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Research Article

Congenital and Blood Transfusion Transmission of Chagas Disease: A Framework Using Mathematical Modeling

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Chagas disease or American trypanosomiasis is an important health problem in Latin America. Due to the mobility of Latin American population around the world, countries without vector presence started to report disease cases. We developed a deterministic compartmental model in order to gain insights into the disease dynamics in a scenario without vector presence, considering congenital transmission and transmission by blood transfusion. The model was used to evaluate the epidemiological effect of control measures. It was applied to demographic data from Spain and sensitivity analysis was performed on model parameters associated with control strategies.

1. Introduction

Chagas disease or American trypanosomiasis is caused by the protozoan parasite *Trypanosoma cruzi*, and it is an important health problem in Latin America. The most effective transmission route is through contact with triatomines bug (the disease vector) feces. Other transmission routes can occur by blood transfusion, organ transplantation, and congenital transmission [1]. Some cases of oral transmission have been reported in Brazil, Venezuela, Colombia, Mexico, Argentina, and Bolivia [2].

The disease presents an initial acute phase, generally asymptomatic, and a subsequent chronic phase, which can present clinical manifestations (cardiac, digestive, and/or neurological) [1]. Since the 1960s the only drugs used in Chagas disease treatment are benznidazole and nifurtimox, which have a great efficiency if the treatment starts early and can control disease progression in chronic cases [1, 3].

Although some Latin American countries, as Argentina, Bolivia, Brazil, Chile, Paraguay, Uruguay, and Peru, have received from the Pan American Health Organization (PAHO) the International Certification of Disease Elimination by the main vector *Triatoma infestans*, the disease is still a challenge [4]. According to the World Health Organization, around 8 million people are infected worldwide and 10,000 people die every year due to disease clinical manifestation [1]. Moreover, it estimates that 25 million people are at risk of acquiring the disease. Around 30-40% of infected people develop cardiomyopathy, digestive megasyndromes, or both [5].

Since 2000, cases of the disease started to be reported in nonendemic countries such as European countries, Canada, USA, Japan, and Australia, due to the large flow of Latin American immigrants [6]. In 2010, the World Health Assembly approved a resolution, WHA 63.20 [7], recognizing the increase in the number of cases and established a way to track

all of the transmission routes. The global cost of the disease is similar to rotavirus or cervical cancer [8].

By 2009, 4,290 cases had been diagnosed in Europe, compared with an estimated incidence ranging from 68,000 to 122,000 cases, hence 95% of cases are nondiagnosed, reflecting the difficulty in tracking infected people [9, 10]. Due to uncertainty about the real number of cases in each country, estimates are based on PAHO [11] and Schmunis et al. 2014 [12].

Spain is the European country with most Latin American immigrants, ranking the second on the world list, after the United States of America [13]. In 2008, there were approximately 4 million immigrants in Spain. 1.5 million of them were born in a country endemic for Chagas disease and, therefore, they are potential carriers of the disease [14]. The first case of the disease by blood transfusion in Spain was detected in 1984, with two more cases in 1995 and 2004 [15]. Cases of congenital transmission were also reported [16, 17].

Due to its silent evolution after infection and the resulting underdiagnoses, there is no complete and reliable data about the disease. Therefore, mathematical models can be a particularly useful tool on the study of disease spread and control.

Several mathematical modeling studies have been done in order to assess different aspects of Chagas disease and control strategies. For instance, Velasco-Hernandez et al. [18] considered a compartmental model with humans, vectors, and transmission by blood transfusion. Inaba and Sekine [19] also considered humans, vectors, and blood transfusion but with infection age dependent infectivity. Congenital transmission was considered by Massad [4], Raimundo et al. [20], and Coffield et al. [21]. Fabrizio et al. [22] explored an interhuman model, considering congenital transmission and blood transfusion transmission.

In this work, we present a novel deterministic compartmental model considering congenital and blood transfusion as the main mode of transmission using demographic data from Spain. The aim is to gain insight into the dynamics of the disease in a scenario without the vector and to evaluate the epidemiological impact through the implementation of control strategies like an improvement on surveillance in blood transfusion and treatment of infected newborns. We also introduced a cure rate for infected individuals to verify how it affects disease dynamics. This cure rate means decrease in the number of parasites inside host, and consequently decreasing the risk of developing clinical manifestation.

2. Materials and Methods

2.1. Model Description. We introduce a deterministic compartmental model for Chagas transmission without the vector presence. The model distinguishes Latin American people from countries with active vector transmission and natives and immigrants from countries without vector transmission. It also splits men and women in different compartments in order to take vertical transmission into account. Therefore, the population is classified into eight compartments:

(1) M_{vh}: healthy men from country with active vector transmission;

(2) M_{vi}: infected men from country with active vector transmission;

(3) M_h: healthy men from country without vector transmission;

(4) M_i: infected men from country without vector transmission;

(5) W_{vh}: healthy women from country with active vector transmission;

(6) W_{vi}: infected women from country with active vector transmission;

(7) W_h: healthy women from country without vector transmission;

(8) W_i: infected women from country without vector transmission.

In the model simulations we analyze the number of individuals over time in each of the compartments. The processes considered for driving their dynamics are the simplest as possible, keeping in mind the essence of the system's structure, the objectives of the model and the questions to be answered. The reasons for looking for such simplicity are various. From a theoretical perspective, a strictly gradual increase in complexity is essential in any model development in order to elucidate the different drivers of the overall dynamics. From a social perspective, this simplicity facilitates the necessary interaction with nonmodelers like community health workers, social scientists, and patients' associations in order to seek real and feasible applications.

The processes considered by the current model are birth, mortality, and flows among compartments. Infections flows are associated with two possible causes: blood transfusion and congenital transmission. Figure 1 shows a flowchart of the model. The assumptions for the dynamics of transmission are the following:

(i) It is assumed that vertical transmission is proportional to the number of infected women. People who are born in Spain will be considered in the without vector compartment, that is, W_i or M_i, even though their family origin is Latin American.

