Edneide Florivalda Ramos Ramalho

Mathematical Models in Epidemiology: Simulating Chagas Disease Transmission and Evaluating the Control Measures

Recife

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UNIVERSIDADE FEDERAL RURAL DE PERNAMBUCO
PRÓ-REITORIA DE PESQUISA E PÓS-GRADUAÇÃO
PROGRAMA DE PÓS-GRADUAÇÃO EM BIOMETRIA E ESTATÍSTICA APLICADA

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Tese julgada adequada para obtenção do título de Doutora em Biometria e Estatística Aplicada, defendida e aprovada por unanimidade em 19/02/2019 pela comissão examinadora

Área de concentração: Biometria e Estatística Aplicada

Supervisor: Dr. Cláudio Tadeu Cristino
Co-supervisor: Dr. Jones Oliveira de Albuquerque and Dr. Daniel López Codina

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I dedicate this work to Edneis Ramalho,
my lovely mom and best friend, who always
support me and make me a better person every day.

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"For since men for the most part follow in the footsteps and imitate the actions of others, and yet are unable to adhere exactly to those paths which others have taken, or attain to the virtues of those whom they would resemble, the wise man should always follow the roads that have been trodden by the great, and imitate those who have most excelled, so that if he cannot reach their perfection, he may at least acquire something of its savour. Acting in this like the skilful archer, who seeing that the object he would hit is distant, and knowing the range of his bow, takes aim much above the destined mark; not designing that his arrow should strike so high, but that flying high it may alight at the point intended."
(Niccolò Machiavelli, The Prince)

Abstract

Chagas disease is one of the 20 Neglected Tropical Diseases, being an important health problem in Latin America, causing around 10,000 deaths due to complications linked to the disease, and affecting around 8 million people worldwide, according to World Health Organization (WHO). The main route of transmission is by the triatomine bug feces. Other transmission routes are blood transfusion and organ transplantation from infected individuals, from mother to child, which is called congenital transmission, by laboratory accident, and by consumption of contaminated food or drink. In the present work, two compartmental deterministic models for Chagas disease transmission were used. This kind of model is based on a system of differential equations which is integrated numerically using computational software. The first model deals only with humans, without the vector presence, considering transmission by congenital and blood transfusion routes. The second one simulates a community with the vector presence in two environments, peridomicile and intradomicile, as well as the presence of the human, domestic animals, competent and non-competent hosts. Simulations were performed to assess different scenarios regarding control strategies. The results of model simulations show that even without the vector presence the disease can be maintained for a long time in a population due to congenital and blood transfusion transmission, the detection and treatment of infected individuals are extremely important in order to avoid future complications dues to the disease, and control measures should be reinforced and maintained in order to reduce the number of new cases. In case of interruption of those controls measures, the simulations show that the system returns very quickly to scenarios similar to that where control measures are not applied.

Key-words: Chagas disease. mathematical models. computational epidemiology. simulation. control measures.

Resumo

A Doença de Chagas é uma das 20 Doenças Tropicais Negligenciadas, sendo um importante problema de saúde na América Latina. De acordo com a Organizaão Mundial da Saúde (OMS), a enfermidade causa mais de 10.000 mortes anuais devido às complicaões associadas à mesma, e afeta cerca de 8 milhões de pessoas em todo o mundo. A principal forma de transmissão é a partir do contato com as fezes do triatomíneo. Outras formas são por transfusão de sangue e transplante de órgãos de pessoas infectadas, da mãe para o filho (transmissão congênita), por acidente de laboratório e consumo de comida ou bebidas contaminadas. No presente trabalho, dois modelos compartimentais determinísticos foram utilizados. Este tipo de modelo é baseado em um sistema de equaões diferenciais que é integrado numericamente a partir de um software computacional. O primeiro modelo lida apenas com humanos, sem a presença do vetor, considerando transmissão congênita e por transfusão de sangue. O segundo modelo simula uma comunidade com a presença de vetores em dois ambientes peridomicílio e intradomicílio, bem como a presença de humanos, animais domésticos, hospedeiros competentes e não-competentes. As simulações foram realizadas para avaliar diferentes cenários referentes às estartégias de controle. Os resultados destas simulações mostram que mesmo sem a presença de vetores a doença pode ser mantida por muito tempo na população devido às transmissões congênitas e por transfusão de sangue, a detecção e tratamento de indivíduos infectados são extremamente importantes a fim de evitar complicações futuras devido à doença, e as estratégias de controle devem ser reforçadas e mantidas a fim de reduzir o número de novos casos. Em caso de interrupção destas medidas de controle, as simulações mostram que o sistema volta muito rapidamente à cenários similares àqueles onde as medidas de controle não são aplicadas.

Palavras-chaves: doença de Chagas. modelos matemáticos. epidemiologia computacional. simulação. medidas de controle.

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1 Introduction

Chagas disease or American trypanosomiasis is an important health problem in Latin America caused by the protozoan parasite *Trypanosoma cruzi*. The disease was named after the Brazilian physician Carlos Justiniano Chagas (1879-1934) who discovered it in 1909 (1).

The most effective transmission mode is through contact with triatomine bug feces, the vector of the disease, also known as "kissing bug" for its characteristic in bite people on face (2). Other transmission modes can occur by blood transfusion, organ transplantation, congenital transmission, laboratory accident or contaminated food or drink (2, 3). Some cases of oral transmission have been reported in Brazil, Venezuela, Colombia, Mexico, Argentina and Bolivia (4).

Chagas disease presents two phases: acute phase – generally asymptomatic, may last up to a few weeks or months, and parasites may be found in the circulating blood – and chronic phase that can lead to long-term consequences as cardiac, digestive and/or neurological. If untreated, infection is lifelong. Following the acute phase, most infected people enter into a prolonged asymptomatic form of disease (called "chronic indeterminate") during which few or no parasites are found in the blood. It is estimated that between 20 to 30% of infected people will develop debilitating and sometimes life-threatening medical problems (3, 2).

The disease cycle inside human body is showed in Figure 1 and is described by the following steps (3):

1. After a blood meal, the vector releases trypomastigotes in its feces near the site of the bite wound.

2. Trypomastigotes enter the host through the wound or through intact mucous membranes, such as the conjunctiva.

3. Inside the host, the trypomastigotes invade cells near the site of inoculation, where they differentiate into intra-cellular amastigotes.

4. Clinical manifestations can result from this infective cycle. The bloodstream trypomastigotes do not replicate.

5. The amastigotes multiply by binary fission and differentiate into trypomastigotes, and then are released into the circulation as bloodstream trypomastigotes.

6. Replication resumes only when the parasites enter another cell or are ingested by another vector.

7. The "kissing" bug becomes infected by feeding on human or animal blood that contains circulating parasites

8. The ingested trypomastigotes transform into epimastigotes in the vector's midgut.

9. The parasites multiply and differentiate in the midgut and differentiate into infective metacyclic trypomastigotes in the hindgut

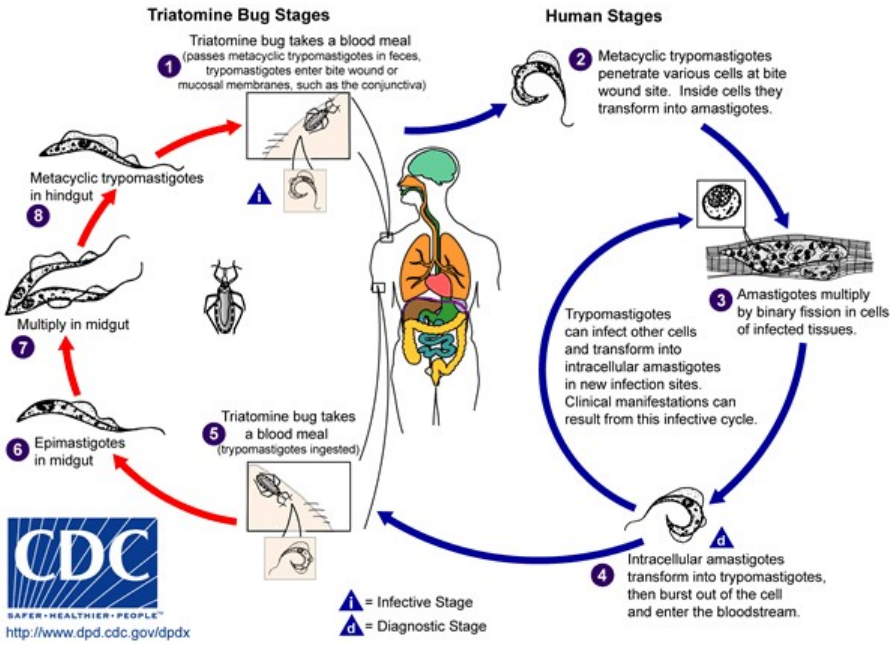


Figure 1 – Chagas Disease cycle in human body and in the vector triatomine bug. Available on ⟨https://www.cdc.gov/parasites/chagas/biology.html⟩.

T. cruzi infect a great diversity of vertebrate host, and over 100 mammalian species have been naturally or experimentally infected with it. Regard to human host, molecular biology techniques have shown that genetically different *T. cruzi* strains may parasitize different organs (5). The triatomine bug thrives under poor housing conditions (for example, mud walls, thatched roofs), so in endemic countries, people living in rural areas are at greatest risk for acquiring infection (3).

During the acute phase of Chagas disease, the diagnosis can be made by observation of the parasite in a blood smear by microscopic examination because a large number of

parasites are present in peripheral blood. In chronic Chagas disease phase, the level of parasitaemia is low, however, it is necessary to use parasite concentration methods. Diagnosis is generally made by testing with at least two different serologic tests. Three conventional tests are widely used: indirect haemagglutination (IHA), indirect immunofluorescence (IIF) and ELISA (3, 5).

Since the 1960 years the only drugs used in Chagas disease treatment are benznidazole and nifurtimox (6), which have a great efficiency if the treatment starts soon and control disease progression in chronic cases (2). Treatment on young infected women or in childbearing age can prevent congenital transmission of *T. cruzi*, furthermore it can prevent future disease complications (7). It is also shown that treatment in newborns have good therapeutics results (8).

There is about 6 to 7 million infected by Chagas world-wide and due to the mobility of Latin Americans around the world, the disease has been detected in the United States of America, Canada, Europe and countries in Pacific Western (2). The global cost of disease is similar to rotavirus disease or cervical cancer (9). Figure 2 displays the global distribution of Chagas disease.

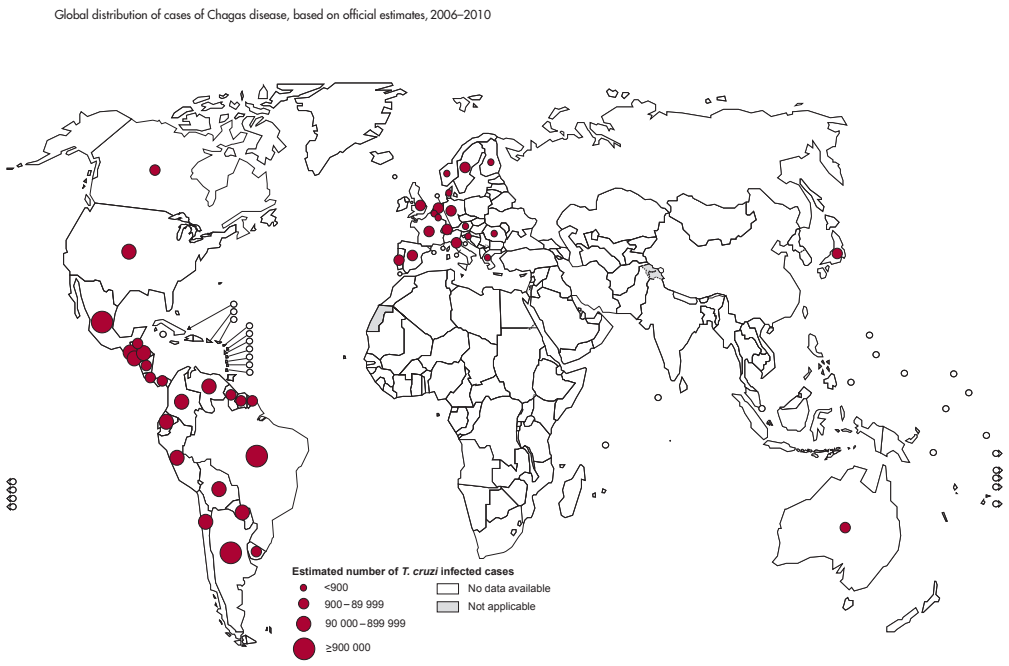


Figure 2 – Global distribuiton of Chagas disease, WHO. Available on:⟨http://www.who.int/chagas/Global_distribution_Chagas_disease_2006_2010.pdf?ua=1⟩

Triatomine bugs are typically found in Southern United States, Mexico, Central America, and South America; and can live indoors, in cracks and holes of substandard housing, or in a variety of outdoor settings including: beneath porches, between rocky structures, under cement, in rock, wood, brush piles, or beneath bark, in rodent nests or animal burrows, in outdoor dog houses or kennels, in chicken coops or houses (3). There are more than 130 different species of triatomine bugs in Latin America (10), at least 40 of them can harbor *T. cruzi*, being potential transmitters of infection (11). *Triatoma infestans*, *Rhodinius prolixus*, *Triatoma dimidiata*, and *Panstrongylus megitus* are the most important domiciliated vectors. *Rhodnius pallescens*, *Triatoma sordida*, *Triatoma brasiliensis*, *T. lenti*, *T. mazzottii*, *T. phyllosoma*, *T. maculata*, and *T. lecticularia* are considered as vectors of secondary importance. *R. domesticus*, *R. ecuatoriensis*, *R. nasutus*, *R. neglectus*, *R. neivai*, *R. pictipes*, *T. lingipennis*, *T. melanocephala*, *T. nigromaculata*, *T. obscura*, *T. platensis*, *T. pseudomaculata*, *T. rubrovaria*, *T. venosa*, *T. vitticeps*, *T. williami*, *E. mucronatus*, *P. diasi*, *P. herreri*, *P. lenti*, *P. lignarius*, *P. lutzi*, *P. rufotuberculatus*, *P. tupynambai*, *M. spinolai* are species usually found in the peridomiciliary environment and, sometimes, inside houses, but generally not colonizing (12).

Some precaution to prevent house infestation include: sealing cracks and gaps around windows, walls, roofs, and doors; removing wood, brush, and rock piles near the house; using screens on doors and windows, and repairing any holes or tears; making sure yard lights are not close to the house, because it can attract the bugs; sealing holes and cracks leading to the attic, crawl spaces below the house, and to the outside; having pets sleep indoors, especially at night; keeping house and any outdoor pet resting areas clean, in addition to periodically checking both areas for the presence of bugs (3).

There is no vaccine for Chagas disease and vector control remained the most effective method of preventing transmission in Latin America. Another important control strategy is screening donated blood, avoiding transmission by transfusion and organ transplantation (2). Improved housing and spraying insecticide inside housing to eliminate triatomine bugs has significantly decreased the spread of Chagas disease in endemic areas of Mexico, Central America and South America (3). Studies conducted in Bolivia and Spain have shown that screening pregnant human from endemic areas and their newborns is better than no screening in terms of costs and quality of life (13).

In this work we make use of mathematical models to study different scenarios in Chagas disease transmission. In this way, it is important to understand what a model is. A model can be understand, as a a miniature representation of something; a pattern of something to be made; an example for imitation or emulation; a description or analogy used to help visualize something that cannot be directly observed; a system of postulates,

data and inferences presented as a mathematical description of an entity or state of affairs. A mathematical model, in turn is a representation in mathematical terms of the behavior of real devices and objects (14). In epidemiology, models uses the language of mathematics to produce a more refine and precise description of the system (15). At present, mathematical epidemiology has a steady presence in the research field. A simple search on Web of Science using the search string: TOPIC: (infectious disease*) AND TOPIC: (mathematical model*) OR TOPIC: (computational model*) AND TOPIC: (epidemio* model) AND TOPIC: (epidemiology) OR TOPIC: (epidemio* mathematic*), shows an increasing number of publications over years (Figure 3).

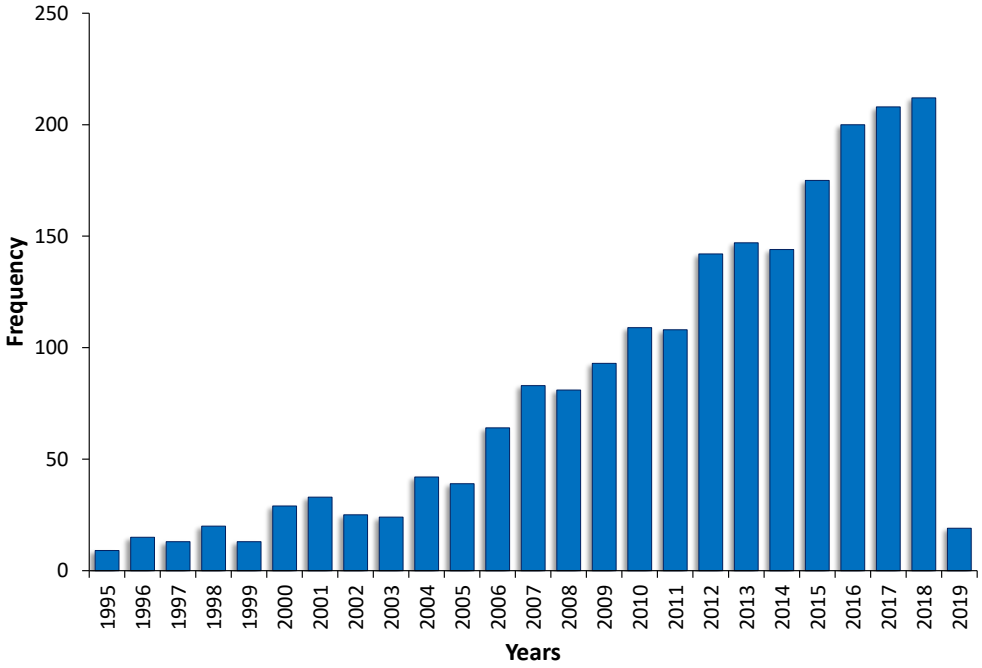


Figure 3 – Number of publications per year from Web of Science using the search string: infectious disease* AND mathematical model* OR computational model* OR epidemio* mathematic*. Accessed in February 22, 2019.

1.1 Aim of the thesis

The aim of this present thesis was to develop tools to manage and control the incidence of Chagas disease, as well as to study different scenarios and impacts of implemented control strategies. This has been carried out from the perspective of compartmental models, that are known as a powerful tool in understanding transmission process, helping on the improvement in decision making in public health policies.

1.2 Thesis Structure

The thesis consists of the following chapters. In this chapter we briefly introduced the main characteristics of Chagas disease and its current status around the world. We also presented the importance of mathematical models in epidemiology, showing the crescent number of publications in this field over time. In the chapter two, we present a literature review to help us to identify research gaps and to build the models proposed on this research. The main compartmental models on epidemiological modeling in literature were also described to give the base in understanding the proposed models. The literature survey focused on mathematical models used in Chagas disease. In the third chapter we use a compartment model to simulate Chagas disease transmission in a scenario without vector presence. Congenital and blood transfusion transmission are considered, and the model is applied to demographic data from Spain, the European countries which receives more immigrants from Latin America – where the disease is mainly found. Treatment of infected newborns and surveillance on blood transfusion are considered as control strategies. In chapter four we develop a compartment model to simulate the disease transmission in a community using information of the state of Pernambuco - Brazil, where a considerable quantity of triatomine bugs were found inside houses. We considered two environment: peridomicile and intradomicile, as well as competent and non-competent animals, bugs, human and domestic mammals. We also considered three strategies for vector control : 1 - house improvement and hygiene, 2 - spraying residual insecticide, and 3 - usage of windows and door screen. Regard to human, we considered treatment of woman in childbearing age as a way to prevent congenital transmission. Finally, the fifth chapter consists of the general conclusions about the work developed and remarks concerning possible future research directions.

