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Epidemiological Aspects of Chagas Disease - a Review

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Abstract

Chagas disease (ChD), also known as American trypanosomiasis, is caused by the trypanosomatid protozoan *Trypanosoma cruzi* (*T. cruzi*) that in its natural life-cycle is transmitted through triatomine vectors. Parasitological studies are useful to confirm acute cases, while the diagnosis of chronic *T. cruzi* infection relies on serological methods. There is no vaccine to prevent the infection, and the treatment is restricted to nifurtimox and benznidazole; and hence, new effective drugs with lower side-effects are urgently needed. The current review updates the facts and phenomena related to ChD, which is becoming an emerging health problem in non-endemic areas too, making the disease a grave global concern.

Keywords: Chagas disease; *Trypanosoma cruzi*; Acute and chronic phases of infection; Triatomine vectors; Anti-*Trypanosoma cruzi* drugs

Introduction

American trypanosomiasis is caused by the protozoan hemoflagellate, *Trypanosoma cruzi* (*T. cruzi*), and is mostly transmitted to humans by triatomine bugs. The disease was discovered in 1909 by the Brazilian physician Carlos Chagas (1879-1934), and hence it is also known as Chagas disease (ChD). The ChD has been recognised by WHO as one of the world's 13 most neglected tropical diseases. *T. cruzi* is restricted to South America, Central America, and parts of North America (Mexico and southern United States), and according to estimates by the World Health Organization (WHO), 10 million people are chronically infected with the parasite, and > 10,000 deaths per year are caused by ChD [1]. The disease was once entirely confined to the region of the Americas – principally Latin America - but it has now spread to other continents.

Two different ecosystems exist for *T. cruzi*: one related to wild triatomine species involving wild mammals (sylvatic transmission cycle), and another dependent on home-dwelling triatomine species involving humans and household animals (domestic transmission cycle). Some triatomine species can infest both domestic and sylvatic sites and may play a bridging role [2].

Vector-borne transmission occurs exclusively in the Americas, and the ChD control programs have focused on preventing transmission of *T. cruzi* (through household insecticide application) rather than active surveillance for infection among human populations at risk. Herein, the ChD updates are due to the SCI and non-SCI based documentation of the disease.

Aetiology

The aetiological agent of ChD is *T. cruzi* - a haemoflagellated protozoan of the Kinetoplastida order and Trypanosomatidae family. *T. cruzi* exhibits well defined wide range of intraspecific genetic diversity. The parasite has six Discrete Typing Units (DTUs), namely, *T. cruzi* I (TcI) and *T. cruzi* II (TcII), having DTUs IIa to IIe [3-5]; *T. cruzi*-I, predominating in the sylvatic transmission cycle, has been associated with human disease in Mexico and Central America, while *T. cruzi*-II prevails in the domestic transmission cycle in most of South America, including Argentina [3].

The *T. cruzi* populations, on the other hand, have been distributed as per the principal zymodemes: Z1, Z2, and Z3 [6,7]; Z1 and Z3 consist of isolates from the silvatic cycle (opossums, armadillos and triatomines), while Z2 comprises isolates from the domestic cycle (humans and domestic animals). Luquetti et al. [8] described the ChD associated zymodeme distribution from Central Brazil where out of 25 patients in acute phase, Z1 was detected in 12 patients and Z2 in 13 patients, while in all 12 patients with chronic form of the disease only Z2 strains were found. The *T. cruzi* I and *T. cruzi* II (DTU IIb) correspond to Miles'zymodemes Z1 and Z2, respectively, and DTUs IIa and IIc are equivalent to Miles'Z3 [4,9]. A new nomenclature for *T. cruzi* has currently been adopted and includes six DTUs: TcI, TcII, TcIII, TcIV, TcV and TcVI, which now are equivalent to TcI, TcIIb, TcIIc, TcIIa, TcIId and TcIIe, respectively [10].

Herrera et al. reported the predominance of *T. cruzi* I in silvatic as well as domestic cycles of the disease in some countries of South America, Central America and in Mexico [11], while in Brazil, *T. cruzi* II (DTU IIb) and hybrids (DTU IId) induce the indeterminate and cardiac forms of ChD. *T. cruzi* I strains induce low parasitemia in human Chagas patients, and in contrast, *T. cruzi* II strains cause human infections with high parasitemia in endemic areas. Also, the host genetics may be involved in susceptibility and play a role in the outcome of ChD [12] occurrence of chronic form of ChD only in few of the infected patients with acute ChD supported this view. It has been reported that in Venezuela, 73.3 % of the 30 chronic chagasic patients had infection with TcI and the remaining with TcIV, and the clinical outcome of people infected with TcI had more severity than those infected with TcIV, suggesting TcI genotype as more pathogenic than TcIV [13].

