# Supporting Text

## Multipathogen models

There is a growing literature on the theory of multistrain pathogen interactions (1–4), which has explored in detail how partial cross-immunity structures population and evolutionary dynamics (5–8). Most of these studies assume that infections are directly transmitted and extend the single-strain $SEIR$ paradigm (9) to multiple strains by categorizing the host population according to immune history (2) or immune status (10). Some models applied previously to dengue have also followed this approach (11, 12), but others (13, 14) have built upon a body of work on vector-borne disease models (15, 16). Here, we adopt a mixed history- and status-based approach within the vector-host framework and extend it in a similar manner to Bartley *et al.* (17) to explicitly consider antibody-mediated mechanisms of interaction between dengue serotypes in the presence of seasonality in vector recruitment.

## Vector-host model

For purposes of illustration, we describe in detail the two-strain model, but this can be easily extended to four (with the number of equations increasing $> 4$-fold).

**Human host population**

Newborns are fully susceptible to either serotype and enter the class of immunologically naive individuals, $S_0$:

$$\frac{dS_0}{dt} = (N_H - S_0)\mu_H - (\lambda_{V1} + \lambda_{V2})\frac{S_0}{N_H} \ . \qquad [1]$$

We make the assumption that the background mortality rate ($\mu_H$) is equal to the birth rate, and the total host population is a constant size, $N_H$. Transmission of the dengue virus from mosquitoes to humans depends on the ratio of infected mosquitoes to the total human population. The variables $\lambda_{V1}$ and $\lambda_{V2}$ are the serotype-specific forces of infection exerted by the vec-

tors, where $\lambda_{Vi} = \alpha_i V_{Ii}$ ($\alpha_i$ denotes the transmission rate, and $V_{Ii}$ represents the total number of vectors infected with serotype $i$). The probability of vector-to-host transmission of serotype $i$ is defined to be $p_i$, so that $\alpha_i = bp_i$, where $b$ is the biting rate of infectious mosquitoes.

After a primary infection with serotype $i$, susceptible individuals enter the exposed (infected but not yet infectious) class, $E_i$, and have a relative probability of contracting an infection with the other serotype simultaneously, modulated by the coinfection parameter, $\phi_j$:

$$\frac{dE_i}{dt} = \lambda_{Vi}\frac{S_0}{N_H} - \phi_j\lambda_{Vj}\frac{E_i}{N_H} - (\sigma_H + \mu_H)E_i \ , \quad i,j = 1,2 \quad i \neq j \ . \qquad [2]$$

After this latent period (average length given by $1/\sigma_H$), individuals become infectious, and if they have not been coinfected, they enter the class, $I_i$, where they continue to have the same chance ($\phi_j$) of becoming coinfected with the other serotype:

$$\frac{dI_i}{dt} = \sigma_H E_i - \phi_j\lambda_{Vj}\frac{I_i}{N_H} - (\gamma_1 + \mu_H)I_i \ , \quad i,j = 1,2 \quad i \neq j \ . \qquad [3]$$

There is limited evidence to suggest that human hosts experience concurrent infections (18), so in most of our analyses, we assume that the likelihood of coinfection is negligible ($\phi_j = 0$). However, the inclusion of the parameter $\phi_j$ allows us to demonstrate how our model relates to previous work (see below). Also, we note that coinfection is not a competitive process within the host in this type of model: if coinfection occurs ($\phi_j > 0$), both infections are allowed to run their course.

Immediately after the infectious period (average length given by $1/\gamma_i$), individuals who have been exposed to only a single infection enter the refractory class, $C_i$, and are temporarily immune to the other serotype:

$$\frac{dC_i}{dt} = \gamma_i I_i - \xi_j\lambda_{Vj}\frac{C_i}{N_H} - (\delta_i + \mu_H)C_i \ , \quad i,j = 1,2 \quad i \neq j \ . \qquad [4]$$

Complete immunity is achieved by setting $\xi_j = 0$ (which is what we generally assume), but partial immunity is easily represented by allowing $0 < \xi_j < 1$.

