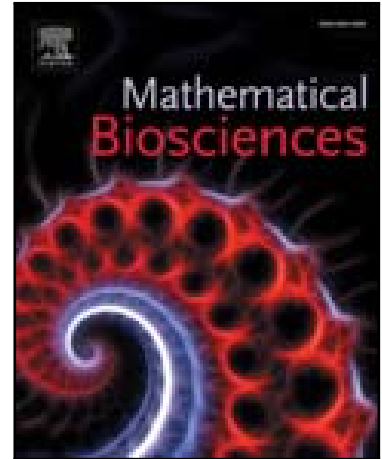# Accepted Manuscript

Analysis of the Optimal Vaccination Age for Dengue in Brazil with a Tetravalent Dengue Vaccine

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Highlights

- Mathematical model to analyse the optimal vaccination age against Dengue in Brazil.

- Use epidemiological data from Brazil.

- Consider both hospitalisation and lethality risks.

- Model possible Dengue Antibody Enhancement.

- Calculations repeated with third and fourth infections asymptomatic.

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Analysis of the Optimal Vaccination Age for Dengue in Brazil with a Tetravalent Dengue Vaccine

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Abstract

In this paper we study a mathematical model to analyse the optimal vaccination age against Dengue in Brazil. Data from Brazil are used to estimate the basic reproduction numbers for each of the four Dengue serotypes and then the optimal vaccination age is calculated using a method due to Hethcote [1]. The vaccine has different efficacies against each serotype. Vaccination that is too early is ineffective as individuals are protected by maternal antibodies but leaving vaccination until later may allow the disease to spread.

First of all the optimal vaccination ages are calculated where there is just one serotype in circulation and then when there are multiple serotypes. The calculations are done using data both assuming constant vaccine efficacy and age-dependent vaccine efficacy against a given serotype. The multiple serotype calculations are repeated assuming that the first infection is a risky infection and that it is not (to model Dengue Antibody Enhancement). The calculations are then repeated when any third or fourth Dengue infections are asymptomatic, so that two Dengue infections with different serotypes provide effective permanent immunity. The calculations are also repeated when the age-dependent risk function (fitted to Brazilian data) is hospitalisation from Dengue and when it is mortality due to Dengue. We find a wide variety of optimal vaccination ages depending on both the serotypes in circulation and the assumptions of the model.

Keywords: Dengue, Vaccination, Optimal Vaccination Age, Age-Structured

Model, Serotype, Risk Function, Mortality, Hospitalisation, Mathematical Model.

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1. Literature Review

Dengue is recognised as one of the most important vector-borne diseases of our time with over 2.5 billion people living in endemic areas and infection numbers estimated as high as 390 million annually [2, 3]. Over the past two decades there has been a noticeable increase in mathematical models describing Dengue transmission dynamics in order to achieve a better understanding of the disease as well as to be able to assess the potential of control measures such as vector-control and vaccinations [4]. The derived transmission models can be broadly categorised as 'single-serotype' models [5, 6, 7] and 'multi-serotype' models [8, 9, 10].

Single-serotype models are usually based on the Ross-MacDonald model, which was derived for the transmission of Malaria by Ross and later extended by MacDonald in the 1950s. These types of models describe both the human and the mosquito populations by separating them into susceptible, infectious and recovered compartments for humans, and susceptible and infectious compartments for mosquitoes. Some models extend the number of compartments for one or both species by including a latency period [6, 7]. While different research questions have led to a multitude of models most are fairly similar to the original Ross-MacDonald model [4]. However, depending on which aspects of the transmission or which type of control measures the researchers aim to investigate the details vary significantly. Considering, for example, vector-control strategies or the effect of temperature on the number of mosquitoes requires a more detailed representation of the vector population than is necessary for models that focus on other issues. Multi-serotype models on the other hand are often concerned with the interaction of the four different Dengue serotypes. Many of these models are based on the assumption of a very short timescale as well as a dense mosquito population so that a direct transmission model can be considered [10].

Understanding the interaction of the four different serotypes is crucial for the understanding of transmission dynamics and for the implementation of control strategies. The World Health Organisation (WHO) has identified the development and implementation of vaccines against Dengue as an important means to reduce the burden of Dengue in their global strategy for Dengue prevention and control 2012-2020 [3]. Accordingly, many researchers

use mathematical models to assess the impact a potential Dengue vaccine may have, or to find a cost-effective vaccination strategy. Modelling the impact of vaccination proves to be very challenging for several reasons. One of the main difficulties is the coexistence of more than one Dengue serotypes in endemic areas resulting in the possibility of consecutive, heterologous infections. While there is little dispute about lifelong immunity to the serotype a person was initially infected with [11], there is less clarity on the interaction between different serotypes. Effects of interaction that have been documented are the short-term cross-immunity after a primary infection [12] even though the length of this protection is not clear [13], as well as more severe symptoms in secondary infections, i.e. Dengue Hemorrhagic Fever or Dengue Shock Syndrome (DHF or DSS), which give rise to the theory of antibody-dependent enhancement (ADE) [14]. It is thought that after a short phase of cross-immunity following an infection a secondary, heterologous infection has a higher virulence caused by antibodies specific to the first serotype. These specific antibodies bind on to the very similar second Dengue serotype allowing the virus entry into its target cells without first inactivating it and are thus enhancing the virulence during a secondary infection. Studies have indeed found that the sequence of serotypes plays an important role in whether an individual develops DHF or DSS rather than the mild symptoms of Dengue Fever and that usually two heterologous infections lead to permanent protection against all serotypes [15, 16]. Based on these observations many models that considered multi-serotype transmission dynamics assume complete immunity after two heterologous infections [17, 18]. Considering these complex interdependencies it is not surprising that there are contradictory conclusions about the effects of vaccination. There is an overall agreement about the potential of vaccines to reduce Dengue Fever cases drastically [6, 17, 19], yet some results indicate that vaccination in the presence of ADE could lead to an increase in the incidence of DHF or DSS under certain conditions [17, 20, 21].

Now that vaccinations against Dengue are becoming a reality with Sanofi Pasteur's Dengvaxia being licensed after twenty years of development as the first Dengue vaccination in the world, it is important to be able to employ the vaccine to protect populations against Dengue Fever and its more severe forms in the best way possible. Some recent vaccination models attempt to do this by finding the most cost-effective strategy or a strategy that will lead to the necessary herd immunity for eradication of the disease [10, 22, 23]. However, considering that ADE might lead to an increase in DHF and

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DSS cases there are a multitude of aspects that need to be considered when introducing a vaccine against Dengue. The WHO recommends the use of Dengvaxia only in highly endemic settings [24]. In very high transmission settings it is recommended to vaccinate individuals aged 9 years, and in high transmission settings individuals between 11 and 14 years on a routine vaccine calendar at 0, 6 and 12 months [25]. However, since the licensure of Dengvaxia there has been an increasing concern about its application particularly in seronegative recipients with some models concluding that in this group the vaccine increases the risk of hospitalisation due to vaccine induced ADE [26, 27, 28]. In fact, Aguiar et al. [29] have shown that for the risk of hospitalisation to be reduced significantly only seropositive individuals should be targeted after immunological screening. They further question whether the vaccine efficacy is mainly correlated with the serostatus rather than with the age of the recipient as indicated in the Dengvaxia efficacy trials [30, 31]. If vaccination of seronegative recipients does indeed lead to ADE and efficacy depends on the serostatus this would mean that the recommendations of the WHO and Sanofi Pasteur might need to be reconsidered as noted by Halstead [26]. Vaccination strategies should therefore be chosen in such a way that the overall risk due to infection is minimised for the entire population. This issue has been addressed by Hethcote [1] for vaccination against Measles by considering a modelling framework to find the optimal vaccination ages that minimise the lifetime expected risk of Measles in a human population. He defined the lifetime expected risk as $E = \int_0^\infty R(a)P(a)da$ where $P(a)$ is the probability of getting infected at age a (in other words if Δa is small and positive the probability that an individual gets infected in the time interval $[a, a + \Delta a]$ is $P(a)\Delta a + o(\Delta a)$). $R(a)$ is the risk of infection at age a, i.e. a function describing the harmfulness of an infection at age a. However, while some of the theory Hethcote used can be applied to the case of Dengue, one has to note that there are significant differences between the two diseases. Measles is usually transmitted directly from person to person, while in the case of Dengue mosquitoes such as the *Aedes aegypti* mosquito function as vectors. The fact that Dengue is a vector-borne disease results in different transmission dynamics and a basic reproduction number R_0 which depends not only on the host but also on the vector species. Since there is only one serotype of Measles, considering Dengue will also require a different definition of the lifetime expected risk due to the coexistence of several serotypes.

Therefore this paper aims to identify the optimal ages of vaccination for Dengue when more than one serotype is present. While the transmission

of the serotypes is considered to take place independently the risk function $R(a)$ is utilised to incorporate observations such as an increased risk of DHF or DSS in certain infection sequences; making it possible to take some of the interactions between the serotypes into account while considering a single-serotype transmission model.

2. Transmission Model

In order to find the optimal age of vaccination against Dengue the first step is to consider the transmission dynamics of a single Dengue serotype. Assuming independent transmission dynamics regardless of how many serotypes are present, this transmission model can then be used to find the lifetime expected risk for a specific vaccination strategy similar to that derived for Measles by Hethcote [1].

For the one-serotype Dengue transmission model the age density of the total human population is divided into 'unaffected', 'infected' and 'recovered' given at age a and time t by $U_H(a,t)$, $I_H(a,t)$, and $R_H(a,t)$ respectively. Note that the category 'unaffected' includes individuals who are passively immune due to maternal antibodies as well as individuals that are susceptible. Similarly the category of 'recovered' comprises individuals that have recovered from natural infection or have been successfully vaccinated. Following Hethcote [1] we will assume that a fraction $C(a)$ of the 'unaffected' individuals at age a are susceptible and that $C(a)$ corresponds to the fraction of susceptible individuals at age a who seroconvert when exposed to the disease or the vaccine. The remaining fraction $1 - C(a)$ of individuals of age a are passively immune, i.e. $1 - C(a)$ represents the fraction of a cohort of individuals who were initially entirely protected by maternal antibodies at birth who still protected at age a. These proportions are estimated from data on the decline of maternal antibodies for each of the four serotypes given in van Panhuis et al. [32]. Therefore passive immunes and susceptibles are given by $(1 - C(a)) U_H(a,t)$ and $C(a)U_H(a,t)$ respectively. Further an infection with any Dengue serotype will lead to an average infectious period $\frac{1}{\gamma_H}$ after which the individual will be immune to that specific serotype for the remainder of their lifetime. The per capita death rate of all humans is taken to be μ_H without any additional deaths due to Dengue based on a very low proportion of Dengue cases leading to death [33]. It will be assumed that the total number of humans N_H remains constant over time.

