Review

Challenges in the management of Chagas disease in Latin-American migrants in Europe

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A B S T R A C T

Chagas disease is endemic in Latin America. Due to migration the infection has crossed borders and it is estimated that 68,000–120,000 people with Chagas disease are currently living in Europe and 30% of them may develop visceral involvement. However, up to 90% of Chagas disease cases in Europe remain undiagnosed. The challenges which have to be overcome in Chagas disease in non-endemic countries are focused on related down barriers to health care access, and related to screening, diagnostic tools and therapeutic management. The aim of this review is to highlight how healthcare management for Latin American migrants with Chagas disease in Europe may be improved. Medical literature was searched using PubMed. No limits were placed with respect to the language or date of publication although most of the articles selected were articles published in the last five years. Chosen search terms were “Chagas disease” AND (“migrants” OR “screening” OR “transmission” OR “treatment”; OR “knowledge” OR “non-endemic countries”); migrants AND (“Public health” OR “Health Service Accessibility” OR “Delivery of Health care”); and “Congenital Chagas disease”. Healthcare management of migrant populations with Chagas disease in Europe has to be improved: -Surveillance programmes are needed to measure the burden of the disease; -screening programmes are needed; -administrative and cultural barriers in the access to health care for migrants should be reduced; -education programmes on Chagas disease should be performed -research on new diagnostic tools and therapeutic options are required. This review highlights the needs of profound changes in the health care of Latin American migrants with Chagas disease in Europe. B. Monge-Maillo, Clin Microbiol Infect 2017;23:290

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Introduction

Chagas disease (CD), caused by the parasite Trypanosoma cruzi, is endemic in Latin America where it is mainly transmitted by triatomine insects. Moreover, CD may also be transmitted congenitally, through blood transfusions and organ transplantation from infected donors, orally through contaminated beverages, and rarely as a consequence of laboratory accidents [1].

It is estimated that around 8 to 10 million people in Latin America are infected with T. cruzi. Currently, due to the large-scale migration from Latin America, CD has crossed borders and it has been estimated that between 68,000 and 120,000 people with CD are currently living in Europe, and 30% of them may develop visceral involvement [1–3]. However, up to 90% of CD cases in Europe remain undiagnosed [4].

Chagas disease is considered one of the main neglected tropical diseases in Latin America that for many years has affected the poor communities living in rural areas of endemic countries and has received little attention. It is currently the leading cause of cardiomyopathy and death due to cardiovascular diseases in patients aged from 30 to 50 years in Latin America [5]. Although the disease was described more than 100 years ago, there are still many challenges to overcome which would significantly improve the healthcare management of immigrant patients with CD. On the one hand, there is a need to improve knowledge about the disease, advancing in aspects of diagnosis, prognosis and treatment. On the other hand, it is necessary to improve the access of the immigrant...
population with CD to the healthcare system and to screening campaigns.

The objective of this manuscript is to go through these challenges and how they might be resolved attending to different aspects: reduction of the CD infra-diagnosis by the implementation of screening programmes, removing barriers to healthcare access of those infected; identification of those patients at risk for visceral involvement, development of effective treatment for chronic cases; or evidence of reliable markers of cure following treatment. For this purpose a medical literature search was done using PubMed. No limits were placed with respect to the date of publication although most of the articles selected were articles published in the last five years. There were no language restrictions. Chosen search terms were “Chagas disease” AND (“migrants” OR “screening” OR “transmission” OR “treatment”); OR “knowledge” OR “non-endemic countries”); migrants AND (“Public health” OR “Health Service Accessibility” OR “Delivery of Health care”); and “Congenital Chagas disease.”

Measuring the real impact of CD in Europe

There are more than three million migrants from areas where CD is endemic living in Europe, mostly in nine countries (Spain, Italy, Portugal, Belgium, France, Germany, the Netherlands, Switzerland and the UK) [4]. Prevalence of CD among the migrant population can vary considerably depending mainly on the prevalence in their country of origin, although, other aspects such as the concrete area of origin and conditions where they have lived have an important influence [6]. In fact, migrants usually come from rural areas, with a lower socioeconomic status than the general population, which probably makes CD prevalence higher than the global prevalence in their country of origin [7]. National infection rates in endemic countries vary from <1% to ~25% in countries such as Bolivia where endemicity is high [8]. Based on the national infection rates of the different countries of origin it was estimated that there were between 68 000 and 120 000 cases of CD in Europe (42 000 living in Spain) [1,2], with a prevalence of chronic CD among Latin American migrants in Europe of 4.2% (0%~15.9%). Based on seroprevalence studies conducted in migrants in Europe, those from Bolivia had the highest prevalence (18.1%), followed by El Salvador (5.6%), Paraguay (5.5%), Nicaragua (4.6%), Honduras (3.7%) and Argentina (2.2%). Prevalence among migrants from other countries was <1% [1–3].

