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Systematic Review

Control and management of congenital Chagas disease in Europe and other non-endemic countries: current policies and practices

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Abstract

OBJECTIVES Identifying pregnant women infected with *Trypanosoma cruzi* is one of the major challenges for preventing and controlling Chagas disease (CD) in non-endemic countries. The aim of this paper was to perform a policy evaluation of the current practices of congenital Chagas disease (CCD) control in non-endemic countries and to propose specific targets for enhanced interventions to tackle this emerging health problem outside the endemic areas of Latin America.

METHODS We conducted a mixed method review of CCD policy strategies by searching the literature in the PubMed, Google Scholar and the World Health Organization (WHO) databases using the key terms 'CCD', 'paediatric Chagas disease' and 'non-endemic countries'; as free text and combined as one phrase to increase the search sensitivity. Reviews, recommendations, guidelines and control/surveillance programme reports were included.

RESULTS Of 427 CCD papers identified in non-endemic countries, 44 matched the inclusion. Although local programmes were launched in different countries with large numbers of Latin American immigrants, there were considerable disparities in terms of the programmes' distribution, delivery, integration and appropriated CCD control strategies. Moreover, Catalonia, Spain is the only region/country with an established systematic monitoring of CCD in pregnant women from Latin American countries.

CONCLUSIONS Given the worldwide dissemination of CD, the nature of its vertical transmission, and the gaps of the current strategies in non-endemic countries, there is an urgent need to standardise, expand and reinforce the control measures against CCD transmission.

keywords congenital infection, Chagas disease, *Trypanosoma cruzi* infection, neglected tropical diseases, poverty, immigrant population

Introduction

Chagas disease (CD) is a parasitic infection caused by *Trypanosoma cruzi*. Endemic vectorial transmission occurs in parts of the southern United States to the south central region of Argentina and Chile [1]. Non-vectorial routes of transmission are congenital, infected blood/blood product transfusions, infected organ transplantation, ingestion of contaminated food or beverages and (rarely) laboratory accidents. Chagas disease affects approximately 8 million people worldwide, with an annual incidence of 41 000 cases and 12 000 deaths [2]. Negative health outcomes of chronic CD and the large disease burden result in a large international economic burden [3]. Early diagnosis and control strategies suggest a favourable cost-benefit ratio [4]. The distribution of CD is highly variable across endemic countries, with the highest prevalence in the poorest areas of Bolivia, Argentina and Mexico [5].

In a meta-analysis, the prevalence of congenital transmission indicated a significant difference between endemic and non-endemic countries, with pooled transmission

rates of 5.0% and 2.7%, respectively [6]. *Trypanosoma cruzi*-infected pregnant women had higher rates of preterm births, low birthweights and stillbirths [6]. Infected babies in non-endemic countries are at risk of not being recognised by obstetricians and neonatologists who are unfamiliar with the disease due to infected babies normally presenting asymptomatically or with subtle manifestations [7]. In rare cases, hepatosplenomegaly, encephalitis, myocarditis, diffuse oedema or anaemia can affect newborns, thereby increasing the risk of misdiagnosis, as the disease may be misdiagnosed as neonatal sepsis or erythroblastosis fetalis [8]. While unrecognised congenital CD (CCD) can be fatal, most cases silently evolve towards a chronic indeterminate phase that is clinically characterised by the lack of symptoms, normal clinical examination and electrocardiographic study, despite having a positive serology for *T. cruzi*.

Congenital infection screening entails a cascade of interventions starting with the identification of at-risk pregnant women and, subsequently, with testing at-risk newborns. CCD in infants is diagnosed through positive serological examinations when infants are older than 9 months, after the maternal anti-*T. cruzi* antibodies have been cleared [9]. When CCD is recognised early, treatment allows for a 90–95% cure rate [10]. Treatment of *T. cruzi*-infected women of childbearing age has showed efficacy in preventing congenital transmission [11, 12], opening a new window for preventive measures of CCD.

