Conquering 'snail fever': schistosomiasis and its control in China

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Schistosomiasis japonica is a serious parasitic disease and a major health risk for more than 60 million people living in the tropical and subtropical zones of south China. The disease is a zoonosis and its cause, the parasitic trematode *Schistosoma japonicum*, has a range of mammalian reservoirs, making control efforts difficult. Current control programs are heavily based on community chemotherapy with a single dose of the highly effective drug praziquantel. However, vaccines (for use in bovines and in humans) in combination with other control strategies are needed to eliminate the disease. In this review, we provide an overview of the transmission, clinical features, pathogenesis, diagnosis, treatment, genetics and susceptibility, epidemiology, and prospects for control of schistosomiasis japonica in China. The threat posed by the Three Gorges Dam may undermine control efforts because it will change the local ecology and associated schistosomiasis transmission risks over the next decade and beyond.

KEYWORDS: China • control • diagnosis • drug treatment • epidemiology • genetics and susceptibility • pathogenesis • schistosomiasis • vaccines

Schistosomiasis (also known as bilharzia) is a chronic and debilitating tropical disease caused by adult blood flukes (parasitic trematode worms) of the genus *Schistosoma* that deposit eggs in blood vessels surrounding the bladder or gut of infected mammalian hosts. *Schistosoma japonicum*, the focus of this review, is currently endemic mainly in China and the Philippines, and causes intestinal and hepatosplenic disease [1–3]. Recent evidence suggests that the burden of disease attributable to *S. japonicum* (and the other major human schistosomes, *Schistosoma mansoni* and *Schistosoma haematobium*) has been under-recognized [4].

Schistosomiasis has a long history in China, disabling and killing millions of Chinese peasants before the new government of the People's Republic began systematic control programs in the 1950s [5,6]. In 1958, Mao Zedong instigated control campaigns, which involved mass mobilization, science, agricultural production, local construction projects and prophylactic measures, fueled primarily by a determination to accelerate China's agricultural development [7]. Despite these remarkable control efforts, and due to attention being diverted away from schistosomiasis, the disease has again become a major burden to the health of the country and remains a formidable

public-health problem there. Progress has been hampered by profound demographic and ecological transformations, resettlement of communities, market-based reforms of the health sector, and the termination of the World Bank loan project on schistosomiasis control in 2001 [8].

The bulk of transmission occurs in the marsh and lake regions of southern China, which cover a vast area of five provinces (Jiangsu, Anhui, Hubei, Jiangxi and Hunan) (FIGURE 1). Endemic foci also occur in the mountainous region of Sichuan and Yunnan, where re-emergence is of growing concern. It is estimated that a million people and over 100,000 bovines are presently infected [9], but these figures could increase due to the Three Gorges Dam across the Yangtze River becoming fully operational in 2009, which may substantially alter the transmission of schistosomiasis both above and below the reaches of the dam [2].

The scope of this article is to review aspects of the clinical features, epidemiology, prevention, treatment, vaccine development and control of schistosomiasis japonica, which, unlike the other human forms of schistosomiasis, is a zoonosis – an infection transmissible from animals to humans – with over 40 species of mammal acting as reservoir hosts [2,9]. The results of control technology advances indicate that a new integrated approach

Figure 1. A map of the Three Gorges Dam showing schistosomiasis endemic foci and the names of various geopolitical divisions.

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to control could lead to eventual elimination of endemic schistosomiasis in China [2,5,9]. However, the threat posed by the Three Gorges Dam may undermine these control efforts because it will change the Yangtze basin ecology and associated schistosomiasis transmission risks over the next decade and beyond [2,6].

***S. japonicum* transmission cycle**

S. japonicum is transmitted through freshwater containing free-swimming larval forms of the parasite called cercariae. These penetrate the skin of humans and a wide range of other animals, including water buffaloes, cattle, rodents, dogs, sheep, pigs and dogs, which act as reservoirs for human transmission [2,9]. The cercariae shed their bifurcated tails and transform their trilaminar tegument into a heptalaminar form adapted to the mammalian environment. Now schistosomula, they leave the skin via the blood vessels and draining lymphatics and reach the lungs. Unlike other trematodes, schistosomes are dioecious (i.e., they have separate sexes), with the adults having a cylindrical body 7–20 mm in length featuring two terminal suckers, a complex tegument, a blind digestive tract and reproductive organs. After several days, the male and female worms

exit the lungs and arrive in the hepatic portal system where they mature, pair up and migrate downstream. The worm pairs reach mucosal branches of the inferior mesenteric and superior hemorrhoidal veins and the females then begin egg production. The process of migration and maturation takes approximately 4–5 weeks, depending on the host species involved. Many eggs pass through the intestinal wall and are discharged in the feces. The eggs of *S. japonicum* are characteristically round with a reduced lateral spine. The life cycle (FIGURE 2) is completed when the eggs hatch and release free-swimming miracidia, which, in turn, reinfect receptive amphibious freshwater snails of the genus *Oncomelania*. The miracidium forms a sporocyst at the site of penetration and this produces daughter sporocysts that migrate to the snail hepatopancreas and asexually produce larval cercariae for daily release into the surrounding water.

