SCREENING AND TREATMENT FOR CHAGAS DISEASE

TECHNOLOGY AND MARKET LANDSCAPE

APRIL 2020

Unitaid
Innovation in Global Health

(Acting as the host Organization for the Secretariat of Unitaid)

ACKNOWLEDGEMENTS

This report was prepared by Robert Luo (Global Health Impact Group), Anisa Leyla Ghadrshenas and Anna Laura Ross (Unitaid). The following individuals and organizations also provided contributions during the development of the landscape: Katerina Galluzzo, Janet Ginnard, Draurio Barreira Cravo Neto and Pablo Vega Rojas from Unitaid; Pedro Albajar Vinas from the World Health Organization; Cary Bern from the University of California at San Francisco; Debi Boeras from Global Heath Impact Group; Sergio Sosa-Estani from the Drugs for Neglected Diseases Initiative; Albert Picado from the Foundation for Innovative New Diagnostics. Graphics and layout supported by Blossom.

CONTENTS

ABBREVIATIONS AND ACRONYMS

CE	Conformité Européenne
CMIA	chemiluminescent microparticle immunoassay
DNA	deoxyribonucleic acid
DTU	discrete typing unit
ECL	electrochemiluminescent assay
ELISA	enzyme-linked immunosorbent assay
EMTCT Plus	elimination of mother to child transmission of HIV, syphilis, hepatitis B, and Chagas
HAI	hemagglutination inhibition assay
HIV	human immunodeficiency virus
ICT	immunochromatographic test
Ig	immunoglobulin
IIF	indirect immunofluorescence
LAFEPE	Laboratório Farmacêutico de Pernambuco
LAMP	loop-mediated isothermal amplification
mg	milligrams
MTCT	mother to child transmission
PAHO	Pan American Health Organization
PCR	polymerase chain reaction
RDT	rapid diagnostic test
SAPA	shed acute phase antigen
T. cruzi	*Trypanosoma cruzi*
TESA	trypomastigote excreted-secreted antigens
US	United States
WHO	World Health Organization

EXECUTIVE SUMMARY

Chagas disease is a vector-borne disease caused by the parasite *Trypanosoma cruzi*. The disease currently affects between 6 and 7 million people worldwide, the majority of whom are in Latin America, where the disease is endemic. This report begins with an overview of Chagas disease epidemiology, global targets, and current diagnostic and treatment guidelines. It then examines the current landscape of technologies used for diagnosis and treatment and relevant market considerations. Diagnostic methods presented include parasitological methods, serological tests, and molecular assays. The two available treatments for Chagas disease, benznidazole and nifurtimox are also presented. The report concludes by summarizing the diagnostic and treatment markets. It identifies the gaps to be filled and the opportunities which may bolster efforts in Chagas disease elimination, including the elimination of mother-to-child transmission.

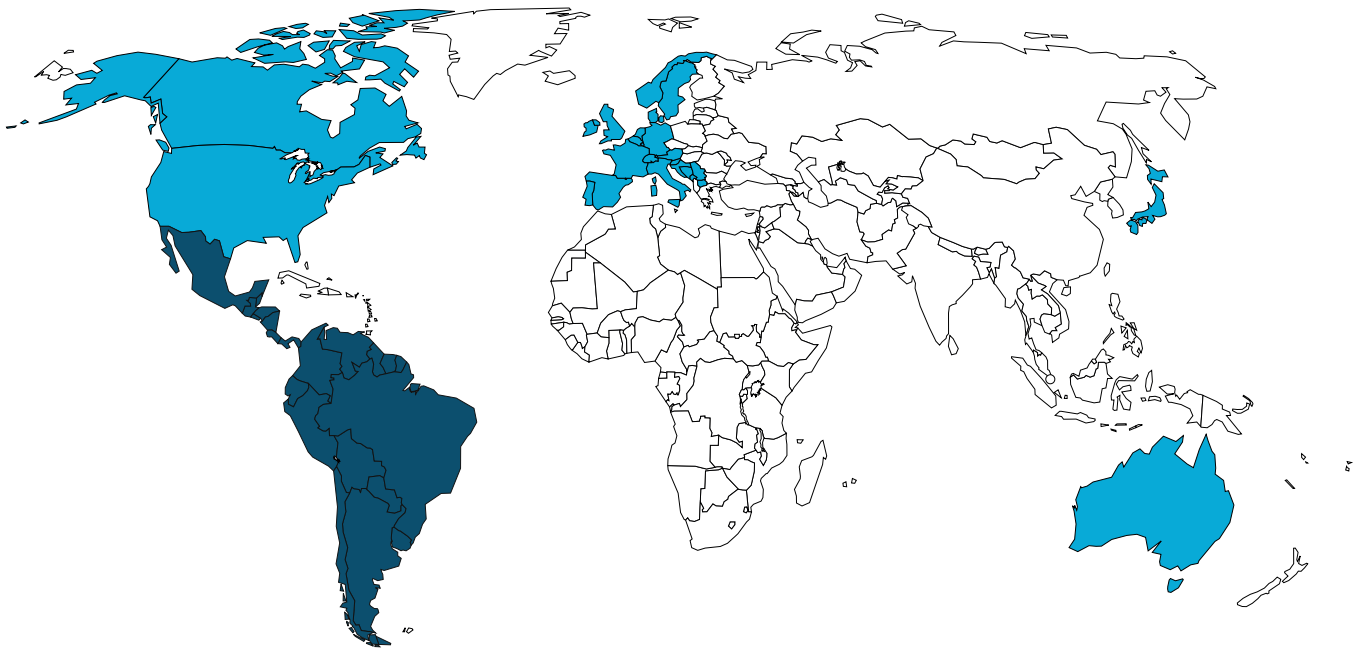
The report points to improvements in the diagnostics market, including the expansion of existing diagnostic tools, new diagnostics for acute and chronic Chagas disease, and better market intelligence and best practices on demand side considerations, such as testing algorithms and demand forecasts. Similarly, for treatment, potential areas include the expansion of existing treatment methods, new and/or shortened treatments for Chagas disease, and improved market intelligence for demand-side treatment needs. Integrated efforts to provide a comprehensive cascade linking Chagas disease diagnosis to effective treatment of the disease will help reduce the global burden of Chagas disease and complement primary prevention methods such as vector control.

Unitaid aims to support the advancement of innovative screening and treatment tools for Chagas disease to enable a paradigm shift in screening and treatment programmes in LMICs, by 1) catalyzing markets for Chagas disease screening and treatment by addressing access barriers for the most promising new technologies; and 2) supporting introduction of these products in selected early-adopter endemic countries through effective delivery channels. Where existing products fail to support countries' efforts to meet global targets, the development of new tests and treatment molecules, or reformulations that meet the needs of specific populations, are needed. The findings of this landscape suggest strong arguments for greater support and attention to the technology and market needs of Chagas disease.

INTRODUCTION

Chagas disease, also known as American trypanosomiasis, is caused by the parasite *Trypanosoma cruzi*. Chagas disease is currently estimated to affect 6 to 7 million people, most of whom live in one of 21 Latin American countries where Chagas disease is endemic.[1] Chagas disease is a vector-borne illness that is transmitted by triatomine insects, often through consumption of contaminated foods or beverages, or following the insect's bite often on sleeping humans. Originally found only in wild animals, Chagas disease eventually spread to humans and domesticated livestock, particularly at the start of the 20th century. Housing conditions can also contribute to the spread of Chagas disease, where triatomine insects can be found living in dwellings with mud walls and/or thatched roofs. The geographic distribution of Chagas disease has also shifted from only rural areas to peri urban and urban centers as well, through increased urbanization, deforestation, and population expansion. Increasingly, international migration has made Chagas disease into a global public health issue, and prevention, diagnosis, and treatment strategies are increasingly important in non-endemic countries as well. Approximately 28,000 new vector-borne cases and over 10,000 deaths occur each year.[2]

FIGURE I World Map of the 21 Countries Endemic for Chagas Diease



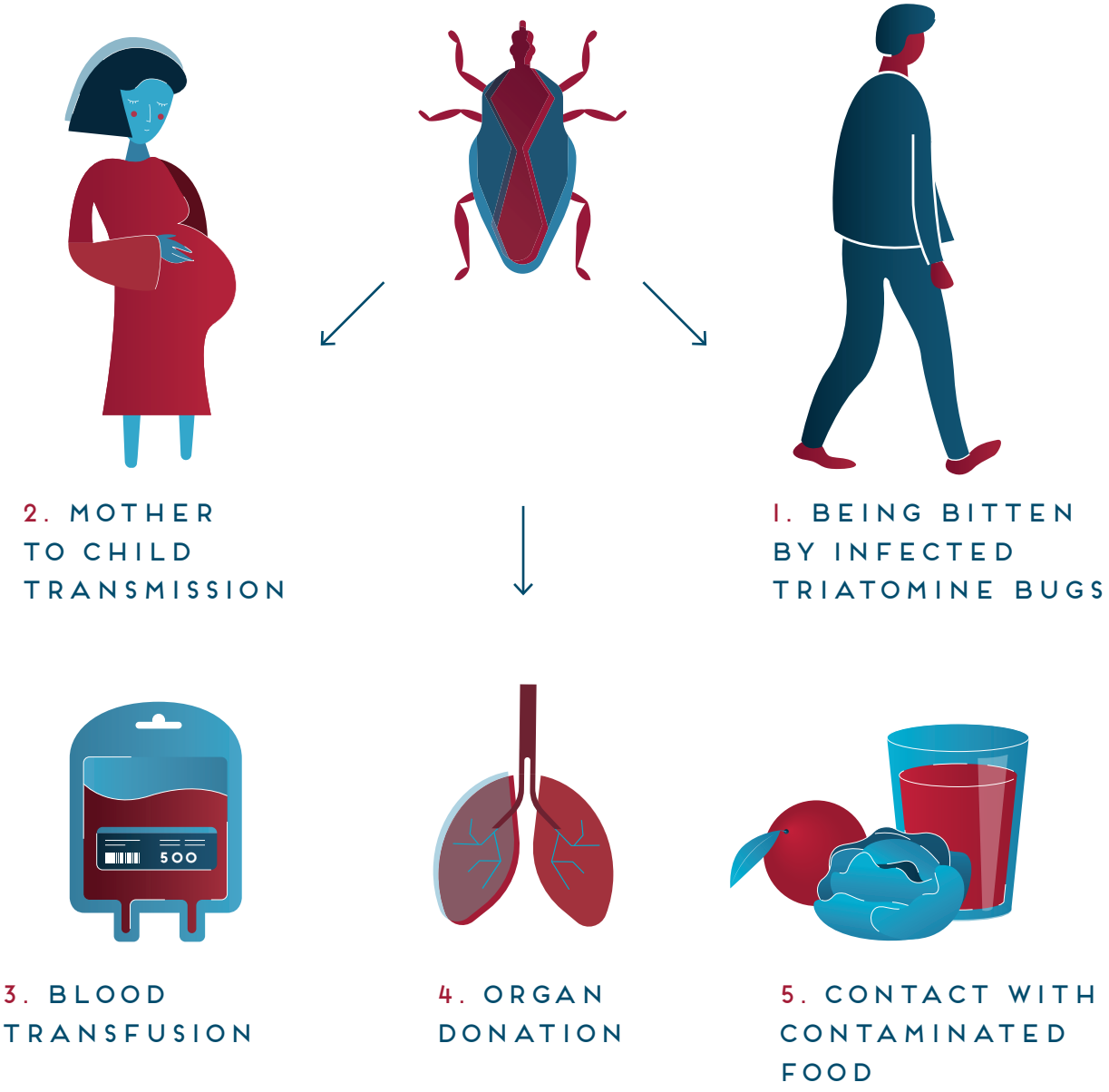
Endemic

Non-endemic but present

21 countries are endemic for Chagas Disease: Argentina, Belize, Bolivia (Plurinational State of), Brazil, Chile, Colombia, Costa Rica, Ecuador, El Salvador, French Guiana, Guatemala, Guyana, Honduras, Mexico, Nicaragua, Panama, Paraguay, Peru, Suriname, Uruguay, and Venezuela (Bolivarian Republic of).