(ii) We considered that the birth rate α is the same for women from countries with and without the vector presence. We also assumed that 50% of the descendants are women and 50% are men, for simplicity.

(iii) If a woman is infected, she has a probability β to infect her son or daughter.

(iv) The parameter γ stands for mortality rate for healthy people. For infected individuals we assumed a mortality rate induced by the disease δ, where $\delta > \gamma$.

(v) Flow among health and infected classes due to blood transfusion is considered as the result of interaction between susceptible and infected people. We considered that there is no difference in the blood and organ donation rate for populations from countries without the vector and for countries with the vector. The parameter τ stands for the yearly blood donation rate.

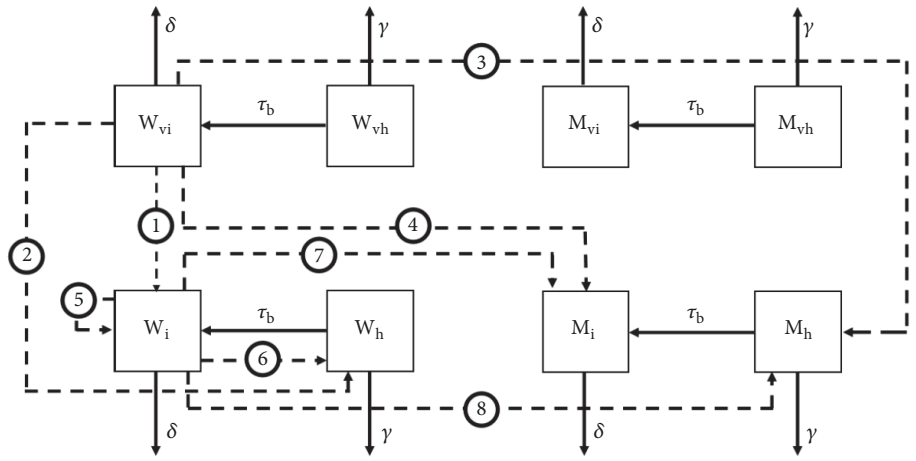

Figure 1: Flow chart for the dynamics of proposed model. Letters inside box indicate the number of individuals in each compartment: infected women from country with vector (W_{vi}), healthy women from country with active vector transmission (W_{vh}), infected men from country with active vector transmission (M_{vi}), healthy men from country with active vector transmission (M_{vh}), infected women from country without vector transmission (W_i), healthy women from country without vector transmission (W_h), infected men from country without vector transmission(M_i), and healthy men from country without vector transmission (M_h). γ is the death rate for healthy people and δ is the death rate for infected people. τ_b is the rate of infection due to blood transfusion. Dashed lines indicate the births. Newborns from W_{vi} can be an infected female (1), healthy female (2), healthy male (3), or infected male (4). The same occur for newborns from W_i that can be infected female (5), healthy female (6), infected male (7), or healthy male (8). Healthy women W_{vh} and W_h only gave birth to healthy newborns (flows not shown).

(vi) We also considered that a proportion p_i of donated blood is potentially contaminated with *T. cruzi*. Once donation has been made, health services carry out controls screening. We considered ξ as the probability of an effective surveillance in screening donated blood samples, thus $1 - \xi$ is the probability that an infected sample will not be detected, reach a receptor, and infect him or her. In this way, the rate at which a healthy person becomes infected with a parasite from an infected person will be proportional to the product $\tau_b = \tau p_i(1 - \xi)$. We also considered that all transfusions are made with the same rate for all individuals.

(vii) We supposed that infected individuals can be cured with a rate C due to treatment. This cure rate means a reduction in the number of parasites inside host, reducing the chances of clinical manifestation. We consider that a yearly percentage d of infected individuals will be diagnosed and receive treatment. Considering e as the treatment effectiveness, we can write $C = e \cdot d$. The detected patients that do not receive any treatment due to different reasons (e.g., reported difficulties in accessing it [29]) are not distinguished from nondiagnosed individuals by the model.

(viii) No migration flows (neither immigration nor emigration) were considered by the model, since they are not relevant for its current purpose.

According to the assumptions above, the model is represented by the following system of ordinary differential equations (1)-(8):

$$\frac{dM_h}{dt} = 0.5\alpha\left(W_h + W_{vh}\right) + 0.5\alpha\left(1 - \beta + \rho\right)\left(W_i + W_{vi}\right) + CM_i - \gamma M_h - \tau_b\left(1 - \xi\right)M_h\left(\frac{I}{N}\right) \quad (1)$$

$$\frac{dW_h}{dt} = 0.5\alpha\left(W_h + W_{vh}\right) + 0.5\alpha\left(1 - \beta + \rho\right)\left(W_i + W_{vi}\right) + CW_i - \gamma W_h - \tau_b\left(1 - \xi\right)W_h\left(\frac{I}{N}\right) \quad (2)$$

$$\frac{dM_{vh}}{dt} = CM_{vi} - \gamma M_{vh} - \tau_b\left(1 - \xi\right)M_{vh}\left(\frac{I}{N}\right) \quad (3)$$

$$\frac{dW_{vh}}{dt} = CW_{vi} - \gamma W_{vh} - \tau_b\left(1 - \xi\right)W_{vh}\left(\frac{I}{N}\right) \quad (4)$$

$$\frac{dM_i}{dt} = 0.5\alpha\beta\left(W_i + W_{vi}\right)\left(1 - \rho\right) - \left(\delta + C\right)M_i + \tau_b\left(1 - \xi\right)M_h\left(\frac{I}{N}\right) \quad (5)$$

$$\frac{dW_i}{dt} = 0.5\alpha\beta\left(W_i + W_{vi}\right)\left(1 - \rho\right) - \left(\delta + C\right)W_i + \tau_b\left(1 - \xi\right)W_h\left(\frac{I}{N}\right) \quad (6)$$

$$\frac{dM_{vi}}{dt} = \tau_b\left(1 - \xi\right)M_{vh}\left(\frac{I}{N}\right) - \left(\delta + C\right)M_{vi} \quad (7)$$

$$\frac{dW_{vi}}{dt} = \tau_b (1 - \xi) W_{vh} \left(\frac{I}{N} \right) - (\delta + C) W_{vi} \quad (8)$$

where $I = W_i + M_i + W_{vi} + M_{vi}$ is the number of all infected individuals and N is the total population.

