Analysis in the need of improvement in the health care system for Chagas disease in Japan

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Abstract

Background

Chagas disease (CD) is emerging as a global health problem. Despite an estimate of 3,000 cases in Japan, there are a lack of policies for control and prevention, resulting in an epidemiological silence with humanitarian and economic consequences. I aim to *i*) analyze the current situation of CD epidemiologically, clinically, and economically; *ii*) characterize the barriers that the populations at risk of CD encounter in accessing the Japanese health care system (HCS); and *iii*) compare a rapid diagnosis test (RDT) with the standard diagnosis.

Methods

This is a cross-sectional study that included participants at risk of CD living in Japan from March 2019 to October 2020. Data were collected in seven different prefectures, focusing on the main populational groups (Brazil, Peru, and Bolivia). To provide a comprehensive approach, I have conducted a system of education throughout the research. Finger-pricks were used to obtain blood for analysis by serological diagnosis and RDT. Quantitative data was obtained from questionnaires/survey with sociodemographic information, risk factors of CD, and barriers in access to the HCS. I calculated the cost-effectiveness of CD screening in the asymptomatic adult migrant population using a Markov state transition model. The identified positive participants were referred to clinical institutions.

Results

The study included 428 participants. Most of the participants were from Brazil (46%, n=195), Bolivia (31%, n=132), and Peru (16%, n=70). The observed prevalence was 1.6% (expected prevalence=0.75%) and among Bolivians was 5.3%. RDT had an agreement of 100% with standard diagnosis ($\varkappa$ =1). The ages of positive participants (n=7) ranged from 45 to 69 years

old; and all were born in Bolivia (Santa Cruz). Six out of seven were asymptomatic. Clinical data were not obtained due to the lack of a follow-up.

Deterministic and probabilistic analysis showed that the screening model was more cost-effective than the non-screening model from a health care and societal perspective (ICER, 200,320 JPY, and 134,147 JPY, respectively).

Female Latin American migrants were at higher risk to avoid a necessary visit to a doctor or health worker (OR=2.30; CI 1.13-4.7). Migrants that live in Japan for more than 10 years are less likely to avoid required visits to health facilities (OR=0.31; CI. 0.10-0.91). Migrants that received information about the HCS from a governmental source were less likely to perceive a worse access to the HCS (OR=0.13; CI 0.02-0.64). Migrants whose communication in Japanese is a barrier and who are not satisfied with the HCS were more likely to perceive worse access to the HCS (OR=3.53; CI.1.37-9.09 and OR=10.06; CI 3.2-31.72, respectively) and avoid seeing a doctor/health worker when they need it (OR= 2.16, CI 1.03-4.52 and OR=10.06, CI 3.2-31.72, respectively).

Conclusion

The CD observed prevalence is more than double compared with the estimated prevalence and is higher in the Bolivian population. Screening for CD is a cost-effective strategy in asymptomatic Latin American adult migrants in Japan. However, barriers associated with their access to HCS include being female, length of stay in Japan, language skills, source of information about the HCS, and satisfaction about the HCS system.

Table of contents

1. List of tables and figures

1.1.Tables

1.2. Boxes

1.3. Figures

2. Abbreviations

CD	Chagas Disease
COVID-19	Coronavirus disease 2019

CEAC	Cost effectiveness acceptability curve
DALYs	Disability adjusted life years
EDTA	Ethylenediaminetetraacetic acid
EHI	Employee health insurance
ELISA	Enzyme-linked immunosorbent assay
GDP	Gross domestic product
HCS	Health care system
ICER	Incremental cost effectiveness ratio
IFA	Indirect immunofluorescence assay
IFI	Indirect immunofluorescence
JICA	Japan International Cooperation Agency
JPY	Japanese yen
LA	Latin American
LAMP	Loop-mediated isothermal amplification
NEKKEN	Institute of Tropical Medicine
NC	Negative control
NHI	National health insurance
NHS	National health system
NPO	Non-profit organization
NTD	Neglected tropical disease
PC	Positive control
PCR	Polymerase chain reaction
PHC	Primary health care
PI	Principal investigator (Inés María Iglesias Rodríguez)
PPP	Purchasing power parity

QALYs	Quality adjusted life years
RDT	Rapid Diagnosis Test
SMU	Saitama Medical University
TPP	Target product profile
UHC	Universal health coverage
WHO	World Health Organization
WTP	Willingness-to-pay

3. Introduction

More than a century after Carlos Chagas discovered Chagas disease (CD), the incidence rate has decreased significantly. However, more than 6 million people are still affected worldwide (PAHO 2021). This prevalence could be underestimated because only 1% of the affected people have the possibility to access the diagnosis and treatment (Instituto de Salud Global 2017). Annually 39,000 new cases occur and 9,000 result from vertical transmission (PAHO 2021). In Latin America, CD represents the tropical disease with the highest burden in disability-adjusted life-years (DALYs), with 806,170 DALYs. (Lee et al. 2013). The global economic burden is about 627 million dollars, of which 10% is attributed to non-endemic countries (Lee et al. 2013). According to these data, the annual cost of the disease worldwide is estimated at 7,200 million dollars, including health expenditures, as well as losses due to premature mortality and lack of income as the cause of DALYs (Instituto de Salud Global 2017). In sum, the disease represents a significant difficult-to-treat and high mortality neglected tropical diseases (NTD) throughout the Western Hemisphere (Perez-Molina & Molina 2018).

In the last years due to migratory flows, the disease has silently crossed the borders of the historical endemic areas into the United States, Europe, and the Western Pacific region (Gascon, Bern & Pinazo 2010). Despite being a globalized disease, CD remains one of the 20 NTD declared by the World Health Organization (WHO).

Despite the resources of developed countries, as are many of the non-endemic countries, the goals to control the disease proposed by WHO have not been achieved, due to the low level of policies and interventions for control and care of CD (WHO 2010). In non-endemic countries, the Latin American (LA) migrant populations face inequalities in terms of access to their social right of health care (Suguimoto et al. 2012; Russell-Miller et al. 2019). In this

perspective, CD monitoring in non-endemic areas can serve as an indicator of healthcare equity (Pinazo & Gascon 2020). The perpetuation of this situation leads to important consequences in humanitarian and economic areas that cannot continue to be neglected.

4. Literature review

4.1. Chagas disease

CD is a parasitic disease caused by the parasite *Trypanosoma cruzi (T. cruzi)*. Most of the burden of the disease is caused by transmission via the insect vector triatomine bug, commonly referred to as the kissing bug for its propensity to bite around the human face. The disease can also be transmitted from mother to child during pregnancy or birth, blood transfusion, and organ transplantation. In recent years, the number of reported cases was increased because of oral transmission through contaminated food with the vector or its feces. Oral transmission is frequently presented as epidemic outbreaks with more potential severe cases than in other ways of transmission. Less frequently, some cases occur due to laboratory accidents (WHO 2019).

4.2. Epidemiology

CD was a disease traditionally confined to the 21 countries that comprise Latin America. However, due to migratory movements, both transoceanic and along the American continents, CD has become a global problem that affects all societal sectors, both in rural and urban areas (Figure 1) (WHO 2021).

The Latin American countries with the highest prevalence are Bolivia (6%), Argentina (4%) and Paraguay (2%). Whereas 42% of the cases of endemic areas of CD reside in Brazil and Argentina (WHO 2015). The non-endemic areas most affected by CD are the United States of

America (USA) and Canada, Europe, and the Western Pacific region (Instituto de Salud Global 2017).

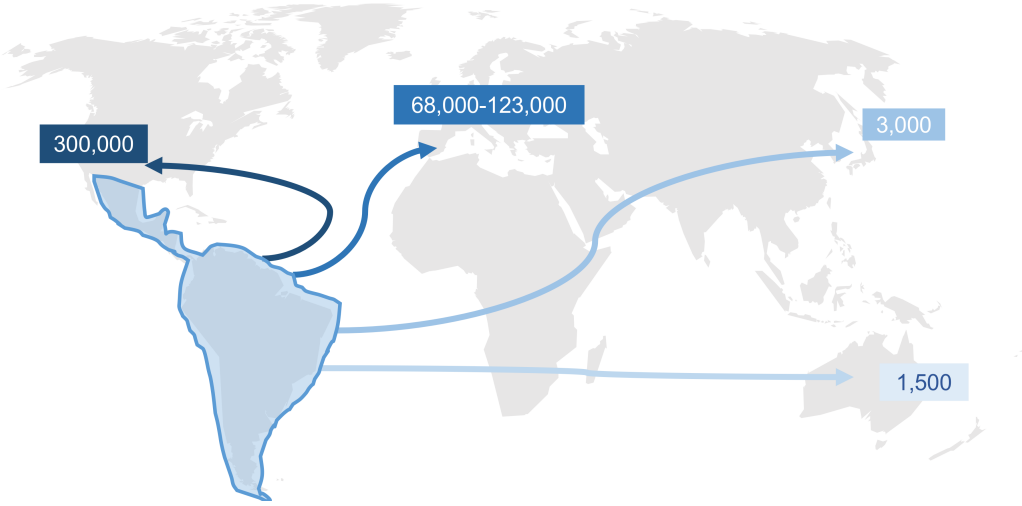

Figure 1. Chagas disease, a global problem.

4.3. Clinical manifestations

The clinical progression of CD involves acute and chronic phases. After the parasite enters the host by one of the transmission routes, the disease can manifest in a symptomatic acute phase (WHO 2021). However, less than 10% of the people infected will develop acute symptoms after infection. Typically, the disease will continue a silent course over decades. Around 30% of the people infected will develop into an asymptomatic chronic phase and the other 70% would remain asymptomatic during their entire life (Roca et al. 2015).

In the chronic phase of CD, the symptomatic disease would occur mostly because of damage in the heart, esophagus, colon, and peripheral nervous system (WHO 2021). Less frequently neurologic complications for the cerebrovascular disease can occur as a primary or secondary outcome to CD cardiomyopathy. The chronic phase can be differentiated by four forms of CD (Table 1). The reactivation of the disease can occur in chronic patients when the immune

system is compromised by other causes such as HIV, leukemia, or transplant patients (Carabarin-Lima et al. 2013).

Table 1. Chronic phase forms of Chagas disease (Nunez et al. 2018; Sabino et al. 2013; (Nunez et al. 2018; Roca et al. 2015; Messenger, Miles & Bern 2015).

Indeterminate form	70% of infected people	○ Defined by a positive result in the serological test without any clinical symptoms or presence of organ damage. ○ Considered infected with the risk of transmission to others. ○ Indeterminate Chagas disease can progress to clinically manifest disease within 10-20 years, at a rate of 1.9% to 7% annually.
Cardiac form	30-40% of symptomatic patients	○ Defined by the presence of at least one typical electrocardiographic abnormality in patients with a positive serological test for *T. cruzi*. ○ The most common clinical manifestation results from electric conduction abnormalities, myocardial contractile dysfunction, arrhythmias, or thromboembolism.
Digestive form	15-20% of the symptomatic (more frequent in Southern Cone)	○ Involvement of the esophagus (from mild achalasia to severe megaesophagus). ○ Colonic involvement (megacolon) can be found.
Combined form	Infrequent	○ Combination of cardiac and digestive involvement.

The comorbidity of CD is associated mainly with the cardiac form contributing to a decrease in productivity years (Nunes et al. 2018). The mortality range varies from 9 to 85%, depending on cardiac damage (Nunes et al. 2018). The leading causes of death are sudden death by arrhythmias, heart failure, and vascular cerebral accidents (WHO 2019, Nunes et al. 2018). As Carlos Chagas illustrated, "individuals, not rarely, die in their youth with apparently a healthy condition and no signs of heart disease" (Chagas & Villela 1922).

4.4. Diagnosis

In the acute phase or reactivation, the most common methods used for diagnosis are direct parasitological diagnostic methods or indirect molecular methods (WHO 2019; Roca et al. 2015). However, because the acute phase rarely has symptoms, most patients would be diagnosed in the chronic phase, at a time where diagnostic methods are not useful because the parasitemia is low and intermittent (Bern 2015).

The diagnosis in the chronic phase is based on indirect methods such as enzyme-linked immunosorbent assay (ELISA), indirect hemagglutination assay (IHA) and indirect immunofluorescence assay (IIF). The standard diagnosis of CD is based on two positive serological tests (WHO Expert Committee 2002). One of the main reasons for conducting a double test is that the sensitivity of serological assays can vary according the geographic origin of the specimens. Antigenic variation between strains can affect the antibody response, resulting in different sensitivities to the serodiagnosis (Umezawa et al. 2004; Caballero et al. 2007; Sosa-Estani et al. 2008).

Even an early diagnosis in the people at risk should be a priority, the actual diagnostic methods used for screening and the therapeutic efficacy for CD are an area requiring

improvement for two main reasons. Firstly, the standard diagnosis is impractical in isolated places where the resources and trained personnel are limited; and in non-endemic countries where CD is an emerging problem in health systems not yet adapted to a globalized world. In the last years as a solution to this problem, the incremented use started of immunochromatography rapid diagnostic test, known as a rapid diagnosis test (RDT). RDT is an easy-to-use diagnostic test without the need for trained personnel or electrical equipment, and offers results in a timely fashion (Sanchez- Camargo et al. 2014). It has shown good results in terms of sensitivity and sensibility (Sanchez-Camago et al. 2014, Égüez et al. 2017; Lozano et al. 2019). However, it has an important sensitivity variability in different geographical areas; and for this reason, to date RDT is just indicated for prevalence studies of chronic CD (PAHO 2018). Secondly, the detection of serological negative conversion to evaluate the therapeutic efficacy is clinical impractical. In response to these deficiencies, the use of molecular diagnostics is increasing in the evaluation of treatments in chronic phases of CD (Besuschio et al. 2017; Alonso-Padilla et al. 2017). Polymerase chain reaction (PCR) is used to detect therapeutic failure; however, it has several limitations. Negative results do not exclude the presence of the parasite, the sensitivity depends on the individual parasitemia level, and the assay requires trained personnel and special equipment. Several lines of investigation are ongoing to explore alternatives for PCR that could supply the current deficiencies in the evaluation of therapeutic efficacy, such as loop-mediated isothermal amplification (LAMP) and several biomarkers, (Besuschio et al. 2017; Porras et al. 2015; Pinazo et al. 2015). Although, none of the alternatives have met the consensus target product profile (TPP) for CD detection assays.

4.4. Treatment

For the treatment of CD, two medications are available: benznidazole and nifurtimox. The efficacy of treatment with these drugs is high in the acute phase or early stages in childhood but drops in chronic stages (WHO 2021). The study BENEFIT found that treating patients with established CD cardiomyopathy has no benefit on cardiac disease patients (Morillo et al. 2015). The actual recommendations for the treatment are summarized in Table 2.

Table 2. Recommendations for Chagas Disease treatment (PAHO 2018; Nunez et al. 2018; Bern et al. 2007; Marin-Neto et al. 2007; Morillo et al. 2015; Viotti et al. 2006; Ribeiro et al. 2012, Pinazo et al. 2011; Fabbro et al. 2014; Fabbro et al. 2007).

Recommended treatment
Acute infections and reactivations.
Vertical infection.
Women of reproductive age*.
Accidental high-risk contaminations**.
Patient in chronic phase younger of 18 years old.
Treatment could be offered
Indeterminate form.
Chronic cardiomyopathy form without established dilated cardiomyopathy (based on a consensus decision between the doctor and the patient).
No recommended treatment
Chronic cardiomyopathy with established dilated cardiomyopathy.

*Previous pregnancy test with negative results and offer contraceptive methods if the patient accepts the treatment.

** Accidental high-risk contaminations: contact with living parasites or cultures thorough skin breakage or mucosal contact.

Aside from the barriers that the patients face in the accessibility and commercialization of the treatment, treatment compliance is low mainly due to the frequent adverse effects. Furthermore, the competition of the treatment course will last almost 60 days with the accumulating decrease of patients that finalize it. The poor tolerability leads to

discontinuation in 9% to 29% of patients (Monge-Maillo et al. 2017) The recent study BENDITA in their preliminary results showed that a shortened treatment could be sufficiently effective with fewer adverse events (DNDi 2019).

4.5. CD in non-endemic countries

Due to the migratory flows, CD has become a problem of global magnitude in areas where the triatomine insect vector is absent (Gascon, Bern & Pinazo 2010). Blood transfusion, organ transplantation, and mother-to-child are the main transmission routes in non-endemic countries (Gascon, Bern & Pinazo 2010). The countries with the highest burden outside of the traditional borders include USA, Spain, Italy, Canada, Japan, and Australia are. In the USA, about 300,000 people are estimated to be affected by CD (Bern & Montgomery 2009). In Europe, CD has an estimated prevalence of 4.2% (95% CI. 2.2-6.7) (Requena-Mendez et al. 2015).

Although thousands of CD cases are estimated in non-endemic areas, few countries analyze their CD situation with epidemiological, clinical, and economic data, being Europe the leader on this. Most non-endemic countries lack effective transmission control programs (Requena-Mendez et al. 2014; Forsyth et al. 2018; Manne-Goehler et al. 2015). The scarce and heterogeneous level of policies for control and prevention in non-endemic countries is notable, and monitoring is mainly confined to blood transfusion control in the countries with higher prevalence (Requena-Mendez et al. 2014). Considering that a potential CD blood transmission is a public health concern, complete coverage of all the countries at risk should be mandatory (Requena-Mendez et al. 2014). The control of the disease by vertical transmission is one of the areas where the effort will yield great benefits (WHO 2010; PAHO 2018). This situation is based on two fundamental pillars, that the treatment of women of fertile age reduces the possibility of vertical transmission (Sosa-Estani et al. 2006; Fabbro et

al. 2014), and that early life treatment has proven to be nearly 100% effective (Pinazo & Gascon 2020). Despite this evidence, control programs are scarce in non-endemic countries (Requena-Mendez et al. 2014; Pinazo & Gascon 2020). Furthermore, considering the risk that transplanted persons acquire an immunosuppression status, measures to avoid it are urgent. In Europe, just three countries (Spain, Italy, and United Kingdom) have a national recommendation to screen all donors (Requena-Mendez et al 2014). Furthermore, the screening of all populations at risk should be a priority to avoid the late diagnosis where the treatment is ineffective. Screening for CD in asymptomatic LA adults living in non-endemic countries is a cost-effective strategy as demonstrated by an economic evaluation of CD screening of LA patients living in Europe (Requena-Mendez et al. 2017).

In non-endemic countries, roughly 1-10% of people with CD are currently diagnosed (Instituto de Salud Global 2017; Basile et al. 2011; Requena-Mendez et al. 2015; Forsyth et al. 2019). Although most of the non-endemic countries are world powers, the level of underdiagnoses can be explained by a complex net where multiple factors are interrupting. First, CD is an emergent disease in non-endemic countries therefore the health system is not adapted, lacking policies for control and care of CD. Second, CD has a silent course that would make it difficult to detect, in addition to the health personnel's lack of awareness. Third, the burden of CD in non-endemic countries is represented by the LA migrant population. This population has several barriers that affect the diagnosis; for example, related conceptions about the disease from the country of origin make CD not considered a priority (Ventura-Garcia et al. 2015; Iglesias-Rodriguez et al. 2019). In addition, the disadvantaged situation of the migrant population compares with the native citizens in access to the host country's health system (Minneman 2012; Suguimoto et al. 2012; Monge-Maillo 2017; Pinazo & Gascon 2020).

Added to this challenging situation, the access to the treatment is surrounded by several barriers in non-endemic countries. For example, most of the non-endemic countries lack approval and commercialization for CD treatment. The approval and commercialization it just the first step in access to treatment. In countries where the treatment has been approved, like the USA, several barriers interfere the access to treatment (Yoshioka et al. 2020). Furthermore, problems of coordination between the sectors, lack of guidelines for CD, the cost assumed by the patients, the social circumstances of the migrant population that influence the difficulty in the follow-up, and lack of qualified professionals are some of the barriers that hamper the objective of treat the people affected of CD (Yoshioka et al. 2020; Romay-Barja et al. 2019).

Despite the important role of sociocultural factors, from the origin and host country, in the level of diagnosis, most of interventions implemented have just a biomedical approach (Ventura-Garcia et al. 2013). Therefore, comprehensive care programs aimed at prevention and detection, diagnosis and treatment of people affected by CD are needed, covering the different dimensions of the disease (biomedical, epidemiological, sociocultural, and political). Transversely, information, education, and communication between the health system and the people affected, including them actively as part of the multidisciplinary approach, are of crucial importance to come out with the necessary changes in the attitudes and practices that allow preventing the transmission or access to the treatment (Sanmartino et al. 2015; Pinazo & Gascon 2020).

Nowadays is Spain the non-endemic country most experienced in developing clinical guidelines, protocols, and policies about the CD. Although national dispersion of these policies for CD has not been reached, Spain has in part of its territory a comprehensive strategy that includes raising public awareness, clinical and social management,

multidisciplinary approach, investigation, and cooperation between departments. This response is not just the most ethical and human, also the most practical and cost-effective (Instituto de Salud Global 2017).

4.6. Japan

Japan is an island country in East Asia with a population of 126 million people in 2020 (Worldometer 2020). The archipelago, made up of 6,852 islands, is considered one of the great powers worldwide. It has a gross domestic product (GDP) per capita of $ 37,654 in 2017, with a correspondingly high standard of living, level of development, safety, and stability (IHME 2019). It has one of the highest life expectancy rates in the world (83.7 years) and the lowest infant mortality rate worldwide (UNDP 2019).

One of the big successes in health in Japan is the foundation of the actual health insurance system to offer Universal Health Care (UHC) in 1961. Nowadays, the Government dedicates 10% of GDP to health spending, which represented 86% of total health expenditure in 2016 (IHME 2019). Even with all these efforts, the current population of Japan is not as homogenous as in the past and the system has become deficient in some minority groups like migrants, not archiving the UHC expected (Shakya et al. 2018; Suguimoto et al. 2012; Yosukawa et al. 2019). It has been reported that Japanese immigration policy prioritizes migrant control over migrant rights, which has a negative impact on migrant health access (Shakya et al. 2018; Suguie et al. 2005; Parikh 2010).

Studies report that there is an inequity in the access to the healthcare system among the migrant population living in Japan (Shakya et al. 2018; Suguimoto et al. 2012). Asylum seekers and migrant workers with expired visas are not covered by the UHC in Japan (Yasukawa et al. 2019). Also, some hospitals deny care to foreign patients who do not have insurance or charge higher medical fees or urging for early discharges of the migrant patients

without insurance (Yasukawa et al. 2019). Furthermore, work by Suguimoto et al indicated that more than half of LA migrants who are full-time workers and should be covered in the Employee Health Insurance (EHI) were not included by their companies with the consequent detriment of benefits as a pension premium (Suguimoto et al. 2012).

The number of migrant residents is expected to increase as the Japanese Government plans to shift policy on migrant workers (Yosukawa et al. 2019), and concomitantly, the number of unfamiliar tropical diseases is expected to increase. The country should host a system that ensures the health of all the residents to avoid humanitarian and economic consequences.

4.6.1. Latin American migration in Japan

Historically Japan is a country where immigration has played a minor role. However, the increase of the aging population and low birth rates force the country into a modification of immigration policies. These measures led to an important influx of descendants of Japanese who emigrated in the 19th century to Latin America. According to the Ministry of Justice of Japan, between 2006 to 2016, between 230,000 and 280,000 people from LA countries migrated to Japan, represented by order Brazil, Peru, and Bolivia (Figure 2) (MOJ 2019). Brazilians alone represent the fifth-largest minority group (n= 204,347; 6%) (e-Stat 2019).

Japan is now the fourth region of the world with more migrant populations from the LA countries after the United States and Canada, Italy, and Spain, with 276,274 residents from LA countries. Aichi, Shizuoka, and Gunma are the prefectures of Japan with the most LA residents (e-Stat 2019).

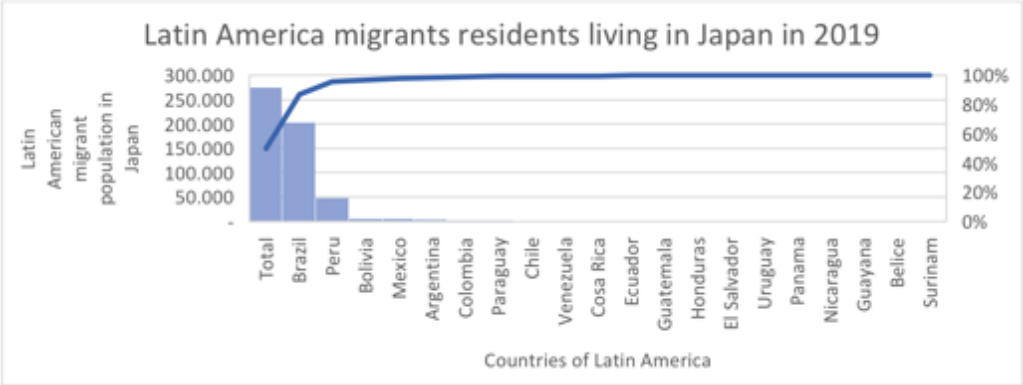

Figure 2. LA migrant residents living in Japan in 2019 (Source: e-Stat 2019).

The LA migrant residents in Japan have some characteristics that should be mentioned compared with other migratory groups. First, most are decedents of Japanese migrants, called 'Nikkei.' Current laws allow Nikkei residents to apply for a long-term resident visa with no restriction of employment (Fielding 2010). Second, as a consequence of the aforementioned, while in the early years of immigration majority of LA migrants were temporary guest employees, and now settle with their families (Goto 2007). Third, in contrast to the occupations of other migrant groups, LA migrants are overwhelmingly manual laborers in the manufacturing industry (Fielding 2010; Suguimoto et al. 2012).

4.6.2. CD in Japan

Due to the many migrants from LA countries, Japan is now in a global category with a large number of CD cases out of the traditional borders, with nearly 3,000 estimated cases for CD (Nara & Miura 2015). Japan is classified as a non-endemic country of CD because is not considered to host the potential vector, the triatomine bug. However, studies reported the presence of *Triatoma rubrofaciata*, a potential vector for CD, in the Western Pacific Region (Dujardin et al. 2015). Recent studies in China highlighted the concern about the possibility of the establishment of CD through globalization, after reporting the presence of *Triatoma*

rubrofaciata in the country (Shi et al. 2020; Liu et al. 2017). There is no published information regarding the geographical distribution of *Triatoma rubrofaciata* in Japan, but an entomological surveillance should be explored due to the presence of many estimated cases of CD. Presently, blood transmission is the only means of transmission recognized by official governmental measures for the control of new cases of CD. In addition, literature published in Japan about CD is scarce and is represented by seven case reports, with no study of prevalence at the national level in the blood banks (Imai et al. 2015; Sayama et al. 2019).

Blood bank prevalence of CD was reported to be 0.02%, but normally blood bank prevalences are underestimated and influenced by selection bias (Sayama et al. 2019). During a retrospective study in blood banks, a case of blood transmission was reported in 2011. At that time no control program for blood donors was implemented in Japan. The donor's blood was transfused to 11 people (Yasukawa 2013). Fortunately, no case of blood transfusion transmission was identified. As a preventive measure, since 2012 the Japanese Red Cross Blood Centers doesn't use blood or produce blood products if the donor or the donor's mother has spent more than 4 weeks in Latin America. This is the only official system preceded by a questionnaire to prevent new cases of CD in Japan.

CD is not included as a disease by the NHS, therefore there are no official interventions for prevention and care, and no official protocols or guidelines. The only possibility to get tested is through an NGO (NGO-MAIKEN) that offers a free screening based on a single RDT test for *T. cruzi* (Chagas DetectTMPlus Rapid Test of Inbios). They provide the RDT screening as part of different activities with different health purposes and are mostly directed to the Brazilian population. These activities take place 3-4 times per year with the capacity to test 20-25 people per day. If a person has a positive result, a digital blood sample is sent to Saitama Medical Hospital, located in the north of Tokyo. There the result is confirmed by a

single ELISA serology (ELISA; Chagas Detect™ Fast ELISA, InBios), as well as the option to perform PCR. If the patient is seropositive, they are considered to be infected by CD and the person would be referred to a doctor at a secondary or tertiary level.

Since there is no clinical specialist in CD in Japan, the follow-up doctor would be selected according to the following criteria: previous experience with CD patients or infectious diseases, proximity to the residence of the patient, and the possibility to request hospital treatment if needed.

Because CD is not included in the NHS the treatment is not approved and commercialized in the country. Japan has a limited stock of nifurtimox and benznidazole, which can be used only in emergency situations. Therefore, when a patient is diagnosed by CD in Japan and the patient is treatable, the treatment should be ordered overseas to the WHO in Geneva by a form signed by the doctor in charge and the director of the hospital. Once the WHO approves the petition, the treatment would be sent (Benznidazole) and will arrive in Japan normally in 2 to 6 weeks. The NHS hospitals can go through this procedure more easily, the reason why the possibility to request the treatment is another factor that is considered to select the doctor and hospital for the patient.

Six people have been identified to have CD from 2012-2019 (Imai et al. 2019). Most were symptomatic patients and not all were treatable. The CD patients in Japan continue their medical follow-up with annual or biannual visits, according to their health condition. In addition, if the patient is a woman with children, the doctor will encourage their testing.

This unofficial system attempts to supply the deficiencies of the government actions to address a real need in Japan. These measures, however, are insufficient, as I will describe. Considering the six blocks of a Health system presented in the WHO Health System Framework (Box 1) - service delivery, health workforce, health information systems, access

to essential medicines, financing, and Leadership/ governance - a working system for CD is almost absent in Japan (WHO 2007).

Box 1. The six building blocks of a health-care system (Source: WHO 2007).

