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ORIGINAL ARTICLE

Modeling Chagas Disease at Population Level to Explain Venezuela's Real Data

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Abstract
Objectives: In this paper we present an age-structured epidemiological model for Chagas disease. This model includes the interactions between human and vector populations that transmit Chagas disease.
Methods: The human population is divided into age groups since the proportion of infected individuals in this population changes with age as shown by real prevalence data. Moreover, the age-structured model allows more accurate information regarding the prevalence, which can help to design more specific control programs. We apply this proposed model to data from the country of Venezuela for two periods, 1961–1971, and 1961–1991 taking into account real demographic data for these periods.
Results: Numerical computer simulations are presented to show the suitability of the age-structured model to explain the real data regarding prevalence of Chagas disease in each of the age groups. In addition, a numerical simulation varying the death rate of the vector is done to illustrate prevention and control strategies against Chagas disease.
Conclusion: The proposed model can be used to determine the effect of control strategies in different age groups.

1. Introduction

Chagas disease, also known as American trypanosomiasis, is a potentially life-threatening illness caused by the protozoan parasite *Trypanosoma cruzi*. Approximately 10 million people around the world are living with Chagas disease and it is among the most neglected tropical diseases in the Americas; Chagas disease ranks near the top in terms of annual deaths and disability-adjusted life years lost [1]. Interestingly, there are a number of striking similarities between people living with Chagas disease and people living with human

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immunodeficiency virus (HIV)/AIDS, particularly for those with HIV/AIDS who contracted the disease in the first 2 decades of the HIV/AIDS epidemic.

The main mode of transmission of Chagas disease in endemic areas is through an insect vector called a triatomine. During the day, most domestic triatomines hide in crevices in walls and rustic roofs. The insects emerge at night, when the inhabitants are sleeping, although in Mexico there is at least one species that is diurnal. Because they tend to feed on people's faces, triatomine are also known as kissing bugs. Triatomines pass *Trypanosoma cruzi* parasites (called trypomastigotes) in feces left near the site of the bite wound. Scratching the site of the bite causes the trypomastigotes to enter the host through the wound, or through intact mucous membranes, such as the conjunctiva. Once inside the host, the trypomastigotes invade cells, where they differentiate into intracellular amastigotes. The amastigotes multiply by binary fission and differentiate into trypomastigotes, which are then released into the bloodstream. The triatomine becomes infected by feeding on human or animal blood that contains circulating parasites [2]. Chagas disease is still considered the most important vector-borne infection in Latin America. It is estimated that between 16 and 18 million humans are infected with *T. cruzi*, with at least 20,000 deaths each year, and 100 million considered at risk [2–4]. Although vector transmission has been controlled to a significant degree, lack of effective medication to treat this disease indicates a failure of the health policies adopted by endemic countries. American trypanosomiasis, tropical in nature, may become an object of interest for highly developed countries in the near future, because of the increasing migration of infected individuals [4,5].

The transmission vector belongs to the subfamily Triatominae (*Hemiptera: Reduviidae*) comprising 130 recognized species, of which about a dozen are commonly involved in transmission of the trypanosome to humans. Other less important forms of transmission include consumption of uncooked food contaminated with feces from infected insects, congenital transmission (from a pregnant woman to her fetus), blood transfusion, organ transplants, and accidental laboratory exposure [2,3,6]. For instance, Alarcón de Noya et al [7] reported a large urban outbreak of orally acquired acute Chagas disease at a school in Venezuela. However, in this article we propose a model focused on the vector as the main transmission factor.

The public health importance of parasites has led to a large amount of literature, exploring their impact on the population dynamics, population genetics and evolutionary biology of human populations. Mathematical models, simpler than the reality, allow us to understand the global dynamic behavior of Chagas in human, animal, and vector populations. Mathematical modeling is often used to study the transmission dynamics of diseases in populations from an epidemiological point of view using different mathematical tools [8,9].

Several interesting mathematical models for the transmission of Chagas diseases have been presented [3,10,11]. For example, Erazo and Cordovez [10] proposed a stochastic dispersal model to study *Rhodnius prolixus* house infestation dynamics in a hypothetical village. In addition, some models [3,11] have been proposed in order to study the evolution of Chagas disease in human populations. A model that includes insecticide spraying and cessation of spraying was presented by Spagnuolo et al [12]. The model predicts that if insecticide use is discontinued, the vector population and the disease can return to prespraying levels in approximately 58 years. Another well elaborated model for the Chagas disease dynamics has been developed using partial differential equations reflecting infection-age-dependent infectivity and considering blood transfusion transmission [13]. In this model difference between the acute stage and the chronic stage is included in the infection-age dependent infectivity. However, from a practical point of view for health institutions, the model includes some parameters difficult to estimate and the model assumes a demographically steady state host population which is not true in many Latin Americans countries where Chagas disease is present. The use of structured population models can make substantial contributions to public health, particularly for infections where clinical outcomes vary over age [14]. Mathematical models have been developed for different type of epidemics where the age plays an important role [8,14–20]. For example, Metcalf et al [14] used an age-structured model for rubella in Costa Rica. The authors showed that the demographic profile of this infection plays a crucial aspect of its public health impact and explored the impact of changing human demography. In order to explore the dynamics of the Chagas disease in human and vector populations we present an age-structured epidemiological type model based on a system of nonlinear differential equations. This mathematical modeling approach allows the investigation of the dynamics of diseases in populations from an epidemiological point of view [8,21]. The age structure of the population plays an important role on the dynamics of the Chagas disease since the *T. cruzi* infection is often lifelong [22–24] and therefore the proportion of infected individuals depends on age. Furthermore, the model allows the generation of a far more realistic heterogeneous fade-out pattern than a homogeneous population model. It is important to note that most infected people are asymptomatic and unaware of the infection [22]. Thus, the proposed model gives a better picture of the relation between the age and prevalence of Chagas disease. In addition, the model is an appropriate framework for both demographic and epidemiological transitions where parameters are based on data ranging from the biological course of infection, basic patterns of

human demography, and specific characteristics of population growth. Furthermore, the age-structured model allows evaluation of public health strategies in the face of changing human demography. For instance, health institutions may want to implement a control program with more focus in specific age groups based on the information provided by the simulation of the model.

The proposed age-structured model consists of the interactions among susceptible and infective individuals of the two species assuming that the horizontal transmission of the disease to humans is only through the contact with infected vectors. In this age-structured model, each age class i of the human population is divided into two subpopulations, susceptible $S_i(t)$ and infectious $I_i(t)$, and the vector population into two subpopulations, susceptible $SV(t)$ and infectious $IV(t)$. It is important to point out that triatomines have six distinct stages of life: five instar ages and an adult stage. In this work, the model equation for the vector was chosen for simplicity. Otherwise, the vector equation might be split into six coupled equations for the different stages of development of the triatomines [12].

In this paper we will apply the age-structured Chagas disease model to data from Venezuela [25]. Venezuela is one of the countries most affected by Chagas disease and the health authorities made a large effort for some years collecting related data. The data we use were taken from the national Chagas Disease Control Programme (CDCP) archives. These data were condensed from monthly and annual reports of the programs ongoing surveillance activities, during the period of 1960−1998 by municipality and State. The data include entomological evaluations carried out by house inspections in rural areas [25].