2 Literature Review

In this chapter, we bring some important information and relevant works on mathematical epidemiology, as well as review some previous models used to study Chagas disease transmission. Different approaches are used as compartmental models, Agent-Based Models (ABM) and cellular automaton. We will briefly discuss these different kinds of models.

2.1 Mathematical models in epidemiology

Mathematical models can be used to understand infectious diseases dynamics and have an important role in epidemiology (16). Epidemiology is the study of the distribution and determinants of disease prevalence in humans (17). Its functions can be enumerated as:

1. Describe the distribution of the disease;
2. Identify the causes or risk factors for diseases;
3. Plan, implement and evaluate detection, control and prevention programs.

Among epidemiology objectives disease control is one of the most important and, it can be reached by preventing the emergence of new cases, curing the existent cases, improving the prognostic and increasing the health level. Models development focus basically in two points, as a predictive tool or as a way of describing and helping in understanding fundamental epidemiological processes (18). In particular, mechanistic mathematical modeling can help in achieving all the epidemiology objectives.

In 1760, Daniel Bernoulli presented the first result in mathematical epidemiology. He was the pioneer in using mathematical models to study infectious disease propagation, in the practice of inoculation against smallpox (19, 20).

P. D. En'ko gave the first contribution to modern epidemiology between 1873 and 1894. He developed a transmission model based on some specific assumptions, but without resorting to previously developed theory (20). He then compared "synthetic epidemics", the numbers of which are calculated using the model to actual outbreaks of measles and scarlet fever in two boarding schools, in St Petersburg (19).

The famous epidemiologist and specialist in malaria Ronald Ross received the Nobel Prize in Physiology or Medicine in 1902 for his work on the life cycle of the malaria parasite, he explained the complete cycle in humans, with the inclusion of the mosquito as a vector and the Plasmodium parasite. Macdonald continued Ross's wor (21). His formulation of mosquito-borne transmission is sometimes referred to as the "Ross–Macdonald model" (19).

In the works of Kermack and McKendrick between 1927 and 1939 (22), the most important result was the threshold theorem, according to which the introduction of infectious individuals within a susceptible population could cause an epidemic only if the density of susceptible exceeds a certain critical value or threshold.

It is worthy to mention some important books that have contributed to the development of mathematical epidemiology, modeling and simulation of infectious disease. *Infectious Diseases of Humans Dynamics and Control* (1992) by Anderson and May (23); *Epidemic Modeling* (1999) by Daley and Gani (24); *Mathematical Epidemiology of Infectious Diseases Model Building, Analysis and Interpretation* (2000) by Diekmann and Heesterbeek (25); *Mathematical Models in Population Biology and Epidemiology* (2001) by Brauer and Castillo-Chávez (26); *An introduction to infectious disease modelling* (2010) by Vynnycky and White (27), and *Modeling infectious diseases in humans and animals* (2011) by Keeling and Rohani (15).

Models can be classified in multiple ways: linear/nonlinear, static/dynamic, discrete/continuous, deterministic/stochastic (28). Furthermore, a wide variety of modeling methodologies exist, ranging from decision analytic models to compartment models, to network models, to agent-based models, and many other types and hybrids along the spectrum of possibilities. Nevertheless, the principle of parsimony specifies that a model should not be more complex than needed (29). Thus, we briefly describe some kind of models used in epidemiology.

In **Compartmental models**, individuals in the population are divided into groups (or compartments) and the model tracks the infection process for these individuals collectively. This kind of model can be deterministic or stochastic. The **Individual-based model (IBM) – or microsimulation model or Agent-Based Modeling (ABM)** – tracks the infection process for every individual in the population. Many individual-based models are also stochastic. **Transmission dynamic model** incorporates contact between individuals in the population and will, therefore, change over time if the number of infectious individuals changes. **Static models** do not explicitly describe contact between individuals. The risk or force of infection, therefore, takes predetermined values. These models are often used when the risk of infection is known. Nevertheless, this kind of

model is not reliable for looking at the effect of interventions involving a reduction in the prevalence of infectious individuals. In **Network models** the network of contacts between individuals is explicitly modeled. The risk of infection for an individual in a network model depends on the person to whom they are connected. Transmission of sexually transmitted infections has been modeled by this kind of model (27). **Cellular automata models** operate on a lattice of sites, with each site generally assumed to hold a single host. Interaction is usually stochastic and with neighboring (4 or 8) lattice sites (15).

In this work, we use compartmental models to study different scenarios in Chagas disease transmission in order to assess the effects of control strategies. In this way, we introduce some of the classical compartment models used in epidemiology, in which a system of Ordinary Differential Equations is applied to describe the dynamics in each compartment. This kind of model is inspired on the work of Kermack and McKendrick (22), who proposed for the first time in 1927, the simplest models involving susceptible, infectious, and recovered individuals (SIR model).

- **SI model**

In this simple compartment model, individuals are divided into susceptible (S) and infected (I) compartments. Once infected, individuals remain in this situation lifelong. Figure 5 shows the flow chart for this model.

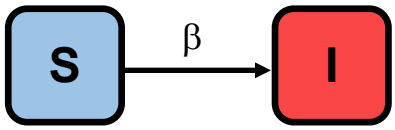


Figure 4 – Flow chart for SI model.

The model is mathematically described for the following system of ordinary differential equations:

$$\frac{dS}{dt} = -\beta SI, \tag{2.1}$$

$$\frac{dI}{dt} = \beta SI, \tag{2.2}$$

where βI is is known as **force of infection**, that is, the rate at which susceptible individuals become infected per unit time. It is also known as the incidence rate or the hazard rate (27).

Although it is an extremely simple mathematical model, it can describe correctly the behavior of some epidemics. In Figure 5 one can notice that, at the end of the simulation, all the individuals contract the infection.

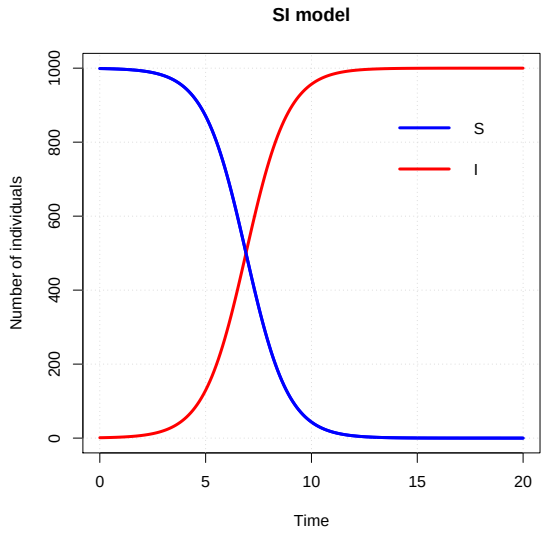


Figure 5 – SI model (Susceptible - Infected) dynamics over time.

- **SIS model**

In this model, recover from infection is followed by an instant return to susceptible S class. Example of some diseases behaving with this characteristic are rotaviruses, sexually, and many bacterial infections (15).

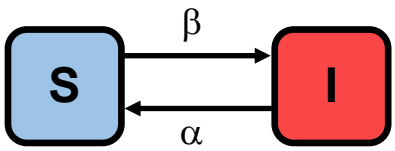


Figure 6 – Flow chart for a SIS (susceptible-infected-susceptible) model.

The system of differential equations representing this model is:

$$\frac{dS}{dt} = \alpha I - \beta SI, \tag{2.3}$$

$$\frac{dI}{dt} = \beta SI - \alpha I, \tag{2.4}$$

where, again, βI is the force of infection and α is the rate at which individuals become susceptible again. Figure 7 shows the dynamics of this model over time.

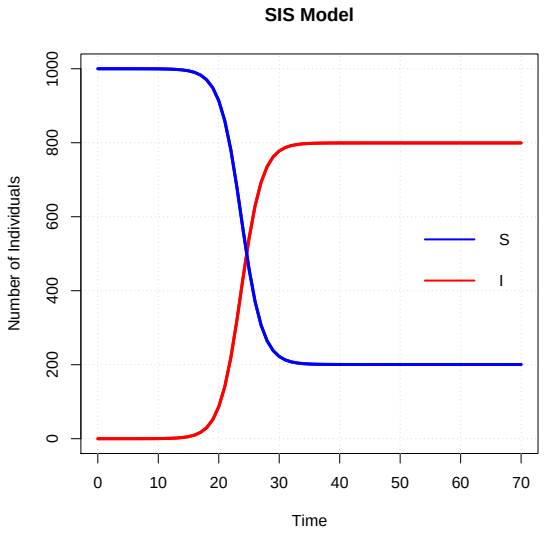


Figure 7 – SIS (susceptible-infected-susceptible) model dynamics over year.

- **SIR model**

In this model, the illness is followed by immunity, typically lifelong. So, there are the compartments susceptible (S), infected (I) and recovered (R). Figure 8 shows the diagrammatic representation for this kind of model.

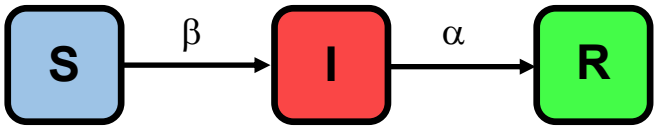


Figure 8 – Flow chart for the SIR model.

The system of differential equations representing this model is:

$$\frac{dS}{dt} = -\beta SI, \tag{2.5}$$

$$\frac{dI}{dt} = \beta SI - \alpha I, \tag{2.6}$$

$$\frac{dR}{dt} = \alpha I, \tag{2.7}$$

where S (susceptibles) represents healthy individuals who can contract the disease. I represents the infected individuals, i. e., individuals who have contracted the disease and now are sick. And finally, R represents the removed/recovered individuals, i. e., those individuals who recovered the disease and no longer can be infected.

In this particular model, proposed by Kermack and McKendrick (22), the main assumptions are that infected people are also infectious; and the total population remains constant. βSI is the number of individuals who become infected per unit time, βI is the force of infection. Individuals leaving the infected compartment by dying or recovering goes to the removed compartment at constant per capita probability per unit of time α called the recovery rate.

Figure 9 displays the model dynamics over time for SIR model.

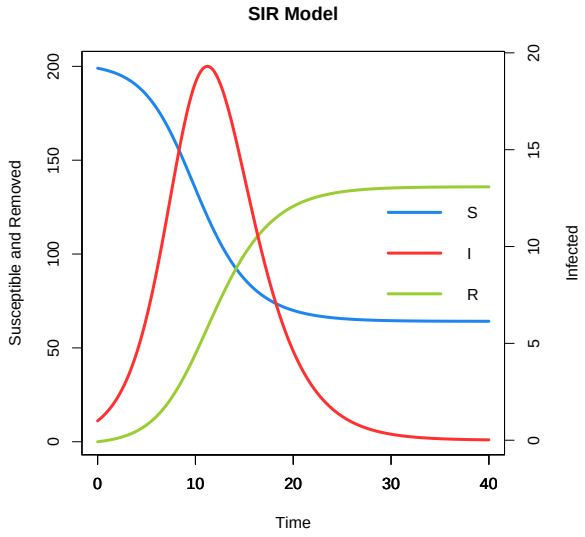


Figure 9 – Plot showing the dynamics for the SIR (susceptible-infected-recovered) model.

- **SEIR model**

In this model, a latent period is taken into account. It is done by introducing the compartment E in a SIR model. This compartment is generally called Exposed class and represents the individuals who are infected but not yet infectious. It is assumed that $1/\alpha$ is the average duration of the latent period. Figure 10 shows the flow chart for this model.

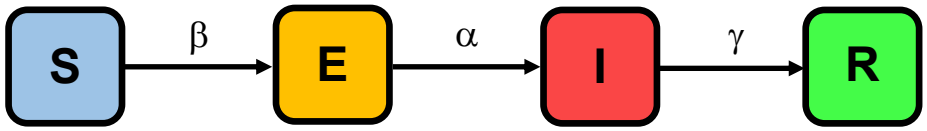


Figure 10 – Flow chart for SEIR (susceptible-exposed-infected-removed) model.

The system of differential equations representing this model is:

$$\begin{aligned}
\frac{dS}{dt} &= -\beta SI, \\
\frac{dE}{dt} &= \beta SI - \alpha E, \qquad (2.8) \\
\frac{dI}{dt} &= \alpha E - \gamma I, \qquad (2.9) \\
\frac{dR}{dt} &= \gamma I, \qquad (2.10)
\end{aligned}$$

where, again, βI is the force of infection, and $1/\gamma$ is the average time to recover from the disease. Figure 11 displays the dynamics of the SEIR model over time.

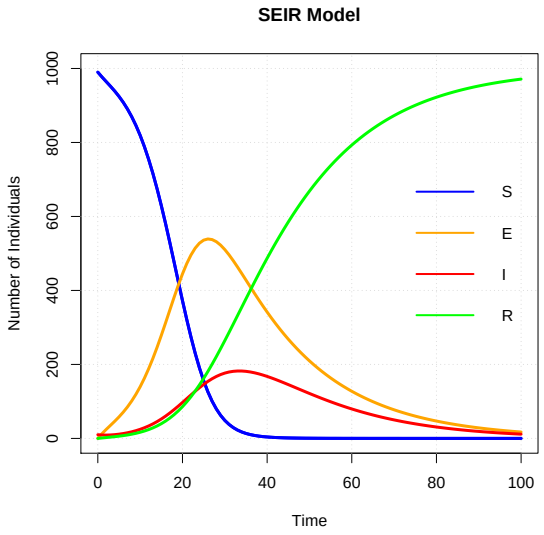


Figure 11 – Plot for SEIR model.

- **Vector-borne model**

Chagas disease is mainly vector-borne transmitted, thus it is important to present a compartment model representing this kind of transmission. The presented model follow the framework founded by MacDonald (21). This model can be adapted for any other vector-borne disease. We represent the vector population by a SI model, and the human population by a SIR model. Figure 12 shows the flowchart for this model.

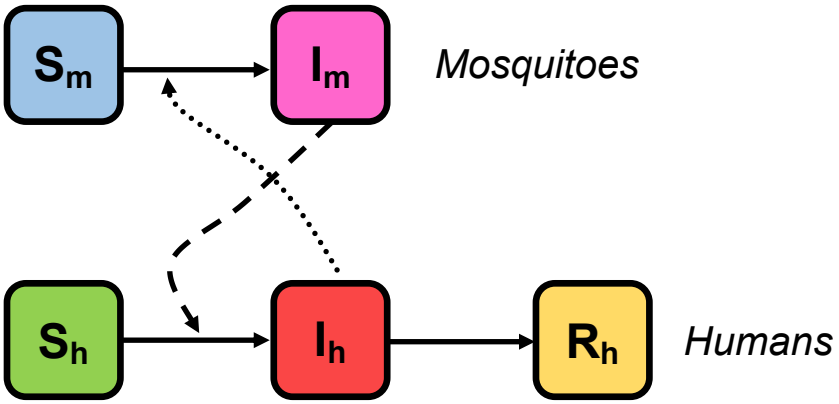


Figure 12 – A flow chart representing a vector-borne dynamics where the compartments are: S_h: susceptible human, I_h: infected human, R_h: recovered human, S_m: susceptible mosquitoes and I_m: infected mosquitoes.

The system of differential equations representing this model is:

$$\frac{dS_h}{dt} = \mu_h - rP_{hm}I_mS_h - \delta_hS_h \tag{2.11}$$

$$\frac{dI_h}{dt} = rP_{hm}I_mS_h - \delta_hI_h - \gamma_hI_h \tag{2.12}$$

$$\frac{S_m}{dt} = \mu_m - rP_{mh}I_hS_m - \delta_mS_m \tag{2.13}$$

$$\frac{I_m}{dt} = rP_{mh}I_hS_m - \delta_mI_m \tag{2.14}$$

where S and I represent susceptible and infected individuals respectively, and the subscripts represent h: human and m: mosquitoes; μ is the number of individuals been born per unit of time; $r = b/N_h$ is the infections rate caused by the contact between an infected human with a susceptible vector (or vice-versa), b is the number of mosquito bites per unit time and N_h the total number of human; δ is the mortality rate; γ_h is the mortality rate for human due to disease; P_{hm} and P_{mh} are the probability of transmission from mosquito to human, and from human to mosquito respectively, assuming values between 0 and 1. As

the population is assumed constant, for simplification, the equation for R_h is not shown, but its value is assessed by the expression $R_h = N_h - S_h - I_h$. Figure 13 displays the dynamics over time for susceptible and infected humans and mosquitoes.

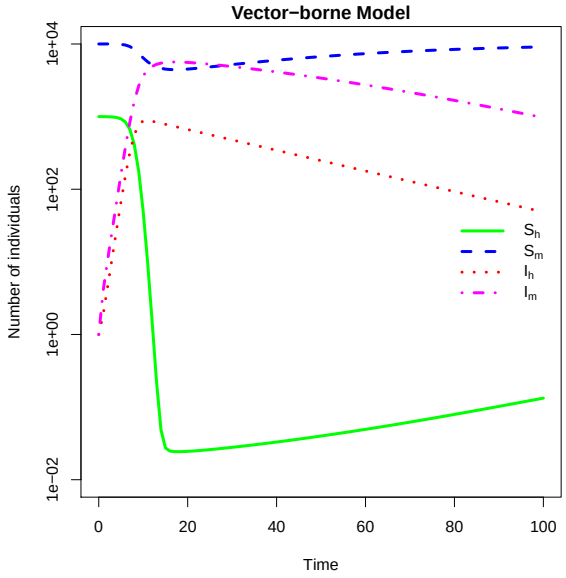


Figure 13 – Graph showing the vector-borne dynamics for susceptible and infected human and mosquitoes.

We only presented some of the classical compartment models. Additional compartments accounting for age structure, host heterogeneity, as well as demography, can be added to those simple compartmental models depending on the questions the model intends to answer.

2.2 Models in Chagas disease

A review on the literature available on mathematical modeling of Chagas disease brought some interesting models with different approaches as compartmental models, agent-based models, and a cellular automaton. We present some of these works below.

Velasco-Hernandez *et al.* wrote two papers in 1991 and 1994, where they used compartmental deterministic model considering hosts and vectors. Transmission by blood transfusion was considered in both works and control by protecting new recruited susceptible hosts was considered (30, 31). Inaba and Sekine (2004) used a compartmental model to study infection-age-dependent infectivity. The authors considered vector and blood transfusion transmission. Stability analysis was performed and an expression for R_0 (the basic reproduction number, that is, the average number of secondary infectious persons resulting from one infectious person following their introduction into a totally susceptible

population) was found (32). A detailed discussion on different models for Chagas disease was performed by Nouvellet *et al.* (2005) that assert *"there is a clear need to develop further standard compartmental models to provide more systematic analysis of the direct and indirect effects that typical domestic community assemblages may have on the risk of disease transmission when it is associated with well-known, domiciliated triatomines species."* (33).

Das and Mukherjee (2006) (34) performed a qualitative study of a model of Chagas disease, where they divided the infected population into the acute and chronic stages and considered transmission only due to vector. Stability and equilibrium analysis were performed, as well as numerical simulations. Massad *et al.* (2008) (35) used compartmental model dividing population in four states, considering infected mother, newborns and treatment and recovery of newborns. Equations were written as a function of age, not of time. Mortality, fertility, and treatment of infected children were considered. R_0 was found and data from WHO and Brazil population was used. Raimundo *et al.* (2010) (36) used compartmental model dividing population into core and non-core groups. Spagnuolo *et al.* (37, 38) used deterministic model based on a system of differential equations considering vectors, human, domestic animals and wildlife population. The impact of insecticide spraying is analyzed by simulation.