Pathology & clinical outcomes

Acute disease

A maculopapular eruption may arise at the site of penetration by the cercariae (FIGURE 3). In migrants or tourists who become infected, skin reactions may develop within a few hours after

infection. However, a rash may appear up to 1 week later. The dermatitis is similar to, but less severe than, swimmers' itch, which develops in sensitized individuals when they are reinfected by species of schistosomes that do not colonize humans (usually the types that colonize birds).

Acute schistosomiasis (Katayama syndrome) is an early clinical manifestation that occurs several weeks postinfection and is common in areas of high transmission rates. A history of contact with contaminated water 14–84 days before presentation is usual. Symptoms are thought to be mediated by the immune complex, and the majority of cases begin with the deposition of an egg (ova) into host tissues. Common symptoms include fever, headache, generalized myalgias, right-upper-quadrant pain and bloody diarrhea. A comprehensive review of acute schistosomiasis is available [10].

Chronic disease

Many of the eggs released by female *S. japonicum* lodge in the tissues of the mammalian host instead of being excreted. Each female worm produces up to 3500 eggs per day and a large proportion of these are trapped within intestinal and hepatic tissues. It is the presence of these retained eggs rather than the worms themselves that cause the principal pathology associated with schistosomiasis [1,3]. Retained eggs contain the miracidium larva that matures over 5 days and remains alive for up to 20 days, secreting enzymes and other toxic products that elicit intense inflammatory responses. Chronic schistosomiasis results from the host's immune response to the eggs and the granulomatous reaction evoked by the antigens they secrete [3,11–14]. The intensity and duration of infection may determine the amount of antigen released and the severity of chronic fibro-obstructive disease. The granulomas destroy the ova but result in fibrotic deposition in host tissues. Most granulomas develop at the sites of maximal accumulation of eggs, the intestine and the liver in the case of *S. japonicum* a characteristic perioval granuloma forms (FIGURE 4), with a necrotic center containing the egg or egg cluster surrounded by epithelioid cells, giant cells and lymphocytes, and an outer layer of plasma cells, eosinophils and fibroblasts. Single eggs are usually reabsorbed but the tissue damage leads to fibrosis. Large egg clusters tend to calcify.

Collagen deposition, cross-linking, contraction and reabsorption are in dynamic balance, and each component is subject to immunoregulation. Most of the information available for schistosomes comes from murine models and indicates that

Figure 2. Lifecycle of schistosomes.

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the determinants of granuloma size may frequently dissociate from those of hepatic fibrosis [1,3,14]. Periportal collagen deposits lead to the progressive obstruction of blood flow, portal hypertension and, ultimately varices, variceal bleeding, splenomegaly and hypersplenism. This periportal fibrosis can be seen on ultrasonography, CT or MRI scans and is characteristic of schistosomiasis. Hepatocellular synthetic function is preserved until the very late stages of disease. Ultrasonography, in addition to clinical examination, is used to detect and quantify hepatosplenic disease based on WHO criteria [3].

Other morbidities

Pulmonary and CNS schistosomiasis (neuroschistosomiasis) are not uncommon with focal or generalized tonic-clonic epilepsy being a typical presentation in *S. japonicum* infection with CNS involvement; focal neurologic deficits may also occur [1,3]. Schistosome infection during childhood causes substantial growth retardation and anemia [1,3]. Successful chemotherapy leads to substantial but incomplete catch-up growth and

Figure 3. Clinical features of acute schistosomiasis: cercarial dermatitis.

Reproduced from [101].

improvement in hemoglobin levels [1,3]. Infected children may also have cognitive impairment and memory deficits, and schistosome infection appears to have adverse effects on both maternal and fetal health [1,3].

Diagnosis

Diagnosis is central to treating schistosomiasis. Case finding and community treatment, assessment of morbidity and evaluations of control strategies all build on the results from diagnostic tests.

Parasitological methods

The detection of *S. japonicum* eggs in the feces is diagnostic of schistosomiasis and is central to its control [5,15]. The rapid, simple and inexpensive Kato–Katz thicksmear stool examination requires 40–50 mg of feces and is widely used in field studies and the national control program in China to determine the burden of eggs in feces [2,5]. The extent of shedding of eggs may fluctuate widely, and as many as three specimens may be required in some patients. The use of formalin-based techniques for sedimentation and concentration may increase the diagnostic yield, but may not be useful in patients with few eggs [2,16]. The miracidium-hatching test has been used extensively by public-health workers in China to rule out *S. japonicum* infection [2]. The test is initiated by the concentration of ova from feces through a nylon tissue bag and suspension in distilled water. Miracidia that hatch from ova are visualized macroscopically, and their presence is diagnostic of infection. In patients with a typical clinical presentation but negative feces specimens, a biopsy of rectal mucosa should be considered for diagnosis [3].