Good health services are those which deliver effective, safe, quality personal and non-personal health interventions to those that need them, when and where needed, with minimum waste of resources.
A well-performing health workforce is one that works in ways that are responsive, fair and efficient to achieve the best health outcomes possible, given available resources and circumstances (i.e. there are sufficient staff, fairly distributed; they are competent, responsive and productive).
A well-functioning health information system is one that ensures the production, analysis, dissemination and use of reliable and timely information on health determinants, health system performance and health status.
A well-functioning health system ensures equitable access to essential medical products, vaccines and technologies of assured quality, safety, efficacy and cost-effectiveness, and their scientifically sound and cost-effective use.
A good health financing system raises adequate funds for health, in ways that ensure people can use needed services, and are protected from financial catastrophe or impoverishment

associated with having to pay for them. It provides incentives for providers and users to be efficient.
Leadership and governance involve ensuring strategic policy frameworks exist and are combined with effective oversight, coalition building, regulation, attention to system-design and accountability

4.6.2.1. WHO health system framework for CD

4.6.2.1.1. Service delivery

The provision of health care to people is known as service delivery. Regarding service delivery, as I will outline in the next section the current health system for CD in Japan, is highly deficient in the WHO key characteristics of comprehensiveness, accessibility, coverage, quality, continuity, person-centeredness, coordination, accountability, and efficiency (Box 2) (WHO 2010).

Box 2. Key characteristics of good service delivery (Source: WHO 2010).

1. Comprehensiveness: A comprehensive range of health services is provided, appropriate to the needs of the target population, including preventative, curative, palliative and rehabilitative services and health promotion activities.
2. Accessibility: Services are directly and permanently accessible with no undue barriers of cost, language, culture, or geography. Health services are close to the people, with a routine

point of entry to the service network at primary care level (not at the specialist or hospital level). Services may be provided in the home, the community, the workplace, or health facilities as appropriate.
3. Coverage: Service delivery is designed so that all people in a defined target population are covered, i.e. the sick and the healthy, all income groups and all social groups.
4. Continuity: Service delivery is organized to provide an individual with continuity of care across the network of services, health conditions, levels of care, and over the life-cycle.
5. Quality: Health services are of high quality, i.e. they are effective, safe, centered on the patient's needs and given in a timely fashion.
6. Person-centeredness: Services are organized around the person, not the disease or the financing. Users perceive health services to be responsive and acceptable to them. There is participation from the target population in service delivery design and assessment. People are partners in their own health care.
7. Coordination: Local area health service networks are actively coordinated, across types of provider, types of care, levels of service delivery, and for both routine and emergency preparedness. The patient's primary care provider facilitates the route through the needed services, and works in collaboration with other levels and types of provider. Coordination also takes place with other sectors (e.g. social services) and partners (e.g. community organizations).

8. Accountability and efficiency: Health services are well managed to achieve the core elements described above with a minimum wastage of resources. Managers allocate the necessary authority to achieve planned objectives and held accountable for overall performance and results. Assessment includes appropriate mechanisms for the participation of the target population and civil society.

1. Comprehensiveness

CD, as for any chronic disease, needs a comprehensive range of healthcare services for prevention, curation, palliation, rehabilitation, and health promotion. However, for CD most of these services are not available in Japan. The only preventable measure is the control of blood banks via a questionnaire that is not completely effective to detect the population at risk living in Japan (Sayama et al. 2019). There is no system for the prevention of transmission through organ transplantation, nor congenital transmission. Congenital cases were documented in Japan more than 5 years ago, and it is estimated that every year new cases occur (Imai et al. 2014). The country lacks an official screening and system of care for the population at risk (Imai et al. 2019). The range of health services for a comprehensive approach of CD is mostly absent.

To supply this gap, an NGO (NGO-MAIKEN) sporadically conducts RDT in different activities directed mainly to the Brazilian population and refers the positive participants to the tertiary level to confirm the results serologically.

2. Accessibility

The role of primary health care (PHC) as a referent and coordinator of the health system is essential to ensure good access (WHO 1978). PHC is an important component in a health system in terms of efficacy, affordability, and proximity to individuals, families, and communities. The importance of PHC is recognized as the coordinator of the population at risk of CD, and in Japan the follow-up of positive cases is restricted to secondary and tertiary care. Furthermore, there is a single hospital (Saitama Hospital) that can perform ELISA for *T. cruzi* detection, under research purposes. The hospital location in Tokyo, an area not included in the 10 first locations for LA migrant residents, is not geographically accessible for the people at risk.

To consider PHC as the routine point of entry to the service, the low prominence of PHC as coordinator in Japan should be considered. Despite the efforts to empower the role of primary care as a coordinator between levels and as the central axis of the Japanese health system, it is far from the current reality (Takamura 2015).

Additionally, the population at risk of CD in Japan is represented mainly by the LA migrant population facing important barriers in access to the health system (Suguimoto et al. 2012). Studies on migrants in Japan reflected an inequity situation of the migrant population in the access to the Japanese health system. This inequity is mainly explained due to the difficulty of the adaptability of the Japanese health system to the rapid globalization in recent years. Factors affecting access to the health system in migrants living in Japan are in part associated with the nature of the migrations of populations; specifically, their low socioeconomic status, their possibilities of improving jobs, ethnicity, communication, and immigration policies (Shakya et al. 2018; Norredam et al. 2011; Igarashi, Horiuchi & Porter 2013; Suguimoto et al. 2012).

3. Coverage

Currently, even though Japan hosts potential congenital, transmission, and transfusion cases, CD is not recognized as a disease and it is not covered by the National Health System (NHS). Consequently, the cost of the diagnosis for a suspected case is normally cover by research funding, if available. The cases identified in the past needed to be considered as cardiopathy of unknown etiology to be covered by at least 70% of the cost by NHS, otherwise the people at risk should pay the services at 100%.

Studies found that LA migrants living in Japan have barriers to the health coverage (Suguimoto et al. 2012). Suguimoto et al. reported that 20% of LA migrants in Japan lack NHI, 55% of the full workers are not receiving the EHI, and nearly 25% are working without a contract with the consequent risk for them and their families. These deficiencies in coverage create a disadvantaged situation in the LA migrant residents in the process of seeking care.

4. Quality

Just six cases of CD were reported from 2012 to 2017, corresponding to a level of diagnosis of 0.2%. Most of the cases (n=5, 83%) were diagnosed in a late-stage, thus reflecting the low vigilance level in the country. Just 33% of the cases reported by Imai et al. (n=2) could be treated with Benznidazole and no study of relatives in the 4 women was described (Imai et al. 2019).

The diagnosis of CD in Japan does not follow the international recommendations by WHO, where two serological diagnosis methods should be performed to confirm a case. In Japan, a single RDT is used as a method of screening for patients suspected of having CD, and if positive is confirmed with a single ELISA (Imai et al. 2019). Most of the people affected for CD are asymptomatic and it is known that the treatment is not effective in advance cases, in

Japan a suspected case is only considered if it has symptoms as cardiomyopathy, echocardiography or electrocardiogram abnormalities, gastrointestinal disorders, megacolon, or megaesophagus, and the patient or the mother was born or raised in a LA country, or had a travel history to Latin America for more than four weeks (Imai et al. 2019).

5. Continuity and coordination

The lack of a protagonist of PHC in the Japanese health system is one of the main barriers for continuity and coordination of the people at risk with chronic diseases as CD that are mostly residing in rural areas of central Japan. PHC could follow-up all the people affected by the indeterminate forms of CD, for its low level of complexity, thereby decreasing the burden in secondary and tertiary care. However, to date the implementation of annual serology at the primary care level is not possible and there is a lack of interlevel communication as well as between other sectors (Takamura 2015).

6. Person-centeredness

Studies have demonstrated that transdisciplinary approaches in the interventions of CD, considering the living conditions of those at risk and their socio-cultural situation, should be integrated to decrease the burden of CD (Ventura-García et al. 2013; Sanmartino et al. 2015; Instituto de Salud Global 2017). However, the actual follow-ups of the current patients in Japan are mostly centered at the biomedical level, and are mostly disease-centered with no participation of other disciplines or the people at risk. A comprehensive approach would offer better outcomes in the system of care of CD (Pinazo & Gascon 2020).

7. Accountability and efficiency

Although CD is the infectious disease with the most burden in DALYs in Latin America, and the screening of CD is considered to be cost-effective in endemic and non-endemic countries,

to date a cost analysis has not been performed in Japan (Requena-Méndez et al. 2017; Ramsey et al. 2014; Sicuri et al. 2011; Stillwaggon et al. 2018). PHC is the most cost-effective resource of a health system; and a screening strategy for CD conducted from PHC should be considered.

4.6.2.1.2. Health workforce. A literature review for this thesis found no studies describing the knowledge of CD by Japanese health personnel. However, due to the high level of underdiagnoses (99.8%) and the low level of knowledge in other non-endemic countries, it is expected that the awareness would be low (Verani et al. 2010; Imai et al. 2019).

4.6.2.1.3. Health information systems. There is no system of information for the population at risk of CD in Japan. Several studies highlighted the importance of a system of information, education, and communication directed to the population at risk that includes the people at risk of CD as main actors (Sanmartino et al. 2015; Pinazo & Gascon 2020; Iglesias-Rodriguez et al. 2020). However, studies demonstrated that most of the migrant population in Japan do not have Japanese language skills regardless of the time spent in the country (Nagamatsu et al. 2020). Accessible systems of information to the target population in their native language should be prioritized.

4.6.2.1.4. Access to essential medicines. The use of Benznidazole or Nifurtimox is not directly available in the country and is ordered overseas only under special request. The approval and commercialization of these drugs is the first step in the access to treat CD (Yoshioka et al. 2019).

4.6.2.1.5. Financing, leadership, and governance.

In 2011, a group of experts highlighted the need for a system of care for CD in Japan (WHO Western Pacific Region 2011). However, ten years later, no new improvements had been

implemented by the Japanese government outside of blood bank protocols. Neither has a health financing analysis of CD been contemplated. Empowerment of the different government and organizations leaders on this subject is important. Japan has a long tradition of collaboration with LA countries through international organizations, such as JICA (Japan International Cooperation Agency), and the health of the LA migrants living in Japan should not be an exception (JICA 2021). Due to the role of the scientific community in providing evidence, the current silence on this subject contributes to perpetuate the neglect.

4.6.2.1.6. A modified WHO health system framework and comprehensive care.

Lazarus and France (2014) included a modified WHO health system framework in which CD care systematically incorporates the perspective of the patients and people at risk in the strategies to strengthen health systems and ensuring the success of the interventions (Figure 3).

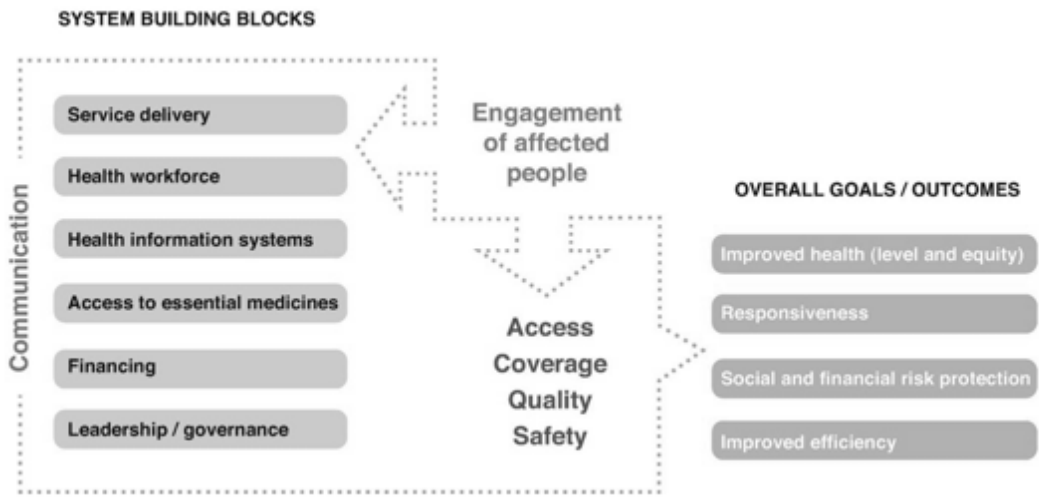

Figure 3. Modified WHO health system framework (Source: Lazarus and France, 2014).

During the last 100 years, CD had been seen as a silent disease. As the writer Eduardo Galeano described, "It does not explode like a bomb, nor sound like a shot. Like hunger, it kills silently. Like hunger it kills the silent, those who live condemned to be silent and die

condemned to oblivion." However, the people affected have a voice and due to the importance of socio-cultural factors in the access for diagnosis, treatment, and care, their involvement in the health system interventions for CD is essential (Ventura-Garcia et al. 2013; Pinazo & Gascon 2020; Sanmartino et al. 2015). The practices or interventions for CD that don't include the population at risk should be avoided. The health system needs to create a bidirectional relationship between the system and the stakeholders (Pinazo & Gascon 2020).

Hence, the ideal approach for CD should incorporate a comprehensive strategy that involves all dimensions of CD - biomedical, political, epidemiological, and socio-cultural - with the implication of a multidisciplinary team (Sanmartino et al. 2015). FINDECHAGAS, an association that includes families, friends, and people affected by CD, works in collaboration with multidisciplinary teams and in 2010 agreed to promote the demands of people affected by CD to overcome the barriers caused by an inadequate comprehensive care. Their goals are summarized in Box 3 (FINDECHAGAS 2018; Pinazo & Gascon 2020).

Box 3. Main principals of the Uberaba Declaration (Source: FINDECHAGAS 2018; Pinazo & Gascon 2020).

We (the affected people associations) recognize that information, education, and communication are essential tools to increase awareness of Chagas disease, to fight stigmatization and indifference, and to guarantee human rights, including prevention and treatment of Chagas disease.
We demand continuity and strengthening of prevention initiatives. We advocate for universal access to clinical and laboratory diagnosis.

We urge universal access to full treatment and follow-up during the acute and chronic phases of the disease.
We support research and development of optimal technologies for the prevention, treatment, and control of Chagas disease.
We maintain that Chagas disease is not a death sentence. It is necessary to know, face, and spread the challenges of people living with the disease. Initiatives to break the cycle that links poverty and disease should be implemented.

In the development of a CD health system, as is the case of Japan, it is important to include the voices of those at-risk of CD in future interventions and policies to develop comprehensive care where no one is left behind.

In summary, the neglect of CD in Japan as risen to a serious level. As a goal of the WHO, the neglected condition of CD should be avoided in non-endemic countries like Japan (WHO 2010). Furthermore, Japan for its historical collaboration with LA countries and its possibility of development and research plays an important role in decreasing the global burden and locally offering a safe system of care to their residents.

5. Purpose of the study and justification

This study aims to characterize the need for improvement of the Health System by analyzing the epidemiological, clinical, and economic situation in Japan with respect to CD and the populations at risk. Also, I aim to analyze the current barriers that the populations at risk have in accessing the Health System. Furthermore, I aim to compare RDT with the current standard diagnosis.

5.1. Epidemiological

The current epidemiological situation of CD remains unknown and the estimation of 3,000 cases in Japan was calculated more than 10 years ago and is likely not representative of the current population at risk living in Japan. To know the current situation of CD, as a preamble of a national protocol, the epidemiological silence in Japan must be broken. This study has as a primary objective to conduct a survey of CD at the national level to estimate the current community-based prevalence. I aim to actualize this data by calculating the estimated and observed prevalence. Furthermore, this study would bring the possibility to analyze the socio-demographic characteristics of the migrant population at risk of CD.

5.2. Clinical

To date the only clinical data published about CD shows an image of a symptomatic disease with a bad prognosis (Imai et al. 2019). However, it is estimated that 70% of the people affected by CD are asymptomatic with the indeterminate form. The situation presented by Imai et al (2019) does not appear to represent the real situation of CD, and the discrepancy can be explained based on a late-diagnosis of symptomatic patients. This research would be community-based, thus participants would be included regardless of their health state.

5.3. Economic

A recent WHO goal states that it is necessary to achieve access to universal comprehensive care for all people infected with *T. cruzi* regardless of their age or disease stage (PAHO & WHO 2018). For this reason, the screening of asymptomatic people and care in CD patients should be accessible for the population at risk. The involvement of CD's early screening program in the NHS could be a first step to increase the coverage in care of LA migrants and therefore indirectly could help to increase the rate of CD diagnosis. This study aims to

analyze the cost-effectiveness of the screening program included in the NHS of Japan, once the epidemiological data is obtained.

5.4. Accessibility to the Japanese health system

Due to the special profile of CD with a chronic and silent course, one of the first priorities should be to ensure access of the population at risk to the health system (Pinazo & Gascon 2020). However, when compared to native citizens, the migrant population has a disadvantaged situation facing several barriers in the process of seeking care (Suguimoto et al. 2012; Shakya et al. 2018). This study aims to analyze the barriers that interferes to the access to the health system in Japan in the LA migrants at risk of CD.

5.5. Diagnostic methods

The protocol for diagnosis of CD in Japan does not follow the standard diagnosis recommended by the WHO, which states that a person would only be considered infected by CD if they have two positive serologies with different antigens for *T. cruzi* (WHO Expert Committee 2002). However, this recommendation is difficult to follow in systems with low resources or systems under construction, as is happening in non-endemic countries like Japan.

The WHO described that the ideal serological test should be performed easily and fast in a single step, should not require special equipment or refrigeration of reagents, must be inexpensive, and with a 100% sensitivity and specificity (WHO Expert Committee 2002). For that reason, the most suitable diagnostic test would be the RDT. Currently, Japan is using the RDT (Chagas DetectTMPlus Rapid Test of Inbios) as a single screening test and confirms the positive cases with a single ELISA. In a comparative evaluation the "Trypanosoma Detect Rapid" (Chagas Detect™Plus Rapid Test of Inbios) had the highest average score, with 44 out of 52 possible points. (Sanchez-Camargo et al. 2014). However, no study has been conducted

in Japan to validate this protocol. To examine the performance of RDT as a potential screening test, I aim to compare the RDT (Chagas DetectTMPlus Rapid Test of Inbios) with the standard diagnostic (two different positive serological test results).

6. Study goals and objectives

Primary

To estimate the expected and observed prevalence of cases of *T. cruzi*-infected people at risk of CD living in Japan.

Secondary

1. The study aims to evaluate the cost-effectiveness of a systematic CD screening in the LA population included in the Japanese national health system.

2. To analyze the socio-demographic characteristic and risk factors of CD of the participants included in the study.

3. To analyze the factors that affect access to the Japanese health system in the LA migrant population.

4. To compare the performance of RDT with the WHO- recommended standard diagnosis (two serological tests positive for *Trypanosoma cruzi*).

7. Methodology

7.1. Study design

This is a cross-sectional study conducted from March of 2019 until October 2020. The study was conducted in four stages represented in Figure 4. Firstly, I created a system of education to provide a comprehensive approach of CD to the population at risk, before, during, and after

the data collection. Secondly, to know the prevalence of CD in the LA migrant population living in Japan, after signing the informed consent, blood samples were collected from the LA migrant population living in Japan, in different governmental, communitarian, cultural, or educational activities directed at the LA population in different prefectures in Japan. The blood samples were analyzed by an RDT and two serological methods to identify positive participants. In the embassy venues, quantitative data was collected from all participants including sociodemographic information, information about risk factors of CD, and the barriers encountered in access to the health system. Thirdly, with the results of the observed prevalence, I calculated the cost-effectiveness of the screening in the asymptomatic adult migrant population as a potential program to be included in the Japanese NHS. Lastly, all participants were informed about their test results and introduced to the appropriate, proximate medical institution. The participants with positive results by the standard diagnosis that attended the clinical institution would be categorize by clinical profile.

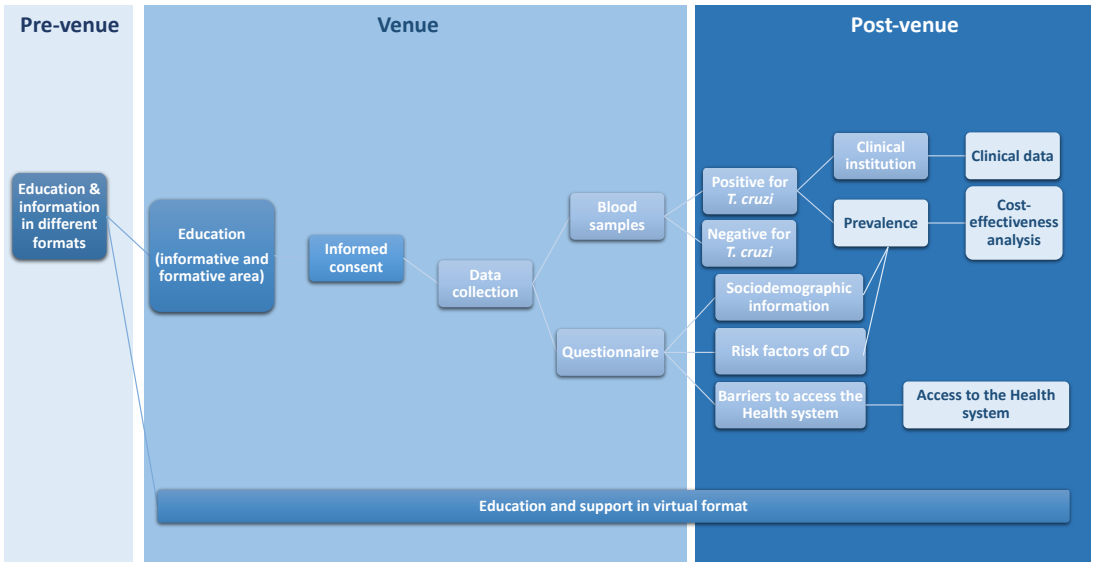

Figure 4. Flow chart of the study design.

7.2. Study areas and study population.

The study included participants at risk of CD living in Japan during the study period. Because this population is mostly represented by LA migrants, we collected the data from the prefectures of Japan with more LA migrant residents, based on the demographic data from Japan official statistics (e-Stats 2019).

Brazil, Peru, and Bolivia represent 90% of LA migrants in Japan. Therefore, the efforts were prioritized working in the close collaboration with the embassies of these three countries. The data collections venues were held according to different activities organized by the LA embassies of Brazil, Peru, and Bolivia across Japan. The activities had multiple purposes, such as educational, cultural, communitarian, governmental activities, and mobile consulate. However, the most frequent venue was the mobile consulates where the migrants came for personal documents procedures. Due the difficulty that the migrants have to attend activities during the weekdays, almost all the embassy activities are organized on weekends as a measure to increase accessibility.

Data were collected from 7 of the 20 prefectures with more LA residents living in Japan (Figure 5) (e-Stats 2019). Nineteen data collections were done within Aichi, Mie, Gunma, Tokyo, Osaka, Hiroshima, and twice in Nagasaki (n=22) (Figure 6). We collected data 6 times with the Brazilian embassy, 6 times with the Peruvian embassy and 7 times with the Bolivian embassy. The personal capacity of the work team was to recruit 20-30 participants in every venue.

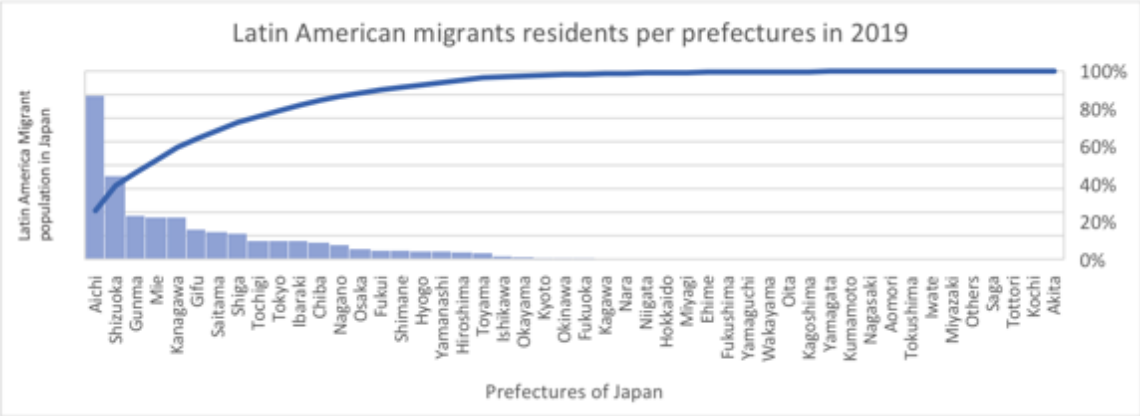

Figure 5. Latin American migrant resident living in Japan per prefectures in 2019

(Source: e-Stats 2019).

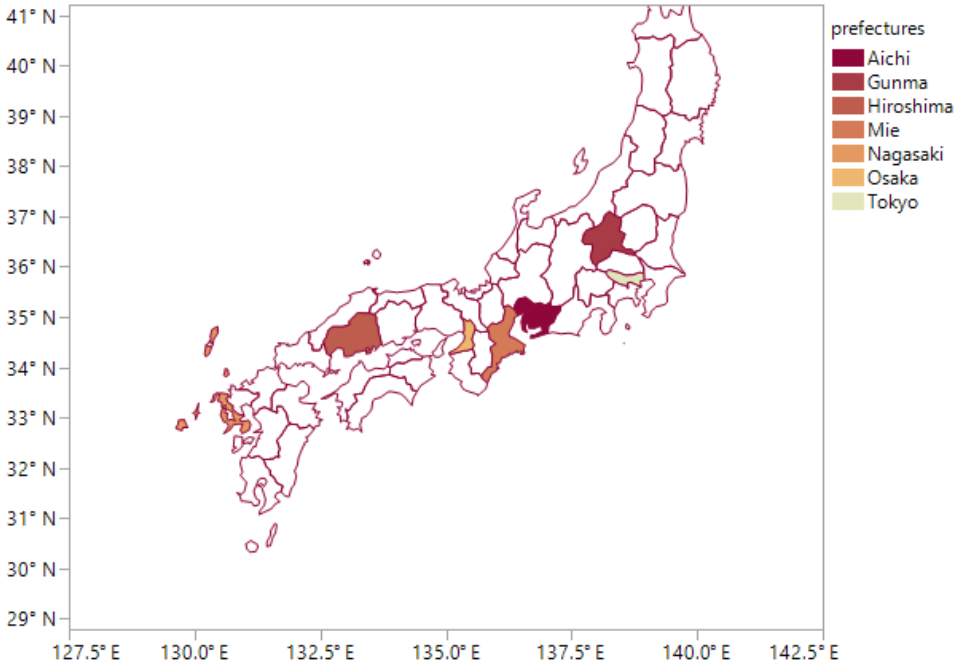

Figure 6. Map of prefectures where data was collected in the study.

LA countries considered endemic for CD are Argentina, Belize, Bolivia, Brazil, Chile, Colombia, Costa Rica, Ecuador, El Salvador, Guatemala, Honduras, Mexico, Nicaragua, Panamá, Paraguay, Peru, Uruguay, Venezuela, French Guiana, Guiana, and Surinam.

7.3. Inclusion and exclusion criteria:

• Subjects of any age who were born in endemic countries for CD and are regular or undocumented residents in Japan.

• Subjects of any age born in non-endemic countries, whose mother was born in a LA country endemic for CD or/and stayed more than four weeks in an endemic country, and currently are residents in Japan.

• Children born in LA endemic countries for CD and adopted by families living in Japan.

The LA migrants from Caribe islands and travelers who spend less than four weeks in LA countries were excluded, because of the low number of cases in CD in these groups.

7.4. Diagnostic tests

7.4.1. Positive case definition and standard diagnosis

Following international recommendations, a participant was considered positive if they have had two serological tests positive, called the "standard diagnosis" (WHO Expert Committee 2002). The standard diagnosis in this study would be considered if two of the following serological tests would be positive: *T. cruzi* IgG CELISA II Enzyme-linked immunosorbent assay (ELISA, Cellabs Pty Ltd, Australia) and Chagas IgG+IgM Indirect Immunofluorescence assay kit (IFA) (IFI, Vircell S.L., Spain). If the results were discordant a third serological test was performed (Chagas Detect™ Fast ELISA kit, InBios International, Inc., USA). Henceforth, the third serological test will be referred to as ELISA-2. The serologic methods were conducted following the manufacturer's instructions described in Appendix 3. Serological diagnostic test.

T. cruzi IgG CELISA II ELISA of Cellabs is a recommended diagnostic test from WHO with a described sensitivity and specificity of 100% (PAHO 2019). The Chagas IgG+IgM Indirect

Immunofluorescence assay kit of Vircell, has a sensitivity of 100% and specificity of 98.6%. The Chagas DetectTM Fast ELISA kit of InBios was used previously in Japan as a diagnosis confirmation tool after a positive result in the RDT, with a sensitivity of 100% and a specificity of 98.9%.

7.4.2. Rapid diagnosis test

The RDT used in the venues is an immunochromatographic assay (Chagas Detect™Plus Rapid Test (Inbios International Inc., Seattle, USA) and was conducted according to the manufacturer protocol (Appendix 3). The RDT of Inbios use a multiepitope fusion protein ITC 8.2 (TcF, SAPA, Pep30, Pep36, KMP11, KMP11, Pep1) (Castro-Sesquen et al. 2021).

The sensitivities and specificities reported in previous studies were 100% to 96.2% and 99.3% to 80.3% respectively (Eguez et al. 2017; Shah et al 2014; Castro-Sesquen et al. 2021). However, the sensitivity highly decreased (less than 60%) in Peruvians samples (Verani et al. 2009). As for other RDT, the performance depends on the geographical area due to the diversity of strains of *T. cruzi* in the LA region. It is for that reason that the WHO in their recent guideline for the diagnosis and treatment of CD don't recommend the use of RDT for diagnosis and keep the recommendation of a standard diagnosis (PAHO 2018). However, this test has been used in Japan during the last 10 years in the activities of the NGO-MAIKEN as single screening tool.

7.5. Research tool (questionnaire)

The questionnaire used contains 40 questions (Appendix 2). The questionnaire included questions related to socio-demographic information, risk factors of CD, risk of transmission, vigilance, and policies, and difficulties in the access to the health system (Table 3).

The questionnaires were based on studies conducted in migrant populations living in non-endemic countries (Jackson et al. 2010; Sanchez et al. 2014; Suguimoto et al. 2012; Shakya et al. 2018; Sheppers et al. 2006). The questionnaires were then translated into the Spanish and Portuguese languages by the author, who is a Spanish native speaker and fluent in Portuguese.

Table 3. Questionnaire variables.

