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American trypanosomiasis

Tripanossomíase americana

Tripanosomiasis americana

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ABSTRACT

Objective: Due to the importance of Chagas disease as a public health problem in Brazil, this study aims to present a review of the epidemiological, treatment and control aspects of Chagas disease in Brazil. **Literature review:** American trypanosomiasis, popularly known as Chagas disease, is considered one of the most important neglected diseases in Latin America. The etiologic agent is *Trypanosoma cruzi*, which is primarily transmitted by hematofagous insects, known as kissing bugs, that belong to the subfamily Triatominae. Besides the primary form of transmission, other forms of transmission have been discovered over the years, such as oral, congenital, blood transfusion, transplant and accidental transmission. It is difficult to diagnose it in the acute phase because it presents generic and non-specific symptoms. It is usually diagnosed in the chronic stage, when the digestive and cardiac systems may be compromised. Since the end of 1960, treatment has been restricted to two drugs, but they are not so effective, and alternative medicines are necessary to improve the treatment and life quality of patients. **Final considerations:** In order to reduce Chagas disease transmission, Latin American countries, especially Brazil, must improve the surveillance system and provide primary care to the population.

Keywords: American trypanosomiasis, Chagas Disease, *Trypanosoma cruzi*, Triatomine, Epidemiology.

RESUMO

Objetivo: Devido à importância da doença de Chagas como problema de saúde pública no Brasil, este estudo tem como objetivo apresentar uma revisão dos aspectos epidemiológicos, de tratamento e controle da doença de Chagas no Brasil. **Revisão bibliográfica:** A tripanossomíase americana, popularmente conhecida como doença de Chagas, é considerada uma das doenças negligenciadas mais importantes da América Latina. O agente etiológico é o *Trypanosoma cruzi*, transmitido principalmente por insetos hematófagos, conhecidos como barbeiros, pertencentes à subfamília Triatominae. Além da forma primária de transmissão, outras formas de transmissão foram descobertas ao longo dos anos, como oral, congênita, transfusão de sangue, transplante e transmissão acidental. É difícil diagnosticá-la na fase aguda porque apresenta sintomas genéricos e inespecíficos. Geralmente é diagnosticado na fase crônica, quando os sistemas digestivo e cardíaco podem estar comprometidos. Desde o final de 1960, o tratamento está restrito a dois medicamentos, mas eles não são tão eficazes, sendo necessárias medicinas alternativas para melhorar o tratamento e a qualidade de vida dos pacientes. **Considerações finais:** Para reduzir a transmissão da doença de Chagas, os países latino-americanos, especialmente o Brasil, devem melhorar o sistema de vigilância e prestar cuidados primários à população.

Palavras-chave: Tripanossomíase americana, Doença de Chagas, *Trypanosoma cruzi*, Triatomine, Epidemiologia.

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RESUMEN

Objetivo: Debido a la importancia de la enfermedad de Chagas como problema de salud pública en Brasil, este estudio tiene como objetivo presentar una revisión de los aspectos epidemiológicos, de tratamiento y control de la enfermedad de Chagas en Brasil. **Revisión bibliográfica:** La tripanosomiasis americana, conocida popularmente como enfermedad de Chagas, es considerada una de las enfermedades desatendidas más importantes de América Latina. El agente etiológico es *Trypanosoma cruzi*, transmitido principalmente por insectos hematófagos, conocidos como vinchucas, pertenecientes a la subfamilia Triatominae. Además de la forma de transmisión primaria, a lo largo de los años se han descubierto otras formas de transmisión, como la oral, la congénita, la transfusión de sangre, el trasplante y la transmisión accidental. Es difícil de diagnosticar en la fase aguda porque presenta síntomas genéricos e inespecíficos. Suele diagnosticarse en la fase crónica, cuando los sistemas digestivo y cardíaco pueden verse comprometidos. Desde finales de la década de 1960, el tratamiento se ha restringido a dos medicamentos, pero no son tan eficaces y se necesitan medicinas alternativas para mejorar el tratamiento y la calidad de vida de los pacientes. **Consideraciones finales:** Para reducir la transmisión de la enfermedad de Chagas, los países latinoamericanos, especialmente Brasil, deben mejorar el sistema de vigilancia y brindar atención primaria a la población.

Palabras clave: Tripanosomiasis americana, Enfermedad de Chagas, *Trypanosoma cruzi*, Triatominos, Epidemiología.

