Modelling dengue vaccination in Singapore

1. Model formulation

We first formulate the base model of dengue transmission. Here base model refers to the standard ODE based compartmental model with all four serotypes but without the incorporation of vaccination and age-group. Once we are done with the base model it would be easier to refine the model with vaccination as well as the age-group.

Most of the previous studies that considered multi-serotypes dengue transmission model or dengue multi-serotype model with vaccination did not consider the mosquito population explicitly to get rid of the high dimensional model. In these model the main assumption that the population is so highly dense that the transmission from human-mosquito-human can be approximated as only human-human transmission. However, in some studies, for example (Ferguson et al., 2016), compared the results in the both the cases and mentioned the difference in is not so significant.

In our model, we consider the mosquito explicitly. Since we will develop an age-stratified model, if we do not consider the human-mosquito interaction explicitly, we have to incorporate the contact matrix, which does not sound good in the context of vector-borne disease modelling. Also note that we only consider female mosquito population in the model. The model can be easily extended by incorporating the aquatic phase of mosquitoes and climate dependency of the entomological parameters. We will consider this in later study, where we will more focus on the combined effect of vaccination and vector control strategies.

In our model, we consider only primary and secondary dengue infection as a staring point as the tertiary or quaternary infections are rarely reported also to avoid model complexity. However, if we have data of such infection in Singapore, we will extend our model.

1.1. *Baseline Multi-serotype dengue model without age-group (without vaccination)*

We divide the human population into following compartments:

Human compartments

- Susceptible to all four dengue serotypes, $S(t)$.
- Symptomatic, $I_i(t)$
- Asymptomatic, $A_i(t)$.
- Life-long immunity from i^{th} serotype but temporarily cross-immune, $(C_i(t))$
- Immune to i^{th} serotype but susceptible to the remaining serotypes $(S_i(i)(t))$
- Immune from serotype (i) but infected with symptoms with serotype (j) (secondary infection), (I_{ij}).
- Immune from serotype (i) but infected with no symptoms with serotype (j) (secondary infection), (A_{ij}).
- Recovered from all infection $(R(t))$

Here $i = 1, 2, 3, 4$. Please note that even though it has been well documented, we avoid the exposed and pre-symptomatic class to reduce the complexity of the model.

We divide the mosquito population into following compartments:

Mosquito compartments

- Susceptible mosquitoes $(S^m(t)$
- Exposed mosquitoes with serotype i $(E_i^m(t))$
- Infected mosquitoes with serotype i, $(I_i^m(t))$

The model now can be expressed as the following set of Ordinary deferential equations:

$$
\begin{aligned}
\frac{dS}{dt} &= \Lambda^h - (\sum_{i=1}^{4} \lambda_i^m + \mu^h)S, \\
\frac{dI_i}{dt} &= \rho_0 \lambda_i^m S - (\gamma_0 + \mu^h) I_i, \\
\frac{dA_i}{dt} &= (1-\rho_0)\lambda_i^m - (\gamma_0 + \mu^h) A_i, \\
\frac{dC_i}{dt} &= \gamma_0 (I_i + A_i) - (\alpha_0 + \mu^h) C_i, \\
\frac{dS_i}{dt} &= \alpha_0 C_i - (\sum_{j \neq i} \eta \lambda_j^m + \mu^h) S_i, \\
\frac{dI_{ij}}{dt} &= \rho_1 \eta \lambda_j^m S_i - (\gamma_1 + \xi + \mu^h) I_{ij}, \\
\frac{dA_{ij}}{dt} &= (1-\rho_1)\eta \lambda_j^m S_i - (\gamma_1 + \mu^h) A_{ij}, \\
\frac{dH}{dt} &= \sum_{i,j;j\neq i} \xi I_{ij} - (\gamma_1 + \delta + \mu^h) H, \\
\frac{dR}{dt} &= \sum_{i,j;j\neq i} \xi \gamma_1 (I_{ij} + A_{ij}) + \gamma_1 H - \mu^h R \\
\frac{dS^m}{dt} &= \Lambda^m - (\sum_{i=1}^{4} \lambda_i^h + \mu^m) S^m, \\
\frac{dE_i^m}{dt} &= \lambda_i^h S^m - (\sigma^m + \mu^m) E_i^m, \\
\frac{dI_i^m}{dt} &= \sigma^m E_i^m - \mu^m E_i^m.
\end{aligned}
\tag{1}
$$

