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Adding a piece to the puzzle of Latin American blood donors and the potential risk of Trypanosoma cruzi transmission in Germany

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Abbreviations

BRK: Bayrisches Rotes Kreuz (Bavarian Red Cross)

CD: Chagas disease

CMIA: Chemiluminescent microparticle immunoassay

COI: Cut off index

DALY: Disease-adjusted life years

ECLIA: Electrochemiluminescence assay

ELISA: Enzyme-linked immunosorbent assay

EU: European Union

HIV: Human Immunodeficiency Virus

ICT: Immunochromatographic test

IFA: Indirect immunofluorescence assay

IHA: Indirect haemagglutination

IgG: Immunoglobulin G

NTD: Neglected tropical disease

PAHO: Pan American Health Organization

PCR: Polymerase chain reaction

PEI: Paul-Ehrlich-Institute

RKI: Robert Koch-Institute

SD: Standard deviation

T. cruzi: *Trypanosoma cruzi*

USD: United States Dollar

WB: Western blot

WHO: World Health Organization

ZTB: Zentrum für Transfusionsmedizin und Zelltherapie, Berlin (Center for Transfusion Medicine and Cell Therapy in Berlin)

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1.1 Author´s Contribution

Before the study´s launch and with my supervisor´s help, I designed the questionnaire, consent form, names list for the retrospective study, and information sheets for enrolled candidates. Then, following the ethics committee´s approval, I started to design a standard operating procedure to carry out the analysis at the Bavarian Red Cross with the help of LG, MP, and EQ. Moreover, I organized the selection and transport of the retrospective samples from Wiesentheid to Munich. Once stored at the Max von Pettenkofer-Institute, I pipetted all samples into aliquots for transportation to the testing facility at Roche in Penzberg. The latter was organized with the help of the Bavarian Red Cross technical staff and DR. Furthermore, I added dilution samples of a positive sample randomly distributed in the set of samples to verify the diagnostic method.

Moreover, I analyzed the retrospective study data with the help of LG and MP. The prospective study was closely monitored throughout the sample period, and subsequent testing and transportation of samples were organized with the support of my supervisors, EQ and DR. Following the launch of the prospective study in Bavaria, I attempted to recruit blood transfusion centers throughout Germany. Unfortunately, I could only recruit the transfusion institute at the Charité in Berlin with the help of the UK, AP, MP, DR, and LG. Therefore, I developed a standard operating procedure for recruiting, transporting, and testing samples from Berlin. Moreover, throughout the study, I attended lab meetings and produced presentations for my supervisors at multiple points during the sample period. Following the completion of the prospective study, I checked and filed all consent forms and questionnaires and then analyzed the data. Lastly, I drafted the first version of the manuscript and helped finalize it with all co-authors´ help. Finally, I archived all the donor’s data and forms in an anonymized manner.

2. Introduction

2.1.1 Aims of the Study

The protozoan parasite *Trypanosoma cruzi* (*T. cruzi*) causing Chagas disease (CD) is a potentially fatal infectious disease. It has compromised blood safety in non-endemic regions such as Europe due to its non-vector-borne risk for transfusional transmission. It is one of 20 neglected tropical diseases (NTD) endemic in 21 Latin American countries (Figure 1), where its transmission is mainly vector-borne. It causes 12,000 deaths annually in the Americas, and increasing migration has spread CD to non-endemic regions worldwide (Lidani et al., 2019; Pan American Health Organisation, 2020). However, data concerning the prevalence and the risk of transfusional transmission in Germany are scarce and patchy. In the first step of bridging knowledge gaps regarding *T. cruzi*, this study aims to quantitatively assess the number of Latin American immigrants from CD endemic countries participating in blood donation and their *T. cruzi* status in two regions of Germany between April 2019 and April 2020: the metropolitan area of Berlin and the state of Bavaria. This study attempts to increase the knowledge base for future decisions about introducing selective screening among blood donors for CD endemic countries in Germany, suggested over 26 years ago by Frank et al. (1997) when adequate screening methods were not yet available. We employed today's diagnostic methods to screen potential at-risk blood donors who were retro- and prospectively screened for *T. cruzi*-specific antibodies. In addition, personal information was prospectively collected on Latin American blood donors born in CD endemic countries via a questionnaire.

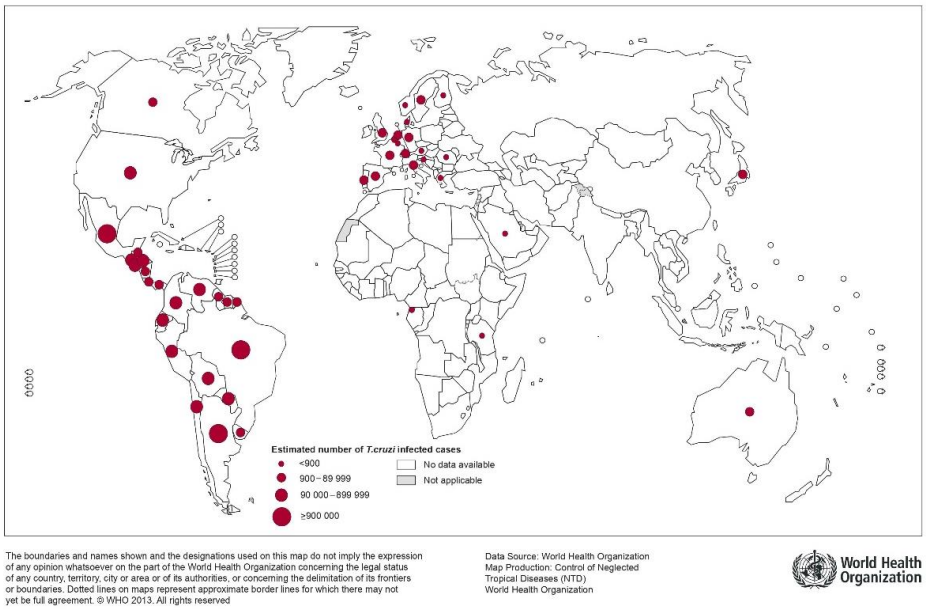

Figure 1 Global distribution of cases of Chagas disease according to the WHO in 2018. *From Chagas Disease (American Trypanosomiasis) by World Health Organisation Map production: Control of neglected tropical diseases (NTD). (https://www.who.int/health-topics/chagas-disease)*

2.1.2 Epidemiology

CD cases worldwide are 6-8 million, with a sizeable geographical variation (World Health Organisation, 2020). For instance, in endemic countries, the prevalence varies between 0.6% in Brazil and 6.1% in Bolivia (Figure 1) (Lidani et al., 2019). The variations in *T. cruzi* seropositivity amongst Latin American migrants has been studied in a multitude of European cities[1] ranging from 2.3% (16/698) in the Canton de Vaud in Switzerland to 23.6% (60/254) in Paris, France (Da Costa-Demaurex et al., 2019; Jackson et al., 2010; Jose et al., 2012; Lescure et al., 2009; Navarro et al., 2011; Pane et al., 2018; Roca et al., 2011). The overall prevalence among Latin American migrants in Europe is 4.2%, according to a meta-analysis of 18 studies in five European countries,[2] with the highest prevalence among Bolivian migrants (Requena-Méndez et al., 2015). In Germany, however, Basil et al. (2011) suggested an estimated CD prevalence of 1.3% to 1.7% among Latin American migrants. As a result, between 1,827 and 2,390 individuals[3] originating from CD-endemic countries could be infected with *T. cruzi* in Germany in 2020 (Basil et al., 2011; Navarro et al., 2017; Statista, 2020).

Furthermore, *T. cruzi* seropositivity has been identified amongst blood donors in Spain (1.91% out of 1,201), France (0.31% out of 972), Switzerland (0.08% out of 1,182), and the UK (0,007% out of 38.585) (Lidani et al., 2019).

