Modelling dengue vaccination in Singapore

1. Age-stratified multi-serotype dengue vaccination model

We divide the human population into following compartments. We use the index a to denote the age-group, i, j to denote the serotype, v to denote vaccinated compartments.

Human compartments (Unvaccinated)

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

Human compartments (Vaccinated)

- Vaccinated Susceptible, $S_v^a(t)$.

- Symptomatic with serotype, $I^a_{vi}(t)$
- Asymptomatic, $A^a_{vi}(t)$.
- Life-long immunity from i^{th} serotype but temporarily cross-immune (to infection), $(C^a_{vi}(t))$
- Immune to i^{th} serotype but susceptible to the remaining serotypes $(S^a_{vi}((t))$
- Immune from serotype (i) but infected with symptoms with serotype (j) (secondary infection), $(I^a_{vij}(t))$.
- Immune from serotype (i) but infected with no symptoms with serotype (j) (secondary infection), $(A^a_{vij}(t))$.
- Hospitalized, $(H^a_v(t))$
- Recovered from all infection $(R^a_v(t))$

Here $i = 1, 2, 3, 4$.

Note that vaccination is introduced to the following compartments: (i) S^a (Sero-negative), (ii) C^a_i (Sero-positive), (iii) S^a_i (Sero-positive), and (iv) R^a (Sero-positive).

Mosquito compartments

We divide the mosquito population into following compartments:

- Susceptible mosquitoes $(S^m(t))$
- Exposed mosquitoes with serotype i $(E^m_i(t))$
- Infected mosquitoes with serotype i, $(I^m_i(t))$