Once this refractory period (average length given by $1/\delta_i$) is over, individuals are assumed to be immune to serotype $i$ but are now susceptible to infection with serotype $j$ and enter the compartment defined by $S_i$:

$$\frac{dS_i}{dt} = (1-\rho_i)\delta_i C_i - \chi_j \lambda_{Vj} \frac{S_i}{N_H} - \mu_H S_i \ , \quad i,j = 1,2 \quad i \neq j \ . \qquad [5]$$

Disease-induced mortality is included by discounting a proportion of those leaving the refractory phase. This is represented by the *per capita* infection-induced mortality probabilities, $\rho_i$. To incorporate one possible consequence of antibody-dependent enhancement, ADE, we introduce the parameter $\chi_j$, so that we can explore the effects of increased susceptibility to infection with the second serotype (by defining $\chi_j > 1$).

For completeness, we now need to define the dynamics of the forces of latency and infection (exerted by the hosts) for pathogen $i$ ($i = 1, 2$), which are represented by $\epsilon_{Hi}$ and $\lambda_{Hi}$, respectively. Additionally, we keep track of all individuals who are no longer susceptible to either infection ($S_{12}$), noting that this compartment may include those who are still exposed or infectious with either serotype (i.e., also included within $\epsilon_{Hi}$ or $\lambda_{Hi}$). The equations for these compartments are given by:

$$\begin{aligned}
\frac{d\epsilon_{Hi}}{dt} &= \lambda_{Vi}\frac{S_0}{N_H} + \eta_i\left(\phi_i\lambda_{Vi}\frac{E_j+I_j}{N_H} + \xi_i\lambda_{Vi}\frac{C_j}{N_H} + \chi_i\lambda_{Vi}\frac{S_j}{N_H}\right) - (\sigma_H+\mu_H)\epsilon_{Hi} \quad [6]\\
\frac{d\lambda_{Hi}}{dt} &= \beta_i\sigma_H\epsilon_{Hi} - (\gamma_i+\mu_H)\lambda_{Hi} \quad [7]\\
\frac{dS_{12}}{dt} &= (1-\rho_2)(1-\rho_x)\left(\phi_2\lambda_{V2}\frac{E_1+I_1}{N_H} + \xi_2\lambda_{V2}\frac{C_1}{N_H} + \chi_2\lambda_{V2}\frac{S_1}{N_H}\right)\\
&\quad +(1-\rho_1)(1-\rho_x)\left(\phi_1\lambda_{V1}\frac{E_2+I_2}{N_H} + \xi_1\lambda_{V1}\frac{C_2}{N_H} + \chi_1\lambda_{V1}\frac{S_2}{N_H}\right) - \mu_H S_{12} \ , \quad [8]
\end{aligned}$$

where $i, j = 1, 2$, and $i \neq j$. The parameter $\eta_i$ allows us to explore the potential for ADE to increase infectiousness of, rather than susceptibility to, secondary infections. We therefore either vary $\eta_i$ and set $\chi_i = 1$ or vary $\chi_i$ and set $\eta_i = 1$. Numerical investigation suggests that there are

only subtle differences between the dynamical outcomes of these alternate assumptions, so we focus on varying $\chi_i$ in the main text (setting $\eta_i = 1$).

An important ingredient of the model for the host population is the assumption that disease-induced mortality occurs during the refractory phase, so that the effective infectious period remains unchanged by mortality as a result of infection. In addition, there is no tradeoff between mortality and transmission in our model, the mechanism for serotype interaction is pure competition for susceptible hosts (19). The consequence of this assumption for ADE is that increased mortality after a secondary infection ($\rho_x > 0$) has no discernible dynamical impact when there are only two serotypes present. The alternate assumption of increased susceptibility after a primary infection (modulated by the parameter $\chi_i > 1$) does, however, induce qualitative dynamical changes.

**Vector population**

There is no strong evidence to suggest that vertical transmission of dengue virus within the mosquito population is important to the transmission cycle between humans and mosquitoes. We therefore assume that mosquito larvae emerge as fully susceptible adults ($V_{Si}$):

$$\frac{dV_{Si}}{dt} = (kN_H(1 - a\cos(2\pi t)) - V_{Si})\mu_V - \lambda_{Hj}\frac{V_{Si}}{N_H}\ , \quad i,j = 1,2 \quad i \neq j\ . \qquad [9]$$

In the absence of seasonality ($a = 0$), recruitment to the susceptible (female adult) vector class is proportional to the human population size, so that the vector population can be related to the average number of mosquitoes per person, $k$. Transmission from humans to mosquitoes depends on the proportion of infected humans. As defined above, $\lambda_{Hi}$ is the serotype-specific force of infection exerted by the hosts, where $\lambda_{Hi} = \beta_i H_{Ii}$ ($\beta_i$ is the transmission coefficient, and $H_{Ii}$ represents the total number of humans infected with serotype $i$). The probability of host-to-vector transmission of serotype $i$ is defined to be $q_i$, so that $\beta_i = bq_i$, where $b$ is the biting rate of noninfectious mosquitoes (assumed to be the same as for infectious mosquitoes).

