Mathematical Modeling of Immunity to Malaria

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ABSTRACT

A comparison of two epidemiological models of immunity to malaria shows that different characterizations of immunity boosted by exposure to infection generate qualitatively different results. Attempts to control disease by reducing transmission or increasing the recovery rate can produce an increase in prevalence in the compartmental model with discrete epidemiological states. However, the parasite density always decreases in response to disease control in the model with continuous epidemiological variables. Each model accounts for some epidemiological patterns. The increase in prevalence seen in the compartmental model is in accord with observed effects of variation in transmission. Parasite suppression in areas of antimalarial drug use is consistent with the effect of an increased recovery rate in the density model. Future work should combine the two approaches, perhaps by using the compartmental model over the low to moderate range of infection rates and switching to the density model at high infection rates. In any case, the validation of models needs to take account of the usage of antimalarial drugs as well as the intensity of transmission.

INTRODUCTION

One of the most complex features of the epidemiology of malaria is the dynamic interaction between infection and immunity. A better understanding of this interaction is important for evaluating the impact of malaria control activities. Perhaps the need for understanding is even greater as we move closer to direct manipulation of immunity with malaria vaccination [6].

The primary concern of this paper is the phenomenon of boosting, which is the maintenance of acquired immunity by continued exposure to infection. A comparison of two models of immunity shows that different formulations of boosting capture qualitatively different epidemiological features. The results combine material previously published in [1], [2], and [5] and new observations on the properties of these models.

A brief discussion of the biology of malaria is required for describing the epidemiology of immunity to malaria. Malaria is caused by a parasitic

protozoan infection. Four different species of the genus *Plasmodium* are known to infect humans; one of these, *Plasmodium falciparum*, causes the most serious illness and is the most widespread in the tropics. This paper will focus exclusively on the population dynamics of *P. falciparum*. The life cycle of the parasite alternates between a female mosquito of the genus *Anopheles* (the vector) and the human host. (See also [2].) Transmission from mosquito to human occurs during a bite by an infectious mosquito. The parasite migrates to the liver and remains latent for several days while replicating. The latent period is followed by penetration of red blood cells and asexual replication within them, resulting in lysis of the cells. Asexual parasites in the blood are responsible for the pathological effects of malaria. Asexual parasites in the blood also give rise to sexual stages called *gametocytes*. Gametocytes are responsible for transmission of the parasite from humans when mosquitoes bite. Fertilization of the parasite occurs in the mosquito gut, and after a short period of replication and development, the cycle of transmission may begin anew.

Epidemiological surveys are based in large part on blood smears in which *asexual parasites* and *gametocytes* may be observed. Blood smears may be classified solely in terms of presence or absence of parasites, or in terms of the density of parasites. Observations which include all forms of the parasite typically reflect asexual parasites, which are more numerous than gametocytes. Clinical symptoms, such as fever or enlarged spleen, may also be included. Because of the dependence of transmission on mosquitoes, epidemiological patterns usually vary with the season.

The epidemiological evidence for immunity to *P. falciparum* malaria comes from areas with intense transmission. For example, consider the results of a baseline survey of two populations in Garki, Nigeria taken during the wet season (season of high transmission). The changes with age reflect the slow acquisition of an immunity that reduces illness but does not completely block infection. The age-specific prevalence (proportion positive) of *P. falciparum* [Figure 1(a)] rises quickly to almost 100% in early childhood and declines slowly into adulthood. The age-specific prevalence of gametocytes [Figure 1(b)] roughly parallels the prevalence of all forms of *P. falciparum* at a lower level. Not shown in the figures, the density of parasites and the severity of illness also decline with age.

The dependence of this immunity on continued exposure is revealed in the effects of malaria control in the study described above. After the baseline period, one population was protected for two wet seasons by insecticide spraying directed against vector mosquitoes and mass drug administration directed against the malaria parasite. In the subsequent wet season, intervention was discontinued (except for additional administration of antimalarial drugs to children under the age of 10 years). During that season, the prevalence of malaria in the (formerly) protected population (P) was higher

