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Workshop report: Schistosomiasis vaccine clinical development and product characteristics

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ABSTRACT

A schistosomiasis vaccine meeting was organized to evaluate the utility of a vaccine in public health programs, to discuss clinical development paths, and to define basic product characteristics for desirable vaccines to be used in the context of schistosomiasis control and elimination programs. It was concluded that clinical evaluation of a schistosomiasis vaccine is feasible with appropriate trial design and tools. Some basic Preferred Product Characteristics (PPC) for a human schistosomiasis vaccine and for a veterinary vaccine for bovine use were also proposed.

1. Introduction

As a follow-up from March 2013 meeting, which was co-sponsored by the National Institute of Allergy and Infectious Diseases (NIAID) and the Bill & Melinda Gates Foundation (BMGF) [1], a schistosomiasis vaccine meeting was conducted in November 2013. The goal of the meeting was to continue discussing how a schistosomiasis vaccine should be used in public health programs, what the desirable Target Product Profile (TPP) for this vaccine should look like, and how a vaccine could be tested in clinical trials should there be one available in the near future. A group of 25 extramural schistosomiasis investigators, concerned intramural investigators, and Program Staff from the NIAID attended the meeting. It was concluded that clinical evaluation of a schistosomiasis vaccine in the field is likely feasible but would be challenging, and mathematical and computational modeling could be a valuable tool for informing the design of a TPP. Some basic product characteristics for a schistosomiasis vaccine for humans and a veterinary vaccine for bovines were proposed to guide early-stage product development. Below is a summary of the workshop discussions and of the further follow-on post-meeting group/subgroup communications and recommendations.

2. Timely opportunities for the schistosomiasis vaccine community

Neglected Tropical Diseases (NTD), including schistosomiasis, continue to be a part of the NIAID's Global Health agenda. Schistosomiasis is an acute and chronic disease caused by three major *Schistosoma* species, *Schistosoma* (*S.*) *mansoni* (*S.m.*), *S. japonicum* (*S.j.*), and *S. haematobium* (*S.h.*). The parasites establish their infection of human host by penetrating human skin in larval form and develop into adult worm in human body. Female worm would release eggs, which are either trapped in the body tissues causing immunopathology in intestinal (for *S.m. or S.j.*) or urogenital (for *S.h.*) organs or passed out in the urine or faeces to continue their life cycle and transmission. Vaccine against schistosomiasis is considered beneficial to the current control programs and a critical tool in achieving the ultimate goal of global elimination of the diseases [1]. The Institute has already established several available preclinical service contract resources and the Vaccine Treatment and Evaluation Unit (VTEU) program to accelerate translational projects into new intervention tools, and it has supported discovery research and early development activities for NTD vaccine candidates, including several schistosomiasis vaccine candidates. In addition, the BMGF strongly supports current schistosomiasis control and elimination strategies and will continue to monitor and landscape advances toward new tool developments, including vaccines. Throughout the meeting presentations, it was apparent that financial support for most of the schistosomiasis vaccine early development mainly stemmed from the Governments and in some cases, some nonprofit organizations (Table 1). In the absence of prominent pharmaceutical involvement and limited support from other prominent organizations, it was highly encouraged that the schistosomiasis research community should actively strive to attract support from other non-conventional R&D investment sources. For example, the hookworm vaccine development effort, which is carried out by the Sabine Vaccine Institute, has attracted support from entities in the helminth endemic country Brazil. While the resource for schistosomiasis vaccine development has been constrained for decades, it was agreed that the community should work together to show unity of purpose, combine strengths, establish collaborations and integration of projects and strategies to maximize resources, and continue to show progress both conceptually and in real-time development effort. As the product development stage moves further downstream and more promising data are available, the development risk can be expected to decrease. More developers are anticipated to join in the mission to ultimately bring products to licensure.

One of the major concerns for the community is the lack of understanding of the potential impact of a schistosomiasis vaccine on the global health. Since mathematical and computational modeling has been utilized to address the impact of new interventions and strengthening of business cases, several investigators presented their modeling tools to assess the vaccine impact on the schistosomiasis control and elimination program. One method [2]

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Table 1
Vaccine candidates in development and funders.

Schistosoma	Vaccine	Development stage	Developer	R&D sponsors
S. haematobium	Monovalent recombinant protein Sh28GST (glutathione S-transferase) with adjuvant (Bilhvax)	Phase III	Inserm & Eurogentec	Inserm, EPLS[a]
S. mansoni	Monovalent recombinant protein Sm14 (fatty acid binding protein) in GLA-SE	Phase I trial completed	Fiocruz	Ministerio da Saude, Fiocruz, WHO
S. mansoni	Monovalent recombinant protein Sm-TSP-2 (tetraspanin surface antigen) with adjuvant	IND-filing, Phase I study on-going	Sabin Vaccine Institute	Blavatnik Charitable Foundation Mort Hyman NIAID
S. japonicum *S. mansoni* *S. haematobium*	DNA prime, recombinant protein boost Sj23 (Tetraspanin) and SjTPI (Glycolytic enzyme)	Field studies in water buffalo and cattle	Univ. of Georgia	Wellcome Trust NIAID NHMRC[b]
S. mansoni	Monovalent recombinant protein Sm-p80 (Calpain) with adjuvant	Preclinical process development	Texas Tech Univ. Health Sciences Center	NIAID Thrasher Research Fund Bill & Melinda Gates Foundation
S. japonicum	Monovalent recombinant protein Sj97 (paramyosin) with adjuvant ISA206	Proof-of-concept in animals	Brown University	NIAID
S. japonicum	Bivalent [SjIR (insulin receptor) or with SjTPI] recombinant proteins with adjuvant	Proof-of-concept in animals	Queensland Institute of Medical Research	NHMRC

