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Transmission dynamics of two dengue serotypes with vaccination scenarios

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ABSTRACT

In this work we present a mathematical model that incorporates two Dengue serotypes. The model has been constructed to study both the epidemiological trends of the disease and conditions that allow co-existence in competing strains under vaccination. We consider two viral strains and temporary cross-immunity with one vector mosquito population. Results suggest that vaccination scenarios will not only reduce disease incidence but will also modify the transmission dynamics. Indeed, vaccination and cross immunity period are seen to decrease the frequency and magnitude of outbreaks but in a differentiated manner with specific effects depending upon the interaction vaccine and strain type.

1. Introduction

Dengue is a vector-borne disease with more than 50 million cases per year [16]. The major vector, *Aedes aegypti*, is located in tropical regions, mainly in urban areas that provide water holding containers that function as breeding sites. There are four dengue serotypes (DEN-1, DEN-2, DEN-3 and DEN-4) that coexist in many endemic areas [21]. Dengue is an emergent infectious disease that can be very severe. Dengue Hemorrhagic fever (DHF) is a life-threatening condition whose development is not well known [6]. One of the main hypothesis that have been put forward to explain it is Antibody Dependent Enhancement (ADE) whereby previous exposure to a Dengue infection may generate a very strong immune response on a secondary infection, thus triggering DHF [19]. In recent years, the development of dengue vaccines has dramatically accelerated [14,24] given the frequent epidemics and morbidity and DHF mortality rates around the world. Vaccination is a cost-effective measure of control and prevention but its development is challenged by the existence of the four viral serotypes, the possibility of ADE and therefore of DHF [22].

Previous mathematical models have incorporated the effect of immunological interactions between the different dengue serotypes in disease dynamics. Infection with a particular serotype is believed to result in life-long immunity to that serotype and temporal cross-protection to the other serotypes. There exists many different models on Dengue population dynamics (e.g. [1,5,13,15,22,23,31]). In a recent paper Coudeville and Garnett [9], propose a compartmental, age structured model with four serotypes that incorporates cross protection and the introduction of a vaccine. Likewise Rodriguez–Barraquer et al. [27], use an age-stratified dengue transmission model to assess the impact of partially effective vaccines through a tetravalent vaccine with a protective effect against only 3 of the 4 serotypes. Other compartmental and agent-based models [8] have found that vaccines with efficacies of 70 – 90% against all serotypes have the potential to significantly reduce the frequency and magnitude of epidemics on a short to medium term.

Many of the published mathematical models include the four dengue serotypes (e.g. [15,17,23]) and deal with the full complexity of the population dynamics that this diversity triggers. In this paper the potential impact of a vaccine is studied through the use of a mathematical model of transmission for two dengue serotypes. In the Americas, Dengue has a typical pattern of presenting a dominant serotype while the others circulate at low densities and in very localized regions of the continent [11]. Dengue epidemics come sequentially thus reducing the basic population dynamics to the competition between two viral strains: the invading and the resident. This is the justification of the model that we study in this paper. On the other hand the introduction of vaccination is founded in the imminent release of a vaccine that has the characteristic of having high efficacy for only three of the four serotypes [6]. In our setting, the vaccination programs that we

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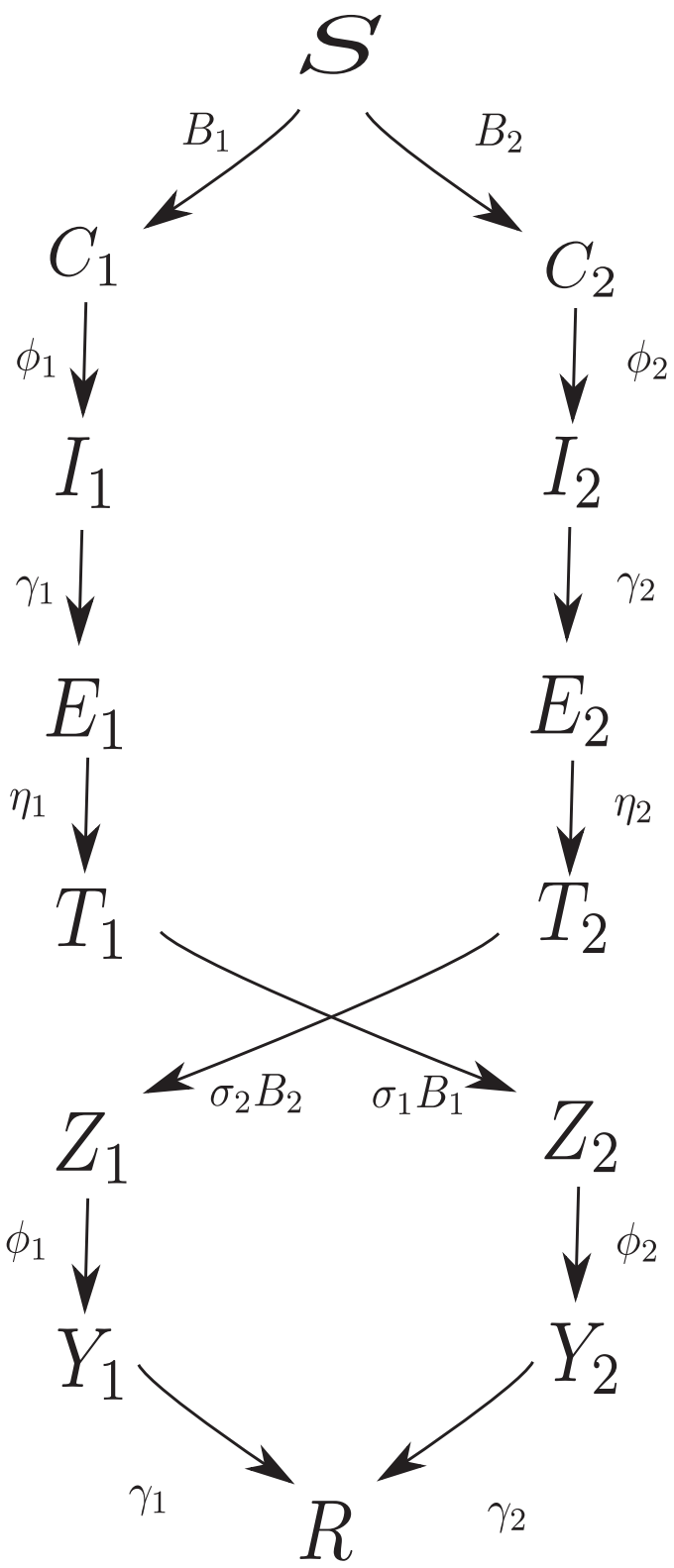

Fig. 1. Basic model without vaccination. S susceptible, C_i infectious in latent stage, I_i infected contagious, E_i temporary cross immunity, T_i susceptibles to strain j already recovered from strain i, Z_i infectious with secondary infection, Y_i infectious and contagious with a secondary infection, R immune to both strains.

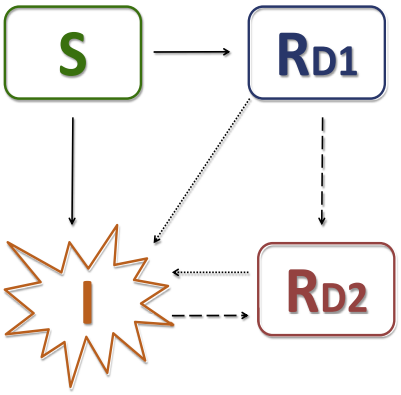

Fig. 2. Basic model with vaccination. D_1 and D_2 doses are applied sequentially; unvaccinated individuals follow a natural route of infection (see Fig. 3). The compartment I represents all infections. The dotted lines represent infections due to failure of the first and second vaccine application. The dashed lines represents the application of the second dose to all susceptible individuals (including those who recovered from a first infection).

study consider the application of one or two doses in the presence of cross protection. In our model the vaccine is assumed to confer higher protection to one serotype than to the second one. The paper is organized as follows. In Section 2 we present a mathematical model for Dengue and the incorporation of the vaccine. In Section 3 we explain the vaccination strategies. In Sections 4 and 5, we present and discuss the numerical results of the vaccination scenarios with different cross immunity periods. In Section 6 we present a statistics summary. Finally, in Section 7 we draw some conclusions about this work.

2. Mathematical model

A basic model for Dengue

In this section we describe the mathematical model for dengue transmission in the presence of vaccination and two co-circulating strains. All human newborns are susceptible to both dengue strains.

The model that we present considers a human host population classified in compartments according to Dengue infection status. We consider the population of individuals that are all fully susceptible to both strains of Dengue. At time $t = 0$ a few infected individuals are introduced and infection process is then triggered.

We call primary infections to those infections that occur in individuals with no previous exposure to either strain; we call secondary infections to those infections that occur in individuals that have been previously exposed to one of the two strains. Let S represents the susceptible individuals, C_i, Z_i the individuals in the latent period of primary or secondary infections for each strain, $i = 1, 2,$ respectively. Likewise, I_i, Y_i are individuals with primary and secondary infections for each of the two strains respectively. E_i are individuals in the state of temporary cross-immunity (temporary immune protection to both strains independent of the strain causing the immediate previous infection), respectively, T_i are susceptible population to dengue strain $j (j \neq i)$. Note that T_i individuals have already recovered from and infection by dengue strain i.

Infection with one serotype has been shown to provide lifelong immunity to that serotype but short-term cross-protection to the other serotypes [7,16]. R represents the immune population to both infections (see Fig. 1).

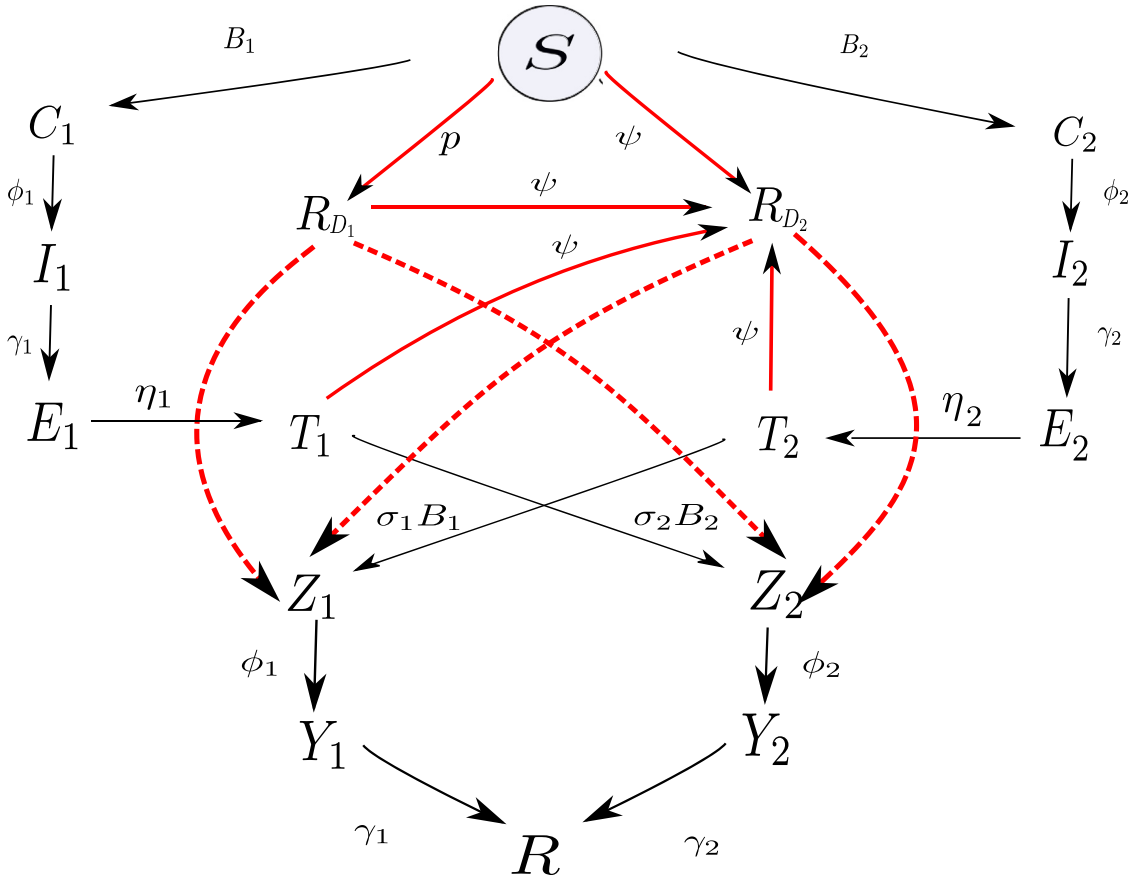

Fig. 3. Complete diagram for the model with vaccination. The compartments R_{D_1} and R_{D_2} indicate vaccinated populations with dose D_1 and dose D_2, respectively. The diagram shows the transitions between states. Black lines represent natural infections. Solid red lines indicate the transitions from those individuals eventually vaccinated. Dashed red lines represent transitions due to failure in protection against either or both strains which results on an inflow to the latent stage in secondary infections ($Z_i, i = 1, 2$). The labels correspond to the rates in the system 1. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

2.1. Incorporating the vaccine

As mentioned in the introduction Dengue is a major global public health problem affecting Asian and Latin America countries. The development of prevention and control measures that focus on epidemiological surveillance and vector control is thus a priority.

