PRACTICAL AND ETHICAL ISSUES IN THE DEVELOPMENT OF A VACCINE AGAINST SCHISTOSOMIASIS MANSONI

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Abstract. Clinical trials to evaluate schistosomal vaccines are in progress. We discuss the desired characteristics of such a vaccine, propose a product profile, and consider the clinical and pre-clinical studies needed for its licensure, within practical and ethical constraints. We believe that licensure of a schistosomal vaccine will be greatly facilitated by resolution of the following issues: identification of the human immunoprotective antigens and mechanisms; induction of the appropriate responses by adjuvanted vaccines; understanding the effect of immunization on immunopathology; development of an improved serologic assay to determine worm burden; generation of approximately $500 million to fund the project; and development of a physical infrastructure with trained professionals in disease-endemic countries to perform Phase III clinical trials. We also believe that development of a schistosomal vaccine, while a long range goal, is possible and desirable, and we have indicated some of the practical steps that will be required to achieve this laudable accomplishment.

INTRODUCTION

One of the cardinal rules of pharmaceutical product development is “Start with the end in mind.” Very early in the development cycle, companies prepare either a product profile or a draft product insert to indicate the desired characteristics of the final product and its consequent advantages over the competition, and/or niche in the armamentarium. This document provides both the goal and the direction of product development. Once these product characteristics have been decided, backward planning then identifies which clinical and pre-clinical studies will be needed to provide supporting data to justify the claims in the product insert. Because most potential pharmaceutical products do not make it to market, the product profile is also used to define Go/No Go criteria for various stages of the development process that then determine if the product is, or can be modified to remain, on the critical path to licensure and success.

A number of investigators are active in the research aspects of schistosomal vaccine candidates, both describing and evaluating potentially protective antigens. Groups headed by Capron and McManus are focused on the development and evaluation of candidate antigens with the ultimate aim of producing a vaccine against schistosomiasis hematobium and japonicum, respectively. The Schistosomiasis Vaccine Development Project (SVDP) has likewise aimed at these goals in relationship to schistosomiasis mansoni. Therefore, we believe it is reasonable to pose the question, “What are the desired characteristics of vaccines against Schistosoma mansoni?” Based on these characteristics one could propose a product profile. The next step would then be to examine the clinical trials and pre-clinical studies that would be required to support the label claims as well as the constraining practical and ethical considerations.

Development of a schistosomal vaccine will be a long process almost certainly with multiple iterations and dead ends. Many of the issues raised by our discussion are currently unresolved. Some practical matters will be decided by scientific reality during product development. For example, otherwise promising antigens may be associated with unacceptable stability, toxicity, or adverse events. The clinical trials team, Institutional Review Boards, and Regulatory Authorities will debate many of the ethical concerns until a consensus is reached. For the purposes of this discussion, we assume that the consensus will be in favor of further development; however this cannot be guaranteed. We present some of the problems to be solved and suggest some possible solutions. This paper is therefore intended to contribute to the discussion of the complexities to be faced during the development of a schistosomal vaccine. We are indebted to P. F. Basch for his seminal contributions to the constructive debate about schistosomal vaccines.

PRODUCT CHARACTERISTICS AND PROFILE

Using a simplified vaccine product insert as a guide, an outline profile for a vaccine against S. mansoni is proposed (Appendix).

Efficacy. In general terms, products must be safe, effective, stable, easily administered, and affordable by the target population. The overarching goal in developing the schistosomal vaccine under discussion is to produce a vaccine that protects people against infection and the consequent morbidity and mortality associated with S. mansoni.

What is the minimum acceptable level of protection from cercarial exposure required of a schistosomal vaccine and how will this value be determined? How one defines protection, that is vaccine efficacy, is important in this context. The generally accepted meaning in the world of vaccinology is VE = (ARU − ARI)/ARU (equation I), where VE is the vaccine efficiency (expressed as a percentage), ARU is the attack rate in the unimmunized, and ARI is the attack rate in the immunized. Thus, hepatitis B vaccines with efficacies greater than 90% absolutely protect this percentage of those people successfully immunized from infection and disease by that virus. However, licensed vaccines do not always provide such high levels of protection and may also seek to ameliorate disease as well as prevent infection. Influenza vaccines prevent illness to viral variants, similar to those in the vaccine, in 70–90% of persons less than 65 years old, but efficacy decreases to 30–40% in elderly populations, especially those in nursing homes yet this is the priority target population of this vaccine. Immunization against influenza in the elderly may not prevent infection and illness, but it does significantly reduce the subsequent morbidity and mortality from complications such as the development of pneumonia, and this is an acceptable, if not ideal, goal. At the present time the situation following schistosomiasis immunization may be consid-
ered analogous to the influenza example. The reason is that the current concept and measurement of vaccine-induced protection to experimental S. mansoni infection in animal models is fundamentally different from vaccine efficacy described by equation I. If two groups of animals, one untreated and the other immunized, are both exposed to the same number of infective cercariae and the number of worms reaching maturity is determined at six weeks post-infection, then protection is defined as \( P = (\text{AWU} - \text{AWI})/\text{AWU} \) (equation II), where \( P \) is protection (expressed as a percentage). AWU is the number of adult worms in the unimmunized, and AWI is the number of adult worms in the immunized.\(^{13}\) Thus, 50% protection means that immunized mice have, on average, 50% fewer worms than unimmunized controls exposed to the same number of infectious cercariae. Such an index is thought to be meaningful in a disease like schistosomiasis where the pathogen, in this case worms, does not divide and replicate in the human host. The concept is strengthened by the idea that morbidity in this disease is generally correlated with the intensity of infection, that is the worm burden.\(^{14}\) Although the two formulae are similar, equation I defines the percentage of the population that is immune to infection, whereas equation II enumerates the reduction in the intensity, or burden, of infection upon exposure.