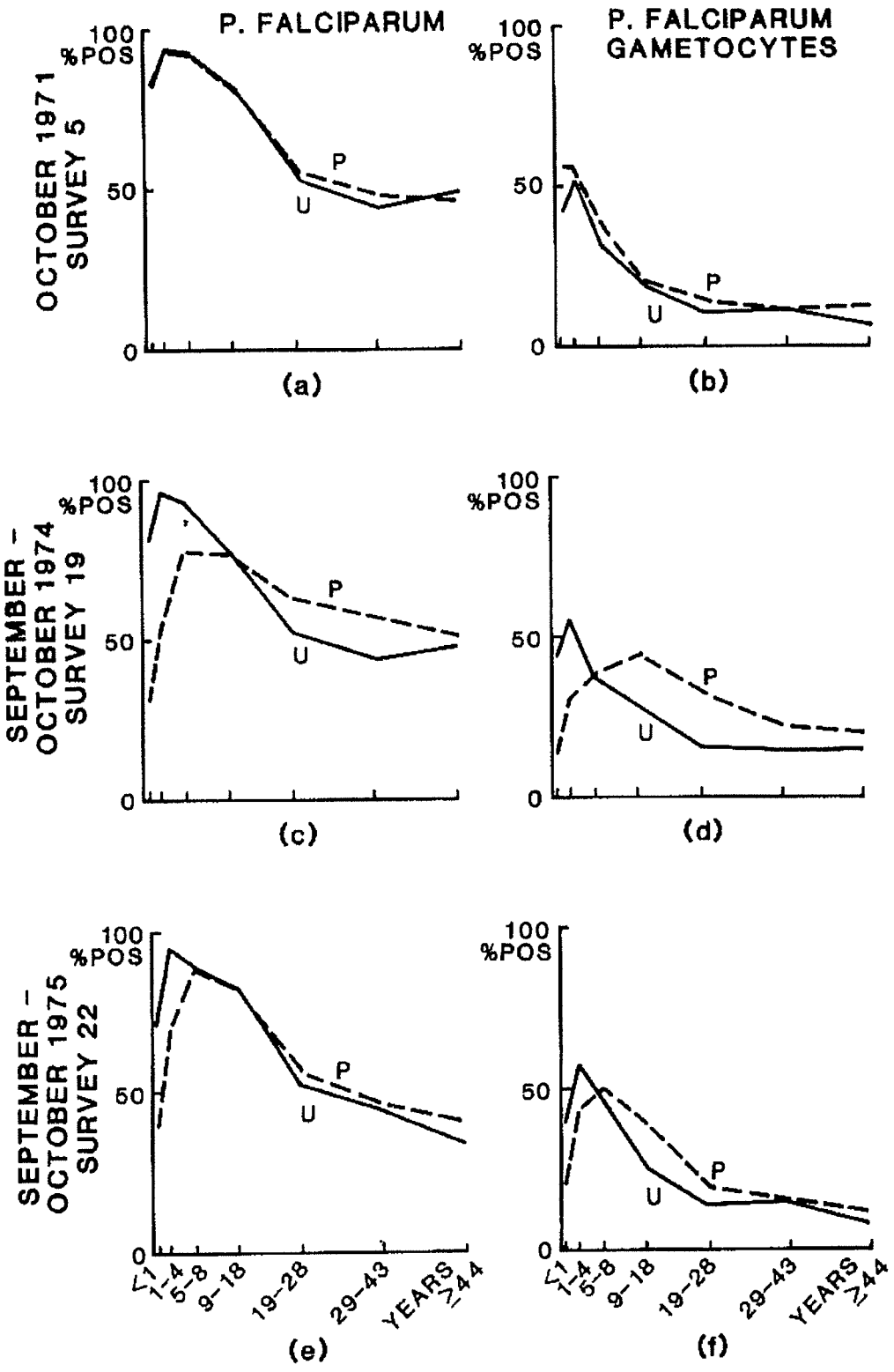

FIG. 1 Age-specific prevalence of *P. falciparum* (any form) and its gametocytes in the wet seasons of 1971 (a, b), 1974 (c, d) and 1975 (e, f) in Garki, Nigeria. As discussed more fully in the text, the unprotected population (*U*, solid line) received no malaria control, while the protected population (*P*, broken line) received malaria control in 1972 and 1973. Reproduced with permission from [7, p. 154].

than in the population (U) which had never received any intervention [Figure 1(c),(d)]. Thus, some immunity was lost during the period of malaria control. However, in the absence of further intervention in the following year, the age-specific prevalence curves of the two populations became more similar [Figure 1(e),(f)]. As the lost immunity was regained, the former epidemiological equilibrium was reestablished.

EPIDEMIOLOGY AND VARYING TRANSMISSION

This section explores how the level of malaria transmission affects age-specific patterns of malaria prevalence and density of asexual parasites. The data are based on cross-sectional surveys which are assumed to represent age-dependent epidemiological equilibria with age measured in years. Both models of immunity follow the experience of a birth cohort. The dynamics of transmission from human to mosquito to human are implicit in the existence of an equilibrium. Levels of transmission are reflected in rates of infection.

