A Model for Chagas Disease with Oral and Congenital Transmission

Daniel J. Coffield Jr., Anna Maria Spagnuolo, Meir Shillor, Ensela Mema, Bruce Pell, Amanda Pruzinsky, Alexandra Zetye

Abstract

This work presents a new mathematical model for the domestic transmission of Chagas disease, a parasitic disease affecting humans and other mammals throughout Central and South America. The model takes into account congenital transmission in both humans and domestic mammals as well as oral transmission in domestic mammals. The model has time-dependent coefficients to account for seasonality and consists of four nonlinear differential equations, one of which has a delay, for the populations of vectors, infected vectors, infected humans, and infected mammals in the domestic setting. Computer simulations show that congenital transmission has a modest effect on infection while oral transmission in domestic mammals substantially contributes to the spread of the disease. In particular, oral transmission provides an alternative to vector biting as an infection route for the domestic mammals, who are key to the infection cycle. This may lead to high infection rates in domestic mammals even when the vectors have a low preference for biting them, and ultimately results in high infection levels in humans.

Introduction

Chagas disease is caused by infection with the parasite *Trypanosoma cruzi* and is a major source of suffering throughout Latin America. The disease leads to organ deformity and early death in about one third of the 8–10 million individuals infected, [1,2]. Vector transmission by reduviids is largely responsible for the spread of *T. cruzi*, with some particular species specialized in domestic infection cycles. Other modes of transmission include blood transfusions, organ transplants, oral transmission, and congenital transmission [3–6].

Although various drugs are under development and testing, current control of the transmission of Chagas disease remains largely based on vector control and blood-bank screening [7–10]. In particular, the Southern Cone Initiative was implemented in the 1990s with the goal of interrupting the transmission of Chagas disease in South American countries through insecticide spraying and blood screening [10–12]. This program has led to a dramatic decrease in transmission in several countries in South America, with some regions now reporting a considerable drop in infections from *Triatoma infestans*, the primary vector, and transmission virtually at zero [13,14]. Additional control measures are treatment for acute Chagas disease and for congenital transmission cases [15].

While insecticide spraying for Chagas vectors has led to a significant decrease in new infections, improved housing, better drugs, and an effective vaccine are needed [16]. In particular, *T. cruzi* infection is likely to remain endemic in sylvatic hosts despite spraying efforts and neither insect control nor current drug treatment is optimal for this disease because of the long life span of infected human hosts, triatomine insecticide resistance, and the ease with which protozoans develop drug resistance [17–20].

Mathematical models for studying Chagas disease dynamics with seasonal insecticide spraying were presented in [21,22]. In this work, we enhance the model in [21], adding the effects of congenital transmission in infected humans and infected dogs and excluding spraying. We also account for oral transmission by allowing the domestic mammals to consume the vectors, as observed experimentally in [23]. The predation term involves a density-dependent consumption rate in the form of a Holling Type II response, similar to that in [4]. There are other likely routes of oral transmission in domestic mammals such as ingesting feces-contaminated food and water or licking feces-contaminated fur. Though the vector consumption is derived on the basis of the animals preying on the vectors, the consumption term can still in some sense account for these other modes since the consumption is dependent on the vector density.

The primary aim of this work is to investigate the significance of the following modes of disease transmission relative to vector biting: 1) oral transmission due to predation, and 2) congenital transmission. In particular, we want to know if these transmission modes play a significant role in human infection and have
implications for disease control. To this end, we study the additional transmission modes as enhancements to the model in [21] for comparison.

The model we present here consists of four nonlinear differential equations that describe the domestic transmission of the disease by predicting the total number of vectors, infected vectors, infected humans, and infected domestic mammals. In [24], a mathematical model for a small population (one household) was described, whereas the model in this work considers a large population (one village). We note that models were recently used in [25,26] to study control issues of the non-domiciliated Chagas disease vectors in the Yucatan Peninsula, Mexico. Those models use difference equations while our model is a classical nonlinear dynamical system. The effectiveness of different control measures was recently studied in [27] using a dynamical system model. Additional modeling and field results can be found in [28–30].

The Methods section gives a detailed description of the model and its parameters. In Results, the model is used to produce simulations of the populations in a hypothetical rural village over thirty years using a baseline parameter set, provided in Table 1. Additional simulations are performed to investigate the model’s sensitivity to various parameters. The Results section also compares simulations of the model presented in this work with the model in [21], which does not consider oral transmission in dogs nor congenital transmission. We conclude with the Discussion.

Methods

In this section, we present a new model for Chagas disease dynamics in a village. Information on pertinent biological processes can be found in [24]. The model represents the overall dynamics of the populations of vectors, infected vectors, infected humans, and infected domestic animals (mammals only) – referred to as ‘dogs’ in our model. In a rural village, there are also non-mammals that act as sources of blood meals but that are not hosts for T. cruzi (i.e., cannot become infected). They will be referred to as ‘chickens’ in our model.

We consider a relatively large representative rural village in South America so that a differential equations model is appropriate. Let the number of humans in the village be \( N \), the number of domestic mammals (dogs) be \( D \), and the number of domestic non-mammals (chickens) be \( C \). These are taken as constants for the sake of simplicity, since we consider a modest time period of 30 years. We denote by \( V = V(t) \) the number of carrier insects living in the houses in the village at time \( t \), the number of infected insects by \( V_i = V_i(t) \), the number of infected humans by \( N_i = N_i(t) \), and the number of infected dogs by \( D_i = D_i(t) \). Each non-infected population, excluding the chickens, is assumed to be susceptible.