Formulating and evaluating the model behavior will help us to find out what information is known and what is unknown, to analyze the relative importance of each one of the parameters, and to understand the system's dynamics, observing the long-term dynamics based on the control actions that are carried out.

3. Results

3.1. Parameter Estimation. In order to evaluate the trends and the important factors on the dynamic system, it is necessary to attribute parameters values used by the model. Thus, the model was fed with available data from Spain. The diversity of model parameters to be fixed required the use of different data sources. After exploring data availability, we chose 2007 as the starting point of the simulation because it guaranteed the access to all necessary information. The sources and obtained values are described below.

3.1.1. Birth Rate and Vertical Transmission. By 2007 birth rate in Spain was 10.9 per 1,000 inhabitants [23]. In a study performed in two maternity clinics in Barcelona, Muñoz et al. [24] reported a prevalence of 3.4% among pregnant Latin American and 7.3% of newborns were infected. Then, we set the birth rate as $\alpha = 0.0109\ \text{year}^{-1}$ and the probability of vertical transmission as $\beta = 0.073$.

3.1.2. Mortality Rates. By 2007 mortality rate in Spain was 8.5 per 1,000 inhabitants [25]. Cunubá et al. [26] published a systematic review about mortality attributed to Chagas disease. The authors found that the annually mortality rate for Chagas patients was twice higher than non-Chagas patients in a moderate clinical group (0.16 (Chagas) *vs.* 0.08 (non-Chagas) with RR = 2.10, 95% CI: 1.52-2.91). Therefore, we set $\gamma = 0.0085$ per year and $\delta = 2\gamma = 0.017$.

3.1.3. Transmission by Blood Transfusion. We defined the rate of transmission by blood transfusion as $\tau_b = \tau p_i$, where τ is the donation rate per year and p_i is the proportion of potentially infected blood samples. The proportion of potentially infected blood samples was reported as 0.67 per 1,000 [27]. The rate of blood donation in Spain in 2007 was 33.4 per 1,000 inhabitants [28]. Then, the rate of infection by blood transfusion τ_b was calculated as 0.00022378 per year.

3.1.4. Control Strategies. Actions to control the increase in new cases of Chagas disease are incorporated into the model ((1)-(8)) by assuming some control parameters. We considered two kinds of control strategies:

(i) Increasing the proportion of infected newborn treated, by means of increasing the parameter ρ on the model simulation.

(ii) Increasing surveillance in blood transfusion, by means of increasing the parameter ξ in the model simulation.

Moreover, we also assumed a cure rate by diagnosing and treating infected individuals. In the model simulation, it was done by increasing the parameter d.

A summary of parameters used in the simulations is listed in Table 1.

3.2. Numerical Simulations. Population in Spain in 2007 was 45,226,803 [30] of which 1,638,694 were immigrants from countries with the vector presence and potential Chagas disease carriers. The estimated number of infected individuals was 53,134. Besides, taking into account the demographic characteristics of the population, the estimated number of infected women in the childbearing age in Spain was 24,000 [24, 27].

Based on that, the initial conditions were set as $M_h(0) = 21,791,055$, $M_i(0) = 0$, $M_{vh}(0) = 792,780$, $M_{vi}(0) = 29,134$, $W_h(0) = 21,792,055$, $W_i(0) = 0$, $W_{vh}(0) = 792,780$, $W_{vi}(0) = 24,000$.

By use of model (1)-(8), we simulated the cumulative number of infected people over time. Numerical simulations were performed using the software R 3.5.0, integrating the system ((1)-(8)) by Runge–Kutta fourth-order method, using the parameters shown in Table 1 and the initial conditions set above. Time step used was one year and time range for simulation was 40 years.

3.3. Total Infected Population. The dynamics of the total number of infected individuals ($I = M_i + W_i + M_{vi} + W_{vi}$) was simulated for 40 years in order to observe the epidemiological behavior given by the model. We observe a decreasing behavior on the total number of infected people along time as shown in Figure 2. This result is due to the higher death rate attributed to infected people and to the fact that migration flows are not considered, thus resulting in a decreasing rate of change in the total number of the infected. At the end of 40 years simulation, there was a 48% reduction in the number of the total infected when compared with the initial value.

3.4. Comparing the Effect of Transmission Routes. Beyond the number of infected people immigrating to the country without vector presence, another quantity of interest is the number of new cases of the disease, i. e., the cumulative number of new infected arising due blood transfusion and congenital transmission, represented by the sum of individuals in the compartments W_i and M_i.

We can compare the difference in the disease dynamics when only one route of infection is considered, as displayed in Figure 3. The results show that congenital transmission has a higher impact than the transmission by blood transfusion, causing 38% more new infections.

3.5. Control Strategies. Two control strategies were considered, as above mentioned, treatment of infected newborns

Table 1: Parameters used in numerical simulation of proposed model (1)-(8).

