SOME MATHEMATICAL MODELS FOR MALARIA

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Abstract

We introduce several enhancements to a cohort model for predicting the parasitemia of malaria. The cohort model has undergone development over half a century by Muench, Aron and May, and Aron. To this we incorporate: time dependent immunity (TDI), temporary immunity, superinfection, and resistant strains of parasites. The TDI model is an attempt to reproduce the extended duration of parasitemia often shown in studies of malaria. We also investigate how superinfection compares as an alternative to TDI in this regard.

All the models have a unique equilibrium and are globally asymptotically stable. We show they are consistent with the dynamics of the disease and obtain remarkably good agreement to the Wilson and Garki Project data sets. We use the TDI model as a baseline study to investigate the individual effects of the parameters.

Among other conclusions we find that the relatively small class of partial immunes are mostly responsible as the link for transmitting the disease to mosquitoes, and that, even though the fraction of mosquitoes harboring resistant parasites may be small environmentally, nevertheless they constitute the major parasite load among infecteds.

Keywords: malaria model, time dependent immunity.

1 Introduction

Malaria is a mosquito-borne infection caused by protozoa of the genus plasmodium. Four species of the parasite, namely: P. falciparum, P. vivax, P. ovale, and P. malariae infect humans. Malaria remains the most important of the tropical diseases, being widespread throughout the tropics, but it also occurs in many temperate regions. It is estimated that 267 million people are presently infected, with 107 million clinical cases annually; the number of countries affected is put at 103 [1].

The parasites are transmitted by the bite of infected female mosquitos of the genus Anopheles. Clinical symptoms such as fever, pain, chills and sweats may develop a few days after an

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infected mosquito bite. The duration of infection depends on such factors as the degree of infection, method and time of treatment, resistivity of parasites to drugs, biology of the host etc. An important aspect of malaria is that where the disease has long been highly endemic, as in many parts of Africa, people are infected so frequently that they develop a degree of acquired immunity, and may become asymptomatic carriers of the infection [2, 3].

The biology of the four species of plasmodium is generally similar and consists of two distinct phases: sexual and asexual. In addition, the asexual phase consists of at least three forms: sporozoites, merozoites, and trophozoites. During the bite by an infected mosquito, parasites in the sporozoite stage enter the victims blood stream carried along with the insects saliva. This must be, at least, its second blood meal as the mosquito itself was infected beforehand. The filimentous and motile sporozoites migrate to the liver and invade a variety of liver cells. Here they replicate giving rise to the merozoite form at about the time the hosts natural defenses begin to attack the infected cells. In about 7 days time, a few tens of thousands of merozoites are released from each infected liver cell into the blood stream. There, the merozoites attack and invade red blood cells whereupon they become the trophozoite form.

This form also undergoes asexual division and in approximately 48 hours, depending on species, bursts the red blood cell releasing more merozoites into the blood stream. This activity is responsible for the clinical symptoms of the disease. These stages are synchronous among broods of the parasite.

Some merozoites differentiate into the sexual forms of the parasite, either male or female, called gametocytes. Gametocytes, which can remain in the blood for more than two years [5], are transmitted to a mosquito during the blood meal of an infected person. Gametocytes complete the life cycle in the gut of the mosquito resulting in sporozoites which migrate to the insects salavary gland to repeat the cycle.

Among the four species of plasmodium, P. falciparum causes the most serious illness and it is the most widespread in the tropics. This paper therefore focuses on the dynamics of P. falciparum malaria, although the analysis is similar for all forms of malaria infections.

Our objective in this work is to compare and enhence several different models predicting the age dependent prevalence of parasitemia. For this purpose we will use common source, multi-compartmental models. This idea is not new; for the purpose of estimating infection and recovery rates, Macdonald [4] used a model in which he assumed the amount of infective material to which the population is exposed remains unchanged. Such models were also introduced in Muench [5], Aron and May [6], and Aron [7, 8]. One factor influencing this choice is that the feedback dynamics from mosquito to man and back to mosquito involves considerable delay, mostly due to the incubation periods of the several forms of the parasite; consequently, the dynamics of the disease over these periods of time are in fact common source, see [9]. Also, in certain cases, it has been observed that the incidence of infected mosquitoes

remains very close to 3 per cent under widely varying circumstances thus constituting an approximately steady threat ([2, 6]).

Common Source Model

The Muench "catalytic" model divides the population into three groups: *susceptibles* or those who may contract the disease, *infecteds* or those infected and experiencing severe symptoms, and *partial immunes* or those infected but experiencing only mild symptoms. The model postulates that the mildly symptomatic can arise only from the severely symptomatic. The mildly symptomatic can not be reinfected as long as their immunity lasts. Hence, as noted, they are often referred to as partial immunes although this group is capable of transmitting the parasite to uninfected mosquitos. Denote by x, y and z, respectively, the relative size of each group; the catalytic, or SIR, model is $\frac{dx}{dt} = -hx$, $\frac{dy}{dt} = hx - ry$, and $\frac{dz}{dt} = ry$. The model tracks the experience of a birth cohort moving through time with t representing the age of the group. The parameter h is the infection rate, and r the acquired immunity rate. Hence $1/h$ is the mean time until infection, and $1/r$ the mean time until immunity. The initial condition is taken as $x(0) = 1$, and $y(0) = z(0) = 0$. It is assumed throughout that

$$x(t) + y(t) + z(t) = 1 \qquad t \geq 0, \tag{1}$$

implying that mortality acts approximately equally on all groups.

