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Using Cascade Charts to Highlight the Impact of Rapid Diagnostic Testing on Chagas Disease Care

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2020

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Abstract

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By Rachel Boxwell

Background: Chagas disease is a neglected tropical disease endemic to South and Central America. It is estimated that 6-7 million people are infected with the Chagas parasite and up to 70 million people are at risk of getting the disease. If left untreated, the parasite can persist for decades, if not the patient's entire life. Of those with Chagas, 30-40% can experience symptoms that affect the cardiac, gastroenterological, and nervous systems. Complications can range from developing a megastomach to sudden death. These symptoms are frequently not attributed to Chagas disease, which allows knowledge about Chagas to go widely unknown and developments to fight the disease few and far between.

Methods: Methods included researching the price of purchasing a rapid diagnostic tests and calculating the number of people that will need to participate in testing to reach 25% coverage of the at risk population in Colombia. This information will be shown using a cascade chart to show the number of participants and the expected results of increased testing and treatment.

Results: To reach 25% testing coverage of the at-risk population in Colombia, 1,204,944 people would need to get tested. Using this number, we made a series of assumptions leading to 105,553 Colombians testing positive for Chagas, and 105,260 people staying to receive their test results. These numbers would lead to 82,103 people receiving Chagas treatment and 51,314 people completing the treatment regimen. We will need 2,403,656 Chagas STAT PAK RDTs (rapid diagnostic test) which would cost $14,421,936 USD. The increased number of people getting tested, and treatment would initially increase DALYs (disability adjusted life years), but eventually there would be a decrease in DALYs.

Conclusion: The implementation of RDTs to reach 25% testing coverage for the at-risk population in Colombia would have impact on how Chagas is treated in Colombia. Chagas is a widely neglected disease and by increasing the number of those diagnosed it will become much more difficult to ignore. The future of Chagas disease testing and treatment lies on the shoulders of those in the health community.

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List of Abbreviations

BCE	Before Common Era
CDC	Centers for Disease Control and Prevention
DALYs	Disability Adjusted Life Years
EBPH	Evidence Based Public Health
FDA	Food and Drug Administration
NGO	Non-Government Organization
NTD	Neglected Tropical Disease
PAHO	Pan American Health Organization
PCR	Polymerase Chain Reaction
RDTs	Rapid Diagnostic Tests
T. cruzi	Trypanosoma cruzi
USD	United States Dollar
WASH	Water, Sanitation, and Hygiene
WHO	World Health Organization

Chapter 1: Introduction

1.1 Rationale

Known as the “silent and silenced disease”, Chagas disease has long been pushed away from the public eye and ignored by international health organizations (WHO, 2023c). With the introduction of World Chagas Disease Day (April 14th), WHO (World Health Organization) has decided to shine a spotlight on the disease that puts up to 70 million people at risk of infection and has infected 6-7 million people globally (PAHO). Without treatment, Chagas disease can develop into chronic Chagas, which can leave up to 40% of those infected with chronic cardiac and gastroenterological conditions, and possibly lead to death (WHO, 2023d). The call to action presented by the WHO promotes the disease’s visibility and recommends that equitable care, improved surveillance, and further education about Chagas in general care be made a priority on the international stage. Technologies regarding Chagas disease have not caught up to match these requests, but improvements, like better testing regimens, can change the impact of the disease forever.

1.2 Problem statement

Limited access to Chagas disease testing has created a system that does not screen for or treat Chagas carrying patients. Implementing the use rapid diagnostic tests (RDTs) will increase the number of people who get tested and seek treatment.

1.3 Purpose statement

The purpose of this study is to measure the overall costs of implementing RDTs in Chagas endemic areas and to assess the impact of increased testing on health outcomes.

Identifying current systems and implementing new strategies to increase testing will encourage more people to seek answers and care for cases of Chagas disease.

1.4 Research question

What is the estimated cost of using rapid diagnostic tests to provide 25% coverage for individuals at risk of developing Chagas disease in Colombia?

1.5 Mission statement

The adoption of rapid diagnostic tests for Chagas disease testing will change the landscape of how Chagas patients are cared for. Cost and availability issues make it rare for people to be tested for Chagas in the first place. By adopting RDT use in endemic countries, like Colombia, the landscape of care can be shifted to empower the people to receive the lifesaving care they need. Twenty-five percent coverage was chosen to provide a more viable example for the plausibility of the study. Calculating the correct number of RDTs to match the eventual goal of WHO, 100%, may drive away potential entities that could provide monetary support for Chagas interventions. By aiming for 25% testing coverage of at-risk individuals, we can develop an estimate of the appropriate number of tests needed and the expected cost. Calculating the perceived costs of producing and using these tests will increase the ability to diagnose and treat thousands of people with this curable parasitic infection.

1.6 Context

Chagas Disease is a parasite that infects the heart, digestive system, and nervous system of its host. It is estimated that as many as 7 million people are infected with this disease, 30,000 new cases of Chagas occur each year in the Americas, and 14,000 people die each year. Up to 70 million people are at risk of contracting the disease (PAHO). The disease is featured in "*Ending*

the neglect to attain the Sustainable Development Goals: A road map for neglected tropical diseases 2021–2030" as one of the 20 most important neglected tropical diseases (NTD) (WHO, 2020).

Chagas disease exists in 3 forms, the acute stage, the intermediate stage, and the chronic stage. The acute stage of the disease happens soon after infection and usually produces little to no symptoms. Complications can occur and inflammation can start around the infection site and travel to the lining of the heart, lungs, and brain (CDC, 2016). The acute stage of the disease has a 5-10% case mortality rate in symptomatic infections (Medeiros et al., 2022). The intermediate or asymptomatic phase can be lifelong or last 10-30 years before turning chronic (De La Rosa et al., 2018). Of those who survive the acute phase, 30-40% of those who have Chagas disease will progress into a phase called "chronic Chagas" and will experience nerve damage and cardiac or gastroenterological diseases (Irish et al., 2022). Illnesses like cardiomyopathy, megacolon, apical aneurysm, and sudden death are common among those with chronic Chagas Disease (PAHO).

Historically Chagas disease is an illness primarily among rural and native populations in endemic countries. Due to urban sprawl and internal migration, cases in cities and well populated areas are becoming more frequent (Alarcon de Noya et al., 2022). Chagas is endemic in South and Central America, with cases beginning to appear in other parts of the world, like the United States, Australia, Japan, and Spain, due to international immigration (Gascon et al., 2010).

Testing has been a long-standing issue when diagnosing Chagas. Currently testing consists of microscopic serological testing for the Chagas parasite (CDC, 2016). Another common way to test for the parasite is by running a polymerase chain reaction (PCR) test

(Matsuda et al., 2009). Both of these means of testing are expensive and results can take weeks to come back, leaving an at-risk population vulnerable to loss to follow up.

Treatment is another difficult aspect of Chagas disease. Medications to treat the disease are difficult to acquire, with both drugs, benznidazole and nifurtimox, only approved for those 2-12 years old or 18 years old or younger, respectively, by the Food and Drug Administration (FDA) (Global Health, 2021). Other treatments can include the use of pacemakers, heart medication, and preventative care as a way to manage the disease (Clinic, 2020).

Chapter 2: Literature review

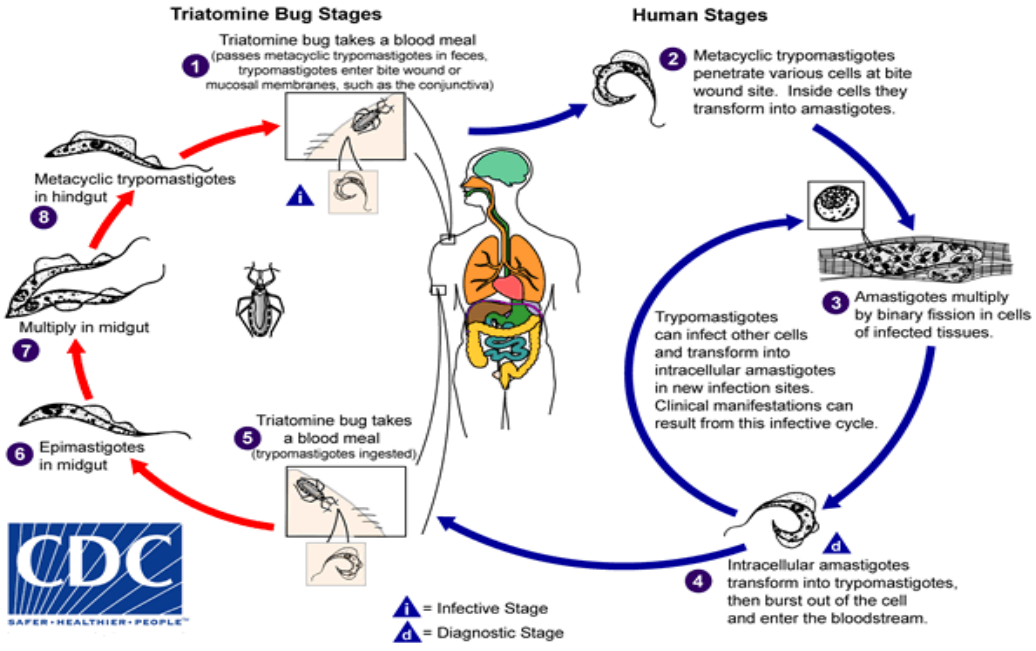
2.1 Disease background

The Trypanosoma cruzi (T. cruzi) parasite is mainly transmitted to humans through the feces of a triatomine bug, also known as the kissing bug. Infection usually occurs after the kissing bug feeds and defecates. Feces are then brushed into the wound or into mucosal membrane and the life cycle of the parasite continues (CDC, 2019). Other routes of transmission include vertical transmission from mother to child, blood and organ donation, and consumption of food or drinks contaminated by kissing bug feces. Triatomine bugs can be found in the wild and near human dwellings. In areas where the bugs are native, they can be found under porches, in cracks around homes, in bush piles, or in dog houses or chicken coops. Kissing bugs that transmit Chagas disease are endemic to 21 countries, including Mexico and all of Central America and South America (Coalition).

