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Modelling American Trypanosomiasis in an Endemic Zone: Application to the Initial Spread of Household Infection in the Argentine Chaco

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Impacts

- Based on official data and field, laboratory and clinical information, we built a mathematical model that provides better understanding of the dynamics of *Trypanosoma cruzi* infection, coupling the interactions among humans, triatomines and dogs.
- The model was applied in a rural household of the endemic zone of Argentine Chaco to study the initial spread of infection.
- The introduction of an infected dog (as the only source of infection) determined fast dissemination of the infection in the triatomine population, whereas the initial number of infected humans had no significant impact on the expected times of appearance of the first infected triatomine or dog.

Keywords:
Trypanosoma cruzi infection; triatomines; dogs; mathematical model; household infection

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Summary

The complex dynamics of *Trypanosoma cruzi* infection (Chagas disease) involves different actors and multiple transmission routes. Based on the information currently available, here, we propose a new and more comprehensive model to better understand the dynamics of the infection. This mathematical deterministic model was formulated considering: (i) the three clinical forms in humans: acute, chronic indeterminate and chronic with determinate pathology, (ii) the three main modes of transmission in the human population: vector-borne, congenital and transfusional, (iii) populations of triatomines and dogs as the main domestic reservoirs of *T. cruzi* and (iv) open populations. A numerical simulation was also performed to estimate the initial spread of the infection in a typical rural household in the endemic zone of the Argentine Gran Chaco. We also analysed the incidence of infected individuals corresponding to each of the three species (humans/triatomines/dogs) over times until the appearance of the first case in the other species. The model predicts that, in the absence of control measures, a few infected individuals are sufficient for the establishment and dispersion of the infection in all the inhabitants of the household. The model proposed and the results obtained allow describing the consequences of the presence of infected individuals in any of the three species considered in the dynamics and the output of the infection.

Introduction

American trypanosomiasis or Chagas disease is a parasitosis caused by the protozoan *Trypanosoma cruzi* (Kinetoplastida, Trypanosomatidae), with difficult diagnosis, management and treatment (WHO, 2013). This disease affects 7–8 million people, determining 14 000 annual deaths and 64–98 million people under risk of infection

over 21 Latin American countries (WHO, 2013) and is becoming an emerging health problem in non-endemic areas because of human movements (OMS, 2008; WHO, 2009, 2013). The transmission routes with epidemiological importance are (i) the contact with triatomine insects (Hemiptera Reduviidae), (ii) the congenital way and (iii) the transfusion of infected blood (WHO, 2002, 2013).

The Gran Chaco, which is a hyperendemic region for Chagas and other neglected diseases, is a 1.3-million km^2 ecoregion including parts of Argentina, Paraguay and Bolivia, with socio-economic features such as (i) high poverty levels, (ii) low population density, (iii) rural populations structures in small sparse villages connected only by worn (and sometimes impassable) pathways and (iv) poor health services. Vector control programs only reach transitory reduction in the level of infection and transmission, with a lack of sustainable surveillance system for sparse and remote rural populations. This region shows high levels of *T. cruzi* maternal prevalence, with high numbers of congenital cases, and some cases of transfusional transmission (Gürtler et al., 2007; Garcia-Bournissen et al., 2009).

Chagas disease develops three clinical forms: acute, chronic indeterminate and chronic with determinate pathology (WHO, 2002; Storino, 2010). The acute form, which lasts 2 months on average, is characterized by high parasitemia and thus a high risk of transmission. Because few infected individuals develop symptoms, almost all of them evolve towards the chronic indeterminate form. In that form, which may last 20–30 years (or even the entire life), although individuals present a lower level of parasitemia, they may infect triatomines or other humans. The 'clinical silence' of this form is an important feature to understand the epidemiology of this disease, even in areas where triatomines are absent. About a third of the chronic indeterminate individuals evolve towards the chronic with determinate pathology form with the most common manifestations of the disease: chronic myocarditis, megaesophagus or megacolon and encephalitic lesions that may have fatal consequences. Infection rates of this form are at their lowest levels because of the age and the sanitary state of the infected individuals.

Cure may be reached by means of anti-trypanosomal drugs, only in the acute form and at the beginning of the chronic indeterminate form (Mady et al., 2008; Freilij et al., 2010). In contrast, in the chronic with determinate pathology form, the evidence of effects in the prevention of new lesions is still controversial (Marin-Neto et al., 2008; Perez-Molina et al., 2009; Muñoz et al., 2011).

Dogs constitute the main domestic reservoir of *T. cruzi* transmission in Latin American endemic areas, determining a serious risk of domestic transmission (Gürtler et al., 1990; Castañera, 1999; Crisante et al., 2006; Estrada-Franco et al., 2006). They acquire the infection mostly by vector-borne and congenital transmissions (Gürtler et al., 1990; Castañera, 1999).

Mathematical models help analyse the dynamics of diseases such as American trypanosomiasis. In addition, they help gain insights into the consequences of model assumptions and enable the researcher to predict the putative results of introducing specific changes at the beginning of simulations and to interpret the spread of the disease under different current scenarios in endemic zones.

Several efforts, focused on the human population, have been made to model Chagas disease (Busenberg and Vargas, 1991; Velasco-Hernandez, 1991, 1994; Canals and Cattan, 1992; Inaba and Sekine, 2004; Das and Mukherjee, 2006; Martorano Raimundo et al., 2010). Each model has brought new advances in the understanding of the dynamics of the disease, although with varying degrees of realism and limited in the estimation of the actual parameters of the processes involved. Some authors considered constant populations over time (Velasco-Hernandez, 1991; Inaba and Sekine, 2004; Das and Mukherjee, 2006). Canals and Cattan (1992) proposed a model in which they added a host animal population, but did not specify the species. Other investigators admitted that models with constant population numbers and without other alternative hosts can be help describe the general trends of the disease but that they are only a very coarse approximation of what actually happens in the field (Velasco-Hernandez, 1991; Inaba and Sekine, 2004). Busenberg and Vargas (1991) included the three main transmission routes (vector-borne, congenital and transfusional) in a SIS model, that is, the human population was divided into susceptible and infected. Martorano Raimundo et al. (2010) reduced their model to congenital Chagas disease because they claimed that this was the only route by which the disease could be acquired in Brazil at that time, and thus classified individuals (women and children) simply as infected (treated or not) and non-infected. The classification of infected humans as acute or chronic (without differentiating between the two chronic forms) has been used in several studies (Velasco-Hernandez, 1991, 1994; Canals and Cattan, 1992). Inaba and Sekine (2004) stratified the population of infected humans by the age of infection.

