Analysis of the Chagas disease situation in Japan: A cross sectional study and cost-effectiveness analysis of a Chagas disease screening program

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The Lancet Regional Health - Western Pacific 2022;00: 100574
Published online xxx
https://doi.org/10.1016/j.lanwpc.2022.100574

Summary

Background Japan is estimated to host 3000 cases of Chagas disease (CD). However, there are no epidemiological data and policies for prevention and care. We aimed to analyze the current situation of CD in Japan and identify possible barriers to seeking care.

Methods This cross-sectional study included Latin American (LA) migrants living in Japan from March 2019 to October 2020. We obtained blood samples to identify participants infected with *Trypanosoma cruzi*, and data about sociodemographic information, CD risk factors, and barriers to access to the Japanese national health care system (JNHS). We used the observed prevalence to calculate the cost-effectiveness analysis of the screening of CD in the JNHS.

Findings The study included 428 participants, most of them were from Brazil, Bolivia and Peru. The observed prevalence was 1.6% (expected prevalence= 0.75%) and 5.3% among Bolivians. Factors associated with seropositivity were being born in Bolivia, having previously taken a CD test, witnessing the triatome bug at home, and having a relative with CD. The screening model was more cost-effective than the non-screening model from a health care perspective (ICER=200,320 JPY). Factors associated with access to JNHS were being female, length of stay in Japan, Japanese communication skills, source of information, and satisfaction about the JNHS.

Interpretation Screening of asymptomatic adults at risk of CD may be a cost-effective strategy in Japan. However, its implementation should consider the barriers that affect LA migrants in access to the JNHS.

Funding Nagasaki University and Infectious Diseases Japanese Association.

Translated abstract

This translation in Japanese was submitted by the authors and we reproduce it as supplied. It has not been peer reviewed. Our editorial processes have only been applied to the original abstract in English, which should serve as reference for this manuscript.

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Keywords: Chagas disease; Migration; Japan

Research in context

Evidence before this study

We did a systematic search on Pubmed. We used the term ("Chagas" AND "Japan" AND ("migrants" OR "immigrants")). The search was restricted to documents in English, Spanish, Portuguese, and Japanese. We found 11 articles, and only five of them were focused on Japan. However, they are restricted to specific areas of Chagas disease improvement in Japan: educative area, blood transfusion transmission, diagnosis development, and clinical case reports. We didn't find any study that evaluate the situation of Chagas disease from the community in Japan.

Added value of this study

This study is the first to deeply analyze the situation of Chagas disease from the community, supported from different perspectives: epidemiological, economic, and health system accessibility data.

Implications of all the available evidence

Our findings provide new epidemiological and economic findings that support the implementation of a screening system of *Trypanosoma cruzi* for the people at risk of Chagas disease in Japan. In addition, this study identifies the barriers of the people at risk of Chagas disease in the access to health care.

Introduction

Chagas disease (CD) is a parasitic neglected tropical disease (NTD) that affects endemic and non-endemic countries.[1] More than 6 million people are estimated to be affected worldwide with most unable to obtain diagnosis and treatment.[1] To decrease the high level of underdiagnosis, the Road Map for NTD established that 75% of people at risk should be diagnosed and treated by 2030.[2]

This recommendation is based on the known benefits of early diagnosis and treatment in all the people at risk of CD.[3,4] However, most of the non-endemic countries with large populations of Latin American (LA) migrants don't have an official system for the affected people.[5–8]

Japan hosts nearly 300,000 LA migrants, mainly from Brazil, Peru, and Bolivia (90%).[9] Most of them are descendants of Japanese who started to migrate to Latin America a century ago.[10] Nowadays they are coming back to Japan to work and settle with their families.[10] It is estimated that nearly 3000 people are infected with *Trypanosoma cruzi (T.cruzi*).[11] However, the county has a low level of policies for control and care.[12,13]

CD is not recognized as a disease in the Japanese National Health System (JNHS) and the only possibility to be tested is through the Non-Governanmental Organisation-MAIKEN. They offer the Rapid diagnosis test (RDT) Inbios Chagas DetectTM Plus Rapid Test (CDP) in events directed mainly to the Brazilian population. In the case of a positive result, they send a blood sample to Saitama Medical University Hospital, where they perform a single serological test for research purposes. If this test is also positive, the person is considered infected with *T.cruzi* and is referred to the JNHS for the follow-up. The treatment (nifurtimox and benznidazole) is not approved or commercialized in Japan. It can be ordered overseas by the responsible hospital through the WHO. Six people, most of them symptomatic, were reported to have been diagnosed during 2012–2017, suggesting a late and low level of diagnosis in the country.[13]

We aimed to analyze the epidemiological, clinical, and economic situation of CD in Japan, barriers that the populations at risk have in accessing healthcare, and to compare RDT-CDP used in Japan with the current standard diagnosis.

Methodology

Study design and study population

This cross-sectional study included participants at risk of CD living in Japan during the study period (April 2019–October 2020).

We considered as people at risk of CD a subject of any age who were regular or irregular resident in Japan during the study period and born or lived long periods (more than one month) in a LA country or whose mother born or lived long periods in Latin America.[11,14]

We estimated our sample size at 400 participants, "based on the rule of threes".[15] To calculate our sample size, we used our updated CD estimated prevalence (0.75%) and a 95% CI (Appendix S1).[9,16]

Study areas

Data were collected along 22 venues in selected areas of the country with a large LA population (Aichi, Mie,

Gunma, Tokyo, Osaka, Hiroshima, and Nagasaki), where the Brazilian, Peruvian and Bolivian embassies held activities of diverse purposes: educational, cultural, communitarian, and governmental events, as well as mobile consulates.

Recruitment method

Previous studies remarked that the interventions directed to people at risk of CD should include a comprehensive approach for the impact and relevance of the socio-cultural dimension of CD.[17–21] Therefore, we created an educational system in Spanish and Portuguese that offer information about CD or planned venues, facilitate communication and support; before, during, and continued after the study concluded. The educational system has a virtual area whose main component was the website "Chagas en Japón" linked to social media[22]; and a physical area in the venues where we conducted CD group discussions based on an activity that demonstrated to increase CD knowledge.[19,18] This discussion was adapted in small groups or individually, for the coronavirus disease (COVID-19) restrictions after March 2020. The stakeholders that work with the LA community in Japan: the embassies, community leaders, Latin-a media, social media influencers, and health professionals spread our information by sharing the website links or broachers.

