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Status of vaccine research and development of vaccines for leishmaniasis

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ABSTRACT

A number of leishmaniasis vaccine candidates are at various stages of pre-clinical and clinical development. Leishmaniasis is a vector-borne neglected tropical disease (NTD) caused by a protozoan parasite of the genus *Leishmania* and transmitted to humans by the bite of a sand fly. Visceral leishmaniasis (VL, *kala-azar*) is a high mortality NTD found mostly in South Asia and East Africa, while cutaneous leishmaniasis (CL) is a disfiguring NTD highly endemic in the Middle East, Central Asia, North Africa, and the Americas. Estimates attribute 50,000 annual deaths and 3.3 million disability-adjusted life years to leishmaniasis. There are only a few approved drug treatments, no prophylactic drug and no vaccine. Ideally, an effective vaccine against leishmaniasis will elicit long-lasting immunity and protect broadly against VL and CL. Vaccines such as Leish-F1, F2 and F3, developed at IDRI and designed based on selected *Leishmania* antigen epitopes, have been in clinical trials. Other groups, including the Sabin Vaccine Institute in collaboration with the National Institutes of Health are investigating recombinant *Leishmania* antigens in combination with selected sand fly salivary gland antigens in order to augment host immunity. To date, both VL and CL vaccines have been shown to be cost-effective in economic modeling studies.

1. About the disease and pathogen

Leishmaniasis is caused by a protozoan parasite of the genus *Leishmania*, of which there are over 20 species that are pathogenic to humans. The disease is vector borne and transmitted to humans by the bite of a sand fly. Roughly 350 million people are at risk, living in areas that are endemic to *Leishmania* parasites. It is estimated that 1.3 million new cases occur annually, adding to the 10–12 million cases found globally [1–3]. The most recent estimates from the Global Burden of Disease Study (GBD) 2010 indicate that more than 50,000 annual deaths result from leishmaniasis and 3.3 million disability-adjusted life years (DALYs) are accrued, ranking leishmaniasis, along with schistosomiasis and hookworm infection, as those neglected tropical diseases (NTDs) with the highest disease burden [4]. A more recent update from GBD 2013 indicates that 62,500 people died from the visceral form of leishmaniasis in 2013 [5], Leishmaniasis has a variety of clinical manifestations, classified according to the clinical syndromes caused by individual species of the parasite: Cutaneous Leishmaniasis (CL) with its disfiguring skin ulcers, caused mostly by the *Leishmania mexicana and Leishmania braziliensis* complexes in the Americas [6] and *Leishmania major* and *Leishmania tropica* in the Middle East and Central Asia; Visceral Leishmaniasis (VL), caused by the *Leishmania donovani* complex, as well as *Leishmania infantum* and *Leishmania chagasi*, also responsible for Post-Kala-azar Dermal Leishmaniasis (PKDL); Mucosal/Mucocutaneous Leishmaniasis (MCL); a severe and chronic mucocutaneous infection [7].

VL (also known as kala-azar) is the third most common parasitic cause of death, after malaria and infantile cryptosporidiosis. Infected individuals present with fever, wasting, anaemia, hepatosplenomegaly, and a depressed immune response, leading to pancytopenia and superimposed infections. The disease can have a case-fatality rate of up to 100% in the absence of treatment. Its sequelae, Post-Kala-azar Dermal Leishmaniasis (PKDL), is a

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Table 1
Development status of current vaccine candidates.

Candidate name/identifier	Reference	Preclinical	Phase I	Phase II
LEISH-F2	[32]			X
LEISH-F3	[33,36]		X	
Various *Lutzomyia* sandfly antigens	[37]	X		
Various second generation protein based vaccines	[22]	X		
Various third generation DNA based and heterologous prime-boost vaccines	[22]	X		

chronic, disfiguring cutaneous condition associated with considerable morbidity and social stigma, in addition to likely contributing to *Leishmania* transmission. Leishmaniasis affects the poorest people living around the Mediterranean Basin, in South-East Asia, East Africa, Afro-Eurasia, and the Americas, and periodic epidemics are known to occur in these areas (Ethiopia [2005, 2006], Kenya [2008], and Sudan [2009–2011]) [3]. An epidemic of VL in Southern Sudan that emerged during the civil conflicts in the 1980s and 1990s is estimated to have killed more than 100,000 individuals [8,9], approximately 10 times the number of deaths from the 2014–15 West African Ebola virus infection outbreak [10].

CL, while not typically a life-threatening infection, is a cause of disfigurement and thus stigma, especially for girls and women. The disease has reached epidemic proportions because of the conflicts and public health breakdowns in Syria (where it sometimes known as "Aleppo evil"), Iraq, Afghanistan and elsewhere in the Middle East and Central Asia, and is widespread in the Americas [11].