Recently, non-vectorial *T. cruzi* infection has been increasingly recognised outside endemic areas [13–15]. Europe, the United States, Canada, Australia, New Zealand and Japan host millions of at-risk Latin American immigrants. Conservative estimates suggest that 80 000 to 120 000 *T. cruzi*-infected immigrants live in Europe, and 300 000 infected immigrants live in the United States. Globally, CD is one of the most neglected tropical diseases; it receives limited attention in non-endemic regions and, consequently, a small number of CD cases have been detected in non-endemic countries in contrast to the burden estimates [16]. Health policies regarding the control of congenital transmission are also lacking in non-endemic countries, and no European country has a specific national policy [17]. However, the recent identification of several cases of congenital infection in Spain has highlighted the need for public health interventions to prevent transmission in non-endemic countries [18–20]. The successes of these CD screening and treatment programmes highlight the benefit of screening programmes in high-risk populations living in non-endemic countries [17].

The aim of this paper was to analyse policy and public health practices critically in terms of CCD control and management in non-endemic countries. Based on our systematic review findings, we propose strategies to improve the handling of this emerging health problem outside the endemic areas of Latin America.

Review

To collect information regarding health policies and practices, we used a sequential method based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for literature review [21] of the following databases: PubMed, Google Scholar and WHO (Figure S1). Reviewers (and co-authors) were selected. Moreover, the references of the retrieved documents were reviewed and selected, if appropriate. The first author selected the reviews, recommendations, guidelines and programme reports, in accordance with their relevance to the research topic, and the co-authors validated the selections (using the inclusion criteria). Information was extracted and analysed by the main author and co-authors from Spain, Italy and Switzerland because of the high burden of CCD in these non-endemic countries.

Ethical approval was not requested because the purpose of the article was to review the available policies and practices of CCD in non-endemic countries, without any specific investigations of human subjects, human material or human data.

The literature search identified 427 articles on CCD studies in non-endemic countries. After excluding those that did not fulfil the inclusion criteria, 44 articles were used for the final review (Table S1).

Canada and United States

Despite the presence of a large community of at-risk persons, the burden of CD in the United States (US) and Canada is still poorly understood. It is unclear how frequent congenital transmission of *T. cruzi* is in the US, although it is known that infected mothers are found there [22]. Currently, there are no data available on the dynamics of vertical transmission over time. To date, only random cases of *T. cruzi* congenital transmission have been described in the US; and none in Canada [23–26]. Using empirical data, Buekens *et al.* have estimated that 1 infected baby would be delivered each year in Canada and 189 in the US [27]. While CCD is recognised as an important health issue in North America, no paper reports on ongoing screening programmes for pregnant women (PW) and their newborns in the US and Canada. One reason

might be the lack of awareness in health professionals, including obstetricians, as reported by Verani *et al.* [7].

Japan

Japan hosts a community of Latin American immigrants (estimated at 300 000 persons), primarily from Brazil and Peru. Estimates of CD burden in Japan are based on limited serologic surveys. Currently, 4 500 affected people might be living in the country. The first case of CCD was described in 2014 [28]. Authors remark that the diagnosis of CD in Japan is difficult because of the low awareness and recognition of the disease by medical staff, the scarcity of epidemiologic and statistical data, and the lack of diagnostic tools, resources and facilities available to help with the differential diagnosis. There are no current screening programmes for CD in Japan to detect chronically infected persons, including Latin American pregnant women and newborns.

Australia and New Zealand

To date, no CCD case has been reported in Australia and New Zealand. Similar to other Western Pacific countries receiving an increasing number of Latin American immigrants, Australia and New Zealand still lack any screening programme for CCD prevention. Model-based estimates showed that Australia and New Zealand could have hosted up to 2000 and 100 infected persons in 2011 and 2006, respectively [29].

Switzerland

Switzerland (primarily its Western French-speaking part) has received an increasing number of Latin American migrants from endemic countries since the mid-1990s. After the identification of two cases of congenital transmission in 2001 and 2006, a serological survey investigated Latin American pregnant women treated at the Geneva University Hospital. It showed that 7/72 (9.7%) overall and 5/30 (16.6%) Bolivians were infected [30]. A larger survey conducted among adults in the community showed an overall prevalence of 12.8% with a prevalence of 26.2% among Bolivians; to date, more than 300 cases of CD have been identified [31].

Subsequently, a systematic screening programme to identify infected LAPW and the transmission of *T. cruzi* to their newborns was implemented in Geneva [32]. The unique screening criterion is Latin American origin. Identification of an infected Latin American pregnant woman prompts the screening of other children and other family members. So far, 10 infected children of different ages have been found in Geneva using this strategy [33]. Note that most infected women and children come from immigrant families living in precarious socioeconomic conditions and lacking health insurance; thus, they face difficulties accessing health care. More recently, Lausanne, the second largest city in Western Switzerland, implemented a similar strategy. However, Switzerland lacks any national health policy regarding CD control and management, including CCD, with the exception of blood donation screening, which was implemented in 2013.