INTRODUCTION

American trypanosomiasis, or Chagas disease, is a chronic and potentially fatal infection caused by the protozoan *Trypanosoma cruzi* Chagas, 1909 (Kinetoplastea, Trypanosomatidae) (CHAGAS C, 1909**)**. According to the World Health Organization (WHO), 6–7 million people are estimated to be infected worldwide, mainly in Latin America. It is considered a neglected tropical disease and one of the main public health problems in Latin America (WHO, 2019). In Brazil, 1,9–4,6 million people are estimated to be infected by *T. cruzi*. Chagas disease is one of the leading causes of death from infectious and parasitic diseases in Brazil (BRASIL, 2022). According to the WHO, the infection caused by *T. cruzi* occurred mainly among wild mammals and triatomines; later on, it started to affect domestic animals and humans, being considered a disease of rural areas (WHO, 2012). The current and rapid environmental changes, added to the uncontrolled migrations of humans and animals, act powerfully as dispersers of parasites.

Current changes in land use and possible changes in temperature, humidity, and rainy seasons could potentially alter *T. cruzi* transmission (GOTTDENKER NL, et al., 2012). Understanding the dynamic variables that influence its transmission, as well as the role played by the fauna in its maintenance, is essential to establishing control measures for this parasite (FLORES-FERRER A, et al., 2019). The precariousness of socioeconomic conditions is also a relevant factor for the transmission of Chagas disease, especially in relation to issues of housing, income, access to health services, and food hygiene. This is reflected in the negligence related to the vulnerable and infected population, which is at greater risk of developing more severe forms of the disease and progressing to death (DIAS JCP, et al., 2016).

Therefore, the work of epidemiological surveillance in the control and prevention of Chagas disease's transmission is fundamental for health awareness and the reduction of infection by *T. cruzi.* Despite the need for greater epidemiological surveillance actions regarding Chagas disease, there are technical and scientific challenges that make it difficult to fight the disease (DIAS JCP, 2007). Due to the importance of Chagas disease as a public health problem in Brazil, this study aims to present a review of the main aspects of Chagas disease in Brazil.

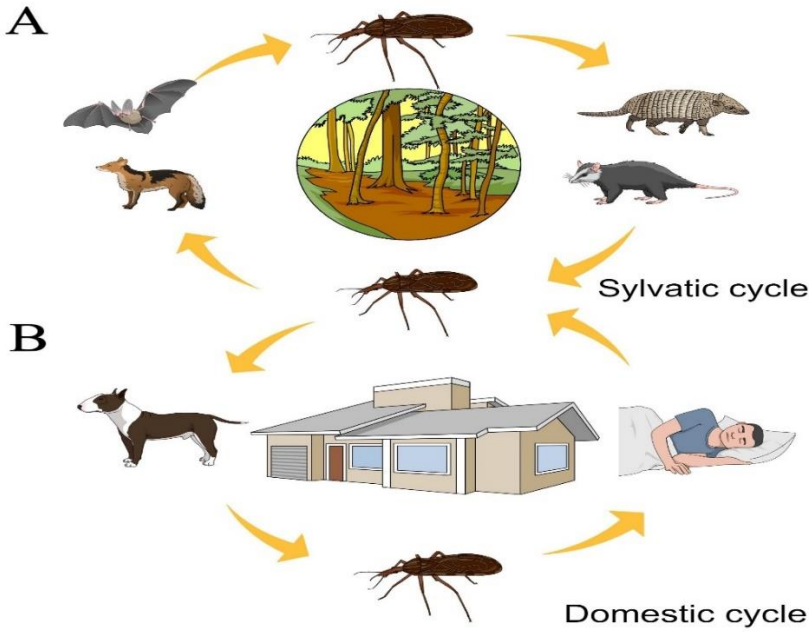
LITERATURE REVIEW

Etiology and life cycle

Trypanosoma cruzi is an obligatorily parasitic flagellate protozoan. It belongs to the class Kinetoplastea, order Trypanosomatida, family Trypanosomatidae, and genus *Trypanosoma*. The protozoan contains a special organelle, the kinetoplast, which is similar to a mitochondria and it's related to the name of the class Kinetoplastea (ADL S, et al., 2018). *T. cruzi* infects several orders of mammals, such as mice, bats, opossums,

dogs, and cats. These animals function as carriers of the parasite, maintaining the wild and domestic cycles of the disease (ÁLVAREZ-HERNÁNDEZ DA, et al., 2018) (**Figure 1**).