We now describe the rate of change of each population in the village per day. The growth rate of the vectors depends on the successful hatching of eggs. As in [22], the egg hatching rate, \( d_h(t) - \tau \), is delayed due to the gestation time of \( \tau \) days. The hatching rate is a product of the following terms: the ratio of adult female vectors to total vectors; the number of eggs laid by an adult female per bite; the successful hatching rate of eggs after \( \tau \) days; the total blood meal supply in human factors; \( b_{supply} \); and the delayed seasonal biting rate \( b(t-\tau) \) prior to hatching. By extracting seasonal data from Castanera et al. [38], we obtain the following values: the ratio of adults to the entire population of triatomines is approximately 11/365 (so we take half that number to be adult females), the fraction of eggs that survive is 0.83, and the number of (eggs/bite)/(fed female) is 20 [37,38]. So, the form of \( d_h \) is

\[
d_h(t-\tau) = (11/365)(1/2)(0.83)b(t-\tau)b_{supply}.
\]

Note that we are assuming \( d_h \) follows the seasonality of \( b \).

Following [24], we use ‘human factors’ as the unit for the total blood supply in the following way: each human represents one human factor, each mammal \( D \) represents \( d_h \) human factors, and each non-mammal \( C \) represents \( c_f \) human factors; then, the total blood supply is given by \( b_{supply} = N + d_hD + c_fC \). We use the standard notation \( f_+ \) and \( f_- \) to denote the positive and negative parts, respectively, of a function \( f = f_+ - f_- \). Vector growth is then modeled by the following delay logistic term

\[
d_h(t-\tau)V(t-\tau) \left(1 - \frac{1}{K} V(t-\tau)\right)^+,
\]

as in [21], where \( K \) is the carrying capacity of vectors in the village houses. The term \( d_h(t-\tau)V(t-\tau) \) is the rate at which vectors hatch at time \( t \) from eggs laid at time \( t - \tau \). The expression \( (1 - V(t-\tau)/K)_+ \) represents the fraction of the food supply that was available to the female vectors at time \( t - \tau \). This assumes that if the vector population at time \( \tau \) days prior to the current time \( t \) was above the carrying capacity, then no eggs are laid. The death rate of the vector population depends on the following three factors: natural mortality, death due to overcrowding or growth beyond the carrying capacity, and death due to being eaten by the dogs. The natural death rate coefficient of triatomines is \( d_m = d_m(t) \) and the coefficient of the death rate of vectors above the carrying capacity is \( d_k = d_k(t) \). These rates are assumed to be periodic functions with a period of one year and are included by adding the following term to the vector growth equation:

\[
-\left(d_h(t)\left(1 - \frac{V(t)}{K}\right)^+ + d_m(t)\right)V(t).
\]

We now consider the death rate of vectors due to consumption by dogs. We use a Holling Type II functional response for the consumption term, defining the per dog consumption rate as

\[
F(V(t)) = \frac{EV(t)}{V(t) + A}.
\]

Here, \( E \) is the maximum number of vectors consumed by one dog per day and \( A \) is the vector number at which dogs consume at the rate of \( E/2 \) vectors per day. This term is similar to one used in [4] where vector consumption by wild animals was considered. Thus, the rate of change in the total vector population within the village is

\[
\frac{dV}{dt} = \left(d_h(t-\tau)V(t-\tau) \left(1 - \frac{1}{K} V(t-\tau)\right)^+ \right.
\]

\[
-\left(d_h(t)\left(1 - \frac{V(t)}{K}\right)^+ + d_m(t)\right)V(t)
\]

\[
-\left(d_k(t)\left(1 - \frac{V(t)}{K}\right) + d_k(t)\right)V(t)F(V(t))
\]

\[
-\left(d_k(t)\left(1 - \frac{V(t)}{K}\right) + d_k(t)\right)V(t)F(V(t)).
\]
Next, we consider the growth rates of the infected populations $V_i$, $N_i$, and $D_i$. We denote by $P_{NV}$ and $P_{DV}$ the probabilities of a vector becoming infected by biting an infected human or an infected dog, respectively. Also, the number of bites per vector per day is given by $b(t) \cdot b_{\text{supply}}$, where $b(t)$ is the same seasonal biting term used to define $d_i$. Since the proportions of those bites that occur on infected humans and infected dogs are $N_i(t)/b_{\text{supply}}$ and $D_i(t)/b_{\text{supply}}$, respectively, the growth rate of infected vectors is

$$b(t)(V(t) - V_i)(P_{NV}N_i(t) + P_{DV}d_iD_i(t)).$$

Table 1. The model parameters and the baseline simulation values.

