# Chagas Disease in Europe


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**Abstract** Chagas disease is an infectious disease caused by the parasite *Trypanosoma cruzi*. It affects approximately seven million people worldwide, most of them in Latin America, where insect vectors that transmit the infection are endemic. Besides, *T. cruzi* can also be transmitted through blood transfusion, organ transplant, and from mother to child. The infection is chronic in a majority of cases and remains asymptomatic for years. It is estimated that ~30% of those chronically infected will end up developing the life-threatening symptoms characteristic of the disease: heart and/or gastrointestinal tract tissue disruptions. In the last decades, large migratory flows between Latin American countries and non-endemic regions like Europe have spread Chagas disease impact. Its silent clinical progression and vector-independent transmission routes entail a health challenge in non-endemic countries too. In this chapter we present the epidemiological status of Chagas disease in Europe as well as the measures being taken to downsize its public health risk and to control the disease.

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## 1 Introduction

Chagas disease is a parasitic infection caused by the protozoan parasite *Trypanosoma cruzi* (*T. cruzi*). Although originally circumscribed to the Americas, where the vectors that generally transmit the infection are endemic, migratory flows in recent decades have spread the disease to non-endemic regions like Europe.

It is estimated that three million people arrived into Europe originating from Latin America (LA) [1]. The distribution of Latin American migrants among European countries has not been homogeneous. In addition to economic factors (chances of finding a job), political factors (ease of entry to countries, old colonial relations, current relationships between origin and reception states), and cultural features (shared language and/or customs) have been very important for migrant distribution [2]. Possibly that is why Spain and to a lesser extent Italy are the countries that have received a greater flow of people from LA (Fig. 1).

Prevalence of Chagas disease in endemic countries is not homogeneous. This has certainly contributed to shape important differences in the prevalence of Chagas disease in European receptor countries accordingly to the origin of migrants. Furthermore, the typology of migratory flows has also varied over time. Most recent migratory flows from LA are basically economic and come from rural areas that are highly endemic for Chagas disease [3].

Emergence of Chagas disease in Europe is manifest from the beginning of this century, as it has been evidenced by several studies [4–6]. Unlike other tropical diseases such as malaria or schistosomiasis, known through previous migratory flows originating in other latitudes and also through traveler's medicine, Chagas disease was unknown to European health professionals. The clinical characteristics of this disease and its variety of forms of transmission have involved new challenges that, especially in those countries that have received a lower flow of people from LA, are still not completely solved. One of the characteristics of this migration is the tendency to feminization, which is relevant in the context of Chagas disease due to the possibility of congenital transmission.

The onset of the economic crisis in Europe in 2008 and the economy improvements seen in some Latin American countries have led to the return of a percentage of this immigration to their countries of origin. Nonetheless, part of this population still remains in Europe, and a percentage of it continued its journey within the European Union (EU), basically from Spain to richer northern countries, less affected by the economic crisis [7]. In any case, this phenomenon has not substantially changed the Chagas disease problem in Europe. It has rather made it more complex, as the preparedness of health systems and the knowledge to manage the disease are not equally set in all European countries. Thereof the importance of generalizing already acquired knowledge to reaching a consensus position for the management and control of Chagas disease in the continent.

