Ashley Barraza

Robichaud

PS 47000

September 7, 2014

Chagas Disease and Poverty in North and Central Americas

Introduction

The relationship between poverty and disease can often be thought of as a cycle in which one results in the other and vice versa. Living in poverty creates conditions in which a person is more exposed to disease, has less access to medical care, and most likely cannot afford medical care if he or she did have access to it. Living with a disease, depending on its degree of severity and what symptoms it manifests, creates conditions which can lead an individual into an impoverished situation. If an individual's health is debilitated to the point where he or she can no longer work, or work as effectively, it becomes more difficult for that individual to support him or herself, unless they are able to rely on family. Parasitic infections are often popular examples of this particular cycle relating poverty to disease.

Parasitic infections are often associated with impoverished areas, especially those populations living in third world countries. However, these infections are also present in poor and marginalized parts of the United States as well. Chagas disease, a Neglected Parasitic Infection in the United States, is caused by the parasite *Trypanosoma cruzi* and has recently been declared an "economic burden" in terms of the costs associated with care of this disease (Lee et al. 2013). Because this disease often infects those already living in poverty, this new finding has raised concerns for the current costs associated with treatment of this disease. The poor living conditions of impoverished communities support the growing conditions for the Triatomine

insect, the disease vector, to live and transmit the parasite to its natural human host. In turn, if not diagnosed and treated early, the long-term effects of Chagas disease can debilitate those infected to the point where they can no longer work or provide income, thus contributing to the poverty already present. The focus of this research project is to investigate the different aspects of Chagas disease and poverty within the southern region of the United States and parts of Mexico, and to address the trajectory of the disease and its impact not only on the United States, but especially those living in impoverished communities that the disease affects the most.

The Parasite

The causative agent of Chagas disease is classified as a trypanosome, which gives rise to its genus name *Trypanosoma*. Trypanosomes are parasites that infect vertebrates, mostly through the use of an arthropod vector. This particular class of parasites is considered successful due to its ability to be found in all classes of vertebrates and in all continents. Once inside the vertebrate host, the parasite exists either in its blood form or its tissue form. Both forms are necessary to the parasite's life cycle: the blood form allows it to migrate throughout the body while the tissue form allows it to grow and live in various different tissues. Although there are a wide variety of trypanosomes that use different vectors and cause different outcomes in their vertebrate hosts, this study focuses on *Trypanosoma cruzi* (Hamilton et al. 2010).

T. cruzi is primarily transmitted via a Triatomine bug, a member of the Reduviidae family and Triatomine subfamily. Although there are up to 140 species of Triatominae, five specific species have been identified as main vectors of *T. cruzi*: *Triatoma cruzi*, *T. brasiliensis*, *Panstronglyus megistus*, *Rhodnius prolixus*, and *Triatoma dimidiata* (Noireau et al. 2010). Triatomines are defined by their ability to ingest blood as a source of nourishment and by their

unique mode of transmitting the parasite into the host. While most parasites that exist in a blood form are typically injected into the host's bloodstream when the arthropod is taking a blood meal, this parasite actually enters the blood through a different route. While the Triatomine bug is taking a blood meal, it simultaneously defecates onto the host's skin. The feces contain *T. cruzi* in its trypomastigote form, and the parasite enters the host's body through the wound site or through mucocutaneous membranes with the help of the host (i.e. scratching or rubbing the feces into the skin).

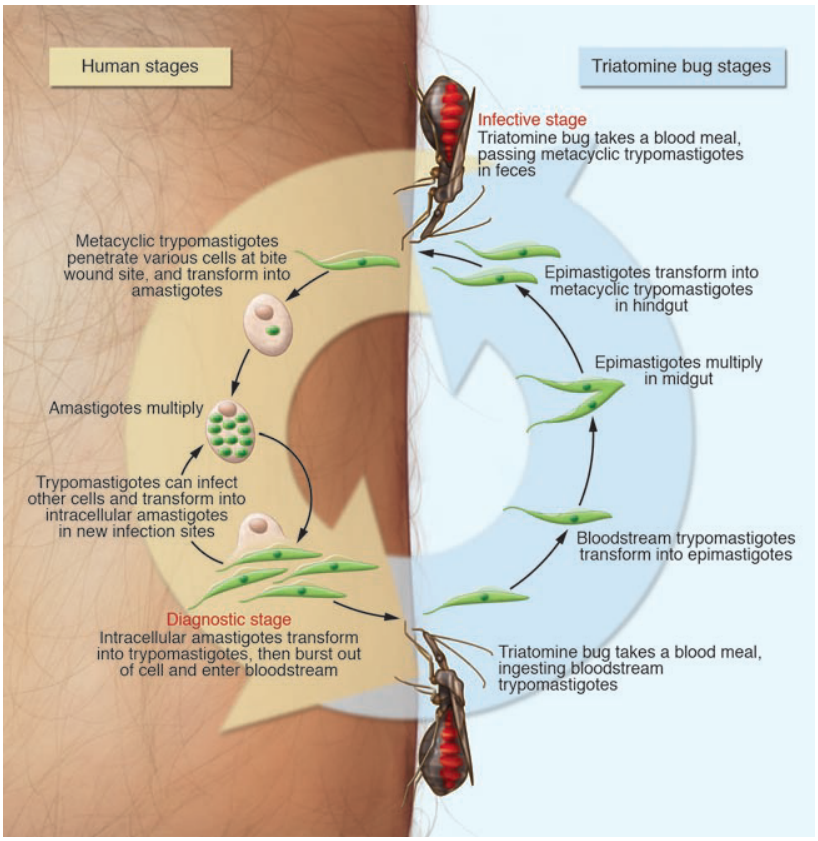

Figure 1: Life cycle of *T. cruzi.* (Stuart et al. 2008)

Life Cycle and Transmission

Once inside the host, the trypomastigotes invade the cells surrounding the wound site and differentiate into the amastigote (tissue form) in order to grow and multiply. It is during this period of replication that the parasites form a cyst. After enough amastigotes have accumulated, the tissue cyst ruptures and the released amastigotes undergo a transformation into the trypomastigote (blood form). The trypomastigotes enter the bloodstream and infect tissues of several different organs. Some of the major organs that are usually infected with trypomastigotes include the heart, the gut, the central nervous system, smooth muscle, and adipose tissue (Stuart et al. 2008). While migrating

throughout the bloodstream to the various different tissues, any Triatomine bug that takes a blood meal can easily ingest the trypomastigotes. Once ingested, the trypomastigotes become epimastigotes in the midgut of the Triatomine, a form in which they can grow and multiply. They transform back into the trypomastigote form and pass through the digestive system of the Triatomine bug so that they can be released via defecation. Certain mammals, such as raccoons and armadillos, are known reservoirs of this parasite. Thus, although they may not contract any disease themselves, they can still spread the disease if the vector is present in the area where the reservoir is found. This is seen in a few different areas within the United States, and has been shown to have higher incidence rates of infected animals than endemic countries, such as Argentina (Milei et al. 2009).

Transmission by the Triatomine vector is the primary form of transmission for this particular parasite, especially in endemic areas, and it is of particular concern from both an epidemiological and socioeconomical perspective. Triatomine bugs are typically found in houses that are generally associated with impoverished areas: those constructed of materials such as mud, adobe, or straw (Milei et al. 2009). The precarious nature of these types of houses presents Triatomine bugs with ideal places to hide and breed before emerging at night in order to have a blood meal from a sleeping host. Inadvertently, the host may even help the parasite enter through the skin by scratching or rubbing the feces into the skin, and ultimately into the wound site. Thus, those living in poor housing conditions often found in impoverished areas of the Americas are at risk of contracting Chagas disease, also known as American trypanosomiasis. Control measures for the vector are currently some of the most effective ways in the spread and rates of this disease can decrease. Vector control and its efficacy will be discussed subsequently.

Vector transmission of *T. cruzi* mostly occurs in areas where several species of the Triatomine insect inhabit, typically in parts of South and Central America. Other modes of transmission exist, and are more prevalent in non-endemic countries, including the United States. Maternal-fetal transmission of *T. cruzi* is the second most common mode of transmission for this parasite. Because the parasites circulate in the bloodstream in order to infect different tissues, and because the maternal blood is circulated to and throughout the fetus during pregnancy through the blood vessels found in the umbilical cord and the placenta, the parasite is able to infect tissues of the fetus as well. Trypomastigotes circulating throughout the bloodstream also becomes a problem for infected individuals that donate to blood banks for transfusions. This type of transmission is not as common anymore, due to the development of serological diagnosis of the disease, which has been implemented in several blood banks throughout endemic countries (Hontebeyrie 2010). When transmission via blood transfusion was common, it was usually due to the fact that the donor was unaware that he or she was infected. This could be due to a variety of reasons, including the donor being an asymptomatic carrier or the fact that he or she was never officially diagnosed with Chagas disease. Similarly, transmission via infected organ donations has also been observed. Currently in the United States, there is no CDC recommendation for serologic testing for *T. cruzi* of donors that wish to donate their organs (Milei et al. 2009). Studies showing data of Chagas disease transmission via organ donation have recommended screening donors in endemic countries for anti-*T. cruzi* antibodies (Milei et al. 2009).