Figure 1 Chagas Disease Global Distribution (DNDi, 2022)

T. cruzi has two life cycles, one in the triatomine bug and one in mammals, in this case, humans. The life cycle in the triatomine bug starts with a blood meal from a Chagas positive animal. The epimastigotes enter the midgut of the kissing bug and begin to multiply. By the time they enter the hindgut they have reached metacyclic trypomastigotes and are now infectious. The kissing bug then takes a blood meal and defecates, leaving the infectious parasite on the skin. A person will then scratch the location or brush the area and pull the feces into an open wound or orifice, leading to the infection of the new host. Once the parasite enters the new host, it penetrates cells around the infection site and becomes an amastigote, infecting the nearby cells. The parasite replicates through binary fission and turns into trypomastigotes which can navigate the blood stream. These can now infect various bodily tissues and turn into intracellular amastigotes, which can reproduce, unlike the bloodstream trypomastigotes. The bloodstream parasites can infect new tissue and replicate again. This cycle of reproduction can lead to clinical manifestation (CDC, 2019).

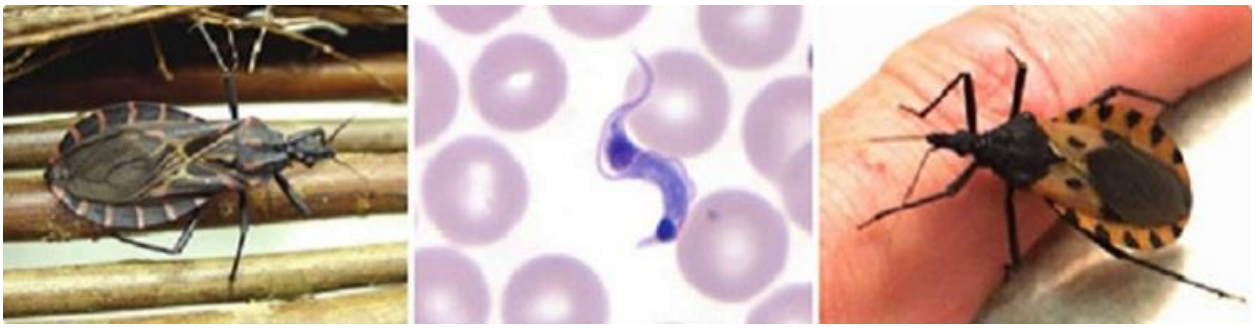
Figure 2 Lifecycle of Chagas Disease (DPDx, n.d.)



Congenital Chagas occurs through vertical transmission, from mother to child, during pregnancy. Due to the nature of the disease, many women get pregnant without knowledge of their status. Treatment of a Chagas infection is discouraged during pregnancy due to the increased risk due to the medications side effects to the fetus. Between 1-10% of babies born to Chagas positive mothers will be born with the disease. To prepare for this, testing women of reproductive age is encouraged (Vázquez et al., 2020). Testing pregnant women during prenatal checkups has become normal in Chagas endemic countries.

Symptoms of Chagas vary from person to person and over time throughout acute, intermediate, and chronic phases. The acute phases can be asymptomatic; symptoms include a mild fever, body aches, diarrhea, vomiting, rashes, and fatigue. These symptoms are common in many other illnesses and are frequently ignored. If the infection is spread through the bite of the kissing bug, there can be swelling and irritation at the site which can lead doctors to a diagnosis. The acute phase is rarely fatal but can be dangerous to children under five and to those with weakened immune systems (CDC, 2022a).

Figure 3 Two types of triatomine bugs (left and right) and the Trypanosoma cruzi parasite from a blood smear test (DPDx, n.d.)



The intermediate phase occurs between the acute stage and the chronic stage. This stage is the most common and around 70% of those infected with intermediate Chagas will experience no symptoms throughout their life and will never be diagnosed or treated for the disease. The remaining 30-40% of those who do not receive treatment during the acute stage will develop chronic Chagas. This population will experience recurring Chagas episodes, usually starting decades after contracting the disease. Of that population 90% of those with recurring symptoms will suffer from heart disease. Thirty percent of those with heart disease symptoms will die from sudden cardiac arrest, without any signs of advanced Chagas disease. Other thromboembolic events are likely to occur including blood clots. Those who do not suffer from sudden cardiac events will lead a life of chronic heart disease; almost 60% of this population will develop cardiomyopathy and die (Haberland et al., 2013).

These symptoms can occur due to an enlarged heart caused by chamber dilatation. The heart walls and septum can become thickened and “patchy” myocarditis is frequently seen. T-cells, B-cells, and macrophages are usually found in nests around the myocarditis as well as interstitial fibrosis and a disruption of normal myocytes. Using a microscope to look for Chagas parasites is successful approximately 10-20% of the time, but new DNA amplification testing identifies Chagas Disease in nearly every Chagas-positive person tested (Haberland et al., 2013). Many of those who die with Chagas-related heart disease will never receive a diagnosis and the cause of death may never be identified.

Other chronic Chagas symptoms include nervous system damage and gastrointestinal disease. The nervous system can be affected during the acute phase of the disease, and symptoms mainly include encephalitis. The symptoms from acute Chagas can reoccur later, during the chronic phase, due to immunosuppression. The majority of chronic Chagas patients will have

little to no signs of neurological distress, although a few will suffer from strokes, brain atrophy, and cerebral thromboembolic events (Oliveira-Filho et al., 2009). Gastrointestinal symptoms mainly include organ dilation, such as, megacolon, megaesophagus, megastomach, and more. These symptoms occur in the gastrointestinal system and are a result of nervous system damage from Chagas (Matsuda et al., 2009).

The most common way to test for Chagas disease is through serological testing. A thick and thin blood smear is taken and is examined under a microscope to look for the parasite (CDC, 2016). This technique is regularly used when testing blood received in donation centers, as the disease is a transfusion transmitted infection (Fearon et al., 2013). The technique is also used when screening pregnant women and those who are trying to have a baby. There is the potential for vertical transmission from mother to fetus so women who are at risk of having Chagas should be tested (CDC, 2021). In recent years PCR tests have been created to check for the disease. While these tests frequently have high specificity and sensitivity, wider distribution of these tests is uncommon (Pinazo et al., 2021). Other signs of Chagas can be found in x-rays and echocardiograms (Acquatella, 2007).

Treatment of Chagas varies based on when the diagnosis is made and which symptoms appear. Benznidazole or nifurtimox should be given soon after the infection and are almost 100% effective if given in the appropriate time frame. Both medications have diminishing efficacy for older infections but should still be administered. These medications cause adverse side effects in up to 40% of adults, while children tolerate the medication better (WHO, 2023a). Other treatments are used to manage symptoms of chronic Chagas, like medications to manage the heart disease, pacemakers, and transplants if applicable. Digestive complications may be treated with diet change, steroids, or surgery (Clinic, 2020).

2.2 Current status

In 2019 the World Health Organization released their *Ending the neglect to attain the Sustainable Development Goals: road map for neglected tropical disease 2021-2030*, known as the Roadmap, to create guidelines on how to handle neglected tropical diseases (NTD) in the coming decade. Chagas disease has been categorized under the "targeted for elimination as a public health problem" grouping. Elimination, in this context, means that there is no incidence of disease in a specified location (Dowdle, 1999). Chagas will likely never be eradicated because the parasite is not human specific. The Roadmap outlined three critical action points to try to reach the goal of elimination. The first critical action point states that each country that has Chagas disease cases should be made aware of the disease as a critical public health issue and establish a monitoring and surveillance system, as well as improve prevention, care, and control. The second critical action point aims to provide better access to information about Chagas and to train health service workers on all levels about the impact of the disease. The final critical action point is to ensure that areas with vector-based transmission comply with surveillance and control, and report findings appropriately (WHO, 2020).

Strategic interventions include improving water, sanitation, and hygiene (WASH) practices, vector control from residual spraying and home improvements to reduce kissing bug dwellings, better testing practices when testing donated blood, and treatment of women and girls of childbearing age to reduce and prevent vertical transmission. Case management is more difficult but is one of the most important aspects. Testing and treating early Chagas cases is key in reducing long term disabilities from Chagas. For those with symptoms of chronic Chagas, having appropriate healthcare to manage symptoms is the difference between life and death.

