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"A Model for Chagas Disease Involving Transmission by Vectors and Blood Transfusion"

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A Model for Chagas Disease Involving Transmission by Vectors and Blood Transfusion

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Models on the population dynamics of Chagas disease are discussed. The effects of vector and blood transfusion transmission are considered and epidemiological data is provided to support model assumptions. Also, the role of density-dependence on the population dynamics of the vector population is explored as well as the existence of non-reproductive insect stages involved in the transmission process. When density dependent effects are neglected, there is a non-oscillatory approach to the endemic equilibrium (local asymptotic stability). When density-dependence effects and vector stage-structure are introduced, limit cycle solutions may be obtained. Results are compared to available field data.

1. INTRODUCTION

Chagas disease or American trypanosomiasis is a vector transmitted disease of tropical America. It is second to malaria in the continent in the number of people infected and at risk (World Health Organization, 1989; Moncayo, 1992). In Fig. 1 prevalence and population at risk are shown. The disease is scattered through all Latin American countries and it is highly endemic in humid tropical regions of the continent. Chagas disease has three stages. The acute stage follows the invasion of the bloodstream by the protozoan *Trypanosoma cruzi*. This stage lasts from one to two months (Texeira, 1979) and infected individuals may or may not show symptoms of the disease. Young children are the population group with the highest incidence and mortality rates (Texeira, 1979). In Fig. 2 a graph of the prevalence of infection in bugs is shown, for a region in Argentina. In this graph the high correlation between the presence of children and the prevalence of infection in the vector population is apparent. After the acute phase, the infected individual enters the chronic stage which has a variable duration that goes from 10 to 20 years (Molyneux and Ashford, 1983; Moncayo, 1986). At its end, for reasons not well known, the disease may

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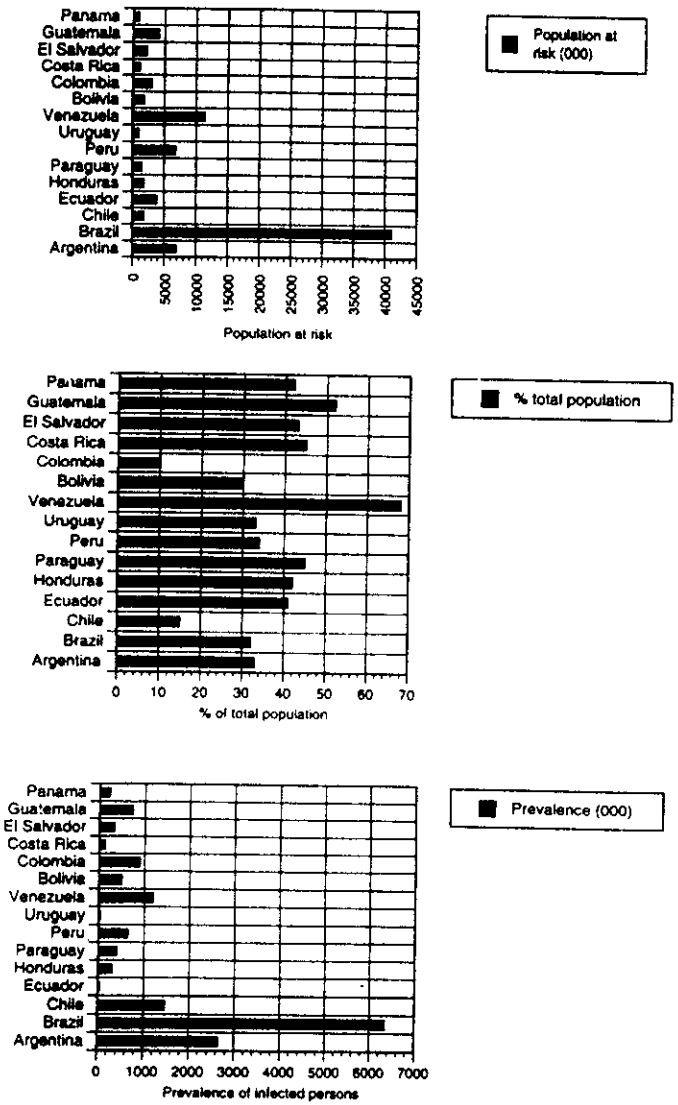

FIG. 1. *Trypanosoma cruzi* infection in Latin America. (a) Data on population and risk 1000). (b) Same data as in (a) but represented as percentage of the total population of :h country. (c) Data on prevalence (× 1000). From Moncayo (1992).

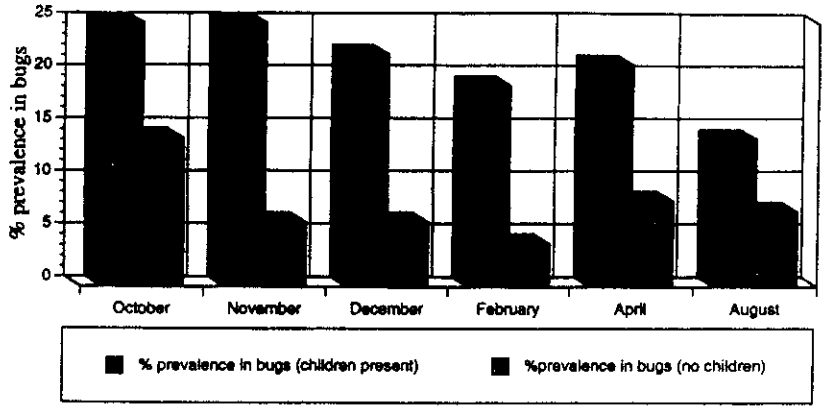

FIG. 2. Association between vector prevalence and the presence of children. From Catala (1991).

follow three different paths: Individuals may develop megasyndromes (Garnham, 1979; Moncayo, 1986; Molyneux and Ashford, 1983); others may present myocarditis which is the terminal form with highest mortality in the group of 20 to 50 years of age. The age-dependent prevalence of the chronic stage has a mode typically in the class of young adults 20–30, 30–45 year old. Infection usually occurs at an early age and thus, the majority of acute cases are children while chronic cases occur in young adults (see Fig. 3).

Finally, individuals may remain asymptomatic for the rest of their lives. Individuals in this group may live an ordinary life although some may die of "sudden death" associated with heart failure produced by the parasite (Texeira, 1979; Brener, 1983, Molyneux and Ashford, 1983).

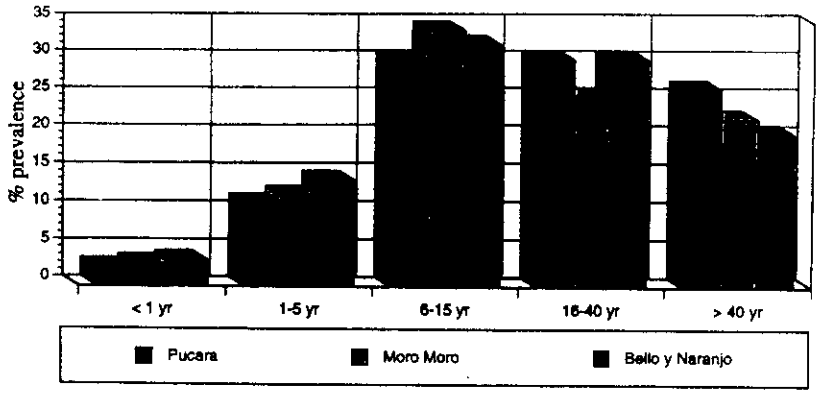

FIG. 3. Age distribution of Chagas disease in three communities in Vallegrande, Bolivia. From Moncayo (1986).

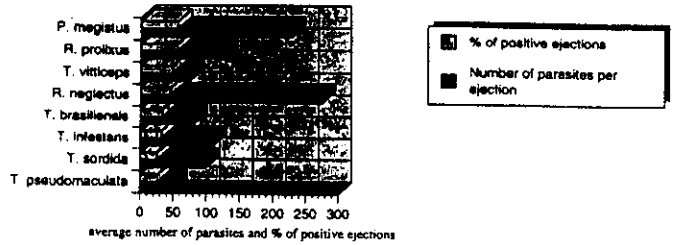

FIG. 4. Average number of parasites and percentage of infective ejections. From Zeledón and Rabinovich (1981).