Pathogenesis

Chagas disease is characterized by two main phases of infection, acute and chronic, both of which can be broken down into different forms. The acute phase can either manifest itself through a nonspecific febrile disease or it will not manifest itself at all, resulting in an

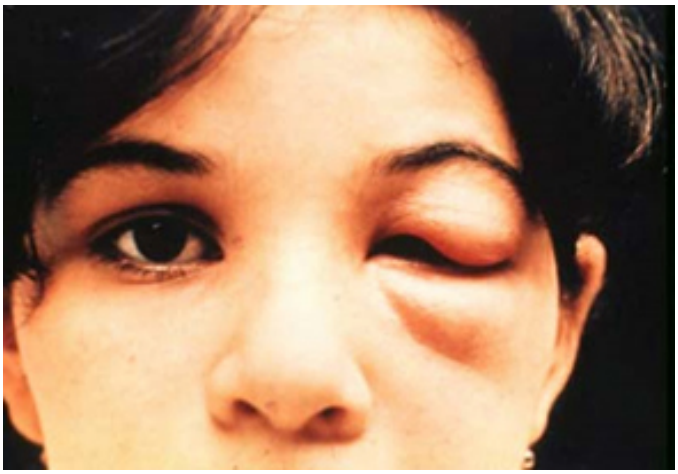

Figure 2: Romaña's sign. (WHO/TDR 1991)

asymptomatic form (Rassi et al. 2010). This phase is observed primarily in children and young adults, and can begin causing clinical symptoms after about one week. Such clinical signs include constant fever, Romaña's sign, edema, and inflammation of infected tissues, and enlargement of lymph nodes, liver, and spleen. The fever is generally accompanied with headaches, malaise, and anorexia, and is usually observed more in children. Romaña's sign, the swelling of an eyelid close in proximity to the parasite's site of entry, is characteristic of Chagas disease. If the wound site is not near the eye, a similar sign can be seen via inoculation chagoma, which is observed through maculonodular erythematous lesion, swelling, and enlarged lymph nodes close to the site of the wound (Rassi et al. 2010). Furthermore, the parasite often travels and invades the heart, causing cardiac problems in 90% of acute infections (Biolo et al. 2010).

The acute phase is generally short-lived, although sometimes it may progress to the chronic phase. Because the acute phase can be asymptomatic or symptomatic with relatively mild symptoms undistinguishable from a general infection, excluding Romaña's sign, this phase largely goes undetected. Having the parasitic infection but being unaware of being infected is primarily the reason why blood banks receive infected blood donations and hospitals receive infected organs. In fact, it has been estimated that approximately 95% of all acute cases are never diagnosed (Coura et al. 2010). In addition, although this phase may be short-lived in some infected individuals, it still poses a problem for vector transmission. Those infected with either

the asymptomatic or the febrile form act as reservoirs of disease. Thus, a Triatomine insect could ingest trypomastigotes from the individual infected with the acute phase and still transmit the parasite to others. Furthermore, if left undiagnosed and thus untreated, the disease could develop into the chronic phase.

Although the acute phase can be quite severe in children, the mortality rate associated with this phase is less than 5% due to the development and administration of effective drugs (Rassi et al. 2010). The chronic phase of Chagas disease, however, exhibits a more severe pathology. This phase appears approximately 2-3 months after the initial infection, at which point any symptoms observed in the acute phase have disappeared. Most chronic cases include the indeterminate form when the parasite is detectable via serological and/or parasitological tests, but is not causing any clinical symptoms. Unless infected individuals receive these tests, most are unaware they still have the parasite. The indeterminate form can last anywhere from 10-30 years, and there is an approximately 40-50% chance of this form progressing to the determinate form (Rassi et al. 2010).

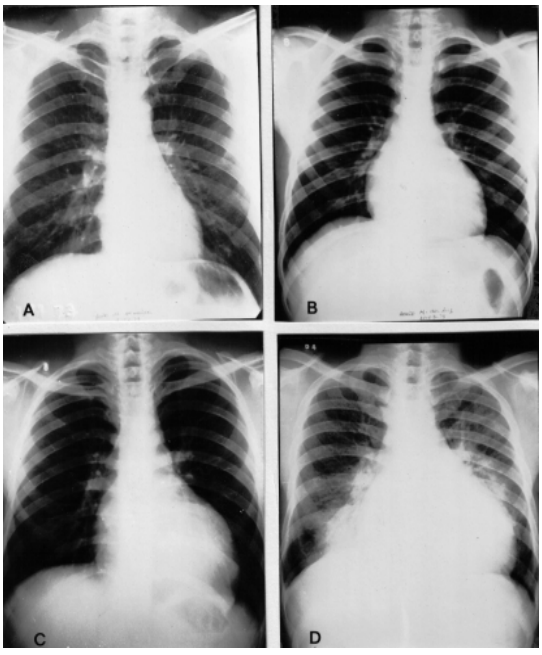

Figure 3: Progression of Chagas cardiomegaly. (A) displays a normal heart while (D) shows a severely enlarged heart (Tarleton et al. 2007).

Whereas the parasite does not cause any symptoms in the indeterminate form, it can either affect the heart, the digestive tract, or both in the determinate form. Of these three, the cardiac form is the most common and the most serious of the determinate forms. The parasite travels to and invades cardiac tissue during the acute phase, causing inflammation of the tissue. During the chronic phase, this inflammation persists and can lead to

arrhythmia, heart failure, and thromboembolism due to tissue damage (Rassi et al. 2010). Although the exact mechanism is still unclear, studies suggest that *T. cruzi* antigens trigger an immune response, which ultimately causes the inflammation (Biolo et al. 2010). Arrhythmia and heart failure can contribute to cardiomegaly, or the abnormal enlargement of the heart, which causes the heart to further decline in normal function. The cardiac form can disrupt normal heart function so severely that it can cause sudden death, the most common cause of death in cardiac chagasic patients (Rassi et a. 2010).

Manifestations of disease similar to those found in the cardiac form also appear in the digestive form. For example, through mechanisms similar to cardiomegaly, organs in the digestive tract can enlarge and result in megaesophagus and megacolon. In megaesophagus, the diameter of the esophagus increases over time, causing difficulty in swallowing, possible regurgitation, and esophageal pain. Eventually, the esophagus could increase in volume and length due to the progression of disease (Rassi et al. 2010). A similar phenomenon occurs in megacolon, where the diameter of the colon steadily increases over time, which could result in constipation and ultimately fecaloma (hardening of feces in the colon, sometime causing obstruction). Although the cardiac form is the most common determinate

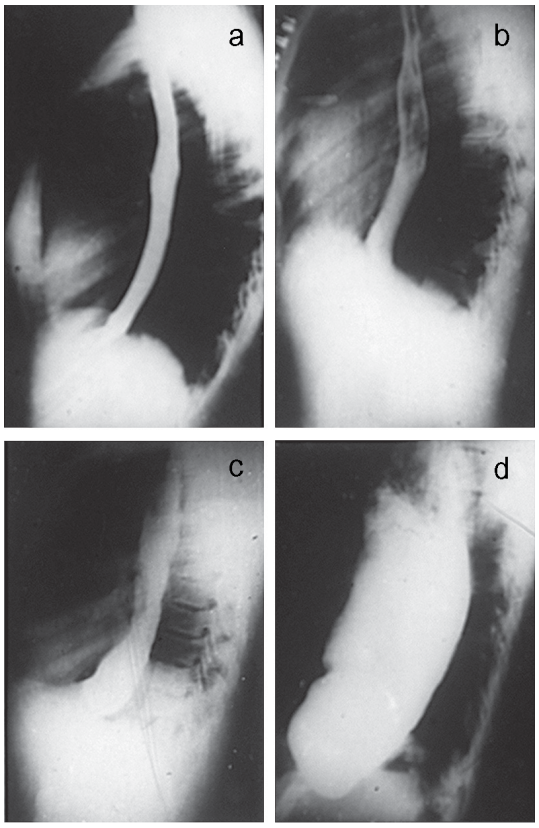

Figure 4: Progression of Chagas megaesophagus. (A) displays a normal esophagus while (D) shows a severely enlarged esophagus (Coura et al. 2007).

form of Chagas disease, oftentimes megaesophagus will precede heart disease in patients with both cardiac and digestive determinate forms (Rassi et al. 2010).

