"Economic Evaluation of Chagas Disease Screening in Spain"

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Authors:

- Iñaki Imaz-Iglesia, MD, PhD, MPH (imaz@isciii.es). Spanish Health Technology Assessment Agency, Instituto de Salud Carlos III. REDISSEC (Spanish Research Network on Chronic Diseases Health Services), Madrid, Spain
- Lucía García-San Miguel, MD, PhD (lucigasan@hotmail.com). Department of Preventive Medicine. Hospital Puerta de Hierro, Majadahonda, Madrid, Spain.
- L. Eduardo Ayala-Morillas, MD, PhD, MPH (leam29@gmail.com). Department of Preventive Medicine. Hospital Clínico Universitario San Carlos, Madrid, Spain.
- Lidia García-Pérez, BScEcon, (lidia.garciaperez@sescs.es). Health Assessment Department, Canary Islands Health Agency. Canary Foundation for Health Research, REDISSEC (Spanish Research Network on Chronic Diseases Health Services), Canary Islands, Spain.
- Jesús González-Enríquez, MD, MPH (jgonza@isciii.es). Spanish Health Technology Assessment Agency, Instituto de Salud Carlos III. REDISSEC (Spanish Research Network on Chronic Diseases Health Services), Madrid, Spain.
- Teresa Blasco-Hernández, PhD (tblasco@isciii.es). National Centre for Tropical Medicine, Instituto de Salud Carlos III, Madrid, Spain.
- María Belén Martín-Águeda, MD, MPH (bmartinagueda@yahoo.es). Department of Preventive Medicine, Hospital Universitario La Princesa, Madrid, Spain.

- Antonio Sarría-Santamera, MD, PhD (asarria@isciii.es). Spanish Health Technology Assessment Agency, Instituto de Salud Carlos III. REDISSEC (Spanish Research Network on Chronic Diseases Health Services). Unit of Preventive Medicine and Public Health, University of Alcala, Madrid, Spain.

1 ABSTRACT:

Although Spain is the European country with the highest Chagas disease burden, the country does not have a national control program of the disease. The purpose of this study is to evaluate the efficiency of several strategies for Chagas disease screening among Latin American residents living in Spain.

The following screening strategies were evaluated: 1) non-screening; 2) screening of the Latin American pregnant women and their newborns; 3) screening also the relatives of the positive pregnant women; 4) screening also the relatives of the negative pregnant women. A cost-utility analysis was carried out to compare the four strategies from two perspectives, the societal and the Spanish National Health System (SNHS). A decision tree representing the clinical evolution of Chagas disease throughout patient's life was built. The strategies were compared through the incremental cost-utility ratio, using euros as cost measurement and quality-adjusted life years as utility measurement. A sensitivity analysis was performed to test the model parameters and their influence on the results.

We found the "Non-screening" as the most expensive and less effective of the evaluated strategies, from both the societal and the SNHS perspectives. Among the screening evaluated strategies the most efficient was, from both perspectives, to extent the antenatal screening of the Latin American pregnant women and their newborns up to the relatives of the positive women. Several parameters influenced significantly on the sensitivity analyses, particularly the chronic treatment efficacy or the prevalence of Chagas disease.

In conclusion, for the general Latin American immigrants living in Spain the most efficient would be to screen the Latin American mothers, their newborns and the close relatives of the mothers with a positive serology. However for higher prevalence immigrant population the most efficient intervention would be to extend the program to the close relatives of the negative mothers.

Keywords: Chagas disease, costs and costs analysis, screening, Spain

2 INTRODUCTION

Chagas disease is an infection caused by the protozoa *Trypanosoma cruzi.* It is spread mostly by insects known as *Triatominae* or kissing bugs. Acute clinical manifestations are usually seen in children. The chronic stage occurs in 10-30% of those infected, 15-20 years after the acute infection. Chronic infection consequences such as myocardial injury, cardiac dilation, arrhythmia, severe conduction abnormalities, and gastrointestinal tract disorders as megaesophagus and megacolon, are irreversible (1-3).

Acute phase diagnosis is usually confirmed by direct visualization of the parasite in the blood (micromethod) or Polymerase Chain Reaction (PCR). In the chronic phase, the parasitemia can be low or absent so serological studies are the most used to detect the infection (1,2).

Treatment reduces acute disease duration, severity, and achieves parasitological cure in a high percentage of cases (2,4). However, at indeterminate or chronic phase there are not suitable markers for measuring parasite eradication. Antibody titers (IgG specific) may remain high for years even though the parasite has been eliminated (4). Moreover, regarding the pharmacological treatment of the chronic disease there is a wide range of efficacy results in the literature, ranging from 8 to 71% (4–6).

Chagas disease is endemic in the Latin American region, with a wide geographic distribution. It is estimated that there may be some 8 million people infected in the world, with an annual mortality of 20,000 (2)(7). In Latin America, Chagas disease has been estimated to be the first tropical and the fourth infectious disease in DALYs (Disability-Adjusted Life Years) (8).

Spain is the European country that receives the largest share of immigrants from Latin America, so it is estimated to be the first European country in Chagas disease burden (5,9). In Spain the regional prevalence of Chagas disease varies depending on the national origin of the immigrant population that has settled in each region (10). It is estimated that, in our country, there may be 90% of under-diagnosis, so most of the infected population do not know their potential risk of develop the chronic disease in the future (9).

Although, in Spain, there is a parasitological control of donated blood and organs, potential vertical transmission continues to be of concern (11). At present, some Autonomous Communities (the country is geographically divided in 17 Autonomous Communities) carry out Chagas screening including a serology test for all pregnant Latin American women, as part of antenatal care, but this practice is not extended to all regions (9). In addition, Chagas disease is not included in the national surveillance system, and there is no national control plan (9,12).

Because of that, we found pertinent to evaluate the efficiency of several strategies for Chagas disease screening of the immigrant population of Latin American residents in Spain and their potential descendants.

3 METHODS

A cost-utility analysis was carried out to compare four screening strategies for Chagas disease in Spain, considering both, the societal and the Spanish National Health System (SNHS) perspective. Costs and events of Chagas disease occurring throughout patient's life were included in the model. Costs were measured in Euros and updated to 2013. The main outcome measurement was quality-adjusted life years (QALYs).

The following four strategies were compared:

A) "Non-screening".

B) "Mother and newborn". All pregnant Latin American women were screened as part of the routine antenatal control. In case of a positive serology test, the newborns were also tested.

C) "Positive mother cluster". This strategy included the previous strategy "Mother and newborn", but added the screening of a cluster of the positive mother. The cluster was defined as the first and second degree relatives of the mother. When the mother's serology was positive, her cluster was tested.