Parameter	Meaning	Value	Source
α	Birth rate (year^{-1})	0.0109	[23]
β	Probability of vertical transmission	0.073	[24]
γ	Mortality rate (year^{-1})	0.0085	[25]
δ	Mortality rate due disease (year^{-1})	0.0017	[26]
τ_b	Rate of infection by infected blood (year^{-1})	0.00022378	[27, 28]
C	Cure rate (year^{-1})	Various	
ρ	Proportion of new born treated	Various	
ξ	Probability of a efficient surveillance	Various	

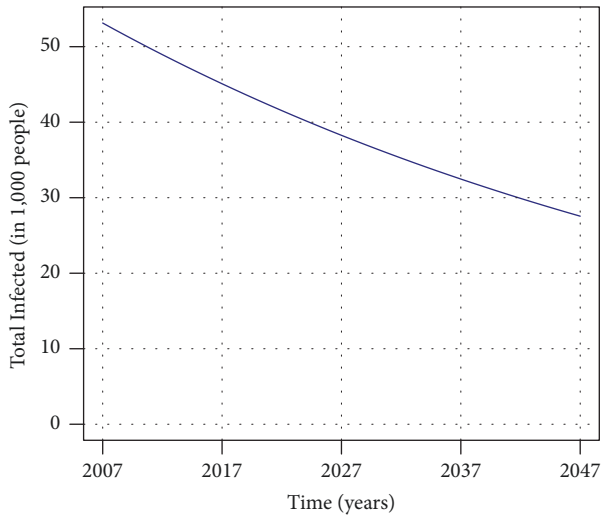

Figure 2: Dynamics on the number of total infected people along 40 years simulation considering death rate due to disease as twice the natural death rate and no migration flows.

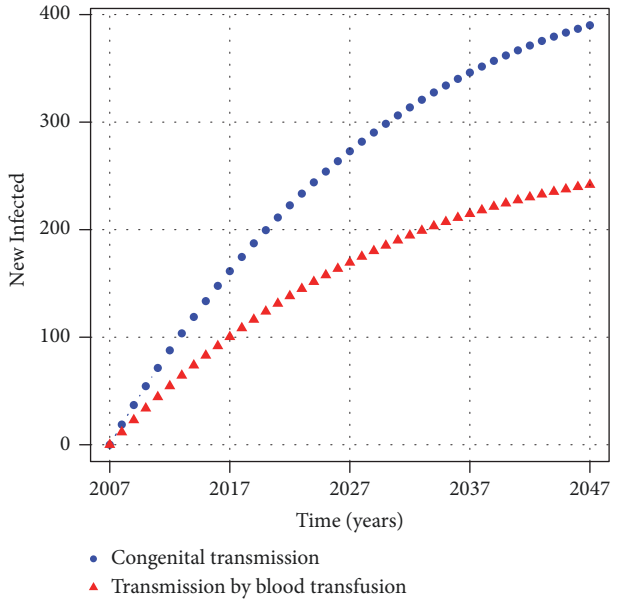

Figure 3: Comparison of the number of cumulative new infections along time when a single transmission route is considered.

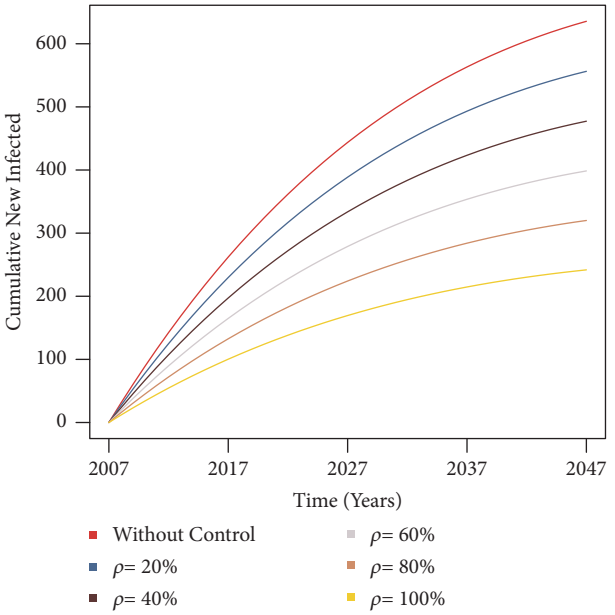

Figure 4: Sensitivity analysis on the cumulative number of newly infected individuals by varying ρ, i.e., the proportion of treatment of infected newborn.

(ρ) and surveillance in blood transfusion (ξ). These strategies were simulated, isolated, and combined.

3.5.1. Considering Only Treatment of Infected Newborns. In this simulation, we evaluated the effect of performing a control strategy only on newborns. The parameter associated with this control strategy is ρ, which represents the proportion of successfully treated infected newborns. This parameter was varied by 20%. The other parameters of the model remained constant as in Table 1, while the parameter ξ representing the control in blood transmission was set to zero. Figure 4 displays the result of this sensitivity analysis in the cumulative number of newly infected individuals.

When comparing these tendencies with the scenario without control (Figure 2), the obtained percentage reductions on the cumulative number of new infected after 40 years are shown in Table 2. Treating 100% of infected newborn means that the cumulative number of newly infected individuals will arise only due to transmission by blood transfusion.

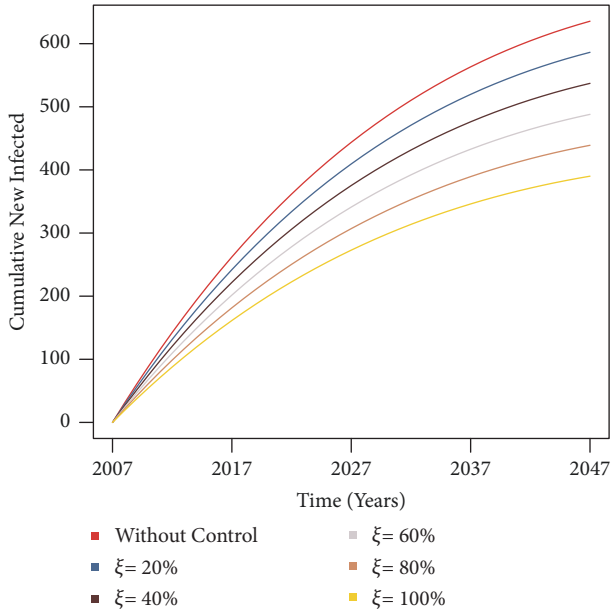

Figure 5: Sensitivity analysis on the cumulative number of newly infected individuals by varying ξ, i.e., the probability of effective surveillance in blood transfusions.

Table 2: Percentage reductions due to variation only in parameter ρ – the proportion of treatment in infected newborn.