Cruz-Pacheco *et al.* (2012) used a compartmental model with humans, vector, dogs and cats, chickens and birds. Considered the transmission by triatomine bites and vertical transmission. Rascalou *et al.* (2012) used SIRS model with people in acute and chronic phases (39). Recruitment rates, mortality rates, acute and chronic phases, treatment and bites per day were considered (40). Coffield *et al.* (2013) used compartmental model considering humans, domestic mammals, and vectors. Oral transmission (dogs eating bugs) and congenital transmission (dogs and human) are considered (41). Pelosse *et al.* (2013) used a SI model with a total of 9 classes involving human and vectors. Three environments were considered: deterministic, stochastic (low) and stochastic (high) (42). Fabrizio *et al.* (2014) considered migration, emigration, birth, mortality, blood transfusion, cure rates and disease stages. The model was applied to Buenos Aires, Argentina (43). Gonzalez-Parra *et al.* (2015) used a compartmental model with a framework for both demographic and epidemiological transitions. The human population is divided into six age groups and parameters were chosen based on available census data from Venezuela (44).

Other approaches besides compartment models were also found in the literature in modeling Chagas disease, as ABM and cellular automaton. An agent-based model was used to model Chagas disease by Devillers *et al.* (2008) for predicting the prevalence of two strains, *T.cruzi I* and *T.cruzi II* during single and mixed infections (45). Galvão

and Miranda (2010) used a three-dimensional multi-agent-based model to understand the participation of different types of cells in the development of Chagas' disease (46). Yong *et al.* (2015) also used an agent-based model to describe host irritability threshold on vector feeding rates. In one scenario, they set raccoons as the only hosts and *T. sanguisuga* as the only triatomine specie. In other, they considered woodrat hosts only, and both species of triatomine bugs - *Triatoma sanguisuga* and *Triatoma gerstaeckeri* (47).

Regarding a cellular automaton model, Slimi *et al.* (2009) used a two-dimensional cellular automaton to simulate a village with houses and arriving of vectors (*Triatoma dimidiata*). Demographic and dispersal parameters reproduce patterns observed in Yucatan, Mexico (48). Cisse *et al.* (2016) also used an epidemiological model based on cellular automaton to simulate the disease spread in homogeneous and heterogeneous environments with competent and non-competent hosts species (49).

3 Congenital and blood transfusion transmission of Chagas disease: a framework using mathematical modeling

The results of this chapter were published on the journal *Complexity* and should be cited as Ramalho, E., Albuquerque, J., Cristino, C., Lorena, V., Gómez i Prat, J., Prats, C. and López, D., 2018. Congenital and blood transfusion transmission of Chagas disease: A framework using mathematical modeling. *Complexity, 2018*. It is available online through the link: ⟨https://doi.org/10.1155/2018/1589016⟩.

In this chapter, a deterministic compartmental model is proposed 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 effects of control measures. It was applied to demographic data from Spain and sensitivity analysis was performed through variations on the model's parameters associated with control strategies.

3.1 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 by congenital transmission (2). Some cases of oral transmission have been reported in Brazil, Venezuela, Colombia, Mexico, Argentina and Bolivia (4).

The disease presents an initial acute phase, generally asymptomatic, and a subsequent chronic phase, which can present clinical manifestations (cardiac, digestive and/or neurological) (2). 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 (6, 2).

Although some Latin American countries, like 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. (35). 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 (2). 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 (50).

Since 2000, cases of the disease started to be reported in non-endemic countries such as European countries, Canada, USA, Japan and Australia, due to the large flow of Latin American immigrants (51). In 2010, the World Health Assembly approved a resolution, WHA 63.20 (52), 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 (9).

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 non-diagnosed, reflecting the difficulty in tracking infected people (53, 54). Due to uncertainty about the real number of cases in each country, estimates are based on PAHO (55) and Schmunis et al. 2014 (56).

Spain is the European country with most Latin Americans 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 (57). The first case of the disease by blood transfusion in Spain was detected in 1984, with two more cases in 1995 and 2004 (58). Cases of congenital transmission were also reported (59, 60).

Due to its silent evolution after infection and the resulting under-diagnoses, there is not complete and reliable data about the disease. Therefore, mathematical models can be a particularly useful tool in 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* (31) considered a compartmental model with humans, vectors and transmission by blood transfusion. Inaba and Sekine (32) also considered humans, vectors and blood transfusion but with infection age dependent infectivity. Congenital transmission was considered by Massad (35), Raimundo *et al* (36) and Coffield *et al* (61). Fabrizio *et al* (43) explored an inter-human 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 the decrease in the number of parasites inside the host, and consequently decreasing the risk of developing clinical manifestation.

3.2 Materials and Methods

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 a country with active vector transmission;
2. M_{vi}: infected men from a country with active vector transmission;
3. M_h: healthy men from a country without vector transmission;
4. M_i: infected men from a country without vector transmission;
5. W_{vh}: healthy women from a country with active vector transmission;
6. W_{vi}: infected women from a country with active vector transmission;
7. W_h: healthy women from a country without vector transmission;
8. W_i: infected women from a 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 non-modelers

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 14 shows a flowchart of the model.

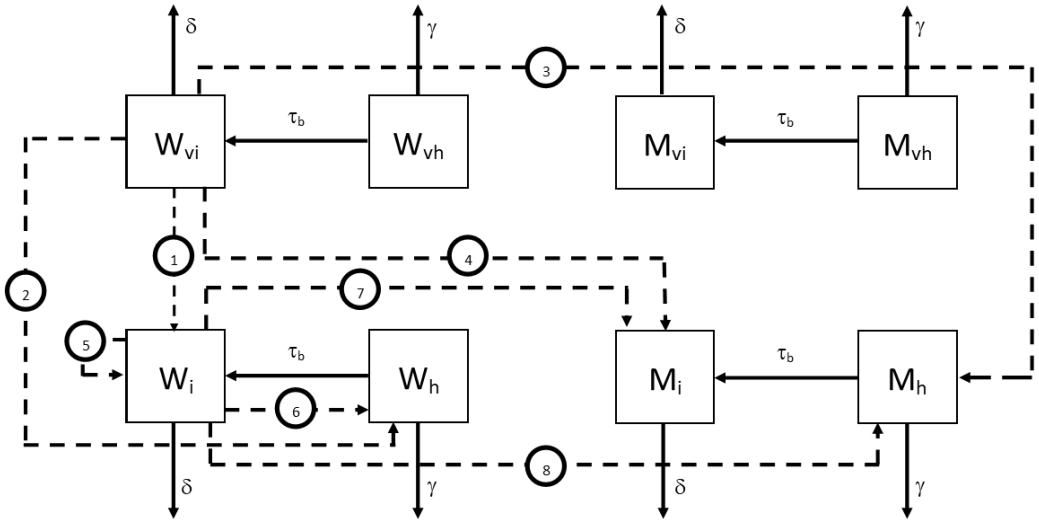


Figure 14 – Flow chart for the dynamics of the proposed model. Letters inside box indicate the number of individuals in each compartment: infected women from country with vector (W_{vi}), healthy women from country with active vector transmission (W_{vh}), infected men from country with active vector 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), 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 births. Newborns from W_{vi} can be an infected female (1), healthy female (2), healthy male (3) or infected male (4). The same occurs 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).

The assumptions for the dynamics of transmission are the following:

- 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.
- 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.

- If a woman is infected, she has a probability β to infect her son or daughter.
- The parameter γ stands for mortality rate for healthy people. For infected individuals, we assumed a mortality rate induced by the disease δ, where $\delta > \gamma$.
- 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.
- We also considered that a proportion of p_i of donated blood is potentially contaminated with *T. cruzi*. Once the donation has been made, health services carry out controls screening. We considered ξ as the probability of 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.
- We supposed that infected individuals can be cured with a rate of C due to treatment. This cure rate means a reduction in the number of parasites inside the host, reducing the chances of clinical manifestation. We consider that a yearly percentage of 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 (62)) are not distinguished from non-diagnosed individuals by the model.
- No migration flows (neither immigration or 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 (3.1) - (3.8).

$$\begin{aligned} \frac{dM_h}{dt} &= 0.5\alpha(W_h + W_{vh}) + 0.5\alpha(1 - \beta + \rho)(W_i + W_{vi}) + CM_i - \gamma M_h \\ &- \tau_b(1 - \xi)M_h\left(\frac{I}{N}\right) \end{aligned} \tag{3.1}$$

$$\begin{aligned}
\frac{dW_h}{dt} &= 0.5\alpha(W_h + W_{vh}) + 0.5\alpha(1-\beta+\rho)(W_i + W_{vi}) + CW_i - \gamma W_h \\
&- \tau_b(1-\xi)W_h\left(\frac{I}{N}\right) \qquad (3.2)
\end{aligned}$$

$$\frac{dM_{vh}}{dt} = CM_{vi} - \gamma M_{vh} - \tau_b(1-\xi)M_{vh}\left(\frac{I}{N}\right) \qquad (3.3)$$

$$\frac{dW_{vh}}{dt} = CW_{vi} - \gamma W_{vh} - \tau_b(1-\xi)W_{vh}\left(\frac{I}{N}\right) \qquad (3.4)$$

$$\frac{dM_i}{dt} = 0.5\alpha\beta(W_i + W_{vi})(1-\rho) - (\delta + C)M_i + \tau_b(1-\xi)M_h\left(\frac{I}{N}\right) \qquad (3.5)$$

$$\frac{dW_i}{dt} = 0.5\alpha\beta(W_i + W_{vi})(1-\rho) - (\delta + C)W_i + \tau_b(1-\xi)W_h\left(\frac{I}{N}\right) \qquad (3.6)$$

$$\frac{dM_{vi}}{dt} = \tau_b(1-\xi)M_{vh}\left(\frac{I}{N}\right) - (\delta + C)M_{vi} \qquad (3.7)$$

$$\frac{dW_{vi}}{dt} = \tau_b(1-\xi)W_{vh}\left(\frac{I}{N}\right) - (\delta + C)W_{vi} \qquad (3.8)$$

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.

3.3 Results

3.3.1 Parameter searching

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.

Birth rate and vertical transmission

By 2007 birth rate in Spain was 10.9 per 1,000 inhabitants (63). In a study performed in two maternity clinics in Barcelona, Muñoz *et al* (8) reported a prevalence of 3.4% among pregnant Latin American and 7.3% of newborns were infected. Then, we

set the birth rate as $\alpha = 0.0109$ year^{-1} and, the probability of vertical transmission as $\beta = 0.073$.

Mortality rates

By 2007 mortality rate in Spain was 8.5 per 1,000 inhabitants (64). Cucunubá *et al* (65) 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 $\delta = 2\gamma = 0.017$.

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 (66). The rate of blood donation in Spain in 2007 was 33.4 per 1,000 inhabitants (67). Then, the rate of infection by blood transfusion, τ_b was calculated as 0.00022378 per year.

Control strategies

Actions to control the increase in new cases of Chagas disease are incorporated into the model (Eqs. 3.1 - 3.8) 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.

Parameter	Meaning	Value	Source
α	Birth rate (year^{-1})	0.0109	(63)
β	Probability of vertical transmission	0.073	(8)
γ	Mortality rate (year^{-1})	0.0085	(64)
δ	Mortality rate due disease (year^{-1})	0.0017	(65)
τ_b	Rate of infection by infected blood (year^{-1})	0.00022378	(66, 67)
C	Cure rate (year^{-1})	Various	
ρ	Proportion of new born treated	Various	
ξ	Probability of a efficient surveillance	Various	

Table 1 – Parameters used in numerical simulation of proposed model.

3.3.2 Numerical simulations

Population in Spain in 2007 were 45,226,803 (68) 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 (66, 8).

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

We simulated the cumulative number of infected people over time. Numerical simulations were performed using the software R 3.5.0 (69), integrating the system (Eqs.3.1 - 3.8) by Runge–Kutta fourth-order method through the package deSolve (70), using the parameters shown in Table 7 and the initial conditions set above. Time step used was one year and time range for simulation was 40 years.

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 15. 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 infected. At the end of 40 years

simulation, there was a 48% reduction in the number of total infected when compared with the initial value.

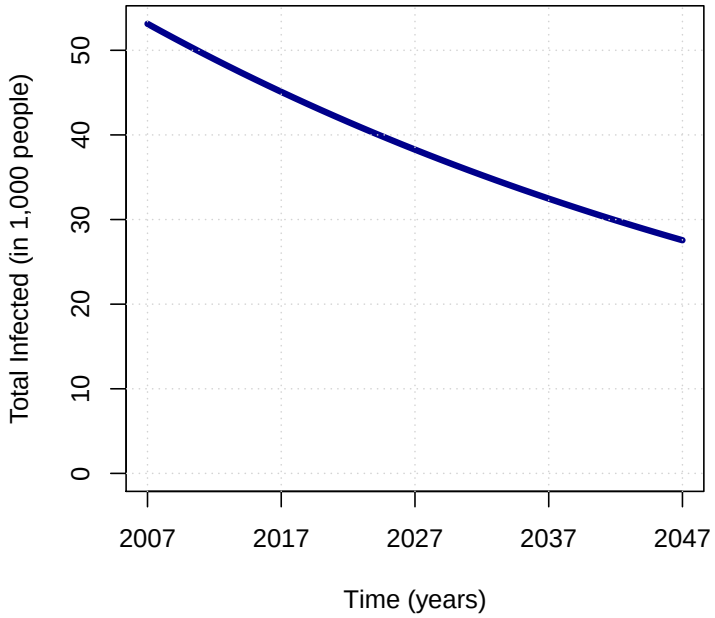


Figure 15 – Dynamics on the number of total infected people along 40 years simulation considering death rate due to disease as twice the natural death rate and no migration flows.

Comparing the effect of transmissions 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 Fig 16. The results show that congenital transmission has a higher impact than the transmission by blood transfusion, causing 38% more new infections.

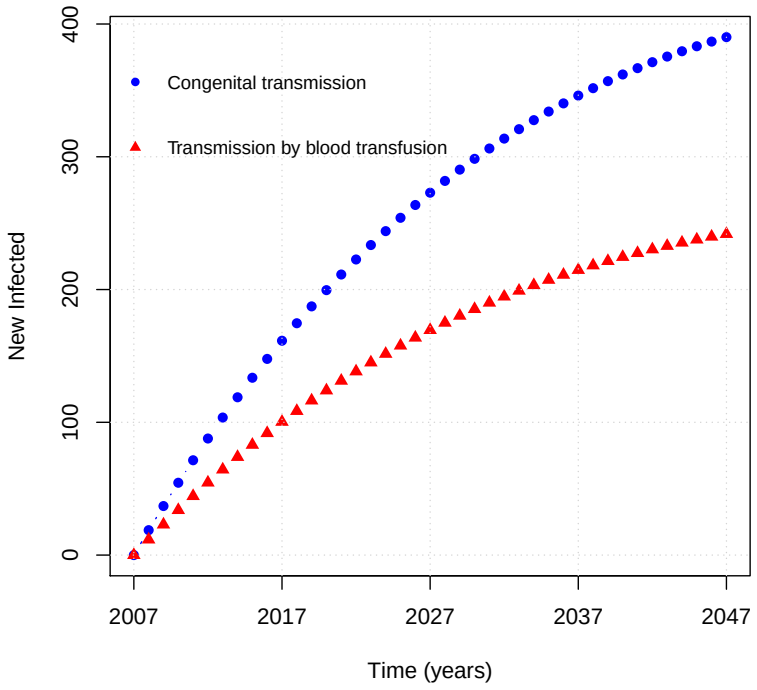


Figure 16 – Comparison of the number of cumulative new infections along time when a single transmission route is considered.

Control strategies

Two control strategies were considered, as above mentioned, treatment of infected newborns (ρ) and surveillance in blood transfusion (ξ). These strategies were simulated isolated and combined.

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 17 displays the result of this sensitivity analysis in the cumulative number of newly infected individuals.

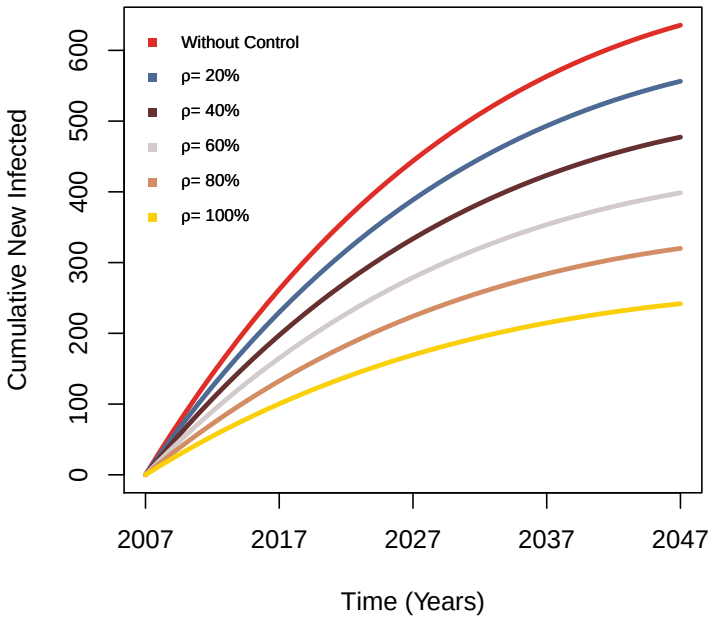


Figure 17 – Sensitivity analysis on the cumulative number of newly infected individuals by varying ρ, i.e., the proportion of treatment of infected newborn.

When comparing these tendencies with the scenario without control (Figure 15), 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.

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

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

Control only in blood transfusion

In this simulation, we evaluated the effect of performing a control strategy only on blood transfusion. Figure 18 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.

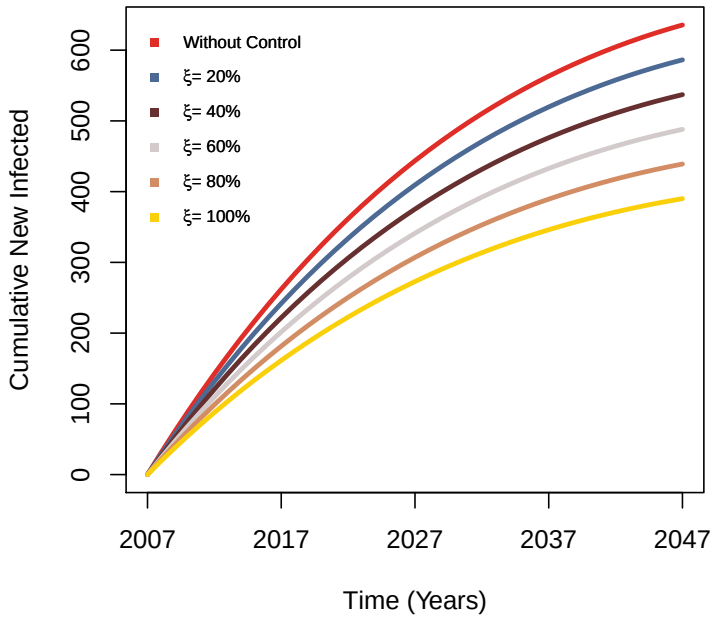


Figure 18 – Sensitivity analysis on the cumulative number of newly infected individuals by varying ξ, i.e., the probability of effective surveillance in blood transfusions.