Considering that mathematical models can only make accurate predictions if all the relevant factors are taken into account, here, we propose a new and more comprehensive model, which includes:

1. Estimation of parameters and a detailed explanation of how these parameters were obtained, gathering the most

relevant information produced in the last years as well as official epidemiological data.
2. The inclusion of the three clinical forms of the disease, which allowed us to show the importance of the chronic indeterminate form of the disease on the dynamics of transmission.
3. The inclusion of the three most important transmission routes of *T. cruzi* in rural endemic areas: (i) vector-borne, (ii) congenital and (iii) transfusional, with differentiated rates according to the form of the disease.
4. The analysis of the consequences of variation in the initial condition (not presented by other models), that is, in the number of infected individuals.

The objectives of this work were to develop, apply and validate this mathematical model of Chagas disease focused on the human population and thus obtain a higher degree of approximation to the real sanitary situation.

Materials and Methods

The model

The human population is partitioned into four compartments: susceptible humans (H_S), humans transiting the acute form (H_A), the chronic indeterminate form (H_I) and the chronic with determinate pathology form (H_P), being $H = H_S + H_A + H_I + H_P$. As usual, the letters for the forms indicate not only the form, but also the size of the subpopulation in that form. For brevity, subpopulation sizes are denoted omitting time. Hence, for example, $H_S(t)$ is denoted H_S. Triatomine and dog populations are partitioned in susceptible and infected (V_S and V_I, for triatomines and D_S and D_I for dogs) with $V = V_S + V_I$ and $D = D_S + D_I$.

We made the following assumptions:

1. All the rates are per capita per unit time (day), except for migrations, which are crude rates.
2. There are immigrations (i) and emigrations (e) of all individuals except for H_A (because of its short time period), denoted m_{HSi}, m_{HIi}, m_{HPi}, m_{VSi}, m_{VIi}, m_{DSi}, m_{DIi}, m_{HSe}, m_{HIe}, m_{HPe}, m_{VSe}, m_{VIe}, m_{DSe}, m_{DIe}
3. *T. cruzi* infection does not affect triatomines in their ecological, physiological or ethological processes and only susceptible triatomines are born.
4. H_A women are considered to give birth to no children because of their short period of time. Birth rates of children from H_S, H_I and H_P mothers are denoted b_{HS}, b_{HI} and b_{HP}, respectively, and q_H is the probability of congenital transmission (assumed the same for all the forms), being $p_H = 1-q_H$. Birth rates of susceptible and infected triatomines and susceptible and infected dogs are denoted b_{VS}, b_{VI}, b_{DS} and b_{DI}, respectively, and q_D is the probability of congenital transmission in dogs ($p_D = 1 - q_D$).
5. We considered i_D as the preference factor of a triatomine to feed on a human with respect to a dog. So, the overall number of hosts available for triatomines (in human terms) is $H + i_D D$. We considered g the mean number of dejections per triatomine per unit time and h the proportion of infected dejections that give rise to infection. Then, an infected triatomine makes ghV_I infectious dejections of which a fraction $\frac{H_S(t)}{H(t)+i_D D}$ is on susceptible humans. That is, the number of new infections of humans per unit time by vector transmission is given by $gh\frac{H_S(t)}{H(t)+i_D D}$. So, $k = gh$ is the transmission rate of *T. cruzi* onto susceptible humans from infected triatomines per unit time.
6. e_A, e_I and e_P denote the mean number of blood transfusions per unit time from H_A, H_I and H_P humans, respectively, and f_A, f_I and f_P the corresponding proportions of infected blood transfusions that give rise to infection in a susceptible human. Then $a_A = (e_A)(f_A)$, $a_I = (e_I)(f_I)$ and $a_P = (e_P)(f_P)$ are the transmission rates by transfusion from H_A, H_I and H_P humans per unit time, respectively. Hence, the term expressing the input of humans infected by blood transfusion per unit time is given by $[a_A H_A(t) + a_I H_I(t) + a_P H_P(t)]\frac{H_S(t)}{H(t)}$.
7. Only H_A and H_I individuals may become cured with rates c_A and c_I, respectively.
8. The transition rates from H_A to H_I, and from H_I to H_P, are denoted r_{AI} and r_{IP}, respectively.
9. The mortality rates for H_S, H_A, H_I, H_P, V_S, V_I, D_S and D_I individuals are denoted d_{HS}, d_{HA}, d_{HI}, d_{HP}, d_{VS}, d_{VI}, d_{DS} and d_{DI}, respectively.
10. o_A, o_I, o_P, o_D are the probabilities for a V_S, to become infected when feeding onto an H_A, H_I, H_P or a D_I, respectively. Hence, $s_A = (g)(o_A)$, $s_I = (g)(o_I)$, $s_P = (g)(o_P)$ and $s_D = (g)(o_D)$ are the transmission rates of *T. cruzi* onto V_S from the corresponding infected individuals per unit time. Therefore, the input of V_I per unit time into the system is given by $\left[\frac{s_A H_A(t)+s_I H_I(t)+s_P H_P(t)+s_D i_D D_I(t)}{H(t)+i_D D(t)}\right] \cdot V_S(t)$.
11. Similarly, o'_D denotes the probability of a D_S to become infected by a triatomine which feeds on it. Therefore, the input of D_I by vectors, per unit time, is expressed as $n_D\, i_D \frac{V_I(t)}{H(t)+i_D D(t)} D_S$, where $n_D = (g)(o'_D)$ stands for the transmission rate of *T. cruzi* to the dogs by vectors.

The system of ordinary differential equations (ODEs), which expresses the temporal changes in the different

compartments caused by infection in the three populations studied, according to the above assumptions, is as follows:

$$\begin{aligned}
\frac{dH_S(t)}{dt} &= (m_{HSi} - m_{HSe}) + \left[b_{HS} - d_{HS} - \frac{a_A H_A(t) + a_I H_I(t) + a_P H_P(t)}{H(t)} - k\frac{V_I(t)}{H(t) + i_D D(t)}\right] H_S(t) \\
&\quad + c_A H_A(t) + (b_{HI} p_H + c_I) H_I(t) + b_{HP} p_H H_P(t) \\
\frac{dH_A(t)}{dt} &= \left[\frac{a_A H_A(t) + a_I H_I(t) + a_P H_P(t)}{H(t)} + k\frac{V_I(t)}{H(t) + i_D D(t)}\right] H_S(t) \\
&\quad - (c_A + d_{HA} + r_{AI}) H_A(t) + b_{HI} q_H H_I(t) + b_{HP} q_H H_P(t) \\
\frac{dH_I(t)}{dt} &= (m_{HIi} - m_{HIe}) + r_{AI} H_A(t) - (c_I + d_{HI} + r_{IP}) H_I(t) \\
\frac{dH_P(t)}{dt} &= (m_{HPi} - m_{HPe}) + r_{IP} H_I(t) - d_{HP} H_P(t) \\
\frac{dV_S(t)}{dt} &= (m_{VSi} - m_{VSe}) + \left[b_{VS} - d_{VS} - \frac{s_A H_A(t) + s_I H_I(t) + s_P H_P(t) + s_D i_D D_I}{H(t) + i_D D(t)}\right] V_S(t) + b_{VI} V_I(t) \\
\frac{dV_I(t)}{dt} &= (m_{VIi} - m_{VIe}) + \left[\frac{s_A H_A(t) + s_I H_I(t) + s_P H_P(t) + s_D i_D D_I}{H(t) + i_D D(t)}\right] V_S(t) - d_{VI} V_I(t) \\
\frac{dD_S(t)}{dt} &= (m_{DSi} - m_{DSe}) + \left[b_{DS} - d_{DS} - n_D i_D \frac{V_I(t)}{H(t) + i_D D(t)}\right] D_S(t) + b_{DI} p_D D_I(t) \\
\frac{dD_I(t)}{dt} &= (m_{DIi} - m_{DIe}) + n_D i_D \frac{V_I(t)}{H(t) + i_D D(t)} D_S(t) + (b_{DI} q_D - d_{DI}) D_I(t)
\end{aligned}$$