The disease is transmitted by hematophagous arthropod (Homoptera: Reduviidae) vectors. Contrary to parasite transmission in malaria, the infective forms of the protozoan are not "injected" to the individual during feeding. The infection occurs by contamination (Molyneux and Ashford, 1983). In Fig. 4 the average number of parasites per ejection and the percentage of ejections with infective forms (trypomastigotes) of the parasite are shown. Notice that for all of the most common anthropophilic species, *T. infestans*, *R. prolixus*, and *P. megistus*, the percentage of positive ejections is above 30%.

Vectors of Chagas disease have a marked tendency to defecate several times while feeding (Molyneux and Ashford, 1983). Infective forms of the parasite go in the feces and can penetrate the skin through the soft tissues of eyes and mouth, or through wounds inflicted by the host him/herself when attempting to aleviate the irritation induced by the vector bite. Infectivity of the vector is not constant throughout the year. Density-dependent insect population growth as well as seasonal variations in temperature and relative humidity contribute to this variable infectivity (Zeledón and Rabinovich, 1981). In Fig. 5, yearly variation of parasite infective forms in *T. cruzi* are shown. Note that there is one infectivity peak per year.

There are other forms of transmission of *T. cruzi* independent of the vector. The most important of these is blood transfusion transmission (Castillo *et al.*, 1984). Prevalence in blood donors in some Latin American countries can reach levels beyond 10% (see Fig. 6) (Schenone *et al.*, 1978; Sagua *et al.*, 1982; Pinto Dias and Brener, 1984; Schenone and Rojas, 1989). Thus, unless careful screening of the blood supply is implemented, horizontal transmission risk is high (WHO, 1985; Moncayo, 1992). The second form of transmission independent of the vector is congenital or vertical transmission but its epidemiological significance is still not well established (Bittencourt, 1984; Bittencourt *et al.*, 1985).

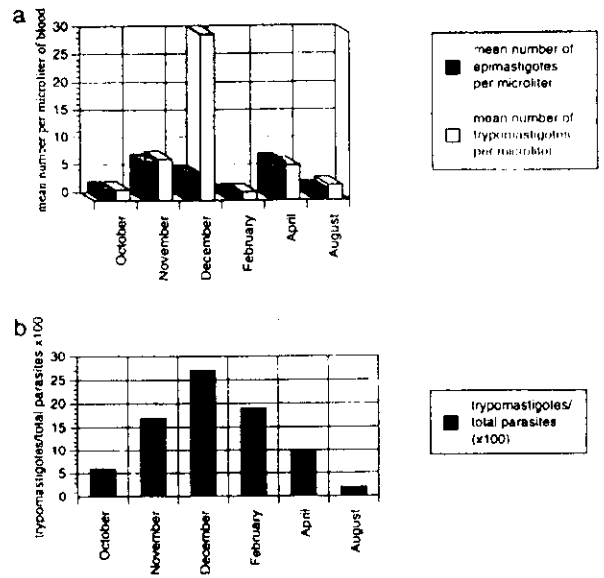

FIG. 5. *Trypanosoma cruzi* forms in feces of infected bugs: (a) mean number of infective (trypomastigote) and reproductive (amastigote) forms per microliter of blood; (b) percentage of the total number of parasites ejected in feces that correspond to the infective form of *Trypanosoma cruzi*. From Giojalas and Gorla (1989).

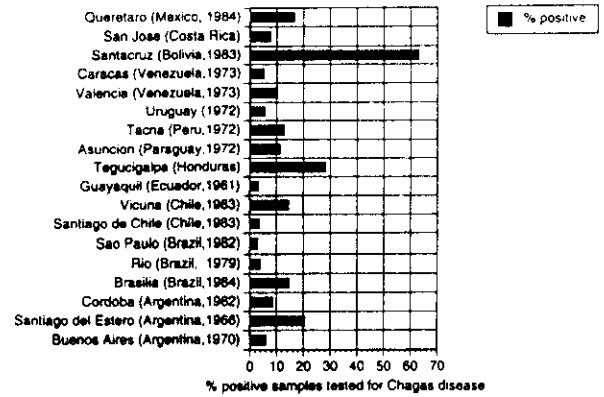

FIG. 6. Percentage of positive blood samples collected in cities of Latin American countries. From Moncayo (1992).

Infection by *Trypanosoma cruzi* existed in wild animal communities prior to human settlement in regions of Latin America that are now endemic (Coimbra, 1988). Chagas disease was a zoonosis that spread into agricultural communities (Coimbra, 1988). The type of human dwellings associated with them were well suited for invasion by insect vectors. This hypothesis is supported by the fact that present day nomadic Indians of endemic egions, are practically free of it. In fact, the number of vector species found in their houses is almost zero (Coimbra, 1988).

There is another factor that plays an important role in disease transmission. The domestic habits of the main vector species responsible for transmission are relatively strong. *Triatoma infestans*, for example, is almost exclusively a domiciliated vector that can hardly be found outside human houses. Other species are not such specialists (Zeledón and Rabinovich, 1981; Starr *et al.*, 1991) but alternate their diet between humans and other (domestic and wild) animals. Others still are only exoparasites of wild mammals with no direct impact on human infection.

Chagas disease, as many other infectious diseases of the tropics, is endemic in regions with weak economies and populations with high annual growth rates (the so-called "Third World" countries). This paper presents simple models for the spread of Chagas disease in such a population. The combined effects of vector and blood transfusion transmission are explored and the consequences of population growth on the dynamics of the disease are assessed.

2. Basic Model

Previous models of Chagas disease transmission are those of Rabinovich *et al.* (1979), Rabinovich and Rossell (1985); Rabinovich and Himschoot (1990), Busenberg and Vargas (1988) and Velasco-Hernandez (1991). The models presented in this paper follow the spirit of the last two where the dynamics of the disease in the human population is analyzed. Busenberg and Vargas (1988) studied Chagas disease under the assumption of a constant proportion of infective vectors but allowing the human host population to grow exponentially as may be the case in Latin American countries with high annual growth rates. They found that there are exponentially stable solutions and no oscillatory behavior is possible when approaching the endemic equilibrium. Velasco-Hernandez (1991) studied the infection under the assumption of constant host population and introducing vector population dynamics. This simple model also shows the existence of an endemic equilibrium point when the basic reproductive number is greater than one. No fluctuating behavior is observed.

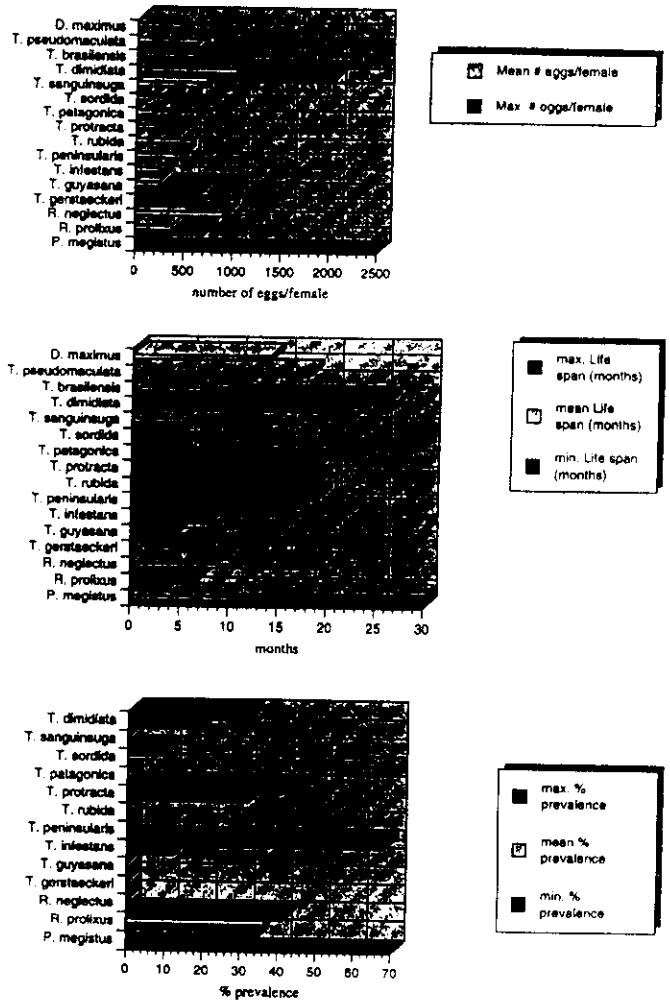

FIG. 7. Parameter values corresponding to the most important species of vectors for Chagas disease: (a) Egg production, (b) longevity, and (c) prevalence of infection of the adult stage in several triatominae species. From Zeledón and Rabinovich (1981).