Nevertheless, and somewhat surprisingly, data concerning CD prevalence in Germany, particularly concerning blood donors, needs to be more comprehensive compared to its European neighbours. Unfortunately, only two relevant studies have followed Franks et al. findings in 1997. Firstly, Navarro et al. (2017) identified 4/43 (9.3%) positive cases among Bolivian migrants in Munich, among whom 12/43 (27.9%) had donated blood in the past, clearly showing the presence of CD in Germany (Navarro et al., 2017; Statista, 2020). In contrast, Flores-Chavez et al. (2018) conducted a cross-sectional study of 4,200 unselected blood samples in 2018 in Germany in which no positive sample was found (Flores-Chavez et al., 2018). However, the significance of these findings is limited as it remains unknown whether *T. cruzi*-exposed donors were included in the study.

In light of this information, the global burden in health care costs is estimated at 627,6 million United States Dollars (USD) per year (Lidani et al., 2019; World Health Organisation, 2020). Moreover, its devastating effects on economies and healthcare are possibly higher than other major infectious or cancer diseases such as rotavirus and cervical cancer (Lee et al., 2013).

[1] Other European cities include Canton of Geneva, Switzerland (130/1,012; 12.8%); Rome, Italy (32/368; 8.7%); Elche, Spain (13/201; 6.5%); Barcelona, Spain (22/766; 2.9%) and Madrid, Spain (44/276; 15.9%) (Da Costa-Demaurex et al., 2019; Jackson et al., 2010; Jose et al., 2012; Lescure et al., 2009; Navarro et al., 2011; Pane et al., 2018; Roca et al., 2011).

[2] Italy, Spain, France, Germany, and Switzerland (Requena-Méndez et al., 2015).

[3] This number was calculated using the number of Latin American migrants originating from CD endemic countries in Germany in 2020, which was 140,565 (Statista, 2020).

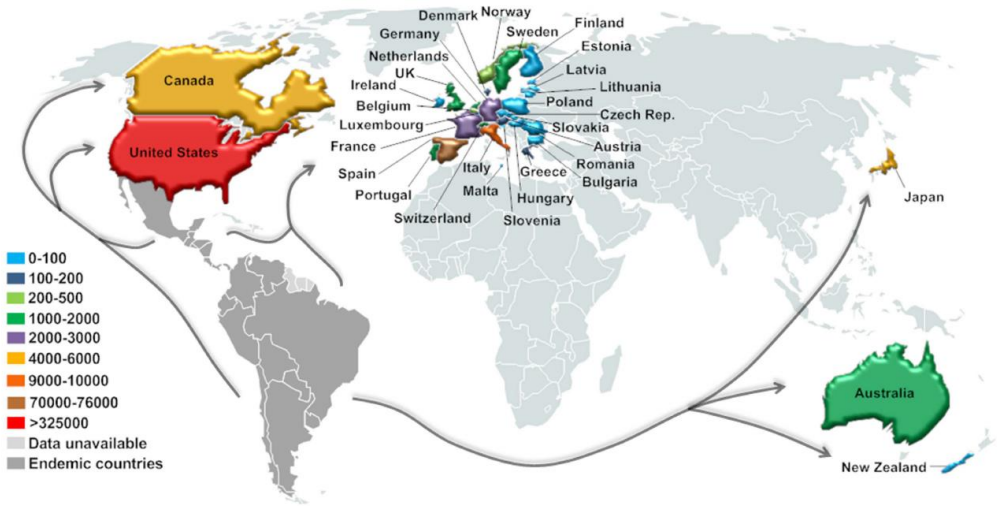

Figure 2 Number of estimated Latin American migrant population infected with T. cruzi based on data between 2006 and 2011. *From "From Discovery to a Worldwide Health Problem"by Lidani et al., 2019, Frontiers in public health, 7, 166.*

2.1.3 Transmission

The most crucial non-vector-borne transmission of *T. cruzi* in non-endemic countries occurs through blood transfusion and has been known since 1973 (Cancino-Faure et al., 2015; Tanowitz et al., 1992). This poses a major global challenge in CD disease control (Lidani et al., 2019). While Belgium, Spain, Switzerland, and the UK have reported transfusion-transmitted infection of *T. cruzi,* this has yet to be observed in Germany, likely due to the lack of data (Lidani et al., 2019).

The probability of transmission depends on the level of parasitemia, the stage of CD, and the type of transfused blood product (Cancino-Faure et al., 2015). The highest risk of transmission lies in the transfusion of platelet concentrates without leukofiltration originating from a donor in the asymptomatic and acute stage of CD due to high parasitemia in the blood (Cancino-Faure et al., 2015). The probability of a permanent infection of the recipient is estimated between 10 and 25% (Angeheben et al., 2015). In addition, blood products stored between -80C° and +4C° may still be infectious when transfused (Martin et al., 2014).

In CD endemic countries, *T. cruzi* transmission mainly occurs vector-borne via infected triatomine bugs such as Rhodnius prolixus, Triatoma infestans, and Panstrongylus geniculatus accounting for 90% of infections (Figure 3) (Alvarez-Hernandez et al., 2018; Pan American Health Organization, 2020). In Latin America alone, 70 million people are at risk for vectorial and non-vector-borne transmission, mainly affecting socioeconomically deprived populations living in rural areas (World Health Organisation, 2020).

The protozoa are transmitted to humans via triatome bugs, feces, and skin irritation near a bite following bloodsucking. Trypanosoma enters the bloodstream through skin lesions favored by itching and subsequent scratching (Figure 3) (Lidani et al., 2019). Finally, *T. cruzi* transmission can occur congenitally through the oral route, laboratory accidents, needle stick accidents, and organ transplantation (Lidani et al., 2019).

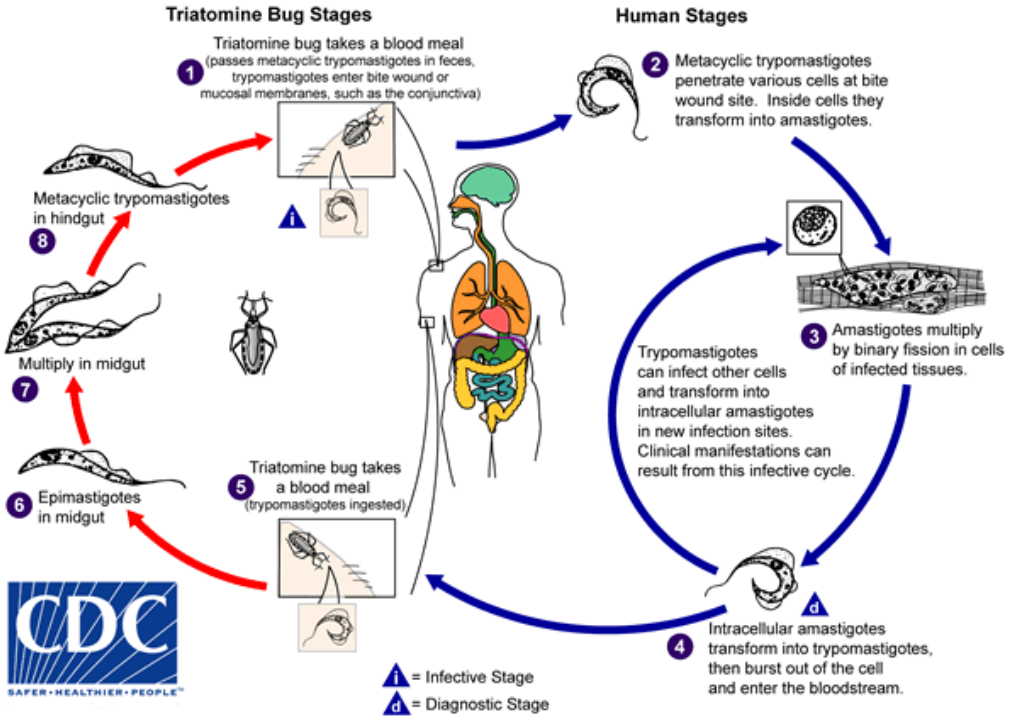

Figure 3 Triatomine bug life cycle. The left-hand side shows the replication cycle of epimastigotes and trypomastigotes in the triatomine bug stages. The right-hand side shows the triatomine cycle in human body cells and the damage caused. *From Parasites American Trypanosomiasis (also known as Chagas Disease) by Global Health, Division of Parasitic Diseases and Malaria, 2019. (https://www.cdc.gov/parasites/chagas/biology.html)*

