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A Systematic Review in Pathogenesis, Epidemiology, and Therapeutic Advances of the Trypanosoma Diseases

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Abstract:- This systematic review offers a comparative analysis of Trypanosoma-related diseases, focusing on African Trypanosomiasis (commonly known as sleeping sickness) caused by *Trypanosoma brucei* and Chagas disease caused by *Trypanosoma cruzi*. These illnesses represent major public health concerns in sub-Saharan Africa and Latin America, impacting millions of individuals. Although significant progress has been made in understanding the life cycles and host interactions of Trypanosoma species, their mechanisms of pathogenesis remain largely unclear. Additionally, current treatment options are limited and often associated with serious side effects. The review examines the epidemiology, clinical symptoms, and recent developments in therapeutic strategies for these diseases. Its findings aim to guide future research and clinical efforts, addressing knowledge gaps and enhancing treatment outcomes for affected communities.

Keywords:- *Sleeping Sickness, Host-Parasite Interaction, Vector-borne Diseases, Immune Evasion Mechanisms, Host Invasion, Global Health Burden.*

I. INTRODUCTION

The genus Trypanosoma, a single-celled protozoan parasites, includes species responsible for diseases of major public health concern, such as African Trypanosomiasis (sleeping sickness) caused by Trypanosoma brucei and Chagas disease caused by Trypanosoma cruzi. These diseases are predominantly found in subSaharan Africa and Latin America, respectively, including 36 countries in subSaharan Africa (Darvin Scott Smith, MD, MSc, 2023) and 21 countries in America according to Pan American Health Organization, affecting millions of people and posing significant challenges to health systems in endemic regions. Despite advances in our understanding of the Trypanosoma life cycle and its interaction with the host immune system, the pathogenesis of these diseases remains poorly understood. Therapeutic options for Trypanosoma infections are limited and often associated with significant side effects such as reactive encephalopathy and nephrotoxicity inmelarsoprol and suramin (WHO., 2023) as well as gastrointestinal and dermatological in Benznidazole and nifurtimox (Bern et al., 2011). Given the complexities of Trypanosoma infections, this systematic review aims to provide a comparative Evaluation of the pathogenesis, epidemiology, and therapeutic advances in the field. By synthesizing the current evidence, this review seeks to evaluate the progress made and inform future research and clinical strategies.

II. METHODOLOGY

We conducted this systematic review following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines to ensure transparency and rigor in the process. PRISMA was used in selecting relevant publications between 2010 to 2024 about the Trypanosome Diseases.

- *Data Sources*

Using the PRISMA guidelines, all relevant published material was carefully selected from multiple widely recognized search databases, Google Scholar, ResearchGate, Elsevier, Springer, and Academia.edu.

- *Literature Search*

To maximize a successful search strategy, the aforementioned databases' search engine used appropriate keywords and Boolean operators such as AND or OR. Three sets of keywords were entered and searched in the online databases. The keywords were categorized into five distinct groups.

First group was focused about the Sleeping sickness like "History of Sleeping Sickness", "African Sleeping Sickness" and "American Sleeping Sickness. Second group focused on the other term for the disease which is Trypanosomiasis like "Tsetse Fly", "African Trypanosomiasis", "Kissing Bugs" and "Chagas Disease". For the third group, it focused in the Therapeutic advances like "Treatment for Sleeping Sickness", "Current drugs for Chagas Disease", "Promising drugs for African Sleeping Sickness", "Diagnosis for Sleeping Sickness" and "Clinical Features of Sleeping Sickness".

Google Scholar, ResearchGate, Elsevier, Springer, and Academia.edu search results were limited to research and review publications authored in English and published between 2010 and 2024. During the initial literature search, all research publications found in databases were selected

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based on their titles, authors, publication dates, and journals to exclude duplicates. To eliminate irrelevant studies, the remaining papers underwent abstract and full text screening for qualifying criteria.

