Malaria prevalence amongst Brazilian Indians assessed by a new mathematical model

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SUMMARY

An alternative way to estimate the endemic level of malaria amongst Brazilian Indians is proposed. This is achieved by estimating the age-related 'force of infection' of malaria (the effective inoculation rate), applying a mathematical model, described elsewhere, to serological data. In addition we present a way to estimate the Basic Reproductive Rate of malaria in the same area. The results have shown a good degree of accuracy in describing the endemic pattern of malaria in the area, and also indicate some relevant aspects of its age distribution related to the design of control strategies.

INTRODUCTION

The quantification of malaria endemicity is a fundamental tool for understanding the distribution of malaria, the dynamics of its transmission, the past and expected changes in transmission resulting from natural and man-made changes, and in particular in the application of malaria control measures [1–3].

Dempster (1848) proposed a system to estimate malaria prevalence by relating the proportion of enlarged spleens to the level of endemicity of malaria in different communities in India [4]. With the identification of the malaria parasite by Laveran in 1880 and the description of its biological cycle by Ross in 1897, entomological data became the central aim of studies on the assessment of transmission and control strategies in the first half of the twentieth century [5].

Notwithstanding the theoretical progress led by the works of Ross and Macdonald [1, 6–9], the practical difficulties of evaluating the entomological parameters under field conditions make this approach cumbersome. So, indirect effects of malarial infection, like the spleen enlargement, as well as direct effects like the presence of parasites in peripheral blood, remained the most used data in studies on malarial prevalence. Current malaria typologies classify the endemic zones according to either the spleen rate (SR) [10] or the parasite rate (PR) [11]

as follows: hypoendemic: SR and PR in children of 2–9 years between 0 and 10%; mesoendemic: SR and PR in children of 2–9 years between 11 and 50%; hyperendemic: SR and PR in children of 2–9 years above 50%; holoendemic: SR in children of 2–9 years and PR in children of 1 year above 75%, and adult SR and PR low.

However, Molineaux (1988) pointed out that both the above typologies are subject to criticism in that (a) they create artificial discontinuities in a natural continuum; (b) they ignore underlying factors; (c) they lump together very dissimilar situations (e.g. low level of malaria resulting either from natural conditions or from the continuous application of control measures); and (d) the 'true' parasitologic picture is often masked by widespread use of antimalarials over and above the effects of increasing immunity with age and the seasonal variation in vector densities [3].

However, as stressed by Molineaux [3], the use of the Basic Reproductive Rate (BRR), defined as the number of secondary infections caused by a single infectious individual in an entirely susceptible population [8], as a malarimetric index depends on the ability to measure it. Direct estimation (using entomological data) is difficult, expensive and imprecise. In the selection of an appropriate control strategy, however, even a rough estimate of the BRR may be invaluable, and a variety of indirect means such as an assessment of the past history of malaria in the area or the determination of the age-specific parasitologic index in combination with serologic profiles can be used in its definition.

The best (most cost-effective) way to collect such information is an indirect estimation of the BRR and has not yet been defined.

The purpose of this paper is to estimate the endemic level of malaria from age-related serological profiles by estimating the age-related force of infection for malaria (the effective inoculation rate) applying a mathematical model described elsewhere [12, 13]. In addition we present a means to estimate the BRR of malaria in this area.

MATHEMATICAL MODELS ON SEROEPIDEMIOLOGY OF MALARIA

Draper [14] was the first author to propose an estimation of the inoculation rate based on age-specific serological data. His model is very simple and states that by plotting the proportion of seropositives in an inverse logarithmic scale against age, one gets a straight line passing through the origin and with inclination μ . The probability, R , of being infected in one year is:

$$R = 1 - e^{-\mu}. \quad (1)$$

Van Druten [15] extended Draper's model and proposed a catalytic approach [16] to estimate the inoculation rates from serological profiles. In this model, the inoculation rate, denoted the 'force of infection' (λ) is seen as the derivative of the intensity function of a non-homogeneous Poisson process [17]. This implies a non-constant force of infection. From the proportion of seropositives ($P(a)$) Van Druten [15] estimated the inoculation rate by the expression:

$$\lambda(t) = \frac{d[-\ln(1 - P(a))]}{dt}. \quad (2)$$

Note that in this interpretation the force of infection is treated as reflecting a past event.

