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Advancing a vaccine to prevent human schistosomiasis

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ABSTRACT

Several candidate human schistosomiasis vaccines are in different stages of preclinical and clinical development. The major targets are *Schistosoma haematobium* (urogenital schistosomiasis) and *Schistosoma mansoni* (intestinal schistosomiasis) that account for 99% of the world's 252 million cases, with 90% of these cases in Africa. Two recombinant *S. mansoni* vaccines – *Sm*-TSP-2 and *Sm*-14 are in Phase 1 trials, while *Smp*80 (calpain) is undergoing testing in non-human primates. *Sh*28GST, also known as Bilhvax is in advanced clinical development for *S. haematobium* infection. The possibility remains that some of these vaccines may cross-react to target both schistosome species. These vaccines were selected on the basis of their protective immunity in preclinical challenge models, through human immune-epidemiological studies or both. They are being advanced through a combination of academic research institutions, non-profit vaccine product development partnerships, biotechnology companies, and developing country vaccine manufacturers. In addition, new schistosome candidate vaccines are being identified through bioinformatics, *OMICs* approaches, and moderate throughput screening, although the full potential of reverse vaccinology for schistosomiasis has not yet been realized. The target product profiles of these vaccines vary but many focus on vaccinating children, in some cases following mass treatment with praziquantel, also known as vaccine-linked chemotherapy. Several regulatory pathways have been proposed, some of which rely on World Health Organization prequalification.
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Q2 Schistosomes are snail-transmitted, water-borne parasitic platyhelminthes (order Trematoda) that are found in fresh water bodies in low- and middle-income countries. Current estimates from the Global Burden of Disease Study 2010 (GBD 2010) suggest that 252 million people are infected with schistosomes, 90% of whom live in sub-Saharan Africa [1]. The World Health Organization (WHO) reports that in 2014 at least 258 million people worldwide required frequent and regular preventive treatment for schistosomiasis [2]. Recently though, the disease even emerged in Europe on the French island of Corsica [3]. Globally two-thirds of the cases are infected with *Schistosoma haematobium* (the cause of urogenital schistosomiasis), one-third with *Schistosoma mansoni* (the cause of intestinal schistosomiasis), and 1% with *Schistosoma japonicum* or *Schistosoma mekongi* (the causes of intestinal schistosomiasis in East Asia). Schistosomiasis, together with hookworm and leishmaniasis, rank as those neglected tropical diseases with the highest disease burden as defined by disability-adjusted life years (DALYs) [1]. While the GBD 2010 estimated that the world lost 3.3 million DALYs from schistosomiasis in 2010 [4], other estimates suggest that DALYs lost may even be an order of magnitude higher if chronic morbidities such as malnutrition, inflammation, and pain are also taken into consideration [5,6]. In addition, there is some evidence that *S. haematobium* may represent an important risk factor for HIV/AIDS acquisition because of the mucosal inflammation and ulceration caused by genital schistosomiasis in tens of millions of girls and women [7,8]. In addition to *S. haematobium*-HIV co-infections, *S. mansoni* and malaria co-infections are also widespread in Africa, and may result in synergistic effects [9].

Schistosomes reproduce by asexual reproduction in freshwater snails and are released in large numbers as infective larvae. In water, these cercariae penetrate the skin of a human

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host, transforming into schistosomulae that migrate through the bloodstream and lungs to the liver where they become adult male-female schistosomes. In the host's mesenteric or bladder venules, the adult schistosomes release their eggs into the tissues before some make their way into the feces or urine. Upon contact with fresh water, the eggs hatch and give rise to miracidia that enter the intermediate hosts, snails.

The pathogenesis of human schistosomiasis begins when eggs destined for exit out of the body through feces or urine, instead become embedded in the tissues of the human intestine or bladder. These trapped eggs subsequently induce inflammation, granulomas, and fibrosis leading to a number of clinical sequelae including hepatic fibrosis and hepatosplenomegaly, hematuria, bladder fibrosis and obstruction, hydronephrosis and chronic renal disease. *S. haematobium* ova can also elicit vaginal or cervical inflammation (so-called "sandy patches") that increases the risk of HIV/AIDS acquisition, such that schistosomiasis is considered an important co-factor in Africa's AIDS epidemic [7]. Moreover, infection with *S. haematobium* is strongly associated with squamous cell carcinoma of the bladder [10]. Chronic schistosomiasis, in addition, can lead to many other sequelae as well, especially in children, including but not limited to anemia, chronic pain, undernutrition, growth failure and cognitive deficits [5,6].

Strategies to control schistosomiasis center on Mass Drug Administration (MDA) of an acylated quinoline-pyrazine known as praziquantel (PZQ). While less than 20% of children who need PZQ MDA actually receive regular treatments, the fact that the prevalence of schistosomiasis may have increased over the last two to three decades [11], suggests that MDA with PZQ alone will not be adequate for the global elimination of schistosomiasis. Indeed, a survey of almost 400 experts on neglected tropical diseases concluded that schistosomiasis may not be eliminated through current approaches [12]. A major reason is that MDA does not interrupt transmission and does not prevent schistosome reinfection. With the added potential for the emergence of PZQ resistance [13,14], there is thus an urgent need for vaccines as an alternative approach to lower the disease burden, limit transmission and mitigate the morbidity of schistosomiasis [15,16].