After the educational activity was conducted, we explained the informed consent in a comprehensive language to the people interested in participating, and those who agreed and signed it were included as participants. All the research was conducted in the native language of the participants: Spanish or Portuguese. The Nagasaki University Institute of Tropical Medicine's Ethics Committee approved this study (number 190110212-3).

Data collection and research tools

After enrollment, we started the data collection with an anonymized questionnaire followed by blood sampling.

The questionnaire was based on previous studies and included 40 questions with socio-demographic information, CD risk factors, related to CD control policies, and accessibility to the JNHS (Appendix S2).[23–27]

We used finger prick to collect the blood samples (600 µl) and to conduct the RDT-CDP which results were recorded in a register. Two different serological tests were performed on all the participants plasma, Chagas IgG+IgM Indirect Immunofluorescence assay kit (Vircell S., Spain) and *T. cruzi* IgG CELISA II ELISA (Cellabs, Australia). A third test (Chagas Detect™ Fast ELISA kit, InBios International, Inc., USA) was only conducted in case of discordant results. All commercial tests were conducted following the manufacturer's instructions. Following the international recommendations, a participant was considered infected with *T.cruzi* if two serological tests were positive, called standard diagnosis.[28]

All the participants chose to get informed of the results by post letter, email, and/or phone call. The letter included a health institution referral to the JNHS in Japanese and an explicative letter in Spanish. The health facilities for the positive participants were selected according to the experience of the doctor/unit in CD. We strongly recommend and facilitate testing the children of the infected women.

Cost-effectiveness analysis model

The cost-effectiveness of CD screening in the asymptomatic LA population living in Japan by the primary health care (PHC) was assessed using a Markov state transition model, primarily based on a published model conducted in Europe in LA migrants.[29]

The model starts with 100,000 individuals at risk of CD at 35 years old, based on the literature of non-endemic countries with more experience in CD.[30] Additionally, we conducted the analysis with the starting age of 43 years, considering our results. According to our results, we considered that 1.7% of them were infected with *T.cruzi*. Every individual can move annually to the different CD health states: indeterminate form, cardiac form, gastrointestinal form, response to treatment, and/or death. We didn't include non-infected or initially symptomatic individuals. Two scenarios were compared in the decision tree (Appendix S3).

1. Screening model. PHC offers the screening of CD to all the people at risk of CD living in Japan. We considered that all the positive cases were treated and included in a life-long follow-up with the necessary periodical visits and interventions. Considering the current barriers to access diagnosis globally, 80% of the individuals in this model will reach the screening and 20% will have the same evolution as in the non-screening model.[17,29,31–33]
2. Non-screening model. We considered that the individuals would follow the natural pathway of CD without any active medical intervention. They will be diagnosed and treated only when they start with symptoms or complications from CD.

The transition probabilities, follow-up details, costs, and Quality-Adjusted Life Year (QALY) information are in Appendix S3-S7.

The Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement can be found in the Appendix S19.

Statistical analysis

The statistical analyses conducted are summarized in Appendix S8.

Role of the funding source
None of the funding sources (Nagasaki University and Infectious Diseases Japanese Association) had any role in the study design, data collection, analysis, interpretation, or writing of the manuscript.

Results

Characteristic of the participants
We recruited 428 individuals were recruited from March 30, 2019, until October 18, 2020. Table 1 summarizes the socio-demographic characteristics. The participants' age ranged from 7 to 82 years old and 4% of them were under 18 years old. The majority of the responders were from Brazil (45.5%, *n*=195), Bolivia (30.8%, *n*=132), and Peru (16.3%, *n*=70). 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) were the top five LA districts of origin. Most responders lived in Japan for more than ten years (Figure 1).

Despite that the majority were familiar with CD (74.3%, *n*=312), only 3.7% (*n*=16) were tested in the past. CD knowledge was significantly lower among Peruvians (*p*-value=0.0001). The participant's characteristics related to risk factors of CD and policies and the knowledge of CD by country are summarized in Appendix S9-10.

Comparing the socio-demographic characteristics of the participants with the LA migrant population living in Japan in 2020, we observed two main differences: age, with a lower representation of the participants under 20 years old, and country of origin, with a larger proportion of Bolivians in our cohort (31%) compared with the proportion represented by Bolivians in the LA migrant population (2%) (Appendix S11).

Prevalence
Seven out of 428 participants were classified as infected with *T.cruzi* by the standard diagnosis, resulting in a total observed prevalence rate of 1.6% (95% confidence interval (95%CI): 0.008–0.033). Bolivians had a prevalence of 5.3% (95%CI: 0.025–0.105; *n*=132). We adjusted the total observed prevalence to a representation of Bolivians of 2% instead of the 31% in our cohort, obtaining an adjusted prevalence of 0.12%. Table 2 shows the prevalence in different groups.

We obtained an agreement of 100% (kappa value of 1) between the results RDT-CDP and the standard diagnosis.

Positive participants and clinical data
The age of the positive participants ranges from 43 and 69 years old. All of them (*n*=7) were from Bolivia (Santa Cruz) and had been living in Japan for more than ten years. All of them had heard about CD, but only three had been tested previously (two in Bolivia and one in Japan) and they had never sought medical care. Just one person referred symptomatology (digestive disorders).