Instead of, or in addition to anti-worm vaccine efficacy, it is also considered that a vaccine that reduces egg production (through fewer worms or fewer eggs produced per worm, that is, anti-fecundity) would be a suitable goal for the development of a schistosomal vaccine.\(^{7}\) While worm perforations as well as egg accumulations are feasible end points in experimental animal studies, only egg quantification in stools or yet to be developed assays for worm and/or egg analytes will be acceptable in human trials. Thus, at this time, the actual measure of efficacy will rest on quantitative egg output and whether this is achieved because of fewer worms or fewer eggs per worm will require the use of future tools.

In experimental systems, what level of anti-worm vaccine efficacy is desirable and achievable for a schistosomal vaccine? Clearly, the most desirable would be a vaccine with greater than 90% classical efficacy. At this time, protection studies are most commonly quantified by equation II and published protection experiments with animal models of schistosomiasis rarely reach such a goal by that measurement. Immunization of mice with one dose of irradiated cercariae generally results in 50–70% partial protection, as defined by equation II, upon subsequent cercarial challenge.\(^{15}\) In some instances this protection can be increased to approximately 90% with four immunizations.\(^{15}\) Subunit vaccines composed of either purified schistosomal proteins or synthetic antigens have in general provided 30–50% partial protection,\(^{4,16–18}\) although this is mouse strain dependent.\(^{19}\) In naturally permis-sive hosts, animal studies have generally demonstrated partial protection, as defined by equation II, with no reports of absolute immunity.\(^{19,20}\)

Do people possess the capacity to be immunized and thus be protected against infection with schistosomiasis? The evidence from field studies, recently reviewed by James and Colley\(^{1}\) and McManus,\(^{3}\) suggests that partial resistance due to infection probably develops in most people. The intensity of infection is generally lower in adults,\(^{20,22}\) and following treatment with praziquantel, adults also display some degree of resistance exhibited as lower intensities upon reinfection.\(^{22,23}\) There are also reports of people who tend to be naturally resistant to infection.\(^{24–27}\) In Brazil, Dessein and others have identified a small group of persons who are homozygous for the so-called SM1 gene on chromosome 5 and who are genetically biased to develop less intense infections.\(^{23}\) Upon stimulation, S. mansoni-specific T cell clones from these people secreted much higher concentrations of interleukin-4 (IL-4) and IL-5 than clones from susceptible people.\(^{27}\) Studies in Kenya indicate that repeated treatment and natural re-exposure of a group of persons results in the development of a spectrum of immunity, from those who are very resistant to reinfection to patients who remain very susceptible (Karanja DM and others, unpublished data). It is possible that vaccine immunization may enhance the naturally occurring protective mechanisms noted in infected people, although it does not have to, i.e., it may result in the stimulation of distinct immune modes of action.

If humans have the capability to be immunized against schistosomiasis, what are the protective antigens and immunoprotective mechanisms? Based mainly on the murine challenge model, a number of candidate antigens have been proposed following immunization with either irradiated cercariae or purified subunits.\(^{4,16–18}\) These antigens usually demonstrate immunoreactivity with sera and peripheral blood mononuclear cells from infected patients.\(^{26}\) Such studies have provided the justification for initiating vaccine development, with the aim of testing one or more candidate antigens in Phase I clinical trials.\(^{7–4}\) However, the human protective antigens are currently unknown and in all likelihood will only be identified by human clinical trials. Similarly, animal studies may not replicate the immunoprotective mechanisms operative in people.\(^{16–19}\) The first vaccines to be tested clinically will be those that demonstrate efficacy in animal models and they may have to be optimized for humans in clinical trials. This situation is not unique in vaccine development. During development of acellular pertussis vaccines in the last 25 years, initial clinical trials indicated that vaccines composed of pertussis toxoid alone were less efficacious than the whole cell pertussis vaccine.\(^{28}\) Consequently, other antigens such as filamentous hemagglutinin, pertactin, and fimbriae were added to the formulations, and subsequent clinical trials demonstrated the requisite efficacy.\(^{28}\) We believe that our current lack of knowledge regarding the nature of the protective antigens and immune mechanisms should not be seen as a stop sign to vaccine development work. Rather, it significantly extends the timeline to licensure of an effective vaccine. Unfortunately, vaccine development is not completed in the laboratory then sent to the clinic for final testing. Clinical development and refinement are integral and essential parts of the process. Consequently, development and licensure of an effective schistosomal vaccine may take a decade or so longer than we would like. However, since the global prevalence of schistosomiasis has remained approximately 200 million for decades,\(^{29}\) even in the presence of efficacious therapeutic drugs, it would seem the time to licensure should not deter moving forward on vaccine development.

