Chagas Disease Epidemiology: From Latin America to the World

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2.1 Introduction

American Trypanosomiasis evokes terms such as zoonosis, ancient, rural, poverty, ranches, palm roofs, chinches, chipos, vinchucas, Latin America, heart disease, lack of effective treatment, pacemaker, etc. It is the "traditional" epidemiology of the infection of man by the parasite *Trypanosoma cruzi* acquired through contact with infected hematophagous triatomines. After sucking human blood, they deposit feces containing very infective metacyclic trypomastigotes that invade skin cells liberating sanguineous trypomastigotes. The latter disseminate and deposit into peripheral tissues such as myocardium, fat, and digestive tract mucosa as amastigotes. Diverse immunopathological mechanisms lead to chronic organ damages.

T. cruzi infection is a consequence of different mechanisms of transmission. Two vectorial-related mechanisms are known, the transcutaneous and the oral routes, the latter following contamination of food with feces of the infected vector or with the incorporation of the vector itself into food. In addition, man-to-man infection occurs through trans-placental transmission, or by contaminated blood product, organ or tissue transfusion or transplant. Less frequently, the accidental form by manipulation of *Didelphis* sp. and infection in the laboratory due to inappropriate handling of infectious biological material [1].

The epidemiology of CD is rapidly evolving and changes have occurred both in and out of traditional endemic areas, i.e., in rural parts of North, Central, and South America. Since the mid-twentieth century, vast flux of migrations pushed millions of

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M.-J. Pinazo Delgado, J. Gascón (eds.), *Chagas Disease*,
https://doi.org/10.1007/978-3-030-44054-1_2

people from rural to urban regions in the context of socioeconomic gradients, political factors, and environmental changes [2]. Following their human hosts, the traditional rural and sylvatic vectors adapted to new environments and new cycles of transmission emerged in so far non-endemic areas of Latin America [3]. Consequently, peri-urban vectorial transmission of *T. cruzi* has been recorded in Argentina [4, 5], Bolivia [6], Brazil [7], Colombia [8], Peru [9], and Venezuela [10]. One consequence was the advent of urban outbreaks following transmission through food-related oral route [11].

Although the transmission mechanisms of the CD are diverse and versatile, Control Programs in Latin America have been mainly based on vector elimination through chemical agents spraying and more recently blood donation screening along with enhanced detection of mother-to-child transmission with early child treatment. Vectorial transmission by the main vector *Triatoma infestans* has decreased in recent decades and even potentially eradicated in some countries such as Chile, Uruguay, Brazil, eastern Paraguay, and in some regions of Argentina [12, 13]. However, vectorial transmission remains very active in Bolivia, Peru, Ecuador, Colombia, Venezuela, the Guyana, large parts of the Central American countries, and Mexico where Vector Control Programs have not been fully consolidated [13]. In absence of sustained monitoring and capacity to rapidly respond, it is likely that currently controlled areas could be re-infested [14].

In addition to the abovementioned changes, the last decades witnessed dramatic changes in transnational human mobility due to a set of factors, including globalization and the development of mass transportation systems. Indeed, large numbers of people moved out of CD endemic areas for political, socio-economical, education-related, or other reasons and settled in countries worldwide previously unaffected and unprepared for tackling this new global health issue.

2.2 Distribution and Burden of the Disease in Non-endemic Countries

The exact geographical distribution of CD and its epidemiology in America have been difficult to determine given the paucity of public health attention, and the limitations of the existing surveillance systems. Despite progress, epidemiological data remain mainly based on assumptions and models with hardly no real-life data at country levels. WHO estimated that 17.4 million persons were infected in 18 countries in 1985 with 100 million (25% of the total population) at risk of infection [15]. Thanks to improvement in living conditions, multi-pronged control programs discussed above and improved access to treatment, the prevalence has been reduced to 8–10 million in 2005 and 6–7 million in 2010 with more than 100 million persons persistently at risk of infection [16, 17]. Argentina, Brazil, Mexico, and Bolivia host the largest numbers of persons infected. The latest estimates suggest that 40,000 new infections and 15,000 deaths of CD occur every year.