D) "Negative mother cluster". This strategy included the previous two strategies, but added screening of the cluster of the negative mother. The cluster was defined as the first and second degree relatives of the mother, but in this strategy, only adults born in Latin America were tested but not children. It was assumed that all children were born in Spain and thus vertical transmission would be unlikely.

3.1 Modelling

A decision tree was built using TreeAge Pro 2011® in order to represent the clinical evolution of the Chagas disease. The population entering the model was Latin American resident in Spain in 2011 and their potential descendants at the moment of the screening. The population was followed from 30 years old (diagnosis average age according to Lee et al. (5)) until the end of their life.

The decision tree started with a decision node, which was divided into the four screening strategies. From all the strategies six branches were set representing six populations with different event probabilities (figure 1).

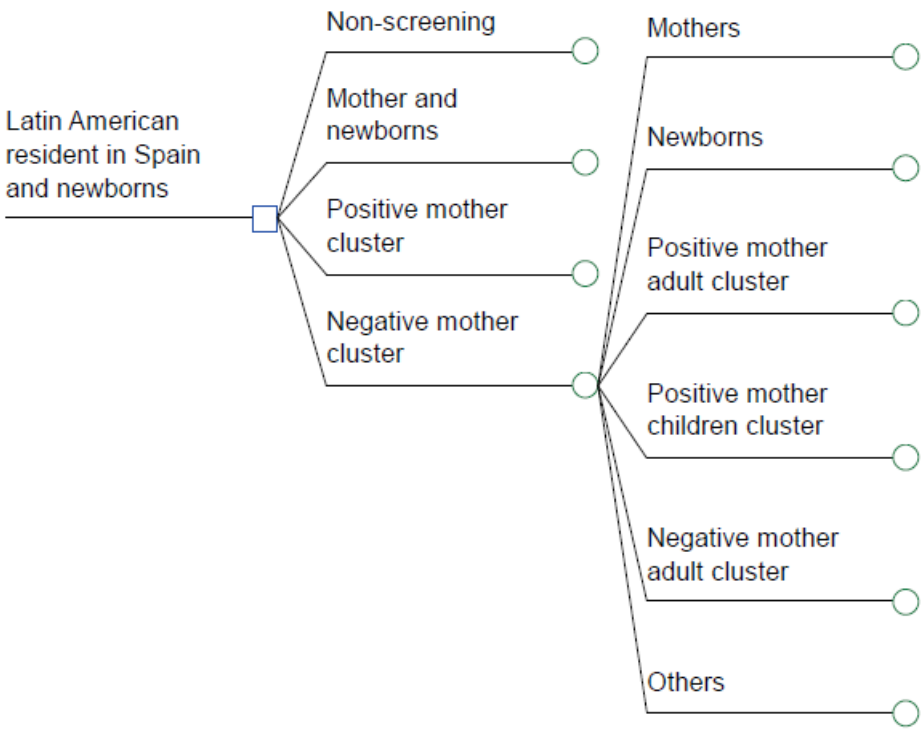

Figure 1. First branches of the decision tree

The populations can be described as follows:

1. Mothers. The Latin American women living in Spain during their childbearing period.

2. Newborns. The potential newborns of those mothers.

3. Positive mother adult cluster. The adult relatives of a mother with a positive serology.

4. Positive mother children cluster. The children relatives of a mother with a positive serology.

5. Negative mother adult cluster. The adult relatives of a mother with a negative serology.

6. Others. The rest of the Latin American population not screened in any strategy.

Populations were estimated as follows:

- Latin American women with childbearing potential (15-49 years) according to the 2011 National Census (13): 685,952 (13).

- Potential newborns: assuming that all women with childbearing potential had the same characteristics as those described by Castro et al in 2011 (14), each one would bear 0.47 children in Spain. Therefore a total number of 322,397 potential newborns (Range: 196,665 – 331,108) was estimated.

- Initial population entering the model: Latin American population (excluding Caribbean islands) living in Spain according to the 2011 National Census (13): 2,130,871 people and their potential newborns (322,397): a total of 2,453,267 people.

- Cluster: "Household composition" of 2.4 persons per every Latin American mother (range 1.8-3) (15) was assumed. It was also assumed that half of the household members would be first and second degree relatives ("Relatives component": 0.5; range: 0.25-0.75), 50% would be adults and 50% children ("Children component": 0.5; range: 0.375-0.625).

Clinical events related with Chagas disease were modeled both for the screened and the non-screened populations in the decision tree. Once a mother is screened can be infected or no infected. The infected could be diagnosed (true positive) or remained undetected (false negative). The infected could be at the indeterminate chronic disease phase (without symptoms) or develop the cardiac or the digestive disease. All diagnosed mothers (true positive and false positive) received treatment and so could develop adverse events. All of the branches ended in a terminal node that represented death (Figure 2).

All the populations have the same branches except for newborns because only they can acquire the acute disease through vertical transmission. In some cases the acute disease can be lethal (Figure 3)