Some of the WHO indicators that are being used to monitor intervention success include having 15 out of 41 countries that have Chagas disease interrupt disease transmission. This includes countries with transmission via transplants, blood transfusions, and congenitally. Another goal is to have 75% antiparasitic treatment coverage to the Chagas-affected population by 2030. Eighteen of twenty-one endemic countries, countries that have vector transmission, will receive verification that there is a decrease of Chagas cases that were acquired at home. An indicator that WHO is hoping to achieve by 2030 is that testing centers will report positive cases of Chagas when testing blood donations and when preparing for an organ transplant in the 41 countries where transmission can occur. The last goal is that at least 15 of the 41 countries will receive reports of interrupted congenital transmission. Each goal will hopefully be met by 2030 (WHO, 2020).

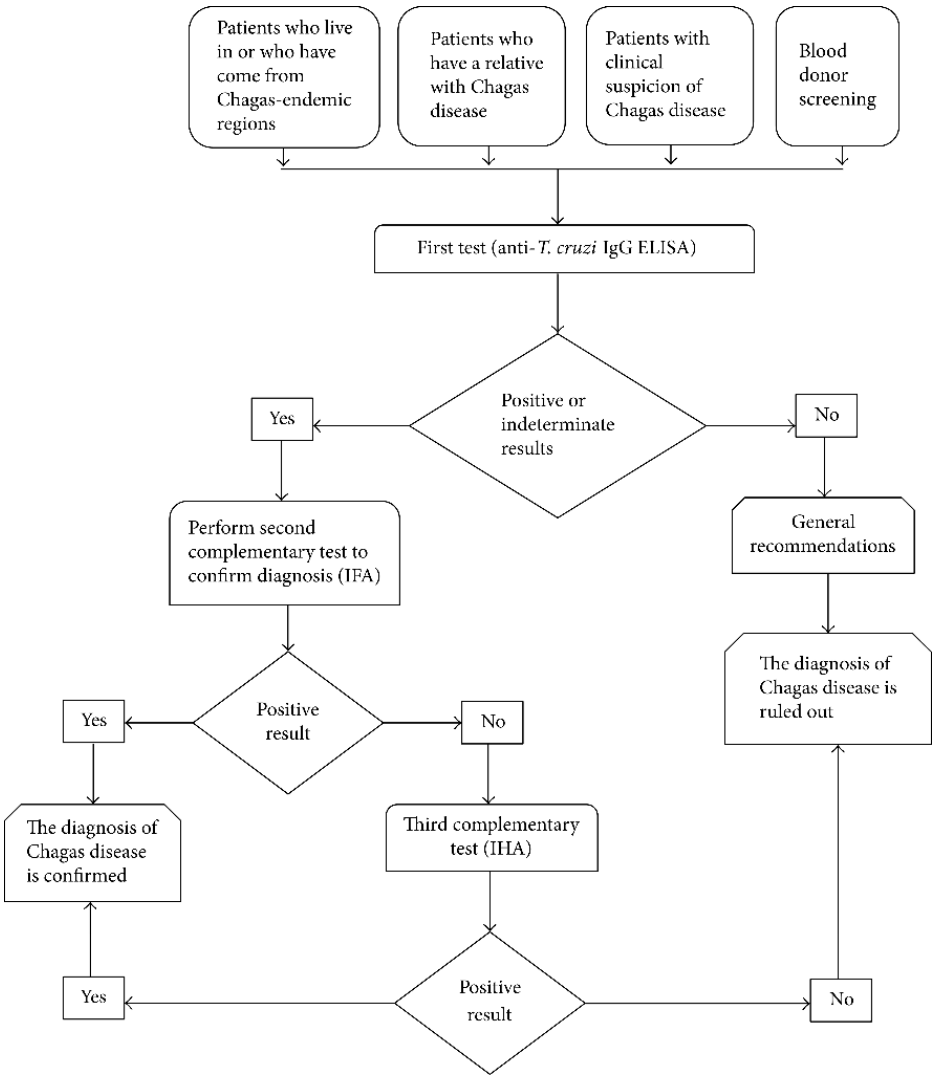
Current WHO assessments show that the health care community has a fair scientific understanding of the disease, however, more research on transmission routes, parasite-host transmission, and characterization of the triatomine bug is needed. There is also a lack of understanding about the best practices to destroy the insects, other preventative measures, information about cardiac symptoms from chronic Chagas, and better knowledge about co-infections, comorbidities, and the survival curve (WHO, 2020). There is also moderate understanding of operational and normative guidance. Although WHO released a guide to end the transmission of congenital Chagas in 2018, an updated document on prevention and control practices is needed, as well as further implementation of congenital and transfusion/transplant policies (WHO, 2018).

Stronger action is required for improved healthcare systems, planning, governance, implementation, monitoring and evaluation, effective intervention, and diagnostics. Improving

awareness in healthcare centers for diagnosis and treatment is key. Chagas has gone from being a rural disease to a more geographically widespread disease due to the constant movement of people. Providers in urban areas need training to recognize Chagas and treat it appropriately. For planning, governance, and implementation, improvements need to be made in screening and diagnosis, and education of case managers to handle cases of chronic Chagas. Monitoring and evaluation needs improvement on screening, surveillance and verification, and increasing the importance of mandatory reporting after a person tests positive. Further research needs to be done on treatment options, including determining the appropriate dosages of benznidazole and nifurtimox, and creating new treatment regimens.

The current status of diagnostics is that it is not available in many critical areas and, if available, is not state of the art. Diagnosis through microscopy for haemoparasites, pathogens that are carried by the blood stream, is not available for Chagas disease. Two tests used to check for antibodies are needed for a diagnosis. Serological RDTs are available but are not frequently used or validated in the field. Polymerase chain reaction (PCR) tests are used to detect the presence of Trypanosoma spp. circulating in the blood. Two to three serological tests are needed for a diagnosis. A shift towards RDTs and automatized tests is needed (Lopez-Albizu et al., 2020). Figure 4 outlines reasons why people go out of their way to get tested, even with the difficulties listed above.

Figure 4 Reasons People Seek Chagas Testing (Olivera, 2017)



WHO has a list of required actions to improve current testing practices. They recommend the creation of a microscopy system that is able to detect haemoparasites, including trypanosomes, using artificial intelligence. WHO also recommends a plan to develop two RDTs,

one with high specificity and one with high sensitivity, to use during field testing. A test needs to be developed that can determine a patient's current Chagas status, another that can assess the best course of treatment, which will eventually reduce overall medical costs, and a test to identify infections transmitted from mothers to their babies. Chemiluminescence developed for lab use should be used to validate the accuracy of any new RTDs (WHO, 2020).

The treatment of Chagas depends on how quickly you get diagnosed after transmission. Treatment in the acute phase calls for the use of anti-parasitic medications, benznidazole and nifurtimox (Lampit). Infants who got Chagas congenitally have a cure rate near 100% if treatment is given early enough. The cure in infants who are in the acute phase have a cure rate of over 60% (Forsyth et al., 2016). A study done in adults has shown a cure rate of 76% in those who receive treatment during the acute stage. The same study showed a cure rate of 8% for those who were treated in the chronic phase (Cançado, 2002).

2.3 Malaria Comparison

Much like Chagas, malaria is a parasitic infection that comes from the bite of an insect. They both affect areas in the southern hemisphere and both, for periods of time, have been ignored by the rest of the world. In recent years, malaria has seen a significant change in how it is studied, tested, and treated. Billions of dollars are spent each year on the study and treatment of malaria (Haakenstad et al., 2019). These funds come from non-government organizations (NGO's), governments, and from personal donors. Chagas disease receives a fraction of the annual funding that malaria receives.

Malaria has been evolving in humans for centuries. Early origins of the malaria parasite can be tracked back 150-200 million years ago in ancient invertebrates (Carter & Mendis, 2002).

Evidence of malaria infections have been noted in Chinese texts from 2700 BCE, Mesopotamia in 2000 BCE, Egypt in 1570 BCE and in many other cultures throughout the centuries. Malaria was referenced in the works of Homer and Hippocrates and has been the focus of medical studies for centuries. The parasite itself was discovered in 1880 by Charles Louis Alphonse Laveran (Cox, 2010).