Once the vaccine is released and applied to a target population, the proportion of the vaccinated population (coverage) is expected to reach 89% of the 2–5 year old class and 69% in the 2–15 year old class after 5 years since the start of the application (these coverage rates correspond to those achieved in Thailand using a combination of catch-up and routine vaccination) [26]. The recommended target age according with SAGE committee (World Health Organization) depends on the seroprevalence of the population, 9 years old if seroprevalence is 90% in that age group; 11 to 14 years old if seroprevalence at 9 years old is less than 90% but above 50% [29].

Currently, the vaccine Dengvaxia (CYD–TDV) by Sanofi Pasteur has been approved in Indonesia and now available in Mexico for vaccination of individuals of 9 to 45 years old (See [32]). The vaccine produced by Sanofi–Pasteur protects against serotypes 1, 3 and 4 but only imperfectly against serotype 2 [28].

We propose a vaccination model that consists of the application of the vaccine in three strategic profiles: one dose vaccine application to all new recruits into the susceptible class (S), one dose after a waiting time of six months to all susceptible individuals including those who recovered from a previous infection by either strain ($S, T_i, i = 1, 2$) and finally the application of both doses.

In our model the vaccine is applied under the following assumptions (see Fig. 2).

1. Vaccination coverage. A fraction p of naive susceptible individuals is vaccinated with a bivalent vaccine. we consider a vaccine coverage $p = 0.8$ [4].
2. Incomplete protection. A proportion p_1 of vaccinated individuals is susceptible to dengue 1 and a proportion p_2 of vaccinated individuals is susceptible to dengue 2.
3. All susceptible individuals (S, T_1, T_2) are vaccinated with a dose after a waiting time of $1/\psi$ days.
4. Vaccinated but unsuccessfully protected individuals can be infected and eventually pass to the fully immune compartment R.

With the previous hypothesis, we set up the following vaccination scenarios labelled as W, D_1, D_2, F:

W: No vaccine application

D_1: One dose vaccine application. A proportion of $p = 0.8$ of all then naive susceptible population is vaccinated. Of these vaccinated individuals, proportions $p_i, i = 1, 2$ remain susceptible (hypothesis 2).

D_2: One dose vaccine application. A vaccine dose is applied after a waiting time of six months to all susceptible individuals including those recovered from a first infection (S, T_1, T_2). Of these vaccinated individuals, proportions $p_i, i = 1, 2$ remain susceptible (hypothesis 2).

F: Two doses vaccine application: a dose application D_1 with a coverage of $p = 0.8$ and a dose application with a delay

Table 1
Definitions and ranges of the main parameters in mathematical model with vaccination [9,31].

Parameter	Description	Chosen values
$1/\mu$	Life expectancy for humans	70 years (25550 days)
$1/\phi_i$	Incubation period	4 to 7 days
$1/\gamma_i$	Duration of disease (infectiousness)	7 to 15 days
$1/\delta$	Life expectancy of mosquitoes	14 to 21 days
$1/\eta_i$	Duration of cross immunity	180 to 270 days
σ_i	Reinfection rate	Undetermined
α_i	Effective contact rate human-mosquito	Undetermined
β_i	Effective contact rate mosquito-human	Undetermined
m_i	Rate death of the disease	Undetermined
q	Recruitment rate of mosquito population	Undetermined
p	First dose vaccine coverage	Undetermined
p_1	Failure probability of vaccine for protection against strain 1	Undetermined
p_2	Failure probability of vaccine for protection against strain 2	Undetermined
$1/\psi$	Period of time for application of the second dose	Undetermined

Table 2
Parameter values for the different vaccination scenarios.

Parameter	W	D_1	D_2	F
p	0	0.8	0	0.8
p_1	0	0.3	0.3	0.3
p_2	0	0.4	0.4	0.4
ψ	0	0	$1/(0.5 \times 365)$	$1/(0.5 \times 365)$

Table 3
Parameters of the population dynamics of dengue [3].

Parameter	Chosen values	Parameter	Chosen values
$1/\mu$	70 years (25550 days)	$1/\phi_1$	4 days
$1/\phi_2$	7 days	$1/\gamma_1$	8 days
$1/\gamma_2$	10 days	$1/\delta$	15 days
$1/\eta_1$	180, 270 days	$1/\eta_2$	180, 270 days
σ_1	0.5	σ_2	0.5
α_1	0.2	α_2	0.2
β_1	0.5	β_2	1.0
m_1	0	m_2	0

of six months D_2 (hypothesis 3). In this scenario, D_2 is also applied to people vaccinated with D_1.

The evaluation of the vaccination scenarios is done through simulations that incorporate heterogeneity in serotype transmission rates. Age-stratified seroprevalence studies suggests that the average transmission intensity and reproductive number of DENV-2 is higher than that of other serotypes [15–27].

The parameters p_1 and p_2 are the proportions of vaccinated individuals that fail to be protected against serotypes 1 and 2, respectively. Therefore, $1-p_1$ and $1-p_2$ represent the protection conferred by the vaccine.

The vaccine schedule is shown in Fig. 2.

The mathematical model with vaccination is the following

$$\frac{d}{dt}S = \mu(1-p)N - (B_1+B_2)S - (\psi+\mu)S$$

$$\frac{d}{dt}R_{D_1} = \mu pN - (p_1B_1+p_2B_2)R_{D_1} - (\psi+\mu)R_{D_1}$$

$$\frac{d}{dt}R_{D_2} = \psi(R_{D_1}+S) + \psi(T_1+T_2) - (p_1B_1+p_2B_2)R_{D_2} - \mu R_{D_2}$$

$$\frac{d}{dt}C_1 = B_1S - (\phi_1+\mu)C_1$$

$$\frac{d}{dt}C_2 = B_2S - (\phi_2+\mu)C_2$$

$$\frac{d}{dt}I_1 = \phi_1C_1 - (\mu+\gamma_1)I_1$$

$$\frac{d}{dt}I_2 = \phi_2C_2 - (\mu+\gamma_2)I_2$$

$$\frac{d}{dt}E_1 = \gamma_1I_1 - (\eta_1+\mu)E_1$$

$$\frac{d}{dt}E_2 = \gamma_2I_2 - (\eta_2+\mu)E_2$$

$$\frac{d}{dt}T_1 = \eta_1E_1 - (\sigma_2B_2+\psi+\mu)T_1$$

$$\frac{d}{dt}T_2 = \eta_2E_2 - (\sigma_1B_1+\psi+\mu)T_2$$

$$\frac{d}{dt}Z_1 = \sigma_1B_1T_2 - (\phi_1+\mu)Z_1 + p_1B_1R_{D_1} + p_1B_1R_{D_2}$$

$$\frac{d}{dt}Z_2 = \sigma_2B_2T_1 - (\phi_2+\mu)Z_2 + p_2B_2R_{D_1} + p_2B_2R_{D_2}$$

$$\frac{d}{dt}Y_1 = \phi_1Z_1 - (\gamma_1+\mu+m_1)Y_1$$

$$\frac{d}{dt}Y_2 = \phi_2Z_2 - (\gamma_2+\mu+m_2)Y_2$$

$$\frac{d}{dt}R = \gamma_1Y_1 + \gamma_2Y_2 - \mu R. \quad (1)$$

The total human population is given by

$$N = S + R_{D_1} + R_{D_2} + C_1 + C_2 + I_1 + I_2 + E_1 + E_2 + T_1 + T_2 + Z_1 + Z_2 + Y_1 + Y_2 + R$$

The dynamics of the vector are given by

$$\frac{d}{dt}V_0 = q(t) - (A_1+A_2)V_0 - \delta V_0$$

$$\frac{d}{dt}V_1 = A_1V_0 - \delta V_1$$

$$\frac{d}{dt}V_2 = A_2V_0 - \delta V_2 \quad (2)$$

with

$$q(t) = q_0(b + k\cos(2\pi t/365))$$

to represent yearly seasonal forcing. V_0 represents the susceptible mosquitoes, and V_1, V_2 the number of mosquitoes infected with

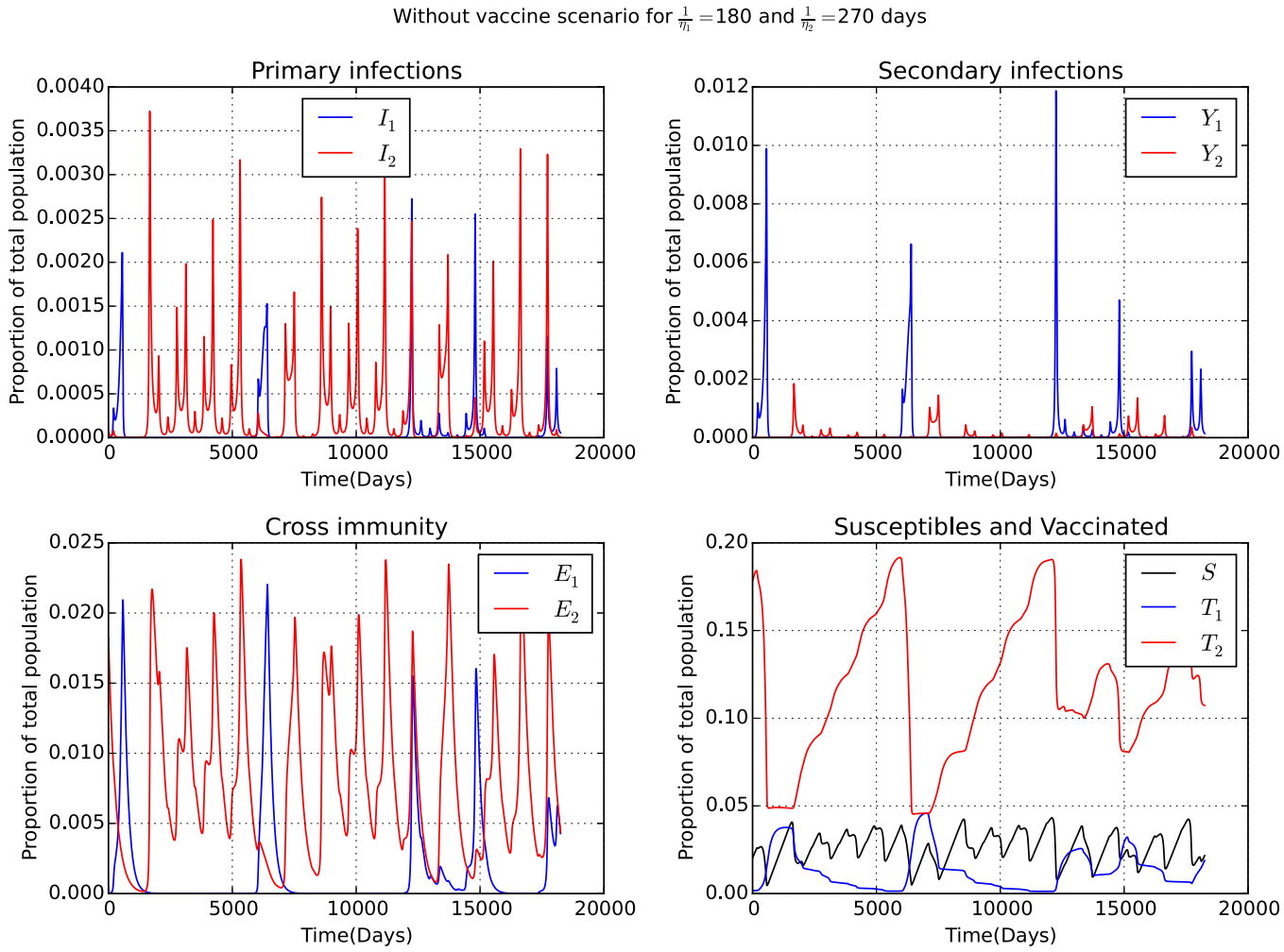

Fig. 4. *Vaccine scenario W.* Numerical results for primary (I_i) and secondary (Y_i) infections, individuals in the temporal cross immunity state (E_i) and susceptibles ($S, T_i, i = 1, 2$). Parameter values: $p = 0$, $p_i = 0$, $\psi = 0$.

strains 1 and 2 respectively. A_1, A_2 represent the forces of infection for strains 1 and 2 in the mosquitoes, respectively. δ is the mosquito death rate. The total mosquito population is $M = V_0 + V_1 + V_2$ (see Table 1 for other parameter definitions and values).