Immunological methods

Antibody detection is quite sensitive and useful in a few specific circumstances, but its use can be limited because antibodies persist after parasitologic cure [2,3,5]. An overview of

immunodiagnosis, including a description of new serologic diagnostic developments in China is available [15]. A positive serologic test may be diagnostic in patients in whom there are no eggs, such as those with Katayama fever [10]. Furthermore, serologic testing is useful in field studies for defining regions of low-level endemicity where individual patients have low egg burdens [5]. Serologic testing may also be useful in determining whether infection has re-emerged in a region after an apparently successful eradication program, and is important for diagnosis in travellers. Commercially available immunodiagnostic kits are generally not as sensitive as multiple fecal examinations and are less specific, due to cross-reactivity with other helminths. Most techniques detect IgG, IgM or IgE against soluble worm antigen or crude egg antigen by ELISA, indirect hemagglutination or immunofluorescence [15]. Detection of circulating adult worm or egg antigens with labelled monoclonal antibodies in serum, urine or sputum in infected individuals is a promising technique that may eventually supersede traditional diagnostic methods [15]. Additional supportive clinical and laboratory evidence of schistosomiasis might include evidence of peripheral-blood eosinophilia, anemia (iron deficiency anemia, anemia of chronic disease or macrocytic anemia), hypoalbuminemia, elevated urea and creatinine levels, and hyperglobulinemia [3].

Biochemical markers of liver fibrosis (procollagen peptides type III and IV, the P1 fragment of laminin, hyaluronic acid, fibrosin, TNF- α R-II and sICAM-1) measured in serum have the potential to provide a highly sensitive and cost-effective method for the assessment of schistosome-induced fibrosis, but are still under investigation [1,17].

Drug treatment

Praziquantel (PZQ), a pyrazinoisoquinoline derivative, is a safe and effective oral drug that is active against all schistosome species; it is the mainstay of treatment and a critical part of community-based schistosomiasis control programs, including those in China [2,5,6,18–21]. Since its discovery in the mid-1970s, its safety and efficacy have ensured its widespread use. It is absorbed well but undergoes extensive first-pass hepatic clearance. PZQ is secreted in breast milk, it is metabolized by the liver and its (inactive) metabolites are excreted in the urine. Side effects are mild and it can be used to treat young children and pregnant women. The drug acts within 1 h of ingestion, although its precise mechanism of action on adult worms is unknown. It appears to trigger titanic contractions in tegumental vacuoles, causing worms to detach from the wall of the vein and die. Schistosome calcium ion (Ca^{2+}) channels are the only moiety so far identified as the molecular target of PZQ, but the evidence remains indirect. In animal models, the presence of host antibodies has been shown to be critical for its efficacy.

Standard treatment of chronic schistosomiasis is 60 mg/kg of PZQ in divided doses; for mass chemotherapy, a single dose (40 mg/kg) is used [3,10]. Treatment failures with this dose have been reported, particularly in areas where schistosomiasis has been recently introduced. Whether this is because the drug works in concert with the host immune response, which has

yet to develop, or is due to migrating larvae not yet susceptible to PZQ, is unknown. As well, there is some evidence, albeit controversial, that resistance to PZQ may be emerging in Africa where there has been heavy exposure to the drug, and where, worryingly, there are reports of *S. mansoni* and *S. haematobium* infections that are unresponsive [1]. There is some laboratory evidence suggesting that drug-tolerant schistosome worms may have altered tegumental architecture, which could limit the effectiveness of the drug. So far, however, patients in many communities have undergone multiple courses of treatment over a period of 10 years or more without a demonstrable loss of efficacy. There have been no reports of the development of tolerance/resistance of *S. japonicum* to PZQ in the clinical treatment of patients in China [20]. In any case, since worm reproduction in the mammalian host is sexual and the generation time is relatively long, resistance is likely to take many years to become an important clinical and public-health issue. Nevertheless, resistance against PZQ in the future cannot be ruled out and research towards development of alternative drugs, such as 4-phenyl-1,2,5-oxadiazole-3-carbonitrile-2-oxide (shown to inhibit a crucial parasite enzyme, thioredoxin glutathione reductase) [22] and mefloquine [23] should be actively encouraged. Other drugs that have been used in the treatment of schistosomiasis are oxamniquine (Vansil®) for *S. mansoni* and metrifonate (trichlorfon) for *S. haematobium* but both are ineffective against *S. japonicum*.

Praziquantel cannot be used for chemoprophylaxis because of its short half-life (1–1.5 h) and because it cannot kill schistosomula (the migrating larvae) that are 3–21 days old. Artemether (ART), which comes from the leaves of the Chinese medicinal plant *Artemisia annua*, and is used for the treatment of malaria, is effective against juvenile schistosomes during the first 21 days of infection in animals and humans [20] and it should kill all immature schistosomula if it is administered every 2 weeks. Accordingly, it has been used as a chemoprophylactic in schistosomiasis-endemic areas in China in high-risk groups, such as flood relief workers and fishermen [5,20]. The doses required are lower than those required for treatment of malaria, but it is unlikely that ART would be used in other regions, such as Africa, where malaria is endemic, because such use might lead to the selection of ART-resistant *Plasmodium falciparum*.

