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Cost-effectiveness of Chagas disease screening in Latin American migrants at primary health-care centres in Europe: a Markov model analysis

Ana Requena-Méndez, Sheila Bussion, Edelweiss Aldasoro, Yves Jackson, Andrea Angheben, David Moore, María-Jesús Pinazo, Joaquim Gascón, Jose Muñoz, Elisa Sicuri



Summary

Background Chagas disease is currently prevalent in European countries hosting large communities from Latin America. Whether asymptomatic individuals at risk of Chagas disease living in Europe should be screened and treated accordingly is unclear. We performed an economic evaluation of systematic Chagas disease screening of the Latin American population attending primary care centres in Europe.

Methods We constructed a decision tree model that compared the test option (screening of asymptomatic individuals, treatment, and follow-up of positive cases) with the no-test option (screening, treating, and follow-up of symptomatic individuals). The decision tree included a Markov model with five states, related to the chronic stage of the disease: indeterminate, cardiomyopathy, gastrointestinal, response to treatment, and death. The model started with a target population of 100 000 individuals, of which 4·2% (95% CI 2·2–6·8) were estimated to be infected by *Trypanosoma cruzi*. The primary outcome was the incremental cost-effectiveness ratio (ICER) between test and no-test options. Deterministic and probabilistic analyses (Monte Carlo simulations) were performed.

Findings In the deterministic analysis, total costs referred to 100 000 individuals in the test and no-test option were €30 903 406 and €6 597 403 respectively, with a difference of €24 306 003. The respective number of quality-adjusted life-years (QALYs) gained in the test and no-test option were 61820·82 and 57 354·42. The ICER was €5442. In the probabilistic analysis, total costs for the test and no-test option were €32 163 649 (95% CI 31 263 705–33 063 593) and €6 904 764 (6 703 258–7 106 270), respectively. The respective number of QALYs gained was 64 634·35 (95% CI 62 809·6–66 459·1) and 59 875·73 (58 191·18–61 560·28). The difference in QALYs gained between the test and no test options was 4758·62 (95% CI 4618·42–4898·82). The incremental cost-effectiveness ratio (ICER) was €6840·75 (95% CI 2545–2759) per QALY gained for a treatment efficacy of 20% and €4243 per QALY gained for treatment efficacy of 50%. Even with a reduction in Chagas disease prevalence to 0·05% and with large variations in all the parameters, the test option would still be more cost-effective than the no-test option (less than €30000 per QALY).

Interpretation Screening for Chagas disease in asymptomatic Latin American adults living in Europe is a cost-effective strategy. Findings of our model provide an important element to support the implementation of *T cruzi* screening programmes at primary health centres in European countries hosting Latin American migrants.

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Introduction

Chagas disease is emerging in Europe, where prevalence has increased enormously during the past 15 years due to migration from Chagas disease endemic countries of Latin America.¹ The global economic burden of Chagas disease has been estimated at about US\$7·2 billion a year, with around 15% of costs pertaining to non-endemic countries, and with the highest cost attributable to cardiovascular disease and early mortality.² 30–40% of chronically infected individuals develop cardiac complications, gastrointestinal complications, or both,³ but most remain indeterminate (asymptomatic for life and with a normal 12-lead electrocardiogram and chest-radiograph).³ Antiparasitic therapy is effective at curing infection in acute, congenital, and early chronic disease.^{4,5}

The current tendency in both endemic and non-endemic countries is to give antiparasitic treatment to chronic asymptomatic adults and patients with early cardiomyopathy.⁶ However, this practice is based on evidence from only one open-label, non-randomised, non-blinded trial and from other longitudinal studies that have shown decreased progression of cardiomyopathy and mortality.^{7,8}

In Europe, transmission from individuals infected with *Trypanosoma cruzi* (*T cruzi*), including from those who are asymptomatic, occurs either vertically or through transfusion of infected blood products or transplantation of infected organs.⁹ Screening programmes are currently recommended in blood-banks and transplant settings and

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Research in context

Evidence before this study

We did a systematic search of PubMed using the search terms ("Chagas" AND ("cost" OR "economic") AND "screening"). We restricted the search to documents available in English and Spanish; the last search was done on Oct 8, 2015. We found four articles that evaluated the cost-effectiveness of control strategies in Latin America all based in vector control strategies, two more articles that evaluated the global cost or the burden of Chagas disease, two studies that evaluated the cost-effectiveness of Chagas disease screening in blood-banks in non-endemic areas, and two economic studies of the screening of Chagas disease in pregnant women and their infants. However, the search did not find any economic studies regarding *Trypanosoma cruzi* screening in asymptomatic chronic adults at the primary care level.

Added value of this study

This study is the first to show the cost-effectiveness of a strategy of Chagas disease screening at primary care level of asymptomatic Latin-American adults living in non-endemic areas.