Vector species of Chagas disease have five nymphal stages previous to the adult stage and all of them are hematophagous. The full life cycle reproductive output (measured as the maximum number of eggs per female) of these organisms is variable and depends on temperature and relative humidity (see Fig. 7).

In the model below we neglect this age/stage structure of the vector population and aggregate in a single compartment all individuals. Later on, this assumption will be somewhat relaxed with the introduction of a maturation delay to account for density-dependent regulation (Schofield, 1982).

The model in this section is a generalization of the malaria model first developed by Ross (1911), Macdonald (1957), Bailey (1982), Rogers (1988), and more recently by Aron and May (1982) and Dietz (1988). We consider a human host population of susceptible individuals, denoted by $S(t)$, which are exposed to *T. cruzi* through the biting of infected vectors, denoted by $V(t)$. We assume that the contact rates between these two populations conform to proportional mixing probabilities. Let a denote the number of bites of infected vectors per but per unit time and b denote the proportion of those bites that produce infection. Ross (1911) showed that we must take into account the ratio of vector numbers to host numbers in order to obtain a reliable description of the transmission process. In the classical models of malaria, both host and vector populations have constant values. However, in regions where Chagas disease is endemic, population growth is significant within the time scale of the infection, and also, the vector population undergoes seasonal fluctuations which are product of syncronization of seasonal trends in temperature and humidity, and possibly, density-dependent regulation. In this model, however, we will only approximate population growth by assuming a constant recruitment rate into the susceptible population. This is certainly a rough, if at all valid, approximation to the exponential growth that endemic areas show. However, it does introduce variable total population size into model and we, therefore, will be able to assess the effects of this assumption in Chagas disease dynamics.

It is reasonable then to take the ratio of host to vector numbers as

$$m(t)=\frac{M(t)+V(t)}{T(t)},$$

where $M(t)$ denotes the number of susceptible vectors at time t, and

$$T(t)=S(t)+A(t)+C(t)$$

with $A(t)$ and $C(t)$ denoting the number of acutely and chronically ill hosts at time t, respectively. In Fig. 8a the year-long variation in the biting rate of *T. infestans* and the associated blood loss rate in an experimental setting

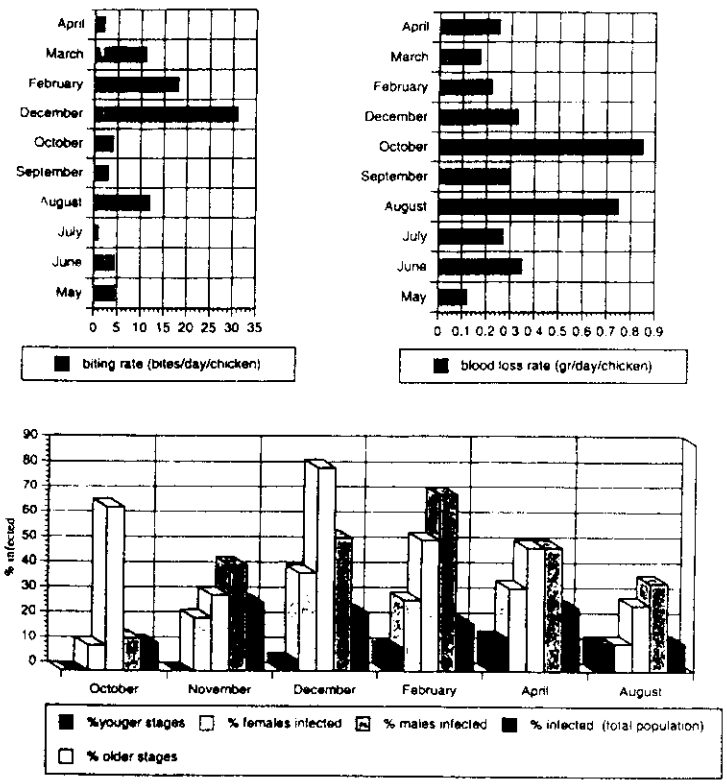

FIG. 8. (a) Daily biting rate (bites per day per chicken) and daily blood loss rate (grams of blood per day per chicken). Only monthly averages are reported. Data form experiments with *Triatoma infestans* performed by Catala (1991). (b) Seasonal changes in the prevalence of infected bugs according to the stage. From Gorla and Schofield (1985).

with chicken is shown. We show in this paper that this periodic behavior is related to periodic changes in $m(t)$ which are driven, in turn, by density-dependent recruitment in the vector species. In Fig. 8b the seasonal changes in seropositive vectors are shown. Note the existence of one prevalence peak per year. In Fig. 9 the variability of prevalence throughout vector species is presented.

We also assume that host contacts with infective vectors are proportional to the frequency of infective vectors $V(t)/(M(t)+V(t))$. This assumption is valid for relatively high population densities. Otherwise a mass action contact rate would be more appropriate. Let σ^{-1} represent the

mean residence time in the acute stage of an infected individual and ν_0, ν_1 the disease-induced death rate of each infective stage respectively. Also, let μ denote the natural death rate of the human population, and δ the corresponding death rate of the vector population regardless of its infected status.

Our model equations are ("'" denotes derivative with respect to time)

$$\begin{aligned} S'(t) &= \Lambda - \left(\frac{\alpha V(t) + h_0 A(t) + h_1 C(t)}{T(t)}\right) S(t) - \mu S(t) \\ A'(t) &= \left(\frac{\alpha V(t) + h_0 A(t) + h_1 C(t)}{T(t)}\right) S(t) - (\mu + \sigma + \nu_0) A(t), \\ C'(t) &= \sigma A(t) - (\mu + \nu_1) C(t), \end{aligned} \tag{1.1}$$

where $P(t)$ is the total vector population. Note that the vector transmission rate in the above equations does not depend on m but, rather, on the ratio of infected vector number to total population density because $\alpha m(V/P) = \alpha(V/T)$. The equations for the vector population are

$$\begin{aligned} M'(t) &= L - \left(\frac{\beta_0 A(t) + \beta_1 C(t)}{T(t)}\right) M(t) - \delta M(t), \\ V'(t) &= \left(\frac{\beta_0 A(t) + \beta_1 C(t)}{T(t)}\right) M(t) - \delta V(t). \end{aligned} \tag{1.2}$$

In the above, Λ and L represent the number of individuals added to the corresponding population per unit time; $\alpha = ab$ and $\beta_i = ac_i$, where c_i is the proportion of bites of susceptible vectors on acute and chronic infective host that result in infection in the vector, $i = 0, 1$, respectively. Also h_0 and h_1 represent the rates of transmission through blood transfusion by the acutely and chronically ill individuals respectively.

Remark. Blood transfusion transmission is being modeled here by assuming that blood donors are randomly chosen from the total population. There is thus no screening and the recipients of blood donations are donating blood themselves at the same rate as anybody else. A more realistic way of modeling this process would be to assume that there is a fixed recruitment of susceptible, acutely and chronically ill individuals respectively into a potential blood donor compartment D (screening). After this screening action, we may assume that only a minor fraction of the infectious individuals will contribute to the transmission of *T. cruzi* to the susceptible population. Given that blood donation is strongly correlated with age and that blood receptors are individuals of very specific health status, one cannot reasonably expect that this way of transmission be of

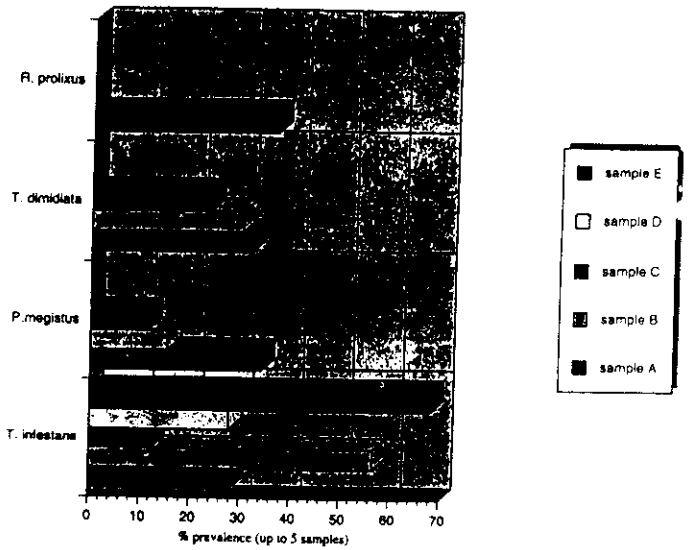

FIG. 9. Infection rates for several species of vectors. Different values for the same species corresponds to different places or times. From Zeledón and Rabinovich (1981).

epidemiological importance relative to the stability or properties of the endemic states. However, since blood transfusion transmission occurs in Chagas disease we have included it in this very simple model to qualitatively evaluate the "sensitivity" of disease dynamics to this process.