2.1.4 Symptoms

Following primary *T. cruzi* infection, the acute phase of CD is characterized by a high level of parasitemia, and infected individuals may show unspecific symptoms (Lidani et al., 2019). These include fever, tachycardia, splenomegaly, hepatomegaly, lymphadenitis, or myalgia in the weeks following primary infection. If infected directly via a vector, CD-specific local symptoms such as the Romaña sign, a subtype of Chagoma, may arise due to the triatome bite and primary replication of *T. cruzi*. In 90% of cases, symptoms cease as parasitemia decreases and the disease enters the chronic phases (Lidani et al., 2019). In this phase, all infected individuals will not show any symptoms. However, after years to decades (up to 30 years), 30% will develop severe gastrointestinal (megacolon, megaoesophagus), cardiologic (cardiomyopathy), and neurological lesions, which can be fatal (Lidani et al., 2019). Severe and lethal gastrointestinal symptoms include colon dilation and may result in severe constipation or esophagus dilatation. Moreover, chronic

Chagasic cardiomyopathy can lead to heart failure requiring heart transplantation (Lidani et al., 2019). These severe symptoms significantly reduce life expectancy, increase mortality, and cause 806,170 DALYs (Lee et al., 2020; Lidani et al., 2019).

2.1.5 Diagnosis

CD diagnosis remains a challenge today as an estimated 95 % of all cases worldwide remain undiagnosed (Basile et al., 2011; Bayona et al., 2019). Infection is diagnosed during the acute phase by identifying parasites in the bloodstream using direct parasitological examinations such as microhematocrit and direct observation microscopy of a blood smear and hemoculture (Alvarez-Hernandez et al., 2018; Lidani et al., 2019; Organización Panamericana de la Salud, 2020). A serological follow-up test using enzyme-linked immunosorbent assay (ELISA), indirect haemagglutination (IHA), or immunofluorescence (IIF) can be used to confirm the diagnosis (Organización Panamericana de la Salud, 2020). Assay confection also includes western blot (WB) (Alvarez-Hernandez et al., 2018). In the chronic phase, CD can be diagnosed using ELISA, immunochromatographic test (ICT), and chemiluminescent microparticle immunoassay (CMIA), to identify anti-*T. cruzi* IgG and Polymerase Chain Reaction (PCR). The diagnostic gold standard combines two serological tests (Lidani et al., 2019; Organización Panamericana de la Salud, 2020). In haemotherapy, the Pan American Health Organisation (PAHO) recommends the ELISA, ICT, or CMIA to screen for CD. Consequently, a single negative result is sufficient for blood donors and hemotherapy (Organización Panamericana de la Salud, 2020). Moreover, further examinations such as echocardiography, Electrocardiogram, chest X-ray, and gastrointestinal endoscopy should be performed to detect complications (Marie & Petri, 2023).

In our study, all serum samples were tested for anti-*T. cruzi* IgG using Roche Cobas e analyzer (Elecsys Chagas), an electrochemiluminescence immunoassay (ECLIA), relying on an anti-*T. cruzi* IgG sandwich complex detected using ruthenium, streptavidin, and a photomultiplier (Figures 4 and 5) (Flores-Chavez, 2018). As a result, the sensitivity and specificity of the assay are given as 100% and 99,9%, respectively, which meets the requirements of the PAHO guidelines concerning CD screening in hemotherapy (Flores-Chavez, 2018; Organización Panamericana de la Salud, 2020). Furthermore, it is an adequate screening method for *T. cruzi* in a non-endemic country with low CD prevalence, such as Germany.

The recombinant antigens employed are derived from flagellar calcium-binding protein, repetitive flagellar antigen, and the cysteine proteinase Cruzipain. Patient samples are added to a mixture containing biotin-labelled and ruthenium-labelled T. cruzi antigens in the first step. This first incubation forms the antibody-antigen immune complex consisting of a ruthenate antigen binding site and a biotinylated antigen binding site, as shown in Figure 4. In the second step, by further incubation, the antibody-antigen immune complex binds to the streptavidin microparticles via biotin, which is transported

to the measuring cell and magnetically attached to the surface of the electrode. Chemiluminescent emission is generated using voltage application to ruthenium which is measured by a photomultiplier. Results are expressed in light counts, then converted into cut-off indices (COI) considering negative controls. The software automatically determines the results based on comparison values obtained during calibration at specific intervals before testing (Flores-Chavez, 2018; Roche Diagnostics, 2019).

A sample with COI<1 is non-reactive and thus considered infectious. Before every testing run, standardized calibration of positive and negative controls was analyzed to ensure calibration and quality control. Furthermore, five additional positive control samples in the dilutions (5fold, 10fold, and 100fold) were added randomly to our study.

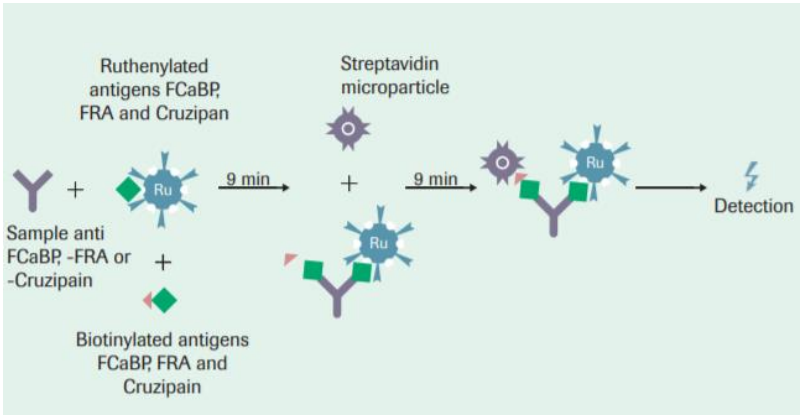

Figure 4 Kinetic of antibody sandwich complex formation in the ECLIA assay used. Both incubations allow the binding of Streptavidin and Ruthenium to the antibodies, which is critical for the measurement technique shown in Figure 5. *From Product Information Elecsys Chagas cobas e analyzers by Roche Diagnostics GmbH, 2019, (https://diagnostics.roche.com/nl/en/products/params/elecsys-chagas.html)*

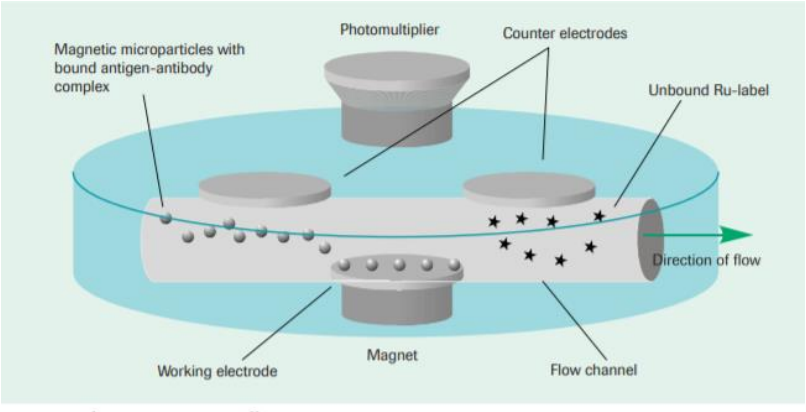

Figure 5 Instrumental arrangement of the ECLIA apparatus for measuring light emission. The antibody sandwich complexes are bound and held in place magnetically due to the streptavidin. For detection, an electrical current is passed through the electrode. *From Product Information Elecsys Chagas cobas e analyzers by Roche Diagnostics GmbH, 2019,* (*https://diagnostics.roche.com/nl/en/products/params/elecsys-chagas.html)*

2.1.6 Treatment

Startlingly, less than 1% of CD patients may receive adequate diagnosis and treatment, even in developed countries such as Germany (Basile et al., 2011; Guggenbühl Noller et al., 2020). If diagnosed in the acute phase, CD can be successfully treated using benznidazole and nifurtimox, the only drugs available today. However, due to the mechanism of action, side effects are considerable, and contraindications include severe liver or kidney disease (Monge-Maillo et al., 2017; Pan American Health Organisation, 2020). Nevertheless, the treatment success rate is 76% for acute infections and 37% for chronic diseases in adults (Cancando et al., 2002; Fabro et al., 2007). Supportive treatment of severe cardiac complications includes pacemakers for heart block and antiarrhythmic drugs for heart failure (Marie & Petri, 2023). For gastroesophageal complications, surgery and injecting botulinum toxin may be used as an ultima ratio (Marie & Petri, 2023).