The obtained percentage reductions in the cumulative number of newly infected after a 40 years simulation, when compared with the without control scenario (Figure 15), are shown in Table 3. When a probability of an effective surveillance reaches 100%, new cases are only due to congenital transmission.

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

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.

Combined control

Sensitivity analysis can also be performed by varying the two parameters associated to control strategies at the same time. Figure 19 shows the results of combined control, by varying ρ and ξ simultaneously.

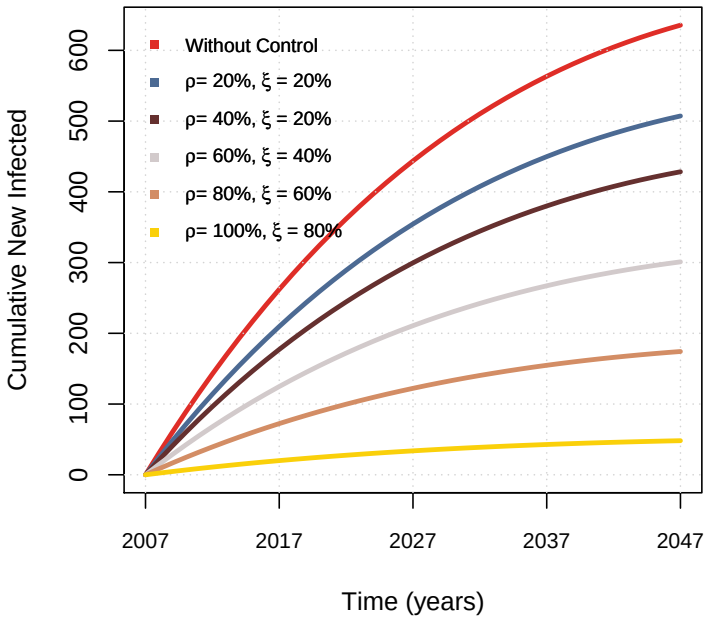


Figure 19 – Sensitivity analysis on the cumulative number of newly infected by applying combined control – increasing proportion of treatment in infected newborns (parameter ρ) and on the surveillance in blood transfusion transmission (parameter ξ).

Percentage reductions on the cumulative number of newly infected when compared with a without control scenario at the end of 40 years simulation is shown in Table 4.

Parameters values	**Reduction**(%)
$\rho = 20\%, \xi = 20\%$	20.2
$\rho = 40\%, \xi = 20\%$	32.6
$\rho = 60\%, \xi = 40\%$	52.6
$\rho = 80\%, \xi = 60\%$	72.6
$\rho = 100\%, \xi = 80\%$	92.4

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).

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% (6).

According to (54), the index of under-diagnosis 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, 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 (54) but also because of other barriers such as health care access limitations or the own miss perception of the disease (62). Therefore, we varied the parameter d between 0 and 25%.

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

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

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

The cumulative number of new infected is strongly affected by the introduction of the cure rate. Figure 20 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.

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

Table 6 – Percentage reductions for each parameter variation.

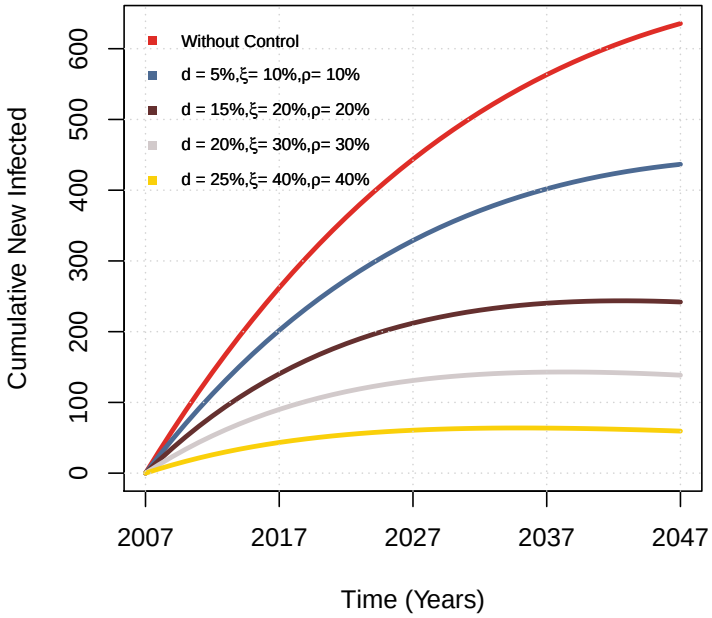


Figure 20 – Sensitivity analysis considering detection and treatment of infected individuals d, treatment of infected newborns ρ and surveillance in blood transfusion transmission ξ.

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 a surveillance in blood transfusion 80% effective. Figure 21 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.

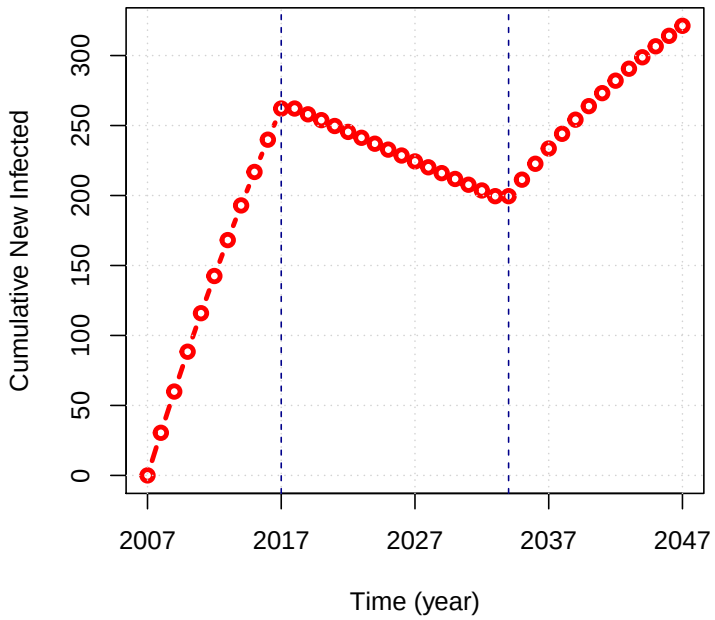


Figure 21 – The result of simulation of interrupted control. Parameters associated with control strategies were: $d = 25\%$ (detection of infected people), $\rho = 80\%$ (treatment of infected newborn) and $\xi = 80\%$ (effectiveness on surveillance in blood transfusion). The control strategies were applied after 10 years of simulation. After 15 years of application, the control strategies were stopped.

3.4 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 15), 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 on the population for a long period of time (71), 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 16). 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 (53). Nevertheless, blood screening should be sustained and it is vital to prevent infection through transfusion and organ transplantation also in non-endemic 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) (52). 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 (58). It can prevent a transfusion by a contaminated blood sample beyond identifying infected people. Simulation results plotted in Figures 17 and 18 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 19). 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 (52). By 2014 only the Tuscany region in Italy had legislation to screen pregnant women from areas considered endemic (9). In Spain, only

Catalonia, Valencia and Galicia regions had protocols in screening pregnant women from Latin America up to 2014 (9). The other countries do not have national programs for disease prevention (72, 73). The adoption of screening protocols is extremely important since the identification and treatment of infected newborns have good therapeutics results (8).

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 (54), 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 (6, 74). Nevertheless, treatment accessibility should be guaranteed for all of the diagnosed patients by eliminating existing barriers (62). Regarding women in childbearing age, detection and treatment also prevent congenital transmission (7, 75).

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 20). 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 (76). 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 21 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 non-endemic 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 (77). In the case of women in childbearing age, treating infected women before a future pregnancy would prevent congenital transmission (75).

Finally, it is also important to point out that the inter- and trans-disciplinary 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 non-experts is feasible.

4 Modeling and simulating Chagas disease transmission in a community: Testing scenarios for Pernambuco - Brazil

In this chapter different aspects are considered to study Chagas disease transmission and control strategies application. The presence of triatomines in two environments (peridomicile and domicile) is taken into account as well as the presence of competent animals, non-competent animals, humans, and domestic mammals. Non-competent animals, such as chicken and turkeys, are not able to acquire the infection. On the other hand, competent animals, such as pigs, horses, cattle, dogs, cats, and a huge variety of wild animals, are able to get infected and, then, participate on disease cycle. The aim of this model is to analyze and quantify the effects of vector control strategies, as well as the treatment of women in childbearing age, on the number of new cases.

4.1 Introduction

The state of Pernambuco, Northeast Brazil, registered the presence of triatomines in 147 of its municipalities, according to an entomological study performed between 2006 and 2007 (78). 18,029 triatomines bugs were analyzed, from 138 municipalities and 8.8% of them were infected with flagellates similar to *Trypanosoma cruzi*. An important and alarming fact is that 91.3% of these triatomines were found inside houses. Amongst the ten different species identified, *T. pseudomaculata*, *T. brasiliensis* and *Pastrongylus lutzi* were the most captured. Silva et al. (78) highlighted that climate change, deforestation, expansion of agricultural areas and attraction to artificial light are factors influencing vector invasion of houses. Besides, 302 acute cases were also reported in 185 municipalities between 2002 and 2013. Mesoregions of Sertão and São Francisco had the highest infection rates (79). The current number of cases is likely to be much larger since mild symptoms on acute phase lead to the infection under-reporting and misdiagnosing.

Although Brazil has received the certificate of elimination of vector transmission due to *T. infestans* in 2006, it is clear that the risk of vector transmission is not completely solved, and other species of triatomines are still representing a risk of house invasion and domiciliation. These facts highlight the importance in strengthening vector control strate-

gies, such as entomological surveillance, community education, chemical control through spraying pyrethroid insecticides, usage of door and windows screen, and improvement of house constructions and hygiene. Moreover, it is also known that the treatment of women in childbearing age prevents the congenital infection, and should also be considered as a strategy to reduce the number of new cases due to vertical transmission (7).

In this chapter, a compartment mathematical model was developed to analyze and understand the impact caused by implementation of the control strategies described above. Besides treatment of women of childbearing age, three vector control strategies are incorporated into the model:

- house improvement and hygiene;
- insecticide application;
- windows and door nets usage.

4.2 Material and Methods

A compartmental model was developed representing a generic rural community in Pernambuco (Northeast Brazil). The transmission was simulated considering human, vectors, competent and non-competent hosts. Two environments are considered, a **peridomicile** and an **intradomicile**. Figure 22 illustrates the elements considered in our model.

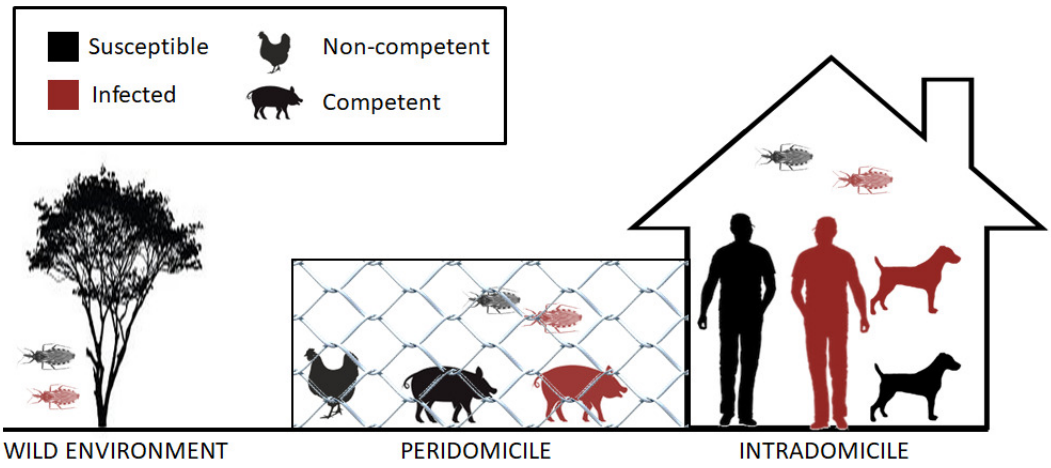


Figure 22 – Illustrative representation of the elements considered in the compartmental model: human, vector, competent and non-competent hosts. All of them can be found in a susceptible or infected epidemiological state. Also two environments were considered, the peridomicile and the intradomicile.

In the peridomicile, we consider the presence of triatomines, competent and non-competent hosts. Triatomine bugs can be placed in one of the two epidemiological states, susceptible or infected. Other assumptions in the peridomicile are:

- A constant number of competent and non-competent hosts were considered, and ξ stands for the proportion of infected competent hosts.
- Λ_v is the number of triatomines entering in peridomicile from wild environment per unit of time, where a proportion of them (ρ), is considered infected.
- Triatomines reproduce with a birth rate of μ_v. A logistic function was used to describe reproduction. In this way, one considered a carrying capacity of K, representing the maximum number of triatomines that can be encountered inside that environment.
- Triatomines die at a mortality rate δ_v, and acquire infection by feeding in an infected competent host, with a force of infection represented by $\beta_v = \frac{bP_{vc}\xi N_c}{N_c+N_{nc}}$. Where b is the vector bite rate, P_{vc} is the probability of infection from competent host to vector, and N_c and N_{nc} are the total population of the competent and non-competent host, respectively.
- Triatomines can move between the two considered environments with movement rates ω – from peridomicile to domicile, and ε – from domicile to the peridomicile environment.

Inside houses (intradomicile environment) one considers vectors (V), domestic animals (D), and humans (H). The dynamics for vectors inside the house is described by the following assumptions:

- Triatomines' reproduction inside the house is equal to that in peridomicile with the exception of the carrying capacity. The carrying capacity inside houses is $k_1(1-\alpha)$, where k_1 represents the maximum number of triatomines the house can sustain, and α ($0 \leq \alpha < 1$) is an index of quality construction and hygiene inside the house. The bigger α is, the better the control associated with house improvement and hygiene is. In this way, there is a reduction in the carrying capacity when control strategy related to house improvement and hygiene is performed.
- Vectors become infected with a force of infection $\beta_{vd} = \frac{b(P_{vh}H_i+P_{vd}D_i)}{N_d+N_h}$ due to contact with infected human (H_i) or domestic mammal (D_i). P_{vh} is the probability of infection from human to vector, P_{vd} is the probability of infection from domestic mammal to vector, N_d and N_h are the total population of domestic mammals and human, respectively.

- Humans can be susceptible or infected. A susceptible human become infected through the contact with an infected vector (V_{di}). The force of infection is given by $\beta_h = \frac{bP_{hv}V_{id}}{N_h+N_d}$, where P_{hv} is the probability of infection from vector to human and, b, N_h, and N_d are as previously defined .

- Humans are born at a birth rate of μ_h and die at a mortality rate of δ_h. An additional mortality rate due to disease, γ_h, is also considered.

- Congenital transmission is considered for humans. The parameter θ represents the probability of congenital transmission. Control regard this kind of transmission is done by providing treatment for infected women in childbearing age, where the parameter $\tau(0 \leq \tau \leq 1)$ represents effectiveness of the treatment.

- Domestic mammals, such as dogs and cats, can be susceptible or infected. They are born at a birth rate of μ_d and die at a mortality rate of δ_d. An additional mortality rate due to disease, γ_d, is considered to the infect domestic mammals.

- Domestic mammals become infected through contact with infected vectors (V_{di}). The force of infection is $\beta_d = \frac{bP_{dv}V_{id}}{N_h+N_d}$, where P_{dv} is the probability of infection from vector to domestic mammal, and the other terms are the same as above-mentioned.

- We assume a homogeneous population, i. e., each individual has the same chance to have contact with the vector, but with different probabilities of becoming infected. We do not consider co-infection due to multiple vectors blood meals.

Figure 23 represents the flow chart for the model described.

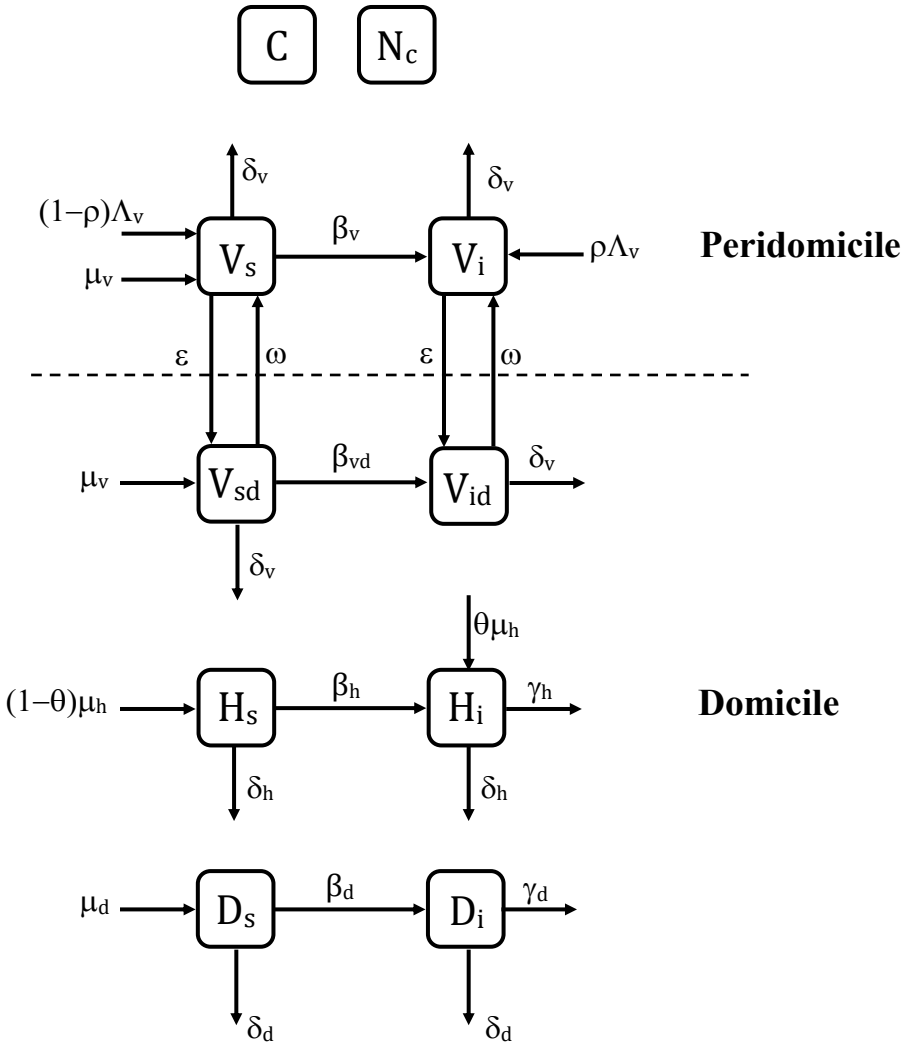


Figure 23 – Flow chart representing the compartmental model for a community. C represents the competent hosts in peridomicile and N_c the non-competent hosts. Both are considered constant, that is why there is no arrow associated with them. V_s and V_i are susceptible and infected vectors in the peridomicile, respectively. V_{sd} and V_{id} represent susceptible and infected vectors inside house, respectively. H_s represents susceptible humans, and H_i infected ones. D_s and D_i represents susceptible and infected domestic mammals respectively. Arrows indicate the flows on the compartments. μ represents birth rates, δ represents mortality rates, γ represents mortality rate due to the disease, β represents the force of infection.

The control strategies considered in the model are:

1. **House improvement and hygiene**. It is represented in the model equations by the parameter $0 \leq \alpha < 1$ which means a decreasing on the carrying capacity for vectors inside the house.

2. **Spraying residual insecticide**. It induces an additional mortality rate δ_{ins} for vectors inside the house.