The forces of infection follow the proportional mixing assumption and are given by

$$A_i = \frac{\alpha_i(I_i + Y_i)}{N} \quad \text{and} \quad B_i = \frac{\beta_i V_i}{M}$$

In our model once a mosquito is infected it never recovers and it cannot be reinfected with a different strain of virus. Secondary infections occur only in the host.

2.2. The basic reproduction number

The basic reproduction number is defined as the number of secondary infections that a single infectious individual produces in a population where all host are susceptible. R_0 is a threshold parameter for the model, such that if $R_0 < 1$ then the Disease Free Equilibrium is locally asymptotically stable and the disease cannot invade the population (eventually the infection dies out), but if $R_0 > 1$, then the Disease Free Equilibrium is unstable and invasion is possible.

Applying the next generation matrix methodology [10], we obtain the basic reproduction number (without vaccination)[1]:

$$R_0 = max\{R_{01}, R_{02}\}$$

$$= max\left\{\sqrt{\frac{\beta_1\alpha_1\phi_1}{\delta(\gamma_1+\mu)(\phi_1+\mu)}}, \sqrt{\frac{\beta_2\alpha_2\phi_2}{\delta(\gamma_2+\mu)(\phi_2+\mu)}}\right\}$$

where β_i/δ represent the number of effective contacts mosquito-to-human during the life time of mosquito, $\alpha_i/(\mu+\gamma_i)$ the number of effective contact human-to-mosquito during the infectious period of human and $\phi_i/(\mu+\phi_i)$ represents the fraction of the time that humans spend in the incubation period of the disease.

When vaccination is introduced the vaccination reproduction number is:

$$R_0^v = max\{R_{01}^v, R_{02}^v\}$$

$$= max\left\{\sqrt{\frac{\beta_1\alpha_1\phi_1(1-p(1-p_1))}{\delta(\gamma_1+\mu)(\phi_1+\mu)}}, \sqrt{\frac{\beta_2\alpha_2\phi_2(1-p(1-p_2))}{\delta(\gamma_2+\mu)(\phi_2+\mu)}}\right\}$$

[1] See Appendix for details.

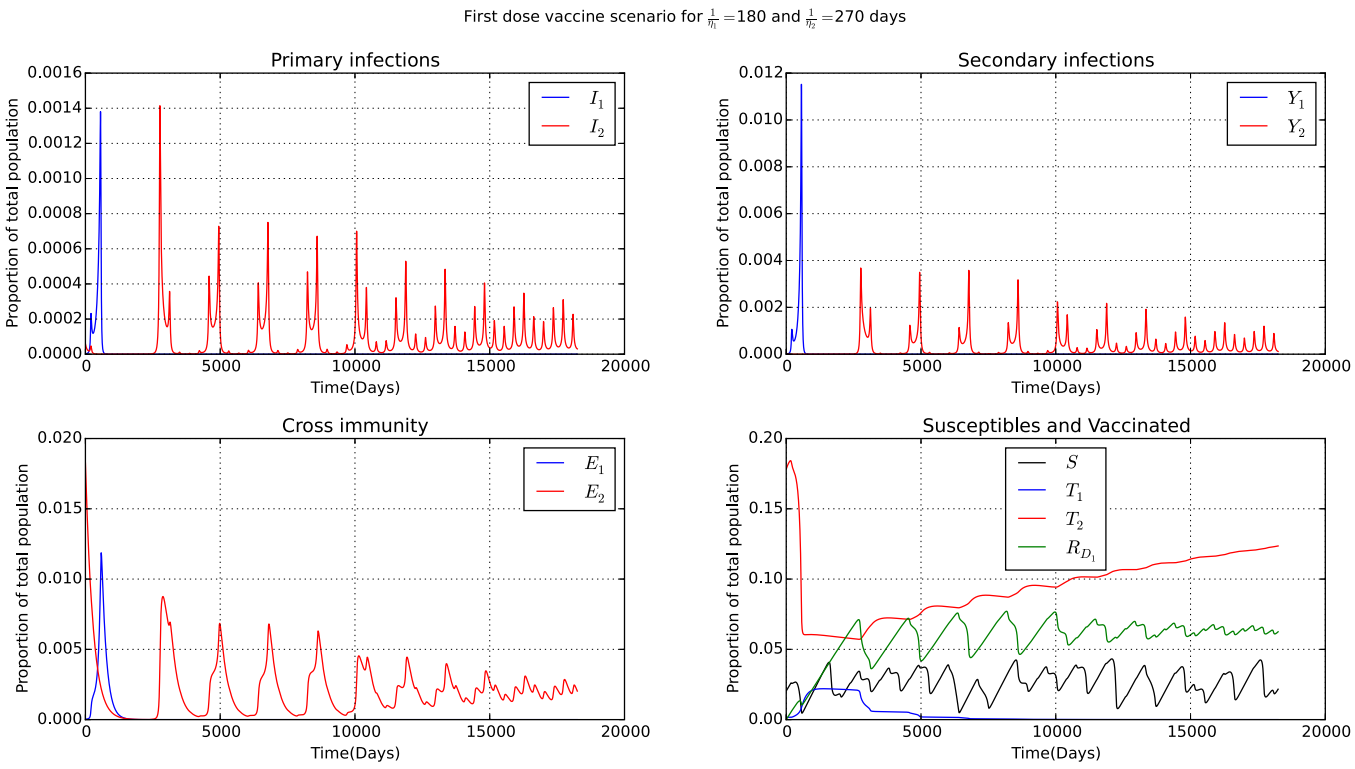

Fig. 5. *Vaccine scenario* D_1. Numerical results for primary (I_i) and secondary (Y_i) infections, individuals in the temporal cross immunity state (E_i), susceptibles (S, T_i), $i = 1, 2$ and vaccinated individuals (R_{D_1}). Parameter values: $p = 0.8$, $p_1 = 0.3$, $p_2 = 0.4$, $\psi = 0$.

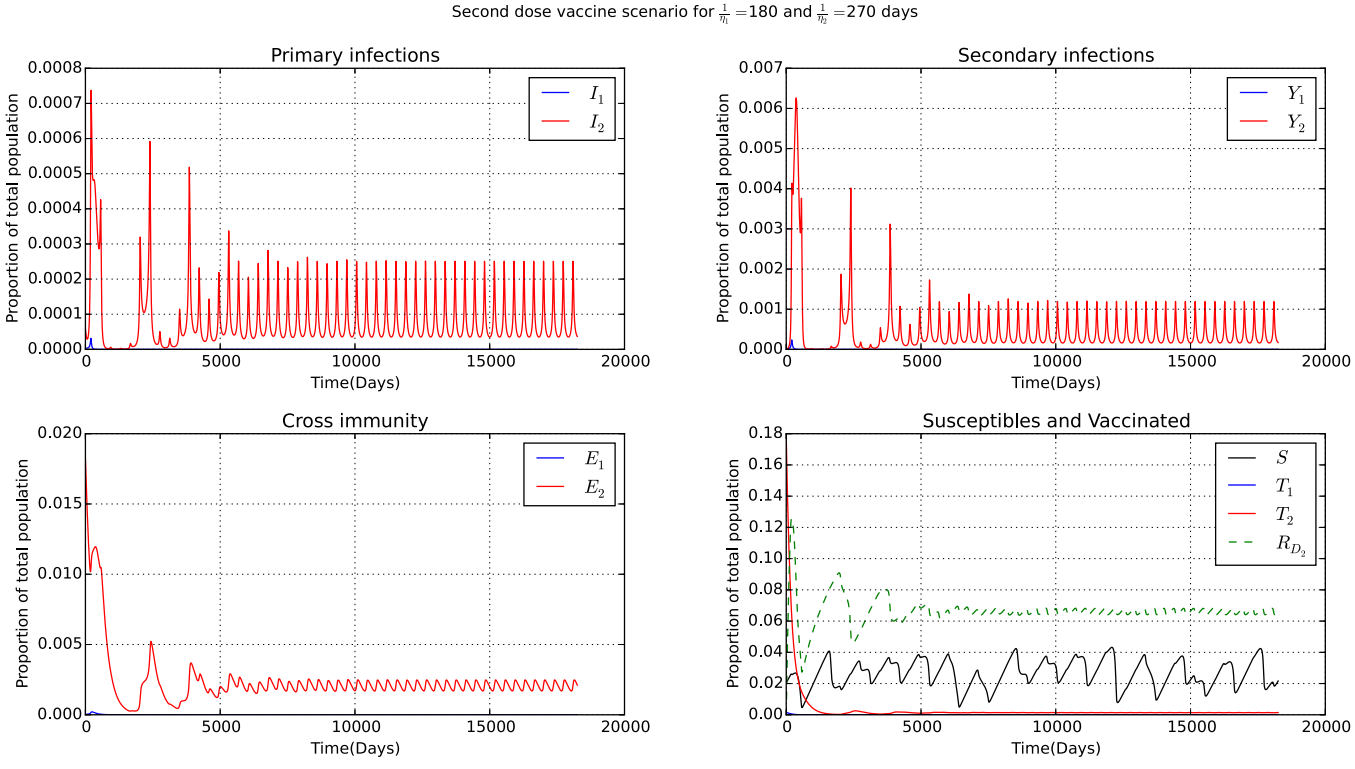

Fig. 6. *Vaccine scenario* D_2. Numerical results for primary (I_i) and secondary (Y_i) infections, individuals in the temporal cross immunity state (E_i), susceptibles (S, T_i), $i = 1, 2$ and vaccinated individuals (R_{D_2}). Parameter values: $p = 0$, $p_1 = 0.3$, $p_2 = 0.4$, $\psi = 1/(0.5 \times 365)$.

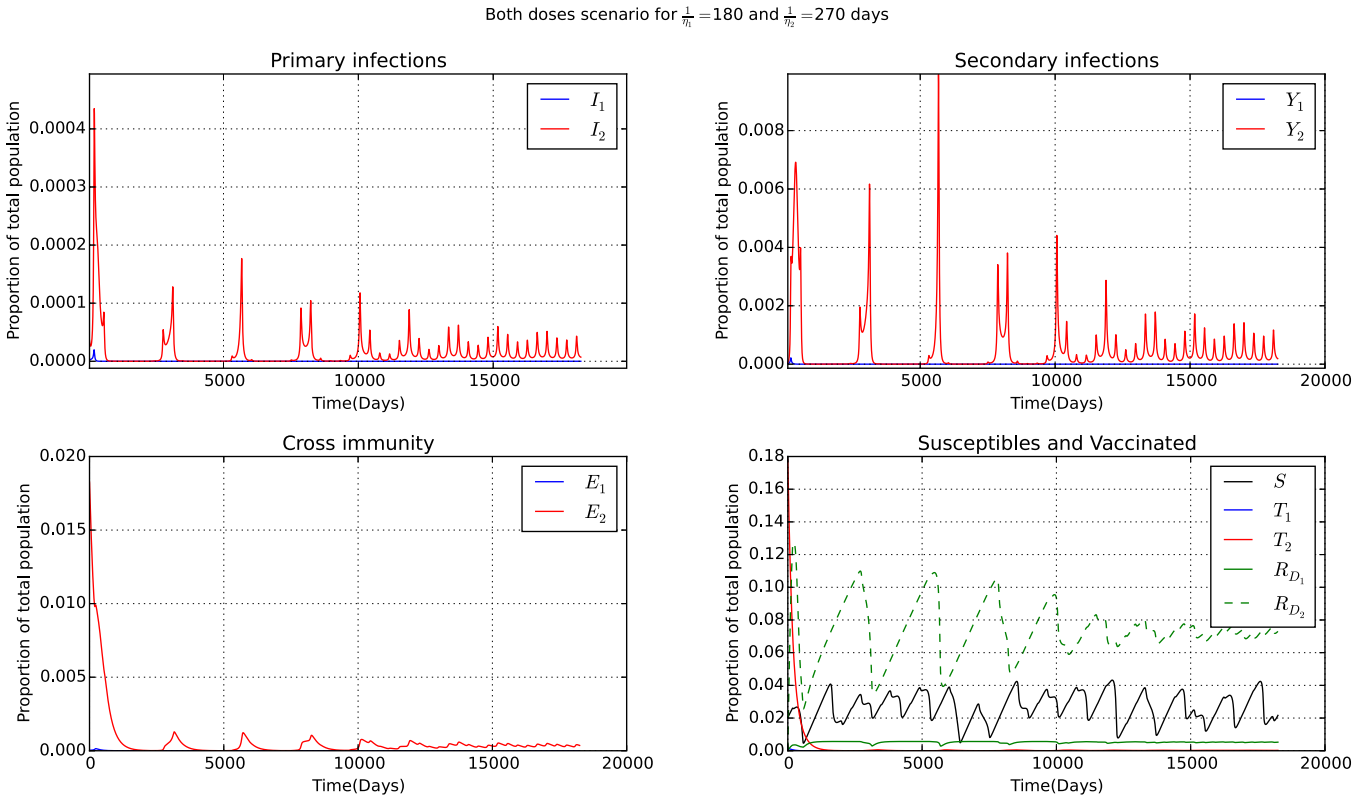

Fig. 7. *Vaccine scenario F.* Numerical results for primary (I_i) and secondary (Y_i) infections, individuals in the temporal cross immunity state (E_i), susceptibles (S, T_i), and vaccinated individuals ($R_{D_i}, i = 1, 2$). Parameter values: $p = 0.8$, $p_1 = 0.3$, $p_2 = 0.4$, $\psi = 1/(0.5 \times 365)$.