	Variables	Question
Socio-demographic	Age	1
	Gender	2
	Education level	4
	Country of origin	5
	Duration of stay in Japan	8
	City of residence	9
	Perspectives of stay	27
Risk factors of CD	Living in rural area	14
	Living in adobe house	15
	Hearing about CD	16
	Knowledge of the vector	17-18
	Having a relative with CD	19
	Risk of blood transfusion infection	21
	Risk of food transfusion infection	22
Risk of transmission	Risk of congenital transmission	3
	Risk of blood transfusion transmission	20
Vigilance and policies	Living in another countries	7
	Tested for CD	10-11
	Treated for CD	12-13
Access to the HCS: Enabling resources	Health insurance	6
	Work conditions	23-26
	Coverage of Health Insurance	28-29
	Price of HCS	30

		Knowledge of HCS	32
		Communication abilities	35,37
		Translation satisfaction	36
		Use of Primary Care as reference	38
	Others	Perceptions towards HCS	31
		Potential access	33
		Unmet utilization of realized access of HCS	34
		Perceived illness	39-40

HCS, Health system; CD, Chagas disease

7.6. Sample size

The sample size was calculated using an actualized estimated prevalence of CD in Japan. The estimated prevalence used in Japan was calculated with the reported prevalence from the WHO in 2010. Since then, the efforts and initiative against the domestic infestation of the vector in the LA houses had a positive impact in the prevalence, with an important decrease in most of the countries. As a result, WHO updated the prevalence in LA in 2015; however, the estimated cases and prevalence in Japan has not been updated. To use a more updated data, as a first step I actualized the estimated prevalence of CD in Japan using the WHO report from 2015 (Table 4) (WHO 2015; e-Stats 2019).

To calculate the estimated prevalence, I divided the total number of estimated cases with *T. cruzi* infection in Japan between the total LA migrants living in Japan, shown as a percentage (Table 4). The number of estimated cases was calculated with the number of LA regular residents from the official statistics of Japan and the estimated prevalence in their country of origin published by the WHO (e-Stats 2019; MOJ 2019; WHO 2015). No additional adjustment was performed for any socio-demographic or risk factors of CD variables.

Van Belle suggest that when the prevalence is low, less than 1%, as is the case of CD prevalence in Japan, the sample size calculation can be based on the "rule of threes". Consequently, considering a prevalence 0.75% and a 95% CI, I estimated a sample size of 400 participants (n = 3 / 0.0075 = 400) (Van Belle 2008).

Table 4. Actualization of the estimated prevalence in Japan (WHO 2015).

	Total number of LA population in Japan (Source e-Stats 2019)	Prevalence in Latin America (%) (Source: WHO 2015)	Estimated cases of Chagas disease in Japan in 2019
Belize	11	0.33	0.04
Cosa Rica	328	0.17	0.55
El Salvador	80	1.30	2.33
Guatemala	216	1.23	2.66
Honduras	190	0.92	1.74
Mexico	5,051	0.78	39.35
Nicaragua	107	0.52	0.59
Panama	114	0.52	0.59
Argentina	3,835	3.64	139.59
Bolivia	5,994	6.10	365.87
Brazil	204,347	0.60	1226.08
Chile	1,153	0.70	8.06
Colombia	2,847	0.96	27.22
Ecuador	278	1.38	3.83
Guayana	19	0.84	0.16
Paraguay	2,117	2.13	45.09
Peru	48,816	0.44	214.30
Surinam	8	0.84	0.07
Uruguay	150	0.24	0.36
Venezuela	513	0.71	3.64
Total	**276,274**	1.21	**2,082.10**
Estimated Prevalence in Japan			**0.75%**

The CD prevalence in the countries of origin has been used by the non-endemic countries to compare the prevalence in their own counties (Requena-Mendez et al. 2014). However, the prevalence in the non-endemic country might differ from the country of origin, because the migrant populations don't migrate in the same proportion as they are represented in their own country. In Japan there are no published demographic data of the origin of the LA migrant population, and the country of origin prevalence would be the most reliable data for comparison.

7.7. Recruitment method

To inform the population about the research activity in the embassy's venues, three different recruitment methods were used. First, the citizens were informed days in advance by the three embassies through their websites/social media regarding when and where the research activity would take place. In addition, in the venues, I informed the migrants that came to do their business. The information was provided in their native language (Spanish/Portuguese) as an educational activity in groups, before the Covid-19 pandemic and by small groups or personally, after the pandemic. Second, informative brochures about CD and venue details (date and place) were provided in two popular magazines directed to the LA community in Japan (Kyodai magazine and Latin-A), in the LA embassies, and in a Clinic of a Peruvian doctor in Nagoya where most of his patients are from Latin America. Third, I used the virtual part of the educational system (website, virtual tools, and social media) to inform about CD and the venue's activities.

To preserve the personal information of the migrants that attended the embassy venue to resolve their personal business, I couldn't have access to the list of number of expected migrants in the embassy activities. Therefore, a potential participants list could not be prepared in advance. I didn't collect information about the reasons for declines to participate

in the research in the venues, nor the recruitment method that influenced participation. The participants that were recruited in the research were mostly people that came to the embassy venues to do some activity or procedure, therefore the participants were recruited mostly by a convenience sampling.

7.8. Educational system

As discussed above, it is essential to consider a comprehensive approach in the interventions of CD for a better outcome due to the important impact of the socio-cultural dimension in the access to the diagnosis (Ventura- Garcia et al. 2013; Sanmartino et al. 2015; Pinazo & Gascon 2020). For that reason, as part of the data collection method I considered essential the inclusion of educational activities with a comprehensive approach directed to the population at risk of CD living in Japan. I created, provided, and coordinated the educational activity based on my previous research experience, my clinical CD experience, and Spanish/Portuguese language competence (Iglesias et al 2020). I offered information, education, communication, and support along the all timeline of the research (before, during, and after data collection) in Spanish and Portuguese.

Along the length of the research, I provided the education in a virtual format. I created and used a website, named 'Chagas en Japón', linked it to social media (Facebook and Instagram) to inform about CD, informed the planned venues, and offered interaction and support in Spanish and Portuguese (Figure 7). The website can be accessed at https://chagasjapon.wixsite.com/website. To adapt to the limitations due to the pandemic of coronavirus disease 2019 (COVID-19) after March 2020, I become more active in using virtual resources and conducting webinars with the LA population. Furthermore, a promotional video was created by the PI in YouTube in Spanish to create awareness about CD in Japan in collaboration with the LA migrant population in Japan. It can be accessed at

https://www.youtube.com/watch?v=LeWgXZdow2g. After the research data collection was finished I remained active on the social media and website.

Figure 7. Website "Chagas en Japón".

To those that attended the embassy activities I offered information about CD venues in two formats: an informative session as a group discussion or/and a formative area with multimedia projection, artistic area for children and adults, games, and informative cartels. The informative session had a comprehensive approach of CD, considering its multidimensionality and demonstrated to increase the knowledge of CD in different areas, as biomedical, epidemiological, political and sociocultural areas of the disease (Figure 8) (Sanmartino et al. 2015; Iglesias-Rodriguez et al. 2020). It preceded the data collection with a duration of 30 min and allow the participants to interact and construct through the group comments and experiences a complete image of the complexity of CD. The materials necessary for the activity were audiovisual material and papers of various colors that were used by the participants during the activity. After the Covid-19 pandemic, in March 2020, due to the difficulty of bringing groups together, the information was adapted to be provided individually or in small groups, keeping the same structure but shortened. The attendance to the informative session was freely decided by the people in the room and was not assessed or

controlled. In addition, informative sessions were conducted online in webinars. The formative area was offered in parallel with the data collection and used different spaces of the venue to offer interactive learning for children and adults (Figure 9). Also, easy access to the website by QR was offered to the participants (Figure 7).

Figure 8. Informative area.

Figure 9. Formative area.

7.9. Data collection method

7.9.1. Venues

After the informed consent was explained in a comprehensive language and signed, the participants were included in the study (Appendix 1, 1a, 1b). The informed consent, as well as the questionnaires were translated into Spanish and Portuguese by the PI. After enrollment, the sample collection was started: a questionnaire that were anonymized by a code number (Appendix 2) and blood samples.

The questionnaire was filled in by the participants in the venue room and when they were completed they proceeded to the blood sample collection. In the case of children under 16 years old, the parents were helping them to complete the questions, as needed. All participants included in the research were fluent in Spanish, Portuguese, or English.

Blood samples were collected from capillary blood by finger prick (600 μl) and stored in capillary tubes with ethylenediaminetetraacetic acid (EDTA) to prevent clotting. Blood samples were kept at 4°C and immediately after data collection were brought to the Institute of Tropical Medicine (NEKKEN). The RDT (Chagas Detect™Plus Rapid Test (Inbios International Inc., Seatttle, USA) was performed in the venue directly from the finger and results were recorded in a register (Appendix 3).

7.9.2. Health institution

All participants were informed of the results by post letter, email, or phone call according to their decision. I facilitated them a point of care in case they wished to consult after their test results.

I sent post-letters to all the positive participants that included the test results and a referral letter to the doctor and the point of care. Also, I called all the positive participants to ensure that they understand the results received by post, to answer possible questions, as well as during the follow-up process. Three health institutions had been selected, according to the experience of the doctor/unit in CD and previous verbal agreement was obtain from the doctor about the acceptance of CD positive patients. Positive participants were referred to one of these health institutions closest to their place of residence. In all cases I recommended testing their relatives, and a stronger recommendation was given to women with children. Information about the data collection schedule was provided to facilitate the test of their relatives.

If a positive participant visited a health facility, then part of the resulting collected blood sample would be sent to NEKKEN from Saitama Medical University (SMU), together with the clinical information, codified with the original code provided in the data collection. However, this information was not possible to obtain due to the lack of follow-up in the positive participants at the time of writing this thesis.

7.9.3. Team roles

The PI (I) was the person involved in the recruitment method, educational system, contacting the embassies and community leaders, explaining and translating the informed consent and questionnaires, resolving questions from the participants, solving encountered problems, conducting the serological testing, informing the results to the participants, referring them to a doctor, and ensuring a telephonic/online follow-up. In addition, I conducted all the analyses.

Dr. Miura from NGO-MAIKEN was the main person involved in blood samples collection and he conducted the RDT in the venue. In the event that he needed a substitute, Dr. Maeda, Dr. Imai, and I extracted the blood samples and conducted the RDT in the venues.

Volunteers with Spanish/Portuguese language skills came to the venues where we expected high influx. They assisted Dr. Miura in the blood sampling or resolved minor questions from the participants.

Dr. Imai conducted the ELISA-2 assays in Saitama Medical University, in two samples where the two serological results conducted in NEKKEN were discordant.

Clara Vazquez Velasquez instructed and supervised me in the serological test analysis from the beginning of the research until April 2020.

Prof. Hirayama supervised directly all the processes in the first two venues. He supervised my activities from Nagasaki University by verbal report after every data collection. In addition, he supervised the financial resources and directly help in problem solving.

7.10. Data Management

7.10.1. Questionnaires

The questionnaires were stored protected by key in NEKKEN and only the PI had access.

7.10.2. Blood samples

After the coded blood samples arrived at NEKKEN, the whole blood sample was separated into plasma and cells, separated through centrifugation for 15 min at 4°C and 3,500 rpm. Plasma and aliquots for cell fraction were frozen at NEKKEN at -80°C. Plasma was used for serological analysis at Nagasaki University. Samples were stored by key in freezers within the Department of Immunogenetics (NEKKEN). A part of the plasma (50 μl) was sent coded by their original code number to SMU where the serological test was conducted in the instance of discordant results.

7.10.3. Data from health institutions

No data was obtained at the moment that this thesis was written from Health Institutions. If data from the health institutions was sent, it was saved with the same safety considerations as the data from the venues.

7.11. Safety Considerations // Test information

The Ethics Committee of NEKKEN of Nagasaki University approved this study with the approval number 190110212-3. All participants gave their informed written consent. All information gathered was coded to ensure anonymity and privacy. All data and samples were coded and protected by key.

Information about the results of the two diagnostic tests was informed to the participants by the PI and referring them for follow-up to a specialist in their area of residence. Because of the lack of resources in Japan about CD, I offered telephone and online support via the website and social media managed by the PI. The website ensures support by active communication and information about CD in their native language.

7.12. Cost- effectiveness methodology

7.12. 1. Model structure

I used a Markov state transition model to evaluate the cost-effectiveness of CD screening in the asymptomatic LA population living in Japan in the PHC centers. The model was mainly based on a Chagas disease state-transition model in Europe (Requena-Mendez et al. 2017). The decision-tree compares two scenarios (Figure 10):

I. **Screening model**. All asymptomatic residents of Japan who were born in Latin America were offered to be screened in the PHC centers. All positive cases were treated and followed up with the necessary periodical visits and interventions. I considered that 80% of the target population will reach the screening and the 20% will remain not screened, considering the potential barriers in the access to CD diagnosis and treatment (Requena-Mendez et al. 2017; Instituto de Salud Global 2017; Ventura-Garcia et al. 2013; Romay-Barja et al. 2020; Monge-Maillo et al. 2017). The 20% followed the same evolution as those in the non-screening model.

II. **Non-screening model**. The LA residents in Japan typically follow the natural path of the disease, and do nothing actively. In that model, just the symptomatic individuals that develop CD symptoms or complications are screened and treated.

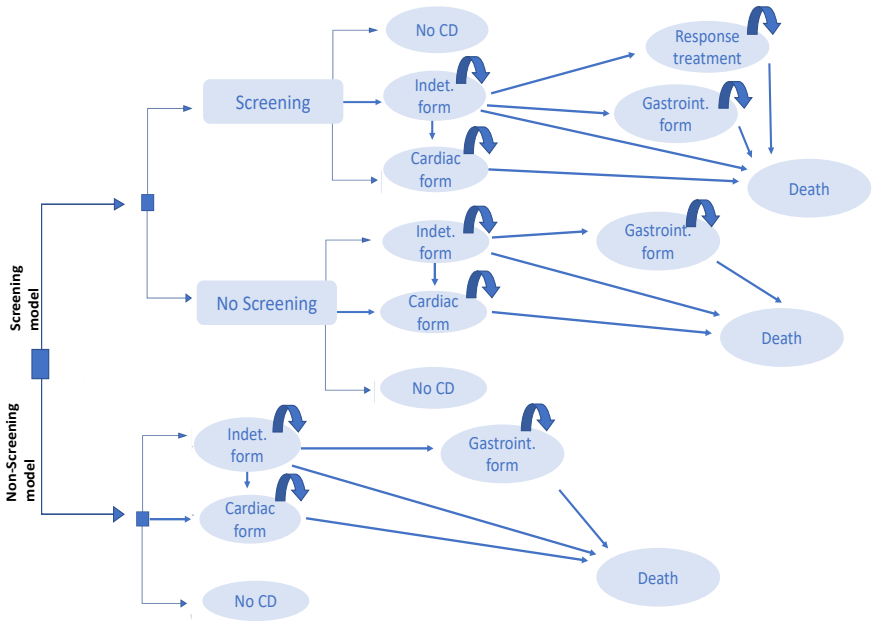

Figure 10. Decision-tree for *Trypanosoma cruzi* screening.
CD, Chagas disease.

The model starts with 100,000 individuals from Latin America, considering that 1.7% (95% CI. 0.008-0.034) were infected with *T. cruzi*. Each infected person can move annually to the different health states of CD according to the transition probabilities. I considered five health states: indeterminate form, cardiac form, gastrointestinal form, response to treatment, and death. The model starts in cycle 0 with individuals at 35 years old (Muñoz et al. 2009). I assumed that 86% were asymptomatic and in those asymptomatic 14% were in the cardiac form and 86% were in the indeterminate form (Salvador et al. 2014). To evaluate if the screening for CD asymptomatic LA migrants of Japan is cost-effective, in the model I didn't include individuals non-infected for CD, nor people initially symptomatic.

7.12. 2. Strategies for the screening and treatment

All individuals in the "Screening model-screening" were under screening, as well as those that became symptomatic in the other models. According to international recommendations, an individual is considered positive if they have at least two positive serological tests, ie, the standard diagnosis (WHO Expert Committee 2002). The standard diagnosis included two serological tests and we assumed that 4% of them would need a third serological test (Salvador et al. 2014; Muñoz et al. 2009; Requena-Mendez et al. 2017). All individuals who were infected with *T. cruzi* continued the evaluation with chest radiography and electrocardiogram. All positive individuals for *T. cruzi* were assumed to be treated with Benznidazole for 60 days and followed up every 2 weeks with blood analysis (Salvador et al. 2013).

7.12. 3. Transition probabilities

The state transition probabilities were based on the literature (Table 5) (Prata 2001; Requena-Mendez et al. 2017; Viotti et al. 2006). The annual probability to move from the indeterminate form to the digestive form was considered to be 0.3% for both options. However, the annual probability to move from the indeterminate form to the cardiac form was 2% in the "Non-screening model" and 0.5% in the "Screening model" (Table 5).

I considered a probability to respond to treatment (serology conversion to negative in previous positive patients) of 20% after 5 years of the treatment (Viotti et al. 2011). According to the literature I considered that 4.2% of individuals in the cardiac form will develop congestive heart failure (Sabino et al. 2013).

The average life expectancy was considered to be the same as for Japanese citizens. Annual mortality rates by age were extracted from the Japanese 2019 abridged life tables (MHLW 2019). The probability of death attributable to indeterminate and digestive form was considered 0% and to cardiac from 3.9% (Rassi et al. 2006).

The transition probabilities of undertaking tests and interventions were based on cost-effectiveness analyses in CD in non-endemic countries, summarized in Table 6 (Requena-Mendez et al. 2017; Imaz-Iglesia et al. 2015).

Table 5. Model input parameters I (probabilities).

Probabilities associated with Chagas disease	Value	SD	Distribution	alfa	beta	Reference
Probability of being asymptomatic	0.858	0.172	beta	2.692	0.446	Requena-Mendez et al. 2017
Probability of being asymptomatic and	0.141	0.028	beta	21.334	129.971	Requena-Mendez et al. 2017

having cardiopathy at the starting point						
Transition probability from the indeterminate to the cardiac form in the treated group	0.005	0.001	beta	24.870	4,949.130	Requena-Mendez et al. 2017
Transition probability from the indeterminate to the cardiac form in the no-screening model	0.020	0.004	beta	24.480	1,199.520	Requena-Mendez et al. 2017
Transition probability from the indeterminate to the digestive form in both groups	0.003	0.001	beta	24.922	8,282.411	Requena-Mendez et al. 2017
Probability of death attributable to CD for parents in the cardiac form for both groups	0.039	0.008	beta	23.986	591.040	Requena-Mendez et al. 2017
Probability of having severe cardiomyopathy (CHF) in the cardiac form	0.042	0.008	beta	23.908	545.330	Requena-Mendez et al. 2017
Probability of death attributable to CD for patients in the cardiac form for both groups	0	0	beta	-	-	Requena-Mendez et al. 2017
Probability of response to treatment	0.200	0.040	beta	19.800	79.200	Requena-Mendez et al. 2017
Probability to have adverse effects in treatment with Benznidazole	0.571	0.1142	beta	10.154	7.629	Pinazo et al. 2010
Weight applied in QALYs	**Value**	**SD**	**Distribution**	**alfa**	**beta**	**Reference**
Healthy patient	1		point estimate			Requena-Mendez et al. 2017
Indeterminate form	0.963	0.093	beta	2.79	0.11	Requena-Mendez et al. 2017
Cardiac form	0.717	0.1434	beta	6.36	2.51	Requena-Mendez et al. 2017

Digestive form	0.800	0.1600	beta	4.20	1.05	Requena-Mendez et al. 2017
Death	0		point estimate			Requena-Mendez et al. 2017
Other parameters used in the model	**Value**	**SD**	**Distribution**	**alfa**	**beta**	**Reference**
Discount rate	0.02		point estimate			Shiroiwa et al. 2017
Threshold efficacy (WTP)	5,000,000		point estimate			Shiroiwa et al. 2009
Probability of death non-attributable to CD	0.00067-1.0		point estimate			MHLW 2020

CD, Chagas disease; WTP, Willingness-to-pay; QALYs, Quality adjusted life years.

Table 6. Model input parameters II (probabilities).

Probability of test being undertaken	Values	SD	Distribution	alfa	beta	Reference
Antiacids	0.50	0.10	beta	12.00	12.00	Imaz-Iglesia et al. 2015
Automatic defibrillator	0.03	0.01	beta	24.22	783.11	Requena-Mendez et al. 2017
Barium X-ray	1.00		point estimate			Requena-Mendez et al. 2017
Benznidazole therapy	1.00		point estimate			Requena-Mendez et al. 2017
Beta-blockers	0.50	0.10	beta	12.00	12.00	Imaz-Iglesia et al. 2015
Beta-blockers (CHF)	1.00		point estimate			Requena-Mendez et al. 2017
Cardiac transplant	0.01	0.00	beta	24.74	2449.26	Requena-Mendez et al. 2017
Chest x-ray	1.00		point estimate			Requena-Mendez et al. 2017
Digestive disease hospitalization	0.06	0.01	beta	23.44	367.23	Requena-Mendez et al. 2017
Digoxin (CHF)	1.00		point estimate			Requena-Mendez et al. 2017
Digoxin	0.50	0.10	beta	12.00	12.00	Imaz-Iglesia et al. 2015
Echocardiogram	1.00		point estimate			Requena-Mendez et al. 2017
Electrocardiogram	1.00		point estimate			Requena-Mendez et al. 2017
Enalapril	0.50	0.10	beta	12.00	12.00	Imaz-Iglesia et al. 2015
Enalapril (CHF)	1.00		point estimate			Requena-Mendez et al. 2017
Endoscopic sphincterotomy	0.01	0.00	beta	24.74	2449.26	Requena-Mendez et al. 2017

Furosemide	0.50	0.10	beta	12.00	12.00	Imaz-Iglesia et al. 2015
Furosemide (CHF)	1.00		point estimate			Requena-Mendez et al. 2017
Heart failure hospitalization	2.35		point estimate			Imaz-Iglesia et al. 2015
Holter	0.30	0.06	beta	17.20	40.13	Requena-Mendez et al. 2017
Intestinal transit study	1.00		point estimate			Requena-Mendez et al. 2017
Manometry	0.05	0.01	beta	23.70	450.30	Requena-Mendez et al. 2017
Mega-viscera surgery	0.01	0.00	beta	24.74	2449.26	Requena-Mendez et al. 2017
Omeprazole	0.50	0.10	beta	12.00	12.00	Imaz-Iglesia et al. 2015
Pacemaker	0.02	0,00	beta	24.48	1199.52	Requena-Mendez et al. 2017
Prokinetic drugs	0.50	0.10	beta	12.00	12.00	Imaz-Iglesia et al. 2015
Screening test (double test)	1.00		point estimate			Requena-Mendez et al. 2017
Screening triple test	0.04	0.01	beta	23.96	575.04	Requena-Mendez et al. 2017
Stress test	0.08	0.02	beta	22.92	263.58	Requena-Mendez et al. 2017
Translator	0.49	0.10	beta	12.21	12.61	Results

CHF, Cardiac heart failure

7.12. 4. Costs

Two scenarios were considered to estimate the costs: societal perspective, and health-care perspective. To estimate the health cost of the visits, tests, and interventions, I used the 2020 edition of the medical fee index for the Japanese healthcare system and the literature (Table 7) (MHLW 2020). Drug costs were obtained for the 2020 edition of the Kyō no chiryō-yaku. (Kyō no chiryō-yaku 2020) These references were used to calculate the adverse events of Benznidazole, considering the approach of Requena-Mendez and colleagues (Table 8) (MHLW 2020; Requena-Mendez et al. 2017).

Because CD has no oversight system in Japan, I used the costs of Benznidazole, serological test, and costs of program uptake based on the study published by Imaz-Iglesia et al. (Imaz-Iglesia et al. 2015). These costs were extrapolated considering the inflation increment, the rate between Japan and Spain according to the WHO Choice cost per bed-day ratio, and the

changing value to Japanese yen (JPY) by the purchasing power parity (PPP) conversion factor (WHO 2010; The world bank 2019).

I used this data to calculate the annual health state costs. In the cases where the probabilities were life-long, I calculated the annual cost using the mean length of life in every state based on previous studies and the Japanese live expectancy age (Imaz-Iglesia et al. 2015; Lee et al. 2013; MHLW 2020). The results of the length of live after 35 years old (mean age) was 49 years for indeterminate form, 22 for digestive form, 10 years for cardiac form.

Table 7. Model input parameters (costs).

Costs estimate	Values	SD	Distribution	alfa	beta	Reference
First medical visit (Primary care)	740.00	148.00	gamma	25.00	29.60	MHLW 2020
First medical visit (Hospital)	2,880.00	576.00	gamma	25.00	115.20	MHLW 2020
Follow-up medical visit	730.00	146.00	gamma	25.00	29.20	MHLW 2020
Chest X-ray	1,230.00	246.00	gamma	25.00	49.20	MHLW 2020
Blood test	1,430.00	247.00	gamma	25.00	49.20	MHLW 2020
Echocardiogram	9,000.00	1800.00	gamma	25.00	360.00	MHLW 2020
Holter	17,500.00	3,500.00	gamma	25.00	700.00	MHLW 2020
Stress test	16,507.80	3,301.56	gamma	25.00	660.31	WHO 2010; PPP;Imaz-Iglesia et al. 2015
Pacemaker	313,400.00	62,680.00	gamma	25.00	12,536.00	MHLW 2020; Soejima et al. 2017
Automatic defibrillator	699,800.00	139,960.00	gamma	25.00	27,992.00	MHLW 2020; Soejima et al. 2017
Cardiac transplant	2,419,180.00	483,836.00	gamma	25.00	96,767.20	MHLW 2020
Heart failure hospitalization	819,415.70	163,883.14	gamma	25.00	32,776.63	Kanaoka et al. 2019; PPP
Barium X-ray	9,600.00	1,920.00	gamma	25.00	384.00	MHLW 2020
Intestinal transit study	9,000.00	1,800.00	gamma	25.00	360.00	MHLW 2020
Manometry	7,800.00	1,560.00	gamma	25.00	312.00	MHLW 2020
Endoscopic sphincterotomy	228,200.00	45,640.00	gamma	25.00	9,128.00	MHLW 2020

Mega-viscera surgery	458,680.00	91,736.00	gamma	25.00	18,347.20	MHLW 2020
Digestive disease hospitalization	360,072.00	72,014.40	gamma	25.00	14,402.88	Kunisima et al. 2018
Screening double test	4,771.04	954.21	gamma	25.00	190.84	WHO 2010; PPP;Imaz-Iglesia et al. 2015
Screening third test	2,385.52	477.10	gamma	25.00	95.42	WHO 2010; PPP;Imaz-Iglesia et al. 2015
Benznidazole therapy	42,796.23	8,559.25	gamma	25.00	1711.85	WHO 2010; PPP;Imaz-Iglesia et al. 2015
Translator	1148,00	229,60	gamma	25,00	45,92	MHLW 2020
Cost of scalling-up	Value	SD	Distribution	alfa	beta	Reference
Personnel (coordinator)	4,644,000.00	928,800.00	gamma	25.00	185,760.00	MHLW 2020
Personnel (technician)	3,417,600.00	683,520.00	gamma	25.00	136,704.00	MHLW 2020
Subsistence	16,507.80	3,301.56	gamma	25.00	660.31	WHO 2010; PPP;Imaz-Iglesia et al. 2015
Travel	1,908,416.22	381,683.24	gamma	25.00	76,336.65	WHO 2010; PPP;Imaz-Iglesia et al. 2015
Computers	3,578,280.42	715,656.08	gamma	25.00	143,131.22	WHO 2010; PPP;Imaz-Iglesia et al. 2015
Office equipment	477,104.06	95,420.81	gamma	25.00	19,084.16	WHO 2010; PPP;Imaz-Iglesia et al. 2015
Meeting	357,828.04	71,565.61	gamma	25.00	14,313.12	WHO 2010; PPP;Imaz-Iglesia et al. 2015
Overheads (15%)	1,884,561.02	376,912.20	gamma	25.00	75,382.44	WHO 2010; PPP;Imaz-Iglesia et al. 2015
Annual costs estimate of drugs	Values	SD	Distribution	alfa	beta	References
Digoxin	3,577.00	715.4	gamma	25.00	143.08	Kyō no chiryō-yaku 2020

Enalapril	5,493.25	1,098.65	gamma	25.00	219.73	Kyō no chiryō-yaku 2020
Beta-blockers	3,686.50	737.3	gamma	25.00	147.46	Kyō no chiryō-yaku 2020
Furosemide	2,336.00	467.2	gamma	25.00	93.44	Kyō no chiryō-yaku 2020
Omeprazol	14,125.50	2,825.1	gamma	25.00	565.02	Kyō no chiryō-yaku 2020
Antacids	2,080.50	416.1	gamma	25.00	83.22	Kyō no chiryō-yaku 2020
Prokinetic drugs	2,153.50	430.7	gamma	25.00	86.14	Kyō no chiryō-yaku 2020

7.12. 4.1. Cost of scaling-up and cost of translation system

The cost of program uptake was considered for the first 5 years of the Screening model-screened (Requena-Mendez et al. 2017; Imaz-Iglesia et al. 2015). The salary of the coordinator and technician were obtained from Japanese official sources and the number of working hours in Japan (MHLW 2020). The Screening model included the cost of translators that would accompany the patient during the medical visits (MHLW 2020). This service was included to overcome the language barrier that affect the access to the health system in the LA migrant population living in Japan. According with the results I considered that 49% of the LA migrants would need a translator.

Table 8. Size effects of Benznidazole.