The force of infection of serotype i affecting human population (denoted by λ_i^m) and the force of infection from humans to mosquitoes (denoted by λ_i^h), are given by following expressions respectively:

$$\lambda_i^h = b\beta_i^h \frac{\chi I_i + A_i + \phi \sum_{j;j\neq i} (\chi I_{ij} + A_{ij})}{N^h}, \tag{2}$$

$$\lambda_i^m = b\beta_i^m \frac{I_i^m}{N^h}. \tag{3}$$

The brief description of the model parameters (without their values and references) are given in Table 1

1.2. Model with vaccination but without age-group

Here we introduce vaccination into the base model (1). Note that the model is based on the vaccination trial data of Dengvaxia in the countries South East Asia and Latin America. The main assumption here is that the vaccination acts like a "natural infection" (Ferguson et al., 2016; Flasche et al., 2016). Here we consider the eligible compartments for vaccinations are: (i) sero-negative ($S(t)$), and (ii) sero-positive ($V_i(t), S_i(t)$).

To better follow the model, we use the superscript v for the state variables and parameters for vaccinated compartments. Also note that some of the parameters related to vaccinated compartments might not be different from that of unvaccinated compartments. However, to make the model more general we designated the vaccine compartments related parameters with v.

We also introduce the parameter $p(t)$ denotes the rate of vaccination in the population which is generally time dependent as it has been reported that the efficacy of Dengvaxia wanes over time. We can model the decay in efficacy by linear or exponential function based on the available trial data.

Now we present the dengue transmission model in the presence of vaccination as follows:

$$
\begin{aligned}
\frac{dS}{dt} &= \Lambda^h - (\sum_{i=1}^{4} \lambda_i^m + \mu^h)S - p(t)S, \\
\frac{dI_i}{dt} &= \rho_0 \lambda_i^m S - (\gamma_0 + \mu^h)I_i, \\
\frac{dA_i}{dt} &= (1-\rho_0)\lambda_i^m - (\gamma_0 + \mu^h)A_i, \\
\frac{dC_i}{dt} &= \gamma_0(I_i + A_i) - (\alpha_0 + \mu^h)C_i - p(t)C_i, \\
\frac{dS_i}{dt} &= \alpha_0 C_i - (\sum_{j \neq i} \eta \lambda_j^m + \mu^h)S_i - p(t)S_i, \\
\frac{dI_{ij}}{dt} &= \rho_1 \eta \lambda_j^m S_i - (\gamma_1 + \xi + \mu^h)I_{ij}, \\
\frac{dA_{ij}}{dt} &= (1-\rho_1)\eta \lambda_j^m S_i - (\gamma_1 + \mu^h)A_{ij}, \\
\frac{dH}{dt} &= \xi \sum_{i,j;j\neq i} I_{ij} + \xi^v(\sum_j I_{vj} + \sum_{i,j;j\neq i} I_{vij}) \\
&\quad - (\gamma_1 + \delta + \mu^h)H, \\
\frac{dR}{dt} &= \gamma_1 \sum_{i,j;j\neq i} (I_{ij} + A_{ij}) + \gamma_1^v \sum_{i,j;j\neq i} (I_{vij} + A_{vij}) \\
&\quad + \gamma_1 H + \gamma_1^v H_v - \mu^h R \\
\frac{dS^m}{dt} &= \Lambda^m - (\sum_{i=1}^{4} \lambda_i^h + \mu^m)S^m, \\
\frac{dE_i^m}{dt} &= \lambda_i^h - (\sigma^m + \mu^m)E_i^m, \\
\frac{dI_i^m}{dt} &= \sigma^m E_i^m - \mu^m E_i^m,
\end{aligned}
\qquad
\begin{aligned}
\frac{dSv}{dt} &= p(t)S - (\sum_{i=1}^{4} \lambda_i^m + \mu^h)Sv, \\
\frac{dI_{vi}}{dt} &= \rho_0^v \lambda_i^m S_v - (\gamma_0^v + \xi^v + \mu^h)I_{vi}, \\
\frac{dA_{vi}}{dt} &= (1-\rho_0^v)\lambda_i^m - (\gamma_0^v + \mu^h)A_{vi}, \\
\frac{dC_{vi}}{dt} &= p(t)C_i + \gamma_0^v(I_{vi} + A_{vi}) - (\alpha_0^v + \mu^h)C_{vi}, \\
\frac{dS_{vi}}{dt} &= p(t)S_i + \alpha_0^v C_{vi} - (\sum_{j\neq i} \eta^v \lambda_j^m + \mu^h)S_{vi}, \\
\frac{dI_{vij}}{dt} &= \rho_1^v \eta^v \lambda_j^m S_{vi} - (\gamma_1^v + \xi^v + \mu^h)I_{vij}, \\
\frac{dA_{vij}}{dt} &= (1-\rho_1^v)\eta^v \lambda_j^m S_{vi} - (\gamma_1^v + \mu^h)A_{vij}, \\
\frac{dHv}{dt} &= \xi^v(\sum_j I_{vj} + \sum_{i,j;j\neq i} I_{vij}) - (\gamma_1^v + \delta + \mu^h)Hv,
\end{aligned}
\tag{4}
$$