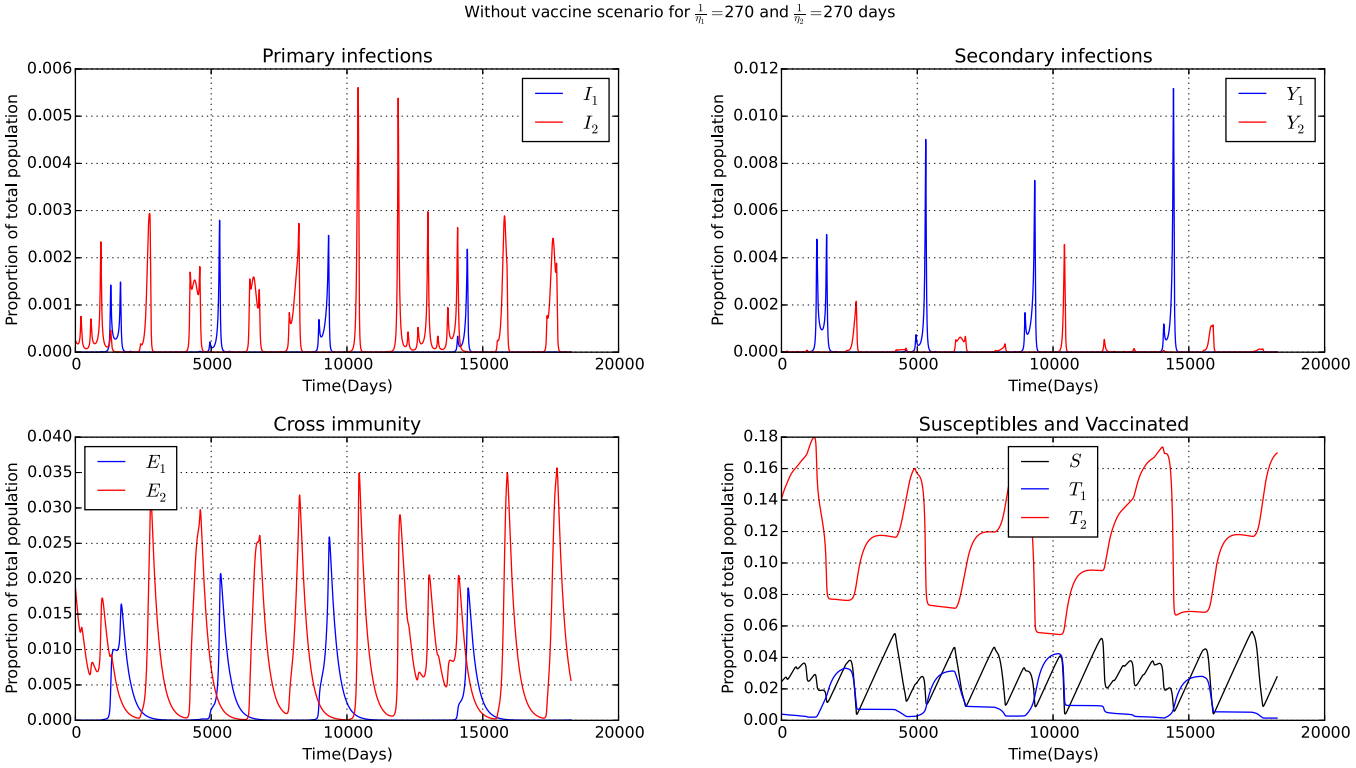

Fig. 8. *Vaccine scenario W.* Numerical results for primary (I_i) and secondary (Y_i) infections, individuals in the temporal cross immunity state (E_i) and susceptibles ($S, T_i, i = 1, 2$). Parameter values: $p = 0$, $p_i = 0$, $\psi = 0$.

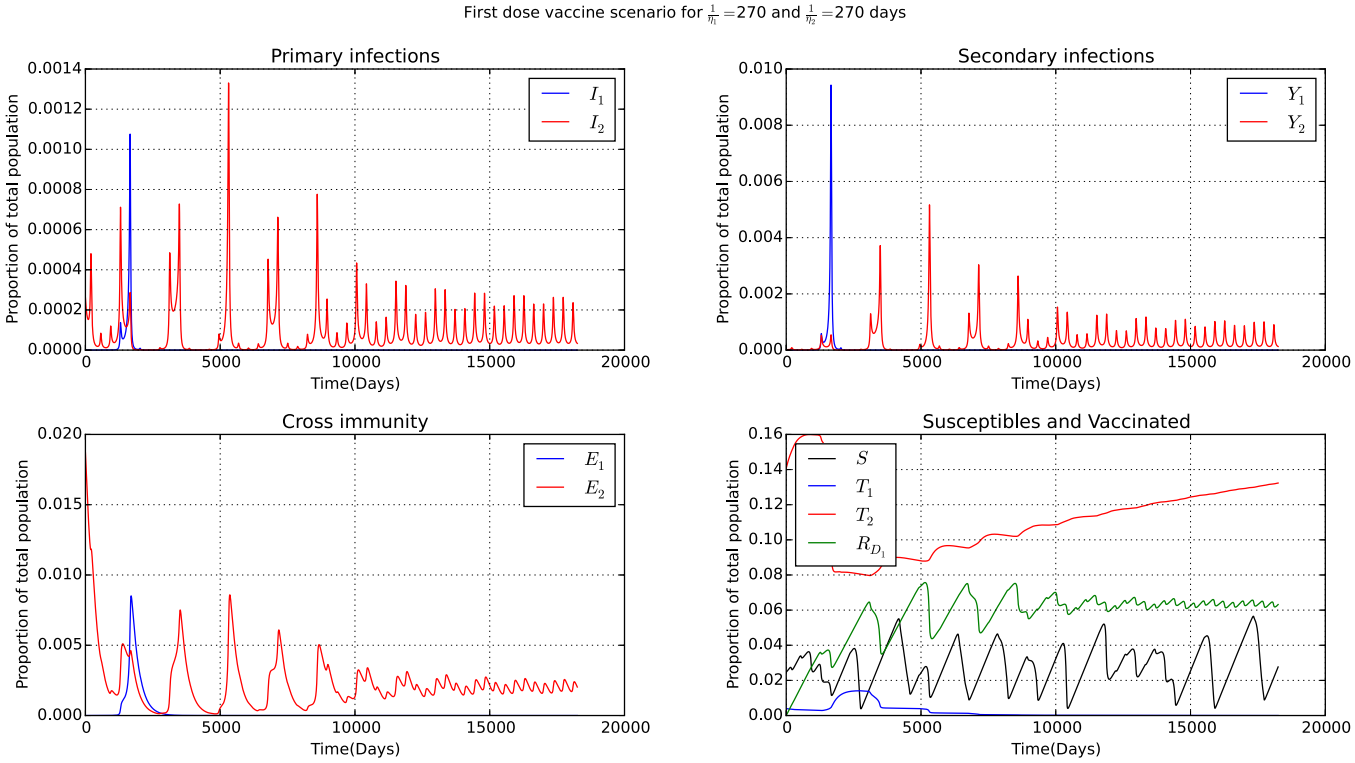

Fig. 9. *Vaccine scenario* D_1. Numerical results for primary (I_i) and secondary (Y_i) infections, individuals in the temporal cross immunity state (E_i), susceptibles $(S, T_i, i = 1, 2)$, and vaccinated individuals (R_{D_1}). Parameter values: $p = 0.8,\ p_1 = 0.3,\ p_2 = 0.4,\ \psi = 0$.

where $p(1 - p_i)$ is the effective coverage against each serotype. Therefore $1 - p(1 - p_i)$ is the proportion of susceptible individuals to serotype i after vaccination.

On another hand, since the model (1) undergoes time-dependent vector population size, we consider the effective reproduction number to take into account the proportion of infections generated during successive periods of time. We use the effective reproduction number approach proposed by Nold (1979) who defined R_t using the mean generation time (see [25]):

$$R^e_{01}(t, \mu) = Tot_1[t, t + \mu]/Tot_1[t - \mu, t]$$

$$R^e_{02}(t, \mu) = Tot_2[t, t + \mu]/Tot_2[t - \mu, t] \quad (3)$$

Where $Tot_i = I_i + Y_i, i = 1, 2$ account for total infections by each strain and μ is the mean generation time.

In Section 5.5 we present the numerical simulations of the effective reproduction numbers where the mean generation time (see [12] for further definitions) is 15 days according to estimations in [2].

3. Scenarios for the dengue vaccination model

The model described in Section 2 will be used to study the impact of vaccination strategies for different efficacy values $(p_i, i = 1, 2)$, transmission intensity $(\beta_i, i = 1, 2)$ and cross immunity periods $(1/\eta_i, i = 1, 2)$. As explained previously, we consider a population of individuals that are all fully susceptible to both strains of Dengue. At time $t = 0$ a few infected individuals are introduced. The infection process is triggered and a vaccine program is applied.

We study the long term dynamics under the following vaccination scenarios:

- Without vaccination (W)
- One dose application only (D_1)
- One dose application only with a delay of six months (D_2)
- Application of both doses (F)

Dose (D_1) is applied to all individuals entering the fully naive susceptible compartment, a second dose (D_2) is applied to susceptible individuals of all types $(S,\ T_1,\ T_2)$ after a waiting time of $1/\psi$ days. Both doses are applied, D_1 is applied to individuals entering the naive susceptible compartment S and D_2 is applied after $1/\psi$ days to all susceptible individuals $S,\ T_1,\ T_2$ and also to those individuals vaccinated with the dose D_1.

We remark that in our model the vaccine has lower efficacy against the serotype with the highest transmission intensity. Thus, $p_1 < p_2$ and $\beta_1 < \beta_2$.

For all scenarios the reproductive number for each serotype assumes $R_{02} > R_{01}$. Likewise, the efficacy of the vaccine against serotype 2 is lower than that for serotype 1. This implies that there is a higher probability of infection from serotype 2 than from serotype 1.

Table 3 shows the baseline parameter values for all simulations. (Table 2).

For the simulations we have chosen cross immunity periods (180 and 270 days) of both serotypes based on the reported information in [9,30]. To study the effect of this cross immunity periods on the asymptotic dynamics, we show four scenarios for each one of the cross immunity periods of 180–270 days and 270–270 days. As previously stated, the vaccine scenarios are W, D_1, D_2 and F.

The numerical simulations were obtained using *Python*. The results are shown after running a transient period of 137 years. After the transient, we assessed the impact of vaccination on the incidence of both serotypes along 50 years.