Costs of benznidazole side effects	**Drug**				**Medical visit**			**Blood analysis**			**General ward day**	**TOTAL**
Source: Pinazo et al. 2010; Requena-Mendez et al. 2017	Sources: Drug price (Kyo no chiryo-yaku 2020), drug and % of prescripton (Requena-Mendez et al. 2017)				Sources: Visit in Japanese hospital: 730 JYP (MHLW 2020), % of extravisit estatated (Requena-Mendez et al. 2017)			Sources: Blood analysis: 1,430 JPY (MHLW 2020) , %. Analysis estimated (Requena-Mendez et al. 2017)			Source: MHLW 2020	
Side effect	Treatment	%	YEN/pill	Number	Total (JPY)	N.extra visit	%	Total (JPY)	Number	%	Total (JPY)		
Headache	Acetaminophen /3 days	30	9	5	3.38								
Skin reactions	Mequitazine/5 mg/ 7 days	100	5.7	13	17.04	2	20	67.16	1	1	3.289		
Skin reactions	Prednisone 10mg/7days	10	9.8	36	8.11								
Asthenia													
Fever	Acetaminophen/2 days	100	9	4	1.80	1	100	36.50	1	100	71.500		
Arthromyalgias	Indomethacin/8h 15 days	5	37.5	30	9.00	2	3	7.01	1	3	6.864		
Arthromyalgias	Prednisone 10 mg/15 days	5	9.8	48	3.76								
Arthromyalgias	Acetaminophen/8h /3 days	50	9	12	8.64								
Paraesthesias													
Gastrointestinal dis	Omeprazol 20mg/ 28 days	30	38.7	28	22.76								
Stomatitis													
Ear involvement													
SUBTOTAL					74.49			110.67			81.653	14,423.00	14689.81

7.12. 5. Productivity loss and consumption

The productivity loss costs were calculated based on the average salary of LA residents and extrapolated by age (MHLW 2020). I included a social fee of 14.75% (National Tax Agency 2020). I considered that a person will be active until 65 years old.

The consumption was obtained from official sources and I excluded the medical care costs to avoid duplication in costs (MHLW 2020).

7.12. 6. Quality adjusted life years (QALYs)

The quality weights applied were 0.9625 for the indeterminate form, 0.717 for the cardiac form, and 0.8 for digestive form, based on the literature (Wilson et al. 2005; Requena-Mendez et al. 2017).

7.13. Statistical analysis

7.13. 1. Prevalence

To calculate the observed prevalence, I divided the total number of cases with *T. cruzi* infection positive identified in the research versus the total participants, shown as a percentage. The expected prevalence was based in the estimated prevalence. It was calculated dividing the total number of estimated cases of *T. cruzi* infection between the total number of LA migrants living in Japan. Details can be found in Table 4 (e-Stats 2019; MOJ 2019; WHO 2015).

7.13.2. Socio-demographic characteristics, risk factors of Chagas and clinical profile

I have analyzed the data descriptively. Due to the small number of positive participants - less than ten - I independently analyzed the association with positive result for each factor using the Fisher exact test. The socio-demographic factors included in the analysis were age, gender, education, country of origin, time in Japan, and having done the CD test previously; the risk factors included were lived in a rural area, lived in a mud house, knowledge about CD, have seen the triatome bug, have seen the triatome bug at home, have a relative affected by CD, have donated blood in the past, and have received a blood donation.

7.13. 3. Accessibility to the Japanese health system.

From the total participants in the cohort, 390 migrants were included who were born in LA countries and were at least 18 years old. From the questionnaires I descriptively analyzed the general characteristics and the answers about access. I conducted a contingency analysis by the Fisher exact test to determine the association between the working condition and source of health insurance, as well as between the working condition and gender.

To examine the factors associated with access to the health-care system, we used a multivariable analysis and a logistic regression model. I fixed the two dependent variables based on studies (Shakya et al. 2018); specifically, (a) if they currently have proper access to a doctor/health worker and (b) if, in the past year, they required but declined to see a doctor/health worker for an illness. The independent variables were chosen based on Andersen's model of access to health care's three primary components of individual and contextual variables (predisposing enabling and need factors) (Jahangir, Irazola & Robinstein 2012; Sheppers et al. 2006; Shakya et al. 2018).

The following independent variables were considered in the study: a) predisposing factors: age, gender, education, and length of stay in Japan; b) enabling factors: employment status,

considered insurance expensive, insurance payment, source of information about the health system, limitation in access due to communication barrier, and health system satisfaction; and c) need factors: self-assessed health condition.

The predictor variables did not show any evidence of multicollinearity. I excluded missing data. The statistical significance was set to $p < 0.05$. JMP Pro was used to conduct the analysis.

7.13. 4. Cost-effectiveness of the screening

Deterministic and probabilistic analyses were conducted using Microsoft Excel (Briggs, Sculpher & Claxton 2006). According to Japanese guidelines, future cost and QALYs were discounted annually at 2% (Shiroiwa et al. 2017). Willingness-to-pay (WTP) and the threshold was set to 5,000, 000 JPY per QALY based on Japanese literature (Shiroiwa et al. 2009). The incremental cost-effectiveness ratio (ICER) between the screening and no-screening models was the primary outcome.

Herein I show the results from a social and health care perspective. However, I based the main analysis on the health care perspective following the recommendations of Japanese guidelines for cost-effectiveness analysis (Shiroiwa et al. 2017). Mean values for each parameter were used for the deterministic analysis. Univariate sensitivity analysis was done with the variation to the mean until +100% or the maximum possible and -99% or the minimum possible. Results were shown in a tornado diagram. A strategy was considered cost-effective if the costs per QALY gained were less than the Japanese threshold (5,000,000 JPY). A threshold analysis was used to estimate the cut-off points of CD prevalence and probability to be screened at which the screening model would not be cost-effective.

Probabilistic sensitivity analysis (PSA) was performed with a WTP range of 0-10,000,000 through Monte Carlo simulations with 10,000 iterations. All probabilistic parameters and utilities were assumed to follow beta distribution; costs were assumed to follow gamma distribution (Briggs, Sculpher & Claxton 2006). For the standard deviation (SD) when data were not available, 20% of the mean values were assumed and 10% in the case of indeterminate form QALYs, based on previous research (Requena-Mendez et al. 2017; Nayagam et al. 2016). The simulations were presented in the ICER scatter plot and the Cost-effectivity acceptability curve (CEAC). The CEAC shows the probability of the screening model to be cost-effective according to the WTP for each QALY.

7.13. 5. RDT/standard diagnosis

I compared RDT with the standard diagnosis. For discrete and continuous variables, frequencies and mean (SD) were used to explain the data. The kappa statistic ($\varkappa$) was used to calculate the agreement between classification tools. (Cohen 1960; Lozano et al. 2019). The $\varkappa$ measure of agreement would take the scale of 0 if the agreement is expected to be observed by chance and 1 if the agreement is perfect (Landis & Koch 1977). A score of 0 indicates no agreement; a score of 0–0.20 indicates poor agreement; a score of 0.21–0.40 indicates fair agreement; a score of 0.41–0.60 indicates moderate agreement; a score of 0.61–0.80 indicates substantial agreement; and a score of 0.81–1.00 indicates practically perfect agreement. The significance level for the analysis was set to 0.05, and JMP pro was used to conduct it.

7.13. 6. Data from health institutions

It was not possible to obtain health data from the health institutions due to the lack of follow-up in the patients that attend the health institutions. Qualitative data could be obtained by phone calls from the positive participants regarding the reason why they stop the follow-up.

8. Results

Four hundred twenty-eight (n=428) participants were recruited from the 30th of March until the 18th of October of 2020 from 7 different prefectures (Gunma, Tokyo, Osaka, Mie, Aichi, Hiroshima, and Nagasaki) over 21 occasions.

8.1.Characteristic of the participants

8.1.1. Socio-demographic characteristic

The participant's ages ranged from 7 to 82 years old, with a mean age of 43.5 (SD. 13.67). Seventeen participants (4%) were under 18 years old and the rest were adults. The percentage of women were slightly higher than men, 59% and 41%, respectively. The majority of women had children (78%, n=187). More than half of the participants had secondary education (53%, n=196). The socio-demographic characteristics are summarized in Table 9.

Table 9. Socio-demographic characteristic.

		mean/N	SD/%	Non- responders
Age		43.5	13.6	7
Gender	Male	177	41.36%	0
	Female	251	58.64%	
Education level	Primary	26	7.05%	59
	Secondary	196	53.12%	
	University	147	39.84%	
Country of origin	Bolivia	132	30.84%	0
	Brazil	195	45.56%	
	Peru	70	16.36%	
	Japan	25	5.84%	

	Paraguay	3	0.70%	
	South Korea	1	0.23%	
	United Kingdom	1	0.23%	
	Colombia	1	0.23%	
Length of stay in Japan	< 5 years	72	17.31%	12
	5-10 years	40	9.62%	
	> 10 years	304	73.08%	
Perspective to came back	Yes	177	44.81%	33
	No	218	55.19%	

Most of the participants were born in Latin America (98.4%, n=401) vs 27 (1.6%) that were born elsewhere outside of Latin America. The participants born outside Latin America had been included because they had at least one of the next conditions: the mother had been born in Latin America or the participant had lived in Latin America for long periods. The participants born in Latin America are represented mainly for three countries: Brazil (45.5%, n=195), Bolivia (30.8%, n=132) and Peru (16.3%, n=70). The top five districts of origin from Latin America were by order: Sao Paulo in Brazil (29%, n=119), Beni in Bolivia (12.6%, n=52), Santa Cruz in Bolivia (11.4%, n=47), Lima in Peru (9.5%, n=39), and Parana in Brazil (6.8%, n=28) (Figure 11).

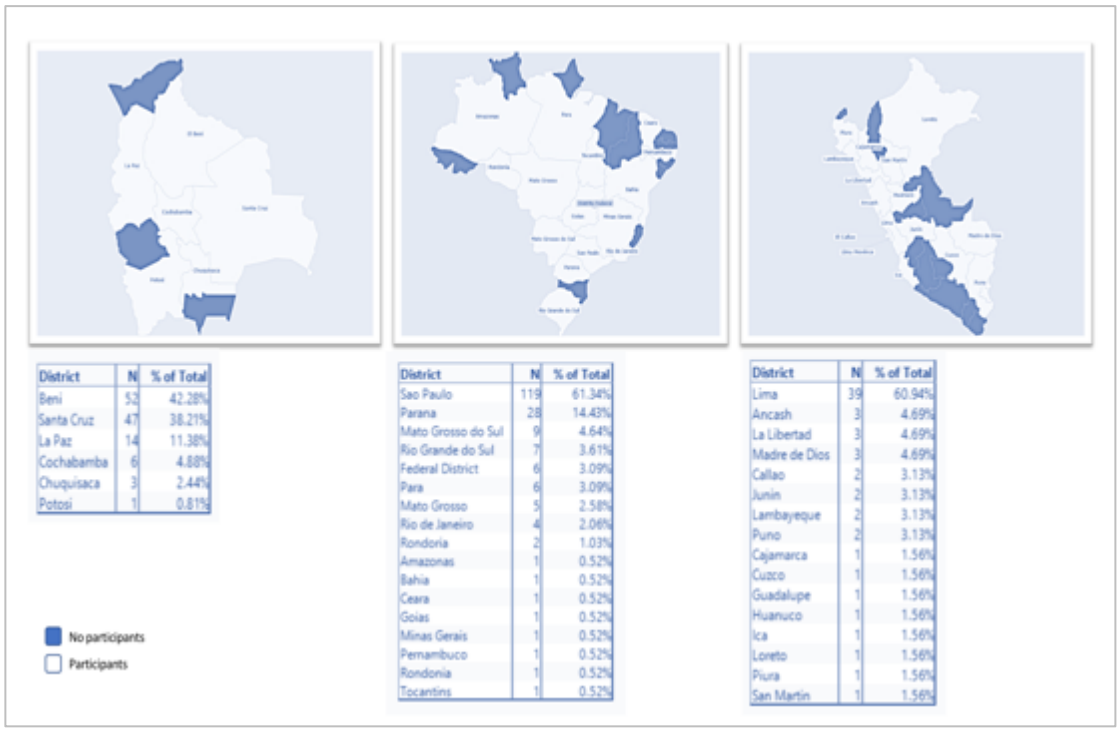

Figure 11. Districts of origin in Bolivian, Brazilian and Peruvian participants.

The majority of those who took part had been in Japan for more than ten years (73%, n=304).

The top three prefectures of residence were Aichi, Mie, and Gunma (Figure 12).

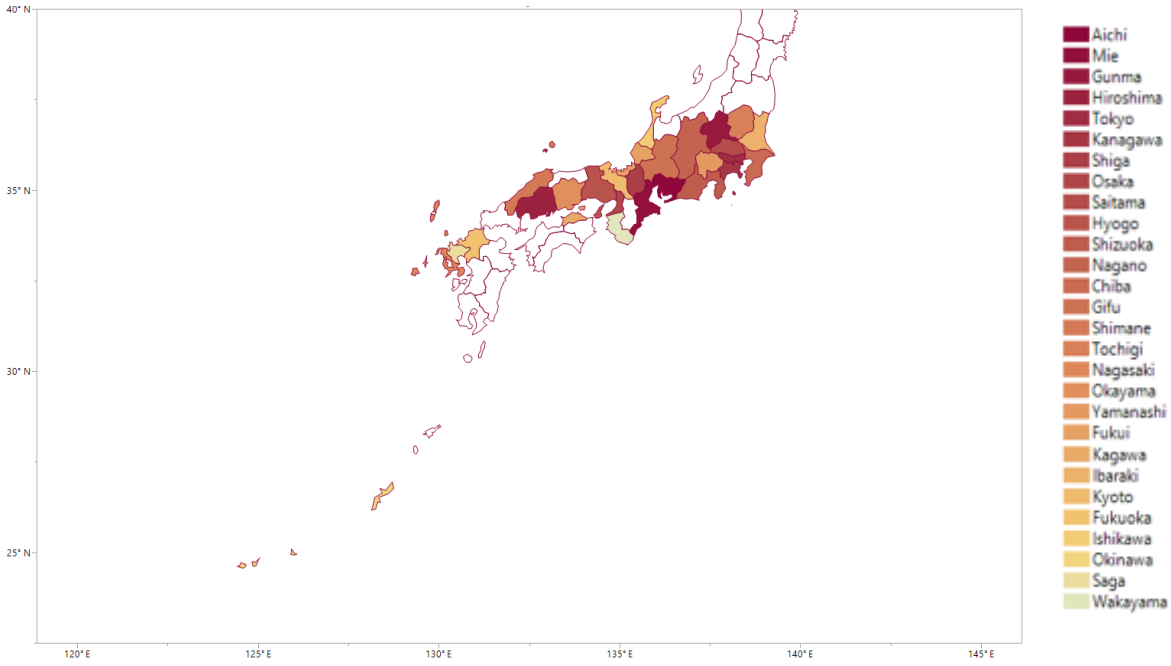

Figure 12. Prefectures of residence in Japan in the participants.

8.1.2. Characteristics of the participants related with risk factors of CD and level of diagnosis and risk of transmission by blood transfusion.

Most of the participants knew about CD (74.3%, n=312) and nearly half had seen the triatome bug (34.2%, n=144). Less than half of the participants had lived in a rural area and less than a fifth of them had lived in a mud house. Thirteen percent (n=52) had a family member affected by CD.

Even though most were familiar with the disease, just 3.7% (n=16) were tested for CD. Fifty-six percent (n=9) of those who were tested received the Chagas test in Bolivia, 25% of them in Japan (n=4), and the rest in Brazil and Paraguay. Table 10 summarizes these characteristics.

Table 10. Characteristics of the participants related with risk factors of Chagas disease, risk of transmission, vigilance, and policies.

	YES n (%)	NO n (%)	NR n
Risk factors of Chagas disease			
Have you ever heard about CD?	312 (74.29%)	108 (25.71%)	8
Have you ever seen this insect?	144(34.20%)	277(65.80%)	7
Have you seen it at home?	44 (10.45%)	377 (89.55%)	7
Had you been lived in rural area?	170 (40.96%)	245 (59.04%)	13
Had you lived in mud house in Latin America?	72 (19.73%)	293 (80.27%)	63
Do you have in your family any member affected by CD?	54 (12.92%)	364 (87.08%)	10
Have you received blood in LA countries?	18 (4.27%)	404 (95.73%)	6
Risk of transmission			
Women with children (women answer)	187 (77.59%)	54 (22.4%)	10
People that have donated blood	126 (29.58%)	300 (70.42%)	320

Vigilance and policies			
Lived in another country	78 (18.22%)	334 (78.04%)	16
Tested for Chagas Disease	16 (3.74%) *	412 (96.26%)	0
Treated for Chagas Disease	1 (0.25%)	400 (99.75%)	27

CD, Chagas disease; LA, Latin American; NR, Non-responders

* Bolivia (n=9, 56.25%). Brasil, Japan and Paraguay (n=7, 43.75%, respectively)

Table 11. Knowledge of Chagas disease by country

Peruvian participants were the group with less knowledge about CD, and less than 30% had heard about CD (Table 11).

Have heard about Chagas disease?				
	Yes	No	Total	p value
Brazilian	172 (89.58%)	20 (10.42%)	192	0.0001
Bolivian	107 (82.95%)	22 (17.05%)	129	
Peruvian	19 (27.94%)	49 (72.0%)	68	
Other	14 (45.16%)	17 (54.84%)	31	
Total	312	108	420	

8.1.3. Socio-demographic characteristics of the participants compared with the Latin American migrant population.

Comparing the socio-demographic characteristics of the participants with the statistics of the LA migrant population living in Japan, we see mainly two differences: age and country of origin (MHLW 2020). The proportion of children under 20 years old is nearly 3 times smaller than in the real population. In addition, the proportion of Bolivians in our cohort represent more than 30% while the real population represents 2% (Table 12).

There were minor differences in gender and prefecture of residence. More women than men participated in the study. Aichi, Mie, and Gunma are among the top four prefectures for residence in both groups, with Aichi having the most LA migrants. However, Shizuoka is the second prefecture where more LA migrants live in Japan, but our cohort takes position number 11. Also, Hiroshima takes fourth place in our cohort and in the LA migrant population takes the place number 9.

Table 12. Socio-demographic characteristics of the participants and the Latin American migrant population (MHLW 2020)

	LA migrants participants		LA migrant population	
	n	%	n	%
Age				
0-20	31	7.36	64,829	23.47
21-40	132	31.35	89,820	32.51
41-60	212	50.36	96,622	34.97
> 60	46	10.93	25,003	9.05
Gender				
Men	177	41.36	14,8320	53.69
Women	251	58.64	12,7954	46.31
Country of origin				
Brazil	195	45.56	20,4347	73.97
Bolivia	132	30.84	5,994	2.17
Peru	70	16.36	48,816	17.67
Others	31	7.24	17,117	6.20
Top 4 prefectures of residence				
Aichi	73	17.05	69,716	25.95
Mie	72	16.82	18,107	6.74
Gunma	62	14.48	18,600	6.92
Hiroshima	49	11.44	3,070	1.14

8.2.Prevalence

8.2.1. Estimated prevalence

In 2019, 276,274 individuals originally from the 21 *T. cruzi* endemic countries of North, Central and South America were living in Japan. Considering the prevalence from WHO 2015, 2,082 migrants were estimated to have Chagas disease in 2019 in Japan, giving a Japan-wide prevalence of 0.75% (Table 4).

Considering the number of diagnosed cases until the moment (n=6) published in previous research, it would give a rate of diagnosis of 0.2% (Imai et al. 2019).

8.2.2. Observed prevalence

Seven out of 428 participants were positive for *T. cruzi* by standard diagnosis, resulting in an overall observed prevalence rate of 1.6% (95% confidence interval (CI) 0.008-0.033) in this cohort. The observed prevalence among Bolivians was 5.3% (95% CI 0.025-0.105; n=132).

Six out of seven positive participants were positive for *T. cruzi* by IFA and ELISA, without discordancy. However, the results were discordant in two participants. The sample number 392 and 374 were positive for *T. cruzi* by IFA but not by ELISA. According to the protocol, ELISA-2 was conducted in the two samples with discordant results. The sample number 392 was positive and the sample number 374 was negative for *T. cruzi*. The results by the different serologic test are summarized in Table 13.

Table 13. Serologic results of positive participants (RDT, IFA, ELISA, ELISA-2).

	74	75	93	96	204	374	390	392
RDT	+	+	+	+	+	-	+	+
IFA	+	+	+	+	+	+	+	+
ELISA	+	+	+	+	+	-	+	-
ELISA-2						-		+
Results	+	+	+	+	+	-	+	+

The Table 14 summarize the different prevalence by population group. The number of children in the cohort represents less than 4%. The prevalence excluding the participants under 18 years old would be 1.7% in the LA migrant population living in Japan and 5.7% in the Bolivian population.

Table 14. Prevalence in the Latin American migrant population living in Japan in different cohorts.

	Seropositive	Total	Prevalence	CI 95%
Latin American migrant population	7	428	1.6%	0.008-0.033
Latin American adult migrant population	7	411	1.7%	0.008-0.034
Bolivian migrant population	7	132	5.3%	0.025-0.105
Bolivian adult migrant population	7	123	5.7%	0.027-0.112
Santa Cruz (Bolivia) migrant population	7	47	14.9%	0.074-0.275

The Figures 13-17 and Table 15 show the result of the serological test.

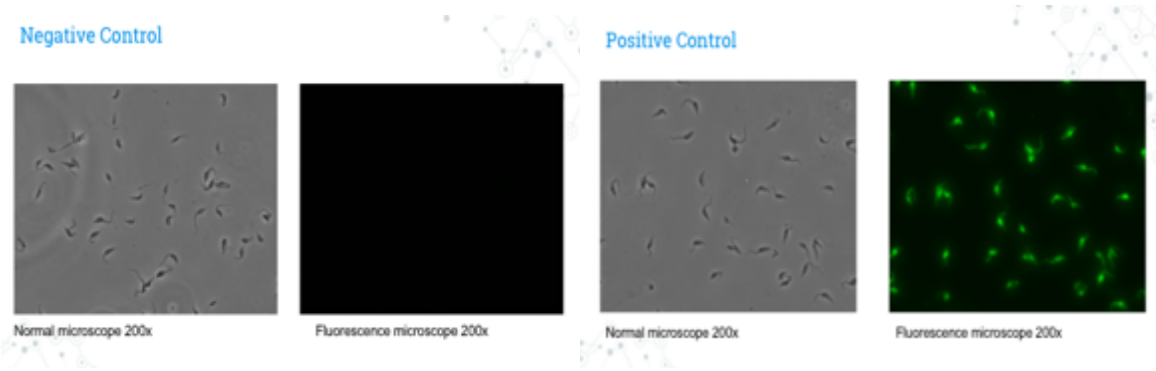

Figure 13. IFA PC (Positive control) and NC (Negative Control).

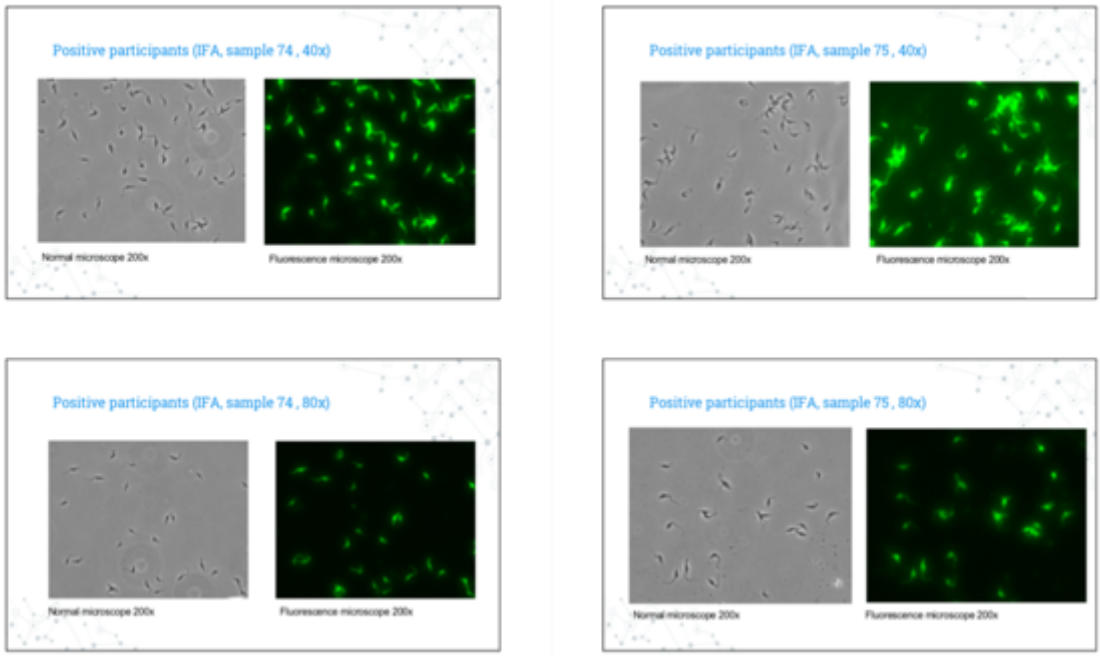

Figure 14. IFA result of positive participants (I)

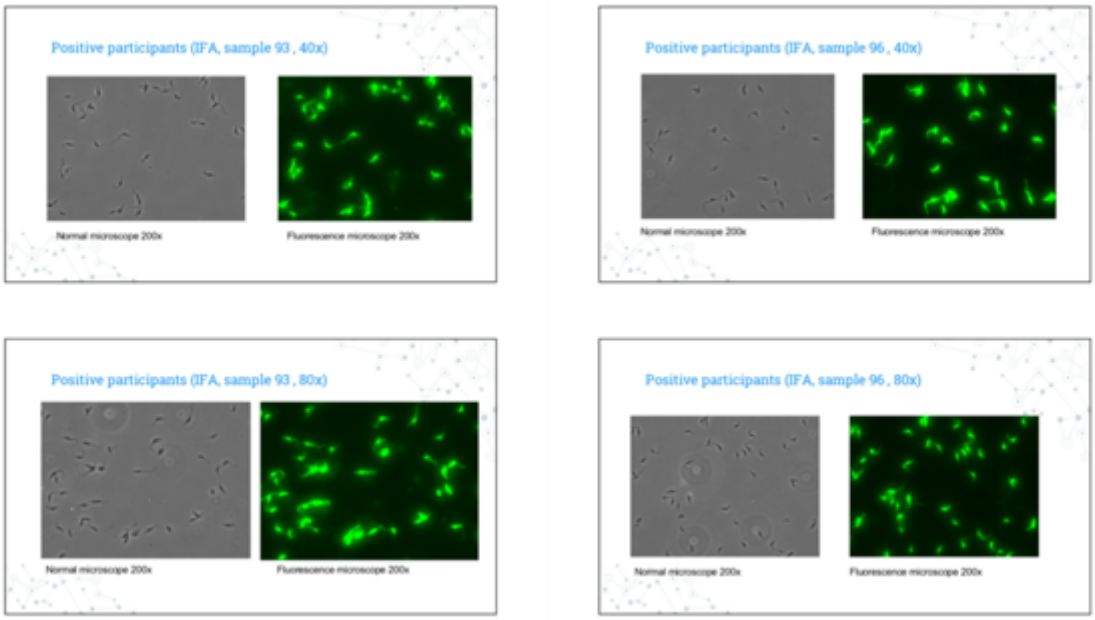

Figure 15. IFA result of positive participants (II).

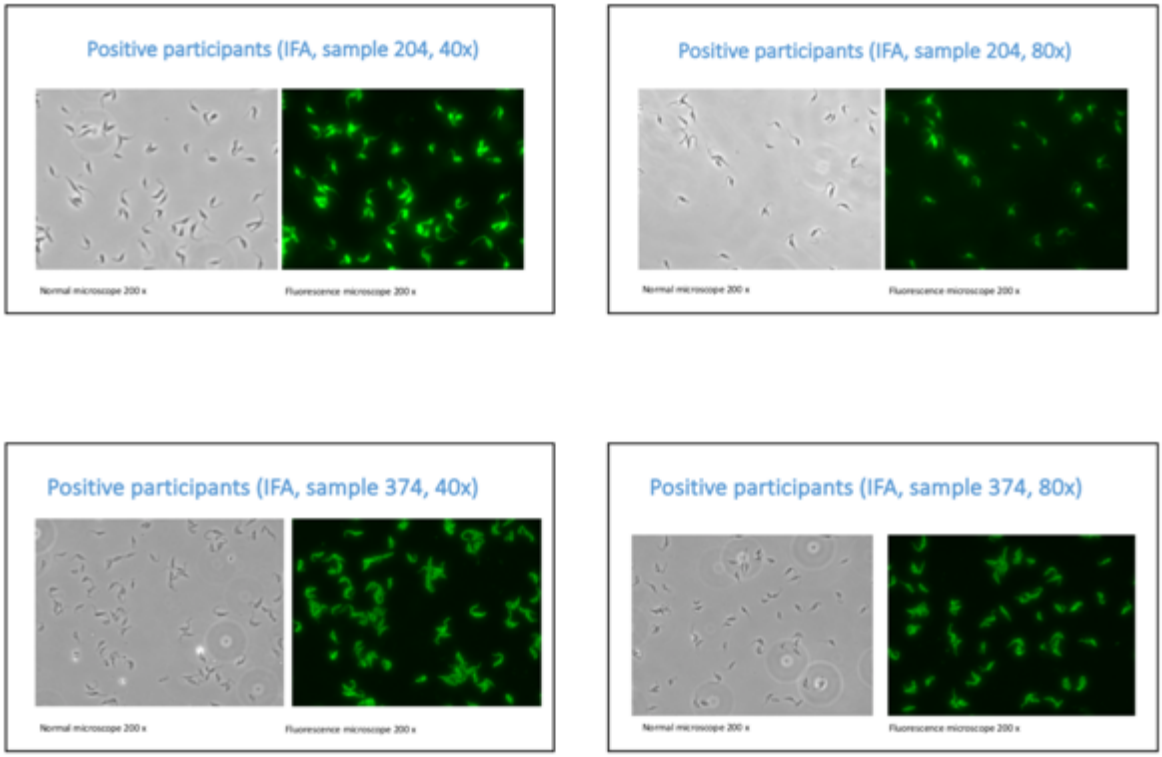

Figure 16. IFA result of positive participants (III).