Application of the model

We applied the model to represent the dynamics of the disease in a typical rural household, belonging to the endemic rural region of the Argentine Gran Chaco including Chaco, Formosa and Santiago del Estero provinces. A typical household has two continuous bedrooms and is built with mud-brick, adobe or mud-stick walls, thatched roofs and floors of beaten earth (Gürtler et al., 1992; Cecere et al., 2004). In this region, the main vector insect of *T. cruzi* is *Triatoma infestans* (Gürtler et al., 1990; Castañera, 1999). We assumed that no control measures of triatomines had been taken and that inter-human transmission may occur. We also assumed that infected humans in this area were transiting the H_I form in 90% of cases and the H_P form in the remaining 10%.

On the other hand, in agreement with previous studies of the feeding profile of triatomines (Gürtler et al., 1997), we considered that the preference for dogs is twice that for humans. This number can be interpreted then as a conversion factor of dogs to human equivalent: a dog, as a host for a triatomine, is equivalent to two humans (that is $i_D = 2$).

Parameter estimation

Human population

Migrations: Mean daily rates of immigration (0.000015) and emigration (0.000019) were obtained from census data (Censo Nacional de Población, Hogares y Viviendas, 2001). Studies in rural communities of the Gran Chaco of Argentina in the absence of vector control have shown high levels of seroprevalence in humans in a range between 17% and 77% (Sosa-Estani et al., 2009; Moretti et al., 2010). We considered that 40% of immigrants are infected with *T. cruzi* and that there are five people in each household. Thus:

$$\begin{aligned}
m_{HSi} &= (0.000015)(5)(0.60) = 0.000045, \\
m_{HIi} &= (0.000015)(5)(0.40)(0.90) = 0.000027 \\
m_{HPi} &= (0.000015)(5)(0.40)(0.10) = 0.000003, \\
m_{HSe} &= (0.000019)(5)(0.60) = 0.000057 \\
m_{HIe} &= (0.000019)(5)(0.40)(0.90) = 0.000034, \\
m_{HPe} &= (0.000019)(5)(0.40)(0.10) = 0.000004
\end{aligned}$$

Birth rates: Official data in the locations considered (Ministerio de Salud de la Nación, 2009) gave $b_{HS} = 0.000058$. Congenital infection in the area was diagnosed in 6–17% of the newborn from infected mothers (Barbieri et al., 2007; Sosa-Estani et al., 2009). We took $q_H = 0.10$ (so $p_H = 0.90$). Mortality related to the congenital infection does not exceed 2% in Argentina (Moya, 1994). If the birth rate of infected individuals is equal to 98% of that corresponding to susceptible women, then $b_{HI} = (0.000058)(0.98) = 0.000057$. Due to the mother's age, we suppose that the birth rate corresponding to H_P women is half of that corresponding to H_I ones. So, $b_{HP} = 0.000029$.

Cure rates: Although the acute form is acknowledged in only 5% of infected individuals (WHO, 2002), treatments with available drugs have an effectiveness of 70–100% (Freilij et al., 2010; Storino, 2010). We assumed that 5% of H_A are detected and that they have a cure rate of 80%, that is, $c_A = 0.000667$. Children at the beginning of the chronic indeterminate form under treatment have shown 63% of negativization in 3–4 years (Sosa-Estani et al., 1998). In asymptomatic adults (H_I), negativization reached 37% in 16 years (Fabbro, 2007). We considered detection of only 5% with an annual possibility of cure during this form of 13%, that is, $c_I = 0.000018$.

Vector-borne transmission: Some studies have calculated that the time elapsed between two successive feeds of *T. infestans* is 6 days (Rabinovich, 1972), whereas others have estimated a range of 2–71 days, depending on the developmental state and temperature (Catala, 1991). The mean life span of first-instar nymphs was estimated in 216–421 days (Perlowagora-Szumlewicz, 1969; Rabinovich, 1972). Here, we considered that triatomines survive for 289 days, with a 6-day lag between feeds and that they bite 48 times through their lives, that is, $g = 0.166090$. Rabinovich et al. (1990) estimated that between 1000 and 2500 potentially infective contacts would be needed to infect a human, that is, that h varies between 0.0004 and 0.001, whereas Cohen and Gürtler (2001) assigned $h = 0.0008$. In the present work, we considered $h = 0.0009$, thus $k = (0.166090)(0.0009) = 0.000150$.

Transmission by blood transfusion: The mean number of annual transfusions per capita in Argentina has been estimated in 0.0233 (Schmunis, 1999). Therefore, $e_I = 0.000063$, $e_A = 0.000011$ and $e_P = 0.000006$ (we assumed that only 10% of the donors were H_P). The estimated risk of transmission per contaminated blood reservoir ranges from 12% to 20% (WHO, 2002). The acute state was given the highest percentage because of its high level of parasitemia: $a_A = (0.000011)(0.20) = 0.000002$, $a_I = (0.000063)(0.12) = 0.000008$ and $a_P = (0.000006)(0.129 = 0.000001$.

Transitions among disease forms: The percentage of H_A cases passing inadvertently to the H_I form has been estimated in 95% (WHO, 2002). So, $r_{AI} = 0.015833$. Annually, 2–5% of H_I evolves towards H_P (Storino, 2010). Considering the central value, $r_{IP} = (0.035/365) = 0.000096$.

Mortality: The death rate in the region considered was 5.9‰ (Ministerio de Salud de la Nación, 2009), so $d_{HS} = (0.0059/365) = 0.000016$. Mortality for the acute form varies between 2% and 3% of infected individuals (WHO, 2002). Adding up natural mortality (i.e. that corresponding to H_S), $d_{HA} = (0.025/60) + 0.000016 = 0.000433$. Mortality for the chronic indeterminate form has values similar to those of the general population (WHO, 2002). So, $d_{HI} = 0.000016$. As for the chronic with determinate pathology form, annual death rates reach 10% (Manzullo and Dairraidou, 1991); then, adding up natural mortality, $d_{HP} = (0.10 + 0.0059)/365 = 0.000290$.