Implications of all the available evidence

Our findings provide an important element to support the implementation of a primary care *T. cruzi* screening programme in European countries hosting Latin American migrants. Other elements should be considered such as the national Latin American migrant profiles, national legislations, and health system characteristics as well as the acceptability of the screening programme.

have already been implemented in some European countries, such as Spain, the UK, and Switzerland.¹⁰ Screening of pregnant women from Latin American endemic countries has also been shown to be cost-effective,¹¹ and has been identified as a priority for Chagas disease control in Europe,¹⁰ although it has not yet been widely implemented.

Among all interventions, the economic value of systematically screening—and treating—migrants from Chagas disease-endemic countries remains unclear. Therefore, we performed an economic evaluation of Chagas disease screening of Latin American patients at European primary care centres. Previous studies have identified primary care centres as key channels through which opportunities arise to identify the infection in patients from Latin America attending the centre for any reason.^{12,13}

Methods

Prevalence of Chagas disease in migrant population

Prevalence was based on country-specific data from a recent systematic review and meta-analysis showing a random effect pooled Chagas disease prevalence of 4.2% (95% CI 2.2–6.8) among Latin-American migrants.¹⁴ The pooled prevalence of Chagas disease by country of origin among Latin American migrants in European countries is summarised in the appendix (p 1). Because the meta-analysis involved studies from France, Germany, Italy, Switzerland, and Spain, only costs from these five countries were included in this economic evaluation. These are also the countries in Europe with the highest number of immigrants from Latin America.

Cost-effectiveness model

We developed a decision-tree to compare the cost-effectiveness of (1) screening all Latin American asymptomatic patients seen at primary health centres, treating the positive cases, and following them up with

periodic visits and interventions (test option) and (2) doing nothing actively but screening and treating only symptomatic individuals that develop Chagas disease complications (no-test option). Within the decision-tree, the natural history of the disease was represented through a Markov model (figure 1), which is considered the most appropriate model for assessing chronic diseases or diseases that progress over time, such as Chagas disease.^{2,15}

The Markov model considered each infected person to be in one of a finite number of health states related to chronic Chagas disease during a 1 year cycle. Every year, each patient either remained in the same state or moved to another one according to defined transition probabilities (figure 1). Costs and utilities in terms of quality-adjusted life-years (QALYs) expectancy, a measure of health outcome that combines the value of length of life and the quality of life into a single indicator,¹⁶ were associated with each of the five states: indeterminate Chagas disease, cardiac form, gastrointestinal form, response to treatment, and death (from any cause). As figure 1 shows, in this model, a patient could not move from treatment response to the cardiac or gastrointestinal forms or from death to any other forms. The model terminated when all patients reached the death state. The model started with a target population of 100 000 Latin American individuals from Chagas disease-endemic countries, and 4.2% (95% CI 2.2–6.8) were assumed to be infected with *T. cruzi*.¹⁴

The first year-cycle of the model (year 0) starts with parameter values taken from the study by Salvador and colleagues,¹⁷ indicating that 85.8% of individuals infected with *T. cruzi* were asymptomatic and that 14.1% of asymptomatic patients were in the cardiac form, whereas the remainder were in the indeterminate form.¹⁷ The mean age of the population was set at 35 years.¹⁸

In the base case analysis, 80% of the target population (patients at risk of Chagas disease) was screened and treated. The remaining 20% followed the same disease pattern as the individuals in the no-test option, which

See Online for appendix

implies that the probability of developing cardiomyopathy was the same in both cases.

Disease states and transition probabilities

In the test option, *T. cruzi* serological screening was applied to all Latin American patients; in the event of a positive result, a chest radiograph and an annual electrocardiogram (ECG) were undertaken. We assumed that no false positive or negative tests occurred. According to the literature, sensitivity of the most widely used serological tests (eg, CLIA recombinant test¹⁹) is virtually 100% and accordingly, some studies recommend that the *T. cruzi* screening should be based on a single unique test when the test done is an ELISA assay.²⁰ However, it is generally held that the infection should be confirmed with a second serological test: this was the screening strategy in our model. We also considered a 4% presumptive false-positive cases with the first test, for which a third screening was then required to resolve potential discrepancies between the first and the second test. Therefore, our screening strategy consisted of a unique serological test in 92%, two tests in 4%, and three tests in 4% of the total population screened. Assumption was made that nobody would refuse the treatment and all positive cases received treatment according to the current clinical practice in non-endemic areas.^{17,18} This entails treatment with the antiparasitic drug benznidazole for 60 days, as per WHO recommendations,²¹ with complete blood count and basic biochemistry monitoring at follow-up visits every 15 days.^{17,18} In the no-test option, only symptomatic patients transitioning to the cardiac or gastrointestinal forms were diagnosed with Chagas disease and treated accordingly.

Based on the literature, the probability of moving from the indeterminate form to the cardiac form was set at 2% a year for the no-test option (progression to cardiomyopathy in untreated patients²²) and at 0.5% for the test option.⁷ The probability of moving to the gastrointestinal form was conservatively considered at 0.3% a year for both options based on little evidence that antitrypanosomal therapy mitigates the risk of progression to intestinal disease.²² The probability of death attributable to Chagas disease was 3.9% in patients with cardiomyopathy and was set at zero in both indeterminate and gastrointestinal forms²³ (appendix p 2). Possibility of reinfection was not considered.