Most of the infected individuals are migrants who acquired the infection in their country of origin and they present in the chronic phase when they arrive in their host countries. Taking into account that around 30% of patients with CD may develop visceral involvement, it could be estimated that between 20 400 and 36 600 Latin American migrants living in Europe may have or develop visceral involvement by CD. However, <10% of these have currently been diagnosed [2,3].

Screening protocols of CD in Latin American migrants

Taking into account the important under-diagnosis of CD in Europe and the possibility of non-vectoral transmission from asymptomatic patients, it seems very reasonable to promote ideal screening programmes focused on: obtaining early diagnosis and treatment of patients; avoiding congenital transmission; and avoiding blood and organ transplantation transmission. In fact a recent study has shown that screening for CD in asymptomatic Latin American immigrants living in Europe is a cost-effective strategy [9].

Undoubtedly, this requires that health access is guaranteed to all LA migrants at risk regardless of their administrative situation. The programme can be conducted either by a primary health centre or by a specialized unit in migrant health or infectious diseases.

The benefits of these targeted screening programmes focus on two main aspects. The first one is that there is a possible benefit of an early diagnosis; follow up and treatment of patients with CD and with no visceral involvement (so-called indeterminate stage of CD) in preventing long-term cardiac or digestive complications. The recent published BENEFIT study has shown that treating patients with established chagasic cardiomyopathy has no benefit on the cardiac disease [10]. However, there are no large and well-planned studies that have demonstrated that treating those patients in the indeterminate phase of CD with no cardiomyopathy could not obtain a benefit over the future visceral involvement. Although there are no randomized controlled studies based on strong outcomes, diagnosis and treatment among those patients in an indeterminate phase of the disease should be considered. On the other hand, most of those screened are women of childbearing age. The diagnosis of CD among these women allows them to be treated and reduces the possibility of congenital CD transmission in further pregnancies, as has been demonstrated in several studies performed in endemic and non-endemic countries [11,12]. A meta-analysis showed that prevalence of congenital transmission in non-endemic countries is about 2.7% (half than in endemic countries) [13]. Moreover, CD during pregnancy can cause higher rates of preterm births, low birthweights and stillbirths [13].

The problem in non-endemic countries is that babies of mothers from CD endemic countries may not be diagnosed because obstetricians and neonatologists are unfamiliar with the disease and so do not suspect it. In these cases, asymptomatic babies infected by T. cruzi may not be diagnosed and their infection will evolve to a chronic indeterminate phase of CD. In other cases, symptoms are misdiagnosed with a neonatal sepsis and if they do not receive adequate CD treatment this can be fatal [11]. Congenital infection screening entails a cascade of interventions beginning by identifying the mothers that are at risk of having CD, followed by testing those newborns from mothers infected by T. cruzi. However, health policies regarding the control of congenital transmission are lacking in most non-endemic countries [14,15]. A recent published review summarises the current policies and practices performed for control of congenital CD in non-endemic countries, including European countries [16]. Screening for congenital CD has been launched in only a few regions of Spain, Italy and Switzerland (Table 1). The direct benefit of screening for congenital CD lies in the efficacy of its prompt treatment. In Bolivia, neonates treated in the neonatal period have 90.7% cure rates [17]. A cost-efﬁcacy study performed in immigrants in Europe has addressed this strategy [18]. Moreover, screening should also be extended to other paediatric periods and children coming from endemic areas or whose mothers have been diagnosed with CD because treatment among those aged <14 years has good tolerance and efficacy [19].

Screening for CD could also beneﬁt those patients with some type of immunosuppression. This can be the case of human immunodeﬁciency virus-infected patients in whom screening and treatment of those co-infected with T. cruzi has been suggested to prevent disease progression and possible reactivation of CD. Moreover, although there is scarce evidence, secondary prophylaxis after a ﬁrst episode of CD in human immunodeﬁciency virus-infected patients has been recommended by most experts [20]. Experience in the management of other cases of immunosuppression, such as those due to neoplasia or immunosuppressive treatments, has shown that all those patients at risk must be screened for CD and treatment and prevention or reactivations must be taken on an individual basis [21].