Figure 1- Transmission cycles of *T. cruzi.* (A) Sylvatic cycle. (B) Domestic cycle.



Note: The layout was developed using the website www.mindthegraph.com.
Source: Soares SBP, et al., 2024.

Trypanosoma cruzi is a multihost pathogen with complex transmission systems that challenge disease control and prevention efforts. Considered a successful generalist parasite, it is capable of infecting almost all cell types of hundreds of vertebrate species distributed from the southern United States to southern Argentina (BRISSE S, et al., 2001). All mammals are susceptible to *T. cruzi*, and about 400 species of wild, synanthropic and domestic mammals are involved in the transmission cycle (NICHOLS MD, et al., 2019). *Trypanosoma cruzi* is known to present a high genetic diversity. Since the end of 1970, different groups classified the parasite into different genotypes, using different diagnostic methods (BRISSE S, et al., 2001). Seven genotypes are recognized, so called Discrete Typing Units (DTUs), named TcI to TcVI and TcBat (ZINGALES B, et al., 2012).

T. cruzi has a heteroxenous life cycle, which consists of intracellular multiplication on the mammalian host and extracellular multiplication on the vector (triatomine). The cycle begins when a triatomine ingests blood infected with trypomastigotes from a mammalian host. The trypomastigotes in the triatomine's stomach migrate to the posterior intestine and differentiate into epimastigotes. The epimastigotes multiply by binary fission and then differentiate into trypomastigotes in the insect's hindgut. The trypomastigotes are eliminated through the triatomine's feces while it is feeding. Metacyclic trypomastigotes enter bite wounds or mucosal membranes, infect cells, and differentiate into amastigotes. Amastigotes multiply by binary fission and breach the cells, releasing trypomastigotes. The trypomastigotes can infect other cells or be ingested by triatomine during their blood meal, restarting the cycle (PÉREZ-MOLINA JA and MOLINA I, 2018).

Transmission

In recent years, the epidemiological patterns of Chagas disease transmission in Brazil have changed a lot due to the advances made in vector control, as well as in ensuring the quality of blood transfusions, measures implemented in the 1990s. In addition, environmental, demographic, economic and social changes, together

with the greater concentration of population in urban areas, also played an important role in this change (DIAS JCP, et al., 2016). In the context of human transmission, oral transmission has been gaining importance after the control of *Triatoma infestans* Klug, 1834, the main vector species of *T. cruzi* in epidemiological importance in Brazil in the past decades. Thus, this is currently the main form of transmission of Chagas disease to humans and occurs through ingestion of food (açaí, bacaba, jaci, sugarcane juice and babassu palm) contaminated with *T. cruzi* from infected triatomines and/or their feces (DIAS JCP, et al., 2016).

It is the mechanism responsible for most acute cases of Chagas disease (from 2005 to 2022), occurring in the form of familial or multi-familial outbreaks, mainly in the Amazon region. Pará is responsible for about 80% of records of oral contamination by fruits typical of the Amazon region and Santa Catarina was the southern state of the country that had the first outbreak described in 2005, probably by sugarcane juice contaminated with the parasite (BRASIL, 2021). The second most recurrent form of transmission currently is vectorial (classical transmission), which occurs through contact with the feces of infected triatomines during or after the insect's blood feeding (PINTO AYN, et al., 2008).

The triatomines are insects commonly known by their hematophagous habits and their potential to act as vectors in Chagas diseases epidemiological cycle (SCHOFIELD CJ and GALVÃO C, 2009). The triatomines are mainly distributed in the Neotropical area and are known by local populations by distinct popular names in Portuguese (e.g., *Barbeiro*), Spanish (e.g., Chipo), English (e.g., Kissing bug) and Native Amerindian languages (SCHOFIELD CJ and GALVÃO C, 2009). This was the main form of transmission reported until 2005 and was responsible for almost all known cases of chronic Chagas disease in the country. Its importance fell from the control strategy established in the country, which aimed to interrupt transmission by vector control at home using insecticides (SANTOS EF, et al., 2020).