3. **Windows and door screen**. $0 \leq q \leq 1$ represents the vector control using door and windows screens, by decreasing the vector movement rate from peridomicile to intradomicile environment.

4. **Treatment of women in childbearing age.** It is done by reducing the vertical transmission by a factor $(1-\tau)$ where τ is the effectiveness of the treatment.

The first three control measures are related exclusively with vector control, the last one is related to the prevention of new vertical cases. The model is described by the following system of differential equations:

$$\begin{aligned}
\frac{dV_s}{dt} &= (1-\rho)\Lambda_v + \mu_v(V_s+V_i)\left(1-\frac{V_s+V_i}{K}\right) - \delta_v V_s - \beta_v V_s \\
&- (1-q)\varepsilon V_s + \omega V_{sd} \qquad (4.1)\\
\frac{dV_i}{dt} &= \rho\Lambda_v - \delta_v V_i + \beta_v V_s - (1-q)\varepsilon V_i + \omega V_{id} \qquad (4.2)\\
\frac{dV_{sd}}{dt} &= \mu_v(V_{sd}+V_{id})\left(1-\frac{V_{sd}+V_{id}}{(1-\alpha)k_1}\right) - \beta_{vd}V_{sd} \\
&- (\delta_v+\delta_{ins})V_{sd} + (1-q)\varepsilon V_s - \omega V_{sd} \qquad (4.3)\\
\frac{dV_{id}}{dt} &= \beta_{vd}V_{sd} + (1-q)\varepsilon V_i - \omega V_{id} - (\delta_v+\delta_{ins})V_{id} \qquad (4.4)\\
\frac{dH_s}{dt} &= \mu_h H_s + (1-\theta)\mu_h H_i + \theta\tau\mu_h H_i - \delta_h H_s - \beta_h H_s \qquad (4.5)\\
\frac{dH_i}{dt} &= \beta_h H_s + \theta\mu_h(1-\tau)H_i - (\delta_h+\gamma_h)H_i \qquad (4.6)\\
\frac{dD_s}{dt} &= \mu_d(D_s+D_i) - \beta_d D_s - \delta_d D_s \qquad (4.7)\\
\frac{dD_i}{dt} &= \beta_d D_s - (\delta_d+\gamma_d)D_i \qquad (4.8)
\end{aligned}$$

where $\beta_v = \dfrac{bP_{vc}\xi N_c}{N_c+N_{nc}}$, $\beta_{vd} = \dfrac{b(P_{vh}H_i + P_{vd}D_i)}{N_h+N_d}$, $\beta_h = \dfrac{bP_{hv}V_{id}}{N_h+N_d}$ and, $\beta_d = \dfrac{bP_{dv}V_{id}}{N_h+N_d}$.

4.2.1 Uncertainty in the parameters

In order to analyze the sensitivity caused on the model output to variation on the parameters we performed a sensitivity analysis. It can help in determining what data need to be collected to reduce uncertainty on the parameters and outputs (80). We used the Latin Hypercube Sampling/Pearson Partial Rank Correlation Coefficient (LHS/PRCC) procedure. Latin hypercube sampling is a scheme for simulating random parameter sets that adequately cover the parameter space. Correlation analysis can be used to investigate how model output is related to input parameters.

For each uncertain parameter in the proposed model, N simulations of the input are selected by LHS sampling scheme. In order to perform the LHS procedure, we need to specify a probability density or distribution function for each uncertain parameter. When data about the parameters are not available the uniform distribution is most appropriate to use as the default. To sample the values for each parameter, each probability density function is divided into N non-overlapping equiprobable intervals (81).

The magnitude and statistical significance of the PRCC indicates that parameter's contribution to the model's prediction is imprecise. Large values of PRCC (> 0.5 or < -0.5) as well as small values of p-values (< 0.05) indicates the most important parameters (Gomero(81), 2012 apud Taylor(82), 1990, p. 13). PRCC values closed to +1 or -1 indicates that LHS parameters strongly influences the model's outcomes.

PRCC values from 0.5 to 0.69 or -0.5 to -0.69 indicate possible contributors; PRCC values from 0.7 to 0.79 or -0.7 to -0.79 indicate very likely contributors to uncertainty; and PRCC values from 0.8 to 0.99 or -0.8 to -0.99 indicate highly likely contributors to uncertainty (81).

LHS/PRCC procedure was run in R (69) using the packages lhs (83) and sensitivity (84).

4.3 Results

4.3.1 Parameters Searching

Whenever possible, parameters values were estimated based on empirical studies for the vectors species *T. brasiliensis*, *T. pseudomaculata* and *Pastrongylus lutzi*. Other parameter values were chosen in a sensible way and based on previous papers.

Vectors

Reproduction rate. Soares et al. 2000 (85) compared some epidemiological char-

acteristics for *T. brasiliensis* and *T. pseudomaculata* under laboratory conditions. They have found instantaneous daily reproductive rates as 0.010, and 0.009 respectively to *T. brasiliensis* and *T. peseudomaculata*. Averaging this two values, we set μ_v as 0.0095 day^{-1}.

Mortality rate. Egg-to-adult life cycle for *T. pseudomaculata* was 212 ± 21 days, and for *T. brasiliensis* was 160 ± 14 days, in laboratory conditions (85). Averaging these two values we can set vector life expectancy as 186 days. In this way, mortality rate can be calculate as the inverse of life expectancy leading as to 0.0054 days^{-1}.

Bite rate. Based on datasets from literature, Nouvellet et al. 2013 (86) found that the bite rate for the main Brazilian vectors *T. brasiliensis* and *T. pseudomaculata* is 0.2 day^{-1}.

Carrying capacity. Previous studies considered a carrying capacity of 50 vectors per person (87),(88). And other studies vary this value. We considered it as ten times food supply for both environment, peridomicile and intradomicile.

Movement rates. Barbu et al. 2009 (89) estimated that 21.1 adult vectors immigrate per year from peridomestic to domestic habitat. Their studies refer to the Yucatan peninsula, Mexico. The authors varied the number of immigrant vectors from 1 to 25 per year. Based on that, we set the number of vectors entering in peridomestic environment Λ_v as 15 vectors per year (0.0411 vectors per day), and the movement rates between peridomestic and dwelling environment (ω and ε) as 21.1 per year, what leads to 0.0578 day^{-1}.

Probability of infection from competent host to vector. Szumlewicz and Muller, 1987 (90) studied the proportion of infected bug after feed on guinea-pigs with chronic Chagas disease for different days of infection by xenodiagnostic tests. Pooled percentages of infection were 41.7% for *T. brasiliensis* and 71.3% for *T. pseudomaculata*. Averaging these two proportions we set the probability of infection from competent host to vector as 0.565.

Probability of infection from dog to vector and from human to vector. Gurtler et al. 1996 (91) found a weighted probability infection for bugs of the specie *T. infestans* fed on dog as 0.3082, and 0.0062 for human.

Human

Birth and mortality rates. According to WHO (92), the average life expectancy at birth of the global population in 2016 was 72.0 years. In this way, we can calculate the mortality rate for humans as the inverse of life expectancy leading to a mortality rate of 3.8052×10^{-5} days^{-1}. By simplicity, we consider the same value for birth rate, meaning that the human population is constant. According Brazilian Health Ministry (93), mortality rates due to Chagas disease in the State of Pernambuco were 1.28 in 2014 and

1.21 in 2015, per 100,000 inhabitants. Thus, we set mortality rate induced by disease as the average of these two values, 1.245 per 100,000 per year (or 3.4110×10^{-8} day^{-1}).

Probability of infection from vector to human. Using datasets from the literature, Nouvellet et al. 2013 (86) estimated the probability of infections transmission from vector (various triatomines species) to human as 5.86×10^{-4} (95%CI: [2.6; 11.0] $\times 10^{-4}$).

Probability of congenital infection. Congenital transmission rate is 0-5.2% (94). We set θ as the upper limit to perform simulations.

Domestic mammals

Birth and mortality rates. We assumed a life expectancy of 8 years for domestic mammals, leading to a mortality rate of 0.0003 day^{-1}. By simplicity, we consider the same value for birth rate. Mortality induced by disease, γ_d was considered the same as for humans.

Probabilities of infection from vector to dog. We considered that the probability of transmission from vector to dog is 0.0009, this value was used in a previous model (40).

Table 7 displays the model input parameters and sources.

Table 7 – Parameters description and values used in simulations.

		Parameter	Meaning	Value	Source
Vector		μ_v	Birth rate	0.0095 day^{-1}	(85)
		b	Bite rate	0.2 day^{-1}	(86)
		K	Carrying capacity in peridomicile	10 times food supply	Assumed
		K_1	Carrying capacity in intradomicile	10 times number of food supply	Assumed
		ω	Movement rate between habitats (from peridomicile to intradomicile)	0.0578 day^{-1}	(89)
		ε	Movement rate between habitats (from intradomicile to peridomicile)	0.0578 day^{-1}	(89)
		ρ	Proportion of infected vector entering on peridomestic environment from wild environment	0.003	Assumed
		Λ_v	Number of immigrants from wild to peridomestic environment	0.0411 individuals $\times$ days^{-1}	(89)
		P_{vc}	Probability of infection from competent host to vector	0.5650	(90)
		P_{vd}	Probability of infection from dog to vector	0.3082	(91)
		P_{vh}	Probability of infection from human to vector	0.0062	(91)
Human		μ_h	Birth rate (day^{-1})	3.8052×10^{-5}	Assumed
		δ_h	Mortality rate (day^{-1})	3.8052×10^{-5}	(92)
		γ_h	Mortality rate induced by disease (day^{-1})	3.4110×10^{-8}	(93)
		P_{hv}	Probabilitity of infection from vector to human	5.8×10^{-4}	(86)
		θ	Probability of congenital transmission	5.2%	(94)
Domestic	**mammals**	μ_d	Birth rate (day^{-1})	0.0003	Assumed
		δ_d	Mortality rate (day^{-1})	0.0003	Assumed
		γ_d	Mortality rate induced by disease (day^{-1})	3.4110×10^{-8}	Assumed
		P_{dv}	Probabilitity of infection from vector to dog	0.0009	(40)

4.3.2 Numerical Simulations

We considered a generic rural community in Pernambuco (Brazilian Northeast) accounting with 1,000 humans (N_h), 300 dogs (N_d), 5000 triatomines (N_v), 125 non-competent hosts (N_{nc}) and 250 competent hosts (N_c). Based on Silva *et al.* 2012 (78), we considered that 91.3% of the triatomines are inside house, and 8.8% of them are infected. All the humans and domestic mammals are considered susceptible. So, we have the following initial conditions: $V_s(0) = 397$, $V_i(0) = 38$, $H_s(0) = 1000$, $H_i(0) = 0$, $V_{sd}(0) = 4163$, $V_{id}(0) = 402$, $D_s(0) = 300$ and $D_i(0) = 0$. The numerical simulation is performed until the system reaches the steady state (approximatelly 137 years), and, then, the control strategies are applied during 45 years. At first, the control strategies are applied individually, and then, combined.

House improvement and hygiene

House improvement and hygiene is modeled as a reduction on the carrying capacity inside home $K_1 = k_1(1 - \alpha)$. It is done by varying the parameter α. We set the values $0 \leq \alpha \leq 0.9$ while maintained the other parameters associated to control, δ_{ins}, q and τ as zero.

Figure 24 shows the effect caused by house improvement and hygiene on the proportion of infected humans, infected domestic mammals, infected vectors inside the house and on cumulative new cases due to vector transmission to humans.

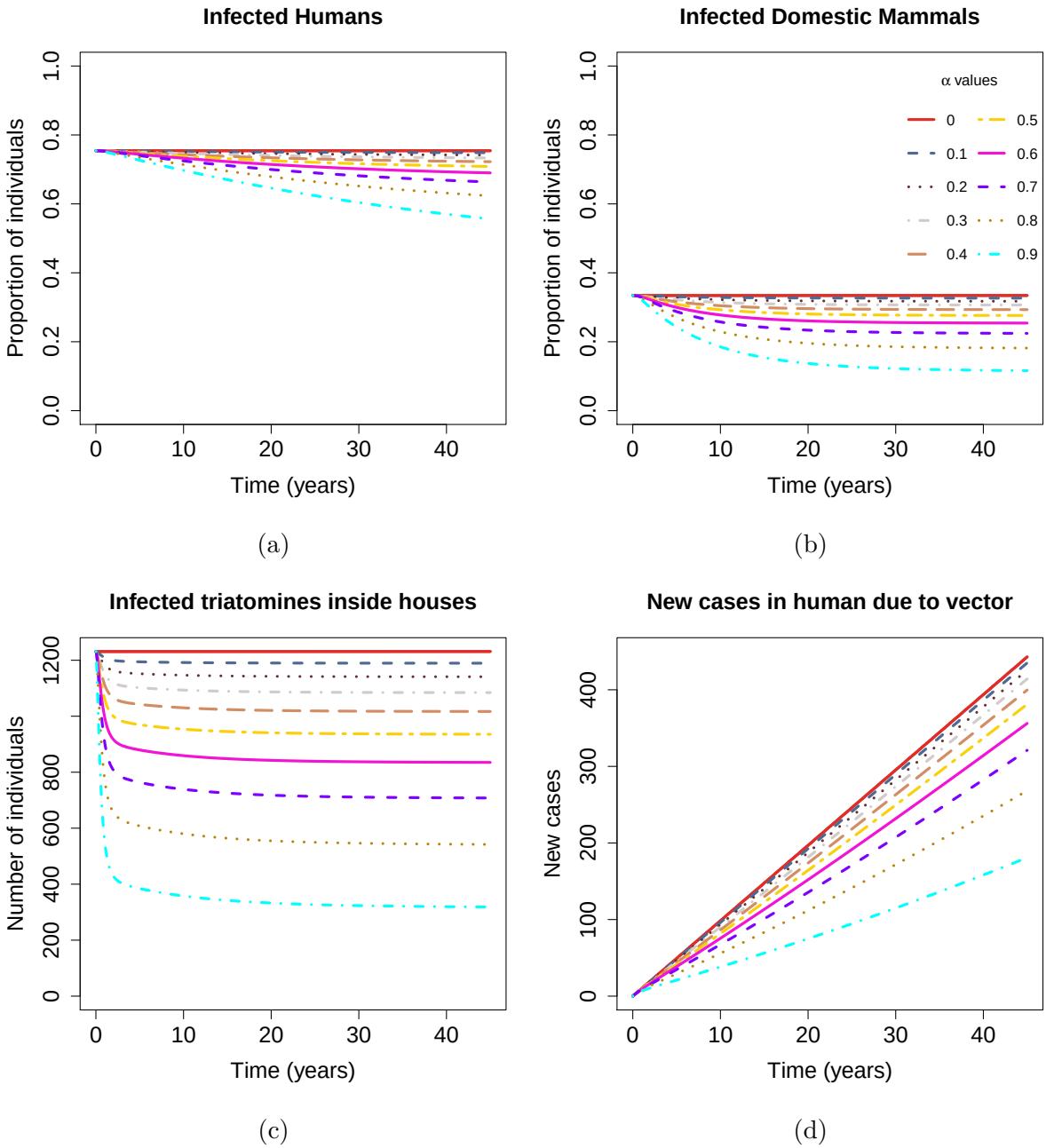


Figure 24 – Effects produced by house improvement and hygiene, represented by the parameter α; in (a) the proportion of infected humans; in (b) the proportion of infected domestic mammals; in (c) the number of infected vectors inside the house; in (d) the cumulative number of new cases in human due to vector infection. α ranges from 0 to 0.9.

Table 8 shows the output at the end of 45 years of simulation for different values of α, representing the effectiveness of house improvement and hygiene.

Table 8 – Proportion of infected humans H_i with respect to the initial population, number of infected vector inside houses V_{id}, proportion between infected domestic mammals D_i and the total population of domestic mammals, and cumulative new cases in human due to vector infection for different values for α, representing the control strategy associated with house improvement and hygiene. Those are values for $t = 45$ years after implementation of control. $\alpha = 0$ means that no control is applied.

α	H_i proportion	D_i proportion	V_{id}	Cumulative new cases in human due to vector
0	0.754	0.334	1231	442
0.1	0.749	0.327	1189	435
0.2	0.742	0.318	1141	425
0.3	0.733	0.307	1084	414
0.4	0.722	0.293	1016	399
0.5	0.709	0.276	935	381
0.6	0.690	0.254	835	356
0.7	0.663	0.224	707	321
0.8	0.623	0.182	542	268
0.9	0.556	0.116	318	180

When the scenario without control is compared to a scenario with 90% of effectiveness in reduction of carrying capacity inside houses, it can be observed that although the number of infected vectors inside house shows a decrease of 74.08%, the prevalence in human decreases in only 26.36%. For domestic mammals, this decrease is of 65.36%. There is a reduction of 59.33% in the cumulative number of new cases in human due to vector infection.

Spraying residual insecticide

Spraying residual insecticide induces an additional mortality rate for vectors inside houses. In the model, this is represented by the parameter δ_{ins} and is simulated as a multiple of vector natural mortality rate. We set values from 0 to 2.5 times the natural mortality rate for vectors. Figure 25 shows the effect of spraying residual insecticide in the intradomicile environment.

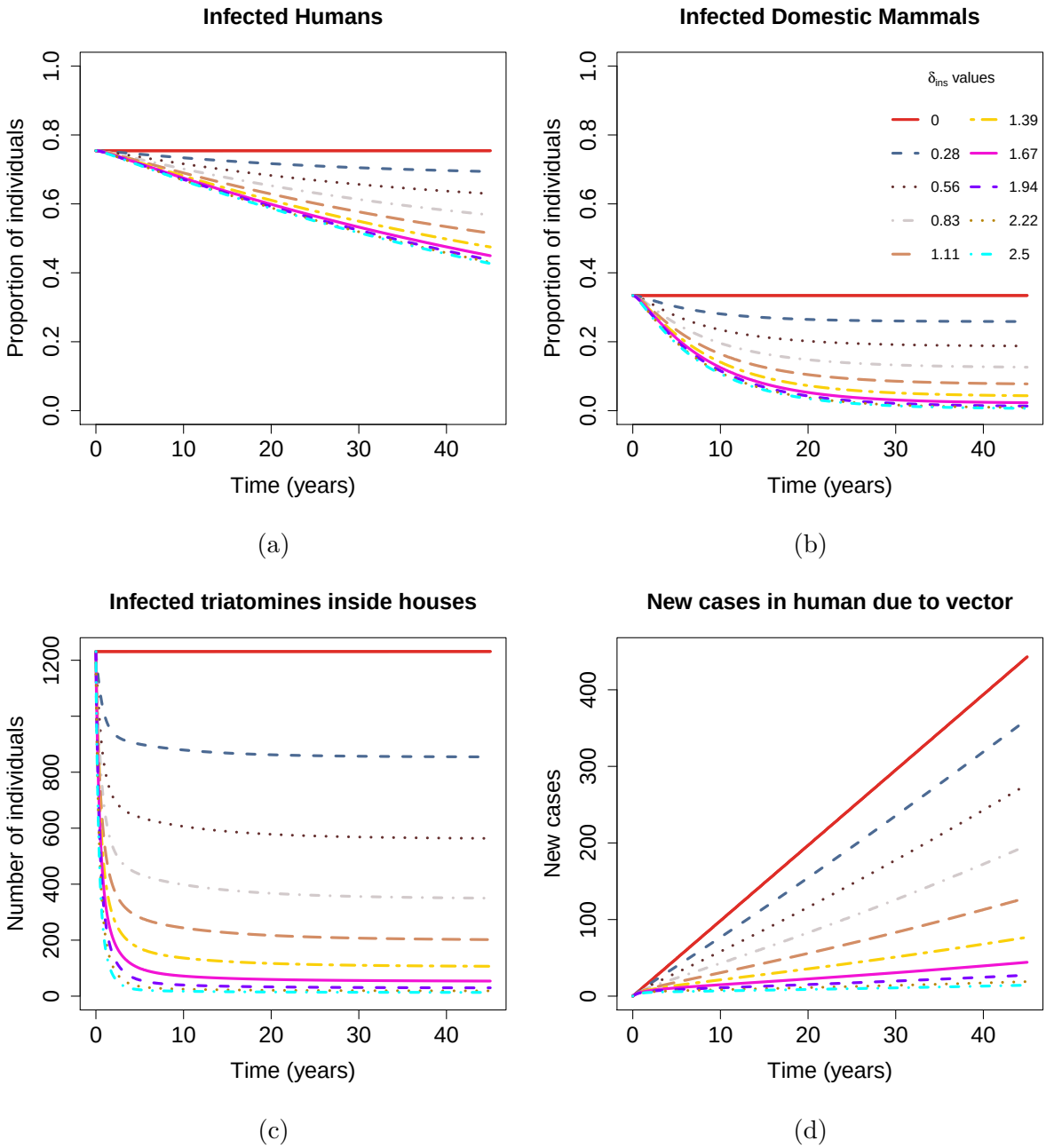


Figure 25 – Effects produced by spraying residual insecticide. Figures show (a) the proportion between infected humans and its population, (b) the proportion between infected domestic mammals and its total population, (c) the number of infected vectors inside the house, and (d) the cumulative number of new cases in human due to vector infection. δ_{ins}, vary from 0 to 2.5 times the natural mortality rate for vectors (δ_v).