At first, we apply the proposed model for the time interval 1961−1971 where we use the only available data of 1958−1968 as the Chagas prevalence for 1961 and the data for 1969−1979 as the prevalence for 1971, i.e. the prevalence reported for 1958−1968 for each age group is assumed as initial condition for 1961−1971 and the prevalence reported for 1969−1979 is assumed to be the real final condition 1961−1971.

The second time interval studied is 1981−1991, where we use the available data for 1980−1989 as the Chagas prevalence for year 1981, and data for 1990−1999 is assumed to be the real prevalence for 1991. The population of Venezuela is rapidly increasing but there is only real demographic data (census) for the specific years 1961, 1971, 1981, 1990, and 2001, which we use to get an approximation of the population for the considered time interval periods. Thus, the model is validated using the Chagas prevalence data from of 1958−1968, 1969−1979, 1980−1989, and 1990−1998 and the available census population data of years 1961, 1971, 1981, and 1990. It is important to note that to the best of our knowledge more recent data regarding Chagas prevalence by age groups are not available and we have chosen old and newer data in order to test the age-structured model. Here, our goal is to show that the model is suitable to understand the dynamics of Chagas disease at population level for the different age groups. Moreover, despite the data not being very accurate, the age-structured mathematical model gives a reasonable explanation of the Chagas disease dynamics at the population level in Venezuela for the aforementioned periods.

In order to better approximate the real scenario we include in the mathematical model a nonconstant total human population. In Venezuela, apart from the change in numbers due to births and deaths, there was a large inflow of population due to immigration in the decade of 1950 [26]. However, it is important to point out that the extensive post-World War II immigration is difficult to study since statistical information is poor or of difficult access [27]. Thus we use an approximation of inflow population using only the total age group real data of censuses for 1961, 1971, 1981, and 1990 from Venezuela. However, from the census data it is clear that immigration or emigration was present for the period 1961−1990. For instance, according to the Dirección Nacional de Identificación y Extranjería (government office) 614,425 cards were issued for foreigners between 1948 and 1961, most from regions not endemic for Chagas disease. When one considers that the population of Venezuela was only about 5 million people in 1950, this inflow population is very important to the dynamics.

2. Materials and methods

In this section, we present the age-structured epidemiological type model based on a system of nonlinear differential equations. In this mathematical model we consider humans and the transmission vectors and we disregard mammal transmitters and nontransmitters. In addition transmission through blood transfusion, organ transplantation, and from mother to fetus are not considered in this first approach because they are not the main means of transmission and also in order to avoid a more complex mathematical model with more unknown parameter values. A similar approach with human and transmission vectors has been taken in other models for the Chagas disease dynamics [13]. In addition, we do not divide the infected population into different compartments for the acute stage and the chronic stage. The acute stage is rather short (1−2 months) in comparison with the length of the chronic stage (10−20 years), so this simplification does not seriously affect the long-term dynamics of Chagas disease [13]. Although several mathematical models for Chagas disease only consider the human and vector populations, we understand that the situation is more complex since probably the main reservoir of the trypanosoma are not humans

but probably rodents or other mammals [28], but tracking the population of infected mammals is clearly not possible. Here we focus in modeling the human age-structure effect without considering other mammals explicitly in a similar way as previous mathematical models [3,11,13,29,30].

Real demographic data (census) for the specific years 1961, 1971, 1981, and 1990 do not include immigration or emigration, but using the total population in each age group it is possible to use linear interpolation to estimate the total population in each age group for each of the years of the simulations. Thus the approximate net inflow for each group is obtained by doing a simple population balance.

It is well-known that the duration of infection is lifelong if it is left untreated [23,24,31]. Martins-Melo et al [32] analyzed all death certificates of individuals who died between 1999 and 2007 in Brazil and found that Chagas disease was mentioned in 53,930 (0.6%) death certificates, with 44,537 (82.6%) as an underlying cause and 9,387 (17.4%) as an associated cause of death. Additionally, it has been presented that 26% of Chagas patients develop right bundle branch block, of whom 7.5% die [33,34]. Since the proposed model focuses on data from the 1960s, it is reasonable to assume that Chagas disease is lifelong. Furthermore, nowadays many rural areas do not have treatments for the disease. Also, Chagas disease has a lifelong chronic phase, during which most infected persons are asymptomatic, and thus clinical information is of little use in identifying infected individuals. Moreover, owing to the extremely low parasitemia during the chronic phase, parasitologic methods are insensitive and in a practical sense are not useful for assembling sizable panels of Chagas-positive specimens and possibly treating them [31]. Based on these facts, life expectancy is assumed to be greater for the susceptible in comparison to the infected population.

There are several population models that may be used to represent the dynamics of the age groups. However, the main idea behind all these models is a population balance analogous to the energy balance used commonly in several areas of science. The variables of an age independent continuous model based on ordinary differential equations are: time-variable t; particular population $v(t)$,which depends on t; birth flow $n(t)$, that is, the number of births per time unit; death flow $d(t)$, and migration flow $f(t)$ defined as $f(t) = fi(t) - fe(t)$, where $fi(t)$ is the immigrant population flow, and $fe(t)$ is the emigrant population flow. Thus, the derivative of $v(t)$ with respect to time can be stated as [35]:

$$\dot{v}(t) = n(t) - d(t) + f(t),\ v(t_0) = v_0. \tag{1}$$

In Eq. 1, t_0 is the initial instant and v_0 is the population at this instant. In addition, if the crude birth rate, $a(t)$, and the crude death rate, $g(t)$, are known, $n(t)$ and $d(t)$ can be obtained as follows: $n(t) = a(t)\cdot v(t)$ and $d(t) = g(t)\cdot v(t)$. Using the census data we have an approximation of the total inflow population, which includes $n(t)$, $f(t)$ and $d(t)$.

The age-structured epidemiological mathematical model is represented by a system of nonlinear ordinary differential equations that includes human population and invertebrate vectors (triatomines) [29]. The human population is divided into six age groups in order to match the available data of Chagas disease. The age groups by years are 0−9, 10−19, 20−29, 30−39, 40−49, and 50+. In this work, the model equation for the vector is divided in susceptible and infected without separating the six distinct stages of life of the triatomines since the time scale of the stages of the triatomines is smaller than the time scale of the transmission process on the human population and in regard to the time simulation periods [12].

In order to construct the model the following notations and hypothesis are taken:

- The total population of humans $N(t)$ is divided into disjoint age classes.
- In each age class i the population of humans $N_i(t)$ is divided into two disjoint subpopulations: those who may become infected (Susceptible $S_i(t)$), and individuals who have been infected ($I_i(t)$).
- Susceptible vectors $SV(t)$: Number of susceptible vectors in the region.
- Infected vectors $IV(t)$: Number of infected vectors in the region.
- Newborns are represented by Λ, the inflow population (immigration or emigration) for each age group i is rs_i and ri_i for susceptible and infected populations respectively.
- The transfer rate between successive age classes c_i is assumed to be the mean length spent by an individual in age group G_i [8,17]. For the last age group G_6, the parameters cs_6 and ci_6 include information regarding life expectancy for the susceptible and infected individuals.
- The population flow rates regarding immigration, emigration, and deaths for each susceptible and infected age classes r_s and r_s are estimated by linear interpolation using the census demographic data. For the last age group G_6, immigration and emigration is included implicitly in the population outflow parameters cs_6 and ci_6.
- Death rates cs_6 and ci_6 for the susceptible and infected populations respectively, are only considered explicitly for the last age group G_6 (50+ years).
- The parameter cs_6 is assumed lower than ci_6 due to the fact that infected individuals have a lower life expectancy since 26% of infected individuals develop right bundle branch block, of which 7.5% die and a report of data between 1999 and 2007 in Brazil that found that Chagas' disease was mentioned in 53,930 (0.6%) of death certificates [32].