| Parameter   | Definition                                      | Baseline Simulation Value | Source                |
|-------------|-------------------------------------------------|---------------------------|-----------------------|
| $V$         | Total number of vectors (vectors/village)       | $V(0) = 23000$           | This study            |
| $N$         | Total number of humans (humans/village)        | 400                       | This study            |
| $D$         | Total number of domestic dogs (dogs/village)   | 100                       | This study            |
| $C$         | Total number of chickens (chickens/village)    | 100                       | This study            |
| $H$         | Total number of houses (houses/village)        | 100                       | This study            |
| $V_i$       | Number of infected humans (humans/village)     | $V_i(0) = 5000$          | This study            |
| $N_i$       | Number of infected humans (humans/village)     | $N_i(0) = 45$            | This study            |
| $D_i$       | Number of infected dogs (dogs/village)         | $D_i(0) = 35$            | This study            |
| $V_{\text{min}}$ | Min. number of vectors (vectors/village) | 2000                      | This study            |
| $d_h$       | Egg hatching rate (1/day)                       | $\frac{1}{2300}$         | Figure 1, [37,38]     |
| $d_m$       | Death rate of vectors (1/day)                   | Seasonal piecewise linear | Estimation from [38], Figure 1 |
| $d_k$       | Death rate of vectors (above $K$) (1/day)       | $d_m/2$                   | This study            |
| $r$         | Delay (days)                                    | 20                        | [38]                  |
| $b(t)$      | (bitess/(day factor))Biting rate                | Seasonal piecewise linear | Estimation from [38,39], Figure 1 in [21] |
| $b_{\text{supply}}$ | $N + d_iD + c_iC$                               | Seasonal piecewise linear | This study            |
| $P_{NV}$    | Human to vector infection probability (per bite)| 0.03                      | [24]                  |
| $P_{DV}$    | Dog to vector infection probability (per bite)  | 0.49                      | [24]                  |
| $P_{VH}$    | Vector to human infection probability (per bite)| 0.00008                   | This study, value unknown |
| $P_{Vh}$    | Vector to dog infection probability (per bite)  | 0.001                     | Estimate from [24]    |
| $d_h$       | Human factor of one dog                         | 2.45                      | [34]                  |
| $c_i$       | Human factor of one chicken                     | 0.35                      | [34]                  |
| $\gamma_N$ | Mortality rate of infected humans (1/day)       | $0.3 \frac{\ln 2}{25.365} + 0.7 \frac{\ln 2}{76.12.365}$ | Estimate from [41,42] |
| $\gamma_D$ | Mortality rate of infected dogs (1/day)         | $\frac{\ln 2}{4.365}$    | Estimate 8 years      |
| $\gamma_Ns$| Mortality rate of susceptible humans (1/day)    | $2 \frac{\ln 2}{76.12.365}$ | Estimate from [41,42] |
| $\gamma_Ds$| Mortality rate of susceptible dogs (1/day)      | $\frac{\ln 2}{6.365}$    | Estimate 12 years     |
| $K$         | Carrying Capacity per village                   | 50,000                    | This study            |
| $d_1$       | First day of fall (day of year)                 | 0                         | March 20              |
| $d_2$       | First day of winter (day of year)               | 91.25                     | June 21               |
| $d_3$       | First day of spring (day of year)               | 182.5                     | September 22          |
| $d_4$       | First day of summer (day of year)               | 273.75                    | December 21           |
| $T_N$       | Congenital transmission probability for infected humans | 0.10                     | [5,15,40]             |
| $T_D$       | Congenital transmission probability for infected dogs | 0.10                     | [5,15,40]             |
| $E$         | Max. number of vectors eaten by a dog per day   | 0.143                     | This study            |
| $A$         | Number of vectors when vector consumption is $E/2$ | 50,000                    | This study            |

doi:10.1371/journal.pone.0067267.t001
We assume that the natural death rate of the infected vectors is also \( d_w(t) \), i.e., carrying the parasites does not affect their life span. Similarly, the death rate due to growth beyond the carrying capacity is \( d_c(t) \).

The death rate of the infected vectors due to predation by dogs is

\[
\frac{F(V(t))DV(t)}{V(t)}, \text{ for } V > 0.
\]

Collecting the terms above, we get the following rate of change for the infected vectors:

\[
\frac{dV_i}{dt} = b(t)(V(t) - V_i(t))(P_{NY}N_i(t) + P_{DV}d_iD_i(t))
- \left( d_i(t) \left( 1 - \frac{V(t)}{K} \right) + d_w(t) \right) V_i(t) - \frac{F(V(t))DV_i(t)}{V(t)}.
\]

We turn now to the infected humans. When bitten by an infected vector, a susceptible human becomes infected with probability \( P_{VN} \). As before, each vector is biting at a rate of \( b(t) \) bites per day, and \( (N - N_i(t))/b_{supply} \) is the fraction of bites that are on susceptible humans. Thus, the natural mortality rate of infected humans is given by \( b(t)P_{YN}(N - N_i(t))V_i(t) \). The natural mortality rates for infected humans and susceptible human are denoted by \( \gamma_{N_i} \) and \( \gamma_{N_s} \), respectively. We assume that human reproduction is independent of infection status, since infected humans typically live beyond reproductive ages. Therefore, the assumption that \( N \) is constant implies that the birth rate for all humans is

\[
\left( \gamma_{N_i} + \gamma_{N_s} - \gamma_{N_i} \right) \frac{N_i(t)}{N}.
\]

Here, the birth rate depends on \( N_i \), which is a consequence of the two preceding assumptions. However, we note that \( \gamma_{N_i} - \gamma_{N_s} \) is small so that \( N_i \) does not vary enough for this dependence to meaningfully affect the model. Furthermore, we investigated multiple other assumptions for the human birth rate, including scenarios for different birth rates of infected humans versus uninfected humans, and the simulation results were virtually indistinguishable in all cases.

We define \( T_{NI} \) to be the ratio, amongst babies born to infected mothers, of infected babies to the total number of babies. Therefore, the rate of change of infected humans is

\[
\frac{dN_i}{dt} = b(t)P_{YN}(N - N_i(t))V_i(t)
+ T_{NI} \left( \gamma_{N_i} + (\gamma_{N_i} - \gamma_{N_s}) \frac{N_i(t)}{N} \right) N_i(t) - \gamma_{N_i}N_i(t).
\]

Under the assumption that both infected and uninfected dogs reproduce at the same rate, the rate of change of infected dogs is similar to that of infected humans, except that we must account for infection caused by the consumption of infected vectors. To this end, let \( P_{VD} \) be the probability that an uninfected dog becomes infected when bitten by an infected vector, let \( P_{VD} \) be the probability that an uninfected dog becomes infected after eating an infected vector, and note that \( D - D_i \) be the susceptible dog population. We also use \( \gamma_{D_i} \) and \( \gamma_{D_s} \) to denote the natural mortality rates for infected dogs and susceptible dogs, respectively. Then, the rate of change of infected dogs is

\[
\frac{dD_i}{dt} = \left( b(t)d_iP_{VD} + \frac{P_{VD}F(V(t))}{V(t)} \right) (D - D_i(t))V_i(t)
+ T_{Di} \left( \gamma_{D_s} + (\gamma_{D_i} - \gamma_{D_s}) \frac{D_i(t)}{D} \right) D_i(t) - \gamma_{D_i}D_i(t),
\]

where \( T_{Di} \) is the probability that an infected dog passes the infection to its offspring congenitally, and the congenital transmission term is similar to the term in the infected humans equation because \( D \) is constant.