Aron and May [6] modified the model to an SIRS type by adding a return path of magnitude γz from the partial immunes back to the susceptibles. Furthermore γ is taken as a function of h in deference to the observation by many, that the greater the endemicity of the disease, the greater the extent of immunity among the population (see e.g. [10]). Thus γ should decrease with increasing h. The exact relationship is in terms of a parameter τ and takes the form

$$\gamma(h) = \frac{he^{-h\tau}}{1 - e^{-h\tau}}, \tag{2}$$

see Fig. 1. It is derived under the assumption that infective exposures arrive as a Poisson process with a mean constant rate of h and that partial immunity lasts an interval of τ units of time. If a person is re-exposed before this time has elapsed, then partial immunity is sustained and another interval of duration τ without exposure is required before return to the susceptible group.

Aron [**?**] further modified the model by adding an immediate return path, ρy, back to the susceptibles following the concept that partial immunity is not immediately acquired. The Aron model then is

$$\frac{dx}{dt} = -hx + \rho y + \gamma(h)z,$$

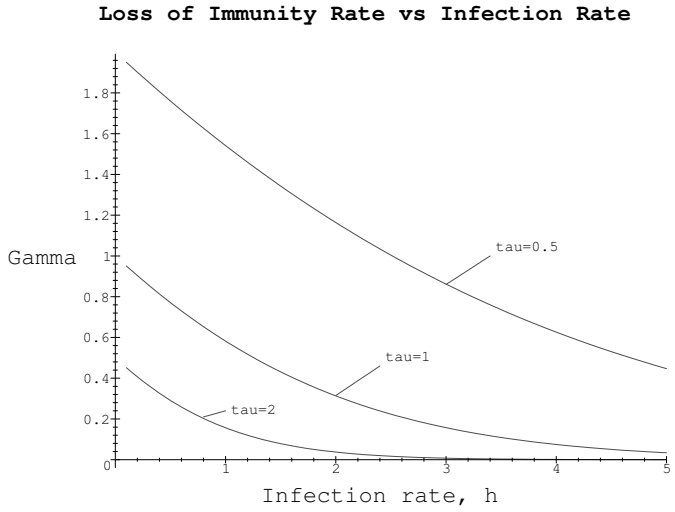

Figure 1. γ as a function of h for various τ.

$$\begin{aligned} \frac{dy}{dt} &= hx - \rho y - ry, \\ \frac{dz}{dt} &= ry - \gamma(h)z. \end{aligned} \tag{3}$$

The *recovery rate* ρ corresponds to how quickly parasites are cleared from the body. High recovery rates are associated with drug treatments.

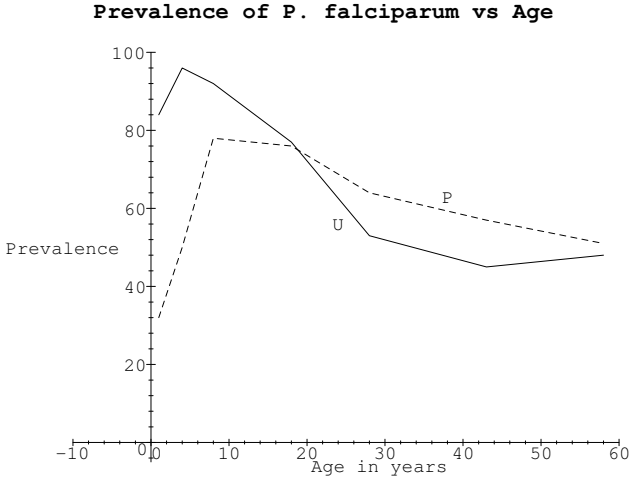

Figure 2. Garki project data. U refers to the controls, P to the treated.

The point of these efforts is to demonstrate qualitative agreement with observed prevalence data as measured by parasitemia. In particular, to predict a certain *cross-over* effect reported by L. Molineaux and G. Gramiccia [11], the "Garki Project" data, see Fig. 2, By aggressively

treating an entire population at risk over a two year period of time, these investigators reported that prevalence decreased at first but then rose to higher levels than controls upon cessation of treatment. That is, the prevalence curves crossed-over each other. Mathematically, this effect is achieved by the aforementioned link between γ and h, equation (2).

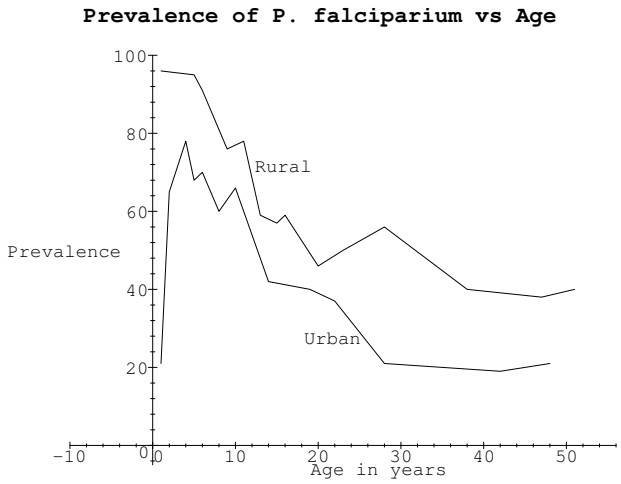

Figure 3. Wilson Data, urban vs rural prevalence

Another relevant data set is reported by Wilson [12] comparing prevalence in urban areas versus that in rural communities. As noted, rural victims have much less access to drugs as compared to their urban counterparts. This accounts for their higher level of prevalence, see Fig. 3. We note the strong similarity between the untreated group in the Garki Project data and the rural group of the Wilson data.

Other factors of concern about the disease include density dependent immunity and superinfection. Aron and May [6] postulate that a density dependent model will be required to accurately model the Garki Project data in particular. The data exhibits extended parasitemia with a prevalance exceeding 50% up to age 28, then becoming nearly constant at the equilibrium level. However model dynamics show parasitemia falling off immediately after peaking out at an early age. But in Section 2 we show that by modifying the immunity term, r to be time dependent, accurate tracking of this data is possible, see Fig. 5. We refer to this as the time dependent immunity (TDI) model. It also tracks Wilson urban data as well, see curve C of Fig. 6.

