Epidemiology of Chagas Disease in Non-Endemic European Countries

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Abstract
Chagas disease results from infection by the protozoan Trypanosoma cruzi and was previously described as an endemic disease focused in populations living in poor rural areas of Latin American countries. Currently, migrant populations and some modes of transmission such as blood and organ donation or vertical transmission from infected mothers to their children have caused the spread of this disease beyond its natural geographical boundaries. In Europe, Spain, with over half of these migrants, is undoubtedly the most important recipient, followed by Italy, France and United Kingdom. However, in non-endemic countries there is no universal screening systems and also physicians are often poorly trained in recognizing this disease. So far, few countries are aware of the emergence of this disease and only few European countries have established changes in their health system to address this disease. The National European Health authorities should take part to this model-of-care, adapting in this new epidemiological scenario with screening this pathology in blood donors, organ donations or vertically from mother to child at birth. These mechanisms are the main forms of human infestation in nonendemic countries and are, therefore, the major targets for reduction of spread.

Key words: Chagas disease; epidemiology; migration

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Background
Chagas Disease (CD) or American trypanosomiasis was described by Carlos Justinoiano Ribeiro Chagas more than a century ago, in 1909. He identified both the causative agent of this infectious disease (Trypanosoma cruzi, T. cruzi) and its transmission vector, and further described the clinical picture of the disorder and possible reservoirs of the parasite.\(^1\) World Health Organization (WHO) classifies CD among the 17 “neglected tropical diseases”.\(^1\)

T. cruzi is a parasite with a wide genetic diversity, which has been grouped by consensus into 6 Discrete Typing Units (DTUs) affecting humans. Some authors have linked these DTUs with different epidemiological profiles or clinical presentations. Current classification of T. cruzi variability is based on DTUs that describe parasites genetically more similar to each other and are identifiable by common genetic, molecular, or immunological markers, constituting relevant units for molecular epidemiology and experimental evolution. There are six main DTUs, each one having distinct biological properties of infectivity, tissue tropism, and drug susceptibility. However, some patients can present infections for mixed DTUs parasites which can be challenging for therapeutic response.\(^2\)

Until recently, Chagas disease was confined to areas of South and Central America where T. cruzi is endemic. This disease is a zoonosis transmitted primarily through secretions from hematophagous triatomine insects. However, the disease can also be transmitted through nonvectorial mechanisms, such as blood transfusions, organ donations, accidental laboratory transmission or vertically from mother to child at birth.\(^3,4\)

In the last 20 years many factors have contributed to a change in the epidemiological profile of CD: the implementation of different initiatives for its control in Latin America (LA), the rise in international travel and migration, urbanisation and internal migration in endemic and non-endemic countries, have favoured the spread of this tropical diseases outside their “original” boundaries.\(^3,4,5\)

At the same time, the epidemiological profile of the disease has changed due to an ageing population and associated comorbidities. Patients with immunosuppressive disorders are particularly susceptible to an altered natural course of the disease with early reactivations and more severe clinical manifestations.\(^6\) The confluence of a disease influenced by changes in ecology and epidemiology, with a long asymptomatic phase and affecting marginalized populations, has resulted in a silent public health crisis. Moreover, only 1% of the globally infected population have access to diagnosis and treatment, which is corresponding with a 99% access gap.\(^5\)

Incidence and prevalence
The prevalence of Chagas disease has decreased from 20 million in 1981 to 8–10 million in 2005. The number of people at risk of infection likewise fell from 100 million to 28 million during the
same time period, mainly as a result of vector control campaigns and blood donation screening and new cases of the illness have reduced from 700,000/year in 1990 to 41,200/year in 2006, and the mortality from 50,000 deaths per year to the current 12,500. However, the number is probably underestimated, since recent projections assign only to North America between 1.3 and 7 million cases.5

There are also marked differences in CD prevalence between endemic countries, with the highest prevalence in the poorest areas of Bolivia, Paraguay, Argentina and Mexico. Bolivia also has the highest rate of T. cruzi infection in the world with a prevalence reported about 6.75 to 15.4%, as well as the highest rate of seroprevalence among tested donors. The next endemic countries in prevalence of Chagas disease are Paraguay (0.69–9.3%), followed by Panama (0.01–9.02%).5

