

Title: The senseless orphanage of Chagas disease.

Abstract.

Introduction: Chagas disease is caused by the parasite *Trypanosoma cruzi*. Endemic in 21 American countries, there are ~7 million people infected, of which 14,000 die every year. Despite this burden, Chagas remains an orphan disease as it mainly affects poor communities with low economic and political power.

Areas covered: there are two drugs available to treat the infection, but both have safety and efficacy issues. Investment in new treatments and other control measures has been historically neglected. This trend is changing and there are novel perspectives to put an end to this senseless orphanage. Research and development agenda of new therapies, diagnostic tools and biomarkers have moved forwards during the last decade; and patients associations have been active in promoting awareness of the disease all along. Besides, the WHO recently declared April 14th as the “World Chagas disease day”, which will increase the visibility of the disease and attract attention internationally.

Expert opinion: efforts must focus in the prevention of new infections, but also in the management of the millions already chronically infected. This will require of an integral approach where increasing the number of trained health workers and generalizing access to diagnosis and treatment will be fundamental.

Keywords: Chagas disease; *Trypanosoma cruzi*; orphan disease; treatment; clinical trials; patients’ associations; World Chagas disease day.

Article highlights.

- Chagas is an infectious disease caused by the parasite *Trypanosoma cruzi* that is endemic in 21 American countries, where reside most of the ~7 million people infected.
- It is mainly transmitted by vectors that proliferate in infra-housing settlements linking the disease to a poor socioeconomic status; and since the affected people are from low-income communities with no political voice Chagas disease treatment and control has been historically neglected.
- There are two drugs to treat the infection: benznidazole and nifurtimox. These are very efficient against the acute stage, but since this is mostly asymptomatic it is not diagnosed. Treatment is provided at the chronic stage, and by then its

efficacy is variable. In addition, both drugs entail long administration regimens that have frequent adverse effects associated.

- Recent advances in more sensitive and specific diagnostics and point-of-care suited technologies, linked to a diversification of the drugs' producers will contribute to generalize access to diagnosis and treatment in the near future. Moreover, Chagas disease is in the clinical trials arena, where alternative regimens of existing drugs as well as new drugs are being evaluated in the search of more efficacious and less toxic treatments.
- Patients' associations have greatly contributed to increase disease awareness and empower those affected by it. Sensitization must continue at all levels to ensure funding for research and development, and to invest in the training of health professionals in order to integrate Chagas disease patients care in the health systems from endemic and non-endemic regions.

1. Introduction.

1.1. Chagas disease origin and epidemiology.

Chagas disease or American trypanosomiasis is a systemic parasitic disease caused by the flagellated protozoan *Trypanosoma cruzi* (*T. cruzi*). The infection is transmitted in the faeces of infected hematophagous vectors such as *Triatoma infestans*, that, upon a bloodmeal, defecate near the bite site or near mucosal tissue [1]. Parasites in the faeces will then gain access to the bloodstream through micro-injuries caused by scratching the bite site or through the mucosa [2]. Oral transmission due to the ingestion of parasite contaminated food or drink has been documented as well [3,4]. Vector-independent transmission routes such as blood transfusion, organ transplant, and congenital have been described too [1]. Another possible route of infection can occur in case of a biohazard incident in the laboratory upon manipulating parasite containing samples [5].

There are over 100 species of transmission-competent insect vectors (family Reduviidae; subfamily Triatominae), which sustain a wild cycle that involves as many mammalian species as hosts and reservoirs [6]. These represent a continuous risk to people in rural endemic areas and make the eradication of the infection an almost impossible task. Vectors find a suitable habitat in adobe-walled houses and thatched roofs, still frequent in many regions of Latin America.

There is paleontological evidence of human *T. cruzi* infection as early as 9,000 years ago in mummies from coastal and low valley sites in northern Chile and southern Peru, and 4,000 years ago in the mesothermal valleys around Cochabamba area, in what is now Bolivia [7–9]. Populations that lived in these areas abandoned their nomadic way of life for a stable one that included wild guinea pig breeding. This settlement favoured vector domiciliation and human infection since triatomine vectors obtained their food very easily from human beings. From these valleys, during the Inca Empire, the vectors and the human disease they transmitted were spread all over the American continent linked to migrations and Inca couriers, called “Chasquis”, who travelled the Inca roads. Spanish chronicles from the 16th and 17th centuries describe the presence of triatomine insects in homes in areas that today would be in Argentina, Bolivia, Chile and Paraguay [10]. Later on, Charles Darwin described the triatomine insects and detailed them biting himself on his “Voyage of the Beagle” in 1835, when he was crossing the Andes from Valparaiso (Chile) to Luxan (Argentina) [11]. But it was not until 1909 when Dr. Carlos Chagas, deployed in a northern area of the state of Minas Gerais in Brazil, first described the parasite, the insect vector and the human disease caused by the infection [12]. The joint full description of the elements driving to a disease, its symptomatology and epidemiological characteristics never before coincided in a single discoverer in the history of medicine. Thus, he was twice nominated to the Nobel Prize; and he was not elected for it neither of them [13].

