

Neglected Parasitic Infections in the United States: Chagas Disease

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Abstract. Chagas disease, which is caused by the protozoan parasite *Trypanosoma cruzi*, can lead to severe cardiac and gastrointestinal disease. Most persons acquire this infection through contact with vector bugs carrying *T. cruzi* in endemic areas of Latin America. Infection can also be acquired by congenital, transfusion, transplantation, and foodborne transmission. Although an estimated 300,000 persons with Chagas disease live in the United States, little is known about the burden of chagasic heart disease. It is not known how often congenital or vector-borne transmission of *T. cruzi* occurs in the United States, although it is known that infected mothers and infected vector bugs are found in this country. Better diagnostic tests and treatment drugs are needed to improve patient care, and research is needed to define transmission risks and develop strategies to prevent new infections and reduce the burden of disease.

BACKGROUND

Chagas disease is caused by the protozoan parasite *Trypanosoma cruzi* and is endemic to the Americas. The parasite causes a vector-borne zoonosis and is capable of infecting many mammalian species, including humans. Most human *T. cruzi* infections are acquired via contact with infected triatomine bugs, when the parasite passed in triatomine feces enters the body through contamination of breaks in the skin or the conjunctiva. Vector-borne transmission can also occur when food or drink is tainted by infected triatomines or their fecal matter. Chagas disease can also be transmitted from mother to child and through blood transfusion and organ or tissue transplantation. An estimated 100 million persons are at risk for infection; most of these persons live in poverty in rural areas of Latin America, and 8 million persons have Chagas disease. Approximately 12,000 deaths are attributed to Chagas disease annually.¹

Chagas disease has two phases, acute and chronic. The acute phase of infection lasts 6–8 weeks after a 1–2 week incubation period, and is often asymptomatic. In some persons, non-specific symptoms or rarely acute myocarditis or meningoencephalitis develop; infants appear to be at higher risk for severe manifestations.² In the absence of treatment, persons enter the chronic phase of infection. Most persons will remain chronically infected and asymptomatic throughout their lives although they are still potential sources of transmission and at risk for reactivation of their infection if immunosuppression occurs. This asymptomatic presentation is the indeterminate form of chronic Chagas disease. The transition to clinical cardiac and/or gastrointestinal disease, the determinate form of chronic Chagas disease, happens after years to decades in approximately 20–30% of chronically infected persons. Progression to determinate disease may depend on host factors, including the host's immune response, and parasite factors, such as strain of infecting *T. cruzi*.^{2,3} The manifestations of determinate chronic Chagas disease are mostly cardiac and include arrhythmias, including heart block,

heart failure, and less frequently stroke, and sudden death. Gastrointestinal megasyndromes can also develop with or without cardiac disease.

Acute phase Chagas disease is diagnosed by identification of the parasite in the bloodstream by microscopic examination or hemoculture of peripheral blood; polymerase chain reaction testing (PCR) can provide earlier and more sensitive indication of circulating parasite but does not confirm the presence of viable parasites because this testing method detects only the parasite genome.⁴ In the chronic phase, the parasite is found sparsely distributed intracellularly in tissues throughout the body and rarely in the blood. Parasitemia is not detectable by microscopy and only intermittently by other more sensitive methods, such as PCR. Chronic phase infections are diagnosed by detection of *T. cruzi*-specific antibodies. The humoral immune response to the parasite is consistently present in infected persons but detectable antibody varies from person to person, and serologic assays can have varying sensitivity possibly due to the infecting strain of *T. cruzi*.^{5–7} No single serologic test is suitable as a gold standard for diagnosis.⁷ Positive results from testing with at least two different serologic assays of differing formats and antigen preparations are required to make a serologic diagnosis of infection.^{7,8}

Two drugs (benznidazole and nifurtimox) are currently available for treatment of Chagas disease. Both drugs are highly effective for treatment of acute phase infections and less so when treating chronic phase infections.^{2,8,9} The goal of treatment of chronic phase infections is to reduce or stop progression of cardiac disease, which does not appear to require parasitologic cure. Antitrypanosomal treatment is less likely to benefit patients with gastrointestinal manifestations, which are typically diagnosed after irreversible damage to intramural neurons has occurred.² Benznidazole and nifurtimox are associated with side effects that can lead to early termination of treatment, although the profile of side effects is different for each.⁹ As of 2013, neither drug has been submitted for U.S. Food and Drug Administration (FDA) approval, but both are available from the Centers for Disease Control and Prevention under investigational protocols. The frequency of side effects, lower effectiveness in chronic infections, and logistical difficulty for physicians wishing to prescribe these drugs create barriers to successful treatment of patients with Chagas disease.

