Introductory Review
Some New Thoughts about Some Old Malaria Models

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ABSTRACT

Simple models for the dynamics of endemic malaria are reviewed. A reanalysis of Ross's models explains Lotka's interpretation of them, and finds a historical context for the vectorial-capacity construction of an inoculation rate. Important epidemiological parameters are scrutinized. Inference problems are discussed concerning estimating mosquito density, recognizing the maternal-antibody effect, choosing among models for superinfection, and accounting for diagnostic error.

1. INTRODUCTION

Ronald Ross, the man who proved that mosquitoes transmit malaria, created the first mathematical model for the disease. Indeed, he created the first *two* mathematical models.

Since Ross, modeling of malaria has flourished, benefiting from thoughtful commentary as well as creative practice. A thorough review by Bailey [5] has recently summarized the field, as have excellent works by others [2, 4, 9].

True, reviews of ongoing science obsolesce quickly; but is another review of malaria modeling due already? I offer here not another comprehensive review but rather a scattering of thoughts in three directions: a few new insights on the evolution of models, starting with Ross's two, with particular attention to inoculation rates; an attempt to clarify vague meanings of some parameters; and a discussion of several inference problems.

A mathematician with no field experience of malaria, I admit to a limited understanding gained by several years' study of data collected as part of the Garki project [49]. My review refers primarily to such endemic *falciparum* malaria. However, I restrict attention to models which lack reference to immunity and which therefore apply at most to infants.

The Appendix contains a glossary of notation, which is drawn principally from the model constructed by Dietz, Molineaux, and Thomas (hereinafter referred to as DMT) for the Garki project [22].

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2. INOCULATION RATES AND THE VECTORIAL CAPACITY

In malaria models, the probability per unit time that an uninfected human becomes infected is called the inoculation rate. This probability depends on the infectiousness of mosquitoes. Nevertheless, it seems possible to avoid modeling disease dynamics in the mosquito population.

DMT modeled the inoculation rate without any dynamical equations for mosquitoes by means of an epidemiological index called the vectorial capacity [22]. Although Ross predated the formal definition of that index, one of his models used the same device. The other model included a differential equation for infected mosquitoes.

In both of Ross's models, the human population size and the density m of mosquitoes (mosquitoes/people) are assumed constant. Let $y(t)$ be the proportion of infected people and $m_{23}(t)$ the density of infected mosquitoes. Then the model in Section 66 of Ross's book is, in current notation,

$$\dot{y} = bm_{23}a(1-y) - ry, \tag{1a}$$

$$\dot{m}_{23} = c(m - m_{23})ay - \mu m_{23}. \tag{1b}$$

The parameters a, b, c, r, and μ are defined in the Appendix. In (1a), $bm_{23}a$ is the inoculation rate.

With a similar updating of notation, the model in Section 27 of Ross's book is the single equation

$$\dot{y} = \left(\frac{bcma^2}{\mu}\right) y(1-y) - ry. \tag{2}$$

Here, the inoculation rate is $(bcma^2/\mu)y$. The combination of parameters in parentheses is a simple vectorial capacity.

Lotka [39] discovered the connection between (1) and (2) by means of a lengthy, classical set of expansions and approximations. In fact, (2) follows from (1) by assuming that the equation for mosquitoes (1b) equilibrates rapidly relative to the equation for humans (1a), as May and Anderson pointed out in a more general context [45].

A singular-perturbation approach helps explain Lotka's discovery. Recalling that m is constant, introduce dimensionless coordinates:

$$t' = rt, \quad \varepsilon = \frac{r}{\mu}, \quad \rho = \frac{ca}{\mu}, \quad z_0 = \frac{bcma^2}{r\mu}, \quad m'_{23} = \frac{m_{23}}{m}. \tag{3}$$

Then letting a dot denote differentiation with respect to t' and dropping

primes, Equations (1) become

$$\dot{y} = -y + \rho^{-1} z_0 m_{23} - \rho^{-1} z_0 m_{23} y,$$
$$\varepsilon \dot{m}_{23} = \rho y - m_{23} - \rho m_{23} y. \tag{4}$$

As $\varepsilon \to 0$,

$$m_{23} = \frac{\rho y}{1+\rho y} \tag{5}$$

Then if $\rho y \ll 1$, substituting (5) into (4) yields

$$\dot{y} = z_0 y(1-y) - y, \tag{6}$$

the dimensionless equivalent of (2).

The Equations (4) have two equilibria. Near the equilibrium (0,0), the eigenvalues of the linearized equations are

$$\lambda_+ = z_0 - 1 + O(\varepsilon),$$
$$\lambda_- = -\varepsilon^{-1} + O(1);$$

and near the nondegenerate equilibrium $(\bar{y}, \bar{m}_{23})$ they are

$$\lambda'_+ = -\frac{(z_0+\rho)(z_0-1)}{z_0(1+\rho)} + O(\varepsilon),$$
$$\lambda'_- = -\frac{\varepsilon^{-1} z_0 (1+\rho)}{z_0+\rho} + O(1).$$

With these expansions in ε, we can understand Lotka's conditions [39, p. 52] for Ross's Section 27 model to approximate his Section 66 model. Quoting Lotka but substituting our notation for parameters:

(1) "ρ/z_0 is small, i.e., if the number of mosquitoes per head of the human population is sufficiently large." The need here in fact is that ρ be small so that $\rho y \ll 1$, as after (5). The mosquito density seems not to matter, except to ensure the "interesting" case of a stable positive equilibrium: That ρ/z_0 be smaller than ρ is equivalent to $z_0 > 1$, the condition for stability of the positive equilibrium; see [4].

(2) "ε is small, i.e., if the rate of recovery among human beings is small as compared with the birthrate (and deathrate) among mosquitoes." This is the singular-perturbation condition.