Currently, we do not know if immunization of people will result in either absolute immunity or a significantly reduced worm burden following re-exposure. The expectation, based on experimental studies, is that initial, small-scale clinical trials of candidate schistosomal vaccines in the field will demonstrate partial protection or perhaps decreased egg produc-
tion and consequently less morbidity. If the current candidate vaccines are found to induce partial protection upon initial clinical trials, what level of protection would be required to justify further development and extensive testing, and how can this be determined? Similar questions can be asked regarding the duration of immunity. Apart from influenza vaccines, which are administered annually because of viral strain variation, most routine vaccines provide protection measured in years to decades. How long should a schistosomal vaccine protect for it to be cost-effective and useful in control programs?

These questions have and will be extensively debated; however, we believe that mathematical modeling should be useful in this context. In a series of multifactorial studies, Woolhouse and others have used mathematical models to estimate the effects of changes in many of the variables affecting transmission, such as water contact and chemotherapy, as well as the duration and efficacy of vaccine-induced protection, on levels of infection. Assuming that immunization induces partial protection, as defined by equation II, for a limited period of time, the model predicted that a long-term effect was more beneficial than short-term protection at a higher level. Their models also indicated that it might be beneficial to delay immunization until school age rather than targeting the young and to combine immunization with initial mass chemotherapy. As clinical trials progress, it will be critical to incorporate more field data into such mathematical models to determine the best strategies both to test and to use a schistosomal vaccine.

Will the efficacy of the vaccine be the same in persons who have never been infected compared with those who have been infected and cured? Will it be possible to protect the latter group? These are very difficult issues that only clinical trials will resolve. However, initial studies in the murine system indicated that effective immunizations with irradiated cercariae were possible in mice cured of a previous infection by praziquantel. In the face of the antigenic onslaught from adult worms and their eggs following infection, the body mounts a vigorous initial response that is later modulated by complex immunomodulatory mechanisms. Very early immune responses in people are believed to be similar to experimental murine infections, such as water contact and chemotherapy, as well as the duration and efficacy of vaccine-induced protection, on levels of infection. Assuming that immunization induces partial protection, as defined by equation II, for a limited period of time, the model predicted that a long-term effect was more beneficial than short-term protection at a higher level. Their models also indicated that it might be beneficial to delay immunization until school age rather than targeting the young and to combine immunization with initial mass chemotherapy. As clinical trials progress, it will be critical to incorporate more field data into such mathematical models to determine the best strategies both to test and to use a schistosomal vaccine.

The advantage might be to focus on what is feasible now and subsequently to capitalize on the continually advancing technologies available later.

Within the context just described, what are appropriate goals for protection from reinfection and duration of immunity for a schistosomal vaccine? If a vaccine cannot provide absolute protection, as defined by equation I, then it should significantly reduce the development of morbidity by only allowing a small number of worm pairs to reach maturity in naturally exposed persons. The relationship between morbidity and intensity of infection is complex and multifactorial; however, it is generally accepted that the fewer worms, the better. Treatment campaigns have significantly reduced mean egg counts and follow up studies have demonstrated reversal of pathology including hepatomegaly, splenomegaly, and Symmers' fibrosis. After three years of annual treatment, the geometric mean egg counts of a group of Sudanese patients decreased from 267 to 14 and the degree of hepatic fibrosis was significantly reduced. Twenty-five percent of the patients reverted to no fibrosis and the percentage with Grades 2 and 3 decreased from 40 to 17. Similarly, in a Madagascan village, mass chemotherapy reduced the geometric mean egg count from 202 to 27, the prevalence of bloody stools from 24.9% to 8.4%, and the prevalence of hepatic morbidity from 28% to 10%. As more data become available, the threshold value for infection intensity below which morbidity is significantly reduced can be refined. If vaccines demonstrate anti-fecundity effects that decrease egg output, infection intensity may have to be determined by circulating antigen concentrations. With respect to the duration of immunity, mathematical models support the concept of vaccine immunity lasting at least five years to be relevant to community health. With those caveats, we propose that a schistosomal vaccine should protect people for at least five years and limit their infection intensity to less than 25 eggs per gram of feces.

Safety. Because most vaccines are administered to generally healthy people, they must have a high degree of safety with a very favorable risk: benefit ratio. It is universally accepted that immunization can frequently result in some degree of both local injection site reactogenicity, such as soreness and erythema, as well as generalized systemic effects such as mild fever, headache, and malaise. Since these effects are most probably the result of immunostimulatory cytokine induction, there are those who would say that these symptoms indicate that the vaccine is working! Thus, the association of similar minimal symptoms at the appropriate frequency with a schistosomal vaccine would be acceptable. The use of dose response studies starting at the lowest doses would minimize untoward effects should they occur and allow for reassessment of the clinical protocol.

It is probable that during initial field clinical trials, some people will be exposed to cercariae and will become infected or re-infected. Because schistosome infection elicits such powerful immunoregulatory effects, what will be the safety ramifications of immunization on any subsequent immunopathologic response to infection, either in persons who have never been infected or those who were cured before immunization? It is also possible, though unlikely, that immunization could exacerbate residual pathology from previously cured infection(s) in the absence of re-exposure. We propose
that animal model studies are warranted to examine the effects of immunization on immunopathology associated with previous or subsequent infections. The situation is further complicated by the fact that untoward effects may not be manifest until a significant time after immunization. These are clearly critical safety issues that will necessitate intense monitoring both during the clinical trials and for a number of years thereafter.

