American Journal of Biology and Life Sciences
2017; 5(5): 39-46
http://www.openscienceonline.com/journal/ajbls
ISSN:2381-3784 (Print); ISSN: 2381-3792 (Online)

Open Science

Current Management Progress and Future Direction of Schistosomiasis: A Review

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To cite this article

C. M. A. Gause Miraj, Wen-Hua Fan, Bainian Feng. Current Management Progress and Future Direction of Schistosomiasis: A Review. *American Journal of Biology and Life Sciences*. Vol. 5, No. 5, 2017, pp. 39-46.

Received: March 13, 2017; **Accepted**: April 27, 2017; **Published**: August 14, 2017

Abstract

Schistosomiasis, also known as snail fever; is a tropical diseases due to the parasite *Schistosoma* trematode worms. It comes second only to malaria as its impact on the society. Around 230 million people are at highly risk in the world. Combines with others such as diarrhea, chronic pain, anaemia, undernutrition, the disease is also a major risk factor for HIV infection in which caused by female urogenital schistosomiasis. The shistosomiasis parasites modulate the immune response of the host once the egg deposition has started. Until now, the most effective antischistosome drug is praziquantel (PZQ). In this review, we discuss some aspects about new antischistosome drug as well as vaccine development.

Keywords

Schistosoma, Oxadiazole-2-oxide Analogues, Antischistosomal Activity, Neglected Tropical Disease

1. Introduction

In 1852, Theodor Bilharz described for the alternately time a scorching parasitic infection (bilharzia, a while later termed schistosomiasis) caused by genus *Schistosoma* which is blood-dwelling trematode fluke worms. Until now, five schistosome species known to infect humans: *S. mekongi* (identified in 1978), *S. intercalatum* (1934), *S. mansoni* (1907), *S. japonicum* (1904), and *S. haematobium* (1852). [1] Approximately 230 million people in 74 countries are infected where 120 million are characteristic, and 20 million withstand severe illness. [2, 3] Africa, the Middle East, the Caribbean, Brazil, Venezuela are generally infected by *S. mansoni*, some part of Africa and the Middle East are also infected by *S. haematobium* where as *S. japonicum* are seen in the Asia like China, Indonesia, and the Philippines.

2. Biology, Life Cycle Features & Transmission

Schistosomes are digenetic trematodes transmitted by free-swimming larval forms of the virus called cercariae. The cercariae plug a proteolytic enzyme, restrained in specialized glands in the front region, to penetrate the skin of humans. Of the ~2700 genera of Digenian parasites, the 13 that constitute the Schistosomatidae are different in four ways: they have two hosts; they are dioecious (having male and female reproductive organs in diverge individuals), they infect their hosts by promptly penetrating the body surfaceand they parasitize the intravascular cubicle. [4]

The female adult worms start producing eggs once the cercariae penetrate the skin. Then eggs were released from the human host to the fresh water environment by urine or feces. These species are transmitted by various kinds of fresh water snails which work as their intermediate hosts.

The cercariae attach and penetrate the human host skin via glandular secretions depends on host site. After penetrate the skin, the parasite lost their tail and formed young schistosomes called schistosomula. [5] The schistosoma dismantle their bifurcated tails and gain access capillaries and lymphatic vessels through the lungs. After all days, the young worms, or schistosomula, made a journey to the portal

venous system, then aged and unite. These worm pairs then migrate to their eventual vascular bed, i.e., the vesical plexus and veins draining the ureters (*S. haematobium*), inferior mesenteric superior mesenteric veins (*S. mansoni*), and superior hemorrhoidal veins (*S. japonicum*) or pair up and sail downstream. Maturation and migration process may take 4 to 6 weeks, which depend on the parasite & host involvement.

Table 1. *Schistosomiasis preventive chemotherapy database reports information.*

Country	Year	SAC Population Requiring PC For SCH Annually	Population Requiring PC For SCH Annually	Reported Number Of People Treated	Age Group	Reported Number Of SAC Treated	National Coverage
China	2014	122,330	122,330	-	-	-	-
Cambodia	2014	42,829	42,829	67,691	SAC and Adults	14,926	34.90%
Lao PDR	2014	25,287	92,613	68,844	SAC and Adults	21,839	74.30%
Indonesia	2014	27,971	27,971	192	SAC and Adults	31	0.10%
Philippines	2014	1,958,978	1,958,978	1,246,615	SAC and Adults	290,450	14.80%

Definitions: SAC(School Age Children, Aged = > 5 and < 15years) population requiring PC(Preventive Chemotherapy) for SCH(Schistosomiasis) annually - estimated number of SAC requiring PC for SCH annually according to the recommended strategy. Population requiring PC for SCH annually - estimated number of individuals requiring PC for SCH annually according to the recommended strategy.