The transmission of CD via blood transfusion has been recognized for decades [22,23]. The possibility of CD transfusion
transmission depends on several factors and varies from 12% to 25% [24]. Only four European countries currently have specific directives regarding blood transfusion transmission of CD: Spain, France, the United Kingdom and Switzerland. In Italy, blood banks are currently following European Union directives 2004/33/CE and 2006/17/CE, which mention CD as an exclusion criterion for donation but do not specify measures that must be taken for those donors potentially infected but never screened for CD. A blood safety protocol is under approval in other countries, including Portugal and Sweden (Table 2). In Portugal, a blood safety protocol is under approval by the Instituto Português do Sangue e da Transplantação and is oriented to exclude all those at-risk donors who have not undergone any diagnostic test. The same is done in Sweden, where all donors who have lived for >5 years in CD endemic countries are excluded from donation [15,23]. Concerning organ transplantation, there are only three countries whose National Transplant Organizations have included a specific section regarding how to control transmission of CD through organ transplantation in their national guidelines [15,25]. In these countries, transplant donors for organ transplantation are routinely screened, although seropositivity for CD might not be a contraindication for certain types of transplantation [15]. Generally the transplantation from those donors with acute CD is contraindicated. The use of the heart (and possibly the intestine) is also contraindicated in donors with CD regardless of the phase of the infection. The viability of other organs among donors with CD is controversial and should be consented by the donor. If finaly transplantation is performed, the recipient should be followed up periodically by parasitological and serological diagnoses methods [25].

As an example of screening programmes, our referral centre provides assistance to migrants [26] and in 2007 a specific clinic was set up for the diagnosis, evaluation, follow up and treatment of patients with CD according to a specific protocol [27]. Since then, around 900 Latin American migrants with CD have attended (97% from Bolivia, 68% women, median age 38.3 years) and 504 initiated antiparasitic treatment (75% completed CD treatment correctly). Moreover, our referral centre in collaboration with non-governmental organizations (NGOs) (Mundo Sano and Salud entre Culturas) [28,29] has promoted three free screening campaigns in non-healthcare settings during weekends and targeted at Bolivians. More than 1100 have been screened and the prevalence of CD was 19.1%.

Removing barriers to healthcare access of those infected

The World Health Organization (WHO) covers ‘The right to Health’, which implies an equal and timely access to health care for all the population. Moreover healthcare services should be financially accessible for all the population including vulnerable groups and should be given with no discrimination [30]. However, the access to the health system for migrants is especially precarious among those who are living in Europe in an irregular administrative situation [31]. Legal status is in many cases an important barrier to access to the healthcare system, but it is not the only one. Migrants also have to face language, cultural and economic barriers to receive care. A project focused on improving services for undocumented migrants in Europe reported how fear of being deported, lack of information about their rights, lack of legal entitlements, cost service and discriminatory attitudes among health professionals can significantly limit the access of migrants to the healthcare system [31]. Generically undocumented migrants in Europe have the right to health under legal conventions adopted by the EU but different ways of interpretation and implementation of these legal conventions are possible [32]. It is difficult to provide adequate screening and health care to migrants with a chronic disease, such as CD, when access to the sanitary health system is limited and not free of charge.

On the other hand, there is a need for health education programmes with information about the disease, modes of transmission and the benefits of early diagnosis among migrants. Several studies have highlighted that there is a lack of knowledge about CD among migrants from endemic countries, especially regarding

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<td>European countries and years of implementation of the screening programmes for congenital Chagas disease transmission [16]</td>
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<th>Country</th>
<th>Year and area of implementation of screening programmes for Chagas disease in pregnant women.</th>
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<tr>
<td>Spain</td>
<td>• Valencia 2009. Total target population 95.4%. Seroprevalence: 11.4%. Congenital transmission rate 11.4%</td>
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<tr>
<td>Spain</td>
<td>• Catalunya 2010: Total target population reached 85% in 2011. Congenital transmission rate in all LA immigrants 5.8% and in the Bolivian community 6.5%</td>
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<tr>
<td>Spain</td>
<td>• Galicia 2012: Seroprevalence in all LA 2% and in the Bolivian community 16%</td>
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<td>Spain</td>
<td>• Madrid 2013: The Study Group in the Community of Madrid called for improvements in the detection of Trypanosoma cruzi in pregnant woman but no systematic screening programme has been established. Screening programmes were implemented by regional organizations of the National Health System</td>
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<tr>
<td>Italy</td>
<td>• Tuscany 2012: establishment of a CCD programme. Screening programmes were implemented by regional organizations of the National Health System. Currently there are no published studies with data from these programmes.</td>
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<tr>
<td>Switzerland</td>
<td>• Geneva 2009: establishment of a CCD programme.</td>
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<td>Switzerland</td>
<td>• Lausanne 2014: establishment of a CCD programme.</td>
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Abbreviations: CCD, congenital Chagas disease; LA, Latin America.