2.1.7 Prevention and Outlook

To prevent transfusional transmission and maintain the highest level of hemovigilance in Germany, all donors must complete a medical questionnaire comprising medical history and traveling activity before donation. Moreover, donors are examined by a medical doctor, and a blood sample is tested for infectious diseases such as Human Immunodeficiency Virus (HIV) and Hepatitis C. In the case of tropical infectious diseases such as malaria, donors are deferred for six months after traveling to an endemic region or if specific symptoms of inflammation develop (Bayerisches Rotes Kreuz, 2023; Ries et al., 2016). Moreover, a negative anti-malaria test must be obtained after a deferral period of 6 months before re-entering blood donation (Bayerisches Rotes Kreuz, 2023).

Transfusion recommendations and guidelines are developed by the “Arbeitskreis Blut,” which comprises representatives from ministries, medical doctors in transfusion medicine, the German red cross, and the pharmaceutical industry and is part of the Federal Ministry of Health. In addition, the Paul-Ehrlich-Institute (PEI) and Robert Koch Institute (RKI) are crucial organizations in ensuring hemovigilance. As a result, guidelines are published regarding issues such as new emerging infectious agents, their diseases, and current scientific findings concerning transfusion medicine and blood Safety (Paul-Ehrlich-Institut, 2023; Robert Koch Insitut, 2023).

Exposure to *T. cruzi* is not routinely screened serologically in German blood banks for the following reasons: i. the epidemiological situation and low prevalence of CD in Germany, ii. the low sensitivity and specificity of available screening tests (Arboprotozoea, 2009). Nevertheless, ongoing migratory waves, and population movements, such as travellers or adoptions, would require frequent and regular data assessment to provide a more accurate picture (Bayona-i-Carrasco and Avila-Tàpies, 2019). Moreover, adequate diagnostics methods to screen for CD are available today. However, while European neighbours such as the UK (1999), Spain (2005), France (2009), Switzerland (2012),

and Belgium (2013) have implemented nationwide screening, there is no standard operating procedure for *T. cruzi* testing nor regulations for blood donors from CD endemic countries in Germany. This includes testing at-risk blood donors born in or having a mother born in Latin America and introducing anti-*Trypanosoma cruzi* antibody testing (Angeheben et al., 2015; Lidani et al., 2019).

Ominously, the estimated number of undiagnosed CD cases in Europe is 68,000 to 122,000, and 2 million people donated blood in Germany in 2022, of which an unknown number have been exposed to *T. cruzi*, posing a potential threat to blood safety (Basile et al., 2011; Bayona et al., 2019; BZgA: Blutspende, 2022). The consequences of a transfusion-transmitted infection of *T. cruzi* are drastic, as all blood products from the index donor must be traced back and destroyed. Moreover, a look-back action must be started in which all patients who have received blood products from the index donor must be tested and treated (Ries et al., 2016). This may be challenging as treatment success highly depends on the stage at which it is diagnosed.

Considering the lack of data, increasing migration, and the availability of adequate diagnostic methods, we have the responsibility and opportunity to end the neglect of CD in Germany, as urged by Frank et al. (1997).

3. Summary (German)

Trypanosoma cruzi ist der Erreger der Chagas-Krankheit, die in Amerika von den südlichen Staaten der USA bis nach Argentinien verbreitet ist. Nach Infektion über den Kot von Raubwanzen verbreiten sich die Trypanosomen im Körper, befallen besonders Herz, Eingeweide und Nerven und können vom Immunsystem sehr schlecht abgetötet werden, sodass es häufig, anfangs zu einem unspezifischen und meist symptomlosen Verlauf kommt. Nach Jahrzehnten der Infektion zeigen etwa ein Drittel der Infizierten klinische Symptome wie Herzmuskelerkrankung, aufgeweitete Speiseröhre oder erweiterten Dickdarm. Die akute Krankheit kann mit den Medikamenten Benznidazol und Nifurtimox behandelt und meist ausgeheilt werden, was bei der chronischen Form seltener gelingt (Lidani et al., 2019).

Trypanosomen werden übertragen durch den Kot von Raubwanzen auf der Haut, welcher bei der Blutmahlzeit abgegeben wird; durch die Nahrung, wenn mit Raubwanzenkot verunreinigtes Gemüse, Säfte oder Früchte verzehrt werden; durch Übertragung von der Mutter auf das Kind während der Schwangerschaft und schließlich durch Transfusion von Erreger-haltigem Blut, Blutprodukten oder Organtransplantation (Lidani et al., 2019).

Trypanosomen werden auch durch Migration von Bewohnern Südamerikas, die sich häufig während der Kindheit infiziert haben, keine Symptome haben und teils Blut spenden in Europa auf andere Menschen übertragen. Durch die Behandlung von infizierten Menschen, Haustieren und Nutztieren in Südamerika nimmt die Gesamtzahl Infizierter langsam ab, während in Europa die Verbreitung dieser sehr seltene Krankheit zugenommen hat (Lidani et al., 2019).

Ziel dieser Studie war es die *Trypanosoma cruzi*-Verbreitung in ausgewählten Blutspendern in zwei deutschen Städten zu untersuchen, um einen aktuellen Wissensstand zum Risiko einer Übertragung zu erhalten; auch ob über Bluttransfusion in Deutschland eine Gefährdung der Empfänger vorliegen kann.

Insgesamt wurden 305 Blutspender als potenziell exponiert erfasst, 267 in der retrospektiven Studie und 38 in der prospektiven Studie in Berlin und Bayern. 267 Proben der retrospektiven und 27 Proben der prospektiven Studie konnten serologisch getestet werden. Die prospektiven-Studie Probanden haben einen Fragebogen zur Erfassung demographischer Daten ausgefüllt

Alle getesteten Proben waren seronegativ für *T. cruzi* spezifische Antikörper. Prospektiv eingeschlossene Probanden hatten einen hohen sozioökonomischen Status sowie einen hohen Bildungsstatus. Das Wissen bezüglich der Chagas-Erkrankung war sehr niedrig, dagegen die Bereitschaft Blut zu spenden hoch. Die Anzahl der Blutspenden hat sich in der Studienpopulation seit 2015 erhöht.

Trotz der noch nicht berichteten transfusionsassozierten *T. cruzi* Infektions-Übertragung in Deutschland, hat sie mit großer Wahrscheinlichkeit unbeobachtet stattgefunden oder es kann in der nahen Zukunft passieren. Risiko-adaptiertes selektive Screening von potenziell exponierten Blutspendern in Deutschland könnte eine Übertragung verhindern und zum aktiven Auffinden von Infizierten beitragen. Zudem sind größere Studien in Deutschland nötig, um die bisherige Vernachlässigung der Erkrankung und seiner Gefahren für die Transfusionssicherheit zu beenden.

4. Abstract

Introduction: Chagas disease (CD) is caused by the *Trypanosoma cruzi* (*T. cruzi*) infection and has become a global health concern due to population mobility and non-vectorial transmission routes. Several countries outside Latin America (LA) have reported transfusion-associated transmission, but equivalent studies in Germany still need to be completed. This study aims to collect first data on the risk of transfusion associated transmission as well as LA blood donors originating from CD endemic countries in Germany.

Materials and methods: A total of 305 blood donors who were assumed to be at risk for *T. cruzi* infection were retrospectively (267) as well as prospectively (38) selected at German blood donation sites in Bavaria and Berlin, and all retrospectively as well as 27 prospectively selected were serologically screened. Prospective study subjects additionally filled out a questionnaire.