(3) "λ_+/λ_- is small, i.e., if the two roots of the characteristic equation for λ are very unequal." This relates to the validity of the distinguished limit

$\varepsilon \to 0$. When taking such a limit, other parameters must remain fixed. When $z_0 > 1$, (0,0) is a saddle point and $(\bar{y}, \bar{m}_{23})$ is a sink. Since $|\lambda_+/\lambda_-| \approx \varepsilon(z_0 - 1)$, that $|\lambda_+/\lambda_-|$ be small is equivalent to the boundedness of z_0 as $\varepsilon \to 0$. It is also the requirement for trajectories in the phase plane to move rapidly to the common unstable manifold of (0,0) and stable manifold of $(\bar{y}, \bar{m}_{23})$. This manifold corresponds to the solution of (5)–(6) and represents, as Lotka pointed out, "the development of a malaria epidemic from a small initial focus" [39, p. 53].

So (1) reduces to (2) when information about *infected mosquitoes* can be traded for information about *all mosquitoes* and *infected people*; that is, when

$$bm_{23}(t)\,a \approx \frac{bcma^2}{\mu} y(t). \tag{7}$$

For more discussion about the qualitative behavior of solutions to (1), see [4] and [35]. Equation (2) can be solved in closed form. For a brief but superbly composed history of Ross's mathematical thinking, see [29].

The models (1) and (2) have experienced amplifications in two principal directions: accounting for the incubation period in mosquitoes, and incorporating temporal variation in the mosquito density m.

The simplest way to model the incubation period is to introduce a constant time delay, say of magnitude N_2, appropriately into the differential equations (1) and (2). For construction of the delay analog of (1) and analysis of its qualitative features, see [4]. For (2), see [16]. I wish to focus on how the incubation delay affects the vectorial-capacity construction of the inoculation rate.

The term "vectorial capacity" was coined by Garrett-Jones [30]. His definition of it included a term involving the incubation lag:

$$C \equiv \frac{bcma^2 \exp(-\mu N_2)}{\mu}. \tag{8}$$

In models, introducing the lag permits resolving infected mosquitoes, m_{23}, into incubating, m_2, and infectious, m_3. Similarly, a compartment for infectious humans, y_1, may be defined. A singular-perturbation analysis in [58] derives, for a pair of models analogous to (1) and (2) but with these more specific compartments, the analog of the approximation (7):

$$bm_3(t)\,a \approx Cy_1(t) \tag{9}$$

Macdonald [45] proposed a model containing an inoculation rate like (9) after Armitage [1] found a similar approximation for the sporozoite rate m_3/m.

Garrett-Jones created the vectorial capacity C independently of any dynamic model to quantify how effectively the mosquito population transmits malaria. Decomposing C helps explain his logic:

mac = rate mosquitoes become infected by biting infectious people;
$\exp(-N_2\mu)$ = probability that a mosquito survives through its incubation period;
ba/μ = number of infecting bites an infectious mosquito delivers.

Thus, according to Garrett-Jones, Cy_1 is the rate at which the current pool of infectious humans generates future infecting bites from mosquitoes. However, bm_3a is the rate at which currently infectious mosquitoes deliver infecting bites. The imperfect match of interpretations reflects the fact that $Cy_1 = bm_3a$ is only an approximation.

The parameter z_0 of (3) becomes C/r when the lag is introduced. Called the basic reproduction rate, it gives the expected total number of new human infections generated by a single case [30]. Since for both (1) and its delay analog the positive equilibrium is stable if and only if the corresponding $z_0 > 1$, manipulation of z_0 has underlain much theory on the control of malaria [42]. Dietz [21] has summarized the severe limitations of this approach. (See also [6], [13], [31], [32], [34], [49, p. 100], [53].)

When temporal variation is introduced into the mosquito density, the vectorial-capacity constructions remain formally unchanged except that the index itself becomes a function of time as m becomes $m(t)$. To model the mosquito population, Dietz [21] and Aron and May [4] suggested three coupled differential equations for m_1, m_2, and m_3 (m_1 is the density of uninfected mosquitoes) driven by a time-varying emergence rate of $\eta(t)$ of young mosquitoes. Nedelman [58] showed how these three equations reduce to one for m_3 driven by time-varying $m(t)$.

For discussion of the qualitative behavior of an analog of (1) which includes periodic emergence of mosquitoes, see [4]. For an analog of (2) with a periodic coefficient, see [10] and [19].

3. INTERPRETATION AND ESTIMATION OF SOME PARAMETERS

I shall discuss four parameters whose meanings suffer interpretively. Two, r and α_1, are recovery rates; the other two, b and c, figure in the inoculation rate.

3A. *THE PARAMETERS r AND* α_1.

r and α_1 are, loosely, the rates of recovery from infection and from infectiousness, respectively. Attempts to account for the magnitude of r make up a large part of the history of mathematical modeling in malaria [28]. However, one can argue that r is not as important, for understanding

transmission and guiding control measures, as α_1. One can argue, too, that r and α_1 have no "true" magnitudes, since their definitions depend on the models in which they appear [5, p. 110].

Cale et al. [11] distinguished between statistical and ecological parameters. Statistical parameters, like regression coefficients, can be assigned values only by fitting the model in which they have been defined. Ecological parameters can be measured independently.

Macdonald defined r as "the proportion of affected people, who have received one infective inoculum only, who revert to the unaffected state in one day" [42]. This sounds ecological: the definition suggests the appropriate experiment. But observing a group of infected people will surely yield fluctuating daily proportions who recover. To extract a constant average proportion is to estimate a constant transition probability for a Markov model. Fine [28] evaluated the assumptions of time homogeneity and Markovianity. The suggested experiment has actually been done; Macdonald and Göckel [43] infer $r = 0.005$ from the data. I believe that people who use r as a parameter intend Macdonald's meaning, even if r's role in their model may best be interpreted otherwise.

In 1950, Macdonald declared that when Ross's single-equation model with constant inoculation rate h,

$$\dot{y} = h(1-y) - ry, \tag{10}$$

is fitted to data on cross-sectional prevalence among infants, the value of r needed is "greatly below that which would be accepted as credible by any malariologist" [40]. Invoking superinfection, he proposed a model which graduated the data with a larger value of r. His model, now called the Macdonald-Irwin model [5, 57], was shown to be inconsistent with his intentions by Dietz [21, 28], who formulated an infinite-server-queue model, now referred to by the name Macdonald-Dietz [5, 56].

Not all malariologists seem unhappy with small values of r for infants. Pull and Grab [62], and Bailey reanalyzing their data [5], were satisfied with inferred "negligible" recovery rates for infants; see Section 4D.