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The mosquito population on the other hand will be divided into 'susceptibles', 'exposed' and 'infectious' given at time t by $S_M(t)$, $L_M(t)$ and $I_M(t)$ respectively. Exposed mosquitoes will become infectious after a latency period τ and stay infectious for the rest of their life. Again we take the per capita death rate to be μ_M for all mosquitoes without any additional deaths caused by the virus.

Table 1: Description of model parameters

Parameter	Significance
q	total rate per unit time at which mosquitoes bite humans,
b	probability per bite that an initially susceptible human bitten by an infected mosquito becomes infected,
c	probability per bite that an initially susceptible mosquito biting an infected human becomes infected,
N_H	total number of humans,
μ_H	natural per capita death rate of humans,
γ_H	per capita recovery rate of humans,
N_M	total number of mosquitoes,
μ_M	natural per capita death rate of mosquitoes,
τ	incubation period in mosquitoes (the extrinsic incubation period),
$A_i \ (i = 1, 2, 3)$	vaccination age for each of the three vaccination stages,
$V_i \ (i = 1, 2, 3)$	vaccinated proportion of the population for each vaccination age

As described in Table 1 we denote q to be the total rate per unit time at which a mosquito bites humans, b to be the probability per bite that an initially susceptible human bitten by an infected mosquito becomes infected and c the probability per bite that an initially susceptible mosquito biting an infected human becomes infected. Then the forces of infection are given by

$$\lambda(t) = qb\frac{I_M(t)}{N_H}, \qquad \text{for humans, and} \qquad (1)$$

$$\lambda_M(t) = qc\frac{1}{N_H}\int_0^\infty I_H(a,t)da \qquad \text{for mosquitoes.}$$

For maximum effectiveness it is recommended that Dengvaxia be given in three separate doses each at least six months apart. Hence in the model

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we assume that we vaccinate fractions V_i of the human population at three vaccination ages A_i $(i = 1,2,3)$ so that the probability of becoming immune due to vaccination at age A_i is $V_i C(A_i)$. Therefore vaccination will result in the matching conditions

$$U_H(A_i + 0, t) = (1 - V_i C(A_i))U_H(A_i - 0, t),$$

where

$$U_H(A_i + 0, t) = \lim_{a \to A_i^+} U_H(A_i, t),$$

and

$$U_H(A_i - 0, t) = \lim_{a \to A_i^-} U_H(A_i, t),$$

for $i = 1, 2, 3$. The model parameters used to describe the transmission dynamics and the vaccination strategy are explained in Table 1.

The transmission model for a single Dengue serotype is therefore

$$
\begin{aligned}
\frac{\partial U_H}{\partial a} + \frac{\partial U_H}{\partial t} &= -\lambda(t)C(a)U_H(a,t) - \mu_H U_H(a,t), \\
\frac{\partial I_H}{\partial a} + \frac{\partial I_H}{\partial t} &= \lambda(t)C(a)U_H(a,t) - (\mu_H + \gamma_H)I_H(a,t), \\
\frac{\partial R_H}{\partial a} + \frac{\partial R_H}{\partial t} &= \gamma_H I_H(a,t) - \mu_H R_H(a,t), \\
\frac{\partial N_H}{\partial a} + \frac{\partial N_H}{\partial t} &= -\mu_H N_H(a,t), \\
N_H(a,t) &= U_H(a,t) + I_H(a,t) + R_H(a,t),
\end{aligned}
\tag{2}
$$

$$
\begin{aligned}
\frac{dS_M}{dt} &= -\lambda_M(t)S_M(t) - \mu_M S_M(t) + \mu_M N_M, \\
\frac{dL_M}{dt} &= \lambda_M(t)S_M(t) - e^{-\mu_M \tau}\lambda_M(t - \tau)S_M(t - \tau) - \mu_M L_M(t), \\
\frac{dI_M}{dt} &= e^{-\mu_M \tau}\lambda_M(t - \tau)S_M(t - \tau) - \mu_M I_M(t), \\
N_M(t) &= S_M(t) + L_M(t) + I_M(t),
\end{aligned}
\tag{3}
$$

with initial conditions

$$U_H(a,0) = U_{H,0}(a), \quad I_H(a,t) = I_{H,0}(a) \text{ for } \tau \in [-\tau, 0], \quad R_H(a,0) = R_{H,0}(a),$$
$$U_H(0,t) = \mu_H N_H , \quad I_H(0,t) = 0, \qquad\qquad\qquad R_H(0,t) = 0,$$

for the human population, and initial conditions

$$S_M(t) = S_{M,0} \text{ for } \tau \in [-\tau, 0], \quad L_M(0) = L_{M,0}, \quad I_M(0) = I_{M,0},$$

for the mosquito population.

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For the sake of simplicity we have assumed a constant death rate. This is a common practice in epidemiological modelling [34]. However a more accurate estimate would be obtained by either a step death function where everyone lives up to a constant age and then dies or by using real demographic estimates for the death rates. This is a topic for further study.

3. Steady-State Force of Infection λ

The next step to find optimal vaccination ages is to derive λ, the force of infection for humans at the steady-state age distribution, from the transmission dynamics. In order to do this we consider the fractions at age a of unaffected, infected and recovered humans rather than the total number (that is the fractions at age a relative to the total population at age a). The fractions will be denoted by the corresponding lower case letters where the subscript H is dropped for the human population. At the steady-state the densities with respect to age of the fractions for unaffected and infected satisfy:

$$
\begin{aligned}
\frac{du}{da} &= -\lambda C(a)u(a), \\
\frac{di}{da} &= \lambda C(a)u(a) - \gamma_H i(a),
\end{aligned}
\tag{4}
$$

with initial and matching conditions

$$
\begin{aligned}
u(0) &= 1, \qquad u(A_i + 0, t) = (1 - V_i C(A_i))\, u(A_i - 0, t), \text{ for } i = 1, 2, 3, \\
i(0) &= 0,
\end{aligned}
$$

respectively where again $U_H(A_i + 0, t) = \lim\limits_{a \to A_i^+} U_H(A_i, t)$, for $i = 1, 2, 3$, and similarly for $U_H(A_i - 0, t)$, while the recovered fraction satisfies $r(a) = 1 - u(a) - i(a)$. This system of ODEs can be solved to give

$$
u(a) = \begin{cases}
e^{-\lambda \int_0^a C(s)ds}, & 0 \leq a \leq A_1, \\
(1 - V_1 C(A_1))\, e^{-\lambda \int_0^a C(s)ds}, & A_1 < a \leq A_2, \\
(1 - V_1 C(A_1))\,(1 - V_2 C(A_2))\, e^{-\lambda \int_0^a C(s)ds}, & A_2 < a \leq A_3, \\
(1 - V_1 C(A_1))\,(1 - V_2 C(A_2))\,(1 - V_3 C(A_3))\, e^{-\lambda \int_0^a C(s)ds}, & A_3 < a < \infty,
\end{cases}
\tag{5}
$$

and

$$
i(a) = e^{-\gamma_H a} \int_0^a \lambda C(s) u(s) e^{\gamma_H s} ds
\tag{6}
$$

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so that the densities of the total numbers of unaffected and infectious are respectively

$$U_H(a) = \mu_H N_H e^{-\mu_H a} u(a),$$

$$I_H(a) = \mu_H N_H e^{-(\mu_H + \gamma_H)a} \int_0^a \lambda C(s) u(s) e^{\gamma_H s} ds. \qquad (7)$$

Note that the equilibrium fraction of infected humans is

$$\frac{1}{N_H} \int_0^\infty I_H(a) da = \frac{1}{\mu_H + \gamma_H} \int_0^\infty \lambda C(a) u(a) \mu_H e^{-\mu_H a} da. \qquad (8)$$

For the human population to reach a steady-state age distribution the mosquito population also needs to be at its equilibrium, therefore the exposed and infectious mosquitoes satisfy

$$L_M + I_M = \frac{cq}{\mu_M} \frac{1}{N_H} \int_0^\infty I_H(a) da \ S_M,$$

$$= \frac{cq}{\mu_M} \frac{1}{N_H} \int_0^\infty I_H(a) da \ (N_M - (L_M + I_M)),$$

from $\frac{dS_M}{dt} = 0$. Hence solving for $L_M + I_M$ gives

$$L_M + I_M = \frac{cqm \int_0^\infty I_H(a) da}{\mu_M + cq \frac{1}{N_H} \int_0^\infty I_H(a) da},$$

where $m = \frac{N_M}{N_H}$ the ratio of mosquitoes to humans. I_M further satisfies

$$I_M = \frac{cq}{\mu_M} e^{-\mu_M \tau} \frac{1}{N_H} \int_0^\infty I_H(a) da \ S_M,$$

$$= e^{-\mu_M \tau} (L_M + I_M)$$

from $\frac{dI_M}{dt} = 0$.

Using these results in the definition of $\lambda(t)$ the steady-state force of infection is given by

$$\lambda = \frac{q^2 bcm e^{-\mu_M \tau} \frac{1}{N_H} \int_0^\infty I_H(a) da}{\mu_M + qc \frac{1}{N_H} \int_0^\infty I_H(a) da}.$$

This expression can be written in terms of the basic reproduction number R_0 which MacDonald [35] found to be

$$R_0 = \frac{q^2 bcm e^{-\mu_M \tau}}{(\mu_H + \gamma_H) \mu_M}, \qquad (9)$$

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so that using (8) for $\frac{1}{N_H} \int_0^\infty I_H(a)da$ the steady-state force of infection satisfies

$$1 = \frac{R_0 \int_0^\infty C(a)u(a)\mu_H e^{-\mu_H a} da}{1 + \frac{qc}{(\mu_H + \gamma_H)\mu_M} \int_0^\infty \lambda C(a)u(a)\mu_H e^{-\mu_H a} da}. \tag{10}$$

4. Serotype-specific Reproduction Numbers

In order to find the steady-state force of infection for a given vaccination strategy using equation (10) for each of the four Dengue serotypes the serotype-specific basic reproduction numbers R_0^i are required. We have found estimates for these reproduction numbers from the initial exponential phase of outbreaks following the approach of Massad et al. [36].