➢ *Inclusions and Exclusions*

All relevant articles included in this review was classified with respect to: (1) studies that tackles about Sleeping Sickness. (2) studies that focuses on Chagas Disease (3) studies that focuses on African Trypanosomiasias (4) studies of the diagnosis in Sleeping Sickness (5) studies of efficacy of current drugs for Sleeping Sickness. It also includes (6) articles that are published as reviews (7) articles published with full text.

Studies are excluded if: (1) article is outdated, (2) articles that are recurring and (3) article does not have available full text.

➢ *Search Results*

A total of 41 articles were identified using Google Scholar, ResearchGate, Elsevier, Springer, and Academia.edu. These online databases' search results were limited to research and review articles that are published between 2010 and 2024, excluding 10 articles that are outdated. Therefore, only 31 research publications remained and were screened according to inclusion criteria. After removing articles based on recurring data and availability in full text, only 17 remained for eligibility. A total of eleven studies were eventually included in the qualitative analysis, while only six studies were included in the quantitative analysis after further screening and evaluating the eligibility based on the contents of titles and abstracts and the availability of full text materials. The PRISMA flow diagram (See Fig. 1) illustrates the steps of study selection and findings.

➢ *Data Extraction*

A total of 41 articles have been viewed and analyzed. The papers that are outdated, dating 2009 and older are eliminated including articles that are recurring. A final total of 17 articles are then undergone for abstract and full text evaluation for qualifying basis.

The information and data extracted from 17 articles includes reported cases of trypanosoma diseases, mode of transmission of the trypanosoma diseases and information about Chagas disease and African Trypanosomiasis (pathogens, vectors, clinical manifestations, diagnosis and treatments).

➢ *Statistical Analysis*

After tabulating and assessing the qualitative characteristics of selected studies, literature is further evaluated for eligibility for quantitative and qualitative analysis.