Diagnosis

Testing for Chagas disease is one of the most important aspects of the disease; due to its complicated nature and the fact that confirmed diagnosis often help with prevention of spread and other control methods. Most infectious diseases rely on clinical data and exams, with laboratory tests as a means of confirmation instead of aiding in the initial diagnosis. Because Chagas disease has an indeterminate form and symptoms in the determinate form that are usually caused by something other than a parasite, using clinical data and exams as the primary sources of information in order to make a diagnosis is faulty. More than half of the infected patients often do not present with any clinical symptoms, and some clinical tests may show normal results (Luquetti et al. 2010). Thus, laboratory testing as a means of diagnosis is essential for Chagas disease.

Different testing techniques are required for the different stages of this particular disease. For the acute phase, the main method of diagnosis has been via microscopy, where a sample of patient blood is observed under a microscope to determine if parasites are present. However, this method is only effective when the parasites are in the blood in large numbers, so during the acute phase. By the time the disease has reached the chronic stages, both indeterminate and determinate, the parasite may be migrating to tissues through the blood, but at levels too low to diagnose (Luquetti et al. 2010). Because viewing blood smears only require a very small amount of

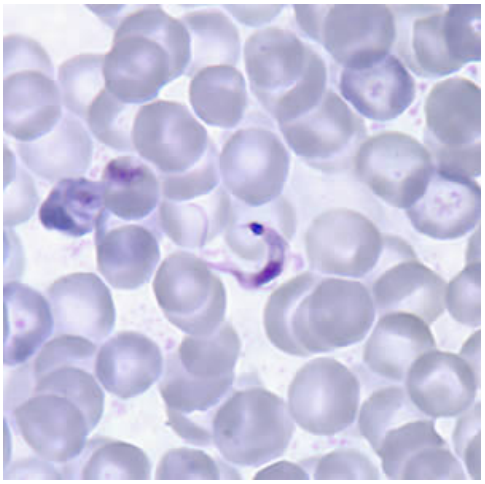

Figure 5: Blood smear with *T. cruzi* trypomastigote present among red blood cells (DPDx 2009).

blood on the slide, it is unlikely that the parasite will be observed via blood smear when there is a small amount of parasites in the blood. Not only are microscopy tests useful during the acute phase, but also they are relatively low cost since the materials used can be found in any hospital laboratory. However, the main drawbacks for this method are the use of high technology due to the use of the microscope and the need for personnel trained in performing microscopic tests in order to correctly read the blood smears (Rosenblatt 2009).

For the chronic phase, the most common test is the enzyme-linked imunnosorbent assay (ELISA), which makes use of a patient's blood serum to detect the presence of a pathogenic substance. If the serum contains the antigen presented by *T. cruzi*, antibodies attached with an enzyme that recognize this antigen will produce an enzymatic reaction, resulting in a change in color. This indicates that the antigen is present, and therefore the parasite is also present. Initially, ELISA tests were known to have high sensitivity but low specificity (Luquetti et al. 2010). This means that although it is great for detecting the presence of the antigen, it is not very specific to the Chagas antigen. Thus, ELISA tests are mainly used for blood bank screenings because they can detect specimens that present a certain antigen; however, it is not specific in determining what specimen the antigen is for. In other words, it detects an antigen's presence in the blood, but it is not necessarily the antigen to *T. cruzi*. Therefore, the ELISA test is mainly to confirm diagnosis of disease rather than to act as a main test for diagnosis (Luquetti et al. 2010). In addition, ELISA tests are generally expensive, need to be done in a laboratory, and need a skilled technician to read the results.

A modified version of the Chagas ELISA test has been developed in order to address these last few issues. This version is a rapid serological test for diagnosing a *T. cruzi* infection by using recombinant proteins in an immunochromatographic assay (Luquetti et al. 2003). By

using recombinant antigens for *T. cruzi*, a single ELISA test for multiple antigens was developed and named the Chagas Stat-Pak. This test has high specificity, high sensitivity, is a one-step process, and produces results that can be read by the naked eye and within a few minutes (Luquetti et al. 2003). This test is ideal for testing large quantities in the field with less technology and relatively low cost. Thus, not only can more people be tested easily, but also more people can be tested easily in areas that might not have a laboratory or that can afford the more expensive tests.

Another test commonly used to diagnose the chronic from of Chagas disease is polymerase chain reaction (PCR). In this test, DNA found in a patient's blood sample is extracted, amplified and compared against the known genome of *T. cruzi* to see if there is any match. If a match occurs, then the results can act as a confirmation of the parasite's presence. Although this test is efficient, accurate, and only take a few hours, it requires a greater degree of technology (Luquetti et al. 2010). This also means that it requires technicians with the skills necessary to run the test and read the results, and it is one of the more expensive diagnostic tools because it needs to take place in a laboratory and uses such high tech equipment.

Treatment

Just as Chagas disease is relatively easy to diagnose during the acute phase, it is also relatively easy to treat during this phase as well. Likewise, treating the disease during the chronic phase is complicated, similar to the complex nature of diagnosing this stage of disease. If Chagas disease is diagnosed during the acute phase, the drugs nifurtimox and benznidazole can be administered in order to kill the parasite and clear the individual of infection. These drugs are effective in treating the parasitic infection but are largely unavailable due the significant side effects that they can cause, such as dermatitis, weight loss, nausea, and polyneuropathy (Coura et

al. 2009). Thus, those wishing to receive treatment for the acute phase must acquire these drugs through the Center for Disease Control and Prevention (CDC), the World Health Organization (WHO)-Bayer Nifurtimox Donation Program, or at specialized clinics that monitor the course of treatment with these drugs (Manne et al. 2013). In addition, administering these drugs to infants infected congenitally has been shown to cure *T. cruzi* infections as well (Clavijo et al. 2012).

Once the infection reaches the chronic phase, nifurtimox and benznidazole lose their efficacy. Treatments are available to alleviate symptoms, but as with all progressive diseases, treatments usually work better the earlier in the disease they are administered. For the cardiac form of the determinate stage, drugs typically used to aid with symptoms of heart failure are also used for this stage of Chagas disease. Such drugs include angiotensin-converting enzyme (ACE) inhibitors and beta-blockers, such as catpopril and enalapril (Biolo et al. 2010). Digoxin is another drug that can be used to alleviate symptoms associated with heart failure, but requires close monitoring due to its potential toxicity to the conduction system within the body (Biolo et al. 2010). To address issues of arrhythmia, implantable cardioverter defibrillators (ICDs) can be used as a means to regulate heart rhythms. Finally, heart transplantation is considered for patients experiencing advanced stages of cardiomegaly. Surgery is often recommended for patients experiencing megaesophagus and/or megacolon, and often includes plastic repair of the esophagus or removal of certain parts of the colon (Pinotti et al. 1993).

Location

Most infections of Chagas disease are limited to the Americas, where the different species of Triatomine insects are widely distributed. The originally endemic countries are those found in South America, such as Argentina, Bolivia, Brazil, Chile, Paraguay, Uruguay, Colombia, Ecuador, Peru, and Venezuela (Moncayo 2009). Although infections still occur in

some of these countries, mostly those in the Andean region, the countries in the Southern Cone region have effectively interrupted vectorial and transfusional transmissions due to an elimination initiative from the governments of the different Southern Cone countries (Moncayo 2009). Different strains and subtypes of *T. cruzi* appear throughout the Americas, and naturally divide this region of the world based on the type of *T. cruzi* (rather than the species of vector) found. For example, about three types of *T. cruzi* are found mostly in the Southern Cone countries of South America, while another type is found in countries north of the Amazon (Patterson 2010). Such countries in this latter area include those in the Andean region as well as Central America and parts of North America, including Belize, Costa Rica, El Salvador, Guatemala, Honduras, Nicaragua, Panama, and Mexico (Moncayo 2009). Non-endemic countries are beginning to emerge with infection rates comparable to those found in South American countries (Patterson 2010). One such non-endemic area is found in the southern region of the United States.