The life-cycle of the parasite represents four cellular forms characterized by the relative positions of the flagellum, kinetoplast and nucleus [14]. (Table 1) describes the features of different life forms of

the parasite. The amastigotes built nests, by several cell divisions, within various tissue cells of human body, and release by rupture of the cells [15]. The macrophages, which generally become attacked by the infective *T. cruzi* trypomastigotes, are recognized as one of the first cell types encountered by the parasite during natural infection, because of the fact of recognition of *T. cruzi* by macrophages through numerous Toll like receptors and lectin receptors; during initial replication, $CD8^+$ T cell infiltration become delayed facilitating parasite survival [16].

Life form	Site of occurrence	Characteristic feature
Metacyclic trypomastigote	Posterior gut of triatomines; representing the infective stage to humans	Nonreplicative, about 20 µm long; with sub terminal kinetoplast
Epimastigote	Multiplies in the triatomid intestine	Replicative form 20 µm in length having a kinetoplast anterior to the nucleus
Bloodstream trypomastigote	Human bloodstream Infective to the vectors	Typically C or U shaped, with centrally located nucleus and kinetoplast at the posterior end
Amastigote	Multiplies within the muscle and cardiac tissue, digestive system, phagocytic cells	Spherical, approximately 2 µm in diameter, with no emergent flagellum

Table 1: *Trypanosoma cruzi* developmental stages.

Epidemiology

The ChD, caused due to the infection of *T. cruzi*, is a traditionally rural Latin American disease; however, infections extend for an extensive geographical area between 42°N in the United States to 43°S in Argentina. The ChD is typically transmitted to humans by triatomine vectors, and in rural areas of Latin America, where the disease is endemic, and poor housing conditions favour vector infestation. Because, the triatomine bugs thrive better in the cracks and crevices of poorly constructed houses and emerge during night for their blood meals facilitating the vectorial transmission of *T. cruzi* among the people. Also, the designation of ChD - a neglected tropical disease - implies its propagation, by poverty, among the most vulnerable populations, requiring continuous medical education [17]. *Triatoma infestans, Rhodnius prolixus, and Triatoma dimidiata* are the three most important vector species responsible for the transmission of *T. cruzi* to humans; *Panstrongylus megistus* is also an important vector from the epidemiological viewpoint [18,19].

It is estimated that in 2008, ChD killed $>10^4$ people [1]. Guedes et al. [20] documented that ChD affects nearly 8 million people, and 28 million people are at risk of acquiring the disease in 15 endemic countries of Latin America. The factors of ChD transmission, as has been demonstrated by Mejía-Jaramillo et al. [21], include high infection rate of people and domestic animals, the construction materials of the houses, the presence of infected triatomines inside human dwellings, the proximity between houses, as well as a sylvatic environment with several triatomine species and wild animals.

Migration has brought infected individuals to cities both within and outside Latin America [22]. Also, the occurrence of ChD in areas where it is not endemic, such as the United States and Europe, is related mainly to the migration of infected people, and thus the disease is an emerging infectious disease in developed countries [23]. Further, it is estimated that roughly 300,167 Latin American immigrants in the USA (where rarely, individuals get infected through autochthonous transmission) are infected with *T. cruzi* [24]. In non-endemic areas, where the vector is lacking, *T. cruzi* can be transmitted through blood transfusions [25], organ and tissue transplants [26], or congenitally from infected mothers to their children [27]. Congenital transmission occurs in 1% – 10% of children born to infected mothers [28]. In 7 Bolivian departments, endemic for ChD, 63% of potential blood donors were found positive for *T. cruzi* antigens [29]. Thus, ChD, currently, is not limited to rural populations in Latin America, as because of the persons migrate to urban areas within countries, and to other parts of the world such as the United States, Canada, Western Europe, Japan, and Australia [30], and as such the disease has become a public health concern.

