Status of Vaccine Research and Development of Vaccines for
Chagas Disease
Prepared for WHO PD-VAC

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.

Chagas disease is one of the world’s most important neglected tropical diseases and a leading cause of disease and poverty in Latin America. An estimated 7-8 million people are infected worldwide with more than 99% of the cases occurring in the Americas, especially in the poorest countries in the region [1-3]. It is transmitted by the parasite Trypanosoma cruzi and the area known as Mesoamerica is one of the hardest hit regions, with up to 6 million cases possibly occurring in North America alone and an additional 800,000 cases in Central America [4, 5]. These cases include up to one million in the southern United States, especially South and Central Texas. For Latin America, based on disability adjusted life years (DALY’s), the disease burden of Chagas disease is five times greater than malaria and is approximately one-fifth that of HIV/AIDS. At present, the greatest number of new cases of Chagas disease occurs in Bolivia, but the disease now is disproportionately affecting the Mesoamerican region (Central America, Mexico, and Texas), with control efforts thwarted by the unique vectors that transmit T. cruzi in this area [2, 5].

Most of the disability and deaths from Chagas disease result from chronic Chagas cardiomyopathy, a condition that develops in approximately 30% of individuals infected with T. cruzi [6]. Maternal-to-child transmission leading to congenital Chagas disease has also emerged as an important route of transmission, especially in Mesoamerica and North America where an estimated 40,000 pregnant women are infected [5, 7]. Chagas disease affects, almost exclusively, the poorest people living in these regions. This is especially because the parasite vector, belonging to the insect family Reduviidae, also referred to as triatomines (also known as the kissing bug) has a propensity to live in poor-quality dwellings, as well as lack of access to essential medicines and vector control practices [2].

Following initial exposure to the T. cruzi parasite (transmitted through exposure to an infected vector vector) patients develop acute infection, which lasts for 4-8 weeks [6]. Virtually all of these acutely infected individuals seroconvert following the acute phase. Of these seroconverters, approximately 60-70% do not develop clinically apparent infection and are considered of indeterminate status, while another 30-40% with initially indeterminate status progress to develop chronic disease (determinate status) characterized by cardiac and gastrointestinal signs and symptoms [6]. The cardiac complications (occurring in 20-30% of patients) are the most severe and are characterized by arrhythmias, aneurysms, and heart failure [6]. Sudden death as a result of ventricular tachycardia and fibrillation accounts for two-thirds of the deaths from Chagas disease, followed closely by heart failure and thromboembolism [6].

Current treatment is dependent on two drugs, benznidazole or nifurtimox, both of which are almost 100% effective, provided therapy is initiated at the onset of infection and the acute phase of the disease. However, very few patients are diagnosed in the acute stages. The efficacy of both drugs for the vast majority of patients with chronic Chagas disease diminishes the longer a person has been infected. Therefore the benefits of medication in preventing or delaying the development of Chagas disease has to be weighed against the long duration of treatment (up to two months) and relatively high rates of adverse reactions that occur in up to 40% of treated patients. Furthermore, the drugs are contraindicated in pregnancy and those with kidney or liver failure. Additionally, specific treatment for cardiac or digestive manifestations may be required. Up to 20% of patients cannot tolerate full treatment courses. There is an urgent need for new control and treatment tools for use in chronic Chagas disease [7-10]. There is no licensed vaccine for Chagas disease and current prevention efforts rely on vector control. Although this has reduced disease incidence, it is not believed that vector control measures alone will be sufficient to eliminate Chagas disease in highly affected areas [11].
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

Several challenges have hindered the development of vaccines against Chagas disease. These include socioeconomic hurdles because Chagas disease is a neglected tropical disease almost exclusively affecting people in poverty and initial scientific concerns over exacerbating pre-existing cardiac lesions by an activation of an autoimmune reaction, based on the erroneous belief that Chagas disease represented an autoimmune disease. Further investigations have shown that it is parasite persistence that is associated with disease progression, and that a strong cellular immune response will need to be induced and encompass CD8+ cell activation and cytotoxic activity in order to control T. cruzi infection through vaccination [11, 12]. Evidence from the testing of a wide range of vaccine formulations over the years that range from whole parasites, to purified or recombinant proteins, viral vectors and DNA vaccines have provided preliminary animal proof-of-concept for vaccination as a preventive and potentially therapeutic strategy. It has been widely noted that the outcome of many vaccines against T. cruzi in animal models depends heavily on the formulation used and the immune response that is induced [11, 12].

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.