In recent times, millions of people at risk have moved across international borders. This trend has accelerated since 1990 and has contributed to disseminate the infection to vector-free, subsequently called non-endemic, regions such as North

America, Japan, Australia, and Western Europe [18]. As for endemic regions, the lack of surveillance systems decreases the ability to provide a comprehensive understanding of the global epidemiological situation. Most estimates rely on epidemiological models based on the number of migrants from each country at risk multiplied by the average infection rates in those countries [17, 19–21].

In Europe, Spain has received the largest number of migrants from endemic areas, but Italy, France, Portugal, Switzerland, and the United Kingdom also host large communities. Initially, most cases were identified in adult migrants suffering severe cardiac damages or reactivation following immunosuppression [22]. In the late 1990s and the early next decade, an increasing number of *T. cruzi* transmission through congenital route and blood transfusion were reported in Europe and the USA [23–25]. This supported the idea of this health issue spreading outside Latin America and to the framing of the concept of non-endemic countries requiring specific responses [15]. Yet, in absence of epidemiological data outside Latin America, it took years before the first public health responses started to be implemented in non-endemic countries with Spain leading the way, soon followed by neighboring countries. To date, Europe has been more responsive to this emerging health problems compared to the USA, Japan, or Australia. The latest estimates pointed to 68,000–123,000 persons infected in Europe [19] and 200,000–300,000 in the USA [26] while Japan, Canada, Australia, and New Zealand were likely to host only a limited number of cases [21].

Given its chronicity and the potentially severe cardiac consequences, CD entails an economic burden of $7 billion per year, similar to or worse than other well-known diseases like rotavirus or cervical cancer [27].

2.3 Factors Affecting the Epidemiology of Chagas Disease in Europe

The origin and geographical clustering of sub-groups of migrants in Europe has had a strong influence over the distribution of cases. Migrant communities tend to cluster geographically according to origin for different reasons, including better support for new arrivants. In addition, Latin American communities have mainly settled in urban areas because of enhanced job activities opportunities. Indeed, migrants from Bolivia and Paraguay show the highest prevalence of infection [28]. In almost all seroprevalence studies, migrants coming from highly endemic areas of Bolivia account for 80% or more of cases.

Spain and Portugal for historical, cultural, political, and economic reasons have been the favored places of entry for the majority of migrants at the turn of the century. Many have acquired European Passport facilitating their integration into the country of destination. Yet, large numbers of them moved out of these countries following the 2008 financial crisis and either returned home or settled in other European countries, highlighting the dynamic, cyclical, and multi-step contemporary migratory patterns. Later on, the rise of restrictive immigration policies and the anti-immigrants rhetoric prevailing in many European countries have also influenced the mobility and distribution of communities. A key aspect pertains to the

vulnerability of labor migrants in Europe who frequently lacked access to social and financial security, usually employed in 3-D (dirty, degrading, and dangerous) and poorly paid jobs. In terms of access to care, migrant's ability to benefit from the public or private health sector widely differs from country to country and across time. Spain for example had initially rather liberal policies until a Royal Decree in 2012 severely limited access to comprehensive health services. In Switzerland, most migrants at risk have no residency permit (undocumented) and the monthly income they generate is not sufficient to cover the cost of the mandatory private health insurance which regulates access to care. In some regions, consulting at a public hospital may represent a consequent danger as health authorities have to denounce irregular migrants to the immigration departments. In many settings, language barriers, the need for out-of-pocket direct payment, geographical distances, and lack of knowledge about how to navigate the healthcare system have contributed restricting the access to medical care.

European host countries were largely unprepared for addressing the new public health and clinical challenges pertaining to the emergence of CD at the turn of the twentieth century. Most countries lacked policy regarding blood donor screening and congenital transmission screening. Still in 2018, most countries hosting substantial numbers of migrants at risk have limited diagnostic capacities and lack scheme facilitating access to anti-parasitic drugs outside the main tertiary health centers. Moreover, health professional's awareness of CD and knowledge about the optimal preventive, diagnostic, and therapeutic strategies remain very limited in Europe. As a consequence, services to communities at risk are mainly delivered by tertiary health centers in the main cities in Europe, complemented with non-governmental organizations in other parts which is largely insufficient to cover the global needs. Of note, specific programs have flourished in a few cities in Spain, Italy, Germany, and Switzerland which usually combine both social and medical strategies to improve the access to diagnosis and treatment.