The variables associated with a positive result were: being born in Bolivia, having taken the CD test before,

		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%	

***Table 1*: Participants socio-demographic characteristics.**

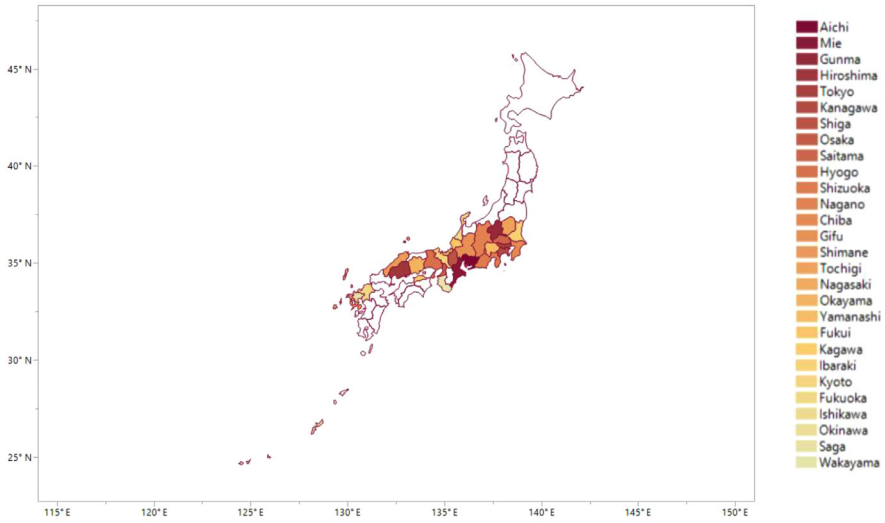

Figure 1. Prefectures of residence in Japan in the participants.

seeing the triatome bug at home, and having a relative with CD (Table 3). The result was communicated until the positive participants sought care passed more than 6 months. The reasons to explain the delay were as follows: prioritization of personal issues, hospital distance, Japanese language skills. Only 3 of them continue the follow-up nowadays. The main reasons expressed to stop the visits were: compartmentalization of the examination in numerous visits with consequences in the increment of cost of the visits and job activity, delays in the treatment access, COVID-19 situation.

Cost-effectiveness

In the deterministic model, for the starting age of 35 years-old and 45 years-old, the cost of the screening was 1,188,513,168 JPY and 1,195,251,834, and in the no-screening 367,303,765 JPY and 324,181,552 respectively. The incremental cost was 821,209,403 JPY and 871,070,282; incremental QALYS of 4099.48 and 2884.65, with an Incremental Cost-Effectiveness Ratio (ICER) of 200,320 JPY and 301,967, respectively (Table 4).

The Probabilistic Sensitivity Analysis showed that the screening model is more cost-effective than the non-screening model. These results are illustrated through the Cost-effectiveness Analysis Curve, where the probability that the screening model was more cost-effective than the non-screening rapidly reached 62% when the Willingness to Pay is more than 250,000 JPY per QALY gained and in the ICER scatter plot graph shows how all the simulated dots are located below and to the right of our threshold line (Appendix S12).

The cost-effectiveness of the screening model will be affected by a drop in the following parameters: 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, a decrease of the people screened in the screening model and a decrease in the prevalence of (Appendix S13-15). Additional cost-effectiveness analysis was conducted with the estimated prevalence (0.75%), showing that the model will be still cost-effective (ICER=393,170.08). The results of the PSA are illustrated in the Appendix S16.

Accessibility to the JNHS

Most of the responders were young adults that actively worked as full time-job in industry, construction, or

		Seropositive	Total	Prevalence	CI 95%
Latin American migrant population	All	7	428	1.6%	0.008–0.033
	Adults	7	411	1.7%	0.008–0.034
Bolivian migrant population	All	7	132	5.3%	0.025–0.105
	Adults	7	123	5.7%	0.027–0.112
	Santa Cruz subgroup	7	47	14.9%	0.074–0.275

***Table 2*: Observed prevalence in different cohorts of the study.**

		Sero-positive n (%)	Sero-negative n (%)	*p*-value
Socio-demographic characteristic	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[a]	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)	
Risk factors of Chagas disease	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 received blood in the past			
	Yes	0 (0)	18 (4.33)	0.7686
	No	6 (100)	398 (95.67)	
Risk OT	Have donated blood donation			
	Yes	2 (28.57)	124 (29.59)	0.6635
	No	5 (71.43)	295 (70.41)	

***Table 3*: Factors associated with Chagas disease Sero-positiveness.**

[a] Japan, Paraguay, Colombia, South Korea, United Kingdom.

OT (of transmission)

	Deterministic model					Probabilistic model			
			Incremental			Probability of cost-effectiveness at willingness to pay (YEN/QALY)			
SA: 35	**Cost (JPY)**	**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%	
Non-Screening	367,303,765	33,546.98							
SA: 45	**Cost (JPY)**	**QALYs**	**Costs**	**QALYs**	**ICER**	**2,500,000**	**5,000,000**	**7,500,000**	
Screening	1,195,251,834	34018.91	871,070,282	2884.65	301,967	100%	100%	100%	
Non-Screening	324,181,552	31134.26							

***Table 4*: Results of deterministic and probabilistic cost-effectiveness analyses for screening for *Trypanosoma cruzi* in asymptomatic adult Latin American migrants living in Japan at the primary health-care level (observed prevalence).**
SA:35, Starting age of 35 years-old; SA:45, Starting age of 45 years-old.

manufacturing. However, nearly 40% (36.4%, *n*=87) of the full-time workers were insured with National Health Insurance rather than the corresponding Employee Health Insurance. The rate of unemployment was 7.42% (*n*=27), represented mostly for women (88.89%, *p*-value ≥0.0001). The participants' characteristics in predisposing, enabling and needed factors are summarized in Appendix S17-18.

In the multivariable regression model (Table 5), the factors associated with access to the JNHS were predisposing and enabling factors. Females had a higher risk of not visiting a doctor when they needed (OR=2.30; 95%CI: 1.13–4.7) and people that lived in Japan for more than ten years were less likely not to visit the clinics when they needed it (OR=0.31; 95%CI: 0.10–0.91). Receiving information about the JNHS from official sources is a protective factor to perceive worse access to the JNHS (OR=0.13; 95%CI: 0.02–0.64). However, the people with difficulties in Japanese communication and the people unsatisfied with the JNHS were more likely to perceive worse access (OR=3.53; 95%CI:1.37–9.09 and OR=10.06; 95%CI: 3.2–31.72, respectively) and don't seek care when they need it (OR= 2.16, 95%CI: 1.03–4.52 and OR=10.06, 95%CI:3.2–31.72, respectively).