- A susceptible human from the population of age group $Si(t)$ transits to the infected subpopulation $I_i(t)$ following an effective contact with a infected vector (at rate β). The value of the transmission rate parameter β depends on the probability that a susceptible human is bitten by the vector.
- A mass incidence action is assumed for human and vector populations. However, it is worth stating that standard incidence models with constant total population (N(t)), are essentially mass action models [8,36].
- Vertical transmission is not assumed in the infected population, i.e., by transmission from mother to fetus.
- Homogeneous mixing is assumed, i.e., all humans of the susceptible subpopulation $S(t)$ have the same probability to become infected [8]. Thus, the transmission parameter β is assumed the same for all age groups.
- The birth rate (inflow population) of the vector is assumed equal to the death rate $\mu_v = d_v$ and the total vector population is normalized to one. Thus the total vector population remains constant [30].

The developed model is given by the following first order nonlinear system of ordinary differential equations:

$$S_1'(t) = \Lambda - c1S_1(t) - \beta S_1(t)VI(t), \tag{2}$$

$$S_2'(t) = c1S_1(t) - c2S_2(t) - \beta S_2(t)IV(t) + rs_2, \tag{3}$$

$$S_3'(t) = c2S_2(t) - c3S_3(t) - \beta S_3(t)IV(t) + rs_3, \tag{4}$$

$$S_4'(t) = c3S_3(t) - c4S_4(t) - \beta S_4(t)IV(t) + rs_4, \tag{5}$$

$$S_5'(t) = c4S_4(t) - c5S_5(t) - \beta S_5(t)IV(t) + rs_5, \tag{6}$$

$$S_6'(t) = c5S_5(t) - cs_6S_6(t) - \beta S_6(t)IV(t), \tag{7}$$

$$I_1'(t) = -c1I_1(t) + \beta S_1(t)VI(t), \tag{8}$$

$$I_2'(t) = c1I_1(t) - c2I_2(t) + \beta S_2(t)IV(t) + ri_2, \tag{9}$$

$$I_3'(t) = c2I_2(t) - c3I_3(t) + \beta S_3(t)IV(t) + ri_3, \tag{10}$$

$$I_4'(t) = c3I_3(t) - c4I_4(t) + \beta S_4(t)IV(t) + ri_4, \tag{11}$$

$$I_5'(t) = c4I_4(t) - c5I_5(t) + \beta S_5(t)IV(t) + ri_5, \tag{12}$$

$$I_6'(t) = c5I_5(t) - ci_6I_6(t) + \beta S_6(t)IV(t), \tag{13}$$

$$\begin{aligned} SV'(t) = \mu_v - kSV(t)(I_1(t) + I_2(t) + I_3(t) + I_4(t) \\ + I_5(t) + I_6(t)) - d_vSV(t), \end{aligned} \tag{14}$$

$$\begin{aligned} IV'(t) = kSV(t)(I_1(t) + I_2(t) + I_3(t) + I_4(t) + I_5(t) \\ + I_6(t)) - d_vIV(t), \end{aligned} \tag{15}$$

where the subscript $i = 1,2,...,6$ denotes different age groups. The parameter $k > 0$ is the transmission rate from infected human to the susceptible vector. Note that the main transitions between groups is due to aging and as in classical mathematical epidemiological models these transitions are proportional to the population and inversely proportional to the mean time spent on each class [8]. Moreover, mortality in the age groups below 50 years are included implicitly in the parameters rs_i and ri_i. However, the main contribution of deaths related to Chagas are taken into account in the parameter ci_6 related to the last age group G_6 (50+ years).

2.1. Equilibrium point for the disease free in the age-structured epidemiological mathematical model

The equilibrium point for the disease free (DFE), was computed from the first order nonlinear system of ordinary differential equations (2)−(15). Equating all the equations to zero and taking into account that $I_i^* = 0$and $IV^* = 0$ one gets,

$$S_1^* = \frac{\Lambda}{c1} \tag{16}$$

$$S_2^* = \frac{\Lambda + rs_2}{c2} \tag{17}$$

$$S_3^* = \frac{\Lambda + rs_2 + rs_3}{c3} \tag{18}$$

$$S_4^* = \frac{\Lambda + rs_2 + rs_3 + rs_4}{c4} \tag{19}$$

$$S_5^* = \frac{\Lambda + rs_2 + rs_3 + rs_4 + rs_5}{c5} \tag{20}$$

$$S_6^* = \frac{\Lambda + rs_2 + rs_3 + rs_4 + rs_5}{cs_6} \tag{21}$$

$$SV^* = \frac{\mu_v}{d_v} \tag{22}$$

2.2. Computation of R_0 for the age-structured epidemiological mathematical model

In order to compute the basic reproduction number R_0 we use the first order nonlinear system of ordinary differential equations (2)−(15). At first we write a new system just using the infected compartments $I_1'(t)$, $I_2'(t)$, $I_3'(t)$, $I_4'(t)$, $I_5'(t)$, $I_6'(t)$ and $IV'(t)$ in matrix form using the methodology proposed by Van den Driessche [49],

$$\dot{x}_I(t) = \mathscr{F}x_I(t) - \mathscr{V}x_I(t)$$

Thus, one gets,

$$\begin{bmatrix} \dot{I}_1 \\ \dot{I}_2 \\ \dot{I}_3 \\ \dot{I}_4 \\ \dot{I}_5 \\ \dot{I}_6 \\ IV \end{bmatrix} = \begin{bmatrix} 0 & 0 & 0 & 0 & 0 & 0 & \beta S_1 \\ 0 & 0 & 0 & 0 & 0 & 0 & \beta S_2 \\ 0 & 0 & 0 & 0 & 0 & 0 & \beta S_3 \\ 0 & 0 & 0 & 0 & 0 & 0 & \beta S_4 \\ 0 & 0 & 0 & 0 & 0 & 0 & \beta S_5 \\ 0 & 0 & 0 & 0 & 0 & 0 & \beta S_6 \\ kSV & kSV & kSV & kSV & kSV & kSV & 0 \end{bmatrix} \begin{bmatrix} I_1 \\ I_2 \\ I_3 \\ I_4 \\ I_5 \\ I_6 \\ IV \end{bmatrix} - \begin{bmatrix} c1 & 0 & 0 & 0 & 0 & 0 & 0 \\ -c1 & c2 & 0 & 0 & 0 & 0 & 0 \\ 0 & -c2 & c3 & 0 & 0 & 0 & 0 \\ 0 & 0 & -c3 & c4 & 0 & 0 & 0 \\ 0 & 0 & 0 & -c4 & c5 & 0 & 0 \\ 0 & 0 & 0 & 0 & -c5 & ci_6 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & d_v \end{bmatrix} \begin{bmatrix} I_1 \\ I_2 \\ I_3 \\ I_4 \\ I_5 \\ I_6 \\ IV \end{bmatrix} \tag{23}$$