Europe is hosting large populations of migrants that were estimated to account for the 8.7% of the total European population in 2010 corresponding to around 4 million people, especially in southern European countries such as Spain and Italy. About 1.4 million of these were in Spain, where 42,000 people (of which 25,000 were women of childbearing age) are estimated to be infected with T cruzi.7,8 Italy is the second country in Europe, with around 390,000 people proceeding from endemic areas and an estimated prevalence rate ranging between 1.7 and 3.1%.9 There are also marked differences in CD prevalence between endemic countries, with the highest prevalence in the poorest areas of Bolivia, Paraguay, Argentina and Mexico. Bolivia also has the highest rate of T. cruzi infection in the world with a prevalence reported about 6.75 to 15.4%, as well as the highest rate of seroprevalence among tested donors. The next endemic countries in prevalence of Chagas disease are Paraguay (0.69–9.3%), followed by Panama (0.01–9.02%).5

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Strasen et al. recently published an estimate of affected people in Europe, indicating that a minimum of about 14,000 to a maximum of about 180,000 cases would be present in Europe. The general prevalence was estimated to be 35 cases per 100,000 inhabitants, with a substantial absence of the disease in Eastern countries to 307 cases/100,000 inhabitants in Spain, 28 cases/100,000 inhabitants in Italy, 25 in Sweden and Portugal and 22 in Switzerland and the Netherlands.7,8

Limited published evidence on the prevalence of CD among Bolivians in Europe revealed a prevalence ranging from 6.8 to 25%, the lowest being the Netherlands and the highest in Spain. Also, when compared to PAHO estimates of national prevalence rates the pooled prevalence of Chagas disease in migrants from Bolivia and from Paraguay living in Europe was significantly higher (prevalence ratio 2.67 and 2.17 respectively).7,8

Nevertheless, this initial distribution is changing due to the economic crisis and currently there is a redistribution or dispersion of LA migration, especially from South Europe to other European countries. Moreover, quite often migrants move to three or more countries in short periods of time. These frequent changes pose a challenge to the health care of these people.

The importance of Chagas disease in this new scenario is directly related to the volume of migration flows received by each host country and the origin of the migrants, due to the distribution of Chagas disease not being homogeneous in endemic countries.11

Mechanism of transmission in non-endemic countries

Congenital transmission rates are estimated to be around 4.7% (range 3.9–5.6) and are significantly higher for mothers with detectable parasitaemia measured by Polymerase chain reaction (PCR). It is estimated that each year between 63 to 115 newborns are infected each year. T. cruzi infected neonates are asymptomatic or exhibit non-specific clinical signs, and obstetrician-gynecologists in non-endemic countries often have limited knowledge of CD and may be less likely to provide the prompt diagnosis and treatment that is crucial for preventing disease progression.11

The risk of mother-to-child transmission is of concern in non-endemic countries. In a study performed in Spain, the rate of prevalence of T. cruzi in LA pregnant women (N=1350) was 3.4% (27% in Bolivian mothers), with 7.3% of infected newborns.11 There are several additional ways that individuals living outside of LA may acquire T. cruzi infection such as through receipt of contaminated blood products or organs, vectorial transmission and laboratory accidents.

Transmission of CD via blood transfusion has been recognised since 1952, although the possibility of this transmission path was first raised by Mazza, in 1936. However, it was only with the advent of the human immunodeficiency virus pandemic (HIV) in the 1980s that blood control programmes were implemented in most LA countries. Also, the migration of affected and asymptomatic individuals from endemic to non-endemic areas may lead to transmission of CD by transfusion anywhere.13

Few studies have been conducted in blood banks in non-endemic countries to assess the risk of transmission in blood banks. In Spain, one study showed that 0.62% of the LA donors (N =1172) were positive for CD, but the percentage increased (10%) when only Bolivian migrants were considered. In other studies between 1% and 5% of blood donors were detected to be positive for CD in the U.S. and Germany. The total number of transfusion-transmitted (TT)-CD cases has been estimated to be between 300 and 800 in the last decades and this is corresponding with a transmission rate per infected blood unit between 10% to 25%.13