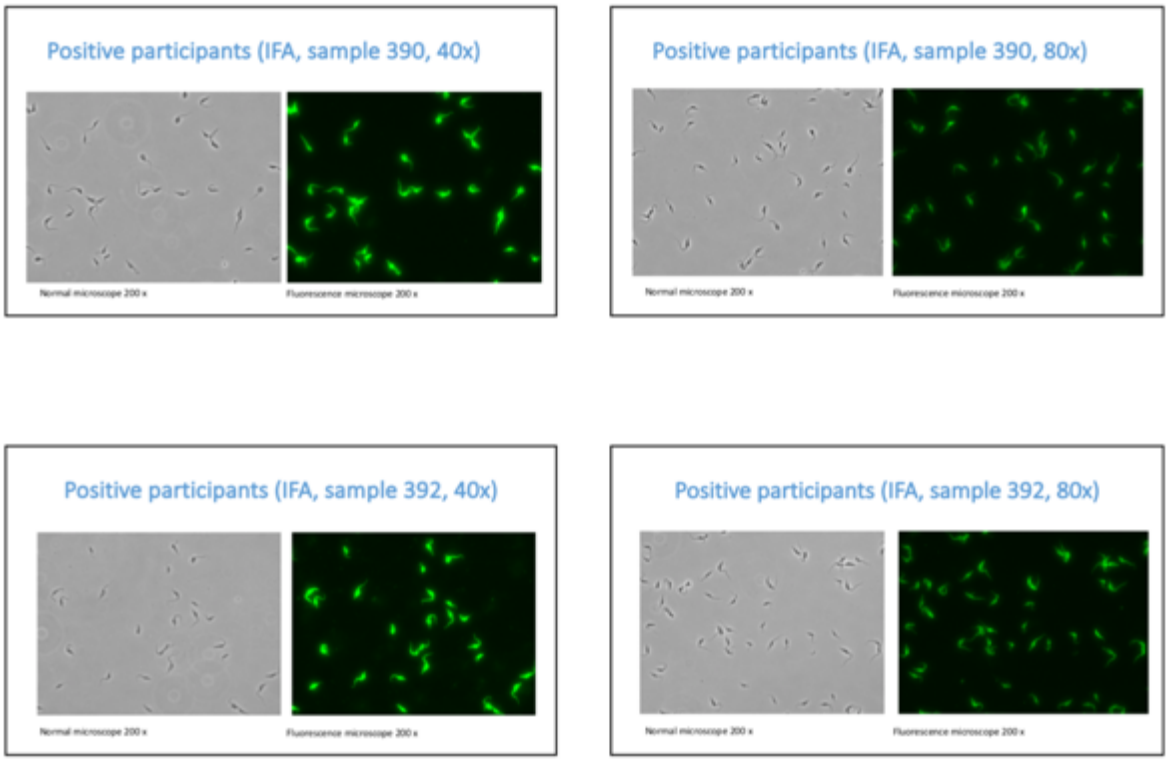

Figure 17. IFA result of positive participants (IV).

Figure 18. ELISA results.

Table 15. ELISA-2 results.

	374	392	Positive control	Negative control
ELISA-2	0.243	3.421	1.813	0.123

8.3. Characteristics of positive participants

The characteristics of positive participants are summarized in the Table 16. The positive participants age ranges from 45 and 69 years old. Four (n=57.1%) were female and three males (n=42.8%). All had secondary education. They were all born in Bolivia (Santa Cruz) and had been in Japan for more than ten years. Three them have been tested before (two of them in Bolivia and one in Japan), but they had never consulted a doctor.

All participants knew about CD. Nearly 60% had lived in rural areas of Santa Cruz (57.1%, n=4) and less than half (42.8%, n=3) had lived in a mud house. Forty-two percent had seen the triatome bug at home and had a relative affected by CD (42.8%, n=3). None had received blood in the past. Three (42.8%, n=3) had a relative affected by CD. Two of the positive participants were second line relatives, although their CD seropositivity was unknown at the time of participation.

Two participants had a history of blood donation (28.5%, n=2), and one recalled that it was in Bolivia. All women participants had children, and screening was recommended for the children. However, just one family came to the venue with the purpose of screening the children (n=3), who were negative for *T. cruzi* by standard diagnosis and RDT.

Just one of the positive participants commented symptomatology (digestive disorders), and the rest referred to be asymptomatic.

Table 16. Characteristics of the positive participants.

	74	75	93	96	204	390	392
Age	45	55	69	59	43	47	41
Gender	Male	Female	Male	Male	Female	Female	Female
Time in Japan	>10 years	>10 years	>10 years	>10 years	>10 years	>10 years	>10 years
Heard about CD	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Seen triatome	No	Yes	Yes	Yes	Yes	No	No
Mud house	No	Yes	Yes	Yes	No	No	No
Rural area	No	Yes	No	No	Yes	Yes	Yes
Have a relative with CD	No	Yes	No	No	Yes	No	Yes
Symptomatology	Digestive	No	No	No	No	No	No
Blood donor	No	No	Yes	Yes	No	No	No
Women with children		Yes			Yes	Yes	Yes

CD, Chagas disease.

Table 17 show the differences between the total participants, Bolivians, and the positive participants.

Table 17. Description summary of Latin American migrants (n=428), Bolivian migrants, (n=132) and positive participants (n=7).

		Total (n=428) N/mean(%/SD)	Bolivian (n= 132) N/mean(%/SD)	Positives (n=7) N/mean(%/SD)
Socio-demographic characteristics				
Age		43.5 (13.6)	41.62 (13.9)	51 (10.16)
Gender	Male	177 (41.36%)	59 (44.70%)	3 (42.86%)
	Female	251 (58.64%)	73 (55.30%)	4 (57.14%)
Education level	Primary	26 (7.05%)	6 (5.77%)	-
	Secondary	196 (53.12%)	53 (50.96%)	7 (100%)
	University	147 (39.84%)	45 (43.27%)	-
Length of stay in Japan	< 5 years	72 (17.31%)	18(14.52%)	-
	5-10years	40 (9.62%)	19(15.32%)	-
	> 10years	304 (73.08%)	87 (70.16%)	7 (100%)
Chagas disease risk factors				
Have you ever heard about CD?	Yes	312 (74.29%)	107 (82.95%)	7 (100%)
	No	108 (25.71%)	22 (17.05%)	-
Have you ever seen this insect?	Yes	144(34.20%)	62(47.69%)	4 (57.14%)
	No	277(65.80%)	68 (52.31%)	3 (42.86%)
Have you seen it at home?	Yes	44 (10.45%)	26 (19.85%)	3 (42.86%)
	No	377 (89.55%)	105 (80.15%)	4 (57.14%)
Had you been lived in rural area?	Yes	170 (40.96%)	57 (44.53%)	4 (57.14%)
	No	245 (59.04%)	71 (55.47%)	3 (42.86%)
Had you lived in a mud house in Latin America?	Yes	72 (19.73%)	36 (31.58%)	3 (42.86%)
	No	293 (80.27%)	78 (68.42%)	4 (57.14%)

Do you have in your family any member affected by CD?	Yes	54 (12.92%)	27 (21.09%)	3 (42.86%)
	No	364 (87.08%)	101 (78.91%)	4 (57.14%)
Have you received blood in Latin America countries?	Yes	18 (4.27%)	8 (6.25%)	-
	No	404 (95.73%)	120 (93.75%)	6 (100%)
Risk of transmission				
Women with children (women answer)	Yes	187 (77.59%)	55 (78.57%)	4 (100%)
	No	54 (22.4%)		-
People who have donated blood	Yes	126 (29.58%)	97 (74.62%)	2 (28.57%)
	No	300 (70.42%)	33 (25.38%)	5 (71.43%)
Vigilance and policies				
Lived in another country	Yes	78 (18.22%)	26 (20.47%)	1 (14.29%)
	No	334 (78.04%)	101 (79.53%)	6 (85.71%)
Tested for CD before	Yes	16 (3.74%)	11 (8.33%)	3 (42.86%)
	No	412 (96.26%)	121 (91.67%)	4 (57.14%)
Treated for CD before	Yes	1 (0.25%)	1 (0.83%)	-
	No	400 (99.75%)	120 (99.17%)	0 (100%)

CD, Chagas disease.

8.4. Analysis of factors associated with positive cases

The factors associated with having a positive *T. cruzi* results by the standard diagnosis were: having been born in Bolivia, having done the CD test in the past, having seen the triatome bug at home, and having a relative affected by CD (Table 18).

Table 18. Factors associated with Chagas disease positive result.

	Sero-positive n (%)	Sero-negative n (%)	p-value
Age			
0-20	0 (0)	31 (7.49)	0.1951

21-40	0 (0)	132 (31.88)	
41-60	6 (85.71)	206 (49.76)	
61 or more	1 (14.29)	45 (10.87)	
Gender			
Male	3 (42.86)	174 (41.33)	0.6848
Female	4 (57.14)	247 (58.67)	
Education			
Primary	0 (0)	26 (7.12)	0.2613
Secondary	4 (100)	192 (52.60)	
University	0 (0)	147 (40.27)	
Country of origin			
Brazil	0 (0)	195 (46.32)	**0.0022**
Bolivia	7 (100)	125 (29.69)	
Peru	0 (0)	70 (16.63)	
Others	0 (0)	31 (7.36)	
Time in Japan			
< 5 years	0 (0)	72 (17.60)	0.5354
5-10 years	0 (0)	40 (9.78)	
> 10 years	7 (100)	297 (72.62)	
Have done CD test before			
Yes	3 (42.86)	13 (3.09)	**0.0014**
No	4 (57.14)	408 (96.91)	
Lived in rural area			
Yes	4 (57.14)	166 (40.69)	0.3074
No	3 (42.86)	242 (59.31)	
Lived in mud house			
Yes	3 (42.86)	69 (19.27)	0.1414
No	4 (57.14)	289 (80.73)	
Heard about CD			
Yes	7 (100)	305 (73.85)	0.1227
No	0 (0)	108 (26.15)	
Have seen the triatome			
Yes	3 (42.86)	141 (34.06)	0.4496
No	4 (57.14)	273 (65.94)	
Have seen the triatome at home			
Yes	3 (42.86)	41 (9.90)	**0.0277**
No	4 (57.14)	373 (90.10)	
Have a relative affected by CD			
Yes	3 (42.86)	51 (12.41)	**0.0489**
No	4 (57.14)	360 (87.59)	
Have donated blood in the past			
Yes	2 (28.57)	124 (29.59)	0.6635
No	5 (71.43)	295 (70.41)	
Have received blood donation			
Yes	0 (0)	18 (4.33)	0.7686
No	6 (100)	398 (95.67)	

8.5.Clinical data

At the time of this writing, clinical data was not possible to obtain from any of the positive participants due to the cessation of follow-ups. During the research period, two out of seven positive participants never answered the phone after multiple phone calls. The rest answered, but just two attended the health institution.

The distance between participant's hometown and the health facilities ranged between 187 and 26 km, with a mean distance of 111 km (SD. 63.02). Just two positive participants visited the assigned health care facility. The patients that attended the visits typically had a shorter distance between their hometown and the health facilities. After more than six months in the follow-up, they give up the health care visits. The principal reasons expressed to stop the follow-ups were: 1) delays in the follow-up due to compartmentalization of examination in numerous visits, 2) influence of the follow-up in the job activity due to the number of visits, 3) absence of information about the treatment by the doctor, 4) bureaucratic delays involved in the treatment access, and 5) COVID-19 pandemic influence. After the barriers referred to by the participants, I decided to refer to a new doctor/hospital and insisted on the importance of the follow-up, but the participants didn't attend.

8.6.RDT/standard diagnosis

RDT was conducted in all the participants (n=428). The image in Figure 19 was taken during the data collection after conducting a RDT with a positive result. Compared with the standard diagnosis the agreement was 100% with a Kappa value of 1 (p value=1).

Figure 19. Image of a positive result by RDT (Chagas Detect™ Fast ELISA kit, InBios).

In comparison with the standard diagnosis, the sensitivity and specificity of the RDT of Inbios was 100% (CI 95%. 59.04-100%) and 100% (CI 95%. 99.13%-100%) (Table 19).

Table 19. Two by two table of positive participants results classification by using the Rapid Diagnosis Test of Inbios and the standard diagnosis.

	Standard diagnosis		
RDT of Inbios	**Positive**	**Negative**	**Total**
Positive	**7**	**0**	**7**
Negative	**0**	**428**	**428**

RDT. Rapid diagnosis test

8.7. Cost-effectiveness

In the base-case analysis, the first-year cycle started with a population of 100,000 LA migrant population, and 1.7% (n=1,700) of them were infected with *T. cruzi*. Most (85.8%, n=1,458.6) were asymptomatic, and 14.1% (n= 205.66) were in a cardiac asymptomatic state. In the screening model, 80% of the asymptomatic LA migrant population (n=79,806.88) successfully accessed the screening.

Figure 20 shows the number of individuals in the five health states for the screening and non-screening model along the time. It can be observed that the number of people in the indeterminate form has declined over time. In the screening model the indeterminate line is discontinuous because 20% of individuals would seroconvert 5 years after finished the treatment (year 5) and pass to the state of "respond to treatment". The number of individuals with the cardiac form was higher in the no-screening model at all timepoints. The graph shows that the number of deaths in the no-screening model has a faster increase over time.

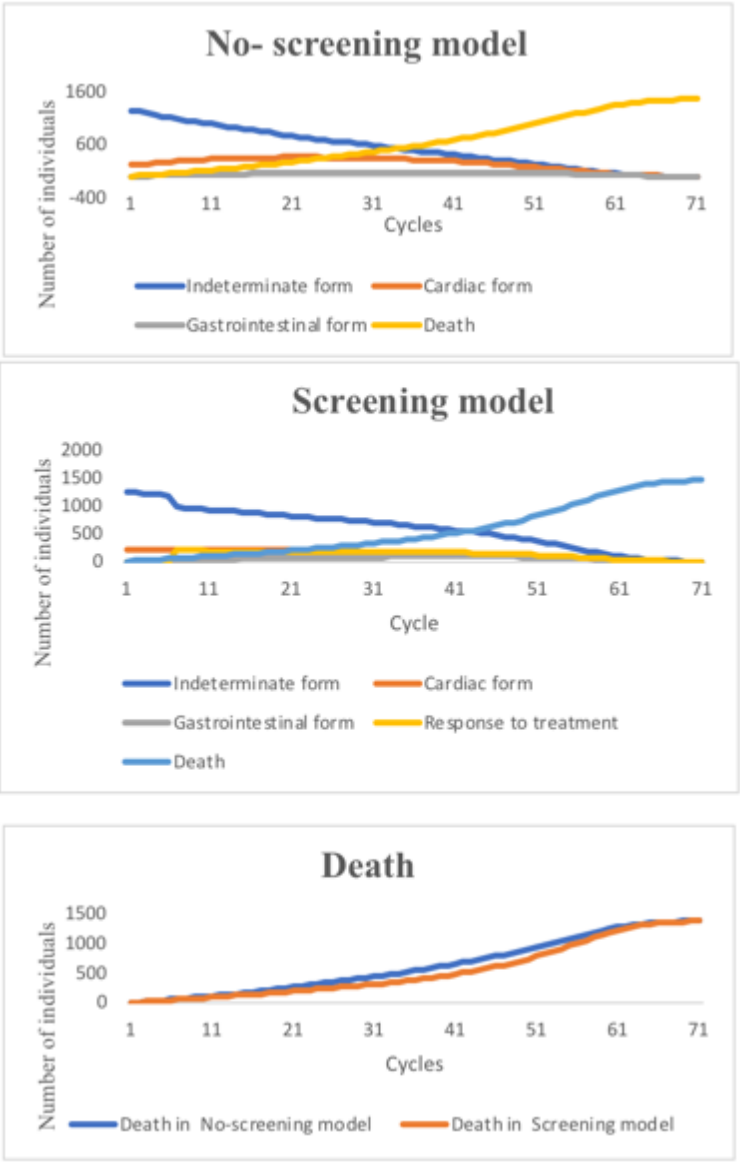

Figure 20. Number of individuals in each state along the cycles in the Markov model.

Table 20 summarizes the results of the deterministic and probabilistic cost-effectiveness studies. We show the cost in the base case: societal perspective and health care perspective. On one hand, from the societal perspective, the cost of the screening model was 14,390,595,018 JPY, whereas this was 13,840,660,990 JPY in the no-screening model, with an incremental cost of 549,934,028 JPY. The respective number of QALYs gained in the screening was 37,646.46 and, in the no-screening was 33,546.98. The incremental cost-effectiveness ratio (ICER) was 134,147 JPY. On the other hand, in the deterministic analysis for the health care perspective, the cost of the screening model was 1,188,513,168 JPY, and this was 367,303,765 JPY in the no-screening model, with an incremental cost of 821,209,403 JPY. The number incremental QALYs was 4099.48. The ICER in the health care perspective was 200,320 JPY.

The PSA showed that screening strategy is more cost-effective than the non-screening strategy in both, the societal and health care perspective.

Deterministic model						Probabilistic model		
Base case			**Incremental**			**Probability of cost-effectiveness at willingness to pay (YEN/QALY)**		
Societal perspective	**Costs (YEN)**	**QALYs**	**Costs**	**QALYs**	**ICER**	**2,500,000**	**5,000,000**	**7,500,000**
Screening	14,390,595,018	37,646.46	549,934,028	4099.48	134,147	100%	100%	100%
No screening	13,840,660,990	33,546.98						
Health care payer perspective	**Costs (YEN)**	**QALYs**	**Costs**	**QALYs**	**ICER**	**2,500,000**	**5,000,000**	**7,500,000**
Screening	1,188,513,168	37,646.46	821,209,403	4099.48	200,320	100%	100%	100%
No screening	367,303,765	33,546.98						

Table 20. Deterministic and probabilistic results of cost-effectiveness analysis for the screening of *Trypanosoma cruzi* in asymptomatic adult Latin American migrants living in Japan at the primary health-care level.

The cost-effectiveness plane (Figure 21. ICER scatter plot) shows the differences in costs and effects between the screening and no-screening model from the health care perspective. The QALYs gained by the screening strategy in comparison with the no-screening are represented on the x-axis and the incremental costs are represented on the y axis. All simulated dots are below and to the right of the threshold limit, showing that the screening model, in comparison to the no-screening model, is more cost-effective.

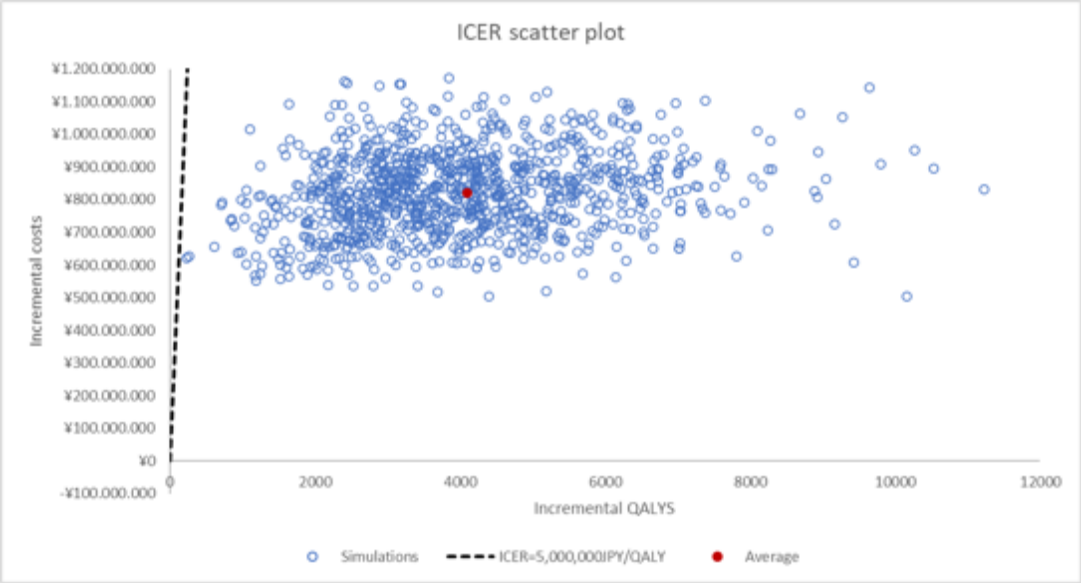

Figure 21. Incremental cost-effectiveness ratio (ICER) scatter plot.

The cost-effectiveness acceptability curve of the health care perspective in Figure 22 (CEAC) shows that the probability that the screening model was more cost-effective than the no-screening, and rapidly rose from zero to 62% when the WTP increased more than 250,000 per QALY gained. Considering that Japan has a WTP of 5,000,000 JPY per QALY, the screening strategy will be 100% cost-effective from the health care perspective.

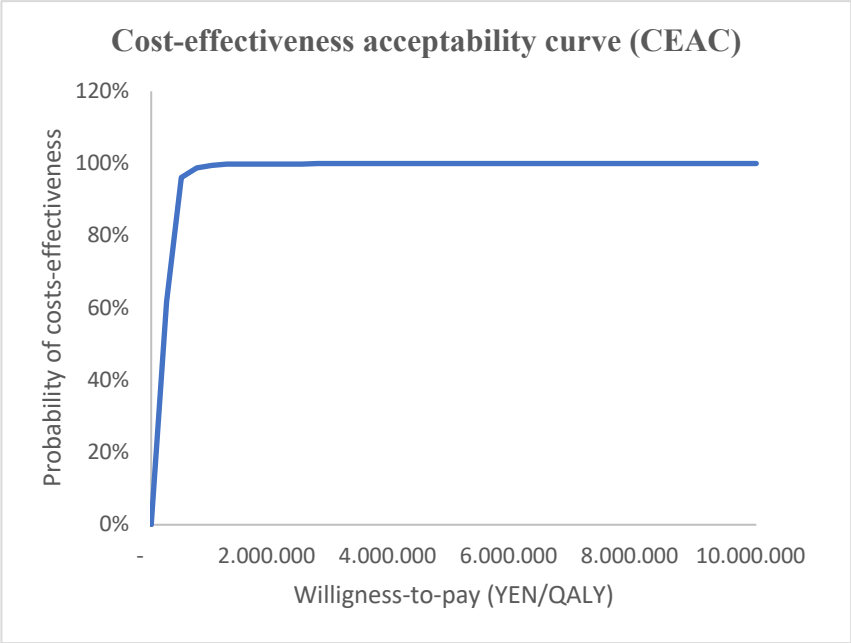

Figure 22. Cost-effectiveness acceptability curve (CEAC).

8.7.1. Univariate analysis

In the univariate sensitivity analysis, the strongest influences on the ICER were a decrease in the utilities of indeterminate and cardiac, the probabilities of response to the treatment, being asymptomatic at the starting point, being asymptomatic and in the indeterminate form at the starting point, probability of being screen in the screening model, and the prevalence of CD. With a 99% drop in these parameters, the intervention would no longer be cost-effective (Figure 23).

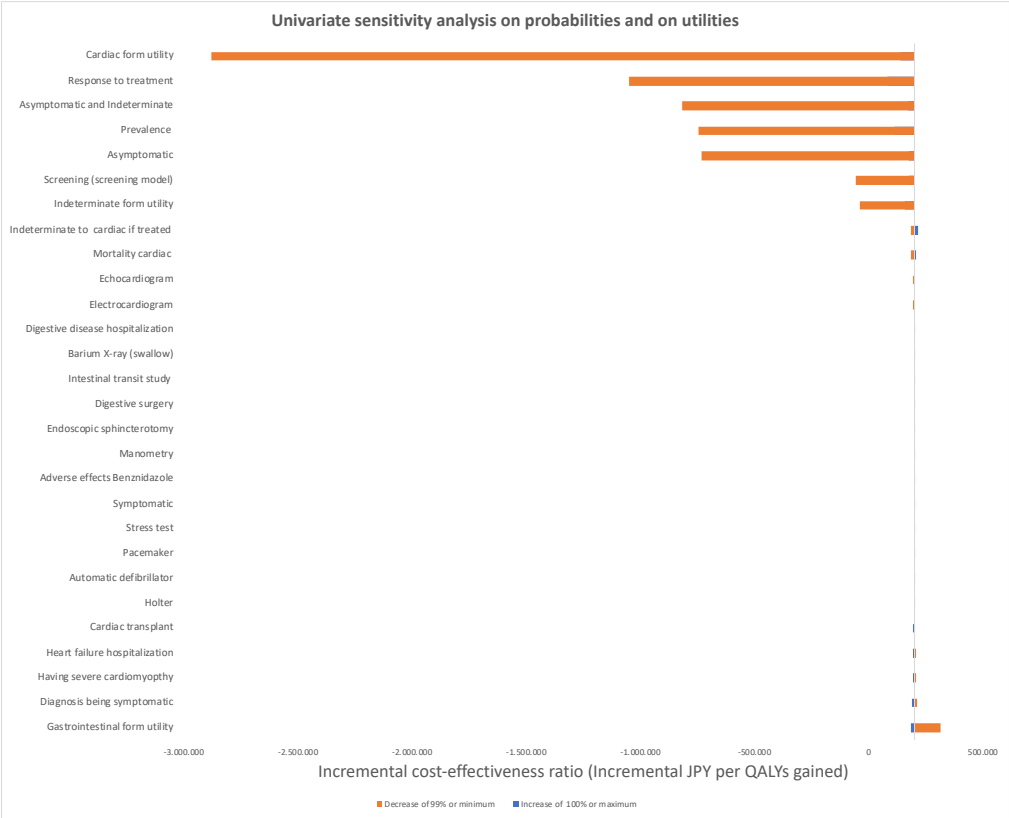

Figure 23. Univariate sensitivity analysis on probabilities and on utilities

CD, Chagas disease.

An increase or decrease in the costs would not change the choice from screening to not screening. However, the ICER was sensitive to the costs of the serology, electrocardiogram, first medical visit in PHC, follow-up medical visit, benznidazole therapy, and translators. The rest of the utilities and costs had a minimum effect on the ICER (Figure 24).

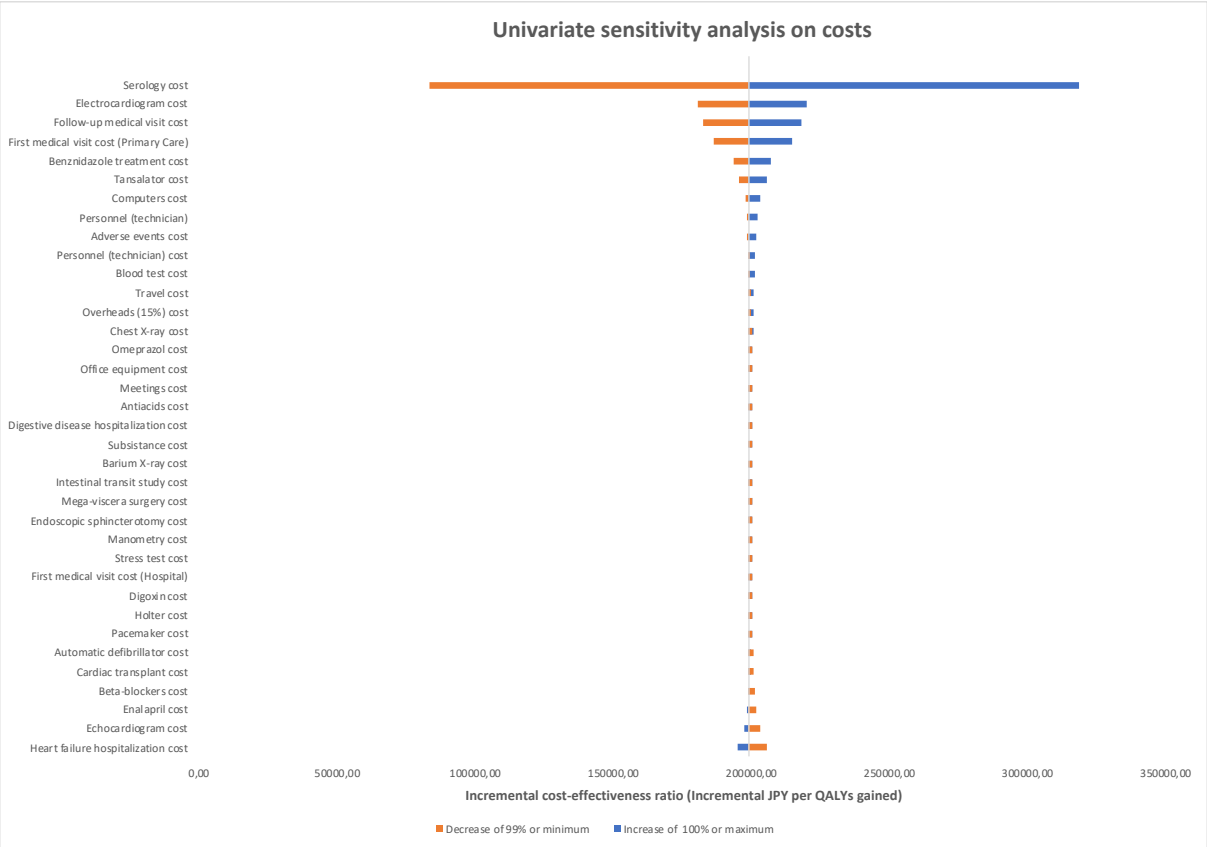

Figure 24. Univariate sensitivity analysis on costs.

8.7.2. Threshold sensitivity analysis of the incremental cost-effectiveness ratio (ICER)

Figure 25 shows that the screening model will be more cost-effective than the non-screening model until a prevalence of 0.43%. A drop in the prevalence below 0.34% will influence the ICER and the screening model will not be cost-effective (ICER=6,113,678.57 with 0.34%).

