I. About the Disease and Pathogen

Basic information on pathogen, including transmission, estimated global disease burden for those at risk, for morbidity and for mortality, including uncertainties/data gaps, geographical distribution, economic burden if available, age groups affected and target groups for vaccination. Existing preventive, diagnostic and treatment measures and their limitations.

Schistosomes are snail-transmitted, water-borne parasitic platyhelminths (order Trematoda). The highest concentration of schistosome infections occurs near bodies of fresh water such as the Lake Victoria in sub-Saharan Africa. Current estimates suggest that 252 million people are infected with schistosomes [1], with approximately two-thirds of the cases caused by *Schistosoma haematobium* (the cause of urogenital schistosomiasis), one-third caused by *Schistosoma mansoni* (the cause of intestinal schistosomiasis), and approximately one percent caused by *Schistosoma japonicum* and *S. mekongi* (causes of intestinal schistosomiasis – a zoonosis - in East Asia). Additional estimates based on a finding that for every egg-positive individual with schistosomes there is an egg-negative individual, have projected that between 400 million and 600 million people could be infected with schistosomiasis. Schistosomiasis together with hookworm and leishmaniasis rank as the leading neglected tropical diseases in terms of disability-adjusted life years (DALYs) [1]. More than 90% of the world’s cases are found in Africa – *S. haematobium* and *S. mansoni* - with the remainder of these cases caused by *S. mansoni* in Brazil and Latin America or both species in areas of the Middle East.

The asexual reproduction of the parasites occurs in the freshwater snails that release large numbers of free-swimming, infective larval schistosomes, known as cercariae, into the water. The cercariae enter the skin, lose their tail and migrate through the bloodstream and lungs reaching the liver. In the liver, they differentiate into male and female schistosomes. Male and female worm pairs migrate through the portal vasculature ending up in the mesenteric or bladder venules. Eggs are released by the worm pairs exiting the body via feces or urine, which then hatch in fresh water. The majority of the human pathology from schistosomiasis occurs when the eggs are unable to exit from the human host. When lodged in the intestinal or bladder wall, eggs induce granulomas and host fibrosis. This can cause hypertension and hepatosplenomegaly in the liver and hematuria, urinary tract infections, hydronephrosis, and kidney failure in the bladder. Eggs from the *S. haematobium* can cause chronic bladder fibrosis or female genital inflammation leading to the formation of so-called “sandy patches” that are risk factors for acquiring HIV/AIDS in Africa. Chronic schistosomiasis is linked with numerous other disease sequelae, especially in children, such as anemia, chronic pain, under nutrition, growth failure, and cognitive deficits [2].

Current treatment and control of schistosomiasis is dependent on solely one drug, acylated quinoline-pyrazine praziquantel (PZQ). With increasing evidence of the disease appearing in new areas, current thinking is that this dependence on chemotherapy alone, given the often silent and undetectable nature of the infection, is inadequate. Although PZQ is highly effective, single-dose chemotherapy is not effective in all patients and the mass treatment with this drug does not prevent reinfection. Furthermore, PZQ is not active against developing forms of the parasite, and in exposed populations in most areas of the disease, within a period of 6 to 8 months following chemotherapy, the disease prevalence returns to its original level. Low cure rates have also been reported, although at the moment actual resistance has only been theoretically demonstrated in lab models and some field isolates. It is known that efficient drug delivery requires significant infrastructure to reach all parts of an area of endemicity. This can make chemotherapy expensive and challenging [3]. Schistosomes do not replicate within their mammalian hosts. Consequently, a non-sterilizing naturally or vaccine-acquired immunity could significantly decrease human pathology and disease transmission.
II. Overview of Current Efforts

A. Biological feasibility for vaccine development

Evidence that vaccine development is biologically feasible including from development of naturally acquired immunity, from vaccine development for related pathogens, from animal models or in vitro data

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 have been found to diminish with age, especially after puberty. However it is apparently unclear if acquired immunity is solely responsible for this observation, and furthermore, the likelihood that such immunity is related to an IgE-mediated mechanism, complicates an approach mimicking this natural immunity.

An alternative vaccinology approach, inducing immunity with attenuated parasites has provided the strongest animal proof-of-concept that vaccines against schistosomiasis is feasible. Vaccination studies with radiation-attenuated cercariae have demonstrated protection in mice (> 90%) and primates (86%) [4-6]. In mice, both cell-mediated and humoral mechanisms appear to operate consecutively (against lung-stage parasites) and immunity can be augmented to very high levels by co-administration of radiation-attenuated cercariae with interleukin 12 (IL-12) as an adjuvant [7, 8]. Although the radiation-attenuated approach is unlikely to be feasible from a human vaccine standpoint, it represents a tool to mine for protective antigens delivered via the recombinant approach.