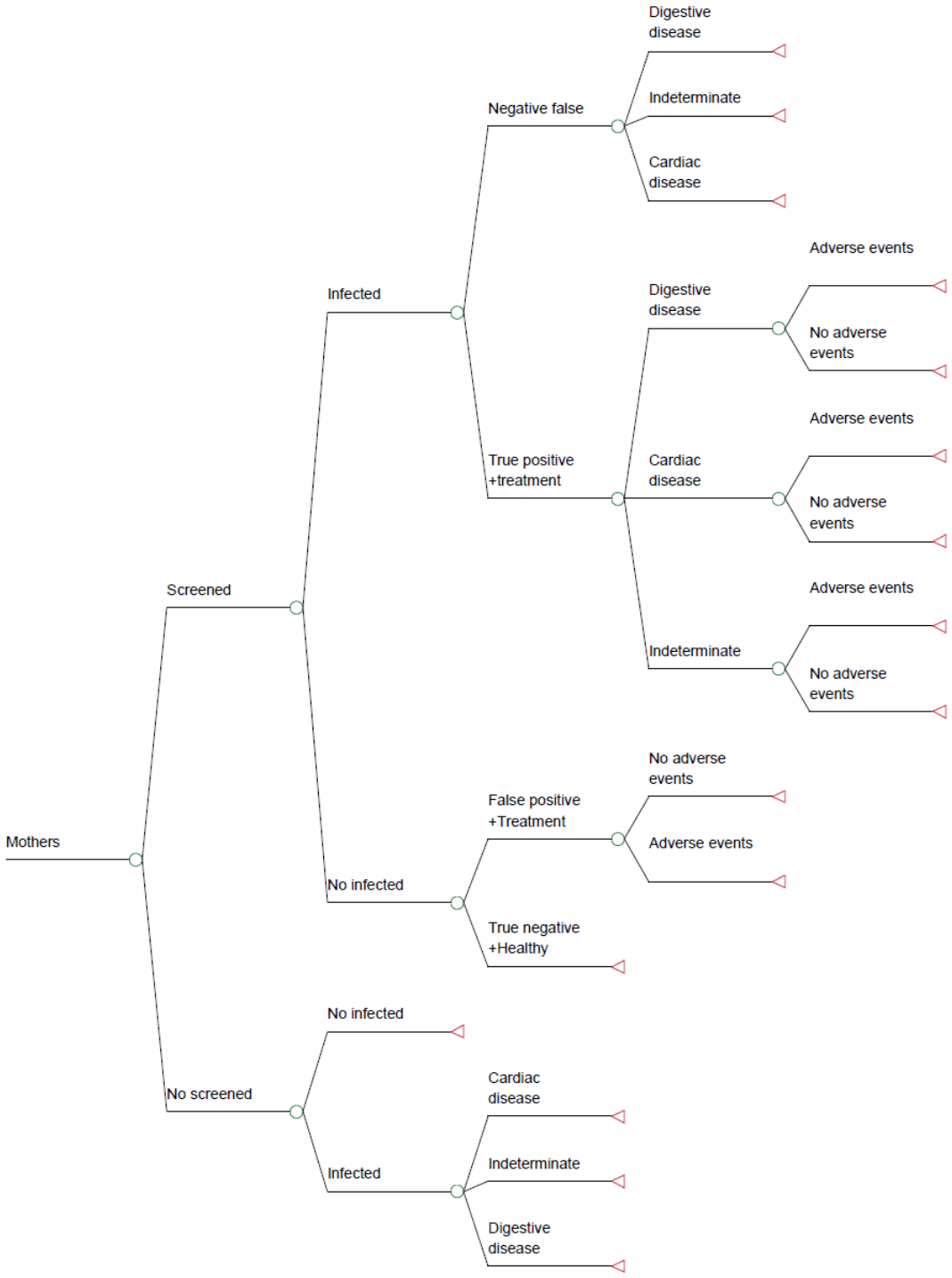

Figure 2. Decision tree for the Latin American women living in Spain during their childbearing period.

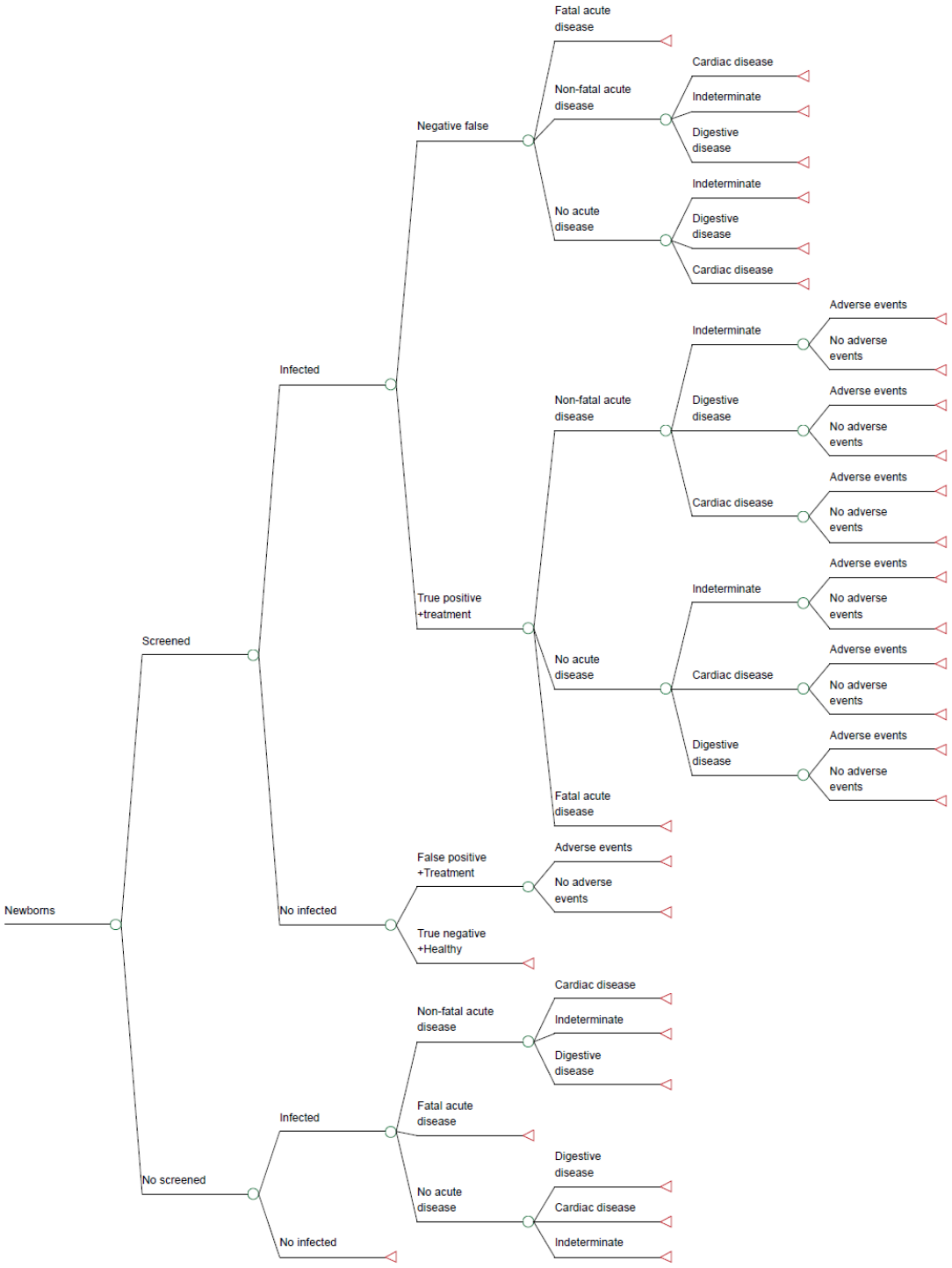

Figure 3. Decision tree for the potential newborns.

3.2 Parameters

Data were obtained from official sources when available (ie. Ministry of Health and National Statistics Institute). Best evidence of medical literature published on PubMed was selected for each case. The sources of information for each parameter are described in the tables below. For each parameter an average and a range of values were estimated. The average value was used for the base case analysis and the range for the sensitivity analysis. When no information was found for the ranges ±10% or ±25% was applied according to the author's criteria.

3.2.1 Disease prevalence and evolution

We applied Chagas disease prevalence by country of origin provided by Basile et al. (10) to the number of Latin American inmigrants by country of origin living in Spain (13), obtaining an average prevalence of 0.0322. That prevalence was adopted for the base case, although the range of prevalence of the Latin American countries provided by Basile et al. was tested in the sensitivity analysis (table 1).