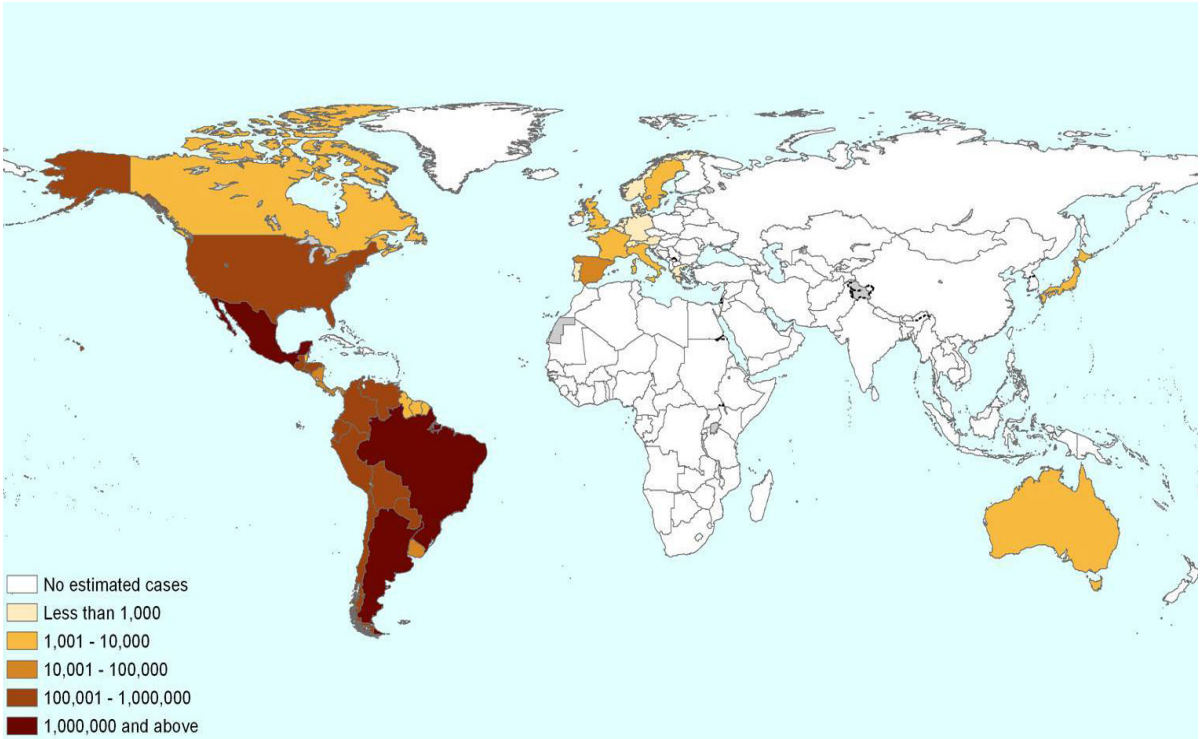

Figure 5: Map estimating global population infected by *T. cruzi* as of 2009 (Guerri-Guttenberg et al. 2008; Schmunis et al. 2007; de Ayala et al. 2009; Paricio-Talayero et al. 2008).

Poverty

The Influence of Poverty on Chagas Disease

As previously mentioned, the Triatomine insect thrives in the Central and South American countries. In order to have enough time to take a blood meal to satisfy the insect, it must stay on its prey for a long enough period of time without being detected. It accomplishes this by hiding during the day and emerging at night to take a blood meal while its prey is sleeping. The Triatomine insect usually hides in cracks and thatched roof-houses typically seen in rural, impoverished communities found in endemic countries (Guhl 2010). Compared to cement walls, cane and adobe walls provide good hiding and breeding places for Triatomine insects (Milei et al. 2009). Thus, living in impoverished areas where the materials used for housing are not sufficient to keep Triatomine bugs outside of the house contributes to a higher prevalence of this disease among poor, rural communities.

Figure 6: Typical houses where Triatomine insects hide in the cracks and nest until night, when they take blood meals from the residents sleeping inside (USAID/Bolivia/PROCOSI 2013).

Poverty can also contribute to the incidence of Chagas disease for reasons typically associated with impoverished communities experiencing disease: lack of health care resources, lack of access to health care, lack of health education, the cost of diagnosis, and the cost of treatment. Typically, rural communities foster an impoverished environment for two reasons: their residents generally have lower incomes, and they lack the resources found in larger cities. Often, such resources include those associated with health care, such as access to health care,

access to high technology required for diagnostic tests, and medical expertise. If people are living in substandard housing in areas where Chagas is endemic, it is likely that they live in areas where there is also no hospital. Furthermore, a study of Latin American doctors has shown that physicians are five times more likely to live and practice in an urban area over a rural area (Miranda et al. 2012). Therefore, if a person is experiencing chagasic symptoms, he or she might not have access to a physician who can diagnose the disease and treat the symptoms.

Even in areas where hospitals and doctors are available, the medical expertise required to correctly diagnose Chagas disease is not always available. This disease is already difficult to diagnose due to its nature: symptoms caused by Chagas disease are often unapparent or similar to those found in other diseases (Pinto-Dias 2010). In fact, Chagas is considered a "silent disease" because infected patients do not present with any major symptoms for years, and by the time they do manifest severe symptoms, it is often too late to treat (Pinto-Dias 2010). The symptoms associated with the determinate form of chronic Chagas disease, such as those pertaining to the heart and digestive tract, could be mistaken for symptoms associated with a different cause. Even in areas where physicians are available, medical expertise is needed to correctly diagnose Chagas disease. While the correct diagnosis of Chagas disease is more common in endemic countries aware of the disease's prevalence, misdiagnosis is more likely to occur in non-endemic countries due to the lack of awareness and the potential of treating infected immigrants from endemic countries.

Lack of health education is another important factor to consider. Without knowledge of the vector and how it transmits disease, what symptoms this disease can cause, and what to do if one suspects they have Chagas or live in an environment conducive to Triatomine habitation, the risk of becoming infected increases for those living in endemic countries. If they are already

infected, then they could miss the opportunity to receive appropriate treatment if they do not believe their symptoms are severe enough. By having this knowledge, those experiencing symptoms and suspecting Chagas disease during the acute phase could receive treatment (assuming they have access to a physician and can receive diagnostic testing), thus curing them from the illness and preventing it from progressing to a debilitating stage.

There are several different tests that could be used in order to diagnose Chagas disease. However, not all of these tests are low in cost, and some of them require high tech equipment that is equally expensive. Tests such as PCR and some ELISA-based tests require high technology and skilled technicians to perform the tests and read the results, thus leading to more expensive diagnostic procedures. Other tests such as the Chagas STAT-Pak do not require a lab setting or skilled laboratory personnel; thus, they are more cost-effective for impoverished communities. Using microscopy as a means for diagnosis is typically not expensive, due to the fact that most hospital laboratories already have the equipment required to run the test. However, if there is no hospital available, those living in rural communities have a more difficult time being tested for Chagas if they exhibit symptoms during the acute phase.

Treatment for Chagas disease can also be a challenge for those infected and living in an impoverished area. Chemotherapy via nifurtimox and benznidazole is mostly unavailable to patients unless they are able to find the specialized clinics in which the drugs are distributed to, which can be difficult for those living in rural areas (Coura et al. 2009). Treatment for the chronic phase generally is expensive and can incur quite substantial medical costs. In Colombia, for example, treatment for chronic Chagas disease can range from $46 - $8,000 per year (Castillo-Riquelme et al. 2008). If patients cannot afford appropriate treatment, then they are at risk of the disease progressing to the point where it can debilitate them.

The Influence of Chagas Disease on Poverty

Depending on the stage and form, Chagas disease can progress to a point that severely affects those infected. The acute stage generally manifests severe disease in young children rather than adults, and if treated during this stage via drug therapy, Chagas can be cured. If the infection is not cleared after the acute stage, most will develop a chronic infection, which can lead to very severe symptoms ranging from enlarged organs to cardiac failure.

The cardiac form of the determinate chronic phase is considered the most severe, as it can cause premature death and can lead to high medical and hospital expenses if treated (Pinto-Dias 2010). In addition, advanced heart disease can weaken individuals to the point where they can no longer work effectively; thus, some lose time from work and therefore lose a means of obtaining income. Furthermore, social factors often associated with those living in poverty can contribute to the likelihood of developing heart disease if an individual is infected with *T. cruzi* (Pinto-Dias 2010). Such factors include alcoholism, undernourishment, and lack of medical attention. Finally, the more severe forms of cardiomyopathy due to Chagas disease often cause death in men 35-50 years of age. If these men had families and if these families depended on their spouse, father, son, or brother to provide a source of income for them, then this often causes other members of the family to find work (Pinto-Dias 2010). This can lead to children leaving school prematurely in order to find work and provide their family with income, which could serve as a partial explanation as to why Chagas disease has been strongly associated with illiteracy (Aras et al. 2002). If the father of the family was infected with Chagas disease, the likelihood of infection increases for the other family members living with him in the same house. Thus, children infected with the disease might be able to survive the acute phase, but if the

infection persists as they grow older, it could result in a chronic infection that could lead them to a debilitated life as well.

