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Supplementary Issue: Disease Vectors

Environmental Changes Can Produce Shifts in Chagas Disease Infection Risk

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ABSTRACT: An epidemiological network contains all the organisms involved (types) in the transmission of a parasite. The nodes of the network represent reservoirs, hosts, and vectors, while the links between the nodes represent the strength and direction of parasite movement. Networks that contain humans are of special interest because they are of concern to public health authorities. Under these circumstances, it is possible, in principle, to identify cycles (closed paths in the network) that include humans and select the ones that carry the maximum probability of human infection. The basic reproduction number R_0 in such a network gives the average number of new infections of any type after the introduction of one individual infected by any type. To obtain R_0 for complex networks, one can use the next-generation matrix (NGM) approach. Every entry in NGM will average the contribution of each link that connects two types. To tease the contribution of every cycle apart, we define the virulence as the geometric mean of the NGM entries corresponding to the links therein. This approach allows for the quantification of specific cycles of interest while it also makes the computation of the sensitivity and elasticity of the parameters easier. In this work, we compute the virulence for the transmission dynamics of Chagas disease for a typical rural area in Colombia incorporating the effect of environmental changes on the vector population size. We concluded that the highest contribution to human infection comes from humans themselves, which is a surprising and interesting result. In addition, sensitivity analysis revealed that increasing vector population size increases the risk of human infection.

KEYWORDS: Chagas disease, next generation matrix, environmental change, mathematical model, epidemiological networks

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Introduction

What changes can be expected in human infection risk produced by shifts in land use and climate? The answer is obviously complicated as some diseases may actually shrink their distributions[1,2] while others can potentially become more common.[3–5] We are particularly interested in investigating infection risk of vector-borne tropical diseases, and among them Chagas disease. Chagas disease in Colombia is transmitted to humans primarily by vectors of the species *Rhodnius prolixus*[6,7] that feed from reservoirs in what has been called the sylvatic cycle. The main reservoir in the wild is *Didelphis marsupialis*, while dogs, pigs, and cats may act as domiciliary reservoirs.[8,9] Humans became part of the transmission network by constructing dwellings close to palm trees, the preferred habitat of the vector. Disease transmission from vectors to humans and reservoirs requires contact with insect feces infected with the parasite *Trypanosoma cruzi*.[10] Transmission to insects from humans and reservoirs occurs when insects seek blood meals.[11] In Colombia, there are 2 people million infected and 8 million at risk.[7]

Current changes in land use and possible shifts in temperature, humidity, and rain seasons can potentially alter

the transmission of *T. cruzi*.[9] Indeed, increased temperature has been linked to shorter insect breeding cycles,[12] while palm tree mono-crops can provide huge areas for insect development. But are these changes in insect population size going to translate into an increased risk of human infection? After all, changes in land use while providing more land for insects could alter the composition of species in the environment (including ecological relations[13,14]) resulting in a different parasite transmission network, which could be either less or more efficient in spreading the disease.[5,15–18]

Unfortunately, measuring the effect of climate or land use change by field experiments might be too slow or extremely complicated.[4] However, epidemiological models can be used to understand the role of different species in disease transmission and the potential effect of environmental changes. Mathematical epidemiological models aim at describing or predicting the average dynamic of the transmission of a disease among members of a particular population.[19–21] An important quantity associated with these models is the basic reproductive number R_0: a threshold value that indicates whether a disease is going to invade the population.[22,23] If multiple populations are involved, R_0 can be computed as the spectral radius of the next generation matrix (NGM). The NGM contains the number of secondary cases of each pair of types involved. Although, given a specific model, obtaining R_0 is straightforward (cf.ref. 23), it does not tell us the contribution of each of the populations involved in the transmission of the parasite.[21,22] In addition, its sensitivity to model parameters is often complicated to derive,[24,25] making it less an attractive tool to investigate the effect of environmental changes.

To overcome these difficulties, we recently proposed an alternative quantity that we called the *virulence*.[26] To compute the virulence, we start by considering the environment as a network where nodes correspond to species and the edges represent relationships between species (ie, who interacts with who). The virulence is defined for a path in the network that starts and finishes at the same node (a cycle). It is clear that changes in the environment can alter the network structure, for example, it can change node densities or it could change the overall connectivity. The virulence of a cycle is the geometric mean of the entries of the NGM for the edges involved in the cycle. The critical virulence, which is the greatest cycle virulence, is telling us that the reproductive capacity of a disease is concentrated on the critical circuit. The critical virulence bounds the basic reproductive number, and being easier to compute, it is more malleable for sensitivity analysis.