Discussion

To the best of our knowledge, this is the first large-scale study out of the blood banks to estimate the prevalence of CD in the people at risk in Japan from the community. The observed prevalence (1.6%) of CD in the study was double the estimated (0.75%) and also exceeds the prevalence reported by the blood bank (0.017%).[34]

In contrast with the previous CD cases reported in Japan, most people infected with *T.cruzi* in our study were asymptomatic.[12,13,35–37] Therefore, we estimate that most people affected with CD are underdiagnosed. According to our results, screening asymptomatic adult migrants from LA from PHC is a cost-effective strategy.

In the univariate sensitivity analysis, the CD prevalence had a strong influence on the ICER and the model would not be cost effective if the prevalence falls down below 0.34%. This will support that the model would be cost-effective even if we use the estimated prevalence (0.75%) instead the observed prevalence.

Because the positive participants were from Bolivia, arise the question of whether the screening should be offered to all LA or only to the Bolivians. On one hand, if the adjusted prevalence (0.12%) would represent the real situation, the screening will be cost-effective only for Bolivians. However, we believe that the adjustment is far to represent the real prevalence for two main reasons. Firstly, it assumes that there are no cases out of Bolivians. However, the Japanese literature reported cases in Brazilians.[12,13,38] Secondly, due to the low endemicity in Sao Paulo and Lima, the main districts of

Variables		Perceived worse access to a doctor/health worker (*N*=390)			Needed to see a doctor/health worker, but did not (*N*= 390)		
		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 communication barrier	No	Ref					
	Yes	3.53	1.37−9.09	**0.008**	2.16	1.03−4.52	**0.039**
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

***Table 5*: Factors associated with the access to the Japanese health care system among adult Latin American migrants in Japan.**

origin of Brazilians and Peruvian respectively, a larger number of participants would be necessary to showcases.[39–42] The results showed that the screening is cost-effective until a prevalence of 0.43%, supporting the inclusion of Bolivians and Peruvians. On the other hand, a country base screening has several disadvantages. Firstly, due to globalization and the urbanization phenomenon, it is difficult to maintain the classification of the people at risk of CD based on the endemic/non-endemic dichotomy.[4,21,43,44] Secondly, nowadays, the representation of migrants from LA in Japan is affected by the facilitation of the immigration of Japanese descendants. However, it might variate according to the migratory regulations.[10] As an additional benefit, the establishment of a system for CD would open the possibility of an extensive analysis of the situation of CD in Japan. Therefore, we support that Bolivian citizens should be prioritized, but the official recommendation should cover all the people at risk of CD, as recommended by the WHO.[2]

Being born in Bolivia was a factor associated with having a positive result in the standard diagnosis (p value= 0.0022). In other non-endemic countries, Bolivians represent the highest number of people affected with CD.[45–50] However, the prevalence of the community in Japan is 4-fold lower (5.3%) than in Europe (22%).[30,46,51–53] This can be explained because most of the Bolivians in Japan came from areas with Japanese colonies, Beni (42.2%) and Santa Cruz (38.2%). Beni is a low endemic area for CD[10,39,53] though Santa Cruz, where all the positive participants are, is one of the most endemic areas of the country, with a 45% in Camiri.[51] Whereas, it is lower (19%) in central-north Santa Cruz regions, where the Japanese colonies are located. but slightly higher than the prevalence of our Santa Cruz Subgroup (14%).[51] To the best of our knowledge, there are no data about the vector situation in the Japanese colonies in LA nor the influence of the distinctive lifestyle maintained in these colonies on the intradomiciliary vector infestation.

PHC-based screening system has been implemented in other non-endemic countries, referring to secondary or higher levels only if necessary.[3,20,54–56] In contrast, in Japan, the previous cases had been followed exclusively by secondary and tertiary levels.[13] The maintenance of this structure contributes to perpetuating the barriers for reaching the LA migrants who work and live under inflexible job schedules in rural areas of the country.[19,25] Even it is reported that the Japanese PHC doesn't have a decisive role as coordinator, Japan has a good public health system responsive to conduct periodically official screenings in the population.[57,58] We believe that these centers can offer CD screening and provide care to asymptomatic individuals in Japan. However, for a successful implementation, Japan will need to consider strategies to overcome the identified barriers that affect the access to medical care in the LA migrant population and the challenges in the diagnosis and treatment of CD.

Even the insurance rate (96.6%) of our responders showed an improvement compared with the results of Suguimoto et al where 20% of the LA were uninsured, still not all the full-time workers are covered with the corresponding Employee Health Insurance, reflecting the continuity of the irregulates in the migrant's job conditions reported for previous researches.[10,25,59–62] Additionally, Language abilities, being a woman, duration of stay in Japan, knowledge source regarding the JNHS, and JNHS satisfaction are all characteristics linked to healthcare access in this study's LA migrant population.

Although Japan increased the number of health interpreters recently, language is reported as a constant barrier independent of the migrant's nationality.[19,26,60,63] According to previous research, the use of cultural mediators could improve the quality of health communication.[64–65]

In our study, women were more likely not to visit a doctor when they need care. Gender social inequities have a negative impact on the process of seeking care worldwide.[66–69] The results showed that LA has a rate of unemployment three-fold higher than the national rate and is mostly women.[70] In addition, it is reported poorer mental health in migrant women living in Japan compared with native populations.[63,71] Because of the critical role of women in the mother-to-child transmission of *T.cruzi*, further research in this area would provide significant benefit.