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<td>European countries with directives regarding blood transfusion transmission of Chagas disease [15]</td>
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<th>Country</th>
<th>Year of implementation of directives regarding control of blood transfusional transmission of Chagas disease.</th>
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<tr>
<td>Spain</td>
<td>• 2005: Real Decreto 1088/2005.*</td>
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<td>United Kingdom</td>
<td>• 2005: Guidelines for the blood transfusion service in: Service UBTT. The Stationery Office (TSO)*</td>
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<tr>
<td>Switzerland</td>
<td>• 2013: Prescriptions du Service de transfusion sanguine CRS*</td>
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* At risk donors are: 1, born or resident in endemic countries; 2, born to mothers native of endemic countries; 3, recipients of blood transfusion in endemic countries. They must be tested for Trypanosoma cruzi infection before blood donation.
transmission and symptoms, as well as many fears and false beliefs [33,34]. Culturally tailored interventions carried out in non-clinical settings could increase the participants’ knowledge and decrease their fears about the diseases and encourage them to undergo screening for T. cruzi [35]. Health education programmes on CD should also be targeted on health professionals to increase screening of migrants. Moreover, patients with CD require a prolonged follow up, which is frequently difficult to perform by many of the Latin American immigrants because of precarious working conditions or because they move to other cities looking for new work opportunities [33].

Developing new tools for diagnosis and test of cure on CD

Chronic CD is diagnosed by two positive serological tests that use different parasite antigens. PCR is not sensitive for diagnosis of chronic CD although it can be used during this phase in cases of discordant serological results, and after therapy as an indicator of treatment failure or as an early marker of resistance [36]. Other diagnostic techniques, such as serology performed on dried blood or rapid diagnostic tests performed on capillary blood, have shown less sensitivity than conventional ELISA techniques [37,38]. Challenges in CD diagnosis and tests of cure that need to be overcome. First is the fact that serological test and PCR determinations for CD are not available for all healthcare providers and national referral units on infectious diseases and microbiology are usually needed. In this cases serology performed on dried blood or rapid diagnostic tests performed on capillary blood, could be considered in certain circumstances [37,38]. Second, there are no surrogate markers of healing that can determine which patients have been cured. Therefore, years of serological and clinical follow up are necessary. Moreover, the lack of healing markers limits the possibility of developing new clinical trials that can evaluate new therapeutic options. Third, there are no markers that can define which patients infected by T. cruzi will develop visceral involvement. These would make it possible to treat only those with high-risk factors for visceral involvement and avoid treatment and toxicity to those two-thirds of infected patients who would never develop cardiomyopathy or gastrointestinal disease. Currently several biomarkers have exhibited potential usefulness for the assessment of response to CD treatment. These biomarkers are related to the parasite itself or to the host response to the presence of the parasite. The research on parasite biomarkers is actually more advanced than the host markers [39]. Regarding parasite biomarkers, nucleic acid amplification techniques are the most common and have demonstrated effectiveness in determining therapeutic failure [40–42]. Studies about host response are mostly focused on immunological and biochemical markers [39]. A recent study has shown that treatment caused changes in the adaptive immunity, leading to a general decrease in inflammatory status. This apparently beneficial response could act as the basis for monitoring new CD drugs [43]. Moreover, complementary non-parasitological tests should be performed on CD patients to determine the presence of visceral involvement. This is especially so when there is a risk of cardiomyopathy. In the next 5 years it is estimated that 200 000 people with CD will die from heart disease and related complications [44]. Therefore, all patients diagnosed with CD should have an electrocardiograph (ECG) and a two-dimensional echocardiogram (ECC) [45] even if they are asymptomatic, because it has been demonstrated that changes in ECG can precede cardiac symptoms [46]. Conversely the study of possible gastrointestinal effects by oesophageal manometry, barium enema or barium swallow seems to be indicated only among those patients who present with digestive symptoms such as dysphagia or constipation among others [47].