The prevalence of the adult cluster of the positive and negative mother was adjusted according to Mott et al. (16), who estimated the increased risk of being infected for the cluster of the positive mother and the decreased risk for the cluster of the negative mother. The general prevalence was multiplied by 2.25 for the positive mother cluster (resulting 0.0724), and was decreased by 0.44 for the negative mother cluster (resulting 0.0141).

For newborns and children cluster of the positive mother the prevalence was assumed to be the vertical transmission rate. It was considered that our population does not have risk of vectorial transmission of the disease.

The proposal of Lee et al. was assumed to estimate the disease evolution parameters (5). According to that study the chronic disease is diagnosed on average at the age of 30 years at an indeterminate phase. Some of the infected persons would live with the indeterminate disease all of their lives without symptoms (52.1 years). Other persons develop a chronic disease, cardiac or digestive, with a mean duration of 24.8 years. The serious chronic disease would have an average duration of 13.2 years. It was assumed the same average life expectancy for Spanish than for Latin American people living in Spain.

The probability of developing acute disease among infected newborns by vertical transmission has been reported between 20 and 35% in two studies. We assumed the median between these two figures. A mortality rate of 1% as published by Mandell et al. was considered (2).

The probabilities of developing chronic disease are varied in the literature. Some authors reported global probabilities of developing chronic disease between 30 and 40% (17–19). Others reported the probabilities separated between cardiac and digestive disease. The cardiac disease is more frequent than the digestive disease. Some authors reported that two thirds of the chronic patients will develop the cardiac and one third the digestive disease (3,20). Others published that the cardiac disease occurred to 20-30% of the chagasic patients (18), and the digestive disease to 10-20% of the chagasic patients (18,21). We adopted the rates published in

the study of the PanAmerican Health Organization (3), where Brazilian data were thoroughly collected. They estimated that a 72.8% of the infected would remain in the indeterminate phase of the disease, while 18.2% would develop the cardiac disease and 9% the digestive disease.

Finally, in most of the cases the utilities were gathered from scientific literature. We had to estimate the value only for acute disease and adverse events.

Table 1. Disease evolution parameters. Average and range values.

Parameter	Base case	Range	References
Chagas prevalence among Latin American resident in Spain	0.0322	0.01-0.1875	(10,13)
Chagas prevalence among adult cluster of the positive mother	0.0724	0.058-0.089	(16)
Chagas prevalence among adult cluster of the negative mother	0.0141	0.0116-0.0174	(16)
Vertical transmission	0.0435	0.014-0.073	(10)
Acute disease probability among infected newborns	0.275	0.206-0.344 [a]	(10,18)
Fatality rate because of acute disease among treated newborns	0.01	0.0075-0.0125 [a]	(2)
Cardiac disease probability	0.182	0.137-0.228 [a]	(3)
Digestive disease probability	0.09	0.068-0.113 [a]	(3)
Indeterminate disease duration (years)	52.1	39.1 – 65.1	(5,22)
Chronic disease duration (years)	24.8	18.6 - 31	(5,22)
Acute disease duration (years)	0.1	0.05 – 0.2	Author's estimation
Treatment duration (years)	0.2	0.1 – 0.3	Author's estimation
Diagnostic process duration (years)	0.13	0.09 – 0.16	Author's estimation
Life expectancy (years)	82.1	78-82.1	(22)
Life years lost because of cardiac disease	4.23	3.2-5.3 [a]	(23)
Life years lost because of digestive disease	3.31	2.5-4.1 [a]	(23)
Life years lost because of fatal acute disease	81	80-82	Author's estimation
Utility for no disease	1		(24)
Utility for indeterminate disease	0.925	0.906-0.944[a]	(3)
Utility for acute disease	0.30	0.23-0.38[a]	Authors' estimate
Utility for fatal acute disease	0	-	Authors' estimate
Utility for cardiac disease	0.72	0.65-0.79[b]	(3,12,24)
Utility for digestive disease	0.84	0.76-0.92[b]	(3)
Utility for adverse event to drug treatment	0.80	0.7-0.9	Authors' estimate

[a] +/- 25%
[b] +/- 10%

3.2.2 Disease diagnosis and treatment

Well acknowledged diagnosis and treatment recommendations for Chagas disease were used (20,25-27). The screening would start for all populations (except newborn), with an antibody test. If the test was positive, a second serology test using different antigens would be carried out for confirmation. Parasitemia detection through capillary concentration or PCR was recommended for newborns during the first two months of life. At nine months old, serology and PCR tests would be carried out simultaneously and if negative, repeated until month 18 of age. Diagnostic accuracy and screening compliance parameters are described in Table 2. The

According to these data the following was estimated for each strategy: number of screened population, number of positives, number of true positives (TP) and positive predictive value (PPV) (Figure 4).

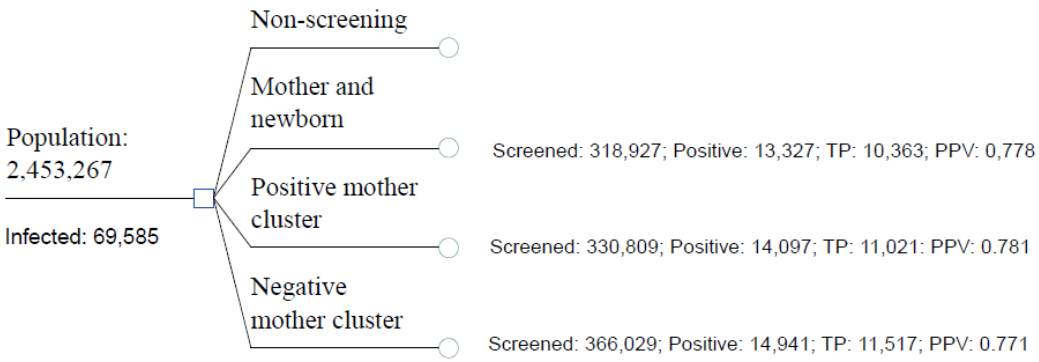

Figure 4. Population size and diagnosis results of the four strategies. TP: true positives; PPV: positive predictive value.

Treatment efficacy, adverse events probabilities and their sources of information are described in Table 2. Treatment recommendations made by Bern et al. are generally followed in Spain, so they were assumed in our study (25). In our model, treatment was indicated for all infected persons. The primary regime was Benznidazole (BNZ) 5-7 mg/kg per day for 60 days, and the alternative regime Nifurtimox (NFX) 8-10 mg/kg per day for 90 days when there was no tolerance to Benznidazole.