Therefore, we can identify the matrices $\mathscr{F}$ and $\mathscr{V}$,

$$\mathscr{F} = \begin{bmatrix} 0 & 0 & 0 & 0 & 0 & 0 & \beta S_1 \\ 0 & 0 & 0 & 0 & 0 & 0 & \beta S_2 \\ 0 & 0 & 0 & 0 & 0 & 0 & \beta S_3 \\ 0 & 0 & 0 & 0 & 0 & 0 & \beta S_4 \\ 0 & 0 & 0 & 0 & 0 & 0 & \beta S_5 \\ 0 & 0 & 0 & 0 & 0 & 0 & \beta S_6 \\ kSV & kSV & kSV & kSV & kSV & kSV & 0 \end{bmatrix}$$

and

$$\mathscr{V} = \begin{bmatrix} c1 & 0 & 0 & 0 & 0 & 0 & 0 \\ -c1 & c2 & 0 & 0 & 0 & 0 & 0 \\ 0 & -c2 & c3 & 0 & 0 & 0 & 0 \\ 0 & 0 & -c3 & c4 & 0 & 0 & 0 \\ 0 & 0 & 0 & -c4 & c5 & 0 & 0 \\ 0 & 0 & 0 & 0 & -c5 & ci_6 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & d_v \end{bmatrix}$$

Therefore, computing the following derivatives,

$\frac{\partial \mathscr{F}_i}{\partial x_j}(0, DFE)$, and $\frac{\partial \mathscr{V}_i}{\partial x_j}(0, DFE)$

one gets the matrices F and V,

$$F = \begin{bmatrix} 0 & 0 & 0 & 0 & 0 & 0 & \beta S_1^* \\ 0 & 0 & 0 & 0 & 0 & 0 & \beta S_2^* \\ 0 & 0 & 0 & 0 & 0 & 0 & \beta S_3^* \\ 0 & 0 & 0 & 0 & 0 & 0 & \beta S_4^* \\ 0 & 0 & 0 & 0 & 0 & 0 & \beta S_5^* \\ 0 & 0 & 0 & 0 & 0 & 0 & \beta S_6^* \\ kSV^* & kSV^* & kSV^* & kSV^* & kSV^* & kSV^* & 0 \end{bmatrix} \tag{24}$$

$$V = \begin{bmatrix} c1 & 0 & 0 & 0 & 0 & 0 & 0 \\ -c1 & c2 & 0 & 0 & 0 & 0 & 0 \\ 0 & -c2 & c3 & 0 & 0 & 0 & 0 \\ 0 & 0 & -c3 & c4 & 0 & 0 & 0 \\ 0 & 0 & 0 & -c4 & c5 & 0 & 0 \\ 0 & 0 & 0 & 0 & -c5 & ci_6 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & d_v \end{bmatrix} \tag{25}$$

In order to simplify the computations, we rely on the reduced domain method of the matrix K, proposed by Diekmann et al [37]. For our particular model, one gets the matrix $K_S = RV^{-1}C$ of 2×2. This matrix, allow us to simplify the computation of the eigenvalues and the reproduction number R_0. At first, we express the matrix F as a matrix product CR, where these matrices are of order (7×2) and (2×7) respectively,

$$F = \begin{bmatrix} 0 & S_1^* \\ 0 & S_2^* \\ 0 & S_3^* \\ 0 & S_4^* \\ 0 & S_5^* \\ 0 & \beta S_6^* \\ kSV^* & 0 \end{bmatrix} \begin{bmatrix} 1 & 1 & 1 & 1 & 1 & 1 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 1 \end{bmatrix} \tag{26}$$

Then, we compute the matrix K_S, as $RV^{-1}C$,

$$K_S = \begin{bmatrix} 0 & \alpha_1 \beta S_1^* + \alpha_2 \beta S_2^* + \alpha_3 \beta S_3^* + \alpha_4 \beta S_4^* \\ & +\alpha_5 \beta S_5^* + \alpha_6 \beta S_6^* \\ k\dfrac{SV^*}{d_v} & 0 \end{bmatrix} \tag{27}$$

with,

$$\alpha_1 = \left(\frac{1}{c1} + \frac{1}{c2} + \frac{1}{c3} + \frac{1}{c4} + \frac{1}{c5} + \frac{1}{ci_6}\right)$$

$$\alpha_2 = \left(\frac{1}{c2} + \frac{1}{c3} + \frac{1}{c4} + \frac{1}{c5} + \frac{1}{ci_6}\right)$$

$$\alpha_3 = \left(\frac{1}{c3} + \frac{1}{c4} + \frac{1}{c5} + \frac{1}{ci_6}\right)$$

$$\alpha_4 = \left(\frac{1}{c4} + \frac{1}{c5} + \frac{1}{ci_6}\right)$$

$$\alpha_5 = \left(\frac{1}{c5} + \frac{1}{ci_6}\right)$$

$$\alpha_6 = \frac{1}{ci_6},$$

where α_i is the mean time that the individuals spent at the infectious stage for the respective age group G_i and the parameter ci_6 includes information regarding the life expectancy.

Computing the eigenvalues of the matrix K_S, one gets,

$$\lambda_1 = \left(\sqrt{k\beta \frac{SV^*}{d_v} \left(\alpha_1 S_1^* + \alpha_2 S_2^* + \alpha_3 S_3^* + \alpha_4 S_4^* + \alpha_5 S_5^* + \alpha_6 S_6^*\right)}, \lambda_2 = -\sqrt{k\beta \frac{SV^*}{d_v} \left(\alpha_1 S_1^* + \alpha_2 S_2^* + \alpha_3 S_3^* + \alpha_4 S_4^* + \alpha_5 S_5^* + \alpha_6 S_6^*\right)} \right)$$

The basic reproduction number R_0 is the dominant eigenvalue, and taking into account that at the disease free equilibrium point $SV^* = 1$, one gets,

$$R_0 = \sqrt{\frac{k\beta}{d_v} \left(\alpha_1 S_1^* + \alpha_2 S_2^* + \alpha_3 S_3^* + \alpha_4 S_4^* + \alpha_5 S_5^* + \alpha_6 S_6^*\right)} \tag{28}$$

Note that the basic reproduction number R_0 increases when the parameters related to the infected process β and k increase as was expected. Moreover, R_0 decreases if the death rate of the vector (mosquitoes) increases. Therefore, this fact can be useful for the control of the Chagas disease as has been done in Brazil.

2.3. Chagas disease data and fitting using the age-structured epidemiological mathematical model

In order to use the age-structured epidemiological model (2)−(15) to simulate the dynamics of Chagas disease in the Venezuelan population, it is necessary to set the parameter values of the model. However, some of the parameter values are not accurately known or are not the same for all regions. The parameter values were chosen based on available data. As mentioned above, the main goal is to construct a mathematical model that could explain qualitative behavior of the Chagas disease dynamics at the population level.

The vector responsible of the transmission of the protozoan parasite, *T. cruzi*, is the adult triatomine. Their life span greatly depends on species, and ranges from 50 days to > 300 days. For comparison, lifespan of females of *Trypanosoma brasiliensis* is about 90−120 days [38], whereas the lifespan of females of *Trypanosoma flavida* ranges from 285 days up to 486 days [3]. Thus, we assume a life time expectancy for the vector to be around 4 months. Therefore, we assume for the vector birth and death rates $\mu_v = 3$/y. Different approaches may be used for these rates such as exponential growth or seasonal functions.

The Chagas disease data have been collected using available cumulative data from the national CDCP archives [25] and include entomological evaluations carried out by house inspections in rural areas [25].