Life Cycle

The life cycle of *T. cruzi* is complex, with different developmental forms in insect vectors (epimastigotes and metacyclic trypomastigotes) and mammalian hosts including humans (non-replicative bloodstream trypomastigotes and replicative intracellular amastigotes) [31,32]. The triatomine vector becomes infected by ingesting circulating parasites (trypomastigotes) in a blood meal from an infected human host. In the mid gut of the vector, the trypomastigotes differentiate into epimastigotes and replicate. The epimastigotes on reaching the hindgut differentiate into infective metacyclic trypomastigotes, which are excreted with the faeces of the vector. In the posterior midgut, epimastigotes attach to perimicrovillar membranes through surface glycophosphatidylinositols and divide by binary fission. Once at the hindgut, epimastigotes weakly attach to the rectal cuticle and transform into metacyclic trypomastigotes [33].

T. cruzi is transmitted by deposits of faecal matter, as infected triatomine vectors take blood meal from sleeping human hosts, on the skin. Itching produced by the vector's bite induces the individual to scratch. Thus, the metacyclic trypomastigotes are allowed to enter into skin lesions or into the conjunctiva; oral ingestion of food or drink contaminated with infected reduviid faeces also cause human infection [34]. Metacyclic trypomastigotes express a stage specific surface glycoprotein of 82 kDa (GP82), a major cell adhesion molecule, responsible in parasite internalization [35].

Once in the human host, the metacyclic trypomastigotes invade the nucleated cells in the localized reticuloendothelial system and connective tissue. In the cytoplasm, metacyclic trypomastigotes differentiate into spherical amastigotes, which replicates by binary fission, with a doubling time of about 12 hours, over a period of 4 to 5 days [36]. When the cell is swollen with amastigotes, they transform into trypomastigotes by growing flagellae, and are released by the rupture of the host cell. The trypomastigotes invade adjacent tissues, and spread by means of the lymphatics and blood stream to distant sites, mainly muscle cells (cardiac, smooth and skeletal) and ganglion cells, where they undergo further cycles of intracellular multiplication [37].

The cycle of transmission is completed when circulating trypomastigotes are taken up in blood meals by triatomine vectors. The sylvatic vertebrates such as armadillo and raccoon, and domestic animals (mainly dogs and cats) serve as the reservoirs for *T. cruzi* [38]. Mejía-Jaramillo et al. [21] demonstrated the occurrence of *T. cruzi* active transmission in Colombia with overlap between the domestic (*Canis lupus familiaris, Felis catus, Sus scrofa* infections) and sylvatic

(*Proechymis semiespinosus, Heteromys anomalus* and *Didelphys marsupialis* infection) transmission cycles of ChD.

Clinical Features

The ChD evolves in phases: acute phase, and chronic phase with indeterminate and determinate forms of the disease [39]. However, Carrasco et al. [13] grouped chronic chagasic patients into 3 stages: Chagas I, Chagas II and Chagas III, the clinical information of which are represented (Table 2). After the initial introduction of the parasite, an incubation period of 7-15 days leads to the acute phase of the disease (characterized by a patent parasitemia), which may last for 4-8 weeks, and in most cases, this is asymptomatic phase. When symptoms occur patients present with fever, malaise, and enlargement of the liver, spleen and lymph nodes. In the particular case of vector-borne transmission, the most recognizable are Romana sign (unilateral painless periorbital oedema at the site of parasite entry), which appears if the entry site is through the conjunctiva, and chagoma (an erythematous oedema in the subcutaneous tissue) - a sign of portal of entry of *T. cruzi* via the skin [13]. In acute phase, severe myocarditis develops rarely, and meningoencephalitis occurs occasionally, especially in children younger than 2 years [32].

The acute phase of untreated ChD is followed by an initially asymptomatic chronic phase known as the indeterminate form of the disease lasting ≥ 10 years. The positive anti–*T. cruzi* serology results, with no symptoms or physical examination abnormalities, and with normal 12-lead electrocardiogram (ECG) features and normal findings on radiological examination of the chest, esophagus and colon are suggestive to indeterminate form of the disease [40,41]. Among the *T. cruzi* seropositive individuals, from Karicna community in Eastern Venezuela, 87.5 % had no signs or symptoms associated with ChD, or abnormalities in their electrocardiograms, chest radiographs, or echocardiograms, and thus were classified as patients with indeterminate phase of the disease [42].