According to Coura et al the greatest expansion of human Chagas disease occurred during the 19th and 20th centuries [14]. This was mainly due to railways development in Brazil and Argentina, and to the related settlement of people in the inland regions of the countries. This expansion lasted until the 1980s, when Chagas disease was reported to be endemic in 21 countries of the American continent, there were 100 million people at risk of acquiring the disease, and more than 17 million were infected [15].

More recently, a second period of disease expansion has occurred as a result of the migration from endemic to non-endemic regions within Latin American countries and to countries in other geographical areas like northern North America and Europe (**Figure 1**). For instance, it is estimated that Europe received around 2 million people from Latin America in the last decades [16]. Current figures of infected people living outside the so-called endemic countries is very difficult to estimate due to the lack of reliable epidemiological studies in the countries of origin of the migrants and the diversity of legal status and access to health care of these people in the host countries. In 2007 Schmunis

estimated that there were between 38,000 and 676,000 *T. cruzi*-infected people in the USA [17]. In Spain, this estimate varies between 47,700 and 67,400 *T. cruzi*-infected people [18]. This latter range is explained by the different seroprevalence rates stated by the Pan American Health Organization (PAHO) in comparison to the values found upon diagnosing pregnant women from Chagas disease endemic countries in maternity wards from Valencia and Barcelona [18,19].

Despite its very important regional and international health impact, Chagas disease belongs to the group of Neglected Tropical Diseases (NTD) listed by the World Health Organization (WHO) [20]. These diseases share certain characteristics: they affect those with fewer resources; they are mostly chronic infections that can cause severe pain and/or lifelong disabilities; they are associated with the exclusion and stigmatization of the people who suffer from them; there are no vaccines and the available drugs to treat them have toxicity and efficacy issues [21].

The fight against Chagas began to be carried out jointly at the sub-regional level in the 1990s with the implementation of initiatives that brought together several countries that were endemic to the disease (Southern Cone, 1992; Central America, 1997; Andean Countries, 1998; Amazon countries and Mexico, 2004) [22]. These initiatives managed to significantly reduce the presence of vectors in households and the transmission of the infection through blood products. Altogether with a general improvement in the living conditions, including architectural improvements in homes that hinder the establishment of the vectors, reduced the estimated number of *T. cruzi*-infected people from 17 million in the 1980s to ~7 million today [1]. While the number of people affected has decreased significantly in recent decades, there are still 25 million people at risk of contracting the disease. Every year there are 30,000 new cases, 9,000 children are born with the disease and 14,000 people die as a result of Chagas disease [23]. Globally, Chagas disease imposes an annual burden of \$627.5 million in health care costs and 806,170 DALY (Disability-Adjusted Life Year) [24,25].

1.2. Clinical features and diagnosis of the infection.

Once a person becomes infected, the motile metacyclic trypomastigotes, which represent the first wave of mammalian infective parasite life forms, enter nucleated cells in blood and tissues and multiply intracellularly upon transforming into replicative amastigotes. These multiply inside the infected cells crowding their cytoplasm and transforming into trypomastigotes, another motile parasite stage that then bursts the

infected host cell and swims away to take the infection elsewhere [26]. The amount of parasites in blood and tissues grows exponentially during the first days of infection and lasts until the immune system develops a specific response to control their dissemination. This acute phase of the disease is 6 – 8 weeks long and is characterized by nonspecific symptomatology that frequently goes unnoticed: fever, headache, asthenia, anorexia, malaise, diarrhoea [1]. Nonetheless, a mortality rate of up to 5% has been reported, especially in children, whereas in oral transmission cases mortality can even be much higher [4,27]. From a microbiological point of view, at the acute phase the parasitaemia is high enough to be detected by direct or indirect classical parasitological techniques [28], or even more sensitively with molecular amplification techniques [29]. Levels of circulating parasites decrease as far as the specific immune response develops, which marks the beginning of the chronic phase.

In the chronic phase of the disease parasitaemia is low and intermittent, but levels of anti-*T. cruzi* type G immunoglobulins (IgG) can be detected in serum, which allows serological diagnosis of the infection. This is asymptomatic in ~70% of the infected people, thereby leading to an indeterminate Chagas disease status [1]. Nonetheless, the remaining ~30% will develop a symptomatic form of the infection with cardiac and/or digestive involvement. Disruptions to heart and/or digestive tract tissues (oesophagus, colon) can be life-threatening if untreated, and it is estimated that in patients with symptomatic Chagas disease the possibility of premature death can reach up to 20% of the cases [30]. In immunocompromised patients, the disease can evolve from an asymptomatic indeterminate chronic phase to a reactivation situation, defined by high parasitaemia, with or without immediate clinical symptoms, which can be detected by parasitological methods [31].