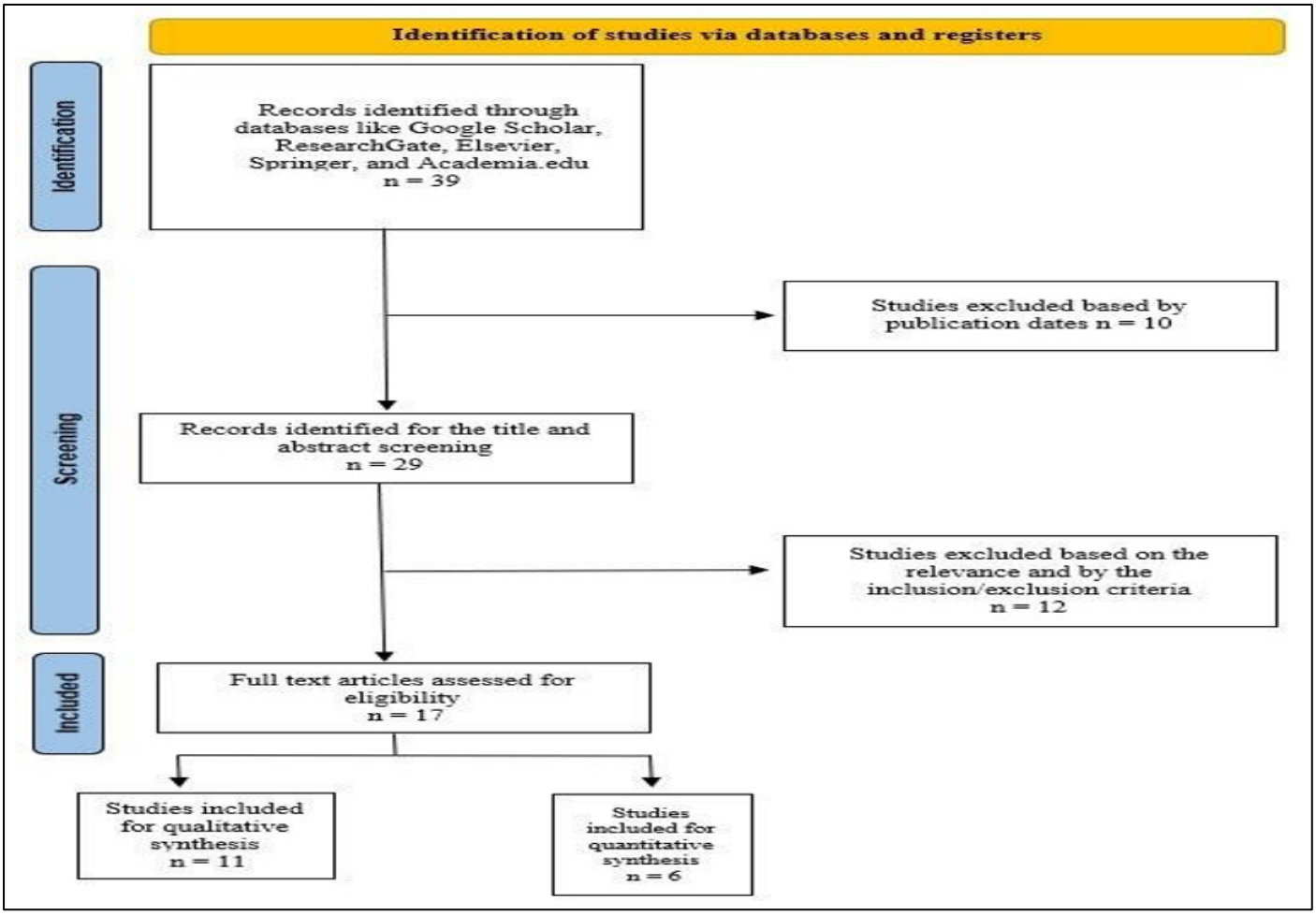

Fig 1 Different Stages of Study Selections and Results Practiced in the PRISMA Flow Diagram

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III. RESULTS AND DISCUSSION

Table 1 Reported Cases of Trypanosoma Disease

Disease	Year	Region	Reported cases	Death's
African Trypanosomias is	2009–2013	Democratic Republic of Congo	82% of global *T. brucei gambiense* cases	3,500 annually (2014)
African Trypanosomias is	2009–2013	Uganda	67% *of T. brucei rhodesiense* cases	Not specified
Chagas Disease	2007	Latin America (e.g.,Bolivia)	Highest prevalence: 6.8% (Bolivia)	12,000 annually
Chagas Disease	Humanitarian Crisis	Venezuela	Increased seroprevalence during crisis	Not specified

The table of reported trypanosomiasis cases highlights significant epidemiological trends and regional disparities in disease burden.

African trypanosomiasis, caused by *Trypanosoma brucei*, primarily affects sub-Saharan Africa, with the Democratic Republic of the Congo (DRC) accounting for 82% of global T. brucei gambiense cases from 2009 to 2013. This concentration reflects endemic transmission facilitated by tsetse flies in the region's environment. Uganda, on the other hand, reported 67% of *T. brucei gambiense* cases. *Brucie rhodesiense* during the same period, reflecting its importance as a focus of the acute form of the disease. Although annual deaths from African trypanosomiasis have declined significantly to 3,500 in 2014 due to improved control measures, the lack of specific mortality data in some regions underscores the need for enhanced surveillance.

Chagas disease, is an anthropozoonosis from the American continent that has spread from its original boundaries through migration (José A Pérez-Molina, PhD, 2018), which is predominantly reported in Latin America, presents particular challenges. Bolivia has the highest prevalence, with 6.8% of the population affected in 2007.

This high burden reflects persistent vectorial transmission by triatomine bugs and limited access to treatment in endemic areas. In humanitarian crises, such as Venezuela, rising seroprevalence highlights the increased risk of transmission due to socioeconomic instability and inadequate public health infrastructure. These findings emphasize the need for region-specific interventions, such as vector control, community education, and equitable access to diagnosis and treatment, to minimize the global impact of trypanosomiasis.