Human to human transmission of Chagas disease can also occur via blood transfusions, organ transplants, and between mother and child during pregnancy or childbirth. Mother-to-child transmission (MTCT) of Chagas disease is estimated to cause about 9,000 new cases in newborns annually.[3] While the majority of infected individuals experience no or only mild non-specific symptoms during the acute phase of infection, if left untreated, Chagas disease can cause severe cardiac , gastrointestinal, or neurologic complications in 30%-40% of individuals during the chronic phase of infection.[1,2]

FIGURE 2 Routes of Transmission for Chagas Disease



Source: https://www.who.int/news-room/fact-sheets/detail/chagas-disease-(american-trypanosomiasis)

As there is no vaccine to prevent Chagas disease, primary prevention of Chagas disease in endemic countries has been most effective through vector control. Programmes to conduct surveillance, improve housing conditions, and perform insecticide spraying of dwellings and areas known to harbor triatomine insects has significantly reduced the number of persons infected with Chagas disease every year.[4] Widespread adoption of testing blood products prior to transfusion has also increased the safety of the blood supply for not only Chagas disease but many other infectious diseases too.[2,4] In parallel, advances in the diagnosis and treatment of acute, congenital, and chronic Chagas disease have occurred as well.[5] New diagnostic technologies have been introduced over the years,[6–8] and drug manufacturers have committed to providing a stable supply of currently available medications for the treatment of Chagas disease.[9,10]

In response to the need for improved visibility on supply-side and demand-side market considerations, Unitaid has conducted this landscape to identify gaps and opportunities in the availability, affordability and accessibility of health products to support control of Chagas disease. The focus of this report is to provide key updates and synthesize currently available information to illustrate important market opportunities and needs related to Chagas disease diagnosis and treatment.

Methodology and Scope

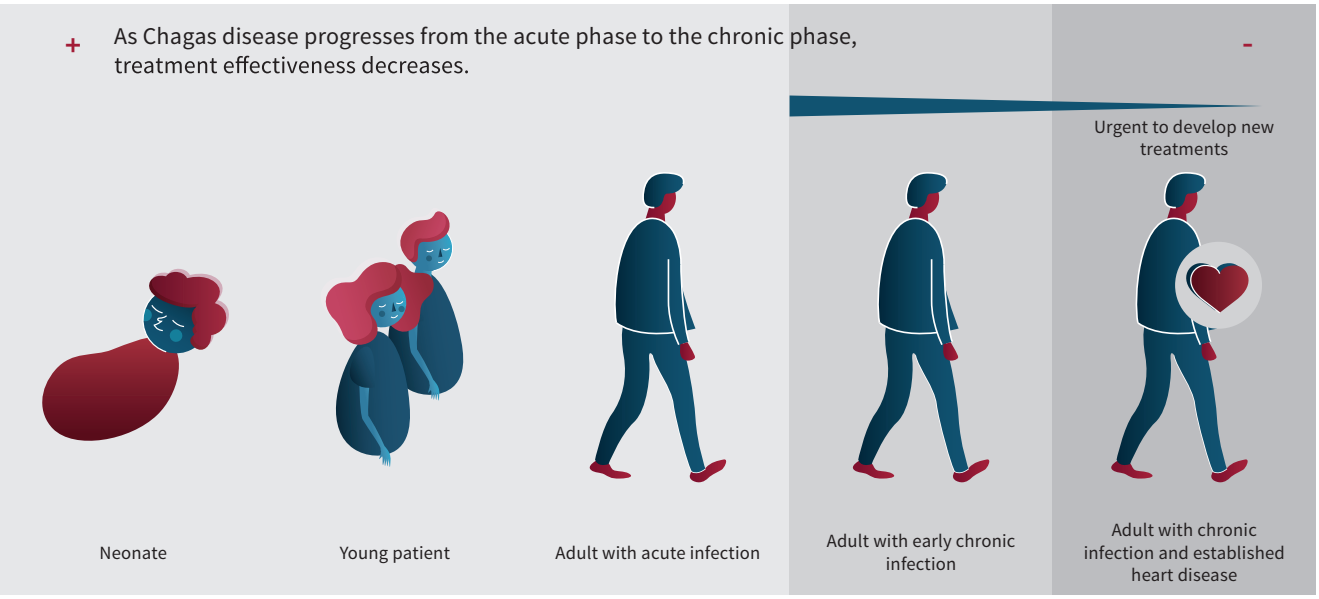
This report was compiled between January-February 2020 drawing from the following sources: previous work conducted by Unitaid, peer-reviewed published literature, conference abstracts, institutional and corporate websites, product instructions for use, and semi-structured telephone interviews with Chagas disease experts from public health, academia, and industry. The product annex was informed by materials from manufacturers and publications on evaluations and clinical trials. Although this report aims to be comprehensive in scope, a major limitation of this report is the potential for oversight and failure to include all products or developments relevant to Chagas disease diagnosis and treatment. This report also focuses on the diagnosis and treatment of acute and chronic Chagas disease itself, including congenitally-acquired Chagas disease, and not on the screening of blood or tissue products, nor on the diagnosis and treatment of Chagas-related cardiac and gastrointestinal sequelae. This report suggests opportunities for interventions that may improve Chagas diagnosis and treatment. However, these suggestions are not meant to be exhaustive, are intended for consideration and to inform further discourse, and do not reflect the scope of potential work to be supported by Unitaid.

Disease Overview

With approximately 75 million people living in areas that are at risk for infection, Chagas disease is one of the most important neglected tropical diseases, causing an estimated

10,000 deaths annually [2], more deaths than any other parasitic disease in Latin America.[1] The overall prevalence of Chagas disease in endemic regions of Latin America is estimated to be between 1%-1.5%, with data showing a wide spectrum of between 0.1% to nearly 50% of people infected depending on the geographic location.[11] Rates of mother-to-child transmission vary across countries, but approximately 5-10% of pregnant women with Chagas disease will also transmit the infection to their newborns.[6] Chagas disease has an initial acute phase lasting 8-12 weeks that can be mild and with non-specific symptoms, which is then followed by a chronic phase where cardiac symptoms may develop anywhere from 10-30 years later in approximately 30% - 40% of individuals. Parasite loads are generally high and detectable during the acute phase, while the chronic phase is distinguished by a low parasite load. Further, treatment efficacy declines as individuals move from the acute phase to the chronic phase, which is why early detection of infection is so critical, and yet so challenging given the lack of specific symptoms and the shorter duration of the acute phase. This is particularly relevant for mother-to-child transmission of Chagas, where the opportunity for treatment efficacy of infected infants is high if pregnant women are provided a timely and definitive diagnosis of their status, and Chagas-exposed infants are offered appropriate and testing and treatment services. Considerations for the treatment of chronic infection are more complicated; estimates show only 10-20% treatment efficacy during this phase. Further, several randomized studies identify adverse health outcomes in individuals with organ damage who receive Chagas treatment while in the chronic phase of infection, suggesting it may be harmful in individuals with certain health conditions. [15] While treatment may not be offered widely to all individuals in the chronic phase, identification of infection through testing facilitates the monitoring for severe complications and symptoms and access to health services that can slow the progression of cardiac disease resulting from chronic Chagas infection. [12]

FIGURE 3 Efficacy of Antiparasitic Treatment



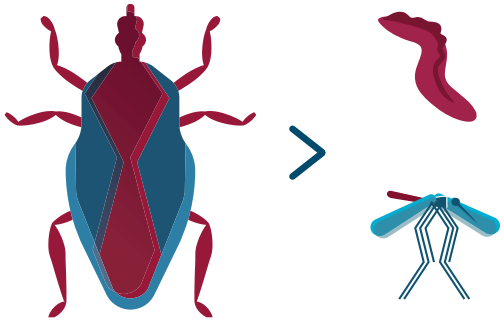
Source: https://www.who.int/chagas/disease/home_treatment/en/

While the benefits of early identification and treatment of Chagas disease during the acute phase are clear, significant gaps remain in coverage rates for diagnosis and treatment of Chagas disease overall. Currently, only 7% of persons with Chagas disease are estimated to be diagnosed and only 1% are treated each year, despite the availability of diagnostic methods and curative treatments.[11,12]

In addition to the health consequences, morbidity and mortality from Chagas disease disproportionately affects rural and poor populations and has both equity and economic consequences. Many people living with Chagas disease are unaware of the infection until much later when clinical problems present, which can accrue significant healthcare costs over the years. Global estimates includes a loss of over 500,000 disability adjusted life years annually and a loss of over US$1 billion dollars in worker productivity that comes from morbidity or premature death.[11]

FIGURE 4 Economic Burden of Chagas Disease

Health burden



75-100 M PEOPLE AT RISK OF INFECTION.
MORE DEATHS THAN ALL OTHER PARASITIC DISEASE COMNÌBINED
in Bolivia, Brazil, Venezuela and Chile

Source: https://www.paho.org/en/topics/chagas-disease

Economic burden

>US$ 6 BILLION
total annual disease cost in Latin America

750,000 WORKING DAYS
lost annually in Latine America alone

Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3763184/

Global Targets for Chagas Disease

Several targets have been established for Chagas disease: by the World Health Organization, through its roadmap for neglected tropical diseases; and by the Pan-American Health Organization (PAHO)'s through its integrated sustainable framework for the elimination of

communicable diseases in the America and its framework for elimination of MTCT of HIV, syphilis, hepatitis B, and Chagas (EMTCT Plus) and the World Health Organization's roadmap for neglected tropical diseases, several targets have been established for Chagas disease:[3,13,14]

- Elimination of MTCT by the year 2020 with at least 90% of children cured of Chagas infection with post-treatment negative serology
- Elimination of transmission of principal intra-domiciliary vectors by the year 2020
- Elimination of Chagas disease in 16 countries by the year 2020, with measures put in place to prevent disease resurgence or reintroduction
- A proposed regional deadline of no neonatal morbidity, through rapid congenital case treatment of infected newborns, new routine prenatal screening, and treatment of at-risk women before pregnancy by the year 2025

These targets are being reviewed and updated for 2020 - 2030, and to achieve these goals, significant scale up in the diagnosis and treatment of Chagas disease will be required, along with continued strengthening of primary prevention methods such as vector control.

Recommended interventions to prevent, diagnose and treat Chagas Disease

Interventions, including vector control, increased awareness and education, blood transfusion screening, and improvements in access to diagnostics and medications can help reduce the reservoir of infected individuals and have contributed to reduce the number of Chagas disease cases and deaths by more than 70% over the last several decades.[2]

In 2018, PAHO also updated clinical practice guidelines for the diagnosis and treatment of Chagas disease as part of its plan of action for the elimination of neglected infectious diseases.[15]. No significant new evidence has come out since the issuance of these guidelines. Many countries have adapted their own set of clinical testing and treatment guidelines from the PAHO guidelines and may include other types of diagnostic products that will be reviewed in the technology landscape section. As described, parasitemia loads vary throughout the different phases of infection, thus guidelines for detection methods require several testing approaches and modalities.[15] As the diagnostic infrastructure, regulatory pathways, and in some cases geographical variations affecting the strain of *T. cruzi* differs across countries, the translations of these guidelines into testing algorithms varies. Treatment options are more standardly adopted by countries, though there is ongoing discourse on the value of treatment in adults with chronic infection, and among which populations of individuals with chronic infection should treatment be prioritized.

Table 1 summarizes the diagnostic and treatment approaches recommended in the guidelines that are relevant to acute and chronic Chagas disease, along with the relevant commodities that were considered to formulate each guideline.

TABLE I PAHO Guidelines for the Diagnosis and Treatment of Chagas Disease

Topic	Guidance	Relevant Commodities
Diagnosis of suspected acute *T. cruzi* infection transmitted congenitally or otherwise	• Direct parasitological tests • Serological follow-up (to evaluate for congenital infection starting at 8 months of age or for seroconversion for all other modes of transmission)	• Microhematocrit • Direct observation • Serological testing (see diagnosis of chronic infection)
Diagnosis of suspected chronic *T. cruzi* infection	• Combination of two serological tests (ELISA, HAI, and IIF) detecting different trypanosome antibodies is better than use of a single test (ELISA, ICT, or CMIA) • Discrepant results can be resolved with a third test • In resource-limited areas, a single ELISA can be considered with positive results confirmed prior to treatment	• ELISA: enzyme-linked immunosorbent assay • HAI: hemagglutination inhibition assay • IIF: indirect immunofluorescence • ICT: immunochromatographic test • CMIA: chemiluminescent microparticle immunoassay
Treatment of acute or congenitally acquired *T. cruzi* infection	• Trypanocidal therapy (including congenital infection)	• Benznidazole • Nifurtimox
Treatment for adults with chronic *T. cruzi* infection and no specific organ damage	• Trypanocidal therapy	• Benznidazole • Nifurtimox
Treatment for children with chronic *T. cruzi* infection	• Trypanocidal therapy	• Benznidazole • Nifurtimox
Treatment for girls and women of childbearing age with chronic T.cruzi infection to prevent vertical transmission	• Trypanocidal therapy (including girls and women of childbearing age to reduce vertical transmission, but excluding women who are already pregnant)	• Benznidazole • Nifurtimox
Treatment for adults with chronic *T. cruzi* infection and specific organ damage	• Treatment is not recommended in this population	

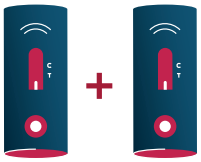
Source: PAHO. Guidelines for the diagnosis and treatment of Chagas disease. Guidelines for the diagnosis and treatment of Chagas disease. http://iris.paho.org/xmlui/bitstream/handle/123456789/49653/9789275120439_eng.pdf?sequence=6&isAllowed=y. Published 2019

Updated recommendations on the diagnosis and treatment of congenital Chagas disease were also released in 2019, following a set of technical meetings convened by WHO.[16] These recommendations highlighted the need to focus on five specific populations for the prevention and control of Chagas disease: girls and female adolescents, women of childbearing age, pregnant women, infants born to infected mothers, and relatives born to infected mothers. Screening and treatment should be applied for all cases of Chagas disease found in these populations.[16]

Technology Landscape - Diagnostics

Current diagnostic approaches for Chagas disease fall into three primary areas: parasitological methods, serological detection of antibodies to parasite antigens, and molecular detection of the parasite.