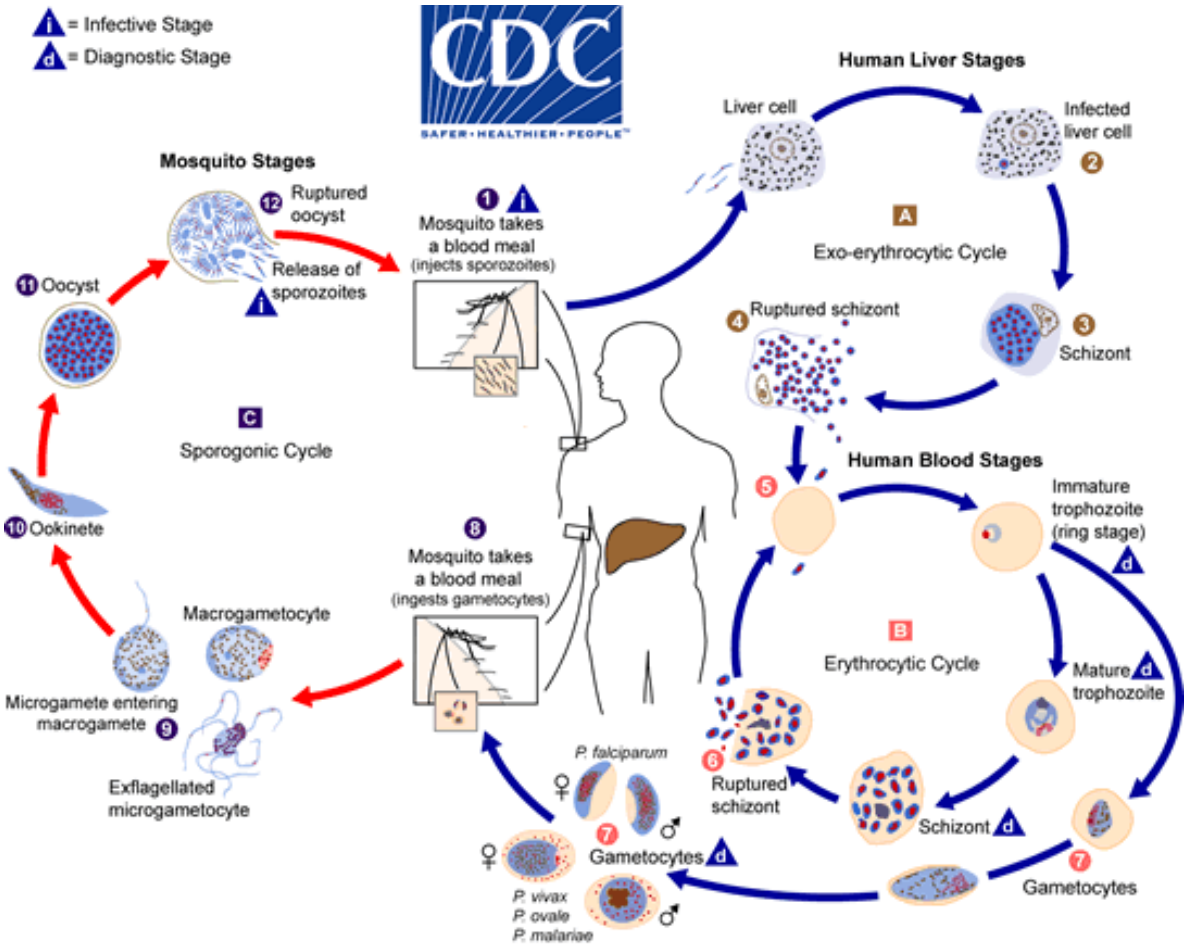
Malaria is a parasitic infection that belongs in the family *Plasmodium.* There are 172 species within the *Plasmodium* family, five of which can infect humans, *P. malariae, P.falciparum, P.vivax, P.ovale, and P.knowlesi (*Talapko*). P.falciparum* is the most common type of malaria, with an annual disease burden of 193.5 million cases (Weiss et al., 2019). The second most common malaria infection is *P.vivax,* with an annual burden of 14.3 million infections (Battle et al., 2019). *P.falciparum* is the most common species in Africa, and accounts for 96% of all malaria deaths (WHO, 2023b). *P.vivax* is the most common species in Latin America.

The disease is spread through the bite of the *Anopheles* mosquito, which injects the parasite into the bloodstream. From there the parasites infect the liver to mature and reproduce. From there the disease enters the blood stage and has clinical manifestations that include symptoms like fever, chills, sweats, nausea and vomiting, as well as other non-specific symptoms. Severe malaria can lead to seizure and coma, acute respiratory distress syndrome, low blood pressure, and kidney injury (CDC, 2023). The malaria parasite life cycle has many similarities to the parasitic life cycle of Chagas disease.

During the liver stage, where growth and reproduction occurs, some types of malaria, *P.vivax* and *P.ovale*, can lay dormant for years (Ashley & White, 2014). This phenomenon can

also be found in Chagas infections, with the disease lying dormant for decades before reinfection occur. Both diseases have parasites living near the organs they frequently infect, the liver for malaria and the heart and digestive muscles for Chagas (CDC, 2022b) (WHO, 2023a).

Figure 5 Malaria Parasite Lifecycle (CDC, 2020)



Malaria can be diagnosed in two ways, microscopy and in more recent years, by rapid diagnostic tests. Microscopy is done using a thick and thin blood smear. Much like Chagas, it requires a microscope and a technician who can read the test correctly. This may make it difficult

to diagnose people who live in non-urban settings because microscopes need power and trained personnel to read the tests (Ngasala et al., 2008).

Development of RDT for malaria took nearly 2 decades and a WHO funded study conducted from 2008-2018. The study tested 332 products in over 8 rounds of testing. Each RDT brand was allowed to make revisions and resubmit for round two. Out of the 332 tests that were submitted, 227 of the RDTs were unique. This testing strategy was done because of the need to expand quality diagnosis results. By 2010, WHO recommended that RDTs were acceptable to use when microscopy is unavailable. The implementation of RDTs shaped donor policies (Cunningham et al., 2019). Competition drives innovation, innovation that encouraged the creation of affordable RDTs and propelled them into wide use. As the development of more malaria RDTs has ramped up, prices have fallen substantially. This evaluation program encouraged manufacturers to embrace competition and improve previous attempts at creating better tests. Ideally in the future, there will be another research expedition for the development of Chagas RDTs at the same level.

2.4 Research question

What is the estimated cost of using rapid diagnostic tests to provide 25% coverage for individuals at risk of developing Chagas disease in Colombia?

Chapter 3: Methods

3.1 Parameters

Measurable parameters for this study will include the number of people getting tested, the number of people receiving a positive test, and the number of people seeking and completing treatment. We will be measuring the cost burden of producing and purchasing the necessary number of Chagas RDTs to improve the rate of screening coverage for at risk populations from 1.35% to 25% coverage (Olivera et al., 2018). Twenty-five percent coverage was chosen to provide a more viable example for the plausibility of the study. Calculating the correct number of RDTs to match the eventual goal of WHO, 100%, may drive away potential entities that could provide monetary support for Chagas interventions. To hit the coverage target of 25%, we will estimate the number of people who will be included in each step of the cascade chart. The number of participants is important because it will influence the number of RDTs that are needed and the total cost of the RDTs.

This economic analysis will be conducted with the support of Evidence Based Public Health (EBPH) principles. EBPH can be described as making the best choices for public health interventions, based on the best scientific data at the time. This is done through scientific experimentation, psychological research, political savvy, and "common sense" (Brownson et al., 2009). By adding economic evaluations to the decision making during public health interventions, it provides a more realistic vision of what the intervention can do in an area, how well it can be sustained, and what the cost will be in the beginning and over time. This will allow for more sustainable interventions and better health outcomes.

3.2 Markov Model and DALYs

We have been using information for our estimates from a Markov Statistical Model analysis that was conducted by Lee (Lee et al., 2013). A Markov Model is an analysis based on the idea that an event happens only because of the event directly before it. This leads to a large number of potential outcomes, as each event can lead to multiple outcomes, which can then lead to hundreds of outcomes. This is applicable in illness because an outcome can only come from the state before it. Lee et al chose to run this model with a one-year cycle. One important parameter in their model includes the probability that someone with an infection will transition between states of illness. The states of illness that were used are as follows; acute disease, indeterminate disease, cardiomyopathy with or without congestive heart failure, megaviscera, and death (Lee et al., 2013).

Each scenario starts with the infection of the disease. For this calculation they use a cycle of one year, with multiple cycles occurring during the length of infection. At the beginning of the model patients will be placed into the acute stage or the asymptomatic stage. If they get tested in time, they can be treated with benznidazole or nifurtimox, and the model will stop at that point. If the person does not get treated, a patient can move into the indeterminate stage, which will then progress either into an asymptomatic infection, or progress to a symptomatic infection. The now-symptomatic patients can have a number of health issues due to the Chagas infection. Once symptomatic, the patient can receive a number of different treatments and continue to live, or the patient could die. If they receive treatment, it could keep them alive longer, or be ineffective and lead to death. Once a patient dies, they are removed from the model. One thousand patients were run through the Markov Model. Within the steps of the model are hundreds of variations of what could happen, leading to a million realizations of the outcome (Lee et al., 2013). A visual

representation of a Markov Model, created for a European immigration testing intervention, is shown below.

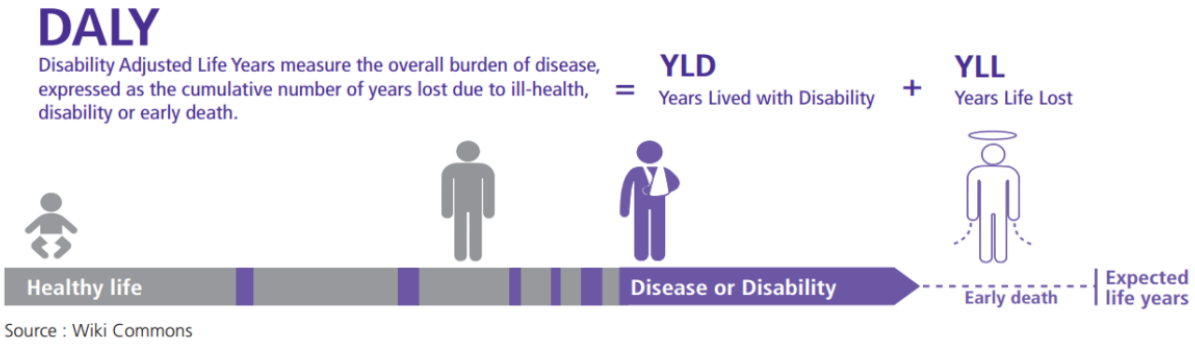
Figure 6 Figure 6: Markov Model of Chagas Screening Programme (Requena-Méndez, 2017)

By using a Markov Model, Lee calculated Disability-Adjusted Life Years (DALYs) (Lee et al., 2013). DALYs are a "time-based measurement" that combines life years lost due to disability and the years lost due to premature death (WHO). The global DALYs for everyone who has Chagas disease, with or without a diagnosis, is 25,398,250. The annual burden for

Chagas disease globally is 806,170 DALYs. The individual yearly burden of Chagas is 0.51 DALYS and the average Chagas sufferer will accrue 3.57 DALYs (Lee et al., 2013).