In Section 3 we modify the Aron model by adding another group, the *temporary immunes* of size w. They differ from the partial immunes in that they are completely cured but still have immunity; they do not infect mosquitos. This group serves as a waiting period between cure and susceptibility. It is unrealistic in some cases to suppose that individuals could be completely cured and become susceptible again immediately. It is seen by this model

that the partial immunes together with the temporary immunes act in exactly the same way as the partial immunes by themselves in the Aron model. Thus the major impact of this model is to indicate that a lesser proportion (than postulated by earlier authors) of the population is directly responsible for the transmission of the disease since the infection is primarily transmitted to mosquitos by the partial immunes. This effect is similar to the "core" endemic subgroup of the population observed by Lajmanovich and York [13] in their gonerrhea study, serving as a reservoir for the infection.

In Section 4 we investigate a superinfection model in which infecteds sustain several broods of parasites due to repeated infectious bites. Our inquiry is whether this model can be an alternative to TDI as a means of extending parasitemia as noted above. Experimentally we were not able to obtain the effect by superinfection alone. However by incorporating a recovery delay for each addtional brood, parasitemia extension reappears.

Section 5 deals with the problem of drug resistant strains of malaria parasites. While the models above deal largely with the natural course of the disease, in this section we assume the entire population is treated. Treatment and control have become more difficult in recent years with the spread of these strains [1, 2, 3]. Drugs such as chloroquine, nivaquine, quinine, and fansidar are used for treatment. More recent and more powerful drugs include mefloquine, and halofantrine. The model is seen to contain some of the previous ones as special cases. Furthermore this $SIRS$ model is likened to describing an infection in which all infecteds have an initial treatment failure with a certain drug.

The problem of drug resistance in malaria has also been examined by other authors, [9, 14]. In [9] the authors study sensitive versus resistant infection allowing for a proportion of hosts to be treated. This leads to the conclusion that competitive exclusion takes place between the strains; which predominates depends on the proportion of hosts treated, the effectiveness of treatment, and the cost of resistance to the parasite in terms of transmission rate. In [14] the study is more of a genetic one tracking the proportion of resistant alleles with up to 50 strains of resistant parasites. An individual is assumed to be infected by several strains at the same time and thus is superinfected. Sensitive strains are assumed to be eliminated in that individual by the drug.

Here we expand on the compartmental model of the earlier sections and in so doing follow the approach taken in [15]. The model predicts, as expected, that the major infection quickly becomes that of the resistant parasite while infection by the sensitive parasite drops nearly to zero. Nevertheless, if the drug is effective, the overall infection drops by about half.

General remarks about the mathematical techniques.

All the models presented here are differential equation systems belonging to the class of compartmental systems with no inflow. The behavior of such systems is well-known. Since the

flow matrix, comprising the right-hand side, is singular with defect dimension 1 (the columns sum to zero), solutions tend to the one-dimensional singular set [16]. However solutions must also satisfy the summation condition (1) and hence remain on the corresponding hyperplane. As a result, solutions tend to a unique globally asymptotically stable equilibrium.

As usual in fitting a model to data, we attempt to minimize least square error. However, here, the least square error depends in a highly non-linear way on the parameters necessitating the use of stochastic search methods. For this we use Genetic Algorithms which is by now, well-studied, see [17].

2 Time Dependent Immunity (TDI) model

We start from the Aron model (3). Understanding that immunity is acquired and develops over time with exposure, we allow the immunity acquisition rate, r to be time dependent, $r = r(t)$. Our assumptions are that immunity is initially nil, $r(0) = 0$, that, upon exposure, there is a startup delay in acquiring immunity, $\dot{r}(0) = 0$ and that immunity tends asymptotically to a limiting value, say r_∞. An embodiment of these principles is contained in the simple differential equation

$$\frac{dr}{dt} = (\text{rate})t(r_\infty - r), \qquad r(0) = 0.$$

Let σ, *exposure*, denote half the rate parameter; solving this differential equation gives

$$r = r_\infty(1 - e^{-\sigma t^2}).$$

A plot of r versus t for various σ is given in Fig. 4.

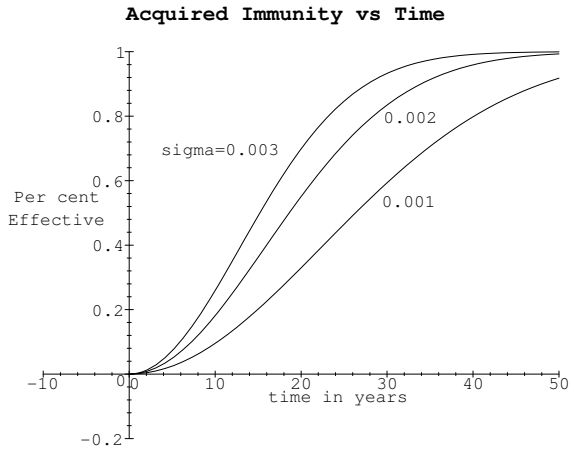

Figure 4. Acquired immunity profile.