Unless the vaccine has therapeutic activity, persons should be negative for *S. mansoni* infection before they are immunized. Chemotherapy is ethically appropriate and combined with immunization may significantly enhance the overall effectiveness of the control program. All vaccine recipients from disease-endemic areas will therefore have to be pre-screened or mass treated. Because of the relative insensitivity of current methods to estimate worm burdens, either by stool egg counts or circulating antigen assays, it is inevitable that some people with undetected or undetectable infections will be immunized. The potential adverse reactions from such an occurrence are currently unknown and should be evaluated, to the degree feasible, in animal models before field clinical trials are initiated. Clinical trials in the field will have to screen patients closely to minimize this complication. Of course, treatment and the consequent death of adult worms will release a bolus of antigens into the circulation that may positively or negatively affect both the safety and efficacy of the vaccine. In regard to this antigenic release, considerable thought needs to be given to the treatment and immunization schedules, and clinical studies may be needed to resolve these issues.

Currently, worm burden is estimated indirectly by several methods. The classic parasitologic determination of stool egg intensity is subject to great variability both from intra-fecal and day-to-day egg counts. Egg excretion is also impaired in immunocompromised persons and may be decreased by anti-fecundity effects of either naturally acquired resistance or immunization. Methods to detect circulating worm or egg antigens in serum, urine, and saliva have shown promise and have even been used to evaluate experimental irradiated cercarial immunization where high numbers of challenge cercariae are used. However, these methods likely do not currently possess the requisite sensitivity and specificity to quantitate worm burdens in vaccine clinical trials, especially when these are low.

We therefore believe that it should be a priority of any schistosomal vaccine plan to develop more sensitive, specific, and quantitative diagnostic tests for circulating adult worm and egg antigens. Such methods would significantly improve the assessment of worm and egg burdens both before and after drug treatment, aid in the determination of vaccine efficacy, and allow determination of anti-fecundity vaccine effects. Since immunization of animal models has demonstrated anti-fecundity effects whereby the egg output of females is reduced, parallel studies of stool egg output and circulating worm and egg antigen concentrations would provide the data needed to evaluate this desired phenomenon in persons following immunization. Of necessity, the diagnostic and vaccine antigens must not cross-react lest immunization results in circulatory clearance of any diagnostic antigen, thereby invalidating the test. The best diagnostic tests for use in this setting would measure analytes that become manifest as early after infection as possible, that are quantifiable and whose concentrations are proportional to worm and/or egg burdens. As previously mentioned, there is currently no serologic test that can evaluate the pathologic development of infection that could be used to monitor for infection/vaccine-related side effects in populations in endemic areas.

In summary, the profile of local, systemic, and severe effects manifest by a schistosomal vaccine should be similar to or better than currently licensed vaccines such as hepatitis B or diphtheria-tetanus toxoids. Vaccines that could be used to monitor for infection/vaccine-related side effects in populations in endemic areas.

Stability and formulation. The areas endemic for *S. mansoni* essentially include Egypt, The Nile Valley, Sub-Saharan Africa, Brazil, and the Caribbean Basin; all locations with warm climates. A vaccine formulation that was routinely stored at 2–8°C but that was stable at 37°C for one month would greatly facilitate distribution and administration, as well as decrease overall costs by elimination of the cold chain. In this respect, much will depend on the protective antigens and any associated adjuvant. The final formulation is usually a compromise designed to maintain the potency and stability of the components in a physiologically compatible medium. For example, freezing destroys the structure and potency of alum-adjuvanted vaccines and thus precludes exploration of lyophilization as a way to improve their stability. Novel technologies are emerging that may enable ambient temperature storage of vaccines. However, the initial goal is to develop an efficacious vaccine; thus, the physicochemical characteristics of the protective antigen(s) and adjuvant will constrain the final formulation at first and may therefore limit storage to the standard 2–8°C.

Many new adjuvants and delivery systems are being developed that hold the promise both to potentiate and to direct vaccine-induced immune responses. Saponins such as QS-21 and Quil-A tend to result in Th-1 responses, in contrast to the alum adjuvants, in which Th-2 responses predominate. The type of response required for protective immunity in people, which will ultimately be decided by Phase II clinical trials, will dictate the choice of adjuvant. If predominantly Th-1 profiles are required, then a proprietary adjuvant formulation will need to be developed or licensed. Field studies have provided some evidence that Th-2 type immunity is associated with the development of partial protection from schistosomal reinfection and possibly genetically determined resistance. If potent vaccine-induced Th-2 responses are required for protection, then alum adjuvants may be appropriate. Alum-adjuvanted vaccines have been widely and safely administered for the past 50 years and have contributed very significantly to the decreased incidence of diseases such as tetanus, diphtheria, and hepatitis B. However, their use has recently been questioned following reports of a potential association with the rare condition of macrophagic myofascitis in France. These claims are controversial and further studies are in progress.

Administration. What is the target population for a schistosomal vaccine? Ideally it would be all persons who are at risk of exposure and negative for *S. mansoni*, irrespective of their previous infection status. Indeed, this concept has been accepted during previous discussions of vaccine indications. The reality is more complex. The mathematical models previously described may argue for delaying immunization until children are school age. However, in the face of the complex immunoregulatory mechanisms initiated by infection, it may not be possible to induce a particular form of...
immunity in previously infected people, either absolutely or for safety reasons related to potential exacerbated immunopathology. Also, as indicated by field studies, adults with schistosomiasis exhibit partial protection following drug treatment and may therefore be in less need of vaccine-induced protection. Thus, for several reasons, the initial target group may be infants and children who have never been infected. Children normally are not heavily exposed to the threat of schistosome infection until they are toddler age;

1 Therefore, this target period is the first two years of life. However, Barakat and others have noted high egg counts in children less than 12 months old who were probably infected by being washed with contaminated water. To achieve its maximal potential in the healthcare setting, any schistosomal vaccine, whether indicated for those never infected, or for all currently negative persons, is likely to stand the best chance if it can be incorporated into the Expanded Program of Immunization (EPI). It will therefore need not to interfere with the efficacy of any of the EPI vaccines with which it is concomitantly administered.