1. Biological feasibility for vaccine development

Immunity as a result of natural exposure to a pathogen is often taken as evidence of the biological feasibility for vaccine development. In the case of human schistosomiasis, rates and intensity of infection tend to diminish with age, especially after puberty. However, it is unclear if acquired immunity is solely responsible for this observation. Furthermore, the likelihood that such immunity is partly due to an IgE-mediated mechanism complicates strategies that try to mimic natural immunity. The goal of immunization, therefore, may not be sterilizing immunity but the long-term reduction of both ova burden in the host tissues and excretion from the host, leading to diminished pathogenicity and reduced transmission, respectively.

The feasibility of schistosomiasis vaccines has been demonstrated in a series of proof-of-concept studies where mice and non-human primates (NHPs) were immunized with radiation-attenuated cercariae, and were found to be protected (with efficacies of >80%) against percutaneous schistosomal challenge [17–19]. Vaccinated mice exhibited both cellular and humoral immune responses to lung-stage parasites [20], and under some circumstances, the co-administration of the cercarial vaccine with interleukin-12 adjuvant improved protective immunity [21,22]. Although an attenuated cercarial vaccine may not be a viable approach in humans due to a number of factors including feasibility of production, quality control, and safety, it represents a model for identifying meaningful correlates of immunity, particularly for the design of a recombinant immunogen.

2. General approaches to vaccine development for low- and middle-income country markets

Schistosomes do not multiply in the human host, and most of the pathology comes as a consequence of the deposition of schistosome eggs in the tissues that lead to end-organ damage associated with fibrosis, inflammation, and bleeding. Current vaccine development strategies aim to prevent schistosome infection and/or reduce ova burden through the interruption of parasite reproduction. Thus, among the major vaccine targets are the migrating schistosomulum stages as well as adult females.

In the 1990s, an independent, WHO/TDR-sponsored evaluation of six *S. mansoni* vaccine candidates in preclinical development found that none achieved better than 40% efficacy in reducing worm load.

Since then the maturing of several new technologies, including *OMICs* (e.g., genomics, proteomics, transcriptomics), microarrays, and immunomic profiling, have helped in the identification of promising new target schistosome antigens [23–25]. However, both inadequate funding and infrastructure for vaccine development have slowed the translation of these antigen discovery technologies to the clinic. Indeed the overall pipeline of human schistosomiasis vaccines currently in clinical trials is extremely modest especially when considering the high disease burden of schistosomiasis and its potential role in Africa's AIDS epidemic.

For *S. haematobium*, a single candidate molecule, Sh28GST (Bilhvax), a schistosome glutathione S-transferase common to the schistosomula and adult stages, is believed to currently be undergoing testing. Early phases 1 and 2 clinical trials conducted in Niger and Senegal have demonstrated an acceptable safety profile and induction of high IgG3 antibody titers that have neutralized Sh28GST activity and reduced egg-production, an effect that could lead to decrease urinary tract pathology and transmission [26,27]. A phase 3 trial to evaluate if the vaccine candidate and PZQ administration would delay pathologic relapses of the S. haematobium infection in infected children was conducted from 2009 to 2012, but no results have been reported yet [28].

There are two vaccine candidates for intestinal schistosomiasis caused by *S. mansoni* in early stage clinical testing. The first comprises the extracellular domain of an integral membrane *S. mansoni* surface protein, *Sm*-TSP-2, that is bound by IgG1 and IgG3 antibodies from individuals that have cleared infection [29]. Preclinical studies in mice have shown that immunization with this protein subunit substantially reduces worm burden. This immunogen has been successfully expressed in yeast (*Pichia pastoris*) for scale-up cGMP production [30,31], and is currently in phase 1 trials in Houston, Texas, USA. A second vaccine candidate in clinical testing is based on Sm14, a fatty acid binding protein from *S. mansoni*, and it was announced that this vaccine will undergo phase 1 trials in Brazil [32]. While not yet in clinical development, Smp80 (calpain) has demonstrated efficacy in Non-Human Primate (NHP) challenge studies, and will also likely advance to the clinic [33]. As Asian schistosomiasis caused by *S. japonicum* is an important zoonosis, there is increased interest here in developing a veterinary vaccine for water buffalo, cattle, and pigs as a potential means toward blocking a transmission to humans [34].

Because several of the antigens under investigation are highly conserved among different species, there is some optimism for advancing a pan-schistosome vaccine, especially for *S. mansoni* and *S. haematobium* co-infection, prevalent in sub-Saharan Africa. In addition, because of the geographic overlap between schistosomiasis and hookworm disease, there have also been early

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