The force of infection of serotype i affecting human population (denoted by λ_i^m) and the force of infection from humans to mosquitoes (denoted by λ_i^h), are given by following expressions respectively:

$$
\lambda_i^h = b\beta_i^h \frac{\left[\chi(I_i + A_i) + \phi \sum_{i,j;j\neq i} (\chi I_{ij} + A_{ij})\right] + \left[\chi^v(I_{vi} + A_{vi}) + \phi^v \sum_{j;j\neq i} (\chi^v I_{vij} + A_{vij})\right]}{N^h}, \tag{5}
$$

$$
\lambda_i^m = b\beta_i^m \frac{I_i^m}{N^h} \tag{6}
$$

The schematic diagram is presented in Figure 1

2. Model with both vaccination and age-group

Finally, we present the transmission model both with vaccination and age-group. Here we introduce the superscript a to denote the age group.

Note that to keep the model more general we also introduce the superscript a in the model parameters. We will fix the parameter values from existing literature or trial data if available or will make assumptions depending on the question or context we are interested in.

$$
\begin{aligned}
\frac{dS^a}{dt} &= \Lambda^{ha} - (\sum_{i=1}^{4} \lambda_i^m + \mu^{ha}) S^a - p(t) S^a, \\
\frac{dI_i^a}{dt} &= \rho_0 \lambda_i^m S^a - (\gamma_0 + \mu^{ha}) I_i^a, \\
\frac{dA_i^a}{dt} &= (1-\rho_0)\lambda_i^m - (\gamma_0 + \mu^{ha}) A_i^a, \\
\frac{dC_i^a}{dt} &= \gamma_0 (I_i^a + A_i^a) - (\alpha_0 + \mu^{ha}) C_i^a - p(t) C_i^a, \\
\frac{dS_i^a}{dt} &= \alpha_0 C_i^a - (\sum_{j \neq i} \eta \lambda_j^{ma} + \mu^{ha}) S_i^a - p(t) S_i^a, \\
\frac{dI_{ij}^a}{dt} &= \rho_1 \eta \lambda_j^{ma} S_i^a - (\gamma_1 + \xi + \mu^{ha}) I_{ij}^a, \\
\frac{dA_{ij}^a}{dt} &= (1-\rho_1)\eta \lambda_j^{ma} S_i^a - (\gamma_1 + \mu^h) A_{ij}^a, \\
a\frac{dH^a}{dt} &= \xi \sum_{i,j;j\neq i} I_{ij}^a + \xi^v (\sum_j I_{vj}^a + \sum_{i,j;j\neq i} I_{vij}^a) \\