To complete the model we prescribe the initial values of the respective populations: \( V_i(0) = V_{ih}, N_i(0) = N_{ih}, D_i(0) = D_{ih} \), together with

\[
V(t) = V_0(t), \quad -\tau \leq t \leq 0.
\]

These equations and conditions form a mathematical model for the domestic dynamics of Chagas disease with oral and congenital transmission:

\[
\frac{dV}{dt} = \frac{d_i(t - \tau)F(t - \tau)}{1 - \frac{V(t)}{K}} V(t - \tau) - \left( d_i \left( 1 - \frac{V(t)}{K} \right) + d_w \right) V - F(V)D,
\]

\[
\frac{dV_i}{dt} = b(V - V_i)(P_{YN}N_i + P_{DV}d_iD_i(t)) - \left( d_i \left( 1 - \frac{V(t)}{K} \right) + d_w \right) V_i(t) - \frac{F(V(t))DV_i(t)}{V(t)},
\]

\[
\frac{dN_i}{dt} = bP_{YN}(N - N_i)V_i + T_{NI} \left( \gamma_{N_i} + (\gamma_{N_i} - \gamma_{N_s}) \frac{N_i(t)}{N} \right) N_i(t) - \gamma_{N_i}N_i(t),
\]

\[
\frac{dD_i}{dt} = \left( b_dP_{VD} + \frac{P_{VD}F(V(t))}{V(t)} \right) (D - D_i)V_i(t).
\]
The coefficient functions $d_h$, $d_b$, $d_m$, and $b$ are one-year periodic since they are seasonally dependent. Also, it is natural to assume that $V_{max} < K$. Note that the delay differential equation (1) for the total vector population is not coupled to the other equations, so it can be solved independently.

**Results**

In this section, we study the effects of the congenital and oral transmission terms, compare the current model with the one in [21]. The Adams-Bashforth Fourth-Order Method was implemented in fortran [31] and verified using Wolfram Mathematica [32]. The figures were generated with Wolfram Mathematica [32].

**Baseline Case**

We first compare the simulation results in a baseline case, similar to the one described in [21], with 100 houses, 400 humans, 100 dogs, and 100 chickens in a representative village. We use a similar parameter set to define our baseline case with the only difference being a new value of 0.35 for $c_f$. See Vector Biting Preference Studies for an explanation. We also add the parameters consistently choose $V_{min}$.

![Figure 1. Vector growth and mortality coefficients.](image)

Figure 1 shows model simulations for the number of vectors, infected vectors, infected humans, and infected dogs over 30 years using the the baseline parameter set with higher initial conditions. We note that all of the populations largely stabilize around a central value and then seasonally oscillate around that value. This is consistent with the endemic nature of the disease in rural villages that do not engage in control measures. Note that the oscillations in the vector populations are much larger than those of the humans and domestic mammals, because of the shorter life span of vectors.

**Vector Biting Preference Studies**

Recently, experimental work in [33] suggests that $d_f$ is about seven times $c_f$. This strongly contradicts earlier estimates found in [34] and used in our previous work [21,22]. We point out that this new study only compares vector preference between dogs and chickens, but does not consider vector preference for humans. Thus, vector preference between humans, dogs, and chickens remains unclear. Moreover, our work indicates that the preference factors substantially affect the dynamics of the infected populations. To address this, we perform simulations over various ranges of $c_f$ and $d_f$. See Figure 4.

Note that for fixed $c_f$ and increasing $d_f$, infection in humans increases and then decreases, attaining its peak for $d_f$ between 2 and 3. Although not shown, the number of infected dogs increases as $d_f$ increases, as expected. This leads to a sharp increase in infected vectors for low $d_f$ values before leveling off later on. See Figure 4. The initial increase in human infections is due to the steep increase in infected vectors which more than compensates for the increased vector preference for dogs. Because the number of infected vectors levels off for large values of $d_f$, it follows that human infection decreases as the vectors primarily bite the dogs. Also, for each fixed $d_f$, human infections decrease as $c_f$ increases. This is expected since chickens are not infective and do not contribute to the infection cycle. Hence a higher $c_f$ just diverts bites from dogs and humans.

In most of the following simulations, we allow $c_f$ to vary and consistently choose $d_f = 7c_f$ due to the relationship found in [33]. In simulations where $c_f$ and $d_f$ are fixed, we choose $d_f = 2.45$ to stay consistent with baseline studies in previous work and correspondingly set $c_f = 2.45/7 = 0.35$. 

![Figure 3 shows model simulations for the number of vectors](image)
Figure 2. Simulation results comparing models. Simulation results of the model in this work (black) and the model without both oral and congenital transmission (gray), from [21], in the baseline case using the parameters in Table 1.
doi:10.1371/journal.pone.0067267.g002

Figure 3. Higher initial conditions. Simulation results of the model with baseline parameters and higher initial conditions.
doi:10.1371/journal.pone.0067267.g003
Effects of Oral and Congenital Transmission

As expected, congenital transmission increases overall infection in humans and dogs. As a result, the number of infected vectors also increases, but not significantly. Estimates of congenital transmission probabilities are readily available and generally in the range of 2–10% [5,15]. For values in this range, the effects of congenital transmission are modest and close to linear as a function of transmission probabilities, Figure 5. We note that a recent article reported dramatically higher congenital transmission probabilities in mice (33–66%) [35]. Simulations of our model with congenital transmission probabilities up to 50% reveal a continued, near-linear effect of vertical transmission on infected humans.

