Supporting Text

Introduction

Figs. 7, 8, and 9 show the effects of changing model parameters τ_{MER}, the lifetime of free merozoites, and *p*, the number of merozoites produced per bursting schizont, for a *Plasmodium vivax* and a generalist model. These three figures show changes in the time to the onset of catastrophic anemia, the peak, and the integrated parasitemia.

Figures 10, 11, and 12 shows changes in *P. vivax* and generalist dynamics that arise from the bystander effect and diserythopoesis (see text).

Figures 13, 14, and 15 display some properties of the steady-state solutions as a function of $\mathbf{f_0}$ for all 3 models.

There are four sections in this supplement: (*i*) Poisson Model of the Fate of Free Merozoites, (*ii*) Limit on Exponential Growth of Parasitemia, (*iii*) Variance in Population Lifespan in a CODE Model, and (*iv*) Steady-State Solutions.

Poisson Model of the Fate of Free Merozoites

As stated in the main text, we assume that there are two competing Poisson processes that affect the fate of a merozoite when it is released from a bursting RBC: (*i*) the merozoite will die or be cleared from circulation at rate $1/\tau_{MER}$; (*ii*) it attaches to an uninfected RBCs at rate ζV. (In our present calculations, we ignored infection of RBCs already infected.) We make the assumption that one of these fates will occur before *V* changes significantly. Then the probability that by time *t* after release neither fate occurs to the merozoite is

$$P_{NH}(t) = \exp(-t\,(1/\tau_{MER} + \zeta V)) \qquad \textbf{[S1]}$$

The probability that neither has occurred by time *t* but the merozoite invades a RBC between time *t* and $t + \Delta t$ (and is not cleared) is

$$\delta P_{INF}(t) = P_{NH}(t)\, \zeta V\, \Delta t\, (1 - \Delta t/\tau_{MER}) \qquad \textbf{[S2]}$$

If $N = t/\Delta t$, then the probability that by time *t*, the merozoite has invaded an RBC (and not died) is

$$P_{INF}(t) = \Sigma_{n=1,N}\, \delta P_{INF}(n\Delta t) \qquad \textbf{[S3]}$$

Taking the limit of $\Delta t \rightarrow 0$ (and $N \rightarrow \infty$), we get

$$P_{INF}(t) = \zeta V\,(1/\tau_{MER} + \zeta V)^{-1}\,[1 - \exp(\,-t\,(1/\tau_{MER} + \zeta V)\,)\,] \qquad \textbf{[S4]}$$

As $t \rightarrow \infty$,

$$P_{INF}(t) \rightarrow \zeta V \tau_{MER}/(\,1 + \zeta V \tau_{MER}\,) \qquad \textbf{[S5]}$$

Consider the free merozoites that reach and infect RBCs. The average number of descendants of those merozoites that also reach and infect RBCs is

$$\begin{aligned} \mathbf{R} &= p\, P_{INF}(t) \;\text{ as } t \rightarrow \infty \\ &= p\, \zeta\, V\, \tau_{MER}\, (1 + \zeta\, V\, \tau_{MER}\,)^{-1} \end{aligned} \qquad \textbf{[S6]}$$

where p is the average number of merozoites released by a bursting RBC. If $\tau_{MER} << \tau_I$, then the merozoites released from a bursting RBC almost certainly will die over a single development cycle unless they infect an RBC by time τ_I after release. Thus **R** is a basic reproductive ratio during a cycle time. Note that $\mathbf{R} \rightarrow p$ as $V\tau_{MER} \rightarrow \infty$.

Limit on Exponential Growth of Parasitemia

$\mathbf{R} = \mathbf{R_0}$ is the basic reproductive ratio when the merozoites are first released from the liver. If the initial release is $\approx 10^4$ to 10^5 merozoites, the merozoite population is dwarfed by the total population of vulnerable RBCs. If $\mathbf{R_0} > 1$, then the parasite count undergoes an initial phase of exponential growth as long as $V \approx V_0$. The question, then, is how long this phase will last. We can set an upper bound on the length of the exponential growth phase. During the initial growth phase, the merozoite count for each generation n is

$$Mer_n \approx \mathbf{R_0}^n\, Mer_0 \qquad \textbf{[S7]}$$

This approximation must certainly break down by the time $Mer_n \approx V_0$. So the upper bound on the duration of the exponential growth phase is

$$T_C = \tau_I\, N_C \qquad \textbf{[S8]}$$

where N_C is the solution to

$$\mathbf{R_0}^{N_C} Mer_0 = V_0 \qquad \textbf{[S9]}$$

This yields

$$N_C = \log(V_0/Mer_0)/\log(\mathbf{R_0}) \qquad \textbf{[S10]}$$

$$T_C = \tau_I \log(V_0/Mer_0)/\log(\mathbf{R_0})$$

Variance in Population Lifespan in a CODE Model

Our discussion in this section resembles those given in refs. 1 and 2, but is repeated here for those readers who are not familiar with compartmental equations. Consider a simple model for the dynamics of a population of individuals that age and then die: initially all the population is in one compartment. As individuals age, they pass from compartment to compartment at an average rate κ. After an individual passes through the last compartment, it dies. Let F be the total number of compartments:

$$dX_1/dt = -\kappa X_1 \qquad \textbf{[S11]}$$

$$dX_n/dt = \kappa(X_{n-1} - X_n),\ 1 < n < F$$

We use initial conditions $X_1(0) = P_0$, $X_n(0) = 0$ for n > 1. Then for $t > 0$ in all compartments:

$$X_n(t) = P_0 \exp(-\kappa t)\ (\kappa t)^{n-1}/(n-1)! \qquad \textbf{[S12]}$$

The rate of individuals dying is

$$r_D(t) = \kappa X_F(t) = \kappa P_0 \exp(-\kappa t)\ (\kappa t)^{F-1}/(F-1)! \qquad \textbf{[S13]}$$