Cultural representations about CD, which both take roots in the culture of origin and evolve with the new experiences overseas, impact on the health seeking behavior of people at risk [29]. Frequently associated with low social position, rurality, and lack of education which might lead to stigmatization of affected people and perceived with fatalism as an incurable infection, it tends to rank low in peoples' health priorities, especially in the context of socioeconomic vulnerability. All these factors combine to explain the low number of cases which have been diagnosed and received medical attention, including treatment, in Europe so far. Indeed, experts estimate that less than 10% of people affected by CD in non-endemic regions have been identified to date, which contributes to fuel the ongoing vertical transmission and highlights the need to implement multi-pronged strategies to curb *T. cruzi* transmission and its toll on human health.

2.4 Risk of Vectorial Transmission in Non-endemic Areas

The most important route of *T. cruzi* transmission worldwide remains vectorial despite the increasing relative importance of congenital and transfusion/transplant routes in areas where vectorial control programs have been deployed. The area of endemicity of CD in America relates to the spatial distribution of hematophagous triatomines of the genera *Triatoma*, *Rhodnius,* and *Panstrongylus*. The disease is maintained in nature as an enzootia. Recently, the rapid encroachment of urban development into wild land, the development of intensive agricultural practices, and the adaptation of vectors to peri-domiciliary and domiciliary environments have increased human contacts with vectors [30]. *Triatoma infestans* is the main vector in South America, probably originated in Bolivia. Its distribution has extended from northeastern Brazil to southern Argentina with some areas under vector control. The same dispersion has occurred with *Rhodnius prolixus*: originating from Colombia and Venezuela, it extended to The Andean region, the Guyana, and Central America [30].

The presence of hematophagous triatomines infected with *T. cruzi* (notably *T. sanguisuga*) has been reported in various Southern States of the United States of America. Zoonotic transmission has led to sporadic autochthonous human cases. Many indigenous triatomine species are susceptible to *T. cruzi* infection, thus making a source of potential vectors to human [31].

In the Old World, eight species of *Triatoma* have been identified as having a potential of transmission to humans. *Triatoma rubrofasciata* has the largest area of distribution worldwide. It spans across North (Mexico, Florida) and South America (Argentina, Brazil, Cuba and most Caribbean islands, French Guiana, Suriname, and Venezuela), Africa (Angola, Democratic Republic of Congo, Guinea-Conakry, Sierra Leone, South Africa, Tanzania, Madagascar, Mauritius, Rodriguez Islands, Seychelles), The Middle East (Saudi Arabia), South Asia and the Western Pacific Region (India-Tamil Nadu, China, Indonesia, Malaysia, Sri Lanka, Singapore, Japan, Philippines, Taiwan, Thailand, Vietnam, Andaman Islands, Tonga, Burma-Myanmar, Cambodia, Carolina Islands, Comoros Islands, Hawaii) [32, 33]. High density of this vector has been found in some urban areas causing frequent stings to humans. It is likely that cargo ship represents the main mode of transportation from the New World to other continents [33].

In recent years, evidence have shown that bedbugs (*Cimex* spp.), that have widely disseminated across the world, may be susceptible to carry *T. cruzi* and to transmit it to mice in experimental conditions [34]. *T. cruzi* is able to survive inside *Cimex* organisms and throughout the insect's molting process guaranteeing the transstadial persistence of *T. cruzi* [35]. Of concern is the fact that *Cimex* has developed resistance to insecticides such as pyrethroid [36].

2.5 Public Health Responses of Non-endemic Countries

The Chagas Disease Control Programs of the different Latin American countries have been supported by the Pan American Health Organization (PAHO) since 1991 and based on the regions diversity four different control initiatives were designated, namely the Southern Cone Initiative, the Initiative of the Andean Region, the Amazonian and the Initiative of Central America [37]. However, since 1981, an increasing number of sporadic cases of CD has occurred in other latitudes which led to the proposal of a WHO-led "Non-endemic Countries Initiative" [37]. Epidemiological surveillance activities have been progressively implemented in blood banks in the United Kingdom (1999), Spain and Italy (2005), the USA (2007), France (2009), and Switzerland (2013) [38, 39]. Of concern, several countries hosting large populations at risk still do not screen blood donors.