Treatment efficacy in the acute phase was estimated to be 97.9% based on several clinical trials that measured parasitological and serological cure with benznidazole or nifurtimox (4). For the chronic disease, the reviews showed very different results. Bruce-Lee (4) estimated the parasitological/serological cure to be 8% with benznidazole or nifurtimox, however the systematic review by Pérez-Molina (6) estimated the clinical cure (defined as no development of clinical events) around 71% only with benznidazole. We assumed that the chronic treatment efficacy could be an average of these two results (39.5%), which is similar to those identified in other economic evaluations (12,17).

Table 2. Diagnostic and treatment of Chagas disease. Average and range values.

DIAGNOSTIC TESTS ACCURACY (0-1)			
	Average	Range	References
Sensitivity antibody test	0.995	0.98-1	(25-27)
Specificity antibody test	0.99	0.98–1	
Sensitivity newborn diagnostic procedure	1	0.9-1	(28)
Specificity newborn diagnostic procedure	1	0.9-1	(28)
SCREENING COMPLIANCE (0-1)			
Pregnant woman	0.95	0.5-1	(29)

Newborn from positive mother		0.99	0.95-1	(29)
Adult cluster positive mother		0.65	0.49-0.81 [a]	Authors' estimate
Children cluster positive mother		0.9	0.75-1	Authors' estimate
Adult cluster negative mother		0.2	0.15-0.25 [a]	Authors' estimate
TREATMENT EFFICACY (0-1)				
Chronic disease		0.395	0.08-0.71	(4,6,24)
Acute disease		0.979	0.65-1	(4,5)
TREATMENT RELATED ADVERSE EVENTS PROBABILITY (0-1)				
Adults				
Benznidazole	Adverse events	0.59 [c]	0.44-0.74 [a]	(30-32)
	Withdrawals	0.23 [c]	0.17-0.29 [a]	
	Severe adverse events	0.03 [c]	0.023-0.038 [a]	
Nifurtimox	Adverse events	0.975	0.73-1	(33)
	Withdrawals	0.395	0.3-0.5 [a]	
	Severe adverse events	0.074	0.056-0.093 [a]	
Children				
Benznidazole	Adverse events	0.58	0.44-0.73 [b]	(34)
	Withdrawals	0.065	0.049-0.081 [a]	
	Severe adverse events	0.018	0.014-0.023 [a]	
Nifurtimox	Adverse events	0.31	0.23-0.39 [a]	(33)
	Withdrawals	0		
	Severe adverse events	0		

[a] +/- 25%
[b] +/- 10%
[c] Average of three studies

3.2.3 Cost estimations

The SNHS perspective considered only the direct medical costs, while the societal perspective considered also the direct and indirect non-medical costs.

3.2.3.1 Medical costs

Costs incurred during the Chagas diagnosis and treatment were estimated and described in tables 3, 4 and 5. Costs related with diagnosis included microbiology tests and consultations. Each population followed different itineraries depending on the results of tests and according to the Chagas diagnosis pathway described previously.

Similarly, the costs related to pharmaceutical treatment and adverse events were estimated including medical visits, control analysis, medicines to treat adverse events (corticoids, antihistaminic and antiemetics) and hospitalization for severe cases weighted by the frequency and type of adverse event.

The costs of pharmacological treatment and their adverse events are summarized in Table 4. The out of pocket medicine expenses were only included in the societal perspective, while the medicine costs incurred by the state health system were included in both perspectives.

Disease management costs of other interventions different from pharmaceutical costs are detailed in Table 5 for every stage of the disease: acute, indeterminate, and chronic disease (cardiac and digestive). The throughout life frequency of attendance to outpatient clinic or need to admission to the hospital were calculated according to published data or investigators criteria.

3.2.3.2 Non-medical costs

Direct non-medical costs included transport costs to attend clinical visits, and home caregiver costs. Indirect non-medical costs included productivity loss of the patient and productivity loss of the parents because of the care for their sick children.

Madrid subway rates were used to estimate public transportation to health centre costs(35). The caregivers fees were estimated according to the annual income of non-qualified staff in Spain for 2011 (36). Furthermore, 33% of full time equivalent (FTE) of caregivers fees for severe cardiac and 20% for digestive disease were estimated.

The productivity loss was estimated to be 5 and 2.5 years for cardiac and digestive disease respectively. The productivity loss costs were calculated on the basis of the average salary of Latin American residents (36) and the average number of working hours in Spain (37) weighted by the unemployment rate of immigrants (38).

Table 3. Cost of the diagnostic process. Average and range values.

Outcome group	**Medical cost (€)** (39,40)		**Non-medical cost (€)** (35-38)	
	Average	**Range**	**Average**	**Range**
Negative mother	20	15-25[a]	0	
Negative newborn	587	326-848	67.5	45.01-90.02
Negative mother adult cluster	199	150-248[a]	38.3	25.5-51.01
Positive mother	253.1	166.7-339.5	38.03	25.5-51.01
Positive newborn	577	326-828	63.76	25.5-102.02
Positive mother adult cluster	253.1	166.7-339.5	38.03	25.5-51.01
Positive mother children cluster	371.1	227.7-514.5	38.03	25.5-51.01

[a] +/- 25%

Table 4. Cost of pharmacological treatment and adverse events. Average and range values.

	Medical costs (€) (41)(39)(40)(42)(43)		**Non-medical costs (€)** (35-38)	
	Treatment cost			
	Average	**Range**	**Average**	**Range**
Benznidazole for adults	179.4	134.5-224.2[a]	137.82	103.4–172.3[a]
Nifurtimox for adults	220	165-275[a]	51.01	38.2–63.7[a]

Benznidazole for children	178.9	134.2–223.7[a]	81.7	61.3–102.1[a]
Nifurtimox for children	256.5	192.4–320.6[a]	51.01	38.3–63.8[a]
	Adverse events			
Adults	444.3	321.1-567.5	39.4	27.01-51.8
Children	65.2	43.5-86.9	22	15-29

[a] +/- 25%

Table 5. Disease management costs. Average and range values (€).