The brief description of the model parameters are given in Table 1

$$
\begin{aligned}
\frac{dS^a}{dt} &= \Lambda^{ha} - (\sum_{i=1}^{4} \lambda_i^m + \mu^{ha}) S^a + a_+ S^{a-1} - a_- S^a - pS^a, \\
\frac{dI_i^a}{dt} &= \rho_1 \lambda_i^m S^a - (\xi_1 + \gamma_1 + \mu^{ha}) I_i^a + a_+ I_i^{a-1} - a_- I_i^a, \\
\frac{dA_i^a}{dt} &= (1-\rho_1)\lambda_i^m S^a - (\gamma_1 + \mu^{ha}) A_i^a + a_+ A_i^{a-1} - a_- A_i^a, \\
\frac{dC_i^a}{dt} &= \gamma_1 (I_i^a + A_i^a) - (\alpha + \mu^{ha}) C_i^a + a_+ C_i^{a-1} - a_- C_i^a - pC_i^a, \\
\frac{dS_i^a}{dt} &= \alpha C_i^a - (\sum_{j \neq i} \lambda_j^{ma} + \mu^{ha}) S_i^a + a_+ S_i^{a-1} - a_- S_i^a - pS_i^a, \\
\frac{dI_{ij}^a}{dt} &= \rho_2 \lambda_j^{ma} S_i^a - (\gamma_2 + \xi_2 + \mu^{ha}) I_{ij}^a + a_+ I_{ij}^{a-1} - a_- I_{ij}^a, \\
\frac{dA_{ij}^a}{dt} &= (1-\rho_2)\lambda_j^{ma} S_i^a - (\gamma_2 + \mu^{ha}) A_{ij}^a + a_+ A_i^{a-1} - a_- A_i^a, \\
\frac{dH^a}{dt} &= \xi_1 \sum_i I_i^a + \xi_2 \sum_{i,j} I_{ij}^a - (\gamma_2 + \mu^{ha}) H^a \\
&+ a_+ H^{a-1} - a_- H^a, \\
\frac{dR^a}{dt} &= \gamma_2 \sum_{i,j} (I_{ij}^a + A_{ij}^a) + \gamma_2 H^a - \mu^{ha} R^a - pR^a \\
&+ a_+ R^{a-1} - a_- 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 I_i^m,
\end{aligned}
\qquad
\begin{aligned}
\frac{dS_v^a}{dt} &= pS^a - (\sum_{i=1}^{4} (1 - \epsilon_{ia}^{\inf -}) \lambda_i^m + \mu^{ha}) S_v^a \\
&+ a_+ S_v^{a-1} - a_- S_v^a, \\
\frac{dI_{vi}^a}{dt} &= \rho_1 (1 - \epsilon_{ia}^{\text{symp}-})(1 - \epsilon_{ia}^{\inf -}) \lambda_i^m S_v^a - (\gamma_1^v + \xi_1 (1 - \epsilon_{ia}^{\text{hosp}-}) \\
&+ \mu^{ha}) I_{vi}^a + a_+ I_{vi}^{a-1} - a_- I_{vi}^a, \\
\frac{dA_{vi}^a}{dt} &= (1 - \rho_1 (1 - \epsilon_{ia}^{\text{symp}-}))(1 - \epsilon_{ia}^{\inf -}) \lambda_i^m S_v^a - (\gamma_1^v + \mu^{ha}) A_{vi} \\
&+ a_+ A_{vi}^{a-1} - a_- A_{vi}^a, \\
\frac{dC_{vi}^a}{dt} &= pC_i^a + \gamma_1^v (I_{vi}^a + A_{vi}^a) - (\alpha^v + \mu^{ha}) C_{vi}^a \\
&+ a_+ C_{vi}^{a-1} - a_- C_{vi}^a, \\
\frac{dS_{vi}^a}{dt} &= pS_i^a + \alpha^v C_{vi}^a - (\sum_{j \neq i} (1 - \epsilon_{ja}^{\inf +}) \lambda_j^m + \mu^{ha}) S_{vi}^a \\
&+ a_+ S_{vi}^{a-1} - a_- S_{vi}^a, \\
\frac{dI_{vij}^a}{dt} &= \rho_2 (1 - \epsilon_{ja}^{\text{symp}+})(1 - \epsilon_{ja}^{\inf +}) \lambda_j^m S_{vi}^a - (\gamma_2^v + \xi_2 (1 - \epsilon_{ja}^{hosp+}) \\
&+ \mu^{ha}) I_{vij}^a + a_+ I_{vij}^{a-1} - a_- I_{vij}^a, \\
\frac{dA_{vij}^a}{dt} &= (1 - \rho_2 (1 - \epsilon_{ja}^{\text{symp}+})(1 - \epsilon_{ja}^{\inf +})) \lambda_j^m S_{vi}^a - (\gamma_2^v + \mu^{ha}) A_{vij}^a, \\
&+ + a_+ A_{vij}^{a-1} - a_- A_{vij}^a \\
\frac{dH_v^a}{dt} &= \xi_1 \sum_j (1 - \epsilon_{ja}^{hosp-}) I_{vj}^a + \xi_2 \sum_{i,j} (1 - \epsilon_{ja}^{hosp+}) I_{vij}^a \\
&- (\gamma_2^v + \mu^{ha}) H_v^a + a_+ H_v^{a-1} - a_- H_v^a, \\
\frac{dR_v^a}{dt} &= pR^a + \gamma_2^v \sum_{i,j} (I_{vij}^a + A_{vij}^a) + \gamma_2^v H_v^a - \mu^{ha} R_v^a \\
&+ a_+ R_v^{a-1} - a_- R_v^a
\end{aligned}
\tag{1}
$$