One model divides the population into three compartments: susceptibles (x), the proportion that are uninfected; infecteds (y), the proportion with severe infections; and immunes (z), the proportion with mild, asymptomatic infections. Individuals are born susceptible to become infected at a rate of h infections per year. They subsequently recover at rate r, becoming susceptible again. Infected individuals may also acquire immunity at a slow rate of q. The effect of boosting is incorporated into the rate at which immune individuals revert to being susceptible. The rate of reversion, γ, is chosen so that the average duration of immunity corresponds to the assumption that immunity lasts until the occurrence of a gap of τ years without exposure. It has been shown in [1] and [2] that γ may be written

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

The monotonically decreasing function in Equation (1) is illustrated in Figure 2. Mortality terms are ignored under the assumption that mortality acts equally on all individuals in the birth cohort. (Only differential mortality is relevant in a model of population fractions.) Although, in fact, mortality rates vary according to disease status, the simpler assumption is a reasonable first approximation for a qualitative analysis of the effect of changes in transmission. The model may then be written

$$\frac{dx}{da} = -hx + ry + \gamma(h)z, \tag{2}$$

$$\frac{dy}{da} = hx - ry - qy, \tag{3}$$

$$\frac{dz}{da} = qy - \gamma(h)z, \tag{4}$$

where $x(a) + y(a) + z(a) = 1$, $x(0) = 1$, and γ is defined in Equation (1).

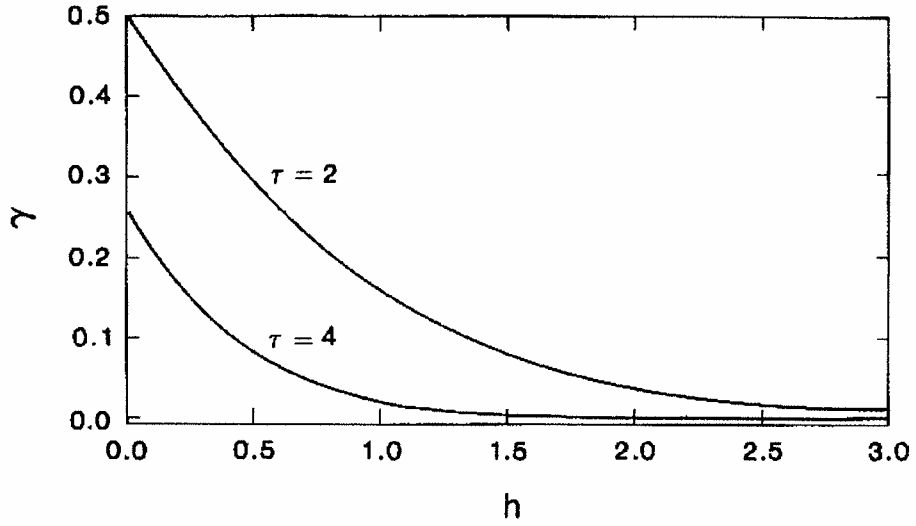

FIG. 2 The rate of loss of immunity, γ, as a function of the infection rate h as defined in Equation (1).

Figure 3 illustrates the possible shapes of the prevalence of infecteds, y, for different values of the rate of infection, h. The prevalence among children always increases with the rate of infection, but the prevalence among adults is highest at intermediate rates of infection. The adult cross-over of the age-prevalence curve with increasing endemicity matches the pattern of acute infection described by Boyd for tropical Africa (Figure 4).

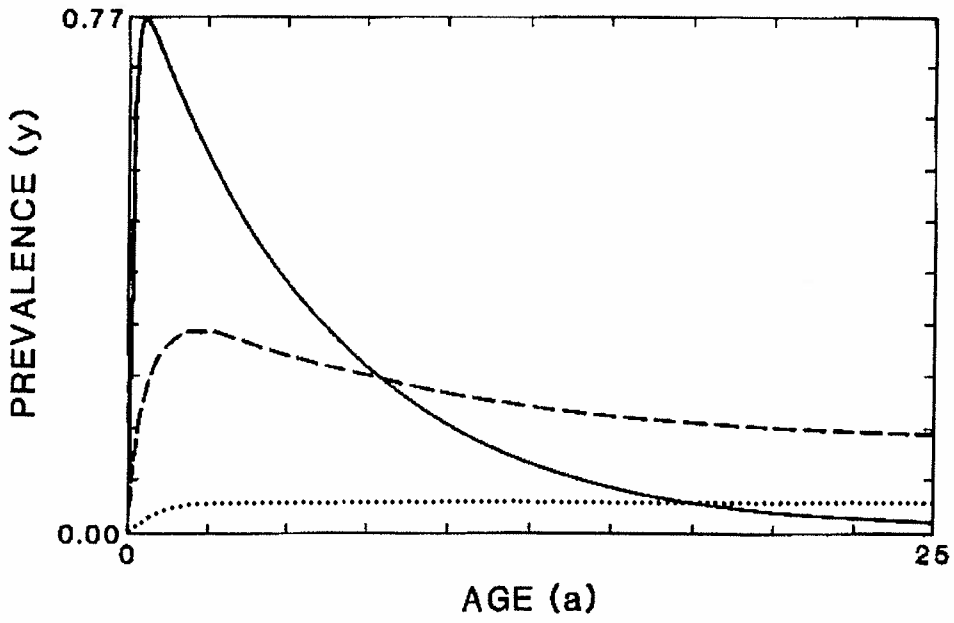

FIG. 3 Prevalence of infecteds, y, as a function of age a for the model defined in Equations (1)–(4). The three curves correspond to different infection rates: $h = 5$ (solid), $h = 0.5$ (broken), and $h = 0.05$ (dotted). The rest of the parameters are $r = 0.8$, $q = 0.2$, and $\tau = 5$.