The diagnostic protocol in Japan is an area of urgent improvement.[71,72] Due to the low number of positive participants and the country homogeneity, we cannot recommend the continuity of the use of RDT-CDP as a screening tool. Besides, RDT-CDP reported bad performance, explained by a possible association between the test sensitivity and the IgG levels, in the Peruvian population who represent 18% of the LA migrants in Japan.[9,73]

As it was reflected through this discussion and in the literature, several barriers affect the seeking behavior in Chagas disease, hindering that the 80% of the population in the screening model reach the screening. However, similar to European countries, the univariate analysis showed that the strategy will be cost-effective even if just 30% of the migrant population would be diagnosed and treated.[29]

We believe that establishing a patient road-map where the visits are compressed in time and frequency, like other non-endemic countries, will improve the diagnostic and treatment procedure.[56,20] Furthermore, providing locations for comprehensive care of CD in selected public health centers with a multidisciplinary team with transcultural and language skills will be essential to overcome the current barriers.[20]

We didn't assess the educational intervention implemented. However, recent research supported that digital tools, such as social media, can be a beneficial health education resource.[74,75]

As limitations, some factors could affect a possible recruitment bias. First, we couldn't obtain the reason of the people that declined to participate or a potential participant list. Second, even though we conducted almost the same number of activities with each embassy and our capacity per venue was the same, we had fewer Peruvian participants. Peruvians had significantly less knowledge about CD. The educational system tried to overcome this barrier, but as described in previous articles, the seeking behavior is influenced by both the previous and the acquired knowledge.[17,19] Third, part of the data collection was conducted during the COVID-19 pandemic and the entrance restrictions in the embassy venue influenced the short number of children in our cohort. Nevertheless, the embassies activities attend the needs of the entire LA population in Japan, ensuring that our cohort was similar to the actual population in other characteristics as gender, place of residence, and job. Fourth, few participants from other countries out of Brazilians, Bolivians, and Peruvians were included in the study. However, this trend mimics the real situation because these three countries represent nearly 95% of the total LA living in Japan.[9]

The cost-effectiveness analysis has some simplifications. We didn't consider the reduction of mother-to-child transmission even this is a priority area worldwide. Due to the lack of data, we assumed the same life expectancy of Japanese for the LA migrants. This could be a very optimistic approach considering that the Japanese had one of the highest life expectancies worldwide and the LA migrant's life conditions differ from Japanese.[10,25,26,39,71,76] However, research showed that the lifestyle of the host country also influences the migrant population.[77,78] Furthermore, studies conducted in Japan reported poor mental health in migrants.[70,79,80] Even though we didn't consider the impact that screening would have on their life due to the limited data in this area. Also, we couldn't include mental health in the need factors of accessibility to the JNHS, for the complexity of obtaining this data in our venues. In addition, there is no data about the quality of life of the CD patients in non-endemic areas and the utilities used were obtained in studies from endemic areas.

To conclude, this study provides important epidemiological and economic findings that support the implementation of a comprehensive CD screening program in the LA migrant population in Japan, particularly among Bolivians. However, additional efforts should focus on overcoming the identified barriers that could affect the implementation of a future system of care for the people affected with CD.

Supplementary appendix [9,16,26–30,60,63,81–98]

Contributors

IMIR, KH contributed to the conceptualization, methodology and validation. IMIR, KH, SM, CV contributed to data curation. IMIR and CV conducted the investigation. The formal analysis was conducted by IMIR, SH, CS. IMIR conducted the software. The study was supervised by KH. IMIR, KH, TM, KI, SM were the project administrators. KH, TM, KI, SM contributed to the funding acquisition and resources. IMIR, KH, CS conducted the visualization, writing and edition. All authors read and approved the final version.

Data sharing statement

The de-identified data are available on reasonable request to the corresponding author.

Editor note

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Declaration of interests

This research was supported by 2019 The Japanese Association for Infectious Diseases Clinical Study Promotion Grant and by the School of Tropical Medicine and Global Health of Nagasaki University. The author IMIR was awarded by Otsuka Toshimi Scholarship Foundation 2019 and 2020. The other authors have declared no conflicting interests.

Acknowledgments

The authors would like to thank the members of the Bolivian Embassy, the Consulate of Peru in Nagoya, and the Brazilian Consulate in Tokyo and Nagoya, that supported the data collection at their activities. Also, NGO-MAIKEN and Saitama Medical University for the help and contribution during the study process.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.lanwpc.2022.100574.

References

1 World Health Organization. Chagas disease (American trypanosomiasis). 2021. http://www.who.int/chagas/disease/en/. Accessed 20 November 2021.
2 WHO. *Ending the Neglect to Attain the Sustainable Development Goals: A Road Map for Neglected Tropical Diseases 2021–2030.* Geneva: World Health Organization; 2020.
3 PAHO. *Guía Para el Diagnóstico y el Tratamiento de la Enfermedad de Chagas.* Washington: Organización Panamericana de la Salud; 2019.
4 Nunes MCP, Beaton A, Acquatella H, et al. Chagas cardiomyopathy: an update of current clinical knowledge and management: a scientific statement from the American heart association. *Circulation.* 2018;138:12. https://doi.org/10.1161/CIR.0000000000000599.

5 Requena-Mendez A, Albajar-Viñas P, Angheben A, Chiodini P, Gascon J, Muñoz J. Health policies to control Chagas disease transmission in European countries. *PLoS Negl Trop Dis*. 2014;8. https://doi.org/10.1371/journal.pntd.0003245.

6 Yoshioka K, Manne-Goehler J, Maguire JH, Reich MR. Access to chagas disease treatment in the united states after the regulatory approval of benznidazole. *PLoS Negl Trop Dis*. 2020;14:1–15.

7 Manne-Goehler J, Reich MR, Wirtz VJ. Access to care for Chagas disease in the United States: a health systems analysis. *Am J Trop Med Hyg*. 2015;93:108–113.

8 Pinto A, Pett S, Jackson Y. Identifying chagas disease in Australia: an emerging challenge for general practitioners. *Aust Fam Phys*. 2014;43:440–442.

9 Statistic of Japan. Portal site of official statitstic of Japan. 2019. https://www.e-stat.go.jp/stat-search/files?page=1&layout=datalist&toukei=00250012&tstat=000001018034&cycle=1&year=20170&month=12040606&tclass1=000001060399. Accessed 29 October 2019.

10 Gotō J. Latin Americans of Japanese origin (Nikkeijin) working in Japan: a survey. *Google eBook*. 2007;7000:50.

11 Nara TA, Miura SA. Current situation of chagas disease in non - endemic countries. *Juntendo Med J*. 2015;61:389–395.

12 Imai K, Maeda T, Sayama Y, et al. Chronic Chagas disease with advanced cardiac complications in Japan: case report and literature review. *Parasitol Int*. 2015;64:240–242.

13 Imai K, Misawa K, Osa M, et al. Chagas disease: a report of 17 suspected cases in Japan, 2012–2017. *Trop Med Health*. 2019;47:38.