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As persons migrate to urban areas within countries and to other parts of the world, Chagas disease has become a public health concern that is not limited to rural populations in Latin America. The United States and endemic Latin American countries face similar challenges, including how to increase disease awareness without increasing stigma as a disease of the poor, how to prevent congenital transmission, and how to stop the development of severe, sometimes fatal cardiomyopathy by increasing the numbers of infected persons receiving appropriate treatment. Better diagnostic tools and antitrypanosomal drugs also are needed, as well as improved access to testing and treatment. To generate effective prevention strategies, we need data to better understand the extent of Chagas disease in the United States. Critical needs include assessment of transmission rate from infected mothers to infants, quantification of the proportion of non-ischemic cardiomyopathy caused by Chagas disease, and evaluation of the risk of vector-borne transmission. In this report, we briefly outline what is known about Chagas disease in the United States, the challenges and gaps in public health knowledge, and suggested ways to address those gaps.

More information on the manifestations of disease can be found at www.cdc.gov/parasites/chagas. Continuing education credits can be obtained through an online course found at www.cdc.gov/parasites/cme/chagas.index.html.

PUBLIC HEALTH IMPORTANCE OF CHAGAS DISEASE IN THE UNITED STATES

In the United States, little evidence is available to document Chagas disease prevalence, assess congenital and vector-borne transmission risk, and quantify the clinical disease burden. Based on immigration estimates for the United States and prevalence estimates in Latin America, more than 300,000 persons with Chagas disease are living in this country; many of these persons do not know that they are infected.¹⁰ An estimated 63–315 babies acquire *T. cruzi* infection congenitally in the United States every year but most infections go undetected and untreated.^{10,11} Based on these estimates, chagasic cardiomyopathy, which can be prevented through early treatment, affects approximately 30,000–45,000 persons in the United States.¹⁰

As of February 2013, only four states (Arizona, Massachusetts, Tennessee, and Texas) were systematically collecting reports of Chagas disease, and there is no national surveillance. Some insight regarding the numbers and distribution of persons with Chagas disease comes from blood donor screening. Although most of the nation's blood supply has been screened since 2007 after licensure of a screening assay, some blood collection centers only started screening blood donations in early 2012 after release of final FDA guidance in late 2010.¹² AABB (formerly the American Association of Blood Banks) has collected reports of positive blood donor testing results voluntarily submitted by member blood collection agencies to their Chagas' Biovigilance Network. As of February 1, 2013, 1,752 blood donors with positive screening test and supplemental test results had been reported to AABB (a map showing the geographic location of positive donors by zip code of residence is available at <http://www.aabb.org/programs/biovigilance/Pages/chagas.aspx>.) Blood

donors who have tested positive for Chagas disease are concentrated in parts of the country where Latino immigrants typically reside.¹³

The potential for transmission of *T. cruzi* from infected mothers to their infants is a significant concern in the United States, and the first documented case of congenital transmission was reported in 2012.^{10,14} This report described an infant born in 2010 with clinical manifestations of congenital Chagas disease, including ascites, pleural effusion, and pericardial effusion.¹¹ Given that most congenital infections are asymptomatic at birth and that symptoms, when present, are non-specific, Chagas disease in infants likely occurs more frequently than recognized in the United States and is under-diagnosed. The prevalence of infection among women of child-bearing age is not known and there have been only small-scale efforts to assess this risk. A study of women delivering at a Houston hospital found that 10 (0.25%) of 4,000 mothers had chronic Chagas disease; 90% of the women had been born in countries other than the United States, most in Latin America.¹⁵ The result of this study was similar to a Houston study conducted 15 years earlier in which 11 (0.3%) of 3,765 pregnant women were found to be infected when tested during prenatal care visits.¹⁶