Diagnostic methods for Chagas disease depend on the stage of the disease. In the acute phase and in reactivations, diagnosis is based on direct detection of parasites in blood either by classical parasitological techniques or by molecular amplification of *T. cruzi* DNA [15,32]. In immunocompromised hosts, the parasite presence can be detected in other fluids such as cerebrospinal fluid (CSF) [31]. Classic parasitological techniques such as the microhematocrit and Strout are based on direct visualization of the parasite under the microscope. These techniques have the advantage of being cheap and simple, but they are operator-dependent and their sensitivity largely decreases in case of parasitaemia levels lower than 40 parasites per ml [33]. In contrast, molecular methods such as the qualitative polymerase chain reaction (PCR) or the quantitative real-time

qPCR are more sensitive and less operator-dependent [34]. Unfortunately, they are not available in most diagnostic centres in endemic regions due to their higher cost and the need for advanced expensive equipment. When available, molecular diagnosis is the recommended method for the diagnosis of congenital Chagas disease, reactivations and acute phase [35,36]. In addition, qPCR is widely used at present to evaluate parasitological clearance after treatment in the context of research and clinical trials investigation [29]. The availability of an easy-to-use point-of-care (POC) molecular-based diagnostic could change the current algorithm of congenital Chagas disease diagnosis, targeting for treatment infected newborns in a much faster fashion than with currently applied algorithms [37]. In this regards, an innovative Loop-isothermal amplification (LAMP) assay aimed to be used as POC test has been recently developed for the detection of *T. cruzi*-DNA [38]. It contains all the required reagents dried-up in the tubes lids and the fact that it relies on an isothermally working polymerase makes it possible to run it without requiring expensive thermal-cyclers [39].

The methods used to diagnose the infection in the chronic phase are serological, mainly based on the detection of specific anti-*T. cruzi* IgGs in serum samples [40]. Despite the advancements in sensitivity and specificity achieved with serological tests based on recombinant parasite antigens, the agreement of two serological techniques that are based on different antigen sets is still recommended to provide a conclusive result [41]. The most used serological method to diagnose chronic Chagas disease is the enzyme-linked immunosorbent assay (ELISA), of which there are many kits commercially available that provide very high sensitivity and specificity [42]. Other conventional serological techniques such as indirect immunofluorescence (IIF) or indirect hemagglutination assay (IHA) are less frequently used than the ELISAs, since they respectively require specific and expensive equipment (i.e. fluorescent microscope for IIF) or have a poorer performance than the former [43]. In terms of POC serological diagnostics, easy-to-use rapid diagnostic tests (RDTs), which are based on immuno-chromatography, are gaining relevance in the last few years. They are simple to use, do not need cold-chain, and can be directly used in the field with a tiny drop of whole blood as sample. Plus, they are capable of yielding a results turnaround to the patient much faster than the ELISAs, while still maintaining a very good performance [44]. In fact, the combined use of two RDTs has been suggested as an alternative to the traditional chronic Chagas disease diagnosis algorithm as far as their use is regionally validated [45,46].

1.3. Chagas disease treatment.

Benznidazole (BNZ) and nifurtimox (NFX) are the only two drugs approved for Chagas disease treatment [1]. They were both developed in the late 1960's and there are no new treatments available since then [47,48]. The effectiveness of these treatments is affected by age, drug dose, stage of the disease, and area of origin of the patient, among other factors [49]. Parasitological and clinical efficacy of treatment in the acute phase in young patients can be up to 100% of the cases, especially in children under one year of age [50,51]. In contrast, when treatment is provided in the chronic phase, its efficacy has been estimated to range between 60% to 80% of the cases upon 12 months follow-up controls with qPCR [52,53]. Nonetheless, clinical efficacy is difficult to assess due to the natural course of the infection and the absence of early markers of treatment response or cure [54,55]. Accordingly to WHO guidelines, only negativization of serological titres can be interpreted as a readout of parasitological cure [15]. Notwithstanding, this serological reversion from positive to negative may take several decades to occur when treatment is administered in the chronic stage of the infection. As a consequence, currently available methodology to assess treatment response in the chronic stage is highly impractical [56].

At present, administration of treatment is indicated for acute cases, congenital infections, reactivations, and those chronic stage infections without symptomatology (indeterminate disease) or with mild cardiac and/or digestive involvement [47,57,58]. The recommended dosage for BNZ regimens is 5 mg/kg/day divided into two doses for 30 to 60 days; whereas for NFX, it is recommended to give 15 mg/kg/day divided into two or three doses for 60 to 90 days [48,59,60].