This leads to what we shall term the TDI model,

$$\begin{aligned} \frac{dx}{dt} &= -hx + \rho y + \gamma(h)z, \\ \frac{dy}{dt} &= hx - \rho y - r_\infty(1 - e^{-\sigma t^2})y, \\ \frac{dz}{dt} &= r_\infty(1 - e^{-\sigma t^2})y - \gamma(h)z. \end{aligned} \tag{4}$$

Our modification of system (3) has no effect on equilibrium values since $r \to r_\infty$ as $t \to \infty$. The equilibrium, in terms of y, is found to be

$$x = \frac{\rho + r_\infty}{h} y \qquad \text{and} \qquad z = \frac{r_\infty}{\gamma} y.$$

But at the same time, solutions must remain on the hyperplane $x + y + z = 1$. Hence the equilibrium value of y satisfies

$$y\left(\frac{\rho + r_\infty}{h} + 1 + \frac{r_\infty}{\gamma}\right) = 1. \tag{4}$$

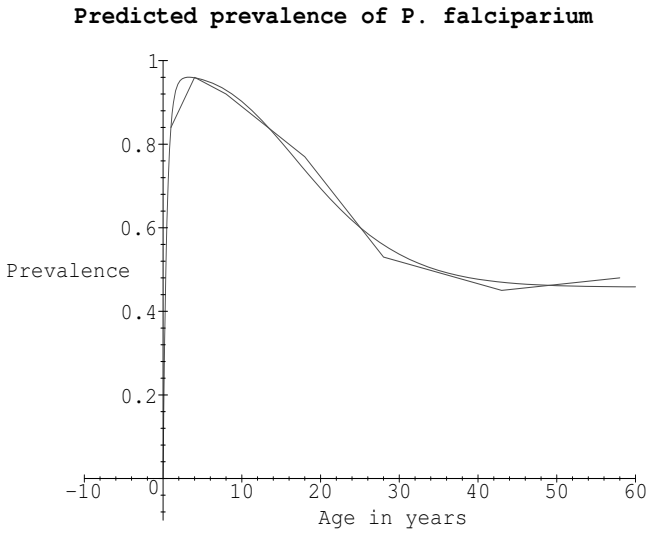

Figure 5. The TDI model versus Garki Project data.

In order to show that this model can predict the Garki Project data, thus addressing a specific query of Aron and May, and for the purpose of obtaining a baseline for further model development, we perform a weighted non-linear least squares fit. The resulting parameters are given in Table 1. Note that for these values, γ as given by (2) is

$$\gamma = 0.104.$$

Hence the mean time as a partial immune is $1/\gamma = 10$ years approximately. The corresponding (relative) equilibrium values are also given. The predicted prevalence curve is shown in Fig. 5 and is compared with the Garki Project untreated incidence data.

Table 1 Time Dependent Immunity Model		
Parameter Specification	Error	Equilibrium values
$h = 1.99$, $\rho = .074$, $r_\infty = .113$, $\tau = 1.5$, $\sigma = .0024$	.003	$\bar{x} = .04$, $\bar{y} = .46$, $\bar{z} = .50$

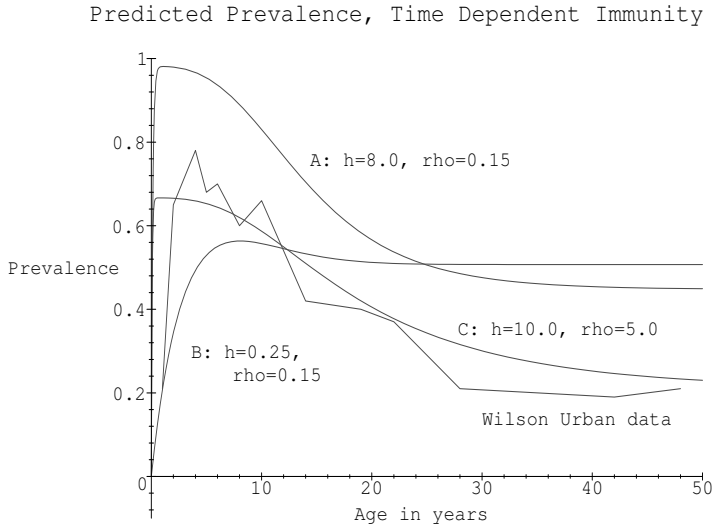

Figure 6. $\tau = 0.6$, $r_\infty = 0.08$, h and ρ as shown.

Note that this time dependent immunity model preserves the cross-over phenomenon and the urban vs rural phenomenon, see Fig. 6. Thus for fixed $\rho = .15$, the curve for high h crosses that for low h, curves A and B. In addition, a high value of ρ, $\rho = 5.0$, gives a profile matching the urban group of the Wilson data, curve C.

Finally, for the parameter set of Table 1, the sensitivity of the equilibrium to parameter fluctuation is given by the Jacobian

$$J = \begin{bmatrix} -.22 & .26 & .18 & -.22 \\ .13 & -.19 & -.28 & -.27 \\ .09 & -.08 & .10 & .48 \end{bmatrix}.$$

The rows are ordered x, y and z and the columns h, ρ, r_∞ and τ. Thus, x is most sensitive to change in ρ, y is most sensitive to change in r_∞, and z is most sensitive to change in τ.

3 Incorporation of Temporary Immunes, Extended Model

Following the idea that there is a period of complete immunity before a partial immune returns to the susceptible class, we extend the model by introducing another population subgroup, of size w, the *temporary immunes*. They differ from the partial immunes in that they are completely cured but still have strict immunity; their immunity is more complete. This group serves as a waiting period between cure and susceptibility, see the transition diagram, Fig. 7.

One advantage of this model is that if the rate of return to the susceptible class should reduce to a small value, that is $\gamma \to 0$, then the entire population accumulates in the z, or partial immunes, group. But it is known that acquired immunity overcomes parasite load with time. The advent of a group having true immunity provides a place for the population in this circumstance.

We assume that the passage from infecteds to partial immunes, and from infecteds to temporary immunes, determined by parameters r and p respectively, depend on the ability to develop acquired immunity. Whether an infected individual goes into the partial immunes or directly to the temporary immunes depends on a number of factors such as the type of parasite, its density and strain and on human physiology.

Our purpose here is to compare predictions of this model with those of the previous ones, particularly the TDI model. The existence of temporary immunes may be of importance to public health officials in that they reduce the load on health services both directly and indirectly by not transmitting the disease.