Dietz, in the same unpublished paper where he analyzed Macdonald's inconsistency, proposed an age-time version of (10) in which the recovery rate $r = r(a)$ increases with age. Age serves as a proxy for immunity. Macdonald's unhappiness with small r's obtained from (10) was that "the common duration of continuous parasitemia (not only basic infection) from one infection must be of the order of three to six years." But that inference, regarding the mean $1/r$, follows only if r is constant. If r increases with age, Macdonald's objection might be circumvented without invoking superinfection.

Weiss and Aron [73] discovered an interesting problem concerning the magnitudes of r when the Macdonald-Dietz model is used as a component of

a larger transmission model such as DMT's. Since the Macdonald-Dietz model describes the process of infection within an individual, death is usually ignored in deriving the model's properties. DMT approximated the Macdonald-Dietz model, without death or other avenue of removal, by means of a differential equation which was then made part of their larger model and onto which was imposed removal by death and immunity. Weiss and Aron showed that if removal is incorporated into the stochastic model first, the recovery rate for the subsequent deterministic approximation differs from the case when the approximation is performed first.

An overtly statistical approach to estimating r (and the incidence rate as well) was adopted by Bekessy et al. [7]. They modeled the infection recovery process as a two-state, continuous-time, time-homogeneous Markov chain. Individuals are classified according to whether a blood sample does not or does contain parasites of *P. falciparum* when examined microscopically. The model was fitted to data from the Garki study [49], a multiwave panel survey. The inferred infinitesimal parameters of the model were interpreted as incidence and recovery rates. Rates were found to vary with age and season.

Singer and Cohen [65] embellished this idea, developing a sampling theory for the estimated rates and for the embeddability of the discrete data in continuous-time models. As Cohen and Singer [14], they considered mixed infections with *P. falciparum* and *P. malariae*. Verma et al. [71] have considered a model similar to that of Bekessy et al., but with the competing risk of "lost-to-followup" adjoined.

α_1, the recovery rate from infectiousness, is less easy to define independently than r, because infectiousness itself is not easily independently assessed. Referring to the standard time-homogeneous Markov assumption (or, equivalently, first-order kinetics), one can estimate $1/\alpha_1$ as the mean duration of infectiousness. Macdonald [42] stated without empirical support that $\alpha_1 = 0.0125\ \text{day}^{-1}$. Likewise without support, Najera [53] accepted this figure, Dutertre [24] doubled it, and DMT [22] took 16% of it. Nobody else has worried about the modeling implications of the duration of infectiousness.

There are not many useful data to help identify α_1. Carter and Gwadz [12] reported that in nonimmune individuals experiencing their first attack, 100% are infectious for about 1 month after onset of infectiousness, 50% for 3 months, and 20% for 1 year. Although these figures contradict an exponential loss rate for infectiousness, an exponential model of these data would need $0.004 \leqslant \alpha_1 \leqslant 0.009$. Boyd [8], Miller [48], and Earle et al. [2] describe individual gametocytemia histories, but there are few such histories and the relationship between gametocytemia and infectiousness is uncertain (see Section 3B).

Gametocytes of *P. falciparum* typically appear 10–15 days after the asexual forms [69, 74]. An additional delay ensues until they are mature enough to infect mosquitoes [69]. Miller [48] demonstrated that fever triggers

gametocytogenesis and that clinical relapses can induce a resurgence of gametocytes after an initial wave has disappeared from the peripheral blood. Smalley et al. [66] claimed that longer-lasting infections produce gametocytes more rapidly as the infection proceeds. But these late gametocytes may be only weakly infectious [69].

I know of only three models with a distinct compartment for infectious humans: those of DMT [22], Dutertre [24], and Elderkin et al. [25]. The latter seems of mathematical but little practical interest in its present form. Neither DMT nor Dutertre incorporated the delays preceding appearance and infectiousness of gametocytes. Only Dutertre allowed relapsing infectiousness. Neither these models nor any others I know of deal with clinical symptoms, such as fever, explicitly.

3B. *THE PARAMETERS b AND c*

b was defined by Macdonald as the proportion of sporozoite-positive bites which infect people [42]. Similarly, c is the proportion of bites on infectious people which infect susceptible mosquitoes.

Historically, inoculation rates have been computed in two ways. The human-biting rate by sporozoite-positive mosquitoes, $m_3 a$, is called the entomological inoculation rate, which I shall here denote h_e. Alternatively, dynamical models have been fitted to cross-sectional prevalences or cumulative prevalence rates in infants, yielding a parasitological inoculation rate h_p. Always $h_e > h_p$, and the ratio h_p/h_e is taken as equal to b; whence, by definition,

$$h_p = bm_3 a,$$

yielding the inoculation rate of Section 2. This definition only makes sense if h_p/h_e is constant, a condition which has apparently never been rigorously tested.

Krafsur and Armstrong [37] found that h_p/h_e did vary when quarterly averages of sporozoite rates and prevalences were used. But to estimate h_p they used the discredited Macdonald-Irwin model [5, 57] to describe inter-quarter prevalence changes. They found $0.06 \leqslant b \leqslant 0.27$ in children and $0.05 \leqslant b \leqslant 0.13$ in adults.

Using a similar approach, Davidson and Draper [20] estimated $b = 0.01$.

Pull and Grab [62] fitted a catalytic model [50] to aggregated cumulative prevalences in infants to estimate h_p. They estimated h_e two ways (see Section 4A), getting two very different values. From the two yearly average h_e's, and h_p which is a yearly aggregate, they concluded that $0.015 < b < 0.026$. In Section 4A, I find similar values from a reanalysis of the data.

Nedelman [58] estimated b from longitudinal records of infants in the Garki [49] study, by assuming that $h_e(t) = bm_3(t)a$ was a time-dependent

incidence rate for a Poisson process of infection and that at most one of the events "infection" or "recovery" could occur during the 10 weeks between successive surveys. His maximum-likelihood estimates of b were 0.012 and 0.086 in the two villages with respectively highest and lowest mosquito densities.