In the numerical results we show the dynamics corresponding to primary I_i and secondary infections Y_i of strains $i = 1, 2$. Recall that S is the compartment of susceptible individuals without previous infection, T_i corresponds to susceptible individuals re-

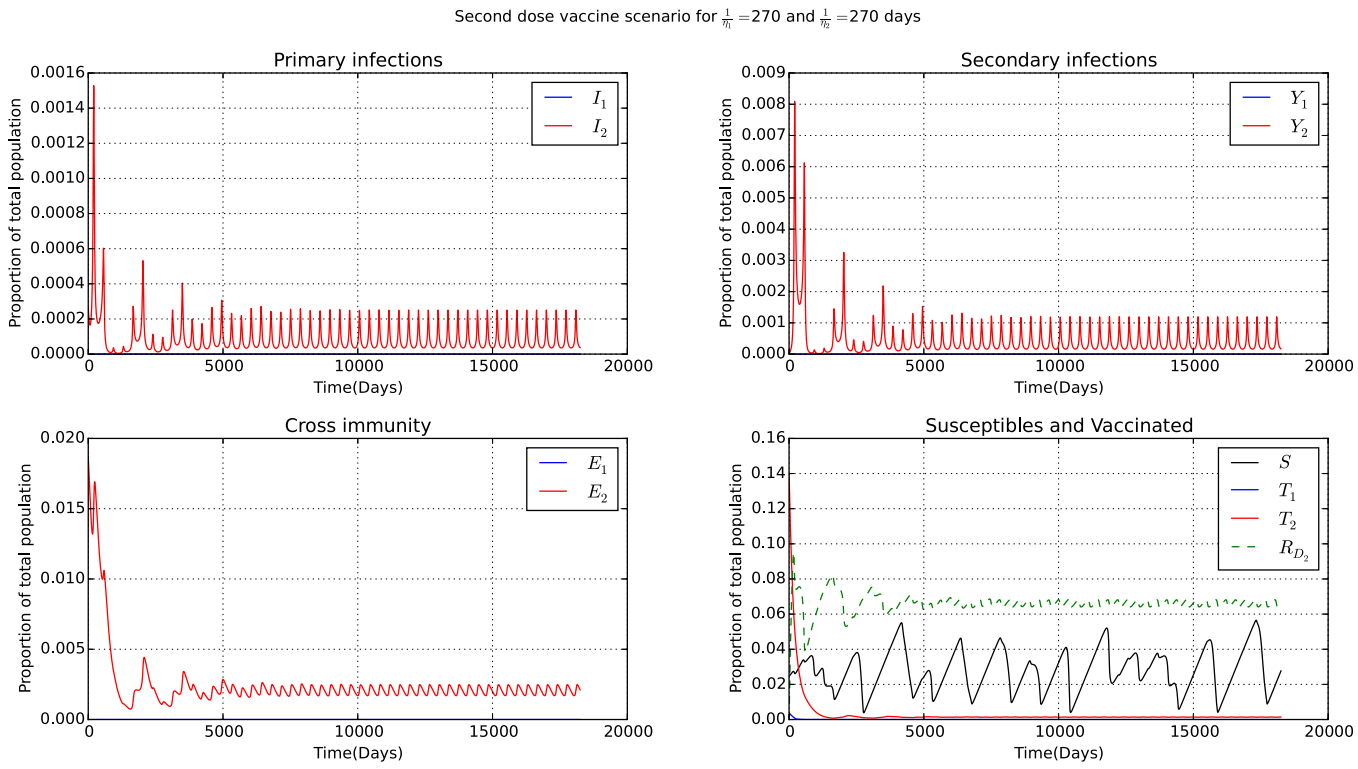

Fig. 10. *Vaccine scenario D_2.* Numerical results for primary (I_i) and secondary (Y_i) infections, individuals in the temporal cross immunity state (E_i), susceptibles ($S, T_i, i = 1, 2$), and vaccinated individuals (R_{D_2}). Parameter values: $p = 0,\ p_1 = 0.3,\ p_2 = 0.4,\ \psi = 1/(0.5 \times 365)$.

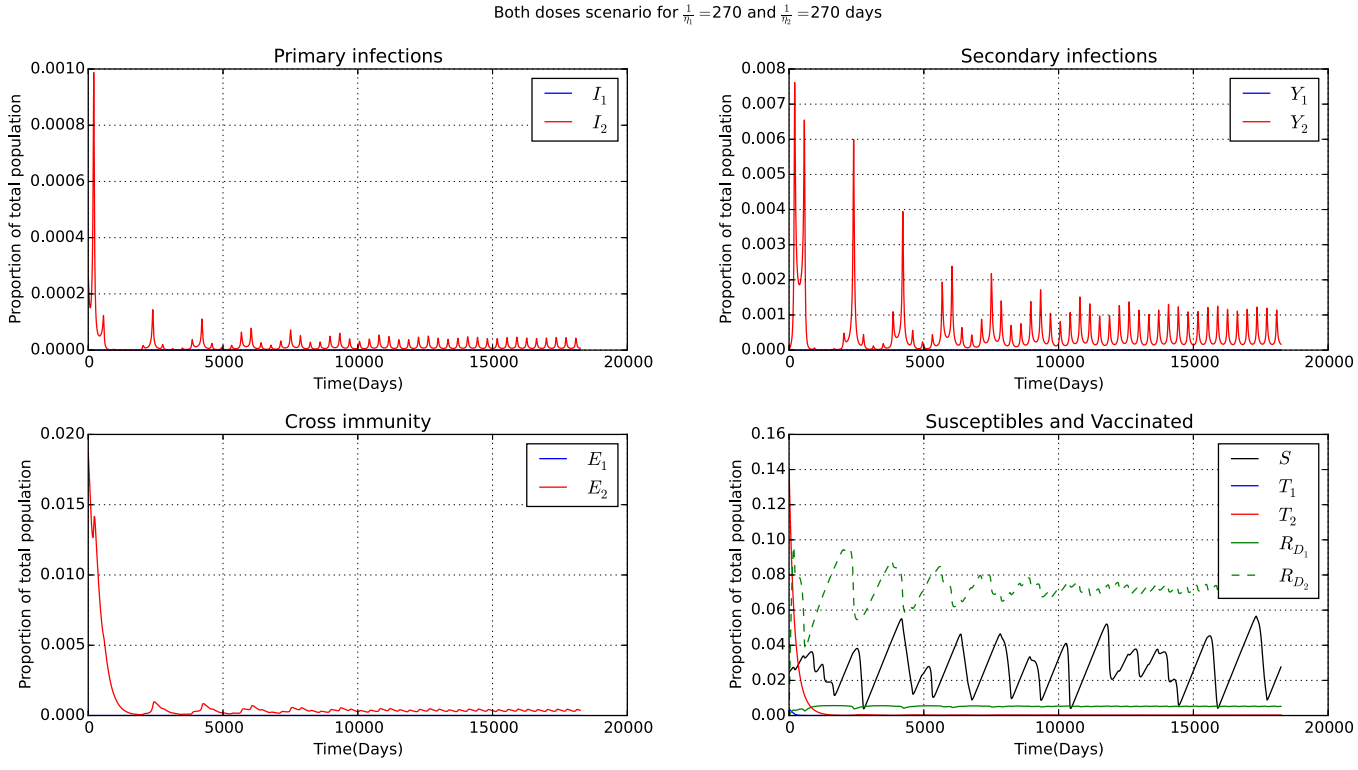

Fig. 11. *Vaccine scenario F.* Numerical results for primary (I_i) and secondary (Y_i) infections, individuals in the temporal cross immunity state ($E_i, i = 1, 2$), susceptibles (S, T_i), and vaccinated individuals ($R_{D_i}, i = 1, 2$). Parameter values: $p = 0.8,\ p_1 = 0.3,\ p_2 = 0.4,\ \psi = 1/(0.5 \times 365)$.

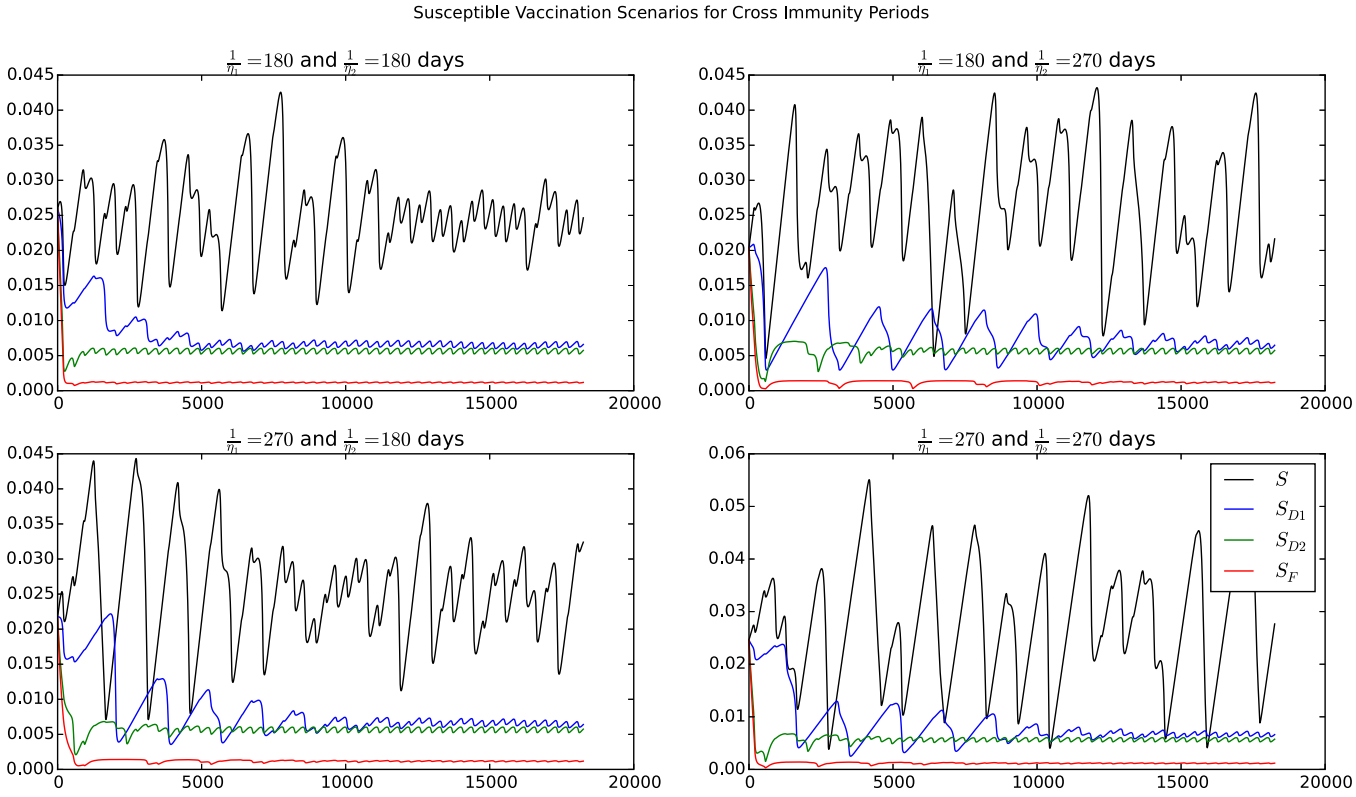

Fig. 12. *Susceptible population under vaccination scenarios.* Numerical results for susceptible individuals for different cross immunity scenarios. S susceptible naive individuals (susceptible to both strains), S_{D_1} susceptible pool of individuals after the application of the first dose, S_{D_2} susceptible pool of individuals left after the application of one dose after 6 months in the susceptible stage. S_F susceptible pool of individuals after the application of both doses. Horizontal axes is in days; vertical axes is the proportion of the population.

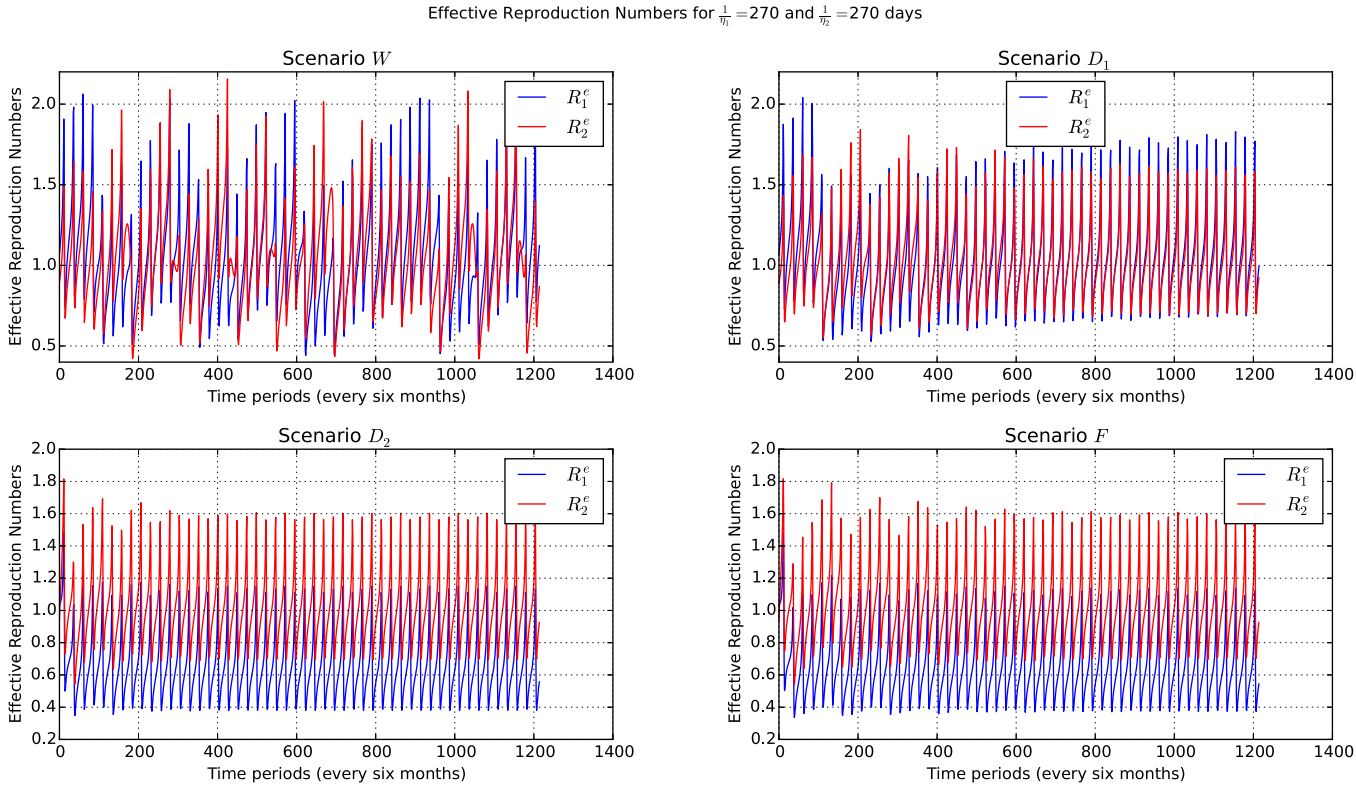

Fig. 13. *Effective reproduction numbers:* $R_{0i}^e(t,\mu), i = 1, 2$ *for* $9-9$ *months of cross immunity periods.* In the horizontal axis is indicated the number of periods of length $\mu = 15$ days. Top left: Without vaccination (W). Top right: One dose vaccine (D_1). Bottom left: One dose vaccine with a delay of 6 months. Bottom right: Both doses (F).

