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Chagas disease in Oklahoma

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Abstract

Chagas disease, caused by infection with the protozoan *Trypanosoma cruzi*, is one of the leading public health problems in the Western Hemisphere. The parasite is mainly transmitted by contact with infected insect vectors but other forms of transmission are important in endemic areas. In the United States, while the disease is largely restricted to immigrants from endemic countries in Latin America, there is some risk of local acquisition. *T. cruzi* circulates in a sylvatic cycle between mammals and local triatomine insects in the southern half of the country, where human residents may be at risk for incidental infection. There are several reported cases of locally-acquired Chagas disease in the United States, but there is a paucity of information in Oklahoma. We present a brief summary of the available data of Chagas disease in Oklahoma to raise awareness and serve as a foundation for future research.

Key Indexing Terms:

Chagas; Trypanosoma; Oklahoma; Benznidazole; Nifurtimox

INTRODUCTION

Chagas disease, caused by infection with the parasite *Trypanosoma cruzi,* is recognized by the World Health Organization (WHO) as one of the neglected tropical diseases. According to data from 2019 and published in the most recent Global Burden of Disease report in 2020,

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DISCLAIMER

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

DECLARATION OF COMPETING INTEREST

The authors of the paper have no conflicts of interest to declare

Chagas disease is one of the leading public health problems in the Western Hemisphere.[1] Although most affected individuals are asymptomatic, morbidity and mortality related to infections are due to cardiac, gastrointestinal, or neurological involvement. Chagas disease affects approximately 5.7 million people in Latin America and over 70 million people are estimated to be at risk.[2] Despite being historically restricted to rural areas of Latin America, Chagas disease is now an emerging public health problem in major cities of Latin America and in regions outside Latin America such as Spain, Italy, Japan, and the United States (U.S.).[3]

The U. S., compared to other countries worldwide, is home to the largest number of immigrants who are infected with *Trypanosoma cruzi*. Based on data from 2005, the Centers for Diseases Control and Prevention (CDC) estimates that approximately 300,000 foreign born immigrants from endemic countries in Latin America are infected, of whom 30,000 to 45,000 have heart disease, and to whom 63–315 infants are born congenitally infected each year.[4] The most recent national estimate is of 238,091 cases of *T. cruzi* infection in the U.S. as of 2012 although it does not include undocumented immigrants who may account for as many as 109,000 additional cases.[5] Importantly, not only immigrants are at risk for the disease in the U.S. *T. cruzi* circulates in a sylvatic cycle between mammals and local triatomine insects in at least 29 states, where human residents may be at risk for incidental infection.[6] In fact, rare cases of locally acquired vector-borne *T. cruzi* infection in the U. S. have been documented, with the first cases of autochthonous infection reported in 1955.[7]

Chagas disease, caused by the protozoan parasite *T. cruzi,* is a vector-borne zoonotic disease. Triatomine insects act as vectors and acquire the parasite when they take a blood meal from an infected mammal. Infected triatomines pass the parasite in their feces when they defecate during or immediately after feeding. The parasites can infect mammals, including humans, by entering new hosts across mucosal surfaces or abraded skin. Furthermore, *T. cruzi* can be spread by blood transfusion, organ transplantation, from mother to fetus, or by ingestion of contaminated food or drink[8] (Figure 1).

Once infection occurs, the host is infected for life. The initial acute phase of the disease is typically asymptomatic, but it may also present as a nonspecific, self-limited mononucleosis-like illness. If the disease is not treated at this stage, it enters the chronic phase of infection. Approximately 60–70% of chronically infected individuals remain asymptomatic which is referred to as the indeterminate form of chronic Chagas disease. The remaining 30–40% of patients will become symptomatic 10–30 years after initial infection – mainly with cardiac or digestive tract (or both) manifestations[8] (Figure 2).

With this report, we summarize the available information about Chagas disease in Oklahoma and provide data that suggest the existence of locally acquired human cases in the State.