A very important issue regarding current therapeutic options for Chagas disease is the safety profile of the two drugs available. It has been described by different authors that between 48% and 86% of the patients treated with BNZ have some kind of adverse effect, resulting in treatment interruptions in 9% to 31% of the cases [61,62]. Similar figures have been reported in the case of NFX [63]. The most frequently observed adverse effects are dermatological, neurological and gastrointestinal, and they are generally mild [61-63]. Much less frequently, there is also a risk of serious life-threatening adverse effects such as severe neutropenia or Dress syndrome [64]. Thus, the paramount importance of setting up and maintaining pharmacovigilance programs to monitor the advent of these side-effects and the readiness to deal with them and minimize their impact in the patients' wellbeing.

Besides the difficulties described, namely long treatments with frequent toxicity burden and the lack of reliable tests to early assess their effectiveness, access to the drugs still hinders the provision of treatment to people with Chagas disease. In 2012, data from WHO estimated that the number of people treated yearly was about 8,500 [65]. This means that since these treatments were launched, they have barely reached ~1% of those affected [66,67]. Looking at it from another point of view, it means that amongst the ~7 million people currently infected by *T. cruzi*, more than 2.1 million will have cardiac or digestive complications, and that around 1 million people could die from this infection. Based on the present treatment success rate of 60% to 80%, if there were universal treatment coverage, 1.2 to 1.6 million of them could avoid the symptomatic form of the disease, live a better life and die from something else.

2. Chagas disease as an orphan disease.

2.1. Why is Chagas disease orphaned?

The term “orphan disease” defines two different but related concepts. It is generally used to define a disease that affects a small number of individuals. Given the current number of people infected with *T. cruzi*, this definition cannot be applied to Chagas disease. However, “orphan disease” is also used as well to name diseases neglected by doctors [68]. This description fits perfectly with the current and past situation of Chagas disease. It can be said that Chagas disease was born orphaned of the attention of the scientific community and political interest. Without going any further, the description of the parasite, vector and human disease at the same time by Dr. Carlos Chagas was a milestone in the history of medicine, which never received the attention or recognition it deserved [13]. This probably had, and still has to do with the socioeconomic characteristics of the affected population. Carlos Chagas himself wrote: "There is an ominous fate in the study of Trypanosomiasis. Each work, each study, points a finger towards a poorly nourished population living in poor conditions; it points to an economic and social problem, which causes them (to the rulers) a tremendous discomfort because it is testimony of (their) inability to solve a tremendous problem [...]. It is a problem of “vinchucas”, which invade and live in poorly constructed, dirty rooms, with ignored, poor, undernourished inhabitants, with no hope or social horizon and that resist to cooperate. Talk about this disease and you will have governments against you" [69]. In 2005, the Uruguayan writer Eduardo Galeano denounced in the book "Chagas, a silent tragedy" the fact that this disease, which takes several years to develop symptoms, affects

mostly poor people, and it is not interesting for the pharmaceutical industry, public opinion, and not even for governments, "...kills in silence [...], it kills the silence: those who live doomed to silence..." [70].

The orphanage of Chagas disease has to do with the fact that it mostly affects poor populations with little power of political pressure, which contributes to a state of invisibility as a health problem in the Americas that leads to a lack of investment in training of healthcare workers, health education of communities, and meagre research and development programs. In addition, it must be highlighted that the impact of the disease itself on the lives of the people affected by it largely contributes to a vicious poverty-disease-poverty cycle, which transforms people at productive age into dependent individuals extending the disease impact onto household economics. On top of that there are structural, psychosocial, clinical and systemic barriers, which make access to treatment a challenging issue for those affected by the disease. Compared to other neglected diseases that particularly target the world's poorest communities, the silence—both political and in the media—surrounding Chagas disease is striking and has delayed the implementation of already available solutions.

Traditionally associated to poor rural areas, Chagas disease used to be a synonym of two very different and, in some ways, contradictory concepts: it meant “death”, and on the other hand “invisibility”, because it is an infection that can be imperceptible for the people who live with it all their lives. These features must drive to strengthen the efforts to promote awareness and training for health staff, and in particular, those who care directly for patients or affected populations [71]. Historically, health professionals in endemic areas were insufficiently aware of the disease impact as they did not acquire the knowledge about how to manage it. This has had a direct impact on the clinical aspects of patient care. The lack of attention towards Chagas disease in Latin American healthcare systems is partly explained by the fact that the books used for the training of health professionals are published in Europe or North America. In these regions, until the migratory phenomena of the year 2000s, Chagas disease was a virtually unknown disease and therefore it was absent or scarcely mentioned in these texts.

On the other side, in academic discussions autoimmunity was long hypothesized to be the major mechanism for chronic Chagas disease pathology [72]. For many years, this hypothesis negatively contributed on the efforts to implement available anti-parasitic treatments and to develop more effective drugs. Fortunately, scientific evidences on the role of the *T. cruzi* parasite as a trigger for tissue damage accumulated over the last three

decades, providing a basis to reconsider this paradigm and to re-introduce anti-parasitic treatment for chronic adult patients. [49,73–75].