Migration and Immigration, Poverty, and Chagas Disease

When those living in poverty are not making enough money to survive, the idea of moving to a different place with more options for better opportunities is always tempting. Both migration and immigration play key roles in the cycle of poverty increasing Chagas disease and Chagas disease increasing poverty. Whether it is moving from one country to another, or simply moving to a different area within the same country, individuals living in impoverished areas of endemic countries are looking for better work opportunities. As they are spreading out across the country and across different continents, they are taking Chagas disease with them.

In countries where Chagas disease is endemic, migration from rural communities to urban areas has caused a shift in where the disease is found. In Brazil, for example, it was observed that approximately 200 urban workers infected with Chagas disease had moved from different rural communities (Pinto-Dias 2013). There are several reasons for moving from the countryside to the city. First, agriculture is the main source of income for those living in rural communities. In places such as Latin America, classical familial agriculture is failing, urban industrialization is increasing, and there has been in an increase in the mass production of agricultural products (Pinto-Dias 2013). Thus, those living in rural communities need to make money where money can be made: by abandoning agriculture and getting a job in an urban area. Second, living in a rural community comes at a price, namely the lack of resources available to the area. Such resources are health care and education, both of which can help individuals better handle their poverty. For example, by having access to health care, individuals can better understand their health and address any issues they may have. In doing so, they can keep

themselves healthier, which can only help them to work harder and/or longer in order to make more money. By receiving an education, individuals open themselves (or their children) up to more job opportunities. Naturally, it makes sense to leave the rural community for an urban one.

The same argument can be made for those wishing to move to a different country in the hopes of finding better opportunities. Some countries simply have poor economies, poor governmental systems, or both, and it would make sense that impoverished people living in these conditions would want to find a way out of them. Thus, moving to a different country with a stable (or even better, a booming) economy, a stable government, or both would create more opportunities for a better job, better access to health care, and better access to education than moving to a different part of the same country. Some of these reasons have contributed to the increased immigration rates from countries in South America (endemic for Chagas disease) to countries in North America (non-endemic for Chagas disease).

Increased immigration from endemic areas to non-endemic areas has contributed to the spread of Chagas disease. Transmission by vector can still occur as long as there is a species of Triatomine in the non-endemic country (Pinto-Dias 2013). However, the more advanced the country, the less likely vectorial transmission is to occur due to better housing conditions, which would not create not good living environments for the insect. Transmission in non-endemic countries can happen in a variety of different ways: through zoonosis (animals not affected by the parasite, but serving as reservoirs), congenital transmission, blood transfusions, and organ donations. The last three methods of transmission are often associated with immigrants and the spread of disease to non-endemic countries (Pinto-Dias 2013).

Epidemiology

Vector Control Methods

Carlos Chagas, the man who discovered the disease named after him, dedicated his life to bringing attention to this disease and advocating the importance of controlling, preventing, and curing it. This disease had become important to him because he had seen how debilitating it could be to people he knew. In fact, he once commented on this by saying that this "new trypanosomiasis reached vast areas…giving rise to a degenerate population seriously jeopardizing the vitality and productivity of rural persons in the country" (Telleria et al. 2010). After several years of hard work, he was able to get the attention of the governmental systems in South American countries and was also able to establish the Centre for the Study and Prevention of Chagas Disease (Telleria et al. 2010). It was not until the late 1940s that the relevance and prevalence of Chagas disease in these countries was finally accepted and realized. At this time, control methods were developed and implemented. Traditional methods of vector control in South American countries included the spraying of insecticides on houses and other buildings that might be suitable places for the Triatomine insect to live (Moncayo 2009).

Currently, control methods in twelve Latin American countries are in place and combine the use of insecticidal spraying with promoting health education. Several of these control programs follow a three-step method that focus on killing the vector. The first step includes the preparatory phase, where mapping and planning of activities takes place. Second, an attack phase is implemented in which houses are sprayed with insecticides and followed up with a second spraying approximately 6-20 months later (Moncayo 2009). Another round of spraying will occur if any problem areas are observed. The third step then focuses on surveillance for

remaining Triatomine bugs and includes the community taking more ownership of control methods to maintain a Triatomine-free area.

Programs following this method have proven to be successful. For example, Brazil showed a 74% decrease of Triatomine prevalence in ten years after establishing such a program. By maintaining this program for 24 years, incidence rates for Chagas disease for children 7-14 years of age decreased to just 0.04% in 1999 (Moncayo 2009). In addition, studies have shown that not only has the program been successful in Brazil, but also is has been highly cost effective. In order to show this, disability-adjusted-life-years (DALYs) were used as a measure of the burden of disease prevented. During the first 20 years of its establishment in Brazil, the program was able to prevent an estimated 89% of potential disease transmission (Moncayo 2009). This correlates to a prevention in the loss of 11,486,000 DALYs, which breaks down to 31% from avoided deaths and 69% from avoided disability (Moncayo 2009). This study also showed that for every $39 (United States dollars) spent by the government on this program, one DALY was gained (Moncayo 2009). Thus, such programs are health investments with a high return.

Other Control and Prevention Methods

Although not all Latin American countries have established vector control programs, most countries do have control methods for blood banks. Such methods include screening for *T. cruzi* via serological tests, which has helped prevent the transmission of Chagas disease by blood transfusion. Testing for the parasite in the blood was made easier through the development of *T. cruzi*-specific antibodies (Hontebeyrie et al. 2010) and has resulted in a decrease in transmission in endemic countries. Unfortunately, non-endemic countries typically do not test for these antibodies, which can contribute to the spread of disease to these countries. The United States, however, found several unexpected cases of Chagas disease in the late 1990s (Hontebeyrie et al.

2010). This led to the CDC mandating all blood donors be screened for *T. cruzi*, which decreased these unexpected incidences of disease.

Preventing the spread of disease via congenital transmission requires attention, as well. The best way to prevent congenital infections is to treat infected girls before they enter their childbearing years (Carlier et al. 2010). Because treating the chronic phase is more difficult than treating the acute phase, preventing congenital transmission can be complicated if an infected woman becomes pregnant. Treatment via drug therapy is not recommended during pregnancy due to potential toxic side effects that could affect the fetus (Carlier et al. 2010). Thus, instead of prevention, there is more of a focus on controlling congenital infections. Testing mothers infected by *T. cruzi* and testing mothers in endemic areas helps physicians to know whether or not they should consider testing the baby once it is born. If the mother is seropositive and the newborn also tests seropositive, then treatment with benznidazole can begin and has shown to cure infants of the disease (Clavijo et al. 2012).

In terms of infectious diseases, preventative vaccines seem to be the ultimate way to prevent a disease from ever being contracted. While no such vaccine currently exists for Chagas disease, research to develop a preventative vaccine is a current and on-going process. Earlier this year, one dog study saw positive responses to a DNA vaccine encoding *T. cruzi* antigens, which decreased parasitemia and did not cause harm to the subjects (Quijano-Hernandez et al. 2013). This study also suggests that it is feasible to develop a similar vaccine that can be used for human infections. Therapeutic vaccines to treat the chronic phase of Chagas disease are also subjects of current research. The Sabin Vaccine Institute and Texas Children's Hospital for Vaccine Development are currently working to develop one such therapeutic vaccine (Dumonteil et al. 2012).

Areas of Focus: Mexico and the United States

The Latin American countries that have utilized vector control programs and blood bank screening have greatly reduced the number of Chagas disease infections. Chagas disease was a large health concern for these countries, but the governmental initiatives to help reduce incidence rates have greatly helped to decrease the number of infections and to control the vector. Non-endemic countries, however, are beginning to realize just how much of a threat this disease could be to them. Because Chagas disease has not been a health concern for these countries in the past, they have no methods of control or programs in place to help prevent transmission. Due to immigration from endemic countries and due to transmission via zoonosis, blood transfusion, and congenital transmission, non-endemic countries have slowly seen the number of Chagas infections rise. Two of these countries are Mexico and the United States.