BRIEF OVERVIEW OF CHAGAS DISEASE IN THE UNITED STATES

Chagas diseases in the U. S. is mainly a disease of Latin American immigrants who acquired the infection in their countries of origin. The burden of the disease caused by autochthonous transmission in the U.S. is unknown and likely underappreciated. The southern half of the

U.S contains triatomines that are capable of supporting the parasitic lifecycle of *T. cruzi*. Contact with triatomines infected with *T. cruzi* has been reported within the U. S. and locally acquired cases of Chagas disease have been identified.[9–11] For example, in Texas approximately 50% of triatomines found near or inside houses were infected with *T. cruzi*.[12] Other forms of transmission such as through blood transfusion, organ transplantation, and congenital infection have also been described in the U.S.[7]

Despite the burden of the disease within the Hispanic community and the increasing number of reported cases of Chagas disease in the U.S., many barriers to care remain. For example, there is a widespread lack of awareness of the disease among public health professionals and clinical providers.[13–15] Additionally, there is an absence of effective screening programs for the disease among those at risk, few clinicians are experienced with its management, and access to care is challenging due to financial and other constraints. Chagas disease is currently a reportable condition in only seven states (Texas, Arizona, Arkansas, Tennessee, Mississippi, Louisiana, and Utah) and Los Angeles county.[16,17]

Eleven species of triatomines are found in the U.S. and ten have been found to be naturally infected with *T. cruzi* with a prevalence of infection as high as that found in Latin America. For eight species, human contact has been documented.[7,11,18,19] Locally acquired Chagas disease might not be as rare an event as previously suspected, as detailed in a recent review of the published cases in the U.S. between 2000 and 2018. The authors found 76 published cases of confirmed or suspected locally acquired disease.[11] Rural residence, history of hunting or camping, and agricultural or outdoor work were suggested as risk factors.[11]

Triatoma sanguisuga *is the most widely distributed species of triatomine in the U. S. Importantly, this species has also been implicated in at least two of the cases of local transmission within the U. S. identified to date*.[18,20,21] *Based on one study, both* T. sanguisuga *and* T. lecticularia *may be effective vectors because approximately one-fourth of the late stage instars or nymphs and female adults of* T. sanguisuga *defecate within 2 minutes of feeding and all instars of* T. lecticularia *defecate within 10 minutes of feeding*.[22]

Based on data from 2005 and assuming a transmission risk of 1%–5%, the annual number of congenital Chagas disease cases in the U.S was estimated to be 63–315 cases. Other reports estimate 166–638 cases annually.[4,23] Although there is no systematic screening to identify congenital Chagas disease in the U.S., these estimates would place its incidence in the range of that for phenylketonuria (254 births per year) or congenital adrenal hyperplasia (121 births per year), which are conditions for which the American College of Genetics recommends newborn screening.[4] Furthermore, an U.S. study showed that universal screening of pregnant women during prenatal care visits or at the time of birth is cost-effective even though only about 12% of pregnant woman are at risk.[24]

Screening for Chagas disease in the U.S. is recommended for individuals born in continental Latin America, who have spent > 6 months in a rural area of Latin America, and/or who report exposure to triatomines.[25] Screening Latin America-born persons in primary care settings has been demonstrated to be highly cost-effective in non-endemic areas such as Europe.[26] The prevalence of Chagas disease among survey participants in a Latin

America born population in Los Angeles County was 1.24% suggesting over 30,000 infected individuals live in the Los Angeles County alone.[27] In another study, the prevalence of infection was 19% among patients with non-ischemic cardiomyopathy residing in Los Angeles, but who had lived in Latin America for at least 12 months.[28]

In the U.S., voluntary blood bank screening for chronic Chagas disease was initiated in 2007 as a safety measure.[29] The Food and Drug Administration (FDA) has approved immunoassays for blood donor testing: Abbott Prism Chagas chemiluminescent assay and the Ortho *T. cruzi* enzyme linked immunosorbent assay (ELISA), both for screening, and the Abbott ESA Chagas Test for confirmatory testing. All these tests detect *T. cruzi* specific IgG antibody. Blood donor testing is performed according to FDA guidance, issued in 2010. All donated units that test positive are retested in duplicate using the same screening test. A repeatedly reactive donation undergoes a confirmatory test by a different assay. Blood donors who have a positive screening result are deferred from donating blood products. For blood donors who tested positive on the screening test but negative on the second confirmatory test, donating blood may be allowed again under specific terms described in the December 2017 FDA guidance reentry testing algorithm.[30] Blood donors who test positive are informed about the likelihood and medical significance of infection with *T. cruzi*. All donors who repeatedly test reactive are counseled to seek a physician's advice.