We can observe that this control strategy seems to be more efficient in reducing the prevalence in humans when compared with the house improvement and hygiene strategy. Table 9 presents the proportion of infected humans, the number of infected vectors in

the intradomicile, the proportion of infected domestic mammals and the number of new cases due to vector transmission to humans, at the end of 45 years simulation, for different values of δ_{ins}.

Table 9 – Effects caused by insecticide on the proportion between infected human (H_i) and the total of human population, the proportion between infected domestic mammals, the number of infected vectors in the intradomicile (V_{id}) and, on the number of new cases in human due to vector infection for different values of δ_{ins}. Those values represent the scenario after 45 years of simulation, supposing an uninterrupted control application. δ_{ins} is written as a function of natural mortality rate for vectors, ranging from 0 (scenario without control) to 2.5 times the vector natural mortality rate.

δ_{ins}	H_i proportion	D_i proportion	V_{id}	Cumulative new cases in human due to vector
0	0.754	0.334	1231	442
0.28	0.694	0.259	854	361
0.56	0.629	0.188	563	276
0.83	0.568	0.126	349	196
1.11	0.515	0.078	201	128
1.39	0.475	0.043	106	76
1.67	0.450	0.023	53	44
1.94	0.437	0.013	29	27
2.22	0.430	0.009	18	18
2.5	0.427	0.007	13	14

Note that the number of vectors inside the houses at the end of 45 years of simulation, decrease in 95.69% when compared with the scenario without control if the induced mortality rate caused by insecticide application reaches 1.67 times the natural vector mortality. It also causes a reduction of 96.83% on the cumulative number of new cases caused by vector transmission. The proportion of infected humans and infected domestic mammals had a decrease of 40.32% and 93.11%, respectively.

Windows and door screen

The usage of windows and door screen works as a physical barrier reducing the migration rate from peridomicile to intradomicile ω by a factor q related to the effectiveness of this control strategy. Figure 26 shows the effect of this control strategy on the proportion of infected human, the proportion infected domestic mammals, the number of infected vectors inside the houses and on cumulative new cases due to vector transmission to human.

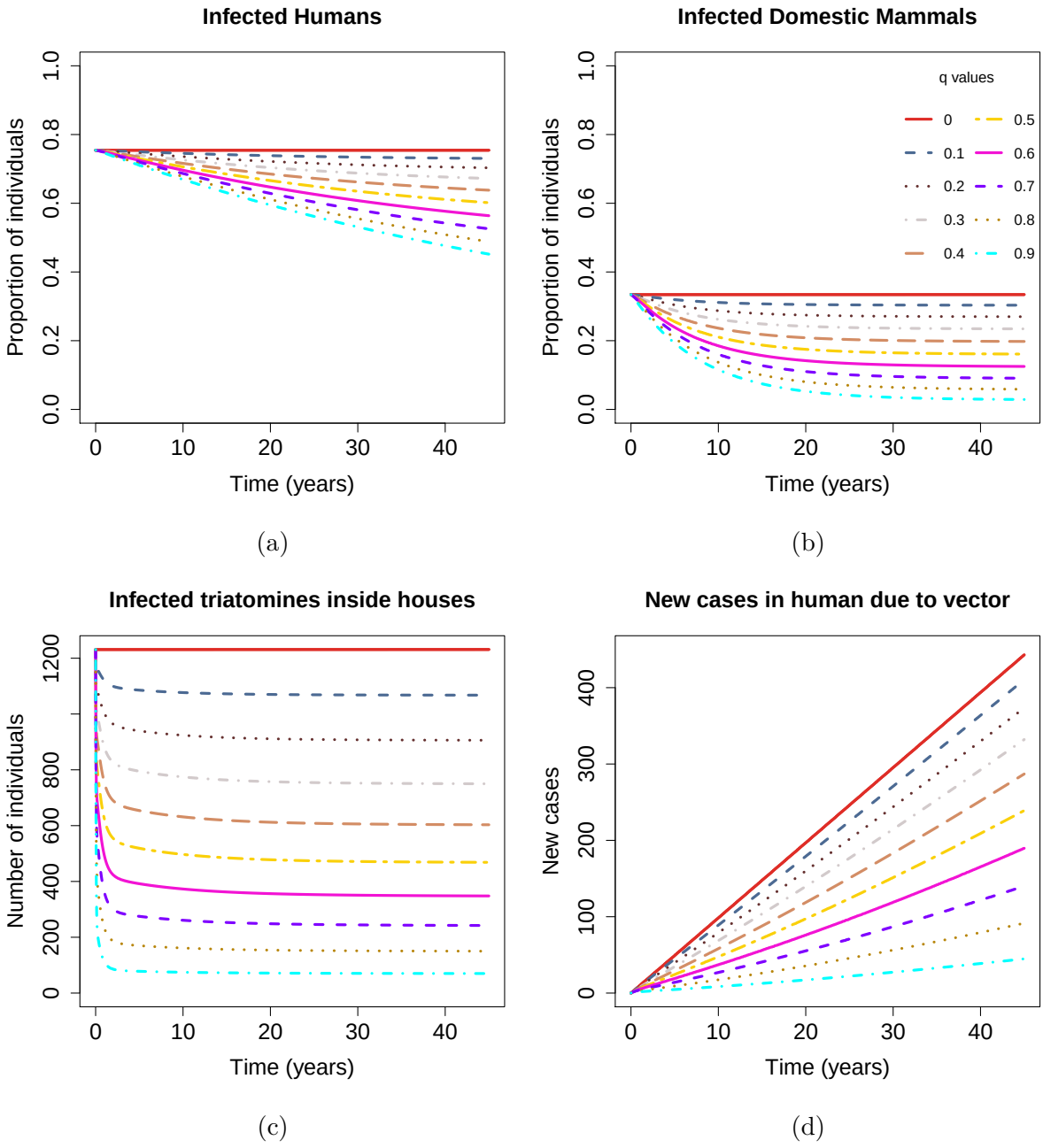


Figure 26 – Effects produced by usage of door and window screen. This control strategy is modeled by varying the vector movement rate from peridomicile to intradomicile by a factor q, representing the effectiveness of this control strategy. The range used was $0 \leq q \leq 1$. Figures show (a) the proportion between infected humans and total human population, (b) the proportion between infected domestic mammals and total population of domestic mammals, (c) the number of infected vectors inside house, and (d) the cumulative number of new cases in human due to vector transmission, for different q values.

Table 10 presents the proportion of infected humans, the number of infected vectors

in the intradomicile, the proportion of infected domestic mammals and the number of new cases due to vector transmission to humans, at the end of 45 years simulation, for different values of q.

Table 10 – Effects caused by usage of windows and door screen on the proportion between infected human (H_i) and total human population, the proportion between infected domestic mammals and total population of domestic mammals, the number of infected vectors in the house (V_{id}) and, the number of new cases in human due to vector infection for different values of q. Those values represent the scenario after 45 years of simulation, supposing an uninterrupted control application. $q = 0$ means a scenario without control.

q	H_i proportion	D_i proportion	V_{id}	Cumulative new cases in human due to vector
0	0.754	0.334	1231	442
0.1	0.730	0.303	1067	410
0.2	0.703	0.270	905	373
0.3	0.672	0.234	749	332
0.4	0.638	0.198	603	286
0.5	0.602	0.161	468	239
0.6	0.564	0.125	348	189
0.7	0.526	0.091	242	140
0.8	0.488	0.059	150	91
0.9	0.452	0.029	70	44

If the effectiveness in the use of windows and door screen reaches 70%, it leads to a reduction of 30.24% on the prevalence in humans, and 72.75% on domestic mammals. Furthermore, the number of infected vectors inside houses decrease by 80.34% and the number of new cases due to vector infection reduces by 68.33%. All those referred reductions are presented after 45 years of uninterrupted control.

Treatment of infected women in childbearing age

The three control strategies previously simulated were related exclusively to vector control. In this section, we introduce and analyze the effect of treatment of women in childbearing age. The treatment effectiveness, τ, is incorporated in the term of births of infected human due to congenital infection, $\theta\mu_h(1-\tau)H_i$. In this way, $\theta\mu_h\tau H_i$ is the rate of change of newborns born from treated women, and this term goes to the susceptible compartment. Although there is not a general agreement whether treatment of women of childbearing age is effective at preventing congenital transmission, some studies support its importance (95, 96). In Figure 27 we observe that the number of new congenital cases is much smaller than the number of new cases due to vector infection, reaching 24 new cases at the end of 45 years, while the number of new cases due to vector transmission reaches

442 new cases for the same period of time, when a scenario without control is considered. Considering the effectiveness of 67% on the treatment of women in childbearing age, the number of new congenital cases is reduced by 66.67%.

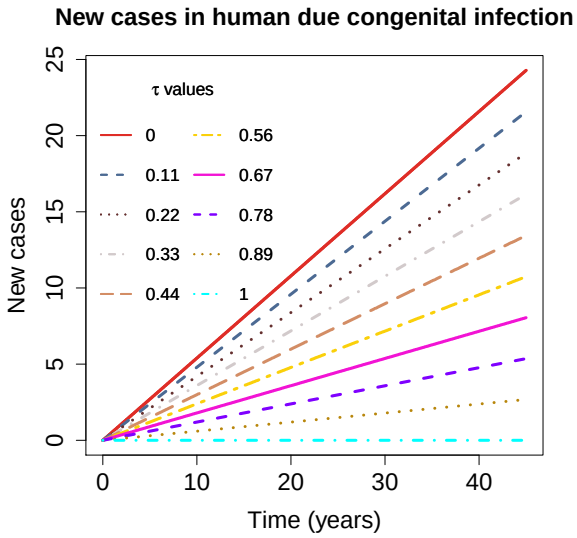


Figure 27 – Effect of treatment of women in childbearing age on the number of new congenital cases. The parameter associated with treatment is τ and, it is in the range $0 \leq \tau \leq 1$. $\tau = 0$ represents the scenario without control and, $\tau = 1$ represents a totally effective control strategy.

Table 11 – Number of new congenital cases on time $t = 40$ years for different values of the parameter θ. This parameter is related to the treatment of women of childbearing age in order to prevent new congenital cases.

τ values	New congenital cases
0	24
0.11	21
0.22	18
0.33	16
0.44	13
0.56	10
0.67	8
0.78	5
0.89	2
1	0

Combined control strategies

So far, we have applied the control strategies in an isolated way. Now, we investigate the effect of combining all the control strategies previously considered. In Figure 28

we observe the effects of combining those control strategies for different parameters combination.

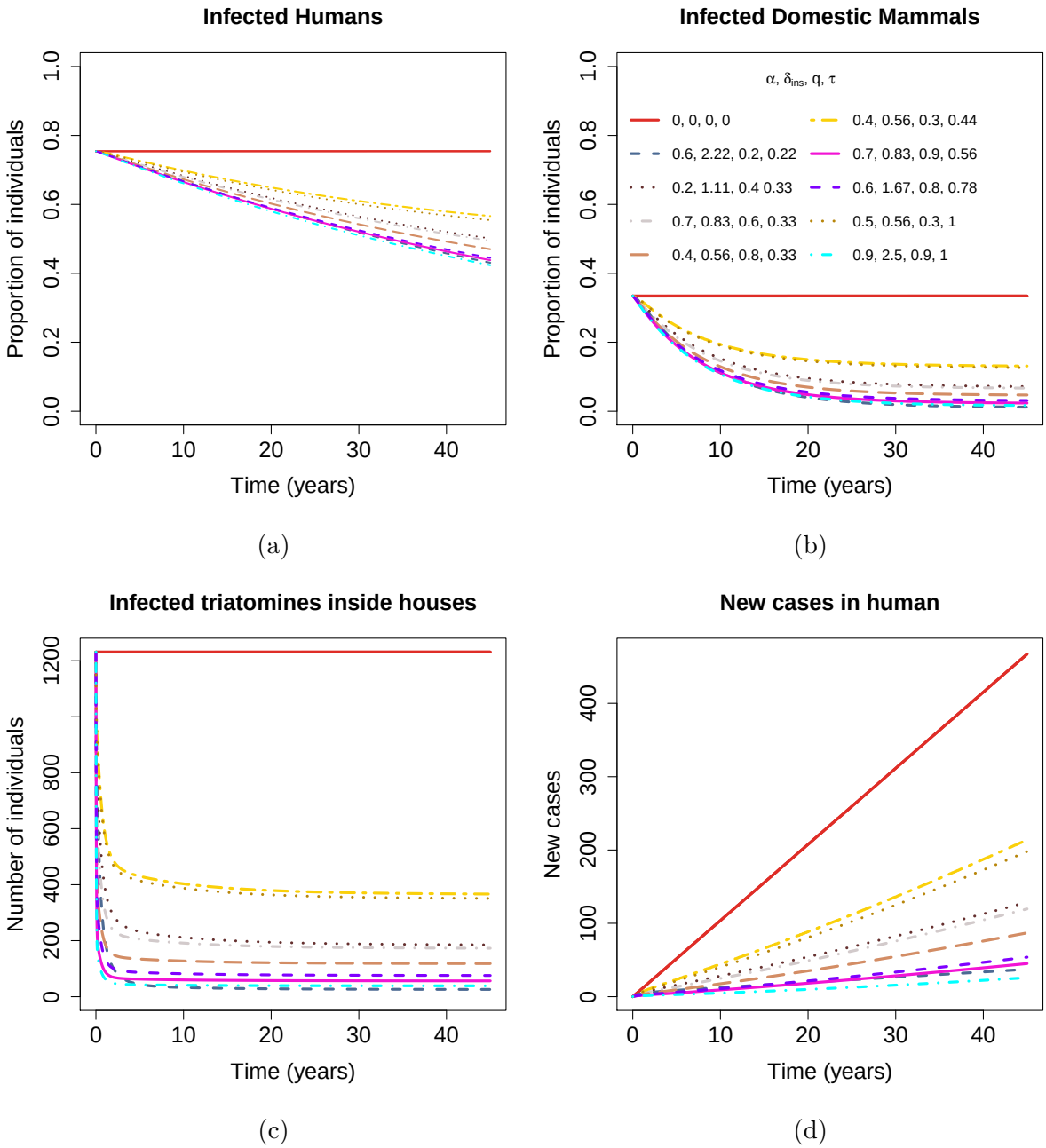


Figure 28 – Effect of combined control strategies: house improvement and hygiene, usage of windows and door screen, and spraying residual insecticides. Figures show (a) the proportion between infected humans and total human population, (b) the proportion between infected domestic mammals and total population of domestic mammals, (c) the number of infected vectors inside house, and (d) the cumulative number of new cases in human due to vector transmission, for different parameters combination.

Table 12 shows the proportion of infected human, proportion of infected domestic mammals, number of infected vectors inside the houses and the number of new cases in humans due to vector infection, at the end of 45 years simulation.

Table 12 – Effects caused by combined control strategies on the proportion between infected human (H_i) and its total population, the proportion between infected domestic mammals (D_i) and its total population, the number of infected vectors in the intradomicile (V_{id}) and, on the number of total new cases (due to vector and congenital) for different values of the parameters α, δ_{ins}, q, and τ. Those values represent the scenario after 45 years of simulation, supposing uninterrupted control application. A scenario without control is represented by setting all the parameters associated with control strategies as zero, i. e., $\alpha = 0, \delta_{ins} = 0, q = 0$, and $\tau = 0$.

α	δ_{ins}	q	τ	H_i proportion	D_i proportion	V_{id}	Cumulative new cases in human
0	0	0	0	0.754	0.334	1231	467
0.6	2.22	0.2	0.22	0.431	0.0112	25	37
0.2	1.11	0.4	0.33	0.501	0.071	185	128
0.7	0.83	0.6	0.33	0.495	0.067	172	119
0.4	0.56	0.8	0.33	0.470	0.047	118	86
0.4	0.56	0.3	0.44	0.566	0.131	366	213
0.7	0.83	0.9	0.5	0.4380	0.023	56	45
0.6	1.67	0.8	0.78	0.445	0.031	75	53
0.5	0.56	0.3	1	0.554	0.126	350	197
0.9	2.5	0.9	1	0.423	0.017	38	25

The combination of control strategies leads to a reduction on the proportion of infected individuals (human, domestic mammals, and vectors) inside the houses and on the number of new cases due to contact with infected vector and to congenital transmission. For the combination $\alpha = 0.4$, $\delta_{ins} = 0.56\delta_v$, $q = 0.8$, and $\tau = 0.33$ there is a reduction of 37.67% on the proportion of infected human, 85.95% on the proportion of infected domestic mammals, 90.41% on the number of infected vectors, and 81.58% on the number of new cases. It shows that, even if the maximum values of parameters are not achieved, different combinations of controls strategies can cause a great effect on the disease transmission.

4.3.3 Combining the control strategies two by two

One can also see the effects of combining the control strategies two by two. We will only apply the control strategies related to vectors, once the number of new cases due to vector infection is much bigger than the new congenital cases. The effects on the

number of new cases due to vector, for each control strategy combination is shown on Figures below.

House improvement and hygiene, and door and windows screen

Combining house improvement and usage of door and windows screen by varying only the parameters α and q in model simulations, we have the result shown in Figure 29.

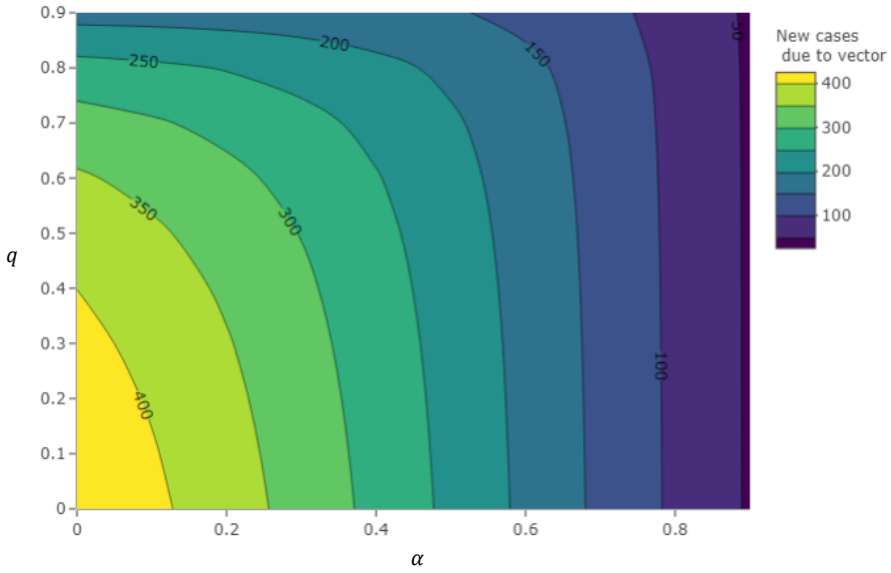


Figure 29 – Contour plot showing the effects caused by combination of house improvement and hygiene, and usage of door and windows screen on the number of new cases due to vector.