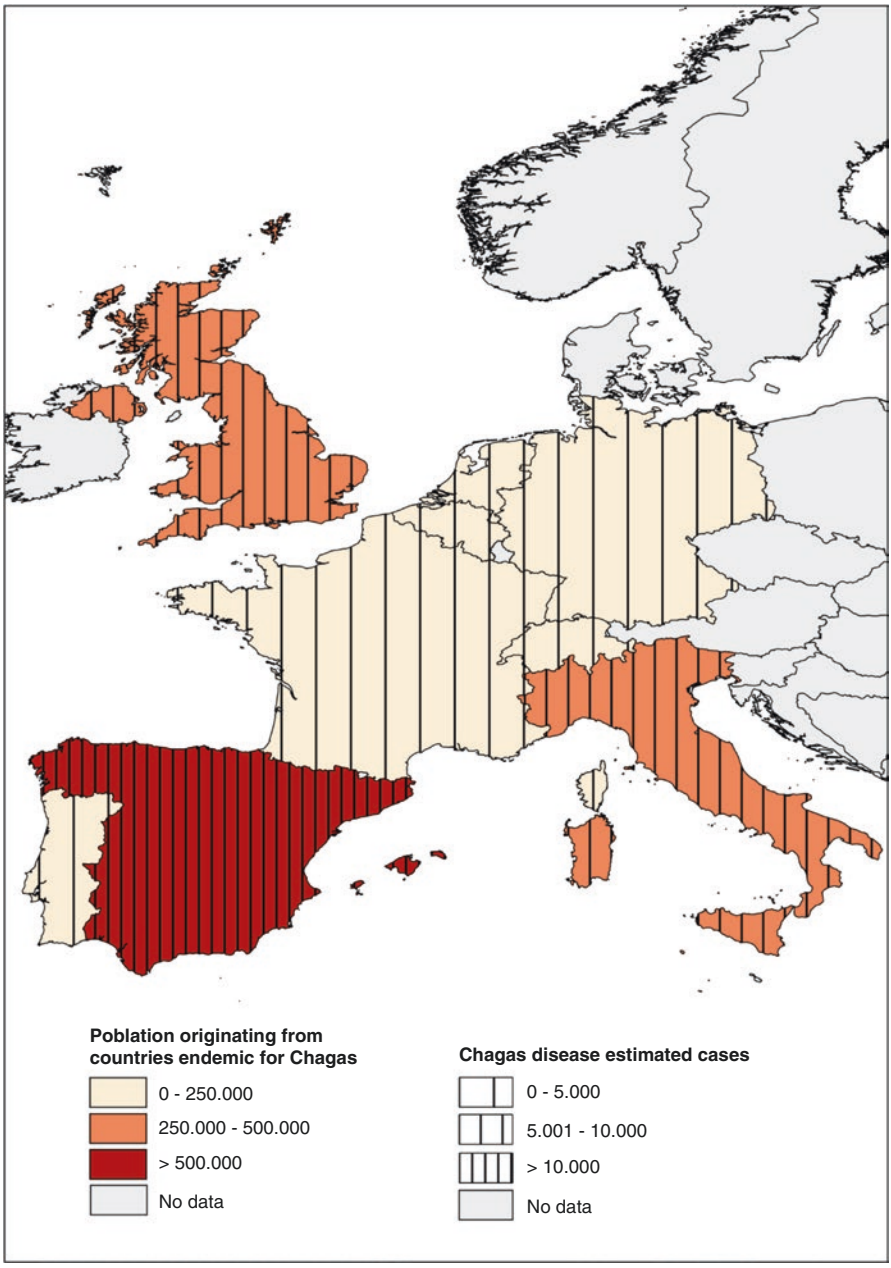


**Fig. 1** Map of Europe: countries that have received migrant population originating from Chagas disease endemic countries shaded according to the legend details; stripes pattern within each country limits indicates the number of estimated cases of Chagas disease per country. Data were extracted from reference [11] to plot the figure. [Photo Credit: Carme Subirà]

## 2 Epidemiology of Chagas Disease in Europe

There are only a few studies conducted in Europe to measure the prevalence of Chagas disease in its countries [8]. Most of the figures currently being handled are estimates based on seroprevalence data from the countries of origin of the migrants and the number of migrants coming from each endemic country [2, 9, 10]. A systematic review identified only 18 prevalence studies as having been made in Europe [8]. Taking into account these studies, around 4.2% of migrants from LA are infected with *T. cruzi*. But in truth, that percentage is very heterogeneous, and it depends on the immigrants' country of origin. For instance, migrants coming from Bolivia had the highest prevalence of Chagas disease (18.1%, 95% CI: 13.9–22.7), followed by those coming from Paraguay (5.5%, 95% CI: 3.5–7.9) [8]. The same review highlighted that prevalence estimates from studies conducted in blood bank screening were considerably lower than those derived from primary healthcare, community level, or antenatal screening [8].