As alluded to above, many recent studies have been based on recombinant protein technology, recombinant viral vaccine vectors, DNA vaccines, and heterologous prime-boost vaccination strategies and have shown strong protection against infection and increased survival of mice. It is believed that for the control of Chagas disease either a preventive vaccine against T. cruzi or a therapeutic vaccine could be of great value [11, 13].

Both vaccine strategies would rely on a skewed immune response toward a T h1-type, leading researchers to believe that the same antigens and vaccine formulations may be used for the prevention of Chagas disease as well as a therapeutic for an ongoing infection. Recent economic modeling has suggested that a therapeutic vaccine for Chagas would be more cost-effective than a preventive vaccine. Indeed, increasing consensus indicates that a therapeutic vaccine -either as a stand-alone product or one used in conjunction with chemotherapeutic agents, so called “vaccine-linked chemotherapy” – is the preferred approach for purposes of human vaccine development [14].

Several different groups are conducting preclinical testing of candidate T. cruzi vaccines [11, 13]. The Sabin Vaccine Institute Product Development Partnership (Sabin PDP) with the Instituto Carlos Slim de la Salud, the Universidad Autónoma de Yucatán, the Laboratorios de Biológicos y Reactivos de México, and the Centro de Investigación y de Estudios Avanzados del Instituto Politécnico Nacional, is advancing a therapeutic vaccine from target selection through process development, scale up and manufacturing [13].

A recent economic analysis concluded that a vaccine would not only be cost-effective, but it could in fact be a cost-saving tool for one of the leading neglected infections of poverty in Latin America. As Chagas disease has been shown to be one of major reasons why Latin America’s “bottom 100 million” or poorest population who cannot escape poverty ($7 billion in economic losses annually) [9, 15], a Chagas disease vaccine represents an important tool for combating both disease and poverty in the Mesoamerican and Latin American region. The advantage of a vaccine compared to benznidazole alone (the major competing product in clinical use) would include: (1) Reductions in toxicities, thereby allowing its use in indeterminate patients; (2) Higher efficacies at preventing cardiac complications; (3) Higher rates of seroreversion to T. cruzi antigens not contained in the vaccine; (4)
Potential use in pregnancy to prevent vertical transmission and congenital Chagas disease; and (5) Reduced incidence of miscarriage and pregnancy complications related to Chagas disease.

Accordingly, two parallel target product profiles (TPPs) are under development. The first is as a stand-alone therapeutic vaccine used for chronically infected individuals that would prevent or delay the onset of Chagas cardiomyopathy. The second is a vaccine for a similar indication but potentially used in conjunction with benzimidazole or other chemotherapeutic agents in order to reduce the drug’s dose, length of treatment, and toxicity and/or create a synergistic effect for efficacy.

An effective vaccine could prevent cardiac complications among the estimated 40,000 new cases of Chagas disease that occur in Latin America annually, avert up to 600,000 DALYs annually that result from cardiomyopathy and gastrointestinal disease, and prevent 10,000 deaths or more annually [1, 3]. In addition, it is expected that a vaccine would serve to reduce child mortality and improve maternal health and pregnancy outcome in Latin American countries and could simultaneously reduce cost of treatment for this disease, while increasing efficacy in treating disease symptoms [9, 15].

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.

Currently no clinical trials have begun for a Chagas disease vaccine. However, national regulatory agencies for endemic countries such as U.S. Food & Drug Administration (FDA), Comisión Federal para la Protección contra Riesgos Sanitarios (COFEPRIS), and Agência Nacional de Vigilância Sanitária (ANVISA) could be engaged. As there is a potential concern of inducing autoimmunity as a result of vaccination, a clinical development strategy could involve the first test of the vaccine in a non-human primate model prior to the first in human trial.

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.

The Sabin PDP is accelerating the development of a bivalent therapeutic vaccine, the first of its kind for the treatment of chronic Chagas disease. It is proposed to be bivalent and comprised of two T. cruzi recombinant proteins. One of the antigens is a unique T. cruzi 24 kDa antigen (Tc24) and the other is a unique T. cruzi surface transialidase (TSA-1). Currently, these candidate antigens are undergoing process development and preclinical testing. The Sabin PDP is also developing alternative candidates to the TSA-1 component, which includes those recently discovered at the University of Texas Medical Branch, the antigens TcG1, TcG2, and TcG4 as possible vaccine candidates in preclinical models. Similarly, the University of Texas at El Paso is pursuing the MASP antigen as a possible vaccine antigen, and it is also being tested in murine models. The University of Georgia is also pursuing vaccine discovery by screening all T. cruzi genes for promising antigens. The Universidade Federal de Santa Catarina as well as the Universidade Federal de Minas Gerais also has active vaccine discovery programs.

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<th>Candidate Name/Identifier</th>
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References