Human serological data of the rural population corresponding to a pioneer period from 1958−1968 accrued from ongoing surveys, serve as baseline data. Prevalence rates, expressed as percentages, were determined for patients testing positive for *T. cruzi* antibodies as numerator data divided by the total number of patients surveyed corresponding to each 10-year age group and confidence intervals were calculated for each age group as well as for the overall prevalence rate for that period [25]. This process was repeated in the same places where control interventions were carried out and the prevalence rates of existing accrued data were computed for the periods 1969−1979, 1958−1968, 1980−1998, and for a shorter period, which grouped the years 1990−1998. In addition, data are presented in 10-year age groups, as filled out by CDCP standard formats. In Table 1 we can see the seroprevalence of Chagas disease by age and time periods.

In order to adjust the age-structured epidemiological model (2)−(15) to simulate the dynamics of Chagas disease in the Venezuelan population to age group time-series data of Chagas seroprevalence only the parameters to be estimated by a fitting process to real data are the Chagas transmissibility β from infected vector to susceptible human and the parameter k that represents the Chagas transmissibility from infected human to susceptible vector. The parameter β depends on the number of bites per unit of time and the transmission probability per bite [3].

At first we apply the proposed model for the time interval 1961−1971, where we use the only available data of the period 1958−1968 as the Chagas prevalence for 1961 and the data from 1969−1979 as the prevalence for 1971. The second time interval studied is the 1981−1991, where we use the available data from 1980−1989 as the Chagas prevalence for year 1981 and data from 1990−1998 as the prevalence for 1991.

In regard to initial conditions for the time interval 1961−1971, we take Chagas prevalence data from the period 1958−1968, and taking into account the population data of Venezuela using the 1961 census for $S_i(t_0)$,$I_i(t_0)$,$SV(t_0)$ and $IV(t_0)$. The data presented in Table 1 are related to particular samples from surveys where the individuals were not taken proportional to the real demographic data. Thus, we are able to compute the

Table 1. Data of seroprevalence (%) of Chagas by age groups from the national Chagas Disease Control Programme archives [25].

Age (y)/period	1958−1968	1969−1979	1980−1989	1990−1998
0−9	20.5	3.9	1.1	0.5
10−19	28.4	9.9	2.4	1.8
20−29	48.9	29.6	12.4	5.9
30−39	62.4	36.1	26.6	16.1
40−49	66.0	49.2	37.5	28.3
50+	65.0	41.1	48.0	43.0

total susceptible and infected population for each age group taking into account real demographic population data from Venezuela in 1961 (Table 2). As final conditions for the simulation period 1961−1971 we rely on the Chagas prevalence data of the period 1969−1979 and real demographic population data from Venezuela in 1971. Note that the simulation interval period 1961−1971 has been chosen according to the only available census demographic data in order to have a good approximation of the age groups population.

In a similar way, initial conditions for 1981−1991 are taken using Chagas prevalence data from 1980−1989 and taking into account real demographic population data of Venezuela using the 1981 census for $S_i(t_0)$,$I_i(t_0)$,$SV(t_0)$ and $IV(t_0)$. As in the previous simulation period the total susceptible and infected population for each age group is computed taking into account real demographic population data from Venezuela in 1981 (Table 2). By contrast, the final condition for the simulation period 1981−1991 for the Chagas prevalence data is taken from 1990−1998 and real demographic population data from Venezuela of 1990. It is important to note that all these real data may include sample errors and are not exactly the detailed data needed it for an accurate demographic model based on differential equations since immigration, emigration and deaths for each age group are not available. Again, here the simulation interval period 1981−1991 has been chosen according to the available census demographic data for each age group. It is important to take relative Chagas seroprevalence in age groups in the real world into account [39].

In order to estimate the population flow rates regarding immigration, emigration and deaths for the susceptible and infected age classes rs_i and ri_i we rely on linear interpolations between initial and final conditions for demographic data of all age group classes for 1961−1971 and 1981−1991. For instance, in Table 2 we can see the positive difference between the population in age group 10−19 years in 1971 and age group 0−9 years in 1961. Note that without immigration or deaths this difference needs to be zero. Thus, based on the census population data we can infer an inflow population between 1961 and 1971. Therefore, we approximate linearly the rate rs_2 as this difference divided by 10 in order to obtain yearly parameter values. A similar process is applied for the different parameters using the census population data. Note that monthly parameter values can also be obtained by simply dividing by 120.

Based on the census population data, we obtain that the largest and positive parameter values are the rs_i for the younger groups only at the first simulation interval period 1961−1971 For the second simulation period 1981−1991 the values of the rs_i are smaller and for the older age groups some are negative reflecting emigration or/and deaths. Thus, for the particular cases considered here we avoid to use parameter values for the ri_i, i.e. we consider that the inflow population is susceptible and the few emigration or deaths corresponds to the susceptible population for age groups G_1, G_2, G_3, G_4, and G_5. For the older age group G_6 (50+ years) the outflow population is considered in both susceptible and infected groups. Further, the outflow infected population rate (deaths and emigration) ci_6 is higher than cs_6 due to the lower life expectancy of the infected individuals [33,34]. We estimate these parameters values considering life expectancy for the Venezuelan population for 1971 and 1990 [40].

Table 2. Census population data of Venezuela for 1961, 1971, 1981, and 1990.

Age (y)	1961	1971	1981	1990
0−9	2,537,416	3,389,570	2,537,416	3,389,570
10−19	1,581,517	3,110,893	1,581,517	3,110,893
20−29	1,169,293	1,647,598	1,169,293	1,647,598
30−39	907,869	1,120,472	907,869	1,120,472
40−49	612,388	839,632	612,388	839,632
50+	715,516	1,040,692	715,516	1,040,692

The fitting process to adjust the age-structured epidemiological model (2)−(15) to the 10-year simulation periods to estimate β and the parameter k is done by the least squares method and using the Nelder−Mead algorithm [41,42]. It is important to note that other parameters may also need to be estimated since values for these parameters are, in some cases, rough approximations. If more parameters are estimated, the number of degrees of freedom of the model is increased and the fitting may improve but computation time will increase. In order to compute the best fitting, we carried out computations with Mathematica (Wolfram, Champaign, IL, USA) and we implemented the function

$$\begin{aligned} &\mathbb{F}:\mathbb{R}^2\to\mathbb{R}\\ &(\beta,k)\to\mathbb{F}(\beta,k)\end{aligned}$$

where β and k are variables such that:

(1) For a given (β, k), solve numerically using the package (*NDSolve[]*) the system of differential equations (2)−(15) and obtain a solution $\widehat{Y}_i(t)=(\widehat{S}_i,\widehat{I}_i,\widehat{SV}$ and $\widehat{IV})$, which is an approximation of the real data solution $Y(t)$.
(2) Set $t_0 = 0$ (fitting process starts at year 1961) and for $t = 10$ (Venezuela), corresponding to 1971 where Venezuelan demographic data are available, evaluate the computed numerical solution for subpopulations $I_i(t)$; i.e. $\widehat{I}_1(10),\widehat{I}_2(10),\widehat{I}_3(10),\ldots,\widehat{I}_6(10)$.
(3) Compute the root mean square (RMS) of the difference between $\widehat{I}_1(10),\widehat{I}_2(10),\widehat{I}_3(10),\ldots,\widehat{I}_6(10)$ (Venezuela) and Chagas disease data modified from Table 1 taking into account the demographic data. This function $\mathbb{F}$ returns the RMS for the Venezuela data, given by: $\text{RMS}=\sqrt{\sum_{i=1}^{6}(\widehat{I}_i(10)-I_i(10))^2/6}$.
(4) Find a global minimum for the RMS using the Nelder−Mead algorithm.