Spain is currently the European country with the greatest number of cases in absolute numbers (between 48,000 and 86,000 people) [2] and in percentage (between 2.7% and 4.9% of the Latin American population) of patients infected with *T. cruzi* (including undocumented immigrants and adopted children) [11] (Fig. 1). In Italy, the seroprevalence of *T. cruzi* infection has been estimated to range between 1.5% and 2.9% depending on whether the seroprevalence estimates used to calculate it are 1990s figures [12] or more recent data from the year 2005 [9]. A serological survey performed by Angheben and coworkers among at-risk population residing in Italy described a 4.3% seroprevalence rate (36 positive participants out of 867) [6]. In Switzerland, up to 2009, a total of 258 cases had been diagnosed, although it is estimated that there may be some 3,000 people infected throughout the country [7]. In the UK, between 6,000 and 12,000 people could have the disease, which would mean a prevalence of 1.3–2.4% [11]. In other European countries that also present Latin American immigration to a lesser extent (Belgium, France, Germany, Holland, or Portugal), absolute numbers are estimated to be below 3,000 infected persons [11] (see Fig. 1). Data from other European countries is not available, although the estimated number of immigrants from LA is much lower than in the countries mentioned above.

In summary, it is estimated that in Europe absolute figures of *T. cruzi*-infected people range between 68,000 and 123,000 [11]. However, up until 2009 only 4,290 cases had been reported [11]. A study carried out in England illustrates the degree of infra-diagnosis that occurs. In this work, the total number of reported cases of *T. cruzi* infection diagnosed in London from 2001 to 2014 was 41, which yielded a prevalence of 0.043% among the Latin American migrants in the city. However, the ratio between the observed and the expected prevalence of *T. cruzi* infection was 3.34%, resulting in an index of underdiagnosis of 96.6% [13].

## 3 Routes of Transmission of *T. cruzi*

The triatomine vectors (order Hemiptera; family Reduviidae) that generally transmit the disease in America are not present in Europe [14]. Vector-independent transmission routes, like organ transplant, blood transfusion, and from mother to child, are of relevance in endemic and non-endemic regions, such as Europe [15].

### *3.1 Blood Banks and Transplants Recipients*

In Europe there have been a few cases of Chagas disease acquired through blood transfusion [16–18]. Although disease acquisition through organ transplant has also been reported [19], no prevalence studies have been published in organ donors.

Regarding blood bank surveillance, a study performed in Spain reported that 0.62% (11/1,777) of blood donors from LA were seropositive to *T. cruzi* antigens [20]. The highest rate (10.2%) was observed in Bolivian people. Other studies from France and Italy showed figures of 0.3% (3/972) and 1.0% (1/102) positive donors, respectively [21, 22]. In contrast, a work performed in the Netherlands showed 0.0% seropositive samples out of 1,333 at-risk donors tested, which mostly were from Suriname and Brazil [23]. Results from these studies come to illustrate the heterogeneous parasite prevalence rates found between different European countries in relation to the immigrants' countries of origin.

### *3.2 Congenital Transmission*

Several studies in pregnant women of Latin American origin have shown that prevalence rates of *T. cruzi* infection range between 1.5% and 4.7% of women [24–29]. In a study performed between 2005 and 2007 at two maternity hospitals in Barcelona (Spain), 3.4% of the LA women were positive for Chagas disease (46 out of 1,350 tested) [27]. Furthermore, a 7.5% rate of *T. cruzi* congenital transmission was found [27]. The incidence of Chagas disease clinical cases due to vertical transmission have been published in several European countries [28–32].