Age-specific probability of death due to any cause was calculated using data from the Spanish Instituto Nacional de Estadística.²⁴ These values are similar across European countries included in our study.²⁵ Response to treatment was defined as conversion to negative of previously positive serology as described elsewhere.^{8,26} Two scenarios were considered: a base-case 20% response to treatment, 5 years after receiving benznidazole, as reported by Viotti and colleagues,⁸ and an assumption of a more optimistic 50% response to treatment, 5 years after receiving benznidazole. Spontaneous positive to negative conversion was not considered.

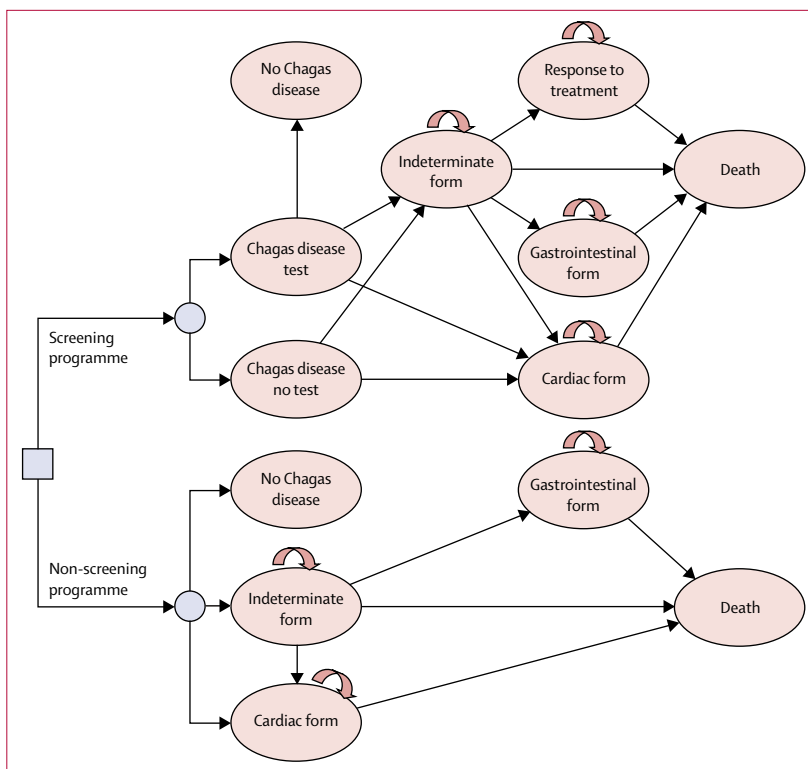


Figure 1: Decision-tree for *Trypanosoma cruzi* screening

We based values of the probabilities of undertaking tests and interventions in the cardiomyopathy and gastrointestinal states on the consensus of data from two different clinical groups. One group is the NHEPACHA network (Nuevas Herramientas para el Diagnóstico y la Evaluación del Paciente con Enfermedad de Chagas) formed by health professionals who are highly experienced in Chagas disease from both endemic (Bolivia) and non-endemic areas (Europe); the second group was composed of a subgroup of researchers from the COHEMI project (Coordinating resources to assess and improve Health status of Migrants from Latin America). Members of the NHEPACHA network provided a value for each parameter, which was then discussed, edited where needed, and validated by the members of COHEMI. The level of uncertainty was increased for these parameters because of the absence of evidence-based data. The probabilities were as follows: echocardiogram 100%, Holter ECG monitor study 30%, stress test 8%, pacemaker 2%, implantable cardioverter-defibrillator 3%, electrophysiology study 3%, and transplantation 1%²⁷ (appendix p 2). Based on the literature, it was established that 4.2% of individuals in this state would develop congestive heart failure²⁸ and therefore require an annual echocardiogram and examination by a cardiologist as well as specific medication (beta-blockers, antihypertensives, and diuretics).

Assumption was made that individuals in the gastrointestinal state would need to undergo small bowel radiographs (100%), barium enema (100%), oesophageal manometry (5%), and surgery (1%; appendix p 2).

Costs

We took the health-care provider perspective to estimate costs. The costs of all visits, tests, drugs, and interventions were taken from the pricelist of Hospital Clínic-Barcelona (Barcelona, Spain), a leading Spanish hospital. The costs of adverse event management were also included (appendix p 7).

To estimate real costs, all values from the pricelist were reduced of an overhead component and, where applicable, of a mark-up of 20%. Costs were extrapolated to France, Germany, Italy, and Switzerland using the WHO Choice cost per bed-day ratios between each country and Spain.²⁹ The ratio for Italy and Spain, for instance, was 1·10 based on a respective per bed-day cost of €476·21 and €433·56. Thus, assuming that a coronary artery bypass costs €5484·68 in Spain, this would cost €6033·15 (= 5484·68×1·10) in Italy (appendix p 7).