Italy

In Europe, Italy has the second largest number of resident Latin American immigrants. Data from 2011 revealed that approximately 380 000 documented and 50 000 undocumented immigrants were allowed into Italy. Latin American migration in Italy has similar features as in the rest of Europe, with a majority of women of childbearing age, irregular distribution of communities across the territory (although partially dependent upon the country of origin: principal destinations are the regions of northern Italy and Lazio, and Rome in Central Italy). The estimated number of CD-affected people ranges between 1300 and 17 000, with an overall estimated incidence of approximately 28 cases per 100 000 inhabitants [34]. The under diagnosis rate ranges from 98.3 to 99%. As of June 2013, a total of 568 patients were unofficially diagnosed in Italy, including one congenital case and three paediatric cases.

The heterogeneous distribution of Latin American communities and the regional organisation of the National Health System in Italy contribute to huge differences in access to health care across the country. In 2012, Tuscany set up a CCD prevention programme, followed by Bergamo in 2013. CCD prevention has also been tackled at the institutional level in Negrar, Roma and Bologna. Currently, there are no published studies with data from these programmes.

Spain

The first prevalence studies of Latin American pregnant women took place in Barcelona, Madrid and Valencia from 2005 to 2009 [20, 35–37]. A few hospitals started to screen Latin American women who gave birth in their reference areas.

Valencia was the first region to start an extended protocol, with the aim to screen all Latin American pregnant women (2009) [38]. This pioneer protocol provided data recovered from the 3 tertiary hospitals in the city of

Valencia, with a total coverage of 95.4% of the target population; the seroprevalence was 11.4% among these women, with a congenital transmission rate of 3.7% [39].

Catalonia was the second region to start screening (2010) and the first region to implement an active centralised surveillance system to identify all infected Latin American pregnant women and follow-up their children. The focal point of this programme is the working group, which is composed of a reference person for every level (from primary healthcare clinics to large hospitals), zone and specialty (microbiologists, midwives, family doctors, paediatricians and obstetricians) responsible for Latin American pregnant women and newborns in their reference area [40]. In the first 2 years of the programme development, 313 Latin American pregnant women were diagnosed with CD in Catalonia, 91.5% of whom were Bolivians. In 2011, 30 of 42 cases with unknown follow-up care were found through the intervention of community health workers (CHW) who helped with active surveillance, education and information activities at paediatric primary care and community levels [41]. The estimated programme coverage rate successfully increased from 65.0% in 2010 to 85.0% in 2011, and the congenital transmission rate was 5.8% among general Latin Americans and 6.5% in the Bolivian community [42].

Galicia became the third region in Spain to implement a protocol for CD screening in Latin American pregnant women in December 2012 [43]. Preliminary data from the main hospital in the southern region of the city showed a prevalence of 2% among all Latin American pregnant women, and 16% in Bolivian pregnant women.

In 2013, the Study Group of CD in the Community of Madrid called for improvements in the detection of anti-*T. cruzi* antibodies in pregnant women from endemic areas because it was the main issue affecting the control of CD in non-endemic area [44].

Other European countries

More than 500 000 people of Latin American origin currently live in Europe, but CD is not yet considered to be a public health problem. Cases of transmission through blood donation, organ transplantation or from mother-to-child have been reported in several European countries, but there are no available data from large countries, such as Germany or the UK, for instance. Current epidemiological data are primarily available from regional surveys from other countries or are extrapolated. Hence, there is great variation in the estimated numbers on the incidence of CD across all European countries [45]. In summary, no data regarding CCD are available from other European countries.

Discussion

Given the global distribution of at-risk people, health professionals worldwide may have to manage a CCD case. However, the frequent absence of surveillance programmes means that many cases are currently missed [15]. This situation reflects not only inadequate health care applied to fatal clinical situations but also the perpetuation and dissemination of CD in new non-endemic areas. Our findings reveal the wide gap between the needs and the current policy and practices regarding the control and management of CCD in non-endemic countries, and they confirm the extent to which CD remains a neglected health issue outside of Latin America.