Triatomine population

Household entry and exit movements: *Triatoma infestans* individuals may have active or passive carriage. Adult *T. infestans* usually disperse by flight (Ward and Baker, 1982; Schweigmann et al., 1988; Schofield et al., 1992) or by walk (Gürtler et al., 1996a) and play an important role in the local spread of *T. cruzi* (Cecere et al., 2004; Abrahan et al., 2011). Domestic animals and humans carry *T. infestans* in their clothes, feathers or hair, contributing to re-infestation of human domiciles. Such passive dispersal by humans is believed to have contributed greatly to the rapid geographical spread of *T. infestans* (Abrahan et al., 2011). So, dispersion plays an important role in the re-colonization process given that, from a few peridomestic residual foci, an entire village may be re-infected (Cecere et al., 2004). We took $m_{VSi} = 0.2$ from a previous study (Rabinovich and Rosell, 1976), assuming that infected bugs enter the household more than the susceptible ones due to the peridomestic conditions (Cecere et al., 2004); so, we estimated that $m_{Vii} = 0.22$. Emigration rates from the household are around 0.10–0.25 bugs/day (Himschoot, 1993). We considered $m_{VSe} = m_{Vie} = 0.21$.

Fecundity: Average fecundity of *T. infestans* fluctuates from 10 to 650 eggs, under rearing conditions (laboratories and poultry) and temperature (Perlowagora-Szumlewicz, 1969; Gorla and Schofield, 1985). Survival probabilities from egg to first-instar nymphs are 0.169–0.177 (Gorla and Schofield, 1989; Cecere et al., 2003). We considered that the birth rate for triatomines is slightly higher than mortality $b_{VS} = b_{VI} = b_V = 0.0125$.

Infectivity: The probability for a triatomine to become infected in a single feed has been estimated in about 0.0032 in a child, 0.0010 in an adult and 0.232 in a dog (Gürtler et al., 1996b). As $g = 0.16609$ (see Vectorial Transmission), $o_A = 0.0032$, $o_I = 0.0010$, $o_P = 0.0010$ and $o_D = 0.2320$, then $s_A = 0.000531$, $s_I = 0.000166$, $s_P = 0.000166$ and $s_D = 0.038533$.

Mortality: Daily mortality rates for each form, from egg to adult, were estimated as 0.08889, 0.03164, 0.01400, 0.03570, 0.02700, 0.00337 and 0.0046 (Castañera et al.,

2003) and the corresponding mean times as 20, 31, 32, 17, 11, 49 and 149 days (Rabinovich, 1972). So, we estimated the daily mortality rate as

$$d_V = d_{VS} = d_{VI} = 1 - \left[(1-0.03164)^{31}(1-0.014)^{32}(1-0.0357)^{17}(1-0.027)^{11}(1-0.00337)^{49}(1-0.0046)^{149}\right]^{1/289} = 0.011078$$

Dog population

Household entry and exit movements: The seroprevalence in dogs, before any intervention in triatomine control, has been determined to be 82.5–100% (Gürtler, 1987; Gürtler et al., 1990). We considered that 90% of dogs are infected with *T. cruzi* and that a dog enters the household every 5 years. Therefore, $m_{DSi} = \frac{0.10}{(5)(365)} = 0.000055$ and $m_{DIi} = \frac{0.90}{(5)(365)} = 0.000493$. Here, we estimated that a dog exits the household every 4.5 years, so, $m_{DSe} = \frac{0.10}{(4.5)(365)} = 0.000061$ and $m_{DIe} = \frac{0.90}{(4.5)(365)} = 0.000548$.

Birth rates: The instantaneous growth rate has been estimated as $r = (0.016/\text{bimester}) = (0.000089/\text{day})$ (Castañera, 1999) and the average dog age as 3 years (Gürtler et al., 1990; Castañera, 1999). Therefore, $b_{DS} = r + d_{DS} = 0.000089 + \frac{1}{(3)(365)} = 0.001002$.

It has been observed that 10% of seropositive dogs are born to seropositive mothers (Castañera et al., 1998). Due to lack of information, we considered that the infection in mothers does not affect birth rates. So, $b_{DI} = 0.001002$ and $p_D = 0.90$.

Infectivity: The probability for a susceptible dog to become infected from an infected triatomine bite was estimated in 0.01 (Castañera, 1999), implying the need for about 100 potentially infectious contacts for the canine to acquire the infection. We incorporated this value in the estimation of n_D. Therefore, $n_D = (0.16609)(0.01) = 0.001661$.

Mortality: As dogs in the region are 3 years old on average (Gürtler et al., 1990; Castañera, 1999), $d_{DS} = \frac{1}{(3)(365)} = 0.000913$. Conservatively, we considered $d_{DI} = d_{DS} = 0.000913$. Table 1 summarizes the parameter estimation.

Sensitivity analysis

A sensitivity analysis was performed to explore the effects of varying all the parameters in the model results. Parameters were varied from values reported from the references and, in cases in that we had only one number we changed them 30% up and down from this base value (Table 1). In some cases, changes were made simultaneously in a group of parameters related to the same process. We compared the responses given by the model at different parameter values in the number of individuals after 3, 6 and 10 years of simulations. In most cases in which changes were detected, these occurred in the number of triatomines (both susceptible and infected) and some cases, in the number of infected humans. As the number of humans in the household was very limited, graphics were performed considering the changes in the number of infected bugs caused by the changes in parameter values.

Results

Numerical resolution of the system of ODEs

We used the Fehlberg fourth–fifth order Runge–Kutta method (Forsythe et al., 1977) to obtain approximate solutions of the ODE system. We represented the dynamics of the disease in a rural household at the endemic region by starting with five humans, three dogs and 30 triatomines. Two of these initial dogs are infected with *T. cruzi*: in this simulation, they are the only source of infection. This is a rather common situation in most of the infected households (Rabinovich et al., 1990; Gürtler et al., 1996b; Castañera, 1999).

