

Dissertation Summary

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

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Background

Chagas disease (CD) is a Neglected Tropical Disease (NTD) caused by the parasite *Trypanosoma cruzi* (*T. cruzi*) that affects more than 6 million people in the world. The disease is mostly transmitted by the vector, kissing bug, which is endemic just in Latin America. However, mother-to-child transmission, blood transfusion, and organ transplantation are other forms of transmission that account for thousands of cases annually worldwide. Each year 39,000 new cases occur and 9,000 results from the congenital transmission.

CD has the particularity of being asymptomatic in almost 90% of the infected people in the acute phase, making difficult the diagnosis and treatment in the early stages. Added to this challenging situation, socio-cultural and political barriers have a strong influence on the alarming level of underdiagnoses. Only 1% of the affected people reach the diagnosis and treatment. Non-treated patients will pass to a silent chronic phase and decades after the infection, 30-40% of them will manifest at least cardiac or/and digestive symptoms that have an important impact on their quality and length of life. CD is the first tropical disease with the highest-burden measured in 806,170 disability-adjusted life-years (DALYs). 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. Situating it as one of the most mortal and intractable NTD in the Western Hemisphere.

Due to the migratory flows in the last decades, CD is emerging as a global health problem worldwide. Japan is one of the countries with more migrant population from Latin American (LA) and it is estimated more than 3,000 cases of CD. However, the country lacks a system of identification, prevention, and care for CD. Furthermore, there is an important gap in epidemiological data that have humanitarian and economic consequences.

This study aims to analyze the need for the improvement of the actual Health System by analyzing the epidemiological, clinical, and economic situation in Japan respect to CD in the population at risk. Also, to analyze the current barriers that the LA migrant population has to access to the Health System. Furthermore, to compare Rapid Diagnosis Test (RDT) with the current standard diagnosis.

Methodology

We conducted a cross-sectional study from March of 2019 until October 2020 that included participants at risk of CD living in Japan during the study period. Data were collected from 7 of the 20 prefectures with more LA residents, focusing on the main populational groups (Brazil, Peru, and Bolivia populations). The study was conducted in 4 stages.

Firstly, we create a system of education with a virtual and physical format to provide information about CD and offer support in Spanish and Portuguese 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, we collected blood samples from the LA migrant population living in Japan in different governmental, communitarian, cultural, and educational activities directed to the LA population in different prefectures in Japan. Finger-prick was used to obtain the blood samples and to conduct the RDT (Chagas Rapid Detect of Inbios) in the venue. After centrifugation of the blood samples, the plasma obtained was analyzed by serological methods to identify the positive participants. Following international recommendations, a participant was considered positive if have two serological test positives for *T. Cruzi* (standard diagnosis method). The serological methods used was *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). In case of discordant results, we conducted a third serological test (Chagas Detect™ Fast ELISA kit, InBios International, Inc., USA). In the venues, quantitative data from questionnaires were collected from all the participants including sociodemographic information, information about risk factors of CD, and about the barriers in access to the health system. Data were described as frequencies and mean for discrete and continuous variables, respectively. To calculate the observed prevalence, we divided the total of cases with *T. cruzi* infection positive in our research between the total participants, shown as a percentage. We used multivariable logistic regression to explore predisposing, enabling, and need factors associated with access to healthcare among the LA adult migrant population. The agreement between RDT and the standard diagnosis method was estimated using the kappa statistic.

Thirdly, with the results of the observed prevalence, we calculated the cost-effectiveness of CD screening in the asymptomatic adult migrant population as a potential program included in the Japanese health system using a Markov state transition model. The model included five states related to the chronic disease: indeterminate, cardiomyopathy, gastrointestinal, response to treatment, and death. It started with a target population of 100,000 individuals of which 1,7% (95% CI. 0.008-0.034) were estimated to be infected with *T.cruzi*. Deterministic and probabilistic analyses (Monte Carlo simulations) were performed, being our primary outcome the incremental cost-effectiveness ratio (ICER). Based on the Japanese literature we set our willingness-to-pay and threshold to 5,000,000 JPY per QALY.