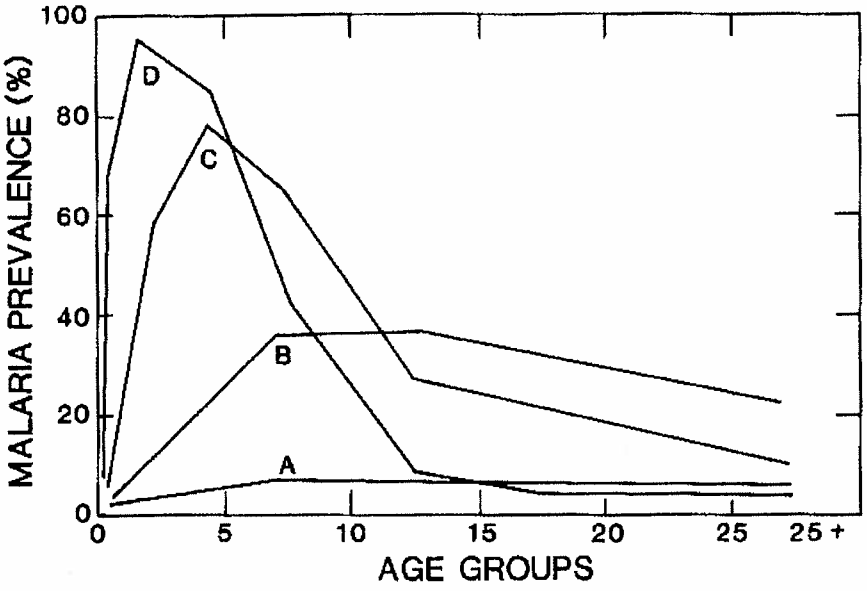

FIG. 4 Prevalence of acute malaria infections versus age in years in stable indigenous populations for differing levels of endemicity: A, low endemicity; B, moderate endemicity; C, high endemicity; and D, hyperendemicity. Modified from [3, p. 571].

In contrast to the discrete epidemiological states of the compartmental model above, the other model uses continuous variables for infection and immunity. At an epidemiological equilibrium, the experience of a birth cohort is characterized in terms of $p(a)$, the density of asexual parasites at age a; $r(a)$, the level of immunity directed against asexual parasites at age a; and $g(a)$, the density of gametocytes at age a. The asexual parasites, p, grow by an influx v and decline according to a rate of clearance $r + r_b$. The rate of clearance is the sum of a background rate, r_b, and the rate r, which represents the effect of acquired immunity. The interaction between infection and immunity is handled by assuming that r increases at a rate proportional to the asexual parasitemia and decreases in the absence of parasitemia. The gametocytes g are produced by the asexual parasites after surviving a developmental period T and are subject to a fixed rate of clearance, δ. (The notation here is slightly different from the original in [5].) The model of the age-specific pattern at equilibrium may then be written

$$\frac{dp}{da} = v - (r + r_b)p, \tag{5}$$

$$\frac{dr}{da} = \alpha p - \beta r, \tag{6}$$

$$\frac{dg}{da} = \gamma p e^{-(r+r_b)T} - \delta g, \tag{7}$$

where $p(0) = r(0) = g(0) = 0$.