According to the WHO, diagnosis of chronic Chagas disease requires testing with two or more diagnostic tests as no one serologic assay has sufficient sensitivity and specificity to be used alone. Two serological tests based on different antigens and/or techniques are used in parallel to increase the accuracy of diagnosis. In some cases, the infection status remains difficult to resolve even after a third test.[31] Several diagnostic serologic kits are FDA cleared, including three ELISA tests and one rapid diagnostic test (InBios Chagas Detect Plus). Several commercial laboratories offer diagnostic serologic testing for Chagas disease, but none offers more than one serologic assay for chronic Chagas disease diagnosis at this time. Currently, CDC's Parasitic Diseases Reference Laboratory is the only laboratory in the U.S. performing two serological assays that meet the WHO recommended method for diagnosis. CDC performs reference laboratory diagnostic testing using the Chagatest recombinant v3.0 ELISA (Wiener, Rosario, Argentina) and a trypomastigote excreted or secreted antigen immune-blot (TESA IB).

A recent review of the performance of the FDA cleared serological tests in the U.S. showed a wide range of sensitivity and specificity that varied according to the country of origin of the person being tested.[32] Importantly, none of these tests had optimal performance characteristics in the population examined and a diagnostic algorithm akin to what is used in syphilis or HIV testing (i.e. highly sensitive screening test followed by a highly specific confirmatory test) is recommended.[32]

Benznidazole and nifurtimox are the only currently available drugs for the treatment of Chagas disease. Both drugs produce side effects in the majority of patients with some toxicities being severe enough to require treatment discontinuation.[25] Prior to 2017, neither drug had been FDA approved and each was released as an investigational new drug (IND) through protocols at CDC. On August 29, 2017, benznidazole obtained FDA approval for

the treatment of Chagas disease in children 2 to 12 years of age.[33] The drug became commercially available May 14, 2018 and as of that date the drug is no longer available through the CDC-sponsored IND program.[33] Nifurtimox was approved by FDA August 7, 2020 for treatment of children birth to less than 18 years of age and became commercially available in October of that year.

CURRENT SITUATION IN OKLAHOMA

The vector

Triatoma sanguisuga *and* T. lecticularia *are the only species identified in Oklahoma. Data regarding the prevalence of* T. cruzi *infected triatomines in Oklahoma are scant. A study of prevalence of* T. cruzi *infection in collected triatomines done in Texas may be relevant to Oklahoma as ecoregions are similar in the two states. Using convenience sampling, over two-thirds of insects were collected from inside or near houses. Of these, over half were infected with* T. cruzi.[12] T. sanguisuga *was one of the three species associated from human dwellings with 26% of a total of 38 specimens of* T. sanguisuga *testing positive for* T. cruzi.[12] *Perhaps more important is confirmation that* T. cruzi *infected triatomines in Texas have been in contact with humans, likely resulting in disease*.[10]

The first surveillance report of *T. cruzi* infection prevalence in kissing bugs in Oklahoma was recently published. In this study, a total of 110 kissing bugs from 22 counties were collected with 20% from 12 counties testing positive for *T. cruzi* DNA. The majority were found indoors or in close proximity to such (e.g. garages). Two specimens tested positive for both *T. cruzi* and human DNA.[34]

Wildlife and domesticated animals

T. cruzi *infection has been reported in both wildlife and domestic mammal species in Oklahoma based on several small studies. One study showed a prevalence of* T. cruzi *infection of 3.6% among 301 owned or impounded dogs in Oklahoma*.[35] *A second study found 5 of 8 (62.5%) raccoons trapped in Tulsa, OK to be infected with* T. cruzi.[36] *In a more recent study pending dissemination via publication, 13.2% of shelter dogs in Tulsa and LeFlore county tested positive for* T. cruzi *(personal communication with Dr. Kelly Allen – Oklahoma State University). These findings confirm that* T. cruzi *exists in a life cycle between insects and both wild and domestic animals. This suggests a potential risk for human transmission because of occupational exposures (e.g., dog catchers, pet groomers, veterinarians, pet owners, raccoon hunters, exotic animal park workers, fur farm workers, etc.) to infected insects and potentially through contact with blood from infected animals*.

In 2017, a total of 361 Mexican free-tailed bats (*Tadarida brasilinesis*) were sampled for *T. cruzi* at three maternity roosts in Oklahoma. One juvenile Mexican free-tailed bat was positive for *T. cruzi* resulting in 0.27% prevalence in the 361 sampled bats. More studies of vector insects and potential mammalian hosts are needed to better understand the epidemiology of this neglected tropical parasite in Oklahoma.[37]

Humans

The epidemiology of Chagas disease in humans in Oklahoma is not defined. There are also no published reports of human contact with competent vectors of Chagas disease in Oklahoma; nevertheless, we have anecdotal evidence to support that this is happening.