In this work, we present a simple mathematical model for Chagas disease transmission and find expressions for the virulence and the critical virulence for the system. In addition, using parameters that are biologically feasible, we identify key cycles in the network. Finally, we investigate the possible impact of an environmental change, modeled as a change in vector population size, by computing the sensitivity and elasticity of the critical virulence to this variable.

Methods

Mathematical model. First we consider a general epidemiological framework for vector-borne diseases to derive the governing equations, but in the Results section, we will derive the parameters specific for Chagas disease in Colombia. The epidemiological system can be described by four different types of carriers of a pathogen: two different kinds of hosts, which we will call R_1 and R_2, a vector V, and humans, H. An epidemiological model for such a system is given by the equations:

$$\frac{dS_V}{dt} = m_V n_V - (\beta_1 I_1 + \beta I_2 + \beta I_H) S_V - m_V S_V \quad (1)$$

$$\frac{dI_V}{dt} = (\beta_1 I_1 + \beta I_2 + \beta I_H) S_V - m_V I_V \quad (2)$$

$$\frac{dS_1}{dt} = m_1 n_1 - b_1 I_V S_1 - m_1 S_1 \quad (3)$$

$$\frac{dI_1}{dt} = b_1 I_V S_1 - m_1 I_1 \quad (4)$$

$$\frac{dS_2}{dt} = m_2 n_2 - b_2 I_V S_2 - m_2 S_2 \quad (5)$$

$$\frac{dI_2}{dt} = b_2 I_V S_2 - m_2 I_2 \quad (6)$$

$$\frac{dS_H}{dt} = m_H n_H + d_H I_H - b_H I_V S_H - m_H S_H \quad (7)$$

$$\frac{dI_H}{dt} = b_H I_V S_H - (m_H + d_H) I_H \quad (8)$$

Where:

- n_j, S_j, I_j are the abundance of the total population, the population of susceptible and the infected individuals, respectively. $j = V$ for vectors, $j = 1$ for hosts of type R_1, $j = 2$ for hosts of type R_2, and $j = H$ for humans. We also have the relation: $n_j = S_j + I_j$,
- m_j are death rates and recruitment rates in each population; they are assumed to be equal so the population size

remains constant. We consider an increased mortality for humans that have acquired the pathogen represented by d_H, so the natural death rate and recruitment rate for humans is given by: $m_H + d_H$;

- β_j and b_j are the infection rates from host or humans to vectors and vice versa, respectively.

Using the assumption that the population size remains constant (so birth and death rates are comparable), we put $S_j = n_j - I_j$, and the system 1–8 collapses to:

$$\frac{dI_V}{dt} = (\beta_1 I_1 + \beta I_2 + \beta I_H)(n_V - I_V) - m_V I_V \quad (9)$$

$$\frac{dI_1}{dt} = b_1 I_V (n_1 - I_1) - m_1 I_1 \quad (10)$$

$$\frac{dI_2}{dt} = b_2 I_V (n_2 - I_2) - m_2 I_2 \quad (11)$$

$$\frac{dI_H}{dt} = b_H I_V (n_H - I_H) - (m_H + d_H) I_H \quad (12)$$

The transmission network is represented by the graph in Figure 1. Arrows contain the number of new infections of type j that are caused by the introduction of an infected individual of every type j. The network is characterized by nodes (populations) and arrows that connect them. A cycle is a path in the network that starts and finishes at the same node. A simple cycle is a cycle that does not enter and leave more than once through any node. Note that we do not include transmission within populations, and vectors move parasites between populations of reservoirs and hosts.