For the purpose of this exercise we envision the vaccine as a pre-filled syringe or a single use vial to be administered with a syringe and needle. Developing technologies such as an oral or mucosal delivery system either by vaccine preparation or through bioengineered foods would also greatly facilitate a large-scale immunization campaign. However these systems are in the development stage with an uncertain timetable for licensure.

Cost. How much will it cost to develop a schistosomal vaccine and who will pay? The current estimate to develop pharmaceutical products and vaccines to licensure is in the range of $500 million. The early stages of pre-clinical development through the first Phase I clinical trial are usually a small portion of this total and can generally be achieved for $5 million to $10 million. From these beginnings, costs rise exponentially such that approximately 50–60% of the total cost is incurred during Phase III clinical trials, the construction and validation of manufacturing capacity, and licensure. Most currently licensed vaccines have been developed outside of tropical disease-endemic countries (DEC). By definition, the large scale, Phase III pivotal clinical studies for a schistosomal vaccine will have to be performed in rural endemic areas where medical and health care facilities are frequently inadequate. To ensure that the trial is performed in compliance with accepted good ethical and clinical practices will most probably require a significant investment in both physical infrastructure and training of highly skilled local personnel, that is the establishment of a Vaccine Treatment and Evaluation Unit (VTEU) and associated field-testing approved sites. An administrative organization to manage and coordinate all aspects of the project will also be necessary. These organizations may need to function for a number of years to monitor the duration of protection and any potential immunopathologic effects. Developing a licensed vaccine is a project for neither the underfunded nor the weak of heart.

A telephone survey by one of us (CWT) determined that none of the six major vaccine producers in the United States was working on the development of a schistosomal vaccine. In the absence of commercial development, the public sector, international agencies, and philanthropic organizations may not have the resources to commit to Phase III trials, licensure, and manufacturing. We suggest that an appropriate strategy is to pursue non-commercial development through Phase II small-scale field clinical trials to generate sufficient safety and efficacy data to demonstrate “proof of principle” and thus justify continuation to large-scale Phase III trials. In the best-case scenario, these data would be used to convince a major vaccine manufacturer to assume the project and proceed to licensure, manufacture, and distribution. It is also possible that licensure may be achieved through currently developing public-private partnerships as are being fostered by WHO/TDR.

Assuming that a vaccine is licensed, who will buy it and at what cost? Apart from a small market for adventurous tourists, international aid workers, missionaries, and possibly military organizations, most of the vaccine will be purchased by, or in conjunction with, Ministries of Health (MOHs) in DEC. Historically, the major vaccine manufacturers have strived to sell their products in the North American and European markets at prices sufficient to recoup development costs and generate a profit. They have then been amenable to two-tier pricing where they supply vaccine at significantly reduced cost to DEC. To keep schistosomal vaccine costs affordable for MOHs in the absence of a market in industrialized countries, alternative financial incentives for commercial manufacturers, such those recently proposed by Lang and Wood and President Clinton’s Millennium Vaccine Initiative are likely to be required.

Other considerations. The development of candidate malaria vaccines has been aided considerably by the use of challenge studies. Laboratory-reared mosquitoes infected with chloroquine-sensitive strains of Plasmodium falciparum are allowed to feed on appropriately immunized volunteers who are followed closely, then treated immediately at the first sign of parasitemia. Are similar studies possible to aid in the development of a schistosomal vaccine? We believe not, despite the availability of safe and effective treatments. To obtain statistically meaningful data from such an experiment, the volunteers would need to be exposed to significant numbers of infective cercariae. Tourists, Peace Corps Volunteers, and soldiers in disease-endemic areas who have become infected frequently demonstrate fever, prostration and general malaise 6–12 weeks after exposure. These patients sometimes develop severe complications such as a transverse myelitis when migrating worms become trapped in ectopic locations and induce intense inflammatory reactions. The current insensitivity of methods to detect developing and adult worms as well as incipient immunopathology would also constrain the requisite close monitoring of these volunteers. It is therefore not planned that volunteer protection studies will be used to further schistosomal vaccine development.