The interactions accompanying this new group, as seen in Fig. 7, are: infecteds and partial immunes can become temporary immunes with rates p and s respectively (cure rates), and temporary immunes become susceptible at the rate ν (true loss of immunity, this could be equal to γ). Thus we have the following model:

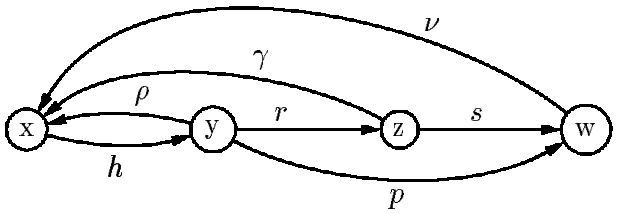

Figure 7

$$\begin{aligned} \frac{dx}{dt} &= -hx + \rho y + \gamma(h)z + \nu w, \\ \frac{dy}{dt} &= hx - \rho y - ry - py, \end{aligned} \tag{6}$$

$$\begin{aligned} \frac{dz}{dt} &= ry - \gamma(h)z - sz, \\ \frac{dw}{dt} &= py + sz - \nu w. \end{aligned}$$

As before, $x(t) + y(t) + z(t) + w(t) = 1$, $x(0) = 1$, and γ is defined in Eq. (2). System (6) is a compartmental system with no inflow and hence, as noted above, solutions tend to the singular set of the flow matrix. These can be given in terms of y and, with relative population size 1, substituted into the total population equation to give

$$y\left[\frac{\rho + r + p}{h} + 1 + \frac{r}{s+\gamma} + \frac{p\gamma + sp + sr}{(\gamma + s)\nu}\right] = 1. \tag{7}$$

If we take the sum $r + p$ in the new model to equal the value of r in the old one, then the outflow from compartment y will be the same between the two models. Similarly by taking γ and ν in the new model equal to γ in the old one, then the inflow to compartment x will be the same as well. Thus the sum $z + w$ of this model will equal z of the TDI model. Hence the effect of the new model will be to refine a fraction of the partial immunes of the old model into temporary immunes. In particular, the dynamics of the infecteds will be unchanged including their equilibrium value. Thus it is not possible to get information about the internal parameter s from incidence data. This can only be elicited from information about the relative size of the temporary immunes.

In Fig. 8 we show the effect of s on the balance between the partial and temporary immunes at equilibrium. The parameter values here are those of Table 1. When $p = 0$, no infecteds become temporary immunes directly but must become partial immunes first. Even in that case, the temporary immunes come to dominate the ratio between the two even for relatively small values of s. Under the condition that $\nu = \gamma$, these equilibrium values are given by

$$z = \left(\frac{r}{\gamma + s}\right) y, \qquad w = \left(\frac{r+p}{\gamma} y - z\right).$$

Since maintence of endemic infection is due to the partial immunes and infecteds, and with most of the immunes in the temporary immunes class, the first line of treatment should be focused on infectads.

In Fig. 9 we show some prevalence plots of the temporary immunes model for the three sets of parameter values shown. The corresponding equilibrium values are given in Table 2.

Table 2 Temporary Immunes Model	
Parameter Specification	Asymptotic equilibrium values
$h = 8$, $\rho = 0.15$	$x = 0.01$, $y = .45$, $z = .17$, $w = .37$
$h = 0.25$, $\rho = 0.15$	$x = .47$, $y = .51$, $z = 0.01$, $w = 0.01$
$h = 10$, $\rho = 5$	$x = .11$, $y = .21$, $z = .13$, $w = .55$

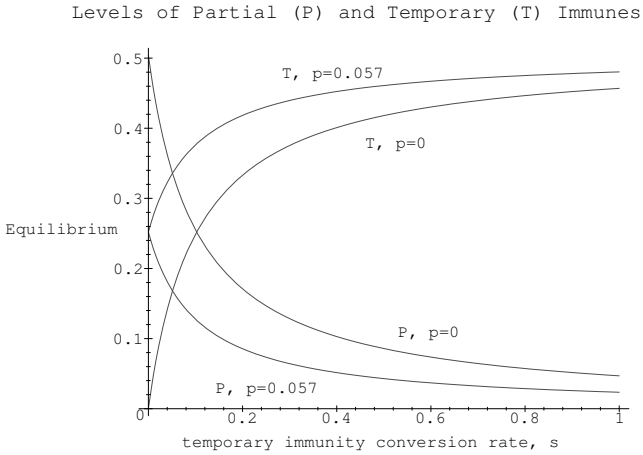

Figure 8, Balance between partial and temporary immmunes as a function of s

4 Superinfection

If an infected individual is re-exposed before recovery, another brood of parasites may result; this is referred to as *superinfection*. Models incorporating superinfection have been previously introduced and studied, [2, 14, 9]. These authors postulate the possibility that a victim could sustain very large numbers of broods, even up to 50, see Fig. 10.

Parasites from different broods can be genetically different but we are assuming here they do not react differently in terms of the model parameters ρ and r. In the next section we will take up the possibility of resistant strains. Therefore the effect of subsequent infections is to increase the parasite load. In this regard, note that with the infection rate parameter $h = 1.99$, the mean time between infectious bites is $1/h$ or about one-half year. On the other hand, with the sum of clearing parameters $\rho + r_\infty = 0.187$, the mean duration, or half-life, of an infection is 5.35 years. Thus one would expect victims to have 5.35/0.5 or nearly 11 broods on average provided the clearing rate remains unaffected by the increased parasitemia.

Previously we introduced the TDI model in an attempt to capture the extended parasitemia and group equilbria shown by the Garki Project data, (prevalance exceeding 50% up to age 28, then nearly constant prevalance at the equilibrium level). The cost in terms of modeling was the addition of a single new parameter, namely σ. Now we ask if superinfection (SI) can also track this data. It may be possible that each new infection serves to delay acquiring immunity and thereby extends the symptomatic stage.