Table 2 Transmission Modes and Age Groups of Trypanosoma Diseases.

	African Trypanosomiasis *(T. brucei gambiense)*		**African Trypanosomiasis *(T. brucei rhodesiense)***		**Chagas Disease (Acute Phase)**	**Chagas Disease (Chronic Phase)**		**Chagas Disease (Humanitarian Crisis)**
Transmission Mode	Vectorial (tsetse bite)	fly	Vectorial (tsetse bite)	fly	Congenital, vectorial, foodborne	Vectorial (kissing bug feces)		Vectorial, foodborne
Age Group Affected	Adults elderly	and	All groups	age	Children and young adults	Adults elderly	and	Immunocom promised, elderly

This table outlines how Trypanosoma diseases are transmitted and the specific populations affected:

African Trypanosomiasis is exclusively transmitted through the tsetse fly and primarily affects adults and Chagas disease demonstrates diverse transmission modes.

- *Acute phase*: Includes congenital (mother-to-child) and foodborne routes.
- *Chronic phase*: Transmission typically ceases, but previously infected individuals suffer long-term complications. The humanitarian crisis in regions like Venezuela reveals increased vectorial and foodborne transmission, particularly impacting vulnerable groups.

Transmission of trypanosomiasis varies by species and region. African trypanosomiasis (*T. brucei gambiense* and *T. brucei rhodesiense*) is transmitted exclusively by the tsetse fly *(Glossina)* in sub-Saharan Africa, affecting adults and the elderly in its chronic form and all age groups in its acute form.In contrast, Chagas disease *(T.cruzi)* involves multiple routes, including vector *(flea)*, congenital, and dietary transmission, making it more prevalent in Latin America and among vulnerable populations, particularly during humanitarian crises. While the acute phase of Chagas disease affects children and young adults, its chronic phase causes serious long-term complications in adults and older adults, emphasizing the need for targeted interventions based on age and vector control measures.

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Table 3 This Table shows the Difference of Two types of Trypanosoma Diseases in Pathogens, Vectors, Geographical Distribution, Clinical Manifestations and Treatment Challenges

Category	African trypanosomiasis	American trypanosomiasis (chagas disease)
Pathogen	*Trypanosoma brucei gambiense* and *Trypanosoma brucei rhodesiense*	*Trypanosoma cruzi*
Vector	Tsetse fly (Glossina)	Triatomine bug("kissing bugs")
Geographical distribution	Sub – Saharan Africa	Latin america, Mexico, and rare cases in the southern united states
Clinical manifestation	Stage 1: Induratedchance, rash, lymphadenopathy Stage 2: Confusion, seizures, coma	Acute phase: fever, fatigue,Romana sign Chronic phase: Cardiomyopathy, Megaesophagus, neurological issues
Analysis	Microscopic examination Serological test Lumbar puncture	Microscopy in acute phase Serological test PCR in chronic phase
Treatment	Stage 1: pentamidine, fexinidazole, suramin Stage 2:melarsoprol, eflornihine, NECT	Benznidazole and Nifurtimox during the acute phase
Challenges	Significant drug side effects, e.g., encephalopathy (Melarsoprol), gastrointestinal issues(NECT0	Reduced treatment efficacy in chronic cases, adverse reactions, contrainications.

➢ *Pathogen and Vectors*

There are many species of trypanosomes, but only two subspecies of the *Trypanosoma brucei* groups are responsible for sleeping sickness: *Trypanosoma brucei gambiense* and *Trypanosoma brucei rhodesiense* (WHO.,2023). Tsetse flies, appropriately referred to as 'Africa's bane', are solely responsible for the cyclical transmission of trypanosomes. Both male and female tsetse flies are obligatory blood suckers and during feeding on an infected animal, parasites are transmitted to humans. Tsetse flies (*Glossina species*) are large, blood-feeding flies that are primarily found in sub-Saharan Africa. Tsetse flies are about the size of a housefly, typically around 8–14 mm in length. They have a characteristic brownish or greyish coloration. Their wings are leathery and they hold them in a distinctive diagonal position over their bodies when at rest. They have a long, sharp proboscis used for feeding on blood.