The phenomenon of granuloma modulation has been documented and studied in human disease and experimental models for more than 35 years. Granulomas formed around freshly deposited eggs later in the disease process are smaller than those formed earlier. Chronic granuloma formation is predominantly under the control of Th-2 cytokines, though the interplay between Th-1 and Th-2 cytokines that results in modulation of the granulomatous response remains controversial. The down-regulation of the initial aggressive granulomatous response to schistosome eggs is thought to be a major part of the establishment of a chronic disease state. Despite this mechanism, some persons progress to severe morbidity characterized by excessive fibrosis and the sequelae
of portal hypertension, hepato-splenomegaly, and esophageal varices.\textsuperscript{88} At times, investigators have posited the development of an anti-pathology vaccine that would limit the granulomatous response from the time the first infection became patent and thereby lead an overall reduction in pathology at later stages of the disease.\textsuperscript{88–90} We believe that with the availability of safe and effective treatment for schistosomiasis, clinical trials to test an anti-pathology vaccine directly are ethically untenable. Consider, in outline, the nature of a clinical trial designed to evaluate the efficacy of an anti-pathology vaccine. A population of schistosome-negative people, who would be expected to have subsequent cercarial exposure, would be split into two groups, one of whom would receive the anti-pathology vaccine, the other a placebo. There is currently no test that becomes indicative early in infection that is predictive of subsequent morbidity and mortality. Consequently, both groups would have to be left untreated for a number of years (10–20) sufficient to determine the severity of schistosome-induced pathology. Since severe morbidity occurs in a relatively small population of infected persons (5–10\%), the size of the study would also need to be quite large to have the power required to determine an effect. Because excellent treatment with praziquantel exists, such a study cannot be ethically contemplated. Although we believe that anti-pathology vaccines \textit{per se} cannot be tested, it is possible that schistosomal vaccines may result in an overall reduction of pathology by virtue of decreasing the intensity of infection,\textsuperscript{14} through a decrease in egg production possibly mediated by anti-fecundity effects,\textsuperscript{62–64} or even by co-stimulation of down-regulatory responses.\textsuperscript{38} Each of these would be a positive outcome of vaccination. Clinical evaluation of vaccinees by ultrasound over time may provide useful data to assess these effects.\textsuperscript{91}

Should a schistosomal vaccine also have therapeutic potential? Current vaccine strategies aim to prevent penetrating cercariae/schistosomulae from reaching maturity and/or decreasing fecundity. If an appropriately formulated vaccine had activity against both larval and adult worms, it would have considerable benefits. Assuming there were no safety issues, it could be given to persons irrespective of their worm burden, would eliminate their current infection and provide future protection. The need for worm-burden pre-screening, drug therapy, and follow up testing before immunization would be removed. Consequent cost savings would be considerable. We are unaware of any experimental data to support the development of a therapeutic schistosomal vaccine. Such a vaccine would be a technical challenge, but the public health rewards in terms of its ultimate implementation could be great.

This discussion has been generally concerned with immunization against \textit{S. mansoni} and thus directly pertains to the situation in Brazil and the Caribbean where it is the major trematode of significance to public health.\textsuperscript{29} Throughout large parts of Africa, the disease-endemic areas of \textit{S. mansoni} and \textit{S. hematobium} overlap, thereby potentially compounding the practicalities of developing a vaccine.\textsuperscript{29} We acknowledge that in these areas, the development of a vaccine against \textit{S. mansoni} may be more difficult because of the consequences that mixed infections may have on vaccine safety, efficacy, and immunopathology.

On the other hand, should there be any cross-protection of the \textit{S. mansoni} vaccine that contributes to resistance to \textit{S. hematobium}, there could be substantial benefits for its use in those regions that are endemic for both diseases. Consideration of how to address these positives and negatives should be included in both immunogenicity studies and eventual Phase III trials. There is currently little in the literature to substantiate such cross-protection, although cross-protection between \textit{S. mansoni} and \textit{Fasciola hepatica} seems more common.\textsuperscript{8,92,93} There may be additional benefits from schistosome-specific immunization. Salmonellosis has been associated with schistosome infection and it is possible that immunity to schistosomiasis might reduce the likelihood of intravascular exposure to \textit{Salmonella spp.}, and impact positively or influence bacterial and viral infections as well.\textsuperscript{94}

\section*{CLINICAL TRIALS}

Clinical trials determine the safety and efficacy of a product then seek to provide data to justify the widest range of indications consistent with the desired product profile. The primary emphasis of all phases of the clinical trials, and on into post-marketing surveillance, should be safety. It has therefore been recommended that in addition to the internal review boards and national regulatory authorities, a specialized, independent safety group be instituted to monitor the whole vaccine development process including manufacturing, clinical trials, adverse events, population epidemiology right through to post-marketing, and long-term surveillance.\textsuperscript{95} It is only with the safety of the target population protected that trials to determine vaccine efficacy can proceed.

\textbf{Phase I.} With safety the overarching concern, all of the institutional review boards, regulatory authorities, and safety monitoring groups will have to approve each study of Phase I clinical trials and the overall sequence before initiation. Within that context, the following sequence of Phase I trials has been proposed by the SVDP: 1) uninfected healthy adults from countries outside the disease-endemic area; 2) previously infected and cured adults from urban areas of disease-endemic countries who are not expected to have contact with cercariae-containing water; 3) previously infected and cured adults from rural areas of disease-endemic countries who are likely to have water contact; and 4) previously infected and cured children from rural areas of disease-endemic countries who are likely to have water contact.

These studies will be dose ranging, always starting with the lowest dose, and will monitor vaccine safety as the highest priority end point. Immunogenicity data, a secondary end point in Phase I, will also be generated. These studies will occur sequentially with the information gained at each stage integrated into the decision-making process on whether and how to proceed. To reiterate, for the purposes of this discussion, we assume that the consensus will be in favor of further development; however, this cannot be guaranteed. Each study in a clinical trial is on the critical path and must be designed to answer specific questions. Study 1 will examine the local reactogenicity and systemic effects of the vaccine in a population immunologically naïve with respect to schistosomal antigens, and will also indicate its immunogenicity. The variables to be examined and the data resulting are summarized in Table 1. The second study will determine safety and the nature of immune responses in a group of persons who have previously responded to schistosomal antigens. It may also indicate if immunization has any untoward effects on
pre-existing pathology or untoward effects due to prior sensitization.