FIGURE 5 Approaches to Testing for Chagas Disease

Optimal diagnostic strategy for suspected chronic *T. cruzi* infection		Optimal diagnostic strategy for suspected acute *T. cruzi* infection transmitted congenitally or otherwise	
			
Microscopy combining 2 serological tests	2 x point of care RDT tests (including laboratory-based and lateral flow)	Microhematocrit centrifuges and direct observation	Serological follow-up starting at 8 months old

Source: PAHO. Guidelines for the diagnosis and treatment of Chagas disease. Guidelines for the diagnosis and treatment of Chagas disease. http://iris.paho.org/xmlui/bitstream/handle/123456789/49653/9789275120439_eng.pdf?sequence=6&isAllowed=y. Published 2019

1) Parasitological detection of *T. cruzi* in blood is used to identify cases of acute infection, including congenital infection, as parasites are typically present in greater numbers in the bloodstream during the first couple months of the infection. Parasitological detection can also be done to investigate potential reactivation of Chagas disease, when parasites return to the bloodstream, especially when a chronically infected person becomes immunosuppressed from other diseases such as HIV or from taking immunosuppressive medications. The following parasitological methods can be used:

Microscopy: Blood samples can be examined under a light microscope to directly detect *T. cruzi*. The simplest but least sensitive methods involve looking at a fresh drop of blood or a simple stained blood smear under a microscope. Concentrating the blood into a thick smear or via a centrifuge (e.g. the microhematocrit method, micro-Strout test, Strout concentration method) and then examining it under a microscope improves the sensitivity of diagnosis.

Microscopy has been the standard of care for the diagnosis of acute infection and congenital infection during the first 8 months of life, when maternal antibodies present in a newborn's bloodstream will confound serological methods. Microscopy can be performed in resource limited settings but do require trained staff and basic laboratory equipment for the preparation and examination of blood samples. The overall sensitivity of microscopy, however, is usually less than 50%.[6] Repeat testing after birth can improve the sensitivity for detection of congenital Chagas disease, as parasite loads in the blood can increase at 1-2 months of age.

Other Parasitological Methods: The presence of *T. cruzi* can also be detected by methods such as xenodiagnosis (exposing uninfected triatomine insects with blood from a patient and subsequently examining the insects under a microscope to look for parasites) and hemoculture (growing and isolating the parasite from a patient's blood sample in a laboratory culture medium). However, these methods require significant laboratory infrastructure, training, and time to perform, and consequently are not commonly used for the diagnosis of acute Chagas disease.

2) Serological detection of antibodies to *T. cruzi* antigens is the most common method to evaluate for chronic infection, since after acute infection, the parasites migrate preferentially into muscle tissue of the heart and gastrointestinal tract and may no longer be found in the bloodstream. Serological detection is also recommended to evaluate infants for congenital Chagas disease after 8 months old of age according to PAHO guidelines, when maternal antibodies should have waned in the infant and blood parasitemia is lower, reducing the sensitivity of PCR.[15] Given the wide genetic diversity of *T. cruzi* across the Americas, with over 6,000 strains grouped into 6 discrete typing units (DTUs), a serological test that performs well in one region may not perform well in another; hence the current PAHO recommendation for two serological tests that utilize different antigens.[15,17]

Serological methods can be divided into two major categories based on the location of testing: laboratory-based testing and point-of-care testing. Currently only laboratory-based serology is currently recommended in the PAHO guidelines, though point-of-care testing was evaluated during the guidelines process and acknowledged for improving the accessibility of testing.[15]

A) *Laboratory-based serology*: Serology testing identifies the presence of *T. cruzi* antibodies in a person's blood sample and can be done through a variety of different technologies. Either whole parasite lysates or one or more recombinant parasite antigens are incubated with a patient blood sample, and detection is performed by measuring reactions between parasite antigens and *T. cruzi* antibodies present in a patient's blood.[18] Measuring the loss of detectable antibodies to *T. cruzi* after treatment, also known as sero-reversion, is a commonly used method to assess treatment efficacy and confirm that a patient has been cured, although this can take months to years to occur after treatment.

Laboratory-based serological tests include the following technologies:

- Enzyme-linked immunosorbent assay (ELISA): a colorimetric reaction is detected when a labeled second antibody reacts with *T. cruzi* antigen-antibody complexes that form when patient antibodies bind to the parasite antigens used in the assay. Reported sensitivities for ELISA typically fall in the range of 94-100%, with specificities between 96-100%.[19–22] Although most often used to detected IgG antibodies to Chagas disease, ELISA methods which detect earlier biomarkers, such as the shed acute phase antigen (SAPA) or IgM antibodies have been used to help diagnose acute and congenital infection.[6] Multiplex ELISA testing covering a series of different Chagas disease biomarkers has also been explored as a way to improve confirmation of chronic Chagas disease.[23]

- Hemagglutination inhibition assay (HAI): the presence of *T. cruzi* antibodies prevents clumping of red blood cells that can been visually evaluated by a laboratory technician. Reported sensitivities are typically lower than ELISA and have ranged from 88-99%, with specificities between 96-100%.[24]

- Indirect immunofluorescence (IIF): a fluorescent reaction is detected when a labeled second antibody reacts to *T. cruzi* antigen-antibody complexes that form when patient antibodies bind to parasite antigens used in the assay. The reported sensitivity and specificity are both around 98%.[24]

- Chemiluminescent microparticle immunoassay (CMIA) and electro chemiluminescent (ECL) assay: Used in automated immunoassay platforms, a chemical reaction occurs in the presence of *T. cruzi* antigen-antibody complexes that form when patient antibodies bind to the parasite antigens used in the assay. This reaction is then detected via optical or electrical methods. Reported sensitivities and sensitivities have been between 99%-100%, prompting discussion on whether a single test on an automated immunoassay platform is sufficient to diagnose and confirm Chagas disease.[25–27]

- Western Blot: *T. cruzi* antibodies are separated and transferred onto a membrane, where a labeled second antibody binds and enables detection. Because reported sensitivities and specificities have been around 100%, Western blot technology has traditionally been considered a confirmatory gold standard for antibody detection. Similarly to SAPA-based ELISA methods, Western blots for earlier serological markers such as IgM antibodies to trypomastigote excreted-secreted antigens (TESA) have been shown to have higher sensitivity than direct parasitological methods.[6,24]

B) *Point of care serology*:

- Immunochromatographic test (ICT) / Rapid diagnostic test (RDT): Lateral flow or blot-based strip, cassette, or membrane containing conjugated antigens/antibodies create a visible chemical reaction in the presence of *T. cruzi* antibodies present in a blood sample that can be read as a visible line or dot. These tests can be done without specialized laboratory staff or equipment and may be performed in decentralized settings in the field or at primary healthcare centers to obtain results at the point of care. A systematic review and meta-analysis of 6 RDTs showed a pooled sensitivity and specificity of 96.6% and 99.3%, respectively, compared to laboratory-based serological testing.[28] A separate PAHO review of 10 RDTs showed sensitivities ranging between 88% and 97%, and specificities between 93% and 100%.[15] Given their performance, they could provide a useful alternative where obtaining laboratory-based serology tests may be difficult. Since test performance can vary by manufacturer and by region, further validations of these tests across different geographies would be useful.[20]

3) Molecular detection of *T. cruzi* has become more common as access to techniques such as the polymerase chain reaction (PCR) has become more widespread for the diagnosis of infectious diseases. Molecular tests look for the presence of *T. cruzi* DNA in a blood or tissue sample. Similar

to parasitological methods, molecular detection is most useful during the acute phase of Chagas disease or during disease reactivation, when parasitemia is highest in the bloodstream. PCR provides higher sensitivity for the diagnosis of acute and congenital Chagas disease compared to microscopy, though it does require more complex laboratory infrastructure and staff trained in molecular techniques. As a result, PCR is not the most widespread or standardized technique for the diagnosis of Chagas disease, despite the high performance of these assays in detecting infection. As detectable parasitemia changes over time, particularly in infants,testing multiple specimens over time is ideal and can increase sensitivity to over 80%, compared to less than 50% for microscopy.[29] Use of clot samples to extract DNA from instead of the entire whole blood sample may also help improve the sensitivity of PCR by concentrating the parasite DNA.[30] A positive PCR result after treatment can also be used to indicate treatment failure, though a negative result cannot necessarily confirm treatment success, particularly in chronic Chagas disease where there may not be any detectable circulating parasite DNA in the blood.

Annex 1 summarizes major characteristics of currently available serological and molecular tests and provides examples of tests used for to diagnose acute and/or chronic Chagas disease.

Emerging diagnostic technologies have focused on improving serological and molecular methods of testing and include the following:

- Parasite antigen detection in urine by nanoparticles has been researched as a method to detect congenital Chagas disease as well as monitor *T. cruzi* parasitemia levels in HIV co-infected individuals.[31,32] A small proof-of-of concept study showed similar sensitivity to PCR for congenital Chagas disease, but no further research has been published on this method since 2016. Ultrasensitive antigen detection methods may be a potential area for future research.

- Simpler isothermal molecular methods, such as loop-mediated isothermal amplification (LAMP), have been studied to provide a molecular diagnostic that requires less laboratory equipment and infrastructure compared to PCR. Samples are incubated with a fluorescently labeled probe at a constant temperature, and results can be read visually. Initial proof-of-concept studies on small sample sizes (<30 patients) have shown that LAMP can detect acute, congenital, and chronic cases of Chagas disease, but further validation is needed to establish the performance of these types of assays, and no commercialization timelines have been published.[33,34] Point of care and near point of care molecular testing has become available for other infectious diseases such as HIV, influenza, and tuberculosis, and have enabled same-day treatment initiation. POC testing could been a future area for Chagas disease research and development as well.

- Improvements in RDTs are being evaluated to determine if their sensitivity and therefore use as a potential confirmatory test for Chagas disease can be increased. A final prototype of one such test is currently under evaluation in South America (DPP Chagas Test, Chembio).

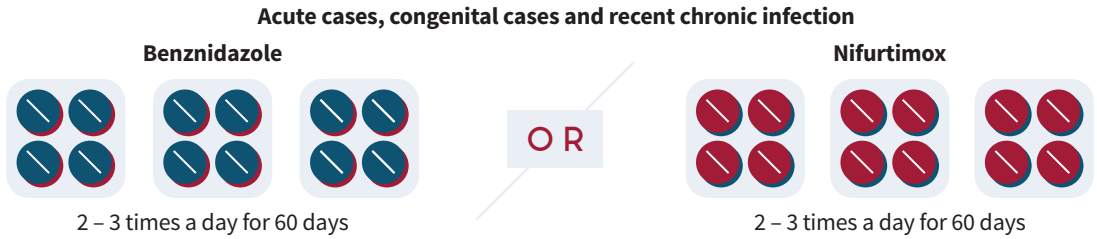
Technology Landscape – Treatment

Two antiparasitic drugs, benznidazole and nifurtimox, are currently the only medications available for treatment of Chagas disease.[35] Both benznidazole and nifurtimox have the highest efficacy during the acute phase of Chagas disease, with cure rates of up to 100% in congenital Chagas disease and up to 80-90% in children and adults.[6,36] Treatment of chronic Chagas disease is much more difficult, with cure rates of between 10-20%, and no significant benefit is seen if a patient already has significant organ damage.[36] A full treatment course typically takes between 60-90 days, with 2-3 doses of tablets taken orally each day. Though the drugs are overall quite safe, the length of treatment increases the frequency of adverse drug reactions and may decrease patient compliance with finishing treatment. Annex 2 summarizes major characteristics of these medications.