Dietz [18] has published recently a comprehensive review of the mathematical approaches as applied to malaria.

Working on similar lines [12, 13, 19] our present study is an application of the theory concerning the estimation of the age-related force of infection from serological data, developed on data from an endemic area, the Xingu Indian Reservation in central Brazil.

The field work was carried out in the period between July and October 1985, as part of a study designed to assess malaria prevalence in the area.

METHODS

Population studied: the Xingu Indian Reservation

The Xingu Indian Reservation is situated in the northern part of Mato Grosso state, in Central Brazil. It is one of the greatest Indian reservations of Brazil approximately 25000 square kilometres in area and with a total population estimated as 4000 inhabitants.

This region is characterized by a huge hydrographic network centred in the Xingu river, and by an ecosystem of transition between savannah and rain forest. The climate is tropical humid with a rainy season from October to March and an average annual temperature of 25 °C.

The northern part of the park, which was the object of this work, is dominated by the rain forest where the sun rays are filtered by the forest canopy without reaching the surface. This provides, with a very humid environment involving rivers and ponds and a high level of soil moisture, almost ideal circumstances for the breeding of the *Anopheles* species. The result is a very high level of malaria endemicity among the indians [19].

Despite the regular DDT spraying of the villages since the mid-1970s, malaria has remained stable in this region [20].

Of the six indian tribes of the northern region of the park amongst all of whom malaria is an important problem, we chose to study the Txucarramaes, the Caiabis and the Suias [19–22].

The target population comprised 1045 individuals. The Txucarramae tribe consists of 371 persons originally from two distinct villages. However, at the time of the survey, the whole Txucarramae population had transferred to a single new village which has caused some increase in malaria transmission among them.

From the total population we took a random sample of 175 individuals, stratified according to age and tribe as shown in Table 1.

Serological and parasitological study

Blood samples were taken by digital puncture and collected on filter paper as described by Guthe, Vaisman and Paris-Hamelin [23] and were tested for IgG antibodies against *P. falciparum* using the Indirect Fluorescence Antibody (IFA) technique by the method of Sulzer, Wilson and Hall [24]. Titres of 20 and above were considered positive. Thick blood smears were processed for the parasitological

Table 1. *Number of individuals of the studied population stratified according to age and tribe*

Age in years	Tribe			Total
	Txucarramae	Caiabi	Suia	
0-1	7	7	3	17
1-2	6	7	6	19
3-4	8	12	5	25
5-9	6	16	7	29
10-14	9	13	7	30
15-24	10	9	8	26
> 25	9	12	8	29
Total	55	76	44	175

Table 2. *Fitting of parameters and statistics of the proportion of age-related seropositives*

Age	Fitted	Observed
1.5	0.06	0.05
3.0	0.10	0.12
7.0	0.32	0.31
12.0	0.74	0.73
19.5	0.96	0.96
> 25.0	0.97	0.97
Fitting parameters	Values	Standard deviation
b ₀	3.26	0.3329
b ₁	-0.316	0.1283
b ₂	-0.0089	0.01181
b ₃	0.000428	0.0002971

study by standard methods, and read by two different experienced workers following the WHO recommendations.

Data from subjects less than 1 year old were not considered because of the influence of maternal antibodies.

The model

The model applied in the current study was described by Burattini [12] and Burattini and colleagues [13] and depends on three basic assumptions: (1) Inoculations occurs in a non-uniform Poisson fashion. This implies, among other things, a non-constant inoculation rate; (2) transmission has not changed dramatically over the period of time corresponding to the age of the eldest individual in the surveyed population; (3) the acquisition of immunity is of Markov type – only the last inoculation determines the level of antibody.