## 4 Chagas Control in Europe and Current Challenges

Chagas disease has a number of connotations that go beyond a simple parasitic infection. In many areas of LA, it is stigmatizing to endure Chagas disease, which makes of it a forgotten disease. The late onset of symptoms, linked to the fact that they are not pathognomonic of infection and are confused with cardiac or

gastrointestinal symptoms of other etiologies, has historically led to a great deal of ignorance. When symptoms do exist, patients' quality of life is impaired. Besides, *T. cruzi* infection does sometimes co-occur with other morbidities and affects other pathological processes. However, despite the high number of people that has arrived from endemic countries, studies on the health status of LA migrants are scarce [33].

In Europe, a major challenge posed by Chagas disease to public health systems and healthcare professionals is the generalized lack of knowledge of the disease, which may preclude an appropriate clinical management of patients. Another big issue is that *T. cruzi* infection is underdiagnosed [11, 13]. Poor access to diagnosis is an acknowledged massive hurdle toward disease control in endemic regions, which is most frequently observed in rural areas that are distantly located from microbiological reference laboratories [34]. Motivated by other features perhaps, but it is a phenomenon that also occurs in Europe despite the availability of wealthier healthcare systems.

## *4.1* T. cruzi *Infection Diagnosis*

Similarly to what is made in endemic countries, the diagnostic algorithms applied in Europe differ depending on whether congenital (acute) or chronic infection is to be diagnosed. In the former, due to potential false-positive confounders from parasite-specific mother-derived immunoglobulins, diagnosis in Europe is largely performed by molecular methods like that described by Piron et al. [35]. Commercial polymerase chain reaction methodologies are also available [29, 36] although at high prices. Since the sensitivity of molecular methods is not perfect, newborns to seropositive mothers (and their kin) must be serologically assayed when maternally derived antibody levels decline. In this regards, an algorithm to reduce the number of tests and restrict serological testing to months 9 and 12 of age of the child has been proposed in order to save costs [37].

At the chronic stage diagnosis is made serologically. At this stage parasitemia is low, and sensitivity of molecular detection is much poorer than indirect detection of anti-*T. cruzi* immunoglobulins in sera. Serological diagnosis involves two assays based on different antigenic sets due to the parasite high antigenic variability. If discordant results are obtained, then a third assay must be performed for tipping the scales. A recent work has questioned this procedure as it reported that a single highly specific and sensitive chemiluminescent assay (Chagas Architect, Abbott) would suffice to discard negative cases and only doubtful positive results ("gray zone") should need to be confirmed by another serological test [38].

In general, the inconveniences faced to get access to Chagas disease diagnosis in Europe are not as cumbersome as those encountered in many areas of endemic regions. However, unawareness of the disease and its characteristic silent clinical progression involves that a large percentage of patients are not timely diagnosed. Thus, specific programs have been set in place to directly bring information and promote disease screening to target populations like immigrants coming from Chagas disease endemic countries [39, 40].

On the other hand, a feature observed upon talking to experts from several European countries was the high level of heterogeneity among diagnostic algorithms used in each place. Certainly, arrival to a consensus could be of great help to standardize the diagnosis and ulterior access to treatment of patients, but also, very importantly, to save costs in the process.

## *4.2 Treatment and Management of Patients*

The two anti-parasitic drugs used to date (benznidazole and nifurtimox) to treat *T. cruzi* infection are available in Europe. However, the routes of acquisition of these drugs may vary from country to country depending on whether benznidazole or nifurtimox is prescribed. Mirroring what occurs in endemic areas, there is also an open debate in Europe about whether all patients infected with *T. cruzi* should or should not be treated. In general, international consensus is followed, which means that anti-parasitic drug treatment is recommended for patients in the acute stage, for those at chronic stage with infection reactivation, and for chronic patients under 50 years of age without clinical symptoms or mild cardiologic compromise (Kushnir level I) [41]. It is especially relevant to treat women at child-bearing age as it has been shown that benznidazole treatment of women before pregnancy significantly reduces the risk of transmission of the infection to their newborns [42, 43]. Whether older patients may receive treatment or not depends on each clinician's judgment. The lack of biomarkers of therapeutic efficacy is certainly a handicap when it comes to establishing more solid consensuses [44].