In animals, combination therapy with PZQ plus ART is safe and results in higher worm-reduction rates than PZQ alone [20,21]. However, a randomized, double-blind, placebo-controlled trial for evaluating combined chemotherapy with PZQ and ART at two different dosages (60 and 120 mg/kg) in the treatment of acute schistosomiasis japonica in China failed to improve treatment efficacy compared with PZQ alone [24]. However, the trial showed that PZQ administered as a dosage of 60 mg/kg (1 day; 3 × 20 mg/kg doses at 4–5-h intervals) to be as effective as the dosage of 120 mg/kg (6 days; 20 mg/kg for each day split into three doses at 4–5-h intervals) that is currently used for treating acute schistosomiasis in China. This result may impact on future schistosomiasis treatment policy in China.

Figure 4. A characteristic perioval granuloma formed around an *Schistosoma japonicum* egg (arrow) in mouse liver (hematoxylin plus eosin stain).

Immunology

It would be impossible to report on progress towards the development of antischistosome vaccines without a description of some basic details of the immunology of schistosomiasis. A number of recent reviews have considered the immunobiology of schistosomiasis, including the nature of the host innate and adaptive responses to schistosomes and the strategies used by the parasites to manipulate such responses [25–31]. An important point to make is that schistosomes are nonreplicating organisms in their mammalian hosts. As a result, a partial, nonsterilizing, naturally acquired or vaccine-induced immunity could potentially decrease human pathology and transmission in areas where schistosomiasis is endemic.

In general, studies in mouse models have established that T-cell-mediated immunity is fundamental to acquired resistance to schistosomes in mice. Much of this protection was shown to be mediated by activated macrophages, and, together with studies of cytokines suggested that a vaccine that induced macrophage-activating Th1 cytokines (IFN- γ and IL-2) may be beneficial in preventing schistosomiasis. However, repeated vaccination with irradiated cercariae produced incremental increases in Th2-mediated (IL-4 and IL-5 predominance) protection, which was transferable to nonvaccinated animals. Studies using B-cell-deficient and cytokine-deficient mice demonstrated that successful antischistosome vaccination required induction of strong Th1 and Th2 responses. Following infection by normal or radiation-attenuated cercariae, the predominant early immune response was Th1-mediated and aimed at the adult worm. Following egg deposition in tissues (6-weeks postinfection for *S. mansoni* or 4–5 weeks for *S. japonicum*), the Th1 response is diminished, being replaced by a prominent Th2-mediated phase. Indeed, it

appears that egg antigens are able to directly suppress the Th1 response, a phenomenon that may also occur in humans. The Th2 response results in an increase in serum IL-5, massive bone and blood eosinophilia and the characteristic granulomatous response aimed at the egg, resulting in collagen deposition, tissue fibrosis and the disease manifestations of schistosomiasis. The precise role of eosinophils in the disease process in the mouse model of infection remains undetermined.

As with the other human schistosomes, longitudinal cohort studies of reinfection rates following curative drug treatment have shown that people living in schistosome-endemic areas acquire some form of protective immunity after years of exposure to *S. japonicum* [1–3,29,30]. However, age-related innate resistance mechanisms may also play an important part in the epidemiology of schistosomiasis [1,31]. Immune correlative studies in various parts of the world suggest that acquired anti-schistosome protective immunity after curative drug therapy is mediated (although not exclusively) by a Th2 response, orchestrated by IgE against adult and larval antigens, which stimulate eosinophils to release cytotoxins targeting schistosomula [1,30,31]. Despite the protective role of IgE, high levels of IgG₄ are also produced during infection, potentially blocking the protective effects of other immunoglobulins. It has been shown that immunity to reinfection is more closely related to the IgE/IgG₄ balance than to the absolute level of each isotype [29,31]. The clinical expression of immunity to schistosome infection is obviously not simply determined by the mere balance between IgE and IgG₄ antibodies. It cannot exclude the participation of additional mechanisms, such as a potential protective role of IgA antibodies in human schistosomiasis; the effector functions of IgA antibodies may be associated with a decrease in female worm fecundity and egg viability [28,29,31]. In addition, it is important to emphasize that the development of a vaccine for schistosomiasis that is dependent on IgE would be potentially problematic, and would probably be impeded by regulatory and safety issues due to potential vaccination-induced anaphylaxis [28]. Therefore, looking at the immune responses of chronically infected individuals, and even those who become refractory by producing IgE after drug treatment, should be approached with caution [28]. Although we still know very little about the protective mechanisms required to engineer an efficacious recombinant vaccine for human schistosomiasis, the analysis of human antibody and cytokine responses to candidate vaccine antigens is potentially a creditable way for establishing *bona fide* vaccine candidates [32]. One such study, carried out over several years in Egypt, focused on ten of the most promising *S. mansoni* vaccine antigens [33]. At various time points, immune responses against the panel of antigens were determined in cohorts of humans living in areas where they were regularly exposed to infection and these results were compared with parasitological diagnosis. Cellular and humoral immune responses were significantly associated with either apparent resistance or with apparent susceptibility to reinfection following chemotherapy. However, only a minority of these responses produced consistent associations and the results were seldom clear-cut. A similar investigation, carried out in the Philippines on *S. japonicum* [34],

confirmed the Egyptian findings, but a straightforward comparison was not possible because some of the antigens tested were different in the two studies. The discovery of the surface-located tetraspanins Sm-TSP-1 and TSP-2 as major candidate vaccine antigens resulted from a combination of protective efficacy data obtained in the *S. mansoni* murine challenge model with their recognition by IgG₁ and IgG₃ antibodies from humans exposed to, but resistant to, schistosomiasis [35]. These human studies are thus instructive for not only identifying the few antigens directly and exclusively associated with resistance, but also for indicating which of these components can be formulated with adjuvants to generate protective responses in animal models [32].