Figure 1 shows the dynamics of the infection in the human population. The total number of humans does not vary with time in 10 years of simulation due to the fact that human inputs, either by immigration or by birth, are offset by the removal either by emigration or by mortality. There is a rapid decrease in the number of susceptible humans, reaching a value close to zero in only 7 years from the beginning of the simulation. In other words, in the absence of members infected with *T. cruzi* at the beginning of the simulation, every human inhabitant thereof (including new ones) will become infected in about 7 years, showing that the number of humans in the chronic indeterminate form describes a curve almost symmetrical with that corresponding to H_S, with respect to an imaginary axis passing through the cut-off of both curves. The graphs of the two curves intersect at 1260 days (3.5 years) of the onset, when almost half of the inhabitants of the household belong to each of these categories of disease. The first H_P individual is expected to appear a little beyond 3600 days (10 years) (continuing the simulation it is expected that this will

Table 1. Estimations of the parameters, information sources used for their calculations and explored range in sensitivity analysis (the unit time is the day)

Parameter	Information source	Estimations	Explored range
m_{HSi}	Censo Nacional de Población, Hogares y Viviendas (2001), Sosa-Estani et al. (2009), Moretti et al. (2010)	0.000045	0.000017–0.000062
m_{HSe}	Censo Nacional de Población, Hogares y Viviendas (2001), Sosa-Estani et al. (2009), Moretti et al. (2010)	0.000057	0.000022–0.000079
m_{HIi}	Censo Nacional de Población, Hogares y Viviendas (2001), Sosa-Estani et al. (2009), Moretti et al. (2010)	0.000027	0.000011–0.000052
m_{HIe}	Censo Nacional de Población, Hogares y Viviendas (2001), Sosa-Estani et al. (2009), Moretti et al. (2010)	0.000034	0.000015–0.000066
m_{HPi}	Censo Nacional de Población, Hogares y Viviendas (2001), Sosa-Estani et al. (2009), Moretti et al. (2010)	0.000003	0.000001–0.000006
m_{HPe}	Censo Nacional de Población, Hogares y Viviendas (2001), Sosa-Estani et al. (2009), Moretti et al. (2010)	0.000004	0.000002–0.000007
b_{HS}	Ministerio de Salud de la Nación (2009)	0.000058	0.000041–0.000075
q_H	Barbieri et al. (2007), Sosa-Estani et al. (2009)	0.10	0.06–0.17
b_{HI}	Moya (1994), Ministerio de Salud de la Nación (2009)	0.000057	0.000040–0.000074
b_{HP}	Moya (1994), Ministerio de Salud de la Nación (2009)	0.000029	0.000020–0.000038
c_A	WHO (2002), Freilij et al. (2010), Storino (2010)	0.000667	0.000467–0.000867
c_I	Sosa-Estani et al. (1998), Fabbro (2007)	0.000018	0.000003–0.000025
k	Perlowagora-Szumlewicz (1969), Rabinovich (1972), Rabinovich et al. (1990), Catala (1991), Cohen and Gürtler (2001)	0.000150	0.000066–0.000166
a_A	Schmunis (1999), WHO (2002)	0.000002	0.000001–0.000003
a_I	Schmunis (1999), WHO (2002)	0.000008	0.000006–0.000010
a_P	Schmunis (1999), WHO (2002)	0.000001	0.000001–0.000002
d_{HS}	Ministerio de Salud de la Nación (2009)	0.000016	0.000011–0.000021
r_{AI}	WHO (2002)	0.015833	0.011083–0.020583
d_{HA}	WHO (2002), Ministerio de Salud de la Nación (2009)	0.000433	0.000303–0.000563
r_{IP}	Storino (2010)	0.000096	0.000055–0.000137
d_{HI}	WHO (2002), Ministerio de Salud de la Nación (2009)	0.000016	0.000011– 0.000021
d_{HP}	Manzullo and Dairraidou (1991); Ministerio de Salud de la Nación (2009)	0.000290	0.000203–0.000377
b_{VS}	Perlowagora-Szumlewicz (1969), Gorla and Schofield (1989), Cecere et al. (2003)	0.012500	0.008750–0.016250
b_{VI}	Perlowagora-Szumlewicz (1969), Gorla and Schofield (1989), Cecere et al. (2003)	0.012500	0.008750–0.016250
s_A	Perlowagora-Szumlewicz (1969), Rabinovich (1972), Catala (1991), Gürtler et al. (1996b)	0.000531	0.000372–0.000690
s_I	Perlowagora-Szumlewicz (1969), Rabinovich (1972), Catala (1991), Gürtler et al. (1996b)	0.000166	0.000116–0.000216
s_P	Perlowagora-Szumlewicz (1969), Rabinovich (1972), Catala (1991), Gürtler et al. (1996b)	0.000166	0.000116–0.000216
s_D	Perlowagora-Szumlewicz (1969), Rabinovich (1972), Catala (1991), Gürtler et al. (1996b)	0.038533	0.026973–0.050093
m_{VSi}	Rabinovich and Rosell (1976)	0.20	0.14–0.26
m_{VSe}	Himschoot (1993)	0.21	0.147–0.273
m_{VIi}	Rabinovich and Rosell (1976), Cecere et al. (2004)	0.22	0.154–0.286
m_{VIe}	Himschoot (1993)	0.21	0.147–0.273
d_{VS}	Rabinovich (1972), Castañera et al. (2003)	0.011078	0.007755–0.014401
d_{VI}	Rabinovich (1972), Castañera et al. (2003)	0.011078	0.007755–0.014401
m_{DSi}	Gürtler et al. (1990)	0.000055	0–0.000086
b_{DS}	Gürtler et al. (1990), Castañera (1999)	0,001002	0.000701–0.001303
b_{DI}	Gürtler et al. (1990), Castañera (1999)	0.001002	0.000701–0.001303
q_D	Castañera et al. (1998)	0.10	0.07–0.13
n_D	Perlowagora-Szumlewicz (1969), Rabinovich (1972), Catala (1991), Castañera (1999)	0.001661	0.001163–0.002159
m_{DSe}	Gürtler et al. (1990)	0.000061	0–0.000107
d_{DS}	Gürtler et al. (1990), Castañera (1999)	0.000913	0.000639–0.001187
i_D	Gürtler et al. (1997)	2	
m_{DIi}	Gürtler et al. (1990)	0.000493	0.000345–0.000641
m_{DIe}	Gürtler et al. (1990)	0.000548	0.000384–0.000712
d_{DI}	Gürtler et al. (1990), Castañera (1999)	0.000913	0.000639–0.001187

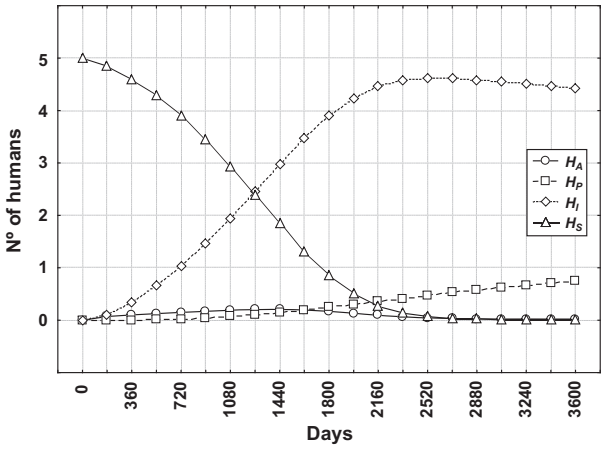

Fig. 1. Human disease dynamics in a rural household of the Argentine Gran Chaco region.

happen in 5400 days, i.e. 15 years). This explains the incipient decline in the number of H_I individuals entering the last form of infection.