Since we will need them later, we write now the equations for the total populations

$$\begin{aligned} T'(t) &= \Lambda - \mu T(t) - \nu_0 A(t) - \nu_1 C(t), \\ P'(t) &= L - \delta P(t). \end{aligned} \tag{2}$$

2.1. *Properties of the Equilibria*

We first analyze the initial spread of the infection into the human population. In the early stages of the disease the total host population is practically constant and also almost all host are susceptible rendering the approximation $S/T = 1$ and $A = 0$. We also can neglect the effect of blood transfusion transmission since most of these infections come from contacts

chronically ill individuals, who are very scarce at the start of the epidemic. Under these assumptions, from Eq. (1.1) we get

$$A(t) = A(0)\, e^{-(\mu+\sigma+\nu_0)t} + \frac{\alpha v_0}{\mu+\sigma+\nu_0}(1 - e^{-(\mu+\sigma+\nu_0)t}),$$

where v_0 is the initial proportion of infective vectors. Not surprisingly, the first epidemic burst of the disease is driven by the influence of the initial size of the infectious vector population represented by the factor $\alpha v_0/\mu+\sigma+\nu_0$ in the second term of the formula for $A(t)$.

To determine the existence and uniqueness of disease-free and endemic equilibrium points we define

$$B(t) = \frac{\alpha V(t) + h_0 A(t) + h_1 C(t)}{T(t)},$$
$$G(t) = \frac{\beta_0 A(t) + \beta_1 C(t)}{T(t)} \tag{3}$$

as the expressions for the force of infection (the rate of acquisition of new infective individuals per unit time) of both populations. In Figs. 7 and 8 typical parameter values are presented which have been gathered from several sources. An effort has been made to provide figures obtained from field conditions. Estimates of parameters obtained under laboratory conditions are used in our simulations only when field data are non-existent or unreliable. Note that a typical value for ν_1 (units day^{-1}) ranges in the interval $1/8000 \leqslant \nu_1 \leqslant 1/4000$ approximately. Thus, ν_1 is two to three orders of magnitude smaller that ν_0 and in what follows it will be taken as zero. We find now expressions for population densities at equilibrium,

$$S^* = \frac{\Lambda}{\mu + B^*}, \qquad A^* = \frac{B^* S^*}{\mu+\sigma+\nu}, \qquad C^* = \frac{\sigma A^*}{\mu},$$

and

$$M^* = \frac{L}{G^*+\delta}, \qquad V^* = \frac{G^* M^*}{\delta}.$$

Substituting the above into the expressions for B and G in (3), we obtain

$$B^* = \frac{\alpha L G^*}{T^*\delta(G^*+\delta)} + \frac{h_0 B^* \Lambda}{T^*(\mu+B^*)(\mu+\sigma+\nu)} + \frac{h_1 \sigma B^* \Lambda}{\mu T^*(\mu+B^*)(\mu+\nu+\sigma)},$$
$$G^* = \beta_0 \frac{B^*\Lambda}{T^*(\mu+B^*)(\mu+\sigma+\nu)} + \beta_1 \frac{\sigma B^* \Lambda}{\mu T^*(\mu+B^*)(\mu+\nu+\sigma)}, \tag{5}$$

where

$$T^* = \frac{\Lambda}{\mu+B^*}\left(1 + \frac{B^*}{\mu+\sigma+\nu} + \frac{B^*\sigma}{\mu(\mu+\sigma+\nu)}\right).$$

In order to find the equilibria of (1) we need to determine the fixed points of the equation

$$u = \Phi(u),$$

where Φ is defined as the RHS of (5) and $u = (B, G)^t$, where t here denotes transpose. At the disease-free equilibrium it is clear that the incidence rate is zero, therefore $\Phi(0,0)$ also vanishes and hence $(B^*, G^*) = (0,0)$ is a fixed point of (5). However, the Jacobian of Φ evaluated at $G = B = 0$ gives

$$D\Phi(0,0) = \begin{pmatrix} \left(\frac{1}{\mu+\nu+\sigma}\right)\left(h_0 + \frac{h_1\sigma}{\mu}\right) & \frac{L\alpha\mu}{\Lambda\delta^2} \\ \frac{\beta_0}{\mu+\nu+\sigma} + \frac{\beta_1\sigma}{\mu(\mu+\sigma+\nu)} & 0 \end{pmatrix}. \tag{6}$$

The dominant eigenvalue of (6) provides us with the basic reproductive number of the infection (Diekman *et al.*, 1990),

$$\mathcal{R}_0 = \tfrac{1}{2}[R_1 + \sqrt{R_1^2 - 4R_2}].$$

where

$$R_1 = \left(\frac{1}{\mu+\nu+\sigma}\right)\left(h_0 + \frac{h_1\sigma}{\mu}\right)$$

and

$$R_2 = \frac{L\alpha\mu}{\Lambda\delta^2(\mu+\nu+\sigma)}\left(\beta_0 + \frac{\beta_1\sigma}{\mu}\right).$$

If $\mathcal{R}_0 > 1$, the map Φ at zero is ejective and hence the parasite may spread in both vector and host populations. If, on the other hand, $\mathcal{R}_0 < 1$ the disease-free equilibrium is locally asymptotically stable. In Fig. 10 simulation results show this asymptotic stability of the endemic equilibrium. Note that the approach is asymptotic and with no oscillations.

Let $S^* = \Lambda/\mu$ and $M^* = L/\delta$ denote the density of the susceptible host and vector population, respectively, at the disease-free equilibrium. Then we can rewrite

$$R_1 = \left(\frac{1}{\mu+\nu+\sigma}\right)\left(h_0 + \frac{h_1\sigma}{\mu}\right),$$

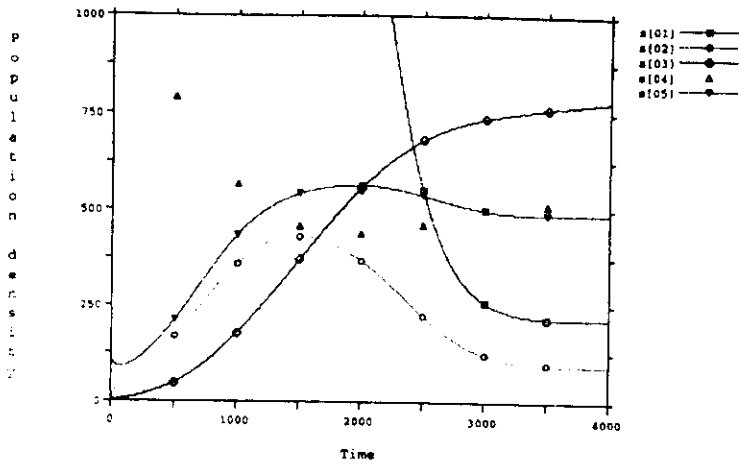

FIG. 10. Simulation of models (1.1) and (1.2) with Runga Kutta 2, fixed time-step solution. The figure shows the first 4000 days of the infection. Notice the epidemic peak in the prevalence of the acute infection A, and the steady rise in the number of chronically infected individuals C. The maximum prevalence in the insect population V, is reached after the corresponding peak in the human acute cases. There is a asymptotic approach to an endemic equilibrium state. The parameter values are $1/\mu = 7000$ d, $h_0 = 0.0001$, $h_1 = 0.001$, $A = 1$, $L = 5$, $\alpha = 0.01$, $\sigma = 0.001$, $1/\delta = 200$, $c_0 = 0.01$, $c_1 = 0.005$, $v_0 = 0.01$ and $v_1 = 0.0001$. The initial conditions $S(0) = 7000$, $A(0) = C(0) = 0$, $M(0) = 900$ and $V(0) = 100$ represent values near to the disease free equilibrium. Symbols are: $S \equiv s[01]$, $A \equiv s[02]$, $C \equiv s[03]$, $M \equiv s[04]$ and $V \equiv s[05]$.