In the case of *S. japonicum*, zoonotic transmission adds to the complexity of control programs, but provides a unique opportunity to develop a transmission-blocking veterinary vaccine (e.g., against bovines) to help prevent human infection and disease. However, studies of protective immunity in bovine schistosome infections are few [36], and, consequently, our knowledge of the immunology of schistosome infections in water buffaloes and cattle is extremely limited. This is particularly the case for water buffaloes where immunological reagents for studying immune responses are relatively scarce. Recent PZQ treatment and reinfection studies of bovines infected with *S. japonicum* in China have indicated that age-related resistance occurs in water buffaloes but not in cattle [37]. Whether this self-cure phenomenon has an immunological basis has yet to be determined. Additional studies on the immunology of bovines represent an important area for future research and will be essential both in selecting *S. japonicum* vaccine antigens and in defining the optimum route of immunization [28,36].

Vaccine development

The control of schistosomiasis requires large-scale population-based chemotherapy in addition to environmental and behavioral modification, but it is difficult and costly to sustain such a program [32]. Consequently, there is a need for a vaccine for long-term prevention. Vaccine development against *S. mansoni* and *S. haematobium* necessitates the use of clinical vaccines for human application. The zoonotic transmission of schistosomiasis japonica allows for a complementary approach for *S. japonicum* involving the development and deployment of a transmission-blocking veterinary vaccine in livestock, particularly bovines, prior to developing a human vaccine should this be necessary. The vaccine would be used in reservoir hosts of *S. japonicum* to potentially reduce transmission to humans. Bovines (cattle and water buffaloes) are the major reservoirs for *S. japonicum* infection in China, with estimates that 75–90% of egg contamination comes from this source – calculations from drug intervention studies and mathematical modeling underpinning the rationale for developing a veterinary vaccine against *S. japonicum* [38,39]. The possibility that this strategy could already pay off is supported by Chinese studies showing that the animal–snail–human transmission cycle is more prominent than the human–snail–human cycle in sustaining the infection [38,40]. Schistosomiasis japonica was once highly prevalent in China in

Table 1. Lead *Schistosoma japonicum* vaccine candidates that have shown efficacy in the mouse model and in reservoir hosts of schistosomiasis japonica.

Antigen (as native protein, recombinant or DNA plasmid)	Abbreviation	Size (kDa)	Stage expressed	Biological function	Worm burden reduction (%) [*] in mouse (other hosts)
Paramyosin	Sj-97	97	Schistosomula, adults	Contractile protein and others	20–86 (17–60, buffaloes/cattle/pigs/sheep)
Triose phosphate isomerase	Sj-TPI	28	All stages	Enzyme	21–33 (42–60, buffaloes/pigs)
23-kDa integral membrane protein	Sj-23	23	Adults	Membrane protein	27–35 (0–59, water buffaloes/cattle/sheep)
Aspartic protease	Sj-ASP	46	All stages	Digestion of hemoglobin	21–40
Calpain large subunit	Sj-calpain	80	All stages	Protease	40–41
28-kDa glutathione S-transferase	Sj-28GST	28	All stages	Enzyme	0–35 (16–69, water buffaloes/cattle/sheep)
26-kDa glutathione S-transferase	Sj-26GST	26	All stages	Enzyme	24–30 (25–62, water buffaloes/cattle/pigs/sheep)
Signalling protein 14–3–3	Sj-14-3-3	30	All stages?	Molecular chaperone	26–32
Fatty acid binding protein	Sj-14	14	All stages?	Binds fatty acids	34–49 (32–59, rats/sheep)
Serpin	Sj-serpin	45	Adults	Serine proteinase inhibitor	36
Very low-density lipoprotein binding protein	Sj-SVLBP	20	Adult males	Binds lipoproteins	34
Ferritin	Sj-Fer	450	All stages?	Iron storage	35 ⁺

When evaluated, reduced egg-hatching capacity of *S. japonicum* eggs into viable miracidia occurred with some vaccines. Cocktails of several of the leading candidates have also been tested.

^{*}Egg reduction (in feces and/or liver) was also recorded with many of the candidates.

⁺Mucosal immunization.

Adapted with permission from [28].

other domestic animals such as pigs but, in recent years, these animals have been of less importance because they are usually restricted to pens, with limited access to the marshland areas [39]. Sheep and goats are also infected but to a far lesser extent, and, as wild animals become rarer, their involvement in transmission can probably be ignored [39].