The parasite is able to survive in labile blood component storage conditions (4°C–22°C) and can also withstand freezing and thawing. The infective capacity of each type of labile blood component is different, with platelets being the most frequently reported means of transfusion transmission and irradiation or leucoreduction did not provide any protection in CD transmission. In Spain, universal blood donation screening for T. cruzi began in 2005. However, in Europe only four more countries (France, Switzerland, United Kingdom and Sweden) have implemented effective measures to control risk of CD infection via blood transfusion.13

Infection rates after solid organ transplantation from an infected donor seem to be lower for kidney transplants (0–18.7%) than they are for liver (29%) or heart transplants (up to 75%). Transmission through bone marrow transplantation has likewise been described in the USA and Spain. Another important point is that T. cruzi-infected individuals may remain asymptomatic for decades before developing symptomology. So far, additional people have already been infected with the parasite following the receipt of a blood or organ donation and are unaware of their infection status.13

Other modes of transmission of this disease in Europe are the adoption of potentially infected children from endemic regions as well as travel to endemic regions. Oral transmission of T. cruzi by tourists traveling in some areas of Latin America, such as the Amazonian region of Brazil, usually occurs due to consumption or ingestion of fresh sugar cane or berry juice made from plants harboring infected triatomine bugs.14
Clinical manifestations and diagnosis

The clinical importance of Chagas disease comes from the 30–40% of infected patients that will develop cardiac and gastrointestinal involvement many years after infection. Although, a proportion of them remain asymptomatic (in a “indeterminate” stage of the infection). However, they may be capable of transmitting the infection to others.\textsuperscript{14}

The acute phase of Chagas disease begins after 1 or 2 weeks of incubation period following inoculation. The acute phase is characterized by parasitemia and subsequent immune response. The level of parasitaemia is high during this phase and is detectable on blood microscopy. PCR also can be utilized for tissue diagnosis during the acute phase as it offers both a qualitative and quantitative assessment of Trypanosoma cruzi burden. The acute phase of Chagas disease has multiple clinical manifestations, the most common of which are nonspecific viral-like signs and symptoms including fever, malaise, and lymphadenopathy. For this reason, many infected individuals are not identified. Patients may manifest cardiac arrhythmias and transient electrocardiographic abnormalities during the acute phase. In $<5\%$ of cases, more severe illness, including myocarditis and meningoencephalitis can occur. During this phase the treatment is most effective and can be curative.\textsuperscript{14}

Twenty to thirty percent of infected individuals will progress from the indeterminate to the determinate phase of the disease and cardiac involvement arises, which is the hallmark of the chronic phase and the most common cause of death in people who die from CD. The diagnosis in this stage is focused on detection of serum antibodies of the parasite. Cardiac complications result from remodeling of the cardiac collagenous matrix and subsequent fibrosis and systolic and diastolic dysfunction, with ultimately, dilated cardiomyopathy associated with ventricular arrhythmias and the potential for sudden death.\textsuperscript{14}

Furthermore, factors such as HIV co-infection, immunosuppressive drugs, transplantation, and neoplastic disease can alter the natural course of the infection.

About 5\% of infants born to women infected with T. cruzi have congenital Chagas disease. Most congenitally infected newborns are asymptomatic or have mild symptoms, although some present with life-threatening disease. The manifestations of symptomatic congenital Chagas disease include prematurity, low Apgar scores, low birthweight, hepatosplenomegaly, anemia, and thrombocytopenia. Severely affected neonates can have myocarditis, meningoencephalitis, gastrointestinal mega-syndromes, anasarca, pneumonitis, and respiratory distress.\textsuperscript{15}

Screening

Unless Chagas disease is suspected, T. cruzi screening is not universal in European countries. Therefore, an estimated 94–96\% of infected individuals in non-endemic areas remain undiagnosed. Consequently, screening should be offered to all LA who might have been exposed to the vector or to contaminated blood products, children whose mothers were born in endemic areas, and to all family members of an index case. These recommendation are particularly relevant for patients who might obtain greater benefits from treatment, such as women of childbearing age, young patients, transplant recipients, and patients who are immunosuppressed.\textsuperscript{13} Additionally, blood, blood products, and organs donated by people from endemic areas should be screened.