and

$$R_2 = \frac{a^2 b(M^*/S^*)}{\delta(\mu+\nu+\sigma)}\left(c_0 + \frac{c_1\sigma}{\mu}\right).$$

In Chagas disease once an individual is infected it never recovers. Thus, after the acute phase, the compartment of chronically ill individuals acts as a compartment of removed individuals as far as the human host population is concerned. There is no recruitment of new susceptibles besides births. The compartment C provides new infections in the vector population. However, these infections will be only a relatively small proportion of the total number since more of the bitings occur in the acute stage composed primarily of children. In fact, we can now derive a formula for the age of first infection following Anderson and May (1991, p. 71). We consider system (1.1) as describing an $S-I-R$ epidemic with no recovery as

described above, and we look at the endemic equilibrium. If we neglect in this case horizontal transmission, i.e., $h = h_0 = h_1 = 0$, we have that at equilibrium the quantity

$$\frac{\alpha V_\infty}{T_\infty}$$

gives the rate of new infections (the subindex "∞" denotes variables at equilibrium). Let $S(t_0)$ be the number of newborn susceptible individuals at time t_0. Thus solving

$$S'(t) = -\frac{\alpha V_\infty}{T_\infty} S(t)$$

we get

$$\frac{S(t)}{S(t_0)} = e^{-(\alpha V_\infty/T_\infty)(t-t_0)}$$

which is the fraction of the initial susceptible population that remains susceptible after $t - t_0$ days. This implies that the average age of infection is given by

$$\mathcal{A} = \frac{T_\infty}{\alpha V_\infty} = \frac{1}{\alpha m_\infty v_\infty},$$

where $m_\infty = P_\infty/T_\infty$, and $v_\infty = V_\infty/P_\infty$.

If we assume no acute stage mortality, $\nu = 0$, then $\mathcal{R}_0 = R_2$ which can be written as

$$R_2 = \mathcal{C}_v\left(ac_0 + \frac{ac_1\sigma}{\mu}\right), \tag{7}$$

where

$$\mathcal{C}_v = \frac{abm_0}{\delta(\mu+\nu+\sigma)}, \qquad (m_0 = M^*/S^*).$$

Using the formula for the age of first infection $\mathcal{A}$, we can rewrite

$$\mathcal{C}_v = \frac{D}{\delta v_\infty \mathcal{A}}\frac{m_0}{m_\infty},$$

where $D = 1/(\mu+\sigma)$. This formula $\mathcal{C}_v$ is really a relative index. It compares the effectiveness of the vector species to transmit the parasite using the ratio of vector numbers to host numbers, before it spreads in the host

population and after the steady state is reached. This formula could be used to evaluate the effectiveness of control strategies by measuring m before and after its application (see, for example, Dye, 1990).

We proceed now with the analysis of the model. As a next step we see that Φ is bounded for all B, G positive. In fact, we have that

$$\Phi_1(B, G) \leqslant B_{max}$$

and

$$\Phi_2(B, G) \leqslant \frac{\beta_0 + (\beta_1 \sigma/\mu)}{1 + (\sigma/\mu)},$$

where

$$B_{max} = \max\left\{\frac{L\alpha\mu}{\Lambda\delta^2}, \frac{h_0 + h_1\sigma/\mu}{1 + \sigma/\mu}\right\}$$

for all non-negative values of G and B. This renders the existence of a non-trivial fixed point for Φ if we assume $\mathcal{R}_0 > 1$. This endemic equilibrium is unique. In fact, if one substitutes the definition of G in the one for B in (5), we obtain a single equation for B, and the problem becomes now to find

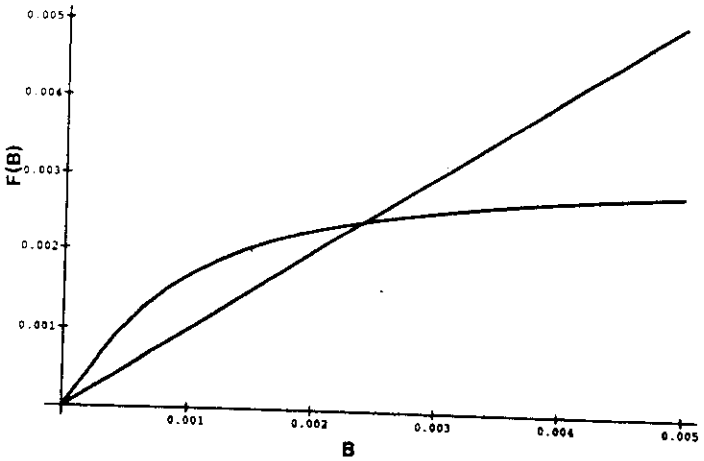

FIG. 11. Existence of the endemic equilibrium point for model Eqs. (1.1)–(1.2) as discussed in the text. Parameter values are the same as in Fig. 10, except now $\alpha = 0.1$. The value of $\mathcal{R}_0 = 3.3$ in this case. Shown are the straight line with unit slope and $F(B)$, the first equation in (5).

a unique fixed point of a one-dimensional mapping $B = F(B)$, which is bounded and continuous. It can be verified, after long and tedious algebra that this new mapping is convex and monotone increasing in R, thus obtaining the uniqueness of the endemic equilibrium, provided $\mathcal{R}_0 > 1$. In Fig. 11 $F(B)$ is shown for a particular set of parameter values.

Given the existence of a unique endemic equilibrium point define

$$\Phi(B, G) = \begin{pmatrix} \Phi_1(B, G) \\ \Phi_2(B, G) \end{pmatrix}$$

where

$$\begin{aligned} \Phi_1 &= \frac{\alpha L G}{T\delta(G + \delta)} + \frac{h_0 B\Lambda}{T(\mu + B)(\mu + \sigma + \nu)} + \frac{h_1 \sigma B\Lambda}{\mu T(\mu + B)(\mu + \nu + \sigma)}, \\ \Phi_2 &= \beta_0 \frac{B\Lambda}{T(\mu + B)(\mu + \sigma + \nu)} + \beta_1 \frac{\sigma B\Lambda}{\mu T(\mu + B)(\mu + \nu + \sigma)}, \end{aligned} \tag{8}$$

where B and G are given in (5) and B^* and G^* represent the incidence functions evaluated at the endemic equilibrium. Note that

$$\Phi(B^*, G^*) = 0.$$

The Jacobian of Φ, $D\Phi$ is a non-negative matrix for all non-negative host and vector population densities. Therefore, $\rho(D\Phi(B^*, G^*))$, the spectral radius of the Jacobian, indicates whether the endemic equilibrium point is locally repelling or attracting.

In order to show the local stability of the endemic equilibrium we treat the case when $h_0 = 0$ and $\beta_1 = 0$. These values determine a transmission process in which the acutely ill individuals can not infect others through contaminated blood, and where chronically ill individuals do not infect susceptible bugs. The assumption can be justified since in Chagas disease the overwhelming majority of new acute cases occurs in children younger than 5 years of age. The incidence rate coming from bits for the adult population is relatively low (P. Himshoot, personal communication). This gives support to the value $h_0 = 0$, since children are not allowed to donate blood. On the other hand, chronically ill individuals reportedly have extremely low concentrations of the parasite in their blood which are usually detected after repeated applications of the method of xenodiagnosis (Perlowagora and Moller, 1979). This method consists in letting "clean" bugs bite on a suspected infected person and then examining the bug's seropositive status. Thus, we may assume $\beta_1 = 0$.

We require $\mathcal{R}_0 > 1$ to ensure the existence of a unique endemic equilibrium. Recall that $\mathcal{R}_0$ is the spectral radius of $D\Phi$ evaluated at the origin.