14 Departament de Salut Direcció General de Planificació i Avaluació. *Protocol for Screening and Diagnosing Chagas Disease in Pregnant Latin American Women and their Newborns Protocol*. editors. 1st ed. 2010 Cham: Generalitat de Catalunya; 2010.

15 Van Belle G. *Statistical Rules of Thumb Van Belle G, Wiley Series in Probability and Statistics*. Cham: Wiley; 2008:49–50.

16 WHO. Chagas diseases in Latin America: an epidemiological update based on 2010 estimates. *Weekly Epidemiological Record*. 6. World Health Organization; 2015:33–44.

17 Ventura-Garcia L, Roura M, Pell C, et al. Socio-cultural aspects of Chagas disease: a systematic review of qualitative research. *PLoS Negl Trop Dis*. 2013;7. https://doi.org/10.1371/journal.pntd.0002410.

18 Sanmartino M, Amieva C, Scazzola MS, Menegaz A. *Hablamos de Chagas: Aportes Para Re-Pensar la Problemática Con Una Mirada Integral*. Buenos Aires: CONICET - Consejo Nacional de Investigaciones Científicas y Técnicas; 2015.

19 Iglesias Rodríguez IM, Mizukami S, Manh DH, et al. Knowledge, behaviour and attitudes towards Chagas disease among the Bolivian migrant population living in Japan: a cross-sectional study. *BMJ Open*. 2020;10:e032546.

20 Sancho FJ, Bernal O, Lazarus JV. Comprehensive Chagas disease care: a global effort. In: Pinazo Delgado MJ, Gascón J, eds. *Chagas Disease*. Cham: Springer International Publishing. Kindle; 2020:342–371. https://doi.org/10.1007/978-3-030-44054-1_12.

21 Sanmartino M, Avaria Saavedra A, de la Torre Avila L. Social approach to Chagas disease: a first step to improve access to comprehensive care. In: Pinazo Delgado MJ, Gascón J, eds. *Chagas Disease*. Cham: Springer International Publishing. Kindle; 2020:112–139. https://doi.org/10.1007/978-3-030-44054-1_12.

22 Chagas en Japon. 2021. https://chagasjapon.wixsite.com/website. Accessed 15 December 2021.

23 Jackson Y, Gétaz L, Wolff H, et al. Prevalence, clinical staging and risk for blood-borne transmission of Chagas disease among Latin American migrants in Geneva, Switzerland. *PLoS Negl Trop Dis*. 2010;4:1–7.

24 Sanchez DR, Traina MI, Hernandez S, Smer AM, Khamag H, Meymandi SK. Chagas disease awareness among Latin American immigrants living in Los Angeles, California. *Am J Trop Med Hyg*. 2014;91:915–919.

25 Suguimoto SP, Ono-kihara M, Feldman MD, Kihara M. Latin American immigrants have limited access to health insurance in Japan : a cross sectional study. *BMC Public Health*. 2012;12:238.

26 Shakya P, Tanaka M, Shibanuma A, Jimba M. Nepalese migrants in Japan: what is holding them back in getting access to healthcare? *Plos One*. 2018;13:e0203645.

27 Scheppers E, van Dongen E, Dekker J, Geertzen J, Dekker J. Potential barriers to the use of health services among ethnic minorities: a review. *Fam Pract*. 2006;23:325–348.

28 WHO. World Health Organization Expert Committee. *Control of Chagas disease*. Brasilia: World Health Organization; 2002.

29 Requena-Méndez A, Bussion S, Aldasoro E, et al. Cost-effectiveness of Chagas disease screening in Latin American migrants at primary health-care centres in Europe: a Markov model analysis. *Lancet Global Health*. 2017;5:e439–e447.

30 Muñoz J, Prat JG, Gállego M, et al. Clinical profile of Trypanosoma cruzi infection in a non-endemic setting: immigration and Chagas disease in Barcelona (Spain). *Acta Trop*. 2009;111:51–55.

31 Global IS. *Una Batalla Por La Salud De Todos. El Liderazgo de España En La Lucha Contra El Chagas*. Barcelona: Instituto de Salud Global; 2017. (in Spanish).

32 Romay-Barja M, Boquete T, Martinez O, Benito A, Blasco-Hernández T. Factors associated with Chagas screening among immigrants from an endemic country in Madrid, Spain. *PLoS One*. 2020;15:1–10.

33 Monge-Maillo B, López-Vélez R. Challenges in the management of Chagas disease in Latin-American migrants in Europe. *Clin Microbiol Infect*. 2017;23:290–295.

34 Sayama Y, Furui Y, Takakura A, et al. Seroprevalence of Trypanosoma cruzi infection among at-risk blood donors in Japan Yusuke. *Transfusion*. 2018;9999:1–8. https://doi.org/10.1111/trf.14999.

35 Imai K, Maeda T, Sayama Y, et al. Mother-to-child transmission of congenital Chagas disease, Japan. *Emerg Infect Dis*. 2014;20:146–148.

36 Satoh F, Tachibana H, Hasegawa I, Osawa M. Sudden death caused by chronic Chagas disease in a non-endemic country: autopsy report. *Pathol Int*. 2010;60:235–240.

37 Ueno Y, Nakamura Y, Takahashi M, et al. A highly suspected case of chronic Chagas' heart disease diagnosed in Japan. *Jpn Circ J*. 1995;59:219–223. https://doi.org/10.1253/jcj.59.219.

38 WHO. *World Health Organization Western Pacific Region. Informal Consultation on Chagas Disease in the Western Pacific*. Nagasaki: World Health Organization; 2011.

39 Manzenreiter W. Living under more than one sun: the Nikkei Diaspora in the Americas. *Contemp Jpn*. 2017;29:193–213.

40 Martins-Melo FR, Ramos AN, Alencar CH, Heukelbach J. Prevalence of Chagas disease in Brazil: a systematic review and meta-analysis. *Acta Trop*. 2014;130:167–174.

41 Ramos-Rincón JM, Ortiz-Martínez S, Vásquez-Chasnamote ME. Chagas disease in pregnant women in the Peruvian Amazon basin. Cross-sectional study. *Front Vet Sci*. 2020;7:1–6.