The oral transmission is more complicated. In the case shown in Figure 5 with a baseline $c_f = 0.35$, the number of infected humans at year 30 changes by at most 4 as $E$ ranges from 0 to 0.15 with a peak attained at approximately 0.07. We note that initially a higher vector consumption rate results in more infections in both humans and dogs, as expected. However, as the consumption rate increases further, the number of human infections actually declines since there are fewer infected vectors feeding on humans, as depicted in Figure 6. Also, the total number of vectors steadily decreases, since more vectors are being consumed as $E$ increases.

Next, we consider oral transmission with higher and lower values of $c_f$, and, correspondingly, $d_f = 7c_f$. Figures 7 and 8 show the four populations as functions of $E$ with all other parameters except $c_f$ and $d_f$ set to their baseline values. We point out that varying $T_N$ and $T_D$ had the same effect on the populations as in Figure 5. In the case where $c_f = 0.1$, the effects of oral transmission are more dramatic with the number of infected humans at year 30 increasing by approximately 30 as $E$ ranges from 0 to 0.15. In comparison, when $c_f = 1.0$, the number of infected humans starts at a significantly lower number and decreases. We observed similar trends with larger $c_f$.

Since the vector preference numbers do not affect the biting rate of the vectors, it follows that the total number of vectors is the same for a fixed value of $E$. So, in each of Figures 6, 7, 8, the graphs for the total number of vectors are identical. However, all infected populations have dramatically different outcomes. More specifically, in all cases, the number of infected dogs increases as $E$ increases, because the dogs are eating more infected vectors. Also, dog infection increases with $c_f$ since $d_f = 7c_f$.

Now, we consider the number of infected humans for the different values of $c_f$. It is interesting to note that the curves for the number of infected humans and infected vectors have the same shape in each instance of $c_f$. We observe that for $c_f$ roughly less than 0.15 (and therefore, $d_f$ roughly less than 1), the curves for infected humans and infected vectors are increasing with $E$ in (0,0.15). However, for $c_f$ roughly in the interval (0.15,1), the curves initially increase before decreasing with the peak moving to the left for higher values of $c_f$. Also, it appears that the peak of each of the $N_i$ curves trails closely behind the peak of the corresponding $V_i$ curves since vector infection drives human infection.

We now explain the decline after the peak for infected vectors, and correspondingly, for infected humans. Recall that $d_f = 7c_f$, so a higher $c_f$ value means a stronger vector preference for dogs and a resulting higher number of infected vectors. However, since the total number of vectors is independent of $c_f$, the ratio $V_i/V$ increases as $c_f$ increases. Also, $V$ is a decreasing function of $E$, making $V_i/V$ even higher for large $E$. Thus, more of the vectors removed through dog predation are infected vectors for higher $c_f$ and $E$ values. Initially as $E$ increases, more dogs become infected which in turn leads to a higher number of infected vectors. But, as $E$ increases further, more infected vectors are being eliminated through vector consumption than are being added through new infections.

Finally, for $c_f$ greater than about 1, the number of infected humans and infected vectors declines as $E$ increases from 0 to 0.15. As in the latter part of the previous case, the high vector preference for dogs leads to a large infected vector population and a high $V_i/V$ ratio. The predation on vectors removes such a high proportion of infected vectors in this case that the number of infected vectors strictly decreases as $E$ increases. Dog infection still increases with $E$, leading to new vector infections, but not enough to overcome those being removed.

Past work has shown that dogs play an important role in the infection cycle. The new model, and particularly the inclusion of oral transmission, demonstrates an even more severe, negative impact of the dogs. In fact, Figures 7 and 8 reveal that high levels of human infection occur in both of the following cases: a high level of dog oral transmission coupled with a low vector biting preference for dogs and chickens; a low level of dog oral transmission coupled with a high vector preference for dogs and chickens. The key observation is that even if vector preference for dogs is low, dogs still become sufficiently infected through oral consumption of vectors than by vector biting. See Figure 9. The figure further reveals that human infection remains high at low $c_f$ and $d_f$ values even when dogs cannot be infected through biting.
Figure 5. Infected humans at year 30 as a function of $E$, $TN_i$, and $TD_i$. The number of infected humans at year 30 as a function of the vector consumption rate $E$ and congenital transmission probabilities $TN_i, TD_i$, (where $TN_i = TD_i$). All other parameters are the baseline values.

doi:10.1371/journal.pone.0067267.g005

Figure 6. Populations at year 30 as functions of $E$. The number of infected humans, infected dogs, vectors, and infected vectors, all at year 30, as functions of $E$. The other parameters are set to the baseline values.

doi:10.1371/journal.pone.0067267.g006
Sensitivity to Consumption

As shown above and in Figure 10, the model is sensitive to the value of \( E \), but only at low values of \( c_f \) and \( d_f \). For example, when \( c_f \approx 0.1 \) and \( d_f \approx 0.7 \), and \( E \) ranges from 0 to 0.15, the number of infected humans changes by about 30. However, the model is not very sensitive to \( E \) for larger values of \( c_f \) and \( d_f \): In fact, for any value of \( c_f \) greater than the baseline value of 0.35, the number of infected humans at year 30 changes by at most 4 as \( E \) varies in the same range (0 to 0.15).