FIGURE 6 Approaches to Treatment for Chagas Disease

Trypanocidal treatment is recommended as Treatment for the following populations/use cases:

- adults with chronic *T. cruzi* infection and no specific organ damage
- children with chronic *T. cruzi* infection
- vertical transmission prevention in girls and women of childbearing age with chronic *T. cruzi* infection
- patients with acute/congenital *T. cruzi* infection



Source: PAHO. Guidelines for the diagnosis and treatment of Chagas disease. Guidelines for the diagnosis and treatment of Chagas disease. http://iris.paho.org/xmlui/bitstream/handle/123456789/49653/9789275120439_eng.pdf?sequence=6&isAllowed=y. Published 2019

Preclinical research studies and clinical trials for new treatments for Chagas disease have taken the following approaches:

- New compounds: Fexinidazole, a drug with efficacy for human African trypanomiasis, is currently in phase II trials for use in Chagas disease.[5] Recent phase II trials of other drugs, such as posaconazole and E1224 (a prodrug of ravuconazole), showed lower efficacy when used alone compared to benznidazole and therefore did not continue to phase III testing.[37,38]
- New combination therapies: Combination therapies of existing Chagas disease drugs plus a second drug, may also be able to improve the efficacy of Chagas disease treatment. A combination study on benznidazole plus E1224 in currently undergoing a phase II clinical trial.[5]

- New treatment formulations: Shorter course regimens of existing Chagas disease medications have been shown to be effective in small pilot studies, and phase I-III clinical trials are underway to validate some of these approaches in both adults and children .[5,39,40]
- Additionally, a phase III clinical trial is currently underway comparing use of nifurtimox to use of benznidazole in a direct head-to-head study, which will help provide more evidence about if they are equivalent or not with regards to efficacy and safety.[5]

Market Landscape - Diagnostics

Current Market Access Overview

An estimated 75 million individuals live in areas that put them at risk for having Chagas disease. Given the high cost of the complications of chronic Chagas disease, screening programmes have been shown to be cost-effective, even in non-endemic settings with a prevalence as low as 0.05%.[41,42] However, despite the large number of people who would benefit from Chagas disease screening and relatively large number of diagnostic tests available from a wide variety of companies and laboratories, uptake of diagnostics for acute and chronic Chagas remains low, with less than 1% of the 6 to 8 million people currently living with Chagas disease estimated to receive treatment each year.[11] Outside of blood transfusion screening programmes and local surveillance and pilot programmes, widespread screening programmes have not been taken to scale, even in the wealthiest countries in the Americas affected by Chagas disease.

Market access barriers and opportunities

Based on the currently available diagnostic technologies and key stakeholder input, several market access barriers and potential opportunities have been identified (Table 2). These fall into the following five areas:

1) Expansion of Existing Diagnostics

Demand and Adoption Barriers: Access to existing diagnostics for Chagas disease is low. While lack of funding to deliver access to optimal testing tools has been identified as one barrier, another barrier remains the lack of evidence on best practices for testing platforms, products and implementation approaches. Country policies reflect a variety of approaches to screening for Chagas disease, but there is limited visibility on demand or targets. No data on overall number of diagnostic tests being used annually, nor on the market share across different diagnostic methods and commercial vs laboratory-developed tests were available for this report. The lack of this information highlights another key barrier, which is the need for standardization and consensus amongst Chagas stakeholders on best practices for diagnostics. Despite the issuance of PAHO guidelines in 2018, different laboratories within countries may use different tests, may develop their own tests, and may follow different diagnostic algorithms.[8] The current PAHO recommendation for two, potentially three, laboratory-based serological tests may also be difficult to implement outside of areas with well-functioning laboratory and patient follow-up

systems. Additional research is needed to determine if only a single serological test or the use of one or two RDTs would work across a range of settings in Latin America.[25,44,45]

Opportunity: Expanding access to and use of current diagnostics could significantly increase the detection of Chagas disease. Interventions that increase market access of currently available diagnostics are likely to have the greatest impact, given the very low utilization of diagnostics for Chagas disease at the present time. To increase demand and adoption of diagnostic tools, there is a need to validate the use of available RDTs in settings where they are most suited, as well as developing operational research to feed into improved algorithms to better guide testing and treatment implementation.

Pilot implementation programmes, such as ones considering 'test and treat' strategies, may provide further programmatic evidence for future scale up of diagnostics at the point of care, and could identify best practices for building a comprehensive care cascade for Chagas disease that links proper diagnosis with completion of treatment (Table 2). Finally, to increase the adoption of PAHO guidance on diagnosing Chagas disease, additional implementation guidance may be needed.

2) New Diagnostics for Acute and Congenital Chagas Disease

Innovation and Availability Barriers: Barriers remain in providing access to diagnostic tools that would enable a timely and accurate result. Given the varying levels of parasitemia and limited sensitivity of microscopy methods, timely and effective testing is critical for those acutely infected with Chagas disease, and in particular for newly infected infants who are exposed to Chagas disease vertically. However, the cost, complexity of testing, and lack of availability in many areas prevents most infants from ever receiving a single test and being linked to effective care and treatment. Additionally, the majority of pregnant women do not receive any screening for Chagas disease, which makes it less likely that their infants would then, too, be screened. In programmes where infants have been given initial screening, loss to follow-up in newborns by 9 months of age has still been over 80%.[46] Additionally, some diagnostic tools, including RDTs, have demonstrated poor performance in specific geographical areas. For example, when the same RDTs were tested in patient specimens from Bolivia and Peru, the sensitivity decreased by 30-50% in Peruvian samples, highlighting the need for validation of tests in different geographical locations.[43]

Opportunity: Detection of acute infection of Chagas disease presents an opportunity to provide timely and effective treatment, in particular for newly infected infants. A new rapid, point of care test for acute Chagas disease, either based on ultrasensitive antigen detection or molecular methods, could benefit both infants and adults by enabling treatment initiation sooner and dramatically reducing loss to follow-up. A survey of over 150 Chagas disease experts identified a point of care tests for congenital Chagas disease as one of the top three diagnostic needs for Chagas disease.[7] Target product profiles have already been created for point of care diagnosis of acute and congenital Chagas disease to help guide these efforts.[47]. Further, the development of a test that can be validated and used across geographies is greatly needed.

3) New Diagnostics for Chronic Chagas Disease

Innovation and Availability Barriers: Current treatment regimens are only effective in approximately 10-20% of cases of chronic Chagas disease, and as such, they are closely monitored when administered to people with chronic Chagas disease.[7] Unfortunately, there is not a standardized diagnostic to determine whether therapies have been effective at clearing the disease. Currently, treatment response is often measured by sero-reversion, or loss of Chagas disease antibodies, which may take years. Clinical trials for Chagas disease drugs use PCR negativity as a surrogate for treatment response, through this only measures the absence of parasite DNA in the blood and cannot measure tissue parasites. The lack of an accurate and easy-to-use diagnostics to determine the success of treatment is a key barrier for people living with chronic Chagas disease. Another barrier in this population is the inability of health workers to determine which individuals with chronic infection are at high risk for progression to cardiac or gastrointestinal disease at the time of diagnosis. By not providing a differentiated diagnosis of the cases which are likely to progress to advanced disease, healthcare workers are often unable to provide adequate clinical care. In settings where resources are limited, this is a challenge in targeting services to those who would benefit from them the most.

Opportunity: A top diagnostic opportunity identified in the survey of Chagas disease experts was the development of a diagnostic for early assessment of treatment response or cure and a test to identify individuals who are likely to develop cardiac or gastrointestinal complications.[7] Since current Chagas disease treatments only cure the minority of chronic Chagas disease cases, a test of cure would identify whether individuals who have received treatment do or do not need additional treatment. Such a test may also help encourage people to get tested and treated, since it would provide proof of cure, something which care providers are not able to inform individuals of currently. Similarly, a test that could identify individuals at high-risk for progression to cardiac or gastrointestinal disease could motivate those persons to start and complete their treatment course. Such technologies could be based on biomarkers measuring the host-parasite response and from a public health perspective, would also enable targeted treatment and prioritization of efforts, which would be particularly beneficial in resource limited settings.

4) Market Forecast for Chagas Disease Diagnostics:

Supply and Delivery Barriers: Currently the diagnostics market for Chagas disease is quite fragmented, with a number of different diagnostics manufacturers and in-house laboratory developed tests being used. Despite a wide variety of diagnostic options, diagnostics uptake has been quite limited, and no accurate estimates or forecasts regarding the current and future diagnostics market have been published. This presents a challenge to current programs, as well as to manufacturers who may be interested to develop products for this market.

Opportunity: Modeling current and future diagnostic needs by country could help plan for scale up of efforts to meet Chagas disease elimination targets and also help plan for anticipated treatment needs as well. Close collaboration between key stakeholders of Chagas programmes, including procurement groups, implementation agencies, normative bodies, and manufacturers, could provide the market intelligence needed to inform appropriate Chagas control targets.

TABLE 2 Diagnostic Market Access Barriers and Opportunities

Area	Access Barriers	Opportunities
Expansion of Existing Diagnostics	• Evidence gaps around performance in different regions • Lack of standardization of diagnostic practices • Need to ensure a complete care cascade, linking diagnosis with treatment	• Validation/Implementation of tests across geographies • Development/Validation of RDTs for inclusion in diagnostic guidelines • Pilot of "Test and Treat" programmes • Evidence on the optimization of testing programs to inform standardization of best practices
New Diagnostics for Acute and Congenital Chagas	• Rapid diagnosis of acute and congenital Chagas disease	• Point of care serological or molecular tests • Validation of tests across geographies
New Diagnostics for Chronic Chagas Disease	• Assessment of treatment response • Risk-stratification for targeted treatment	• New methods for assessing who needs treatment and who has been cured
Market Forecast for Diagnostics	• Fragmented market with limited uptake of numerous commercial and laboratory developed tests	• Modeling current and future diagnostic needs by country • Improved collaboration between key stakeholders

Market Landscape – Treatment

Current Market Access Overview

Benznidazole is currently produced by Grupo Insud (Argentina; trade name: Abarax; the group includes Chemo Group and Exeltis, with shareholder stake in Laboratorio Elea) and by LAFEPE (Laboratório Farmacêutico de Pernambuco, Brazil). According to information provided by the manufacturer, Abarax is distributed worldwide in over 15 different countries, excluding Brazil, which is supplied by its domestic manufacturer LAFEPE. The price of benznidazole varies by region, but cost estimates typically range between US$40-$50 for a full treatment course in endemic countries, and US$250-$300 in non-endemic countries. Over one million tablets of benznidazole were sold in 2019, representing over 10,000 treated patients. Both adult and pediatric formulations of benznidazole are available in numerous Latin American countries, with the pediatric formulation also approved in the United States for children between 2-12 years of age. The Mundo Sano Foundation has also committed to donating benznidazole free of charge for treatment of congenital Chagas disease in all countries who request support via a joint WHO/PAHO collaboration, though scale up has been limited, primarily due to low case-finding rates of Chagas disease in newborns.

Nifurtimox is currently produced by Bayer (Germany) and Gador (Argentina). According to information provided by Bayer, the company has provided nifurtimox free of charge through a donation programme with WHO over the last 2 decades. Over the last five years, individuals in 18 endemic countries have received nifurtimox, and over 1 million tablets were provided in 2019. A new pediatric formulation is also currently under review by the U.S. Food and Drug Administration for use in children starting from birth. As the drug has been entirely donated,

there is no pricing information available for nifurtimox, though that may change if private markets, such as the United States, begin purchasing the drug once it is registered there. No published data is available yet for nifurtimox produced by Gador.

Based on distribution numbers of benznidazole and nifurtimox, an estimated 20,000-30,000 persons received treatment for Chagas disease in 2019, which aligns with estimates that less than 1% of persons with Chagas disease infection currently receive treatment.[11] No estimates are available on the proportion of congenital, pediatric, and adult cases this would represent. WHO is currently working on compiling available treatment data and plans to release additional information later in 2020 regarding treatment numbers for Chagas disease.

Market Access Barriers and Opportunities

Based on the two treatment options currently available and key stakeholder input, several market opportunities, needs, and potential innovations have been identified (Table 3). These fall into the following three areas:

1) Expansion of Existing Treatments

Demand and Adoption Barriers: Compared to the number of people infected with Chagas disease, the number of persons treated every year is strikingly low. A constellation of challenges limits the reach of current treatments, including poor linkage from diagnosis to care and treatment programs, lack of sustained political will around Chagas disease in the face of many other competing health priorities, limited awareness among providers and patients to screen and treat for Chagas disease, and difficulties in convincing patients to take several months of treatment in complicated dosing structures, when they are perhaps asymptomatic, especially when the majority of individuals will not have complications, when the drugs can have adverse side effects, and when the majority of chronic disease patients who are treated may not be cured or even know if the treatment has been effective.

Opportunity: Several opportunities exist to address barriers to treatment demand, access and uptake. New educational campaigns, data on the treatment efficacy of different regimens, and shorter course and easier to tolerate treatment formulations may all help alleviate some of these factors. Additionally, linking testing to treatment is critical to reduce loss to follow-up and to illustrate how testing and treatment programmes can be implemented in different geographic settings.

2) New Treatments for Chagas Disease

Innovation and Availability Barriers: The current treatments for Chagas disease themselves also have limitations. Even when individuals are diagnosed and initiated onto treatment, there can be low adherence and treatment completion rates, particularly among infants where caretakers may not always have the resources or ability to bring them back to a health center for clinical care and treatment.[6,48] In addition current treatment regimens are unable to be used during pregnancy, which limits their capacity to prevent mother to child transmission, and their lower efficacy rates in chronic Chagas disease, where the burden of disease is highest, compared to acute disease.