Function $\mathbb{F}$ takes values in $\mathbb{R}^2$ (β and k) and returns a positive real number, the RMS that measures the closeness of the scaled infectious population, provided by the model, to time-series data. Hence, we can try to minimize this function using the Nelder−Mead algorithm, which does not involve the computation of any derivative or gradient, which is impossible to know for function $\mathbb{F}$. In order to find a global minimum, we take several initial different points for Nelder−Mead algorithm in the domain $[0,1]\times[0,1]\subset\mathbb{R}^2$. We stored all the minima obtained and, among them, the values of β and k that minimize the function $\mathbb{F}$. In other words the Nelder−Mead algorithm return the best value of β and k which gives the minimum of the RMS. Note that the same procedure is used for the simulation period 1981−1991 but different parameter values are obtained for β and k.

3. Results

In this section, we simulate the dynamics of the population with Chagas disease from Venezuela using the age-structured epidemiological model (2)−(15). At first, the numerical simulation of the model are applied with real data from the country of Venezuela for 1961−1971. The second numerical simulation of the age-structured model is for 1981−1991, taking into account real Chagas disease and demographic data for this period. Numerical computer simulations are presented to investigate the suitability of the age-structured model to explain the real data regarding prevalence of Chagas disease in the age-groups. In addition, a numerical simulation reducing the transmission coefficients as a result of health policies was run to show that the model can be used by health institutions for the evaluation of prevention and control strategies against the Chagas disease in several regions.

For the first period the numerical result of the model is compared with the real data for 1958−1968 and 1969−1979. For the second period, the model is implemented with more recently real data from 1980−1989 and 1990−1998. The last scenario is a hypothetical one, where we assume that a health program is implemented to eliminate the main vector in order to curtail the vector transmission [5]. All the parameters and simulations used in this section are in years scale.

In order to perform the numerical simulations we assume that Venezuelan population life expectancies for the first period 1961−1971 were 64 years and 59 years for the susceptible and infected populations, respectively [40]. We assume as initial condition for the human population

Table 3. Initial conditions for 1961−1971.

Age (y)	Susceptible	Infected
0−9	$S_1(0)=(2537416-I_1(0))$	$I_1(0)=(2537416*0.205)$
10−19	$S_2(0)=(1581517-I_1(0))$	$I_2(0)=(1581517*0.284)$
20−29	$S_3(0)=(1169293-I_3(0))$	$I_3(0)=(1169293*0.489)$
30−39	$S_4(0)=(907869-I_4(0))$	$I_4(0)=(907869*0.624)$
40−49	$S_5(0)=(612388-I_5(0))$	$I_5(0)=(612388*0.66)$
50+	$S_6(0)=(715516-I_6(0))$	$I_6(0)=(715516*0.65)$

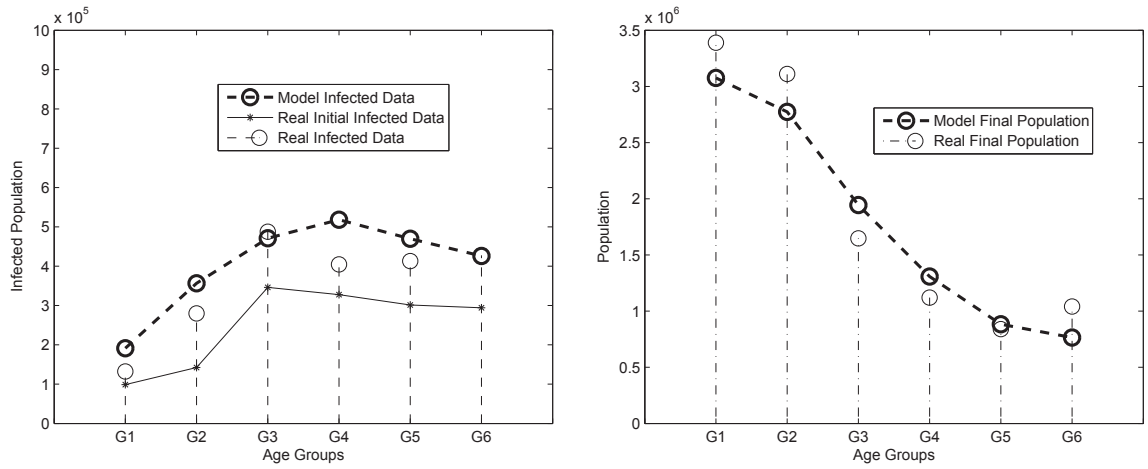

Figure 1. Result of the numerical simulation of the dynamics of the population with Chagas disease from Venezuela using the age-structured epidemiological model (2)−(15). The results of the model related to seroprevalence of Chagas are compared with the real data for 1961−1971 for the different age groups.

the values presented in Table 3 and for the vector population the proportions $SV(0) = 0.99$ and $IV(0) = 0.01$. The parameter values of the r_i are computed using the change of the population between the censuses of 1961 and 1971. The parameter values for β and k given by the model fitting to real data are small, in the order of 10^{-10}. However, as t can be seen in the Figures 1 and 2 the age-structured epidemiological model (2)−(15) explains or reproduce the Chagas disease prevalence data for the different age groups relatively well.

Figure 1 is a numerical simulation for the dynamics of the population with Chagas disease from Venezuela using the age-structured epidemiological model (2)−(15) for the period 1961−1971. As can be observed on the left of Figure 1, the model adjusts the seroprevalence of Chagas disease relatively well for the different age groups despite the underlying assumptions of the constructed model and lack of well known data. For this particular time period a normalized RMS deviation or error equal to 0.2407 was obtained despite the above mentioned factors. In addition, the profile of the Chagas disease prevalence by age is similar to the profile of other regions presented in other studies [43−45]. It can be observed in Figure 2 that the maximum prevalence in other regions also occurs at middle age (around age 40 years).

Additionally, the right of Figure 1 shows that the dynamics of Venezuelan population by age groups for 1961−1971. As can be observed, the underlying age-structured population model (2)−(15) forecasts the real data population profile well despite the assumptions and roughness of the data. Finally, Figure 3 shows the dynamics for the total susceptible and infected human Venezuelan population. This behavior for the Chagas disease at the population level can be observed for real data in Table 1.