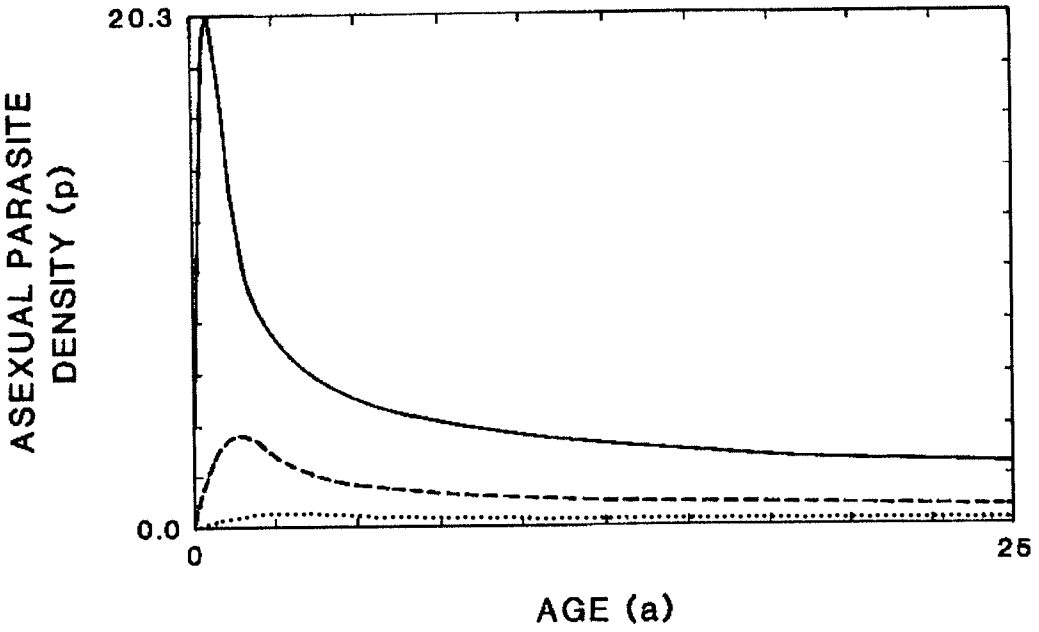

FIG. 5 The density of asexual parasites, p, as a function of age a for the model defined in Equations (5)–(7). The three curves correspond to different rates of parasite influx: $\upsilon = 50$ (solid), $\upsilon = 5$ (broken), and $\upsilon = 0.5$ (dotted). The rest of the parameters are $r_b = 0.66$, $\alpha = 0.2$, $\beta = 0.005$, $\gamma = 0.5$, $T = 1$, and $\delta = 0.4$.

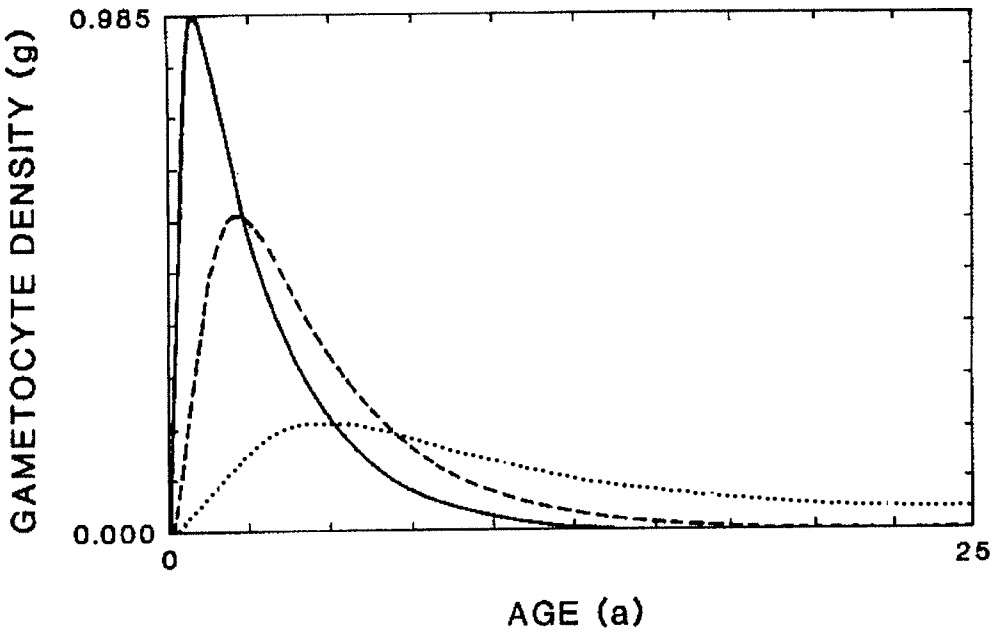

FIG. 6 The density of gametocytes, g, as a function of age a for the model defined in Equations (5)–(7). The three curves correspond different rates of parasite influx: $\upsilon = 50$ (solid), $\upsilon = 5$ (broken), and $\upsilon = 0.5$ (dotted). The rest of the parameters are $r_b = 0.66$, $\alpha = 0.2$, $\beta = 0.005$, $\gamma = 0.5$, $T = 1$, and $\delta = 0.4$.

The analysis in [5] considered an overall model of transmission in which v was replaced by $V\int_0^\infty \mu e^{-\mu x} g(x)\,dx$, where V represents the transmission potential of the mosquito vector population and $\mu e^{-\mu x}$ represents the age structure of the human host population. However, the authors did not show the effect of changes in v on the shape of the age-dependent equilibrium. In this model, changes in transmission do not result in crossovers of the age-dependent equilibria for asexual parasites (Figure 5). The compartmental model (Figure 3) seems to characterize different levels of endemicity better than does the density model (Figure 5). However, it is of interest to note that the age-dependent patterns of gametocytes generated by the density model do show a crossover (Figure 6). The qualitative patterns of the asexual parasites which cause illness are thus different from the qualitative patterns of the gametocytes which are responsible for transmission. Patterns of asexual parasites and illness (the focus of this paper) should be carefully distinguished from patterns of gametocytes.