Chronic stage	Clinical information			
	DTUs	Symptoms	Diagnosis	Involvement
Chagas I	TcI: 6 (20 %); TcIV: 7 (23.33 %)	Absence of cardiac damage	ELISA positive; xenodiagnostic positive	Domestic and sylvatic cycles
Chagas II	TcI: 5 (16.66 %); TcIV: 1 (3.33 %)	Evidence of myocardial damage	ELISA positive; xenodiagnostic positive	Domestic and sylvatic cycles
Chagas III	TcI: 11 (36.66 %); TcIV: nil	Presence of severe cardiac damage and congestive heart failure	ELISA positive; xenodiagnostic positive	Domestic and sylvatic cycles

Table 2: Clinical presentation of chronic Chagasic disease stages [13].

It has been reported that 70-80 % of infected persons undergo the indeterminate form throughout life, and 20–30% of infected persons have disease progression to determinate form over years to decades [36]. Usually 10-20 years later during the chronic phase serious symptoms of the disease emerge, when the patients undergo determinate form and develop cardiac complications (cardiac form: cardiomyopathy), 15-20 % suffer digestive disorders (digestive form: mainly megaesophagus and megacolon) or both (cardiodigestive form), and < 5 % develop the neurological form of the disease [36,43].

The clinical features of megaesophagus include chest pain, dysphagia, cough and regurgitation; hypersalivation, parotid enlargement and repeated aspiration may also occur, while constipation and abdominal pain are the typical symptoms of patients with megacolon, however, in patients with advanced megacolon, obstruction, perforation, and sepsis may develop [44]. The most serious and common manifestation of chronic *T. cruzi* infection is the chagasic cardiac disease, the earliest sign of which includes the conduction system abnormalities (right bundle branch block and left anterior hemiblock), and with the progression of the disease patients may develop atrial and ventricular arrhythmias, left ventricular dysfunction, thromboembolic events, dilated cardiomyopathy and congestive heart failure with a risk of sudden death [45]. Echocardiography with chronic chagasic heart patients reveals left ventricular dilatation and wall dysfunction, dyssynergic segments, ventricular aneurysm (apical or other), low ejection fraction (if <50 %) and valve disease, and dilatation and dysfunction of right ventricle [46,47]. (Table 3) represents the clinical features, diagnosis and management of two chronic Chagasic cardiomyopathy cases.

When *T. cruzi* transmission occurs from mother to child across the placenta and through the birth canal, the infection causes abortion, prematurity and organic lesions in the foetus [15]. Congenital *T. cruzi* infection has no specific clinical signs; the 10-40 % of newborns who are symptomatic might have low birth weight, hepatosplenomegaly, respiratory distress, cardiac failure, or meningoencephalitis [28].

Diagnosis

The acute ChD is diagnosed by identification of the parasite in the bloodstream (circulating trypomastigotes) by direct microscopic examination [30,49]. Light microscopy detects *T. cruzi* in Giemsa or Wright stained samples of blood with thin smears showing clear parasitic morphology; blood concentration techniques (microhematocrit or Strout tests having sensitivity 80-90%) can increase the probability of finding the parasites [50]. The microhematocrit facilitates detection of *T. cruzi* in the 'buffy coat' prepared from patient blood in heparinized capillary tubes, by centrifugation, while the Strout method consists of serum collection, by centrifugation, from the blood sample, following one hour incubation at 37°C, and microscopic examination of the precipitate from the serum on second centrifugation.

The ChD reactivation can be detected when a positive Strout test indicates the presence of *T. cruzi* in blood or in tissue samples from a patient presenting signs and symptoms of disease, and thus

microscopic evidence of *T. cruzi* is currently accepted as the gold standard for reactivation confirmation. Romana sign allows facile symptomatic diagnosis in up to half of the cases showing overt manifestations of acute disease [51]. Inflammation of the myocardium can be detected by CMR (cardiac magnetic resonance) on patients with ChD, including in patients in the subclinical phase [52].

Patient	Clinical presentation	Diagnosis and management
Male (76 years old)	Case with conduction disorders; grade III cardiomegaly with cardio- thoracic index 0.57 on chest radiography; cardiac dilatation and left heart ejection fraction of 40 % on cardiac ultrasound	ELISA and indirect hemagglutination tests positive for antibodies to *T. cruzi* Management: digoxin, furosemide, spironolactone, isosorbide and pravastatin
Female (60 years old)	Case with progressive heart failure; grade IV cardiomegaly with cardiothoracic index 0.7 on chest radiography; severe atrial and moderate ventricular dilatation with ejection fraction of 35 % on cardiac ultrasound	ELISA, indirect hemagglutination and immunofluorescence tests positive for ChD Management: digoxin, furosemide, captopril, sosorbide and acetylsalicylic acid and pravastatin

Table 3: Clinical presentation, diagnosis and management of chronic Chagas cardiomyopathy [48].