Study 3 will potentially introduce the variable of reinfection to the trials, albeit in very small numbers of volunteers. Safety concerns will again be paramount, but useful ancillary data on antibody- and cell-mediated immune responses, similar to Study 2, will be generated. Patients will likely be observed very closely for a week or so after immunization then actively followed every month to monitor and treat adverse events that might occur upon any subsequent exposure and/or reinfection. Passive self-reporting and facile access to the VTEU will be actively encouraged. A monthly follow-up would, of necessity, require a stool and circulatory antigen examination, and mandate immediate treatment of any positive test results. This regimen could need to continue for up to two years, depending on the local reinfection rate. Ultrasound evaluations at appropriate times would also be performed. This study may therefore yield very preliminary data regarding time to first reinfection, an intermediate, not ideal substitute for protection and intensity of infection. Seasonal exposure patterns will also have to be considered. For example, persons residing in the Nile Delta during the winter will face little cercarial exposure until the following spring. In any case, patient numbers will be too small to provide the power to calculate any meaningful efficacy results. Assuming favorable safety and immunogenicity data to that point, the above study would be repeated in children who are assumed to be eventually the primary target population.

**Phase II.** Upon successful completion of Phase I studies, between 80 and 100 adults and children will have been immunized with various doses of the schistosomal vaccine. We will have answers to many safety issues, knowledge of vaccine-induced immune responses in previously infected and uninfected individuals, plus perhaps some very preliminary indication of vaccine efficacy. Phase II studies to examine more clearly the safety of the appropriate dose, immunization schedule and generate more efficacy data in both previously infected and uninfected children and infants can then be designed (Table 2). The studies in uninfected children and infants will be critical because this will be the first time that immunization with schistosomal antigens precedes potential cercarial exposure. Phase II clinical trials will seek to optimize the antigen dose, the number of doses, and their timing. Safety will still be of paramount concern with the trials conducted at the highest ethical standards.

There have been active discussions if it will be possible to determine the efficacy of a schistosomal vaccine.\(^1\)–\(^7\) Such studies will only be appropriate if the initial studies have demonstrated vaccine safety following natural cercarial exposure, and there is sufficient evidence of a potential protective effect. The Egyptian Government currently conducts annual surveys of schoolchildren in the Nile Delta for schistosomiasis positivity followed by treatment with praziquantel.\(^9\)\(^6\) An argument can therefore be made that a clinical trial could be timed appropriately to coincide with the Government’s campaign. Following annual diagnosis and treatment, children would be immunized with a schistosomal vaccine that already had data to support its safety, immunogenicity, and potential protective efficacy. The one-year follow up, also timed in such a way to include the primary transmission season, would then assess infection/reinfection rates and infection intensity and treat any positives. Ultrasound evaluation of morbidity would also be performed. Obviously, such a plan would not proceed unless approved by all the institutional and regulatory authorities. Phase II studies will also indicate if the vaccine/adjuvant formulation and the type of immune response generated (Th-1 or Th-2) elicit protection. If protection is not demonstrated, reformulation plus additional Phase I and II trials may be required to optimize efficacy.

**Phase III.** Because of the many factors influencing the incidence of schistosome infection, the design of Phase III clinical trials will be clinically and epidemiologically challenging. However, with the notable exception that schistosomiasis is treatable, many of the issues to be faced in this respect have

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**Table 1**

Summary of the proposed studies and resulting data comprising the Phase I clinical trials for a schistosomal vaccine*  

<table>
<thead>
<tr>
<th>Study number</th>
<th>Non-DEC, normal adults</th>
<th>DEC urban, adult, infected and cured</th>
<th>DEC rural, adult, infected and cured</th>
<th>DEC rural, child, infected and cured</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticipated cercarial exposure</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Number of subjects</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Safety data regarding Reactogenicity</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Systemic effects</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>“Old” pathology</td>
<td>NA</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>New pathology, postinfection</td>
<td>NA</td>
<td>NA</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Immunogenicity</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Protection data</td>
<td>–</td>
<td>–</td>
<td>±</td>
<td>±</td>
</tr>
</tbody>
</table>

* Variables for each study are antigen dose response. DEC = disease-endemic countries; NA = not applicable.

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**Table 2**

Summary of the proposed studies and resulting data comprising the Phase II clinical trials for a schistosomal vaccine*  

<table>
<thead>
<tr>
<th>Study number</th>
<th>DEC rural, child, never infected</th>
<th>DEC rural, child, infected and cured</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticipated cercarial exposure</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Number of subjects</td>
<td>80–100</td>
<td>80–100</td>
</tr>
<tr>
<td>Safety data regarding Reactogenicity</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Systemic effects</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>“Old” pathology</td>
<td>NA</td>
<td>+</td>
</tr>
<tr>
<td>New pathology, postinfection</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Immunogenicity</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Protection data</td>
<td>±</td>
<td>±</td>
</tr>
</tbody>
</table>