EPIDEMIOLOGY AND VARYING ANTIMALARIAL DRUG USAGE

This section explores how the level of antimalarial drug usage affects age-specific patterns of malaria prevalence and density of asexual parasites. The compartmental model and the density model of the previous section are used without modification. Levels of antimalarial drug usage are reflected in rates of recovery (r for the compartmental model and r_b for the density model). The data in this section are cross-sectional surveys from Tanganyika (Tanzania) in which the region of lesser endemicity displays a lower prevalence and density of malaria at every age (Figure 7). Although it seems at first that Figure 7 directly contradicts Figure 4, the differences are affected by the widespread availability of antimalarial drugs in urban Tanga [Figure 7(b)] and the lack of pharmaceuticals in isolated, rural Gombero [Figure 7(a)].

The age-specific densities of both asexual parasites (Figure 8) and gametocytes (Figure 9) generated by increasing r_b in the density model reveal that parasites are suppressed in the younger age groups and little affected in the older age groups. The age-specific prevalence of infecteds (Figure 10) generated by increasing r in the compartmental model shows reductions in the younger age groups and increases in the older age groups. Since Figure 7 does not display a crossover, the density model is more successful than the compartmental model in this setting. This reversal illustrates the utmost importance of the knowledge of malaria control activities in the interpretation of malaria surveys.

The effect of antimalarial drugs is especially relevant for models of the epidemiology of malaria in the 1980's. The expansion of health-care facilities in many developing countries has served to provide access to antimalarials,

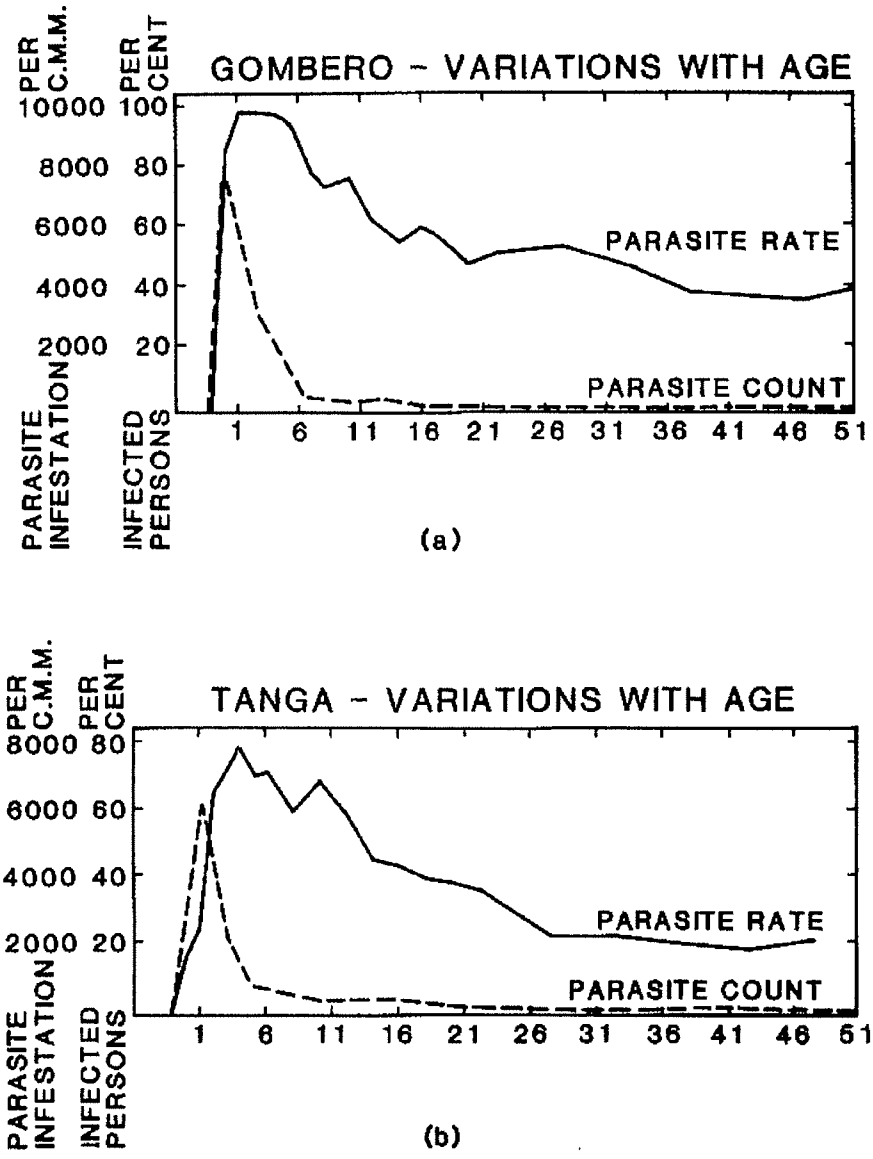

FIG. 7 Age-specific prevalence (parasite rate) and density (parasite count) of malaria in (a) Gombero, a rural area, and (b) Tanga, an urban area in Tanganyika. Reproduced with permission from [8, p. 603].

particularly chloroquine. The dominating effect of anitmalarial drugs is indicated in one recent study of malaria in Papua New Guinea, in which the level of endemicity correlated inversely with the use of chloroquine measured by the Dill-Glazco urine test (Table 1). The dynamics are complicated when transmission is high enough to result in acquisition of immunity and when antimalarial drug usage is high enough to reduce the densities of parasites and malaria mortality. The situation is further complicated by the spread of drug-resistant malaria parasites. The problem of integrating drug use and transmission control into epidemiological models of immunity to malaria should receive more attention.