In 2010, a female reported seeing “bedbugs” on the ceiling of her apartment. The insects displayed the habit of congregating around her bed. One morning, she found some of the insects bloated with blood and noticed over 20 insect bites on her arms and torso. Although the insects were not available for examination by an entomologist, the pictures of the insects were highly suggestive of adults and fourth and fifth instars of *Triatoma sanguisuga*. The finding of nymphs means that the complete lifecycle of the insect likely was occurring inside the house – considered evidence of infestation.[38] The presence of infestation increases the potential for exposure to bugs and, if the bugs are infected, to the parasite.

Additional sightings occurred in Oklahoma City during the winter of 2012–2013 and were different in that only the adult form of *T. sanguisuga* was found in a house in the metro area of Oklahoma City – considered an incidental intrusion of a sylvatic species– and no bites from the insect were reported. It is important to note that for intrusion to occur an active cycle occurring around houses needs to exist.[38]

The Oklahoma State Health Department was also informed of two additional encounters between insects capable of transmitting the disease and humans in the Oklahoma City County area (Personal communication with Dr. Kristy Bradley, former State Epidemiologist). In addition to the above-mentioned encounters, one of us (N.I.A.H) has evaluated three specimens collected in the Oklahoma City metropolitan area. All specimens were sent to CDC for identification and testing for infection with *T. cruzi*. The insects were identified as *T. sanguisuga* but were not infected with the parasite.

Following FDA guidance, Oklahoma blood donors are tested for Chagas disease. The Oklahoma Blood Institute (OBI) is responsible for 80–85% of the blood supply for the state with most donors residing in Oklahoma. The OBI has been screening for Chagas disease since 2007 using the Ortho ELISA assay initially and then the Abbott assay since January 7, 2013. The “confirmatory test” has been changed periodically. The radioimmune precipitation assay (RIPA) was used from 2007 until September of 2014 when it was replaced by the Abbott ESA Chagas Assay. According to a study by Manne-Goehler et al., there were an estimated 1,407 immigrants living with Chagas disease in Oklahoma as of 2012 and 17 blood donors from Oklahoma with Chagas disease were reported to AABB (formerly American Association of Blood Banks) between January of 2007 and September of 2013.[5]

Studies in Texas reported an estimated 5.5–7.5% of *T. cruzi* infected blood donors acquired the disease locally[39] and 1/6,500 Texas blood donors tested positive for *T. cruzi* infection.[40] Given the ecological similarities between Texas and Oklahoma, we attempted to identify locally acquired infections among Oklahoma blood donors in a case control study enrolling donors who had tested positive for the disease as cases and age and geographic location matched as controls. We collaborated with the OBI to contact every donor who had tested

positive for Chagas disease since screening was implemented January 1, 2007. Our study was approved by the OU Health Sciences Center and the OBI Institutional Review Boards, respectively. In a letter sent by the OBI, positive donors were given the option of enrolling in the study by calling a pre-specified phone number. Donors were interviewed by telephone, after providing verbal consent, to determine eligibility for participation in the study.

To be included in the study the donor had to be age 18 years or older and have had at least one positive test for Chagas disease performed at the OBI. Exclusion criteria included: living in an endemic country for > 6 months, born to a mother who lived in an endemic country for > 6 months, pregnancy, receipt of a blood transfusion, organ or tissue transplant from someone who was known to have Chagas disease or who was known to have lived in an endemic country for at least 6 months, and non-English speakers. Those who did not meet eligibility criteria or declined to participate were offered access to additional diagnostic testing and expert consultation.

After obtaining written, informed consent, the participants were interviewed in person to identify potential forms of exposure. Blood was collected and sent to CDC for confirmation of *T. cruzi* infection using serological testing detailed above. Age matched neighbors living within a 1 block radius were enrolled as controls and were interviewed with the same questionnaire and tested for *T. cruzi* infection (performed at OBI).

