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Review

The Human Hookworm Vaccine

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ABSTRACT

Hookworm infection is one of the world's most common neglected tropical diseases and a leading cause of iron deficiency anemia in low- and middle-income countries. A Human Hookworm Vaccine is currently being developed by the Sabin Vaccine Institute and is in phase 1 clinical testing. The candidate vaccine is comprised of two recombinant antigens known as *Na*-GST-1 and *Na*-APR-1, each of which is an important parasite enzyme required for hookworms to successfully utilize host blood as a source of energy. The recombinant proteins are formulated on Alhydrogel® and are being tested in combination with a synthetic Toll-like receptor 4 agonist. The aim of the vaccine is to induce anti-enzyme antibodies that will reduce both host blood loss and the number of hookworms attached to the gut. Transfer of the manufacturing technology to the Oswaldo Cruz Foundation (FIOCRUZ)/Bio-Manguinhos (a Brazilian public sector developing country vaccine manufacturer) is planned, with a clinical development plan that could lead to registration of the vaccine in Brazil. The vaccine would also need to be introduced in the poorest regions of Africa and Asia, where hookworm infection is highly endemic. Ultimately, the vaccine could become an essential tool for achieving hookworm control and elimination, a key target in the 2012 London Declaration on Neglected Tropical Diseases.

Contents

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1. Background

Hookworm infection is a leading cause of iron-deficiency anemia in rural areas of the world's poorest countries [1]. An estimated 700 million people chronically harbor hookworms in their intestines—most of these people survive on less than $1–2 per day, a benchmark threshold for defining global poverty [1,2]. Indeed, hookworm infection is considered to be among the two most common chronic infections of the "bottom billion" and based on disability-adjusted life years (DALYs) lost, it is the most important neglected tropical disease (NTD) and the second most important parasitic infection (after malaria) [2,3].

Hookworms can live for years in the human intestine where they feed on host blood. Most of the morbidity is due to chronic blood loss that results in iron-deficiency anemia and hypoalbuminemia [1]. Recent evidence points to hookworm infection emerging as an important global threat to maternal–child health. Both children and pregnant women are especially vulnerable because of their higher iron demands and lower baseline iron reserves [4,5]. Children with moderate and heavy hookworm infections develop growth stunting and intellectual, cognitive, and educational deficits [4]. As they become adults entering the workforce, individuals with chronic hookworm infection experience substantial reductions in wage-earning potential [6]. Moreover between one-quarter and one-third of pregnant women in Africa are infected with hookworms, which can result in severe anemia, increased maternal morbidity and mortality, and fetal loss or prematurity [5]. Thus, hookworm infection is a major impediment to achieving Millennium Development Goals (MDGs) and targets for ameliorating poverty and improving maternal and child health [4].

Adding to the disease burden resulting from hookworm infection is the observation made in sub-Saharan Africa that there is extensive geographic overlap with malaria, and hookworm–malaria co-infections are widespread [7]. The effect of concurrent hookworm and malaria infections on the severity of anemia has been shown to be additive or synergistic, and malaria infections on the incidence of anemia have been shown to be synergistic and increase the risk of severe and profound anemia [8].

A Human Hookworm Vaccine is being developed by the product development partnership (PDP) of the Sabin Vaccine Institute [9,10]. The vaccine is being designed to target *Necator americanus*, the hookworm species responsible for approximately three-quarters or more of all human hookworm infections [11]. The eventual goal is to license a vaccine that contains two recombinant hookworm antigens, *Na*-GST-1 and *Na*-APR-1, which are formulated on an aluminum hydroxide adjuvant (Alhydrogel®). Clinical testing will evaluate whether an additional adjuvant, an aqueous formulation of a synthetic Toll-like receptor 4 (TLR 4) agonist (glucopyranosyl lipid A [GLA-AF]), will be required to achieve acceptable immunogenicity [9].

Na-GST-1 is a 24 kDa recombinant *N. americanus* glutathione-*S*-transferase expressed in yeast (*Pichia pastoris*) [12,13], while *Na*-APR-1 is a 45 kDa recombinant *N. americanus* aspartic protease expressed in tobacco plants. For safety and stability reasons, *Na*-APR-1 was modified through site-directed mutagenesis to produce a recombinant protein devoid of proteolytic activity [14,15]. Preclinical proof-of-concept that both recombinant *Na*-GST-1 and *Na*-APR-1 can induce protective efficacy has been demonstrated though challenge studies conducted in laboratory animals (reviewed in [9]).

- *Na*-GST-1 has been manufactured at pilot scale according to current Good Manufacturing Practices (cGMP). Following regulatory submissions in the United States and Brazil, *Na*-GST-1 is currently in phase 1 clinical trials in healthy adult volunteers in the United States and Brazil.
- *Na*-APR-1 has also undergone cGMP manufacture at pilot scale. An investigational new drug (IND) filing for this antigen formulated on Alhydrogel® will be submitted to the United States Food and Drug Administration and the Brazilian regulatory agency (the Agencia Nacional de Vigilância em Saúde) in late 2012 or 2013.

Following phase 1 testing of each hookworm vaccine candidate antigen in adults and children, they will be combined into a single product, assuming that both have been shown to be safe and immunogenic. This co-formulated product will be tested in phase 2b and 3 studies in hookworm-endemic regions of Brazil and likely sub-Saharan Africa to evaluate its efficacy in preventing moderate and heavy infections and the resulting intestinal blood loss and anemia. In addition, early in clinical development a proof-of-concept challenge trial is being considered in hookworm-naïve adult volunteers who are vaccinated and then challenged with infective *N. americanus* larvae. Previous studies of experimental hookworm infection have demonstrated that it is feasible, safe, and reasonably well tolerated (depending on the dose of infectious larvae) [16–18]. This vaccination-challenge trial would be conducted after the initial phase 1 trials of each recombinant antigen in adults to provide an early indication of their potential efficacy.

The target product profile of the Human Hookworm Vaccine includes the following important features [9]:

1. The vaccine is intended for children under the age of 10 years who are at risk for acquiring moderate and heavy hookworm infections in endemic areas of developing countries.
2. The vaccine will be administered by intramuscular injection up to two doses and will require storage between 2 °C and 8 °C.
3. The vaccine can be administered concurrently with other childhood vaccines such as the measles vaccine.
4. Vaccine efficacy of at least 80% in preventing moderate and heavy hookworm infections caused by *N. americanus*.

Widespread use of an effective Human Hookworm Vaccine would significantly improve global public health and as outlined below could also become a critical technology for the eventual elimination of hookworm infection in low- and middle-income countries. Such a vaccine has been described as an 'antipoverty vaccine' because of its potential to improve the economic development of affected populations in addition to its positive impact on health [10]. In addition, due to the synergistic effect of concurrent infection with malaria and hookworm on incidence of anemia, using the vaccine in sub-Saharan Africa could potentially also reduce the burden of disease due to *Plasmodium falciparum*.

2. Main barriers and challenges

Licensure and global access to the Human Hookworm Vaccine will face significant scientific, programmatic, and commercial challenges, as described below.

2.1. Scientific challenges

Currently there are no licensed anthelminthic vaccines for humans. Two experimental schistosomiasis vaccines are undergoing early stage clinical testing in Brazil and sub-Saharan Africa [19,20], while the Human Hookworm Vaccine is the only vaccine in clinical development for hookworm infection. Hookworms are complex multicellular parasites, so that producing an efficacious vaccine against this helminth is in some respects an even more formidable challenge than producing vaccines against