In general, under the above assumptions, the spectral radius has the form

$$\rho(D\Phi(B, G)) = \tfrac{1}{2}(-A_0 + \sqrt{A_0^2 + 4A_1}) \tag{9}$$

where

$$A_0 = \frac{\mu(\mu+\nu+\sigma)[LG\alpha\mu\nu + GA\delta h_1\sigma + A\delta^2 h_1\sigma]}{A\delta(G+\delta)(B\mu+\mu^2+\mu\nu+B\sigma+\mu\sigma)^2}$$

and

$$A_1 = \frac{L\alpha\beta_0\mu^3(B+\mu)(\mu+\nu+\sigma)^2}{A\delta(G+\delta)^2(B\mu+\mu^2+\mu\nu+B\sigma+\mu\sigma)^3}.$$

Thus as the incidence rates B and G increase, system (1) approaches the endemic equilibrium, the spectral radius $\rho(D\Phi)$ decreases and actually tends to zero provided, of course, that $\mathcal{R}_0 > 1$. In Fig. 12 we show $\rho(D\Phi(B^*, G^*))$ as a function of B and G. A continuity argument extends this result for β_1, h_0 positive and small.

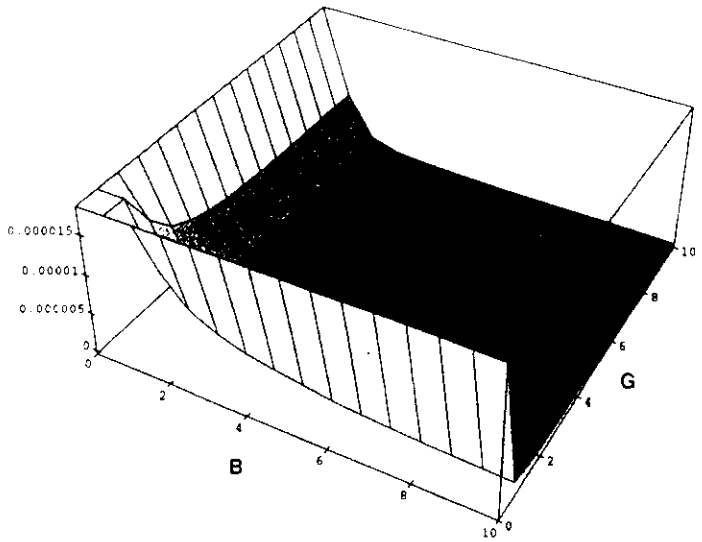

FIG. 12. Graph of $\rho(D\Phi)$ as a function of B and G. Parameter values are as in Fig. 10 except now $\alpha = 0.01$. The value of $\mathcal{R}_0$ is 1.13. The graph shown is truncated near (0, 0). As the value of B and G increase the value of $\rho(D\Phi)$ decreases very quickly below one.

The model analyzed so far shows the local asymptotic stability of the endemic equilibrium with both vector and host populations approaching it without oscillations. However, it is known that the density of the bug population follows an non-constant pattern (Gorla and Schofield, 1985; Zeledón and Rabinovich, 1981) that may be caused by purely density dependent effects (Schofield, 1982) or by seasonal environmental factors (Zeledón and Rabinovich, 1981) in regions with ample climatic fluctuations. In the next section, we generalized the model to account for density-dependent factors.

3. The Effect of Density-Dependence

Model (1) assumes a density-dependent regulation of parasite spread in the bug population. The incidence rate of the disease in this population decreases as the number of the available uninfected populations decreases. Schofield (1980) reports, however, that other important factor that regulates population growth is egg-to-adult developmental time and, in a lesser degree, female reproductivity. This author also indicates that for a constant susceptible host recruitment, both factors are density-dependent regulated.

Model (1) as it stands predicts the existence of a locally asymptotically stable endemic equilibrium as shown in Fig. 10.

To allow for egg-to-adult density dependent regulation we use the approach of Nisbet and Gurney (1982). We assume

1. all eggs take τ units of time to develop into sexually mature adults,
2. the rate of egg production by the adult population depends only on its current size,
3. the probability of an egg surviving and producing an adult depends on the size of the subpopulation within the same stage or age class.

Following Nisbet and Gurney (1982) we set $se^{-P(t-\tau)/P_0}$ as the probability that an egg laid at time t will survive to time $t+\tau$ where P denotes the density of the vector population and P_0 is the population density at which density dependent effects start acting. Let ϕ be the rate of egg production. Then we redefine L in equation (1.2) as

$$\phi s e^{-P(t-\tau)/P_0}.$$

Now we assume that once the eggs hatch, it takes about θ days for the nymphs to become susceptible individuals. It is known (Zeledón and Rabinovich, 1981) that first instar nymphs are hematophagous. However,

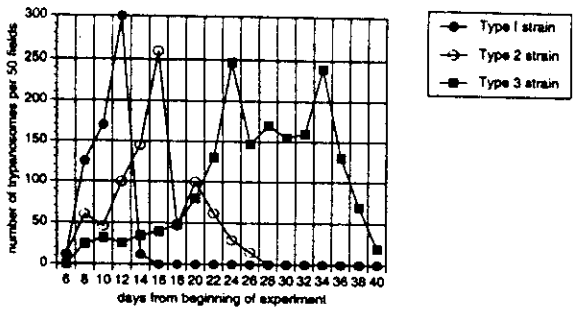

FIG. 13. Patterns of parasitaemia in three strains of *T. cruzi*. From Andrade (1979).

the volume of blood ingested is small compared with the blood intake of later stages (Schofield, 1982) and moreover, significant levels of parasitaemia in adult *Triatoma infestans* appear, on average, after 6 days (Andrade, 1979) (Fig. 13). In general, some time θ has to pass before infected bugs can have any impact on disease transmission. We take $\theta < \tau$.

The equations for the human population stand (same as (1.1)):

$$\begin{aligned} S'(t) &= \Lambda - \left(\frac{\alpha V(t) + h_0 A(t) + h_1 C(t)}{T(t)}\right) S(t) - \mu S(t) \\ A'(t) &= \left(\frac{\alpha V(t) + h_0 A(t) + h_1 C(t)}{T(t)}\right) S(t) - (\mu + \sigma + \nu_0) A(t), \\ C'(t) &= \sigma A(t) - (\mu + \nu_1) C(t). \end{aligned} \tag{10.1}$$

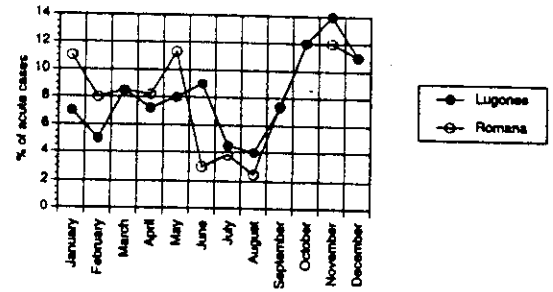

FIG. 14. Percentage of the total population with the acute disease in two regions of the Argentinian Chaco. From Giojalas *et al.* (1989).

In the new model, equations for M and V in (1.2) are replaced by

$$\begin{aligned} M'(t) &= \phi s e^{-P(t-\tau)/P_0} P(t-\tau) - \left(\frac{\beta_0 A(t) + \beta_1 C(t)}{T(t)}\right) M(t-\theta) - \delta M(t) \\ V'(t) &= \left(\frac{\beta_0 A(t) + \beta_1 C(t)}{T(t)}\right) M(t-\theta) - \delta V(t). \end{aligned} \tag{10.2}$$

In (10.1) we have introduced the average duration $1/\nu_0$ and $1/\nu_1$ for the acute and chronic stages which are of the order of 2 months and 10 to 20 years respectively.

The equation for the total vector population P is obtained by adding up both equations in (10.2). The resulting equation has been analyzed by Nisbet and Gurney (1982) and it can show a variety of behaviors. Following Nisbet and Gurney (1982) we know that there exists a unique non-trivial equilibrium $P^* = \ln(\phi s/\delta)$. This equation can also give rise to limit-cycle behavior with cycle amplitude determined by the product $\tau\delta$. In Fig. 7 some typical developmental times for several species of triatominae vectors are presented.

A set of simulations was run with two sets of parameter values that represent two typical triatominae vectors, *T. infestans* and *Rhodnius prolixus*. The former has a longer life span and the onset of reproductive activity occurs after 160 days after hatching. In contrast, the other species has a shorter life span and, consequently, sexual maturity occurs around 70 days after hatching (Zeledón and Rabinovich, 1981). The value of the delay θ is the same for both typical vectors and set to a value of 20 days, approximately 14 of which correspond to the egg stage.