The observation of b's variation among villages in Garki [49, 58], and Krafsur and Armstrong's observation that b differs between adults and children, suggest that immune processes affect b. Manson-Bahr and Apsted [44] and Macdonald [42] suggested that mosquitoes' sporozoite doses would vary inversely with local endemicity because of community gametocytemia levels. Dutertre [24] and Aron [3] considered possible effects of heterogeneity in b. Aron showed how heterogeneous susceptibility could produce a drop in measured susceptibility during periods of intense transmission.

Analogously, c may as well stand for "chimera." Mosquitoes display genetic heterogeneity in susceptibility [69]. Regarding humans, fundamental to a definition of c must be a definition of "infectious." But because of poorly understood immune processes and patterns of parasite development, infectiousness cannot be equated with gametocytemia. Although infectiousness increases, on average, with gametocyte density in the blood, the literature is replete with anecdotal anomalies [12, 23, 36]. Infectiousness may depend on the duration of infection [69].

In several studies, mosquitoes were permitted to bite infected volunteers, after which the mosquitoes were dissected. Muirhead-Thomson [51] conducted a study where individuals who infected any mosquitoes at all with *P. falciparum* infected an average of 0.24 of the *A. gambiae* which bit them. Boyd [8] displayed the record of an induced *P. falciparum* infection, where, during the period when any mosquitoes were infected, on average 0.48 of mosquitoes which bit became infected.

Draper [23], reviewing the literature, exhibited three data sets on infectiousness of persons with *P. falciparum* gametocytemia. The data do not permit identification of possible noninfectious gametocytemias, but proportions of mosquitoes acquiring infections averaged 0.51, 0.47, and 0.09. Similarly, Smalley and Sinden [67], observing four patients with *P. falciparum* gametocytemia, reported that on days 1–4 of gametocytemia, an average 0.64 of biting mosquitoes were infected; on days 11–12, an average 0.072 were infected.

Nedelman [58] estimated c by fitting a differential equation for mosquito dynamics and the corresponding vectorial-capacity approximation to estimates of m and m_3 from the Garki study [49]. He found that both equations for m_3 graduated the data equally well but that $c = 0.48$ for the differential equation and $c = 0.38$ for the vectorial-capacity approximation. However, these two estimates did not differ significantly when sampling variability was accounted for.

4. INFERENCE PROBLEMS

In this section I shall discuss four unrelated issues involving model-related inference: estimating mosquito density, recognizing the maternal-antibody effect, choosing among models for superinfection, and accounting for diagnostic error.

4A. *COUNTING MOSQUITOES*

Validation and application of any inoculation-rate models require counting some component of the mosquito population. The five components which have appeared in models discussed in Section 2 are the emergence rate η, and the densities m, m_1, m_2, and m_3.

Gillies [33] described how the pre-gravid rate serves as an index of emergence. His work should vex anyone who fits a smooth model to sparse entomological data. In a Tanganyikan village, he discovered that after each heavy rain new emergents flooded the local *A. gambiae* population, drastically perturbing the age structure and lowering the sporozoite rate. He also found the estimated pre-gravid rate sensitive to collection site and delay until dissection.

To count mosquitoes, entomological surveys typically use one or more of four methods to catch mosquitoes: knockdown, where mosquitoes resting inside a dwelling are collected following morning spraying; exit-trap, where mosquitoes are caught leaving through the window of a hut during the night; night-bite, where mosquitoes biting human baits are captured; and outdoor-trap, which is as it sounds. For more details about these techniques, see [52], [59], and [64].

Mosquito counts must be translated into relevant density estimates for insertion into models. The night-bite counts are direct estimates of ma. This human-biting rate may also be estimated from the knockdown and exit-trap counts by examining mosquitoes' stomachs for human blood. When Pull and Grab [62] estimated ma both ways, the two estimates differed considerably, the second estimate consistently less than the first although tracking its sixfold seasonal variation.

Estimating m_3, or the sporozoite rate m_3/m, is difficult because of the small numbers of infectious mosquitoes. To estimate m_3/m, mosquitoes are dissected and their salivary glands are inspected for sporozoites, a tedious procedure. But a new process, exploiting monoclonal antibodies, may enable larger sample sizes [75].

4B. *SEASONALITY AND AGE-DEPENDENT SUSCEPTIBILITY*

Although mosquito densities vary seasonally in many parts of the world, modelers have frequently ignored this inconvenience. In two studies, a catalytic model [50] (first-order kinetics) with constant h_p was fitted to data

on cumulative prevalence in infants aggregated over 1–2 years [61, 62]. In both cases, the data appeared sigmoidal rather than exponential. This sigmoidicity was attributed to the maternal-antibody effect: newborns are protected by maternal antibodies which cross the placenta but which gradually degrade, rendering infants more susceptible as they age.

Might not the sigmoidal appearance of the data be an artefact of the time aggregation? Probably not if the study was well designed, possibly yes otherwise.

Consider a field study lasting from time $t = 0$ to time $t = T$. Suppose that all infants born between 0 and T are followed until they first become infected. Let U_β be the age at which an infant, born at time β, first becomes infected, and let $F(u;\beta)$ be the cumulative distribution function for U_β,

$$F(u;\beta) = \Pr\{U_\beta \leqslant u\}$$

If $h(t,u)$ is the inoculation rate for an infant of age u at time t, then

$$F(u;\beta) = 1 - \exp\left(-\int_0^u h(\beta+s,s)\,ds\right).$$

A cumulative incidence curve from aggregated data estimates

$$\bar{F}(u) = E(F(u;B)),$$

where the expectation is over the birth date B.

Assume that births occur according to a time-homogeneous Poisson process. Then the conditional distribution of B, given that $0 \leqslant B \leqslant T$, is uniform. Hence,

$$\bar{F}(u) = T^{-1}\int_0^T \left[1 - \exp\left(-\int_0^u h(\tau+s,s)\,ds\right)\right] d\tau.$$

To be sigmoid, $\bar{F}$ must satisfy $\bar{F}''(0) > 0$. Now,

$$\bar{F}''(0) = T^{-1}[h(T,0) - h(0,0)] + T^{-1}\int_0^T [h_2(\tau,0) - h^2(\tau,0)]\,d\tau,$$

where $h_2(t,u) = \partial h(t,u)/\partial u$. If T is a multiple of one year and $h(t,u)$ is seasonally periodic in t, then $h(T,0) - h(0,0) = 0$. Then in order for $\bar{F}''(0) > 0$, we would need $h_2(\tau,0) > h^2(\tau,0) > 0$ on average—that is, susceptibility must increase with age around birth. This is consistent with the maternal-antibody hypothesis. Good sampling design would be to start and end the study in the season of lowest transmission levels to ensure $h(T,0) - h(0,0) \approx 0$.