Massad et al. [36] found an expression for the estimate of R_0 by linearisation of the differential equations for the age-independent proportions of infected humans and infectious mosquitoes at the beginning of an epidemic. The expression for R_0 in terms of λ where λ is the exponential growth rate at the beginning of an outbreak is given by

$$R_0 = \frac{(\lambda + \mu_M)(\lambda + \mu_H + \gamma_H)}{(\mu_H + \gamma_H)\mu_M}. \tag{11}$$

The parameter values $\mu_M = 2.50 \times 10^{-2}$ day^{-1}, $\mu_H = 3.72 \times 10^{-5}$ day^{-1}, and $\gamma_H = 0.14$ day^{-1} were chosen from the literature [37, 38]. λ can be found by fitting the number of new cases from an outbreak to an exponential curve for datasets of each serotype.

We used Dengue case numbers separated by serotype provided by the Brazilian Ministry of Health (SINAN) to find the first twelve weeks of each major outbreak in Brazil in the years from 2000 to 2014. We then found the corresponding outbreak period in each of five regions (North, Northeast, South, Southeast and Centre-West) to obtain upper and lower bounds for the growth rate λ and hence upper and lower bounds for the serotype-specific basic reproduction numbers for each of the Dengue virus serotypes (denoted DENv1–DENv4) and each outbreak. While there were four major outbreaks during the surveyed period for DENv1–DENv3, DENv4 only re-emerged in Brazil in 2010 [39] and is responsible for two major epidemics in 2012 and 2013. The mean of the basic reproduction numbers of the considered outbreaks are taken as the serotype-specific reproduction number, while the lowest and highest values in the regions are considered upper and lower

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Table 2: Serotype-specific Basic Reproduction Numbers

Serotype	R_0	lower bound	upper bound
DENv1	3.3939	1.1898	4.2732
DENv2	2.4726	1.3141	5.3608
DENv3	3.2421	1.3621	7.2837
DENv4	3.2066	1.6684	3.5919

bounds. The resulting serotype-specific reproduction numbers with upper and lower bounds from the regions are given in Table 2.

Note that these results highly depend on which weeks are considered to correspond to the initial phase of an outbreak. This cannot be determined exactly and usually differs for each of the regions due to different climatic conditions. However, the results seem to be in agreement with previous estimations of basic reproduction numbers for Dengue [40, 41].

5. Lifetime Expected Risk E

Using the above transmission model with the given vaccination ages we now want to find the lifetime expected risk E for an individual that is born into the population in order to choose vaccination ages that will minimise this risk. The risk will be the total risk from infection that an individual is exposed to during their lifetime, i.e. the probability $P(a)$ of getting infected at any given age a, multiplied by the risk $R(a)$ an infection at this age poses, multiplied by the probability $e^{-\mu_H a}$ of being alive at age a. This definition of the lifetime expected risk differs from that used by Hethcote [1] which does not include the survival probability and thus leads to overestimation. Hethcote's definition of the lifetime risk was also used by Massad et al. [42] in designing vaccination programs against Rubella, by Zanetta et al. [43] in designing optimal vaccination ages for Measles and by Amaku, Coudeville and Massad [44] in designing vaccination programs against Dengue [44]. While in many countries Dengue is primarily considered a childhood disease it does affect people of all ages [11]. In fact, as is the case with many diseases, the risk associated with infection while fairly low for young adults and middle-aged people significantly increases again at older ages. Also as we shall see later when we are considering the risks such as hospitalisation, including the survival probability can make a big difference. However, this increased risk should not be overrated in comparison to the risk of Dengue at young ages

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since few people live very long lives and it is therefore important to include the survival probability when calculating the lifetime expected risk.

For a scenario where only one serotype exists we know from the transmission model that the risk of getting infected at age a is given by $\lambda C(a)u(a)$ where λ is the steady-state force of infection found as described in the previous section. Therefore the lifetime expected risk from Dengue when only one serotype, e.g. the serotype DENv1, is in circulation is:

$$E^1 = \lambda_1 \int_0^\infty R_1(a)C_1(a)u_1(a)e^{-\mu_H a}da. \tag{12}$$

When considering more than one serotype with independent transmission dynamics the lifetime expected risk becomes the sum of the risks of possible infection successions. The independence of the transmission of each serotype means that the probability of getting infected with serotype i at age a is $\lambda_i C_i(a)u_i(a)$ while the probability of not having been infected up to age a corresponds to $u_i(a)$, the proportion of unaffected at age a, and hence the probability of having been infected up to age a is $1 - u_i(a)$ for each serotype. Therefore for two serotypes the probability $P_{ij}(a)$ of getting infected with serotype i at age a after previously having been infected with serotype j is given by

$$P_{ij}(a) = \lambda_i C_i(a)u_i(a)(1 - u_j(a)),$$

while the probability $P_{i\bar{j}}(a)$ of getting infected with serotype i at age a without ever having been infected with serotype j is

$$P_{i\bar{j}}(a) = \lambda_i C_i(a)u_i(a)u_j(a).$$

The risk functions $R_{ij}(a)$ and $R_{i\bar{j}}(a)$ describe respectively the risk that an infection with serotype i poses after having been and not having been infected with serotype j before. We will denote the expected risk of getting infected with serotype i at age a by

$$E_i^{\mathrm{last}}(a) = R_{ij}(a)P_{ij}(a) + R_{i\bar{j}}(a)P_{i\bar{j}}(a)$$

so that the lifetime expected risk for two coexistent Dengue serotypes, e.g. serotypes 1 and 2, is

$$E^{12} = \int_0^\infty \left[E_1^{\mathrm{last}}(a) + E_2^{\mathrm{last}}(a) \right] e^{-\mu_H a}da. \tag{13}$$

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Similarly for three serotypes the probabilities of getting infected with serotype i at age a after previous infections with serotypes j and k, previous infection with serotype j only, or no previous infection are given by

$$P_{ijk}(a) = \lambda_i C_i(a) u_i(a)(1 - u_j(a))(1 - u_k(a)),$$
$$P_{ij\bar{k}}(a) = \lambda_i C_i(a) u_i(a)(1 - u_j(a)) u_k(a), \text{ and}$$
$$P_{i\bar{j}\bar{k}}(a) = \lambda_i C_i(a) u_i(a) u_j(a) u_k(a)$$

respectively. The corresponding risk functions are denoted by $R_{ijk}(a)$, $R_{ij\bar{k}}(a)$, $R_{i\bar{j}\bar{k}}(a)$ respectively and the expected risk from getting infected with serotype i at age a by

$$E_i^{\text{last}}(a) = R_{ijk}(a) P_{ijk}(a) + R_{ij\bar{k}}(a) P_{ij\bar{k}}(a) + R_{i\bar{j}k}(a) P_{i\bar{j}k}(a) + R_{i\bar{j}\bar{k}}(a) P_{i\bar{j}\bar{k}}(a).$$

The lifetime expected risk for three Dengue serotypes, e.g. serotypes 1, 2 and 3, is then

$$E^{123} = \int_0^\infty \left[E_1^{\text{last}}(a) + E_2^{\text{last}}(a) + E_3^{\text{last}}(a) \right] e^{-\mu_H a} da. \tag{14}$$

Note that for $P_{ijk}(a)$ and the associated risk $R_{ijk}(a)$ the order of the previous infections with serotypes j and k is not relevant. This is the case because independently of the order of previous infections an individual with this history is expected to have antibodies against both serotypes j and k for the remainder of their life.

For four Dengue serotypes the probabilities of infection with serotype i after three heterologous previous infections, two heterologous previous infections, one heterologous previous infection, or no previous infection are analogously given respectively by

$$P_{ijkl}(a) = \lambda_i C_i(a) u_i(a)(1 - u_j(a))(1 - u_k(a))(1 - u_l(a)),$$
$$P_{ijk\bar{l}}(a) = \lambda_i C_i(a) u_i(a)(1 - u_j(a))(1 - u_k(a)) u_l(a),$$
$$P_{ij\bar{k}\bar{l}}(a) = \lambda_i C_i(a) u_i(a)(1 - u_j(a)) u_k(a) u_l(a), \text{ and}$$
$$P_{i\bar{j}\bar{k}\bar{l}}(a) = \lambda_i C_i(a) u_i(a) u_j(a) u_k(a) u_l(a)$$

with corresponding associated risk functions $R_{ijkl}(a)$, $R_{ijk\bar{l}}(a)$, $R_{ij\bar{k}\bar{l}}(a)$ and $R_{i\bar{j}\bar{k}\bar{l}}(a)$. The expected risk from infection with serotype i at age a in this case is defined as

$$E_i^{\text{last}}(a) = R_{ijkl}(a) P_{ijkl}(a) + R_{ijk\bar{l}}(a) P_{ijk\bar{l}}(a) + R_{ijl\bar{k}}(a) P_{ijl\bar{k}}(a) + R_{ikl\bar{j}}(a) P_{ikl\bar{j}}(a)$$
$$+ R_{ij\bar{k}\bar{l}}(a) P_{ij\bar{k}\bar{l}}(a) + R_{ik\bar{j}\bar{l}}(a) P_{ik\bar{j}\bar{l}}(a) + R_{il\bar{j}\bar{k}}(a) P_{il\bar{j}\bar{k}}(a) + R_{i\bar{j}\bar{k}\bar{l}}(a) P_{i\bar{j}\bar{k}\bar{l}}(a)$$

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so that the expected lifetime risk when all four Dengue serotypes coexist is given by

$$E^{1234} = \int_0^\infty \left[E_1^{\text{last}}(a) + E_2^{\text{last}}(a) + E_3^{\text{last}}(a) + E_4^{\text{last}}(a) \right] e^{-\mu_H a} da. \qquad (15)$$

The associated risk functions $R(a)$ are an important factor when minimising the lifetime expected risk and need to be chosen so that the adverse effects due to infection at age a are measured. One possible choice is the probability of hospitalisation due to infection for any given age, but also the probability of severe symptoms, or the probability of death could be used. If infection is considered to be equally serious at any age or the risk is simply considered to be getting infected $R(a) = 1$ can be chosen. When several serotypes coexist the risk functions can also be used to incorporate the fact that an infection with any serotype is usually harmless if no heterologous infection was acquired before, hence for two serotypes $R_{i\bar{j}}(a) = 0$ could be used if an infection which does not lead to DHF or DSS is considered to be harmless. Similarly the risk functions $R(a)$ can be used to incorporate no symptomatic Dengue infections after the second. If two heterologous infections are assumed to result in no subsequent symptomatic Dengue infections $R_{ijk}(a) = 0$ can be used in the case of three serotypes and $R_{ijkl}(a) = R_{ijk\bar{l}}(a) = 0$ in the case of four serotypes.