Benznidazole is the most widespread drug due to its availability. The regime indicated for adults involves a 5 mg/kg daily dose (up to a maximum of 400 mg per day) administered in two doses for 60 days. In children, benznidazole should be indicated with an 8–10 mg/kg daily administered in two or three doses for 60 days as well. A pediatric formulation of benznidazole has been successfully assessed in a clinical trial and will be produced soon in Argentina [45, 46]. Nifurtimox should be prescribed at a 15 mg/kg daily dose for children and 8–10 mg/kg for adults in three doses for 60 days [15]. Nifurtimox daily accumulated dose should not surpass 600 mg. Both drugs are well tolerated by children, and even a more specific age-related dosing has been proposed [47]. Once treatment is initiated, patients are regularly observed for the onset of adverse drug reactions (ADRs) which are mostly skin-related manifestations, digestive disorders, and general ADRs like headache, asthenia, and fever [48]. ADRs such as muscular-articular and neurological complains are less common [48, 49]. Nonetheless, in a very low percentage of cases, hospitalization is required, and updated clinical guidelines are of major importance to closely monitor these events [48, 49].

Patients' access to diagnosis and treatment within Europe differs accordingly to the health systems of each country and the personal status of immigrants (legal entitlements). For instance, in Spain universal access to the healthcare system facilitates the entry of patients into the system. Despite this, there are other bar-

riers (work schedules, permits, language, unfamiliarity with rights, entitlements, and the overall health system gaps in health literacy, social exclusion, and direct and indirect discrimination) that hinder their care [50]. On the other hand, health systems of recipient countries should ensure that health professionals are aware of the existence of Chagas disease and have adequate clinical guidelines. In Spain, the most affected European country, a series of clinical guidelines and consensus documents have been produced and published in national and international journals with the aim to help health professionals to know about Chagas disease and to provide protocols for chronic Chagas cardiologic and digestive disease [51–53]. The management of Chagas disease has been as well documented in the context of primary healthcare [54] and under immunosuppression conditions like in patients with HIV/AIDS [55] or organ and tissue transplants recipients [56].

Patient management after access to diagnosis and treatment is not easy. In one study focusing on process of care for Chagas disease in Italy, less than 30% of patients completed treatment with dropouts along the cascade of care. The authors concluded that there is an urgent need to involve affected communities and local regional health authorities to take part in the model of care, adapting it to the local needs [57]. Probably similar facts occur in other European countries. In complex cases with advanced disruption of heart and/or gastrointestinal tract tissues, the referral to specialists in cardiology or gastroenterology should follow the usual circuits of the different health systems.

## 5 Efforts to Control Transmission

### *5.1 Blood Banks*

Most European countries follow the EU Directive 2004/23/EC on safety and quality of blood. In this document, an antecedent of Chagas disease is specified as a permanent exclusion criterion for homologous donors. But there are many patients at risk of *T. cruzi* infection who have never had a screening test and therefore do not know whether or not they carry and may transmit the parasite. Only France, Spain, and the UK currently have a legal regulation that makes explicit the screening of *T. cruzi* prior to donation; this includes not only migrants from endemic areas but also children born to mothers of endemic areas and persons who have received transfusions in endemic countries [58–60].

Italy is in the process of approving a new law in the parliament that allows systematic screening in patients at risk of infection [61]. The legislation in Sweden directly excludes people who have lived more than 5 years in countries endemic to the disease, although they do not refer to children of mothers born in endemic areas [62]. As a rule, donation is excluded in Switzerland in case of diagnosis of Chagas disease, but some cantons such as Geneva and Vaud have now implemented unofficial screening measures at the hospital level. There is no data from other European countries, although the Latin American presence in these countries is practically nonexistent.

## 5.2 Transplants

The use of donor organs with acute infection is contraindicated, and the use of a donor heart with chronic infection is also contraindicated. However, the use of other organs from donors with chronic infection has a relative contraindication. If transplantation is decided, periodic monitoring of the recipient should be recommended using parasitological and serological methods [56].