In connection with the lack of awareness of health care workers, the neglect of Chagas disease also involves health decision makers. It was not until 1986 that the first regional program for the control of Chagas disease was established in Tupiza, Bolivia [76]. Since then, national Chagas programs have been implemented in the region, with the creation of diagnostic and treatment guidelines, which are not always coincident [77–80]. Finally, in 2018, the first consensus guideline at regional level was endorsed by PAHO/WHO [41]. Before that, discrepancies in the indications for treatment in different national guidelines meant that, for example, treatment was not universally recommended in patients over 19 years of age with an indeterminate chronic form of the disease, which clearly represents a missed treatment opportunity. The reason for not recommending treatment in adult patients was mainly due to the lack of an early cure marker, since the only cure marker currently accepted is serological negativization and this can take decades to occur [36].

Perhaps the sole exception to the absence of specific attention to Chagas disease was the regional implementation of vector control programs. This, together with the improvement in housing habitability conditions (although these were not specifically aimed at controlling the disease), led to a 40% decrease in the number of people affected over time: from the ~17 million in the 1980s to the ~10 by the end of last century and ~7 million today [23]. However, vector control programs have been irregularly implemented in the region, and become an incomplete and inefficient strategy unless they are not accompanied by other specific measures for disease control such as providing information and education to the community, training healthcare personnel, and enabling widespread access to diagnosis and treatment.

2.2. Need of tools to improve disease control and management.

Tools to detect anti-*T.cruzi* immunoglobulins at the chronic stage and parasitological and/or molecular diagnostics for the diagnosis of acute infection are nowadays available [81,82]. Despite they provide valuable information on the infection status, they cannot inform on the clinical prognosis of the disease neither on the treatment efficacy (or spontaneous cure) in a short period of time [54]. As already mentioned, a positive serological result takes many years to become negative upon administration of treatment and no re-exposure to the infection. Thus, it is not possible to rely on current

serological tests in order to address response-to-treatment timely. On the other hand, although molecular-based techniques are highly sensitive to assess acute *T. cruzi* infection status, treatment administration usually occurs during the chronic stage when parasitemia is low and intermittent. By then a positive qPCR result at follow-up will indeed indicate a treatment failure event, but a negative outcome cannot rule out the presence of undetected tissue hidden parasites that could relapse later on. Thereby, the lack of appropriate biomarkers to early assess response to treatment greatly limits overall the opportunity to give an accurate response to patients about the efficacy of their specific treatment. In addition, this shortage also hinders the evaluation of the efficacy of new therapeutic strategies tested through clinical trials. These are major barriers towards generalizing access to diagnosis and treatment, and strong reasons to consider Chagas disease an orphan disease.

The aim of several ongoing studies is to identify and validate markers to early address disease prognosis and/or therapeutic response. These studies have evaluated both parasite-derived markers [83–85], as well as host-derived ones [86–89]. The latter could be classified into three main groups: (i) immunological markers (cytokines) elicited by the host cellular response to the infection; (ii) biochemical biomarkers, such as hypercoagulability markers, fragments of apolipoprotein A1 (ApoA1), or transforming growth factor beta (TGF β); and (iii) inflammatory markers of cardiac damage (e.g. type-B natriuretic peptide (BNP) or highly-sensitive protein C), which have been perhaps the most studied of all and unfortunately were not very good to follow disease progression [90]. Very recently, the use of cytokine IL17A as biomarker of treatment response has generated expectation [91], but further studies should be implemented to better characterize and validate them, especially in chronically infected adult population. On the other hand, expectations have been as well deposited on a promising group of parasite-derived biomarkers, which mostly encompass parasite surface molecules [83–85,92]. The future availability of different types of long-awaited early response-to-treatment biomarkers, and the corresponding tests based on them will be crucial to “un-orphan” Chagas disease.

2.3. Advancements towards improved therapeutic interventions.

No new treatments for Chagas disease have been approved since the 1970s. As indicated above, BNZ and NFX are the only medications available for the treatment of *T. cruzi* infection. However, despite belonging to the list of essential medicines of the WHO,

they are available to less than 1% of the infected individuals [66,67]. Other challenges to face include their safety profile and variable efficacy accordingly to the stage of the disease they are administrated. BNZ production has had many ups and downs during the last decades. Roche was its only manufacturer until 2003, when it stopped production and commercialization. Then, it transferred the manufacturing technology and rights to the Brazilian government, which assigned the production of BNZ to the Public Pharmaceutical Laboratory of the State of Pernambuco (LAFEPE) (**Figure 2A**). Then BNZ production stopped from 2003 to 2008. LAFEPE was at that time the only producer of BNZ in the world. However, LAFEPE did not have the Good Manufacturing Practices (GMPs) certification for the production of the drug, which prevented the possibility of commercialization to other countries and there was a dramatic shortage. In 2011, the Argentine pharmaceutical laboratory ELEA began the production of BNZ (**Figure 2A**), becoming the only producer of BZN able to commercialize it through the PAHO fund. Nowadays, LAFEPE and ELEA (with its North American subsidiary EXELTIS), can produce and distribute BNZ, but being the only two companies in the market, competition will hardly influence price regulation so as to have BNZ at an affordable price. Similarly occurs with NFX, which is produced by Bayer and GADOR, and in most endemic countries is only accessible for treatment through donations to national Chagas programs (**Figure 2B**).