Both simulations show persistent oscillation in all four subpopulations, the ones with larger amplitude corresponding to the vector. In general, the trend for both sets of simulations is an steady increase in the number of people in the chronic stage, and very mild oscillations, when compared with the ones in the vector population, in both susceptible and acute-stage individuals. This trend contrasts sharply with the results presented in Sections 2 and 3, where a non-oscillatory approach to the endemic equilibrium is always achieved. In Fig. 14 we show one-year data on the prevalence of acute cases in Northern Argentina (Giojalas *et al.*, 1990) which supports the existence of oscillatory behavior. The vector of Chagas disease in this region is *T. infestans*. This data also apparently shows the existence of two peaks per year in number of acute cases. In Fig. 15 a two-year simulation of our model, for two different vector species, produces instead, only one peak per year. We argue that this is in rough agreement with the data on Fig. 14 if one samples on a interval of time that includes the lowest number of cases. If this is done two peaks will appear in this window, one in each end of the interval. However, the population dynamics of the vector

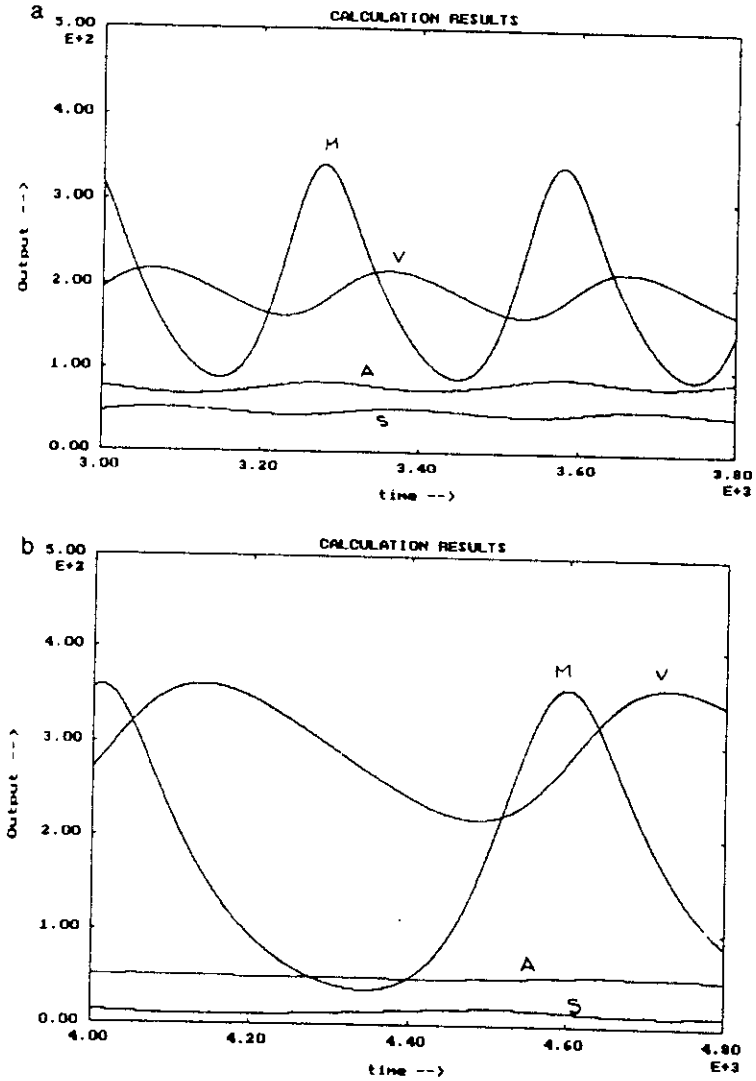

FIG. 15. Simulation of models (10.1) and (10.2) for 800 days. (a) Parameter values as in Fig. 10 but with $1/\delta = 200$, $\tau = 70$ and $\theta = 20$. The maturation delay is close to that presented by *T. infestans*. The chronic cases are way above the graph and are not shown. Notice that fluctuations appear for the remaining compartments although those corresponding to the

suggest, according to our model, that one peak of acute cases should exists annually.

The model also shows that oscillations in the population of the insect vector may arise solely by the action of density-dependent effects in the recruitment rate of new susceptible individuals. Note that right after the peak in the number of susceptible vectors, there is a second peak this time of the number of infected vectors, θ days apart from the first.

The basic reproductive number $\mathcal{R}_0$ is still the same for model (10.1), (10.2) given the small values for ν_1.

4. Blood Transfusion Transmission

In this section we analyze the role of horizontal transmission in Chagas disease. This transmission form is becoming a health threat in Latin America because of the rapid urbanization of the rural population (Moncayo, 1992). We, however, refer the reader to the Remark in Section 2 for the justification of the modeling of this factor.

The main problem associated with this form of transmission arises from the long period of infectiousness associated with the chronic stage. In Table I we show some typical data on seropositive infectious individuals 17 or more years after emigrating outside endemic areas. In urban centers the importance of transmission through vector contact is negligible and thus we only consider the equations for the human host with $\alpha = \beta_0 = \beta_1 = 0$.

On the other hand we assume that the proportion of asymptomatic individuals in the acute stage is low and thus horizontal transmission is only important through contacts with the chronically ill. Then we take $h_0 = 0$ and $h_1 = h$. The new equations describe a $S - E - I$ type model with vital dynamics. These are

$$\begin{aligned} S'(t) &= \Lambda - \left(\frac{hC(t)}{T(t)}\right) S(t) - \mu S(t) \\ A'(t) &= \left(\frac{hC(t)}{T(t)}\right) S(t) - (\mu + \sigma + \nu)\, A(t), \\ C'(t) &= \sigma A(t) - \mu C(t), \end{aligned} \tag{11}$$

human host are very mild. In the figure S and A denote the susceptible and acute stage hosts, while M and V denote the susceptible and infected vectors respectively. (b) Simulation of Eqs. (10.1)–(10.2) for 800 days. The maturation delay is $\tau = 150$ days and $1/\delta = 365$, as in *R. prolixus*. The bug population fluctuates with higher amplitude than in the previous simulation. In the figure S and A denote the susceptible and acute stage hosts, while M and V denote the susceptible and infected vectors respectively.

TABLE I

Seropositive Status of Chronically Infected Patients and Time of Residence Outside Endemic Area[a]

Xenodiagnosis	Average age	Years outside endemic area
Positives	31.7 years (range 4–56)	17.3 years (range 3–43)
Negatives	36.24 (range 12–64)	15.3 (range 1–44)

[a] From Coura (1988).

where we assume no disease induced mortality in the chronic compartment. The analysis of section 2.1 follows through, providing us with the existence and uniqueness of an endemic equilibrium point of the basic reproductive number

$$\mathcal{R}_0 = \frac{h\sigma}{\mu(\mu+\nu+\sigma)} \tag{12}$$

is greater than one.

$\mathcal{R}_0$ depends linearly on h and thus changes on this parameter reflect in the same way on changes on the basic reproductive number. Since σ is large compared with μ and ν we have that the quotient $\sigma/(\mu+\nu+\sigma)$ is approximately equal to one. Thus the magnitude of $\mathcal{R}_0$ depends on the ratio h/μ which one would expect to be very small. Notice that in this model we are actually averaging blood transfusion transmission over the whole population. Since only a very small fraction of it receive donated blood the ratio h/μ must be small forcing the value of the basic reproduction number (12) to be less than one. As an example, suppose that the mean life span of the host population is 50 years. Then $\mathcal{R}_0 \approx 50h$ which implies that in order for the parasite to spread in the population by blood transfusion, $h > 0.02\text{yr}^{-1}$ which is a very high value. Since blood transfusions are performed only on a relatively small group of the general population it is not expected that Chagas disease could maintain an endemic level in this way.