From the contour plot (Figure 29) one can observe that, in order to make the number of new cases due to vector reaches less than 50 after 45 years, parameters associated with both control strategies should be set as their maximum values, which is, somewhat, laborious if we take into account that this combined control is applied for public health systems.

House improvement and hygiene, and spraying insecticide

Combining house improvement and spraying insecticide, i. e., varying only the parameters α and δ_{ins} in model simulations, we have the result shown in Figure 30.

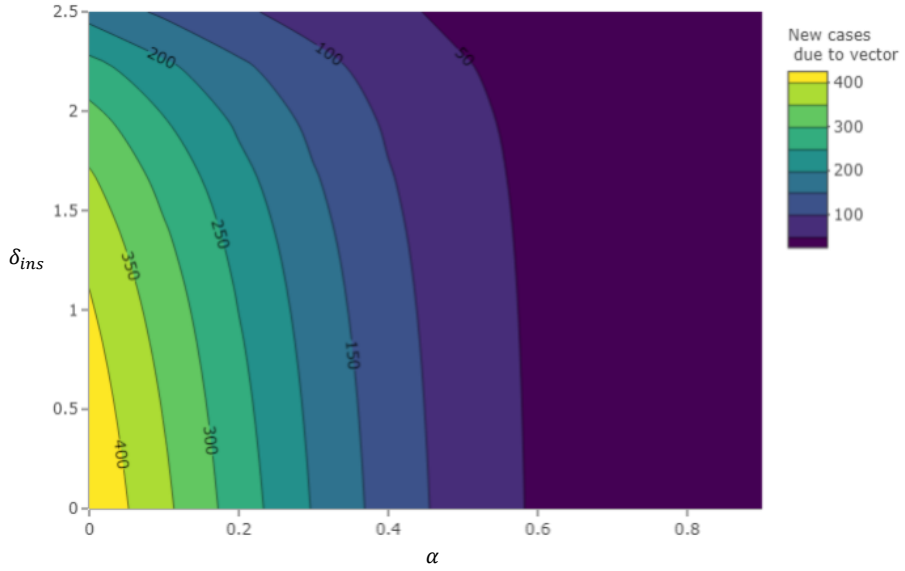


Figure 30 – Contour plot showing the effects caused by combination of house improvement and hygiene, and spraying insecticides on the number of new cases due to vector.

The result shown on the contour plot for this combination is more optimistic than the previous one. The number of new cases can reach values smaller than 50 forα values a bit smaller than 0.6 in combination with all the range for δ_{ins}, which seems more feasible to be implemented than the previous combination.

Spraying insecticide, and door and windows screen

Combining spraying insecticide and usage of door and windows screen, i. e., varying only the parameters δ_{ins} and q in model simulations, we have the result shown in Figure 31.

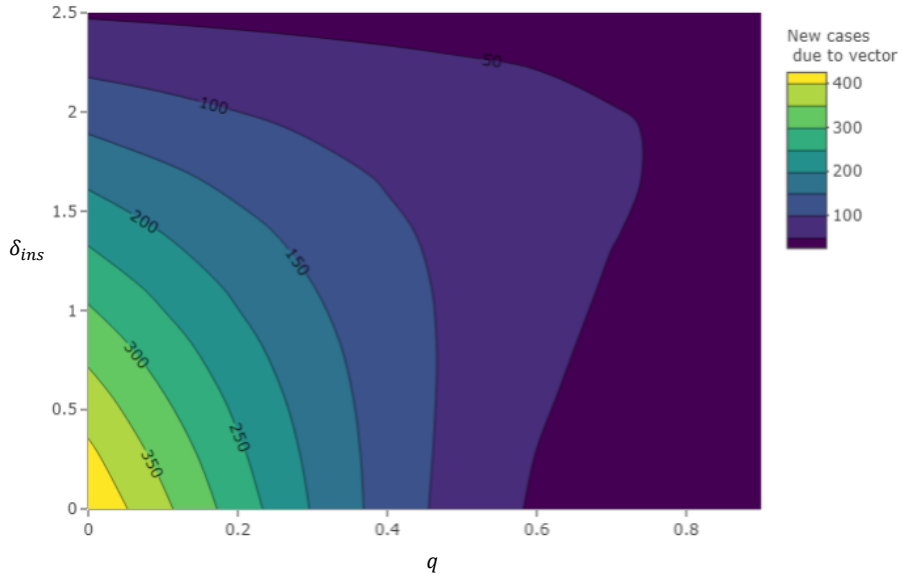
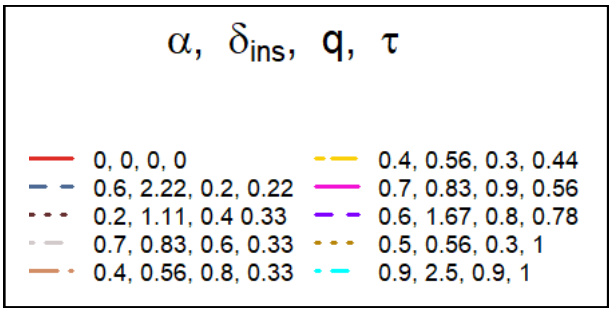


Figure 31 – Contour plot showing the effects caused by combination of spraying insecticides and usage of door and windows screen on the number of new cases due to vector.

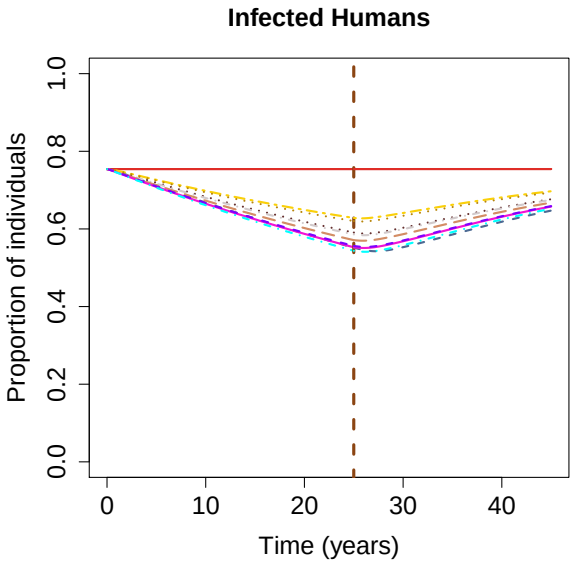
The contour plot (Figure 31) shows that, even if q is set around 0.6 and 0.7, its combination with δ_{ins} values around 1.5 and 2 results in more than 50 cases at the end of 45 years. The combinations two by two shows different scenarios. In an epidemiological point of view, the best combination is the one who results in smaller number of new cases, but it also depends on the cost-effectiveness to apply those combinations. The contour plots can help on making decisions towards these issues.

Interrupted Control

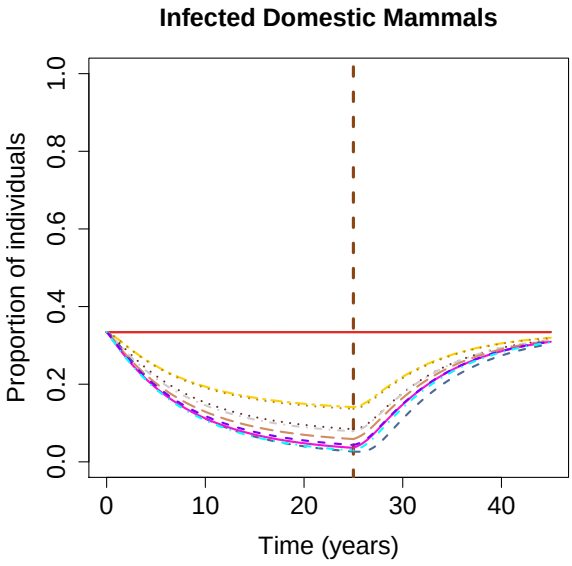
On the previous analysis we assumed that the control strategies were performed continuously, although it is known that it is not always feasible. In order to test the effect of interruption of the control strategies, we simulated a combined control application for 25 years , and then the control was stopped. Figure 32 displays the effect of control interruption for the proportion of infected humans, the proportion of infected domestic mammals, the number of infected vectors inside house and the cumulative number of new cases in human due to vector infection.



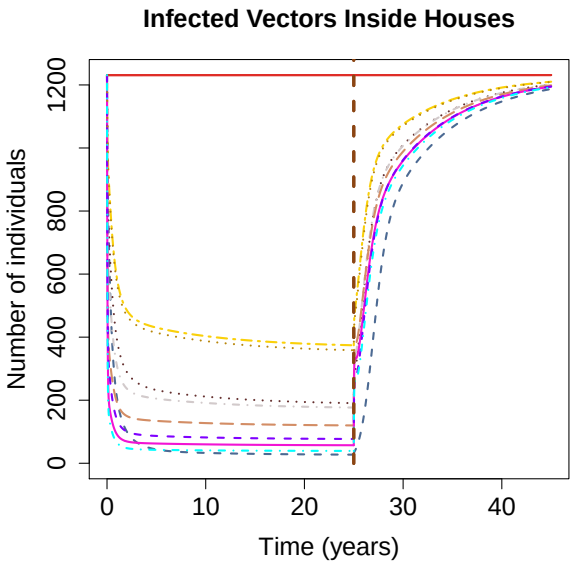
(a)



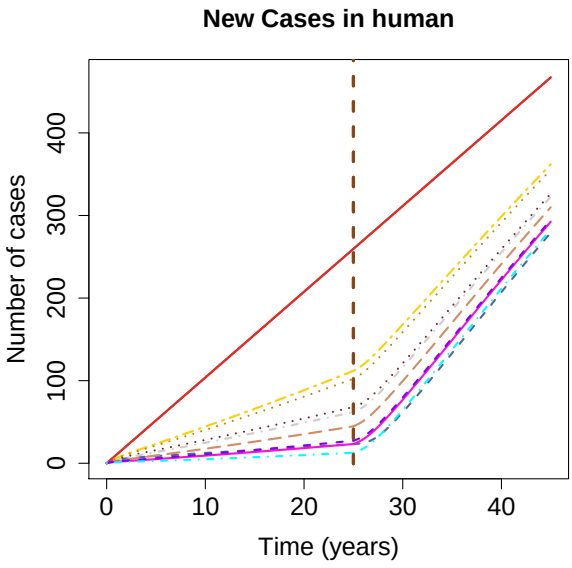
(b)



(c)



(d)



(e)

Figure 32 – Combined control strategies applied during 25 years, then, were interrupted. Figures show (a) parameter values; (b) proportion of infected humans; (b) proportion of infected domestic mammals; (c) infected vectors inside house; (d) cumulative number of new cases in humans.

Once control is interrupted, the proportions of infected human and mammals, the number of infected vectors inside house and the cumulative new cases in human get closer to the values observed in scenario without control. Table 13 shows these quantities at the end of 25 years (the last year of control application) and at 45 years (15 years after the control strategies are interrupted). For example, even if the most efficient control is applied, i. e., when all the parameters associated with control reach their maximum values ($\alpha = 0.9$, $\delta_{ins} = 2.5\delta_v$, $q = 0.9$, $\tau = 1$), the proportion of infected human, the proportion of infected domestic mammals, the number of infected vectors inside houses, and the cumulative new cases have a 19.85%, 9.62%, 29.56%, and 22.58% increase in their numbers after 15 years of control interruption.

Table 13 – Table showing the the proportion of infected human with respect to the total population, the proportion of infected domestic mammals with respect to the total population, the number of infected vectors inside house, and the cumulative new cases in human. The control is applied during 25 years, and then, is interrupted. At the end of 45 years, the numbers are closer to the scenario without control.

	α	δ_{ins}	q	τ	H_i **proportion**	D_i **proportion**	V_{id}	**New cases in human**
Time = 25 years	0	0	0	0	0.754	0.334	1231	467
	0.6	2.22	0.2	0.22	0.647	0.304	1187	279
	0.2	1.11	0.4	0.33	0.677	0.314	1201	326
	0.7	0.83	0.6	0.33	0.675	0.314	1201	322
	0.4	0.56	0.8	0.33	0.668	0.312	1198	309
	0.4	0.56	0.3	0.44	0.697	0.320	1210	361
	0.7	0.83	0.9	0.5	0.658	0.309	1194	292
	0.6	1.67	0.8	0.78	0.659	0.310	1195	294
	0.5	0.56	0.3	1	0.694	0.320	1209	355
	0.9	2.5	0.9	1	0.652	0.308	1192	283
Time = 45 years	0	0	0	0	0.754	0.334	1231	467
	0.6	2.22	0.2	0.22	0.647	0.304	1187	279
	0.2	1.11	0.4	0.33	0.677	0.314	1201	326
	0.7	0.83	0.6	0.33	0.675	0.314	1201	322
	0.4	0.56	0.8	0.33	0.668	0.312	1198	309
	0.4	0.56	0.3	0.44	0.697	0.320	1210	361
	0.7	0.83	0.9	0.5	0.658	0.309	1194	292
	0.6	1.67	0.8	0.78	0.659	0.310	1195	294
	0.5	0.56	0.3	1	0.694	0.320	1209	355
	0.9	2.5	0.9	1	0.652	0.308	1192	283

4.4 Uncertainty on the model parameters

Some of the parameters in our model are not known exactly, we use baseline values, shown on Table 7, to perform the simulations. The uncertain parameters are: $\rho, \Lambda_v, \varepsilon, \omega, b, P_{vc}, \xi, P_{hv}, P_{vh}, P_{vd}, P_{dv}, K_{,h}, K_1$. In order to take into account the parameters uncertainty we perform a sensitivity analysis to find the most important parameters determining the model behavior as consequence of changes on them. In order to do that, an efficient tool employed is the Latin Hypercube Sampling/Partial Rank Correlation Coefficient (LHS/PRCC). Latin hypercube sampling is a scheme for simulating random parameter sets that adequately cover the parameter space. Correlation analysis can be used to investigate how model output is related to input parameters. Partial Rank Correlation Coefficients (PRCC) effects to each input variable. The parameters with large PRCC values (> 0.5 or < -0.5) are the most important. In our analysis we sampled the parameters from an uniform distribution and the range for each uncertain parameter were considered as 50% above and below the baseline values.

One of the output quantity we are interested in is the cumulative number of new cases due to the vector infection. Therefore, we performed the LHS/PRCC analysis for this quantity, for the different values of the parameters associated with vector control, α, q, and δ_{ins}.

House improvement and hygiene

Considering the house improvement and hygiene as the only control strategy applied we vary the α-values, from 0 to 0.9. For each α-value, 100 parameters combination are sampled by LHS. Figure 33 displays the effect on the number of cumulative new cases due to vector for different α values and for the 100 simulations. A box-plot show the variation on the number of new cases for the 100 simulations on each value of α. The red line represents the average behavior of the cumulative number of new cases due to vector, when the parameters assumed their baseline values.

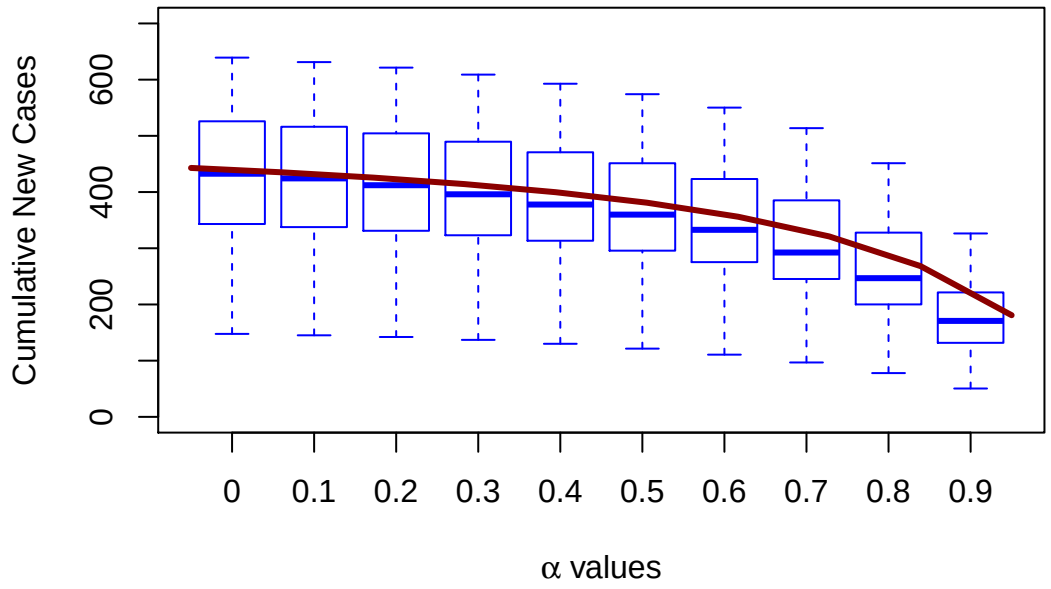


Figure 33 – Cumulative number of new cases for different effectiveness on house improvement and hygiene, represented by the parameter α. For each value of α, 100 simulations of the model were performed using Latin Hypercube Sampling for uncertain parameters. The red line represents the average behavior of the cumulative number of new cases when the parameters assume their baseline values.

Figure 34 shows the Partial Rank Correlation Coefficients for the 14 dimension uncertain parameters.We observe that the parameter b is a possible contributor to uncertainty in the model (PRCC = 0.6601), being the most sensitive among the fourteen parameters. Table 14 shows the output from PRCC analysis.

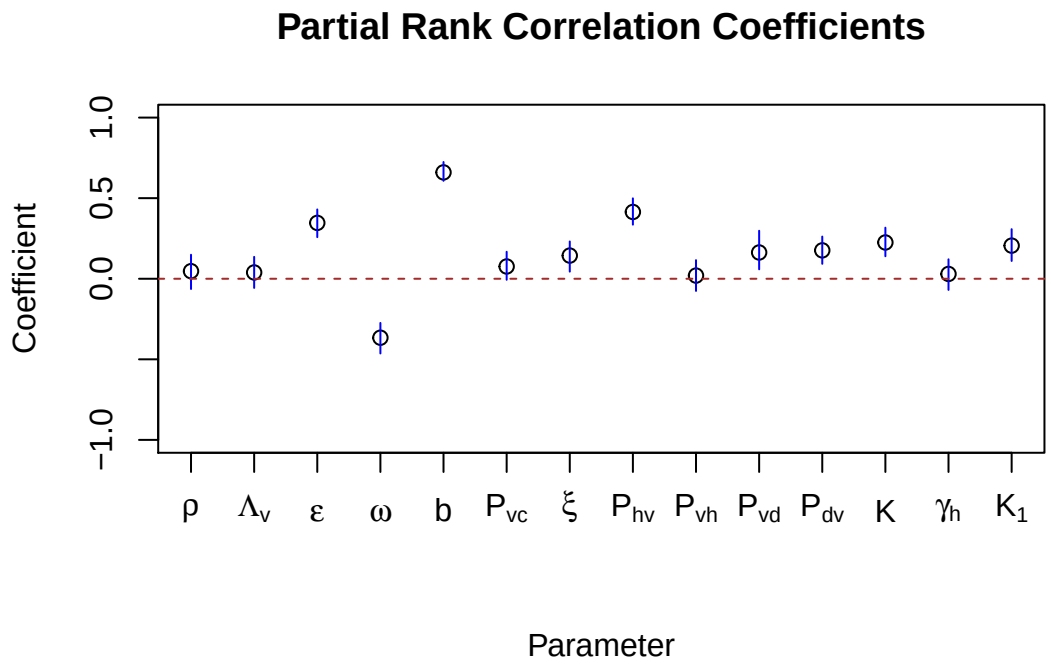


Figure 34 – Partial Rank Correlation Coefficients for the 14 parameters dimension.