Some additional specific health policies targeting CD transmission exist at national or local level in Europe. National guidelines for solid organ transplant in Italy, Spain, and the United Kingdom specifically mention the need to screen for CD in donors and recipients at risk [40]. Three autonomous communities in Spain, one region in Italy (Tuscany), and some health institutions in neighboring countries have health policy for the screening of congenital transmission in pregnant women at risk and their babies [40]. In most of the European countries that do not have specific programs for CD, the rules and recommendations of the Council of Europe are followed [41]. Extra-European countries such as Australia and Japan have very limited policies, whereas the USA which hosts the largest number of infected people outside the endemic area has no other policy than blood donor screening [42].

We present below three examples of non-endemic countries with different risks of *T. cruzi* transmission to highlight the challenges pertaining to the control of the CD.

The responses in the United States of America are characterized by large heterogeneity across States and their limited scope. In 2007, blood donors screening was introduced in the USA. After 10 years, 2300 infected donors have been identified [43], mainly in Arizona, Massachusetts, Tennessee, and Texas [39]. According to the Center for Diseases Control (CDC), only seven states acted to control CD blood-donation transmission. During the 2008–2013 periods, Massachusetts complemented blood donors screening by a program of medical care to affected people but surveillance was discontinued in 2014. In 2008, there were reports of triatomines naturally infected with *T. cruzi* in Arizona, where active case detection and surveillance was implemented. Mississippi initiated actions in 2010 to determine if the cases detected in blood banks were caused by local autochthonous transmission or imported. Other States such as Tennessee, Arkansas, Louisiana, and Texas initiated active search for triatomines and naturally infected reservoirs along with medical attention to the infected persons [43]. The USA has an estimate of up to 315 congenital cases per year, but since there is no systematic search for congenital infection, it is likely that most cases remain undetected [43]. Overall, the response is largely insufficient to cover the transmission risk and to provide affected people with adequate medical care, especially in regions where most people at risk live such as California. One concern is that a significant proportion of people at risk has

no health insurance and sometimes lacks residency status which hampers access to medical care. Moreover, access to diagnostic procedures and anti-parasitic treatment is severely restricted. A positive note is the registration of benznidazole for the treatment of children.

Spain hosts the largest community of Latin Americans in Europe [44, 45]. In 2011, it was estimated that 2,090,695 Latin Americans were living in Spain in the early twenty-first century, of which 47,738 and 67,423 could be infected with *T. cruzi* [19, 28, 42]. Spain implemented blood donors screening in 2005 and subsequently put into practice policies to identify and prevent transmission by organ and tissue donation and from mother to child. Yet, responses widely differ from region to region and do currently not allow for a full coverage of risk nationwide [28]. In different regions, community-based interventions have been deployed to increase the participation to screening programs. Like in the USA, access to preventive and curative care for the most vulnerable migrants has been threatened by changes in laws.

China has yet to identify the first CD case on its territory but it hosts populations of vectors with transmission potential. The National Institute of Parasitic Diseases at the Chinese Center for Disease Control and Prevention started research in southern China in 2016 based on the concern of the expansion of CD to non-endemic countries and the increasing mobility of potential infected Latin American migrants. A resident of Foshan city in Guangdong Province has found five adults and a nymph which were morphologically and molecularly identified as *T. rubrofasciata* [32]. This vector has been found in other latitudes naturally infected with *Trypanosoma cruzi* and *T. conorhini* [33], hence the growing concern about the possibility of establishment of infection in this very populated region of China. Epidemiological surveillance is based on vector surveillance since there are no health policies related to screening in blood banks, transplants, and congenital infection. The Center for Disease Prevention and Control in Guangdong province has appealed on social media for the public to look out for South American "kissing bugs," even offering free health consultations to the inhabitants who catch triatomines [46].

2.6 Final Remarks

Although the hematophagous triatomine vectors of the American Trypanosomiasis have disseminated to the world since ancient times and that an increasing number of countries worldwide report CD cases, the importance of this disease as a global public health issue has yet to be emerged, notably in Western non-endemic countries ill prepared to face such challenges.

As a testimony of CD inclusion in the list of neglected tropical diseases by the WHO, the public health and clinical challenges remain largely unmet by health authorities and health professionals, even more so in countries where migrant populations at risk suffer inequity in accessing to their social rights such as access to care. In this regard, tackling CD in non-endemic countries can be seen as an indicator of health equity.

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