3. Pathology & Morbidity

Schistosomiasis progresses in three different phases: acute, chronic, and advanced phase. The acute phase is characterized by different kind of symptoms and a high cellular immune response to schistosome antigens especially those from the parasite's eggs. Chronic morbidity was attributed to the healing of granulomata by fibrosis and calcification at the sites of oval entrapment, deposition of schistosomal antigen-antibody complexes in the renal glomeruli or develops secondary amyloidosis. The acute infection may occur within 14–84 days after a prime exposure to contaminated water[6] one of the symptoms is called as Katayama syndrome which is due to immune system response when schistosomula antigens form a T helper type 1 (Th1) cell-driven inflammatory process (involving interleukin-1, interleukin-6 cytokines and tumour necrosis factor). [7, 8] The inauguration of Katayama fever is rapid, with flu-like symptoms such as fever, fatigue, myalgia, complexity, and nonproductive cough. Patients often experienced with marked patchy pulmonary infiltrates, peripheral eosinophilia, and elevated immunoglobulin E. In the situation of *S. japonicum*, it is also associated with either a super-infection or a hypersensitivity process. Patients may retrieve suddenly after 2–10 weeks and develop more consistent contagion characterized by weight loss, dyspnea, diarrhea, diffuse abdominal pain, hepatomegaly, and generalized rash. [6]

Bowel lesions such as ulceration, pseudopolyps, and microabcesses can be occurring due to the gastrointestinal schistosomiasis caused by *S. japonicum*, *S. mansoni, S. mekongi*. The worms transmit as intimidate within the mesenteric veins but are consciences to favor certain locations to lay eggs, consistently in clusters. Egg clusters act of process and incite mucosal inflammation, hyperplasia, ulceration, microabscess formation, blood loss, and pseudopolyposis. [9, 10] Superficial abdominal blood vessel dilatation, spleen increase, and bleeding-prone esophageal varices will shown as clinical signs. [2] Lower abdominal pain is frequent, repeatedly colicky, and generally referred to the left lower quadrant. Diarrhea is common, consistently with occult blood.

Haematuria is well-known sign of urogenital schistosomiasis associated with S. haematobium. Late disease manifestations further include proteinuria (often nephrotic syndrome), bladder calcification, ureteric obstruction, slight bacterial irritation in the urinary tract, renal colic, hydronephrosis, and renal failure. Granulomatous inflammation also caused by *S. haematobium* eggs inserted in the ureteral and vesical walls. Due to systemic immunological effects and local genital tract, urogenital schistosomiasis, for both sexes, a major risk factor for HIV. Schistosomal co-infection commit hasten HIV disease development in individuals earlier infected with HIV, and accelerate viral transmission to sexual partners. [11]

4. Diagnosis

The infection could be detected by several ways including microscopy, egg identification, serology and radiologic findings but also with Non-specific findings like anemia (from chronic blood loss), thrombocytopenia (from splenic sequestration) as well as eosinophilia. Both serological and immunological tests are satisfying in confirming the infection. Microscopic examination of excreta (stool, urine) rest the gold standard for diagnosis of schistosomiasis albeit with some limitations. [2] Quick diagnosis of the species except *S. haematobium*, stool samples are studied for the survival of microbe eggs for a Kato-Katz thick smear or rapid Kato techniques. [12] It has specificity of 100% nonetheless its sensitivity varies with prevalence and term of infection, as readily as with the number of stool specimens collected and slides prepared for microscopy. The Miracidium Hatching Test (MHT) is a traditional approach to assessing *S. japonicum* infection. This test has been widely used in China for more than four decades. [13]