6. Results

We now present optimal vaccination ages for Dengue obtained numerically by evaluating the expressions for the lifetime expected risk introduced in Section 5. In order to find this risk the steady-state force of infection λ needs to be computed for each serotype separately since our model assumes independent transmission dynamics irrespective of the number of serotypes in circulation. While most of the parameters required for the calculations are equal for all serotypes, the basic reproduction numbers are different. These serotype-specific reproduction numbers were found from the initial phases of major outbreaks in Brazil from 2000 to 2014 as discussed in Section 4. The death rates μ_H and μ_M of humans and mosquitoes, as well as the recovery rate γ_H for humans were already used to calculate the basic reproduction numbers and are given in Section 4. The remaining model parameters $m = 1.5$ (the number of vectors per host), $\tau = 7$ days (the latency period in mosquitoes), $b = 0.6$ and $c = 1$ (the transmission probabilities from mosquitoes to humans

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and vice versa), which are needed to find the biting rate q from eq. (9) and hence λ, are taken from literature [37, 45]. b, c and τ are assumed to be equal for all serotypes. m is taken as the middle value of the range given in [45].

Dengvaxia, currently the only available vaccine against Dengue, is licensed for individuals aged between 9 and 45 years and is being administered in three doses with 6 months between each dose. Based on this strategy we consider fractions V_i to be vaccinated at ages A_1, $A_2 = A_1 + 6$ and $A_3 = A_1 + 12$ months. However, we allow vaccination to start between the ages of 0 and 900 months, i.e. immediately after birth up to the age of 75 years. This interval is chosen in order to determine whether the prevailing guidelines make it possible to achieve minimal lifetime expected risk. The fractions V_i are assumed to be equal for each dose but incorporate the efficacy of the vaccine. Dengvaxia is a tetravalent vaccine and thus aims to protect against all four serotypes. However, in two separate phase three trials [30, 31] the vaccine efficacy was not only found to be dependent on the serotype, but these serotype-specific efficacies were also found to be different for the age-groups of participants under 9 years and 9 years or older. The efficacies obtained from the pooled data as presented by Hadinegoro et al. [30] are summarised in Table 3. The vaccinated fractions V_i for each serotype are then calculated using the relation $V_i = 1 - (1 - eff)^{\frac{1}{3}}$ where eff is the vaccine efficacy for that serotype as given in Table 3. When considering the change in efficacy based on the age-groups the fraction vaccinated at each dose will depend on the age at which the dose is administered, i.e. $V_1 = V_2 \neq V_3$ if $A_1 \in [8, 8.5)$ years and $V_1 \neq V_2 = V_3$ if $A_1 \in [8.5, 9)$ years. The results we present below will consider both constant efficacies and efficacies by age-groups as in Table 3.

Table 3: Vaccine Efficacies as found by Hadinegoro et al. [30]

Serotype	age-independent eff	under 9 years eff	9 years or older eff
DENv1	54.7%	46.6%	58.4%
DENv2	43.0%	33.6%	47.1%
DENv3	71.6%	62.1%	73.6%
DENv4	76.9%	51.7%	83.2%

The optimal vaccination strategy will highly depend on what is considered to be the risk of Dengue. An infection with Dengue can progress without noticeable symptoms or, as mentioned before, severe symptoms leading to

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DHF, DSS, and even to death can be observed. Hethcote [1] noted in his paper on Measles vaccination that setting $R(a) = 1$ describes a scenario where getting infected by itself is already considered undesirable. For the case of Dengue this choice is not particularly reasonable since many cases are asymptomatic [46] and thus do not pose a significant threat to the infected individual. We will therefore examine how the optimal vaccination ages are influenced when the risk of an infection is taken to be the probability of being hospitalised due to the severity of the symptoms, or of dying due to an infection. Note that there is some degree of correlation between these two risk measures since most Dengue cases leading to death are treated in hospital prior to death.

There are several other factors worth considering when it comes to calculating the lifetime expected risk. In most endemic areas there are several of the serotypes co-circulating and while infection with a given serotype leads to lifelong immunity it is possible for individuals to be infected with any of the other serotypes after a short period of cross-immunity. Many scientists think that these secondary infections are indeed more dangerous than an initial infection [14] and some argue that there is enough evidence that third and fourth infections do not lead to symptomatic cases [15, 16]. We want to explore the optimal vaccination ages when the actual transmission dynamics agree with these theories. For both of the chosen risk-measures we will therefore find the optimal vaccination ages for the case of risk-free primary infections, no subsequent symptomatic Dengue infection after a secondary infection and the combination of both of these, i.e. the only risky infection is considered to be the secondary one. The results are presented in the next two subsections first for hospitalisation and subsequently for lethality. In these subsections all cases that require vaccination outwith the range of 9-45 years for which Dengvaxia is licensed to minimise the lifetime expected risk are re-examined to compare with the minimum lifetime expected risk that can be achieved by vaccinating in this age-range.

6.1. Hospitalisation

To begin with we consider the risk of Dengue to be the probability of hospitalisation. Burattini et al. [47] used data provided by SINAN to evaluate the cases of hospitalisation by age. We used their data to find the risk function $R(a)$ describing the undesirability of Dengue in terms of hospitalisation by fitting a piecewise function and assuming the risk to remain constant for ages above the highest age of the recorded data. The hospitalisation

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percentage is clearly highest at young (0-20 years) and old ages (>70 years) with much lower values inbetween. In fact, the risk increases exponentially for adults. We therefore determined the piecewise risk function to be of the form:

$$R(a) = \begin{cases} 0.09201ae^{-0.1828a}, & 0 \leq a < 20, \\ 0.02440e^{0.02356a}, & 20 \leq a < 100, \quad \text{for risk of hospitalisation.} \\ 0.02440e^{0.02356\cdot100}, & 100 \leq a < \infty, \end{cases}$$

(16)

Table 4 summarises the optimal vaccination age A_1 in months along with the obtained minimal lifetime expected risk E for vaccination aiming at the reduction of the risk of hospitalisation due to Dengue. The scenarios considered for each specific combination of serotypes are constant efficacy and efficacy based on whether a dose is given before or after the age of 9 years, risky and risk-free primary infections for combinations of at least two serotypes, and asymptomatic tertiary and quaternary infections for combinations of three or four serotypes. Below we discuss the findings presented in Table 4 in detail. Note that while the simulations were carried out for vaccination ages between 0 and 900 months the results presented cover ages between 0 and 300 months for combinations with several coexisting serotypes since the optimal vaccination ages are all fairly low and the behaviour at older vaccination ages is similar to the one that can be observed for a single serotype in existence as presented in Figure 1.

Even though in most endemic areas there are several Dengue serotypes present we first investigate the optimal vaccination ages for each of the serotypes individually. The consequences of the vaccine efficacy and the basic reproduction number are of particular interest in this case. Figure 1 shows the lifetime expected risk as a function of the age at which the first dose of vaccine is administered for each of the serotypes. Figure 1a corresponds to unchanged vaccine efficacies and Figure 1b to vaccine efficacies by age-groups as given in Table 3.

Assuming that the efficacy is the same at any age we can observe from Figure 1a that the lifetime expected risk for all four serotypes reaches its minimum for relatively young vaccination ages, i.e. it is first reached if the initial vaccination dose is given between 9 and 22 months. However, for DENv1 and 2 the lifetime expected risk increases immediately after the optimum is reached, which is not the case for DENv3 and 4. For these two serotypes the
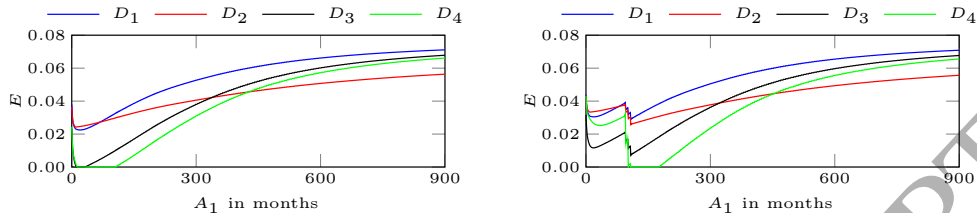
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Table 4: Optimal vaccination age A_1 in months and minimal lifetime expected risk E for vaccination aimed at reducing the risk of hospitalisation due to Dengue. All simulations were done for constant efficacy and efficacy based on age-groups as given by Table 3. Further the impact of considering a primary infection to be free of risk was considered for scenarios where at least two serotypes coexist. Simulations for three and four coexisting serotypes were carried out both for symptomatic and asymptomatic tertiary and quaternary infections, where asymptomaticity reflects that two heterologous infections effectively confer permanent cross-immunity.

	efficacy constant				efficacy based on age-groups			
	1st infection risky		1st infection risk-free		1st infection risky		1st infection risk-free	
	A_1	$E \times 10^{-2}$	A_1	$E \times 10^{-2}$	A_1	$E \times 10^{-2}$	A_1	$E \times 10^{-2}$
DENv1	22	2.25			109	2.91		
DENv2	9	2.42			109	2.60		
DENv3	12-31	0			108	0.74		
DENv4	13-106	0			108-176	0		
DENv12	16	4.70	122	2.85	109	5.51	109	2.53
DENv13	22	2.25	31	1.49	109	3.65	109	1.64
DENv14	22	2.25	105	1.39	109	2.91	174	1.15
DENv23	12	2.43	31	1.68	109	3.34	109	1.72
DENv24	13	2.44	106	1.58	109	2.60	175	1.39
DENv34	13-31	0	13-31	0	108	0.74	108	0.37
DENv123	16	4.70	31	4.00	109	6.25	109	3.72
DENv124	16	4.70	106	3.72	109	5.51	173	3.19
DENv134	22	2.25	31	1.94	109	3.65	109	2.02
DENv234	13	2.44	13	2.18	109	3.34	109	2.17
DENv1234	16	4.70	31	4.34	109	6.25	109	3.95
DENv123	16	2.62	122	1.84	109	4.08	109	1.55
DENv124	22	2.60	122	1.60	109	3.48	166	1.23
DENv134	22	1.15	33	0.84	109	2.33	109	0.69
DENv234	22	1.24	32	0.94	109	1.93	109	0.76
DENv1234	16	1.20	73	0.80	109	2.91	109	0.61

Row groups: DENv12–DENv1234 (first set) = symptomatic; DENv123–DENv1234 (second set) = asymptomatic; the lower block corresponds to 3rd and 4th infections.