In the last 15 years, the recorded vector transmission data are generally reported in the extra domiciliary environment (with accidental exposure to the sylvatic cycle of the parasite) or by visitation of sylvatic vectors to households, without their vector domiciliation (basic form of generation of outbreaks by transmission orally in rural areas). Probably, the majority of cases reported without identification of the probable form of transmission of the disease (ignored form) in recent decades, occurred from vector transmission, however, it is not possible to attribute these numbers to it, since the carrier of the disease did not know the form of its contagion. Other form of transmission occurs when there is a blood transfusion or organ transplantation from infected donors to healthy recipients. Due to the mandatory clinical-epidemiological and serological screening in most endemic countries for blood donation candidates, there was a large reduction in this form of transmission in Brazil as well as in Latin America. In the country, in the 1960s and 1970s, the average prevalence of reactive serology for *T. cruzi* among candidates for blood donation was 8.3%, decreasing to 0.18% in 2010 (DIAS JCP, et al., 2016).

Vertical transmission, also known as congenital or maternal-infant transmission, occurs through the passage of parasites from women infected with *T. cruzi* to their babies during pregnancy or childbirth. Although it is still a neglected form of transmission, congenital transmission is now one of the main routes of infection in countries that have controlled vector transmission through surveillance, improved housing standards and implemented universal screening in blood banks (BRASIL, 2004). In non-endemic countries, it is currently considered the main source of new cases of Chagas disease (WHO, 2019). Accidental transmission can occur through contact with injured skin, mucous membranes (oral or ocular) or self-inoculation with material contaminated by *T. cruzi* during the handling of contaminated triatomines, mammals, cultures, aerosols and blood. Accidents of this type of transmission may be related to laboratory accidents, work to capture triatomines in the field, or handling of wild game meat, for example (DIAS JCP, et al., 2016).

Clinical manifestations

Chagas disease occurs in two phases: the acute phase and the chronic phase. The acute phase starts after an incubation period of 1-2 weeks and usually lasts 3-4 months. It can be asymptomatic or symptomatic. In the latter case, symptoms start with local manifestations, such as Romaña's sign (periocular edema) and chagoma (a painful subcutaneous nodule at the site of infection). Other symptoms include fever, headache,

malaise, hepatosplenomegaly and lymphocytosis. In some rare cases, it can cause meningoencephalitis or myocarditis (CARLIER Y, et al., 2011). After the period of the acute phase, the symptoms disappear and the patient enters the chronic phase, which is characterized by a latent period of 10—30 years in which the patients are asymptomatic and radiological and cardiological exams are normal. About 30% of the patients remain in this stage for the rest of their lives. This stage is called the indeterminate chronic phase (BERN C, 2015). The determinate chronic phase is characterized by the development of cardiological or gastrointestinal symptoms or, in some cases, the infection of these two systems.

It's estimated that 15–45% of the patients develop the Cardiac Chagas disease, which is characterized by dilation of cavities, ventricular hypertrophy, arrhythmias, contractile disorders, myocarditis and chronic cardiac insufficiency. Cardiac Chagas disease is the main cause of sudden death, heart failure and thromboembolism (PRATA A, 2001). Gastrointestinal Chagas disease affects about 10% of the patients in the chronic phase and it is more common in South America. It causes destruction of Intramural parasympathetic neurons, hypertrophy of the muscle layers and progressive loss of contractile capacity. This leads to impairment of the food transit along the digestive tract. The symptoms include dysphagia, odynophagia, oesophageal reflux, weight loss, aspiration, cough, and regurgitation (ÁLVAREZ-HERNÁNDEZ DA, et al., 2018). The accumulation of food in the cardia causes esophagus dilatation, or megaesophagus. The feces transit is also affected by the denervation. The accumulation of feces in the colon leads to colon dilatation, or megacolon. Other symptoms include persistent constipation, fecaloma, volvulus, and bowel ischaemia (PÉREZ-MOLINA JA and MOLINA I, 2018).

Diagnosis

A laboratory diagnosis is necessary to confirm the infection by *T. cruzi.* The methods of diagnosis are different depending on the phase of the disease. In the acute phase, parasitological exams are usually recommended because there is a high level of parasitemia and high levels of nonspecific antibodies. In the chronic phase, serology is most common due to the low parasitemia and high levels of specific antibodies (DE LANA M, et al., 2016). Direct parasitological methods are usually done in the acute phase and include an exam of fresh samples, thick film, a micro-staut test and a microhematocrit. Indirect parasitological methods are common in the chronic phase and include xenodiagnosis and blood culture (ÁLVAREZ-HERNÁNDEZ DA, et al., 2018). Serology tests are most common in the chronic phase, and it is necessary to have at least two different tests to confirm the diagnosis. If the two tests are inconclusive, a third test is performed. ELISA, indirect immune-fluorescence, or indirect hemagglutination assays are usually used in this stage of infection. Western blot is also performed when the other serological tests are discordant (LÓPEZ-MONTEON A, et al., 2019).