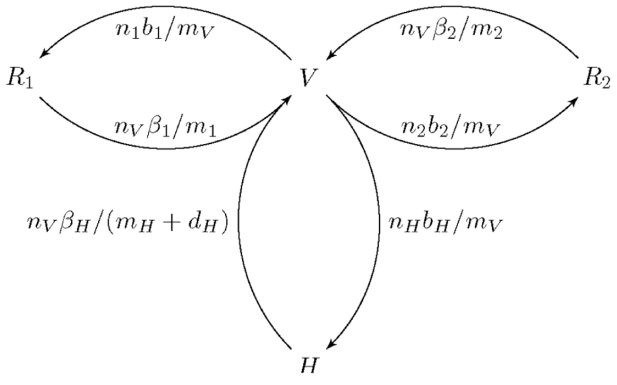

Figure 1. Directed graph associated with the system. Two different types of reservoirs ([R_1] and [R_2]), vectors (H), and humans (H) are considered in this model. Note that arrows connect populations that can transmit the parasite to each other; self-infection is not possible in this model. Transmission rates are represented by β_j's, population densities by n_j's; birth and death rates by b's and m_j's, respectively. A *cycle* is a path that starts and finishes at the same node. A *simple cycle* only crosses once every node but the start and finishing node.

The NGM contains the number of new infections produced in each type in the system by an infected individual of every other type. Thus, in each entry of the NGM, we have the term associated with the arrow in the directed graph. The NGM for the system described in Figure 1 is given by:

$$\text{NGM} = \begin{bmatrix} 0 & \frac{n_V \beta_1}{m_1} & \frac{n_V \beta_2}{m_2} & \frac{n_V \beta_H}{m_H + d_H} \\ \frac{n_1 b_1}{m_V} & 0 & 0 & 0 \\ \frac{n_2 b_2}{m_V} & 0 & 0 & 0 \\ \frac{n_H b_H}{m_V} & 0 & 0 & 0 \end{bmatrix}$$

The basic reproductive number R_0 is the average number of infections produced by the contribution of the whole network. If R_0 is greater than 1, the disease will establish itself in the population.[27] Therefore, R_0 is a quantitative approximation for long-term infection risk of the network. R_0 can be computed from the NGM by finding the largest eigenvalue of the NGM.[28] The contribution of every cycle to R_0 is an important aspect of disease transmission: it will tell us the relative weight of a path for this network's infection risk.

Based on previous work[26] and using ref. 29, we established that the *virulence* of a cycle μ(NGM), or the contribution to R_0 from a given cycle, can be computed by taking the geometric mean of every entry of the NGM involved in the cycle. Furthermore, there is a cycle that contributes the most ($\mu_{\max}$(NGM)) to the reproductive capacity of the disease, and we call its virulence the *critical virulence*.

The simple circuits in our network are:

$R_1 \to V \to R_1$, $R_2 \to V \to R_2$, $H \to V \to H$,

with respective virulence equal to:

$$\sqrt{\frac{n_V \beta_1 n_1 b_1}{m_1 m_V}}, \quad \sqrt{\frac{n_V \beta_2 n_2 b_2}{m_2 m_V}}, \quad \sqrt{\frac{n_V \beta_H n_H b_H}{(m_H + d_H) m_V}}.$$

The value $\mu_{\max}$(NGM) is obtained by finding among all these simple circuits in the graph the greatest one.

Elasticity and sensitivity. We now assume that the abundance of vectors, n_V, is the main variable linked with the environment, either via a change in temperature or a shift in land use. Thus, we measure the elasticity and sensibility of $\mu_{\max}$(NGM) to n_V, $E(\mu_{\max}(\text{NGM}), n_V)$, and $S(\mu_{\max}(\text{NGM}), n_V)$ as:

$$E(\mu_{\max}(G), n_V) = \left| \frac{\partial \text{In}\, \mu_{\max}(G)}{\partial \text{In} n_V} \right| = \left| \frac{n_V}{\mu_{\max}(G)} \frac{\partial \mu(G)}{\partial n_V} \right| \quad (13)$$

and

$$S(\mu_{\max}(G), n_V) = \left| \frac{\partial \mu_{\max}(G)}{\partial n_V} \right|. \quad (14)$$