Mexico

Although some studies show estimated incidence rates for Chagas disease in Mexico close to those in endemic countries, it appears as though the country is not taking precautions. One study estimated approximately 6 million cases of Chagas disease found in Mexico, making it one of the most important vector-borne neglected tropical diseases in this country (Hotez et al. 2012). However, actual prevalence rates in Mexico are not known because there is no official reporting of cases (Carabarin-Lima et al. 2013). In addition to a lack of official reporting, Mexico lacks a vector control program, despite the fact that about 8 species of Triatomine insects living in this area are capable of transmitting disease (Patterson et al. 2010). Furthermore, there appears to be debate on how to diagnose *T. cruzi* infections in blood banks and maternity wards in this country, which could lead to lower numbers of incidence rates because these patients or donors were never screened and therefore never diagnosed (Carabarin-Lima et al.2013).

There have also been problems with drug administration and health education in this country as well. Reports have shown that the drugs commonly used to treat Chagas disease during the acute phase are not on Mexico's essential medicine list (although they are listed on the WHO list) nor do these drugs have market authorization in Mexico (Manne et al. 2013). This makes it difficult for those infected and diagnosed to receive the necessary drug therapy in an adequate amount of time. These drugs can be obtained for infected Mexican residents, but only through the WHO-Bayer Nifurtimox Donation Program. This can take time, delaying therapy and potentially allowing the disease to worsen over time. Furthermore, there appears to be a lack of awareness and understanding of the disease not only among the populations at risk, but also among physicians and other health care workers (Manne et al. 2013). This has led to decreased surveillance of Chagas disease and some unwillingness to treat patients when medicinal therapy is available.

International institutes, such as the WHO, believe Chagas disease to be a threat on an international level. Mexico, however, does not seem to see this threat nationally, despite the fact that their estimated prevalence rates are comparable to those found in endemic countries. While issues with official reporting of this disease can contribute to this apparent lack of concern due to national authorities not knowing true incidence rates within the country, other national issues could be taking precedence in terms of national concern. For example, the drug war in Mexico is a huge national concern, with over 60,000 drug war deaths in only six years (Grillo 2013). It is difficult to establish control programs and other initiatives to reduce infection rates of any disease when the government is concerned with other pressing issues. Chagas disease targets a population that is poor and dependent upon governmental public actions, so surveillance and

reduction strategies will suffer until the disease becomes a political priority (Pinto-Dias et al. 2010).

The United States

Although there has been some debate as to the actual numbers of *T. cruzi* infections in the United States, it is evident that not only does Chagas disease exist within the country, but also it is considered a threat as well (Milei et al. 2009). Some studies estimate approximately 1 million Americans are infected with *T. cruzi*, while others think this number is actually closer to 300,000 infected (Hotez et al. 2012). No vector control program exists within the United States, even though approximately eleven species of Triatomine insects capable of transmitting disease live in the U.S. Because houses in the U.S., even for those living in poor populations, are typically built out of materials that do not allow for Triatomine invasion, transmission via vector is not as common as in other countries. However, several animal reservoirs exist in this country and infection among animals is considered extremely high (Patterson et al. 2010). These reservoirs include armadillos, raccoons, opossums, and even domestic dogs. Chagas disease is zoonotic, meaning the vector can transmit the parasite from a non-human host to a human. Thus, humans are at risk of contracting the disease if the vector carrying the parasite is able to take a blood meal from humans, considering the fact that houses in the United States are not conducive to Triatomine infestation.

Immigration is one of the main causes of spreading Chagas disease in the United States, especially since it is a first-world country with a decently stable government and better economic opportunities when compared to countries in Central and South America. In 2006, approximately 6 million immigrants from Mexico came to the United States, and it is estimated that 30,000 – 400,000 of these immigrants could have been infected with *T. cruzi* (Schmunis

2007). In 2007, it was estimated that 2% of the 17 million immigrants from Latin America to the United States could be infected with disease, resulting in a similar number of approximately 300,000 infections. With the Triatomine species prevalent in the United States, introducing infected individuals to a non-endemic area with no vector control measures in place creates an increased possibility for infection.

Due to its proximity to Mexico, most incidences of Chagas disease have been observed in states bordering Mexico as well as states bordering the Gulf Coast. These states include California, New Mexico, Arizona, Texas, Louisiana, and Florida, although cases have also been observed in states higher up along the Atlantic Coast, such as Massachusetts (Patterson et al. 2010). Of the 254 counties in Texas, infected vectors and hosts have been observed in 82 of them, with the greatest concentration of these counties in the southern region of the state (Hotez et al. 2012). Currently, Texas does not have control methods such as testing pregnant women for congenital infections or reporting any positive infections (Hotez et al. 2012). Although houses in this region of the country are not made out of substandard materials, the South's warmer climate can often contribute to the spread of disease. People living in impoverished areas that cannot afford air conditioning resort to leaving their windows open in an effort to feel more comfortable inside their house. This creates an opportunity for Triatomine insects to infect people while they are sleeping at night.

Due to the asymptomatic nature of the indeterminate phase, and to the mild, flu-like symptoms experienced during the acute phase in adults, those infected with Chagas disease are susceptible to misdiagnosis. This is especially true in non-endemic countries, where the disease is not seen as much of a threat. In the United States, heart disease is the leading killer of American citizens (Hoyert et al. 2011). Heart disease is also a manifestation of advanced Chagas

disease once it has progressed to the chronic determinate cardiac form. Thus, although heart disease may be the ultimate diagnosis when a patient visits his or her physician, the cause of heart disease could be misunderstood. Obesity has been linked as risk factor for developing heart disease, both of which have been problems within the United States (Krauss et al. 2000). Obesity has also been linked to those living in poverty within the United States, as populations living in poor areas often do not have access to fresh and healthy foods (Levine 2011). Thus, poverty can contribute to obesity, and obesity can contribute to heart disease. However, poverty can also contribute to the transmission of Chagas disease, and Chagas disease can also contribute to heart disease. Thus, the number of correctly diagnosed cases of heart disease due to *T. cruzi* infections becomes difficult to determine among individuals living in impoverished areas that are also at risk for Chagas disease transmission, either due to vector prevalence or increased presence of Latin American immigrants.

Analysis and Advocacy

Importance of Chagas in the United States and Mexico

The increase in incidence rates for Chagas disease in the United States has contributed to an increase in attention to the disease. Chagas disease has recently been referred as an "economic burden" due to the estimated cost of treatment for those infected, and has also been thought of as the "new HIV/AIDS of the Americas" due to some similarities between the two diseases (Lee et al. 2013, Hotez et al. 2012). Although there are not enough cases for Chagas disease to be considered an imminent threat at this point, the fact that it has gained national attention suggests that a threat could emerge unless measures are taken to prevent and control the spread of disease within the United States.

Using statistical modeling, one study has shown that on average, an infected individual can incur health care costs up to $474 (U.S. dollars) annually and $3500 over a lifetime (Lee et al. 2013). This study also showed that the economic burden due to productivity loss caused by Chagas disease is approximately $900 million within the United States, and an average of 28,000 DALYs accrued (Lee et al. 2013). The more DALYs that accumulate, the more life-years a particular country is estimated to have lost due to death or disability caused by a certain disease. Mexico was shown to have the third highest DALY burden by having an estimated 114,000 (Lee et al. 2013). The global economic burden of Chagas disease was estimated to be approximately $700 billion. To put these numbers into perspective, this means that the global burden Chagas disease creates a cost burden comparable to or exceeding the global burdens of cervical cancer and cholera (Lee et al. 2013). With these estimates, this study suggests that more attention should be directed towards Chagas prevention and control mechanisms, including research for a preventative vaccine. Even though there is a similar burden from Chagas disease as there is from human papillomavirus (HPV), the World Health Organization Expanded Program for Immunization has given more attention to the HPV vaccine that is already established than it has to research efforts to develop a vaccine for Chagas disease (Lee et al. 2013). This study also suggests that Chagas disease should be given more attention globally simply based on the number of DALYs accrued, since much of the disease burden is due to the premature deaths and productivity loss of those infected.

Chagas disease has historically been shown to affect those living in impoverished communities, and this phenomenon is still observed today in non-endemic countries such as Mexico and the United States. In 2012, Mexico had a poverty rate of 45.5%, meaning that just under half of the population is living at or below the poverty line (Wilson 2013). Thus, just

under half of the population is technically at risk for living in areas in conditions conducive to contracting Chagas disease. In 2011, 11.7 million Mexicans lived in the United States, with over half of the immigrants living in either California or Texas (Stoney et al. 2013). Furthermore, Mexican-born immigrants were more likely to live in poverty at that time than native-born residents of the United States (Stoney et al. 2013). Increasing the number of immigrants increases the chances of transmitting Chagas disease to those living in the southern parts of the United States, where the immigrants tend to reside. Because there is such a strong link between poverty and Chagas disease, and because immigrants to the United States have been found to be more likely to live in poverty, infected immigrants are more likely to contribute to the spread of disease in the impoverished areas that they live in.