The model consists of the following steps:

(1) Fitting the age-related proportion of seropositives, $P(a)$, to a continuous function with the form:

$$P(a) = \frac{1}{1 + e^{K(a)}}, \tag{3}$$

where $K(a)$ is a polynomial whose parameters and fitting statistics can be seen in

Table 2. We did not consider data from age below one year because of the influence of maternal antibodies.

(2) The estimation of the age-related inoculation rate (force of infection), $h(a)$ according to the equation:

$$h(a) = \frac{dP(a)/da + P(a)/\tau}{1 - P(a)}, \quad (4)$$

where τ means the average period of time in years individuals remain seropositive without reinfection. The full description of equation (4) can be found in Burattini [12] and Burattini and colleagues [13];

(3) This inoculation rate is then applied to a compartmental model whose structure is as follows:

$$\frac{\partial X}{\partial t} + \frac{\partial X}{\partial a} = -h(t, a)X(t, a) + rY(t, a) + \gamma Z(t, a), \quad (5)$$

$$\frac{\partial Y}{\partial t} + \frac{\partial Y}{\partial a} = h(t, a)X(t, a) - (r + \delta)Y(t, a), \quad (6)$$

$$\frac{\partial Y'}{\partial t} + \frac{\partial Y'}{\partial a} = \delta Y'(t, a) - \phi Y'(t, a), \quad (7)$$

$$\frac{\partial Z}{\partial t} + \frac{\partial Z}{\partial a} = \phi Y'(t, a) - \gamma Z(t, a), \quad (8)$$

where $X(t, a)$, $Y(t, a)$, $Y'(t, a)$ and $Z(t, a)$ stands for the proportion of susceptibles, parasite positives and seronegatives, parasite positives and seropositives, and parasite negatives and seropositives, respectively, and r , δ , ϕ and γ are the transition rates between the compartments, whose values are presented in Table 3. According to the initial assumption 2 the time derivatives can be omitted from equations (5)–(8). This system of first order ordinary differential equations was numerically integrated through a 4th order Runge–Kutta algorithm [25].

The average age of acquisition of the first infection $A(I^{st})$ was calculated according to the following equation:

$$A(I^{st}) = \int_0^\infty ah(a)e^{-\nu(a)}da, \quad (9)$$

where

$$\nu(a) = \int_0^a h(a)da. \quad (10)$$

The Basic Reproductive Rate, R_0 , defined above, is related to the average inoculation rate as given by Macdonald [26]:

$$h = \frac{R_0 \phi Y^* (-\ln(p))}{a Y^* - \ln(p)}, \quad (11)$$

where Y^* is the average number of parasite positive individuals, p is the probability of a mosquito surviving through one whole day, a is the average number of men bitten by one mosquito in 1 day and ϕ as above.

Table 3. *Epidemiological parameters*

Parameter	Value	Description
p	0.90 [27]	Probability of surviving/mosquito/day
a	0.05 [27]	Average number of bites/mosquito/day
δ	4.0 year ⁻¹	Rate of development of antibodies
ϕ	0.35 year ⁻¹	Clearance rate of parasitaemia
r	0.0 year ⁻¹	Spontaneous recovery rate
τ	10 years	Average duration of seropositivity
γ	1/ τ [12, 13]	Rate of losing protective immunity

Table 4. *Age-related proportion of positives to thick blood smear and the IFA technique*

Age in years	Parasite rate	Seropositives
1-2	0.10	0.05
3-4	0.04	0.12
5-9	0.04	0.31
10-14	0.06	0.73
15-24	0.20	0.96
> 25	0.21	0.97

Fig. 1. Results of the fitting procedures for the serological data. The crosses represent the actual values whereas the continuous line represents the function fitted to data.

The epidemiological parameters are summarized in Table 3. The entomological parameters p and a were taken from the literature [27].