Intervention	Unit cost (range)	Frequency x years (range)	Average	Range	References
ACUTE DISEASE					
Medical costs					
Hospitalization	4,275	1	4,275	3,206 - 5,344	(39)
TOTAL			4,275	3,206 - 5,344	
Non-medical costs					
Transport	6	2 (1-3)	12	6 - 18	
Parents productivity loss due to children hospitalization	39	2 (1-3)	78	39 - 117	
TOTAL			90	45 - 135	
INDETERMINATE DISEASE					
Medical costs					
First medical visit	130	1	130		(39)
Follow-up medical visits	78	0.5 x 51.1	1,992.9	822.9 - 3,162.9	(39)
Electrocardiogram	16.73	0.5 x 51.1	427.4	176.5 - 678.4	(40)
TOTAL			2,550	1,129 – 3,971	
Non-medical costs					
Transport	6	0.5 x 52.1	159.3	69.3 – 249.3	(35)
Productivity loss for medical visits	39	0.25 x 52.1	517.9	225.3 – 810.5	(36-38)
TOTAL			677.2	294.60 – 1,060	
CARDIAC DISEASE					
Medical costs					
First medical visit	130	1	130		(39)
Follow-up medical visits	78	[10.6 + 3 (2-4)] x 13.2	3,915.6	2,886 - 4,945	(39)
Electrocardiogram	16.7	1 x 24.8	414.9		(12,40)
Chest x-ray	13.4	1 x 24.8	333.6		(12,39)
Digoxin	14	0.5 (0.33-0.66)	6.9	4.6 - 9.2	(12,44-46)
Enalapril	84.2	0.5 (0.33-0.66)	41.7	27.8 - 55.6	
Furosemide	10.5	0.5 (0.33-0.66)	5.2	3.5 - 6.9	
Doppler ultrasound	60.7	0.2	301.2		(12,40)
Holter	170.2	0.01	1.7		
Stress echocardiography	69.2	0.08	5.5		
Pacemaker	10,915 (8,525-13,304)	0.03 (0.02-0.04)	300.1	170.5 - 465.6	(12,39,47,48)
Automatic defibrillator	32,717 (28,112-37,323)	0.03	981.5	843.4 - 1,120	(12,39)
Cardiac transplant	82,326	0.01	823.3		
Heart failure hospitalization	3,545	2.35 (0.33-4.38)	8,344	1,175 - 15,512	(23,39)

Digestive disease hospitalization	5,645	0.06 (0.02-0.10)	321.8	84.7 - 558.9	
TOTAL			15,927	7,206 - 24,684	
Non-medical costs					
Transport	6	[11.6 + 3 (2-4)] x 13.2	307.2	230.4 – 384	(35)
Caregivers	5,771	13.2 x 0.33 (0.166-0.666)	25,392	12,696 - 50,785	(36)
Productivity loss due to medical visits	39	0.5 x 12 (9-15)	234.08	175.6 – 292.6	(36-38)
Productivity loss due to illness	8,269	1 x 0.3 (0-2)	2,481	0 - 16,537	(36,38)
TOTAL			28,414	13,102 - 67,999	
DIGESTIVE DISEASE					
Medical costs					
First medical visit	130	1	130		(39)
Follow-up medical visits	78	[0.5 (0.25-1) x10.6)] + [0.5 (0.25-1) x 13.2]	928.2	464-1,856	
Barium x-ray	13.5	0.2	2.7		(12,39)
Intestinal transit study	13.5	0.2	2.7		
Mega-viscera surgery	8,970 (6,259-11,680)	0.052 (0.05-0.055)	470	313 - 642	(3,24,39)
Digestive disease hospitalization	5,645	0.322 x 3.8 (1-6.6)	6,907	1,818 – 11,997	(14,23)
Heart failure disease hospitalization	3,545	0.015 x 7.1 (1-13.2)	377.5	53.2 - 701.9	
Omeprazol	37.2	0.5 (0.33-0.66)	18.4	12.3 - 24.5	(12,49-51)
Antiacids	41.1	0.5 (0.33-0.66)	20.4	13.6 - 27.1	
Prokinetic drugs	27.7	0.5 (0.33-0.66)	13.7	9.1 - 18.3	
TOTAL			8,872	2,818-15,403	
Non-medical costs					
Transport	6	[0.5 (0.25-1) x 11.6)] + [(1 (0.5-2) x 13.2]	77,4	38,7-154,8	
Caregivers	5,771	13.2 x 0.2 (0.1-0.4)	15,235	7,618-30,471	(36)
Productivity loss due to medical visits	39	11.1 x 0.5 (0,25 – 1)	108	54-217	(36-38)
Productivity loss due to illness	8,268.7	0.1 (0-2)	827	0-8,269	(36,38)
TOTAL			16,248	7,711-39,111	

AE: Adverse events

3.2.3.3 *Cost of developing the screening program*

Costs of a potential program for Chagas screening to implement in the SNHS were estimated by the investigators (table 6). The expenses included cost of personnel (gross salaries) and other costs needed to coordinate activities in the regions. The costs were based on the “Carlos III” Health Institute official rates. The costs of developing the screening program were applied to the three screening strategies but not to the “Non-screening” strategy.

Table 6. Cost of developing the screening program. Average and range values.

Intervention	Unit cost (€)	Frequency	Average (€)	Range (€)
Personnel (Coordinator)	37,524	5 years	187,620	140,715 – 234,525
Personnel (Technical)	31,110	5 years, 2 people	311,100	233,325 – 388,875
Subsistence costs	8,000	5 years	40,000	30,000 - 50,000
Travel	15,000	5 years	75,000	56,250 – 93,750
Computer equipment	2,000	3 equipment	6,000	4,500 – 7,500
Office equipment	1,500	5 years	7,500	5,625 – 9,375
Meetings	7,900	5 years	39,500	29,625 – 49,375
Sub-total			666,720	500,040 – 833,400
Carlos III (15%) overheads			100,008	75,006 – 125,010
TOTAL			766,728	575,046 – 958,410

3.3 Analysis

The strategies were compared using the incremental cost-utility ratio (ICUR). This indicator provides the cost of gaining one QALY with the implementation of a certain strategy in comparison with other. The ICUR was calculated for both societal and SNHS perspective. Although there is no an established ICUR threshold for health technology introduction in Spain, €30,000 per QALY was assumed as it was the most quoted figure in the Spanish literature (52). An annual discount for costs and results of 3% (range 0-5) was applied.

A deterministic and univariate sensitivity analysis test in all of the model parameters from the societal perspective was carried out using the range of values already described. The societal perspective was used as reference for the sensitivity analyses because included all variables, while the SNHS perspective excluded the non-medical cost variables.

4 RESULTS

4.1 Base Case

The results of the base case from both societal and SNHS perspectives are shown in figures 5 and 6 and tables 7 and 8. In both perspectives the “Non-screening” strategy was dominated by the other three screening strategies because resulted more expensive and less effective than the others. Among the three screening strategies the “Negative mother cluster” was the most effective while the most expensive.

Assuming a threshold for health technology introduction of €30,000 per QALY, the most efficient strategy from both perspectives would be the “Positive mother cluster”. To adopt the “Negative mother cluster” instead of the “Positive mother cluster” resulted in an ICUR value higher than the threshold. From the societal perspective the “Negative mother cluster” would achieve an

additional QALY in comparison with the “Mother and newborn” strategy at a cost of 38,013 € per patient.

The average utility of the base case from the SNHS perspective was similar to the societal perspective, but the average costs were reduced. From the SNHS perspective to adopt the “Negative mother cluster” instead of the “Positive mother cluster” would achieve an additional QALY at a cost of 30,844 € per patient.