An estimated 30,000–45,000 persons likely have cardiomyopathy caused by Chagas disease in the United States.¹⁰ Since the mid-1960s, individual cases and small case series of cardiomyopathy caused by Chagas disease in Latin American immigrants have been reported but no assessment of the overall burden of disease had been made.^{17,18} Two recent studies of Latino immigrants with non-ischemic cardiomyopathy were conducted in New York City and Los Angeles. In these two studies, 13% (5 of 39 patients enrolled) and 16% (15 of 93 patients enrolled) of cases were attributable to Chagas disease.^{19–21} These results support the assumption that Chagas disease is an important cause of cardiomyopathy among Latin American immigrants in the United States. The development of heart disease may be slowed or prevented by early antitrypanosomal treatment, making Chagas disease a potentially preventable cause of heart disease in this population.^{2,8}

Vector bugs, infected animals, and the parasite *T. cruzi* are found in many parts of the southern half of the United States and rare vector-borne infections acquired domestically have been reported in humans.²² There are at least 11 species of triatomine bugs capable of transmitting *T. cruzi* in the United States, and in some areas more than 50% of triatomine bugs were found to be infected with the parasite. These bugs are found predominantly in areas where wildlife are common, unlike the peridomestic habitat of the triatomine species in Central and South America. Numerous animals can be infected and serve as a reservoir including woodrats, possums, raccoons, armadillos, and skunks.²³ Domestic dogs may also become infected and manifest clinical cardiac disease; however, their role as reservoirs in the United States is not defined.²³ Only 23 human cases of domestically acquired vector-borne Chagas disease have been reported since 1955.^{22,24–30} Of these cases, six were acute infections in five infants or young children and one adult.^{24,26–30} The remaining 17 cases were asymptomatic chronic infections, including 16 cases identified in a study of blood donors who had tested positive for *T. cruzi* infection during 2006–2010.^{22,25} The authors extrapolated their data to the wider

blood donor population, estimating that one of 354,000 U.S. blood donors might have acquired *T. cruzi* infection in the United States.²² Transmission risk to humans is likely very low and geographically restricted in the United States, and the areas where there may be a higher risk of autochthonous infection are not well defined.

GAPS IN CURRENT KNOWLEDGE AND FUTURE DIRECTIONS

High-quality data are needed to help develop strategies to minimize the health impacts of Chagas disease. As the map of blood donor testing results suggests, persons with Chagas disease are living in many parts of the United States, although often concentrated in certain areas. To efficiently target interventions to control Chagas disease, detailed information on the epidemiology of this disease is needed, including sex and age distribution, risk history such as history of birth or long-term residence in a country where transmission of *T. cruzi* occurs, and presence of clinical manifestations. Formal reporting at the state and local levels would assist efforts to understand the distribution of Chagas disease but may not provide a complete picture. Special studies are needed to generate the evidence base to design interventions to reduce the numbers of infected infants born every year, prevent the progression to serious clinical manifestations, and protect persons from vector-borne infections in the United States. Such studies would include conducting and then evaluating community-based screening surveys in areas with high concentrations of Latino immigrants to demonstrate the efficiency of that approach to identify persons with Chagas disease who are asymptotically infected.

Identifying maternal infection is the critical first step to finding those babies who should be monitored for congenital infection in the first year of life. Maternal screening should lead to appropriate treatment of the mother and identification and treatment of infected children, reducing the number of people at risk for progression to serious disease and further vertical transmission. Understanding the extent and distribution of Chagas disease in women of child-bearing age is needed to design a cost-effective strategy for this intervention. The results of the previously mentioned studies of high-risk pregnant women argue for larger and more generalizable studies to develop appropriate public health interventions.