&\quad - (\gamma_1 + \delta + \mu^{ha}) H^a, \\
\frac{dR^a}{dt} &= \gamma_1 \sum_{i,j;j\neq i} (I_{ij}^a + A_{ij}^a) + \gamma_1^v \sum_{i,j;j\neq i} I_{vij^a} + A_{vij}^a) \\
&\quad + \gamma_1 H^a + \gamma_1^v H_v^a - \mu^{ha} R^a \\
\frac{dS^m}{dt} &= \Lambda^m - (\sum_{i=1}^{4} \lambda_i^h + \mu^m) S^m, \\
\frac{dE_i^m}{dt} &= \lambda_i^h - (\sigma^m + \mu^m) E_i^m, \\
\frac{dI_i^m}{dt} &= \sigma^m E_i^m - \mu^m E_i^m,
\end{aligned}
\qquad
\begin{aligned}
\frac{dS_v^a}{dt} &= p(t) S^a - (\sum_{i=1}^{4} \lambda_i^m + \mu^{ha}) S_v^a, \\
\frac{dI_{vi}^a}{dt} &= \rho_0^v \lambda_i^m S_v^a - (\gamma_0^v + \xi^v + \mu^{ha}) I_{vi}^a, \\
\frac{dA_{vi}^a}{dt} &= (1-\rho_0^v)\lambda_i^m - (\gamma_0^v + \mu^{ha}) A_{vi}^a, \\
\frac{dC_{vi}^a}{dt} &= p(t) C_i^a + \gamma_0^v (I_{vi}^a + \ldots - (\alpha_0^v + \mu^{ha}) C_{vi}^a, \\
\frac{dS_{vi}^a}{dt} &= p(t) S_i^a + \alpha_0^v C_{vi}^a - (\sum_{j\neq i} \eta^v \lambda_j^m + \mu^{ha}) S_{vi}^a, \\
\frac{dI_{vij}^a}{dt} &= \rho_1^v \eta^v \lambda_j^m S_{vi}^a - (\gamma_1^v + \xi^v + \mu^{ha}) I_{vij}^a, \\
\frac{dA_{vij}^a}{dt} &= (1-\rho_1^v)\eta^v \lambda_j^m S_{vi}^a - (\gamma_1^v + \mu^{ha}) A_{vij}^a, \\
\frac{dH_v^a}{dt} &= \xi^v (\sum_j I_{vj}^a + \sum_{i,j;j\neq i} I_{vij}^a) - (\gamma_1^v + \delta + \mu^{ha}) H_v^a,
\end{aligned}
\tag{7}
$$

The force of infection of serotype i affecting human population (denoted by λ_i^m) and the force of infection from humans to mosquitoes (denoted by λ_i^h), are given by following expressions respectively:

$$
\lambda_i^h = b\beta_i^h \frac{\left[\chi \sum_a (I_i^a + A_i^a) + \phi \sum_{a,i,j;j\neq i} (\chi I_{ij}^a + A_{ij}^a)\right] + \left[\chi^v \sum_a (I_{vi}^a + A_{vi}^a) + \phi^v \sum_{a,i,j;j\neq i} (\chi^v I_{vij}^a + A_{vij}^a)\right]}{N^h}, \tag{8}
$$