The second scenario considered here is for the time interval 1981−1991, which is implemented using more

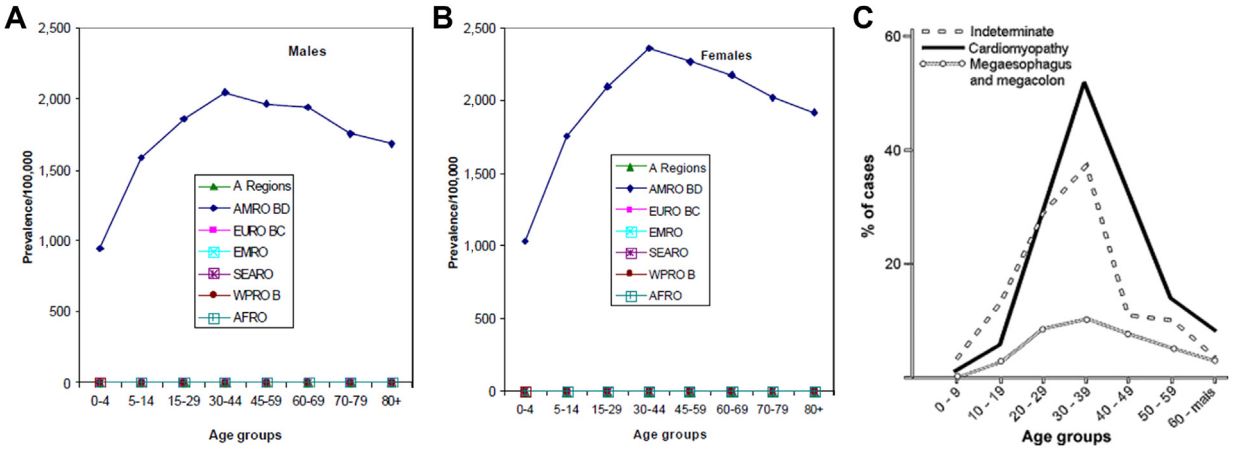

Figure 2. (A), (B) Chagas disease prevalence rates, age group and sex, broad regions, 2000 [45]. (C) Distribution of 510 cases of chronic Chagas disease from different states in Brazil according to clinical forms and age groups [43,46].

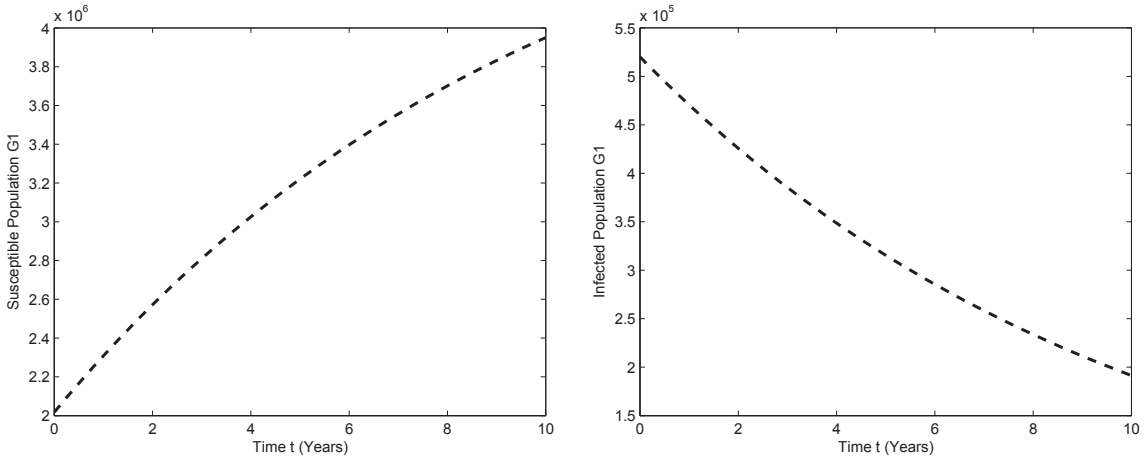

Figure 3. Numerical simulation of the dynamics of the population with Chagas disease from Venezuela using the age-structured epidemiological model (2)−(15) for the susceptible $S_1(t)$ and infected $I_1(t)$ subpopulations.

recent real data from 1980−1989 and 1990−1998. In this case, the Chagas prevalence data and the demographic dynamics are different but the same proposed model can be used with only changes on the parameters values Λ, β, k, cs_6, ci_6, and r_i. Venezuelan population life expectancies have increased and are assumed to be 70 years and 64 years for the susceptible and infected populations, respectively [40]. Thus, these values imply that the parameter values are $cs_6 = 1/20$ and $ci_6 = 1/14$. In this case, the parameter values of r_i are computed using the change of the population between the censuses of 1981 and 1990. We assume as initial condition for this period the values presented in Table 4 and for the vector population the proportions $SV(0) = 0.99$ and $IV(0) = 0.01$.

In the second period considered here, the main change regarding the Chagas disease is that the numerical value of the Chagas transmission β, from vector to human has been increased to 1.7510^{-2} in order to fit the Chagas prevalence data for 1991. Figure 4 shows a numerical simulation for the dynamics of the population with Chagas disease from Venezuela for 1981−1991. As can be observed on the left, the model adjusts relatively well the seroprevalence of Chagas disease for the different age groups despite the underlying assumptions of the constructed model and not well known data. The right of Figure 4 shows the dynamics of Venezuelan population by age groups for the period 1981−1991. The underlying age-structured population model (2)−(15) forecasts the real population data profile relatively well, despite the assumptions and roughness of the data used. This forecast may be improved using a similar age-structured population model but with more complex real data. For instance, we may use parameters that depend on time in order to have a more detailed underlying structured population model. However, as mentioned above, this is out of the scope of this paper.

For the last scenario, we assume that a health program is implemented to eliminate the main vector in order to curtail the vector transmission [5]. For this scenario, the death rate of the vector d_v is increased. Thus, the vector population is no longer constant as it is assumed for the other previous scenarios, instead the vector population is decreasing due to the elimination program. Figure 5 shows a numerical simulation for the dynamics of the population with Chagas disease from Venezuela for 1990−2020. The model predicts low prevalences for the younger age groups and a decrease of the total infected population in accordance with other studies [25,47]. This health program is effective since the prevalences are lower in comparison to the results without the program. Finally, Figure 6 shows that the total population is higher when the program to eliminate the vector is implemented due to the increase of the life expectancy of the human population.

Table 4. Initial conditions for 1981−1991.

Age (y)	Susceptible	Infected
0−9	$S_1(0) = (4004686 - I_1(0))$	$I_1(0) = (4004686 * 0.011)$
10−19	$S_2(0) = (3438926 - I_2(0))$	$I_2(0) = (3438926 * 0.024)$
20−29	$S_3(0) = (2686001 - I_3(0))$	$I_3(0) = (2686001 * 0.124)$
30−39	$S_4(0) = (1714530 - I_4(0))$	$I_4(0) = (1714530 * 0.266)$
40−49	$S_5(0) = (11142088 - I_5(0))$	$I_5(0) = (1114208 * 0.375)$
50+	$S_6(0) = (1558384 - I_6(0))$	$I_6(0) = (1558384 * 0.48)$

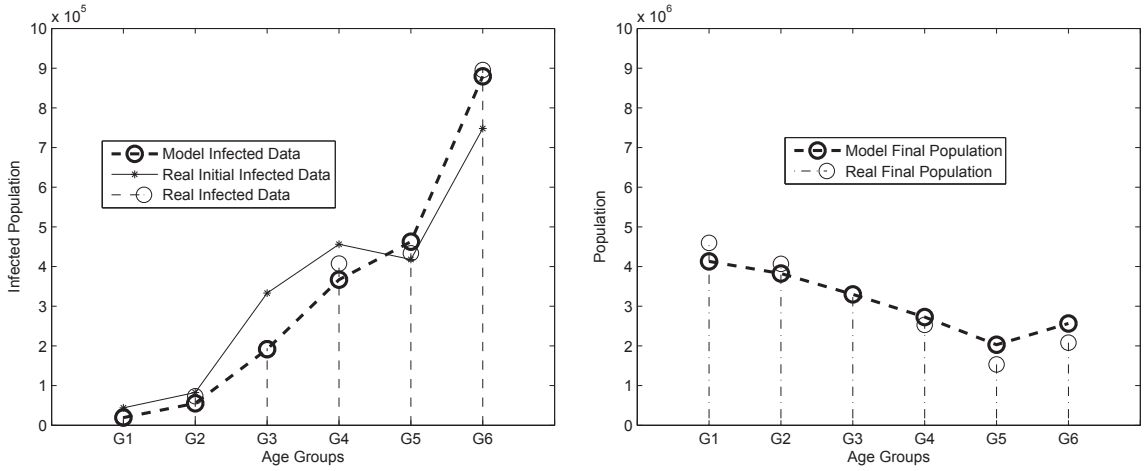

Figure 4. Result of the numerical simulation of the dynamics of the population with Chagas disease from Venezuela using the age-structured epidemiological model (2)−(15). The results of the model related to seroprevalence of Chagas are compared with the real data for 1981−1991 for the different age groups.