Lastly, all participants were informed about their test results and introduced to the appropriate medical institution, considering the proximity to their residence area. The participants with positive results in our serological test that attended the clinical institution referred were categorized by clinical profile.

Results

Characteristic of the participants

428 participants were included in our study. The participant's ages ranged between 7 and 82 years old, with a mean age of 43.5 (SD. 13.67). Seventeen participants (3.9%) were under 18 years old and the rest were adults. Most of the participants were originally born in LA (n=401, 98.4%) vs 27 (1,6%) that were born outside Japan. The participants born outside Japan had been included because they had at least one of the next conditions: the mother had born in LA or the participant have lived in LA for long periods. The participants born in LA are represented mainly for three countries: Brazil (45.5%, n=195), Bolivia (30.8%, n=132) and Peru (16.3%, n=70). Most of the participants were living in Japan for more than 10 years (73%, n=304). The participants place of residence in Japan were located in 29 out of the 47 different prefectures of Japan. The top three prefectures of residence were Aichi, Mie and Gunma. Most of the participants heard about CD (74.3%, n=312) and one third of them have seen the triatome (34.2%, n=144). However, just 3.7% (n=16) were tested by CD.

Prevalence

Considering the prevalence in LA countries proposed by WHO 2015, 2,082 migrants were estimated to have CD in 2019 in Japan, giving a Japan-wide estimated prevalence of 0.75%.

In our cohort, 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 prevalence among Bolivians was 5.3% (95% CI 0.025-0.105; n=132). 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.

The positive participant age ranges from 45 and 69 years old. Four of them (n=57.1%) were female and 3 males (n=42.8%). All of them were born in Bolivia (Santa Cruz) and are living in Japan for more than 10 years. Just one of them commented symptomatology (digestive disorders), rest referred to be asymptomatic. All of them have heard about the CD. Nearly 60% have lived in rural areas of Santa Cruz (57.1%, n=4) and less than half (42.8%, n=3) have lived in a mud house. Forty-two percent of them had seen the triatome at home and have a relative affected of CD (42.8%, n=3). None of them had donated blood in the past. All the women have children. The screening was recommended for all the women's children. However, just the family of one woman came to the venue with the purpose of screening and all of the children screened (n=3) were negative for *T. cruzi* by standard diagnosis.

RDT/Standard diagnosis

RDT of Inbios was conducted in all the participants (n=428). Compared with the standard diagnosis we had an agreement of 100%. Kappa value of 1 (p value=1).

Clinical data

All the participants involved in this study have been informed about the results. However, the clinical data was not possible to obtain due to the lack of follow-up in the positive participants. The principal reasons expressed

for the participants that attended the visits and stop the follow-up were: 1) delays in the follow-up due to compartmentalization of examination in numerous visits; 2) absence of information about the treatment by the doctor; 3) influence of the follow-up in the job activity due to the number of visits 4) bureaucratic delays involved in the treatment access 5) COVID-19 pandemic influence.

Cost-effectiveness

The deterministic and probabilistic analysis shows that the screening model was more cost-effective than the non-screening model from a health care perspective and societal perspective. 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. 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.

Accessibility to the Japanese health system

We include 390 participants from our cohort after excluding the participants not born in LA and the participants under 18 years old. The following predisposing and enabling factors were significantly associated with access to health care in our multivariable regression model. Predisposing factors. Females LA migrants were at higher risk to not visit a doctor or health worker when they need it (OR=2.30; CI 1.13-4.7). On the other hand, people that live in Japan for more than 10 years are less likely to not visiting the health facilities when they need them (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 do not see 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 observed prevalence of CD is more than double compared with the estimated prevalence (1.6% vs 0.75%, respectively). This prevalence is higher if we consider only the Bolivian population (5.3%). Screening for CD in asymptomatic LA adults migrants residents in Japan is a cost-effective strategy. However, there are several factors that affect the access to the health care system for LA migrants living in Japan. Being female, length of stay in Japan, language skills, source of information about the health system, and satisfaction about the health care system are factors associated with their access to health care.

Japan may need to consider the inclusion of CD as a disease for control and care in the Japanese Health system. However, for the correct implementation, it would be useful to consider measures to avoid the current barriers in the healthcare access in the LA migrant population.