According to the price list published by PAHO in its strategic fund reference prices [93], the estimated cost of BNZ treatment for an adult is ~100 USD [94,95]. In any case, it is yet incredible that when there is access to the drugs, this is often through complicated drug application processes that sometimes involve weeks or months until having them delivered. Such application processes are not usually accessible to primary care physicians who are most aware of the needs and responsible for their prescription. The immediate consequence is that a doctor in an endemic country sadly may not have the chance to offer treatment in case of need.

The troubles with the drugs' production and distribution listed beforehand relate to the neglect of the disease by the political statement, as much as with the lack of commercial interest of pharmaceutical companies. The latter has a large impact on the research and development of new drugs for Chagas disease too. Although it affects a large number of people, their very low purchasing capacity makes the potential market unattractive to pharmaceutical companies' drug discovery efforts. Thereby, with no revenue foreseen it is complicated that private initiatives take the risk to invest in anti-*T.*

cruzi drug development. However, some non-profit initiatives in recent years are leading a change in this regard [96]. After decades without any movement at all, in the past few years up to three clinical trials evaluating new drugs for Chagas disease have been carried out [52,97,98]. In all cases, posaconazole and ravuconazole (its prodrug E1224) failed to yield the level of parasitological clearance achieved by the gold-standard BNZ [52,97,98]. Even so, the fact that these clinical trials took place is hopeful by itself. To illustrate the difficulty of conducting clinical trials in some endemic areas, it should be enough to point out that the first clinical trial conducted in the history of Bolivia was the mentioned E1224 [52]. Although the outcome of such experience did not contribute to change the treatment of Chagas disease, it left a mark in the country in terms of acquired experience and training of the personnel involved. These are key features towards the performance of both current and future studies, such as FEXI, BENDITA and TESEO among others [99]. Similarly, although the results from the BENEFIT trial were controversial, it marked a milestone in Chagas disease clinical research being the first Phase III study ever performed [99]. In this regards it represented a major advancement in the field as it established a large multinational clinical network for its performance that involved institutions from several Latin American countries.

Amongst the new drugs under evaluation for Chagas disease treatment, perhaps the most promising is fexinidazole (FEXI). Notably, its use for the treatment of African trypanosomiasis, a parasitological disease caused by *T. cruzi* closely related protozoan species *T. brucei gambiense* and *T. b. rhodensiense*, has been very recently approved [100,101]. At present, there are pending results of a Phase II study evaluating FEXI administration to chronic Chagas disease patients [102]. An observed increased scientific interest, altogether with the improvement of the drug discovery techniques, hold promise towards finding a better drug for Chagas [103]. Nonetheless, currently ongoing efforts will need to be sustained and paired with an adequate investment, otherwise there is a high risk of a slow and inefficient progression [104].

2.4. Patients' involvement.

Regarding the patient's active role, there have been some significant advances in the last decade. In 2010, more than 20 associations from all over the world gathered to create the International Federation of Associations of People Affected by Chagas Disease (FINDECHAGAS). Members of the associations that are part of FINDECHAGAS chose to be identified as "affected" people and not as "infected". In deciding to be represented

through non-stigmatizing word choice, the members of FINDECHAGAS are promoting a transformation in the way we traditionally look at those who suffer these kinds of diseases.

The need of increasing awareness about Chagas disease is a common gap for both patients and health staff. To fill this gap, both communities must work together. On 28th April 2015, the Food and Drug Administration (FDA, United States of America) held a public meeting to hear people with Chagas disease about their condition, its impact on their daily life, and their perspectives on approaches to treating the disease. In this meeting, besides patients and patient advocacy organizations, there were various stakeholders in the drug development process, health care providers, academic experts and industry experts. From the patient's point of view, the most important input provided was the significant lack of awareness and understanding of Chagas disease by the healthcare community. Patients participants identified struggling with fear of future symptoms, social isolation, difficulty in finding others to discuss their experiences with, and the frustration of living with a condition that was not well understood [105].

In the last assembly of FINDECHAGAS, held in Veracruz (Mexico) in 2018, patients associations brought back again the need to be more visible, the need to be listened to [71]. They requested the support of all health stakeholders and especially from the Chagas disease Global Coalition in order to submit the petition of a Chagas disease World Day to the World Health Assembly. This submission was approved, and the official day was voted in the WHO's 72nd World Health Assembly in May 2019. Next April 14th 2020 will be the first official global day for Chagas disease (**Figure 3**) [106]. That very same day in 1909, doctor Carlos Chagas made the first diagnosis of the disease to the child Berenize Soares in Minas Gerais, Brazil [107].