Results: All samples tested seronegative for *T. cuzi* specific antibodies. Prospectively enrolled study subjects all had high socio-economic status including good education. Knowledge regarding CD was limited but willingness to donate frequently was high. Blood donation rates from donors born in LA countries seem to increase since 2015.

Discussion: Although no transfusion associated *T. cruzi* infection has been documented in Germany, it has likely already happened unnoticed, or might happen in the near future. Performing risk-adapted serology-based blood donor screening in Germany could avoid transfusion-associated transmission events as well as contribute to active case detection. Moreover, larger, and ongoing studies are needed to increase the evidence base as well as end the neglect of CD in Germany.

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Adding a piece to the puzzle of Latin American blood donors and the potential risk of *Trypanosoma cruzi* transmission in Germany

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Introduction: Chagas disease (CD) is caused by the *Trypanosoma cruzi* (*T. cruzi*) infection and has become a global health concern due to population mobility, as well as non-vectorial transmission routes. Several countries outside Latin America (LA) have reported transfusion-associated transmission, but equivalent studies in Germany are lacking. This study aims to collect first data on the risk of transfusion associated transmission as well as LA blood donors originating from CD endemic countries in Germany

Materials and methods: A total of 305 blood donors who were assumed to be at risk for *T. cruzi* infection were retrospectively (267) as well as prospectively (38) selected at German blood donation sites in Bavaria and Berlin, and all retrospectively as well as 27 prospectively selected were serologically screened. Prospective study subjects additionally filled out a questionnaire.

Results: All samples tested seronegative for *T. cuzi* specific antibodies. Prospectively enrolled study subjects all had high socio-economic status including good education. Knowledge regarding CD was limited but willingness to donate frequently was high. Blood donation rates from donors born in LA countries seem to increase from 2015.

Discussion: Although no transfusion associated *T. cruzi* infection has been documented in Germany, it has likely already happened unnoticed, or will do in the near future. Performing risk-adapted serology-based blood donor

screenings in Germany could avoid transfusion-associated transmission events as well as contribute to active case detection. Moreover, larger, and ongoing studies are needed to increase the evidence base as well as end the neglect of CD in Germany.

KEYWORDS

blood banks, blood donor screening, *Trypanosoma cruzi*, Chagas disease, transfusion, transmission, Germany

Introduction

Chagas disease (CD) is a potentially fatal infection caused by *Trypanosoma cruzi* (*T. cruzi*). It is endemic in 21 Latin American (LA) countries with devastating effects on health and economies, possibly higher than that of other major infectious or chronic diseases (e.g. rotavirus or cervical cancer) (Lee et al., 2013). CD has become a global health issue due to population movements and several non-vectorial transmission routes, and is now prevalent in non-endemic areas such as Europe (Lidani et al., 2019). Moreover, it is one of the most neglected tropical diseases where less than 1% of those affected may receive adequate treatment even in rich countries such as Germany (Basile et al., 2011; Guggenbühl Noller et al., 2020).

Data concerning CD in European countries is scarce and patchy: Estimates state that roughly 4,6 million LA migrants live in Europe and that there may be between 68,000 to 122,000 undiagnosed cases of CD (Basile et al., 2011; Bayona-i-Carrasco and Avila-Tàpies, 2019). It is very difficult to identify the number of undocumented migrants although they may account for the highest CD prevalence rates (Jackson et al., 2010). Ongoing migratory waves, together with other population movements, such as travelers or adoptions, would require frequent and regular data assessment in order to provide a more accurate picture (Bayona-i-Carrasco and Avila-Tàpies, 2019). In 2020, a total of 140,565 immigrants from CD endemic LA countries were officially registered in Germany (Statista, 2021), undocumented migrants and migrants with European citizenship have to be counted on top of this.

Due to migrant groups participating in blood donation programs within their host countries, transfusion transmitted *T. cruzi* infections have already been described in non-endemic countries like Australia, Canada, Spain, and the USA (Angheben et al., 2015). Reacting to this, several countries (e.g. Belgium, France, Spain, Switzerland, and UK) have implemented nationwide screening of at-risk blood donors for *T. cruzi* specific antibodies (Angheben et al., 2015; Lidani et al., 2019). In Germany, only one study has been published so far with a total of 4,391 blood donors being screened as negative in 2015-2016 (Flores-Chavez et al., 2018). However, the study likely included only few to no blood donors at risk for CD. According to current regulations in Germany, blood donors including those at risk for CD are not screened serologically for *T. cruzi*. In 2009, recommendations by the German Advisory Committee Blood stated as reasons (i) the lack of data justifying such screening measures, (ii) the epidemiological situation and low prevalence of CD in Germany, and (iii) the low sensitivity as well as specificity of available screening tests (Arboprotozoea, 2009). Following regulations, individuals with a known *T. cruzi* infection and/or having received blood transfusions from CD endemic countries are excluded from blood donations. Additionally, individuals are put on hold for six months after visiting or living in malaria endemic regions, which excludes a relevant fraction of individuals at risk of acute CD due to the significant overlap of both protozoa (Arboprotozoea, 2009).

The primary aim of our study is to collect first data on the risk of transfusional *T. cruzi* transmission in Germany. Moreover, it should improve knowledge about the population of LA blood donors born in endemic countries for CD. For this, selected blood donors were retro- as well as prospectively screened for *T. cruzi* specific antibodies and personal information was prospectively collected on LA blood donors born in CD endemic countries *via* a questionnaire.

Materials and methods

Ethical considerations

The study protocol was approved by the Institutional Review Board at the Ludwig-Maximilians-University in Munich, Germany (opinion dated 19 September 2018, number 18-458) prior to study initiation and adhered to the most recent version of the Declaration of Helsinki.

Retrospective study

We compiled a list of common Brazilian/Portuguese and/or Spanish surnames in LA by consulting multiple databases and national registries (Supplemental Data 1). We took spelling variants into account and excluded surnames also frequent in German (e.g. Jordan, Leon, Martin, or Reis). We utilized this in order to enrich the list of blood donors originating from LA countries with CD endemic geographic regions and thus those at increased risk of *T. cruzi* infection. For at least five years, EDTA plasma reserve samples of all active blood donors are kept in the Bavarian Red Cross central blood bank (Wiesentheid, Germany). Thus, in February 2019, we took plasma samples belonging to donors with listed names within the timeframe between January 2014 and January 2019 in a pseudonymized manner, including additional information on age range and sex.

Prospective study

We recruited participants in the prospective study at different Bavarian Red Cross blood collection sites across Bavaria and the centralized blood transfusion services of the Institute of Transfusion Medicine, Charité University Hospital, Berlin between April 2019 and April 2020. We used the compulsory standard medical questionnaire prior to blood donations in order to identify donors aged 18 and older as well as born in one of the 21 LA countries with CD endemic geographic regions. We informed those potential study subjects about our study and enrolled all individuals that gave oral and written informed consent to the responsible medical doctor on site. Once enrolled, study subjects filled out a study questionnaire and we kept a 5 mL serum sample during the blood donation process which was stored at -20°C until screening for *T.cruzi* specific antibodies was performed.

Screening for *T. cruzi* specific antibodies

We screened all retro- as well as prospectively collected plasma/serum samples for anti-*T. cruzi* IgG using the licensed Elecsys Chagas assay on a cobas e 411 analyzer by Roche diagnostics as described previously (Flores-Chavez et al., 2018). Sensitivity and specificity were shown to be 100.0% and 99.9%, respectively (Flores-Chavez et al., 2018), thus meeting the requirements of the Pan-American Health Organization guidelines concerning *T. cruzi* screening in hemotherapy (Organización Panamericana de la Salud, 2019). In addition to the standardized calibration of the cobas e analyzer prior to every test cycle, a total of five serum samples from known CD patients were added as positive controls in three distinct dilutions (5-, 10-, and 100-fold). A cut-off index for reactivity of 1.0 was used according to the instructions of the manufacturer.

Data analysis

Pseudonymized data was entered in Microsoft Excel, anonymized once the necessity of look back procedures could be excluded, and then analyzed using SPSS version 27.