Results

Model parameters. Chagas disease in Colombia could be grossly characterized by the transmission of *T. cruzi* to vectors of the species *R. prolixus* (V) and sylvatic reservoirs such as *D. marsupialis* (R_1) and domestic animals, like dogs or pigs (R_2) and humans (H). The amount of parasite transmission between the nodes in this network is quantified by the virulences defined in the previous section. In order to compare these expressions, we use data from the literature (actual number choices detailed in the Discussion section) and some simple manipulations to reduce the amount of unknowns. To this end, we start by dividing NGM by n_V to get the relative abundance to vectors, instead of the absolute abundance. Using an estimate of 1 domestic animal per 1000 vectors, 1 human per 1000 vectors, and 1 sylvatic reservoir every 2000 vectors we get:

$$\frac{n_1}{n_V} = 0.0005$$

and

$$\frac{n_2}{n_V} = \frac{n_H}{n_V} = 0.001$$

Mortality rates can be estimated from life expectancy. We use and estimate a 2-year life expectancy for R_1, 1 year for V, 3 years for R_2, and 70 years for H. Thus,

$$m_V = 1;\ m_1 = 0.5;\ m_2 = 0.3$$

and

$$m_H = 0.015$$

Disease-induced death rate in humans can be estimated by assuming a decrease in life expectancy of an average of 20 years. Therefore:

$$d_H = 0.005$$

In the model, disease transmission rates have units of new infections per susceptible per unit of time. Because they are difficult to estimate, it is more convenient to express them as relative odds of infection. Thus, we further divide NGM by β_H (infection rate of vectors after a human encounter) and determine the relative difficulty of transmission compared to this route. We estimate that infection of vectors after a contact with an R_2 is equally probable that an infection after a human contact, but can be twice as probable from R_1 since they interact continuously in the sylvatic cycle. Thus,

$$\frac{\beta_1}{\beta_H} = 2$$

and

$$\frac{\beta_2}{\beta_H} = 1$$

Infection of H, R_1, and R_2 from V tends to be less efficient since it requires contact with insect feces. We also assumed that $b_H < b_1 < b_2$ based on the number of contacts and reported incidences. Thus,

$$\frac{b_H}{\beta_H} : \frac{b_1}{\beta_H} : \frac{b_2}{\beta_H} = \frac{1}{100} : \frac{1}{10} : \frac{1}{5}$$

Virulence and critical virulence. Using the expressions for virulence and the set of parameters derived in the previous section and varying β_H between 10^{-5} and 1, we found that the virulence and R_0 vary linearly between:

$$2 \times 10^{-7} < \mu(R_1 \to V \to R_1) < 2 \times 10^{-2}$$

$$1.7 \times 10^{-7} < \mu(R_2 \to V \to R_2) < 1.7 \times 10^{-2}$$

$$2.24 \times 10^{-7} < \mu(H \to V \to H) < 2.2 \times 10^{-2}$$

$$3.4 \times 10^{-7} < R_0 < 3.4 \times 10^{-2}$$

for $n_V = 1$ (ie, per vector). The critical virulence (see ref. 26,29) is $\mu_{\max}(\text{NGM}) = \mu(H \to V \to H)$

$$\mu_{\max}(\text{NGM}) \le R_0 \le \sqrt{3}\, \mu_{\max}(\text{NGM})$$

Elasticity and sensitivity. $E(\mu_{\max}(\text{NGM}), n_V)$ and $S(\mu_{\max}(\text{NGM}), n_V)$ for β_H between 10^{-5} and 1, and $n_V = 1$ are:

$$1.1 \times 10^{-7} < S(\mu_{\max}(\text{NGM}), n_V) < 1.1 \times 10^{-2}$$

$$E(\mu_{\max}(\text{NGM}), n_V) = 0.5$$

Discussion

In this work, we presented a simple mathematical model that contains some of the features that characterize the transmission of *T. cruzi* between sylvatic, domestic, and human populations. We consider three simple cycles: (i) $R_1 \to V \to R_1$, (ii) $R_2 \to V \to R_2$, and (iii) $H \to V \to H$. Other cycles are missing, for example, humans can have transmission via blood transfusion,[30] insect nymphs could eat contaminated feces from adults,[30] or domestic animals could eat insects.[31]

In addition, there are multiple other sylvatic populations involved, including reptiles and birds that do not host the parasite but feed the insects.[32] However, the cycles considered are the best known and might be responsible for the greatest portion of parasite transmission.[30,32]

Model parameters. With the simple structure shown in Figure 1, we had to estimate a total of 10 parameters and the densities for each population involved. Population densities were normalized by insect population, so we estimated relative abundances. Reports suggest that *D. marsupialis* can have densities of two to three individuals per km^2.[31] For the same area, we found reports of 2000 insects (100 insects per palm times 20 palms).[33] Similarly, we estimated that in rural areas, the density of humans and domestic animals is around six per km^2. The values for the virulence for every cycle and R_0 are reported per insect.