This has a maximum at time $t_{MX} = (F - 1)/\kappa$, the time when most of the population has progressed into the final compartment. Define the quantity $\sigma = (F - 1)^{1/2}/\kappa$. Using the infinite series representation of $\ln(1 + x) = \Sigma_n (-1)^{n-1} x^n/n$, we find that for small enough time interval Δt:

$$\ln(r_D(t_{MX} + \Delta t)/r_D(t_{MX})) = -(1/2)\Delta t^2\sigma^{-2} + (1/3)\Delta t^3\sigma^{-3} - (1/4)\Delta t^4\sigma^{-4} + \ldots \quad \textbf{[S14]}$$

In particular, if $\Delta t = +\sigma$ or $-\sigma$:

$$\ln(r_D(t_{MX} + \sigma)/r_D(t_{MX})) = -1/2 + (1/3)\,(F - 1)^{-1/2} - (1/4)(F - 1)^{-1} + \ldots$$

$$\ln(r_D(t_{MX} - \sigma)/r_D(t_{MX})) = -1/2 - (1/3)\,(F - 1)^{-1/2} - (1/4)(F - 1)^{-1} - \ldots \quad \textbf{[S15]}$$

Eqs. **S14** and **S15** show that as F gets larger, t_{MX} fixed, $r_D(t)$ approaches Gaussian function of t centered about t_{MX} with variance $\sigma = (F - 1)^{1/2}/\kappa = t_{MX}\,(F - 1)^{-1/2}$. If F = 10, $r_D(t_{MX} + \sigma) \approx 0.66\, r_D(t_{MX})$ and $r_D(t_{MX} - \sigma) \approx 0.52\, r_D(t_{MX})$. For F = 100, $r_D(t_{MX} + \sigma) \approx 0.63\, r_D(t_{MX})$ and $r_D(t_{MX} + \sigma) \approx 0.58\, r_D(t_{MX})$.

The nominal lifespan of an individual is $\tau = F/\kappa$; then

$$\sigma^2 = t_{MX}^2/(F - 1) = \tau^2(F - 1)/F^2$$

$$= (\tau^2/F)(\,1 - 1/F). \quad \textbf{[S16]}$$

If $F >> 1$, τ fixed, we can use the approximation $\sigma \approx \tau/F^{1/2}$.

Steady-State Solutions

The steady-state solutions obtained by setting all the time derivatives in the CODE models to zero have analytic forms for all three models. The steady-state solutions show both unifying themes and differences due to the age structure of the attack strategies. For all three models, the free merozoite count is given by

$$Mer_S = xF_V/(\zeta\,\tau_V) \quad \textbf{[S17]}$$

where τ_V = 120 days, τ_R, or τ_S for the generalist, *P. vivax* or *P. malariae* models respectively. F_V is the number of compartments that describe the susceptible RBC stage. The dimensionless number x is the solution to

$$F_v x/(1 - (\,1 + x)^{-Fv}) = f_0\, E_{T0}\, \tau_{Mer}\, \zeta\, (p - 1) \quad \textbf{[S18]}$$

Thus, the variance in the duration of a susceptible RBC affects the steady-state solution. The right hand side can be written as $\mathbf{R_0}(p - 1)/(p - \mathbf{R_0})$. Since the left-hand side $\rightarrow$ 1 as $x \rightarrow 0$, $\mathbf{R_0}$ must be > 1 for there to exist a non-trivial steady state (i.e. a real, positive solution for x).

The infected and susceptible RBC steady-state counts for all three models are

$$IE_S = (\tau_{IE}/\tau_V)\, f_0 E_{T0} (1 - (1 + x)^{-Fv}) \qquad \textbf{[S19]}$$

$$Vs = 1/((p - 1)\, \zeta\, \tau_{MER}) \qquad \textbf{[S20]}$$

Note that $V = Vs$ gives $\mathbf{R} = 1$ in Eq. **1** in the main text, as expected.

For the *P. malariae* and generalist models, the steady-state count of nonsusceptible RBCs is

$$N_S = (1 - f_0)\, E_{T0}, \qquad \textbf{[S21]}$$

which is independent of the behavior of the susceptible fraction of RBC. However, the *P. vivax* model is very different from the other two in that the steady-state count of the non-susceptible RBCs is highly dependent on the susceptible RBCs:

$$N_S = (1 - f_0)\, E_{T0}\, (1 + x)^{-FR} \qquad \textbf{[S22]}$$

$U_S = N_S + Vs$ is the total uninfected RBC population during steady-state. If the simulation is not stopped when U declines to the threshold value for catastrophic anemia U_A (which we take arbitrarily as 75% of U for a healthy host), the total uninfected RBC count, U, approaches U_S. The value of U_S tells us nothing about the transients in U, however: even if $U_S > U_A$, U can drop below U_A before U stabilizes at U_S.

References for Supplementary Material

1. Lloyd, A. L. (2001) *Proc. R. Soc. London Ser. B* **268**, 847- 854.

2. Lloyd, A. L. (2001). *Proc. R. Soc. London Ser. B* **268**, 985- 993.