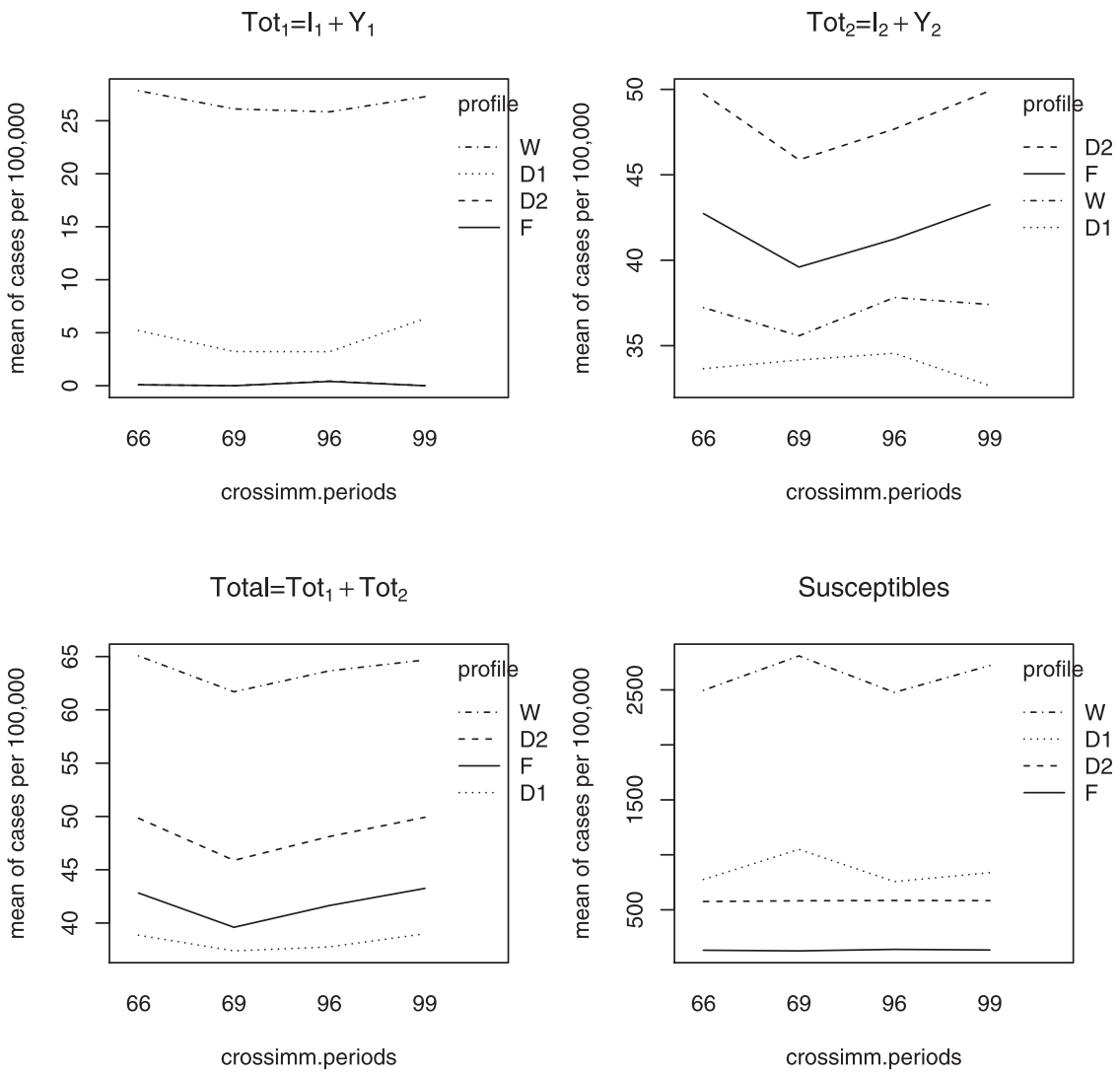

Fig. 14. Interaction plots of the effect of vaccine profiles and cross immunity periods on the means every six month along 50 years. Top left: Total infections by serotype 1. Top right: Total infections by serotype 2. Bottom left: Total infections. Bottom right: Susceptibles. Only the effect of vaccine profile on the reduction of means of $Tot_i, i = 1, 2$ and of those of susceptibles is statistically significant ($p - value < 0.05$). Both factors, taken independently, are statistically significant in the reduction of total infections ($Total = Tot_1 + Tot_2$).

covered from infection by strain i and prone to acquire dengue strain j (with $j \neq i$) and E_i individuals in the state of temporary cross-immunity after infection by strain i.

In the following sections we use the term *strong* strain to designate strain 2 which has the highest reproductive number.

4. Vaccination scenarios with cross immunity periods of 180 and 270 days for each strain

4.1. Without vaccine scenario W

In Fig. 4 we see in primary infections that both strain outbreaks exhibit desyncrhonized behaviour. The frequency of the outbreaks by the strong strain (I_2) is considerably higher (one order of magnitude) than those of the other. (Fig. 8)

In secondary infections, although the outbreaks Y_2 reduce their frequency, the proportion of infected individuals Y_1 increases about ten times compared to its proportion in primary infections. Besides, the highest peaks of T_2 (susceptibles to strain 1 only) trigger the outbreaks Y_1.

4.2. One dose vaccine scenario D_1

In primary and secondary infections there is only one outbreak by the weak strain I_1, while the proportion of infections I_2 decreases after the highest peak around 10 years and reaches more regular oscillatory pattern after 41 years. (Fig. 5)

On the long term, the effect of the first vaccine application is the prevention of outbreaks by the weak strain and the appearance of yearly outbreaks in primary and secondary infections by the strong strain (I_2, Y_2). In this scenario the vaccine protects effectively against strain 1 but it fails to protect against the strong strain, allowing yearly outbreaks.

4.3. One dose vaccine scenario D_2

In this scenario, only the dose (without the application of the first dose) with a delay of 6 months is applied.

In primary infections there is only one negligible outbreak by the weak strain I_1, while the proportion of infections by the strong strain I_2 reaches regular yearly outbreaks (Fig. 6).

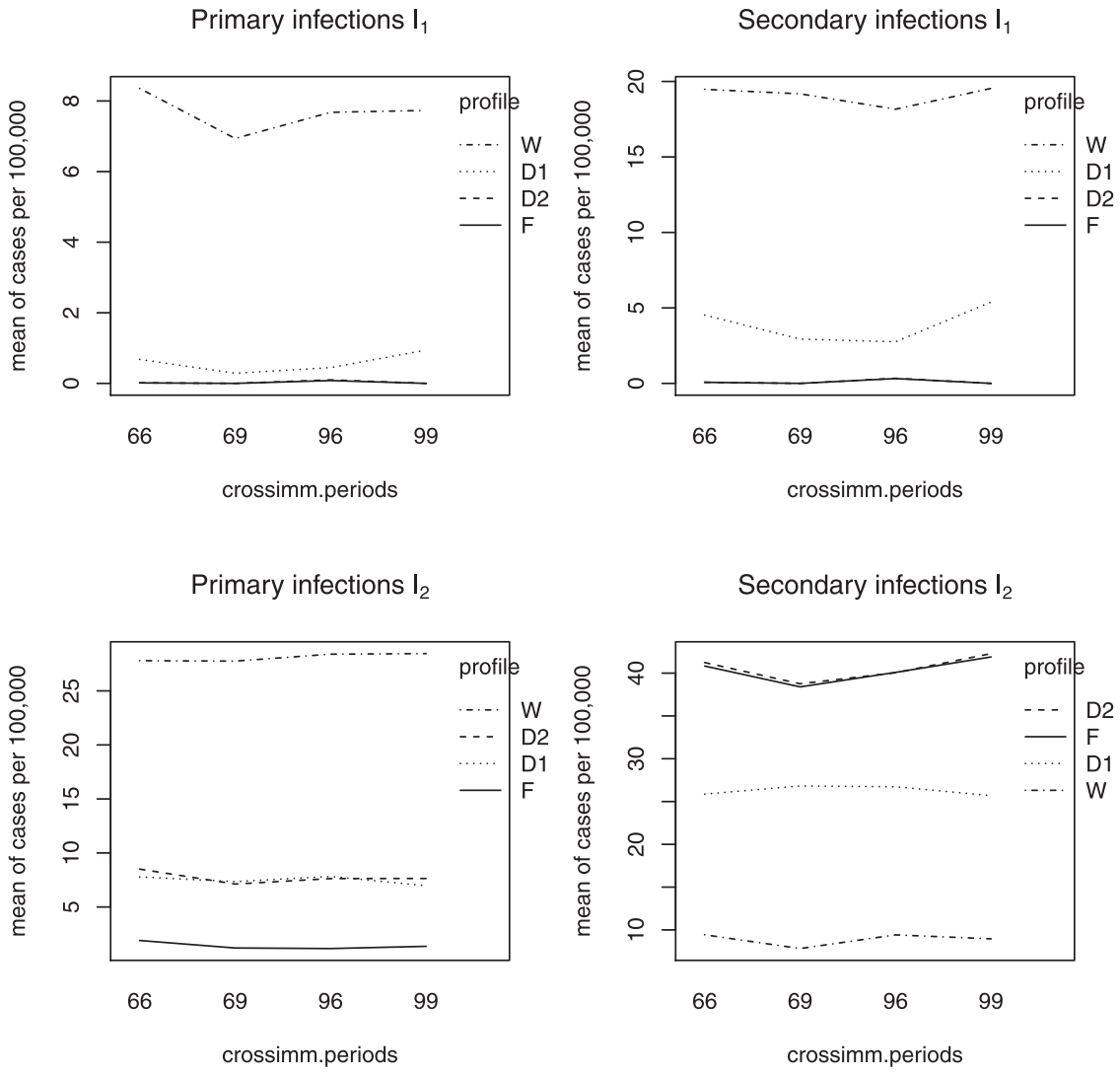

Fig. 15. Interaction plots of the effect of vaccine profiles and cross immunity periods on the means every six month along 50 years. Top left: Primary infections by serotype 1. Top right: Secondary infections by serotype 1. Bottom left: Primary infections by serotype 2. Bottom right: Secondary infections by serotype 2.

The vaccine effect has the following characteristics: first, it diminishes completely the outbreaks by strain 1 in both levels of infection, but it fails to prevent outbreaks by the strong strain. Second, unlike the scenario D_1, scenario D_2 reduces to almost zero the pool of susceptible individuals $(T_i, i = 1, 2)$ prone to acquire infection by both strains strain. However, in this scenario the vaccine also fails to protect against the strong strain, allowing yearly outbreaks Y_2.

4.4. *Both vaccine doses scenario* F

In the scenario where both doses of the vaccine are applied, the long term effect is the prevention of outbreaks of primary and secondary infections by the weak strain (I_1, Y_1), while the proportion of primary infections by the strong strain I_2 reaches regular oscillations after about 41 years. Compared to scenarios D_1 and D_2, in scenario F, the vaccine delays the occurrences of the outbreaks (I_2, Y_2) for the first 25 years.

On the other hand, in this scenario, the vaccine fails to prevent outbreaks by the strong strain (Y_2) despite the negligible pool of susceptibles to acquire either strain as a secondary infection $(T_i, i = 1, 2)$ (Fig. 7).

5. Vaccination scenarios with cross immunity periods of 270 days for both infections

In this section the simulation results, where the cross immunity periods are 270 days for both the weak and the strong serotypes [30], are presented for the previous four vaccine scenarios (W, D_1, D_2, F)

5.1. *Without vaccine scenario* W

As before, we present scenario W as a baseline for the other cases.

In this scenario, the effect of considering temporal cross immunity of 270 days for both strains results in desynchronized dynamics and less frequent outbreaks than those occurring when the cross immunity periods are 180 – 270 days.