Unfortunately, the results of this study cannot show the predicted DALYs after the implementation of RDT. The formula for calculating DALYs is shown below in Figure 7. As the formula shows, I would need to find the years lived with disability and the lives lost due to Chagas disease. This is information that I will not be able to obtain after the implementation of RDTs due to the limited research on the impact of mass testing campaigns for Chagas disease. We will be able to estimate whether or not there will be an increase or reduction and DALYs due to the trends that are estimated to occur post intervention.

Figure 7 Formula to Calculate DALYs (NCCID, 2015)



DALYs = Years of life lost due to premature mortality (YLL) + Years lived with disability (YLD)

3.3 Test Selection

My literature review identified 10 RDTs that were used in studies from 2014-2023. Of those ten RDTs, only five are still available today. Those five include Chagas STAT PAK, (Chembio Diagnostics), Chagas Detect Plus (InBIOS International Inc.), WL-Check RDT

(Wiener Laboratorios), OnSite Chagas Ab Rapid Test (CTK Biotech), and BiolineChagasAb Rapid (Standard Diagnostics Inc.). I was able to contact 4 of the companies, Chembio Diagnostics, InBIOS International Inc, Wiener Laboratorios, and CTK Biotech. Out of the four I contacted, I received a response from Chembio Diagnostics. Chembio Diagnostics shared that these tests are only used in small research studies, but they were nice enough to let me know that each test is sold for $6 USD. They were not able to disclose the overall cost of production for each test.

Because the cost of producing Chagas STAT PAK is proprietary information, I will be using the average cost of malaria RDT's, including parts and production and human labor when distributing the test. The average cost of a malaria test is $2.19 USD, with $1.51 going toward parts and production and the other $0.68 going to labor (Du et al., 2020). Due to the parameters of this study, we will be using the cost of production, $1.51, for the malaria RDTs to calculate measures that can be scaled to the cost of the Chagas STAT PAK RDT. Production costs for Malaria tests are $1.51, which is 68.95% of $2.19. Because each Chagas STAT PAK is sold for $6, we are assuming that 68.95% of those costs are from the parts and production costs, and that the production costs are $4.14.

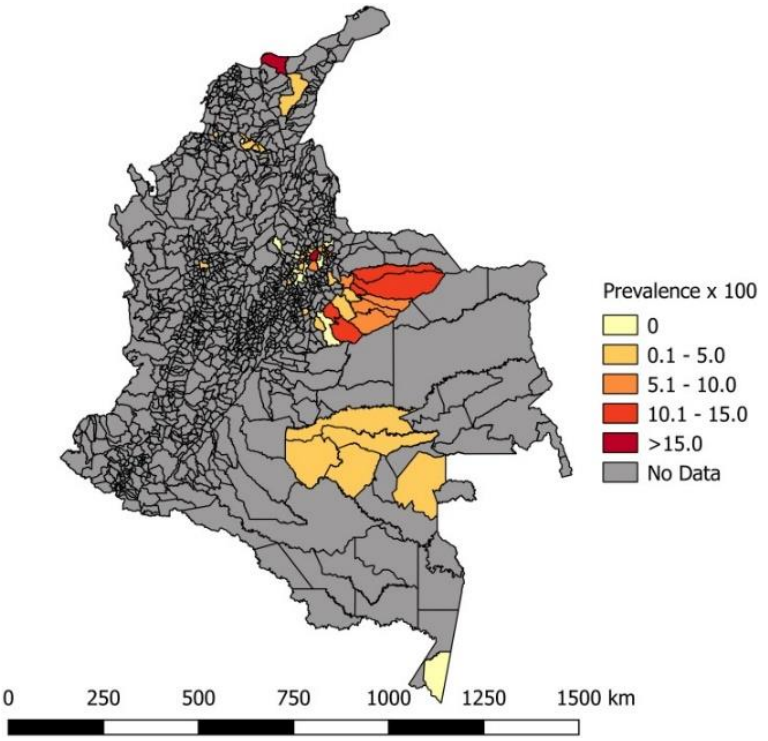
Due to the nature of the disease, we will assess the money saved from diagnosing and treating patients during the acute stage of Chagas. Testing and treating intermediate and late-stage Chagas will have less of an impact on lifespans because detection and treatment in later stages mainly includes symptomatic management and there is no cure once the chronic stage begins and symptoms start to appear. The invention of the internal pacemaker in 1958 and subsequent improvements have led to an increased lifespan for those suffering from cardiac symptoms due to Chagas disease (Clark et al., 2014).

The prices discussed above are current and are subject to change as time progresses. The cost of RDTs change over time, usually becoming less expensive for the purchaser (Wittenauer et al., 2022). This can be accounted for with better manufacturing, bulk pricing, and the cost of materials becoming less expensive. This study calculated the prices for the total number of tests that are needed to receive an accurate diagnosis. This study is not meant to show the cost of RDTs for the population at risk and is not intended to be a guide on how much money should be spent by the family on Chagas testing or to show the government what amount of the national budget should be allocated for the use of RDTs. The perspective of our analysis is that of the manufacturer.

3.4 Data Collection

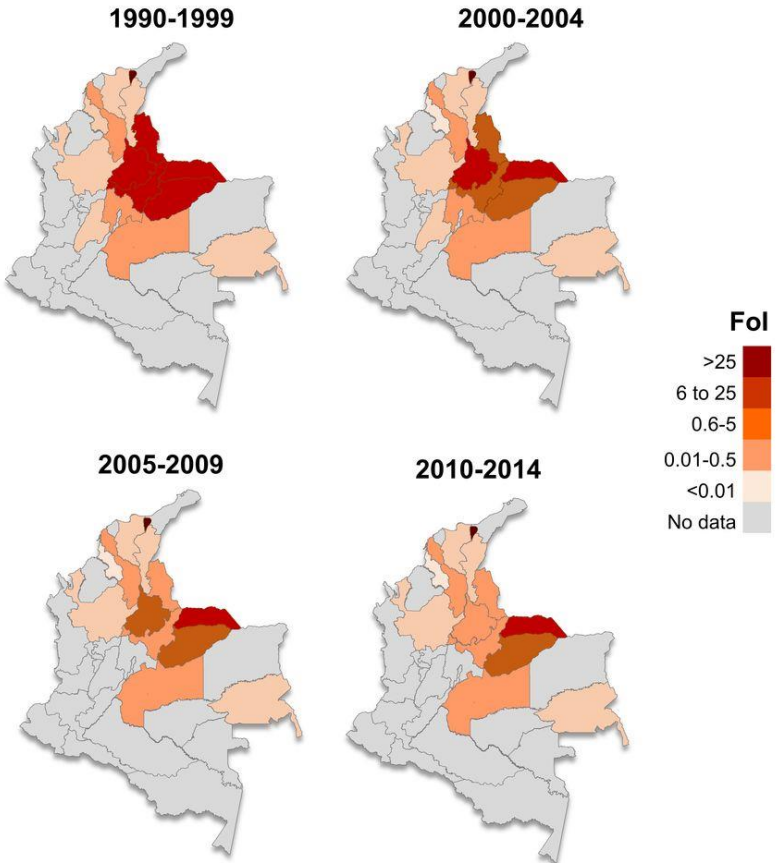
For this study, I chose to use data from Colombia due to the length of time Chagas has been reported and the consistency of the reports. Compared to other Chagas endemic countries, Colombia has reported Chagas over a longer time period, 2014-2023, thus providing a more robust data set. However, underreporting in Colombia is common. There are an estimated 437,960 cases of Chagas in Colombia, with approximately 4,813,543 Colombians at high risk of catching the disease (Olivera et al., 2018). In 2019, Colombia had a total of 5,426.21 DALYS (Network, 2020). The estimated yearly cost of Chagas in Colombia is approximately $13,100,000 USD, with the cost breakdown including direct and indirect medical costs, and other indirect costs like absenteeism, presenteeism, and premature death (Olivera & Buitrago, 2020).

Figure 8 Distribution of reported Chagas cases, 2007-2017 (Olivera, 2019)



The vast majority of Chagas cases are shown to be in the Casanare and Santander municipalities, with the highest proportion of cases residing in the top of the Magdalena municipality. This map lacks data about Chagas disease in the majority of the country. This is due to the limited reporting to the Colombian government, and the minimal amount of data that is collected, overall, for Chagas disease (Olivera et al., 2018).