The serological diagnosis offers high performance characteristics in *T. cruzi* antibody detection; Malan et al. [53] depicted the high specificity and sensitivity of three IgG ELISAs (CeLLabs *T. cruzi* ELISA, hemagen Chagas' kit and IVD research Chagas' serum microwell ELISA) and MarDx indirect immunofluorescent assay (IFA). The CRA (cytoplasmic repetitive antigen) and FRA (flagellar repetitive antigen) proteins from *T. cruzi* have been used in studies on the diagnosis of ChD; an ELISA-based diagnostic test that used either of CRA antigens achieved 100 % sensibility and specificity, while FRA antigen showed a lower sensitivity of 91.5 % with a specificity of 60 % [54]. The IgM IFA is useful for detection of IgM-specific *T. cruzi* antibodies; a positive IgM IFA result is indicative of acute infection [55], and hence an IgM assay could be an important diagnostic tool. The iron-superoxide dismutase excreted by *T. cruzi* (Fe-SODeCRU or SODeCRU) has proven strongly immunogenic and highly specific, and the agreement between the results for ELISA-SODeCRU and Western blot-SODeCRU was almost 100 % [56]. However, a single serologic test cannot be a gold standard for diagnosis of ChD, and for serologic diagnosis of *T. cruzi* infection testing with at least two different serologic assays, demonstrating positive results of the test sample, of different formats and antigen preparations are essential [30,49].

The most potential diagnostic tool for *T. cruzi* infection is PCR, which relies on amplification of DNA target sequences of the parasite, *T. cruzi*. The test is based on the detection of *T. cruzi* DNA sequences in patients' blood samples. Brasil et al. [57] 2010 reported two main target regions of *T. cruzi* DNA amplification: nuclear satellite DNA (ns- DNA) - a family of highly repetitive nuclear DNA sequences named E13, that is distributed over most of the parasite chromosomes; and Kinetoplast DNA (K-DNA). PCR targeted against repetitive *T. cruzi* sequences (330 bp minicircle variable region on the kinetoplastid genome, K-DNA, and intergenic spacer of the spliced leader genes, SL-DNA) as a sensitive laboratory test for diagnosis in clinical practice, as has been reported by Diez et al. [58].

To investigate congenital infection, infants born to seropositive mothers should be tested within the first 2 months of life by microscopic examination or PCR testing of cord and/or peripheral blood [45]. In a comparison of two diagnostic techniques in patients with chronic ChD, PCR showed 100 % specificity and 70-75% sensitivity, and a western-blot technique using trypomastigote excreted-secreted antigen (TESA), had 100 % sensitivity and 99.2 % specificity [59].

Treatment

The two nitroheterocyclic compounds with proven efficacy against ChD include benznidazole (N-benzyl-2-nitroimidazole-1-acetamide) and nifurtimox (4[(5-nitrofurfurylidene) amino]-3-methylthiomorpholine-1,1-dioxide); both the drugs are almost 100 % effective in curing the disease if treated promptly at the onset of the acute phase [1]. However, the drugs (benznidazole and nifurtimox) are not recommended for pregnant women or people with kidney or liver failure, and nifurtimox is contraindicated for patients having neurological or psychiatric disorders [1].

Adult patients can be treated with benznidazole (5-7 mg/kg/day) in two divided doses for 60 days, or with nifurtimox (8-10 mg/kg per day) in three divided doses for 90 days [40]. For the treatment of children, benznidazole (5-10 mg/kg daily) in two or three divided doses for 60 days, or nifurtimox (15 mg/kg daily) in three divided doses for 60-90 days, preferably after meals are recommended; for adults, daily treatment with 5 mg/kg benznidazole or 8-10 mg/kg nifurtimox is recommended for the same duration as for children [60]. Benznidazole treatment of congenital infection is highly effective, with cure rates >90 % when instituted in the first few weeks of life [28]. The children of < 12 years of age can be treated with benznidazole (10 mg/kg/day) [35]. Other potentially beneficial drugs, such as allopurinol or itraconazole, do not have a high enough degree of clinical efficacy, as compared with nifurtimox or benznidazole; posaconazole is a promising drug, but expensive [61].