Suppose that in fact $h_2(\tau,0) \equiv 0$—that is, there is no age dependence in susceptibility at birth. Then

$$\bar{F}''(0) = T^{-1}\left\{[h(T,0)-h(0,0)] - \int_0^T h^2(\tau,0)\,d\tau\right\},$$

which could be positive if T is not a multiple of one year or if there is a marked departure from periodicity.

I have refitted Pull and Grab's cumulative-prevalence data using the age- and time-dependent inoculation rate

$$h(t,u) = [b(m_3a)(t-10)][1-e^{-\lambda(u-10)}]. \tag{11}$$

The human-biting rates of infectious mosquitoes, $(m_3a)(t)$, were obtained from Table 6 of [62]. The time lag of 10 days accounts for incubation delay. b and λ, a decay constant for the maternal-antibody effect, were found by maximum-likelihood fitting to the data in Table 2 of [62].

It is not clear what a correct likelihood for those data might be. The "susceptible infants examined" were not members of a cohort but were instead equiaged members of several cohorts combined. I decided to treat the 12 age classes as independent. Letting

$$\bar{F}(u;b,\lambda) = 1 - 365^{-1}\int_0^{365}\exp\left(-b\int_{10}^{u}h(t,\tau)\,dt\right)d\tau,$$

$$(u_0,u_1,u_2,\ldots,u_{12}) = (10,30,60,\ldots,360)$$

$$= \text{endpoints of age intervals,}$$

the number of new infections out of the number of never infected infants in the ith age class was taken to be a binomial sample with probability of "success"

$$p_i(b,\lambda) = \frac{\bar{F}(u_i;b,\lambda)-\bar{F}(u_{i-1};b,\lambda)}{1-\bar{F}(u_{i-1};b,\lambda)}.$$

The overall likelihood was the product of the 12 binomial likelihoods.

Maximum-likelihood estimates $\pm$ standard errors estimated from the information matrix are

$$\hat{b} = 0.0223 \pm 0.0028, \qquad \hat{\lambda} = 0.0192 \pm 0.0046.$$

The Pearson chi-square measure of fit is 11.1 on 10 degrees of freedom. When the final four age categories, where sample sizes are small, are combined, the chi-square is 9.41 on 7 degrees of freedom.

For comparison (actually first, before being reprimanded by a reviewer), I ignored the question of sampling distributions and fitted the model by least

squares, matching $\bar{F}(u)$ at $u = 20,45,75,\ldots,285$ to the cumulative prevalences reported in Table 4 of [62]. The least-squares estimates are $b_{ls} = 0.0195$ and $\lambda_{ls} = 0.0565$. Visually, the fit looks good (Figure 1).

Thus, the fit of this model is consistent with a maternal-antibody effect. The model does not prove the existence of such an effect, since other aspects of infant behavior might also provide protection [54]. Moreover, whereas congenital transfer of antibodies against sporozoites and blood stages is well documented [46, 54], the presence of antibodies against malaria parasites does not necessarily confer clinical immunity [15, 17, 38, 68, 72].

The maximum-likelihood estimate of λ matches the disappearance rate of maternal IgG from an infant's plasma, as reported in [26]. However, the least-squares estimate of λ seems more consistent with the rate of decline of specific malaria-antibody titers reported in [46]. The authors of the latter study argue that the observed rapid decline may have been due to above average rates of antibody utilization.

Molineaux and Gramiccia inferred from the data of the Garki study that "maternal antibody probably does not delay significantly the acquisition of the first infection" [49, p. 159]. But the Garki study's surveys were 10 weeks apart. This low resolution may have hidden an effect if it was there. They did, however, conclude from the data that recovery rates are higher among infants, and they attributed that phenomenon to maternal antibodies.

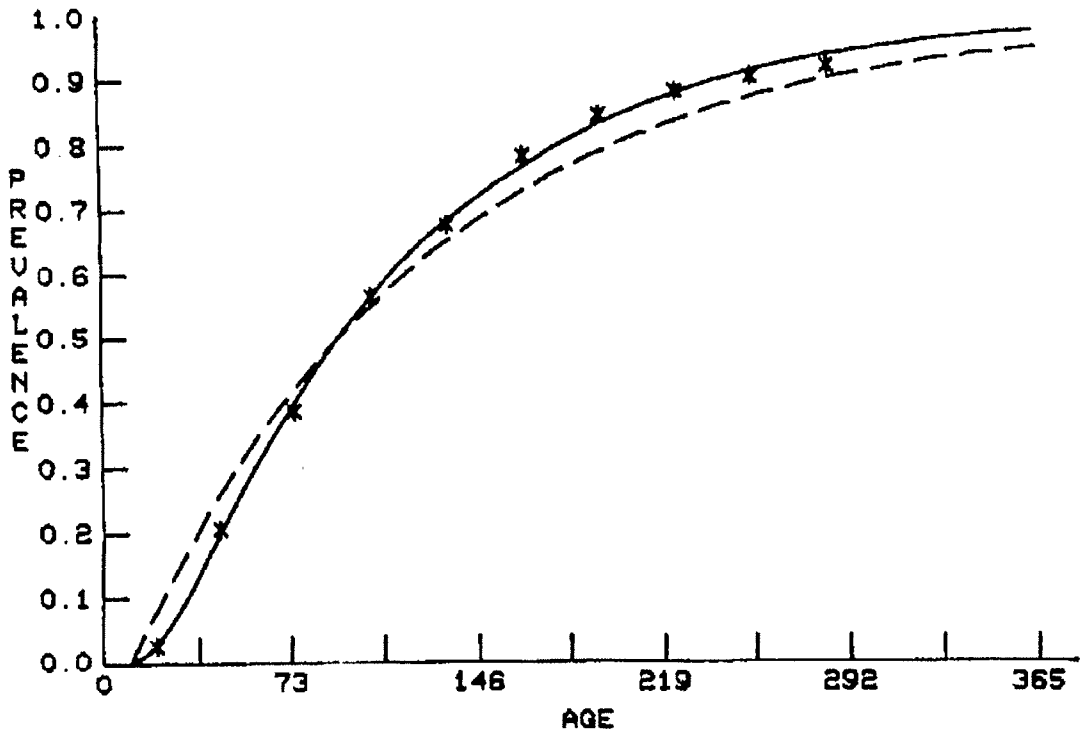

FIG. 1. Pull and Grab's [62] cumulative-prevalence data (*) fitted by their time-independent catalytic model (dashed) and the least-squares fit of the age-time model of Section 4B (solid).