A high level of protection against *S. japonicum* infection has been attained in mice, water buffaloes and pigs when the animals were immunized with irradiated cercariae, with both Th1 and Th2 responses probably contributing to protection [36,41,42]. Vaccination can be either targeted towards the prevention of schistosome infection or to the reduction of parasite fecundity. A reduction in worm numbers is the gold standard for antischistosome vaccine development, with the migrating schistosomulum stage likely to be the major vaccine target of protective immune responses [36,41,42]. However, as schistosome eggs are responsible for both pathology and transmission, a vaccine targeted at parasite fecundity and egg viability is also relevant [29,31,36,41].

Coordinated laboratory and field research has identified a set of well-defined *S. japonicum* molecules with protective potential, with a view to developing a recombinant-protein,

synthetic-peptide, or DNA vaccine. Some of the leading *S. japonicum* vaccine candidates (as recombinant protein and/or DNA vaccines) are presented (TABLE 1). A majority are membrane proteins, muscle components or enzymes, and further details of the characteristics and efficacy of these and other vaccine candidates can be found elsewhere [28,36,41,43]. Recent studies in water buffaloes of the protection afforded by *S. japonicum* recombinant proteins (e.g., paramyosin [Sj-97] and GST-26 [Sj-GST26]) [28] and DNA plasmids (triose phosphate isomerase [Sj-TPI] and 23-kDa integral membrane [tetraspanin] protein [Sj-23]) [44] have yielded encouraging results, indicating the feasibility of developing a transmission-blocking vaccine for use in reservoir hosts.

The current *S. japonicum* vaccine candidates may not prove to be the most effective and it is, therefore, important to continue to identify new target antigens. Complete sequencing of the *S. japonicum* genome, the generation of a large schistosome transcriptome database and postgenomic technologies, including DNA microarray profiling, proteomics, glycomics, immunomics and the application of RNA interference (RNAi), can provide the necessary ancillary information [45–50]. These new approaches in antigen discovery have the potential to identify a new generation

of vaccine target molecules that may induce greater potency than the current candidate schistosome antigens [28]. Molecules containing signal peptides and signal anchors as predictors of excretory–secretory products, including enzymes and components exposed on the schistosome tegument (including receptors) that interact directly with the host immune system, are highly relevant targets for study [51]. Some causation is necessary, however, as the *S. japonicum* homologue of the surface-located tetraspanin Sm-TSP-2, discussed earlier and regarded as a major candidate vaccine antigen for *S. mansoni* [35], showed at best only very moderate protection in immunized mice, probably due to the high level of polymorphism of this molecule, which reduces its potential as a vaccine candidate [52].

In addition, the selection of a suitable adjuvant and delivery system to aid in the stimulation of the appropriate immune response are critical steps on the path to the development and employment of successful antischistosome vaccines, and a number of different approaches have been tested, with some success [28,53]. Immunogenicity relies on antigenic access to particular pathways promoting the secretion of cytokines from antigen-presenting cells and other cells. This can now be achieved artificially by using immunomodulating agents, live microbiological carriers or DNA technology. The new lines of immunomodulators include a variety of agents, such as lipopeptides, saponins, muramyl dipeptides, CpG oligodeoxynucleotides and lipopolysaccharide, which could provide clues as to how vaccines should be formulated [53]. Understanding the mechanisms whereby these novel adjuvants work will no doubt facilitate the production of more effective vaccines.

Genetics & susceptibility to schistosomiasis

Genetic background plays a pivotal role in determining the susceptibility to and outcome of schistosome infections [54–59]. Segregation analysis revealed that susceptibility to infection is controlled by the *SM1* gene locus that has been linked to the 5q31–q33 chromosome region comprising the genes *IL-4*, *IL-5* and *IL-13* [60,61] although other polymorphisms in genes of the type 2 cytokine pathway may also be important [62]. Furthermore, two single nucleotide polymorphisms (SNPs) within *IL-5* have been associated with the development of symptomatic infection with *S. japonicum* in a Chinese population [59]. Another study indicated that the segregation of a codominant gene (*SM2*) could account for the familial distribution of severe schistosomiasis. Linkage analysis indicated that this gene occurred within the 6q22–q23 region, with polymorphisms close to and in the *IFNGR1* gene [57]. A later study confirmed linkage of severe schistosomiasis with the *IFNGR1* locus, and also suggested a possible association with the interleukin *IL-13/IL-4* region and the *TGF-β1* gene [54]. Furthermore, IFN-γ production by egg antigen-stimulated peripheral blood mononucleocytes correlates with protection against severe schistosomiasis *mansoni* [63] and two polymorphisms in *IFN-γ* have been found to be associated with advanced hepatic disease [56], consistent with the antifibrogenic role of IFN-γ and the low IFN-γ production by subjects with severe disease [56,64]. IFN-γ is also associated with protection

against peripheral fibrosis in humans infected with *S. japonicum*, whereas IL-10 protects against severe hepatic central fibrosis, and it is likely the two fibrotic outcomes are under different genetic control [65].

Associations have also been reported between the clinical manifestations of chronic schistosomiasis and gene alleles within the MHC, although no consistent picture has emerged from these studies [55].

