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Status of vaccine research and development of vaccines for Chagas disease

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1. About the disease and pathogen

Chagas disease (American trypanosomiasis caused by *Trypanosoma cruzi*) is a vector-borne parasitic infection transmitted by triatomines (kissing bugs), today considered one of the most important neglected tropical diseases globally (NTDs) [1].

1.1. Global disease and economic burden

An estimated 7–8 million people are infected worldwide with almost all of the cases occurring in the Americas, predominantly in the poorest countries in the region [2–4]. However, revised estimates taking into consideration underreporting and poor diagnosis suggest that the number of total worldwide Chagas cases is much closer to 9–10 million [5,6]. Further estimates are that Chagas disease is responsible for 10,600 deaths per year in addition to 97,500 years lived with disability (YLDs) [5,7]. In total, combining years of life lost and YLDs, Chagas disease causes approximately 0.6 million disability adjusted life years (DALYs), a measure integrating a disease's morbidity and mortality [4,5,8]. According to the World Health Organization, currently the largest number of people living with Chagas disease are found in focal areas of poverty within Latin America's three wealthiest countries: Argentina (1.5 million), Brazil (1.2 million), and Mexico (0.9 million), while the highest prevalence of the disease (in terms of percentage of the population infected with *T. cruzi*) is seen in Bolivia (6.104 cases per 100 people) [7]. Chagas disease has also become "globalized" with thousands of cases also found in Southern Europe, Australia, and Japan [9]. Also, of particular concern are the large numbers of cases in the southern United States, especially Texas where emerging evidence indicates a significant level of autochthonous transmission [10,11].

Despite its global importance in the most affected Western Hemispheric countries, it is estimated that only a small percentage of Chagas disease patients are diagnosed and receive access to essential medicines and other healthcare [12]. Patients with Chagas disease typically live in extreme poverty and represent a highly vulnerable population. The poor who live in the Western Hemisphere's wealthiest countries, including Argentina, Brazil, Mexico, and the United States are especially neglected, a concept consistent with the tenets of "blue marble health" [13]. Moreover, Chagas also has an important impact on veterinary public health, with canines and sylvatic mammals serving as important reservoir hosts.

In addition to its global health impact, Chagas disease has been demonstrated to be one of the largest causes of why Latin America's poorest population, the "bottom 100 million", remain impoverished ($7 billion annual losses to the economy) [14,15].

1.2. Natural history and clinical disease

Typically, the *T. cruzi* protozoan parasite enters its vertebrate hosts with insect faeces deposited into fresh bite sites, mucosal surfaces or other skin breaks. In its trypomastigote form the parasite then can invade cells such as fibroblasts, macrophages, and epithelial cells, thus largely evading the host's immune system. Within its mammalian host the parasite then transforms into its intracellular amastigote form, and concomitant with the eventual rupture of these host cells, blood-form trypomastigotes are released. The cycle is completed when triatomines take up trypomastigotes during subsequent feedings, and the parasite develops into the epimastigote form in the midgut, which multiplies by binary fission, and back into trypomastigotes in the hindgut [16].

Exposure to the *T. cruzi* parasite results in the development of an acute infection, which is often asymptomatic and lasting for 4–8 weeks, but can also be characterized by a rather telling localized swelling at the site of infection (Chagoma), or a special form of

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conjunctivitis (Romaña's sign). Virtually all of these acutely infected individuals seroconvert to *T. cruzi*, but approximately 60–70% of these individuals do not progress to clinically apparent disease (*indeterminate status*), while the remaining 30–40% move on to develop the chronic form of the disease (*determinate status*), concomitant with the appearance of cardiac and/or gastrointestinal signs and symptoms. Cardiac complications in particular, occurring in 20–30% of patients, cause the most severe morbidity and mortality and are characterized by arrhythmias, aneurysms, and heart failure. Ventricular tachycardia and fibrillation leading to sudden death are connected to two-thirds of the mortalities from Chagas disease, followed closely by heart failure and thromboembolism [17]. Pathological findings in chronic Chagasic gastrointestinal disease include dilatation and muscular hypertrophy of the colon or the oesophagus, as well as injury to the parasympathetic nervous system [18].

While most of Chagas disease occurring in the Americas is transmitted by triatomines, there is now also evidence for increasing maternal-to-child transmission of the disease, resulting in congenital Chagas disease. Hundreds of thousands of pregnant women in the Americas now live with Chagas disease, while maternal-to-child transmission of *T. cruzi* leading to congenital Chagas disease has resulted in 8668 documented neonates infected in Latin America (in 2010), with Mexico having the largest number of cases of congenital Chagas disease [7], though these estimates do not likely represent the true number of cases due to poor detection of the disease [19,20].