Trypanosoma cruzi, is a parasitic protozoan that is the causative agent of Chagas disease. Kissing bugs (Triatomine bugs) are a group of blood-feeding insects belonging to the family Reduviidae, specifically the subfamily Triatominae. These bugs in the order Hemiptera differ from most other blood-feeding vectors by developing from egg to adult via nymphs that appear similar to adults but lack a pupal stage. Kissing bugs are typically large, ranging from 1.5 to 4 cm in length, depending on the species. They have flattened, oval-shaped bodies with long, slender legs. Their proboscis (mouthparts) is adapted for piercing the skin of mammals to feed on blood. The color varies by species, but they often have a brown or reddish-brown body with distinctive markings along the edges. Furthermore, kissing bugs are primarily night feeders, coming out during the night to search for a blood meal. They are attracted to warm-blooded animals, including humans, and typically bite areas with thinner skin such as around the face, which is why they are called "kissing" bugs. After feeding, they often defecate near the site of the bite, and the feces can contain the Trypanosoma cruzi parasite.

➢ *Geographical Distribution*

Trypanosoma brucei gambiense is endemic in West and Central Africa. *Trypanosoma brucei rhodesiense* is restricted to East and Southeast Africa. These ranges do not overlap, although in Uganda both subspecies are co-endemic, with *Trypanosoma brucei gambiense* found near the northern border and *Trypanosoma brucei rhodesiense* is found in the central and southern regions of that country. The *Trypanosoma brucei gambiense* are more prevalent, in the period from 2009– 2013, 82% of gambiense HAT cases were reported from the Democratic Republic of Congo, while in the last 5 years (2009–2013), 67% of the *Trypanosoma brucei*. African Trypanosomiasis caused around 3,500 deaths, down from 34,000 in 1990. More than 80% of these cases are in the Democratic Republic of Congo rhodesiense cases reported to have happened in Uganda (Franco et al., 2014).

During Venezuela's humanitarian crisis, vectorial transmission has begun occurring in areas where it had previously been interrupted, and Chagas disease seroprevalence rates have increased. In 2007, PAHO published the following data regarding the countries most affected by Chagas disease where Bolivia has the highest prevalence with 6.8% (López-Céspedes et al., 2012).Chagas disease was once entirely confined to continental rural areas of the Americas. Due to increased population mobility, most infected people now live in urban settings and the infection has been detected in 44 countries (including Canada, the United States of America, and many European and some Western Pacific, African and Eastern Mediterranean countries).

➢ *Clinical Manifestation*

The clinical manifestations of African trypanosomiasis can vary depending on the stage of infection (early or late) and the species of Trypanosoma involved (*T. brucei gambiense or T. brucei rhodesiense*). It includes skin rashes and swelling of lymph nodes, particularly the cervical lymph node. If untreated, the infection progresses to the central nervous system, leading to more severe manifestations including the most characteristic symptom,

involving periods of deep sleep during the day (drowsiness) and insomnia at night and seizures and coma due to brain involvement.

Chagas disease manifests in two stages: acute and chronic. The clinical manifestations vary depending on the stage of infection, as well as the organs affected. The acute stage is often mild or asymptomatic, but some individuals may exhibit noticeable symptoms including Fever as one of the most common symptoms in the acute phase and fatigue and malaise which is a generalized feeling of being unwell. The chronic phase can be asymptomatic for many years, but over time, the parasite causes damage to various organs, particularly the heart such as Chronic Chagas Cardiomyopathy as one of the most serious long-term complications, characterized by heart failure, arrhythmias, and dilated cardiomyopathy. This can eventually lead to sudden death due to arrhythmias or progressive heart failure and digestive system such as gastrointestinal manifestations including Megaesophagus which is an enlargement and loss of motility of the esophagus, leading to difficulty swallowing (dysphagia) and regurgitation.