Results

Retrospective study

From January 2014 to January 2019, a total of 3,514,501 blood donations were drawn from 647,561 donors by the Bavarian Red Cross at their donation sites. We selected a total of 296 donors (0.05%) by cross-checking the name list of common Brazilian/Portuguese and/or Spanish names in LA countries with CD endemic geographic regions (Figure 1; Supplementary Data 1). We were able to obtain 267 (90.2%) of the corresponding EDTA plasma reserve samples in order to perform *T. cruzi* antibody screening (Figure 1). Of those, 71/267 (26.6%) study subjects were selected for having frequent Brazilian/Portuguese names, 171/267 (64.0%) for frequent Spanish names, and 25/267 (9.4%) for names that are common in both languages. Sex was nearly equally distributed with 128/267 (47.9%) being females and 123/267 (46.1%) study subjects belonged to the age group 18-29 years at the time of blood donation. Table 1 provides a more detailed description regarding age range and sex of the retrospective study population. All study subjects' samples were non-reactive (highest measurement 0.26) for *T. cruzi* specific IgG, while all positive controls were reactive in all dilution steps.

Prospective study

From April 2019 to April 2020, a total of 545,754 blood donations were drawn from 263,762 donors by the Bavarian Red Cross at all blood donation sites across Bavaria. In the same time frame, a total of 8,718 blood donations were drawn from 6,386 donors at the Institute of Transfusion Medicine, Charité University Hospital, in Berlin. A total of 38 study subjects could be enrolled in this prospective study consisting of 34 individuals from across Bavaria and 4 from Berlin (Figure 2). Of those, the names of 24/38 (63.2%) enrolled study subjects were included on the name list (Supplementary Data 1) used for the retrospective study and thus would have been detected by using this screening methodology. Questionnaire data was available for all 38 study subjects, while *T. cruzi* antibody screening could only be performed on 26 of them due to a transport associated loss of 12 serum samples. Donors of

lost samples were contacted, asked to send a blood sample for testing, and one donor could be resampled. Of the 27 samples screened for *T. cruzi* specific IgG, all were non-reactive (highest measurement 0.11), while all positive controls were reactive in all dilution steps. Table 2 provides information on study subjects in our prospective study. Most participants belonged to the age group 18-29 (22/38; 57.9%) and the study population consisted of slightly more males (23/37; 60.5%). Study subjects were born in a variety of countries with CD endemic geographic regions, with Brazil (13/38; 34.2%), Mexico (9/38; 23.7%), Argentina (4/38; 10.5%), and Colombia (4/38; 10.5%) being the most frequent (Table 2; Figure 3). Two study subjects were born in Bolivia, the country with the highest prevalence of CD per 100,000 inhabitants worldwide, and both tested serologically negative. As expected, considering the country of origin, more study subjects stated Spanish as their mother tongue (24/38; 63.2%) than Portuguese (14/38; 36.8%). The vast majority of study subjects (37/38; 97.4%) grew up in a LA country with CD endemic geographic regions and nearly all of them resided there (36/37; 97.3%) prior to emigrating to Germany. Most study subjects kept their nationality of origin (32/38; 84.2%), whereas some (6/38; 15.8%) adopted the German nationality in addition to their original nationality. Most study subjects (22/38; 57.9%) immigrated to Germany from 2015 to 2019, the others immigrated between 1980 and 2013 (Figure 4). All donors grew up in larger cities with more than 100,000 inhabitants and were living in houses made out of stone or concrete. A total of 24/37 (64.9%) had heard about CD in their country of birth, but only 8/38 (21.1%) could correctly describe three typical symptoms. Some 21/30 (70.0%) correctly indicated that CD could possibly be transmitted *via* the triatomine feces but only 12/30 (40.0%) knew that it could be transmitted *via* transfusion of blood and blood derivates, while 6/38 (15.8%) did not know any ways of transmission. Only 9/38 (23.7%) had seen a triatomine bug

TABLE 1 Age ranges and sex for retrospective study subjects.

	Female	Male	Total
Age ranges			
18-29	63 (51.2%)	60 (48.8%)	123
30-39	35 (48.6%)	37 (51.4%)	73*
40-49	26 (53.1%)	23 (46.9%)	49
50-59	11 (57.9%)	8 (42.1%)	19
60-69	3 (100.0%)	0 (0.0%)	3

*Sex information was unavailable for one study subject aged 30-39.

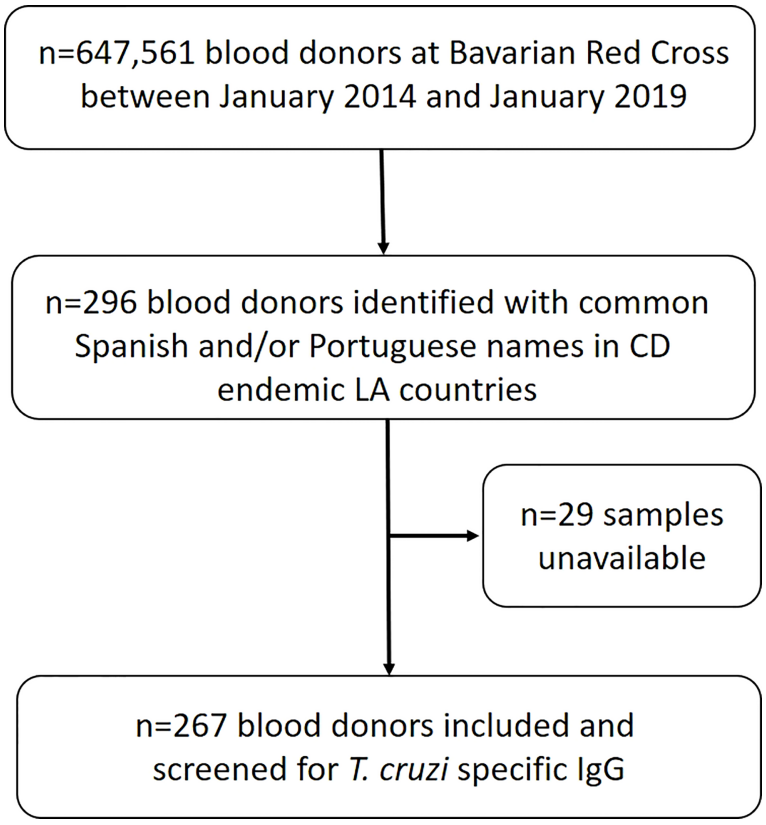

FIGURE 1
Selection algorithm of study subjects in the retrospective study.

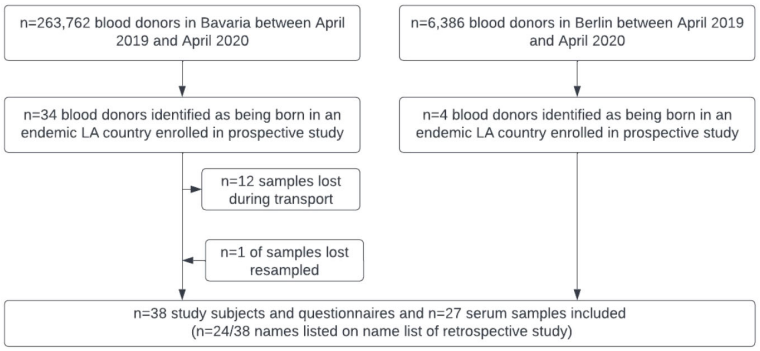

FIGURE 2
Selection algorithm of study subjects in the prospective study.

during their housing in LA and 2/37 (5.4%) knew someone suffering from CD in their LA country of birth. Most study subjects (25/38; 65.8%) had already donated blood prior to study inclusion and of those, 7/25 (28.0%) had donated in Germany and 18/25 (72.0%) in LA, respectively. All study subjects were highly educated and socio-economically advantaged: All had finished at least secondary schooling and a total of 24/38 (63.2%) were in possession of a university degree.