Costs of programme uptake (appendix p 8) were estimated based on data published by Imaz-Iglesia and colleagues³⁰ for Spain. These costs included, among others, programme coordination, equipment, travel, and meetings for a period of 5 years. Because human resources represented the major cost associated with programme uptake, estimates from Spain were extrapolated to the other countries by applying the purchasing power parity (PPP) conversion factor.³¹ Finally, the cross country average and the relative variability were used in the model. No additional programme recurrent costs were computed beyond the first 5 years of uptake. Costs were discounted by 3%.¹⁹ Because there was no information in the hospital pricelist about traded and non-traded components of costs, in a further scenario, all costs, not only those associated with programme uptake, were PPP adjusted with the exclusion of drug costs, which can be considered traded goods (appendix p 2).

QALYs

In the model, length of life resulted from the combination of a series of parameters, in particular the probability of dying (all causes) and of dying due to Chagas disease. The quality weights (utilities) applied were 0·9625 for the indeterminate form and 0·7171 (average between 0·769 for mild cardiomyopathy and 0·6651 for severe cardiomyopathy) for the cardiomyopathy and gastrointestinal forms.³² QALYs, like costs, were discounted by 3%.³²

Data analysis

The model was estimated by applying deterministic and probabilistic analyses in Microsoft Excel. Deterministic analysis was done with mean values for each parameter (appendix p 2). Univariate sensitivity analysis was done

by varying the mean value of each parameter to both +100% and -99% or to the minimum or maximum feasible value (eg, 0 and 1 if parameters were probabilities). Results of the univariate sensitivity analysis were shown in a tornado diagram. Three scenarios alternative to the base case were depicted: one with a response to treatment of 50% (base case 20%); a second one with a prevalence of Chagas disease of 20%, corresponding, roughly, to the one estimated among Bolivian immigrants (base case 4·2%); and a third one with PPP adjustments for all costs excluding drug costs. A threshold analysis allowed the estimation of the cutoff points of Chagas disease prevalence and of probability of screen and treat at which the choice between the test and no-test options would switch. A strategy was considered to be cost-effective if the cost per QALY gained was less than the currently accepted threshold in Europe of €30 000.^{33,34}

For the probabilistic analysis, parameters were included as probability distributions. Probabilistic distributions were assigned to parameters based on good research practice.³⁵ Because individual data were not available in most cases, the standard deviation (SD) of each parameter was assumed to be 20% of the mean values (appendix p 2), which is an accepted variance to construct parameter ranges for probabilistic sensitivity analysis when variance is unknown.³⁶ For QALYs, an SD of 10% was considered for the indeterminate form's quality weights because this phase is perceived to be quite homogeneous across people infected with *T cruzi*: in the indeterminate phase, the infection is asymptomatic and patients are well. In the case of clinical service costs, the SD was based on estimated costs for each of the five countries.

Probabilistic analysis was performed through Monte Carlo simulations. The number of iterations needed to produce stable results was based on the graphical representation of the cumulative average net monetary benefits (threshold level×incremental effects - incremental costs). Simulations were graphically presented in the cost-effectiveness plane³⁷ and as acceptability curves.³⁸ The cost-effectiveness plane plots all Monte Carlo simulations produced with respect to QALYs gained and incremental costs, allowing visualisation of the confidence area delimited by the 95% confidence ellipses. Acceptability curves show the probability of the test option to be cost-effective according to theoretical policy-maker willingness to pay for each QALY gained.

The study followed the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement (appendix p 9).

Role of the funding source

The funder of the study (the European Commission) had no role in the study design, data collection, data analysis, data interpretation, or writing the report. All authors had full access to all study data and had final responsibility for the decision to submit for publication.

Results

For the cost-effectiveness model, figure 2 shows the number of individuals present at each cycle (year) in each of the five health states for the test (figure 2A) and no-test (figure 2B) options. At the first cycle of the target population of 100 000, 4.2% ($n=4200$) had Chagas disease, 85.8% of them ($n=3604$) were asymptomatic, and 14.1% ($n=505$) of them had an underlying cardiomyopathy despite being asymptomatic. Considering an 80% probability of being screened, 3099 individuals were finally screened in the base case analysis. The number of individuals in the indeterminate form decreased over time (figure 2A; dark blue line). In the test option the line is discontinuous because 5 years after treatment (year 5), 20% of individuals would seroconvert and move to response to treatment (figure 2A; orange line). The number of individuals with the cardiac form (figure 2B; green line) was higher in the no-test option at all timepoints. The number of deaths in the no-test option increased faster over time (figure 2C).

Results of the deterministic and probabilistic cost-effectiveness analyses are reported in the table. For the deterministic analysis, the total cost in the test option was €30 903 406, whereas this was €65 974 03 in the no-test option, with a difference of €24 306 003. However, the respective number of QALYs gained in the test option was 61820.82 and in the no-test option was 57354.42. The incremental cost-effectiveness ratio (ICER) was €5442.