➢ *Analysis*

African trypanosomiasis includes symptoms such as fever, headache and fatigue in both *Trypanosoma brucei gambiense* and *Trypanosoma brucei rhodesiense*. According to Cleveland Clinic, advanced symptoms cause confusion and trouble walking and make it difficult to stay awake. Late during African trypanosomiasis, trypanosomes appear in the interstitial fluid of many organs, including the myocardium and eventually the central nervous system which can cause seizures and coma (Chelsea Marie, William A. Petri, Jr., 2022).

The diagnosis of African Trypanosomiasis includes Microscopic Examination where it relies on the identification of trypanosomes in body fluids, such as blood, lymph node aspirate, or cerebrospinal fluid (CSF). Another test is called Serological Tests: Serological tests, such as the card agglutination test for trypanosomiasis (CATT), can be used for population screening in endemic areas. Lumbar Puncture (spinal tap) is essential for staging the disease and assessing the involvement of the central nervous system.

According to Mayo Clinic, in acute phase, it usually has no symptoms but when they do occur, the person suffers mild and flu-like including fever, fatigue, headache, swollen lymph nodes, muscle aches, loss of appetite, swelling at the bite site (chagoma) and Romaña's sign which is a severe swelling around one eye, often accompanied by conjunctivitis. It could lead to chronic phases which include serious complications such as Cardiomyopathy, Megaesophagus, Megacolon and Neurological issues including seizures, paralysis and mental impairment.

The diagnosis of Chagas trypanosomiasis varies from the phases of the disease. Acute phases have high levels of parasitemia that's why it usually undergoes microscopy which can be detected in blood smears. In chronic stage, Serological tests which detect ls antibodies against the parasite in the blood. Multiple tests are often used to confirm the diagnosis. And PCR which is used to detect the parasite's DNA in blood or other tissues (Center for Disease Control and Prevention, 2010).

➢ *Treatment and Challenges*

Treatment in African Trypanosomiasis varies by what stage the disease. For stage 1, Pentamidine is used to treat *Trypanosoma brucei gambiense* infection in children under 6 years old and those weighing less than 20 kg. Fexinidazole is a newer oral drug effective against both diseases. And Suramin which is also effective against both subspecies in the first stage but has significant side effects. For the second stage, Melarsoprol is the drug of choice for treating *Trypanosoma brucei rhodesiense* infection in the second stage, but it has serious side effects, including encephalopathy.

Eflornithine is also used to treat *Trypanosoma brucei gambiense* infection in the second stage, but it requires intravenous administration and can cause side effects. Additionally, Nifurtimox-Eflornithine Combination Therapy (NECT) is a more effective and safer alternative to eflornithine alone for treating *T. b. gambiense* infection in the second stage (Center for Disease Control and Prevention, 2014).

Chagas disease can be treated with benznidazole or nifurtimox (WHO., 2024). Both medicines kill the parasite and are fully effective in curing the disease if given early in the acute phase, including in case of congenital transmission. Their efficacy diminishes, however, the longer a person has been infected; also, adverse reactions are more frequent in older age. Adults with infection, especially those with no symptoms, should be offered treatment because antiparasitic medicines can also prevent or curb disease progression. Benznidazole and nifurtimox should not be administered to pregnant women or people with kidney or liver failure. Nifurtimox is also contraindicated for people with a background of neurological or psychiatric disorders.

Table 4 The Table Lists Several Research Articles on Chagas Disease and African Trypanosomiasis**.**

Article Title	Focus	Author(s)	Year	Source/References
Trypanosomiasis cruzi and Chagas 'disease in the united states'	Epidemiology and impact in the U.S.	Bern, C., k jos, S, Yabsley, M.J	2011	Clinical Microbiology reviews
'Overview of the diagnostic methods used in the field for human african trypanosomiasis	Diagnostic methods for African trypanosomiasis	Bonnet,J. Boudot,C. and Courtioux, B.	2015	BioMed Research International
' The detection and treatment of human African trypanosomiasis	Detection and treatment of sleeping sickness	Bouteille, B. And Buguet, A.	2012	Research and Report in Tropical Medicine