Opportunity: Existing treatments would be complemented by new medications with characteristics such as higher cure rates, better tolerability and improved safety profiles, particularly if formulated for use in pregnant women and children. Shortened treatment regimens of new or existing treatment molecules may address adherence challenges. A target product profile has been suggested for new Chagas disease medications, which can be used as a starting point for the ideal characteristics of a new drug, including high efficacy against all *T. cruzi* subtypes.[49]

3) Market Forecasting for Chagas Disease Treatment

Supply and Delivery Barriers: With only two treatments available and a limited number of manufacturers in operation, the current treatment market has been an area of focus for both the pharmaceutical companies as well as WHO and PAHO in their efforts to provide access to medications. The number of individuals treated and number of medications provided has risen over time, and supply chains have become much more stable. Despite these steps forward, treatment uptake remains limited and variable across different countries, as local registrations expire, health departments prioritize other challenges, and funding for Chagas disease programmes continues to be limited.

Opportunity: Market forecasting that can better model current and future treatment needs could assist with scale up efforts, prevent expiration of unused medicines, and help ensure availability and access to treatment in each country. Close collaboration between key stakeholders of Chagas programmes, including procurement groups, implementation agencies, normative bodies, and manufacturers, will provide the market intelligence needed to support Chagas control targets.

TABLE 3 Treatment Market Access Barriers and Opportunities

Area	Access Barriers	Opportunities
Expansion of Existing Treatments	• Lack of awareness • Evidence gaps regarding currently available treatments • Overcoming psychosocial barriers to treatment	• New educational tools • Data on efficacy of different treatment regimens
New Treatments for Chagas Disease	• Limited efficacy for treatment of chronic Chagas disease • No ability to treat pregnant women until after delivery	• Drugs with higher cure rates for chronic disease • Antiparasitic treatments safe in pregnancy and for children. • Shorter course, easier to tolerate treatments
Market Forecasting for Treatment	• Limited and varied usage of currently available treatments	• Modeling current and future treatment needs by country • Improved collaboration between key stakeholders

CONCLUSION

Over the last few decades, significant advances have been made in the prevention, diagnosis, and treatment of Chagas disease; however, significant progress still needs to be made in order to meet global and regional Chagas disease elimination targets, and to end mother-to-child transmission of the disease. With less than 1% of persons infected with *T. cruzi* estimated to receive diagnosis and treatment, the market stands wide open for expansion of currently available technologies and treatments and the introduction of new innovations. These efforts will complement continued prevention efforts for Chagas disease focused on vector control. The substantial economic and health consequences of Chagas disease, coupled with the disproportionate burden on poor and marginalized communities creates a strong imperative to bring attention and action to this neglected tropical disease. Renewed political will, together with commitment of funders, and increased awareness of the disease at all levels of society is critical to ensuring the prevention and elimination of Chagas disease and expanding the reach of live-saving diagnostics and treatments.

REFERENCES

1. Chagas disease. https://www.who.int/news-room/fact-sheets/detail/chagas-disease-(american-trypanosomiasis). Accessed January 29, 2020.
2. PAHO. Chagas disease. https://www.paho.org/hq/index.php?option=com_topics&view=article&id=10&Itemid=40743&lang=en. Accessed January 29, 2020.
3. PAHO. EMTCT Plus. 2017.
4. CDC. Chagas Disease. https://www.cdc.gov/parasites/chagas/index.html. Published April 12, 2019. Accessed February 24, 2020.
5. Alonso-Padilla J, Cortés-Serra N, Pinazo MJ, et al. Strategies to enhance access to diagnosis and treatment for Chagas disease patients in Latin America. Expert Rev Anti Infect Ther. 2019;17(3):145-157. doi:10.1080/14787210.2019.1577731
6. Messenger LA, Bern C. Congenital Chagas disease: current diagnostics, limitations and future perspectives. Curr Opin Infect Dis. 2018;31(5):415-421. doi:10.1097/QCO.0000000000000478
7. Picado A, Angheben A, Marchiol A, et al. Development of Diagnostics for Chagas Disease: Where Should We Put Our Limited Resources? PLoS Negl Trop Dis. 2017;11(1):e0005148. doi:10.1371/journal.pntd.0005148
8. PATH. Diagnostic Gaps and Recommendations for Chagas Disease. https://path.org/resources/diagnostic-gaps-chagas-disease/. Accessed January 29, 2020.
9. Kratz JM. Drug discovery for chagas disease: A viewpoint. Acta Trop. 2019;198:105107. doi:10.1016/j.actatropica.2019.105107
10. Ribeiro V, Dias N, Paiva T, et al. Current trends in the pharmacological management of Chagas disease. Int J Parasitol Drugs Drug Resist. 2019;12:7-17. doi:10.1016/j.ijpddr.2019.11.004
11. Ribeiro I, Sevcsik A-M, Alves F, et al. New, improved treatments for Chagas disease: from the R&D pipeline to the patients. PLoS Negl Trop Dis. 2009;3(7):e484. doi:10.1371/journal.pntd.0000484
12. PAHO. Diagnosis and Treatment of Chagas disease in 21 endemic countries: the Americas, 2010-2016. 2018.
13. PAHO. An integrated, Sustainable Framework to Elimination of Communicable Diseases in the Americas. 2019. http://iris.paho.org/xmlui/handle/123456789/51106.
14. WHO. Accelerating work to overcome the global impact of neglected tropical disease. A roadmap for implementation. 2012.
15. PAHO. Guidelines for the diagnosis and treatment of Chagas disease. Guidelines for

the diagnosis and treatment of Chagas disease. http://iris.paho.org/xmlui/bitstream/handle/123456789/49653/9789275120439_eng.pdf?sequence=6&isAllowed=y. Published 2019. Accessed January 29, 2020.

16. Carlier Y, Altcheh J, Angheben A, et al. Congenital Chagas disease: Updated recommendations for prevention, diagnosis, treatment, and follow-up of newborns and siblings, girls, women of childbearing age, and pregnant women. PLoS Negl Trop Dis. 2019;13(10):e0007694. doi:10.1371/journal.pntd.0007694

17. Brenière SF, Waleckx E, Barnabé C. Over Six Thousand *Trypanosoma cruzi* Strains Classified into Discrete Typing Units (DTUs): Attempt at an Inventory. PLoS Negl Trop Dis. 2016;10(8):e0004792. doi:10.1371/journal.pntd.0004792

18. WHO. Anti-Trypasosoma cruzi Assays. 2010. https://www.who.int/diagnostics_laboratory/publications/anti_t_cruzi_assays.pdf. Accessed February 4, 2020.

19. Brasil PEAA, De Castro L, Hasslocher-Moreno AM, Sangenis LHC, Braga JU. ELISA versus PCR for diagnosis of chronic Chagas disease: systematic review and meta-analysis. BMC Infect Dis. 2010;10:337. doi:10.1186/1471-2334-10-337

20. Caicedo Díaz RA, Forsyth C, Bernal OA, et al. Comparative evaluation of immunoassays to improve access to diagnosis for Chagas disease in Colombia. Int J Infect Dis IJID Off Publ Int Soc Infect Dis. 2019;87:100-108. doi:10.1016/j.ijid.2019.07.022

21. Brasil PEAA do, Castro R, Castro L de. Commercial enzyme-linked immunosorbent assay versuspolymerase chain reaction for the diagnosis of chronic Chagas disease: a systematic review and meta-analysis. Mem Inst Oswaldo Cruz. 2016;111(1):1-19. doi:10.1590/0074-02760150296

22. Afonso AM, Ebell MH, Tarleton RL. A systematic review of high quality diagnostic tests for Chagas disease. PLoS Negl Trop Dis. 2012;6(11):e1881. doi:10.1371/journal.pntd.0001881

23. Granjon E, Dichtel-Danjoy M-L, Saba E, Sabino E, Campos de Oliveira L, Zrein M. Development of a Novel Multiplex Immunoassay Multi-cruzi for the Serological Confirmation of Chagas Disease. PLoS Negl Trop Dis. 2016;10(4):e0004596. doi:10.1371/journal.pntd.0004596

24. Álvarez-Hernández DA do, Franyuti-Kelly GA, Díaz-López-Silva R, González-Chávez AM, González-Hermosillo-Cornejo D, Vázquez-López R. Chagas disease: Current perspectives on a forgotten disease. In: ; 2016. doi:10.1016/j.hgmx.2016.09.010

25. Pérez-Ayala A, Fradejas I, Rebollo L, Lora-Pablos D, Lizasoain M, Herrero-Martínez JM. Usefulness of the ARCHITECT Chagas® assay as a single test for the diagnosis of chronic Chagas disease. Trop Med Int Health TM IH. 2018;23(6):634-640. doi:10.1111/tmi.13063

26. Praast G, Herzogenrath J, Bernhardt S, Christ H, Sickinger E. Evaluation of the Abbott ARCHITECT Chagas prototype assay. Diagn Microbiol Infect Dis. 2011;69(1):74-81.

doi:10.1016/j.diagmicrobio.2010.08.019

27. Flores-Chavez MD, Sambri V, Schottstedt V, et al. Evaluation of the Elecsys Chagas Assay for Detection of *Trypanosoma cruzi*-Specific Antibodies in a Multicenter Study in Europe and Latin America. J Clin Microbiol. 2018;56(5). doi:10.1128/JCM.01446-17

28. Angheben A, Buonfrate D, Cruciani M, et al. Rapid immunochromatographic tests for the diagnosis of chronic Chagas disease in at-risk populations: A systematic review and meta-analysis. PLoS Negl Trop Dis. 2019;13(5):e0007271. doi:10.1371/journal.pntd.0007271

29. Messenger LA, Gilman RH, Verastegui M, et al. Toward Improving Early Diagnosis of Congenital Chagas Disease in an Endemic Setting. Clin Infect Dis Off Publ Infect Dis Soc Am. 2017;65(2):268-275. doi:10.1093/cid/cix277

30. Mayta H, Romero YK, Pando A, et al. Improved DNA extraction technique from clot for the diagnosis of Chagas disease. PLoS Negl Trop Dis. 2019;13(1):e0007024. doi:10.1371/journal.pntd.0007024

31. Castro-Sesquen YE, Gilman RH, Galdos-Cardenas G, et al. Use of a novel chagas urine nanoparticle test (chunap) for diagnosis of congenital chagas disease. PLoS Negl Trop Dis. 2014;8(10):e3211. doi:10.1371/journal.pntd.0003211

32. Castro-Sesquen YE, Gilman RH, Mejia C, et al. Use of a Chagas Urine Nanoparticle Test (Chunap) to Correlate with Parasitemia Levels in *T. cruzi*/HIV Co-infected Patients. PLoS Negl Trop Dis. 2016;10(2):e0004407. doi:10.1371/journal.pntd.0004407

33. Besuschio SA, Llano Murcia M, Benatar AF, et al. Analytical sensitivity and specificity of a loop-mediated isothermal amplification (LAMP) kit prototype for detection of *Trypanosoma cruzi* DNA in human blood samples. PLoS Negl Trop Dis. 2017;11(7):e0005779. doi:10.1371/journal.pntd.0005779

34. Rivero R, Bisio M, Velázquez EB, et al. Rapid detection of *Trypanosoma cruzi* by colorimetric loop-mediated isothermal amplification (LAMP): A potential novel tool for the detection of congenital Chagas infection. Diagn Microbiol Infect Dis. 2017;89(1):26-28. doi:10.1016/j.diagmicrobio.2017.06.012

35. Chatelain E. Chagas disease drug discovery: toward a new era. J Biomol Screen. 2015;20(1):22-35. doi:10.1177/1087057114550585

36. Sulleiro E, Muñoz-Calderon Aq, Schijman AG. Role of nucleic acid amplification assays in monitoring treatment response in chagas disease: Usefulness in clinical trials. Acta Trop. 2019;199:105120. doi:10.1016/j.actatropica.2019.105120

37. Torrico F, Gascon J, Ortiz L, et al. Treatment of adult chronic indeterminate Chagas disease with benznidazole and three E1224 dosing regimens: a proof-of-concept, randomised, placebo-controlled trial. Lancet Infect Dis. 2018;18(4):419-430. doi:10.1016/S1473-3099(17)30538-8

38. Morillo CA, Waskin H, Sosa-Estani S, et al. Benznidazole and Posaconazole in Eliminating Parasites in Asymptomatic *T. Cruzi* Carriers: The STOP-CHAGAS Trial. J Am Coll Cardiol. 2017;69(8):939-947. doi:10.1016/j.jacc.2016.12.023

39. Álvarez MG, Hernández Y, Bertocchi G, et al. New Scheme of Intermittent Benznidazole Administration in Patients Chronically Infected with *Trypanosoma cruzi*: a Pilot Short-Term Follow-Up Study with Adult Patients. Antimicrob Agents Chemother. 2016;60(2):833-837. doi:10.1128/AAC.00745-15

40. Sosa-Estani S, Viotti R, Segura EL. Therapy, diagnosis and prognosis of chronic Chagas disease: insight gained in Argentina. Mem Inst Oswaldo Cruz. 2009;104 Suppl 1:167-180. doi:10.1590/s0074-02762009000900023

41. Sicuri E, Muñoz J, Pinazo MJ, et al. Economic evaluation of Chagas disease screening of pregnant Latin American women and of their infants in a non endemic area. Acta Trop. 2011;118(2):110-117. doi:10.1016/j.actatropica.2011.02.012

42. Requena-Méndez A, Bussion S, Aldasoro E, et al. Cost-effectiveness of Chagas disease screening in Latin American migrants at primary health-care centres in Europe: a Markov model analysis. Lancet Glob Health. 2017;5(4):e439-e447. doi:10.1016/S2214-109X(17)30073-6

43. Verani JR, Seitz A, Gilman RH, et al. Geographic variation in the sensitivity of recombinant antigen-based rapid tests for chronic *Trypanosoma cruzi* infection. Am J Trop Med Hyg. 2009;80(3):410-415.