Molecular methods have also been used to diagnose Chagas disease due to their high specificity and sensitivity in the acute phase. PCR and qPCR, as well as genotypification markers, are most used molecular methods for diagnosis. Biochemical markers can also be used, but they have low specificity and sensitivity and function as indicators of cardiomyopathy for chronic Chagas heart disease (BALOUZ V, et al., 2017). Over the last few years, some other methods have been developed to diagnose Chagas disease. Loop isothermal AMPlification (LAMP) and Recombinase Polymerase Assay (RPA) are two new molecular methods that showed results similar to and effective as PCR but are easier to perform and cheaper than PCR.

Rapid diagnostic tests (RDTs) are serological tests that have been produced lately, showing efficiency and good cost benefit since they are cheap, easy to store, easy to perform and provide results quickly. RDTs have been produced in several endemic countries and they are a good alternative for places that don't have access to labs (ALONSO-PADILHA J, et al., 2019). A recent study showed that some RDTs, including a test developed in Brazil by Fiocruz, presented high diagnostic ability (ITURRA JAD, et al., 2023). The use of these RDTs can provide access to diagnosis for vulnerable populations and access to treatment.

Treatment

Benznidazole is the first-choice drug in Brazil to treat Chagas disease, and nifurtimox can be used as an alternative in cases of intolerance or lack of response to treatment with benznidazole (DIAS JCP, et al., 2016).

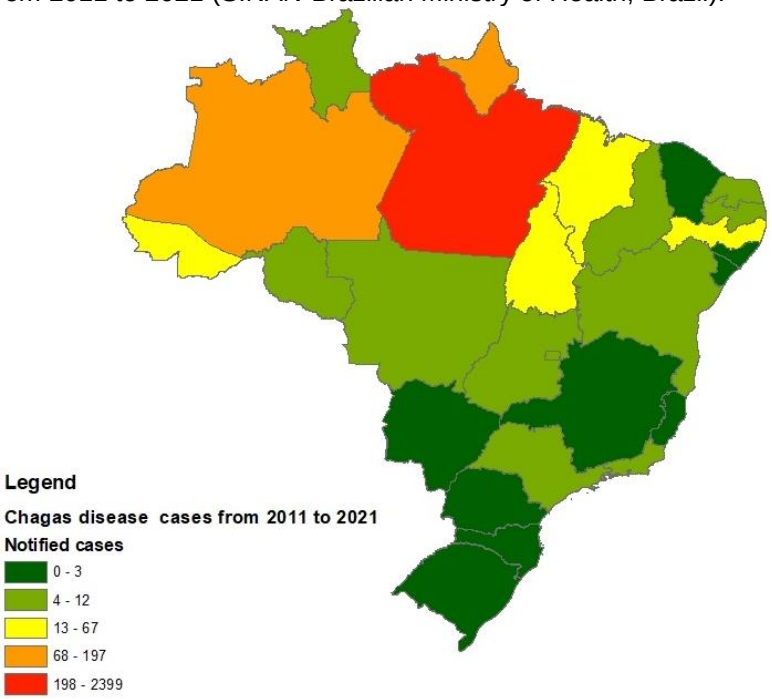
Both have side effects, such as hypersensitivity, bone marrow depression, and peripheral polyneuropathy. In some cases, the occurrence of side effects requires suspension of the treatment. In addition, supportive care is crucial in managing symptoms and complications of Chagas disease, including pain relief, antipyretics for fever reduction, anticoagulants, pacemakers, and fluid management to maintain proper hydration and electrolyte balance (DIAS JCP, et al., 2016). Drug repurposing has gained attention as a viable strategy, with some existing medications demonstrating potential antiparasitic activity against *T. cruzi* (URBINA JA, 2015). An example is Amiodarone, an antiarrhythmic that showed efficacy against *T.cruzi,* especially when combined with other drugs, such as itraconazole (BENAIM G, et al., 2021).