Parameters	Description	Value	References
Λ^h	Constant recruitment rate of human population	$\mu_h N^h$	
N^h	Total human population	5.45 million	
μ^h	Natural death rate of human population	$\frac{1}{83} year^{-1}$	
Λ^m	Constant recruitment rate of mosquito population		
μ^m	Natural death rate of mosquito population	$\frac{1}{3} week^{-1}$	
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	2	
ρ_1	Fraction of infected who are symptomatic upon primary infection	0.25	
ρ_2	Fraction of infected who are symptomatic upon secondary infection	0.6	
$\frac{1}{\gamma_1}$	Infectious period of primary infection	12 days	
$\frac{1}{\gamma_2}$	Infectious period of secondary infection	12 days	
α	Duration of cross-protection	1-3 years	
ξ_1	Rate of hospitalization for primary infection		
ξ_2	Rate of hospitalization for secondary infection		
$\frac{1}{\sigma^m}$	Extrinsic incubation period	10 days	
p	Rate of vaccination		
ϵ_{ia}^{inf-}	Vaccine efficacy against infection for sero-negatives		
ϵ_{ia}^{inf+}	Vaccine efficacy against infection for sero-positives		
ϵ_{ia}^{symp-}	Vaccine efficacy against symptoms for sero-negatives		
ϵ_{ia}^{symp+}	Vaccine efficacy against infection for sero-positives		
ϵ_{ia}^{hosp-}	Vaccine efficacy against hospitalization for sero-negatives		
ϵ_{ia}^{hosp+}	Vaccine efficacy against hospitalization for sero-positives		
a_+	Rate of ageing in		
a_-	Rate of ageing out		

Table 1: Description of parameters for the model (1).

Force of infection

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:

$$\lambda_i^h = b\beta_i^h \frac{\left[\sum_a (\chi I_i^a + A_i^a) + \sum_{a,j;j\neq i} (\chi I_{ij}^a + A_{ij}^a)\right] + \left[\sum_a (\chi I_{vi}^a + A_{vi}^a) + \sum_{a,j;j\neq i} (\chi I_{vij}^a + A_{vij}^a)\right]}{N^h}, \tag{2}$$

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

We consider the contribution of asymptomatic individual in the force of infection. We assume that the infectiousness of symptomatic is higher than that of asymptomatic, and we denote the relative infectiousness of symptomatic individuals by χ.

Antibody dependent enhancement

We incorporate ADE into the model as intensity of severity of the disease. It is reflected through the rate of hospitalization. We use ξ_1 and ξ_2 to denote the rate of hospitalization of primary and secondary cases respectively. We consider $\xi_2 > \xi_1$ to capture the increase in the severity of the disease due to ADE. For vaccinated compartments, the corresponding hospitalization rates will be modified according to the vaccine efficacy against hospitalization. Also the fraction of symptomatic infection are different for primary (ρ_1) and secondary infection (ρ_2). We keep $\rho_2 > \rho_1$ in the model.

Incorporation of vaccine efficacy

We consider efficacy of vaccination against (1) infection, (2) symptoms, and (3) hospitalization. We kept all the efficacy parameters to be age, serotype and sero-status dependent for completeness. However, we can relax the dependency on these factor depending on the available data and modify accordingly.

Parameters in vaccinated compartments

We assume that at a rate p, eligible individuals will be vaccinated and move to the vaccinated compartments. We only kept recovery rate of primary and secondary infections among vaccinated individuals, i.e, γ_1^v and γ_2^v and temporarily cross-immune period ($\frac{1}{\alpha^v}$). However, it is most likely that there is no evidence that these parameters differs depending the vaccination status of the individuals, in that case we assume same value as the parameters corresponding to unvaccinated compartments.

Age transition

We have now incorporated age transition between the age groups. The parameter a_+ denotes rate of "ageing-in" and a_- denotes the rate of "ageing-out" from a specific age-group. The value of this parameter is simply calculated as the inverse of the length of the specific age-group.