$$
\lambda_i^m = b\beta_i^m \frac{I_i^m}{N^h} \tag{9}
$$

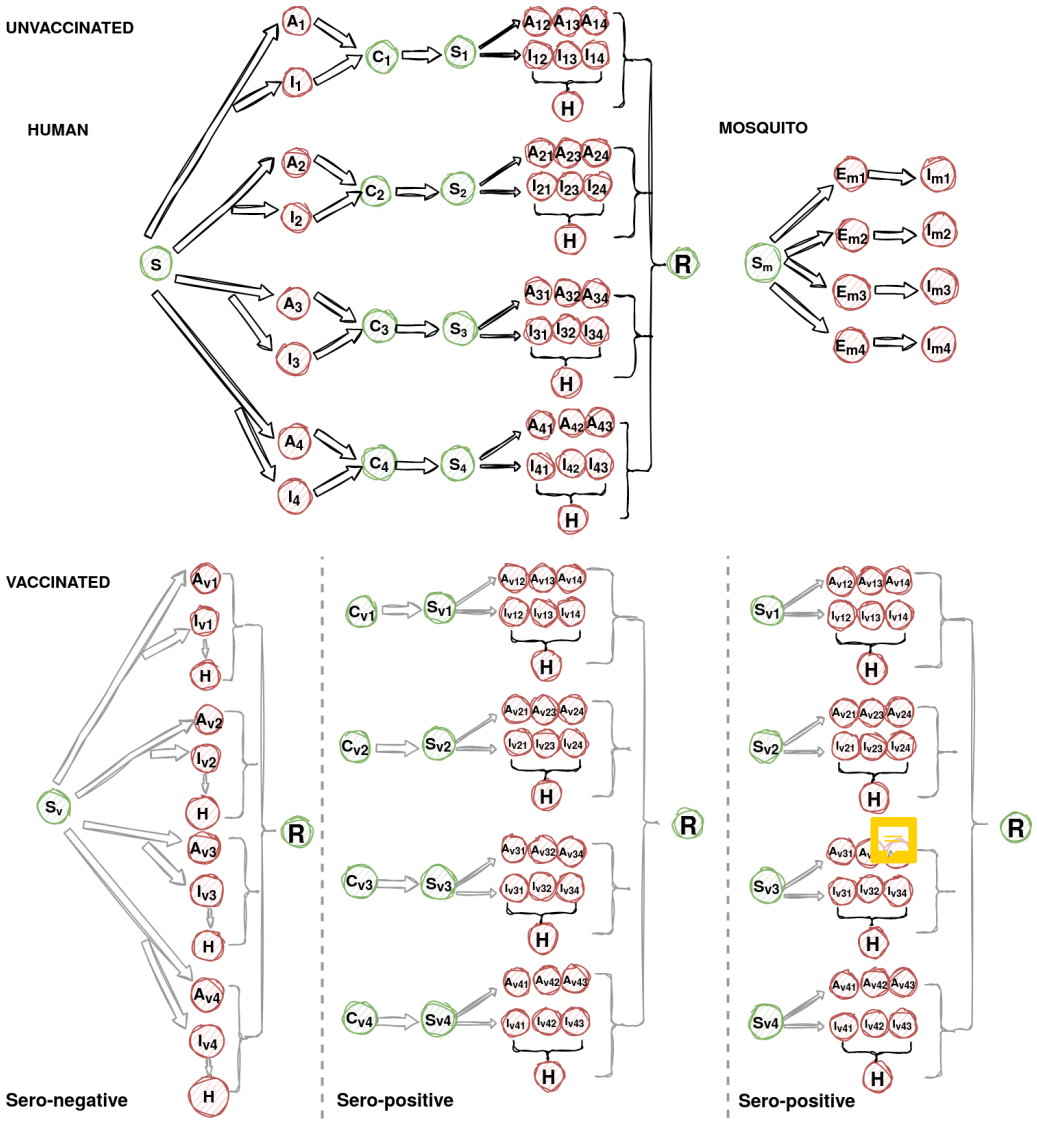

Figure 1: Schematic of a multi-serotype dengue transmission model with vaccination. The rate parameters and the natural birth/death, disease related death from hospitalized are not mentioned in the figure.

From the trial data carried out in South-East Asia and Latin America, the waning of vaccine efficacy over the time is observed. Therefore, incorporation of waning efficacy into model is essential.

References

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Parameters	Description	Value	References
Λ^h	Constant recruitment rate of human population		
N^h	Total human population		
μ^h	Natural death rate of human population		
Λ^m	Constant recruitment rate of mosquito population		
μ^m	Natural death rate of mosquito population		
δ	Disease induced death rate		
b	biting rate		
β_i^m	Transmission probability from mosquito infected with i^{th} serotype to human		
β_i^h	Transmission probability from human infected with i^{th} serotype to mosquito		
χ	Relative infectiousness of symptomatic compared to asymptomatic individuals		
ϕ	Enhancement of infectiousness due to ADE		
η	Enhancement of susceptibility due to ADE		
ρ_0	Fraction of infected who are symptomatic upon primary infection		
ρ_1	Fraction of infected who are symptomatic upon secondary infection		
$\frac{1}{\gamma_0}$	Infectious period of primary infection		
$\frac{1}{\gamma_1}$	Infectious period of secondary infection		
ξ	Rate of hospitalization		
$\frac{1}{\sigma^m}$	Extrinsic incubation period		
$p(t)$	Rate of vaccination		

Table 1: Description of parameters for the model (**??**). Note that the parameters related to vaccinated groups presented in (4) are denoted by the same notations as that of unvaccinated group but with the superscript v. For example, ρ_0^v denotes the fraction of sero-negative individuals who become symptomactic upon dengue infection.