B. General approaches to vaccine development for this disease for low and middle income country markets

What are the scientific approaches and indications and target/age/geographic groups being pursued? What public health needs will these vaccines meet if successfully developed? Where there are several different possible indications/target groups, how much consensus is there as to prioritization between these for vaccine development in LMIC.

Vaccine development strategies against schistosomes currently target the prevention of infection and/or the reduction of parasite reproduction. Schistosomes do not multiply in the human host and pathology of the disease results from the eggs deposited by the reproducing worms. The worm burden is also thought to affect the human host’s immune system in a deleterious manner, compromising immune responses to other infections [9]. Among the major disease targets for vaccination are the migrating schistosomulum stages, as well as adult female worms that release tissue-destructive eggs. In addition, vaccines that would specifically reduce parasite reproduction and egg viability may also be a desirable goal.

Most current approaches have focused on exploiting molecular and recombinant technology to identify possible protective antigens from stage-specific parasites and deliver these purified extracts or recombinant constructs in various formulations. An independent preclinical evaluation of six potential candidates against *S. mansoni* in mice was sponsored by WHO/TDR in the 1990s; none of the candidates reached to 40% or better worm load reduction target. Although knowledge on immunity to the disease is limited and limits the ability to ascertain protective antigens with assurance, completion of schistosome “omics” projects for high throughput identification of candidates, coupled with studies in animal vaccination experiments have identified a couple of promising target that are being developed as vaccine candidates.

For urogenital schistosomiasis, vaccination experiments in primates identified an antigen shared between the schistosomula and adult schistosome stages of *S. haematobium*, Sh28GST, which been shown in human studies to induce IgG3 that is associated with decrease in egg-production in *S. haematobium* infection, an effect that if successfully reproduced, could lead to decrease urinary tract pathology and transmission [10]. Early phase 1 and 2 clinical trials have shown an acceptable safety profile and induction of high titers of antibodies that neutralized Sh28GST activity and the vaccine
will undergo phase 3 testing soon [11].

For intestinal schistosomiasis, there are two vaccines in early stage clinical testing, including an integral membrane \textit{S. mansoni} surface protein, Sm-TSP-2, has also been identified, and has shown to reduce worm burden in mice by 60-70%. The antigen is also recognized by IgG1 and IgG3 from naturally resistant human subjects, who are not chronically infected [12]. Sm14 is another \textit{S. mansoni} antigen that is undergoing clinical testing, while Smp80 (calpain) has shown great promise in non-human primates. For Asian schistosomiasis caused by \textit{S. japonicum}, there is interest in developing a veterinary vaccine for water buffalo, cattle, and pigs as a potential means towards a transmission blocking approach for humans.

Because several of these antigens are highly conserved among different species, there is interest in developing a pan-schistosome vaccine. In addition, because schistosomiasis geographically overlaps with hookworm, where they are co-endemic there is additional interest in developing a multivalent vaccine that targets both helminth parasites [13].

The general approach for vaccine development is to target school aged children in endemic areas in Africa and Brazil. The development of a vaccine would require a relatively low cost and efficacious vaccine with a suitable shelf-life for the low to middle income countries. An additional and important potential benefit would be through targeting urogenital schistosomiasis caused by \textit{S. haematobium}, a vaccine could reduce HIV/AIDS transmission in Africa.

III. Technical and Regulatory Assessment

Highlight perceived positive/negative aspects in clinical/regulatory pathways e.g. well established product development and regulatory pathway to licensure, accepted immune correlates and/or functional assays, accepted surrogate efficacy endpoints, existence of well accepted animal or challenge models, agreed trial designs and endpoints. Possibilities to develop case for correlates/surrogates should be included.

The pathway for WHO endorsement for these candidate vaccines would be to generate a 40% or better reduction in challenge-derived worm burdens relative to non-immunized controls. The available schistosome antigens and prototype vaccine formulations induce 40 to 50% protection in animal models with the standard readouts looking at reduced worm burden or egg production and viability. The challenge is translating these antigens with similar or superior protection in humans. The development of a vaccine with suitable efficacy is the greatest challenge for schistosomiasis vaccines.

The immune correlates of protection for a schistosomiasis vaccine are thought to be observed in IgG1 and IgG3 antibody recognition of the antigens. The standard animal model for screening potential antigens is the mouse model used to test the efficacy of schistosomiasis vaccines.