* Variables: Study 5: optimal antigen dose, optimal number of doses; study 6: optimal antigen dose, optimal number of doses, optimal timing of immunization relative to chemotherapy. DEC = disease-endemic countries; NA = not applicable.
been considered in the design of clinical trials for acquired immunodeficiency syndrome (AIDS) vaccines and may serve as useful models. Some of the common factors in vaccine clinical trials include behavioral changes that increase or decrease infection exposure-risk and susceptibility, and vaccines that may be partially protective and population mobility affecting study attrition rates. Estimation of the sample size for a Phase III trial must take into account these factors, as well as considerations specific to schistosomiasis such as overall disease incidence, time to develop immunity, the duration of immunity, age differential in the rates of reinfection, climatic changes, plus the expected efficacy. A thorough epidemiologic picture of the target population will therefore be necessary. Indeed, it may very well be that extended Phase II trials are required to provide an estimate of vaccine efficacy so that an appropriately sized Phase III trial can be designed. Although positivity for human immunodeficiency virus (HIV) will almost certainly be an exclusion criterion in Phase I and 2 trials, it may have to be considered in a large Phase III trial that involved adolescents and adults.

Randomized, double-blind, placebo-controlled trials are the gold standard for estimating the efficacy and safety of products in Phase III testing. Classical randomization has been at the level of the individual, though it has been argued that the community should be the unit of randomization. Community-randomized trials may more closely reflect the pattern of vaccine usage in a healthcare setting and may also elucidate patterns of herd immunity that result from immunization. Recent analysis of the factors that determined the ability to detect specific end points in a pneumococcal vaccine trial in The Gambia concluded that individual as opposed to community randomization would be better in that setting.

A similar detailed analysis of the patterns and disease incidence in communities proposed for Phase III schistosomal vaccine trials would clearly be indicated. It may also be relevant to examine different statistical approaches to determine which would be most appropriate in the design and decision-making process for this Phase III trial. The ultimate trial design will have to be rigorous, but potentially flexible, to account for the realities of field studies but still be able to deliver reliable results capable of supporting licensure.

In the product profile, we defined many criteria required of the final vaccine. The large-scale Phase III trials provide the definitive data upon which licensure is based. The most critical studies will examine efficacy and safety in at-risk infants, children, adolescents, and adults, whether previously infected or not. If it is planned to administer the schistosomal vaccine in conjunction with the EPI, many trials will be required to demonstrate no impairment of the immune response to each of the individual EPI vaccine antigens plus no increase in the type, frequency, and severity of adverse events of those vaccines. Phase III trials are extensive but they are all designed to support the label claim of the final vaccine and determine its utility, in this case, in controlling infection and morbidity by *S. mansoni*.

CONCLUSION

For a large multicellular organism such as *S. mansoni* to live, reproduce, and thrive for many years in the portal circulation of humanity in the face of all our innate and acquired immune defense mechanisms is a remarkable achievement. Similarly, the licensure of a safe, effective, and affordable schistosomal vaccine to defeat this adversary will require a technical *tour de force*. None of us underestimates the challenges that lie ahead. Nor do we intend that this effort should supplant the use of currently effective control programs with available drugs. Rather, these short and long range approaches to schistosomiasis control need to go forward in parallel, and work in scientific synchrony. In this paper we have tried to define the necessary characteristics of a schistosomal vaccine and thereby indicate at least the initial outline of the practical steps that will be required for us all to reach this goal.

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REFERENCES


APPENDIX
PROPOSED PRODUCT PROFILE FOR A SCHISTOSOMIASIS MANSONI VACCINE

Description. Product will be a sterile vaccine containing T and B lymphocyte-stimulating antigenic determinants from the trematode parasite Schistosoma mansoni. Each 0.5 ml dose will contain the antigen with or without adjuvant in a physiologically compatible buffer. The product may be free of a bacteriostatic preservative.

Administration. Either intramuscular or subcutaneous needle injection.

Indications and usage. The vaccine will be indicated for immunization against infection caused by S. mansoni. Immunization is recommended for 1) infants, children, adolescents, and adults never previously infected with S. mansoni who are at risk of contact with contaminated water; 2) infants, children, adolescents, and adults previously infected with S. mansoni who have been treated and cured of their infection but remain at risk; and 3) international travelers, military personnel, and expatriates in disease-endemic countries identified as being at increased risk.

Use with other vaccines. Compatible for concomitant administration with diphtheria and tetanus toxoids and pertussis (DTP), oral live poliovirus (OPV), inactivated poliovirus (IPV), measles mumps rubella (MMR), Haemophilus influenzae b (Hib), yellow fever, and hepatitis B vaccines using separate sites and syringes for injectable vaccines.

Contraindications. Limited to hypersensitivity to any component of the vaccine.

Warnings. If vaccine is used in persons with malignancies or those receiving immunosuppressive therapy or who are otherwise immunocompromised, the expected immune response may not be obtained. Patients who develop symptoms suggestive of hypersensitivity after an injection should not receive further injections of the vaccine.

Precautions. Patients must test negative for S. mansoni infection by a sensitive diagnostic method. Patients who test positive should be treated with chemotherapy and demonstrated to be negative.

Adverse reactions. Local and systemic adverse reactions must be less than or equivalent to currently licensed vaccines such as hepatitis B. No exacerbation by vaccine of pre-existing or subsequent disease pathology upon re-exposure or re-infection. No induction of autoimmunity.

Dosage and administration. For either intramuscular or subcutaneous administration.

How supplied. Supplied as 0.5 ml in a single dose vial or a pre-filled syringe.

Storage. Ideally would have routine storage at 2–8°C. The product may be stable for > 12 months at 2–8°C.

Costs. Comparable to hepatitis B.