In the univariate sensitivity analysis, the structural parameters of the model, such as the probabilities of screening and treatment, Chagas disease prevalence, and proportion of asymptomatic individuals, had the strongest influence on the ICER (appendix p 11). In particular, a drop in the probability of screening and treatment (from 80% to 10%) would determine the intervention to be largely not cost-effective (ICER €57 000 per QALY gained). With a 99% drop in Chagas disease prevalence and in the probability to be asymptomatic down to 0.042% and 0.858%, respectively, the intervention would no longer be cost-effective. Neither an increase nor a decrease in any other parameter would change the choice from test to no-test option. However, the ICER was sensitive to utilities used for QALYs estimates and to the probability of transplant and of response to treatment (appendix p 11) as well as to costs of pacemaker, automated defibrillator, and transplant. Costs associated with medical visit, echocardiogram, and benznidazole affected the ICER to a lesser extent (appendix p 11). The results were also affected by the discount rate used (appendix p 11). Most probabilities and costs (appendix p 11) had a negligible effect on the ICER.

In the threshold analysis, figure 3A shows that even with a drop in Chagas disease prevalence to 0.05%, the test option would still remain more cost-effective than the no-test option (less than €30 000 per QALY gained). Below this critical value the ICER would rapidly increase to infinity. The cost-effectiveness ratio increased with decreased probability of screening and treatment

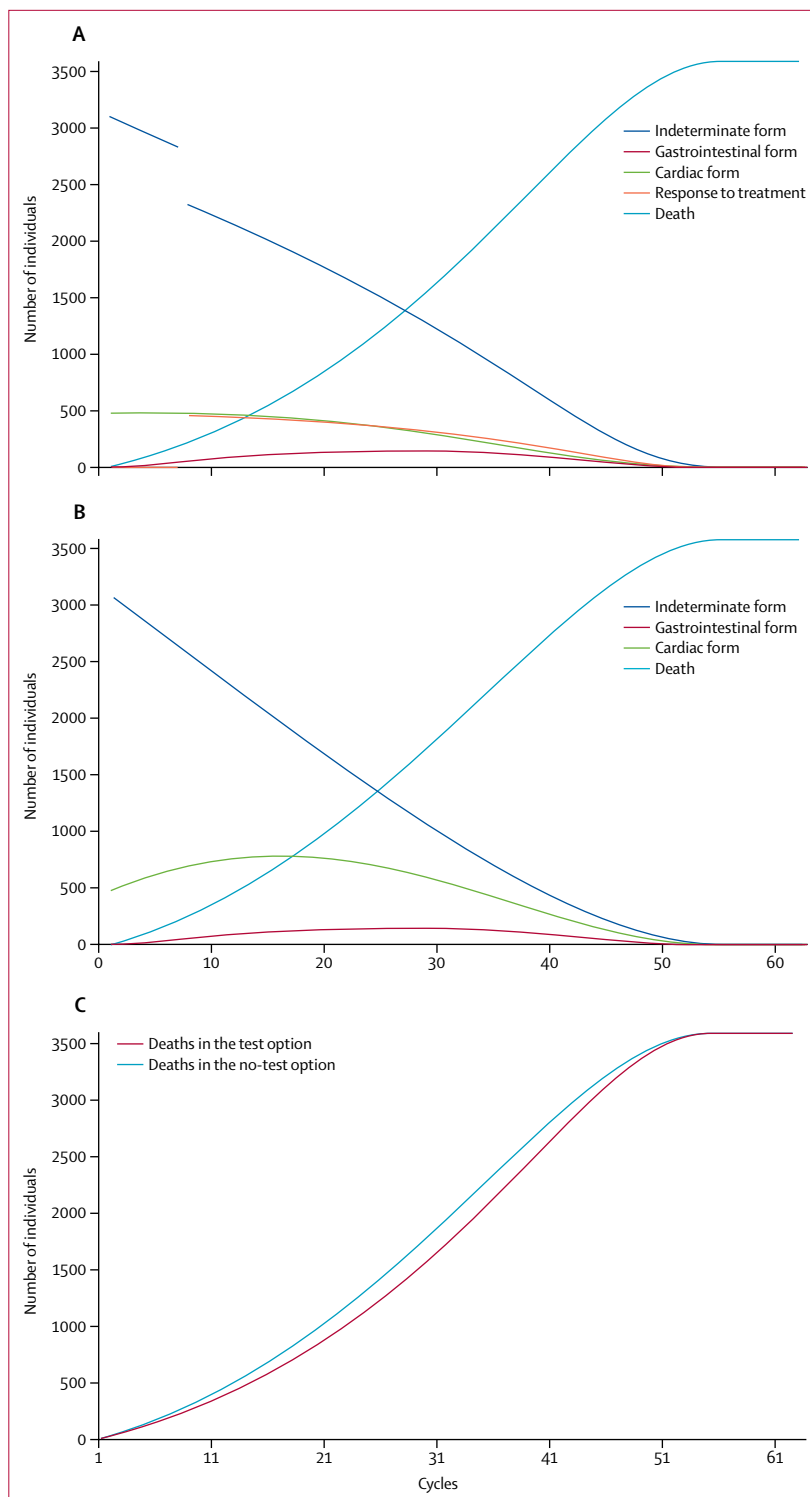


Figure 2: Markov model—number of individuals in each state at each cycle. Test option (A), no-test option (B), and detail of number of deaths in the test and no-test option (C). In (C) cycles start at 1 because there are no deaths at cycle 0.