In primary infections there are four large outbreaks by the weak strain I_1 while the outbreaks of the strong one I_2 occur with higher frequency. In secondary infections there are also four outbreaks of the weak strain Y_1 of considerably higher proportion than of

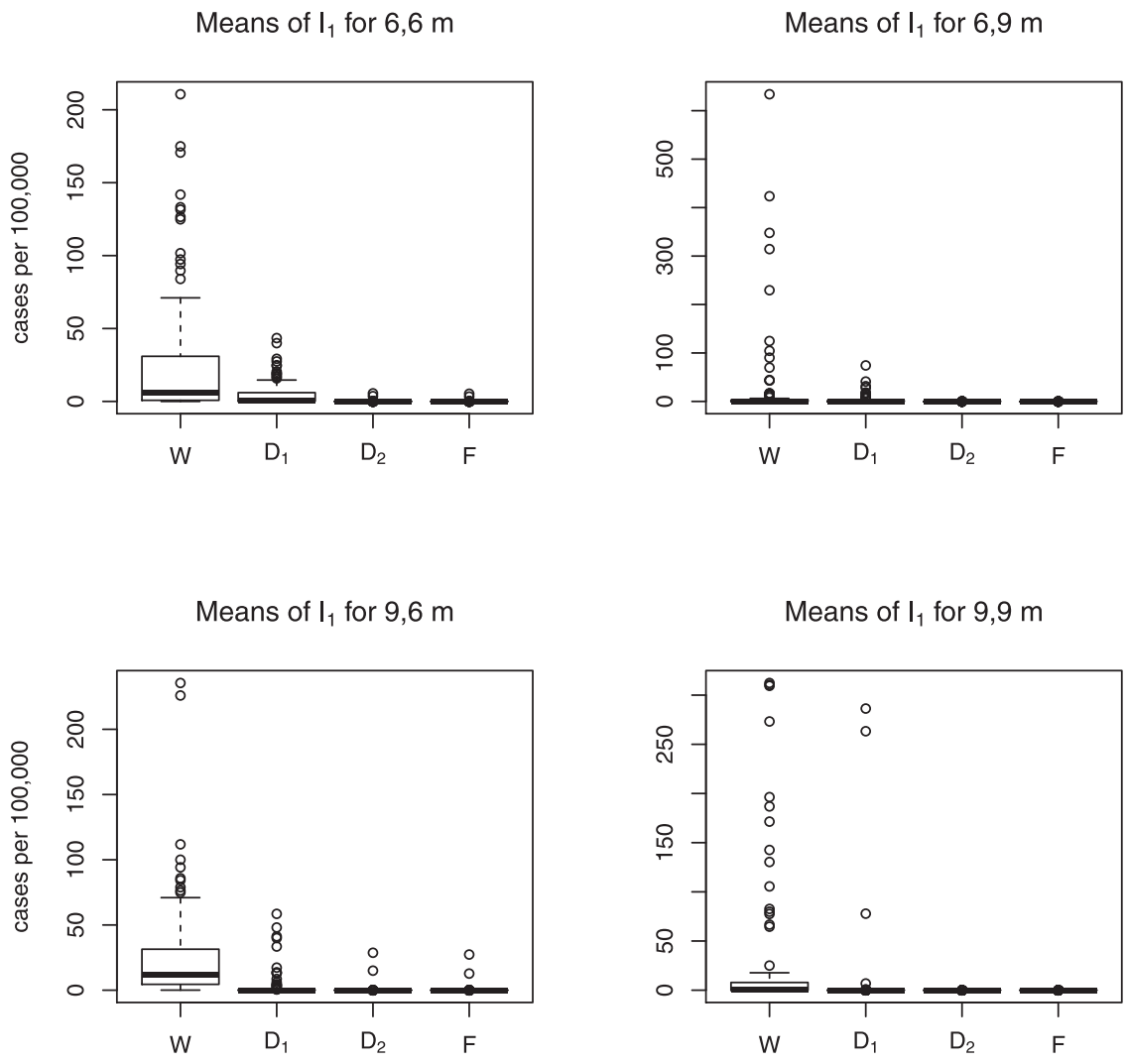

Fig. 16. Effect of vaccine profiles and cross immunity periods on the means of total infections by serotype 1. These means were obtained every six month along 50 years (cases per 100,000) for four pairs of cross immunity periods. Top left: six months for both serotypes. Top right: Six and nine months for serotype 1 and 2. Bottom left: Nine and six months for serotype 1 and 2. Bottom right: Nine months for both serotypes.

those by the strong strain Y_2. For this cross immunity periods, unlike the $180-270$ days of cross protection case, the proportions of primary and secondary infections are about the same order of magnitude.

Also, the outbreaks in secondary infections occur when the highest pool of recovered from primary infections (T_1, T_2) are reached. The highest proportion of susceptibles is that of T_2, which promotes higher outbreaks by strain 1 in secondary infections (Y_1).

5.2. One dose vaccine scenario D_1

In the scenario where the first dose of the vaccine is applied, the long term effect on the disease is, on one hand, the prevention of outbreaks by the weak strain in primary infections with only one large outbreak about 6 years after vaccine implementation. Whereas, infections by the strong strain tends to reach a regular oscillatory pattern after about 27 years. This effect is seen in both levels of infection (I_2, Y_2).

On the other hand, the vaccine effectively protects against strain 1 but it fails in protection against the strong strain. Thus, in scenario D_1, despite the increment of the pool of susceptibles (T_2) to acquire strain 1, the outbreaks by this strain (Y_1) are prevented, unlike the yearly outbreaks occurrence by strain 2 (Y_2) despite of the negligible pool of susceptibles (T_1) (Fig. 9).

5.3. One dose vaccine scenario D_2

In this scenario the vaccine dose is applied with a delay of 6 months. In this case, the long term effect is the prevention of primary and secondary outbreaks I_1, Y_1, while in both levels of infection I_2, Y_2 tend to yearly cyclic outbreaks after about 11 years of the vaccination program is implemented (Fig. 10).

On one side, the scenario D_2 leads to a faster regularization of the dynamics of infections by the strong strain and also diminishes the susceptible pool $T_i, i = 1, 2$ compared to scenario D_1.

In contrast, the delay in the dose application undergoes a failing in protection against the strong strain. Thus, there are

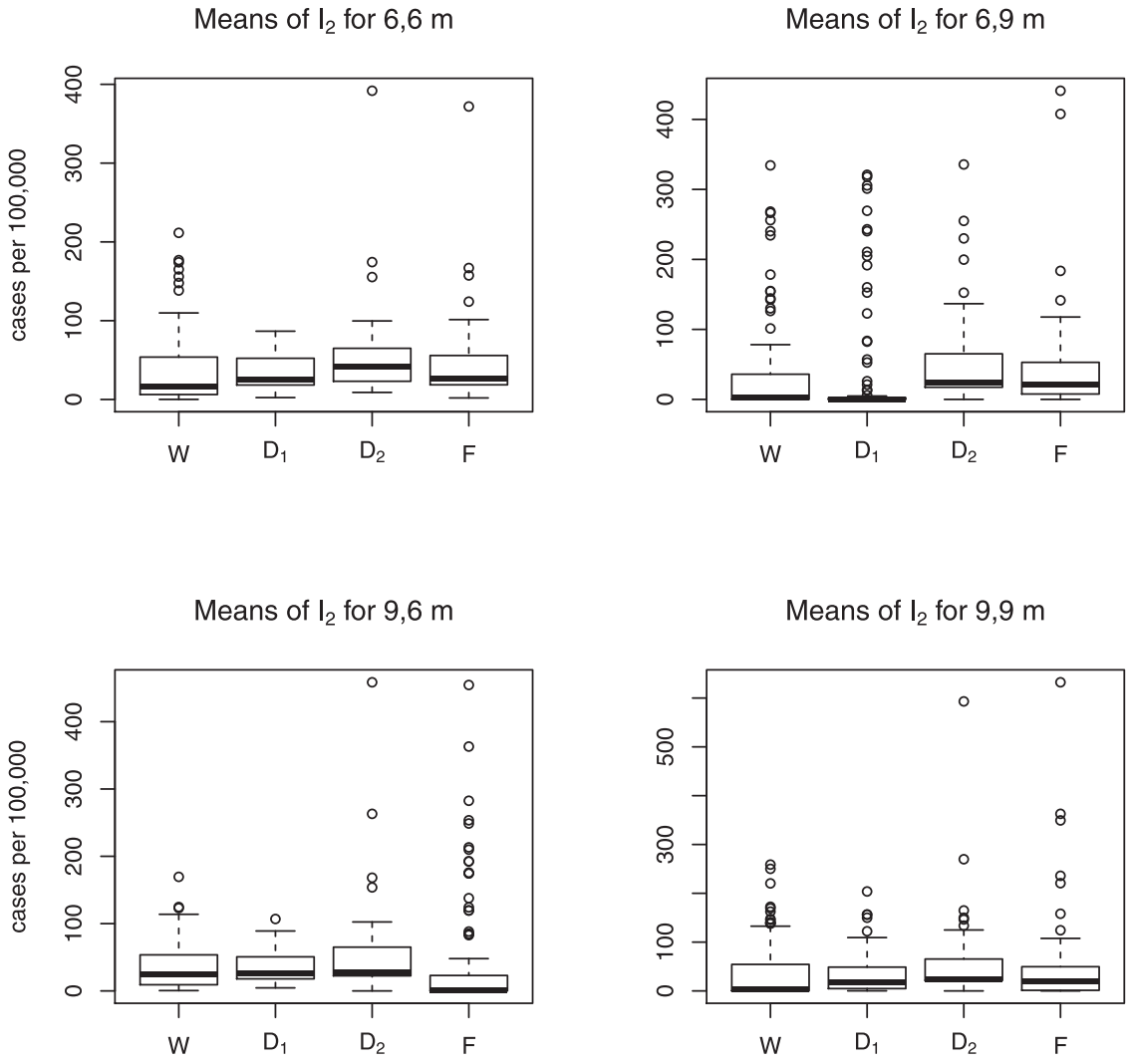

Fig. 17. Effect of vaccine profiles and cross immunity periods on the means of total infections by serotype 2. These means were obtained every six month along 50 years (cases per 100,000) for four pairs of cross immunity periods. Top left: six months for both serotypes. Top right: Six and nine months for serotype 1 and 2. Bottom left: Nine and six months for serotype 1 and 2. Bottom right: Nine months for both serotypes.

yearly outbreaks by strain 2 although the pool of susceptibles (T_1, T_2) tends to zero in the first 5 years of the vaccination campaign.

5.4. *Both vaccine doses scenario* F

In the scenario where both doses of the vaccine are applied, the long term effect is the prevention of outbreaks by the weak strain (I_1, Y_1). In contrast, the effect on secondary infections by the strong strain is the regularization of its dynamics in primary infection producing yearly outbreaks about 25 years. This strategy has a better effect on the reduction of the proportions of primary than in secondary infections.

Besides, in secondary infections, the both vaccine doses application fails to protect against the strong strain since there are yearly outbreaks by strain 2 although the pool of susceptibles (T_1, T_2) tends to zero in the very first years. (Fig. 11)

Finally, in Fig. 12 we present the available pool of susceptible individuals in each vaccination scenario.

5.5. *Effective reproduction numbers*

We present the numerical simulations for the effective reproduction numbers for cross immunity periods of 9 months for both strains since this case is representative of the regular behaviour that the application of the vaccine induces in each of the scenarios (D_1, D_2, F). The vaccine regularizes the outbreaks after about a 400 weeks transient.

As an approach, we use the definition of effective reproduction number given in (3), section (2.2):

$$R^e_{0i}(t,\mu) = Tot_i[t, t+\mu]/Tot_i[t-\mu, t] \qquad i = 1, 2$$

It is noteworthy that the effective reproductive numbers which accounts for infections occurred in periods of $\mu = 15$ days shows regular cyclic peaks (new infections) although vaccination prevents outbreaks by the weaker strain (see Fig. 13).

6. Summary statistics

In this section we present summary statistics based in our numerical simulations.

Means were obtained every six months over a period of 50 years for the variables: total infections by each serotype ($Tot_i = I_i + Y_i, i = 1, 2$), total infections ($Total = Tot_1 + Tot_2$) and susceptible individuals. The vaccine profiles and cross immunity periods are as in the previous sections.

6.1. Total infections

An ANOVA was performed for the means of total infections by each strain $Tot_i, i = 1, 2,$ total infections ($T = Tot_1 + Tot_2$) and Susceptibles along 50 years using as factors: the vaccine scenarios (W, D_1, D_2, F) denoted as profiles and the cross immunity periods denoted as crossimm.periods[2].

The reduction of the mean of serotype 1 total infections (Tot_1) is the result of either the application of only the secondary dose or the application of both vaccine doses (Top Fig. 14). While for the reduction of the mean of total infections by serotype 2 (Tot_2), only the primary dose application is necessary (Top right Fig. 14). Primary dose application reduces the six month means of total infections (Bottom left Fig. 14).