The mosquito vectors can acquire multiple infections and progress through a latent stage, $\epsilon_{Vi}$, before they become infectious. Unlike human hosts, the vectors do not recover, so their force of infection ($\lambda_{Vi}$) is only depleted by mosquito mortality:

$$\frac{d\epsilon_{Vi}}{dt} = \lambda_{Hi}\frac{V_{Sj}}{N_H} - (\sigma_V + \mu_V)\epsilon_{Vi}\ , \quad i,j = 1,2 \quad i \neq j \qquad [10]$$

$$\frac{d\lambda_{Vi}}{dt} = \alpha_i\sigma_V\epsilon_{Vi} - \mu_V\lambda_{Vi}\ . \qquad [11]$$

**Approximation leading to direct-transmission ADE models**

To make the link to direct-transmission ADE models, the vector force of infection can be roughly approximated by solving for equilibrium values of the vector population:

$$\lambda_{Vi} \approx \frac{\alpha_i k \sigma_v \lambda_{Hi}}{\mu_v(\sigma_v + \mu_v)}$$

(under the assumption that recruitment to the susceptible vector population is constant and on the same timescale as the infection process, such that $V_{Si} \approx kN_H$). The approximation results in a scaling of the host transmission parameter $\beta_i$ so that the new "direct transmission" parameter $\beta_i' = \frac{\alpha_i\beta_i k\sigma_v}{\mu_v(\sigma_v+\mu_v)}$. Using this approximation, most previous models investigating the interactions of multiple pathogens within a single host population are obtained as limiting cases of certain parameters. In particular, the lower dimensional models studying ADE analyzed by Ferguson *et al.* (11) and Cummings *et al.* (20) can be derived if $1/\sigma_H \to 0$ and $\phi_i = \xi_i = \chi_i = 1, \eta_i > 1$.

**Extension to include temporary ADE**

For simplicity, the model presented above assumes that any enhancement after a period of temporary ADE is permanent. To incorporate temporary ADE as explored in Fig. 2, we need to add two new compartments ($A_i$) with additional parameters, $\omega_i$, which represent the rate at which cross-enhancing antibody levels from serotype $i$ wane to neither protective nor enhancing levels. We also need to make adjustments to the differential equations for the $S_i$ and $\epsilon_{Hi}$. These

modifications are given by:

$$\frac{dA_i}{dt} = (1-\rho_i)\delta_i C_i - \chi_j \lambda_{Vj}\frac{A_i}{N_H} - (\omega_i + \mu_H)A_i \quad [12]$$

$$\frac{dS_i}{dt} = \omega_i A_i - \lambda_{Vj}\frac{S_i}{N_H} - \mu_H S_i \quad [13]$$

$$\frac{dS_{12}}{dt} = (1-\rho_2)(1-\rho_x)\lambda_{V2}\left(\xi_2\frac{E_1+I_1}{N_H} + \phi_2\frac{C_1}{N_H} + \chi_2\frac{A_1}{N_H}\right) + (1-\rho_2)\lambda_{V2}\frac{S_1}{N_H}$$
$$+(1-\rho_1)(1-\rho_x)\lambda_{V1}\left(\xi_1\frac{E_2+I_2}{N_H} + \phi_1\frac{C_2}{N_H} + \chi_1\frac{A_2}{N_H}\right) + (1-\rho_1)\lambda_{V1}\frac{S_2}{N_H}$$
$$-\mu_H S_{12} \quad [14]$$

$$\frac{d\epsilon_{Hi}}{dt} = \lambda_{Vi}\left(\frac{S_0}{N_H} + \xi_i\frac{E_j+I_j}{N_H} + \phi_i\frac{C_j}{N_H} + \chi_i\frac{A_j}{N_H} + \frac{S_j}{N_H}\right) - (\sigma_H + \mu_H)\epsilon_{H1}\ , \quad [15]$$

where $i, j = 1, 2$ and $i \neq j$.

## Parameter Values

Table 1 presents the fixed demographic and epidemiological parameter values used in the model simulations, along with a range and source of these estimates. Figs. 13 and 14 demonstrate the sensitivity of model predictions to changes in $R_0$, in the absence and presence of pathogen interaction, respectively.


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