If a cohort of individuals is infected-by sharing contaminated blood from a blood bank, the prevalence of the infection will decrease very slowly. To see this consider positive disease-induced death rates v_0, v_1. Suppose that at time $t = t_0$ we manage to get $h = 0$. This gives

$$A(t) = A(t_0)\, e^{-(\mu+\sigma+v_0)(t-t_0)}.$$

Then, after substituting into the equation for C in (11) we have

$$C(t) = e^{-(\mu+v_1)(t-t_0)}\left[C(t_0) + \frac{A(t_0)}{\mu+\sigma+v_0}\left(1 - e^{-(\mu+\sigma+v_0)(t-t_0)}\right)\right].$$

Because $\mu+\sigma+v_0 > \mu+v_1$ the second exponential above vanishes faster than the first for large t. Therefore

$$\frac{C(t)}{C(t_0) + A(t_0)/\mu+\sigma+v_0} = e^{-(\mu+v_1)(t-t_0)}$$

denotes the proportion of individual remaining chronically ill after $t - t_0$ units of time. The mean residence time in this compartment is

$$\frac{1}{\mu+v_1}.$$

5. Control Strategies

In this section we briefly explore the effect of an control program in the transmission dynamics of Chagas disease. Great effort has been put into the development of vaccines to prevent infection by *T. cruzi*. There are several promising possibilities but all are in experimental phase. Other control measures (see Molineaux, 1988) tend to physically limit the availability of susceptible host to bugs by changing the sanitary conditions that allow house infestation by infected bugs. These two are radically different control measures with very different implications for transmission dynamics according to our model. The net effect of any potential vaccine is to reduce the number of new infections resulting from infected bug bites. Consequently, if no other vector control measures are introduced, the number of bugs per host will not change. The vaccine reduces only b, the proportion of bites by infected vectors that result in host infection. This can induce a decrease in $\mathcal{R}_0$.

Other control strategies involve improving sanitary conditions and behavior that put individuals at risk (Moncayo, 1986). These strategies physically interfere with the transmission process by actually removing a proportion of susceptible individuals from the vector availability pool. Let p be the fraction of the newly recruited population of susceptibles protected by this second control strategy against the parasite. Assume that vector mortality is independent of this control strategy. In this case the first equation in (1.1) becomes

$$S'(t) = A(1-p) - \left(\frac{\alpha V(t) + h_0 A(t) + h_1 C(t)}{T(t)}\right) S(t) - \mu S(t),$$

and consequently, the basic reproductive number now is given by

$$\mathcal{R}_0 = \tfrac{1}{2}(R_1 + \sqrt{R_1 + 4R_2})$$

with

$$R_1 = \left(\frac{1}{\mu + \nu + \sigma}\right)\left(h_0 + \frac{h_1\sigma}{\mu}\right),$$

and

$$R_2 = \frac{a^2 b(M^*/S_p^*)}{\delta(\mu + \nu + \sigma)}\left(c_0 + \frac{c_1\sigma}{\mu}\right),$$

where now $S_p^* = \Lambda(1-p)/\mu$.

It is surprising that the model predicts an increase in the magnitude of the basic reproductive number, rather than a decrease, when a fraction $p < 1$ of the susceptible population is protected from vector contact. In fact, unless $p = 1$, an control program based in the removal of susceptible individuals where vector transmission is strong will only make things worse. The transmission process from infected vector to host depends on the ratio m of vector numbers to host numbers. The net effect of the control program is to remove a fraction of the vector blood supply and, consequently, to increase the number of insects per remaining susceptible host, that is, vectors are forced to search for food increasing the infection risk of the proportion of susceptibles not implementing the control method. Therefore, there is a net increase of $\mathcal{R}_0$.

The assumption of vector mortality independence on the control strategy is the responsible for this result. The assumption is highly criticizable since improvement of sanitary conditions will surely increase egg and perhaps nymphal mortality. Nevertheless, in houses with high infestation rates, much of the adult and late nymphal stages of the vector population are likely to escape and survive while the control strategy is being implemented reducing the effect of the control measure on its mortality. The formula for the basic reproductive number indicates that it is more effective as disease control strategy, to reduce the vector population than to improve sanitary conditions of only a fraction of the host population. *T. cruzi* has multiple reservoirs in other mammal and bird species, and the insect vector is facultative in its host preference. This implies that for a period of time, removing a fraction p of susceptible host by the improvement of sanitary conditions will bring about a decrease in m. However, if direct control of the bug population is not implemented, eventually m will increase and thus the disease will spread even faster than before. This is a plausible mechanism for the production of epidemic outbreaks reported by Gorla (1991)

6. Conclusions

Chagas disease is a major disease in Latin America, it is a disease of the poor (Pinto Dias, 1985). It is nevertheless surprising that in one of the most authoritative books on the subject of transmission of infection diseases recently published, *Trypanozoma cruzi* is not even mentioned (Anderson and May, 1991). Chagas disease has been mainly a Latin American research subject with the bulk of a very abundant literature published in Spanish or Portuguese.

Carlos Chagas (Chagas, 1911) identified triatominae insects as carriers of the parasite around 1909 in the state of Minas Gerais, Brazil, practically at the same time when Ronald Ross was revolutionizing epidemiology with his studies on Malaria transmission. In fact, Carlos Chagas has already emphasized the importance of the domiciliary habits of the adult female mosquito in Malaria transmission, as early as 1906 (Romaña, 1979). The etiology of the disease that later was named Chagas disease, however, was not accepted by the prevailing medical establishment until around 1930 (Romaña, 1979), 24 years after its discovery. Once the foundations of the etiology and basic transmission mechanisms were established, the true dimension of its prevalence began to appear. As mentioned in Section 1, Chagas disease is a endemic Latin American infection that threatens approximately 90 million people (Moncayo, 1992).

In this paper we have studied the basic population dynamics and transmission mechanisms of the disease. We have also explored plausible density-dependent mechanisms of fluctuations in bug population abundance. Vector population biology is tightly coupled to the environment, specially to changes in temperature and humidity and variable infectivity of bug bites can also be described by time dependent recruitment, as in the malaria model of Aron and May (1982), or biting rate. However, the introduction of density-dependence in egg to adult development can account for the annual fluctuations in vector infectivity and in the prevalence of the acute stage in the host.

Chagas disease vectors have five nymphal stages before reaching reproductive maturity. These nymphal stages are hematophagous and hence contribute to disease transmission. In this paper we have attempted to introduce these two factors into the population dynamics of the disease. Equations (1.1) and (1.2) are modified by introducing a maturation delay to account for the stage structure in vector reproduction, and a "blood-sucking" delay to account for the hematophagous nature of all vector strages. These two delays produce annual peaks in the population density of susceptible and infective vectors, and susceptible and acutely infective hosts. The prevalence of the chronically ill hosts shows a steady increase to a constant level without significant fluctuation.

We have also compared the relative efficiency of blood transfusion and vector transmission. The former is relatively inefficient. For example, in a population growing at 2% per year with a life expectancy of 50 years, the horizontal transmission rate would have to be as large as the growth rate (see discussion following Eq. (11)). Given that blood transfusions are only performed under special health-related circumstances including countries with high seroprevalence in the blood supply, we would not expect Chagas disease to reach endemic proportions purely as consequence of blood transfusion transmission. However, if the majority of cases produced by this form of transmission is through blood donated by chronically infected individuals, the number of cases would disappear very slowly as Eq. (15) shows.

Control measures have been also explored with our model. The main control form should include control of vector numbers and improvement of sanitary conditions. This obvious conclusions targeted to disease eradication, is not so "obvious" when its practical implementation is needed. For example, in regions of Argentina and Mexico where Chagas disease is endemic, the triatominae vectors are not recognized by the people as a health threat. Children play with them and when insect control is performed it is frequently limited to the collection by hand of all individuals that can possibly be found (author's personal field observation). Given the economic hardship of Latin American countries this situation is not likely to improve in the short term. So it is necessary to have, at the very least, a measure of the strength and rate of spread of the parasite in any given population at risk. According to our formula for $\mathscr{C}_v$, basic parameters needed are μ^{-1}, the life expectancy of an individual host; δ, the life expectancy of the main vector population; $\mathscr{A}$ the age of first infection; v_∞, the prevalence of infection in the bug population; and the number of vectors per host before and after the application of the control measure, m_0 and m_∞.

Finally, we point out some of the factors important in disease transmission that have not been treated here. Perhaps the most important one is the neglect of host age-structure. As Fig. 2 shows, the prevalence of *Trypanosoma cruzi* in vectors is strongly correlated with the presence of children in the household, and chronic stage individuals are mainly young adults. This aspect of the disease deserves a more detailed analysis and will be published elsewhere. The other problem is house infestation and its relation to alternative wild mammal reservoirs (Bertoglia *et al.*, 1984; Burchard *et al.*, 1984). The number of bugs per home is a known risk factor that can reach incredibly high numbers. Also, species of triatominae differ in their affinity towards human blood and can shift hosts.

Chagas disease is a major health problem in the American continent and Latin America would be greatly benefit from the contributions that, in particular, mathematical epidemiologists of North America and Europe could provide. The discovery of the etiology of Chagas disease is almost as old as that of malaria but its population dynamics is basically unexplored.

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