3. Perspectives to get Chagas disease un-orphaned.

One of the most powerful arguments to get the attention of governments is to focus on the huge economic consequences of maintaining this disease and its tremendous public health impact ignored, neglected. The estimated economic burden of Chagas disease was calculated between 6,500 and 7,190 million dollars per year [24]. These figures would justify by themselves that governments and policy makers believed that investing on Chagas disease control measures can be a way to improve the health of the population and, at the same time, improve the country's economy [108,109]. For example, a cost-benefit study of a congenital Chagas detection program conducted in Bolivia concluded

that with an investment of 1.5% of the annual socioeconomic cost of all congenital Chagas cases it would be possible to diagnose and treat all children born in Bolivia with this infection [110].

The fight against Chagas disease can benefit from the Sustainable Development Goals (SDGs), which involved setting out a new roadmap on NTDs for the next decade, with specific targets to advance towards the control of Chagas and ultimately its elimination as a public health challenge. Chagas disease is included implicitly in some targets of SDG Goal 3, which is related to health issues. Particularly, Chagas disease is directly addressed in target 3.3: "...on the end of epidemics of Neglected Tropical Diseases by 2030"; and indirectly in other targets such as: target 3.4 ("...reduce mortality from noncommunicable diseases..."), target 3.8 ("...achieve universal health coverage..."), and due to its congenital transmission route also by target 3.7 ("...ensure universal access to sexual and reproductive health care services..."), plus target 11.1 ("...adequate, safe and affordable housing...") [111].

In addition, institutional coordination will be fundamental at the transnational level in endemic areas as well as in non-endemic countries. For example, interventions regarding vector control, information and education of the communities or diagnosis and treatment in an area such as the Gran Chaco, which includes vast extensions of Bolivia, Paraguay and Argentina, will be much more efficient the better coordinated and the more similar they are in between those countries. Maintaining vector surveillance and control programs is yet at the frontline of the fight against Chagas, so they must be solidly maintained and expanded to areas where it is not applied now. Based on this premises, it should be possible to implement more advanced control strategies [112].

Like many other infectious diseases, Chagas disease must be controlled through comprehensive programs that offer a broad range of interventions in addition to case management (diagnosis and treatment). These include Chagas disease information and education to the communities and widespread training of healthcare personnel. For the latter it will be essential to make efforts to include specific training on Chagas disease for health professionals in the curricula of schools and universities. This will allow creating a foundation on which to establish control and management programs as well as it will generate a prepared scientific community that is better connected with the reality of its environment. Although it is very important, counting with well-informed health professionals will not change the reality of the disease, all of a sudden bringing it to the focus of the common interest. For this, information, education and communication (IEC)

actions with civil society are yet very necessary to find tools that can help control the disease and manage its daily impact [113].

If we assumed that of all of the above said (greater government interest, coordinated transnational policies, trained professionals and a very involved civil society) is eventually achieved, there would still be a lot of work to do in terms of improving access to diagnosis and medications. It must be highlighted that there are already many diagnostic tools and two drugs available for this purpose. Notably, we can count as well with positive experiences of training primary health doctors, in procedures where they concentrate efforts on the access to diagnosis and treatment, and are in connection to other specialists in case their intervention would be necessary [112]. Such a strategy could partly mitigate the current problems of access to diagnosis and treatment experienced by a population that is frequently dispersed geographically and with little accessibility to hospital care.

The implementation of this kind of initiatives would yet leave us with an insufficiently studied disease from which there is much to be understood (e.g. its pathophysiology); that lacks of a vaccine; for which the only available chemotherapeutic options have a worrying safety profile where frequent adverse effects are observed; and that has no biomarkers available for the evaluation of therapeutic response nor any to diagnose disease progression. Thus, in-depth knowledge will be much needed towards the control and adequate management of Chagas disease impact. This will undoubtedly require of an unambiguous investment in research and development of biomarkers, locally adapted diagnostic algorithms, and new therapeutic interventions, including the search for an effective vaccine.

As an orphan disease, Chagas disease treatment should be benefited by accelerated procedures to facilitate marketing authorization and drug availability. These procedures can be priority review, fast-track approval and accelerated approval. However, no such legislative benefits regarding orphan drugs exist in any of the endemic countries. From the USA as well as the countries of the European Union, where these mechanisms do exist, an impulse is needed to recognize Chagas as an orphan disease. This could boost the use of legal resources available that could help facilitate marketing authorization and drug availability.