Apart from very few specific regions, there is no national programme targeting at-risk populations. Unawareness of CD generally persists decades after the first cases have been identified in non-endemic countries. Several factors may contribute to this situation, including the fact that CD predominantly affects the poorest migrant populations whose needs frequently receive less attention from national healthcare systems. Another factor is the disease itself, as the absence of symptoms during the early stage fails to generates clinical and public heath alarms, unlike other congenital infections.

Reviewing the current programmes for CCD control in Europe (namely, Spain, Italy and Switzerland at different levels, see Table S1), a few commonalities can be identified to develop a surveillance strategy. First, it is widely recognised that identifying all affected children implies testing all pregnant women at risk for the infection. If pre-conception testing is not feasible, then screening should be implemented during standard antenatal care as the minimum. Moreover, all children who were born to seropositive mothers or received transfusions should be tested not only within the first month of life but also from 9 months of age [46]. Follow-up during the first year of life is essential to identify CCD cases. Indeed, serology is useless in the first months of life in presence of maternal antibodies and a significant proportion of newborns are initially negative at direct parasitological tests or PCR. Therefore, most cases are detected later, when maternal antibodies clear and the presence of antibodies indicates that they are from the baby. Moreover, follow-up is a major challenge in CCD control because these migrants are often very poor, and adherence to the post-natal screening strategy is economically demanding [47]. In Catalonia experience [40, 41] shows that the suc-

cess of follow-up care depends on good health networks established between primary care centres and tertiary hospitals, which promote extensive counselling of the mothers and emphasise the relevance of control even in asymptomatic and apparently healthy children. Efforts to enhance community involvement and education are likely to contribute to improved adherence to screening recommendations and the implementation of such recommendations within primary healthcare structures [47].

Early diagnosis is important because within the first year of life, treatment is well tolerated, and the response rate approximately 100% [10]. Siblings and relatives of children with congenital infection should also be screened to detect and treat infections as early as possible before the development of organ damage [48].

In its first report on neglected diseases, WHO recognised that the dissemination of CD to areas previously considered to be non-endemic presents a serious public health challenge [15] and expressed concern about the control of CCD in places where health professionals have little knowledge or experience of it.

The simplest and most pragmatic approach to control CCD is pre-conception and early antenatal or neonatal diagnosis. We suggest that the following measures be taken:

- Primary prevention of congenital transmission through systematic serological detection of all Latin American women of childbearing age and treatment provisions before conception [11];
- Secondary prevention through systematic detection of Latin American pregnant women through prenatal screening by standard serology, emphasising the need to incorporate the detection of *T. cruzi* infection in the group of vertically transmitted infections (the so-called TORCH complex);
- Tertiary prevention through timely detection of congenital infection in neonates of infected mothers within the first year of life; systematic treatment and follow-up of all detected congenital infections (control strategy of current congenital infection and prevention of a following second generation congenital infection); and
- Systematic investigation and management of infection in the siblings and relatives of infected mothers/newborns and the participation of CHW in the affected populations to afford this problem in non-endemic countries.

From an epidemiological and public health point of view, a global control strategy to increase congenital and paediatric CD detection needs to be implemented urgently. This should aim to

- Strengthen community information, education and communication through CHW, patients associations and other professional intervention as a fundamental step towards an integrated CCD control strategy at public health level;
- Improve awareness, education and training of healthcare workers at different levels and to facilitate cooperation among the primary health care, hospital and public health actors;
- Gather data and monitor the health risks as migrant populations profile rapidly change in non-endemic areas due to the high migrant mobility in times of economic constraints.

Conclusions

According to WHO, the strategy to control CCD in non-endemic countries should be based on two pillars: first, by interrupting transmission. Treating girls and women of childbearing age can prevent or diminish transplacental transmission [11]. The treatment and cure of newborn girls can also avoid congenital transmission to second generations. Secondly, by providing health care to patients (i.e. diagnosing and treating infected newborns based on a global information and surveillance system, which is urgently awaited), updating epidemiological information, implementing control measures and monitoring programmes (i.e. in practice, mapping CCD management in non-endemic countries through community health actions). This would improve control of CCD.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. A PRISMA flow diagram for searching review articles for congenital Chagas disease in non-endemic countries.

Table S1. Strategies for controlling congenital Chagas disease in non-endemic geographical regions.

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