A total of 140 letters were sent to potential participants who had at least one positive test for Chagas disease; twelve letters were returned with no forwarding address. Twelve donors returned the call and expressed willingness to participate but five were lost to follow up and could not be enrolled. Of the seven participants and two controls enrolled, six participants and both controls tested negative for *T. cruzi* infection at CDC and OBI, respectively. One participant had a positive Weiner ELISA at 2.271 (negative < 0.270; positive > 0.330, and indeterminate 0.270–0.330) and negative TESA IB. A second sample was submitted, and the Weiner ELISA was again positive at 2.271, the TESA IB was negative and an IFA was performed as a “tie breaker.” The IFA was negative at a titer of 1:16 (positive if ≥ 1:32).

During study interviews, the individual stories of the participants revealed important challenges with managing Chagas disease in the U. S. including Oklahoma. Lack of awareness is widespread in U.S. health care providers.[13–15] The seven participants who had tested positive for *T. cruzi* when donating blood were informed by OBI of that result and the need to consult their health care provider for further guidance. All but one had a follow up test at a private diagnostic laboratory. Some of the participants took their results to their primary provider and were told that the disease does not exist in the U. S. Some participants sought a second opinion but had difficulty in finding a healthcare provider aware of the current situation of Chagas disease in the U. S.

Outside of the study, we provided care for a female adult Chagas disease patient born and raised in Oklahoma City. She was initially seen in our clinic in 2018 and her infection was confirmed by testing at CDC. She was diagnosed with the indeterminate form of Chagas disease. Her mother was born and raised in Peru and had immigrated to the U.S. several decades ago. Her mother had been diagnosed with Chagas disease affecting the central

nervous system in the setting of immunosuppression which prompted testing of her children. Our patient had never traveled abroad other than to a resort in Mexico for a few days. She had not lived in any other state or in rural Oklahoma. She denied encounters with triatomine bugs, had not received a blood transfusion, and did not have a profession that would place her at risk of acquiring the disease. We hypothesize that the most likely route of transmission was congenital, making this the first reported case of congenitally acquired Chagas disease in Oklahoma.

Adequate access to care for Chagas disease in the U. S. is limited.[41] The immigrant population, which carries the burden of the disease, is especially vulnerable for a variety of reasons, including lack of awareness and knowledge among U.S. health care providers.[13–15,42] CDC only released 2–3 treatment courses for Oklahoma under their IND-sponsored protocol since it was implemented in October 2011 and until May 2018. Another patient in Oklahoma exemplifies the barriers to Chagas disease care encountered by the Hispanic immigrant population in the U.S. In 2015, a patient originally from Guatemala presented to the clinic seeking a second opinion. He had lived in the U.S. for close to 4 decades and tested positive for the disease when he donated blood in 2013. His health care provider advised the patient to return to Guatemala for treatment citing inability to offer access to treatment. The patient quit his job and returned to his home country. Treatment with nifurtimox was started but the planned treatment course could not be completed due to limited availability of the medication, a common situation in some Latin American countries that could increase the risk for development of drug resistance.[43] He returned to Oklahoma after spending 6 months in Central America.

CONCLUSIONS

Although substantial progress in the control of domestic transmission of the disease has been accomplished, Chagas disease continues to be a major public health problem in endemic countries.[44] For example, there are still regions in Latin America where greater than 95% of the population older than 30 years of age and close to 20% of the pregnant women population are infected by the parasite.[45,46]

Several factors including but not limited to poverty, political instability, violence, and climate change have spurred migration of humans from endemic to non-endemic areas of the world. In the U.S. and only considering foreign born immigrants from endemic countries that are legally in the country, an estimated 238,092 people live with *T. cruzi* infection. If undocumented immigrants are considered, the estimated total number of cases will increase to between 326,000 and 347,000.[5] Taking into account the most recent prevalence data of Chagas disease in Latin America,[2] the U.S. is home to more people infected with *T. cruzi* than 16 of the 21 endemic Latin American countries. Approximately 16.3% of Oklahoma residents (i.e. 645,000 people) were born outside of the U.S. with most originating from Mexico (approximately 110,000 people). There is also a relatively large community from Guatemala, Honduras, El Salvador, Argentina, and Venezuela totaling close to 20,000 people from these 5 countries.[10] Oklahoma ranks 27th in regards to the states with the most people living infected with *T. cruzi* with estimated cases greater or similar to states where Chagas disease is a reportable condition[5,16] and similar to the number of infected people living in

Belize.[2] The total annual cost to the State, taking into account the most recent estimate of 1,407 infected immigrants, is of approximately $18,641,343 – $24,540,594.[5,44]