(figure 3B) up to a critical value of about 20%—for lower values the ICER increased exponentially.

	Deterministic analysis					Probabilistic analysis				
	Costs €	QALYs	Δ Costs €	Δ QALYs	ICER	Costs € (95% CI)	QALYs (95% CI)	Δ Costs € (95% CI)	Δ QALYs (95% CI)	ICER (95% CI)
Base case estimate										
Test	30 903 406	61 820·82	24 306 003	4466·39	5442	32 163 649 (31 263 705– 33 063 593)	4758·62 (4581·31– 4935·93)	25 258 884 (24 551 659– 25 966 109)	6405·38 (6159·9– 6650·86)	6840·75 (6255·75– 7425·75)
No test	6 597 403	57 354·42	6 904 764 (6 703 258– 7 106 270)	59 875·73 (58 191·18 –61 560·28)
All potentially non-traded cost PPP adjusted										
Test	20 695 827	61 820·82	16 342 853	4466·39	3659·07	21 127 781 (20 539 624– 21 715 938)	63 238·46 (61 423·77– 65 053·15)	16 678 850 (16 217 740–17 139 960)	4680·95 (4502·78– 4859·11)	4666·93 (4490·93– 4842·93)
No test	4 352 974	57 354·42	4 448 931 (4 317 232– 45 80 631)	58 557·52 (56 885·95– 60 229·08)
QALYs and ICER have been estimated under the base case scenario of 20% response to treatment. QALYs=quality-adjusted life-years. ICER=incremental cost-effectiveness ratio. Δ=incremental. PPP=purchasing power parity.										
Table: Deterministic and probabilistic results of the cost-effectiveness analysis for <i>Trypanosoma cruzi</i> screening at primary health-care level										

The ICER decreased to €5235 per QALY gained for a calculated Chagas disease prevalence of 20%. With a higher response to treatment of 50%, the ICER decreased to €4243 per QALY gained. With all costs, excluding drug costs, being PPP adjusted, the ICER decreased to €3704 per QALY gained (appendix p 1).

In the probabilistic analysis, about 1500 random iterations of the cost-effectiveness model were required to achieve stable results. Thus, with 2000 iterations the results of the model can be considered stable (appendix p 13). Separate simulations were undertaken for costs, for QALYs, for their respective differences, and for the ICER.

For a target of 100 000 individuals, the total cost of screening, benznidazole treatment, follow-up of positive patients plus the costs corresponding to patients who developed cardiac and gastrointestinal involvement and the cost of the scaling-up of the screening programme was €32 163 649 (95% CI 31 263 705–33 063 593) in the test option and €6 904 764 (6703 258–7106 270) in the no test option. The respective number of QALYs gained were 64 634·35 (95% CI 62 809·6–66 459·1) in the test option and 59 875·73 (58 191·18–61 560·28) in the no-test option (table). The ICER was €6840·75 (95% CI 6255·75–7425·75) per QALY gained. With PPP adjustment of all costs, the ICER was €4666·93 (95% CI 4490·93–4842·93).

The cost-effectiveness plane (appendix p 14) shows the differences in costs and effects between the test and no-test options. The x axis represents the QALYs gained by the option test in comparison with the no-test option, whereas the y axis represents the incremental costs. All the simulation dots are situated below and to the right of the threshold limit (yellow line on appendix p 14) indicating that the test option, in comparison with the no-test option, is cost-effective.

The acceptability curve (appendix p 15) shows that, below a theoretical willingness to pay of about €5000 per

QALY gained, the probability that the test option was more cost-effective than the no-test option was zero. This probability rapidly increased from zero to 1 when augmenting the willingness to pay from €5000 to €7000 per QALY gained. The probability remained equal to 1 at any higher willingness to pay level.

Discussion

Our model found that screening for *T cruzi* in asymptomatic adults at risk of being infected, treating and following up those testing positive, is a cost-effective strategy in European countries with the highest number of immigrants from Latin America. The cost per QALY gained is much lower than the currently accepted threshold of €30 000 per QALY in Spain³³ and other European countries;³⁴ furthermore, it is no higher than that reported for other common infectious diseases in migrants in Europe such as hepatitis B or C.³⁹

Our findings were robust to wide ranges of parameter alterations both deterministically and probabilistically. The cost-effectiveness reported in this study is based on the pooled Chagas disease prevalence of 4·2% estimated for Latin American migrants in Europe in a recent meta-analysis.¹⁴ The high heterogeneity of prevalence in Latin American migrants from different countries, and even different regions within each country, complicates the interpretation of our results. For example, Chagas disease is more prevalent in migrants from Bolivia and Paraguay than from Brazil and Peru, and prevalence rates also vary by host country depending on the origin of migrants.¹⁴ Italy, for instance, has a high proportion of people from Andean countries, whereas Spain has received immigrants from both Andean and non-Andean countries.⁴⁰ Other sociodemographic characteristics, such as level of education and socioeconomic status, also vary. Finally, changes in migratory flows also need to be considered because they

could change the scenarios contemplated in the near future. Dynamic models that consider demographic and migration flows could therefore be a reasonable strategy to adapt the results of this study to different contexts.