(a) The optimal vaccination age A_1 is 22, 9, 12-31 and 13-106 months for DENv1, 2, 3 and 4 respectively.

(b) The optimal vaccination age A_1 is 109, 109, 108 and 108-176 months for DENv1, 2, 3 and 4 respectively.

Figure 1: The lifetime expected risk E for endemic areas with a single serotype in circulation given as a function of vaccination age A_1 in months which corresponds to the age at which the first of three doses is given. **(a)** shows the risk for constant vaccine efficacies, while **(b)** shows vaccine efficacies depending on the age groups <9 years and $\geq$ 9 years as shown in Table 3. The risk function is given by equation (16).

lifetime expected risk can be reduced to zero if the first dose of vaccination is given at any age between 12 and 31 months, and 13 and 106 months respectively. Further Figure 1a shows that the lifetime expected risk obtained for DENv2 stands out since the curve is much flatter than those for the other serotypes and as a result the lifetime expected risk of getting hospitalised due to an infection with serotype 2 is the highest for all serotypes at young vaccination ages but the lowest if vaccination is initiated later on. These observations can be explained by looking at Tables 2 and 3 to compare respectively the basic reproduction numbers and vaccine efficacies for the four serotypes. The efficacy is lowest for DENv2, followed by DENv1 and with quite significantly higher values by DENv3 and 4, on the other hand the basic reproduction number is by far the lowest for DENv2 with a value of approximately 2.5, while DENv3 and 4 have similar basic reproduction numbers of roughly 3.2 and DENv1 has the highest at almost 3.4. Vaccination leads to a reduction in cases of natural infections the extent of which depends on the effectiveness of the vaccine and the age at which it is administered. If, for example, vaccination is first given late in life the reduction in natural infections may not be significant even if the efficacy was 100% since most people will have already had the infection by the time they get vaccinated, this can be observed in Figure 1a since for all serotypes the lifetime expected risk is very flat at ages above 750 months (62.5 years) independently of the effectiveness of the vaccine. The number of natural infections for each of the serotypes is correlated with the basic reproduction number, therefore what can be seen

from Figure 1a is that while the number of infections for DENv2 is lower due to the lower basic reproduction number the efficacy for this serotype is fairly low as well and therefore the number of infections is only slightly reduced even if the vaccination is started at young ages leading to a comparably flat lifetime expected risk. Similarly the higher efficacy for serotypes 3 and 4 leads to a reduction in cases of these infections which for vaccination at young ages is so significant that the risk of hospitalisation can be reduced to zero. On the other hand at older ages after many natural infections have already occurred the higher efficacy does not reduce the number of infections significantly so that at these ages the lifetime expected risk is higher than for DENv2. For serotype 1 the fairly low efficacy but high basic reproduction number means that only vaccination that takes place very early to prevent many infections can reduce the lifetime expected risk below that of DENv2.

For constant efficacy the optimal vaccination ages are all below 9 years of age which under the current license for Dengvaxia cannot be satisfied, we therefore restrict the possible vaccination strategies to be initiated between 108 and 539 months so that all three vaccination doses are administered before an individual reaches age 46 years. Figure 1a indicates that under these restrictions the optimal vaccination ages for all four serotypes should be 9 years, i.e. 108 months, the exact results from the simulations, owing to the flat objective function and the use of (possibly inaccurate) numerical integration, are 109 months for DENv1, 3 and 4 and 108 months for DENv2. The minimum lifetime expected risk under the age-constraint of the license is significantly higher for all four serotypes, with an increase compared to the values found for optimal vaccination ages of approximately 47% and 24% for DENv1 and 2, the risk for DENv3 and 4 can be entirely eliminated if vaccination starts at 12 and 13 months, while it is 1.05×10^{-2} and 4.19×10^{-4} respectively if the license restrictions are considered. Table 6 on page 38 summarises the comparison of the lifetime expected risk achieved at optimal vaccination age to that achieved under the license restrictions for all scenarios where it differs.

If instead we consider the vaccine efficacy to depend on whether a dose is given before or after 9 years of age Figure 1b has several interesting features while the main observations of the case for constant efficacy are transferable. When none of the vaccination doses is given to children 9 years or older (i.e. $A_1 < 96$ months) the lifetime expected risk is higher than found for constant efficacy with the same vaccination ages since the overall efficacy is lower for all serotypes as can be seen from Table 3. Once the age of the first dose

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increases to 96 months the third dose has the efficacy given in Table 3 for children aged 9 or older and the lifetime expected risk drops since the efficacy of the third dose is now much higher, i.e. significantly more infections will be prevented with the final dose if it is administered to children of at least 9 years. The same happens again once the second dose is administered at age 9 or above and one last time when all three vaccination doses are administered in this age-group. These three drops are obvious in Figure 1b. For $A_1 \geq 108$ months only the efficacy of the second age-group is relevant and it can be observed that the efficacy for DENv4 is is in fact so high in this age group that the lifetime expected risk of an infection with DENv4 is zero if vaccination is initiated between the ages of 108 and 154 months. The optimal vaccination ages are 109 months for DENv1 and 2 and 108 months for DENv3, again we believe that due to the numerical integration the simulation results can be understood in such a way that the minimal lifetime expected risk in all these cases is achieved once the efficacy for all three doses is that for 9 and older.

In summary in an endemic area with only a single serotype in circulation the ages for which Dengvaxia is currently licensed (9-45 years) would be much too high if vaccine efficacy is age-independent, whereas if the efficacy does change at 9 years of age the optimal vaccination ages we found match the licensed ages. Note that while the optimal ages for constant vaccine efficacy lie outside the licensed ages the age-dependent efficacy cases are more realistic and all optimal vaccination ages relating to this are within the permitted range.

Now we will examine the much more realistic cases of several coexisting serotypes in an endemic region. We want to find the optimal vaccination ages for all possible combinations of co-circulating serotypes and investigate how strongly the age depends on whether a primary infection is considered dangerous or not. We in fact expect the optimal vaccination age to be significantly impacted by this since in the case where no risk is attached to a primary infection vaccination will only be beneficial if an individual is likely to get at least two heterologous infections during their lifetime. Results for two, three and all four co-circulating serotypes are shown in Figures 2 to 4 respectively. As before the vaccine efficacy for Figures 2a, 3a and 4a is assumed to be age-independent and for Figures 2b, 3b and 4b the efficacy is based on age-groups of younger than 9 and 9 or older. In both cases the graph at the top shows results when all infections are equally risky, while the bottom graph corresponds to a primary infection being free of risk since an initial infection with any serotype does not lead to significant symptoms.

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For the bottom plots the risk functions for a primary infection are therefore taken to be $R_{i\bar{j}}(a) = 0, R_{i\bar{j}\bar{k}}(a) = 0$ and $R_{i\bar{j}\bar{k}\bar{l}}(a) = 0$ respectively.

To begin with let us consider an endemic area where two serotypes are present. From Table 4 we can see that the optimal vaccination age A_1 depends on the risk associated with a primary infection whether efficacy is based on age-groups or not. When the efficacy is constant and all infections have the same risk the optimal ages range from 12 months for the co-circulation of DENv2 and 3 to 22 months for DENv1 and 3, while the risk for DENv3 and 4 is in fact zero for A_1 between 13 and 31 months, i.e. for the ages at which both the risks for DENv3 and DENv4 were found to be eradicated. On the other hand, if a primary infection is risk-free the ages for all combinations of two serotypes apart from DENv3 and 4 significantly increase and range from 31 months for DENv1 and 3 (and DENv2 and DENv3) to 122 months for DENv1 and 2. For these serotype-combinations the combined efficacy is fairly low so that while the average age is increased due to vaccination not enough infections are prevented and the lifetime expected risk is higher if vaccines are administered too early. The reason for the optimal age being unchanged for DENv3 and 4 lies with the high efficacy for both these serotypes since the number of prevented primary infections and secondary infections is so significant that the risk can be eliminated.