Figure 9 "Maps illustrating spatiotemporal changes in force-of-infection (FoI) of Chagas disease in Colombia (1990–2014). Color intensity represents the magnitude of the FoI (per 1000 population at-risk per year); for departments in grey there are no available seroprevalence data. (Cucunubá, 2017)



Any country-wide data on Chagas is difficult, if not impossible, to find. The best data I could find came from Colombia's *Boletín Epidemiológico* (epidemiological bulletin), a weekly publication about infectious diseases in Colombia. Weekly articles from 2006 on are posted online on the Institution of Health webpage. These bulletins can be found under the Transparency and Access to Public Information tab. They began reporting on Chagas in week 6 of 2014. The data that was provided from 2014 through week 18 of 2017 was thorough and offered a good amount of insight. The data included characteristics of those who tested positive,

including age, location, sex, and ethnicity (Salud, 2016). The data that was available between 2014-2017 showed similar numbers of Chagas cases; 1,143 cases in 2014, 887 in 2015, 927 in 2016, and 1086 cases in 2017.

Between the end of 2017 and the end of 2018, the yearly report for the numbers of Chagas cases decreased to just 12 cases (Salud, 2018). In 2019, there were 273 reported cases (Salud, 2019), 2020 had 18 total cases, but this can be attributed to the beginning of COVID-19 pandemic, 2021 had 30 reported cases, and 2022 had 270 cases of Chagas disease. These bulletins are released weekly and the numbers for 2023 are already higher than the years 2018, 2020, and 2021, combined. National conflict, displaced citizens, (HRW, 2018) high inflation (Insider, 2018) and unemployment (Marchiol et al., 2017), could be some of the reasons why the level of data being reported decreased so drastically.

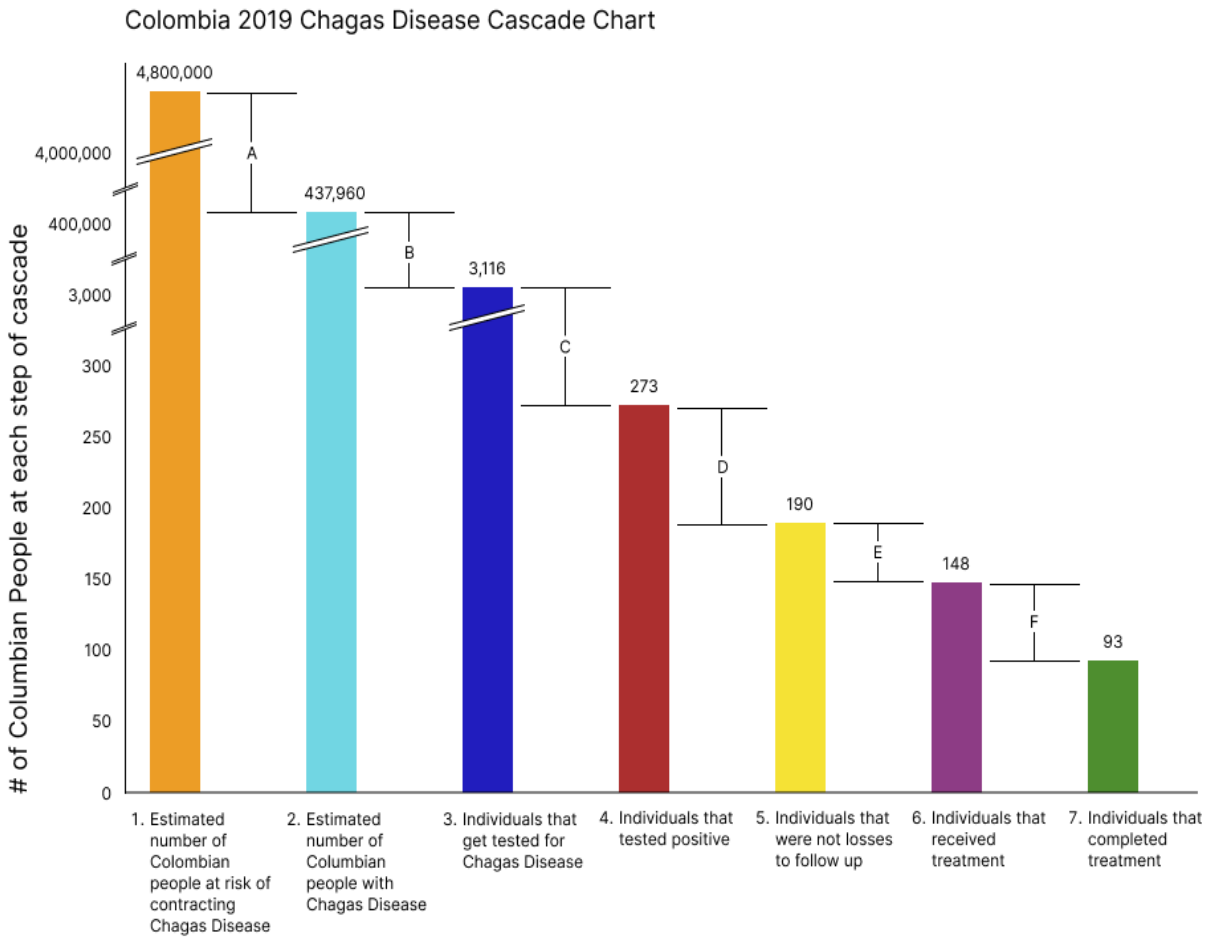
3.5 Cascade Charts

To illustrate the status of Chagas that occurs with different testing approaches, I developed a cascade chart. A cascade chart is a visual aid that represents and "evaluates outcomes across stages of patient engagement in a health system (Subbaraman et al., 2020)." It shows the visual gaps and steps that are taken to achieve the best estimate of the number of participants engaging in Chagas testing. The chart values take the best estimates of Chagas disease at different points in the testing strategy. The cascade for the current approach is the first result illustrated in the results section. We then illustrate the change in the cascade using RDTs rather than the microscopic approach.

Chapter 4: Results

4.1 Current Cascade Chart

Figure 10 Cascade Chart of Chagas Disease Testing and Treatment, 2019 (current testing strategy)



Step 1: The number of people who are at risk of developing Chagas disease in Colombia (Olivera et al., 2018). With Colombia's population being approximately 51.52 million, 9% of people who live in Colombia are at risk of developing Chagas disease (Bank, 2022). At-risk individuals tend

to live in areas where Chagas transmission is occurring and who live in homes that are susceptible to the triatomine bugs (Clinic).

A large gap was seen in the number of people who are at risk of developing the disease, and who were actually diagnosed with the disease.

Gap A: This shows the difference between the number of Colombian's that are at risk of developing Chagas disease, 4.8 million, to the estimated number of people who are infected with Trypanosoma cruzi.

The next step highlights the estimated number of people with Chagas disease in Colombia.

Step 2: According to the World Health Organization there are an estimated 437,960 cases of Chagas in Colombia (WHO, 2015b). The majority of these people will not get tested in their lifetime and 30-40% of this population will develop cardiac, gastrointestinal, and nervous system problems from the infection (CDC, 2019).

The next gap underlines the differences between the number of people who have the disease and those who are getting tested for the disease.

Gap B: The drop in numbers between the number of people estimated to have Chagas disease in the country, 437,960, to the number of people who were tested in 2019 (Olivera et al., 2018). By

knowing that there were 273 cases of Chagas disease in 2019, it allows us to make assumptions on other aspects of the data.

The previous gap leads into the beginning of our assumptions, as there is limited data on the positivity rate for Chagas testing.

Step 3: A study of an indigenous population in Colombia showed that testing for Chagas found a positivity rate of 8.76% (Kann et al., 2022). Under this assumption we can estimate 3,116 people were tested for Chagas disease in Colombia in 2019.

Under the assumption set forth with step 3, we can see the differences in the number of people that were tested and how many tests are positive.

Gap C: Indicates the positivity rates of tests given in Columbia in 2019.

The next step shows the number of positive individuals after testing.

Step 4: The known number of individuals that tested positive for Chagas in 2019, 273, according to the *Boletín Epidemiológico, Week 52, 2019* (Salud, 2019).

The next gap indicates the number of people who were lost to follow up during or after testing.

Gap D: Shows the drop of those who were lost to follow up. Loss to follow up can happen when test results take longer to get back to the patient. I could not find information on lab result time in Colombia so used estimates from a New York lab that reports between 1-8 days after testing (Laboratories, 2017). This potentially impacts why the loss to follow up rate falls at 30.4% (Hyson et al., 2021).

The next step shows the population thus far into the cascade.

Step 5: The number of people who are left after those who tested negative and those who were lost to follow up are removed from the population is 190.

The next gap shows the loss of patients that will and will not seek care.

Gap E: According to a 2008 study, 22% of patients who received a positive Chagas test, and have knowledge about the results, will choose not to seek care (Castillo-Riquelme et al., 2008). This could be due to affordability issues, time commitment problems, expectations that the infection will improve or "go away," and distrust within the healthcare system itself (Taber et al., 2015).

The following step highlights the number of people who received treatment.

Step 6: The number of people who are receiving treatment for Chagas Disease is 146.

There are a number of reasons people do not complete treatment; gap F discusses some of the reasons.

Gap F: The reduction of those who received but did not finish treatment. The two drugs available for Chagas treatment, nifurtimox and benznidazole, can lead to unpleasant side effects, including, hair loss, rash, nausea, abdominal pain, headaches, insomnia, fatigue, and many others. Because of this, the completion rate for the medications ranged from 25 to 96.3%, we will use a study by Jackson that shows the treatment completion rate is 62.5% (Jackson et al., 2020).

We will transition to step seven which shows the number of people who completed treatment.

Step 7: The number of people who tested positive for Chagas at the beginning of this chart and managed to complete treatment, is 93.