Searching natural anti-Chagas agents as alternative to the currently available treatment agents (nifurtimox or benznidazole) with limited therapeutic potential and associated serious side effects [45, 62], has been a goal. It has been reported that the cysteine protease inhibitors are among the most investigated drug candidates against *T. cruzi* [63]. Bellera et al. [64] demonstrated the anti-*T. cruzi* activity of levothyroxine (a traditional hormone replacement therapy for patients with hypothyroidism) that also had dose dependent inhibition of cruzipain, the major cysteine protease essential for replication of the intracellular form of *T. cruzi* and plays role in host-parasite interactions [65]. Varela et al. [66] demonstrated the in vitro anti-*T. cruzi* activities of two secondary metabolites from *Aristeguietia glutinosa* (Lam.: Asteraceae) hydro-ethanolic extract (IC_{50} = 19.6 µg/mL): (+)-15-hydroxy-7-labden-17-al (capable of inhibiting the parasitic mitochondrial dehydrogenases activity) and (+)-13,14,15,16-tetranorlabd-7-en-l7,12-olide (capable of inhibiting biosynthesis of parasite membrane sterols) showing IC_{50} values 3.0 and 15.6 µg/mL,

respectively, and reported such active principles displaying low toxicity against murine macrophages, poor hemolytic activity and absence of mutagenicity, as well as decreasing in parasitemia in murine acute model of ChD.

Genes et al. [67] reported that prodigiosin produced from the gram-negative bacteria *Serratia marcescens* could be a good candidate for the treatment of ChD. Bahia et al. [68] showed experimentally the fexinidazole (1H-imidazole, 1-methyl-2-((4-(methylthio)phenoxy) methyl)-5-nitroimidazole) as an effective oral treatment of acute and chronic forms of ChD caused by benznidazole (2-nitroimidazole-(Nbenzil- 2-nitzo-1-imidazoleacetamide) -susceptible, -partially resistant and -resistant *T. cruzi*, and thus illustrated the potential of the agent as a drug candidate for the treatment of human ChD.

Since, the side effects of currently available anti-chagasic drugs, benznidazole and nifurtimox, are time- as well as dose- dependent [69], combination therapy may help improve treatment efficacy with the drugs by reducing dosage (from synergistic effect), treatment duration and toxicity, and preventing potential development of parasitic resistance to the available treatments [70]; the *in vitro* and *in vivo* activities of azole derivatives in combination with benznidazole and other compounds implicated in sterol biosynthesis have already been reported synergistic against *T. cruzi* [71], giving hope in the development of cost-effective, non-toxic treatment protocol for ChD.

Prevention and Control

Since there is no vaccine for ChD, vector control should be the most effective method of preventing the disease in endemic areas, while in non- endemic areas control strategies should be focused on preventing transmission from blood transfusion, organ transplantation, and mother-to-baby. Thus, non-endemic countries require implementation of the preventive policies related to blood transfusion, organ transplantation and congenital cases [72,73]. Since, the blood transfusion and organ transplantation (from infected people), which remain the secondary route of *T. cruzi* transmission in endemic regions, are the prime modes of transmission of the parasite in non-endemic areas (where insect vector has been controlled, or is absent), in order to reduce infections by blood or organ transplants, it is important to screen donated blood and organs for the presence of parasites [74]. Moreover, implementation of the guidelines, as per the WHO guidelines, in controlling blood banks and organ transplant systems to eliminate the risk of ChD transmission is essential. Early detection and prompt treatment of cases and congenital cases may help reduce the disease burden. The triatomine bugs live under poor housing conditions, basically within the cracks or crevices of mud walls, and hence in rural endemic countries, where there is a great risk of acquiring infection with *T. cruzi*, the spread of ChD can be decreased by improved housing.

Concluding Remarks

A century after its discovery [75], ChD remains a major neglected tropical disease, affecting millions of *T. cruzi*–infected people in countries of endemicity and emerging in non-endemic regions as a result of migratory movements of human population. The most important problems in the outcome of ChD are the unavailability of vaccine for the disease and the limitation of existing drugs (nifurtimox and benznidazole) for treatment, which is effective against recent infection. Moreover, emergence of benznidazole resistant *T. cruzia* strains showing cross-resistance to nifurtimox has been reported [76]. The problems associated with the available drugs [77,78], and the lack of alternative medications underline the imperative need to develop new strategies for chemotherapy against the disease. Before that ChD control is mainly based on the elimination of triatomine vectors. Finally, the congenital transmission is a kind of ChD transmission that may lead to global dissemination of the disease, and hence control measures of such mode should be established as a public health priority in all endemic regions [79].

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