Although rates are lower in the United States compared to Mexico, poverty still exists and is of national concern. In 2012, the poverty in the United States was 15%, the poverty rate in Texas was 17.9%, and the poverty rate for Hispanics in Texas during this time was 25.9% (Macartney et al. 2013). The increased number of Chagas disease transmissions in the United States, and mostly in Texas, could potentially contribute to increased poverty rates as well. Advanced cases of the chronic form of Chagas disease can debilitate those working jobs with high physical demands. Thus, if advanced disease debilitates those working to the point where they can no longer carry out their usual duties without compromising their health, then they must find another job while having no source of steady income. Ultimately, this process can contribute to an increase in poverty.

Current Model for Eradication

Due to the economic burden that Chagas disease imposes on both the United States and Mexico and due to the potential increase in poverty resulting from disease, measures need to be

taken in order to control current cases through treatment and to prevent further transmission from taking place. Programs focusing on vector control in endemic countries have been successful in decreasing their infection rates for Chagas disease, but the disease is not completely eradicated from these countries. Furthermore, these programs need to be sustained in order to continue being effective so that the vector does not reemerge in areas where it has been killed off. Sustainable programs combining vector control with health education and continuing surveillance can offer hope for eradication of Chagas disease in countries that are either endemic or non-endemic for the disease.

One type of program currently exists, but is focused on eradicating onchocerciasis. This parasitic disease affects those living in rural populations of sub-Saharan Africa, and is also transmitted via an insect vector. This program has a community-directed component, which has proven to be successful in areas where health systems are weak and under-resourced (Sambo et al. 2011). This component stresses the education of the public about onchocerciasis by allowing health workers to visit with communities in order to explain the concept of community-directed treatment. The community decides if they would like to take part in this strategy and designates community-directed distributors (CDDs). These individuals are then trained by the health worker to administer Ivermectin, the drug used to treat the disease by killing the parasite. The community also decides dates in which the drug could be effectively distributed to those living in the community. The CDD would meet with the health worker to obtain the drug before giving it to the members of the community. This way, the drug is brought to those infected rather than making those infected figure out ways to get to the nearest medical facility, which might not even have the appropriate drug for treatment. This process of drug distribution takes place once a year, since the drug is only effective for a year at a time (Sambo et al. 2011). This component

of the program would need help with funding, either from the national government or from a non-governmental development organization.

Although community involvement is a key component to this particular program, other components are necessary to ensure the successful eradication of onchocerciasis. For example, there is a vector elimination program that relies on the use of insecticides. In addition, monitoring and evaluation of current practices within the program are constantly taking place in order to identify weak areas so that they can be addressed. Finally, there is a focus on sustainability and ownership. Not only does the organization funding the program need to take ownership, but it also needs to ensure that the program is sustainable. If either the vector elimination component or the community-directed treatment component decreases in maintenance over time, then onchocerciasis will never be eradicated. Eradication is a group effort, and programs must be able to sustain long periods of time until the ultimate goal is accomplished.

Suggestions for Control and Prevention Methods

The model of control strategies for onchocerciasis has made progress, but still requires more time until the disease is eradicated from sub-Saharan Africa. This model can serve as a great starting point for programs focusing on eradicating Chagas disease, but it does have some limitations. For example, onchocerciasis causes symptoms affecting the skin that are visible and easy to see. Chagas disease manifests itself in a variety of different ways, and is often difficult to diagnose without testing. Therefore, the community-directed treatment method might not be applicable to a program for Chagas disease since many of those infected might not know that they are infected. Furthermore, Ivermectin appears to be an approved drug for treating onchocerciasis. Both nifurtimox and benznidazole are difficult to obtain and the FDA in the

United States currently has not approved either drug. Unless the CDC or the WHO-Bayer Nifurtimox Donation Program is able to supply drugs for these programs, the community-directed treatment component might not be a viable option.

This model, however, introduces the importance of education and the community to an eradication program. A community component could be implemented as part of an eradication program that also includes vector elimination. The purpose of this community component would be to inform those living in areas of risk for transmission about the vector, how it transmits disease, and what the symptoms are. By knowing this information, members of the community who are at risk can take precautions in order to reduce transmission and will hopefully be more likely to visit their physician and request testing if they are experiencing symptoms consistent to those found in Chagas disease. Because this disease is so difficult to diagnose due to its complicated nature with either general symptoms or no symptoms at all, the earlier an infection is brought to the attention of a physician, the earlier the infection can be diagnosed, treated, and hopefully cured before it progresses. Educating expecting mothers can also help control the disease. Although transmission cannot be prevented once an infected woman becomes pregnant, the newborn can be tested after birth. If positive for the disease, the infant can then receive treatment and can be cured of the disease before it ever becomes advanced. Initiatives aimed at educating the community could be accomplished via health day programs at schools and health fairs within the community. Targeting children in school is especially important, as the acute phase can be fatal to this age group if they are infected with the parasite.

Programs aiming to eradicate Chagas disease should also focus on surveillance, evaluation, and sustainability. Surveillance of community programs and of vector elimination programs is crucial in order to evaluate what is effective and what needs improvement. In

addition, whoever is funding or running the programs needs to take ownership by ensuring its sustainability and encouraging monitoring and evaluation of the program. Again, making sure that the programs are able to continue year after year is important. Programs should be maintained and should strive to improve until the disease is eradicated, with no more Triatomine vectors and no more reported infections. This could be difficult for Chagas disease, however, because those infected that are unaware that they are infected could act as reservoirs for transmission.

In addition to control programs, the eradication of Chagas can be achieved by a combination of advancements. First, rapid diagnostic testing, such as the Chagas STAT-Pak, would make it easier to diagnose more people in a short amount of time. These could be particularly effective for those living in impoverished areas, especially if health workers were able to bring these tests to those living in areas at risk for transmission. That way, if those living in impoverished areas lacked access to a hospital or to a hospital that had inexpensive testing, this could reduce the burden and complication of being tested. In addition, continued screening of all blood and organ donors is essential in order to keep transmission rates via blood transfusion and organ donation low.

While education of those at risk for contracting Chagas disease is important, it is equally important for medical personnel to also be educated on the disease: how it is transmitted, what the symptoms are, and what treatment is currently available. Misdiagnosis is a concern with this disease in which the pathology is complicated to diagnose unless physicians have an idea of what they might be looking for or dealing with. This is especially important for physicians in Mexico and the southern region of the United States. Because these areas are not considered endemic for this disease but have experienced increasing incidence rates, physicians should be educated on

how the disease manifests itself through the symptoms it causes. If physicians are more aware of Chagas disease, they might be more likely to test for it if patients present with symptoms consistent with this illness.

Finally, research is also important for the control, prevention, and possible eradication of disease. Research is needed in order to develop more diagnostic tests that have both increased sensitivity and specificity. Research is also needed to improve the current drugs available so that they can be easier to access and distribute, and have less significant side effects. New drugs that could target alleviating or relieving symptoms associated with the chronic stages of Chagas disease would also be important in developing. Lastly, the ultimate form of easy prevention is the use of a preventative vaccine. If such a vaccine could be developed, then it could be administered to those at risk of contracting the disease. Community programs could set dates in which members of the community could be vaccinated, so that nobody would ever have to be at risk for disease.

Conclusion

Chagas disease has a long history, existing in Latin American countries for over a century and now emerging in non-endemic countries such as the United States. This neglected parasitic infection affects those living in poverty, and can contribute to increases in poverty. Symptoms are often general and unspecific in the early phase of the disease while asymptomatic forms of disease can occur in the late phase, making it difficult to diagnose and to treat. Unless more control measures are instituted to control current infections and prevent the transmission of more, the impoverished populations of the Americas at risk for contracting Chagas disease are susceptible to never escaping the cycle of poverty.

Works Cited

Aras, Roque, et al. "Prevalence of Chagas' disease in Mulungu do Morro northeastern Brazil." *Arquivos brasileiros de cardiologia* 78.5 (2002): 441-443.

Bern, Caryn, et al. "Trypanosoma cruzi and Chagas' disease in the United States." *Clinical microbiology reviews* 24.4 (2011): 655-681.

Biolo, Andréia, Antonio L. Ribeiro, and Nadine Clausell. "Chagas Cardiomyopathy—Where Do We Stand After a Hundred Years?." *Progress in cardiovascular diseases* 52.4 (2010): 300-316.