6.2. Primary and secondary infections

The six month means over a 50 years period were computed and an ANOVA performed. In this case, the effect of the vaccine profile (as one the factors) is statistically significant for both primary and secondary infections by each serotype.

This reduction of the mean for both primary and secondary infections by serotype 1 results from the application of either only the secondary dose or both vaccine doses (Top Fig. 14). In contrast, primary infections by serotype 2 is reduced only when both vaccine doses are applied. Note that the reduction of the mean of secondary infections by serotype 2 is achieved by the primary dose alone.

A summary of these results are shown in Figs. (16) and (17) (Fig. 15).

7. Conclusions

We have numerically explored the asymptotic and dynamical behaviour of a two-strain Dengue model under the application of a vaccine.

The model incorporates heterogeneity regarding transmission of both strains and efficacy of the vaccine against each one. In particular, the vaccine is assumed to have a lower efficacy against the serotype with the highest transmission intensity (strain 2 in the model). This assumption implies that a large numbers of hosts might be well protected against the weaker serotype (strain 1) but not against the stronger serotype (due to its higher transmission rate).

In contrast to Coudeville and Garnett [9], we compare the effect of each dose application assuming a fixed coverage of 80%. The target population is composed of susceptible individuals to which one out of three possible vaccination scenarios is applied. These are: a one dose vaccine application (D_1) at $t = 0$ to individuals entering to the susceptible compartment; a one dose vaccine application with a delay of six months (D_2) to all susceptible individuals ($S, T_i, i = 1, 2$); and the application of both doses of the vaccine (F). Each vaccine profile is applied taking two combinations of cross immunity periods: 180–270 and 270–270 days for each strain respectively.

In the baseline scenario W, the pool of susceptibles (T_1, T_2) remaining after a primary infections directly drives the size and frequency of outbreaks in secondary infections.

In scenario D_1, the vaccine effectively prevents outbreaks by the weak strain. Whereas, in scenarios D_2 and F, the vaccine reduces the pool of susceptibles to acquire a secondary infection by either strain but fails to prevent outbreaks by the strong strain in secondary infections, allowing yearly outbreaks (Y_2).

The statistical analysis also indicates that the application of the first vaccine dose considerably reduces (around 85%) the average incidence of strain 1 infections, whereas it only reduces around 9% the mean incidence by strain 2 for the two cross immunity combinations.

The other vaccine profiles, although effective against strain 1, lead to an increase in the mean incidence of secondary infections by strain 2. These cases could present clinically riskier secondary infections. In general the overall effect of the single vaccine application after 6 months (D_2) in the susceptible class ($S, T_i, i = 1, 2$) or the application of both doses (F), is the prevention of outbreaks by the weak strain together with the stabilization of recurrent outbreaks by the stronger strain. Thus, both vaccination profiles although considerably reduce the pool of susceptibles also produce increments in the proportion of secondary infections by the strong serotype [26].

Based on our results, the period of cross-immunity plays a crucial role in each of the scenarios. For the scenario without vaccination, with the longest period of cross-immunity for both strains, the frequency of the outbreaks decreases.

Moreover, despite an increase in secondary infections by serotype 2 for the single vaccine application after 6 months in the susceptible class or the application of both doses to all individuals, the largest overall reduction in incidence of both strains occurs when the cross immunity period is 270 days for the strong strain. And, with equal cross immunity periods (270 days) the yearly outbreaks appear faster of the outbreaks by strain 2 compared to the other cases.

On the long term, the three vaccination strategies seem to reduce the proportion of primary infections by both strains, F is the most favourable scenario since it also reduces the pool of susceptibles to acquire a secondary infections. This reduction is statistically significant in the means of proportions of total infections by each serotype ($Tot_i = I_i + Y_i$). In all vaccine scenarios, the vaccine induces periodic yearly outbreaks of the strong strain.

Acknowledgements

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[2] In this section, cross immunity periods of 180 − 180, 180 − 270, 270 − 180, 270 − 270 days for both serotypes are labelled as 6 − 6, 6 − 9, 9 − 6, 9 − 9 months.

Appendix A. Basic reproduction number R_0

The basic reproduction number is defined as the number of secondary infections that a single infectious individual produces in a population where all hosts are susceptible. It provides an invasion criterion for the initial spread of the virus in a susceptible population.

A.1. Reproduction number without vaccination

The set bounded by the total host and vector population

$$\Omega = \{(S, C_1, C_2, I_1, I_2, E_1, E_2, T_1, T_2, Z_1, Z_2, Y_1, Y_2, R, V_0, V_1, V_2):$$

$$S + C_1 + C_2 + I_1 + I_2 + E_1 + E_2 + T_1 + T_2 + Z_1 + Z_2 + Y_1 + Y_2 + R \leq N,$$

$$V_0 + V_1 + V_2 \leq M\}$$

the disease-free equilibrium is given by $E_0^* = (S^*, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, V_0^*, 0, 0)$.

According to the notation of P. van den Driessche and Watmough [10], we calculate the matrices F and V^{-1} evaluated in E_0^*.

$$F = \begin{pmatrix} 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \frac{\delta\beta_1}{M} & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \frac{\delta\beta_2}{M} \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \frac{T_2\beta_1\sigma_1}{M} & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \frac{T_2\beta_1\sigma_1}{M} \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & \frac{V_0\alpha_1}{N} & 0 & 0 & 0 & \frac{V_0\alpha_1}{N} & 0 & 0 & 0 \\ 0 & 0 & 0 & \frac{V_0\alpha_2}{N} & 0 & 0 & 0 & \frac{V_0\alpha_2}{N} & 0 & 0 \end{pmatrix},$$

$$V^{-1} = \begin{pmatrix} \frac{1}{\mu+\phi_1} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & \frac{1}{\mu+\phi_2} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ \frac{\phi_1}{(\mu+\gamma_1)(\mu+\phi_1)} & 0 & \frac{1}{\mu+\gamma_1} & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & \frac{\phi_2}{(\mu+\gamma_2)(\mu+\phi_2)} & 0 & \frac{1}{\mu+\gamma_2} & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & \frac{1}{\mu+\phi_1} & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & \frac{1}{\mu+\phi_2} & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & \frac{\phi_1}{(\mu+\gamma_1)(\mu+\phi_1)} & 0 & \frac{1}{\mu+\gamma_1} & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & \frac{\phi_2}{(\mu+\gamma_2)(\mu+\phi_2)} & 0 & \frac{1}{\mu+\gamma_2} & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \frac{1}{\delta} & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \frac{1}{\delta} \end{pmatrix}$$

By construction FV^{-1} is the next-generation matrix and set $R_0 = \rho(FV^{-1})$ where ρ denotes the spectral radius of a matrix.

$$FV^{-1} = \begin{pmatrix} 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \frac{S\beta_1}{M\delta} & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \frac{S\beta_2}{M\delta} \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \frac{T_2\beta_1\sigma_1}{M\delta} & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \frac{T_2\beta_2\sigma_2}{M\delta} \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ \frac{V_0\alpha_1\Phi_1}{N(\mu+\gamma_1)} & 0 & \frac{V_0\alpha_1}{N(\mu+\gamma_1)} & 0 & \frac{V_0\alpha_1\Phi_1}{N(\mu+\gamma_1)} & 0 & \frac{V_0\alpha_1}{N(\mu+\gamma_1)} & 0 & 0 & 0 \\ 0 & \frac{V_0\alpha_2\Phi_2}{N(\mu+\gamma_2)} & 0 & \frac{V_0\alpha_2}{N(\mu+\gamma_2)} & 0 & \frac{V_0\alpha_2\Phi_2}{N(\mu+\gamma_2)} & 0 & \frac{V_0\alpha_2}{N(\mu+\gamma_2)} & 0 & 0 \end{pmatrix}$$

where $\Phi_1 = \frac{\phi_1}{\mu+\phi_1}$, $\Phi_2 = \frac{\phi_2}{\mu+\phi_2}$, $S = N$, $V_0 = \frac{q}{\delta}$ and thus, the basic reproduction number is

$$R_0 = max\{R_{01}, R_{02}\} = max\left\{\sqrt{\frac{\beta_1\alpha_1\phi_1}{\delta(\gamma_1+\mu)(\phi_1+\mu)}}, \sqrt{\frac{\beta_2\alpha_2\phi_2}{\delta(\gamma_2+\mu)(\phi_2+\mu)}}\right\}$$

This expression is a generalization of the Ross–Macdonald basic reproductive number to the case of two strains, frequency-dependent contact rates and variable population size in both host and vector.

A.2. Reproduction number with vaccination

The set bounded by the total host and vector population with vaccination

$$\Omega = \{(S, R_p, R_s, C_1, C_2, I_1, I_2, E_1, E_2, T_1, T_2, Z_1, Z_2, Y_1, Y_2, R, V_0, V_1, V_2) :$$

$$S + R_p + R_s + C_1 + C_2 + I_1 + I_2 + E_1 + E_2 + T_1 + T_2 + Z_1 + Z_2 + Y_1 + Y_2 + R \leq N,$$

$$V_0 + V_1 + V_2 \leq M\}$$

The disease-free equilibrium is given by $E_0^* = (S^*, R_p^*, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, V_0^*, 0, 0)$.

$$F = \begin{pmatrix}
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \frac{S\beta_1}{M} & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \frac{S\beta_2}{M} \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \frac{p_1 R_p \beta_1}{M} & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \frac{p_2 R_p \beta_2}{M} \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & \frac{V_0\alpha_1}{N} & 0 & 0 & 0 & \frac{V_0\alpha_1}{N} & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & \frac{V_0\alpha_2}{N} & 0 & 0 & 0 & \frac{V_0\alpha_2}{N} & 0 & 0
\end{pmatrix},$$

$$V^{-1} = \begin{pmatrix}
\frac{1}{\mu+\psi} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -\frac{p_1 R_p \beta_1}{V_0 \delta(\mu+\psi)} & -\frac{p_2 R_p \beta_2}{V_0 \delta(\mu+\psi)} \\
\frac{\psi}{\mu^2+\mu\psi} & \frac{1}{\mu} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -\frac{p_1 R_p \psi \beta_1}{V_0 \delta \mu(\mu+\psi)} & -\frac{p_2 R_p \psi \beta_2}{V_0 \delta \mu(\mu+\psi)} \\
0 & 0 & \frac{1}{\mu+\phi_1} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & \frac{1}{\mu+\phi_2} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & \frac{\phi_1}{(\mu+\gamma_1)(\mu+\phi_1)} & 0 & \frac{1}{\mu+\gamma_1} & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & \frac{\phi_2}{(\mu+\gamma_2)(\mu+\phi_2)} & 0 & \frac{1}{\mu+\gamma_2} & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & \frac{1}{\mu+\phi_1} & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & \frac{1}{\mu+\phi_2} & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & \frac{\phi_1}{(\mu+\gamma_1)(\mu+\phi_1)} & 0 & \frac{1}{\mu+\gamma_1} & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & \frac{\phi_2}{(\mu+\gamma_2)(\mu+\phi_2)} & 0 & \frac{1}{\mu+\gamma_2} & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \frac{1}{\delta} & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \frac{1}{\delta}
\end{pmatrix}$$

the next generation matrix is given by

$$FV^{-1} = \begin{pmatrix}
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \frac{S\beta_1}{q} & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \frac{S\beta_2}{q} \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \frac{p_1 R_p \beta_1}{q} & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \frac{p_2 R_p \beta_2}{q} \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & \frac{q\alpha_1\phi_1}{\delta N(\mu+\gamma_1)(\mu+\phi_1)} & 0 & 0 & \frac{q\alpha_1}{\delta N(\mu+\gamma_1)} & 0 & \frac{q\alpha_1\phi_1}{\delta N(\mu+\gamma_1)(\mu+\phi_1)} & 0 & \frac{q\alpha_1}{\delta N(\mu+\gamma_1)} & 0 & 0 \\
0 & 0 & 0 & \frac{q\alpha_2\phi_2}{\delta N(\mu+\gamma_2)(\mu+\phi_2)} & 0 & \frac{q\alpha_2}{\delta N(\mu+\gamma_2)} & 0 & \frac{q\alpha_2\phi_2}{\delta N(\mu+\gamma_2)(\mu+\phi_2)} & 0 & \frac{q\alpha_2}{\delta N(\mu+\gamma_2)} & 0 & 0
\end{pmatrix}$$

where $S = \frac{\mu(1-p)N}{\mu+\psi}$, $R_p = \frac{\mu p N}{\mu+\psi}$, and thus, the basic reproduction number with vaccination

$$R_0^v = max\{R_{01}^v, R_{02}^v\} = max\left\{\sqrt{\frac{\beta_1\alpha_1\phi_1(1-p(1-p_1))}{\delta(\gamma_1+\mu)(\phi_1+\mu)}}, \sqrt{\frac{\beta_2\alpha_2\phi_2(1-p(1-p_2))}{\delta(\gamma_2+\mu)(\phi_2+\mu)}}\right\}$$

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