Control

Over the past 50 years, China has placed a high priority on the control of schistosomiasis, which has resulted in a substantial reduction in human prevalence [8]. Despite these achievements progress appears to be stagnating as national surveys of schistosomiasis showed that the prevalence of schistosomiasis infection in humans in areas in which it is endemic had not substantially changed from 1995 (4.9%) to 2004 (5.1%) [66]. Past efforts to control the amphibious *Oncomelania* snail populations through chemical mollusciciding or modification of snail habitats have often resulted in environmental pollution [66]. After over 20 years of experience, it is generally agreed that morbidity control through population-based PZQ chemotherapy, although it is the mainstay of current schistosomiasis control programs in China and elsewhere, does have some limitations. PZQ compliance can be erratic and mass treatment does not prevent reinfection. This occurs rapidly in exposed populations with a history of endemicity, such that within a period of 18–24 months following chemotherapy, the prevalence returns to its baseline level [3]. Furthermore, efficient drug delivery can require a substantial infrastructure to regularly mass treat endemic populations. This can make chemotherapy an expensive and often impractical approach. In China, there is the additional challenge that transmission control necessitates interventions targeting animal reservoirs, particularly buffaloes [38–40]. Moreover, in situations of ongoing high transmission and interrupted chemotherapy campaigns, severe ‘rebound morbidity’ in terms of hepatosplenic disease is now well documented for schistosomiasis, contributing to the disease burden [3,67].

Spatial epidemiology, geographical information systems (GIS), remote sensing (RS; using Landsat Thematic Mapper images), and the use of advanced Bayesian based spatial statistics have become important tools in China’s national schistosomiasis control program over the past 10–15 years [9,68–70]. Predictions of infection risk are mainly made by the application of the normalized difference vegetation index or land surface temperature to predict *Oncomelania* habitats [71]. A study conducted by Guo and colleagues in 2005 employed RS and GIS techniques to identify habitats of *Oncomelania hupensis* in the Poyang Lake area [69]. Multi-temporal Landsat Thematic Mapper 5 satellite images were used to derive land-use types from the dry and wet seasons, as well as to extract the NDVI. The derived environmental features were used to develop a composite model that predicted an estimated 709 km² of marshlands in Poyang Lake as potential habitats for *O. hupensis*. In a further step, the predicted snail habitats were used as centroids, and buffer zones were established around them. Villages with an overall prevalence of *S. japonicum*

below 3% were located more than 1.2 km away from the centroids. A gradient of high-to-low prevalence was observed with increasing distance from centroids. Results of the developed model proved an important tool for identifying high-risk areas of schistosomiasis japonica.

Mathematical modeling of schistosomiasis has important implications when considering options for control [72]. Models can predict the spread of disease, the utility of various strategies for treatment coverage and the impact of vaccines [72]. The future elimination of schistosomiasis as a public health problem in mainland China will no doubt rely on a combination of various control options, such as drug treatment regimes, environmentally friendly mollusciciding, vaccination, environmental modification, health education and improved sanitation. Mathematical models will assist in estimating the effect of these combined strategies and the costs of control [39].

The ecology of central and southern China is changing drastically as a result of the construction of the Three Gorges Super Dam (FIGURE 1) [2,70,73,74]. Emergences or re-emergences of schistosomiasis have resulted from other large-scale hydroprojects, such as the Gezira–Managil Dam in Sudan, the Aswan Dam in Egypt, the Melkasadi Dam in Ethiopia, and the Danling and Huangshi Dams in China [1]. It is predicted that the Three Gorges Dam will impact considerably on the distribution and transmission of schistosomiasis [2,70,73,74]. The Chinese Government began work on this giant impoundment across the Yangtze River in the 1950s; in 2003 the Dam was closed to a height of 135 m. In 2009, it will become fully operational, reaching its full height of 185 m and begin to generate 18,600 MW of power for approximately 10% of China [70,74]. It will also help to control the lower Yangtze floods, which cause much-feared periodic disasters. However, it will create a lake behind the dam that will stretch 600 km upriver, with shorelines suitable in many areas for the establishment and propagation of the intermediate snail hosts and *S. japonicum* transmission. The lake will be located between the two key transmission zones of *S. japonicum* – Sichuan and Hubei–Hunan. The downstream schistosomiasis-free buffer is only 40 km and the upstream buffer is 500 km. The resettlement of over one million people into areas settled by 19 million people along the lake, as well as increased river traffic, could introduce both parasites and intermediate hosts into the lake. The lake will provide an opportunity for hybridization by two sub-species of the intermediate host, *O. h. robertsoni* in Sichuan and *O. h. hupensis* in Hubei [2], with unpredictable consequences. If schistosomes become established in the lake, they would be difficult to eradicate.