Several new drugs have been developed to treat Chagas disease, such as the compound A3K2A3, a dibenzylideneacetone, which demonstrated high efficacy in fighting tripomastigotes and epimastigotes of *T. cruzi* (PERON F, et al., 2017). Brazil and other Latin American countries have been studying plant extracts as an alternative treatment for Chagas disease (GARCÍA-HUERTAS P, and CARDONA-CASTRO N, 2021). Vaccine development is another promising avenue of research, aiming to prevent infection and disease progression by stimulating the host's immune response (MARTINS-MELO FR, et al., 2016). Furthermore, identifying novel drug targets, such as enzymes and proteins critical to the survival and reproduction of *T. cruzi*, may lead to the development of more effective and better-tolerated drugs in Brazil (URBINA JA, 2015). Therefore, continued research in these areas is essential to improving Chagas disease treatment and reducing its impact on public health.

Epidemiology

Chagas disease remains a significant public health issue in Brazil, with an estimated 1.2 million cases and around 6,000 deaths reported annually (MARTINS-MELO FR, et al., 2014). The spatial distribution of Chagas disease in Brazil demonstrates considerable regional variation, with a higher prevalence observed in the Southeast, Northeast, and North regions (MARTINS-MELO FR, et al., 2018) (Figure 2). These differences can be attributed to triatomine vectors, ecological conditions, and regional socioeconomic disparities (LEITE G, et al., 2010).

Figure 2 - Spatial distribution of Chagas disease cases in Brazil, from 2011 to 2021 (SINAN-Brazilian Ministry of Health, Brazil).



Note: The map was constructed using ArcGis software version 10.8.2. **Source:** Soares SBP, et al., 2024.

Various demographic, environmental, and socioeconomic factors contribute to the risk of Chagas disease in Brazil. Poor housing conditions, particularly in rural areas, provide favorable environments for triatomine insects, the primary vectors of *Trypanosoma cruzi* (DIAS JCP, et al., 2016). Deforestation disrupts the natural habitat of triatomines, leading to their migration to peri-urban and urban areas (COURA JR, 2015). Additionally, urbanization can contribute to Chagas disease transmission as human populations encroach upon natural environments (DIAS JCP, 2003). Furthermore, socioeconomic disparities influence the distribution and transmission of Chagas disease, with a higher prevalence observed in areas characterized by lower income and limited access to healthcare (LEITE G, et al., 2010).

Brazil has implemented various control programs to combat Chagas disease, with some notable successes. Insecticide spraying campaigns have significantly reduced the presence of triatomine vectors in many areas, contributing to the decrease in transmission (DIAS JCP, 2003). Housing improvement programs, such as replacing traditional mudbrick and thatched-roof structures with more modern materials, have also been used to reduce vector-borne transmission. Blood screening measures, implemented in the 1980s, have substantially reduced the risk of transmission through blood transfusions (DIAS JCP and SCHOFIELD CJ, 1998). Despite these efforts, challenges remain, and continued vigilance and adaptation of control strategies are necessary further to reduce the Chagas disease burden in Brazil.

The epidemiology of Chagas disease in Brazil has undergone significant changes in recent years. Implementing control measures, such as insecticide spraying and blood screening, has reduced vector-borne and transfusion-related transmission (DIAS JCP and SCHOFIELD CJ, 1998). However, new risk factors have emerged, including oral transmission through contaminated food and beverages and the expansion of triatomine vectors into urban and peri-urban areas (SANTANA KS, et al., 2011). Furthermore, climate change and habitat modifications have altered the distribution and ecology of triatomine vectors, potentially impacting Chagas disease transmission dynamics (CORRÊA-DO-NASCIMENTO GS and LEITE G, 2023). These changing patterns call for continuous surveillance, the adaptation of control strategies, and the reinforcement of health education to prevent the re-emergence of Chagas disease in previously controlled areas (DIAS JCP, et al., 2016).

FINAL CONSIDERATIONS

Chagas disease continues to be a major health problem in Latin America. Although Brazil showed progress in controlling the disease, especially due to the virtual elimination of the main vector and rigorous protocols to avoid transfusion/transplant transmission, there is still a lot to do to improve disease control. Vector control should be sustained, developing new interventions for secondary vectors. Health education and training of the health professionals should be done regularly, so they can also inform the population about Chagas disease. The control of oral transmission should be improved and continued, especially in the North region of Brazil, where most cases occur nowadays. It's a region where there are low-income populations, which usually don't have access to the health system. So, it's necessary improve the access to diagnosis and treatment for these vulnerable populations. The stock of the two drugs should be normalized in the Brazilian public health system, so the population can start or continue the treatment properly. The development of new drugs is crucial to the treatment of Chagas disease, to have more efficient drugs for the acute and chronic phases of the disease as well as more comfortable drugs for the patients. New diagnosis methods are also necessary. Only by combining health care and surveillance will Brazil be able to reduce Chagas disease transmission.