4C. *IDENTIFIABILITY OF SUPERINFECTION*

In Section 3A, we saw how Macdonald preferred a model for superinfection to explain observed data on cross-sectional prevalence among infants. However, neither the model (10) nor any of its competitors have been proven with data. As long as time variation of the inoculation rate is ignored and recovery rates are not known *a priori*, leaving h and r as free parameters, any of the models can be made to fit a typical prevalence curve.

Aron and May [4] pointed out that if superinfection of any nontrivial sort obtains, then observed recovery rates should decrease as infection rates increase. They presented some evidence that rates do so behave. But, as they conceded, measuring recovery rates without a model poses other problems.

What if longitudinal infection patterns among infants are examined without ignoring time variation of the inoculation rate? Might the superinfection process be identifiable? Suppose we have available a set of longitudinal records, such as from the Garki project. For I infants the record for the ith infant consists of

$$\left\{\beta_i,(s_{i1},w_{i1}),\ldots,(s_{in_i},w_{in_i})\right\},\qquad 1\leqslant i\leqslant I, \tag{12}$$

where

β_i = birth date of ith infant;
n_i = number of surveys at which the ith infant was observed;

$$s_{i1}<s_{i2}<\cdots<s_{in_i}$$

are the times of those n_i surveys; and $w_{i1},\ldots,w_{in_i}$ are the observed states ($w=0$ if uninfected, $w=1$ if infected). For one of the superinfection models, let $q(w_{i1},\ldots,w_{in_i};\beta_i,s_{i1},\ldots,s_{in_i})$ be the likelihood of such a record. The model's overall likelihood is then the product of such contributions from each of the I infants.

To see how these likelihoods might be computed for each model, let us define the models as stochastic processes. Let $X(t)$ be the number of distinct broods of infection harbored by an infant at time t. Then $X(t)\in\{0,1\}$ for Ross's model and $X(t)\in\{0,1,2,3,\ldots\}$ for Macdonald and Dietz's. Define the transition probabilities

$$P_{ij}(\tau,t)=\Pr\left\{\,X(t)=j\,|\,X(\tau)=i\right\}.$$

Let $W(t)$ be the observable state of an infant at time t: $W(t)=0$ if the infant is parasitologically negative, $W(t)=1$ if positive. For the Ross model, $W(t)=X(t)$, and the Markov character of the process permits easy computation of the relevant likelihoods. Indeed, Nåsel [55] found the transition

probabilities $P_{ij}(\tau, t)$, and with them

$$q(w_1, \ldots, w_n; \beta, s_1, \ldots, s_n) = P_{0y_1}(\beta, s_1) \prod_{j=2}^{n} P_{y_{j-1}y_j}(s_{j-1}, s_j).$$

For the Macdonald-Dietz model, $W(t) = 0$ if $X(t) = 0$, but $W(t) = 1$ if $X(t) \geq 1$. The $W(t)$ process is not Markovian, and computation of the likelihoods does not appear tractable.

Consider two approximations to the $W(t)$ process [60]. The first approximation defines quasi transition probabilities $Q_{ij}^{(1)}(\tau, t)$ for $W(t)$ as follows:

$$Q_{00}^{(1)}(\tau, t) = P_{00}(\tau, t),$$

$$Q_{01}^{(1)}(\tau, t) = 1 - Q_{00}^{(1)}(\tau, t),$$

$$Q_{10}^{(1)}(\tau, t) = \frac{\sum_{j=1}^{\infty} P_{0j}(\beta, \tau) P_{j0}(\tau, t)}{\sum_{j=1}^{\infty} P_{0j}(\beta, \tau)},$$

$$Q_{11}^{(1)}(y, t) = 1 - Q_{10}^{(1)}(\tau, t).$$

These functions do not define a continuous-time Markov process. However, for a fixed β and a fixed set of subsequent observation times, they do determine a discrete-time Markov chain. They are readily computable [60], and the likelihood q can then be computed as with the Ross model.

The second approximation defines the continuous-time, bivariate Markov process $(W(t), Z(t))$ where $W(t)$ is as before, $Z(t) = 0$ if $W(t) = 0$, and otherwise $Z(t)$ is defined by the following transition rules:

$$Q_{(0,0),(0,0)}^{(2)}(\tau, t) = P_{00}(\tau, t),$$

$$Q_{(0,0),(1,j)}^{(2)}(\tau, t) = \begin{cases} 1 - P_{00}(\tau, t), & j = \text{Round}\left(E\left(X(t) | X(\tau) = 0,\ X(t) \geq 1\right)\right), \\ 0 & \text{otherwise,} \end{cases}$$

$$Q_{(1,j),(0,0)}^{(2)}(\tau, t) = P_{j0}(\tau, t),$$

$$Q_{(1,j),(1,k)}^{(2)}(\tau, t) = \begin{cases} 1 - P_{j0}(\tau, t), & k = \text{Round}\left(E\left(X(t) | X(\tau) = j,\ X(t) \geq 1\right)\right), \\ 0 & \text{otherwise.} \end{cases}$$

Here, Round(x) is the integer nearest to x. Thus, if the process moves to a state of observable infection, then Z moves to the (rounded) conditional expected value of X, given that X is not zero. The succeeding transition is then governed by the transition probabilities obtained by assuming that $X = Z$. See [60] for more details.