Chagas disease continues to be a neglected disease, both in Latin American and non-endemic countries such as the U.S. The disease mainly affects people living in poverty in Latin America and the immigrant and vulnerable population in developed countries. Challenges in diagnosing and treating Chagas disease are therefore similar in both endemic and non-endemic regions. Lack of funding for education of both people at risk and healthcare providers, provision of screening programs (i. e. pregnant woman), assurance of access to culturally sensitive healthcare for those chronically infected, and distrust in the government programs are some of the most important barriers that we identified in Oklahoma and which are also shared by other states in the nation.[41,47]

Further research in Oklahoma might focus on identifying the risks for infection in domesticated animals and humans. There is also a pressing need to better understand the prevalence of the disease in specific patient populations such as foreign-born immigrants from endemic areas in Latin America and pregnant women. Finally, efforts to study the burden of cardiomyopathy attributed to Chagas disease in Oklahoma, especially among those originating from endemic areas, is also recommended.

Improving the care of those infected by the parasite in Oklahoma needs to be urgently addressed. Awareness of the disease in the healthcare community can be improved by partnerships between health departments, universities, and other professional organizations. Many of the important public health aspects of the disease could be addressed by making Chagas disease in animals and humans a reportable condition in Oklahoma.

The implementation of published screening guidance,[25,48] improvement of access to testing, and the creation of a patient registry and referral network to centers with the infrastructure needed to provide culturally-competent care irrespective of the insurance or immigration status will help address some of the barriers to care. Investment in this might reduce the fragmentation of care and unify efforts to address Chagas disease across institutions and stimulate needed research of this neglected entity. In the interim, patients that have tested positive for the disease can schedule an appointment in the Infectious Diseases Institute in the University of Oklahoma Health Sciences Center. Furthermore, the Oklahoma State University is currently collecting triatomine insects from Oklahoma and surrounding areas and testing them for the presence of *T. cruzi* and the origin of the insect's most recent blood meal.

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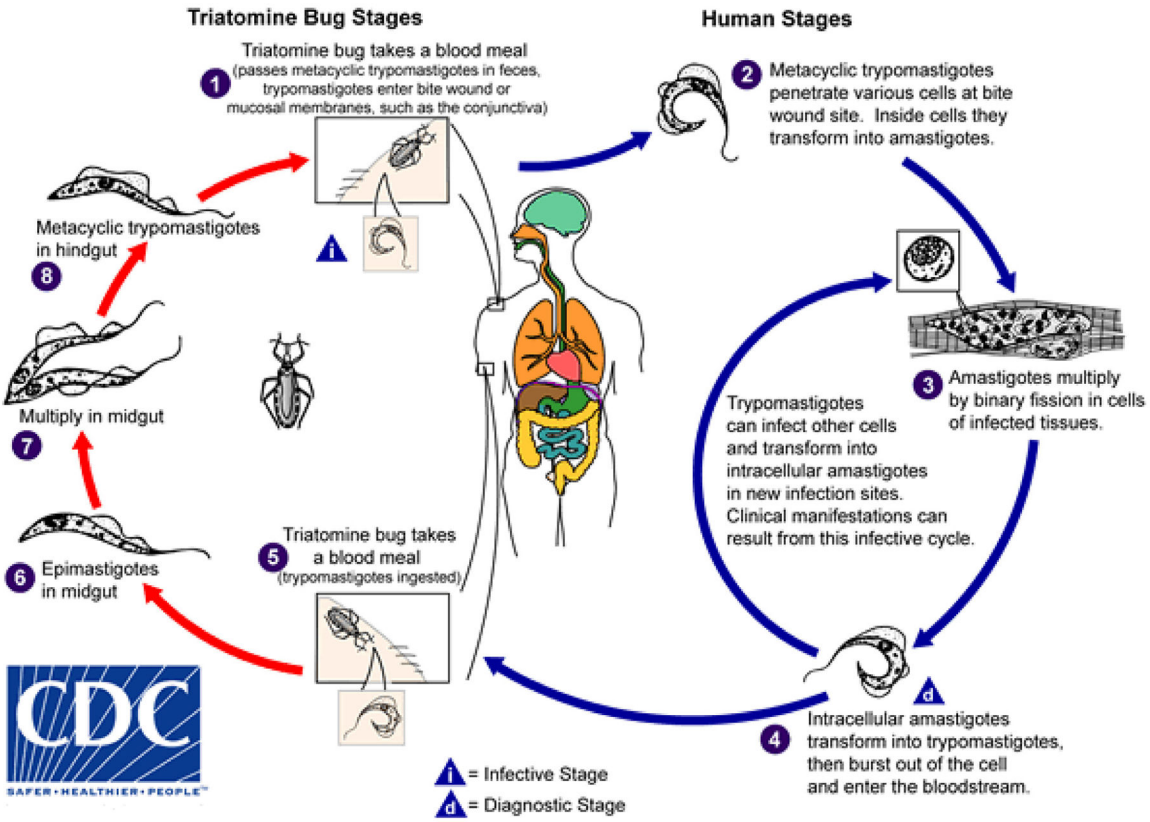