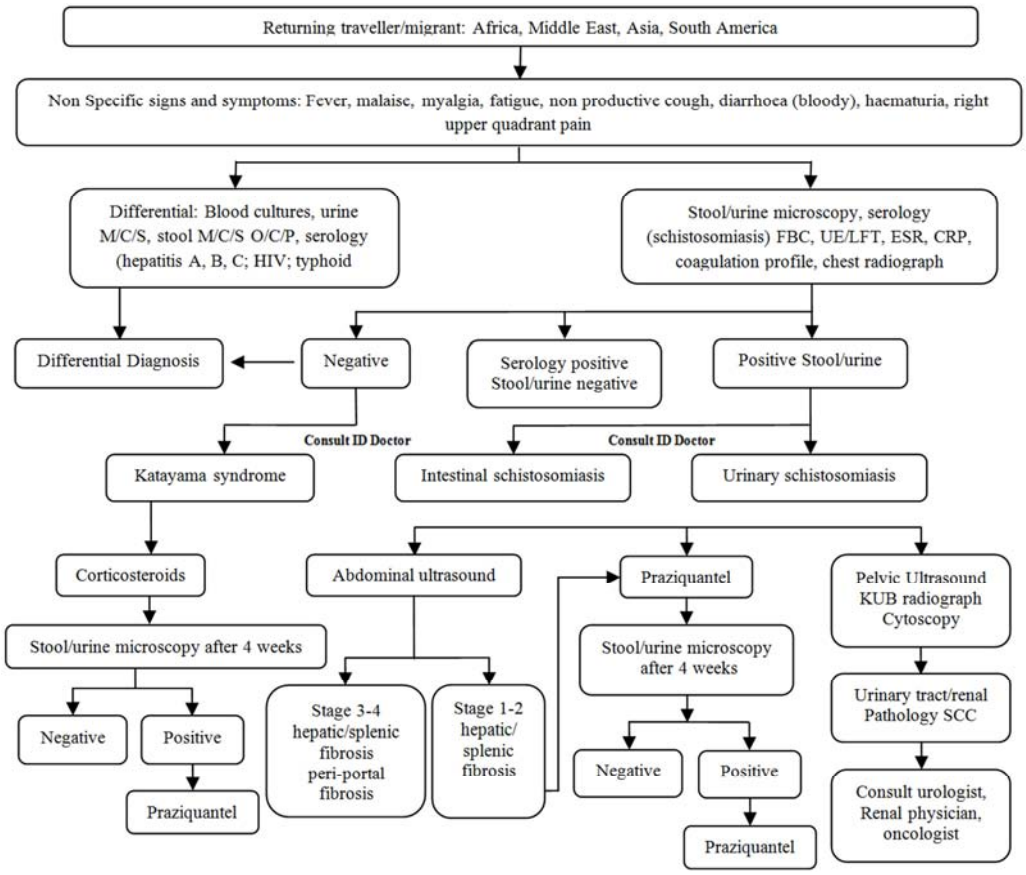


Figure 1. *Diagnostic and treatment algorithm.*

[M/C/S=microscopy/culture/sensitivity; O/C/P=ova/cysts/parasites; FBC=full blood count; UE/LFT=urea, electrolytes, and liver function test; ESR=erythrocyte sedimentation rate; CRP=C-reactive protein; ID doctor=infectious diseases doctor; KUB=kidney, ureter, and bladder; SCC=squamous cell carcinoma.]

To identify *S. haematobium* infection, egg detection in urine is standard. It is particularly helpful in high-prevalence settings, and eggs are identified by their length and shape. During low transmission settings, the investigated slides should be increased to valid the technique's sensitivity. Tests will return negative results around the migration phase preceding egg excretion.

Serologic tests can identify antischistosomal antibodies in serum samples. To diagnose schistosome infection Serologic tests (e.g. Circumoval Precipitin test and Indirect Hemaglutination Assay [14]) were extended to identify the survival of antibody against different schistosome stages. [15]