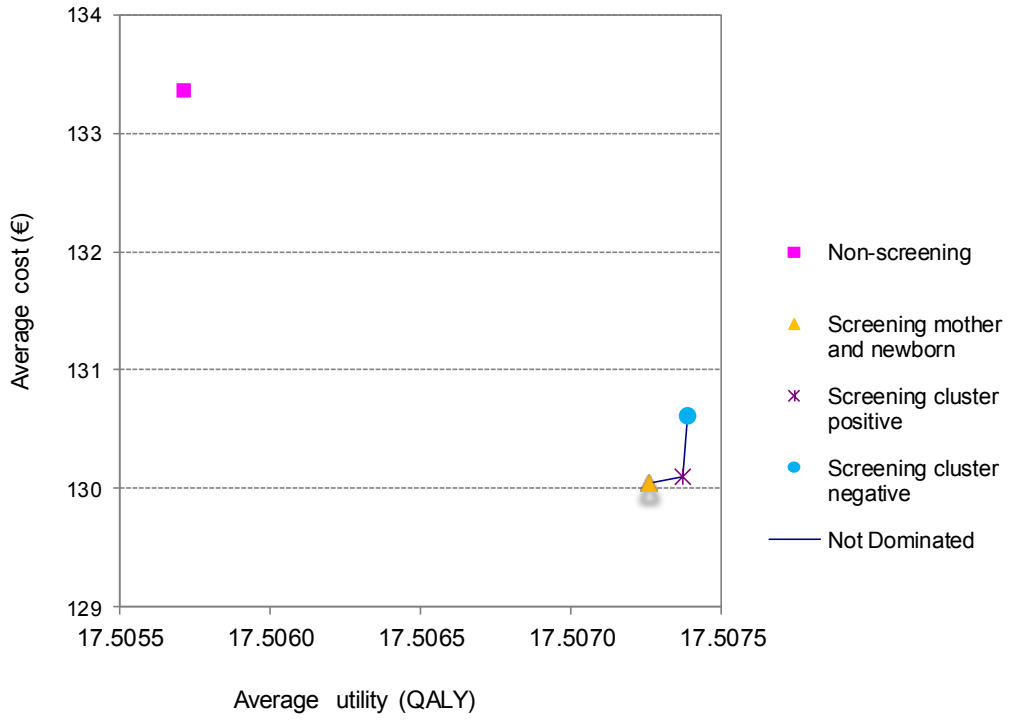

Figure 5. Cost-utility analysis results of the base case from the societal perspective.

Table 7. Base case results of the four screening strategies from the societal perspective.

Strategy	Average Cost (€)	Incremental Cost (€)	Average Utility (QALY)	Incremental Utility (QALY)	Average Cost-Utility	ICUR[a] (€/QALY)
Mother and newborn	130.035872	-	17.507259	-	7.427540	
Positive mother cluster	130.082152	0.046281	17.507375	0.000116	7.430135	399
Negative mother cluster	130.603294	0.521142	17.507389	0.000014	7.459896	38,013
Non-screening	133.359859	2.756565	17.505714	-0.001675	7.618076	Dominated

[a] ICUR: Incremental Cost-Utility Ratio comparing each strategy with the previous one

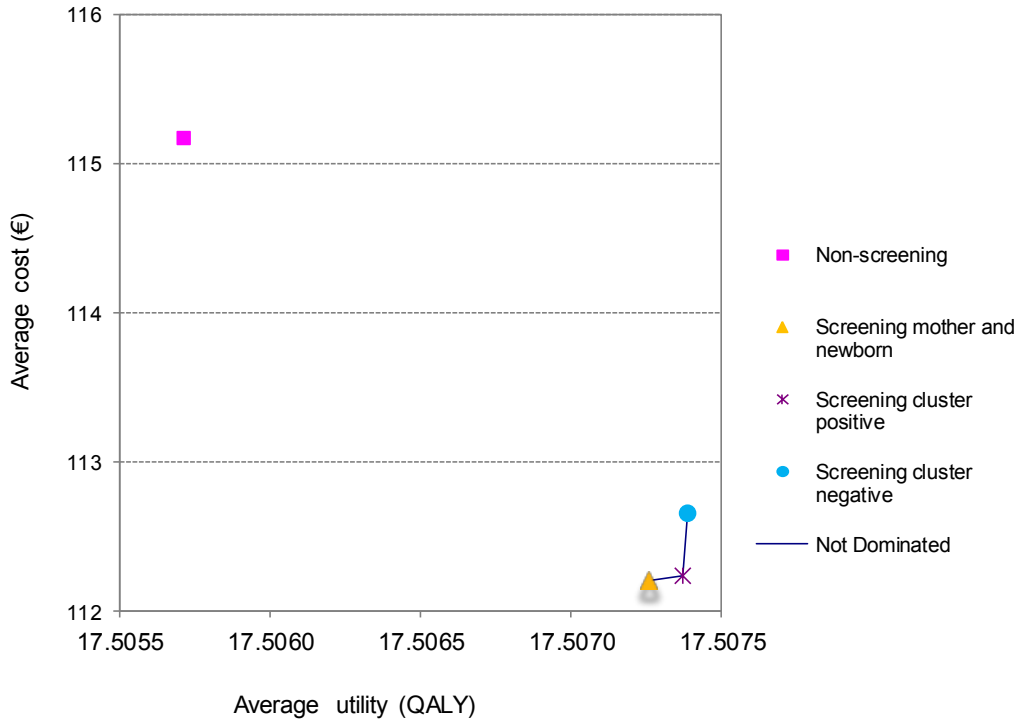

Figure 6. Cost-utility analysis results of the base case from the SNHS perspective.

Table 8. Base case results of the four screening strategies from the SNHS perspective.

Strategy	Average Cost (€)	Incremental Cost (€)	Average Utility (QALY)	Incremental Utility (QALY)	Average Cost-Utility	ICUR[a] (€/QALY)
Mother and newborn	112.196073	-	17.507259	-	6.408546	
Positive mother cluster	112.231032	0.034958	17.507375	0.000116	6.410500	301
Negative mother cluster	112.653892	0.422860	17.507389	0.000014	6.434648	30,844
Non-screening	115.168853	2.514962	17.505714	-0.001675	6.578929	Dominated

[a] ICUR: Incremental Cost-Utility Ratio comparing each strategy with the previous one

4.2 Sensitivity Analysis

The test of all the variables through sensitivity analysis produced important changes on the ICUR values in ten of the variables (table 9). The reduction of the values of two variables ("Chronic treatment efficacy" and "Chagas prevalence") made the "Non-screening" the most efficient strategy. Value changes in other eight variables made "Negative mother cluster" into the most efficient strategy.