44. Egüez KE, Alonso-Padilla J, Terán C, et al. Rapid diagnostic tests duo as alternative to conventional serological assays for conclusive Chagas disease diagnosis. PLoS Negl Trop Dis. 2017;11(4):e0005501. doi:10.1371/journal.pntd.0005501

45. Shah V, Ferrufino L, Gilman RH, et al. Field evaluation of the InBios Chagas detect plus rapid test in serum and whole-blood specimens in Bolivia. Clin Vaccine Immunol CVI. 2014;21(12):1645-1649. doi:10.1128/CVI.00609-14

46. Alonso-Vega C, Billot C, Torrico F. Achievements and challenges upon the implementation of a program for national control of congenital Chagas in Bolivia: results 2004-2009. PLoS Negl Trop Dis. 2013;7(7):e2304. doi:10.1371/journal.pntd.0002304

47. Porrás AI, Yadon ZE, Altcheh J, et al. Target Product Profile (TPP) for Chagas Disease Point-of-Care Diagnosis and Assessment of Response to Treatment. PLoS Negl Trop Dis. 2015;9(6):e0003697. doi:10.1371/journal.pntd.0003697

48. Carlier Y, Sosa-Estani S, Luquetti AO, Buekens P. Congenital Chagas disease: an update. Mem Inst Oswaldo Cruz. 2015;110(3):363-368. doi:10.1590/0074-02760140405

49. Rao SPS, Barrett MP, Dranoff G, et al. Drug Discovery for Kinetoplastid Diseases: Future Directions. ACS Infect Dis. 2019;5(2):152-157. doi:10.1021/acsinfecdis.8b00298

ANNEX IA. PRODUCT PROFILES OF COMMERCIALLY AVAILABLE RAPID DIAGNOSTIC TESTS*

CHAGAS DETECT™ PLUS RAPID TEST	
Manufacturer	InBios International, Inc.
Product Photo	
PRODUCT SPECIFICATIONS	
Intended Use Summary	Rapid test for the detection of IgG antibodies to T*rypanosoma cruzi*, useful for diagnosis of Chagas disease
Target User of Test	Primary healthcare worker, Laboratory technician
Target Population	Persons under evaluation for chronic Chagas disease
Level of Health System	All levels, including clinic setting, field setting, and hospital-based laboratory
Analyte/Biomarker Detected	IgG antibodies to T*rypanosoma cruzi*
Materials provided	Test devices, gold solution, chase buffer type A
Materials required but not provided	Microsafe capillary tubes or pipettor, timer, lancets or phlebotomy supplies, alcohol wipes, gauze
Sample Type	Whole blood, serum
Sample Volume	5 microliters
Time to Result	20 minutes
Result Output	Visible red line
Protocol Complexity/ # of steps	1. Add specimen to sample pad 2. Add one drop of gold solution 3. Wait 5 minutes 4. Add one drop of chase buffer type A 5. Read results in 15 minutes
Controls	Visible internal red control line
Shelf Life	24 months
Storage	20-30°C

* Several other RDTs in development have the potential to eliminate the need for multiple tests and are in the pipeline, but limited information is publicly available. This includes the RT-Bio two line cassette developed by Fiocruz and currently under review by ANVISA.

PRODUCT PERFORMANCE	
Sensitivity/Specificity	-Product insert study 1: 100% sensitivity, 100% specificity in 200 negative matched serum and whole blood samples from US -Product insert study 2: 100% sensitivity, 100% specificity in 542 negative matched serum and whole blood samples from Chile -Product insert study 3: 96.6% sensitivity in 473 serum samples, and 97.0% sensitivity in 473 matched whole blood samples from persons previously diagnosed with Chagas disease in Chile -Product insert study 4: 100% sensitivity, 87.1% specificity in 108 serum samples from Bolivia, with 98.7% sensitivity, 96.8% specificity in 108 matched whole blood samples -Product insert study 5: 99.2% sensitivity, 96.7% specificity in 243 serum samples from pregnant women in Bolivia, with 95.1% sensitivity, 98.3% specificity in 243 matched whole blood samples -Product insert study 6: 100% sensitivity, 98.4% specificity in 200 pediatric serum samples from Bolivia -2014 published study: 96.2% sensitivity, 98.8% specificity in 388 whole blood samples and 99.3% sensitivity, 96.9% specificity in 585 serum samples from Bolivia[1] -2017 published study: 100% sensitivity, 99.3% specificity in 342 serum samples from Bolivia[2] -2019 published study: 98.4% sensitivity, 87.1% specificity in 685 whole blood samples from Bolivia[3] -2019 published study: 97.4% sensitivity, 92.3% specificity in 800 plasma samples from US blood donors[4]
Invalid Rate	None reported
Restrictions on Use	Single use test, do not add excess gold solution, do not read results after 20 minutes of total test time
PRODUCT AVAILABILITY	
Regulatory Status	CE mark / US FDA clearance
Other Country Registrations	Information available from manufacturer on request
Countries Where Available	Information available from manufacturer on request
Pricing	Information available from manufacturer on request
REFERENCES	
Data Sources	Product insert, Peer-reviewed literature, Manufacturer input

1. Shah V, Ferrufino L, Gilman RH, et al. Field evaluation of the InBios Chagas detect plus rapid test in serum and whole-blood specimens in Bolivia. Clin Vaccine Immunol CVI. 2014;21(12):1645-1649. doi:10.1128/CVI.00609-14

2. Egüez KE, Alonso-Padilla J, Terán C, et al. Rapid diagnostic tests duo as alternative to conventional serological assays for conclusive Chagas disease diagnosis. PLoS Negl Trop Dis. 2017;11(4):e0005501. doi:10.1371/journal.pntd.0005501

3. Lozano D, Rojas L, Méndez S, et al. Use of rapid diagnostic tests (RDTs) for conclusive diagnosis of chronic Chagas disease - field implementation in the Bolivian Chaco region. PLoS Negl Trop Dis. 2019;13(12):e0007877. doi:10.1371/journal.pntd.0007877

4. Whitman JD, Bulman CA, Gunderson EL, et al. Chagas Disease Serological Test Performance in U.S. Blood Donor Specimens. J Clin Microbiol. 2019;57(12). doi:10.1128/JCM.01217-19

CHAGAS STAT-PAK ASSAY	
Manufacturer	Chembio Diagnostic Systems, Inc.
Product Photo	
PRODUCT SPECIFICATIONS	
Intended Use Summary	Screening test for the detection of antibodies to *Trypanosoma cruzi*, used in the diagnosis of Chagas disease
Target User of Test	Primary healthcare worker, Laboratory technician
Target Population	Persons under evaluation for chronic Chagas disease
Level of Health System	All levels, including clinic setting, field setting, and hospital-based laboratory
Analyte/Biomarker Detected	Antibodies to *Trypanosoma cruzi*
Materials provided	Test devices, microsafe tubes for fingerstick whole blood, sample diluent
Materials required but not provided	Timer, sterile single use lancets or phlebotomy equipment, sterile alcohol swabs, pipettor for serum, plasma or venous whole blood, centrifuge for serum or plasma preparation
Sample Type	Whole blood, serum, plasma
Sample Volume	10 microliters – whole blood 5 microliters – serum, plasma
Time to Result	15 minutes
Result Output	Visible pink/purple line
Protocol Complexity/ # of steps	Add specimen to sample well Add six drops of diluent to sample well Read results in 15 minutes
Controls	Visible internal pink/purple control line
Shelf Life	24 months
Storage	8-30°C
PRODUCT PERFORMANCE	
Sensitivity/Specificity	-Product insert study 1: 98.5% sensitivity, 96.0% specificity in 350 serum samples from Brazil -Product insert study 2: 100% sensitivity, 98.6% specificity from 352 serum samples from Honduras, Venezuela, Bolivia, and Argentina -Product insert study 3: 99.8% sensitivity, 100% specificity in 5998 serum samples from Honduras, El Salvador, and Nicaragua -2008 published study: 93.4% sensitivity, 99.0% specificity in 1913 fingerstick whole blood samples from Bolivia[1] -2008 published study: 94.6% sensitivity, 99.0% specificity in 2495 umbilical cord blood samples in Argentina, Bolivia, Honduras, and Mexico[2]

	-2009 published study: 99.3% sensitivity, 100% specificity in 320 serum samples from Honduras[3] -2009 published study: 87.5% sensitivity, 100% specificity in 93 serum samples from Bolivia; 26.6%-33.0% sensitivity (depending on user), 99.6% specificity in 332 serum samples from Peru[4] -2009 published study: 94.7% sensitivity, 97.3% specificity in 2484 whole blood samples from Bolivia[5] -2010 published study: 95.2% sensitivity, 99.9% specificity in whole blood and 96.0% sensitivity, 99.8% specificity in serum from 125 Latin-American migrants in Switzerland[6] -2011 published study: 95.3% sensitivity, 99.5% specificity in 375 serum samples from Argentina[7] -2014 published study: 87.2% sensitivity, 93.2% specificity in 424 serum samples from Japan, France, Spain, United States, Argentina, Brazil, Colombia, Costa Rica, and Mexico[8] -2017 published study: 100% sensitivity, 99.3% specificity in 342 serum samples from Bolivia[9] -2019 published study: 97.7% sensitivity, 97.4% specificity in 685 whole blood samples from Bolivia[10]
Invalid Rate	None reported
Restrictions on Use	Single use test, do not read results after 15 minutes or add excess sample volume
PRODUCT AVAILABILITY	
Regulatory Status	CE mark
Country Registrations	Colombia, Bolivia, Mexico,Peru, Guatemala, Honduras, El Salvador, Chile , Paraguay
Countries Where Available	Bolivia, Paraguay, Honduras, Chile
Pricing	US$2.15/test, lowest price PAHO-Strategic Fund
REFERENCES	
Data Sources	Product insert, Peer-reviewed literature, Manufacturer input

1. Roddy P, Goiri J, Flevaud L, et al. Field evaluation of a rapid immunochromatographic assay for detection of *Trypanosoma cruzi* infection by use of whole blood. J Clin Microbiol. 2008;46(6):2022-2027. doi:10.1128/JCM.02303-07

2. Sosa-Estani S, Gamboa-León MR, Del Cid-Lemus J, et al. Use of a rapid test on umbilical cord blood to screen for *Trypanosoma cruzi* infection in pregnant women in Argentina, Bolivia, Honduras, and Mexico. Am J Trop Med Hyg. 2008;79(5):755-759.

3. Ji MJ, Noh JS, Cho BK, Cho YS, Kim SJ, Yoon BS. [Evaluation of SD BIOLINE Chagas Ab Rapid kit]. Korean J Lab Med. 2009;29(1):48-52. doi:10.3343/kjlm.2009.29.1.48

4. Verani JR, Seitz A, Gilman RH, et al. Geographic variation in the sensitivity of recombinant antigen-based rapid tests for chronic *Trypanosoma cruzi* infection. Am J Trop Med Hyg. 2009;80(3):410-415.