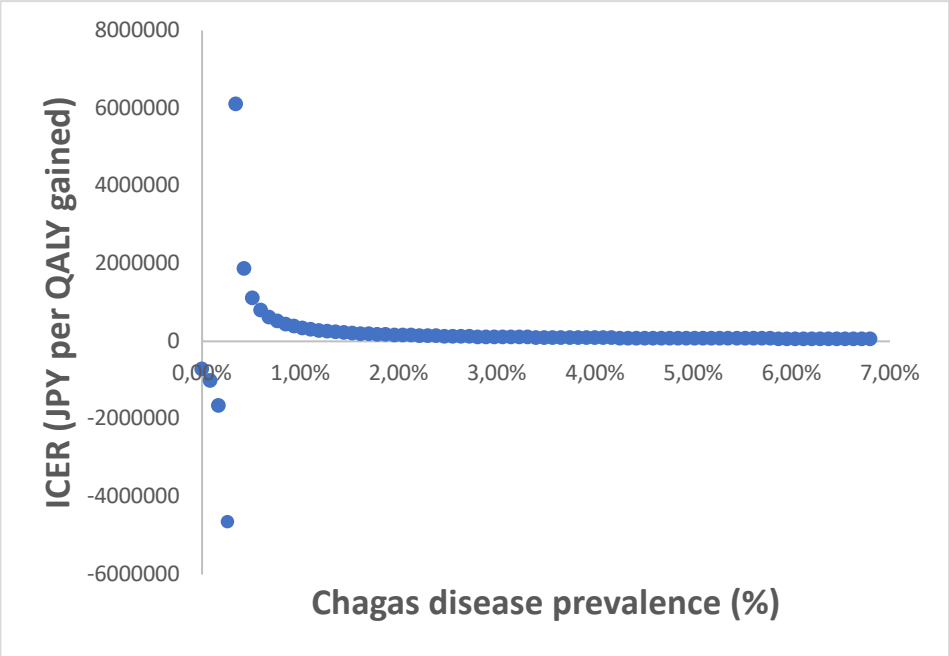

Figure 25. Relationship between ICER and Chagas disease prevalence.

A drop in the screened people below 30% will affect negatively the ICER and the screening model will not be cost-effective (Figure 26).

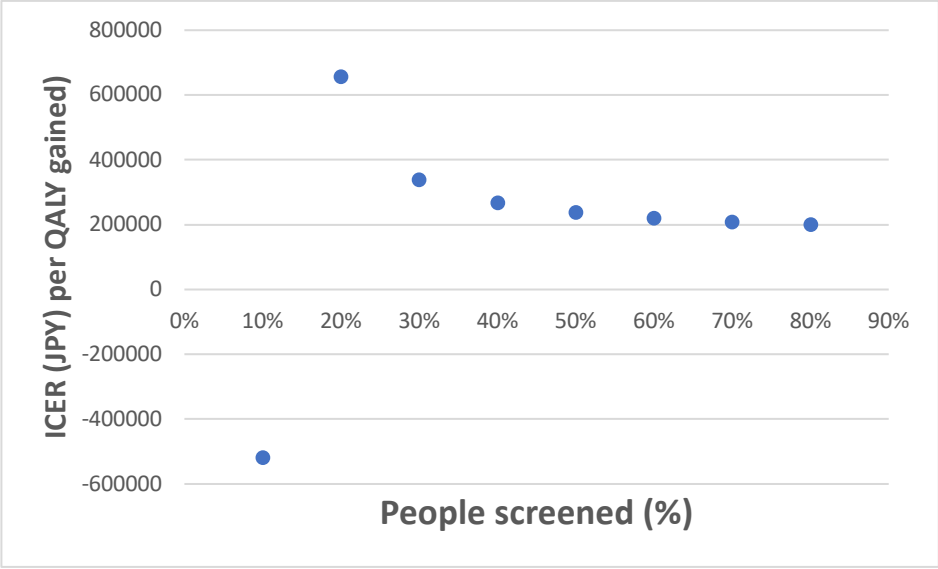

Figure 26. Relationship between ICER and screened people.

Figure 27 shows that the screening model will be cost-effective even if the number of symptomatic people diagnosed with CD drops to 0% in the non-screening model.

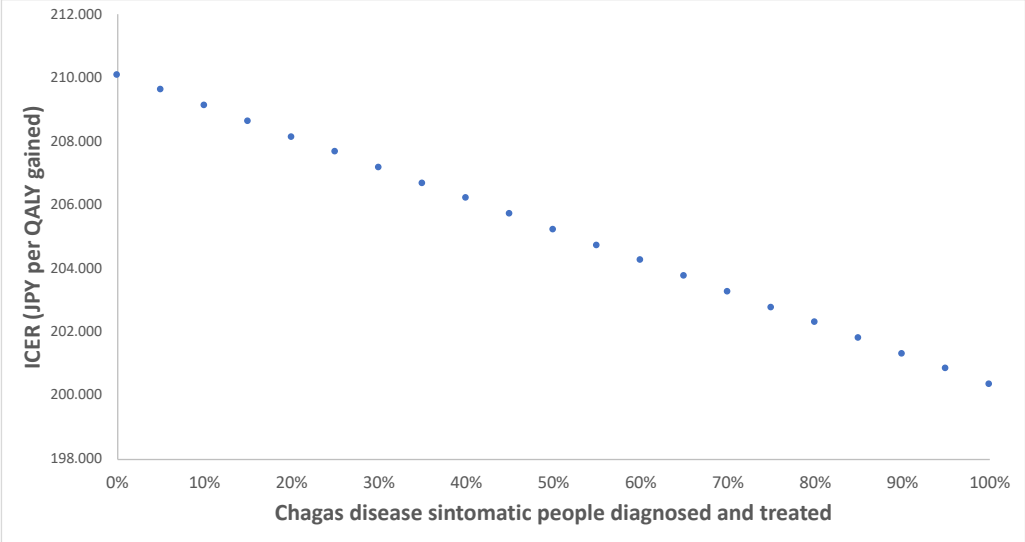

Figure 27. Relationship between ICER and Chagas disease symptomatic people diagnosed and treated.

8.8.Accessibility to the Japanese health system

I included 390 participants from the cohort after excluding participants not born in Latin America and participants under 18 years old.

8.8.1. Predisposing factors

The responders had a mean age of 45 years old (SD 11.7), of which roughly 60% were women. More than half had obtained secondary education (54.6%). Nearly half (49.7%, n=194) came from Brazil, followed by Bolivians (31.5%, n=123), and Peruvians (17.6%, n=69). Just 1% (n=4) came from other LA countries. Seventy-four percent had been in Japan for more than a decade (n=280).

8.8.2. Enabling factors

8.8.2.1. Job conditions

Most of the responders work a full-time job (67.6%, n=246) and had remained in the same company for more than 3 years (63.5%, n=183). The rate of unemployment was 8% of the responders unemployed (7.42%, n=27) and most were women (88.89%, p-value=<0.0001 (Table 21). Most responders worked in industry, construction, or manufactoring (n=59.4%, n=157).

Table 21. Work condition by gender in Latin American migrants in Japan.

		Full time	Part time	Self-employment	Unemployment	Student	Retired	Total	P-value
Males	n (%)	123 (50%)	9 (19.15%)	13 (41.94%)	3 (11.11%)	2 (33.33%)	4 (57.14%)	154 (42.31)	<0.0001
Females	n (%)	123 (50%)	38 (80.85%)	18 (58.06%)	24 (88.89%)	4 (66.67%)	3 (42.8%)	210 (57.69)	

8.8.2.2. Health insurance

Most responders were insured (93.52%, n=361), and most commonly EHI or NHI. However, more than 5% of the responders were uninsured. Nearly 40% (36.4% n=87) of the full-time employees were receiving NHI instead of the corresponding EHI (Table 22).

More than half of the responders thought that the cost of health insurance was expensive for them (55.74%, n=204). Nevertheless, most of the responders paid the health insurance regularly (96.6%, n=346).

Table 22. Sources of health insurance in Japan for Latin American migrants based on their employment situation.

	Employees health insurance	National health insurance	Late Elders' Health Insurance	Others	P-value
	n (%)	n (%)	n (%)	n (%)	
Full time	130 (54.39%)	87 (36.40%)	2 (0.84%)	20 (8.37%)	<0.0001
Part time	20 (43.48%)	26 (56.52%)	0 (0.00%)	0 (0.00%)	
Self-employment	9 (30.00%)	21 (70.00%)	0 (0.00%)	0 (0.00%)	
Others (unemployed, student, retired)	5 (14.29%)	22 (62.8%)	3 (8.57%)	5 (14.29%)	
Total	164 (46.86%)	156(44.57%)	5 (1.43%)	25 (7.14%)	

8.8.2.3. Health system

In general, 88% (n=326) of the responders were satisfied with the care received in the Japanese Health Institutions and they perceive that they have good access to the health system (85.9%, n=323). However, almost 25% of the responders needed to see a doctor during the last year and they did not for some reason (24%, n=90) (Table 23).

Most of the responders received information about the health system in Japan from the City Hall/Government or a relative (35.9%, n=135). Less than 40% of the responders have a family doctor as a referent (36.7%, n=141) (Table 23).

8.8.2.4. Communication in Japanese

Nearly half of the responders needed a Japanese translator during the visit to the health facilities and the lack of fluency in Japanese limited their access to the health system in 36% of the responders. Most of the responders that needed to make use of translators were satisfied with their work. However, nearly 20% were not satisfied with the translations (Table 21).

8.8.3. Need factors

Most responders self-assessed their health status in good condition (75.07%, n=286), and just 14.5% suffer from a chronic illness (Table 21).

Table 23. Predisposing, enabling, need factors, satisfaction of the health system and access to the health system (adults migrants born in Latin American migrants living in Japan). N=390

Variables		n/mean	%/SD	NR
Predisposing factors				
Age		45	11.71	7
Education	Primary	16	4.77%	55
	Secondary	183	54.62%	
	University	136	40.59%	
Gender	Male	159	40.76%	0
	Female	231	59.23%	
Time in Japan	<5 years	64	16.93%	12
	5-10 years	34	8.99%	
	>10 years	378	74.07%	
Enabling factors				
Occupation	Industry, construction or manufactory	157	59.47%	126
	Education	8	3.03%	
	Translator	4	1.52%	
	Housekeeper (unpaid)	16	6.06%	
	Housework and care (paid)	7	2.65%	
	Health and science	8	3.03%	

	Busyness/autonomous	4	1.52%	
	Other	60	22.73%	
Work condition	Full time	246	67.58%	26
	Part time	47	12.91%	
	Self-employment	31	8.52%	
	Unemployed	27	7.42%	
	Student	6	1.65%	
	Retired	7	1.92%	
Years employed by the current employer	0-2	105	36.46%	102
	3 or more	183	63.54%	
Term of contract with the company (months)	1-2	45	16.42%	116
	3-6	55	20.07%	
	7-24	86	31.39%	
	No written contract	88	32.12%	
Do you have HI in Japan?	No	25	6.48%	4
	Yes	361	93.52%	
Insurance type	Employees Health Insurance	173	47.01%	22
	National Health Insurance	162	44.02%	
	Late Elders' Health Insurance	6	1.63%	
	Others	27	7.34%	
Insurance payment	Regular	346	96.65%	32
	Irregular	12	3.35%	
Do you think that the cost of HI is expensive for you?	No	162	44.26%	24
	Yes	204	55.74%	
How did you receive information about the HS in Japan?	Relative	112	29.79%	14
	Friend	37	9.84%	
	City Hall/Government	135	35.90%	
	Others	55	14.63%	
	Still don't have information	15	3.99%	
	More than one source	22	5.85%	
Do you need of Japanese language interpreter during visit	No	194	50.79%	8
	Yes	188	49.21%	

to health facilities (including a relative)?				
Are you satisfy with the translation of language interpreters?	No	54	19.29%	110
	Yes	226	80.71%	
The fact that you can't communicate limit your access to the doctor?	No	225	64.10%	39
	Yes	126	35.90%	
Do you have a referent doctor of routine as family doctor?	No	243	63.28%	6
	Yes	141	36.72%	
Satisfaction of the Health System				
Are you satisfied with the care received in Japanese Health Centers?	No	44	11.89%	20
	Yes	326	88.11%	
Potential access and Unmet utilization or realized access of Health System				
Do you think that you have a good access to a doctor /health worker?	No	53	14.10%	14
	Yes	323	85.90%	
In the past year, needed to see a doctor/health worker, but didn't?	Yes	90	24.00%	15
	No	285	76.00%	
Need factors (perceived illness)				
Self-rated health status	Good/very good/excellent	286	75.07%	9
	Poor/fair	95	24.93%	
Do you have any chronic disease?	No	325	85.53%	10
	Yes	55	14.47%	

HI: Health Insurance; HS: Health system; NR. Non-responders

8.8.4. Access to the health care system

In the multivariable regression model (Table 24), the following predisposing and enabling factors were significantly associated with access to health care. None of the need factors were found significant.

Predisposing factors. Females LA migrants were at higher risk to not visit a doctor or health worker when in need (OR=2.30; CI 1.13-4.7). On the other hand, people that live in Japan for more than ten years are less likely to not visit the health facilities when in need (OR=0.31; CI. 0.10-0.91).

Enabling factors. The people that received information about the health system from the city hall or government were less likely to perceive worse access to the health system (OR=0.13; CI 0.02-0.64). However, the migrants whose communication in Japanese is a barrier and the migrants who are not satisfied with the health system were more likely to perceive worse access to the health system (OR=3.53; CI.1.37-9.09 and OR=10.06; CI 3.2-31.72, respectively) and they also do not see a doctor/health worker when they needed it (OR= 2.16, CI 1.03-4.52 and OR=10.06, CI 3.2-31.72, respectively).

Table 24. Factors associated with access to health care among adult migrants born in Latin America living in Japan.

		Perceived worse access to a doctor/health worker (N=390)			**Needed to see a doctor/health worker, but did not (N= 390)**		
Variables		OR	95%CI	p value	OR	95%CI	p value
Predisposing factors							
Age		2.14	0.20-22.50	0.465	3.09	0.42-22.53	0.323
Gender	Male	Ref.					
	Female	1.11	0.46-2.68	0.809	2.30	1.13-4.7	**0.021**

Education	Primary	Ref.					
	Secondary	0.26	0.042-1.67	0.158	3.57	0.26-48.46	0.339
	University	0.30	0.04-2.11	0.231	3.44	0.24-49.10	0.361
Length of stay in Japan	5-10 years	Ref.					
	>10 years	0.36	0.09-1.43	0.146	0.31	0.10-0.91	**0.034**
	<5 years	0.16	0.02-1.00	0.050	0.34	0.09-1.25	0.105
Enabling factors							
Employment status	Full-time (and self-employed)	Ref.					
	Part-time	1.36	0.39-4.76	0.626	0.54	0.18-1.59	0.266
	Student	0.99	0.04-22.45	0.995	0.44	0.02-7.81	0.578
	Others (unemployed and retired)	4.32	0.92-20.27	0.062	0.30	0.05-1.60	0.106
Considered insurance expensive	Yes	Ref.					
	No	2.09	0.76-5.77	0.151	0.62	0.30-1.29	0.202
Insurance Payment	Regular	Ref.					
	Irregular	0.83	0.14-4.74	0.830	1.00	0.17-5.72	0.995
Source of information about the health system	Friend	Ref.					
	Relative	0.44	0.11-1.66	0.225	0.50	0.16-1.58	0.241
	City hall/government	0.13	0.02-0.64	**0.012**	0.48	0.15-1.52	0.212
	Others	0.75	0.17-3.32	0.704	0.68	0.18-2.50	0.562
	Still no information	0.52	0.07-3.70	0.516	1.78	0.26-12.16	0.553
	Combined	0.55	0.06-4.89	0.593	0.78	0.12-4.85	0.797
Limitation in access due to	No	Ref					
	Yes	3.53	1.37-9.09	**0.008**	2.16	1.03-4.52	**0.039**

communication barrier							
Health system satisfaction	Yes	Ref.					
	No	10.06	3.2-31.72	**<0.0001**	10.06	3.2-31.72	**0.006**
Need factors							
Self-rated health status	Good/very good/excellent	Ref.					
	Poor/fair	0.72	0.25-2.05	0.540	1.18	0.53-2.63	0.681

9. Discussion

This is the first large-scale study outside of blood banks to assess the prevalence of CD in Japan. The CD observed prevalence in the study (1.6%) was double the estimated prevalence (0.75%). It also exceeds the prevalence found in blood donors from LA in a blood bank study in Japan (0.017%) (Sayama et al. 2019). As it was described in previous studies, the blood donor prevalence is influenced by selection bias, and as a result, used to underestimate the prevalence (ElGhouzzi et al. 2010; Prion et al. 2008; Kitchen, Hewitt & Chiodini 2012; Custer et al. 2012; Brien et al. 2013).

The data reported about CD in Japan, outside of blood banks, was limited to a few cases reports of symptomatic patients (Imai et al. 2019; Imai et al. 2014; Satoh et al. 2010; Imai et al. 2015). Therefore, this might be the tip of the iceberg due to the silent and chronic profile of CD in most of the infected people in non-endemic countries.

Previous research showed an alarming level of underdiagnoses in Japan, situating it as one of the non-endemic countries with a higher level of underdiagnoses for CD (Imai et al. 2019). In Europe the level of underdiagnoses is less than 10%, whereas in Japan less than 0.2% of the

affected people for CD reach the diagnosis and treatment (Instituto de Salud Global 2017; Imai et al. 2019). According to the results, the level of underdiagnoses could be larger. Therefore, a system for CD is a priority that Japan cannot continue neglecting. This is not just the most humanitarian response, but also the most cost-effective. This study demonstrated that the screening of asymptomatic adult LA migrant population is a cost-effective strategy. The study supports that the implementation of *T. cruzi* screening programs at the PHC level might be considered as a strategy to increase the diagnosis and treatment of CD.

9.1. Screening system of asymptomatic adults at risk of CD in Japan from PHC

There is clear consensus that the early diagnostic and treatment should be provided within a primary health care setting, with referrals to a secondary or tertiary care facilities only when necessary (Pinazo & Gascón 2020; Sosa-Estani et al. 2021; Echeverría et al. 2020; Nunez et al. 2018). PHC contains the essential characteristic required to overcome the inherent difficulties associated with a multidisciplinary problem, such as CD, where the socio-cultural factors play an important role in the diagnosis and follow-up. PHC is not just the most affordable resource in a health system, it is the most accessible to the population facilitating the connection of individuals with their community and their environment (WHO 1978). Even though in Japan the currently diagnosed cases of CD are still exclusively followed and treated in secondary and higher levels (Imai et al. 2019). Considering that most of the LA migrant population live in rural areas of Japan with constraining job schedules, keeping the current structure contributes to the maintenance of barriers for reaching the population at risk. Spain, one of the non-endemic countries with more policies for CD and better control of the disease, supports a system of screening from PHC with a published guideline for the follow-up from PHC level in non-symptomatic patients (Roca Saumell et al. 2015). Japan has not developed a

strong PHC level and has a weak connection between levels, despite Japan having a good public health system in charge of conducting periodically official screenings systems in the population in the public health centers. These centers count on primary health care professionals and can be a good alternative for the screening of CD.

Although Japan has a good system of annual health check-ups in the workplace, CD screening in the employment setting should be avoided because it could lead to potential discrimination towards LA migrants. Discrimination related to the employment setting and mistreatment has been reported in endemic and non-endemic areas (Ventura et al. 2013; Sanmartino 2009; Sanmartino et al. 2015). Nowadays, Argentina has a law that prohibits the screening of CD in workplaces to avoid employment-related discrimination (Gobierno de Argentina 2007). Following the principle of non-maleficence in medicine ("primum non nocere"), CD programs should avoid any risk of human rights abuse or discrimination.

Therefore, I conducted the cost-effectiveness analysis following the current recommendations where the screening of asymptomatic adult individuals at risk of CD will be done from PHC (Takamura 2015; Kato et al. 2019). Based on the results and the current international recommendations, I believe that Japan will benefit from the development and empowerment of PHC for CD control. Therefore, the inclusion of PHC as coordinator of a future system for CD, screening and providing care to the asymptomatic individuals at risk of CD.

9.2. Positive cases

According to the results, all positive participants were from a single country, Bolivia, and from the same district, Santa Cruz. In addition, one of the factors associated to have a positive

result for CD is being born in Bolivia (p value= 0.0022). This result was expected because Bolivia has the highest prevalence of CD worldwide (6.1%) and most of the cases reported in non-endemic countries and migrants in non-endemic countries are in the Bolivian population (WHO 2015; Salvador et al. 2013). In the study, the prevalence increases to 5.3% in the Bolivian group, similar to the estimated country prevalence (6.1%) (WHO 2015). However, it is lower than the prevalence reported in other non-endemic countries in the Bolivian population. A meta-analysis conducted in European countries reported a prevalence in the community of 22%, 4-fold higher (Alonso-Vega, Billot & Torrico 2013; Coll O et al. 2018; Muñoz et al. 2009; Requena-Mendez et al. 2015). One possible explanation is that in the European studies, Bolivians came mostly from Cochabamba, Chuquisaca, and Santa Cruz and the positive cases are mostly from hyperendemic areas of Chagas, as Chupisaca and Tarija, in the Bolivian Chaco (Favila Escobio et al. 2015; Requena-Mendez et al. 2015; Gascon, Bern & Pinazo). However, the Bolivian migrants in Japan mostly came from the areas where the Japanese colonies are located, Beni (42.2%) and Santa Cruz (38.2%) (Manzenreiter, 2017). Beni is not a high endemic area of CD; in contrast, the south of Santa Cruz is one of the most endemic areas of the world for CD with a reported seroprevalence of *T. cruzi* of 45% in Camiri (Alonso-Vega, Billot & Torrico 2013). Whereas, the central and north regions of Santa Cruz, where most of the Bolivian migrants in Japan came from (due to the presence of two Japanese colonies), have prevalences around 20% (Alonso-Vega, Billot & Torrico 2013). The prevalence in the Santa Cruz subgroup (14%) is similar to other non-endemic countries with patients from this district (19.6%) and slightly inferior to the prevalence in central Santa Cruz, Bolivia (19%) (Fabila Escobio et al. 2015; Alonso-Vega, Billot & Torrico 2013). Another possible explanation for this difference could be due to the differential characteristic of the LA migrants residing in Japan. For European countries the migratory regulations are same for all LA migrants, while in Japan the current migration laws facilitate the migration of

Japanese descendant's respect to non-descendants. This inequity affects the migration flows into Japan where the LA migrant population is composed mainly from Japanese descendants and their families (Goto J. 2007). I didn't assess how many of the participants were Japanese descendants. However, most of the participants were originally from four main areas in Latin America (Sao Paulo in Brazil, Lima in Peru, and Beni and Santa Cruz in Bolivia) where the Japanese created their colonies more than 50 years ago and remain as areas of residence of many of them (Manzenreiter 2017). To date there are no studies about the CD vector situation conducted in the Japanese colonies. However, due to the maintenance of a Nikkei diaspora in LA countries through family structures and social institutions of association, education, rules, and rites, make the Japanese colonies a distinctive place from the rest of the LA society (Manzenreiter 2017). It could influence a lower prevalence in the cohort compared with the one seen in other non-endemic countries migrant population.

Factors associated with a CD positive status were being Bolivian, having a relative affected by CD, having seen the triatome at home, and having been tested before. Having a relative affected and being familiar with the triatome were factors described in previous studies and they are considered part of the risk factors to have CD (Custer et al. 2012; Muñoz et al. 2009; Roca et al. 2011). They are recommended to be included in the anamnesis in a patient with CD. The fact that the people that were tested in the past have more risk be diagnosed with CD, highlights the positivity that Japan hosts known cases that are not formally receiving care and follow-up. During the research some participants commented that due to their knowledge about CD they tried to seek care in Japan, but were unsuccessful due to lack of awareness in the health providers and lack of a system of care. In addition to a non-existent system, as reported in previous studies, factors such as stigmatization or normalization of the disease

could be influencing the care seeking behaviour of people at risk of CD (Avaria-Saavedra & Gomez i Prat 2008).

No cases were identified in Brazilians or Peruvians. Due to the small sample size of Peruvians (n=70), the low prevalence in the home country (0,44%), and that most of them came from Lima, an area that is not high endemic for CD, the results were expected. However, considering the estimated prevalence of Brazilians (0.6%) and the inclusion of nearly 200 participants, between 1 or 2 positive cases were expected to be found in the study. In addition, a study conducted ten years ago found a prevalence in Brazilians living in Japan nearly of 2% (WHO 2011). However, no positive cases were identified in the Brazilian group. One possible explanation could be that the great improvement that Brazil made in eliminating the intradomicile vector in the last ten years, with a consequent decrease of the cases notified in the whole country, had an influence in the prevalence of the Brazilians in Japan (Fabila Escobio et al. 2015; Martins-Melo et al 2014). Another possibility is due to the place of origin of the migrants. The estimated prevalence represents a national prevalence, but most of the new cases of CD in Brazil are in the northwest and north areas of Brazil (Fabila Escobio et al. 2015; Martins-Melo et al 2014). However, most of our participants (76%) come from the Southern regions, Sao Paulo, and Parana, where the prevalence is lower. The clarification of the real prevalence of the Brazilian population in Japan is an important area for future research because Brazilians represent two-thirds of the LA population.

9.3. Cost-effectiveness analysis

The observed prevalence is higher than expected, but all the positive participants (n=7) were from Santa Cruz, Bolivia, and the study population is over-represented with Bolivians (31%)

compared with the proportion of Bolivians in the LA migrant population in Japan (2%). When the observed prevalence is adjusted, the adjusted prevalence is 0.12%. If the real prevalence were 0.12% then the screening would no longer be cost-effective. This assumption would consider that Bolivians are the only group with cases of CD and the strategy will be only cost-effective for Bolivian migrants. However, this decrease in the prevalence as a result of the adjustment seems to be far from representing the real population for several reasons. First, I can't assume that there are not cases in other countries. As previous studies showed, there are Brazilian patients affected with CD living in Japan and larger cohorts will probably show cases in LA countries other than Bolivians (Imai et al. 2019; WHO 2011). Second, the prevalence in the Santa Cruz sub-group (14%) and the prevalence observed in a previous study in the Brazilian population (1.9%), show that the prevalence obtained is very similar to the prevalence in the areas of origin of the participants in Latin America, being in Santa Cruz 19% and in Sao Paulo and Parana 2.3% (WHO 2011; Fabila Escobio et al. 2015; Alonso-Vega, Billot & Torrico 2013; Martins-Melo et al 2014). Therefore, even though it is difficult to predict, the real prevalence probably would mimic the same tendency as in the subgroups mentioned and perhaps being slightly inferior to the expected one (0.75%).

Due to the homogeneity of the positive participants in the country of origin, arise the question if the screening should be applied to all LA groups or just to the Bolivian population. The design of the cost-effectiveness model doesn't contemplate cross-country differences and can be applied to different LA countries groups changing the prevalence value. The results show that the systematic screening strategy will continue to be cost-effective even with an increase of prevalence of more than 5.7%, supporting the screening and treatment of the adult Bolivian population. Also, it will be cost-effective with a decrease in prevalence (until 0.43%). These results support the screening in Brazilian and Peruvian groups, considering that the estimated

prevalence is 0.6% and 0.44%, respectively. Even in the cohort, no participant was positive other than Bolivians, but I believe that a larger number of participants probably will report cases in these groups. The results show that most of the migrants from Brazil and Peru came from low endemic areas, thus influencing a lower prevalence than the estimated in these groups. Additionally, cases of CD in the Brazilian population have been reported in Japan (Imai et al. 2019). A study conducted in the Brazilian population in Japan with more than 1,000 participants reported a prevalence of 1.9% in 2010 (WHO 2011). Therefore, I believe that the screening should be prioritized in the Bolivian population, without excluding other LA groups. As additional benefit, the establishment of a screening system would give the possibility to do a deeper analyze of the real prevalence of CD and status of the people affected in the LA migrant population. In addition, a cost-effective analysis is an important tool to prioritize the health strategies, but it is not the only one. Avoiding the screening and treatment of potential people at risk of CD, knowing the benefit of an early diagnosis, would not be ethical neither humanitarian.

Additionally, a system based on screening LA migrants according to their nationality has several disadvantages. First, it will easily fail in considering the CD country's prevalence heterogeneity since it will require deep knowledge about CD. It will complicate the implementation of the screening during the clinical practice (Requena-Mendez et al. 2017). Secondly, a screening based upon countries is difficult to apply in a globalized world. The increase of the migratory flows in the last years inside of Latin America changed the traditional risk map of CD and modified the areas that were considered endemic and non-endemic. Nowadays, most of the people at risk live in urban areas (WHO 2021). Following the human host, the vector can be found in periurban areas and the concept of CD is no longer attached to ruralism (Nunez et al. 2018; Moscatelli et al. 2015; Urdaneta-Morales et al. 2014;

Araujo-Jorge et al. 2009; Briceño-León 2007; Bayer et al. 2009). With the decrease of domestic infestation, the congenital transmission is scaling up as one of the most common causes of transmission of CD (Nunez et al. 2018; Pinazo & Gascon 2020). Furthermore, the current representation of the LA migrant population in Japan is influenced by the migratory regulations which can be easily modified according to the socio-economical needs of the nation in the future. As Sanmartino et al. said we should be alert of the social changes and transformation of the individuals that consult (or not) and the health system should reflect these transformations (Pinazo & Gascon 2020). In this context, it will remain obsolete to maintain the traditional dichotomies as tools for CD to classify a person of risk: endemic/non-endemic, rural/urban, healthy/ill, poor/not poor, ignorant/expert, patient/agent (Pinazo & Gascon 2020). Therefore, I support that the country of origin should be considered only as a first step in order to prioritize strategy in a system under-construction but the official recommendation should include all the people at risk, as it was recommended by the last road map for NTD of WHO (WHO 2020). A comprehensive system will consider the migratory history at the individual level, including people at risk of CD, instead of being restricted to the born place.

The cost-effectiveness model included two assumptions that could be too optimistic to achieve. First, I assumed that 100% of the people that will become symptomatic will be diagnosed and treated in the non-screening model. This approach may not mimic the current diagnosis trend, considering that Japan is one of the CD non-endemic countries with a higher level of underdiagnoses. However, the results showed that the percentage of symptomatic people diagnosed with CD in the non-screening model has minimal influence in the ICER and the screening model will continue being cost-effective with a drop until 0%. Second, the base case analysis of the model considered that 80% of the people included in the screening model-

screened will be diagnosed. Also, the model assumed that all the people with a serological positive result for *T. cruzi* will be treated. However, this is a very optimistic approach due to the numerous barriers that non-endemic countries have been reported due to unprepared systems for emergent disease, such as CD (Pinazo & Gascon 2020; Manne-Goehler et al. 2015; Forsyth et al. 2018; Yoshioka et al. 2020; Monge-Maillo et al. 2017; Di Girolamo et al. 2011; Iglesias-Rodriguez et al. 2020). These barriers can be divided into two groups: structural barriers that impede the access to the diagnosis, treatment, and comprehensive care of people affected with CD due to limited governmental public health infrastructure, resources, and interventions; and barriers as migrants that impede their access to the health system due to inequities compare with the native population in job conditions and opportunities, socioeconomic status, communication, lack of transcultural education of the health providers, and immigration policies. A study conducted in Madrid (Spain), a city where the diagnosis is free and accessible through PHC, reported that less than 50% of the Bolivian population reached the diagnostic and at the national level this number is less than 10% considering the whole LA population (Romay-Barja et al. 2019). Barriers inherent to the multidimensionality problem of CD and barriers that affect exclusively the migrant population in the host country intertwine, making the 80% a heroic number to reach. Nevertheless, the same as for European countries, in the univariate analysis the strategy will continue being cost-effective even if just 30% of the migrant population would be diagnosed and treated (Requena-Mendez et al. 2017).