The main difficulty is their inability to discriminate between past and current active infection. However, a negative result can rule out infection in endemic population. To identify the circulating antigens two promotors technics are used, they are circulating Anodic Antigen (CAA) and Circulating Cathodic Antigen (CCA). [16] They were tested in fieldbased surveys, definitely for preschool children due to the complexity to derive consecutive stool samples, and provided a more sensitive and quick testing for intestinal schistosomiasis (Figure 1). [17] Recently, a point-of-care (POC) urine assay test using CCA has been evaluated in five countries in term to confirm its use as a future diagnostic screening tool. POC testing of urine with CCA was discovered more important than the Kato-Katz technique in sensing low intensities of *S. mansoni* infection. [18] A study on population aged between 9 and 12 years old shown that 72% of measure by POC-CCA was like to 50% measure by Kato-Katz, whereas, 46% POC-CCA measure was like to 10% Kato-Katz prevalence. [19] Commercially accessible CAA/CCA kits, with first-class sensitivity (98%) and specificity (100%), have been put to use to detect both *S. mansoni* and *S. haematobium* disease in serum and urine samples. [20]

Many special tests and procedures commit to help the diagnosis, especially if no eggs are found in the stool or urine, which is consistently the situation in intuitive schistosomiasis. Several method used such as cystoscopy, colonoscopy, endoscopy, and liver biopsy for tissue biopsyl. In integral principle, chest X-rays, CT scan, MRI, and echocardiograms may be used to verify the size of the infected area in various organs.

5. Treatment Status

Historically, antischistosomal agents against *S. haematobium* or *S. mansoni* (hyacanthone, metrifonate, oxamiquin and others) or against *S. japonicum* (niridazole,

antimonials) have been used but lately discontinued due to their narrow therapeutic windows. Praziquantel(PZQ), a pyrazinoisoquinoline derivative,is the most effective oral drug that cure against all schistosome species. [21] The drug is absorbed well and undergoes extensive first pass hepatic clearance. It is secreted in breast milk and its metabolites (which are inactive) are excreted in the urine. The mechanism of action is unknown, although data shown it causes schistosomes to develop tetanic contractions and tegumental vacuoles; affected worms lose their hold on the vein wall, and then washed upstream to the liver, and die.

Recently, published 52 clinical trials showed that a dosage of 30-60 mg/kg praziquantel (PZQ) compared with placebo, made a cure rate of around 76% (range from 67-83%) for human schistosomiasis. Several Studies of PZQ against *S. mansoni* and *S. haematobium* among school children, at a dosage of 40 mg/kg, resulted in cure rates of 60.9%–88.6% and 39.8%–88.9%, [22] respectively. In children aged ≤7 years, 77.6% of treatment-naive children were treated well of *S. mansoni* infection, in which rate is low on such children who have treated before with PZQ. [23] Several dosage of PZQ at 40 mg/kg, which cure the schistosomiasis from 41.9% to as high as 100%, those individuals who also infected with *S. mansoni*, while other *S. haematobium* infection, cure rated 53.1%–88.0%, not vary much from the single dose. [24] Dosage at 60 mg/kg against *S. japonicum* in the Philippines didn't reach the goal to achieve efficacy to treat schistosome infection (92.61% versus 97.03%). Looking for distance coverage and aiming to recover compliance of preschool children (aged 6-5 years) around mass care campaigns targeting schistosomiasis, the WHO provided evident areas with a syrup formulation of PZQ. This syrup gave similar efficacies to crushed PZQ tablets in the benefit of this special age group. [25]

However, with practically single drug used for desolate patient administration and community-based morbidity approach, interference to praziquantel manage emerge and spread. [26] The shortcoming of PZQ is the circumstance that it is not active against juvenile schistosomes. [27] As a preventive drug, praziquantel is not useful at all. It also show side effects such as dizziness, rash, nausea, abdominal pain, pruritus, headache and drowsiness which could be connected with the result of worm death rather than the drug itself. [28]

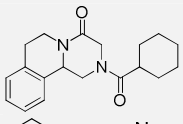
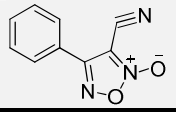
Some antimalarial drugs were discovered to have several antischistosomal properties, such as the artemisinin, produced by combining trioxolanes, and mefloquine. They are effective against the juvenile stages of schistosome species yet are few and far between working well against mature worms. Artemisinin was introduced for the treatment of schistosome in the early 1990s. Combination therapy of arteminisin and PZQ, make a great cure rate of 84% (range 64%-91%). The result suggests that alternative treatment should be explored. Study show as beta-methyl ether of artemether, synthesized by the Shanghai Institute of Materia Medica of the Chinese Academy of Sciences, can kill schistosomula over the first 21 days after they enter the body. [29] However, a combination therapy for acute *S. japonicum* have failed to improved treatment efficacy compared with PZQ alone. [30]