For the sake of brevity, the corresponding plots for triatomines and dogs are not shown. The population of triatomines, both susceptible and infected with *T. cruzi*, presents an exponential growth. At first, the speed of the increase is slow, but after 5 years, it is more pronounced, especially the percentage of infected triatomines, which varies from 56% in 6 months to 65% in 10 years (V_I being equal to 3254).

The number of dogs in the household tends to increase from 3 to 4, being all of them infected.

Sensitivity analysis

In all cases, we found, in the range considered, that the responses in the variable values (number of individuals inside the eight compartments studied) were linear.

If changes are made in each individual parameter of the human population, the system responds with exactly the same numbers of individuals. Moreover, the same numbers are observed for the eight state variables when (i) the parameters of congenital and transfusional transmission are decreased to the minimum values (lower values proposed in the literature or a decrease of 30% in their values) and (ii) the cure rates are considered at the maximum values (the largest value given by the literature or an increase of 30% in that value) simultaneously. The only subtle difference is that in making these changes simultaneously, the first human infected appears 5 years later (in the model with the estimated parameters this happens at 708 days and in the model with modified parameters at 713 days).

The increase in the parameter of the input of susceptible triatomines to the house (m_{VSi}) increases the number of bugs and the number of infected people. A decrease of 20% in this value (0.16 instead of the original value of 0.20) generates fewer infected humans in each time considered (decreasing in one individual the corresponding value in the base of 2, 4 and 5 infected people at 3, 6 and 10 years) and even a 93% decrease in the number of total triatomines after 10 years. Figure 2a shows the variations in the number of infected triatomines (V_I) at 3 years of simulations in response to% changes in m_{VSi} from the base value.

In contrast, simultaneously increasing the number of triatomines leaving the house (m_{VSe} and m_{VIe}) decreases the number of infected individuals in the three species studied. With a 10% increase, at 3 years, would be obtained 22% of the number of triatomines that would be generated according to the estimated parameters (Fig. 2b) and only one infected human (with the base values, it would be two), while at 6 years, only would get 6% of the bugs that would be generated with the base values and two infected humans (with the base values, it would be four).

If the value of m_{VIi} is decreased by 20% (from 0.22 to 0.176), the number of triatomines decreases with time; at 3 years, it would be lower than the initial number (Fig. 2c), generating only two infected humans after 10 years.

Also, substantial changes in the values of the system variables are generated by changes of the birth rate of triatomines ($b_{VS} = b_{VI}$). A decrease of 10% (from 0.0125 to 0.01125) generates a quarter of triatomines with respect to the base values at 3 years and fewer infected humans (after 10 years, this would generate three infected humans). In contrast, an increase of 10% after 3 years quadruplicates the number of triatomines (even V_I), generating four infected humans (two, with the base values) (Fig. 2d).

Increases in the mortality rate of triatomines ($d_{VS} = d_{VI}$) drastically reduce the number of bugs and therefore the domiciliary infection. An increase of 10% decreases in one-third the number of triatomines and also decreases in 1 the number of infected humans at 3 years. In contrast, for the same time, a 10% of decrease in the mortality rate of triatomines triplicates the number of bugs (including V_I) and increases in 1 the number of infected humans (Fig. 2e).

Simultaneous changes in the rates of transmission of *T. cruzi* infection from humans to triatomines (s_A, s_I and s_P) do not change the numbers of individuals in the system. However, increasing the transmission rate from dogs to triatomines (s_D) increases the number of V_I; a decrease of 30% causes a decrease of only 13% in the number of V_I at the different times studied. The total number of triatomines and humans infected in each time studied are not altered with changes in s_D. Figure 2f shows the variations in the number of infected triatomines (V_I) at 3 years of simulations in response to % changes in s_D from the base value.

Regarding dogs, individuals changes in m_{DSi} and m_{DIi} do not generate changes in the results, except for a slight

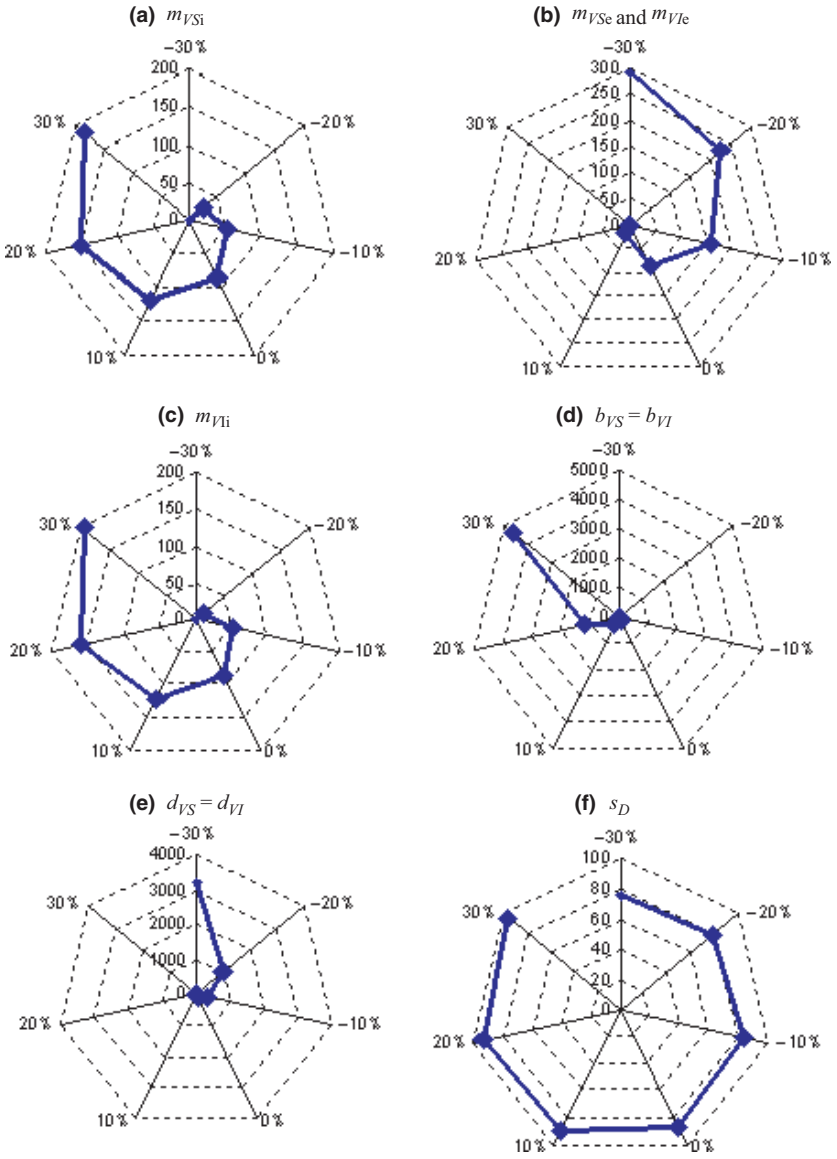

Fig. 2. Variations in the number of infected triatomines (V_I) at 3 years of simulations in response to changes in parameter values.

long-term tendency to increase V_I and decrease V_S. If $m_{DSi} = 0$ (Gürtler et al., 1990), 1791 susceptible and 3225 infected triatomines would be obtained but if this parameter increases by 80% (Gürtler et al., 1990), these values are 1741 and 3262, respectively, being the values obtained with the base numbers 1762 and 3274, respectively. In contrast, changes in m_{DSe} and m_{DIe} generate a slight tendency to decrease the number of V_I: a decrease to 0 in m_{DSe} generates 3282 V_I and an 80% increase produces 3229 infected triatomines after 10 years. These changes do not alter the number of infected humans in the house, in comparison with the base values.