Discussion

To the best of our knowledge, this study is the first to examine blood donors from LA countries with CD endemic geographic regions and the associated risk for *T. cruzi* transmission in Germany. No *T. cruzi* infections were detected among the 293 screened blood donors. Several European countries such as Spain, the UK, Switzerland and France have implemented screenings of blood donors at risk for *T. cruzi* infection (Angheben et al., 2015). Studies carried out in Spain and France have shown a prevalence of at risk blood donors to be 0,66% in Spain and 0,31% in France, respectively (Piron et al., 2008; El Ghouzzi et al., 2010). In addition, several transfusion-associated *T. cruzi* infections have been described in non-endemic countries (including several European countries), of which some were detected after the implementation of serological blood donor screenings and associated look-back procedures (Flores-Chávez et al., 2008; Kessler et al., 2013; Angheben et al., 2015; Blumental et al., 2015; Ries et al., 2016).

As we had no possibility to identify the risk for CD or the country of birth in retrospect, we used a list of common Brazilian/Portuguese and/or Spanish names in CD endemic LA countries as a proxy for LA origin that resulted in screening 267 blood donors who had donated over a time period of five years. By applying the same name list to our 38 prospective study subjects, a total of 24 (63.2%) would have been detected retrospectively. We therefore assume that the 267 retrospectively identified blood donors include a significant fraction of individuals who were actually born in CD endemic LA countries. A limitation of this approach is that LA blood donors with high risk of *T. cruzi* infection could have been missed due to the exclusion of surnames also common in Germany or name changes (e.g. after marriage or adoption) and Portuguese as well as Spanish citizens without risk could have been falsely included.

In the prospective study, all 38 study subjects who enrolled over a time period of 12 months were born in a CD endemic LA country. We could not identify the number of blood donors born in a LA country with CD endemic geographic regions who were identified but refused to take part in our prospective study. As this was not included in the original study protocol and we were unable to gather this information in retrospect, it has to be mentioned as a shortcoming. The small number of blood donors and blood donation centers included and some samples being lost during transport also impacts the informative value of our study.

One of the strengths of our prospective study is that we collected additional data on study subjects *via* questionnaires. Higher socio-economic status is correlated with less risk for *T. cruzi* infections (Hotez and Gurwith, 2011): With 24 out of the 38 prospectively enrolled study subjects (63.2%) having a university degree and the rest having at least finished secondary schooling, study subjects all had high socio-economic status. In addition, all 38 study subjects grew up in cities >100,000 inhabitants situated in housing with little risk of insect vector colonization and only two reported having known someone suffering from CD in their country of birth. The country of birth also influences the likelihood of CD infection (Bern et al., 2019) and only two of our participants were born in Bolivia. In the light of this information, it is not surprising that no infection was detected in our prospective cohort. Enrolled subjects from Mexico, Argentina, Bolivia and Paraguay were slightly overrepresented percentagewise in our study cohort (Figure 3). Subjects from Colombia and Peru were slightly underrepresented and the biggest subject group from Brazil

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TABLE 2 Questionnaire data of prospective study subjects.

	Female	Male	Total
Age range			
18-29	7	14	22*
30-39	2	8	10
40-49	2	1	3
50-59	1	0	1
60-69	2	0	2
Country of birth			
Brazil	6	7	13
Mexico	1	7	9*
Colombia	0	4	4
Argentina	1	3	4
Venezuela	2	1	3
Bolivia	2	0	2
Peru	2	0	2
Paraguay	0	1	1
Arrival in Europe			
2019-2020	1	3	4
2017-2018	4	5	10*
2015-2016	3	5	8
2010-2013	1	4	5
2000-2009	1	6	7
1980-1999	4	0	4
Highest educational status			
Secondary school	5	5	10
Vocational training	2	2	4
University degree	7	16	24*
Has seen a triatomine bug inside their housing in LA			
Yes	2	6	9*
No	12	17	29
Knows someone with CD in LA**			
Yes	1	1	2
No	13	21	35*
Heard about CD in country of birth**			
Yes	10	14	24
No	4	8	13*
Ways of CD transmission			
Triatomine bug	6	15	21
Sexual intercourse	1	2	3
Blood transfusion	5	7	12
Mosquito	1	3	4
Mother to child	1	3	4
Juice consumption	1	1	2
Organ transplantation	1	5	6
Physical contact	1	2	3
Don't know	1	4	6*
No answer	4	4	8
Infected can feel healthy**			
Yes	6	6	12

(Continued)

TABLE 2 Continued

	Female	Male	Total
No	1	3	4
Don't know	7	13	20
Most common CD symptoms			
No correct symptom	9	14	24*
1 correct symptom	1	1	2
2 correct symptoms	0	4	4
3 correct symptoms	4	4	8
Would donate organs			
Yes	13	19	33*
No	0	0	0
Don't know	1	4	5
Previously donated blood			
In country of origin	8	9	18*
In Germany	1	6	7
No	5	8	13
Received blood transfusion(s)			
Yes	1	0	1
No	13	23	37*

*Sex was unavailable for one study subject aged 18-29.
**Not all participants answered those questions so numbers don't add up to 38.
CD, Chagas disease; LA, Latin American.

was accurately represented (Figure 3). However, the sample size was too small in order to draw relevant conclusions out of these differences.

A way of reducing the already limited likelihood of transfusional as well as transplantational *T. cruzi* transmission in Germany is to raise awareness about CD among individuals at risk for CD, e.g. LA migrants or travellers having lived in LA countries at risk of CD that are or eventually could become donors. Once diagnosed with CD, they would be excluded from donations and thus render this method of transmission unlikely. Among our prospectively enrolled study subjects —having both high socio-economic status and education— general knowledge about CD was low: e.g. most study subjects (24/38; 63.2%) could not even correctly mention one common symptom of CD and 13/37 (35.1%) study subjects hadn't heard of CD in their country of birth. These findings are in agreement with a previous study performed among

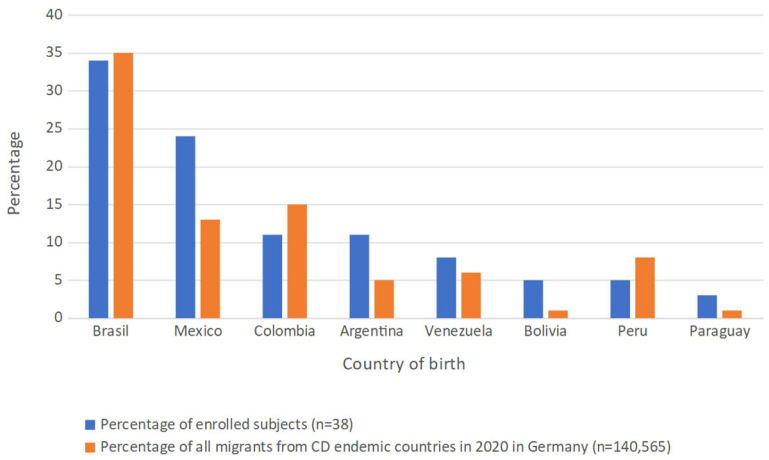

FIGURE 3
Comparison between the percentages of enrolled subjects and total registered immigrants from that country in Germany in 2020.

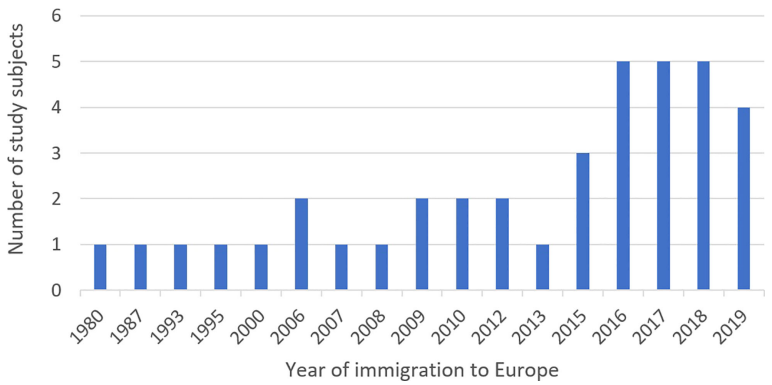

FIGURE 4
Year of immigration to Europe for all prospectively enrolled study subjects.

Bolivians living in Munich, Bavaria, Germany (Navarro et al., 2017). Continuing efforts to raise awareness about CD with at-risk individuals as well as health care personnel might lead to increased diagnoses and with this to a decreased risk of infection transmission. It is likely that less than 1% of individuals at risk of CD receive adequate care in Germany at the present time (Basile et al., 2011; Guggenbühl Noller et al., 2020). All of this data forms a strong argument for targeted, innovative, as well as continued information, education, and communication campaigns in regard to CD.