In Spain, a study showed that doing a screening in pregnant women for early detection and treatment to children infected by T. cruzi was cost-effective. In other European countries, there are some other punctual initiatives from some centers for the control of newborns whose mothers are infected with T. cruzi. Due to the high efficacy of specific T. cruzi treatment in newborns (of nearly 95\%), programs for the control of Chagas disease via congenital transmission should be implemented in all countries to screen pregnant women coming from endemic areas with the objective of early treating the infected newborns.\textsuperscript{16}

PCR is indicated for diagnosis of acute and congenital infection and is deemed a useful method for monitoring response to treatment or infection reactivation after transplantation.

Treatment

Nowadays, many issues in the management of T. cruzi infection are challenging, including the high rate of underdiagnosis in endemic and non-endemic countries, uncertainties regarding the natural history and prognosis of asymptomatic patients, the scarcity of drugs with a favourable efficacy and safety profile, and the absence of reliable methods to monitor patients to confirm parasite elimination after treatment.

Currently only two antiparasitic drugs are available for treatment of CD: benznidazole and nifurtimox. These antiparasitic therapies have proven efficacy in clearing T. cruzi infection in acute, congenital and early chronic disease. The acute phase of the disease has rates of parasitological cure of 60–80\%.\textsuperscript{3} Nevertheless, the effectiveness of treatment seems to decrease in relation to the time elapsed from primary infection. Even in the absence of infection reactivation, parasiticidal treatment could be recommended in patients with neoplasms and chronic T. cruzi infection with therapeutic failure, since it has the potential benefit to prevent reactivation. Therefore, an early disease detection and intervention is crucial in all patients.\textsuperscript{18}

Another problem is that less than 30\% of patients completed treatment with dropouts along the cascade of care, in part due to adverse events of the current antiparasitic drugs and lack of proper accessibility to sanitary systems of these patients.

Future perspectives

Development of an effective vaccine or new improved therapies are crucial, and perhaps the most important next step in the fight with this disease. Another important point for preventing and controlling CD is the identification of pregnant women infected with T. cruzi. Early diagnosis and control strategies suggest a favourable cost-benefit ratio in preventing congenital transmission. Due to the substantial side effects and unclear teratogenic risks of available trypanocidal medications and a lack of other therapeutic options, there is no reliable method for preventing congenital infection. The treatment and cure of the affected newborn needs to be implemented and can also avoid transmission to second generations. However, health policies regarding the control of congenital transmission are also lacking in so many non-endemic European countries.\textsuperscript{19}

In fact, a multidisciplinary approach is essential to address this health problem that is multifaceted, which includes the coordination of various control programs (vector, vertical, blood banks, transplant), and the attention to affected people (primary care, different specialists). Moreover, the decision makers must decide priorities within their competence in face of other health problems and coordinate with professionals working in the field and with the people affected. Also is important to train health professionals in non-endemic countries the basics of care of patients affected with CD.
However, after decades of improvements in surveillance, treatment, and vector-eradication strategies, effective elimination of the disease in the near future is becoming an increasingly attainable goal. Further, there is no national framework for the control and management of CD and treatment is only available in a few countries or tertiary hospitals. There is an urgent need to involve affected communities and local regional health authorities to take part to this model-of-care, adapting it to the local epidemiology. The European health authorities should take steps in advocating for a change in the current paradigm.

Conclusion

Chagas disease, no longer confined to poor rural areas of Latin America, is now a worldwide public health concern and will remain so for the foreseeable future. Assessing the true burden and public health implications of Chagas disease in European countries is crucial for design and planning public health interventions to improve the health of migrants affected with this disease and control their transmission in European Countries.

Declarations of Interest

The author has no conflicts of interest to declare.

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The author declares she abides by the requirements for ethical publishing in biomedical journals.

Abbreviations

T. Cruzi: *Trypanosoma cruzi*.
CD: Chagas Disease.
DTUs: Discrete Typing Units.
WHO: World Health Organization.
LA: Latin American.
PCR: Polymerase chain reaction.

References