Limited data suggest that Chagas disease may contribute to up to 16% of non-ischemic cardiomyopathy in at risk Latino populations in the United States, which could potentially be prevented with early identification and treatment. Large-scale studies are needed to assess the burden of cardiac disease, define the population at risk, and quantify the costs associated with unrecognized chagasic heart disease. These data would inform cost-effective strategies to ensure that symptomatic patients receive care appropriate for their infection and asymptomatic patients are preemptively screened and treated for chronic infection before serious disease develops.

A critical gap is lack of understanding of the risk of domestic vector-borne transmission and how autochthonous infections contribute to congenital infection and cardiac disease burden. Studies should be conducted in areas known to have triatomines infected with *T. cruzi*, to define how

often autochthonous vector-borne transmission occurs and the risk factors for infection. These studies should include determinations of the presence and *T. cruzi* infection rate in triatomine bugs and animal reservoirs within the same geographic area as an assessment of human infection risk. Consideration of autochthonous vector-borne *T. cruzi* infection among patients with cardiomyopathy in these same areas will help quantify the role of these infections in the overall Chagas disease burden. Understanding how much autochthonous transmission is occurring and who is at risk are critical to development of prevention strategies to protect persons from vector-borne infection.

Several critical tools are needed for better recognition and treatment of Chagas disease. Better performing diagnostic tests and validated rapid screening tests are needed not only in the United States but worldwide. In the United States, three serologic tests have been approved or cleared by the FDA for patient diagnosis,³¹ as of 2013, only one was available for purchase through U.S. distributors. Rapid tests, which would enable bedside testing of pregnant women at risk for chronic Chagas disease, have been studied in some countries of Latin America but not in the United States where the population at risk is composed of persons from many different endemic areas who may be infected with antigenically different strains of the parasite. As of 2013, FDA has not reviewed any rapid tests. The frequency of treatment drug side effects, lower drug effectiveness in chronic infections, and logistical difficulty for physicians wishing to prescribe drugs create barriers to successful treatment of patients with Chagas disease. New drugs that are effective, safe, and readily available are needed. Hopefully new treatment options will become available soon as a result of international drug development efforts.

What we can do now, even before the studies and surveys to best inform policies and practices are conducted, is increase awareness and knowledge of Chagas disease with health education that is accurate and useful. Most persons with chronic Chagas disease are unaware of their infection. Chagas disease is known as a disease of poverty in rural Latin America, and immigrants who have improved their family's socioeconomic status may be reluctant to accept that they are at risk because of perceived stigma. Despite the substantial number of infected persons in the United States, most U.S. health care providers are not familiar with Chagas disease.^{32,33} This lack of familiarity leads to under-diagnosis and under-reporting. Health care providers must consider this diagnosis for their patients and request appropriate testing; lack of awareness leads to missed opportunities to offer treatment that may prevent congenital transmission and the development of serious manifestations of infection in both mothers and congenitally infected infants. Public health reporting relies on health care provider awareness; currently many cases of Chagas disease are only reported to state health departments if the person donates blood and is screened for the infection as part of routine blood safety procedures. Increasing awareness of Chagas disease in at risk populations without increasing stigma and improving expertise in health care providers would lead to more people with Chagas disease being diagnosed and receiving appropriate care and better case detection. Efforts to improve the health of the U.S. Hispanic/Latino population should include Chagas disease. Chagas disease should be added to the curricula at

medical schools and to the preventive medicine agenda for primary care practitioners.

The situation in the United States is unique compared with that in other countries where Chagas disease is confined to immigrants: the United States has both the largest estimated number of immigrants with Chagas disease and uncommon but documented domestic vector-borne transmission. In addition to ensuring that immigrants with Chagas disease receive appropriate clinical management to prevent disease progression and possible congenital transmission, we need to better define domestic vector-borne risk to develop the necessary prevention strategies. Although blood donor screening and limited formal surveillance are a good start to addressing these issues, much more must be done. Research is needed to inform prevention strategies and address the challenges outlined here; the first step is to increase knowledge and awareness of this disease among health care providers, public health professionals, and the public. Successful control of Chagas disease in the United States will be built on collaborations and partnerships to address these challenges.

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