This is no longer the case if efficacy is assumed age-dependent both for risky and risk-free primary infections because the combined efficacy is lower in this case until all doses are given to children aged at least 9 years and therefore too many natural infections to eliminate the risk already occur before the higher efficacy is achieved. The optimal vaccination age in these cases is therefore 108 months. For risky primary infections the remaining serotype combinations require vaccination at 109 months, while for risk-free ones the combinations of DENv1 and 4 and DENv2 and 4 have optimal vaccination ages 174 and 175 months respectively. In any case the lifetime expected risk is lower if a primary infection is considered risk-free since only subsequent infections contribute to the risk. As was the case for a single serotype age-dependent efficacy results in optimal vaccination ages of approximately 9 years for every scenario, for constant efficacy the optimal vaccination ages under the restrictions of the current license are 109 months for all combinations apart from DENv1 and 2 when primary infections are risk-free which leads to minimal lifetime expected risk at 122 months as before as shown in Table 6. The lifetime expected risk increases up to 93% compared to the values found for low vaccination ages in all cases where elimination of

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the risk was not possible, for the combination of DENv3 and 4 it increases from zero to 1.09×10^{-3} for risky primary infections and to 5.05×10^{-3} for risk-free ones. Note that these results indicate that the specific combination of serotypes in an endemic region needs to be considered before vaccination programmes can be chosen adequately independently of whether efficacy is age-dependent or not, particularly when primary infections are risk-free.
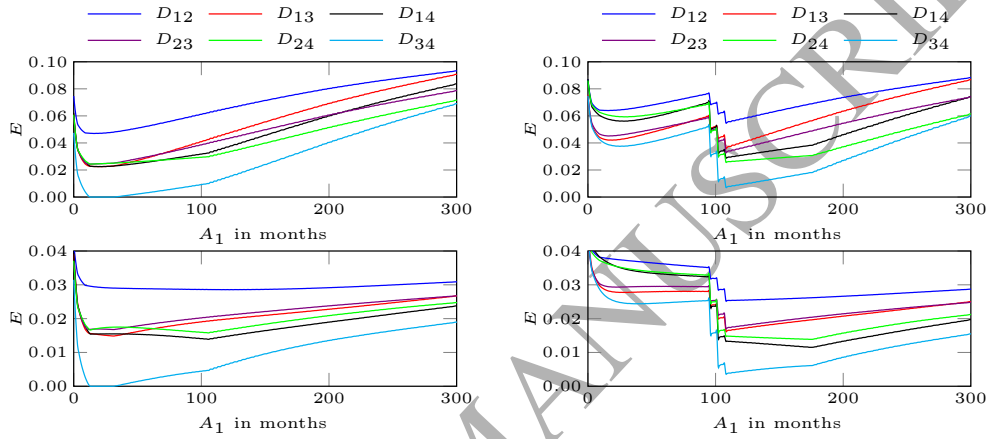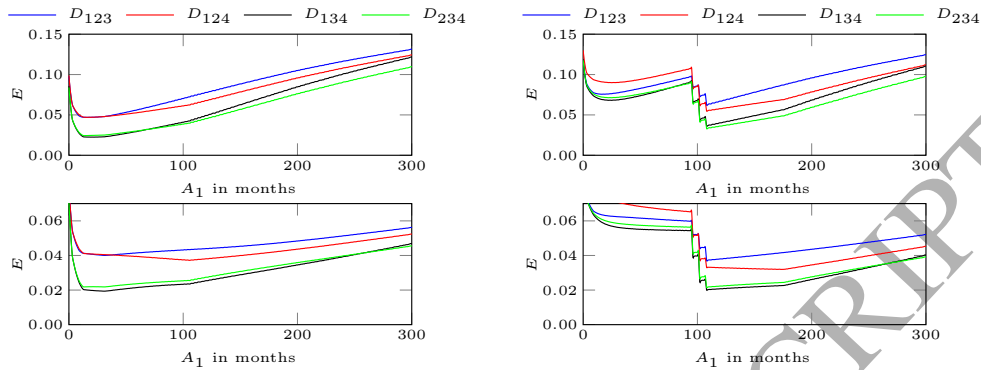

(a) Top: The optimal vaccination age A_1 is 16, 22, 22, 12, 13 and 13-31 months for DENv12, DENv13, DENv14, DENv23, DENv24 and DENv34 respectively. Bottom: The optimal vaccination age A_1 is 122, 31, 105, 31, 106 and 13-31 months for DENv12, DENv13, DENv14, DENv23, DENv24 and DENv34 respectively.

(b) Top: The optimal vaccination age A_1 is 109 months for combinations DENv12, DENv13, DENv14, DENv23 and DENv24, and 108 months for DENv34 respectively. Bottom: The optimal vaccination age A_1 is 109, 109, 174, 109, 175 and 108 months for DENv12, DENv13, DENv14, DENv23, DENv24 and DENv34 respectively.

Figure 2: The lifetime expected risk E for endemic areas with two serotypes in circulation given as a function of vaccination age A_1 in months which corresponds to the age at which the first of three doses is given. **(a)** shows the risk for constant vaccine efficacies, while **(b)** shows vaccine efficacies depending on the age groups <9 years and ≥ 9 years as shown in Table 3. The graphs at the top show results for each infection having the risk function given by equation (16), while the ones at the bottom assume $R(a) = 0$ for a primary infection. DENvij denotes the co-circulation of serotypes i and j.

For three and four serotypes co-circulating the results are fairly similar to those of two serotypes as can be seen from Figures 3 and 4. For constant efficacy the optimal vaccination ages increase for risk-free primary infections. The only scenario where the age is unchanged is the co-circulation of DENv2, 3 and 4 due to the combination of high efficacies for DENv3 and 4 and low basic reproduction number of DENv2. For risky primary infections the age ranges from 13 to 22 months, while for risk-free ones the age ranges from 13 to 106 months if efficacy is constant. For efficacy based on the age-

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(a) Top: The optimal vaccination age A_1 is 16, 16, 22 and 13 months for DENv123, DENv124, DENv134 and DENv234 respectively. Bottom: The optimal vaccination age A_1 is 31, 106, 31 and 13 months for DENv123, DENv124, DENv134 and DENv234 respectively.

(b) Top: The optimal vaccination age A_1 is 109 months for all combinations DENv123, DENv124, DENv134 and DENv234 respectively. Bottom: The optimal vaccination age A_1 is 109 for DENv123, DENv124 and DENv234 respectively, and 173 months for DENv134.

Figure 3: The lifetime expected risk E for endemic areas with three serotypes in circulation given as a function of vaccination age A_1 in months which corresponds to the age at which the first of three doses is given. **(a)** shows the risk for constant vaccine efficacies, while **(b)** shows vaccine efficacies depending on the age groups <9 years and ≥ 9 years as shown in Table 3. The graphs at the top show results for each infection having the risk function given by equation (16), while the ones at the bottom assume $R(a) = 0$ for a primary infection. DENvijk denotes the co-circulation of serotypes i, j and k.

groups risky primary infections all lead to optimal vaccination age of 109 months and risk-free ones to ages between 109 and 173 months and the drops caused by the increased efficacy are again obvious. It is noteworthy that near-optimal vaccination can be achieved for a much larger age-range if a primary infection considered free of risk and efficacy is constant when all four serotypes are present. The same is true for certain combinations of fewer serotypes such as DENv1, 3 and 4 or DENv1 and 2. If efficacy is based on age groups near-optimal lifetime expected risk is indeed achieved for wider age-ranges in almost every case. The increase in optimal age for risk-free primary infections is because vaccination is only sensible if individuals are infected at least twice, so that vaccination is ideal if it reduces the number of secondary infections. It can also be seen from these results that the current ages for which Dengvaxia is licensed are much too high to achieve minimal lifetime expected risk unless efficacy depends on the age at which each dose is given. By limiting the possible vaccination ages to conform to the current license again the vaccination should take place at approximately 9 years of

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age, i.e. in all cases the age increases to 109 months with lifetime expected risk increases varying significantly as presented in Table 6, e.g by less than 1% for DENv1, 2 and 4 with risk-free primary infections but up to 95% for the combination of serotypes 1, 3 and 4 when primary infections are risky.
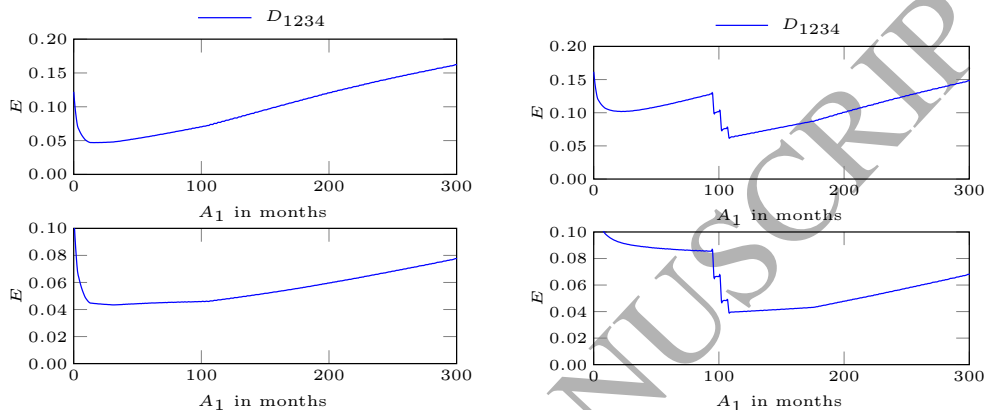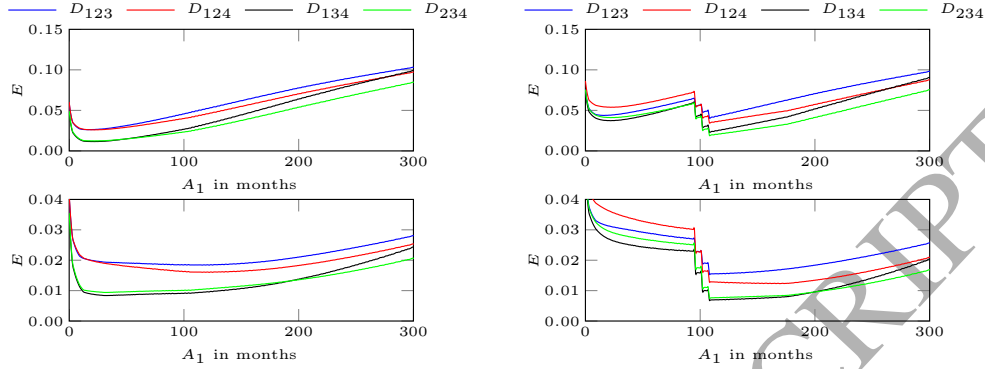

(a) Top: The optimal vaccination age A_1 is 16 months. Bottom: The optimal vaccination age A_1 is 31 months.