Testing these ideas required implementing the model as a simulation rather than as a differential equation. When the number of infected compartments, n, is even modestly large, the differential equation solver slows unacceptably. By contrast the time for a simulation run is independent of n; instead it depends, in a linear fashion, on the simulated population size. Furthermore, changing n involves no more than specifying its new value. In testing the

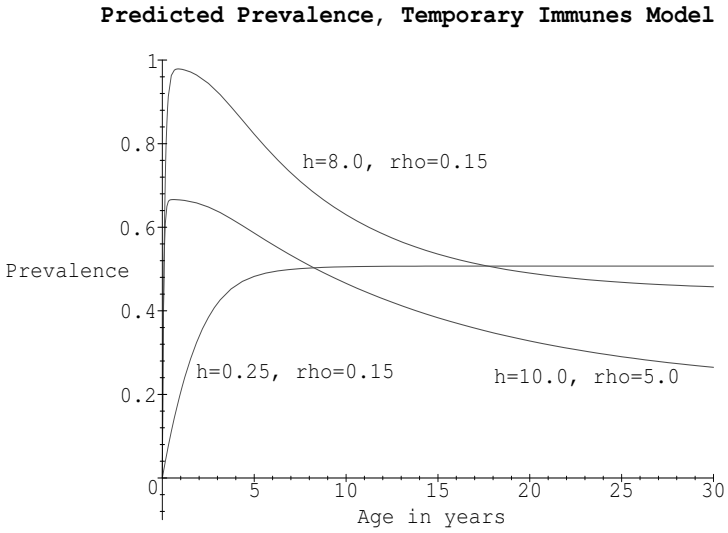

Figure 9. $\tau = 0.6$, $r + p = 0.08$, h and ρ as shown.

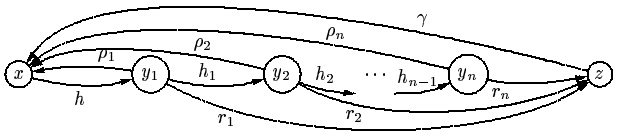

Figure 10, y_1, y_2, ..., y_n denote the infected subgroups.

simulation against the differential equation for the TDI model, accurate results were generated with population sizes as small as 1000. Such runs took 2.3 seconds. Runs with population size 10,000 took 23 seconds.

Turning now to the question of the dynamics of the SI model, first note that each infected compartment (except the last) entails three parameters, h_k, ρ_k and r_k, see Fig. 10. These must bear a close relation to h, ρ, and r, respectively, of the Aron model. For example setting $h_k = h$, $\rho_k = \rho$ and $r_k = r$ for all k, introduces no new parameters except the number of infected subcompartments itself. However this change by itself cannot alter the dynamics of the combined infected subgroups. Just as in the temporary immunes model above, with these parameter choices the inflow to z from the combined infecteds and the outflow from x remains the same and we have, effectively, the Aron model. Hence what the number of subgroups ought to be and how the infecteds are distribution among them cannot be determined from the Garki or Wilson data.

Indeed, just as Aron and May predict, were not able to track the Garki data and maintain the equilibria for any choice of h, ρ, or r. Furthermore, depending on the number of subgroups, nearly all, infecteds tended to the last subgroup (when $h_k = h$ for all k). Thus under the stated conditions, it is concluded that the SI model is not consistent with malaria incidence

data.

In regard to the distribution of infecteds among the subgroups, we studied this fixing parameter values as in the baseline TDI model, see Table 1. In line with the half-life calculation above, after the 16th subgroup, population falls off to low numbers. The exception to this is when the number of subgroups is 30 or less, then there is a population blow-up in the last subgroup, larger as the number of subgroups decreases.

If adding infected subgroups by itself cannot extend parasitemia, it is still possible to make adjustments to the SI model, along the lines of the TDI model, that captures extended parasitemia, reproduces the observed equilibriums and even spreads the infection approximately equally over the several subgroups. This occurs if the transition from one subgroup to the next progressively decreases and the recovery time from each subgroup progressively increases. Both these are justifiable. Extending overall recovery time from later subgroups with more broods makes sense due to their greater parasite load. (Note this is not the same thing as saying the time spent in later subgroups is longer, part of the process of acquiring immunity has already been paid in previous subgroups, see the next.) A decreasing probability of moving from one subgroup to the next subgroup could be the result of remaining for less time in later subgroups due to having spent time acquiring immunity in previous subgroups.

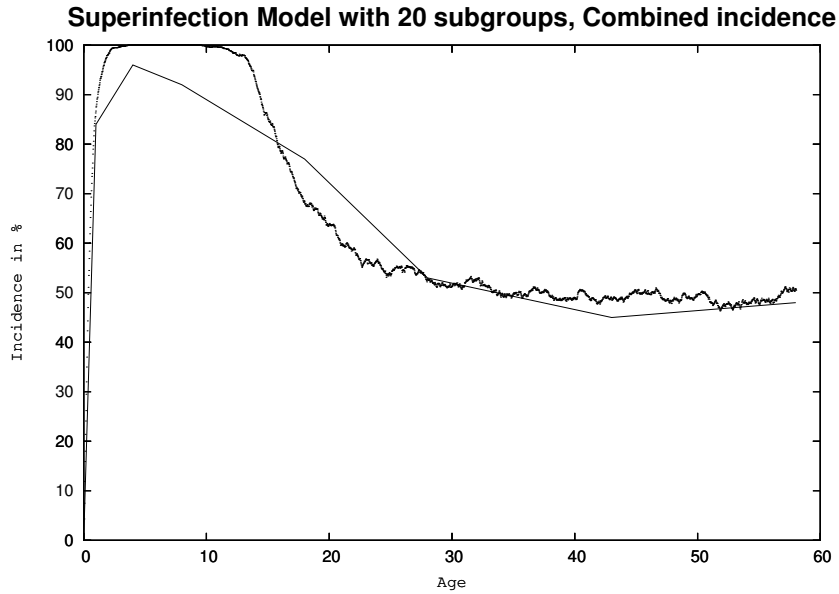

Figure 11, SI with $\sigma = 0.071$, $a = 0.96$, $t_h = 12.0$ and h, τ, r_∞, and ρ as in TDI model