ρ values	Reduction (%)
20%	12.5
40%	24.9
60%	37.29
80%	49.64
100%	61.95

Table 3: Percentage reductions in the number of new cases due to variation in parameter ξ – the probability of an effective surveillance in blood transfusion.

ξ values	Reduction (%)
20%	7.75
40%	15.49
60%	23.22
80%	30.93
100%	38.63

3.5.2. Control Only in Blood Transfusion. In this simulation, we evaluated the effect of performing a control strategy only on blood transfusion. Figure 5 displays the result of sensitivity analysis on the cumulative number of newly infected individuals by varying the probability of an effective surveillance ξ on blood transfusions, while the other parameters remain constant and the parameter associated with the control of infected newborn ρ is set to zero.

The obtained percentage reductions in the cumulative number of the newly infected after a 40 years simulation, when compared with the without control scenario (Figure 2), are shown in Table 3. When a probability of an effective surveillance reaches 100%, new cases are only due to congenital transmission.

Table 4: Percentage reductions in the number of new cases due to variation in both parameters associated with control strategies – ρ (percent of infected newborn treated) and ξ (probability of an effective surveillance in blood transfusion).

Parameters values	Reduction (%)
ρ = 20%, ξ = 20%	20.2
ρ = 40%, ξ = 20%	32.6
ρ = 60%, ξ = 40%	52.6
ρ = 80%, ξ = 60%	72.6
ρ = 100%, ξ = 80%	92.4.

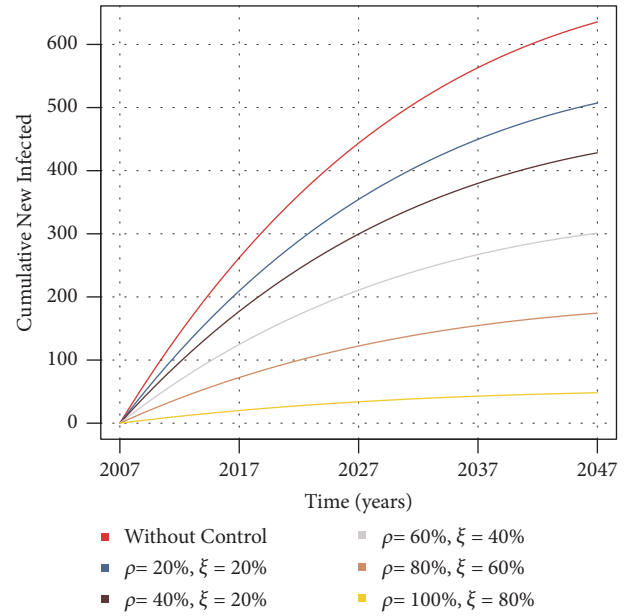

Figure 6: Sensitivity analysis on the cumulative number of newly infected by applying combined control: increasing proportion of treatment in infected newborns (parameter ρ) and on the surveillance in blood transfusion transmission (parameter ξ).

3.5.3. Combined Control. Sensitivity analysis can also be performed by varying the two parameters associated to control strategies at the same time. Figure 6 shows the results of combined control, by varying ρ and ξ simultaneously. Resulting percentage reductions on the cumulative number of newly infected when compared with a without control scenario at the end of 40 years simulation are shown in Table 4.

We also explored the effect of a certain cure rate on the dynamics of infected individuals. The effectiveness due to treatment with nifurtimox and/or benznidazole in patients in the chronic indeterminate phase of Chagas disease is about 7-8% [3].

According to [10], the index of underdiagnosis in Spain is in the range 92.0-95.6%. It justifies the low values considered for the percent of detected individuals in model simulation,

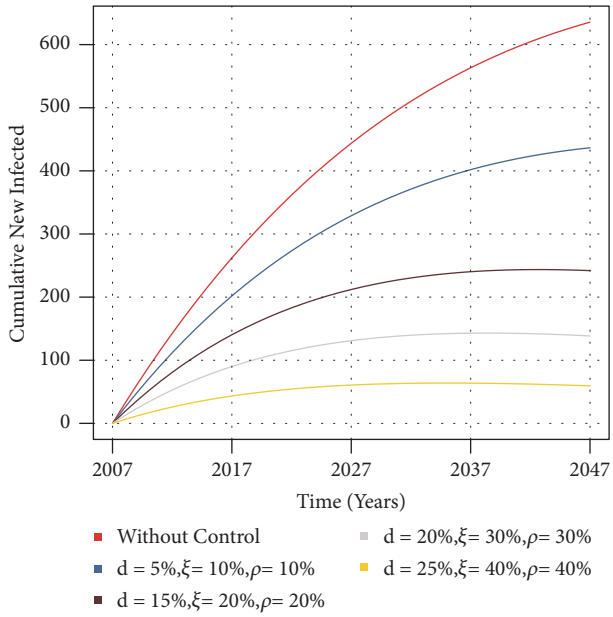

Figure 7: Sensitivity analysis considering detection and treatment of infected individuals d, treatment of infected newborns ρ, and surveillance in blood transfusion transmission ξ.

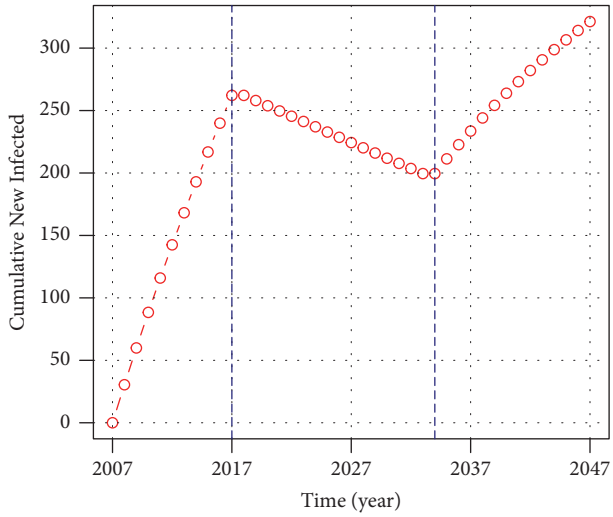

Figure 8: The result of simulation of interrupted control. Parameters associated with control strategies were $d = 25\%$ (detection of infected people), $\rho = 80\%$ (treatment of infected newborn), and $\xi = 80\%$ (effectiveness on surveillance in blood transfusion). The control strategies were applied after 10 years of simulation. After 15 years of application, the control strategies were stopped.

included in the parameter d. Based on that, we set the treatment effectiveness as $e = 7.5\%$ and varied the detection and treatment of infected individuals d. The cure rate is assessed as $C = 7.5\% \cdot d$.