5. Chippaux J-P, Santalla JA, Postigo JR, et al. Sensitivity and specificity of Chagas Stat-Pak test in Bolivia. Trop Med Int Health TM IH. 2009;14(7):732-735. doi:10.1111/j.1365-3156.2009.02288.x

6. Chappuis F, Mauris A, Holst M, et al. Validation of a rapid immunochromatographic assay for diagnosis of *Trypanosoma cruzi* infection among Latin-American Migrants in Geneva, Switzerland. J Clin Microbiol. 2010;48(8):2948-2952. doi:10.1128/JCM.00774-10

7. Barfield CA, Barney RS, Crudder CH, et al. A highly sensitive rapid diagnostic test for Chagas disease that utilizes a recombinant *Trypanosoma cruzi* antigen. IEEE Trans Biomed Eng. 2011;58(3):814-817. doi:10.1109/TBME.2010.2087334

8. Sánchez-Camargo CL, Albajar-Viñas P, Wilkins PP, et al. Comparative evaluation of 11 commercialized rapid diagnostic tests for detecting *Trypanosoma cruzi* antibodies in serum banks in areas of endemicity and nonendemicity. J Clin Microbiol. 2014;52(7):2506-2512. doi:10.1128/JCM.00144-14

9. Egüez KE, Alonso-Padilla J, Terán C, et al. Rapid diagnostic tests duo as alternative to conventional serological assays for conclusive Chagas disease diagnosis. PLoS Negl Trop Dis. 2017;11(4):e0005501. doi:10.1371/journal.pntd.0005501

10. Lozano D, Rojas L, Méndez S, et al. Use of rapid diagnostic tests (RDTs) for conclusive diagnosis of chronic Chagas disease - field implementation in the Bolivian Chaco region. PLoS Negl Trop Dis. 2019;13(12):e0007877. doi:10.1371/journal.pntd.0007877

ONESTEP CHAGAS RAPIDIP™ INSTATEST	
Manufacturer	Cortez Diagnostics
PRODUCT SPECIFICATIONS	
Intended Use Summary	Detection of antibodies to *Trypanosoma cruzi*
Target User of Test	Laboratory technician
Target Population	Persons under evaluation for chronic Chagas disease
Level of Health System	Laboratory setting
Analyte/Biomarker Detected	Antibodies to *Trypanosoma cruzi*
Materials provided	Test devices, chase buffer
Materials required but not provided	Pipettor, timer, test tubes, alcohol wipes, phlebotomy supplies, centrifuge
Sample Type	Whole blood, Serum
Sample Volume	20 microliters of whole blood 10 microliters of serum
Time to Result	10 minutes
Result Output	Visible red line
Protocol Complexity/ # of steps	1. Add sample to test strip area beneath arrow 2. Add 3-4 drops of chase buffer into test tube 3. Place test strip into test tube 4. Read results in 10 minutes
Controls	Visible red internal control line
Shelf Life	
Storage	20-30°C
PRODUCT PERFORMANCE	
Sensitivity/Specificity	
Invalid Rate	
Restrictions on Use	Single use test, do not read results after more than 15 minutes
PRODUCT AVAILABILITY	
Regulatory Status	CE mark
Other Country Registrations	
Countries Where Available	
Pricing	
REFERENCES	
Data Sources	Product insert

ONSITE CHAGAS AB COMBO RAPID TEST	
Manufacturer	CTK Biotech
PRODUCT SPECIFICATIONS	
Intended Use Summary	Detection of IgG antibodies to T*rypanosoma cruzi*
Target User of Test	Primary healthcare worker, Laboratory technician
Target Population	Persons under evaluation for chronic Chagas disease
Level of Health System	All levels, including clinic setting, field setting, and hospital-based laboratory
Analyte/Biomarker Detected	IgG antibodies to *Trypanosoma cruzi*
Materials provided	Test devices, droppers, sample diluent
Materials required but not provided	Timer, lancets or phlebotomy supplies, alcohol wipes
Sample Type	Whole blood, serum, plasma
Sample Volume	40-50 microliters of whole blood 20 microliters of serum or plasma
Time to Result	15 minutes
Result Output	Visible coloured line
Protocol Complexity/ # of steps	
Controls	Visible coloured internal control line
Shelf Life	
Storage	2-30°C
PRODUCT PERFORMANCE	
Sensitivity/Specificity	-Product insert study 1: 92.9% sensitivity, 100% specificity -2009 published study: 97.9% sensitivity, 98.8% specificity in 320 serum samples from Honduras[1] -2014 published study: 90.1% sensitivity, 91% specificity in 424 serum samples from Japan, France, Spain, United States, Argentina, Brazil, Colombia, Costa Rica, and Mexico[2]
Invalid Rate	None reported
Restrictions on Use	Single use test
PRODUCT AVAILABILITY	
Regulatory Status	CE mark
Other Country Registrations	
Countries Where Available	
Pricing	
REFERENCES	
Data Sources	Manufacturer website, Peer-reviewed literature

1. Ji MJ, Noh JS, Cho BK, Cho YS, Kim SJ, Yoon BS. [Evaluation of SD BIOLINE Chagas Ab Rapid kit]. Korean J Lab Med. 2009;29(1):48-52. doi:10.3343/kjlm.2009.29.1.48

2. Sánchez-Camargo CL, Albajar-Viñas P, Wilkins PP, et al. Comparative evaluation of 11 commercialized rapid diagnostic tests for detecting *Trypanosoma cruzi* antibodies in serum banks in areas of endemicity and nonendemicity. J Clin Microbiol. 2014;52(7):2506-2512. doi:10.1128/JCM.00144-14

SD BIOLINE CHAGAS AB RAPID TEST	
Manufacturer	Abbott
PRODUCT SPECIFICATIONS	
Intended Use Summary	Screening test for the detection of antibodies to *Trypanosoma cruzi*
Target User of Test	Primary healthcare worker, Laboratory technician
Target Population	Persons under evaluation for chronic Chagas disease
Level of Health System	Clinics and laboratories
Analyte/Biomarker Detected	Antibodies to *Trypanosoma cruzi*
Materials provided	Test devices
Materials required but not provided	Pipettor, timer, phlebotomy supplies, alcohol wipes
Sample Type	Whole blood, serum, plasma
Sample Volume	100 microliters
Time to Result	15 minutes
Result Output	Visible coloured line
Protocol Complexity/ # of steps	1. Add specimen to sample well 2. Read results in 15 minutes
Controls	Visible coloured internal control line
Shelf Life	24 months
Storage	1-30°C
PRODUCT PERFORMANCE	
Sensitivity/Specificity	-Product insert study 1: 99.3% sensitivity, 100% specificity in 280 samples from Honduras -2014 published study: 90.7% sensitivity, 94% specificity in 424 serum samples from Japan, France, Spain, United States, Argentina, Brazil, Colombia, Costa Rica, and Mexico[1]
Invalid Rate	None reported
Restrictions on Use	Single use test, do not read results after 15 minutes
PRODUCT AVAILABILITY	
Regulatory Status	CE mark
Other Country Registrations	
Countries Where Available	Brazil, Argentina, Colombia, Mexico
Pricing	
REFERENCES	
Data Sources	Product insert, Peer-reviewed literature, Manufacturer input

1. Sánchez-Camargo CL, Albajar-Viñas P, Wilkins PP, et al. Comparative evaluation of 11 commercialized rapid diagnostic tests for detecting *Trypanosoma cruzi* antibodies in serum banks in areas of endemicity and nonendemicity. J Clin Microbiol. 2014;52(7):2506-2512. doi:10.1128/JCM.00144-14

SERODIA CHAGAS TEST	
Manufacturer	Fujirebio
PRODUCT SPECIFICATIONS	
Intended Use Summary	Particle agglutination *Trypanosoma cruzi* antibody test
Target User of Test	Laboratory technician
Target Population	Persons under evaluation for chronic Chagas disease
Level of Health System	Laboratory setting
Analyte/Biomarker Detected	Antibodies to *Trypanosoma cruzi*
Materials provided	
Materials required but not provided	
Sample Type	
Sample Volume	25 microliters
Time to Result	120 minutes
Result Output	Visible particle agglutination
Protocol Complexity/ # of steps	
Controls	
Shelf Life	
Storage	2-8°C
PRODUCT PERFORMANCE	
Sensitivity/Specificity	-2014 published study: 94.2% sensitivity, 94.7% specificity in 424 serum samples from Japan, France, Spain, United States, Argentina, Brazil, Colombia, Costa Rica, and Mexico[1]
Invalid Rate	
Restrictions on Use	Single use test
PRODUCT AVAILABILITY	
Regulatory Status	Not CE marked
Other Country Registrations	
Countries Where Available	Argentina only
Pricing	
REFERENCES	
Data Sources	Manufacturer website, Peer-reviewed literature

1. Sánchez-Camargo CL, Albajar-Viñas P, Wilkins PP, et al. Comparative evaluation of 11 commercialized rapid diagnostic tests for detecting *Trypanosoma cruzi* antibodies in serum banks in areas of endemicity and nonendemicity. J Clin Microbiol. 2014;52(7):2506-2512. doi:10.1128/JCM.00144-14

SIMPLE CHAGAS WB TEST	
Manufacturer	Operon
Product Photo	
PRODUCT SPECIFICATIONS	
Intended Use Summary	Detection of antibodies specific to *Trypanosoma cruzi*
Target User of Test	Primary healthcare worker, Laboratory technician
Target Population	Persons under evaluation for chronic Chagas disease
Level of Health System	All levels, including clinic setting, field setting, and hospital-based laboratory
Analyte/Biomarker Detected	Antibodies to *Trypanosoma cruzi*
Materials provided	Test devices, lancets, blood collection pipette, dilution buffer
Materials required but not provided	Timer, alcohol wipes
Sample Type	Whole blood, Serum, Plasma
Sample Volume	25 microliters of whole blood 125 microliters of a 1:15 dilution of serum
Time to Result	10 minutes
Result Output	Visible red line
Protocol Complexity/ # of steps	1. Add sample to circular window 2. Wait 30-60 seconds 3. Add two drops of dilution buffer 4. Read results in 10 minutes
Controls	Visible blue internal control line
Shelf Life	
Storage	2-30°C

PRODUCT PERFORMANCE	
Sensitivity/Specificity	-Product insert study 1: 94% sensitivity, 96% specificity in 92 blood samples in Spain -Product insert study 2: 93.2% sensitivity, 99.1% specificity in 501 blood samples in Spain -2011 published study: 86.3% sensitivity, 94.4% specificity in 276 fingerprick blood samples from Latin American migrants in Spain[1] -2012 published study: 91.5% sensitivity, 93.6% specificity in 282 venous blood samples, and 86.4% sensitivity, 95% specificity in finger-prick blood samples from Latin American migrants in Spain[2] -2014 published study: 84.9% sensitivity, 70.7% specificity in 424 serum samples from Japan, France, Spain, United States, Argentina, Brazil, Colombia, Costa Rica, and Mexico[3]
Invalid Rate	None reported
Restrictions on Use	Single use test, follow test timing, do not submerge test into the blue area of the test strip
PRODUCT AVAILABILITY	
Regulatory Status	CE mark
Other Country Registrations	
Countries Where Available	
Pricing	
REFERENCES	
Data Sources	Product insert, Peer-reviewed literature

1. Navarro M, Perez-Ayala A, Guionnet A, et al. Targeted screening and health education for Chagas disease tailored to at-risk migrants in Spain, 2007 to 2010. Euro Surveill Bull Eur Sur Mal Transm Eur Commun Dis Bull. 2011;16(38). doi:10.2807/ese.16.38.19973-en

2. Flores-Chavez M, Cruz I, Nieto J, et al. Sensitivity and specificity of an operon immunochromatographic test in serum and whole-blood samples for the diagnosis of *Trypanosoma cruzi* infection in Spain, an area of nonendemicity. Clin Vaccine Immunol CVI. 2012;19(9):1353-1359. doi:10.1128/CVI.00227-12

3. Sánchez-Camargo CL, Albajar-Viñas P, Wilkins PP, et al. Comparative evaluation of 11 commercialized rapid diagnostic tests for detecting *Trypanosoma cruzi* antibodies in serum banks in areas of endemicity and nonendemicity. J Clin Microbiol. 2014;52(7):2506-2512. doi:10.1128/JCM.00144-14

STICK CHAGAS TEST

Manufacturer	Operon
Product Photo	
PRODUCT SPECIFICATIONS	
Intended Use Summary	Detection of antibodies specific to *Trypanosoma cruzi*
Target User of Test	Laboratory technician
Target Population	Persons under evaluation for chronic Chagas disease
Level of Health System	Laboratory setting
Analyte/Biomarker Detected	Antibodies to *Trypanosoma cruzi*
Materials provided	Test devices, dilution buffer
Materials required but not provided	Pipettor, tubes, timer, alcohol wipes, phlebotomy supplies, centrifuge
Sample Type	Serum
Sample Volume	150 microliters of a 1:15 dilution of serum
Time to Result	10 minutes
Result Output	Visible red line
Protocol Complexity/ # of steps	1. Prepare 1:15 dilution of serum by adding 35 microliters of serum to 500 microliters of dilution buffer 2. Place the test vertically in the diluted serum 3. Read results in 10 minutes
Controls	Visible blue internal control line
Shelf Life	
Storage	8-25°C

PRODUCT PERFORMANCE	
Sensitivity/Specificity	-Product insert study 1: 94.5% sensitivity, 88.9% specificity in 265 serum samples from persons possibly affected by Chagas disease -Product insert study 2: 100% sensitivity, 91.9% specificity in 329 serum samples from blood banks and from persons suspected to have Chagas disease in Spain -Product insert study 3: 93.3% sensitivity, 97% specificity in 265 serum samples from Brazil -Product insert study 4: 98.8% sensitivity, 96.2% specificity in 1143 serum samples from Brazil -Product insert study 5: 91% specificity in 100 serum samples from persons with various diseases, >99% specificity in 49 serum samples from healthy persons -2012 published study: 100% sensitivity, 97.9% specificity in 251 well-characterized serum samples, and 100% sensitivity, 91.6% specificity in 450 uncharacterized serum samples from Latin American migrants in Spain[1]
Invalid Rate	None reported
Restrictions on Use	Single use test, follow test timing, do not submerge test into the blue area of the test strip
PRODUCT AVAILABILITY	
Regulatory Status	CE mark
Other Country Registrations	
Countries Where Available	
Pricing	
REFERENCES	
Data Sources	Product insert, Peer-reviewed literature