Varying Dog and Chicken Levels

We now investigate the effects of changing the number of chickens and dogs in the village and their preference factors, while setting all other parameters to their baseline values. For fixed \( c_f \), the number of infected humans increases as the number of chickens increases, Figure 11. Although chickens are not infectious, a higher chicken population means a higher blood supply available to the vectors, resulting in higher vector prevalence. This leads to more bites on dogs and humans and increased infected populations.

Similarly, for a fixed value of \( c_f \), the number of infected humans increases as the number of dogs increases, Figure 11. The effect on \( N_i \) of increasing the number of dogs is more dramatic than the effect of increasing the number of chickens because dogs are infectious. As can be seen in both cases, the number of infected humans initially increases with increasing \( c_f \) before decreasing once \( c_f \) is beyond about 0.3—0.4.

Larger Blood Supply Cases

We now consider a more realistic village, see [36], where each house in the village has 5 humans, 2 dogs, and 18 chickens. All other parameters are taken to be the baseline values. The primary effect of the increased populations is a larger blood supply available to the vectors. Correspondingly, the total number of vectors is significantly higher than in the baseline case. See Figure 12. All of the infected populations are significantly higher and a greater percentage of all populations become infected.

Discussion

This work presents a new model with seasonally dependent coefficients for the domestic transmission of Chagas disease, building upon the work in [21]. The model includes transmission through vector biting along with the new infection routes of congenital transmission in humans and domestic mammals as well as oral transmission in domestic mammals through consumption of infected vectors. Simulations indicate that oral transmission plays an important role in the infection cycle while the effect of congenital transmission is more limited.

The inclusion of congenital transmission in humans directly leads to more human infections. However, because both the birth rate and the probability of the infection passing from mother to
child are relatively low, vertical transmission in humans leads to only a few new infections over 30 years in a village of 400. We note that the choice to have a constant human population limits the model's flexibility in choosing the birth rate and thus it is perhaps artificially low. Clearly, the effects of congenital transmission in humans would be more severe in villages with higher birth rates. On the other hand, since dogs have a relatively higher birth rate than humans, congenital transmission in dogs might be expected to substantially influence the number of infected dogs and indirectly increase the number of infected humans. However, the dogs become so easily infected by other transmission routes that the inclusion of congenital transmission does not significantly affect dog infections. In particular, simulations show that the infected dog population quickly stabilizes at a high level of infection (usually around 60%-90% infected). The inclusion of congenital transmission does slightly increase the peak dog infection level, but not enough to substantially affect human infection.

The effects of oral transmission in dogs are more dramatic and complex than that of congenital transmission. Furthermore, the significance of the oral transmission is strongly tied to the vector biting preference numbers. For high values of $c_f$ and $d_f$, most of the dogs become infected through biting without oral transmission, though increasing the dog's consumption rate does moderately increase the number of infected dogs (Figure 8). However, in this case, the increased consumption causes a decline in the infected vector population, and correspondingly, in the infected human population. These declines are small though, which demonstrates that vector biting drives infection when the vectors strongly prefer to feed on dogs.

Alternatively, oral transmission is the driving force behind the infection cycle when $c_f$ and $d_f$ are low (Figure 7). In this case, vector biting alone leads to only about 15% of the dogs being infected after 30 years. However, adding oral transmission dramatically increases all of the infected populations and the level of infection is very sensitive to the dog’s maximal consumption rate, $E$. As noted in Results, the number of human infections in a representative village of 400 increases by about 30 infections over 30 years of simulation as $E$ is increased from 0 to the baseline value of one per week. This means that with significant oral transmission in dogs, human infection will remain high even if the vectors have a low preference for biting the dogs. Since the probability of transmission from dogs to vectors is significantly higher than the probability of transmission from humans to vectors, see Table 1, we know that the dogs are primarily responsible for infecting the vectors. In turn, the size of the infected vector population directly drives the number of human infections. So, when $d_f$ is low, oral transmission is the key route of dog infection, whereas biting is more important when $d_f$ is high. In either case, our simulations show that the level of dog infection remains high, resulting in a substantial number of human infections. This result is noteworthy because it suggests that the disease will persist at high levels even if measures are taken to deter the vectors from biting the dogs, e.g. using insecticide collars.

It is well-known and widely reported that domestic mammals are a major player in the infection cycle and the main reservoir of
the parasite. Our work strengthens these conclusions and further demonstrates the need to remove mammals (dogs, cats, etc.) from the domestic settings. This is not a new control recommendation, but our simulations, and particularly the inclusion of oral transmission, show the fundamental, negative role the mammals play in causing human infections over a wide range of vector biting preferences. In fact, our simulations show that the infections persist endemically even with a small number of dogs (0.2 dogs/home). This is consistent with [34], where it was found that a 100% effective control method on at least 88% of the dogs would be needed to achieve a basic reproductive number smaller than 1.

In our model, the infection dies out with no dogs. And even if a total removal of domestic mammals is infeasible, reducing their numbers will likely lead to fewer human infections. As shown in Results, the number of infected humans only increases with the number of dogs in our model. This contrasts with the model in [24], where it was found that human infection declines when each household has more than two dogs, allowing the dogs to sufficiently divert vectors away from the humans. In our model, more dogs means a higher blood supply available to the vectors, and correspondingly, more vectors and higher infected populations. However, we note that we do see a similar decline in human infections as the vector biting preference for dogs increases beyond about 2.5 human factors. See Figure 4.

We note that this work uses a predation term to model the oral transmission in dogs, and this term may not appropriately account for other likely routes of oral transmission such as licking of feces-contaminated fur and ingesting feces-contaminated food or water.

A weakness of this work is that the parameters are coming from different studies. However, data from the same studies do not...