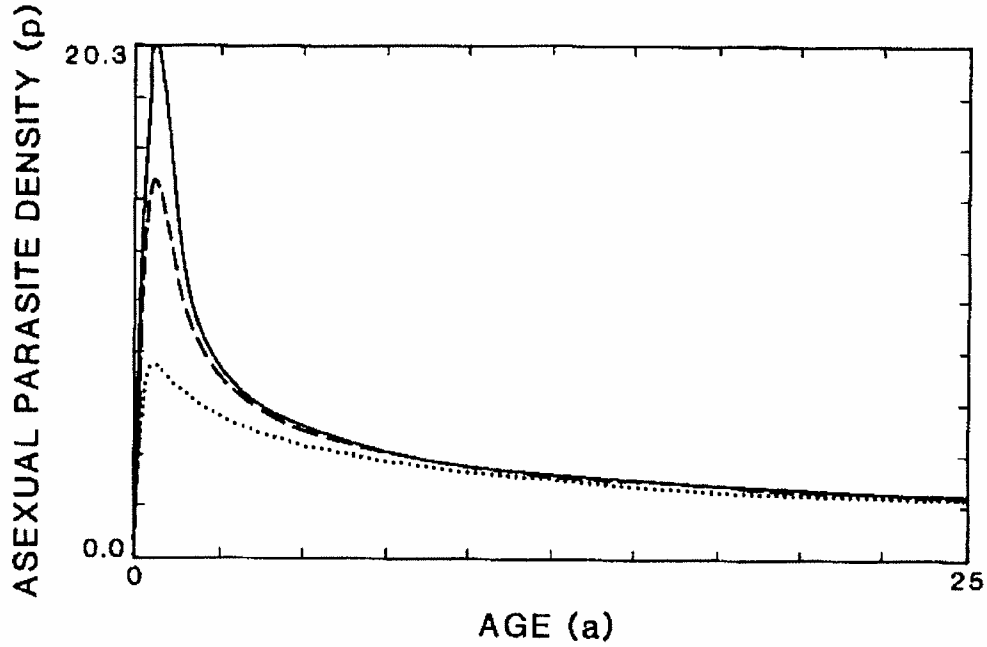

FIG. 8 The density of asexual parasites, p, as a function of age a for the model defined in Equations (5)–(7). The three curves correspond to different background rates of clearance: $r_h = 0.66$ (solid), $r_h = 1.98$ (broken), and $r_h = 5.94$ (dotted). The rest of the parameters are $\upsilon = 50$, $\alpha = 0.2$, $\beta = 0.005$, $\gamma = 0.5$, $T = 1$, and $\delta = 0.4$.