1. Flores-Chavez M, Cruz I, Nieto J, et al. Sensitivity and specificity of an operon immunochromatographic test in serum and whole-blood samples for the diagnosis of *Trypanosoma cruzi* infection in Spain, an area of nonendemicity. Clin Vaccine Immunol CVI. 2012;19(9):1353-1359. doi:10.1128/CVI.00227-12

WL CHECK CHAGAS TEST	
Manufacturer	Wiener Lab
Product Photo	
PRODUCT SPECIFICATIONS	
Intended Use Summary	Rapid test for the detection of antibodies to antibodies to *Trypanosoma cruzi*
Target User of Test	Primary healthcare worker, Laboratory technician
Target Population	Persons under evaluation for Chagas disease
Level of Health System	All levels, including clinic setting, field setting, and hospital-based laboratory
Analyte/Biomarker Detected	Antibodies to *Trypanosoma cruzi*
Materials provided	Test devices, sodium phosphate buffer, capillary whole blood sample collection device (in some kit sizes)
Materials required but not provided	Pipettor, timer, lancets or phlebotomy supplies, alcohol wipes, gauze
Sample Type	Whole blood, serum, plasma
Sample Volume	40 microliters
Time to Result	25-35 minutes
Result Output	Visible pink/purple red line
Protocol Complexity/ # of steps	1. Add specimen to sample well 2. Wait 10-15 seconds 3. Add three drops of buffer 4. Read results in 25-35 minutes
Controls	Visible internal pink/purple red control line
Shelf Life	18 months
Storage	2-30°C

PRODUCT PERFORMANCE	
Sensitivity/Specificity	-Product insert study 1: 93.9% sensitivity in panel of 326 positive samples -Product insert study 2: 94.0% sensitivity in 83 positive samples from children in endemic areas -Product insert study 3: 98.6% sensitivity in panel of 72 positive samples -Product insert study 4: 100% sensitivity in panel of 106 positive plasma samples and 91.5% sensitivity in 106 matched whole blood samples -Product insert study 5: 97.9% specificity in 1419 serum, plasma, and whole blood samples -Product insert study 6: 98.1% specificity in 313 blood bank samples -2014 published study: 88.7% sensitivity, 97% specificity in 424 serum samples from Japan, France, Spain, United States, Argentina, Brazil, Colombia, Costa Rica, and Mexico[1] -2014 published study: 87.3% sensitivity, 98.8% specificity in 241 whole blood samples and 95.7% sensitivity, 100% specificity in 238 serum samples in Argentina[2]
Invalid Rate	None reported
Restrictions on Use	Single use test, do not read results after 35 minutes
PRODUCT AVAILABILITY	
Regulatory Status	CE mark
Other Country Registrations	
Countries Where Available	
Pricing	
REFERENCES	
Data Sources	Product insert, Peer-reviewed literature, Manufacturer input

1. Sánchez-Camargo CL, Albajar-Viñas P, Wilkins PP, et al. Comparative evaluation of 11 commercialized rapid diagnostic tests for detecting Trypanosoma cruzi antibodies in serum banks in areas of endemicity and nonendemicity. J Clin Microbiol. 2014;52(7):2506-2512. doi:10.1128/JCM.00144-14

2. Mendicino D, Stafuza M, Colussi C, Barco M del, Streiger M, Moretti E. Diagnostic reliability of an immunochromatographic test for Chagas disease screening at a primary health care centre in a rural endemic area. Mem Inst Oswaldo Cruz. 2014;109(8):984-988. doi:10.1590/0074-0276140153

ANNEX IB. PRODUCT PROFILES OF OTHER COMMERCIALLY AVAILABLE DIAGNOSTIC METHODS

LABORATORY-BASED SEROLOGICAL TESTS	
Test Examples (Manufacturer)	Architect Chagas, ESA Chagas (Abbott) Bioelisa Chagas (BioKit) Chagas ELISA (Vircell) Chagas IgG ELISA CE (CTK Biotech) Chagas III (Bios Chile) Chagatek (Lemos) Chagatest (Wiener) Elecsys Chagas (Roche) Hemagen Chagas Kit (Hemagen) Immunocom II (Orgenics) NovaLisa Chagas (NovaTec) Pathozyme Chagas (Omega)
COMMON PRODUCT CHARACTERISTICS	
Intended Use	Detection of IgG antibodies to *T. cruzi*, typically to aid in the diagnosis of chronic Chagas disease
Target user of test	Laboratory technician
Target Population	Persons under evaluation for chronic Chagas disease
Setting	Hospital-based laboratory
Analyte/Biomarker Detected	IgG antibodies to various *T. cruzi* antigens
Equipment/Components	ELISA instrument and test kits (both automated and non-automated systems are available)
Sample Type(s)	Serum, Plasma
Sample Volume	5-20 microliters
Test Capacity	96 samples (most common)
Time to Result	Hours
Result Output	Qualitative, Quantitative (signal/cutoff ratios)
Protocol Complexity	Moderate complexity lab test
Infrastructure Requirements	Clinical laboratory

Controls	Positive and negative kit controls
Shelf Life	1-2 years
Storage	Refrigeration
Regulatory Status	CE mark
Pricing	As low as a few dollars per test, plus cost of instrumentation and maintenance
REFERENCES	
Data Sources	Product inserts, Scientific literature

Note: Since the majority of the tests listed are test kits that can be run on various immunoassay instruments, individual product profiles are not provided, as laboratories will need to verify product performance and characteristics based on the instrument they are using.

1. WHO. Anti-Trypasosoma cruzi Assays. 2010. https://www.who.int/diagnostics_laboratory/publications/anti_t_cruzi_assays.pdf. Accessed February 4, 2020.
2. PATH. Diagnostic Gaps and Recommendations for Chagas Disease. 2016. https://path.org/resources/diagnostic-gaps-chagas-disease/. Accessed January 29, 2020.
3. Afonso AM, Ebell MH, Tarleton RL. A systematic review of high quality diagnostic tests for Chagas disease. PLoS Negl Trop Dis. 2012;6(11):e1881. doi:10.1371/journal.pntd.0001881
4. Álvarez-Hernández DA do, Franyuti-Kelly GA, Díaz-López-Silva R, González-Chávez AM, González-Hermosillo-Cornejo D, Vázquez-López R. Chagas disease: Current perspectives on a forgotten disease. Rev Med Hosp Gen Mex; 2016. doi:10.1016/j.hgmx.2016.09.010
5. Brasil PEAA do, Castro R, Castro L de. Commercial enzyme-linked immunosorbent assay versus polymerase chain reaction for the diagnosis of chronic Chagas disease: a systematic review and meta-analysis. Mem Inst Oswaldo Cruz. 2016;111(1):1-19. doi:10.1590/0074-02760150296

MOLECULAR TESTS*	
Test Examples (Manufacturer)	RealCycler CHAG (Emelca) RealStar Chagas PCR (Altona) Tryanosoma cruzi Real-Time PCR Detection Kit (Viasure)
COMMON PRODUCT CHARACTERISTICS	
Intended Use	Detection of *T. cruzi* DNA, typically to aid in the diagnosis of acute or congenital Chagas disease
Target user of test	Laboratory technician
Target Population	Persons under evaluation for acute/congenital Chagas disease
Setting	Hospital-based laboratory
Analyte/Biomarker Detected	*T. cruzi* DNA sequences
Equipment/Components	PCR instrumentation, DNA extraction methods, and Chagas test kits (no automated systems currently available)
Sample Type(s)	Extracted DNA from blood
Sample Volume	5-20 microliters of extracted DNA
Test Capacity	Typically 24-96 samples, dependent on PCR instrument used
Time to Result	Several Hours
Result Output	Qualitative
Protocol Complexity	High complexity molecular lab training required
Infrastructure Requirements	Molecular diagnostics laboratory
Controls	Positive and negative controls
Shelf Life	1-2 years
Storage	Refrigeration required (2-8°C)
Regulatory Status	CE mark
Pricing	Typically $5-$50 per test plus cost of instrumentation and maintenance
REFERENCES	
Data Sources	Product inserts, Scientific literature

Note: Since the tests listed are test kits that can be run on various PCR instruments, individual product profiles are not provided, as laboratories will need to verify product performance and characteristics based on the instrument they are using.

1. PATH. Diagnostic Gaps and Recommendations for Chagas Disease. 2016. https://path.org/resources/diagnostic-gaps-chagas-disease/. Accessed January 29, 2020.

2. Afonso AM, Ebell MH, Tarleton RL. A systematic review of high quality diagnostic tests for Chagas disease. PLoS Negl Trop Dis. 2012;6(11):e1881. doi:10.1371/journal.pntd.0001881

3. Álvarez-Hernández DA do, Franyuti-Kelly GA, Díaz-López-Silva R, González-Chávez AM, González-Hermosillo-Cornejo D, Vázquez-López R. Chagas disease: Current perspectives on a forgotten disease. Rev Med Hosp Gen Mex; 2016. doi:10.1016/j.hgmx.2016.09.010

4. Brasil PEAA do, Castro R, Castro L de. Commercial enzyme-linked immunosorbent assay versus polymerase chain reaction for the diagnosis of chronic Chagas disease: a systematic review and meta-analysis. Mem Inst Oswaldo Cruz. 2016;111(1):1-19. doi:10.1590/0074-02760150296

* Several other molecular methods are in development and have the potential to increase access to testing, particularly at the point-of-care, but limited information is publicly available.

ANNEX 2. PRODUCT PROFILES OF COMMERCIALLY AVAILABLE TREATMENT METHODS

BENZNIDAZOLE	
Manufacturer(s)	Grupo Insud (Chemo Group, Exeltis, Laboratorio Elea), LAFEPE (Brazil only)
PRODUCT SPECIFICATIONS	
Intended Use	Treatment of Chagas disease
Target Population	Paediatric and Adult patients
Available Dosages	12.5mg, 100mg
Treatment Regimens	Weight-based dosing, twice a day, for 60 days
Adverse Drug Reactions	Allergic dermatitis, Peripheral Neuropathy, Weight loss, insomina and bone-marrow suppression
Country Availability	Distributed in over 15 countries from 2015-2019
Pricing	Estimated $40-50 for full treatment course in endemic regions, $250-$350 in non-endemic regions
Procurement	Purchased through local distributors Donation programme for congenital Chagas
REFERENCES	
Data Sources	Product insert, Manufacturer input, Peer-reviewed literature

1. Álvarez-Hernández DA do, Franyuti-Kelly GA, Díaz-López-Silva R, González-Chávez AM, González-Hermosillo-Cornejo D, Vázquez-López R. Chagas disease: Current perspectives on a forgotten disease. Rev Med Hosp Gen Mex; 2016. doi:10.1016/j.hgmx.2016.09.010
2. Kratz JM. Drug discovery for chagas disease: A viewpoint. Acta Trop. 2019;198:105107. doi:10.1016/j.actatropica.2019.105107
3. Ribeiro V, Dias N, Paiva T, et al. Current trends in the pharmacological management of Chagas disease. Int J Parasitol Drugs Drug Resist. 2019;12:7-17. doi:10.1016/j.ijpddr.2019.11.004

NIFURTIMOX	
Manufacturer(s)	Bayer, Gador (Argentina only)
PRODUCT SPECIFICATIONS	
Intended Use	Treatment of Chagas disease
Target Population	Paediatric and Adult patients
Available Dosages	30mg, 120mg
Treatment Regimens	Weight-based dosing, 3-4 times a day, 60-90 days
Adverse Drug Reactions	Weight loss, Polyneuropathy, Nausea, Vomiting, Headache, Dizziness
Country Availability	Distributed in over 15 countries from 2015-2019
Pricing	Free of charge, via Bayer donation programme through WHO
Procurement	Worldwide donation programme (Bayer)
REFERENCES	
Data Sources	Product insert, Manufacturer input, Peer-reviewed literature

1. Álvarez-Hernández DA do, Franyuti-Kelly GA, Díaz-López-Silva R, González-Chávez AM, González-Hermosillo-Cornejo D, Vázquez-López R. Chagas disease: Current perspectives on a forgotten disease. Rev Med Hosp Gen Mex; 2016. doi:10.1016/j.hgmx.2016.09.010
2. Kratz JM. Drug discovery for chagas disease: A viewpoint. Acta Trop. 2019;198:105107. doi:10.1016/j.actatropica.2019.105107
3. Ribeiro V, Dias N, Paiva T, et al. Current trends in the pharmacological management of Chagas disease. Int J Parasitol Drugs Drug Resist. 2019;12:7-17. doi:10.1016/j.ijpddr.2019.11.004


Unitaid
Innovation in Global Health