The schematic diagram is presented in Figure 1

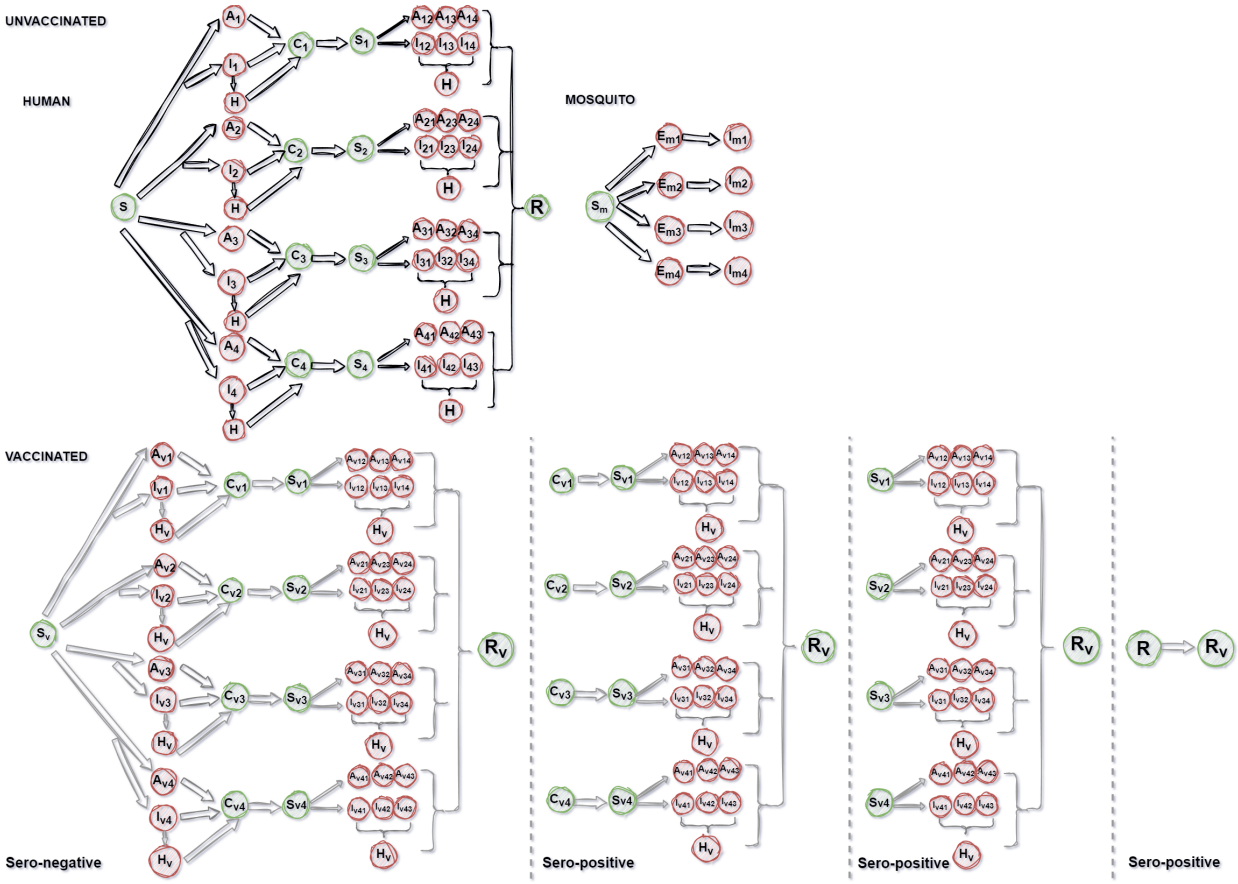

Figure 1: Schematic of a multi-serotype dengue transmission model with vaccination.

	DENV1	DENV2	DENV3	DENV4
> 9 yrs	58.4 (47.7 - 66.9) P:(100/200) ; D:(10/50)	47.1 (31.3 - 59.2)	73.6 (64.4 - 80.4)	83.2 (76.2 - 88.2)
< 9 yrs	46.6 (25.7 - 61.5)	33.6 (1.3 - 55.0)	62.1 (28.4 - 80.3)	51.7 (17.6 - 71.8)