Developing an effective and less toxic treatment for the chronic phase of CD

The only drugs approved for CD are benznidazole and nifurtimox, which were launched in the 1970s. They both share some characteristics: better tolerated by children than by adults, more efficacious during the acute phase of the infection, and variable susceptibility depending on the T. cruzi discrete typing units [48]. There is enough evidence to support that parasitic persistence may be one of the causes of the progression of CD towards cardiomyopathy and therefore treatment with benznidazole and nifurtimox during the chronic phase may reduce its development [49]. However, the published results of the BENEFIT clinical trial have demonstrated that once the cardiomyopathy has occurred, treatment has no effect on its progression [10].

Chagas disease has been treated with the same two drugs since the 1970s, with lack of interest in research by private laboratories. This is reflected also in the fact that <10% of publications on CD are related to clinical trials [48]. Moreover, in 2012 the stocks of benznidazole ran out for several months due to an insufficient production by a pharmaceutical laboratory (LAFEPE). This resulted in thousands of patients in the world not having access to treatment [50]. No paediatric formulation was available until recently, in 2011. Moreover, the tolerability of benznidazole is poor and around 50% of patients have adverse reactions during benznidazole treatment, leading to discontinuation in 9%–29% of patients, even though most reactions are reversible and only <1% are severe [27,51]. Drug-toxicity management includes stopping the administration of BNZ or nifurtimox and adding antihistaminic drugs. A few alternative drugs have been tested in some studies, like the randomized open-labelled clinical trial that evaluated the efficacy of posaconazole versus benznidazole. As a result, it was observed that posaconazol was not as effective as benznidazole in chronic Chagasian patients [52]. In contrast, itraconazole showed an improvement in ECG outcome in chronic patients, although these results were from a limited cohort in Chile [53]. In mouse models it has been observed that posaconazole and itraconazole have a synergistic effect when added to benznidazole for treating CD in an acute phase [54]. However, a recently published study has reported no benefit in the association of posaconazole to benznidazole in patients with CD in an indeterminate phase [55]. Ravuconazole (E1124) has been tested in a phase 2 double-blind, randomized controlled trial to evaluate its safety and efficacy in patients with chronic indeterminate CD in Bolivia. E1124 was found to be ineffective in monotherapy; however, it holds promise for use in combination with other existing drugs as it showed strong positive activity during treatment [56]. All of these findings have led research to focus on the possibility of combined therapies that could increase efficacy and reduce benznidazole doses and toxicity. Some new compounds based on natural products, molecules specifically designed to inhibit a particular enzyme, chemically modified existing molecules to increase their anti-trypanocidal activity and drugs used for other diseases may become good alternatives for CD treatment [48,50]. Until then, there is much to do to improve the efficacy and tolerability of CD treatment.

Conclusions

Healthcare management of migrant populations with CD in Europe could be improved in several ways.

- CD is a hidden disease in Europe and it is an important public health issue. There is a need of surveillance programmes to measure the real burden of the disease in Europe. Much is needed to be done to reduce the CD infra-diagnosis in Europe by
performing systematic targeted screening programmes. The target population is Latin American women of childbearing age; Latin American pregnant women and their newborns; and all Latin American migrants from Bolivia. The advantages of these screening programmes could be: obtaining early diagnosis and treatment of patients; avoiding congenital transmission and; avoiding blood or organ transplantation transmission.

- Administrative and cultural barriers in the access to health should be reduced, facilitating health care for migrants regardless of their administrative situation and providing financially accessible health services. It is difficult to develop screening and treatment strategies when the access to the sanitary health system is limited. Ideally, care of patients with CD should be done by primary health physicians in coordination with referral centres by performing screening, detecting visceral involvement, offering treatment when it is indicated and, offering prolonged follow up for all those patients diagnosed with CD.

- Education programmes on CD should be given to Latin American migrants to increase their knowledge of the disease, reduce fears and increase the number of at-risk individuals who request CD screening.

- Investing in research for developing new diagnostic tools and prognostic markers and supporting initiatives to find new therapeutic options that are more effective and less toxic for patients with chronic CD should be a priority.

### Transparency declaration

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