9.4. Barriers that affect the inclusion of a CD system in Japan

Additional efforts should be implemented to overcome the current barriers. The latest recommendations from the WHO indicate that establishing a simpler diagnosis protocol is

one of the measures that would increase the level of diagnoses (WHO 2020; Marchiol et al. 2017). However, contradictorily, the WHO still demands the use of two positive serological tests (standard diagnosis) to consider a patient positive for CD (WHO 2018). Therefore, it is still necessarily the standard diagnosis in the screening of CD. As a future objective, the WHO aims to validate the effectiveness of RDT for screening and develop the affordable ones due to their potential as TPP (WHO 2020). In Japan in response to the lack of a system for CD and the difficulties to follow the requirements of the standard diagnosis, the cases reported by Imai et al. don't follow the current standard diagnosis for CD and used RDT as a screening tool followed by a single ELISA in the positive cases (Imai et al. 2019). To examine the performance of RDT, I have compared it with the results of standard diagnosis with a concordance of 100%. However, the number of positive participants and the homogeneity in their country of origin were not enough to recommend it as a single screening tool in Japan. RDT (Chagas Detect™Plus Rapid Test of Inbios) performed very well in Bolivia and could be used in the Bolivia population, although they didn't have good sensitivity in the Peruvian population (Shah et al. 2014; Verani et al. 2009). Considering that the second most numerous group of LA migrants in Japan are Peruvians and the bad performance of a different RDT in Peruvian populations in previous research with a high possibility of false-negative, Japan should be cautious in generalizing the use of RDT as a single screening tool, as it has done until now. Furthermore, due to the strain variation of *T. cruzi*, recent studies proposed the use of at least two RDT in countries in which RDT showed a good performance like Bolivia (Lozano et al. 2019). Studies with more positive participants would be necessary in Japan to validate the use of RDT for screening. The implementation of an official screening strategy from the health facilities would increase the diagnosis level and help to identify more positive cases in the different LA countries groups, bringing the opportunity to

validate the RDT in larger numbers of samples from a more geographically diversified population.

In the study, none of the positive patients reached a conclusive diagnosis of their status of CD. Only the two positive participants with the less geographical distance between their hometown and the hospital reached the health care point. The distance to health facilities is described as an important factor impeding access in previous studies (Forsyth et al. 2018; Di Girolamo et al. 2011; Marchiol et al. 2017). Based on the literature a follow-up by PHC in the indeterminate form could increase access to care for its geographical proximity (Pinazo & Gascón 2020; Sosa-Estani et al. 2021; Echeverria et al. 2020; Nunez et al. 2018). Both participants withdrew at the follow-up. They stated that the delays and compartmentalization in numerous visits affected their job activity, thereby influencing their decision to stop the visits. In addition, to simplify and bring up to date diagnostic algorithms to improve access, several studies showed that to shorten the time to diagnosis is a necessary strategy to achieve better outcomes in the follow-up (Marchiol et al. 2017; WHO 2020; Pinazo & Gascon 2020) None of the positive participants in the research accessed the treatment of CD. The participants claimed lack of information about the treatment and bureaucratic delays in access. The barriers that experienced the positive participants have been already described as areas of improvement in CD in endemic and non-endemic countries (Marchiol et al. 2017; Yoshioka et al. 2020; Romay-Barja et al. 2019). To achieve the 75% of coverage in the antiparasitic treatment proposed for WHO by 2030, Japan will need to consider the establishment of a patient road map or guideline that leads the health professionals, simplifying the diagnosis and treatment process. In addition, the establishment of diagnosis, treatment, and comprehensive care points with health personnel trained in CD and LA cultural skills, distributed in the prefectures where the majority of migrants live, would increase the

accessibility and diagnosis rates. Furthermore, if the diagnostic tests are compacted in time, reducing the number of visits, as was done in European countries like Spain or Italy, it would help to decrease the loss of follow-up.

In addition to the structural barriers for the diagnosis and treatment of CD, the LA population living in Japan faces barriers that make it difficult for their access to the health system. Considering the access to the health system from the potential (perceive better access to the health system) and realized access to health (utilization of the services when needed), the LA migrant population in Japan have better potential access to health than other migrant groups in Japan, such as Nepalese (86% and 30%, respectively) (Shakya et al. 2018). This difference could be explained by the special profile of the LA migrant population in Japan. Due to the advantage of most of them for long-term visas, they settle in Japan with their families which offers support and information about the health system (Fielding 2010; Goto 2007). Almost 30% of the responders received information about the health system from their relatives. Also, the study found a higher rate of insured migrants than in previous research. A study conducted on LA migrants in Japan showed that 20% of LA were uninsured (Suguimoto et al. 2012). However, in the research, most of the participants were insured (93.5%) and most of them pay it regularly (96.6%) even the payment was considered expensive for more than half of them. The fact that the study of Suguimoto et al. was limited to a single city in Japan (Nagahama city, Shiga) could reflect a problem geographically constrained (Suguimoto et al. 2012). On the other hand, I agree with the results of Sugimoto et al. that not all full-time workers are covered with the EHI and almost 35% of them are enrolled in the NHI. This may reflect the reported poor conditions and irregularities in the job offered by the work companies to LA migrants in Japan, described as “5K” positions – Kiken (dangerous), Kitanai (dirty), Kitsui (heavy), Kibishii (difficult), and Kirai (despicable) (Kawamura L, 2008; Goto

2006; Suguimoto et al. 2012; NHK 2021). Thirty years after the change in the immigration law that increased the influx of the LA migrant population, they remain as unskilled professionals working in the manufacturing industry. Japan does not facilitate the migration of unskilled professionals to strengthen the economy, but the Japanese descendants are an exception. Consequently, the second most numerous group of unskilled professionals in Japan are South Americans (Manzenreiter 2017).

Controversly to the potential access, the realized access of the LA migrant population is poor, similar to other migrant populations in Japan and other countries of Asia (Ismayilova et al. 2015; Shakya et al. 2018). Almost one-fourth of the LA migrant population didn't visit the doctor when in need.

As demonstrated in previous studies, the LA migrant population faces barriers to access the health system (Iglesias-Rodriguez et al. 2020; Suguimoto et al. 2018). Language skills, being women, length of stay in Japan, information source about the health system, and satisfaction of the health care system are factors associated with access to the healthcare system in the LA migrant population in this study.

Even though most of the participants had lived in Japan for more than 10 years, nearly half of them (49%) need a translator when visiting a doctor, and 40% considered that the Japanese language skills affected their access to the health system. Language is a constant barrier reported for many studies conducted in the different migrant groups in Japan, regardless of the time in Japan or nationality (Nagamatsu et al. 2020; Iglesias-Rodríguez et al. 2020). It is for that reason that I decided to include service translators in all the visits in the screening model and the results showed that their cost has minimal influence in the ICER and even an

increase in the cost of translators, the screening will still be a cost-effective strategy. In Japan, the number of health interpreters increased during the last years, but they lack cultural competence and the migrants prefer being accompanied by a friend or relative (Iglesias-Rodríguez et al. 2020; Scheppers et al. 2006). In the research, nearly 20% of the people that used interpreters are not satisfied with their translations. In other non-endemic countries with a long tradition of migration flows, the health service includes the figure of cultural mediators, who have great competence not just interpreting the language, but also the culture, and offer better outcomes (Verrept 2019; Abubakar et al. 2018).

Women were less likely to visit a doctor when they need it. Gender social inequities were reported to have a significant impact in the access to health system, reducing the health-seeking behavior in migrant women worldwide (WHO 2017; Ismayilova et al. 2015; Schoevers et al. 2009; Malmsi et al. 2010). The results shows that the rate of unemployment in the responders is three-fold compared with the national rate and most of them are women (88.89%) (The world bank 2021). However, these results contrast with previous studies about the behavior in seeking CD diagnosis in the LA migrant population (Ventura-Garcia et al. 2013; Minerman et al. 2012). These studies described a higher tendency of women in seeking care with respect to men. It was described that the LA women tend to prioritize family health over their own (Rojas-Guyler et al. 2016). The possibility of vertical transmission can explain this gender difference to seek a diagnosis for CD. There is little information available regarding the health and seeking behavior of LA migrant females in Japan. Recent studies suggested poor mental health and inequities compared to the native population in the preventive health programs in the women migrant population living in Japan (Miller et al. 2019; Nagamatsu et al. 2020). Further studies in this area would have great benefit due to the important role of women in the mother-to-child transmission of CD.

Migrants that have lived in Japan for more than 10 years are more likely to visit the health care point when they need it compared with the migrants that are in Japan for shorter periods. It was described in previous studies that the length of stay in Japan is a barrier to well-being and access to the health system in migrants (Miller et al. 2019; Shakya et al. 2018). This supports the assimilation theory of migration, where the process of acculturation is highly influenced by the length of stay and progressive acquiescence of language proficiency (Dhadda & Greeene 2018; Russell Miller et al. 2019).

The source of information about the health system and the level of satisfaction are factors that influence the access to the Japanese health system of the LA migrant population. Receiving information from governmental sources is a factor that can improve the access to the health system. However, just 36% of the migrants received the information from an official source. The lack of Japanese skills and that most of them tend to settle with families or cluster for the job type, could influence the source of information. Information about the health system is essential to increase access to the health system and is a key cornerstone that influences the seeking behavior (Romay-Barja 2020; Navarro et. al 2011; Blasco Hernandez et al. 2016). Official information programs in Spanish and Portuguese could help to reduce the barriers in access to the health system. Previous studies described how an adequate health communication, in which the patient is actively involved, influenced patient satisfaction with better outcomes not just in the access to the health system, but also in the adherence to treatment and medical recommendations (Schouten et al. 2020; Igarashi et al. 2013).

9.5. Comprehensive care

Throughout this discussion, I have focused on the biomedical and political barriers that influenced the problem of CD in Japan. However, the global emergence and perpetuation of CD depend mainly on the socio-cultural aspect (Ventura-Garcia et al. 2013; Di Girolamo 2011; Sanmartino et al. 2015). To avoid a narrow and incomplete approach to CD, the interventions to decrease the burden should include the socio-cultural dimension. This has a special nuance in non-endemic countries where the socio-cultural concepts from the country of origin and host country intertwine. In Japan, CD is still a difficult concept for the LA migrants to integrate into their Japanese reality due to the lack of a tangible link between Japan, a country that inspires security and wellbeing, and the invisible problems of Latin America, like CD (Iglesias-Rodriguez et al. 2020). Due to this additional complexity, to reach better outcomes it is essential that we work with (and not only "for") the people at risk. As described by Ventura-Garcia et al. "Both researches focused on incorporating people's experience and needs into policies and interventions in endemic and non-endemic countries and the development of preventive and/or control actions conducted with attention to affected individuals beyond medical spaces are crucial" (Ventura-Garcia et al. 2013). Specific programs have started to combine social and medical strategies to improve the access to diagnosis and treatment in Spain, Italy, Germany, and Switzerland (Pinazo & Gascon 2020). Japan, as an advance and world-recognized medical service, should consider acquiring a compressive approach for a CD where all the dimensions are included (epidemiological, biomedical, political, and socio-cultural).

To consider a social approach, I developed an educational system throughout this research with the objective of inform, interact, and include the people affected as main actors. As Sanmartino et al. indicated, it is essential "a dialogical educational perspective that allows individuals and communities to analyze, decide, and lead contextualized prevention and

promotion actions about their health" (Sanmartino, Mateyca & Pastorino 2020). I didn't assess the impact of these interventions. However, the informative activity conducted in the venues had a comprehensive approach and it was demonstrated to increase the knowledge of CD in previous research conducted in Bolivian migrants in Japan (Iglesias-Rodriguez et al. 2020). To my knowledge, the virtual system that was created is the first resource in Spanish and Portuguese about CD in Japan. The website link was incorporated in the official website of the Bolivian embassy as a pop-up and it had 1,216 visits (viewed the 10th of February of 2021). It is linked to social media, Facebook, and Instagram. I have experienced the utility of social media to interact with the participants, connect with the community, inform about the venues, resolve concerns about CD, and inspire other scientific groups. Recent studies demonstrated that the use of social media can be a new educational resource for health problems (Stelefson et al. 2020; Smith & Denali 2014). The inclusion of an expert patient as a leader of these activities, as was done in other non-endemic countries, will ensure continuity and development (Claveria Guiu et al. 2017).

In summary, this study provides the first insight of the situation of CD in Japan from the LA community. Due to the limited number of participants, it would be difficult to reflect a real prevalence of CD from the whole LA migrant population, especially in Brazilian and Peruvian groups. However, the findings clearly show that the prevalence in Bolivian migrants is high and most of them are in an asymptomatic state. Therefore, strategies to offer an early and comprehensive care outside of the blood banks should be further explored in Japan. As a preamble, the screening of asymptomatic adults would be a cost-effective strategy in populations with a prevalence higher than 0.43% and can be considered in the Bolivian population.

9.6. Limitations

As limitations, during the recruitment process I couldn't obtain any information from the people that declined to participate in the study, therefore it would be difficult to estimate factors that could influence a possible selection bias. However, even though we conducted almost the same number of data collections with every country activity and our capacity in every venue was the same, we had less participants in the Peruvian venues. One factor that differentiates the participants by the country group is the knowledge about CD. Peruvians had significantly less knowledge about CD than Brazilians and Bolivian. This could be a factor that influences participation in the research. Although I tried to cover this bias through the educational activity, it is likely that people with previous knowledge about CD and that are aware of the benefits of an early diagnosis would be more willing to participate. Most of the Brazilians had received information in the school in Brazil, and Bolivians in their home country live very close to the reality of CD due to the high prevalence in the country. However, less than 30% of Peruvians knew about CD compared more than 80% of Brazilians and Bolivians. As described in previous research, the seeking behavior of migrants depends both on the knowledge acquired in their home country and the host country (Iglesias et al. 2020; Ventura-Garcia et al 2013). One-third of this study was conducted during the COVID19-pandemic, thereby influencing the low participation of infants in the cohort. Due to the limitations to protect the privacy of the migrants, we couldn't do a random sampling with a prelist of participants and the sampling were done with the people that attended the embassy venues, being more a convenience sampling. This sampling has potential bias. However, the embassies activities attend the needs of the entire LA migrant population, offering their services to a heterogenous population, thus being our cohort very similar to the real population in terms of gender, place of residence and job. The main limitation was the

low inclusion of children in our study, caused by the measure to decrease the number of people that enter in the room after the pandemic in March 2020.

As I argued within the discussion, the observed prevalence might be overestimated due to the high representation of Bolivians in our cohort compared with the real migrant population, thus having an important impact on the cost-effectiveness analysis. However, the results of the cost-effectiveness analysis show that it would remain cost-effective to maintain the screening if the group prevalence is 0.43%. Therefore, it would be cost-effective for Bolivians, and probably for Brazilians and Peruvians if we considered their estimated prevalence at 0.6% and 0.44%, respectively. The cost-effectiveness analysis didn't consider the impact of screening on the reduction of congenital transmission of CD. The quality weights were obtained from studies conducted in Latin America and I didn't consider the impact of the diagnosis of CD on the quality of life of the infected people. The screening program can have an impact on the mental health of the CD-positive people and affect their work area due to discrimination (Forsyth 2017; Sanmartino 2009). Unfortunately, there is not much research in this area, thus it is difficult to measure. Due to absence of data on the probabilities of undertaking tests and interventions in the different CD, most of the parameters was taken from the experts' opinions used in previous cost-effectiveness analysis in Europe (Requena-Mendez et al. 2017). Due the lack of data in the mortality of the LA migrant population living in Japan, I assumed that the length of life of the migrant population would be same as Japanese population, as it was assumed in other CD economic analysis conducted in non-endemic countries (Imaz-Iglesia et al. 2015; Requena-Mendez et al. 2017). This could be an optimistic approach considering that Japanese has one of highest life expectancies worldwide and the life conditions of migrants in Japan differ from the native citizens (Shakya et al. 2018; Suguimoto et al. 2012; Miller et al. 2019; Manzenreiter 2017).

On the other hand, studies support that migrant populations who settle in new countries modify their lifestyle compared with the origin population (Petroni et al. 2018; Tsugane 1992). This could have an impact to increase the life expectancy of the LA migrants living in Japan.

Studies conducted in Japan showed that the migrant population has poor mental health influenced by the migration process (Russell Miller et al. 2019; Takubo et al. 2020; Koyama et al. 2016). However, I didn't include mental health variables in the need factors of the Andersen's model for access to health system due to the difficulty of obtaining this data in the venue's format. Finally, as the information in questionnaires was self-reported, there is a risk for reporting bias in the personal information.

9.7. Future research

To adopt a system for CD in Japan, a greater involvement of the scientific community is necessary. First, the screening of women in fertile age at risk of CD and their children should be a priority for research, for the well-known benefits of prompt treatment for CD (WHO 2020). To follow the WHO recommendation and validate an effective point-of-care diagnosis for infants, future studies should evaluate the cost-effectiveness of this intervention and understand which are the barriers that interfere in the access of LA migrant women to the health system. Second, the results show that the screening of CD conducted for PHC is a cost-effective strategy. However, nothing is known about the knowledge and capacity of Japanese health personnel for CD and the willingness of PHC to assume the coordinator role. Third, to improve access for CD, a guideline should include a simpler diagnosis protocol and a strategy to overcome the current barriers in treatment. The factors that impede the implementation of the treatment is an area of urgent intervention. Fourth, the inclusion of the people affected by

CD, individually and through patient associations, as main actors in the problem of CD, is an essential resource in non-endemic countries (Marchiol et al. 2017). In comparison with other non-endemic countries, Japan lacks representation of the people affected by CD in the decision-making process for interventions for CD. Social media could offer a strategic tool to involve the young population and reach a community geographically dispersed across Japan. Exploring the factors that influence the empowerment of the CD patients as leaders could be a strategy of great impact in the level of diagnosis and as a long-term resource of support. Finally, *Triatoma rubrofaciata*, a potential vector for CD, is circulating in different countries of Asia, including Japan (Dujardin et al. 2015; Hieu et al. 2019; Shi et al. 2020; Liu et al. 2017). The presence of *T. cruzi* in Japan highlights the need for entomological surveillance.

10. Conclusion

The observed prevalence of CD in the LA migrant population living in Japan is more than double the estimated prevalence, and is higher in the Bolivian population. Screening of LA adult migrants living in Japan is a cost-effective strategy. However, to achieve the screening, the Japanese health system should consider several barriers that impede access to the health system. The level of Japanese language skills is a key factor that influences the access of the LA migrant population to the health system. Also, being female, length of stay in Japan, source of information, and satisfaction of the health system are factors associated with access to the healthcare system in the LA migrant population.

The findings of this research provide important epidemiological and economic findings that support the implementation of *T. cruzi* screening program at the PHC level in Japan. The inclusion of a multidisciplinary and comprehensive approach to this program could be a wise policy enriched from the learnings from more experienced countries.

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13. Conflicts of interest

I declare no conflict of interest

14. Appendices list

Appendix 1 Informed consent

Appendix 1a. Assent

Appendix 1b. Informed consent for parents.

Appendix 2. Questionnaire

Appendix 3. Serologic diagnostic test

Appendix 4. The CHEERS checklist (Husereau et al. 2013)

Appendix 5. The GREET checklist 2016a (Phillips et al. 2016)

Appendix 6. The CROSS checklist (Sharma et al. 2021)

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Appendix 1. Informed consent

Name of the participant:

This informed consent form is for Latin American immigrants living in Japan who are invited to participate in an investigation entitled

"Analysis in the need of improvement the health care system for Chagas disease in Japan".

This research protocol, human rights, and safety were reviewed and approved by Institutional Review Boards of Nagasaki University Institute of Tropical Medicine and Saitama Medical University, and each dean of the institution.

- Principal Investigator (PI): Inés María Iglesias Rodríguez
- Name of supervisor: Prof. Kenji Hirayama
- Other collaborating researchers: Dr. Sachio Miura, Takuya Maeda, Shusaku Mizukami.
- Name of the organization: Nagasaki University (School of Tropical Medicine and Global Health) and Institute of Tropical Medicine (NEKKEN)
- Collaborating Organization: Latin American Embassies in Japan and NPO- MAIKEN organization. Department of Microbiology and Department of Infectious Disease and Infection Control, Saitama Medical University, Saitama, Japan. Clinical Laboratory Medicine, Saitama Medical University Hospital.

Part I: Information sheet

Introduction: I'm Ines Iglesias, Ph.D. student at the University of Nagasaki. I am doing research on Chagas disease in the migrant population living in Japan. I am going to give you information and I invite you to be part of this investigation. You do not have to decide today whether or not to participate in the investigation. Before deciding, you can talk to people. This consent form may contain words that you do not understand. Please, ask for help for the compression if you need it.

Purpose of the investigation: Chagas disease affects more than 7 million people in the world, especially in Latin America. Due to the current migratory flows, in Japan it is estimated 3,000 people affected by Chagas, but the exact figure is unknown. We want this study to help to know the real situation in Japan and this helps to create policies to improve the current situation.

Type of research intervention: This investigation will involve a small prick on the finger to

obtain a few drops of blood that will be later analyzed in the laboratory. The result will be informed by the PI . It also involves a few brief questions in a questionnaire about information about you. If you concern about the infection of Chagas disease, we can introduce appropriate medical institution.

Procedures

1. Questionnaire (5min)

2. Blood Sample (5 min) We will obtain 1 blood sample (600 μL) for conduct the diagnostic methods. We will conduct three serologies methods and two molecular diagnostic tests. The molecular diagnostic methods would be polymerase chain

reaction (PCR) and the DNA based diagnostic method loop-mediated isothermal amplification (LAMP).

The blood sample and the data obtained during this research procedure will be used only for this research, and will be destroyed after 5 years, when the research is completed.

Selection of participants: You are being invited to participate in this research since the source of origin is at risk of Chagas disease.

Voluntary participation: Your participation in this research is completely voluntary. It is your choice whether to participate or not. If you choose not to participate, all the services you receive will continue and nothing will change. You have the right to refuse or withdraw. You do not have to participate in this research if you do not want to, and choosing to participate will not affect you in any way. You will withdraw this study at any time. **If you** withdraw this study, your information and specimens will be deleted according to your desire. However, this rule does not apply to all cases where the research article has already been published.

Duration: The investigation is carried out during 3 years in total, but your participation is only today.

Risks: The incision to take the blood sample may be painful at the time and some people may feel dizzy. Although it is rare, bruising may appear in the area and pain days later.

Benefits: You don't receive any benefit directly. If you concern about the infection of Chagas disease, we can introduce appropriate medical institution.

Cost: You do not need to bear an cost, and will not be rewarded.

Confidentiality: The information we collect from this research project will remain private. Only the investigators will know what your information is and we will close that information with a

padlock and a key. Your information will be anonymizes to be not specified your private information. Your private information will not be shared or given to anyone, except the PI.

Who to contact: If you have any questions, you can ask now or later. If you wish to ask questions later, you may contact any of the following: chagasjapon@gmail.com or 095-819-7800. This proposal has been reviewed and approved by the NEKKEN

Ethics Committee of the Nagasaki University (Japan), which is a committee whose task is to ensure that the participants of the investigation are protected against any damage.

Sample storage method and utilization of other research: The blood samples and the data obtained during this research procedure will be closely storage in Nagasaki University Institute of Tropical Medicine (NEKKEN), and will be disposed as medical wastes (blood samples) and deleted (data) after termination of the storage period. However, the blood samples and the data may be used for the other research or provided for other research institutions upon obtaining new approval by Institutional Review Boards. The blood samples and the data will be storage after 5 years, when the research is completed. It is possibility that the sample storage period will be extended, if other research will be conducted.

Management Policy for Conflicts of interest and research fund : This research protocol was reviewed and judged by Conflict of Interest Management Committee of Nagasaki University Institute of Tropical Medicine and Saitama Medical University, there are no conflict of interest, which leads to disadvantage of participants or unfairly evaluation of research.

This research is conducted using the following research grant:

- Name: 2019 The Japanese Association for Infectious Diseases Clinical Study Promotion Grant

Information disclosure: The research results will be published and reported as academic conference presentation with the anonymization to prevent your and your family name being specified.

Part II: Consent certificate

I have been invited to participate in this research on Chagas disease in the migrant population living in Japan. I have read the above information, or have read it to me.

I have had the opportunity to ask questions about it and all the questions that have been asked have been answered to my satisfaction. I give my voluntary consent to participate in this study.

Name of the participant_____

Participant's signature _____ Date _____ Day / month / year ___ / ___ / _____

*** If I am illiterate,** I have witnessed the accurate reading of the consent form for the prospective participant, and the individual has had the opportunity to ask questions. I confirm that the individual has freely given consent.

Write the name of the witness_____ Thumbprint of the participant Signature of the witness _____ Date _____ Day / month / year

Statement by the researcher / person taking the consent I have read the information sheet for the possible participant with precision, and in the best way I could, I made sure that the participant understood that the following will be done:

1..

2..

3.

I acknowledge that the participant had the opportunity to ask questions about the study, and all the questions asked by the participant have been an answer.

Part III: Document declaring the withdrawal of consent

Nagasaki University Institute of Tropical Medicine (NEKKEN)

"Analysis in the need of improvement the health care system for Chagas disease in Latin American migrant population living in Japan".

To Nagasaki University Institute of Tropical Medicine (NEKKEN)

To Kenji Hirayama

I inform you the withdraw consent to this research.

I withdraw consent to following contents with marked.

□ My sample and specimen are used of research.

□ My personal information are used of research with the anonymization.

□ My sample and specimen are storage and will provide the other research in the future.

Name of the participant _____

Participant's signature _____ Date _____ Day / month / year ____ / ____ / _____

Appendix 1a. Assent

Name of the participant:

This informed consent form is for Latin American immigrants living in Japan who are invited to participate in an investigation entitled

"Analysis in the need of improvement the health care system for Chagas disease in Japan".

This research protocol, human rights, and safety were reviewed and approved by Institutional Review Boards of Nagasaki University Institute of Tropical Medicine and Saitama Medical University, and each dean of the institution.

- Principal Investigator (PI): Inés María Iglesias Rodríguez
- Name of supervisor: Prof. Kenji Hirayama
- Other collaborating researchers: Dr. Sachio Miura, Takuya Maeda, Shusaku Mizukami.
- Name of the organization: Nagasaki University (School of Tropical Medicine and Global

Health) and Institute of Tropical Medicine (NEKKEN)

- Collaborating Organization: Latin American Embassies in Japan and NPO- MAIKEN organization. Department of Microbiology and Department of Infectious Disease and Infection Control, Saitama Medical University, Saitama, Japan. Clinical Laboratory Medicine, Saitama Medical University Hospital.

Part I: Information Sheet

Introduction: I'm Inés Iglesias, Ph.D. student at the University of Nagasaki. I am doing research on Chagas disease in the migrant population living in Japan. I am going to give you information and I invite you to be part of this investigation. You do not have to decide today whether or not to participate in the investigation. Before deciding, you can talk to people. This consent form may contain words that you do not understand. Please, ask for help for the compression if you need it.

Purpose of the investigation: Chagas disease affects more than 7 million people in the world, especially in Latin America. Due to the current migratory flows, in Japan it is estimated 3,000 people affected by Chagas, but the exact figure is unknown. We want this study to help to know the real situation in Japan and this helps to create policies to improve the current situation.

Type of research intervention: This investigation will involve a small prick on the finger to obtain a few drops of blood that will be later analyzed in the laboratory. The result will be informed by the PI. It also involves a few brief questions in a questionnaire about information about you. If you concern about the infection of Chagas disease, we can introduce appropriate medical institution.

Selection of participants: Because Chagas disease affect also to the children and they respond almost 100% to the treatment, your participation is very important.

Participation is voluntary: Your participation in this research is completely voluntary. It is your
choice whether to participate or not. If you choose not to participate, all the services you receive will continue and nothing will change. You have the right to refuse or withdraw. You do
not have to participate in this research if you do not want to, and choosing to participate will
not affect you in any way. You will withdraw this study at any time. **If you** withdraw this study, your information and specimens will be deleted according to your desire. However, this rule does not apply to all cases where the research article has already been published.

Duration: The investigation is carried out during 3 years in total, but your participation is only today.

I have checked with the child and they understand that participation is voluntary

_____

Procedures:

1. Questionnaire (5min)

2. Blood Sample (5 min) We will obtain 1 blood sample (600 μL) for conduct the diagnostic methods. We will conduct three serologies methods and two molecular diagnostic tests. The molecular diagnostic methods would be polymerase chain reaction (PCR) and the DNA based diagnostic method loop-mediated isothermal amplification (LAMP).

The blood samples and the data obtained during this research procedure will be used only for

this research, and will be destroyed after 5 years, when the research is completed.

I have checked with the child and they understand the procedures _____

Risks: The incision to take the blood sample may be painful at the time and some people may feel dizzy. Although it is rare, bruising may appear in the area and pain days later.

Discomforts: Can hurt a little in the finger but normally it is just for some minutes.

I have checked with the child and they understand the risks and discomforts ____

Benefits: You don't receive any benefit directly. If you concern about the infection of Chagas disease, we can introduce appropriate medical institution.

I have checked with the child and they understand the benefits_____

Confidentiality: The information we collect from this research project will remain private. Only the investigators will know what your information is and we will close that information with a padlock and a key. Your information will be anonymizes to be not specified your private information. Your private information will not be shared or given to anyone, except the PI.