REFERENCES

1. ADL S, et al. Revisions to the Classification, Nomenclature, and Diversity of Eukaryotes. Journal of Eukaryotic Microbiology, 2019; 66: 4-119.
2. ALONSO-PADILLA J, et al. Strategies to enhance access to diagnosis and treatment for Chagas disease patients in Latin America. Expert Review of Anti-infective Therapy, 2019; 17(3): 145-157.
3. ÁLVAREZ-HERNÁNDEZ DA, et. al. Chagas disease: Current perspectives on a forgotten disease. Revista Médica del Hospital General de México, 2018; 81(3): 154-164.

4. BALOUZ V, et al. Chagas Disease Diagnostic Applications: Present Knowledge and Future Steps. Advanced Parasitology, 2017; 97: 1-45.
5. BENAIM G, et al. Rationale for use of amiodarone and its derivatives for treatment of chagas' disease and leishmaniasis. Current Pharmaceutical Design, 2021; 27: 1825–1833.
6. BERN C. Chagas' Disease. New England Journal of Medicine, 2015; 30(373): 456-66.
7. BRASIL. Agência Nacional de Vigilância Sanitária. Manual técnico para a investigação da transmissão de doenças pelo sangue. Brasília: Ministério da Saúde; 2004.
8. BRASIL. Guia de Vigilância em Saúde/ Ministério da Saúde, Secretaria de Vigilância em Saúde. Departamento de Articulação Estratégica de Vigilância em Saúde. 2022.
9. BRASIL. Ministério da Saúde. Nota Informativa nº 9/2020-CGZV/DEIDT/SVS/MS. Recomendações para adequações das ações de vigilância e cuidado ao paciente com doença de Chagas frente à situação epidemiológica da COVID19. Brasília: Secretaria de Vigilância em Saúde, 2021.
10. BRISSE S, et al. Characterization of large and small subunit rRNA and mini-exon genes further supports the distinction of six *Trypanosoma cruzi* lineages. International Journal of Parasitology, 2001; 31(11): 1218-26.
11. CARLIER Y, et al. Congenital Chagas disease: recommendations for diagnosis, treatment and control of newborns, siblings and pregnant women. PLoS Neglected Tropical Diseases, 2011; 5(10): 1250.
12. CHAGAS C. Nova tripanozomiaze humana: estudos sobre a morfolojia e o ciclo evolutivo do *Schizotrypanum cruzi* n. gen., n. sp., ajente etiolojico de nova entidade morbida do homem. Memórias do Instituto Oswaldo Cruz, 1909; 1(2): 159-2018.
13. CORRÊA-DO-NASCIMENTO GS e LEITE G. Current and paleoclimate models for an Atlantic Forest kissing bug indicate broader distribution outside biome delimitations. Frontiers in Ecology and Evolution. 2023; 10.
14. COURA JR. The main sceneries of Chagas disease transmission. The vectors, blood and oral transmissions: a comprehensive review. Memórias do Instituto Oswaldo Cruz, 2015; 110(3): 277-82.
15. DE LANA M, et al. *Trypanosoma cruzi* e doença de Chagas. In: Neves DP. Parasitologia Humana. São Paulo: Editora Ateneu, 2016; 91-117.
16. DIAS JCP, et al. II Consenso brasileiro em doença de chagas. Epidemiologia e Serviços de Saúde, 2016; 25: 7-86.
17. DIAS JCP e SCHOFIELD CJ. Controle da transmissão transfusional da doença de Chagas na Iniciativa do Cone Sul. Revista da Sociedade Brasileira de Medicina Tropical, 1998; 31(4): 373-83.
18. DIAS JCP. Doença de Chagas: Sucessos e desafios. Cadernos de Saúde Pública, 2003; 22: 2020-2021.
19. FLORES-FERRER A, et al. *Trypanosoma cruzi* transmission dynamics in a synanthropic and domesticated host community. PLoS neglected tropical diseases, 2019; 13(12): 0007902.
20. GARCÍA-HUERTAS P e CARDONA-CASTRO N. Advances in the treatment of Chagas disease: Promising new drugs, plants and targets. Biomedicine & Pharmacotherapy, 2021; 142; 112020.
21. GOTTDENKER NL, et al. Host life history strategy, species diversity, and habitat influence *Trypanosoma cruzi*vector infection in changing landscapes. PLoS Neglected Tropical Diseases, 2012; 6(11): 1884.
22. ITURRA JAD, et al. A multicenter comparative study of the performance of four rapid immunochromatographic tests for the detection of anti-*Trypanosoma cruzi* antibodies in Brazil. Frontiers in Medicine (Lausanne), 2023; 10: 1031455.
23. LEITE G, et al. Influence of the landscape on dispersal of sylvatic triatomines to anthropic habitats in the Atlantic Forest. Journal of Biogeography, 2010; 38: 651 – 663.
24. LÓPEZ-MONTEON A, et al. More than a Hundred Years in the Search for an Accurate Diagnosis for Chagas Disease: Current Panorama and Expectations. Current Topics in Neglected Tropical Diseases [Internet], 2019.
25. MARTINS-MELO FR, et al. Mortality from neglected tropical diseases in Brazil, 2000–2011. Bulletin of the World Health Organization, 2016; 94(2): 103-110.
26. MARTINS-MELO FR, et al. Prevalence of Chagas disease in Brazil: A systematic review and meta-analysis. Acta Tropica, 2014; 130: 167-174.
27. MARTINS-MELO FR, et al. The burden of Neglected Tropical Diseases in Brazil, 1990-2016: A subnational analysis from the Global Burden of Disease Study 2016. PLOS Neglected Tropical Diseases, 2018; 12(6): 0006559.
28. NICHOLS MD, et al. *Trypanosoma cruzi* in a Mexican Free-Tailed Bat (*Tadarida brasiliensis*) in Oklahoma, USA. Journal of Wildlife Diseases, 2019; 55(2): 444-448.
29. PÉREZ-MOLINA JA e MOLINA I. Chagas disease, Lancet. 2018; 391: 82-94.
30. PERON F, et al. Effects of (1E,4E)-2-Methyl-1,5-bis(4-nitrophenyl) penta1,4-dien-3-one on *Trypanosoma cruzi* and Its Combinational Effect with Benznidazole, Ketoconazole, or Fluconazole. Biomed Research International, 2017; 2017: 1-11.