Recombinant vaccines are mostly being expressed in low-cost bacteria or eukaryotic expression systems. The selected antigens require processing through the endoplasmic reticulum due to their expression sites in the parasite (i.e., secreted or anchored in the tegument), which can be difficult. Antigen identification and successful protective results will not be sufficient if a GMP scale-up manufacture cannot be performed on the antigen [3]. Selecting the appropriate adjuvant and delivery platform to stimulate the correct immune response is important to ultimately produce an efficacious anti-schistosome vaccine. The factors listed above must be taken into consideration for low to middle income countries when selecting antigen strain, production feasibility and cost per dose.

IV. Status of vaccine R&D activities

Summarize status of vaccine design, pre-clinical and clinical trial activity, including platforms, vectors, and adjuvants. Note academic, government, biotech and industry entities engaged. Summarize antigenic targets (if subunit approaches). Section on major advances in last 3-5 years, including key opportunities highlighted by recent science developments in the area.

Although there remains no current commercially available vaccines for schistosomiasis, the various antigens and candidates in clinical trials are listed in Table 1 and Table 2.
The combination of public databases that provide the *S.mansoni* and *S. japonicum* transcriptomes and such techniques as DNA microarray profiling, proteomics, glycomics, and immunomics provide the opportunity to provide new vaccine target molecules with increased potency/efficacy than current schistosome antigens. A significant advancement is the successful application of RNA interference (RNAi) to schistosomes. This technique has been able to determine the functions of schistosome genes/proteins and which ones are essential for survival and reproduction. If antigens were able to silence the expression of numerous *S. mansoni* genes, it would validate their importance as targets for vaccines and new drugs.

Table 1: Species, Vaccines and antigenic targets in Clinical Trials

<table>
<thead>
<tr>
<th>Parasite species targeted</th>
<th>Vaccine</th>
<th>Major antigens/adjuvants</th>
<th>Sponsor</th>
<th>Primary Endpoint</th>
<th>Status</th>
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<tbody>
<tr>
<td><em>Schistosoma haematobium</em></td>
<td>Bilhavx</td>
<td><em>Sh28GST</em> (28-kDa recombinant glutathione-S-transferase) Alum formulation</td>
<td>Institut Pasteur and INSERM</td>
<td>Looking for safety/efficacy of the vaccine. Immunogenicity was evaluated by antibody production, capacity of sera to inhibit enzymatic activity of the antigen.</td>
<td>Completed Phase 2, initiating Phase 3.</td>
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<tr>
<td><em>Schistosoma mansoni</em></td>
<td>Sm-TSP-2 schistosomiasis vaccine</td>
<td>Sm-TSP-2 (9-kDa recombinant tetraspan) Alhydrogel® ± GLA</td>
<td>Sabin Vaccine Institute Product Development Partnership/ Division of Microbiology and Infectious Diseases / National Institutes of Health / Baylor College of Medicine Vaccine and Treatment Evaluation Unit</td>
<td>Looking for safety/efficacy of the vaccine. The immunology aspect will look at the IgG level by ELISA.</td>
<td>Initiating Phase 1 trial in USA in 2014 at Baylor College of Medicine.</td>
</tr>
<tr>
<td><em>S. mansoni</em></td>
<td>Sm-14 schistosomiasis vaccine</td>
<td>Sm-14 (14-kDa recombinant fatty acid binding protein) with the adjuvant GLA</td>
<td>Oswaldo Cruz Foundation (Fiocruz)</td>
<td>The primary target of the study is to determine the safety and tolerability of the vaccine in healthy adults. The immunological properties monitored are seroconversion and cellular immune responses.</td>
<td>Active status, the study is ongoing but not recruiting patients [14].</td>
</tr>
</tbody>
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Table 2: Development Status of Current Vaccine Candidates (POC = Proof of concept trial) [3]

<table>
<thead>
<tr>
<th>Candidate Name/Identifier</th>
<th>Preclinical</th>
<th>Phase I</th>
<th>Phase II</th>
<th>POC</th>
<th>Phase III</th>
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<tbody>
<tr>
<td>SmTSP-2c (tetraspanin D)</td>
<td>X</td>
<td></td>
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<tr>
<td>SmTSP-1</td>
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<tr>
<td>Sh-GST28</td>
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<td>X</td>
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<td>Sm14e</td>
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<td>Sm28-GSTe</td>
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<td>Sm28-TP1e</td>
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<td>CT-SOD</td>
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References