42 Sugie Y, Kodama T. Immigrant health issue in Japan: the global contexts and a local response to the issue. *Tor Public Health*. 2005;1:1–22.

43 Sanmartino M. Tener Chagas en contexto urbano: concepciones de varones residentes en la region de la Plata (Argentina). *Rev Bioméd*. 2009;20:216–227.

44 Moscatelli G, Berenstein A, Tarlovsky A, et al. Urban Chagas disease in children and women in primary care centres in Buenos Aires, Argentina. *Mem Inst Oswaldo Cruz*. 2015;110:644–648.

45 Angheben A, Anselmi M, Gobbi F, et al. Chagas disease in Italy: breaking an epidemiological silence. *Eurosurveillance*. 2011;16:1.

46 Requena-Méndez A, Aldasoro E, de Lazzari E, et al. Prevalence of Chagas disease in Latin-American migrants living in Europe: a systematic review and meta-analysis. *PLoS Negl Trop Dis*. 2015;9:1–15.

47 Ramos JM, Ponce Y, Gallegos I, Flóres-Chávez M, Cañavate C, Gutiérrez F. *Trypanosoma cruzi* infection in Elche (Spain): comparison of the seroprevalence in immigrants from Paraguay and Bolivia. *Pathog Global Health*. 2012;106:102–106.

48 Romay-Barja M, Boquete T, Martinez O, et al. Chagas screening and treatment among Bolivians living in Madrid, Spain: The need for an official protocol. *PLoS One*. 2019;14:e0213577. https://doi.org/10.1371/journal.pone.0213577.

49 Salvador F, Treviño B, Sulleiro E, et al. Trypanosoma cruzi infection in a non-endemic country: epidemiological and clinical profile. *Clin Microbiol Infect*. 2014;20:706–712.

50 Perez-Molina JA, Molina I. Chagas disease. *Lancet*. 2018;391:82–94. https://doi.org/10.1097/01.JAA.0000547749.92933.6a.

51 Alonso-vega C, Billot C, Torrico F. Achievements and challenges upon the implementation of a program for national control of congenital Chagas in Bolivia: results 2004–2009. *PLoS Negl Trop Dis*. 2013;7. https://doi.org/10.1371/journal.pntd.0002304.

52 Coll O, Juncosa T, Verge M, et al. Prevalence and vertical transmission of trypanosoma cruzi infection among pregnant Latin American women attending 2 maternity clinics in Barcelona, Spain. *Clin Infect Dis*. 2018;48:1736–1740. https://doi.org/10.1086/599223.