[a] EPLS: Centre de Recherche Biomedicale, Espoir Pour La Sante.
[b] NHMRC: Australia National Health and Medical Research Council.

was to develop a clinical and economic outcome model to profile the costs, followed by developing an economic/operational model for each potential intervention, and subsequently link these models to a schistosomiasis transmission model to assess the impact of each intervention (in this case, vaccine) on transmission. The other method was to evaluate the impact of an intervention (e.g., vaccine) on transmission by studying the basic reproductive number R_0, defined as the average number of female offspring produced (that develop into adult worms) by one fertile female worm throughout her lifetime in the absence of density-dependent constraints, or by using mating probability in a stratified worm burden model, a compartment model that distributes human infectious burden among different infection intensity strata based on the observed field data [3]. Moreover, the group agreed that an important utility for the modeling is to guide the development of TPPs based on the desirable economic value or public health endpoint of a particular vaccine. Examples were presented to illustrate this application, such as the economic modeling for Visceral Leishmaniasis [4] or Chagas' disease [5]. The modeling of schistosomiasis vaccine is still at its infant stage and many more researches are needed. Given the complexity of the schistosome biology and multiple existing interventions for the control and elimination program, some basic critical parameters worth incorporating were proposed: parasite species (*S.m./S.h.*); targeted parasite life-stages; level and duration of efficacy; costs of production and distribution; targeted population; and the types of vaccines (e.g., anti-fecundity or anti-infection). Similarly, several other possible vaccine or vaccination-related features were suggested for consideration. For example, immunity may not be complete and vaccine effects may be short-lived; prior infection/treatment can boost vaccine effects; and vaccines could affect worm fecundity and male to female balance or disrupt the balance between immunoregulation and immunopathology.

3. Vaccine candidates for schistosomiasis

Recent progress in schistosomiasis vaccine development was discussed (Table 1). Several forms of vaccines are on the horizon. Bilhvax3, a vaccine candidate based on *S.h.* parasite protein glutathione S-transferase Sh28GST, which prevents both clinical and parasitological recurrences of *S.h.* infection in children, is currently under Phase III of human clinical evaluation [6]. The panel also noted other vaccine candidates that reduce worm burden and egg outputs of *S.m.* infection in small animals and in some cases non-human primates (NHP) (e.g., *S.m.* proteins fatty acid binding protein Sm14, Tetraspanin Surface Protein antigen TSP-2, and calpain protein Sm-p80) [7–11], or kill established worms (Sm-p80) [12]. These candidates would most likely be developed as human prophylactic vaccines for susceptible populations in endemic areas. Currently, the Sm-p80 or the *S.j.* Insulin Receptor protein SjIR-based vaccine has also been shown to preferentially reduce female worm burden and reduce egg shedding in animals. The strong anti-fecundity impact of this type of vaccine provides additional transmission blocking benefits. Other vaccines like *S.j.* parasite proteins Tetraspanin Sj23/Glycolytic enzyme SjTPI, paramyosin Sj97, and SjIR-based vaccines, all of which have been tested in small animals and showed protection against *S.j.* infection [1,13–16], are being further tested in water buffalo prior to any human clinical trial. These vaccines would most likely first be developed as veterinary vaccines for bovines, which indirectly reduce parasite transmission to humans and thus potentially serve as transmission-blocking vaccines for human populations.

The types of vaccines needed for global control and elimination programs were further discussed. Since schistosomes have a complex life cycle involving different developmental stages (e.g., cercariae, schistosomulae, adult worm) migrating through and residing in a variety of anatomical sites in the human host coupled with the prolonged time for disease induction and manifestation, the traditional term of infection cannot be clearly and easily elucidated for "schistosome infection", as, for example, is clearly defined for an acute viral infection for which the timing or the anatomical site for infection or disease presentation are well known. As a result, there was apparent confusion in the schistosomiasis vaccine field about the terminology of a therapeutic vaccine vs. a prophylactic/preventive vaccine. Some investigators tended to define the therapeutic vaccine based on the infection status of the host (i.e., a vaccine intended for infected individuals) while others preferred to define a therapeutic vaccine based on the targeted biological stage of the parasite (i.e., a vaccine which exhibits efficacy against established adult worms in a chronic infection). Traditionally, a