RESULTS

Table 4 shows the proportion of positives for the thick smear tests and the IFA, distributed according to age.

The fitting of $P(a)$ shown in Figure 1 derives from the figures shown in Table 2.

Fig. 2. Theoretical estimate of the age-dependent inoculation rate ($h(a)$).

Fig. 3. Result of the numerical simulation of the model, showing the age dependence in the proportion of persons in each compartment and in the serological and parasitological prevalence levels. $\square$, X; +, Y; $\diamond$, Y'; $\triangle$, Z; $\times$, (Y' + Z); $\triangle$, Y + Y', where X, Y, Y', Z, (Y' + Z) and (Y + Y') stands for the proportion of susceptibles, parasite positives but yet seronegatives, parasite positives and seropositives, recovered seropositives, total seroprevalence and the total parasite prevalence levels, respectively.

Fig. 4. Retrieved seroprevalence level. Squares represent the actual data and continuous line the result of the simulation.

Fig. 5. Retrieved parasite prevalence level. Squares represent the actual data and continuous line the result of the simulation.

The age-dependent inoculation rate, $h(a)$ calculated according to equation (4) is shown in Figure 2.

The result of the numerical integration of equations (5)–(8) is shown in Figure 3. This figure shows the simulation of the age-dependent dynamics of malaria in the studied area.

Table 5. *Calculated age of first infection and basic reproductive rate (R_0)*

h	1.72 year ⁻¹	Average inoculation rate
$A(I^*)$	2.74 years	Average age of 1 st inoculation
R_0	26.76	Basic Reproductive Rate
Y^*	0.20	Average parasite rate at equilibrium

Figures 4 and 5 show the age-related proportion of positives to serological and parasitological tests, respectively, retrieved by the model and compared to the original data.

Finally, the results of the calculation of the average age of first infection and the basic reproductive rate are presented in Table 5.

DISCUSSION

A large amount of editorial space has been devoted to the problem of the epidemiology of malaria and its measurement. For a comprehensive review see Wernsdorfer and McGregor [28].

The endpoint of malaria transmission measurement is commonly some epidemiological index, such as the prevalence of malaria infection, the incidence of malarial illness, or the entomological inoculation rate [29]. The latter index, although the more useful is also the most difficult to obtain. Direct measurement of $h(a)$, the inoculation rate, involves counting mosquitoes, examining their stomachs for human blood and dissecting their salivary glands in the search for sporozoites, which are indeed extremely difficult procedures, prone to errors. Therefore, alternative ways to estimate the effective inoculation rate, the most indicative index of malaria transmission, are desired.

As mentioned in the introduction, age-related serological studies are probably the best (most cost-effective) ways to assess malarial prevalence, provided the data are properly treated [3].

In this paper we have applied a simple method to estimate the effective inoculation rate from serological data, which has been described previously [12, 13]. The model proposed involves several simplifications, namely: (1) we assume that transmission in the area is in a steady-state, that is temporal variation is negligible; (2) the dynamics of immunity considered in the model are much simplified. In particular we assumed that only the last inoculation, and the time elapsed since then, determines the seropositivity rate at survey time; (3) the estimation of the inoculation rate was based on a two compartment structure. Nevertheless, it has been used in a four compartment model; (4) the transition rates δ , ϕ and r were arbitrarily assumed as age-independent, and finally (5) the specific mortality due to malaria was neglected. Detailed discussions of these simplifications have been published recently [12, 13].

Probably the most important simplification for this area is concerned with the steady-state assumption. Actually, it is believed that malaria prevalence has probably changed in the last 20 years, although not sufficiently to alter the endemic pattern of the studied area.

Despite the above simplifications, the model has been shown to be reliable and feasible enough for practical purposes as can be seen from the results.