31. PINTO AYN, et al. Fase aguda da doença de Chagas na Amazônia brasileira: estudo de 233 casos do Pará, Amapá e Maranhão observados entre 1988 e 2005. Revista da Sociedade Brasileira de Medicina Tropical, 2008; 41(6):602-14.
32. PRATA A. Clinical and epidemiological aspects of Chagas disease,The Lancet Infectious Diseases, 2001; 1(2): 92-100.
33. SANTANA KS, et al. Spatial distribution of triatomines (Reduviidae: Triatominae) in urban areas of the city of Salvador, Bahia, Brazil. Geospatial Health, 2011; 5(2): 199-203.
34. SANTOS EF, et al. Acute Chagas disease in Brazil from 2001 to 2018: A nationwide spatiotemporal analysis. PLoS Neglected Tropical Diseases, 2020; 14: 8.
35. SCHOFIELD CJ e GALVÃO C. Classification, evolution, and species groups within the Triatominae. Acta Tropica, 2009; 110(2-3): 88-100.
36. URBINA JA. Recent clinical trials for the etiological treatment of chronic Chagas disease: advances, challenges and perspectives. Journal of Eukaryotic Microbiology, 2015; 62(1): 149-156.
37. WHO. WORLD HEALTH ORGANIZATION. Chagas disease (American trypanosomiasis). Research priorities for Chagas disease, human African trypanosomiasis and leishmaniasis. 2019.
38. WHO. WORLD HEALTH ORGANIZATION. Technical report of the TDR Disease Reference Group of Chagas Disease, Human African Trypanosomiasis and Leishmaniasis. Geneva: World Health Organization, 2012.
39. ZINGALES, B et al. The revised *Trypanosoma cruzi* subspecific nomenclature: rationale, epidemiological relevance and research applications. Infection, Genetics and Evolution, 2012; 12(2): 240-53.