---

Figure 9. Infected humans and infected dog populations at year 30 in different scenarios. The infected human and infected dog levels after 30 years in different scenarios where dogs can be infected through vector biting only, oral consumption only, or both biting and consumption. Here $d_i = 7c_f$ and all other parameters are set to the baseline values.

doi:10.1371/journal.pone.0067267.g009
currently exist. Although the simulation results are highly sensitive to the vector biting preferences for dogs and chickens, which are largely unknown, the primary control implication—eliminating domestic mammals—is independent of these parameters. That is, domestic mammals should be removed from the homes even if vector preference for them is low. Furthermore, due to recent work in [33], we have drastically changed the relationship between $d_f$ and $c_f$ as compared to our previous work [21,22]. Yet, the overall dynamics are very similar to our previous work and dogs remain the driving force of the infection cycle.

The dynamics of Chagas disease are indeed complex, so in addition to validation of the model, there are several open issues that are of interest for further study. First, we point out that human infection levels might be higher than in the simulations, because we did not include blood transfusions or oral transmission in humans, though recent outbreaks (e.g. feces in juice) indicate that the latter may be a significant source of human infection. Additionally, the effects of wild vectors and the disease in the wildlife were not investigated. We also did not directly consider vector mortality due to consumption by domestic non-mammals. Finally, the dynamics for the total human and domestic animal populations could be studied, which would allow for investigation of immigration and contact between neighboring villages.

**Acknowledgments**

The authors would like to thank the reviewers for their insightful comments and suggestions which improved the manuscript.

**Author Contributions**

Conceived and designed the experiments: DJC AMS MS. Performed the experiments: DJC AMS EM BP AP AZ. Analyzed the data: DJC AMS MS.

![Figure 10](https://plosone.org/doi/10.1371/journal.pone.0067267.g010)

**Figure 10.** Infected humans at year 30 as a function of $E$ and $c_f$. The number of infected humans at year 30 as a function of $E$ and $c_f$, where $d_f = 7c_f$ and all other parameters are set to the baseline values.

doi:10.1371/journal.pone.0067267.g010

![Figure 11](https://plosone.org/doi/10.1371/journal.pone.0067267.g011)

**Figure 11.** Infected humans at year 30 with different numbers of chickens and dogs. The figure shows the effects of changing the number of chickens and dogs on the number of infected humans in the village at year 30. Note that $d_f = 7c_f$ and all other parameters are set to their baseline values.

doi:10.1371/journal.pone.0067267.g011
EM BP AP AZ. Contributed reagents/materials/analysis tools: DJC AMS MS EM BP AP AZ. Wrote the paper: DJC AMS MS.

References

1. Organizacion Panamericana de la Salud (2006) Estimacion cuantitativa de la enfermedad de Chagas en las Americas. Washington DC: PAHO Publishing.
2. Schofield CJ, Jennin J, Salvatella R (2006) The future of chagas disease control. Trends Parasitol 22: 383–386.
3. Camandaroba ELP, Pinheiro Lima CM, Andrade SG (2002) Oral transmission of Chagas disease: Importance of Trypanosoma cruzi biobreeder in the intragastric experimental infection. Rev Inst Med Trop Sao Paulo 44: 97–103.
4. Kribs-Zaleta CM (2006) Vector Consumption and Contact Process Saturation in Sylvatic Transmission of T. Cruzi. Math Popul Stud 13(2006): 135–152.
5. Kribs-Zaleta CM (2010) Alternative Transmission Modes for Trypanosoma Cruzi. Math Biosci Eng 7(3): 657–673.
6. Roellig DM, Ellis AE, Yabsley MJ (2009) Oral transmission of Trypanosoma cruzi with opposing evidence for the theory of carnivory. J Parasitol 95: 360–364.
7. Garg N, Bhatia N (2005) Current status and future prospects for a vaccine against American trypanosomiasis. Expert Rev Vaccines 4(6): 867–880.
8. Rodrigues CJ, de Castro SL (2002) A critical review on Chagas disease chemotheraphy. Mem Inst Oswaldo Cruz 97(1): 3–24.
9. Schmunis GA (1999) Prevention of transfusional Trypanosoma cruzi infection in Latin America. Mem Inst Oswaldo Cruz (Suppl 1): 93–101.
10. Schmunis GA, Cruz JR (2003) Safety of the blood supply in Latin America. Mem Inst Oswaldo Cruz (Suppl 1): 405–411.
11. Schmunis GA (1999) Prevention of transfusional Trypanosoma cruzi infection in Latin America. Mem Inst Oswaldo Cruz (Suppl 1): 93–101.
12. Schmunis GA, Cruz JR (2003) Safety of the blood supply in Latin America. Mem Inst Oswaldo Cruz (Suppl 1): 405–411.
13. Dias JC (2007) Southern Cone Initiative for the elimination of domestic populations of Triatoma infestans and the interruption of transfusional Chagas disease. Historical aspects, present situation, and perspectives. Mem Inst Oswaldo Cruz 102(Suppl 1): 11–18.
14. Massad E (2008) The elimination of Chagas disease from Brazil Epidemiol Infect 136: 1153–1164.
15. Gürler RE, Segura EL, Cohen JE (2003) Congenital transmission of Trypanosoma cruzi infection in Argentina, Emerg Infect Dis 9(1). Available:

http://www.cdc.gov/ncidod/EID/vol9no1/02-0274.htm. Accessed 29 May 2013.
16. Bonfey A (2003) Chagas disease: current epidemiological trends after the interruption of vectoral and transfusional transmission in the Southern Cone countries. Mem Inst Oswaldo Cruz 98: 577–591.
17. Buckner FS, Wilson AJ, White TC, Van Voorhis WC (1998) Induction of resistance to azole drugs in Trypanosoma cruzi. Antimicrob Agents Chemother 42: 3245–3250.
18. Diotaiuti L, Pereira AS, Loiola CF, Fernandes AJ, Schofield JC, et al. (1995) Inter-relations of sylvatic and domestic transmission of Trypanosoma cruzi in areas with and without domestic vectorial transmission in Minas Gerais. Mem Inst Oswaldo Cruz 90: 443–448.
19. Murta SM, Romanha AJ (1998) In vivo selection of a population of Trypanosoma cruzi and clones resistant to benznidazole. Parasitology 116(Pt 2): 165–171.
20. Vasena CV, Picollo MI, Zerba EN (2000) Insecticide resistance in Brazilian Triatoma infestans and Venezuelan Rhodnius prolixus. Med Vet Entomol 14: 51–55.
21. Spagnuolo AM, Shillor M, Kingsland L, Van Voorhis WC, et al. (2003b) A Logistic Delay Differential Equation Model for Chagas Disease with Interrupted Spraying Schedules. J Biol Dyn 6(2): 377–394. doi:10.1080/17513758.2011.537896.
22. Spagnuolo AM, Shillor M, and Stryker GA (2011) A Model for Chagas Disease with Controlled Spraying. J Biol Dyn 5(4): 299–317.
23. Reithinger R, Ceballos LA, Stariolo R, Davies CR, Gurtler RE (2005) Chagas disease control: deltamethrin-treated collars reduce Triatoma infestans feeding success on dogs. Trans R Soc Trop Med Hyg 99: 502–508.
24. Cohen JE, Gurtler RE (2001) Modeling household transmission of American trypanosomiasis. Science 293: 694–698.
25. Barbé C, Dumontel E, Gourbiè`re S (2009) Optimization of Control Strategies for Non-Domiciliated Triatoma dimidiatata Chagas Disease Vector in the Yucata n Peninsula, Mexico. PLoS Negl Trop Dis 3(4): e416. doi:10.1371/journal.pntd.0000416.
26. Gourbiè`re S, Dumontel E, Rabinovich JE, Minkoue R, Menu F (2008) Demographic and Dispersal Constraints for Domestic Infestation by Non-
27. Cruz-Pacheco G, Esteva L, Vargas C (2012) Control measures for Chagas disease. Math Biosci 237; 49–60.
28. Rabinovich JE, Himshoot P (1990) A population-dynamics simulation model of the main vectors of Chagas' Disease transmission, Rhodnius prolixus and Triatoma infestans. Ecol Modell 52; 249–266.
29. Rabinovich J, Schweigmann N, Yohai V, Wisnevesky-Colli C (2001) Probability of Trypanosoma cruzi transmission by Triatoma infestans (Hemiptera: Reduviidae) to the opossum Didelphis albiventris (Marsupialia: Didelphidae), Am J Trop Med Hyg 65(2); 125–130.
30. Rabinovich JE, Wisnevesky-Colli C, Solarz ND, Gurtler RE (1990) Probability of Chagas disease by Triatomine infestans (Hemiptera: Reduviidae) in an endemic area of Santiago del Estero, Argentina. Bull World Health Organ 68(6); 737–746.
31. GNU Compiler Collection website. Available: http://gcc.gnu.org/fortran. Accessed 2013 May 28.
32. Wolfram website. Available: http://www.wolfram.com. Accessed 2013 May 28.
33. Gurtler RE, Ceballos LA, Ordoñez-Krasnowski P, LANati LA, Stariolo R, et al. (2009) Strong Host-Feeding Preferences of the Vector Triatoma infestans Modified by Vector Density: Implications for the Epidemiology of Chagas Disease. PLoS Negl Trop Dis 3(5): e447.doi:10.1371/journal.pntd.0000447.
34. Gurtler RE, Cecere MC, Lauricella MA, Cardinal MV, Kitron U, et al. (2007) Domestic dogs and cats as sources of Trypanosoma cruzi infection in rural northwestern Argentina. Parasitology 134; 69–82.
35. Hall CA, Pierce EM, Wimsatt AN, Hobby-Dolbeer T, Meers JB (2010) Virulence and vertical transmission of two genotypically and geographically diverse isolates of Trypanosoma cruzi in mice. J Parasitol 96(2): 371–376.
36. Cardinal MV, Lauricella MA, Marcet PL, Orozco MM, Kitron U, et al. (2007). Impact of community-based vector control on house infestation and Trypanosoma cruzi infection in Triatoma infestans, dogs and cats in the Argentine Chaco. Acta Trop 103(3): 201–211.
37. Gorla DE, Schoffield CJ (1985) Analysis of egg mortality in experimental populations of Triatoma infestans under natural climatic conditions in Argentina. Bull Soc Vector Ecol 10: 107–117.
38. Castanera MB, Aparicio JP, Gurtler RE (2003) A stage-structured stochastic model of the population dynamics of Triatoma infestans the main vector of Chagas disease. Ecol Modell 162; 33–53.
39. Catalá S (1991) The biting rate of Triatoma infestans in Argentina. Med Vet Entomol 5(3): 325–333.
40. Kribs-Zaleta CM (2010) Estimating Contact Process Saturation in Sylvatic Transmission of Trypanosoma cruzi in the United States. PLoS Negl Trop Dis 4; e656.
41. The World Factbook website. Available: https://www.cia.gov/library/publications/the-worldfactbook/geos/ar.html. Accessed 29 May 2013.
42. Rassi Jr A, Rassi A, Marin-Neto JA (2009) Chagas heart disease: pathophysiological mechanisms, prognostic factors and risk stratification. Mem Inst Oswaldo Cruz 104 (Suppl 1): 152–158.