(b) Top: The optimal vaccination age A_1 is 109 months. Bottom: The optimal vaccination age A_1 is 109 months.
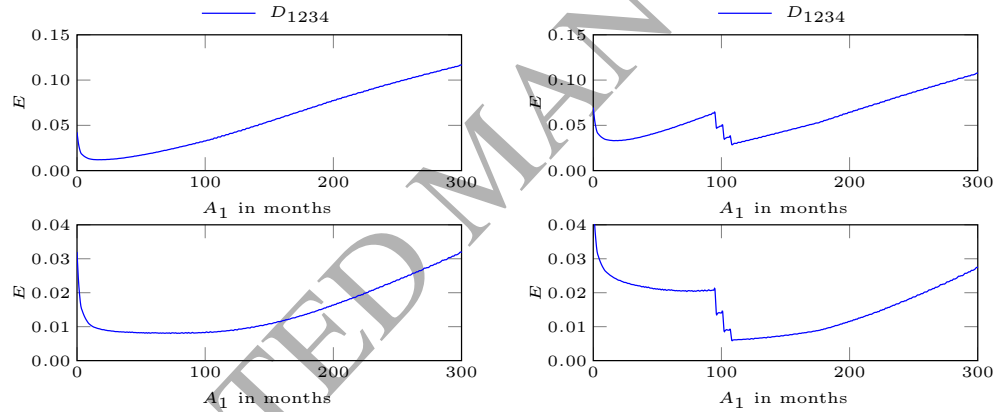
Figure 4: The lifetime expected risk E for endemic areas with all four serotypes in circulation given as a function of vaccination age A_1 in months which corresponds to the age at which the first of three doses is given. **(a)** shows the risk for constant vaccine efficacies, while **(b)** shows vaccine efficacies depending on the age groups <9 years and ≥ 9 years as shown in Table 3. The graphs at the top show results for each infection having the risk function given by equation (16), while the ones at the bottom assume $R(a) = 0$ for a primary infection.

Many models so far assume complete immunity after two infections with heterologous serotypes [17, 18] based on studies reporting that third and fourth infections do not cause clinical disease [15, 16, 48]. We will therefore investigate how the optimal vaccination ages for three and four coexisting serotypes change. This will change the risk function for getting infected which is used to calculate E for third and fourth infections such that $R_{ijk}(a) = 0$ for three and $R_{ijk\bar{l}}(a) = 0$ and $R_{ijkl}(a) = 0$ for four co-circulating serotypes. Asymptomatic third and fourth infections will certainly lead to a lower lifetime expected risk since only primary and secondary infections contribute to it. Note that asymptomatic third and fourth infections implies that vaccination after a secondary infection will no longer have any effect. Our results are shown in Figure 5. We can immediately see that the lifetime expected risk is indeed lower if third and fourth infections are asymptomatic and that

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(a) Top: The optimal vaccination age A_1 is 16 months for DENv123, and 22 months for DENv124, DENv134 and DENv234 respectively. Bottom: The optimal vaccination age A_1 is 122, 122, 33 and 32 months for DENv123, DENv124, DENv134 and DENv234 respectively.

(b) Top: The optimal vaccination age A_1 is 109 months for all combinations DENv123, DENv124, DENv134 and DENv234 respectively. Bottom: The optimal vaccination age A_1 is 109 months for DENv123, DENv134 and DENv234 respectively, and 166 months for DENv124.

(c) Top: The optimal vaccination age A_1 is 16 months. Bottom: The optimal vaccination age A_1 is 73 months.

(d) Top: The optimal vaccination age A_1 is 109 months. Bottom: The optimal vaccination age A_1 is 109 months.

Figure 5: The lifetime expected risk E for endemic areas with three or four serotypes in circulation given as a function of vaccination age A_1 in months which corresponds to the age at which the first of three doses is given. It is assumed that secondary infections lead to no subsequent symptomatic infections for all other serotypes so that $R_{ijk}(a) = 0$ for third and $R_{ijkl}(a) = 0$ and $R_{ijk\bar{l}}(a) = 0$ for fourth infections. **(a)** and **(c)** show the risk for constant vaccine efficacies for three and four serotypes, while **(b)** and **(d)** show vaccine efficacies depending on the age groups <9 years and $\geq$ 9 years as shown in Table 3. The graphs at the top show results for each primary and secondary infection having the risk function given by equation (16). The ones at the bottom assume $R_i(a) = 0$ for a primary infection.

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there is fairly little change in optimal vaccination ages in comparison to the previous results independently of the number of serotypes circulating or whether efficacy is constant or based on age-groups. The only exceptions to this are DENv1, 2, 3 and all serotypes coexisting if efficacy is constant and primary infections are risk-free. In these two cases the assumption of asymptomatic third and fourth infections leads to an increased optimal vaccination age. However, in both cases the lifetime expected risk is in fact near-optimal for a significant age-range that includes similarly low ages as found for the same combinations if third and fourth infections are symptomatic. For three serotypes from Figure 5a we can see that if the vaccine efficacy is constant and a primary infection is risky the optimal ages are still very low between 16 and 22 months, while for risk-free primary infections the optimal vaccination ages range from 32 to 122 months. Similarly for four serotypes Figures 5c and 5d show that the optimal vaccination ages are 16 and 73 months for risky and risk-free primary infections for constant efficacy. The optimal age if efficacy is age-dependent is 109 months for all four serotypes and for all combinations of three serotypes apart from DENv1, 2 and 4 co-circulating for risk-free primary infections which requires vaccination at 166 months. Again we compare the achieved lifetime expected risk at the best age to that achieved if the age is limited to the license. As was the case for symptomatic tertiary and quaternary infections we only need to consider the case of constant efficacy since all results for age-dependent efficacy already satisfy the restriction, the results are similar albeit the percentage increase of the lifetime expected risk is much higher in some cases as can be seen in Table 6.

6.2. Lethality

In this section we consider lethality as the risk of a Dengue infection, i.e. the goal of vaccination is to reduce the probability of death due to Dengue for the population. We found the risk function based on lethality from unpublished data [49] similarly to that for hospitalisation in Section 6.1. The risk of lethality is always significantly lower than that of hospitalisation as expected. However, if considering lethality the risk for individuals at older ages is significantly higher than for any other age-group including children and teenagers which is not the case for hospitalisation. The risk of lethality

is given by:

$$R(a) = \begin{cases} 6.995 \times 10^{-4} ae^{-0.2418a}, & 0 \le a < 20, \\ 3.236 \times 10^{-5} e^{0.06633a}, & 20 \le a < 100, \\ 3.236 \times 10^{-5} e^{0.06633 \cdot 100}, & 100 \le a < \infty, \end{cases} \quad \text{for risk of death.} \quad (17)$$

Table 5 presents the optimal vaccination age A_1 in months along with the obtained minimal lifetime expected risk E for vaccination aiming at the reduction of the risk of death due to Dengue. In this section we discuss the findings presented in this table in detail in the same manner as for the risk of hospitalisation.
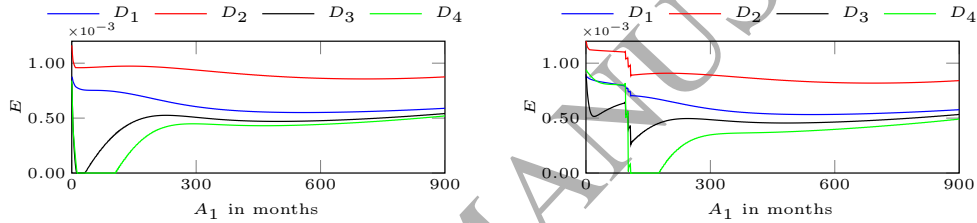
(a) The optimal vaccination age A_1 is 557, 706, 12-31 and 13-106 months for DENv1, 2, 3 and 4 respectively.

(b) The optimal vaccination age A_1 is 544, 693, 108 and 108-176 months for DENv1, 2, 3 and 4 respectively.

Figure 6: The lifetime expected risk E for endemic areas with a single serotype in circulation given as a function of vaccination age A_1 in months which corresponds to the age at which the first of three doses is given. **(a)** shows the risk for constant vaccine efficacies, while **(b)** shows vaccine efficacies depending on the age groups <9 years and ≥ 9 years as shown in Table 3. The risk function is given by equation (17).

Again we start by finding optimal ages for the theoretical scenario of a single Dengue serotype in circulation in order to compare the effect of a constant or age-group based vaccine efficacy for each serotype and restrict the vaccination ages to conform to the license if necessary to evaluate the impact of the licensed age-range as presented in Table 6. The corresponding results are shown in Figures 6a and 6b respectively. For the efficacy being equal at all ages we can see that the lifetime expected risk due to death is eradicated at the same ages as was the case for hospitalisation for DENv3 and 4 if there is no age-restriction. The optimal vaccination ages for serotypes DENv1 and 2 on the other hand are much higher, i.e. 557 months for DENv1 and 706 months for DENv2 and even at these high vaccination ages the lifetime expected risk of death due to serotypes 1 and 2 remains higher than that

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Table 5: Optimal vaccination ages A_1 in months for the initial of three doses and minimal lifetime expected risk E for vaccination aimed at reducing the risk of death due to Dengue. All simulations were done for constant efficacy and efficacy based on age-groups as given by Table 3. Further the impact of considering a primary infection to be free of risk was considered for scenarios where at least two serotypes coexist. Simulations for three and four coexisting serotypes were carried out both for symptomatic and asymptomatic tertiary and quaternary infections, where asymptomaticity reflects that two heterologous infections effectively confer permanent cross-immunity.

	efficacy constant				efficacy based on age-groups			
	1st infection risky		1st infection risk-free		1st infection risky		1st infection risk-free	
	A_1	$E \times 10^{-4}$	A_1	$E \times 10^{-4}$	A_1	$E \times 10^{-4}$	A_1	$E \times 10^{-4}$
DENv1	557	5.51			544	5.32		
DENv2	706	8.57			693	8.19		
DENv3	12-31	0			108	2.71		
DENv4	13-106	0			108-176	0		
DENv12	643	14.12	735	9.49	628	13.57	728	9.02
DENv13	31	7.56	31	5.30	109	9.76	616	5.41
DENv14	106	7.41	105	5.07	176	6.72	176	4.54
DENv23	22	9.59	12	6.70	109	11.61	706	8.59
DENv24	22	9.59	13	6.65	109	8.90	176	6.95
DENv34	13-31	0	13-31	0	108	2.71	108	2.12
DENv123	31	17.15	643	13.82	575	18.20	636	13.16
DENv124	106	17.12	636	13.55	176	15.79	616	12.60
DENv134	31	7.56	31	6.88	109	9.76	108	8.61
DENv234	22	9.59	13	8.70	109	11.61	109	10.62
DENv1234	31	17.15	31	16.65	109	18.66	575	16.51
DENv123	288	7.12	428	2.95	278	6.77	417	2.77
DENv124	280	6.79	423	2.81	109	5.89	400	2.49
DENv134	31	3.61	334	2.06	109	3.69	319	1.79
DENv234	31	4.54	423	2.55	109	4.34	400	2.25
DENv1234	36	2.94	219	1.46	109	2.87	215	1.20