The detection and treatment of infected patients are difficult, mainly due to the asymptomatic characteristics of the disease [10] but also because of other barriers such as health care access limitations or the own misperception of the disease [29]. Therefore, we varied the parameter d between 0 and 25%.

Table 5: Percentage reductions on the total number of infected individuals by varying the proportion of detection and treatment of infected individuals d.

d values	Reduction (%)
$d = 5\%$	13.93
$d = 15\%$	36.23
$d = 20\%$	45.11
$d = 25\%$	52.76

Table 6: Percentage reductions for each parameter variation.

Parameters	Reduction (%)
d = 5%, ξ= 10%, ρ= 10%	22.63
d = 15%, ξ= 20%, ρ= 20%	48.78
d = 20%, ξ= 30%, ρ= 30%	60.51
d = 25%, ξ= 40%, ρ= 40%	69.75

Percentage reductions in the total number of infected individuals from the initial year simulation to 40 years are shown in Table 5.

The cumulative number of new infected is strongly affected by the introduction of the cure rate. Figure 7 displays the sensitivity analysis by varying the parameters ρ, ξ, and d. The corresponding percentage reductions when compared with the scenario without control at the end of 40 years simulation for each parameter combination are displayed in Table 6.

3.5.4. Interrupted Control. Another interesting scenario explored by our model was the simulation of interrupted control. We simulated the cumulative number of new cases by applying control strategies after ten years without control, followed by a control period of 15 years, and interrupted again after this period. We used a detection proportion of 25%, a treatment success of 80% of infected newborns, and surveillance in blood transfusion 80% effective. Figure 8 displays the result. In the first ten years, the number of new cases increases because there are more infected people in the population. When control strategies are performed, the number of new cases decreases because infected people are treated avoiding transmission by congenital and blood transfusion routes. When the control strategies are stopped, the number of new cases start increasing again, since there will be more infected newborns and people infected by blood transfusions over time.

4. Discussion

In this work, we used a compartmental mathematical model to evaluate the dynamics of Chagas disease in a scenario with vector absence, where the transmission can only occur through congenital or blood transfusion routes.

Our results show that, although the total number of infected individuals presents a decreasing behavior (Figure 2), in 40 years its reduction reaches less than half of its initial value, even assuming a death rate for infected individuals as twice the rate for healthy people and no immigration. It means that if the disease is not taken seriously, it can be present in the population for a long period of time [31], even with the vector absence, generating a burden to the public health system which should be prepared to provide patient care and conduct an adequate treatment in order to prevent the long-term disease manifestations.

According to the model, transmission exclusively due to blood transfusion has a smaller impact on the number of new cases when compared with the transmission exclusively due to congenital route (Figure 3). Low prevalence in blood banks in countries with vector absence, oftentimes by self-exclusion of Latin American immigrants in transfusion services, can explain this fact [9]. Nevertheless, blood screening should be sustained and it is vital to prevent infection through transfusion and organ transplantation also in nonendemic countries. Optimizing blood transfusion safety and screening is one of the resolutions of the World Health Assembly for the control and elimination of Chagas disease (WHA 63.20) [7]. In Spain, the control strategy is based on selective donor screening from a questionnaire and it has been implemented since 2005. Donations from at-risk individuals are accepted and the blood is tested [15]. It can prevent a transfusion by a contaminated blood sample beyond identifying infected people. Simulation results plotted in Figures 4 and 5 display the application of isolated control strategies. They show that, even if all infected newborns are treated or if a totally effective surveillance in blood banks is reached, the reduction on the number of new cases when compared with a scenario without control is not 100% achieved.

The model simulation also shows that application of combined control strategies (i.e., treatment of infected newborns and effective surveillance in blood transfusion) can lead to a more significant reduction in the number of new cases when compared with a scenario without control (Figure 6). For instance, treating 80% of infected newborns and having 60% of effectiveness on surveillance in blood banks entails 72.6% less new infections when compared with a scenario without control. It is important to highlight that, although there are standard protocols to deal with the disease control, the quality of the service is very important and sometimes difficult to be measured. In this sense, the study of patients' perceptions and experiences should be included in such protocols in order to increase the quality assessment of services. This fact justifies the values used on our parameters associated with control strategies, varying from 20% to 100% on the effectiveness.

Regarding congenital transmission, an important fact to mention is that the majority of Latin American immigrants in Italy, Japan, Switzerland, Australia, and New Zealand are women in childbearing age, highlighting the importance of programs to screen pregnant women. These programs lead to an early detection of congenital transmission, as stated in World Health Assembly [7]. By 2014 only the Tuscany region in Italy had legislation to screen pregnant women from areas considered endemic [8]. In Spain, only Catalonia, Valencia, and Galicia regions had protocols in screening pregnant women from Latin America up to 2014 [8]. The other countries do not have national programs for disease prevention [32, 33]. The adoption of screening protocols is extremely important since the identification and treatment of infected newborns have good therapeutic results [24].

Although the detection of infected people is difficult due to the asymptomatic characteristic of the disease leading to an underestimation on the number of current cases [10], our model tested the effect of a cure rate due to treatment. This cure rate can be understood as a reduction in the number of parasites inside the host body. Treatment in chronic cases can reduce long-term complications caused by the disease [3, 34]. Nevertheless, treatment accessibility should be guaranteed for all of the diagnosed patients by eliminating existing barriers [29]. Regarding women in childbearing age, detection and treatment also prevent congenital transmission [35, 36].