Oxamniquine is an aminoethyltetrahydroquinolone derivative, which is effective against only to *S. mansoni*, mostly the adult worms, and male worms are more sensitive to the drug. [31] Oxamniquine is also rapidly absorbed like PZQ, reached its plasma concentration in 1-4 hours upon intake. A study in Brazil shown that, oxamniquine have similar effect as praziquantel due to its safety and efficacy by cure rate detected by stool examination.

In addition, corticosteroids are also being administered as adjuvant therapy in cases of neuroschistosomiasis [32] and alsothere is a case report of their use in urinary schistosomiasis. [33] Corticosteroids reduce the immune response, hence prevent excessive granulomatous inflammation and tissue damage. [34] Anticonvulsants are used to treat seizures associated with cerebral schistosomiasis but long term use is not reported.

The dependence on a single drug for schistosomiasis control may evolve the drug-resistant parasites. PZQ resistant parasites have already identified in the laboratory. The urgent need of new antischistosomal agents to control the emergence of PZQ resistance must be top priority. The problem has attracted considerable attention in recent years. The PZQ modification can be done in different ways like synthesis of the PZQ, new design of pharmacophore, derives new compound from large-scale screening. But lack knowledge of *in-vivo* target of PZQ, pharmacophore process is hampered. WHO is working on some large-scale screening program. PZQ derivatives with a chloroacetyl group, and amide group in position 2 showed better worm killing activity than PZQ. [35]

Table 2. *Worm-killing activity on S. japonicum adult worms in vitro (PZQ and Oxadiazole-2-oxide) [37].*

Compound	Structure	Conc. (µm)	Number of Worms	killing Activity*		
				24 H	48 H	72 H
1640	-	-	8	0.00%	0.00%	0.00%
1% DMSO	-	-	9	0.00%	0.00%	0.00%
PZQ		10	8	0.00%	0.00%	0.00%
		25	7	14.3%	28.6%	42.9%
		50	9	22.2%	22.2%	44.4%
		100	7	28.6%	42.9%	71.4%
1,2,5-Oxadiazole-2-oxide		10	9	0.00%	0.00%	11.1%
		25	8	25.0%	62.5%	62.5%
		50	8	75.0%	87.5%	87.5%
		100	8	100%	100%	100%

4-phenyl-1,2,5-oxadiazole-3-carbonitrile-2-oxide (commonly 4- phenyl-3-furoxancarbonitrile or furoxan), have shown good activity against the schistosome species. [36] Oxadiazoles n-oxide also known as nitric oxide (NO) donors, which give NO in the presence of physiological levels of thiols. During the treatments stages, furoxan was administrated at 10 mg/kg to *S. mansoni* infected mice, in which it kill both the adult and juvenile worms. The author suggests that the antischistosomal activity of oxadiazole-2-oxide (furoxan) is connected with the donation of nitric oxide(NO) because of the target enzyme. [36] While recently published another paper suggest that the antischistosomal activity of the furoxan (Oxadiazole-2-oxide) does not only depend on NO production or inhibiton of thioredoxin glutathione reductas e(TGR) activity. [37]

Until now, so many new compounds have shown activity against different species of schistosome, but none of them havent come out as a drug yet. Everyday new researches are going on developing a potential candidate for schistosome treatment. Oxadiazole-2-oxide(furoxan) maybe one of the best candidates although so many experiments yet have to be done.

6. Current Status for Vaccine Development

Over the last three decades, intensive efforts have been related to the acknowledgment of vaccine candidates, a process to a great extent facilitated all availability of schistosomegenomic, proteomic andtranscriptomic. [38] The key question is whether human (and reservoir hosts, in the situation of *S. japonicum*) can transpire immunity to schistosome infection or not. Vaccination with irradiated cercariae generate the development of effector responses that can range from Th1-type cell mediated response to parasite-specific antibodies and all of these responses help to kill the worms. [39] In mice, a predoinantly T-helper 1 (Th1) process in the speedily stages of infection shifts to an egg-induced Th2-biased profile, and imbalances between these responses run to severe lesions. [40] The identification of interleukin-13 (IL-13) receptor serve as central regulators of disease development in schistosomiasis was a great achievement. [41]