1.3. Current approaches to treatment

Current treatment is dependent on two drugs, benznidazole or nifurtimox, both of which are highly effective, provided therapy is initiated at the onset of infection and during the acute phase of the disease. However, very few patients are diagnosed in the acute stages because these stages are often silent, or because the patients do not have access to proper diagnosis and treatment. The efficacy of both drugs for many patients with chronic Chagas disease diminishes the longer a person has been infected. In fact, a recent randomized trial of patients showing evidence of Chagasic cardiomyopathy failed to show any benefit for patients treated with benznidazole versus an untreated control cohort when it came to the progression of cardiac clinical deterioration [21]. 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 for 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 [22,23]. Given this current situation, there is an urgent need for a new treatment strategy is crucially needed for chronic Chagas disease, including a safe and effective vaccine.

2. Overview of current efforts

2.1. Biological feasibility for vaccine development

Currently there are at least two major potential Target Product Profiles (TPPs) for a Chagas disease vaccine (Box 1). The first is a prophylactic vaccine that would prevent acute infection and the second is a therapeutic vaccine for patients that have seroconverted and are at the indeterminate stage. It is widely noted that a therapeutic or preventative *T. cruzi* vaccine would be highly beneficial in controlling Chagas disease [23,24]. A preventative vaccine if used in highly endemic areas could potentially prevent acute infection (especially in a hyperendemic setting found in some parts of Latin America) but is unlikely to interrupt disease transmission because of the large number of animal reservoirs and zoonotic hosts, typically found in these endemic areas. A therapeutic vaccine administered alone or in combination with chemotherapy would be used to prevent or delay the onset of Chagasic cardiomyopathy in patients who have seroconverted to *T. cruzi* infection and are at the indeterminate or early determinate stage [15]. Hence a third TPP would include the use of a therapeutic vaccine used in conjunction with benznidazole or other newly developed antiparasitic drugs. Some investigators refer to this combination as "vaccine-linked chemotherapy".

Box 1: TPPs for Chagas disease vaccine
Preventive Chagas disease vaccine
Therapeutic Chagas disease vaccine in patients with indeterminate infection
Therapeutic Chagas disease vaccine linked to anti-parasitic chemotherapy ('vaccine linked chemotherapy')

Cost-effectiveness studies have been conducted on both the preventive and therapeutic vaccine TPPs [14,15,25]. While both are considered cost-effective, the therapeutic vaccine is considered more cost-effective and cost-saving and therefore more economically dominant [15]. There is as yet no consensus among the community of Chagas disease researchers on the urgency for developing a prophylactic vaccine. However, there is general agreement on the need for new therapeutic anti-trypanosomal products that go beyond the currently available drugs, benznidazole and nifurtimox.

Both scientific and socioeconomic challenges have hindered the development of vaccines against Chagas disease. Chagas disease is an NTD almost exclusively affecting people in poverty and thus there has been an absence of market incentive for pharmaceutical companies to undertake research and development on a vaccine. In addition, initial safety concerns over exacerbating pre-existing cardiac lesions through activation of an autoimmune reaction, based on earlier assertions that there is an important autoimmune component to Chagas disease pathogenesis. However, most investigators currently believe that it is parasite persistence that is associated with disease progression, and that a strong $CD8^+$ T cell immune response will need to be induced, encompassing either interferon-gamma or cytotoxic activity, or both, in order to control *T. cruzi* infection through vaccination [18,22,23].

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 pre-clinical proof-of-concept for vaccination as a preventive and potentially therapeutic strategy. It has further been observed that the efficacy of *T. cruzi* vaccines in pre-clinical models will be greatly influenced by the vaccine formulations used and their resulting immune response [22,23]. Along these lines, many preclinical models have been employed in the study of Chagas disease, most of which include rodents, dogs, and non-human primates (NHP). The advantages of rodent models, most commonly mice, are lower cost for housing and handling, and a shorter lifespan resulting in quicker results. However, it is often difficult for the murine systems to completely reflect the pathology seen in human Chagas disease. Canine and NHP models often more successfully mimic the human responses and pathologies observed, but, with their longer lifespan, experimental results are often delayed. In addition, ethical concerns that surround their use and the

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