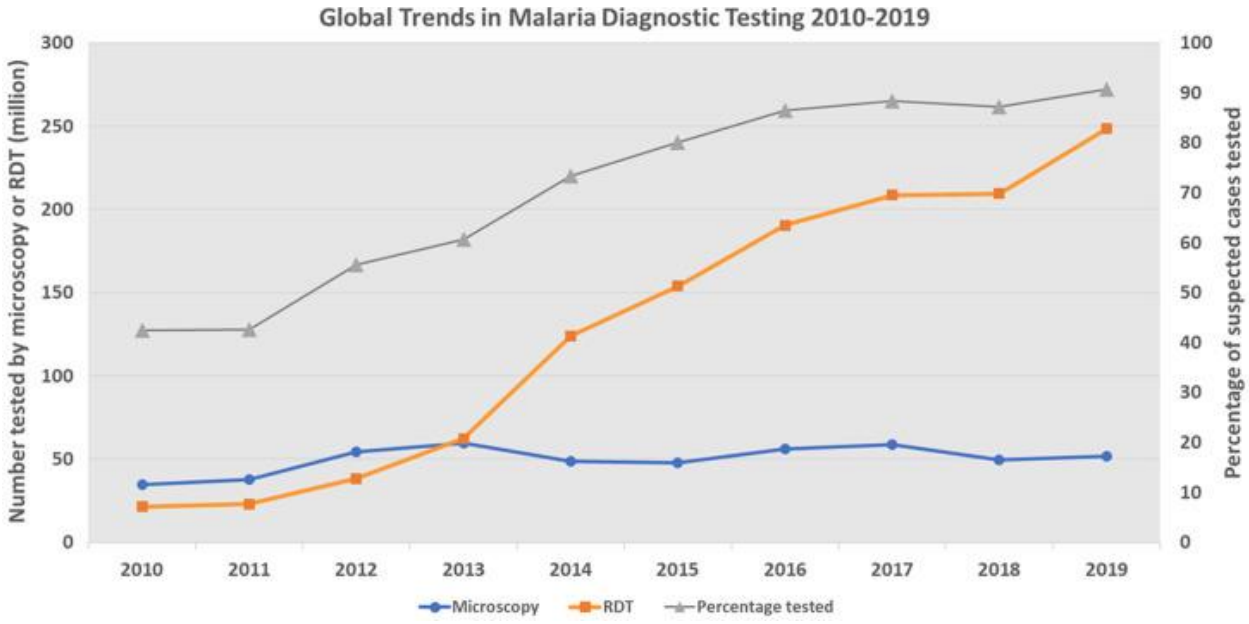
I will not be adding a section on how well the treatments work because it varies greatly depending on who is taking them. The medication works best in younger patients, as they experience fewer side effects and are usually within the acute stage of the disease (Altcheh et al., 2011). Approximately 100% of those who receive either nifurtimox or benznidazole during the acute stage of infection will be cured (PAHO, 2017). A study focusing on adults who were taking the medication during the chronic stage can experience parasitological clearance of around 82% at various doses, with 7% withdrawing from the study due to side effects. Seventy percent of participants experienced adverse events due to the medication. Further studies are still needed to support these results (Torrico et al., 2021).

This cascade chart highlights multiple issues within the testing and treatment of Chagas patients, however; by implementing rapid diagnostic tests for Chagas disease, the number of people receiving a diagnosis can skyrocket, leading to faster treatments and better health outcomes.

4.2 Increased RDT Use

To check the impact of wider use of RDTs, we will return to the malaria comparison. From 2010- 2018, there was a 133% increase in testing rates for suspected malaria cases in sub-Saharan-Africa. This was mainly attributed to the introduction of rapid diagnostic tests (Aidoo & Incardona, 2022).

Figure 11 Global Trends in Malaria Diagnostic from 2010-2019 (Aidoo, 2021)



Between 2008-2015 there was 1.35% screening coverage of at risk populations for Chagas disease in Colombia (Olivera et al., 2018). The percentage of testing being this low can

be partially attributed to the difficulty of finding a location that provides testing and the lack of coverage of testing costs from insurance providers (Caicedo Díaz et al., 2019). By removing these barriers, more Colombians will get tested, which will lead to more diagnosis and faster treatment. The increase in testing will come with an increase of the total healthcare costs surrounding Chagas disease, but it will save lives and reduce the number of DALYs for the country. The annual cost of chronic Chagas in Colombia is $175,016,000 USD (Marchiol et al., 2017).

4.3 Cascade Chart with RDT intervention

To get 25% screening coverage for the at-risk population we need to consider that current testing is done exclusively through traditional testing measures. Using the data collected and analyzed from 2019, we are assuming the screening coverage of at-risk populations was approximately 00.06%. We can assume that the testing coverage will stay stable, using current methods.

For our cascade chart we will start with the number of people who will need to be tested for Chagas disease to reach 25% coverage of the at-risk population. The total population of individuals at risk of contracting Chagas disease is 437,960 (WHO, 2015b). That total number of people to reach that is 1,204,944. We will be using the same principles from the original chart to calculate the number of people that participate in each following step.

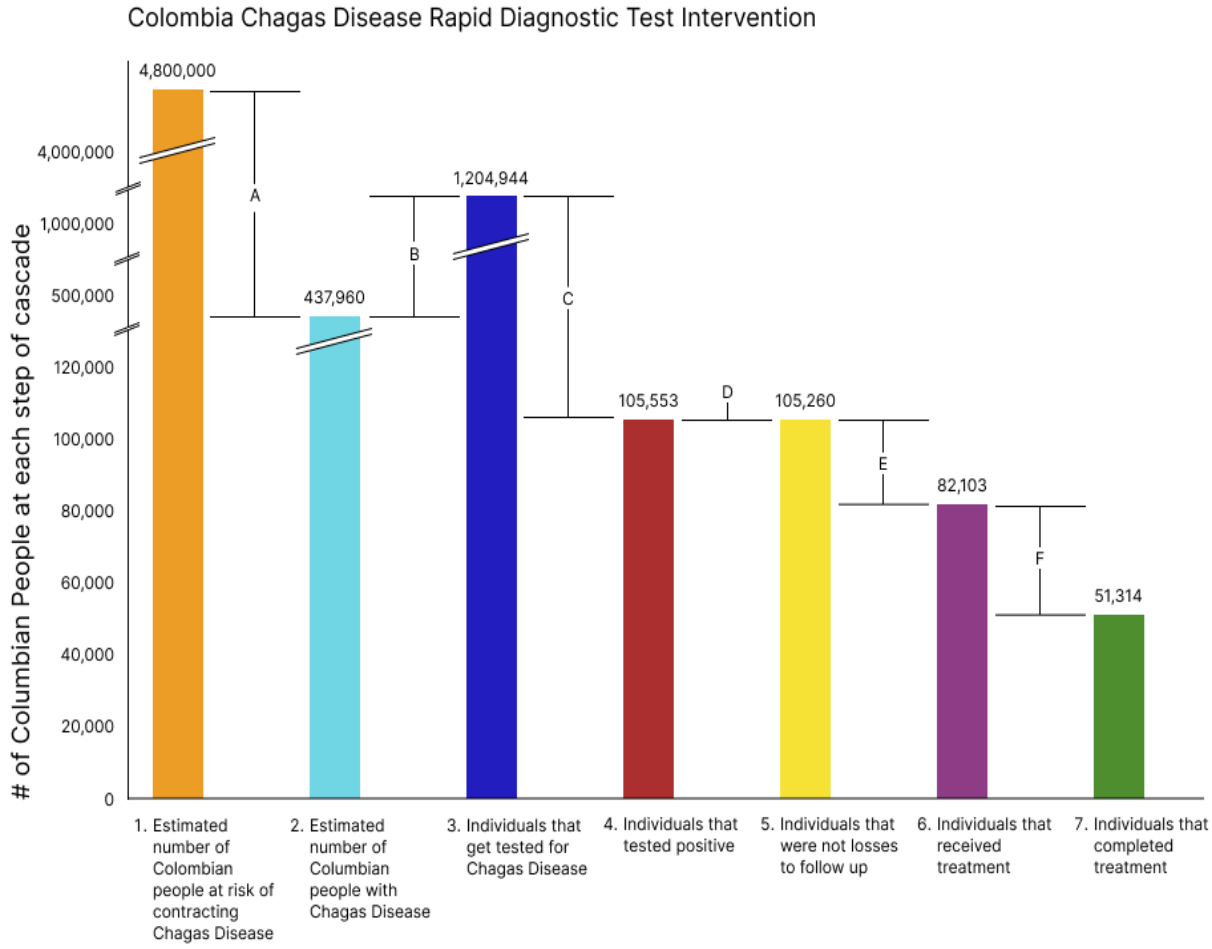
A total of 2,403,656 Chagas STAT PAK RDTs are needed for 25% coverage of at risk populations, because two positive tests are needed for a Chagas diagnosis because a single test does not have adequate specificity and sensitivity (Mendicino et al., 2019). Based on 2019 numbers, 3,116 tests will be done using traditional testing measures. Continuing use of some of

the traditional testing methods will reduce the number of Chagas STAT PAK RDTs needed to reach the desired 25% testing coverage of at-risk individuals.