Together with IgE, valuable levels of IgG4 are produced over helminth infection. Preliminary information was sooner released of a important correlation between susceptibility to re-infection by *Schistosoma mansoni* in humans and increased production of IgG4 to defined schistosomeantigens. [42] The production of IgG4 and IgG2 antibodies in high scale increased the tendency for re-infection. From these studies, it was concluded that immunity to reinfection was preferably closely familiar to the IgE/IgG4 balance than to the confirmed level of each isotype. Both IL-4 and IL-13 production was depend on the response of IgE and IgG4 initially, although it has lately been found that the production of IgG4 antibodies is precise in an antigen specific context by IL-10 and IFN-γ produced by Th0 cells. [43] It suggests that IgE and IgG4 can be separate in confrontation of their reported dependence on IL-4. The assumed role of IL-10 in the preferential induction of an IgG4 reaction should be sitting in the broader perspective of the general properties about cytokine. Indeed it is soon readily established that IL-10 prevents APC dependent IgE synthesis and IgE-dependent cytokine preserve from host cells, activation of eosinophilsalso the release ofIL-5. [44]

Table 3. *Schistosome vaccine candidates.*

Antigen and Reference	Short Form	Size kDa	Stage Expressed	Particular Property	Claimed Protection (%)			IP Status	Institute- Development
					Mouse	Rat	Other		
Glutathione-S-transferase	GST	18	All Stages	Enzyme	30-60	40-60	40 (baboon)	Patented	Institut Pasteur de Lille, France
Paramyosin	Sm97	97	Somula Adult	Muscle Protein	30			Public domain	Cornell/CWRU/NIAID, USA
Irradiated vaccine antigen no. five	IrV-5	62	All Stages	Muscle Protein	50-70	95	25 (baboon)	Patented	Johns Hopkins School of Medicine, Baltimore, USA
Triose Phosphate isomerase (TPI)	MAP-4	28	All Stages	Synthetic Peptide	30-40			Public domain	Harvard School of Public Health, Boston, USA
Membrane antigen Sm23	MAP-3	23	All Stages	Synthetic Peptide	40-50			Public domain	Johns Hopkins/Harvard
Fatty-acid-binding protein	Sm14	14	Somula	Membane Antigen	65		90-100 (rabbit)	Patented	Oswaldo Cruz Foundation, Rio de Janeiro, Brazil

To express the protective antigens, plasmid DNA has been used specifically on *S. japonicum*. DNA vaccines inspire both T-cell and B-cell (or antibody-mediated) immune responses and are here with particularly delectable for schisto some vaccine development. The discipline and production of DNA vaccines are satisfying and economical. Animals in which B-cell–T-cell interactions are compromised separately targeted deletion of CD80 and CD86, or CD154 (CD40L) also reject to ensure TH2 responses afterwards infection, during it is vague whether B cells are at fault for this effect.

World Health Organization (WHO) approved six vaccine candidates until now (Table 3). Among them, the 28 kDa glutathione-S-transferase (GST) appears the excellent characterized and the practically promising molecule, once under verify in phase II clinical trials. [45] The approximately important contributions of these studies have

been the exhibit *in vivo* of the protective act of IgE6 and eosinophils. [46] GST, also recognizes as enzyme, was firstly cloned from a cDNA library from *S. mansoni* and named Sm28GST21. The molecule has been crystallized [47] thus has been disclosed its 3-dimensional structure possible(Table 4). The gene encoding for Sm28GST has been completely sequenced leading to a chain of studies toward the control of protein expression. [48] It is our aspiration that functionally significant antigens will perform as efficient targets for a schistosome vaccine, in which schistosomes act closely with their host, transmission functions such as immune evasion, nutrient uptake and attachment. We presume that host-exposed schistosome proteins that undertake such imperative functions will be effective targets for a schistosomiasis vaccine. [49]