53 Araújo-Jorge TC De, Medrano-Mercado N. Chagas disease in Bolivia: a brief review of the urban phenomena. *Rev Biomed*. 2009;20:236–244.
54 Sosa-Estani S, Colantonio L, Segura EL. Therapy of Chagas disease: implications for levels of prevention. *J Trop Med*. 2012;2012. https://doi.org/10.1155/2012/292138.
55 Echavarría NG, Echeverría LE, Stewart M, Gallego C, Saldarriaga C. Chagas disease: chronic chagas cardiomyopathy. *Curr Probl Cardiol*. 2021;46(3):1–16.
56 Roca Saumell C, Soriano-Arandes A, Solsona Díaz L, Gascón Brustenga J. Documento de consenso sobre el abordaje de la enfermedad de Chagas en atención primaria de salud de áreas no endémicas. *Aten Prim*. 2015;47:308–317.
57 Takamura A. The present circumstance of primary care in Japan. *Res Artic Open Access Qual Prim Care*. 2015;23:262–266.
58 Shinji T, Kenichi O, Tomofumi S. Topics : recent topics in public health in Japan review public health center (Hokenjo) as the frontline authority of public health in Japan : contribution of the national institute of public health to its development. *J Natl Inst Public Health*. 2020;69:2–13.
59 Parikh NS. Migrant health in Japan : safety-net policies and advocates' policy solutions 日本における移民の健康 —— 安全策と擁護側の解決策. *Asia-Pacific J*. 2010;8:1–15.
60 Sugie Y, Kodama T. Immigrant health issue in Japan: the global contexts and a local response to the issue. *Toronto Public Health*. 2005;1:1–22.
61 Kawamura L. The multiple identities of the Nikkei community. Brazilian migrations: social and cultural networks between Brazil and Japan. Discover Nikkei 2008; http://www.discovernikkei.org/es/journal/2008/12/3/multiplas-identidades/.
62 NHK. Watashitachi wa gaijin janai (Nós Não Somos Gaijin) – a história dos 30 anos de risos e lágrimas dos brasileiros no Japão. https://www6.nhk.or.jp/nhkpr/post/original.html?i=27075. Accessed 11 November 2021.
63 Nagamatsu Y, Barroga E, Sakyo Y, Igarashi Y, Hirano O Y. Risks and perception of non-communicable diseases and health promotion behavior of middle-aged female immigrants in Japan: a qualitative exploratory study. *BMC Women's Health*. 2020;20:1–9.
64 Verrept H. What are the roles of intercultural mediators in health care and migrants in the WHO European Region? Evidence for health and well-being in context. *What are the roles of intercultural mediators in health care and migrants in the WHO European Region? Evidence for health and well-being in context*. 64. World Health Organization Europe; 2019.
65 Abubakar I, Aldridge RW, Devakumar D, et al. The UCL–Lancet commission on migration and health: the health of a world on the move. *Lancet*. 2018;392:2606–2654.
66 WHO. *Women on the Move: Migration, Care Work and Health*. Geneva: World Health Organization; 2017. Licence: CC BY-NC-SA 3.0 IGO.
67 Ismayilova L, Nim H, Stacey L, Louisa NE, Assel G, Rozental Y. Mental health and migration: depression, alcohol abuse, and access to health care among migrants in Central Asia. *J Immigr Minor Health*. 2014;16:1138–1148.
68 Schoevers MA, Van Den Muijsenbergh METC, Lagro-Janssen ALM. Self-rated health and health problems of undocumented immigrant women in the Netherlands: a descriptive study. *J Publ Health Policy*. 2009;30:409–422.
69 Malmusi D, Borrell C, Benach J. Migration-related health inequalities: showing the complex interactions between gender, social class and place of origin. *Soc Sci Med*. 2010;71:1610–1619.
70 The World Bank 2020, Unemployment rate in Japan. International Labour Organization, ILOSTAT database. https://data.worldbank.org/indicator/SL.UEM.TOTL.NE.ZS?locations=JP. Accessed 10 Februry 2021.
71 Miller R, Tomita Y, Ing K, Ong C, Shibanuma A. Mental well-being of international migrants to Japan: a systematic review. *BMJ Open*. 2019. https://doi.org/10.1136/bmjopen-2019-029988.
72 Imai K, Murakami T, Misawa K, Fujikura Y, Kawana A. Parasitology international optimization and evaluation of the ARCHITECT Chagas assay and in-house ELISA for Chagas disease in clinical settings in Japan. *Parasitol Int*. 2021;80:102221.
73 Verani JR, Seitz A, Gilman RH, et al. Geographie variation in the sensitivity of recombinant antigen-based rapid tests for chronic trypanosoma cruzi infection. *Am J Trop Med Hyg*. 2009;80:410–415.
74 Smith M-K, Denali DL. Social media in health education, promotion, and communication: reaching rural Hispanic populations along the USA/Mexico border region. *J Racial Ethnic Health Disparities*. 2014;1:194–198.
75 Stellefson M, Paige SR, Chaney BH, Chaney JD. Evolving role of social media in health promotion: updated responsibilities for health education specialists. *Int J Environ Res Public Health*. 2020;17. https://doi.org/10.3390/ijerph17041153.
76 UNDP United Nations Development Programme, Human Development Reports, Japan. http://hdr.undp.org/en/countries/profiles/JPN#. Accessed 20 August 2019.
77 Tsugane S. Ecological, H & studies of Japanese immigrants and their descendants in South America. *Jpn Hyg Mag*. 1992;47:775–784.
78 Petroni TN, Nunes DP, Duarte, et al. Non-Japanese, Japanese and Japanese descendant older adults in the health, wellbeing and aging study: functional and health conditions *Rev Bras Epidemiol*. 2018;2:1–12.
79 Takubo Y, Nemoto T, Iwai M, et al. Demographic and clinical characteristics of foreign nationals accessing psychiatric services in Japan: a multicentre study in a metropolitan area. *BMC Psychiatry*. 2020;20:1–10.
80 Koyama A, Okumi H, Matsuoka H, Makimura C, Sakamoto R, Sakai K. The physical and psychological problems of immigrants to Japan who require psychosomatic care: a retrospective observation study. *BioPsychoSocial Med*. 2016;10:1–10.
81 Wilson LS, Strosberg AM, Barrio K. Cost-effectiveness of Chagas disease interventions in Latin America and the Caribbean: Markov models. *Am J Trop Med Hyg*. 2005;73:901–910.
82 Imaz-Iglesia I, Miguel LGS, Ayala-Morillas LE, et al. Economic evaluation of Chagas disease screening in Spain. *Acta Trop*. 2015;148:77–88.
83 Lee BY, Bacon KM, Bottazzi ME, Hotez PJ. Global economic burden of Chagas disease: a computational simulation model. *Lancet Infect Dis*. 2013;13:342–348.
84 Ministry of Health, Labour and welfare. Various information for medical fee. 2020; http://shinryohoshu.mhlw.go.jp/shinryohoshu/kaitei/doKaiteiR02;jsessionid=47B1C5A3D82D0FF2E67C962AB9C72CD8. Accessed 20 November 2020.
85 Pinazo MJ, Muñoz J, Posada E, et al. Tolerance of benznidazole in treatment of Chagas' disease in adults. *Antimicrob Agents Chemother*. 2010;54:4896–4899.
86 Kamae I, Thwaites R, Hamada A, et al. Health technology assessment in Japan : a work in progress. *J Med Econ*. 2020;23:317–322.
87 Hasegawa M, Komoto S, Shiroiwa T, Fukuda T. Formal implementation of cost-effectiveness evaluations in Japan: a unique health technology assessment system. *Value Health*. 2019;23:43–51.
88 Ministry of Health, Labour and welfare. Abridged life tables for Japan. 2019; https://www.mhlw.go.jp/english/database/db-hw/lifetb19/index.html. Accessed 19 November 2020.
89 WHO. *WHO-CHOICE Estimates of Cost for Inpatient and Outpatient Health Service Delivery*. World Health Organization; 2010. https://www.who.int/choice/cost-effectiveness/inputs/country_inpatient_outpatient_2010.pdf?ua=1.
90 The World Bank. PPP conversion factor, private consumption. 2019. http://data.worldbank.org/indicator/PA.NUS.PRVT.PP. Accessed 28 November 2020.
91 Soejima K, Asano T, Ishikawa T, et al. Performance of leadless pacemaker in japanese patients vs. Rest of the world: results from a global clinical trial. *Circ J*. 2017;81:1589–1595.
92 Kanaoka K, Okayama S, Nakai M, et al. Hospitalization costs for patients with acute congestive heart failure in Japan. *Circ J*. 2019;83:1025–1031.
93 Kunishima H, Ito K, Laurent T, Abe M. Healthcare burden of recurrent Clostridioides difficile infection in Japan: a retrospective database study. *J Infect Chemother*. 2018;24:892–901.
94 Urabe A, Shimada K, Kawai S. *Kyō no chiryō-yaku. Kaisetsu to Binran*. 2020th ed. Tokyo, Japan: Nankodo Co., Ltd; 2020.
95 Cohen J. A coefficient of agreement for nominal scales. *Educ Psychol Meas*. 1960;20:37–46.
96 Sáez-Alquezar A, Junqueira ACV, Durans A, et al. Application of who international biological reference standards to evaluate commercial serological tests for chronic Chagas disease. *Memorias do Instituto Oswaldo Cruz*. 2020;115:1–8.
97 Jahangir E, Irazola V, Need RA. Enabling, predisposing, and behavioral determinants of access to preventative care in Argentina: analysis of the national survey of risk factors. *PLoS One*. 2012;7. https://doi.org/10.1371/journal.pone.0045053.
98 Briggs A, Sculpher M, Claxton K. *Decision Modelling for Health Economic Evaluation*. United Kingdom: Oxford University; 2006.