There are few European countries with a current legislation that considers transplants and Chagas disease. But in the EU directives on organ transplantation, there is no mention of Chagas disease [63]. It only points out that it is necessary to investigate certain epidemiological situations that may affect the suitability of the transplant and that may imply a risk in the transmission of some disease. In Italy, since 2012, a legal regulation has been approved obliging the screening of *T. cruzi* in donors at risk [64]. In Spain, although the legislation concerning this issue is vague [65], the National Transplant Organization (ONT) has made some official recommendations [66].

## 5.3 Congenital Transmission

It is of special interest the management of *T. cruzi* infection in pregnancy, during which, although it is of vital importance to carry out the diagnosis, it is not possible to administer treatment to the pregnant woman. Treatment in newborns is highly effective, and the early treatment during the first months of life will prevent future complications of the disease, thereby the great relevance of adequately diagnosing mothers before delivery. Diagnosis of *T. cruzi* infection during pregnancy will allow careful monitoring of the affected women and early control of the newborns, which should be immediately treated in case the parasite is transmitted. Several studies have shown that congenital transmission control programs are cost-effective in endemic countries [67]. In European countries, where health systems are widely established and health economics less stringent, timely screening of pregnant women suspected of at risk of infection should be mandatory. Furthermore, preventive widespread diagnosis and treatment of *T. cruzi*-infected women in child-bearing age has been shown to be beneficial to control transmission of the infection during pregnancy [42, 43]. For this particular group of patients, it would then be very advisable to implement diagnostic algorithms to limit the transmission and save newborns from receiving treatment.

In some areas of Spain, specifically in Catalonia and Valencia, and in Tuscany in Italy, control measures for *T. cruzi* infection in pregnant women at risk of infection and control programs of newborns have already been approved by regional governments [68–70]. In other regions of several European countries (at least four in Spain, three in Italy, one in Germany, two in Switzerland, and two in Portugal, and there might be more the authors do not currently know about), there are local initiatives, generally promoted by hospitals or research centers, implemented for the early detection of *T. cruzi* infection in pregnant women and the screening of newborns born to positive mothers. However, up to now there is yet no official recommendation or guide at national or EU levels.

## 6 Conclusions

1. Population movements during the last decades between Chagas disease endemic countries in Latin America and Europe have contributed to extend the impact of the disease, which should now be considered an emerging infectious disease due to the number of cases registered and its relevance as public health threat.
2. There are between 68,000 and 123,000 people infected with *T. cruzi* in Europe, a majority of them residing in Spain, Italy, the UK, and France.
3. The distribution and epidemiology of the infection in Europe is very heterogeneous and depends on the origin of the immigrants received by each country.
4. There is a lack of knowledge of the disease and how to manage it clinically, which entails a public health risk in countries where it is a new challenge.
5. Access to diagnosis is still shaded by the stigma that accompanies this disease, which along with miscommunication and unawareness complicate widespread testing of at-risk populations.
6. Diagnostic algorithms are diverse and may lead to delays in treatment administration to congenital cases as well as to excessive costs due to cost-ineffectiveness.
7. Although treatment with benznidazole and nifurtimox is generally widely available, there are still issues that preclude access to it, most importantly the huge level of underdiagnosed cases.
8. Treatment is highly effective and well tolerated by children, and it should therefore be administered to them as soon as a positive diagnosis is known.
9. Transmission routes in non-endemic regions are vector-independent (blood transfusion, organ transplant, and from mother to child), and control measures must be put on place for each of them correspondingly.
10. Blood bank screening in European countries most affected by Chagas disease is well established. Serological testing of at-risk organ donors is not that obvious.
11. Control of congenital transmission should be particularly enforced due to the great benefits it provides. Both by early identifying potentially infected newborns and immediately treating them, as well as preventively treating women at child-bearing age to reduce chances of vertical transmission of the parasite.

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