The at-times rapidly changing landscape of migratory movements poses challenges to blood banks and other institutions alike. The number of donors should be maximized while maintaining the highest levels of hemo-vigilance. Although there has never been a documented case of transfusional *T. cruzi* transmission in Germany, we should take heed of the aphorism "absence of evidence is not evidence of absence": That it cannot be ruled out that transfusional transmission has likely taken place or that it could take place in the future. That no case had been documented to date might easily be due to the absence of appropriate donor screening, as seen in other European countries (Angheben et al., 2015). The increasing popularity of Germany among LA migrants and their participation in the blood donation system (Navarro et al., 2017), makes a strong case for the undertaking of additional and larger investigations like this one, as well as for direct implementation of risk-adapted serology-based blood donor screening in Germany. These measures could avoid potentially fatal transfusion-associated CD as well as contribute to active case detection and thus help to end the neglect of CD in Germany. Germany, together with all other member states of WHO, endorsed the new road map for neglected tropical diseases 2021-2030 in the 73rd World Health Assembly in November 2020 (WHO, 2020). One of the objectives is the verification of the interruption of transfusional *T. cruzi* transmission and by implementing an appropriate national protocol Germany could verify this much before 2030.

In summary, this first attempt to describe the German landscape of LA blood donors born in countries with CD endemic geographic regions suggests a generally higher socio-economic status and thus reduced overall risk of *T. cruzi* infection compared to the general population in their countries of birth. Although, no transfusion associated *T. cruzi* infection has been documented in Germany so far, it likely could have already taken place unnoticed or will do in the near future. A risk-adapted serology-based blood donor screening in Germany could avoid transfusion-associated *T. cruzi* transmission, maximize the number of donors, as well as contribute to active case detection and thus help to end the neglect of CD in Germany. At the very least, more and larger studies are needed to increase the evidence base. The rapidly changing landscape of migratory movements remains challenging and calls for constant surveillance until CD is eliminated or no longer a neglected tropical disease.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by institutional review board at the Ludwig-Maximilians-University in Munich, Germany. The patients/participants provided their written informed consent to participate in this study.

Author contributions

LG and MP provided funding for the study. LG and MP designed the study. EQ, FW, UK, AP, and PA-V commented on the study protocol. JU was responsible for recruitment with the help of LG, EQ, FW, UK, AP, and MP. DR supervised laboratory analyses. JU analyzed the data with the help of LG and MP. JU drafted the first manuscript version. All authors contributed to the article and approved the submitted version.

Acknowledgments

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Conflict of interest

Author DR is employed by Roche Diagnostics GmbH, Penzberg, Germany.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcimb.2022.1014134/full#supplementary-material

SUPPLEMENTARY DATA SHEET 1
List of common Brazilian/Portuguese and/or Spanish surnames in CD endemic Latin American countries.

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Supplementary Data

The following supplementary data has been published.

In order to retrospectively select blood donors potentially born in or to mothers from CD endemic LA countries with increased risk for *T. cruzi* infection, we compiled a list of common Brazilian/Portuguese and Spanish surnames in CD endemic LA countries.

As Brazil is the only Portuguese-speaking country in LA that is endemic to CD, we included 100 frequent Brazilian surnames. However, the surname Reis was also frequent among German names and thus removed from the list.

We initially included 226 frequent surnames for Spanish names in CD endemic LA countries. However, we subsequently removed the names Jordan, Leon, Martin, and Martins due to overlap with German names.

A total of 22 surnames overlapped between the lists of Spanish (222) and Brazilian/Portuguese (99) surnames. Thus, the final list of prevalent Brazilian/Portuguese and Spanish surnames in CD endemic LA countries possessed 299.

Common Brazilian/Portuguese surnames in Brazil (n=77):

Abreu, Almeida, Alves, Amaral, Amorim, Anjos, Antunes, Araujo, Assuncao, Azevedo, Baptista, Barbosa, Barros, Batista, Borges, Branco, Brito, Cardoso, Carneiro, Carvalho, Coelho, Correia, Costa, Crunha, Esteves, Faria, Ferreira, Figueiredo, Fonseca, Freitas, Gaspar, Goncalves, Guerreiro, Henriques, Jesus, Leal, Leite, Loureiro, Lourenco, Macedo, Machado, Magalhaes, Maia, Matias, Matos, Meideros, Melo, Monteiro, Moraes, Moreira, Mota, Moura, Nascimento, Neto, Neves, Nogueira, Oliveira, Pacheco, Paiva, Punheiro, Pinho, Pires, Ramos, Raposo, Ribeiro, Santana, Silva, Simoes, Soares, Souza, Sa, Tavares, Teixeira, Valente, Vaz, Vicente, Vieira

Common Spanish surnames in CD endemic LA countries (n=200):

Acosta, Aguilar, Aguilera, Aguirre, Alarcon, Aliaga, Alonso/Alonzo, Alvarez, Anez, Antelo, Antezana, Apaza, Aramayo, Arancibia, Aranibar, Araya, Arce, Arias, Arteaga, Avila, Ayala, Baez, Balderrama, Barrientos, Bejarano, Beltran, Benitez, Blanco, Bustillos, Caballero, Cabrera, Caceres, Calderon, Calle, Camacho, Cardenas, Cardozo, Carlos, Carrasco, Carvajal, Castillo, Cespedes, Chambi, Chavez, Choque, Claros, Claure, Coca, Colque, Condori, Contreras, Cordova, Cortes/Cortez, Cossio, Crespo, Cuellar, Daza, Delgadillo, Delgado, Dorado, Duran, Encinas, Escobar, Espinosa/Espinoza, Ferrufino, Flores, Franco, Fuentes, Galeano, Gaviria, Gil, Gimenez, Gonzales, Gutierrez, Guzman, Herbas, Heredia, Hernandez, Herrera, Hinojosa, Huanca, Hurtado, Ibanes/Ibanez, Iglesias, James, Jimenes/Jiminez, Justiniano, Landivar, Laura, Ledezma, Limachi, Llanos, Loayza, Loza, Luna, Maldonado, Mamani, Martinez, Medina, Medrano, Mejia, Melgar, Menacho, Mendoza, Mercado, Molina, Montano, Montero, Morales, Morell, Moreno, Moscoso, Munoz, Murillo, Navarro, Nina, Nogales, Orellana, Ortega, Ortis/Ortiz, Pacheco, Padilla, Paniagua, Parada, Paredes, Paz, Pena, Peredo, Perez, Poma, Ponce, Ponze, Prado, Quiroga, Quiros/Quiroz, Quisbert, Quispe, Ramirez, Ramos, Reyes, Ribera, Rios, Rivera, Rivero, Roca,

Rojas, Romero, Rubio, Ruiz, Salas, Salazar, Salinas, Salvatierra, Sanches/Sanchez, Sandoval, Sanz, Saravia, Saucedo, Sejas, Sepulveda, Serrano, Siles, Silva, Soliz, Soria, Sosa, Soto, Suares/Suarez, Tapia, Teran, Terceros, Terrazas, Ticona, Ticonas, Torrico, Vaca, Valdes/Valdez, Valdivia, Valencia, Valenzuela, Valverde, Vargas, Vasquez, Vega, Veizaga, Velarde, Velasco, Velasques/Velazquez, Vera, Villalba, Villarroel, Villca, Villegas, Zabala, Zambrana, Zapata, Zeballos, Zembrano, Zenteno, Zurita

Common Brazilian/Portuguese and Spanish surnames used in CD endemic LA countries (n=22):

Andrade, Campos, Castro, Cruz, Dias/Diaz, Domingues/Dominguez, Duarte, Fernandes/Fernandez, Garcia, Gomes/Gomez, Lima, Lopes/Lopez, Marques/Marquez, Mendes/Mendez, Miranda, Nunes/Nunez, Pereira, Pinto, Rocha, Rodrigues/Rodriguez, Santos, Torres

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