Our model results are in accordance with this fact since the detection and treatment of infected people have an impact on the cumulative number of new infections (Figure 7). One important strategy to track infected people is by active surveillance in primary care and community action in order to identify pregnant women and follow up their children [37]. Even with a great effort to conduct this kind of strategy, in some cases, infected people can be lost. The simulations results show that there is a reduction in the number of total infected people by 52.76% if 25% of infected people are detected and treated when compared with a scenario without control. The detection and treatment also reduce the number of new cases when combined with treatment of infected newborns and surveillance on blood transfusions. For example, detecting 25% of infected individuals, treating 40% of infected newborns, and having a surveillance in blood banks 40% efficient, the number of new cases is almost 70% smaller when compared with a scenario without control. It is important that the control strategies are sustained; otherwise, the disease elimination will take even longer to be achieved. Figure 8 displays a result of a simulation where the control is applied for a limited period and it is then interrupted. During the period where control applications are performed, the number of new cases decreases, but it starts increasing again when control stops.

The model was applied to Spain, a country without the vector presence, but it could be similarly applied to other countries with vector absence in order to carry out a diagnosis of the current epidemiological situation and determine the order of magnitude of such control strategies' effects.

It should be recalled that a model is a simplified description of reality. Consequently, it entails necessary simplifications in order to focus on the stated aims. The proposed model was sufficient to show the importance of sustaining the control strategies considered in order to advance steadily towards the disease elimination. Otherwise, it will be present in a population for a long time causing long-term clinical manifestation and a burden on the public health system.

Other aspects can be also explored in future works as, for example, the introduction of migrations rates. Nevertheless, although migration flows have a straightforward effect on

Chagas disease dynamics in nonendemic countries, they are usually unpredictable and difficult to control. Therefore, *in silico* experiments could be used for exploring different scenarios and proposing possible actions to revert those negative epidemiological effects. Another control strategy that could be incorporated into the model for its testing is the screening of specific collectives in order to detect (and treat, if necessary) new asymptomatic cases among at-risk populations [38]. In the case of women in childbearing age, treating infected women before a future pregnancy would prevent congenital transmission [36].

Finally, it is also important to point out that the inter- and transdisciplinary work among modelers, health practitioners, community health workers, patients' associations, and other context-specific actors is essential for generating and implementing effective tools for decision making and public health control policies. In that sense, the development of simple models and user-friendly simulation platforms will guarantee that this necessary collaboration between modeling experts and nonexperts is feasible.

5. Conclusions

Mathematical models can be used as a valuable tool to explore different scenarios related to disease spread, as well as to estimate the epidemiological impact when control strategies are implemented. Interdisciplinary collaboration is extremely important in this context since it can improve decision making for the implementation of public policies in order to reduce the disease burden in public health.

Data Availability

The epidemiological and demographic data supporting this study are from previously reported studies and datasets, which have been cited. The processed data is available from the corresponding author upon request.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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References

[1] *WHO, World Health Organization. Chagas Disease (American trypanosomiasis)*, 2017, http://www.who.int/mediacentre/factsheets/fs340/en/.

[2] "The importance of the multidisciplinary approach to deal with the new epidemiological scenario of Chagas disease (global health)," *Acta Tropica*, vol. 151, pp. 16–20, 2015.

[3] P. A. S. Junior, I. Molina, S. M. F. Murta et al., "Experimental and Clinical Treatment of Chagas Disease: A Review," *The American Journal of Tropical Medicine and Hygiene*, vol. 97, no. 5, pp. 1289–1303, 2017.

[4] E. Massad, "The Elimination of Chagas' Disease from Brazil," *Epidemiology and Infection*, vol. 136, pp. 1153–1164, 2008.

[5] A. Rassi Jr., A. Rassi, and J. A. Marin-Neto, "Chagas disease," *The Lancet*, vol. 375, no. 9723, pp. 1388–1402, 2010.

[6] C. Di Girolamo, C. Bodini, B. Marta, A. Ciannameo, and F. Cacciatore, "Chagas disease at the crossroad of international migration and public health policies: why a national screening might not be enough," *Eurosurveillance*, vol. 15, no. 37, 2011, Eurosurveillance.

[7] World Health Organization (WHO), *Chagas disease: control and elimination. Resolutions and Decisions WHA 63.20*, WHO, Geneva, 2010, http://www.who.int/neglected_diseases/mediacentre/WHA_63.20_Eng.pdf.

[8] A. Requena-Méndez, P. Albajar-Viñas, A. Angheben et al., "Health Policies to Control Chagas Disease Transmission in European Countries," *PLOS Neglected Tropical Diseases*, vol. 8, no. 10, p. e3245, 2014.

[9] A. Requena-Méndez, E. Aldasoro, E. de Lazzari et al., "Prevalence of Chagas Disease in Latin-American Migrants Living in Europe: A Systematic Review and Meta-analysis," *PLOS Neglected Tropical Diseases*, vol. 9, no. 2, p. e0003540, 2015.

[10] L. Basile, J. Jansa, Y. Carlier et al., "Chagas disease in European countries: the challenge of a surveillance system," *Chagas disease in Europe*, vol. 16, no. 37, 2011.

[11] Organización Panamericana de la Salud, *Estimación cuantitativa de la enfermedad de Chagas en las Américas. Spanish*, 2006, http://www.bvsops.org.uy/pdf/chagas19.pdf.

[12] G. A. Schmunis and Z. E. Yadon, "Chagas disease: a Latin American health problem becoming a world health problem," *Acta Tropica*, vol. 115, no. 1-2, pp. 14–21, 2010.

[13] M. Navarro, B. Navaza, A. Guionnet, and R. López-Vélez, "Chagas Disease in Spain: Need for Further Public Health Measures," *PLOS Neglected Tropical Diseases*, vol. 6, no. 12, 2012.