Table 4. *Development Status of Current Vaccine Candidates.*

Candidate Name/Identifier	Preclinical	Phase I	Phase II
SmTSP-2*c* (tetraspanin D)		X	
SmTSP-1	X		
Sm29	X		
Sm23	X		
Sm-p80	X		
Sh-GST28			X
Sm14*e*		X	
Sm28-GST*e* X		X	
Sm28-TPI*e*		X	
Sm97 paramyosin*e*		X	
CT-SOD	X		

Tetraspanins, also called tetraspans, have four transmembrane domains, found on the surfaces of eukaryotic cells, including B and T cells. Sm23 is a tetraspanin [50] expressed in the tegument of *S. mansoni* and is a well known of the fundamentally tested WHO/TDR vaccine candidates. [51] Sm23 is practically efficacious when delivered as a DNA vaccine [52] and does not confer protection as a recombinant protein when formulated with alum. Upon administration, the reduction in egg burden from 50–61% and protection ranging from 29–61% in mice. [53]

7. Prevention and Control

So far, the fundamental means of preventing *Schistosoma* infection is avoiding contact with fresh water infested by all of Schistosome parasites. In cases when there is brief accidental contact mutually infected water, vigorous towel drying is advised to help prohibit the cercariae from penetrating the skin. Fine-mesh filters may also be used to filter the cercariae possibly contained in the water. Insect repellants such as DEET(N,N-Diethyl-meta-toluamide) may be applied topically to prohibit cercariae from penetrating the skin, yet this is not a literally reliable measure. The WHO has recommended preventive chemotherapy as a approach for morbidity act that will help minimize the break, extent, and severity of the consequences of infection. [1]

At present time, control of schistosomiasis is based on drug assistance, snail control, improved sanitation and health education. Population-based chemotherapy allows rapid gains, nonetheless needs purposeful long-term project to assure sustainability and progression to the more troublesome stages of infection and transmission control. [54] Praziquantel, a most trusted drug, treat the human infection, is a great discovery for control strategies on chemotherapy. In 2010, overall 108 million school-aged children required treatment, and only 21 million were given treatment (19%). It was far below the target stated in the resolution. The report come from 28(55%) of 51 countries where preventive chemotherapy against schistosomiasis should have been applied. [55]

A studies in the People's Republic of China, where shown that the comparative molluscicidal efficacy of two formulations of niclosamide, use of 50% niclosamide ethanolamine salt wettable powder resulted in 88% snail mortality meanwhile 4% niclosamide ethanolamine powder caused 93% mortality in the snail population. For molluscicide to be capable in eliminating snails, dosing must be done at least twice a year. [56] One successful example of combining diverse strategies to constitute an integrated act program was the National Schistosomiasis Control Programme implemented in the People's Republic of China in 2004. This program aimed to cut the figure of infection in humans to<5% by 2008 and to <1% by 2015. The strategies recommended by the WHO for clear of soil-transmitted helminths and for schistosomiasis are the related, starting with morbidity control. Thus, integrating the control program of these infections can be cost-effective.

8. Conclusion and Future Direction

There is an urgent need for integrated control programs, and preventive chemotherapy. In case, there is a requirement for efforts to achieve better health education, to provide water and adequate sanitation (especially the use of toilets). Since, there has been limited interest in the considereration of a multiepitope approaches and multivalent antigen. Before a brilliant decision can be made on adjuvant selection, a broad understanding of the desired immune response (phenotype) is necessary.

The challenge for researchers who desire to improve the treatment process of schistosomiasis will include to determine best antigens and to response the praziquantel resistance. The chemotherapy should be effectively carried out on both aged and larval schistosomes. The vaccines that intend either the human host or, in the situation of *S japonicum* or *S mekongi*, the animal reservoir hosts. Moreover, there are mRNAs encoding latter, putatively secreted proteins without experienced homologues that are lodged in the tegument membrane, and these have sooner or later to be explored. The immune system is largely helpless of resisting prime infection, and intervention to super infection takes ages to develop. So, the presence of the host seems to depend on the immunity to derive a suitably balanced TH response that is qualified to produce granuloma development, discourage debilitating acute disease, and reduce fibrosis and tough morbidity around chronic infection.

Amazingly, most (>90%) infected individuals in endemic areas look to successfully make this. Future work using DNA microarray analyses and enriched genetics promises to disclose much about how this balance is achieved. However, it will still require decades or longer before these vaccines can be commercially available. While the world waits, integrated act initiatives must continue.

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