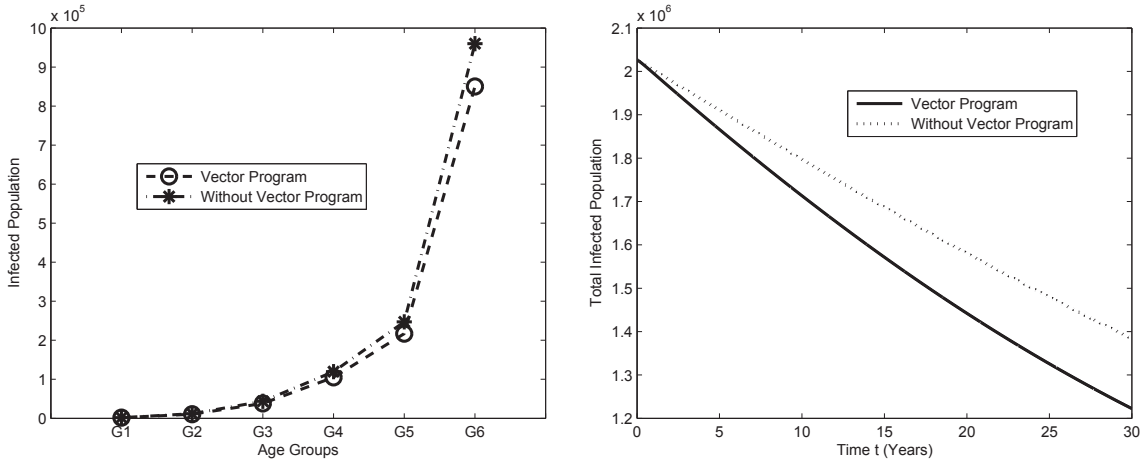

Figure 5. Result of the numerical simulations of the dynamics of the population with Chagas disease from Venezuela when a program to eliminate the main vector is implemented ($d_v = 3$). The results are for the period 1990−2020 for different age groups.

4. Discussion

In this paper we constructed an age-structured epidemiological model for Chagas disease for the human population and including the vector population. This model includes interactions between human and vector populations that transmit Chagas disease. The human population is divided into age groups in order to obtain more detailed information in the exploration of the dynamics of the disease at population level. We applied this proposed model to available data from the country of Venezuela for two periods 1961−1971 and 1981−1991, taking into account real demographic data for these periods. Demographic data were taken from the censuses 1961, 1971, 1981, and 1990 in order to match with the available Chagas disease prevalence data from the Venezuelan population. To the best of our knowledge more recent data regarding Chagas prevalence by age groups are not available and we choose old and newer data in order to test the age-structured model. It was shown that the model is suitable to understand the dynamics of Chagas disease at population level for the age groups and may be used in different regions or periods with different parameter values.

The age-structured epidemiological type model presented is based on a system of nonlinear differential equations. Numerical computer simulations show the suitability of the age-structured model since the model adjusts or reproduces the seroprevalence of Chagas disease relatively well for the different age groups despite the underlying assumptions of the constructed model. In order to avoid an initial complex model, some rough approximations were made regarding vector and human populations. The numerical simulations of the dynamics of the different age groups regarding Chagas disease shows that the dynamics of the susceptible and infected populations behave similar to the prevalence of Chagas disease real data since the susceptible population increases and the infected decreases. These dynamics are in good agreement with the worldwide tendency for

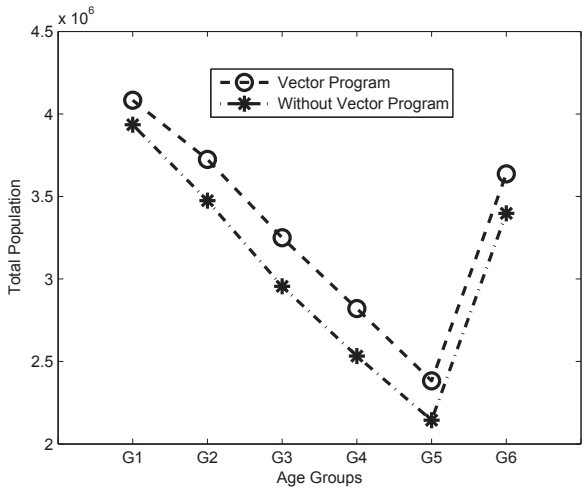

Figure 6. Result of the numerical simulation of the dynamics of the population with Chagas disease from Venezuela when a program to eliminate the main vector is implemented ($d_v = 3$). The results are for the period 1990−2020 for the different age groups.

the last 50 years [6,48]. The model was tested with real data from Venezuela using two periods. The first period considered here is from 1961 to 1971 using Chagas data collected in the intervals 1958−1968 and 1969−1979. The second period considered was 1980−1990 using Chagas data of intervals 1980−1989 and 1990−1998. In both periods the age-structured model approximate the real data well regarding Chagas prevalence in the population of Venezuela. Finally, we simulated the period 1990−2020 by assuming a health program to reduce the main vector in order to curtail the vector transmission. The model in this case predicts low prevalences for the younger age groups and a decrease of the total infected population in agreement with other studies. Furthermore, the effectiveness of the program was tested positively since the prevalences are lower in comparison to the results without the program. It is important to note that in the real world a program to reduce the vector may be expensive since the insects that carry *T. cruzi* to humans in some Andean countries are not strictly domiciliated [48].

The main advantage of the age-structured approach proposed here is that Chagas disease can be studied taking into account the specific demographics of the population, which can be a main factor in the eradication of this disease since the *Trypanosoma cruzi* infection is lifelong. The usage of structured population models can make substantial contributions to public health, particularly for infections where clinical outcomes vary over age. The model allows generation of a far more realistic heterogeneous fade-out pattern than a homogeneous population model. In addition, the model is an appropriate framework for both demographic and epidemiological transitions where parameters may be based on data ranging from the biological course of infection, basic patterns of human demography, and specific characteristics of population growth.

The model developed here can be improved using more details such as age structure of the vectors or taking into account the stage of the Chagas disease on the individuals. In addition, more detailed demographics factors can be added to increase the complexity and the accuracy of the model. Work along these lines is in progress. Finally, it is important to mention the significance of the model from a health point of view since it could help health institutions to design the optimal strategies to control the Chagas disease in the human populations and in the vector population, which are the main factors in the spread of the disease. Additionally, in a spraying program, the best location may be inferred based on the demographic profile of the susceptible population.

Conflicts of interest

All authors have no conflicts of interest to declare.

Acknowledgments

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