[14] M. Piron, M. Vergés, J. Muñoz et al., "Seroprevalence of *Trypanosoma cruzi* infection in at-risk blood donors in Catalonia (Spain)," *Transfusion*, vol. 48, no. 9, pp. 1862–1868, 2008.

[15] A. Angheben, L. Boix, D. Buonfrate et al., "Chagas disease and transfusion medicine: A perspective from non-endemic countries," *Blood Transfusion*, vol. 13, no. 4, pp. 540–550, 2015.

[16] C. Riera, R. Fisa, C. Martin, A. Guarro, M. Castro, J. M. Jorba et al., "Congenital transmission of *Trypanosoma cruzi* in Europe (Spain): a case report," *The American Journal of Tropical Medicine and Hygiene*, vol. 75, no. 6, pp. 1078–1081, 2006.

[17] J. Muñoz, M. Portús, M. Corachan, V. Fumadó, and J. Gascon, "Congenital *Trypanosoma cruzi* infection in a non-endemic area," *Transactions of the Royal Society of Tropical Medicine and Hygiene*, vol. 101, no. 11, pp. 1161-1162, 2007.

[18] J. X. Velasco-Hernández, "A model for Chagas disease involving transmission by vectors and blood transfusion," *Theoretical population biology*, vol. 46, pp. 1–31, 1994.

[19] H. Inaba and H. Sekine, "A mathematical model for Chagas disease with infection-age-dependent infectivity," *Mathematical Biosciences*, vol. 190, no. 1, pp. 39–69, 2004.

[20] S. M. Raimundo, E. Massad, and H. M. Yang, "Modelling congenital transmission of Chagas' disease," *Biosystems*, vol. 99, pp. 215–222, 2010.

[21] D. J. Coffield Jr., A. M. Spagnuolo, M. Shillor et al., "A Model for Chagas Disease with Oral and Congenital Transmission," *PLoS ONE*, vol. 8, no. 6, 2013.

[22] M. Fabrizio, N. J. Schweigmann, and N. J. Bartoloni, "Modelling inter-human transmission dynamics of Chagas disease: analysis and application," *Parasitology*, vol. 141, pp. 837–848, 2014.

[23] "The World Bank, Birth rate, crude (per 1,000 people)," https://data.worldbank.org/indicator/SP.DYN.CBRT.IN?locations=ES.

[24] J. Muñoz, O. Coll, T. Juncosa et al., "Prevalence and vertical transmission of *Trypanosoma cruzi* infection among pregnant latin american women attending 2 maternity clinics in Barcelona, Spain," *Clinical Infectious Diseases*, vol. 48, no. 12, pp. 1736–1740, 2009.

[25] "The World Bank, Death rate, crude (per 1,000 people)," https://data.worldbank.org/indicator/SP.DYN.CDRT.IN?locations=ESview=chart.

[26] Z. M. Cucunubá, O. Okuwoga, M.-G. Basáñez, and P. Nouvellet, "Increased mortality attributed to Chagas disease: a systematic review and meta-analysis," *Parasites & vectors*, vol. 9, p. 42, 2016.

[27] R. A. Gallastegui, C. C. Izaguirre, E. C. Brustenga et al., "Enfermedad de Chagas y Donación de Sangre," *Ministerio de Sanidad y Política Social*, 2009, Ministerio de Sanidad y Política Social.

[28] J. A. García-Erce, A. Campos, and M. Muñoz, "Blood donation and blood transfusion in Spain (1997-2007): the effects of demographic changes and universal leucoreduction," *Blood Transfusion*, vol. 8, p. 100, 2010.

[29] M. Navarro and J. J. de los Santos, "Access to Chagas disease treatment in non-endemic countries: the case of Spain," *The Lancet Global Health*, vol. 5, p. e577, 2017.

[30] "The World Bank, Population, total," https://data.worldbank.org/indicator/SP.POP.TOTL?locations=ES.

[31] J. Coura and P. Vinas, "Chagas disease: a new worldwide challenge," *Nature*, pp. 56-57, 2010.

[32] Y. Jackson and F. Chappuis, "Chagas disease in Switzerland: history and challenges," *Eurosurveillance*, vol. 16, 2011.

[33] K. Imai, T. Maeda, Y. Sayama et al., "Chronic Chagas disease with advanced cardiac complications in Japan: Case report and literature review," *Parasitology International*, vol. 64, no. 5, pp. 240–242, 2015.

[34] D. L. Fabbro, M. L. Streiger, E. D. Arias, M. L. Bizai, M. Del Barco, and N. A. Amicone, "Trypanocide treatment among adults with chronic Chagas disease living in Santa Fe City (Argentina), over a mean follow-up of 21 years: Parasitological, serological and clinical evolution," *Journal of the Brazilian Society of Tropical Medicine*, vol. 40, no. 1, pp. 1–10, 2007.

[35] S. Sosa-Estani, E. Cura, E. Velazquez, C. Yampotis, and E. L. Segura, "Etiological treatment of young women infected with *Trypanosoma cruzi*, and prevention of congenital transmission," *Journal of the Brazilian Society of Tropical Medicine*, vol. 42, no. 5, pp. 484–487, 2009.

[36] D. L. Fabbro, E. Danesi, V. Olivera et al., "Trypanocide Treatment of Women Infected with *Trypanosoma cruzi* and Its Effect on Preventing Congenital Chagas," *PLOS Neglected Tropical Diseases*, vol. 8, no. 11, p. e3312, 2014.

[37] A. Soriano-Arandes, L. Basile, H. Ouaarab et al., "Controlling congenital and paediatric Chagas disease through a community health approach with active surveillance and promotion of paediatric awareness," *BMC Public Health*, vol. 14, no. 1, 2014.

[38] A. Requena-Méndez, S. Bussion, E. Aldasoro et al., "Cost-effectiveness of Chagas disease screening in Latin American migrants at primary health-care centres in Europe: a Markov model analysis," *The Lancet Global Health*, vol. 5, no. 4, pp. e439–e447, 2017.