A review of seven malaria RDTs interventions showed that the loss to follow up between taking the test and receiving a prescription for antimalarials was between 0.0%-2.5% (Odaga et al., 2014). One of the seven reports did not include this information and was not included in the reporting of this information. Four of six remaining studies reported 0.0% loss to follow up, one reported 0.3% loss to follow up, and one reported 2.5% loss to follow up. Due to the speed of results from RDTs, as few as 30 minutes, I believe it is safe to assume that it has a 0.0% loss to follow up during the test result period (Lozano et al., 2019).

The cascade chart below shows the impact of implementing RDTs for 25% testing coverage for the at-risk population in Colombia.

Figure 12 Cascade Chart of Chagas Disease testing and Treatment, 25% Coverage



Step 1: This shows the number of the people that are at a heightened risk of developing Chagas disease, 4,800,000. (Olivera et al., 2018).

The gap shows a large gap in the number of people who are at risk of developing the disease, and who actually have the disease.

Gap A: shows the difference between the estimated number of Colombians at risk of getting Chagas disease and the estimated number of Colombians who have Chagas disease. Nine point one two percent (9.12%) of people who are at risk of developing Chagas disease are estimated to have it.

The next step highlights the estimated number of people with Chagas disease in Colombia.

Step 2: The estimated number of people living in Colombia who have Chagas disease, 437,960, according to WHO (Olivera et al., 2018).

The next gap underlines the differences between the number of people who have the disease and those who will be tested for the disease using RDTs.

Gap B: The increase of number of people that will need to be tested to reach 25% testing coverage in comparison to the number of people who are infected with Chagas.

There is a large jump between the number of people who have the disease and those who will need to be tested to reach 25% testing coverage.

Step 3: The number of people who will need to be tested to reach the desired coverage, 1,204,944.

The large drop that Gap 3 shows indicated the estimated positivity rate of these tests.

Gap C: The change in the number of people being tested to the number of people who are positive after being tested for Chagas, assuming a 8.76% positivity rate (Kann et al., 2022).

This step shows the number of cases the RTDs will diagnose.

Step 4: The actual number of positive cases of Chagas disease after testing using rapid diagnostic tests, 105,553.

Only a small change is shown for Gap D.

Gap D: The change in the number of people who stayed long enough to receive test results.

The number of people is approximately the same, with limited losses to follow up.

Step 5: The number of people who were not a loss to follow up, due to the short response time of RDTs, approximately 30 minutes (Lozano et al., 2019). The numbers between step 4 and 5 are nearly identical, 105,553 for Step 4 vs. 105,260 for Step 5. They differ because some of the people who received a positive test result were tested in the traditional way and will experience a 30.4% loss to follow up (Hyson et al., 2021).

The next gap discusses the drop in participants from step 5 to Step 6.

Gap E: The gap represents the number of people who received their test results and decided to seek treatment.

The next step discusses how we estimated the number of people who do not seek treatment.

Step 6: The fall in the number of people is due to the 22% of individuals who will not seek treatment for Chagas after receiving a positive test (Castillo-Riquelme et al., 2008). That number is 82,103 people. This could be due to the cost of the treatment, the length of time of the treatment, or fears about the side effects of the drugs available.

The gap indicates the drop in participation between those who start treatment and those who did not complete treatment.

Gap F: This gap comes from the number of people who did not complete treatment.

The differences in participation numbers between Step 6 and Step 7 is significant.

Step 7: As stated above, the completion rate can vary greatly among the populations receiving treatment. We used 62.5% from the Jackson study, but the study also indicated that completion rates have been recorded between 25%- 96.3% (Jackson et al., 2020). This leaves 51,314 people who completed treatment for Chagas disease.

4.4 Findings

The total number of people who were tested and followed the cascade down to drug completion is 51,354 people, a massive increase from the testing that occurred in 2019. I did not calculate the total number of people who were cured from the treatment, due to the variation of effectiveness of nifurtimox and benznidazole.

WHO states for RDTs to be used in the field, two tests are needed (WHO, 2020). To account for this, the number of Chagas STAT PAK RDTs ordered will need to be double the population being tested. That will bring the number ordered from 1,204,944 to 2,403,656.

The current cost of 2,403,656 Chagas STAT PAK RDTs, at $6 USD a unit, is $14,421,936 USD, and $9,951,135.84 USD will go towards production costs. Estimated costs of Chagas disease in Colombia in 2017 was 13.1 million USD (Olivera & Buitrago, 2020). While the cost of these tests eclipses the previous total cost of Chagas in the country, the implementation of these tests will aid in decreasing DALYs and will decrease overall healthcare costs over time.

I expect the burden of Chagas DALYs to increase in time immediately after the testing campaigns. This is expected because increased testing will identify more people with Chagas, and events like disability and deaths that were once accredited to other events will now, correctly, be assigned to Chagas disease. DALYs will eventually decrease due to fewer people developing chronic Chagas and experiencing fewer disabilities that come with cardiac, digestive, and nervous system damage, reducing the disability aspect, and years lived with disabilities. This intervention will also prevent deaths due to Chagas in the acute and chronic phases, lowering the years of life lost (Larson, 2013). Both of these factors will eventually lower DALYs caused by Chagas disease.

Chapter 5: Limitations, Conclusion, and Discussion

5.1 Limitations

Limitations are plentiful when it comes to this study. There is not a lot of information, data, or research on Chagas disease. It infects tens of thousands of people a year, but the true horrors of this disease occur 10-30 years after the original infection (PAHO). It is not uncommon that the first sign of chronic Chagas disease is sudden death, usually related to a cardiac event (Keegan et al., 2020). Forty-three percent of seropositive, cardiac related deaths due to Chagas disease do not have Chagas listed as a contribution to death (Capuani et al., 2017).

Limited transmission in high income countries creates another barrier to the treatment of Chagas disease. In the United States there are an estimated 300,000 cases of Chagas disease, frequently occurring in immigrants from endemic countries (WHO, 2015a). Approximately 27%–68% of US physicians are not confident their knowledge of Chagas disease is up to date (Stimpert & Montgomery, 2010). If high income countries, with advanced health systems, have limited knowledge of the disease, the rest of the world may have far less knowledge.

Chagas disease is mainly a disease that thrives in rural areas and affects poor populations in Central and South America (Sartor et al., 2017). In recent years there has been a shift in Chagas cases originating in urban environments due to urban Triatoma populations that carry the parasite (Carbajal-De-La-Fuente et al., 2022). Chagas is mainly in areas that are easy to ignore in a population that could not afford treatment even if they wanted it. This made it easy to put Chagas on the “back burner” and forgotten for so long.

Country level research and record keeping on Chagas disease has been an issue for decades. Most countries do not have a surveillance system in place that allows for thorough tracking. Countries like Colombia, as mentioned earlier, receive data about Chagas annually, but that data appears to be severely underreported based on the expected number of Chagas cases.

5.2 Conclusion and Discussion

Despite the costs of ordering enough RDTs for 25% testing coverage being more expensive than the total Chagas expenditure for Colombia, thinking about the future of Chagas testing will be crucial in the next few years. WHOs "*Roadmap for Neglected Tropical Diseases*" stated that increased testing for Chagas is a required action to continue the push towards Chagas elimination. It specifically mentions the need for RDTs that can be used in the field. These tests will help with surveillance initiatives and will help improve medical care by promoting early treatment (WHO, 2020).

Due to limited demand and current small-scale production of Chagas RDTs, creating a large-scale operation to produce over 2 million tests is a seemingly impossible task. In an ideal world the World Health Organization would hold another study competition, similar to the one held for the creation of a malaria RDT, to encourage the creation of new tests. The malaria competition brought in over 227 unique rapid diagnostic tests. It pushed innovators globally to create better options for a malaria test and led to RDTs being a major part in the fight against malaria-related deaths (Cunningham et al., 2019).

Chagas disease will need an intervention, similar to the malaria one, to promote the use of RDTs, increase the production of new tests, and ultimately drive the price for each test down. Testing currently needs expensive equipment and trained technicians to make a diagnosis, reducing access to those in rural areas (Figueredo et al., 2021). Testing using RDTs, ideally,

would not be expensive, creating availability for those without access to a metropolitan area. Currently the cost for two Chagas STAT PAK tests is 12 USD. The average Colombian income in 2021 was $6,190 (Statista, 2023). These tests are “affordable” to the average Colombian but are an unnecessary expense to many who do not have symptoms of Chagas.

Implementing RDT use will improve Chagas testing, which will impact the number of people that are receiving treatment, which will impact the number of people who are cured of the disease. Testing is a crucial first step when managing a disease and better testing options will allow for better overall care. An increased number of positive tests will help make international news, ideally, and bring in further investors who will help the fight against Chagas. WHO has outlined that RDTs are necessary for the future of Chagas disease elimination and should be responsible in promoting the creation of new Chagas rapid diagnostic tests.

In recent years Chagas has gained the attention of public health heavy hitters. WHO has designated April 14th as World Chagas Disease Day (WHO, 2023d). This day was chosen because it is the anniversary of when Carlos Chagas first discovered the disease in 1909 (Steverding, 2014). There has been considerable improvement in Chagas diagnostics and treatment in the century since its discovery, however, these positive changes have not kept up with current technology and is leaving those who suffer from the disease in the shadows. The creation of World Chagas Disease Day puts the disease into the public eye and promotes knowledge about the disease, which can mean the difference between life and death. This push in education about Chagas is necessary and important, but more research needs to be done and more funding is necessary to fight the good fight, as it will be what brings us to the ultimate goal for Chagas disease, elimination.

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