The inoculation rate, seen in Figure 2, shows a marked increase in malaria exposure with age, which is in accord with current epidemiological beliefs for the area. Also, from this curve we can assess the average age of the first infection, 2·7 years, which can be used as a rough indicator of the transmission pattern of the area. For instance, this age could suggest a peri-domiciliary transmission of malaria. However, it should be noted that people who are most exposed (24 years) have the greatest level of activities in the forest. Finally, the slight decrease in malaria transmission believed to have occurred in that area in the last 20 years may have caused an overestimate in the rate of increase of the inoculation rate with age.

The result of the numerical integration of the model can be seen in Figure 3, which shows the dynamics of malaria in the area. It can be noted that the model provides insights that may be useful in the design of control strategies. The figure shows that the higher proportion of susceptibles and the peak of parasitaemia are related to the lower ages (< 15 years), which should be monitored more carefully as this fraction of the population is subject to the highest risk of morbidity and mortality. On the other hand, it is clear that individuals over 15 years of age, although subject to lower risk of morbidity and mortality still have parasitaemias, and are perhaps the most important parasite reservoir contributing significantly to the maintenance of endemicity. Finally, the very low proportion of individuals with parasitaemia without antibodies shows that our estimation of $h(a)$ using a two compartment structure is justified.

The retrieving capacity of the model is shown in Figures 4 and 5. The agreement for serological data is almost perfect. In contrast, for parasitological data the agreement seems poor. However, it should be recognized that parasitological data are subject to influences that limit their use as a malariometric index. The apparent overestimate of parasite rate shown in Figure 5 is probably due to technical problems in its assessment and, more importantly and significantly, due to widespread use of chemotherapy, mainly in children. In fact, the surprisingly low levels of parasitaemia found are incompatible with the serological prevalence. As comprehensively discussed in the literature the use of parasite rate as commonly defined, mainly in areas subject to heavy chemotherapy schedules, may cause gross underestimate of malaria endemicity level [3, 5, 30–32]. Assuming that the model parasite rate is correct, and that parasitological data are underestimated mainly due to treatment, one can estimate the treatment rate of the area, as shown in the Appendix.

Finally, the Basic Reproductive Rate estimated for the area points to a stable and meso- to hyperendemic situation, which is in accord with current beliefs.

The above considerations point to a situation in which malaria transmission occurs mainly outdoors, probably in the village neighbourhood, like the forest edge, the river margins and the cultivated fields. Therefore, besides the classical methods, control strategies should be directed to the development of studies designed to provide an understanding of human habits that may influence contact rates with the vector, which could serve as a guide to the application of educational campaigns. Also, an active search for cases should be periodically performed, mainly in the adult fraction of the target population.

In conclusion, our results are most encouraging in pointing to the use of

Fig. A 1. Age-dependent treatment level estimated according to equation A 3.

mathematical models, as applied to serological data, as a useful tool for the estimation of malaria prevalence and the design of control strategies.

APPENDIX

In this appendix we show how to estimate an age-dependent chemotherapy rate.

Let $Y_0(a)$ be the observed and $Y_e(a)$ be the estimated parasite rate (note that $Y_e(a) = Y(a) + Y'(a)$).

Let $C(a)$ be the age-related chemotherapy rate to which the population is submitted. Then, $Y_0(a)$ and $Y_e(a)$ obey the following equations:

$$\frac{d}{da} Y_0(a) = h(a) X(a) - (\phi + C(a)) Y_0(a), \quad (\text{A } 1)$$

$$\frac{d}{da} Y_e(a) = h(a) X(a) - \phi Y_e(a), \quad (\text{A } 2)$$

from which we have:

$$C(a) = \frac{\phi[Y_e(a) - Y_0(a)] + d/da[Y_e(a) - Y_0(a)]}{Y_0(a)}. \quad (\text{A } 3)$$

The results of equation (A 3), with $Y_0(a)$ and $Y_e(a)$ as described above, can be seen in Figure A 1.

Although the above analysis was intended to serve as an illustration of the

proposed theory, the results shown in Figure A 1 are in good agreement with the current epidemiological beliefs for the area.

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