Chemotherapy is the main treatment for all three major forms of leishmaniasis, and is generally effective. However, factors such as high costs, toxicity, and long-term and complicated regimens compromise most chemotherapeutic options, though the development of new therapies may start to alleviate these concerns [3,12]. In terms of the public health control or elimination of leishmaniasis, the major approach has relied on sand fly vector control. Indoor residual spraying has been key to sand fly control in many areas, but there is concern about the emergence of dichlorodiphenyltrichloroethane (DDT) resistance, especially in highly endemic areas such as in Bihar state, India [13], where insecticide spraying or bed nets are difficult to sustain due to the large number of sand flies and potential reservoirs for parasite transmission [12,14]. Dogs are significant reservoirs for *L. major* (a cause of CL in the Middle East and elsewhere), *L. infantum* (a cause of CL and VL in southern Europe, and elsewhere), and *L. chagasi* (a cause of VL in Brazil) [3,15].

Ultimately, the development and delivery of a vaccine could represent one of the most cost effective means of controlling or eliminating CL or VL. At least two cost effectiveness modelling exercises have been published. With regards to CL it has been estimated that using a vaccine that provides protection for 10 years at 70% efficacy within seven countries of Latin America: Bolivia, Brazil, Colombia, Ecuador, Mexico, Peru and Venezuela could prevent 41,000–144,000 cases of CL, for less than what currently recommended treatments cost [16]. For VL even a vaccine that provides protection for only five years at 50% efficacy would still be cost effective as compared to current treatments which has also been confirmed *via* a similar study for VL in Bihar State [16,17]. However, there is an urgent need to model CL and VL (as well as MCL) vaccines across a wide range of scenarios, including different levels of parasite transmission and parasite ecologies.

2. Overview of current efforts

2.1. Biological feasibility for vaccine development

A pivotal argument for the development of a vaccine for leishmaniasis is that the majority of people who recover from infection become immune [12,18,19]. Further proof of biological feasibility of vaccine development (at least for CL) is provided by an ancient practice that pre-dates modern vaccinology, "leishmanization" [12,14]. Widely practiced in the Middle East and Central Asia, individuals were immunized using thorns or sharp instruments to introduce live (whole-cell) parasites to artificially simulate a cutaneous infection, in an unexposed site on the body so as to prevent the risk of facial lesions through natural infection. Leishmanization vaccines have been developed and were in use in various countries (former Soviet Union, Central Asia, Israel, and Iran) and remain the only group of leishmaniasis vaccines to show efficacy in humans. However, issues pertaining to standardization and control of the dose and strain identity, the occurrence of persistent lesions and the risk of disseminated leishmaniasis in immunocompromised individuals, limit the actual deployment of this approach. As an alternative to employing live *Leishmania* parasites, attempts have been made to use killed whole parasites together with the BCG vaccine, but so far this approach has not achieved significant success, in terms of levels of protection [20]. Many pre-clinical models including murine, canine, and hamster for both CL and VL have been developed and are used extensively for assessing vaccines and adjuvants for Leishmaniasis. These models provide a wealth of information related to cellular immunity and have facilitated *in vivo* studies of the mechanism of action of numerous adjuvants [21].

There is currently no licensed vaccine against human leishmaniasis, and although several vaccines have advanced to clinical trials, most are still in early research and development (Table 1) [14,18,22]. Ideally an effective vaccine against leishmaniasis will elicit long-lasting immunity, thereby limiting chemotherapy usage, and involve a balanced T_H1- and T_H2-mediated immune response from vaccination [18,23].

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

Since live, whole-cell Leishmanization strategies are no longer seen as a viable vaccine strategy due to safety concerns, vaccine development approaches have now evolved to killed, inactivated parasite vaccines, or even the insertion of suicidal cassettes directly into the Leishmania genome [12,14,18,22]. These vaccines have focused on CL and VL with inconsistent clinical results [12,14,24]. Currently, the emphasis of the so-called second generation vaccines is on the subunit/recombinant protein approach using a range of adjuvants to augment the immunogenicity of the selected antigens [12,14]. As mentioned earlier, the evidence that parasite control and protective immunity is dependent on T_H1 immune responses has been helpful for research in this area. Leishmania antigens that induce protective immune responses in mice, hamsters, and dogs, have been identified and various combinations of these antigens are being tested as recombinant proteins [25]. Although vaccines targeting T cell-dependent immunity for protection have been more difficult to develop compared to those targeting antibody-mediated immunity, progress in the development of safe and effective adjuvants presents novel options for improved formulations. Alternatively, antigens delivered as DNA

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