'Diagnosis, msnagement and treatment of chronic chagas' gastrointestinal disease'	Chagas disease diagnosis and treatment	Pinazo ,M. J,. et al.	2010	Gastroenterologia y Hepatoogia
'The epidemiology of Chagas disease in the Americas"	Epidemiology of Chagas in latin America	Cucunuba, Z,M., et al.	2024	The Lancet Regional Health - Americas
"African trypanosomiasis(sle eping sickness: Human African trypanosomiasis;HA T)	African trypanosomiasis epidemiology and clinical features	Chelsea Marie, William A. Petri,JR.	2022	Medscape
"*Trypanosomiasis cruzi* population dynamics in central Ecuadorian Coast"	*Trypanosoma cruzi* population studies	Costales,J. A., et al.	2015	Acta Tropica
" Chagas screening and treatment among Bolivians living in Madrid, spain"	Screening and treatment in non- endemic areas	romay , Barja,M., et al.	2019	Plos One

The table highlights basic investigative articles on Chagas disease and African Trypanosomiasis, centering on different perspectives such as the study of disease transmission, conclusion, treatment, and population considerations. For Chagas malady, articles just "Like the epidemiology of Chagas infection within the Americas" by Cucunuba et al. (2024) dive into its predominance over Latin America, whereas investigate by Pinazo et al. (2010) centers on the incessant conclusion and treatment perspectives, emphasizing the gastrointestinal impacts. Another critical think about by Romay et al. (2019) examines Chagas screening and treatment in non-endemic regions, displaying the significance of tending to transient wellbeing needs, such as Bolivians living in Spain.

For African Trypanosomiasis, investigate just like the 2015 article by Cap et al. investigates progressed demonstrative strategies, Contributing to way better illness administration in endemic locales. Essentially, Bouteille and Buguet (2012) give bits of knowledge into the location and treatment of resting affliction, a basic issue in African open wellbeing. Collectively, these thoughts illustrate a comprehensive approach to understanding and overseeing Trypanosoma diseases, emphasizing territorial impacts, inventive demonstrative instruments, and custom-made treatment methodologies. These commitments are crucial for handling ignored tropical maladies, particularly in resource-limited settings.

IV. CONCLUSIONS

African Trypanosomiasis and American Trypanosomiases are both caused by Trypanosoma. They differ significantly in their pathogenesis, with African Trypanosomiasis primarily affecting the central nervous system, with a focus on the brain and spinal cord. and American Trypanosomiasis primarily affects the heart, gastrointestinal system, and, to a lesser extent, the peripheral nervous system. Significant differences exist in their respective vectors, geographical distribution, and the resulting impact on human health. Vector Survivability and Density on both tsetse flies (*Glossinidae*) in Africa and kissing bugs (Triatominae) in Latin America share characteristics that make them vulnerable to control efforts. Both species are slow- reproducing, limiting their capacity to repopulate areas where their abundance has been reduced. This, combined with their limited genetic variability, makes them less adaptable to control interventions, such as insecticide resistance. However, the density of vectors can vary significantly depending on environmental factors and human activities. The distribution of tsetse flies in Africa is heavily influenced by climate and vegetation, with specific species adapted to different habitats. The distribution of kissing bugs in Latin America is similarly influenced by environmental factors, with species adapted to different climates and habitats. The distribution of Chagas disease mirrors this, with higher prevalence in rural areas with poor housing conditions that provide suitable bugs. breeding grounds for kissing. While both diseases are caused by trypanosomes, they differ in their causative agents, vectors, clinical manifestations, and therapeutic approaches. Although both trypanosoma diseases are zoonosis, where the animal reservoir plays a key role, the interruption of the disease's transmission is not deemed feasible. Therapeutic advances in treating both African and American immune response is essential for developing new and innovative therapeutic approaches.

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