A major question regarding the implementation of a *T. cruzi* screening programme is whether the intervention should target all Latin American migrants or just specific high-risk groups. If pooled prevalence rates such as that used in our study are considered, the decision is easier because cross-country differences do not have to be contemplated. Our results show that systematic screening is a cost-effective strategy in countries where the prevalence of infection in the population being screened is above 0.05%. Another strategy might be to implement screening by country of origin according to a threshold above which this practice is recommended. The ICER of €6280 per QALY obtained for a threshold prevalence of 1% is acceptable, but it would only be applicable to migrants from Argentina, Bolivia, El Salvador, Honduras, Mexico, Nicaragua, and Paraguay. Furthermore, such a system might be complicated to implement in clinical practice, because it would require health professionals to be familiar with Chagas disease prevalence rates according to country of provenance. This system also still fails to take account of important within-country heterogeneity.

Interestingly, the acceptability curve shows that policy-makers should be willing to pay at least about €5000 per QALY gained. Any investment lower than this minimum value would not lead to a cost-effective result. Legislative differences across Europe represent another challenge in the implementation of Chagas disease screening programmes, because not all undocumented migrants have free or full access to health care, and therefore huge proportions of the at-risk population could be excluded.

Our study considered the costs of intervention uptake to the national level, including human resources to coordinate the programme as well as equipment. The inclusion of such costs was conservative because the diagnostic tests needed to detect Chagas disease might not require additional structural costs to national health systems, and furthermore, laboratories would not need additional equipment to test for Chagas disease in most European countries.

The results of our cost-effectiveness study were based on a treatment efficacy of 20%.⁸ However, we also contemplated a more optimistic rate of 50%, which substantially improved the ICER, based on new data for PCR follow-up testing suggesting that the efficacy of benznidazole (or at least the antiparasitic efficacy) in chronic Chagas disease could be higher than previously believed.⁴¹

In the base case analysis, the model considered that 80% of the target population would be finally screened and treated. This high coverage level is optimistic because it is unlikely that the 80% of target population can be reached at primary health centres without

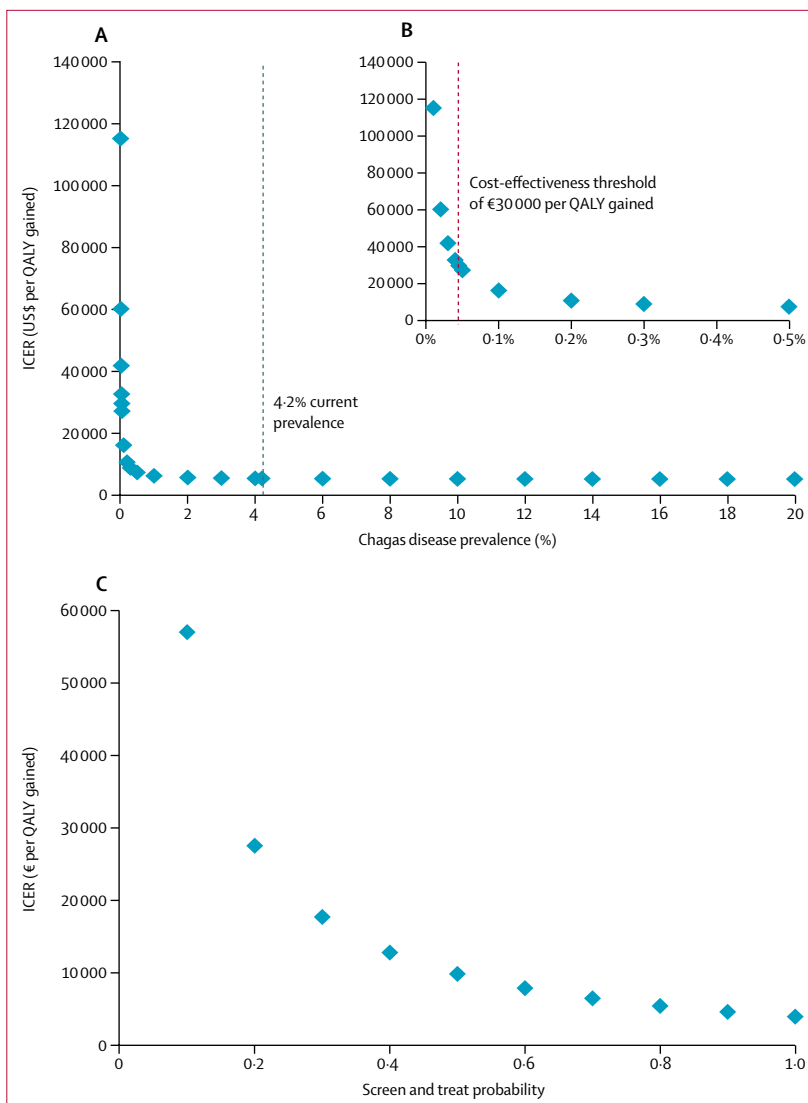


Figure 3: Threshold sensitivity analysis of the incremental cost-effectiveness ratio (ICER)