Table 14 – Output from PRCC analysis for the cumulative number of new cases due to vector infection. The 95% confidence interval is also shown for each parameter.

Parameters	**PRCC**	**min. c.i.**	**max. c.i.**
ρ	0.0470	-0.0638	0.1489
Λ_v	0.0389	-0.0570	0.1358
ε	0.3467	0.2581	0.4303
ω	-0.3659	-0.4639	-0.2742
b	0.6601	0.6075	0.7244
P_{vc}	0.0760	-0.0065	0.1675
ξ	0.1438	0.0439	0.2316
P_{hv}	0.4143	0.3355	0.4990
P_{vh}	0.0197	-0.0758	0.1155
P_{vd}	0.1629	0.0583	0.2980
P_{dv}	0.1760	0.0925	0.2618
K	0.2251	0.1395	0.3169
γ_h	0.0297	-0.0694	0.1207
K_1	0.2055	0.1104	0.3076

Usage of door and window screen

Figure 35 shows the sensitivity analysis for different q values. For each value, 100 simulations of the model were performed and the parameters were selected by Latin

Hypercube Sampling.

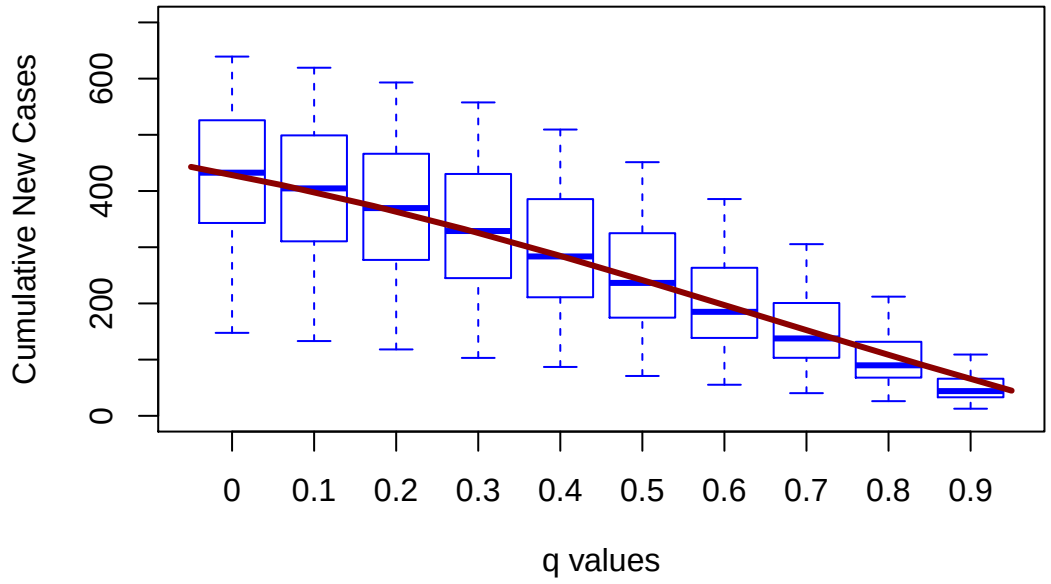


Figure 35 – Cumulative number of new cases for different effectiveness on the usage of door and window screen, represented by the parameter q. For each value of q, 100 simulations of the model were performed. For each simulation the parameters were generated using Latin Hypercube Sampling.

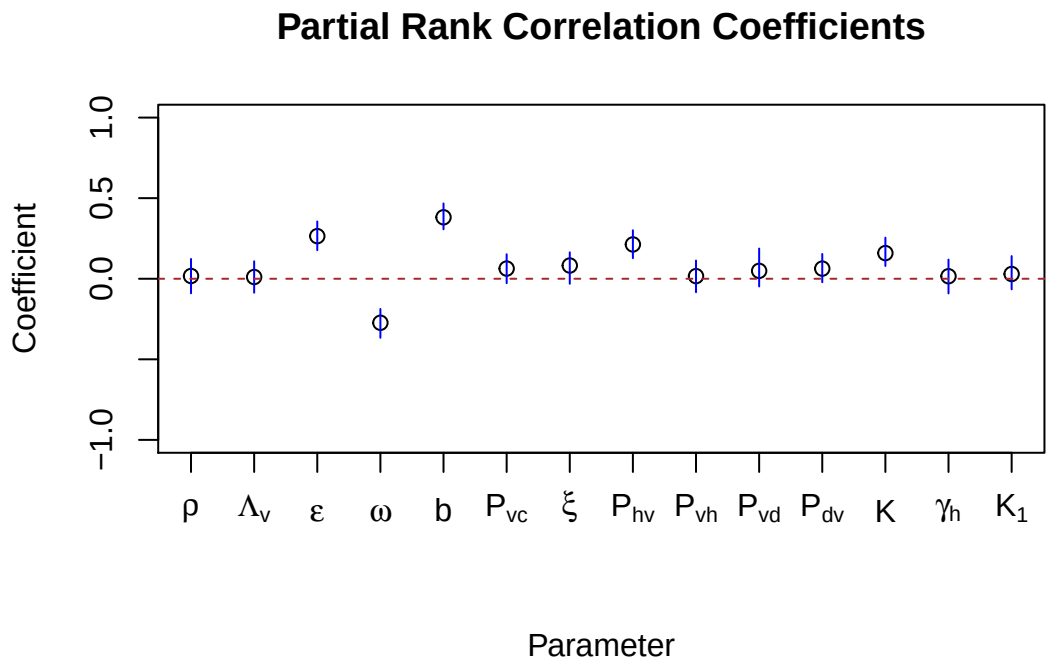


Figure 36 – Partial Rank Correlation Coefficients for the 14 parameters dimension for different q values.

The parameters with bigger PRCC are $b, \omega,$ and ρ, respectively 0.3814, -0.2732, and 0.2643 as shown in Table 15. But, as these values are lesser than 0.5, they do not contribute for the uncertainty on the number of new cases.

Table 15 – Output from PRCC analysis for the cumulative number of new cases due to vector infection and 95% confidence interval for each uncertain parameter.

Parameter	**PRCC**	**min. c.i.**	**max. c.i.**
ρ	0.0170	-0.0904	0.1230
Λ_v	0.0107	-0.0867	0.1084
ε	0.2643	0.1770	0.3556
ω	-0.2732	-0.3665	-0.1876
b	0.3814	0.3067	0.4674
P_{vc}	0.0631	-0.0275	0.1521
ξ	0.0821	-0.0314	0.1640
P_{hv}	0.2129	0.1274	0.3009
P_{vh}	0.0162	-0.0838	0.1132
P_{vd}	0.0489	-0.0478	0.1876
P_{dv}	0.0628	-0.0218	0.1537
K	0.1591	0.0791	0.2548
γ_h	0.0155	-0.0913	0.1191
K_1	0.0294	-0.0656	0.1406

Spraying insecticide

Figure 37 shows the sensitivity analysis for different δ_{ins} values. For each value, 100 simulations of the model were performed and the parameters were selected by Latin Hypercube Sampling.

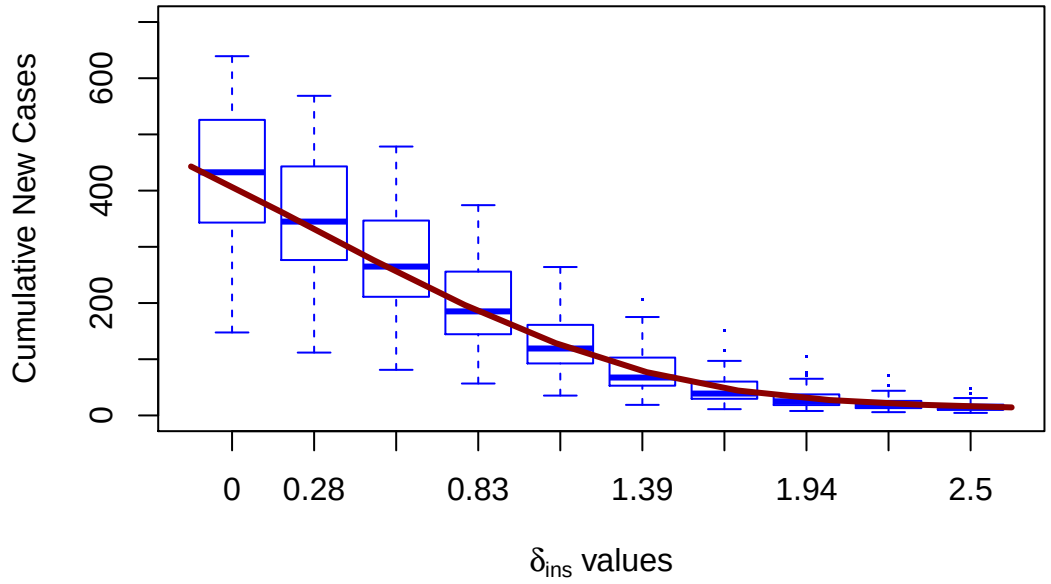


Figure 37 – Cumulative number of new cases for different

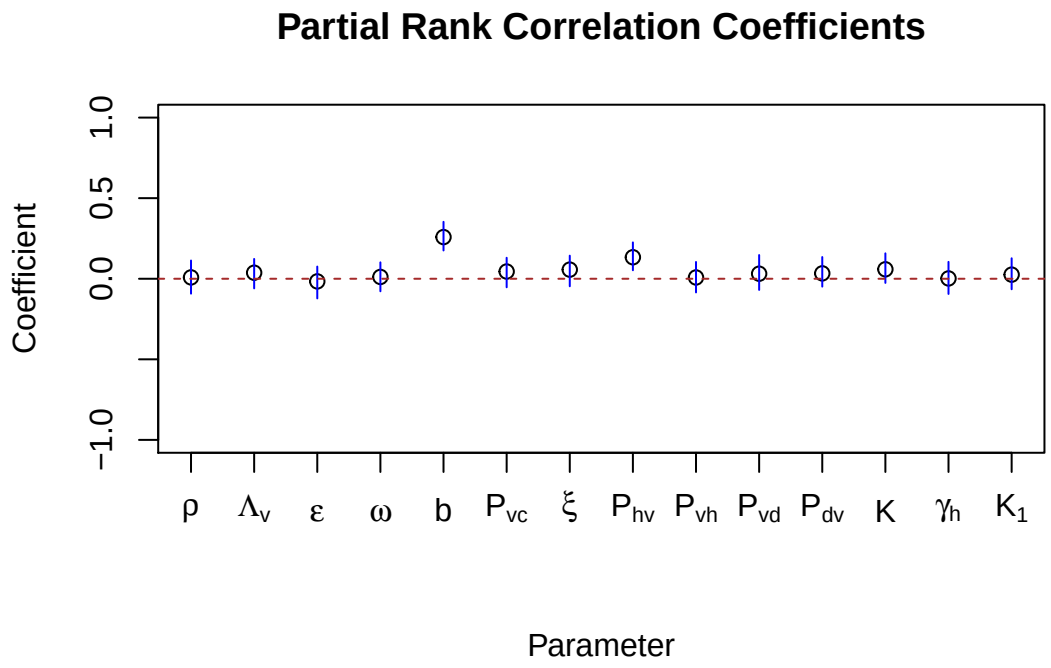


Figure 38 – Partial Rank Correlation Coefficients for the 14 parameters for different values of δ_{ins}.

Table 16 – Output from PRCC analysis for the cumulative number of new cases due to vector infection and 95% confidence interval for each uncertain parameter.

Parameter	**PRCC**	**min. c.i.**	**max. c.i.**
ρ	0.0084	-0.0926	0.1131
Λ_v	0.0373	-0.0598	0.1229
ε	-0.0165	-0.1221	0.0756
ω	0.0112	-0.0779	0.1018
b	0.2585	0.1753	0.3533
P_{vc}	0.0448	-0.0531	0.1303
ξ	0.0566	-0.0467	0.1433
P_{hv}	0.1334	0.0526	0.2256
P_{vh}	0.0079	-0.0850	0.1042
P_{vd}	0.0312	-0.0694	0.1471
P_{dv}	0.0333	-0.0489	0.1347
K	0.0585	-0.0260	0.1577
γ_h	0.0020	-0.0945	0.1047
K_1	0.0254	-0.0652	0.1270

None of the parameters for this specific control strategy presented a PRCC significant value. Therefore, none of the values seems to introduce uncertainty on the output of

interest.

In general, we identified the bite rate and the vector's movement rates as the most important parameters in our model. It means thata

4.5 Discussion

Although Brazil has received the certificate of elimination of vector transmission by *T. infestans* in 2006 by PAHO (Panamerican Health Organization), the presence of other species – as *T. brazilienses*, *T. pseudomaculata* and *Pastrongylus lutzi* – mainly in Brazil Northeast, persists and represents a risk of infection for humans. Brazilian Northeast is also an endemic region serving as dispersion center of *T. brasiliensis*, considered the most difficult triatomine to control (97).

Our results show that by implementing control strategies in a continuous way, one can reduce the number of new cases due to vector infection, the number of vectors inside house and the proportion of infected individuals and domestic mammals over time. However, isolated application of control strategies has a lesser impact on the reductions of those quantities. For example, even with a 90% effectiveness on house improvement and hygiene, the reduction of human prevalence is only 10.98% at the end of 45 years, and 27.95% on the number of new cases in human. These values are 22.11% and 53.80%, respectively, if a 78% of effectiveness is considered in usage of door and windows screen. The individual control strategy that seem more effective is spraying residual insecticide. By considering an induced rate mortality due to insecticide as 1.67 times the natural vector mortality rate, the human prevalence is decreased by 37.9% and the number of new cases due to vector reduces by 88.55% for the same period of time.

When the vector control strategies are combined, the effect on the prevalences in humans and domestic mammals, on the number of vectors inside house and, on the cumulative new cases due to vector infection is stronger. For example when there is an effectiveness on house improvement of 10%, spraying insecticide generates an induced mortality rate of 1.86 times of vector natural mortality and the effectiveness on usage of windows and door screen reach 22%, the proportion of infected humans is reduced by 36.84%, the proportion of infected domestic mammals is reduced by 94.74%, the number of infected vectors inside houses are reduced by 98.85% and the number of new cases due to vector infection is reduced by 90.86%. It highlights the importance of combined control strategies in order to eliminate the vector transmission, one of the goals of the London Declaration 2020.

Although the number of vectors inside house are greatly reduced with vector

control strategies, the disease may persist in the human population for a long period of time due to the long disease course. Hence, it is important to detect and treat infected individuals. Screening and treating women of childbearing age at risk of being infected and consequently infected their children is an important strategy to be considered, once anti-parasitic treatment can prevent congenital cases (98). In this way, we also incorporated this strategy in our model simulation. Our results show that it is possible to reduce the number of new congenital cases by detecting and treating women of infected of childbearing age. A 67% effectiveness on detecting and treating women of childbearing age, for example, leads to a reduction of 66.70% on the number of the cumulative new congenital cases after 45 years of implementing this control strategy.

Our results also show the importance of maintenance control strategies, once it is stopped, the number of new cases due to vector infection, proportion of infected individuals and vectors inside house tend to return to the scenario without control as is shown in Figures 32. The results show that combined control strategies can reduce significantly the number of vectors inside house, mainly due to application of residual insecticide that can eliminate triatomine colonies. But, houses can always be re-invaded from the silvatic and peridomestic habitats (85). Thus, there is a need for constant vigilance and effective control programs. In a study performed in Ceará (Brazilian Northeast), even after house restoration and insecticide spraying, the lack of suervision have led to a rapid recover of triatomine population, after two-three years (99).

As a simplified description of reality, mathematical models have limitations and can not explore all the complexities associated with biological systems. Nevertheless, their simple description about complexity problems can lead to important results in order to improve decision-making policies. Other aspects can be also incorporated in future models, such as, using the distance between the two considered environments – peridomicile and domicile – as factor to determine vector invasion to houses; consider the presence of human and domestic mammals in the peridomicile, model the insecticide effect in different ways such as an exponential decay on effectiveness over time, and search for reliable data from communities in Pernambuco in order to reduce uncertainty in parameter estimation and model validation.

5 Conclusions

5.1 General conclusions

At the beginning of this work we presented the main characteristics of Chagas disease and its importance as one of the Neglected Tropical Diseases. Although its endemic area is concentrated in Latin America, the mobility of Latin Americans around the world make it present in European, North America and Pacific Western countries. We also described the importance of the mathematical models in epidemiology, emphasizing the compartmental models, as they were used in this thesis to study different scenarios on the disease transmission.

On the first model we used compartmental mathematical model to investigate Chagas disease transmission due to congenital and blood transfusion routes. This model was applied to Spain, since it is the non Latin American country which receive more Latin American immigrants. We found that congenital transmission generates more new cases than transmission due to blood transfusion, and that when control strategies are performed, as effective surveillance in blood transfusion and treatment of infected newborns, have a great impact on the reduction of new cases. On the flip side, if these control strategies are interrupted, the number of new cases can increase again. Besides the prevention of new cases, it is important to highlight that detection and treatment of infected people are also important in order to prevent long term complications.

The second model considered Chagas disease transmission in a rural community accounting with peridomicile and intradomicile environments, triatomine bugs, competent and non-competent hosts, humans, and domestic mammals. We used information from Pernambuco to set up some of the model parameters. Vector control strategies were performed, as improvement of houses and hygiene, usage of windows and door screens, and spraying insecticides. According to the numerical simulations, spraying insecticides is more effective in reducing the number of new cases, the proportion of infected human and domestic mammals, and the number of triatomine bugs inside houses. Combined those control strategies also is beneficial in reducing these values. Treatment of women in childbearing age was also performed as a strategy to reduce the number of new congenital cases, and it is effective. Again, interrupting the control strategies are problematic, because the disease dynamics return rapidly to a scenario where there is no control strategies

application.

Although the models applied were simple, the epidemiological results showed that mathematical models can be used as valuable tools to estimate epidemiological impacts on the implementation of control strategies, improving decision making in public health policies in order to reduce the disease burden. Multidisciplinary work among modelers, health practitioners, community health workers, patient associations and other important actors in this context are extremely important.

5.2 Perspectives and future work

Mathematical models are simplified description of reality, in this way, they have limitations. On the first model we can introduce migrations rates to try to track the difference on the disease dynamics over time. On the second model we can use the distance between the peridomicile and intradomicile environments as a strategy to prevent bugs invasion and domiciliation in the intradomicile, consider movement of humans and domestic mammals on both environments (intradomicile and peridomicile), and model insecticide effect with different approaches, for instance, as exponential decay over time. The dynamics proposed can also be explored by stochastic models. Searching for real data for a specific community in Pernambuco in order to check all the model assumptions, the parameters values, and validate the model will be incorporated in future works.

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