Increasing the birth rate of dogs ($b_{DS} = b_{DI}$), the number of V_I increases, decreasing the number of V_S, although the total number of triatomines remains constant at each time studied. A 30% increase in these parameters generates 3589 triatomines infected after 10 years. In contrast, an increase in the dog mortality rate ($d_{DS} = d_{DI}$) increases the number of V_S and decreases the number of V_I (a 30% decrease generates 3570 V_I and a 30% increase generates 2610 V_I after 10 years), but the number of infected humans is not altered.

Changes in the rate of transmission of the infection from the triatomine to the dog (n_D) or by congenital transmission in dogs (q_D) do not altered the system numbers.

Influence of the initial number of infected humans on the expected time until the first infection appears in dogs and triatomines

As the number of infected humans increases (being the only source of initial infection in the household), the mean times until the appearance of the first infected triatomine and the first infected dog decrease slightly (Table 2). When the infected dogs are present in the house, the expected time to until the first infected triatomine is about 4 months. It may be seen that even H_I (with low levels of parasitemia) are able to infect triatomines. When triatomines are present, the expected time for the first dog to become infected is 1 year. Besides, the time until the appearance of the first infected triatomine is affected by the feeding preference pattern.

Influence of the initial number of infected dogs on the expected time until the first infection appears in humans and triatomines

The introduction of an infected dog in the household determines a fast dissemination of the infection in triatomines, even when the dog is the only source of initial infection (Table 3). Starting with 30 triatomines, the time until the appearance of the first infected triatomine varies between 2 and 6 days, depending on the prevalence of dogs. We found that with an equal number of dogs in the household, the expected times until the appearance of the first infected human and the first infected triatomine decrease with the increase in the initial value of D_I. In contrast, if the initial number of dogs increases, the human takes longer to be infected, probably because the bugs prefer to feed on dogs. When the source of infection is a dog, the expected times until the first triatomine becomes infected are much lower than when that source is a human.

Influence of the initial number of infected triatomines on the expected time until the first infection appears in humans and dogs

The initial number of infected triatomines had a strong impact on the time until the appearance of the first infected human or dog (Table 4). Besides, the first dog is infected 4–13 times faster than the first human.

Table 2. Effect of the initial number of infected humans on the expected time of appearance of the first infection in dogs and triatomines

Initial number of humans		Expected time until the appearance of the first infected triatomine (days)	Expected time until the appearance of the first infected dog (days)
Infected	Susceptible		
1	4	120	390
2	3	115	386
3	2	111	382
4	1	107	378

Table 3. Effect of the initial number of infected dogs on the expected time until the appearance of the first infection in humans and triatomines

Initial number of dogs		Expected time until the appearance of the first infected human (days)	Expected time until the appearance of the first infected triatomine (days)
Infected	Susceptible		
1	0	631	4
1	1	675	4
2	0	643	2
1	2	737	5
2	1	708	3
3	0	691	2
1	3	800	6
2	2	772	3
3	1	756	2
4	0	745	2

Table 4. Effect of the initial number of infected triatomines on the expected time until the appearance of infection in humans and dogs

Initial number of triatomines		Expected time until the appearance of the first infected human (days)	Expected time until the appearance of the first infected dog (days)
Infected	Susceptible		
9	21	769	179
24	6	717	80
30	30	473	55
50	50	332	31
80	80	240	19

Comparison with field data

Some field data collected from households in localities in a rural region of the Santiago del Estero province (27°12′30″ S, 63°02′30″W) in 1982 and 1984 (Gürtler, 1987) were compared with our model predictions. In these locations, no official campaign of triatomine control had been made. Households where 100 or more triatomines were collected (4 h/person of capture) with the help of a house irritant were selected. This approach reflects the situation in which triatomine and host populations are in a hypothetical endemic state. Table 5 summarizes the epidemiological information in comparison with the predictions of our model.

According to Table 5, the numerical resolution of the ODE system provides values similar to those of the observations obtained from the field work in similar situations, that is, without control of triatomines.

Our results are consistent with that found in several previous works: (i) in rural villages of Northwest Argentina,

Table 5. Epidemiological data in households in Santiago del Estero province and results predicted by the model

Mean number (standard deviation) of individuals per household and percentage of *Trypanosoma cruzi* infection in Santiago del Estero province (RC1 and RC2) versus results of the model simulation (RS1 and RS2*)

	Humans		*Triatoma infestans*		Dogs	
	Number (SD)	% infection (SD)	Number (SD)	% infection (SD)	Number (SD)	% infection (SD)
RS1	5	50	165	63	3	100
RC1	7 (2.4)	60 (19.4)	164 (42.1)	64 (15.7)	3 (1.4)	100 (0)
RS2	5	68	253	63	3	100
RC2	6 (3.0)	66 (24.4)	222 (64.3)	60 (25.8)	3 (1.3)	100 (0)

SD, standard deviation.

*RS1 corresponds to results after 1200 days of simulation and RS2 corresponds to results after 1500 days of simulation.

the overall proportion of domiciliary *T. infestans* infected with *T. cruzi* was found to be about 49–82% (Rebozolan and Terzano, 1958; Gürtler et al., 1998); (ii) in another work, the median number of dogs per dog-owning household was found to be 3 and the change in overall population size not being significantly different from 0 over the 4 years of research (Castañera et al., 1998); (iii) in several surveys, seropositive dogs living in infested rural settings of the Argentine Chaco had a higher rate of detectable parasitemia: 82–100% (Wisnivesky-Colli, 1982; Gürtler et al., 2007); (iv) new human cases of *T. cruzi* occurred 2–3 years after the initial detection of domestic re-infestation in the house, and cases among dogs preceded the first child case (Gürtler et al., 2007).