A reduction in the "Chronic treatment efficacy" from 39.5% (base case) to 8% turned the "Non-screening" into the cheapest and the most effective strategy, and therefore dominates the three screening strategies. However, an increase of the "Chronic treatment efficacy" to 71% converts the "Negative mother cluster" into the most efficient strategy.

An increase in the Chagas prevalence of the screened population made the "Negative mother cluster" the most efficient strategy. However, if we screened population with a prevalence of 0.005 none of the screening strategies would be efficient and the "Non-screening" strategy would dominate the others.

For the rest of the variables changes in their values reduced the ICUR (38,013 €/QALY) more than a half, turning the "Negative mother cluster" into the most efficient strategy instead of "Positive mother cluster".

Table 9. Sensitivity Analysis for the societal perspective.

Variable	Value		ICUR (€/QALY)			
			Negative mother cluster	Positive mother cluster	Mother and newborn	No screening
Chronic treatment efficacy	Higher value	0.71	1,120	0	Dom*	Dom
	Base case	0.395	38,013	399	0	Dom
	Lower value	0.08	Dom	Dom	Dom	0
Chagas prevalence	Higher value	0.1875	0	Dom	Dom	Dom
	Base case	0.0322	38,013	399	0	Dom
	Lower value	0.005	Dom	Dom	Dom	0
Specificity	Higher value	1	3,814	272	0	Dom
	Base case	0.99	38,013	399	0	Dom
	Lower value	0.98	Dom	650	0	Dom
Indeterminate disease utility	Higher value	0.94375	5,954	261	0	Dom
	Base case	0.925	38,013	399	0	Dom
	Lower value	0.91	Dom	688	0	Dom
Cardiac disease probability	Higher value	0.2275	7,109	0	Dom	Dom
	Base case	0.182	38,013	399	0	Dom
	Lower value	0.1365	Dom	2,972	0	Dom
Risk decrease of being infected for cluster of negative mother	Higher value	0.55	10,195	399	0	Dom
	Base case	0.44	38,013	399	0	Dom
	Lower value	0.33	Dom	399	0	Dom
Relatives component	Higher value	0.75	205,778	399	0	Dom
	Base case	0.5	38,013	399	0	Dom
	Lower value	0.25	11,031	398	0	Dom
Digestive disease probability	Higher value	0.1125	13,699	119	0	Dom
	Base case	0.09	38,013	399	0	Dom
	Lower value	0.0675	Dom	882	0	Dom
Adverse events utility	Higher value	0.9	Dom	396	0	Dom
	Base case	0.8	38,013	399	0	Dom
	Lower value	0.7	16,504	401	0	Dom
Treatment duration	Higher value	0.3	16,503	401	0	Dom
	Base case	0.2	38,013	399	0	Dom
	Lower value	0.1	Dom	396	0	Dom

* Dominated

5 DISCUSSION

According to our results, implementing a screening strategy for Chagas disease in Spain is cost-effective. The non-screening strategy would not be acceptable under both the societal and the healthcare system perspectives. Among the tested strategies, the most efficient strategy would be to extent the antenatal screening of the Latin American mothers to the relatives of the positive mother (strategy "Positive mother cluster"). The screening to the relatives of the negative mother would not be efficient unless some variables were modified.

In that sense, the Chagas prevalence is one of the more important factors. The sensitivity analysis has shown that the screening to higher prevalence populations would increase the efficiency up to the most extensive program, which is the "Negative mother cluster". The prevalence of Chagas disease is very different among people coming from different Latin-American countries. The Bolivians are the most affected people with a prevalence of 18.75% in immigrants living in Europe (10,53–55), while the rest do not differ significantly from base case. Bolivians represents 14% of Latin American population living in Spain (13), distributed heterogeneously throughout the country. The results would suggest that the implementation of the "Negative mother cluster" would be the most efficient strategy to Bolivians while for the rest of Latin American immigrants the most efficient intervention would be the "Positive mother cluster".

We found also other uncertainties in the parameters related with Chagas disease that could affect our results. The efficacy of chronic disease treatment is not well established. The literature review has not provided consistent results and the variation is very wide. Moreover, an accurate biological marker to determine parasitological cure after treatment is still unavailable. According to our results a low treatment efficacy value (8%) would make not worthy any screening intervention regarding Chagas disease on Latin American population living in Spain.

On the other hand the official data on the population of Latin American people living in Spain may not correspond with the reality as the migration balance is currently negative and a percentage of immigrants have obtained Spanish nationality (13). Our model used a static cohort until the end of life, no taking into account migratory movements or future infection risks because of travels back to origin countries for holidays. Similarly, transfusion or transplant risk was not considered.

The calculation of the number of newborns and clusters from fertile women of the cohort are based on studies that may vary throughout the period (14,15). Our model assumed that the SNHS would cover the immigrants' healthcare necessities indefinitely, but their access to healthcare has been considerably limited recently (56). Adherence to the screening program was estimated according to current data, but probably it will be increased in the future due to a rising concern about Chagas disease in society (29).

The costs of developing the screening program are also uncertain. Although they were designed by experts on public health and tropical medicine, it could have modifications at the moment of implementation. Anyway, important changes in their values did not produced sensitive variations on the cost-utility ratio.

As far as we know, this study is the first to assess the extension of Chagas screening to others than Latin American pregnant women and their newborns in a developed country. The economic evaluation published by Sicuri *et al* in 2011 (12) evaluated three strategies based on

two models, one for the Latin American women resident in Spain and another one for their newborns. They found that to screen both Latin American women and their newborns is more cost-effective than non-screening. Our study, however, compares four strategies based on a unique model including all Latin American population that is estimated living in Spain. Our results indicate that to carry out the screening only in mothers and newborns would imply that most of the affected people would remain undiagnosed.

Our study aims to provide useful information to support decision making in Spain regarding the design and implementation of national strategies for prevention and treating Chagas. However the decision to incorporate a new program or technology depends on the Public Health priorities and economy of the nation. Some countries use explicit cost-effective thresholds to establish priorities but it is not the case of Spain, where there is no a standard threshold for technology incorporation (57).

In summary, our results indicate that in Spain it would be efficient to implement a screening program to control Chagas disease in the Latin American population living in the country. There are several possibilities for those programs, which can differ in extension, adherence or target population, among other variables. The population of Latin American mothers and their newborns has been at the moment the most targeted population for these programs. However, the efficiency to extend the program to other populations had not been evaluated. Our results would indicate that for the general Latin American immigrants the most efficient would be to screen the Latin American mothers, their newborns and the close relatives of the mothers with a positive serology. However for higher prevalence population, as Bolivians, the most efficient intervention would be to extend the program even to the close relatives of the negative mothers.

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