Relationship between ICER and Chagas disease prevalence (A); detail of the relationship between ICER and Chagas disease prevalence when disease prevalence is between 0 and 0.5% (B); and relationship between ICER and probability of screen and treat (C). QALY=quality-adjusted life-years.

additional effort and additionally optimistic that this 80% would accept the screening and remain adherent to treatment. Not surprisingly, in the univariate sensitivity analysis, a decrease in this parameter had the largest effect on ICER increase. However, even with 20% coverage the ICER remained below €30,000 per QALY gained. Slightly below 20% coverage the ICER increased exponentially, implying that 20% represents a lower boundary below which the intervention does not add any benefit to the current strategy of screening and treating only symptomatic cases.

The model incorporates several simplifications. We assumed that all individuals who accepted the screening would receive and adhere to antiparasitic treatment. No

evidence has been published on the acceptance and adherence to Chagas disease treatment. However, in our clinical experience, almost nobody has ever refused the treatment. Some patients might experience difficulties in adhering completely to the antiparasitic treatment for several reasons, including side-effects. However, even with a relevant reduction of efficacy of the treatment, the strategy to test remained cost-effective in our model.

The model did not include a state for individuals negative for Chagas disease; equally, it did not include individuals initially symptomatic. Indeed, the model was specifically constructed to decide whether asymptomatic individuals likely to have been exposed to the infection in the past should be tested, treated, and followed up.

No evidence is available on the probabilities of doing tests and interventions in the cardiac and gastrointestinal forms. This absence is because Chagas disease is still an emerging health problem in non-endemic countries. In endemic areas, tests and treatments currently used in non-endemic countries might not be available because of insufficient resources. To overcome this knowledge gap, we estimated key clinical parameters by experts' opinion, leaving a large uncertainty around their true values. However, these parameters did not have a large effect on our model and should not have led to inaccurate results.

Response to treatment was only considered in individuals with the indeterminate form of the disease, whereas patients with Chagas disease and cardiac or gastrointestinal involvement were not allowed to convert to a seronegative condition after treatment. Recent results of the BENEFIT trial support this premise showing that benznidazole treatment for chronic Chagas cardiomyopathy did not reduce cardiac clinical deterioration through 5 years of follow-up.⁴²

Transition from the gastrointestinal to the cardiac form was also not allowed, and it was therefore assumed that no patients simultaneously developed cardiac and digestive complications. Additionally, we contemplated the same treatment for severe cardiomyopathy for all patients. Standard deviation for parameters was set at 20% for all parameters except QALYs in the indeterminate form (10%). This was done under the assumption that the indeterminate phase is quite homogeneous across people infected with *T. cruzi*. This is different from the quality of life of patients in the cardiac and gastrointestinal forms. Cardiac and gastrointestinal problems are associated with a wide spectrum of manifestations, from less severe to very severe signs and symptoms. As a consequence; the associated quality of life has a wider range of uncertainty.

As mentioned earlier, the variability of the nationalities of migrants coming from endemic areas living in each European country might also be a limitation when interpreting the results and providing recommendations in each country.

Quality weights used were not elicited from individuals affected by Chagas disease across Europe but derived from a previous study in which utilities were equally not

directly measured.³² Little knowledge is available about the quality of life of patients with Chagas disease from endemic areas⁴³ and no knowledge from non-endemic areas. The measurement of quality of life of patients with Chagas disease in non-endemic areas should be set as a priority in the research agenda.

Finally, we did not consider the potential negative effect of a positive *T. cruzi* test on an individual's quality of life. Knowledge that the individual has the disease could negatively affect quality of life, at least in the short term. However, this is difficult to measure in practice.⁴⁴

Our study did not assess the effect of screening and treatment on the reduction of the vertical transmission of *T. cruzi* infection;⁴⁵ this could be another important benefit of screening at-risk women of childbearing age.

Screening asymptomatic adult Latin American migrants for Chagas disease in western Europe and treating *T. cruzi*-seropositive individuals with antiparasitic therapy and following them up in the long term is a cost-effective strategy. Our findings provide an important element to support the implementation of a primary care *T. cruzi* screening programme. However, other factors should be considered such as the heterogeneity of national legislations and of health system characteristics as well as users' acceptability of the screening programme.

Contributors

AR-M and ES were involved in the study design, literature search, data collection, extraction, analysis and interpretation, and writing of the report. SB was involved in the data analysis. YJ, AA, DM, M-JP, and JG were involved in the data interpretation. JM did the study design and data interpretation.

Declaration of interests

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