For progressive delay we utilize the TDI modification but with a half-life normalization and an increasing delay exponent. Thus, for the kth subgroup put

$$\rho_k = \rho(1 - e^{-\sigma(t/t_h)^k}) \quad \text{and} \quad r_k = r_\infty(1 - e^{-\sigma(t/t_h)^k}).$$

where t_h denotes the half-life parameter. For infection we introduce an infection rate "attenuating" factor a, $0 < a \leq 1$,

$$h_k = a^k h.$$

Note that as $t \to \infty$, $\rho_k \to \rho$ and $r_k \to r_\infty$ for all k. Hence by taking ρ and r_∞ as in the TDI model, this model preserves equilbria since the h_k serves only to rearrange infecteds among the brood distinguishing subgroups. With these modifications, the SI model is no longer in contrast to TDI, but an extension of it.

Using the TDI baseline parameters for h, ρ, r_∞ and τ, and taking $\sigma = 0.071$, $t_h = 12.0$ and $a = 0.96$ we get the dynamics shown in Fig. 11 with 20 infected subgroups.

5 Resistant Strain Model

Next we consider the effect of distinguishing resistant infecteds; that is, we identify individuals infected with parasites that are resistant to drugs. Because the dynamics of the mosquito population operates on a faster time scale than that of the human population, [9], we do not include the mosquito population in our model.

In this section we assume that all infected individuals receive treatment. Treatment consists in the administration of chloroquine or other 4-aminoquinoline derivatives. It is well known that these popular drugs do not have any significant activity against the exoerythrocite or gametocite stage of malaria parasites. We assume that sensitive infecteds respond quickly to treatment and return to the susceptible class. On the other hand, individuals infected with a resistant strain do not respond to this treatment and, since mortality is not a factor, must necessarily acquire immunity and pass through the immune group before returning to the susceptibles. In this setting, it is still possible that a small number of sensitive infecteds become partial immunes, and that a small number of resistant infecteds return directly to the susceptibles. But we ignore these effects so as to be able to examine the relationship between this model and the previous ones.

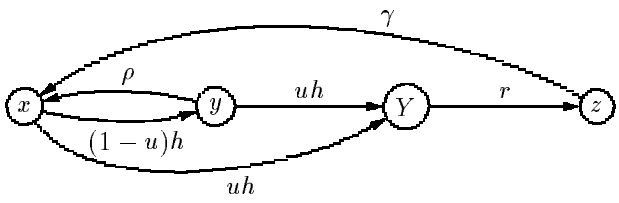

Figure 12

Let y represent the infecteds stricken with sensitive parasites only and Y those stricken with resistant parasites and, possibly, sensitive strains as well. Let u be the probability that, when an individual is infected, it is with a resistant strain of the parasite, with or without

sensitive strains, and let $1-u$ be the complementary probability, that is the probability that an individual is infected with sensitive strains only. With the rest of the notations as before, we have the following sensitive-resistant strain model, see Fig. 12,

$$\begin{aligned} \frac{dx}{dt} &= -hx + \rho y + \gamma z, \\ \frac{dy}{dt} &= (1-u)hx - \rho y - uhy, \\ \frac{dY}{dt} &= uhx + uhy - r_\infty(1-e^{-\sigma t^2})Y, \\ \frac{dz}{dt} &= r_\infty(1-e^{-\sigma t^2})Y - \gamma z, \end{aligned} \tag{8}$$

where γ is a function of h as in (2), $x(0)=1$ and

$$x(t)+y(t)+Y(t)+z(t)=1. \tag{9}$$

The transition from y to Y with per capita rate uh results in superinfection as discussed in the previous section.

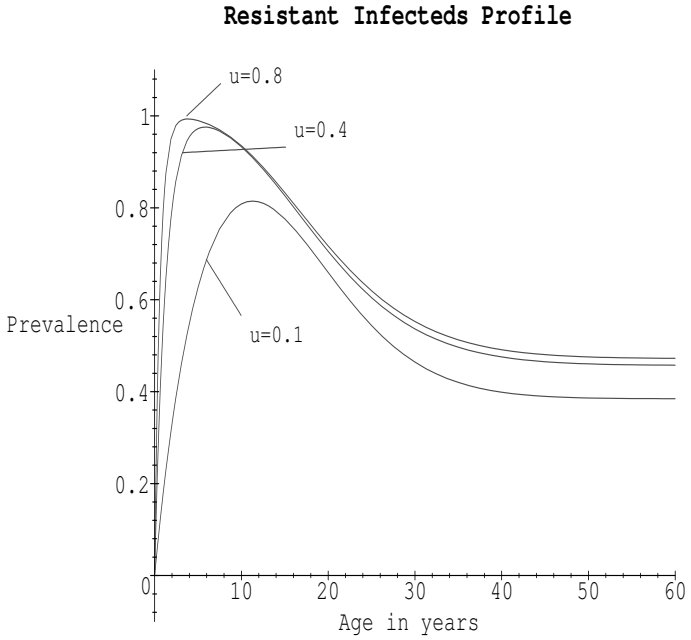

Figure 13. Parameter values as in Table 1 except $\rho = 5$.

This model is not equivalent of any of the previous ones even though the only new parameter here is u, the fraction of resistant infections. If $u = 0$ there results a simple SIS

model between susceptibles an infecteds. And if $u = 1$ there results an SIRS model among the susceptibles, resistant infecteds and immunes equivalent to that of Aron and May [6]. From this point of view, the $SIRS$ model could be seen as describing a situation in which all infecteds have an initial treatment failure with certain drugs and in which the only means of recovery is by a slow acquisition of immunity. Furthermore if $\gamma \equiv 0$, (that is, if immunity is acquired but not lost) then this model becomes the Muench catalytic model described in the introduction. Although this model differs from the Aron model, if $u = 1$ it behaves like the Aron model for small ρ.