Let L_R, L_{M1}, and L_{M2} be overall likelihoods for the Ross model and the two approximations to the Macdonald-Dietz model. We can compare the models by means of the likelihood ratios

$$\lambda_1 = \frac{L_R}{L_{M1}}, \qquad \lambda_2 = \frac{L_R}{L_{M2}}.$$

The models were fitted to data from two villages in the Garki study: Sugungum, where mosquito densities were highest, and Rafin Marke, where mosquito densities were the lowest. The time varying inoculation rate was taken to be Cy_1 (see Section 2) with ma, μ, N_2, and $y_1(t)$ as in [58]. The product $\gamma = bc$ of susceptibility parameters was left free. Also left free was the recovery rate r. So fitting the models means maximizing the likelihoods with respect to r and γ, using data of the form (11) from Sugungum ($I = 31$) and Rafin Marke ($I = 17$).

Results are displayed in Table 1. Clearly, on the basis of the likelihood ratio, no model is favored by these data. Thus, incorporating time dependence seems not to help the identification problem.

4D. *MISDIAGNOSIS*

The analysis in the preceding section assumed that the parasitological data were accurate. In fact, many epidemiologists believe that such data sets suffer from significant rates of false-negative diagnosis.

Several investigators have considered the effects of misdiagnosis on inference. Singer and Cohen [65] quantified how misdiagnosis biases rates estimated from the model of Bekessy et al. [7] when all who are infected have the same probability of being misdiagnosed.

To offset the problem of false diagnosis in estimating prevalence, Aron [3] proposed repeated blood examinations. She assumed that each individual is characterized by a probability of positive diagnosis when infected. This detectability varies among individuals, but it is fixed for a given individual for all examinations. Further assuming that separate examinations constitute independent trials, she demonstrated how, in the work of Bekessy et al., the

TABLE 1

	Sugungum			Rafin Marke		
	r	γ	λ	r	γ	λ
Macdonald-Dietz, Approx. 1	.0071	.0077		.0036	.0492	
			$\lambda_1 = 1.005$			$\lambda_1 = 0.986$
Ross	.0028	.0093		.0024	.0687	
			$\lambda_2 = 1.003$			$\lambda_2 = 1.012$
Macdonald-Dietz, Approx. 2	.0074	.0076		.0047	.0503	

variation of the rate estimates with age may be explained by age dependence of the detectabilities. She also discussed parameter estimation and validity testing for her model.

Another study in which the possibility of diagnostic error was considered is that of Pull and Grab [62], whose data were reanalyzed by Bailey [5] and Verma, et al. [70]. Pull and Grab applied Ross's model (10), modified to incorporate misdiagnosis, to cross-sectional prevalence data for infants. Their modified model is

$$\begin{aligned} \dot{z} &= h(1-z) - rz, \\ y &= kz, \end{aligned} \tag{13}$$

where z is the true cross-sectional prevalence and y the observed.

The model (13) assumes that diagnostic errors are independent over time. The rise and fall of parasite densities in the blood above and below thresholds of detectability may generate an important time dependence. Consider a model where y_+ and y_- are observed positives and false negatives, satisfying

$$\begin{aligned} \dot{y}_+ &= h[1-(y_- + y_+)] - ry_+ - \sigma_+ y_+ + \sigma - y_-, \\ \dot{y}_- &= \sigma_+ y_+ - \sigma_- y_- - ry_-. \end{aligned} \tag{14}$$

The solution to (14) satisfying $y_+(0) = y_-(0) = 0$ is

$$\begin{aligned} y_+(t) = \frac{h}{(h+r)} \{ & c_1 - c_2 \exp[-(h+r)t] \\ & -(c_1 - c_2)\exp[-(r+\sigma_+ + \sigma_-)t] \}, \end{aligned}$$

where

$$c_1 = \frac{\sigma_- + r}{\sigma_- + \sigma_+ + r} \qquad c_2 = \frac{\sigma_- - h}{\sigma_- + \sigma_+ - h}.$$

As discussed in Section 4A, Pull and Grab estimated h independently of their model (13) by curve-fitting the solution of

$$\dot{y} = h(1-y)$$

to time-aggregated cumulative prevalences. They found $\hat{h} = 0.0084$ day^{-1}. Bailey, using maximum likelihood, obtained $\hat{h} = 0.0089$. Verma et al. [60], using maximum likelihood but making an apparently unjustified assumption about censoring, found $\hat{h} = 0.0069$.

Pull, Grab, and Bailey then fitted (13) to time-aggregated cross-sectional prevalences by adjusting the two parameters k and r. Not surprisingly, given the discussion of Section 4B, they were able to graduate the data well, finding $k = 0.7$, $r = 0.0007$ (Pull and Grab) and $k = 0.637$, $r = 0$ (Bailey). Thus, they estimated that more than a third of all infected infants are misdiagnosed, and the recovery rate r is virtually nil.

I have refitted Pull and Grab's cross-sectional prevalence data with an age-and-time version of (12):

$$\frac{d}{du}z(u;\beta) = h(\beta+u,u)[1-z(u;\beta)] - rz(u;\beta),$$
$$z(10;\beta) = 0,$$
$$y(u) \doteq k \times 365^{-1}\int_0^{365} z(u;\beta)\,d\beta,$$

where $z(u;\beta)$ is the true proportion of all infants, born at time β, who are infected at age u; and $y(u)$ is the observed prevalence, as in (13). The inoculation rate $h(t,u)$ is as in (11), with b and λ replaced by the maximum-likelihood estimates from Section 4B.

As in Section 4B, the sampling model was product binomial, with the data coming from the final three columns of Table 1 in [62]. Letting

$$(\tilde{u}_1, \tilde{u}_2, \ldots, \tilde{u}_{12}) = (20,45,75,\ldots,345)$$
$$= \text{midpoints of age intervals},$$

the number of positive infants out of the number examined in the ith age class was taken to be a binomial sample with probability of "success" $y(\tilde{u}_i)$.

In the strip $0 \leqslant r < \infty$, $0 \leqslant k \leqslant 1$, the likelihood is maximized at $k = 1$, $r = 0.00735$. The estimated standard error of r is 0.00043. The Pearson chi-square measure of fit is 18.04, corresponding to $0.05 < p < 0.10$ on either 10 or 11 degrees of freedom. When the model is fitted by least squares, using b_{ls} and λ_{ls} in h and fixing $k = 1$, the least-squares estimate of r is 0.00710. Figure 2 displays the least-squares fit.