Mortality rates came from life expectancy reported in the literature. However, the experimental reports vary even within species; thus, we use approximate life spans in years. We found that *R. prolixus* lives for about a year[12,34] and *D. marsupialis* for about two years.[8] For humans, we used life expectancy of 70 years and assume the disease would shorten the life span by 20 years on average.[7,10]

Transmission rates were expressed as proportions to the transmission rate from humans to vectors. There are some reports that suggest that β's (parasite transmission via blood meals) are higher than b's (parasite transmission via contaminated feces).[30] Because the rates of transmission are difficult to measure and they are critical for model results, we vary β_H between 10^{-5} (1 out of 100.000 encounters results in an infected vector) and 1 (1 out of 1 encounter results in an infected vector) and kept the proportions constant to explore the behavior of the critical virulence. We believe that this range contains the biologically feasible values for the transmission rate.

Virulence and critical virulence. We found with the model that the cycle $H \rightarrow V \rightarrow H$ is the critical cycle because it has the maximum virulence. The virulence for this cycle is 12% higher than the virulence of $R_1 \rightarrow V \rightarrow R_1$ and 30% higher compared to $R_2 \rightarrow V \rightarrow R_2$, for all values of β_H. We also computed R_0 and found that extremely low values of β_H produce $R_0 = 3.4 \times 10^{-7}$. Thus, a population in the order of millions of insects per km^2 is needed to maintain the disease. On the other hand, when $\beta_H = 1$, $R_0 = 3.4 \times 10^{-2}$, and only 100 insects per km^2 would be enough to maintain the disease in the population. This last number is greatly exceeded in many endemic areas.

This finding is interesting because very often health authorities target insect eradication, which is very important, but this study suggests that additional efforts should be made to identify people infected and provide them with treatment, not only for ethical reasons, but also because having humans infected is what contributes the most to disease establishment, at least in this simple model.

Elasticity and sensitivity. Climate and many other local environmental conditions are likely to have a large impact on vector-borne diseases, as survival, development, and physiological rates of vectors and hosts are often related to abiotic variables.[35] In addition, climatic factors will, to a large extent, determine where a vector species can persist, and the same applies for many host species, therefore climate change could expand or diminish the areas where the disease can establish.[25]

Sensitivity analysis provides a way to measure how small changes in the parameters translate into variations in the critical virulence.[24,36] We found that vector densities increase the critical virulence linearly for $10^{-5} \leq \beta_H \leq 1$. Sensitivity analysis showed that a 50% change in critical virulence can be expected after a small perturbation of insect population's size. The elasticity corroborated that this relation is maintained for the whole range of β_H. This suggests that insect population densities play a prominent role in human infection. If they change because of land use shifts or climate variations, we could expect different patterns of disease transmission.

Conclusions

We conclude that insect population densities, as expected, play an important role in human Chagas disease infection risk. Sensitivity and elasticity analysis revealed that a small change in insect densities could translate into 50% increase in the number of human secondary cases. If changes in land use or climate produce changes in insect population sizes, then human infection risk is expected to change in a steep manner. In addition, we found that the simple cycle $H \rightarrow V \rightarrow H$ contributes the most to Chagas disease establishment. These findings, taken together, suggested to us that it is important to actively screen human populations for infection while continuing the efforts to keep insect densities low. This is important for Colombia because only a small proportion of the population infected is diagnosed when donating blood or by health systems and historically strong effort has been directed to house improvement for insect eradication.

Author Contributions

Conceived and designed the experiments: JMC, CS. Contributed to the writing of the manuscript: JMC, CS. Agree with manuscript results and conclusions: JMC, CS. Jointly developed the structure and arguments for the paper: JMC, CS. Made critical revisions and approved final version: JMC, CS. Both authors reviewed and approved of the final manuscript.

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