Discussion

This work presents the first model considering the three clinical forms of Chagas disease and the interaction with dogs and triatomines. Processes influencing the dynamics of the infection were considered including more realistic transitions between forms. Changes in the number of individuals in each form of the human population are due to births, deaths, migration, acquisition of infection and healing, differentiated by form. In the triatomine and canine populations, changes in the number of susceptible and infected individuals are due to births, deaths, migration and the acquisition of infection (in triatomines by the bite of infected humans in different forms of the disease and infected dogs, and in canines by the contact with infected triatomines or congenitally). This involved 40 different processes and the estimation of 50 parameters. This effort included the most relevant information gathered in field, laboratory and clinical works and the most recent official data.

We also analysed the consequences of changing the initial conditions of infection: (i) we found a mild effect of the variation in the initial number of infected humans on the expected time of appearance of the first infection in dogs and triatomines and confirmed triatomine preference for dogs (Table 2), (ii) we found a meaningful contribution of the initial number of infected dogs on the expected time of appearance of the first infection in humans and triatomines (Table 3), (iii) we found that the effect of the initial number of infected triatomines on the expected time of appearance of infection in humans and dogs (Table 4) confirms that population sizes and infection rates of triatomines are positively associated with the number of infected dogs per household (Gürtler et al., 1996b, 1997, 1998).

We corroborated the importance of taking into account the three disease forms in humans and found that the chronic indeterminate form is the one that most influences the dynamics of the infection. This was tested in a household of an endemic rural area. In the absence of infected humans at the beginning of the simulation, half of the people acquire this form of infection in 3.5 years, H_I keeps growing and then begins to decrease due to the evolution of H_I individuals to H_P ones. The particular features of the chronic indeterminate form, that is, its long duration and its lack of easy-to-detect symptoms, contribute more to the dispersion of the infection than any other form, as shown by the numerical resolution of the ODE system. Human and dog population sizes remain constant but triatomines grow exponentially, partly because no carrying capacity was allowed in the model. Nevertheless, after 10 years, 5016 triatomines mounted in the house, 3254 of them infected, which is a plausible number in the endemic area without vector control (Gürtler et al., 1997; Castañera, 1999). The great influence of dogs in the dispersion of the infection is stressed because dogs become infected faster than humans, especially because of the low expected times to the appearance of the first infected triatomine when an infected dog is introduced. A single infected dog in the house (being the only source of infection of *T. cruzi*) generated the first infected triatomine in less than a week. This reinforces the consideration that the dog is an effective sentinel of the vectorial transmission of *T. cruzi* in endemic rural areas (Gürtler et al., 1990; Castañera et al., 1998).

One of the limiting factors of the model proposed is the consideration of the parameters constant time-independent magnitudes. It is for this reason that the simulation ranges over only 10 years.

The model responses to perturbations in its parameters allowed us to increase our understanding of the model behaviour.

The model suggests that if measures taken are only to reduce transfusion and congenital transmissions and simultaneously increase the cure rates, the number of infected individuals will not be altered in any of the three species (humans, triatomines and dogs). Because infection by *T. cruzi* is a parasitic infection, there is no vaccine to generate immunity in humans and current drugs do not create resistance. Therefore, if a person is cured and the house conditions remain unchanged, he/she would become infected again mainly by the vectorial route.

The model is sensitive to changes in parameters that express the input and output of triatomines in and out of the house. We confirmed the dominant role of immigration in the domestic infestation by *T. cruzi*. A key source of this domestic reinfestation is the peridomestic triatomine population (Cecere et al., 2004; Abrahan et al., 2011).

The quantitative change observed in the number of infected individuals before changes in fertility and mortality of triatomines suggests that a key control measure is to prevent eggs from hatching (both in the house and in peridomestic structures) and increase their mortality by bugs control methods. We conclude that it is essential that the house and the peridomestic areas do not provide favourable conditions for domiciliation of triatomines and that the availability of refuges and cracks in ceilings and walls of the house should be avoided by plastering them in a complete way. The same treatment should be applied in peridomestic sites, restricting the structures that can be colonized by triatomines (Cecere et al., 2004; Gürtler et al., 2007).

The contact of triatomines with dogs must be avoided. Dogs or other highly infectious vertebrates must be kept outside the house, because they are a source of *T. cruzi* infection to other species, including humans (Gürtler et al., 1998; Cohen and Gürtler, 2001).

Our results agree with those of other models of transmission of American trypanosomiasis in rural houses centred in the populations of triatomines or dogs.

Rabinovich and Rosell (1976) built a model in which after a couple of years, 100% of the human population of the house was in the chronic condition, but did not distinguish between the two chronic forms in humans. In Rabinovich and Himschoot (1990) and Himschoot (1993) simulation models, bug population reached the carrying capacity after 3–5.5 years and remained in that value over remaining 10–20 years of the simulation, with 60–65% of infection. In our model, this change in the number of triatomines is reached in 4.25–4.5 years, with 64–65% of infection.

Cohen and Gürtler (2001) concluded that eliminating infected dogs from a household with infected people is nearly sufficient to extinguish transmission of *T. cruzi*, barring the introduction of infected dogs, children or bugs. With additional dogs, more bugs are diverted from feeding on humans because bugs prefer to feed on dogs. After 1700 days (4.7 years) from the beginning of the simulation, our model predicts 213 infected triatomines on average, whereas after 1860 days (i.e. 5 months later), it predicts 268 infected triatomines. The importance of having at least one infected dog in the house on the infection spread is shown in Table 4.

Other models of transmission of American trypanosomiasis are focused on the human population. Busenberg and Vargas (1991) were pioneers in modelling Chagas disease but did not estimate any model parameter. Velasco-Hernandez (1991), Canals and Cattan (1992), and Das and Mukherjee (2006) concluded that the disease tends to reach an endemic equilibrium point (first statement) and that early detection of cases is important for the eventual eradication of the disease (second statement). Our model projections, in turn, agree with that first statement, but not with the second, because we considered the dog as an alternative host and, as shown in Table 3, only one infected dog as the only infection source generates the first infected triatomine in only 1 week and the first infected human in the household in 2 years. Unlike that found in our model, another work by Velasco-Hernandez (1994) showed that the population of triatomines remained constant through the simulation, although the ratio of infected triatomines was similar to ours. Inaba and Sekine (2004) suggest that reducing the ratio of the density of vectors to the density of humans to control the transmission must be highly effective. They also suggest that, from a realistic point of view, many factors are still neglected in their model. For example, the existence of reservoir host animals living around humans would play a very important role in the spread of the disease. We showed this in our model.

Therefore, we conclude that the permanent removal of triatomines in conjunction with other measures, such as avoiding the interaction of a reduced number of triatomines with domestic dogs followed by early detection and treatment of human acute cases, is the best ways to control the transmission. However, these measures are difficult to implement, because improving the household conditions and spraying the houses and peridomestic areas regularly are costly and triatomines are becoming resistant to insecticides (Toloza et al., 2008; Gurevitz et al., 2012).

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