In addition to the problems posed by the new lake, the downstream area will undergo massive changes in ways that could also affect schistosomiasis. Downstream flows will be higher in winter and lower in summer, and the annual flooding will be prevented. The marshlands will expand. Silt deposition will change and some areas will become more suitable for intermediate host snails, and other areas less so. The current two transmission seasons may become one long season with the absence of the annual floods, which drown the adult snail intermediate hosts. The transmission season may also be further extended by

climate change, with the temperature remaining above the optimal 10°C required for miracidia release for longer. It has also been estimated by Yang *et al.* that climate change has expanded the potential schistosomiasis transmission area by 41,335 km², translating to an additional 20.7 million people at risk, via the shifting of the historical 0–1°C January isotherm from 33°15' N to 33°41' N [75]. Furthermore, two lakes forming part of the proposed South–North water transfer project are located within this new transmission area and may pose additional challenges for control [75]. These factors are certain to alter the distribution and endemicity of schistosome infection in ways that are currently unpredictable. Seto and colleagues [70] believe that overall snail densities may decrease with lower and more-stable water levels, but the density of infected snails and corresponding human infections may increase due to colocation of bovine grazing areas, snail habitat and human activity that may occur with more-stable water levels.

Expert commentary & five-year view

The collective effort to understand and control schistosomiasis japonica in China over the last 50 years has been enormous. In those areas where it was possible, the transmission environment has been modified to make it insusceptible to the snail hosts. Toxic drugs were used to cure infection and those infected were followed for years until cure was certain. Great progress was made and the huge toll taken on affected human populations now has been greatly reduced. Dwarfism, impoverishing incapacity to work in rural areas and widespread premature death are now a thing of the past. The tenacity and dedication of the thousands of schistosomiasis control workers, farmers, government cadres and public health officials were central to this massive control effort.

In some areas, elimination was not successful. However, advances in chemotherapy with PZQ and (probably) artemether now make it possible to cure and prevent both parasite infection and associated fibro-obstructive disease. But, in areas of continued transmission, it is not possible to remove the parasite from the environment. Thus, chemotherapy needs to be administered repeatedly to protect communities, a process that must eventually lead to community fatigue and possibly to drug resistance.

The inability to eradicate the parasite from large areas of the lake and marshland zones of the middle Yangtze and its upper reaches, together with ecological changes soon to arise throughout the Yangtze basin due to the complete closure of the Three Gorges Dam in 2009 make it imperative to develop new strategies for control. Foremost among these is the development and deployment of human and animal vaccines.

Given the breadth of the international efforts to generate anti-schistosome vaccines, there is considerable optimism about possible future success. However, these vaccines will be only one component of an integrated schistosomiasis control program. Combining vaccination with chemotherapy would reduce overall morbidity in conjunction with limiting the impact of reinfection. Although induction of consistent, high-level protection has not been recorded for any of the current bovine vaccine candidates,

the reported level of approximately 50% protection should be sufficient for a combined chemotherapy-bovine vaccination approach that would provide an effective control strategy for schistosomiasis. Bovine vaccination, in concert with other control efforts [8,66], may make the Chinese goal of reducing human prevalence below 1% by 2015 achievable [5,6].

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Key issues

- Schistosomiasis, caused by *Schistosoma japonicum*, has a long history in China and was named the 'god of plague' in the 1950s by former chairman Mao Zedong.
 - Unlike the African forms, schistosomiasis japonica is a zoonosis, which complicates control efforts.
 - The bulk of transmission occurs in the marsh and lake regions of southern China comprising five provinces (Jiangsu, Anhui, Hubei, Jiangxi and Hunan), with other endemic foci in the mountainous regions of Sichuan and Yunnan.
 - Clinical features in schistosomiasis range from fever, headache and lethargy to severe portal hypertension, hepatosplenomegaly and premature death.
 - The disease is diagnosed parasitologically with the Kato-Katz thicksmear stool examination and immunologically with antibody/antigen-detection tests – ELISA, indirect hemagglutination or immunofluorescence.
 - Praziquantel is the therapeutic drug of choice and represents the cornerstone of control. A new drug, artemether, could be used as a chemoprophylaxis for travellers and high-risk groups with significant water contact, such as fishermen.
 - Immunologically, schistosomiasis largely stimulates a Th2-mediated (IL-4 and IL-5 predominance) response in humans under the orchestration of IgE and eosinophils.
 - Vaccination is needed for long-term prevention and integrated control. Both human and bovine vaccines comprising recombinant proteins, synthetic peptides and DNA constructs are being explored.
 - S. japonicum* recombinant proteins (e.g., paramyosin [Sj-97] and GST-26 [Sj-GST26]) and DNA plasmids (triose phosphate isomerase [Sj-TP1] and 23-kDa integral membrane protein [Sj-23, a tetraspanin]) have yielded encouraging levels of protection in bovines.
- Genetic background plays a pivotal role in determining susceptibility to infection and disease. The *Schistosoma mansoni* 1 (*SM1*) gene locus that has been linked to the 5q31–q33 chromosome region comprising the genes *IL-4*, *IL-5* and *IL-1*, and a codominant gene (*SM2*) on the 6q22–q23 region, with polymorphisms close to and in the IFN- γ receptor 1 (*IFNGR1*) gene have been implicated with the infection and familial distribution of severe schistosomiasis.
- The Three Gorges Dam represents a new threat to control but, through integrated efforts, including drug treatment, the use of a vaccine and other control options, this challenge can be met in the 21st Century.

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