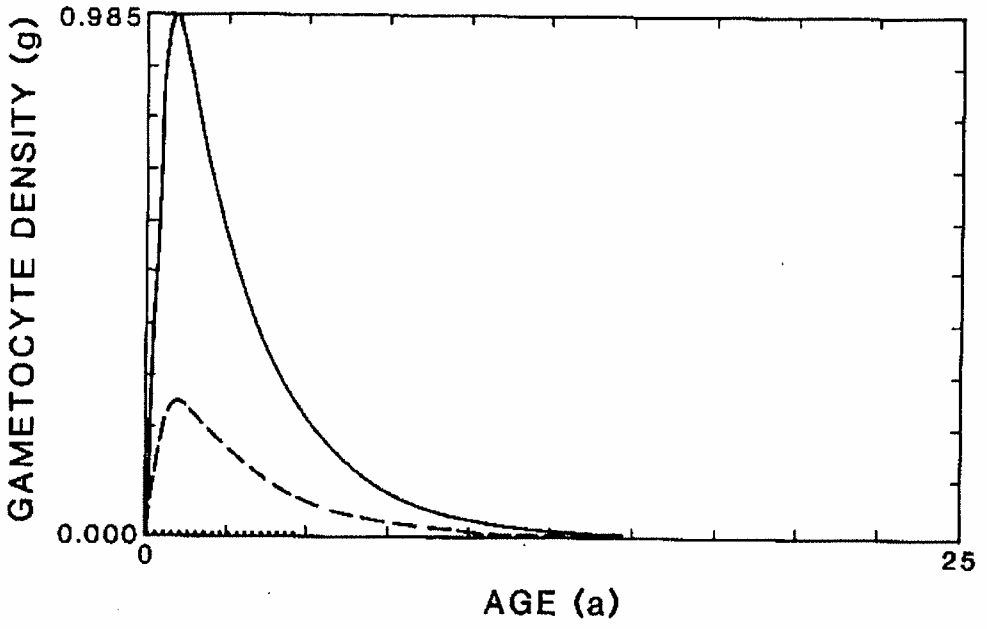

FIG. 9 The density of gametocytes, g, as a function of age a for the model defined in Equations (5)–(7). The three curves correspond to different background rates of clearance: $r_h = 0.66$ (solid), $r_h = 1.98$ (broken), and $r_h = 5.94$ (dotted). The rest of the parameters are $\upsilon = 50$, $\alpha = 0.2$, $\beta = 0.005$, $\gamma = 0.5$, $T = 1$, and $\delta = 0.4$.

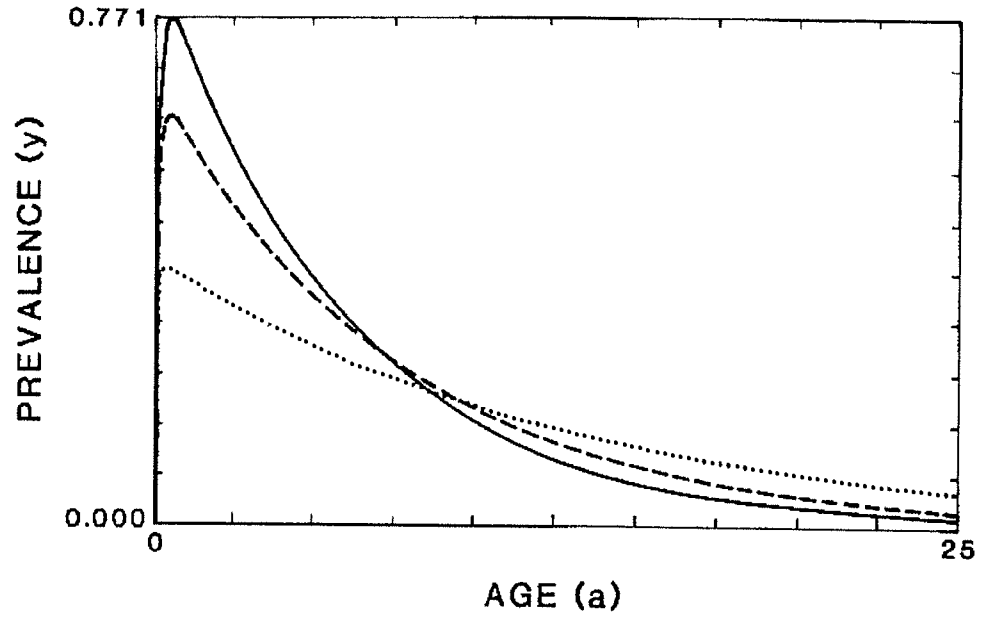

FIG. 10 Prevalence of infecteds, y, as a function of age a for the model defined in Equations (1)–(4). The three curves correspond to different recovery rates: $r = 0.8$ (solid), $r = 2.4$ (broken), and $r = 7.2$ (dotted). The rest of the parameters are $h = 5$, $q = 0.2$, and $\tau = 5$.

TABLE 1

Malaria in Papua New Guinea[a]

Area	Percentage positive for parasites (1–4-yr-olds)	Percentage positive Dill-Glazco test (all ages)
1	46.9	16.4
2	47.9	11.6
3	61.9	9.3

[a]Wet-season figures from Table 6 and Table 9 in [4].

CONCLUSION

A comparison of two different approaches to the dynamics of acquired immunity to malaria has highlighted the strengths and weaknesses of each. Both approaches incorporate the need for reexposure to maintain immunity, but they produce qualitatively different results. The potential for reduced transmission to increase the prevalence of malaria (Figure 4) is captured by the compartmental model but not the density model. However, only the density model generates the suppression of malaria observed (at least in the short term) from widespread antimalarial drug use (Figure 7).

The differences between the two approaches may be due in part to different measures of malaria. Wilson surveyed parasites (Figure 7), while

Boyd examined enlarged spleens (Figure 4). Since the density model was designed for the study of parasites and the compartmental model was designed for the study of illness, their respective successes might reflect real differences between the dynamics of parasites and the dynamics of illness.

It may also be that each model is appropriate for different ranges of infection rates. When people have a lot of time to clear infections before becoming reinfected, a compartmental model is a natural framework. When infection rates are so high that virtually everyone harbors parasites, a density model makes sense.

These conclusions suggest the need for further work. Features of compartmental malaria models should be combined with features of density malaria models. Ultimately, models of immunity need to take account of the effect of antimalarial drugs as well as the effect of transmission.

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