It is clear that the definition of resistant parasites is with respect to a particular antimalaria drug against certain parasites. Thus the parameter u is a function of the effectiveness of the antimalaria drug against the particular parasite. Since strains resistant to the 4-aminoquinolines have been reported from nearly all parts of the world where malaria is endemic, it follows that u cannot be zero in all situations where these drugs are the object of consideration.

The general equilibrium points of the degenerate system (8) are given in terms of z by

$$x = \frac{\gamma(\rho + uh)}{uh(\rho + h)}z, \quad y = \frac{\gamma(1-u)}{u(\rho+h)}z, \quad Y = \frac{\gamma}{r_\infty}z.$$

As in the previous models, since solutions must lie on the hyperplane (9), we have a unique asymptotic equilibrium.

To illustrate the effect of u, in Fig. 13 we plot some prevalence profiles for the resistant infecteds (the number of sensitive infecteds is very small, see below) for various values of u. In this figure we assume that all parameters are as in the baseline TDI model, Table 1, except recovery rate ρ which taken to be much higher. We see from the figure that the profiles are relatively insensitive to u (provided it is not zero).

Next we examine graphically some predictions of this model in relation to the previous ones. With parameter values as in the TDI baseline model, and $u = 0.8$, see next, we get the equilibrium point

$$x = .020, y = .233, Y = .359, z = .387.$$

Alternatively, using reference [18] it is possible to estimate model parameters specific to the Nsukka region of Nigeria. These estimates are: $h = 0.5$, $\rho = 0.8$, $r_\infty = 0.2$, $\tau = 0.6$, and $u = 0.8$ (σ is not needed for equilibria). The corresponding equilibrium point is

$$x = .250, y = .021, Y = .541, z = .188.$$

The population of the region is about 2 million.

Solution curves for both y and Y in Fig. 14 are for the parameter values shown. In the figure the subscript refers to a particular parameter set, thus y_1, y_2, and y_3 correspond to Y_1, Y_2, and Y_3 respectively. The corresponding equilibria are given in Table 3.

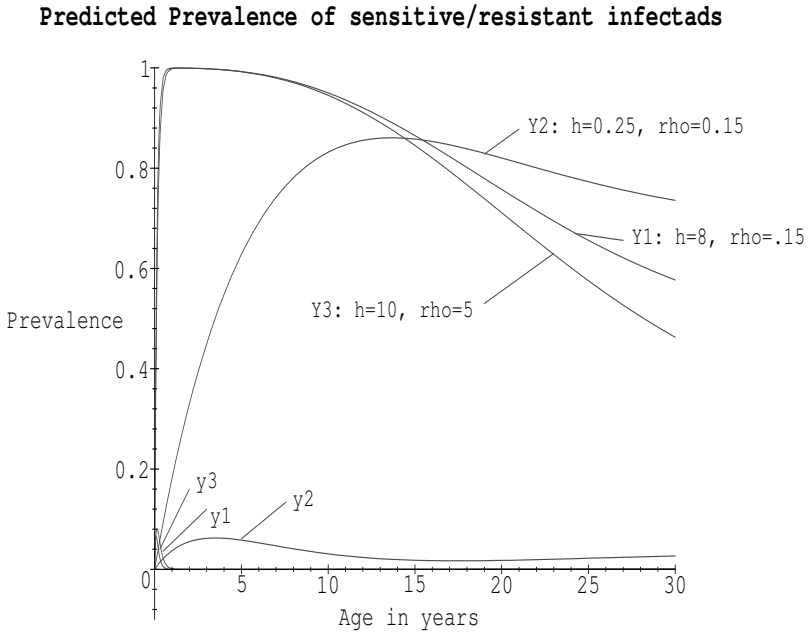

Figure 14, $r_\infty = 0.08$, $\tau = 0.6$, $\sigma = .0024$, $u = 0.8$, h and ρ as shown.

It is seen from the figure that for small ρ, the resistant curves Y_1 and Y_2 resemble the corresponding curves in Fig. 6. Thus in this setting the first two sets of parameters could be seen as describing a situation in which infecteds are treated initially with a drug that has very little impact on the disease. The third curve Y_3 still shows that if u is large, sensitive infecteds diminishes. However this curve cannot be related directly to the corresponding Aron/TDI curve in Fig. 6. This is due to the fact that ρ is high. Since recovery through treatment by drugs does not confer immunity in most cases, if the drug treatment is highly effective, then Y is small and this model is as if $u = 0$.

Table 3 Sensitive-Resistant model	
Parameter Specification	Asymptotic equilibrium values
$h = 8$, $\rho = 0.15$	$x = .01$, $y = 0$, $Y = .45$, $z = .54$
$h = 0.25$, $\rho = 0.15$	$x = .24$, $y = .03$, $Y = .69$, $z = .04$
$h = 10$, $\rho = 5$	$x = 0$, $y = 0$, $Y = .24$, $z = .76$

An observation which follows from the equilbrium equations and illustrated in Table 3, is that for large ρ (treatment is widely administered and effective) most of the population will be in the immune class. This occurs even if infection rate h is large.

Also noticeable from all the models is that τ or ν more or less controls infection. With increasing τ (or ν in the extended model), γ tends to 0 and the entire population eventually enters the corresponding immune class regardless of the magnitudes of the other parameters. This observation leads us to postulate that the most effective control/curative method is that of boosting the rate of acquiring immunity and minimizing immunity loss.

As previously mentioned, u is a function of the effectiveness of the antimalaria drug against a particular strain. It is hoped that this work will stimulate interest in the distribution of antimalaria drugs for all possible strains.

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