Compensation: If you get hurt we will be taking care of you.

Who to Contact: If you have any questions, you can ask now or later. If you wish to ask

questions later, you may contact any of the following: Inés Iglesias chagasjapon@gmail.com or 095-819-7800. This proposal has been reviewed and approved by the NEKKEN Ethics Committee of the Nagasaki University (Japan), which is a committee whose task is to ensure that the participants of the investigation are protected against any damage.

Sample storage method and utilization of other research: The blood samples and the data obtained during this research procedure will be closely storage in Nagasaki University Institute of Tropical Medicine (NEKKEN), and will be disposed as medical wastes (blood samples) and deleted (data) after termination of the storage period. However, the blood samples and the data may be used for the other research or provided for other research institutions upon obtaining new approval by Institutional Review Boards. The blood samples and the data will be storage after 5 years, when the research is completed. It is possibility that the sample storage period will be extended, if other research will be conducted.

Management Policy for Conflicts of interest and research fund: This research protocol was reviewed and judged by Conflict of Interest Management Committee of Nagasaki University Institute of Tropical Medicine and Saitama Medical University, there are no conflict of interest, which leads to disadvantage of participants or unfairly evaluation of research.

This research is conducted using the following research grant:

- Name: 2019 The Japanese Association for Infectious Diseases Clinical Study Promotion Grant

Information disclosure: The research results will be published and reported as academic conference presentation with the anonymization to prevent your and your family name being specified.

If you choose to be part of this research I will also give you a copy of this paper to keep for yourself. You can ask your parents to look after it if you want.

PART II: Certificate of Assent

I have read this information (or had the information read to me). I have had my questions answered and know that I can ask questions later if I have them.
I agree to take part in the research.

OR

I do not wish to take part in the research and I have not signed the assent below._____(initialed by child/minor)

Only if child assents:
Print name of child _____
Signature of child: _____
Date:_____
day/month/year

If illiterate:

I have witnessed the accurate reading of the assent form to the child, and the individual has had the opportunity to ask questions. I confirm that the individual has given consent freely.

Print name of witness (not a parent) _____ AND Thumb print of participant
Signature of witness _____
Date _____
Day/month/year

I have accurately read or witnessed the accurate reading of the assent form to the potential participant, and the individual has had the opportunity to ask questions. I confirm that the individual has given assent freely.

Print name of researcher_____

Signature of researcher_____

Date_____

Day/month/year

Statement by the researcher/person taking consent

I have accurately read out the information sheet to the potential participant, and to the best of my ability made sure that the child understands that the following will be done:

1.

2.

3.

I confirm that the child was given an opportunity to ask questions about the study, and all the questions asked by him/her have been answered correctly and to the best of my ability. I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily.

A copy of this assent form has been provided to the participant.

Print Name of Researcher/person taking the assent_____

Signature of Researcher /person taking the assent _____

Date _____

Day/month/year

Copy provided to the participant _____(initialed by researcher/assistant)

Parent/Guardian has signed an informed consent ___Yes ___No _____(initialed by researcher/assistant)

Part III: Document declaring the withdrawal of consent

Nagasaki University Institute of Tropical Medicine (NEKKEN)

"Analysis in the need of improvement the health care system for Chagas disease in Latin American migrant population living in Japan".

To Nagasaki University Institute of Tropical Medicine (NEKKEN)

To Kenji Hirayama

I inform you the withdraw consent to this research.

I withdraw consent to following contents with marked.

□ My sample and specimen are used of research.

□ My personal information are used of research with the anonymization.

□ My sample and specimen are storage and will provide the other research in the future.

Name of the participant _____

Participant's signature _____ Date _____

Day /

month / year / /

Appendix 1b. Informed consent for parents

Name of the participant:

This informed consent form is for Latin American immigrants living in Japan who are invited to participate in an investigation entitled

"Analysis in the need of improvement the health care system for Chagas disease in Japan".

This research protocol, human rights, and safety were reviewed and approved by Institutional Review Boards of Nagasaki University Institute of Tropical Medicine and Saitama Medical University, and each dean of the institution.

- Principal Investigator (PI): Inés María Iglesias Rodríguez
- Name of supervisor: Prof. Kenji Hirayama.
- Other collaborating researchers: Dr. Sachio Miura, Takuya Maeda, Shusaku Mizukami.
- Name of the organization: Nagasaki University (School of Tropical Medicine and Global

Health) and Institute of Tropical Medicine (NEKKEN)

- Collaborating Organization: Latin American Embassies in Japan and NPO- MAIKEN organization. Department of Microbiology and Department of Infectious Disease and Infection Control, Saitama Medical University, Saitama, Japan. Clinical Laboratory Medicine, Saitama Medical University Hospital.

PART I: Information Sheet

Introduction: I'm Inés Iglesias, Ph.D. student at the University of Nagasaki. I am doing research on Chagas disease in the migrant population living in Japan. I am going to give you information and I invite your child to be part of this investigation. You do not have to decide today whether or not your child will participate in the investigation. Before deciding, you can talk to people. This consent form may contain words that you do not understand. Please, ask for help for the compression if you need it.

Purpose of the investigation: Chagas disease affects more than 7 million people in the world, especially in Latin America. Due to the current migratory flows, in Japan it is estimated 3,000 people affected by Chagas, but the exact figure is unknown. We want

this study to help to know the real situation in Japan and this helps to create policies to improve the current situation.

Type of Research Intervention. This investigation will involve a small prick on the finger to

obtain a few drops of blood that will be later analyzed in the laboratory. The result will be informed by the PI. It also involves a few brief questions in a questionnaire about information about you. If you concern about the infection of Chagas disease, we can introduce appropriate medical institution.

Procedures and Protocol

1. Questionnaire (5min)

2. Blood Sample (5 min) We will obtain 1 blood sample (600 μL) for conduct the diagnostic methods. We will conduct three serologies methods and two molecular diagnostic tests. The molecular diagnostic methods would be polymerase chain reaction (PCR) and the DNA based diagnostic method loop-mediated isothermal amplification (LAMP).

The blood samples and the data obtained during this research procedure will be used only for

this research, and will be destroyed after 5 years, when the research is completed.

The blood samples and the data obtained during this research procedure will be used only for this research, and will be destroyed after 5 years, when the research is completed.

Selection of participants: Your child is being invited to participate in this research since the source of origin is at risk of Chagas disease.

Voluntary participation: The participation of your child in this research is completely voluntary. It is your choice whether to participate or not. If you choose not to participate, all the services him/her receive will continue and nothing will change. You have the right to refuse or withdraw. Your child doesn't have to participate in this research if you or your child do not want to, and choosing to participate will not affect you in any way. You will withdraw this study at any time. **If your child** withdraws this

study, the information and specimens will be deleted according to your desire. However, this rule does not apply to all cases where the research article has already been published.

Duration The investigation is carried out during 3 years in total, but he/her participation is only today.

Risks The incision to take the blood sample may be painful at the time and some people may feel dizzy. Although it is rare, bruising may appear in the area and pain days later.

Benefits: The child don't receive any benefit directly. If you concern about the infection of Chagas disease, we can introduce appropriate medical institution.

Cost: You do not need to bear a cost, and will not be rewarded.

Confidentiality The information we collect from this research project will remain private. Only the investigators will know what your information is and we will close that information with a padlock and a key. Your information will be anonymizes to be not specified your private information. Your private information will not be shared or given to anyone, except the PI.

Who to Contact If you have any questions, you can ask now or later. If you wish to ask questions later, you may contact any of the following: Inés Iglesias chagasjapon@gmail.com or 095-819-7800. This proposal has been reviewed and approved by the NEKKEN Ethics Committee of the Nagasaki University (Japan), which is a committee whose task is to
ensure that the participants of the investigation are protected against any damage.

Sample storage method and utilization of other research: The blood samples and the data obtained during this research procedure will be closely storage in Nagasaki University Institute of Tropical Medicine (NEKKEN), and will be disposed as medical wastes (blood samples) and deleted (data) after termination of the storage period.

However, the blood samples and the data may be used for the other research or provided for other research institutions upon obtaining new approval by Institutional Review Boards. The blood samples and the data will be storage after 5 years, when the research is completed. It is possibility that the sample storage period will be extended, if other research will be conducted.

Management Policy for Conflicts of interest and research fund : This research protocol was reviewed and judged by Conflict of Interest Management Committee of Nagasaki University Institute of Tropical Medicine and Saitama Medical University, there are no conflict of interest, which leads to disadvantage of participants or unfairly evaluation of research.

This research is conducted using the following research grant:

- Name: 2019 The Japanese Association for Infectious Diseases Clinical Study Promotion Grant

Information disclosure: The research results will be published and reported as academic conference presentation with the anonymization to prevent your and your family name being specified.

PART II: Certificate of Consent

Certificate of Consent

I have read the foregoing information, or it has been read to me. I have had the opportunity to ask questions about it and any questions that I have asked have been answered to my satisfaction. I consent voluntarily for my child to participate as a participant in this study.

Print Name of Participant_____
Print Name of Parent or Guardian_____
Signature of Parent or Guardian _____
Date _____
Day/month/year

If illiterate

A literate witness must sign (if possible, this person should be selected by the participant and should have no connection to the research team). Participants who are illiterate should include their thumb print as well.

I have witnessed the accurate reading of the consent form to the parent of the potential participant, and the individual has had the opportunity to ask questions. I confirm that the individual has given consent freely.

Print name of witness_____ AND Thumb print of parent

Signature of witness _____

Date _____

Day/month/year

Statement by the researcher/person taking consent

I have accurately read out the information sheet to the parent of the potential participant, and to the best of my ability made sure that the person understands that the following will be done:

1.

2.

3.

I confirm that the parent was given an opportunity to ask questions about the study, and all the questions asked by the parent have been answered correctly and to the best of my ability. I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily.

A copy of this ICF has been provided to the participant.

Print Name of Researcher/person taking the consent_____

Signature of Researcher /person taking the consent_____

Date _____

Day/month/year

An Informed Assent Form will_____ OR will not _____ be completed.

Part III: Document declaring the withdrawal of consent

Nagasaki University Institute of Tropical Medicine (NEKKEN)

"Analysis in the need of improvement the health care system for Chagas disease in Latin American migrant population living in Japan".

To ~~Dean of~~ Nagasaki University Institute of Tropical Medicine (NEKKEN)

To Kenji Hirayama

I inform you the withdraw consent to this research.

I withdraw consent to following contents with marked.

□ My sample and specimen are used of research.

□ My personal information are used of research with the anonymization.

□ My sample and specimen are storage and will provide the other research in the future.

Name of the participant _____

Participant's signature _____ Date _____

Day /

month / year ___ / ___ / _____

Appendix 2. Questionnaire **Code** ☐

1. Age……
2. Gender: Male ☐ Female☐ Others ☐ ……
3. If you are a woman, have you had children? YES☐ NO☐
4. Education level. Primary / Secondary /University
5. Country of origin. …….. City……
6. Do you have health insurance in Japan? YES☐ NO☐
7. Have you lived in any other country? YES☐ NO☐ Which one?.....
8. How long have you lived in Japan?
   Less than 5 years / more than 5 years/ more than 10 yeas
9. In witch city of Japan do you live?.....
10. Have you been tested for Chagas disease? YES☐ NO☐
11. Do you remember which test?.....
12. Have you been treated for Chagas disease? YES☐ NO☐
13. Do you remember which treatment?.....
14. In your country of origin, have you ever lived in rural areas? YES☐ NO☐
15. Have you lived in a house made of mud material "adobe"? YES☐ NO☐
16. Have you ever heard about Chagas disease? YES☐ NO☐
17. Have you ever seen this insect (kissing bug)? YES☐ NO☐
18. Have you seen it at home? YES☐ NO☐
19. Do you have in your family any member affected by Chagas? YES☐ NO☐
20. Have you ever donated blood? YES☐ NO☐ In witch country? ……
21. Have you ever received a blood donation in a Latin American country? YES☐ NO☐
22. Have you ever consumed one of these natural foods?

a. acaí	b. jucara
c. Bacaba	d. Wine of palma
e. Mandarina juice.	f. sugar cane juice

---

23. Occupation ……
24. Work condition
    a. Full time
    b. Part time
    c. Self employmened
    d. Unemployed
    e. Student
    f. Retired

25. Years employed by the current employer: a. 0-2. B. 3 or more
26. Term of contract with employer (months)
    a. 1-2
    b. 3-6
    c. 7-24
    d. No written contract
27. Do you have perspective to came back to your country for living? YES□ NO □
28. Which insurance do you have?
    a. Employees Health Insurance
    b. National Health Insurance
    c. Late Elders Health Insurance
    d. Others
29. Payment of the health insurance
    a. Regular b. Irregular (Not paid for a year or more)
30. Do you think the cost of health insurance is expensive to you? YES□ NO □
31. Are you satisfied with the care received in Japanese in Health Centers? YES□ NO □
32. How did you receive information about the Health System in Japan?
    a. Relative/family
    b. Friend
    c. City Hall/Government of Japan
    d. Others
    e. Others
    f. I don't have information still
33. Do you perceive a good access to the doctor/health worker? YES□ NO □
34. In the past year, have you needed to see a doctor/health worker, but you did not? YES□ NO □
35. Do you need Japanese language interpreter during the visits to health facilities (including a family member)? YES□ NO □
36. Are you satisfy with the translation of language interpreters? YES□ NO □
37. The fact that you can't communicate limit your access to the doctor? YES□ NO□
38. Do you have a fix doctor as family doctor? YES□ NO □
39. Self-rated health status
    a. Good/very good/excellent
    b. Poor/fair
40. Do you have any chronic disease? YES□ NO □

Name:

Address:

Telephone:

Email:

Appendix 3- Serologic diagnostic

Serologic diagnostic test

ELISA test: T. Cruzi IgG Celisa II of Cellabs

T. Cruzi IgG Celisa II was performed as instructions by the PI and Prof.Clara Alejandra Vasquez Velasquez. After bringing all reagents to room temperature (18-25°C), we prepared the Wash Buffer and removed the required number of Celisa Plate strips. We prepared 1/100 dilution of the positive control, negative control, and the patient sample in Wash Buffer ensuring proper mixing.

Then, 100 µL of this dilution (patient sample, positive control, and negative control) was put into individual microwells. We included two positives and two negatives in each assay. We cover and incubate for one (1) hour at room temperature (RT) in a humid chamber. In the last 10 minutes of the incubation period, we prepared the working strength Conjugate, adding 5µL of Enzyme Conjugate to 995µL of Wash Buffer and mix thoroughly. Then, we washed the wells manually (empty contents from the wells and refill with the wash buffer. We repeated the process a further three (3) times. After the fourth wash, we inverted wells dry on absorbent tissue).

After, we added 100µL of Conjugate to each well and incubate for thirty minutes (30 minutes) at RT in a humid chamber. In the last 10 minutes of the incubation period, we prepared the working strength Substrate. We added 50µL of Substrate Chromogen to 950µL of Substrate Buffer and we mixed thoroughly. Then we washed the wells manually as previously. Then, we added 100 µ L of fresh Substrate and incubate it in the dark (covered) at room temperature for 15 minutes. We added 50 µ L of Stopping Solution.

The results were read photometrically within 30 minutes of stopping the reaction read absorbance of all wells including all the controls at 450nm on an ELISA reader. A positive result was considered values more than 0.8. Values between 0.5 and 0.8 will be considered as past infection or current low-level infection. Values between 0.25 and less than 0.5 will be considered that contain antibodies, but the level is lower than the generally accepted significant level. Values of less than 0.25 will be considered negative.

Chagas IFA (Indirect immunofluorescent assay) of Vircell.

Chagas IFA of Vircell was performed as instructions by the PI and Prof. Clara Alejandra Vasquez Velasquez. The samples were diluted 1/40 and 1/80 by adding 10 µL of sample to 390 µl of PBS (1/40 dilution). Then will make two-fold dilutions with 50 µL of PBS (1/80 dilutions). We applied 20 µL of 1/40 and 1/80 dilutions in two slide wells for the negative and positive controls. The slide was incubated for 30 minutes at 37°C in a humid chamber. The slide was rinsed briefly with a gentle stream of PBS and immerse for ten minutes in PBS. Next, the washed slide was briefly dipped into distilled water. We allowed the slide to dry and then add 20 µL of anti-human IgT FITC conjugate solution to each well. We repeated previous steps of incubation, rinse with PBS, rinse with MiliQ and slide dry. After adding a small drop of mounting medium to each well and carefully cover with a coverslip, the slide was read as soon as possible in a fluorescence microscope at 400× magnification. If necessary, the samples were further analyzed with up to 1/2048 dilutions if some of the samples are positive.

Chagas Detect™ Fast ELISA (ELISA-2)

Chagas Detect™ Fast ELISA was performed as instructions by Dr. Imai. Eight µL of plasma was diluted with 192 uL of Sample Dilution Buffer. After, 100 µL of diluted samples were added into each well, and incubate well at 37°C for 30 min. After the incubation, each well will be washed six times with 300 µL of Wash Buffer.
After the wash step, 100 µL of Ready to Use Enzyme Conjugate-HRP for CD was added into each well and incubated the well at 37°C for 30 min. After the incubation, each well was washed six times with 300 µL of Wash Buffer.
After the wash step, 100 µL of Liquid TMB Substrate was added into each well and incubated the well at room temperature for 10 min. After the incubation, the reaction was stopped by adding 50 µL of Stop Solution into each well. The palate was read immediately by using Varioskan® Flash (Thermo Scientific, Massachusetts, USA) at 450 nm. Positive cut-off values were determined Optical Density (OD) > 0.500, according to the manufacturer instructions.

Chagas Detect™Plus Rapid Test (CDP of Inbios)

Chagas Detect™Plus Rapid Test (Inbios International Inc., Seatttle, USA) was performed by Dr. Miura, Prof. Maeda, Dr. Imai and the PI. It is a rapid immunochromatographic strip assay for the qualitative detection of human lgG antibodies of T. Cruzi. It was used as RDT in the venues following the manufacturer's instruction. After finger prick, some drops of whole blood were used directly on the strips. The strips were introduced in a plastic recipient prepared with 3 drops of the reagent. After 15 min at room temperature, results were interpreted by eye. Results were recorded as negative, weak positive, or positive.

Appendix 4- The CHEERS checklist (Husereau et al. 2013)

Section/item	Item No	Recommendation	Reported on:
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	-
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	Abstract, page 3-4.
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study.	4. Literature review (page 24-37) and 5. Purpose of the study and justification (page 38-40)
		Present the study question and its relevance for health policy or practice decisions.	6. Study goals and objectives, page 40.
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	7.12.1. Model structure, page 56-58,
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	7.12.1. Model structure, page 56-58.
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	7.12.4. Costs, page 62, line 2-3.
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	7.12.1. Model structure page 56-57 and section 7.12.2 in page 58, line 10-20.
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	7.12. 1. Model structure, page 58, line 5.
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	7.13. 4. Cost-effectiveness of the screening, page 69, line 10.
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	7.13. 4. Cost-effectiveness of the screening, page 69, line 12-13
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	7.12.1. Model structure, page 56-58.
	11b	*Synthesis-based estimates*: Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	-
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	-
Estimating resources and costs	13a	*Single study-based economic evaluation:*Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity	Sections:7.12.3, 7.12.4., 7.12.5. and 7.12.6., page 59-67

		costs.	
	13b	*Model-based economic evaluation:* Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	-
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	7.12. Costs, page 62-66.
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	7.12.1. Model structure, 58-59, Figure 10. 7.13. 4. Cost-effectiveness of the screening, page 71, line 13-15
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	7.12.1. Model structure, page 56-58. 7.13. 4. Cost-effectiveness of the screening, page 69-70. 7.12.3 Transition probabilities, page 59-62.
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	7.13. 4. Cost-effectiveness of the screening, page 69-70.
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	Table 5 and Table 6, page 59-62.
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	Table 7, page 63-65. Table 8, page 66. Section 8.7., page 93-95
Characterising uncertainty	20a	*Single study-based economic evaluation:* Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).	Section 8.7.1 page 95-97
	20b	*Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	-
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed	Section 8.7.2., page 93-97

		variability in effects that are not reducible by more information.	
Discussion			
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	9.Discussion, page 105-126 9.6. Limitations, page 123.
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	12. Fundings, page 129.
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	13. Conflicts of interest, page 129.

For consistency, the CHEERS statement checklist format is based on the format of the CONSORT statement checklist

Appendix 5- The GREET checklist 2016[a] (Phillips et al. 2016)

BRIEF NAME	Reporte on:
1. INTERVENTION: Provide a brief description of the educational intervention for all groups involved [e.g. control and comparator(s)].	7. Methodology, 7.8. Educational system, page 50-52.
WHY - this educational process	7. Methodology, 7.8. Educational system, page 50, line 6-15
2. THEORY: Describe the educational theory (ies), concept or approach used in the intervention.	7. Methodology, 7.8. Educational system, page 51, line 6-10.
3. LEARNING OBJECTIVES: Describe the learning objectives for all groups involved in the educational intervention.	7. Methodology, 7.8. Educational system, page 51, line 8-10.
4. EBP CONTENT: List the foundation steps of EBP (ask, acquire, appraise, apply, assess) included in the educational intervention.	7. Methodology, 7.8. Educational system, 50-52.
WHAT	
5. MATERIALS: Describe the specific educational materials used in the educational intervention. Include materials provided to the learners and those used in the training of educational intervention providers	7. Methodology, 7.8. Educational system, page 51, line 12-13
6. EDUCATIONAL STRATEGIES: Describe the teaching/learning strategies (e.g. tutorials, lectures, online modules) used in the educational intervention.	7. Methodology, 7.8. Educational system, page 50 and 52.
7. INCENTIVES: Describe any incentives or reimbursements provided to the learners.	-
WHO PROVIDED	
8. INSTRUCTORS: For each instructor(s) involved in the educational intervention describe their professional discipline, teaching experience/expertise. Include any specific training related to the educational intervention provided for the instructor(s).	7. Methodology, 7.8. Educational system, page 50, line10-12.
HOW	
9. DELIVERY: Describe the modes of delivery (e.g. face-to-face, internet or independent study package) of the educational intervention. Include whether the intervention was provided individually or in a group and the ratio of learners to instructors.	7. Methodology, 7.8. Educational system, page 50-53.
WHERE	
10. ENVIRONMENT: Describe the relevant physical learning spaces (e.g. conference, university lecture theatre, hospital ward, community) where the teaching/learning occurred.	7. Methodology, 7.8. Educational system, page 51.
WHEN and HOW MUCH	
11. SCHEDULE: Describe the scheduling of the educational intervention including the number of sessions, their frequency, timing and duration.	7. Methodology, 7.8. Educational system, page 51.
12. Describe the amount of time learners spent in face to face contact with instructors and any designated time spent in self-directed learning activities.	7. Methodology, 7.8. Educational system, page 51.
PLANNED CHANGES	
13. Did the educational intervention require specific adaptation for the learners? If yes, please describe the adaptations made for the learner(s) or group(s).	-
UNPLANNED CHANGES	

14. Was the educational intervention modified during the course of the study? If yes, describe the changes (what, why, when, and how).	7. Methodology, 7.8. Educational system, page 51, line 16
HOW WELL	
15. ATTENDANCE: Describe the learner attendance, including how this was assessed and by whom. Describe any strategies that were used to facilitate attendance.	7. Methodology, 7.8. Educational system, 51, lie 16-17
16. Describe any processes used to determine whether the materials (item 5) and the educational strategies (item 6) used in the educational intervention were delivered as originally planned.	-
17. Describe the extent to which the number of sessions, their frequency, timing and duration for the educational intervention were delivered as scheduled (item 11).	7. Methodology. Page 42, line 15.

Appendix 6- CROSS checklist (Sharma et al. 2021)

Section/topic	Item	Item description	Reported on:
Title and abstract	1a	State the word "survey" along with a commonly used term in title or abstract to introduce the study's design.	Abstract, page 3, line 15.
	1b	Provide an informative summary in the abstract, covering background, objectives, methods, findings/results, interpretation/discussion, and conclusions.	Abstract, page 3
Background	2	Provide a background about the rationale of study, what has been previously done, and why this survey is needed.	4. Literature review (page 24-37) and 5. Purpose of the study and justification (page 37-40)
Purpose/aim	3	Identify specific purposes, aims, goals, or objectives of the study.	6. Study goals and objectives (Page 40)
Study design	4	Specify the study design in the "Methods" section with a commonly used term (e.g., cross-sectional or longitudinal).	7. Methodology, 7.1 Study Design, page 40-41.
Data collection methods	5a	Describe the questionnaire (e.g., number of sections, number of questions, number and names of instruments used).	7.5. Research tool (questionnaire), page 46, line 10-13 and Table 3.
	5b	Describe all questionnaire instruments that were used in the survey to measure particular concepts. Report target population, reported validity and reliability information, scoring/classification procedure, and reference links (if any).	7.5. Research tool (questionnaire), page 45-46. 7.3. Inclusion and exclusion criteria, page 44, line 1-8.
	5c	Provide information on pretesting of the questionnaire, if performed (in the article or in an online supplement). Report the method of pretesting, number of times questionnaire was pre-tested, number and demographics of participants used for pretesting, and the level of similarity of demographics between pre-testing participants and sample population.	-
	5d	Questionnaire, if possible, should be fully provided (in the article, or as appendices or as an online supplement).	Appendix 2
Sample characteristics	6a	Describe the study population (i.e., background, locations, eligibility criteria for participant inclusion in survey, exclusion criteria).	7.2. Study areas and study population, page 42-43. 7.3. Inclusion and exclusion criteria, page 44, line 1-8.
	6b	Describe the sampling techniques used (e.g., single stage or multistage sampling, simple random sampling, stratified sampling, cluster sampling, convenience	7.7. Recruitment method, page 49-50.

Section/topic	Item	Item description	Reported on:
		sampling). Specify the locations of sample participants whenever clustered sampling was applied.	
	6c	Provide information on sample size, along with details of sample size calculation.	7.6. Sample size, page 48-49 and Table 4.
	6d	Describe how representative the sample is of the study population (or target population if possible), particularly for population-based surveys.	7.6. Sample size (page 47-48) and Table 12 in section 8.1.3 (page 75-76)
Survey administration	7a	Provide information on modes of questionnaire administration, including the type and number of contacts, the location where the survey was conducted (e.g., outpatient room or by use of online tools, such as SurveyMonkey).ven7	7.9.1. Venue (page 53, line 8-9)
	7b	Provide information of survey's time frame, such as periods of recruitment, exposure, and follow-up days.	7.1. Study design (page 40, line 19)
	7c	Provide information on the entry process: –>For non-web-based surveys, provide approaches to minimize human error in data entry. –>For web-based surveys, provide approaches to prevent "multiple participation" of participants.	-
Study preparation	8	Describe any preparation process before conducting the survey (e.g., interviewers' training process, advertising the survey).	-
Ethical considerations	9a	Provide information on ethical approval for the survey if obtained, including informed consent, institutional review board [IRB] approval, Helsinki declaration, and good clinical practice [GCP] declaration (as appropriate).	7.11. Safety considerations (page 57, line 8-12)
	9c	Provide information about survey anonymity and confidentiality and describe what mechanisms were used to protect unauthorized access.	7.11. Safety considerations ((page 56, line 10-14)
Statistical analysis	10a	Describe statistical methods and analytical approach. Report the statistical software that was used for data analysis.	7.13 Statistical analysis, section 7.13.2 in page 68 and section 7.13.3 in page 69.
	10b	Report any modification of variables used in the analysis, along with reference (if available).	7.13 Statistical analysis, section 7.13.2 in page 68 and section 7.13.3 in page 69.
	10c	Report details about how missing data was handled. Include rate of missing items, missing data mechanism (i.e., missing completely at random [MCAR], missing at random [MAR], or missing not at random [MNAR]), and methods used to deal with missing data (e.g., multiple imputation).	Page 69, line 4-5.
	10d	State how non-response error was addressed.	-

Section/topic	Item	Item description	Reported on:
	10e	For longitudinal surveys, state how loss to follow-up was addressed.	-
	10f	Indicate whether any methods such as weighting of items or propensity scores have been used to adjust for non-representativeness of the sample.	-
	10g	Describe any sensitivity analysis conducted.	-
Respondent characteristics	11a	Report numbers of individuals at each stage of the study. Consider using a flow diagram, if possible.	8. Results, page 71, line 2
	11b	Provide reasons for non-participation at each stage, if possible.	-
	11c	Report response rate, present the definition of response rate or the formula used to calculate response rate.	Table 9 (page 71-72), Table 10 (page 74-75) and 23 (page 100-101).
	11d	Provide information to define how unique visitors are determined. Report number of unique visitors along with relevant proportions (e.g., view proportion, participation proportion, completion proportion).	-
Descriptive results	12	Provide characteristics of study participants, as well as information on potential confounders and assessed outcomes.	8. Results (page 71-104)
Main findings	13a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates along with 95% confidence intervals and *p* values.	8. Results (page 71-104)
	13bmu	For multivariable analysis, provide information on the model building process, model fit statistics, and model assumptions (as appropriate).	Section 7.13.3 in page 68, from line 14 until page 69 line 6. 8. Results (page 103-105)
	13c	Provide details about any sensitivity analysis performed. If there are considerable amount of missing data, report sensitivity analyses comparing the results of complete cases with that of the imputed dataset (if possible).	-
Limitations	14	Discuss the limitations of the study, considering sources of potential biases and imprecisions, such as non-representativeness of sample, study design, important uncontrolled confounders.	9.6. Limitations, page 123.
Interpretations	15	Give a cautious overall interpretation of results, based on potential biases and imprecisions and suggest areas for future research.	9. Discussion, page 105-126.
Generalizability	16	Discuss the external validity of the results.	9. Discussion, page 105-126.
Role of the funding source	17	State whether any funding organization has had any roles in the survey's design, implementation, and analysis.	12. Fundings, page 129.

Section/topic	Item	Item description	Reported on:
Conflict of interest	18	Declare any potential conflict of interest.	13. Conflict of interest, page 129.
Acknowledgements	19	Provide names of organizations/persons that are acknowledged along with their contribution to the research.	11. Acknowledgments, page 127.