Carabarin-Lima, Alejandro, et al. "Chagas disease (American Trypanosomiasis) in Mexico: an update." *Acta tropica* (2013).

Carlier, Yves, et al. "Maternal-fetal transmission of Trypanosoma cruzi." *American Trypanosomiasis-Chagas Disease-One Hundred Years of Research* (2010).

Castillo-Riquelme, Marianela, et al. "The costs of preventing and treating chagas disease in Colombia." *PLoS neglected tropical diseases* 2.11 (2008): e336.

CDC. Romaña's sign. "Other NTDs." *Centers for Disease Control and Prevention*. Centers for Disease Control and Prevention, 06 June 2011.

Clavijo, N. A., et al. "Prevalence of Chagas disease in pregnant women and incidence of congenital transmission in Santa Cruz de la Sierra, Bolivia." *Acta tropica* (2012).

Coura, José Rodrigues. "Chagas disease: what is known and what is needed-A background article." *Memórias do Instituto Oswaldo Cruz* 102 (2007): 113-122.

Coura, José Rodrigues. "Present situation and new strategies for Chagas disease chemotherapy: a proposal." *Memórias do Instituto Oswaldo Cruz* 104.4 (2009): 549-554.

Coura, José Rodrigues, and José Borges-Pereira. "Chagas disease: 100 years after its discovery. A systemic review." *Acta Tropica* 115.1 (2010): 5-13.

de Ayala, Ana Pérez, et al. "Chagasic cardiomyopathy in immigrants from Latin America to Spain." *Emerging infectious diseases* 15.4 (2009): 607.

DPDx. "*T. cruzi* trypomastigote in a thin blood smear stained with Giemsa." *DPDx - Trypanosomiasis, American Image Library*. N.p., 2009.

Dumonteil, Eric, et al. "Accelerating the development of a therapeutic vaccine for human Chagas disease: rationale and prospects." *Expert review of vaccines* 11.9 (2012): 1043-1055.

Grillo, Ioan. "Drug War No More." *nytimes.com*. The New York Times, 27 Nov. 2013.

Guerri-Guttenberg, Roberto A., et al. "Chagas cardiomyopathy: Europe is not spared!" *European heart journal* 29.21 (2008): 2587-2591.

Guhl, Felipe, and Arthur Aufderheide. "2 Chagas Disease in Pre-Colombian." *American Trypanosomiasis: Chagas Disease One Hundred Years of Research* (2010): 25.

Hamilton, Patrick B., and Jamie R. Stevens. "Classification and Phylogeny of." *American Trypanosomiasis: Chagas Disease One Hundred Years of Research* (2010): 321.

Hontebeyrie et al. "23 Other Forms of Transmission." *American Trypanosomiasis: Chagas Disease One Hundred Years of Research* (2010): 583.

Hotez, Peter J., et al. "Chagas disease:"the new HIV/AIDS of the Americas"." *PLoS Neglected Tropical Diseases* 6.5 (2012): e1498.

Hotez, Peter J., et al. "Texas and Mexico: sharing a legacy of poverty and neglected tropical diseases." *PLoS Neglected Tropical Diseases* 6.3 (2012): e1497.

Hoyert, Donna L., and Jiaquan Xu. "Deaths: preliminary data for 2011." *Natl Vital Stat Rep* 61.6 (2012): 1-65.

Krauss, Ronald M., et al. "AHA dietary guidelines revision 2000: a statement for healthcare professionals from the Nutrition Committee of the American Heart Association." *Circulation* 102.18 (2000): 2284-2299.

Lee, Bruce Y., et al. "Global economic burden of Chagas disease: a computational simulation model." *The Lancet infectious diseases* (2013).

Levine, James A. "Poverty and Obesity in the US." *Diabetes* 60.11 (2011): 2667-2668.

Luquetti, Alejandro O., et al. "Chagas' disease diagnosis: a multicentric evaluation of Chagas Stat-Pak, a rapid immunochromatographic assay with recombinant proteins of *Trypanosoma cruzi*." *Diagnostic microbiology and infectious disease* 46.4 (2003): 265-271.

Luquetti, A. O., and G. A. Scmunis. "Diagnosis of Trypanosoma cruzi infection." *American tripanosomiasis (Chagas disease) one hundred years of research. E-book. Amsterdam: Elsevier* (2010): 743-792.

Macartney, Suzanne, Alemayehu Bishaw, and Kayla Fontenot. "Poverty rates for selected detailed race and hispanic groups by state and place: 2007–2011." *American Community Survey Briefs* 11.2 (2013).

Manne, Jennifer M., et al. "Barriers to Treatment Access for Chagas Disease in Mexico." *PLoS neglected tropical diseases* 7.10 (2013): e2488.

Milei, José, et al. "Prognostic impact of Chagas disease in the United States." *American heart journal* 157.1 (2009): 22-29.

Miranda, J. Jaime, et al. "Stated Preferences of Doctors for Choosing a Job in Rural Areas of Peru: A Discrete Choice Experiment." *PloS one* 7.12 (2012): e50567.

Moncayo, Álvaro, and Antonio Carlos Silveira. "Current epidemiological trends for Chagas disease in Latin America and future challenges in epidemiology, surveillance and health policy." *Memórias do Instituto Oswaldo Cruz* 104 (2009): 17-30.

Noireau, François, and Jean-Pierre Dujardin. "7 Biology of Triatominae." *American Trypanosomiasis: Chagas Disease One Hundred Years of Research* (2010): 149.

Paricio-Talayero, José María, et al. "Vigilancia epidemiológica de la transmisión vertical de la enfermedad de Chagas en tres maternidades de la Comunidad Valenciana." *Enfermedades Infecciosas y Microbiologia Clinica* 26.10 (2008): 609-613.

Patterson, James S., and Felipe Guhl. "5 Geographical Distribution of." *American Trypanosomiasis: Chagas Disease One Hundred Years of Research* (2010): 83.

Pinotti, H. W., et al. "The surgical treatment of megaesophagus and megacolon." *Digestive Diseases* 11.4-5 (1993): 206-215.

Pinto-Dias, J., and C. Schofield. "Social and medical aspects: Morbidity and mortality in general population." *American trypanosomiasis Chagas disease. One hundred years of research. First edition. London: Elsevier* (2010): 45-54

Pinto-Dias, João Carlos. "Human Chagas Disease and Migration in the Context of Globalization: Some Particular Aspects." *Journal of tropical medicine* 2013 (2013).

Quijano-Hernández, Israel A., et al. "Preventive and therapeutic DNA vaccination partially protect dogs against an infectious challenge with< i> Trypanosoma cruzi</i>." *Vaccine* (2013).

Rassi, A., J. M. Rezende, and A. O. Luquetti. "Clinical phases and forms of Chagas disease." *American trypanosomiasis (Chagas disease). One hundred years of research. 1st edition. Burlington (MA): Elsevier Inc* (2010): 709-41.

Rosenblatt, Jon E., L. Barth Reller, and Melvin P. Weinstein. "Laboratory diagnosis of infections due to blood and tissue parasites." *Clinical infectious diseases* 49.7 (2009): 1103-1108.

Sambo, Luis. "APOC...In Brief." *APOC Magazine*. World Health Organization, Dec. 2011.

Schmuñis, Gabriel A. "Epidemiology of Chagas disease in non endemic countries: the role of international migration." *Memórias do Instituto Oswaldo Cruz* 102 (2007): 75-86.

Schmuñis, Gabriel. "Status of and cost of Chagas disease worldwide." *The Lancet infectious diseases* 13.4 (2013): 283-284.

Stoney, Sierra, and Jeanne Batalova. "Migration Information Source - Mexican Immigrants in the United States." *The Migration Information Source*. Migration Policy Institute, Feb. 2013.

Stuart, Ken, et al. "Kinetoplastids: related protozoan pathogens, different diseases." *The Journal of clinical investigation* 118.4 (2008): 1301.

Tarleton RL, Reithinger R, Urbina JA, Kitron U, Gürtler RE. The challenges of Chagas Disease-- grim outlook or glimmer of hope. *PLoS Med. 2007 Dec;4(12):e332.*

Telleria, Jenny, and Michel Tibayrenc, eds. *American trypanosomiasis: Chagas disease one hundred years of research*. Access Online via Elsevier, 2010.

USAID. "A Partnership Fights Chagas Disease." *U.S. Agency for International Development*. USAID, 09 Aug. 2013.

Wilson, Christopher. "Mexico's Latest Poverty Stats | Wilson Center." *Mexico's Latest Poverty Stats – Wilson Center*. Wilson Center, 12 Aug. 2013.