FIGURE 1.

Chagas disease: life cycle of *Trypanosoma cruzi*

Content: This illustration depicts the life cycle of the trypanosome, *Trypanosoma cruzi*, the causal agent of American trypanosomiasis, also known as Chagas disease. For a complete description of the *T. cruzi* life cycle, paste the following address in your address bar: https://www.cdc.gov/dpdx/trypanosomiasisamerican/index.html. (From Centers for Disease Control and Prevention [CDC], Atlanta, GA. Content Providers: CDC/ Alexander J. da Silva, PhD; Melanie Moser, 2002).

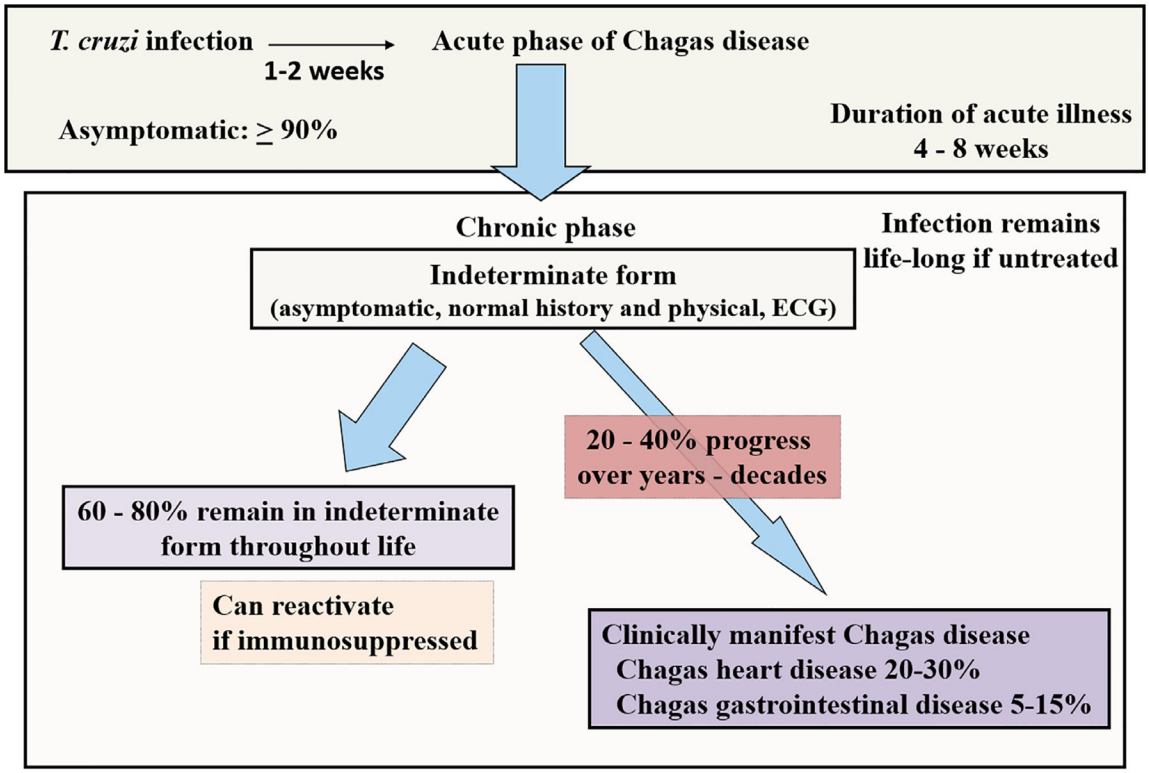

FIGURE 2.
Natural History of Chagas Disease in Humans.