Expert Opinion

For the last two decades, Chagas disease is slowly leaving anonymity and beginning to have a higher presence in the public health landscape. This is in part related to the healthcare attention change associated to population movements of the late 20th and early 21st centuries. Europe became a destination for around 2 million people originating from Chagas disease endemic countries, and management of the disease became a challenge for European health care systems and research groups. This challenge is now reflected in the performance of clinical trials centered on treating *Trypanosoma cruzi* infections. Nonetheless, only 3 out of the 47 Chagas disease interventional clinical trials registered have evaluated the use of drugs different from BNZ and NFX [99]. Moreover, despite this very welcomed wave of clinical studies, to date there is no new treatment that has yet passed Phase II of evaluation. As a result, it is very unlikely that a new anti-*T. cruzi* drug becomes available within the next 5 years. However, what these trials have very well established is that currently available drugs can indeed be used in a primary health care context with good results.

In the diagnosis arena, there has been as well a remarkable progress. Conventional serological tests such as the ELISAs based on recombinant antigen sets now provide a very high sensitivity and specificity. There is as well a plethora of RDTs based on immuno-chromatographic techniques commercially available that could be used as POC diagnostics for the chronic infection. Some of them have shown a performance comparable to the ELISA tests, with the advantage over conventional methods of being very simple to use and well-suited to work in the field. However, while serological methods are the standard of use in the chronic stage, sensitive and reliable methods to diagnose the acute stage of the infection are still missing. Molecular diagnostics such as the real-time qPCR are very sensitive for the detection of the circulating parasites during the acute phase, but the reagents' costs and the requirement of expensive equipment and highly-trained personnel are yet disadvantages to overcome towards their implementation in endemic regions with low resources. Innovative developments such as the LAMP assay could represent a solution to this problem providing the sensitivity of a molecular-based detection of the parasite in a POC test suitable for healthcare facilities with poorly equipped laboratories.

Despite the aforementioned advances, a major problem towards an improved management and control of Chagas disease is still the lack of biological markers of disease prognosis and cure. Accordingly to the WHO recommendation, only the serological reversion from positive to negative status evaluated by conventional serology

is accepted as cure marker. But this is most impractical as it can take several years or even decades to occur upon treatment administration. Undoubtedly this is a field of research that needs more investment, as to date there is not a well-defined set of biomarker candidates, neither for the prognosis of the disease pathology or for the evaluation of treatment response.

In contrast, a remarkable feature to highlight within the last few decades is the growing involvement of patients and affected population in spreading disease awareness. More than 20 patients' associations form the International Federation of Associations of People Affected by Chagas Disease (FINDECHAGAS). The common main objective of these associations is to make Chagas disease more visible, to increase the awareness about it. In this context, the World Health Assembly recently approved to declare April 14th as the international day of Chagas disease. It is expected that this will help to attract further attention on this public health problem and commit countries with affected populations to accomplish and maintain Chagas disease control interventions. In relation to the former, there is yet an urgent need to specifically train healthcare workers in the disease management, both in endemic as well as in non-endemic regions. The consensus guideline issued by the PAHO - WHO for the diagnosis and treatment of Chagas disease patients could be used as a basis for healthcare professionals training.

Overall, the funding and political measures required towards the availability of: (i) well-established and widespread vector control mechanisms; (ii) safer and more efficacious drugs, especially against the chronic stage; (iii) reliable and practical diagnosis algorithms that are better suited to the reality of highly endemic regions distant from reference laboratories; (iv) biomarkers to early assess cure and/or disease progression; and (v) adequately trained and prepared healthcare personnel and health systems, they must all be accompanied by the commitment of governments and international institutions that nurture trans-national cooperation. Ensure a generalized access to Chagas disease diagnosis and treatment is a pending subject that deserves the compromise of all involved actors (patients' associations, academia, pharmaceutical companies, governments, international agencies,...) in order to grant all aforementioned features to the affected populations as soon as possible.

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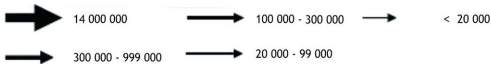
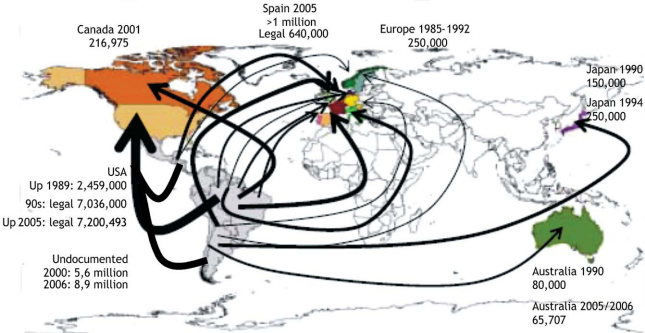
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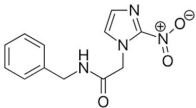
****This article describes the Bolivian platform for the comprehensive care of adults with Chagas disease, which was created in 2009 thanks to funds from the**

Spanish international cooperation. The established strategy has been very successful to provide a solution to unmet demands in the care of Chagas disease patients, greatly improving access to diagnosis and treatment.

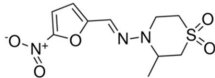
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A



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FINDECHAGAS