Thus, the likelihood approach suggests that in fact misdiagnosis is *not* a problem and that the recovery rate r was even larger, with this non-superinfection model, than Macdonald's favored value of 0.005. The curve-fitting approach demonstrates that the alternative age-time model with $k = 1$ is at least as good as the original model of Pull and Grab. These authors may have had other reasons for believing that large numbers of infants were misdiagnosed. However, in the Garki study [25, 57], misdiagnosis was assumed to be a problem only for older persons who had developed immunity after repeated exposure.

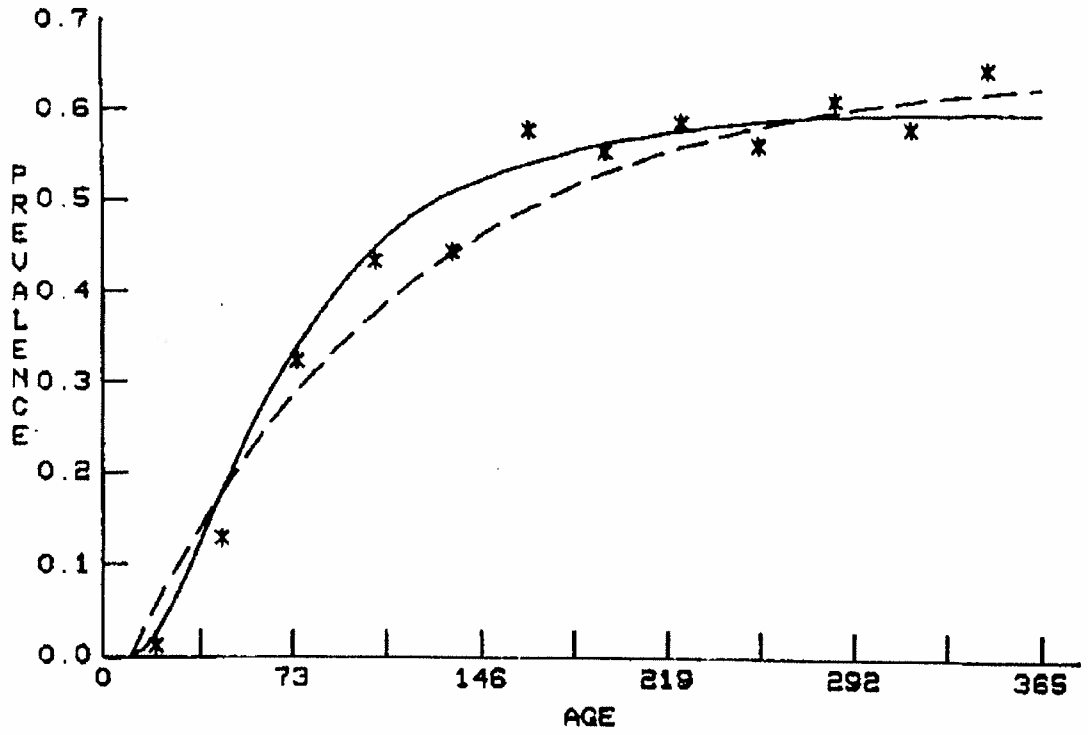

FIG. 2. Pull and Grab's [62] cross-sectional prevalence data (*) fitted by their time-independent catalytic model (dashed) and the least-squares fit of the age-time model of Section 4D (solid).

5. DISCUSSION

Diverse issues in mathematical modeling of malaria have been considered.

A search for historical roots of the vectorial-capacity construction of the inoculation rate was motivated by the fact that Dietz, Molineaux, and Thomas used the device in their path-breaking work [22]. The approximation (9) has never been tested with adequate data, although it is plausible, given certain parameter values.

The mathematical ease with which such parameters can be manipulated distracts from the vagueness of their epidemiological interpretations. When applying dynamic models to data, a lesson from regression analysis is important: the interpretation of a parameter depends on what else is in the model. On the other hand, as malaria modeling becomes more applied, another lesson is worth remembering: if the purpose of the model is to predict, then considerable statistical uncertainty in the parameters is tolerable, provided the model predicts well with a useful class of inputs; so why worry much about interpretation?

And malaria modeling is becoming more applied. As *dynamic* models come to be used for purposes other than the study of *equilibria*, more sophistication regarding inference from data will be called for. Bailey [5] has raised the banner of statistical rigor behind which modelers and data collectors should rally.

APPENDIX. NOTATION

a = human-biting rate of mosquitoes,

b = proportion of bites by infectious mosquitoes on susceptible humans which result in infection,

c = proportion of bites by susceptible mosquitoes on infectious humans which result in infection,

C = vectorial capacity,

$h, h(t), h(t, u)$ = inoculation rate,

h_e = inoculation rate determined from entomological data,

h_p = inoculation rate determined from parasitological data,

k = proportion of true infections which are misdiagnosed, in Pull and Grab's model,

m_1, m_2, m_3 = density of susceptible, latent, and infectious female mosquitoes, respectively,

$m_{23} = m_2 + m_3$,

$m = m_1 + m_2 + m_3$,

N_2 = incubation delay in mosquitoes,

n_i = number of surveys at which an infant is observed,

r = recovery rate from parasitemia,

s_{ij} = date of the jth survey for the ith infant,

U_β = duration until first patent infection for an infant born at time β,

w_{ij} = state of the ith infant at the jth survey,

y = proportion of the human population who are infected, in models not discriminating between infected and infectious,

y_+ = proportion who are correctly diagnosed as infected,

y_- = proportion who are misdiagnosed as uninfected,

y_1 = proportion of the human population who are infectious,

z_0 = basic reproduction rate,

α_1 = recovery rate from infectiousness (humans),

β = birth date of an infant,

$\gamma = bc$,

$\varepsilon = r/\mu$, singular perturbation parameter,

η = emergence rate of mosquitoes,

λ = first-order decay constant for the maternal-antibody effect,

λ_+, λ_- = eigenvalues of Ross's equation linearized about an equilibrium,

μ = death rate of mosquitoes,

$\rho = ca/\mu$,

σ_+, σ_- = transition rates between y_+ and y_-.

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