(Row-group labels at left: the DENv123–DENv1234 rows are grouped under "3rd and 4th infections", with the first set labelled "symptomatic" and the second set labelled "asymptomatic".)

of death due to the other two serotypes for similar vaccination ages. This is because of the low efficacy of the vaccine for DENv1 and 2 as well as the high risk of death at older ages. Vaccination aims to decrease the number of infections in the population but increases the average age of infection. Therefore, the optimal vaccination age needs to be chosen so that the benefit of fewer infections outweighs the higher risk if those infections that do occur are at more dangerous ages. Since the efficacy of the vaccine for DENv1 and 2 is fairly low the number of cases will not be reduced as much as for the other serotypes so that vaccination at older ages is more effective. On the other hand the efficacy for DENv3 and 4 is large enough to stop the spread of these serotypes if it is administered early enough. The optimal vaccination ages for DENv1 and 2 are therefore above 45 years, while those for DENv3 and 4 are below 9 years. If the age-range of the license is applied the obtained ages are 538, 539, 108 and 109 months for DENv1, 2, 3 and 4 respectively, i.e. taking the limited precision of the simulations into account the vaccination age can be taken to be 9 years if the optimal one is found to be below this age and 539 months if it is is found to be above this age as can be seen from Table 6. As shown in Figure 6a the percentage increase from the minimal lifetime expected risk is significantly below 1% and approximately 1.6% for DENv1 and DENv2 respectively with the age-restriction applied, for DENv3 and 4 not being able to vaccinate at early ages leads to lifetime expected risks of 3.65×10^{-4} and 1.73×10^{-5} and therefore the license makes it impossible to achieve eradication as is the case otherwise. For efficacy based on age-groups the optimal vaccination age is $A_1 = 108$ months for serotype 3 and $A_1 = 108\text{-}176$ months for serotype 4 similarly to the case of hospitalisation. For serotypes 1 and 2 optimal results are achieved at age $A_1 = 544$ and 693 months respectively which are still very high vaccine ages. The results of restricting the ages to between 108 and 539 months again leads to vaccination ages at the upper limit of the range with hardly any impact on the lifetime expected risk achieved as shown in Table 6. The license restriction only makes it possible to achieve good results for hospitalisation if efficacy is assumed age-dependent. This is not the case for lethality since the achievable lifetime expected risks are very close to the minimal ones for all serotypes when efficacy is age-dependent, and for serotypes 1 and 2 if efficacy is constant. However, if efficacy is assumed constant and DENv3 or 4 are considered to circulate restricting the age leads to comparably bad results.

Now we want to find the optimal vaccination ages for several co-circulating serotypes. Again we will consider how the assumption of a primary infection

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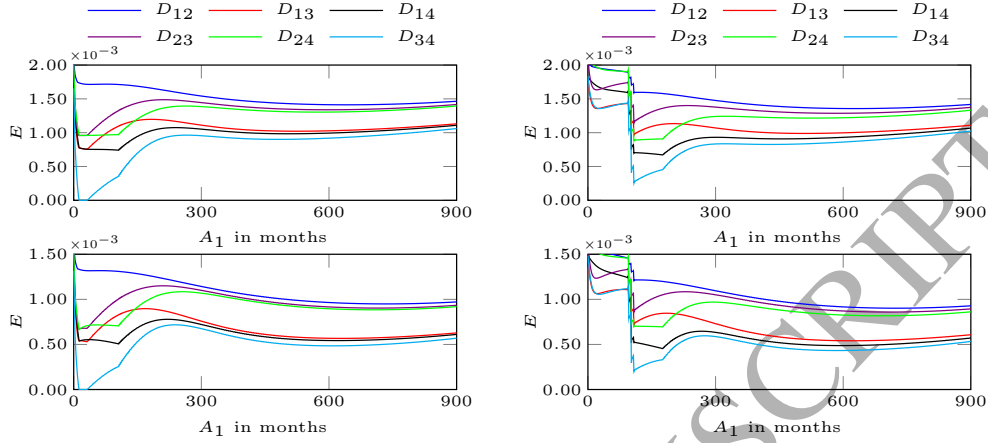
(a) Top: The optimal vaccination age A_1 is 643, 31, 106, 22, 22 and 13-31 months for DENv12, DENv13, DENv14, DENv23, DENv24 and DENv34 respectively. Bottom: The optimal vaccination age A_1 is 735, 31, 105, 12, 13 and 13-31 months for DENv12, DENv13, DENv14, DENv23, DENv24 and DENv34 respectively.

(b) Top: The optimal vaccination age A_1 is 628, 109, 176, 109, 109 and 108 months for DENv12, DENv13, DENv14, DENv23, DENv24 and DENv34 respectively. Bottom: The optimal vaccination age A_1 is 728, 616, 176, 706, 176 and 108 months for DENv12, DENv13, DENv14, DENv23, DENv24 and DENv34 respectively.
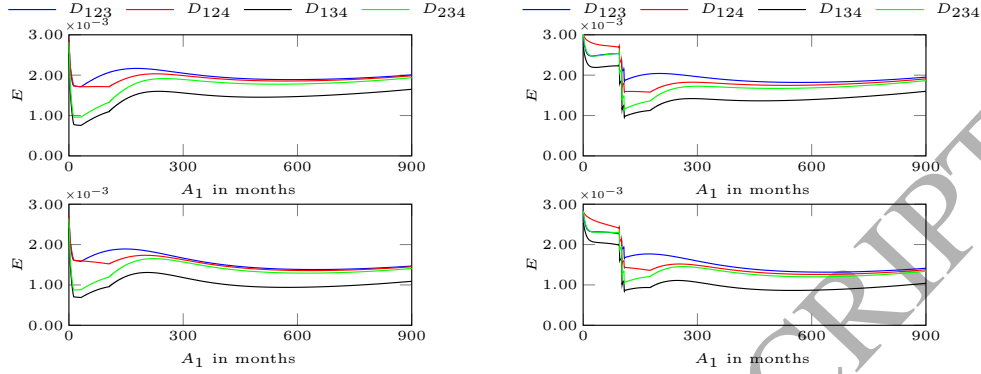
Figure 7: The lifetime expected risk E for endemic areas with two serotypes in circulation given as a function of vaccination age A_1 in months which corresponds to the age at which the first of three doses is given. **(a)** shows the risk for constant vaccine efficacies, while **(b)** shows vaccine efficacies depending on the age groups <9 years and ≥ 9 years as shown in Table 3. The graphs at the top show results for each infection having the risk function given by equation (17), while the ones at the bottom assume $R(a) = 0$ for a primary infection. DENvij denotes the co-circulation of serotypes i and j.

being risk-free affects the optimal ages. The results corresponding to risky primary infections are shown at the top of Figures 7a to 9b and those for risk-free ones at the bottom.

For two coexisting serotypes in an endemic area the optimal vaccination ages very much depend on the serotypes present independently of whether a primary infection is considered risky and whether efficacy is based on age-groups or assumed constant. If serotypes 1 and 2 are coexisting the optimal ages are very high with 643 and 735 months for risky and risk-free primary infections respectively and constant efficacy, similar results are obtained for age-dependent efficacy. For serotypes 1 and 4 coexisting the corresponding ages are 106 and 105 months which is still fairly high and for age-based efficacy the age is 176 months in both cases. All remaining combinations require vaccination between 12 and 31 months if efficacy is constant and serotypes 3 and 4 can be eradicated if vaccination is started at any age between 13 and

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31 months. For age-dependent efficacy these serotype combinations lead to optimal vaccination ages of 108 or 109 months if primary infections are risky and ages between 108 and 706 months otherwise. Interestingly when the results for risky and risk-free primary infections are compared a decrease in optimal ages in some of the cases for constant efficacy can be observed, while age-dependent efficacy leads to an increase in most cases with some ages being unchanged. The results for serotype combinations excluding DENv2, in comparison to those where DENv2 is present can clearly be distinguished in Figures 7a and 7b since those including DENv2 tend to lead to a higher lifetime expected risk due to the low efficacy of serotype 2. Many of the optimal ages found for two serotypes are either below 9 years or above 45 years, so that restricting the ages to the license result in increases from the minimal lifetime expected risk between approximately 0.5 and 39%, apart from serotypes 3 and 4 coexisting for which the risk could be eradicated at young ages, but can now only be reduced to between 2.12×10^{-4} and 3.82×10^{-4} depending on whether efficacy is constant or age-dependent and whether primary infections are risky. The optimal vaccination ages are again the lowest or highest possible in most cases, however, while for hospitalisation ages below 9 years would increase to 9 years and ages above 45 years decrease to 45 years this is no longer the case here, e.g. DENv1 and 3 require vaccination at 31 months for risky and risk-free primary infections and constant efficacy, however limiting the age to between 9 and 45 years results in an optimal age of 519 and 538 months.

We will now consider endemic areas where there are three of four serotypes present. For combinations of three serotypes we can see from Figure 8 that combinations including serotype 2 again lead to a higher lifetime expected risk than that of DENv1, 3 and 4 due to the low efficacy for this serotype. Further the optimal vaccination ages for risky primary infections are between 22 and 106 months for constant efficacy and between 109 and 575 months for age-dependent efficacy. Most of these ages increase if primary infections are considered risk-free to between 31 and 643 months for constant efficacy and 108 and 636 months for age-dependent efficacy, with the combination of DENv2, 3 and 4 being an exception if efficacy is constant where the optimal vaccination age is 13 months for risk-free primary infections. For all four serotypes coexisting and a constant efficacy the the optimal vaccination age is 31 months for both risky and risk-free primary infections. If efficacy is age-dependent the corresponding optimal ages are 109 and 575 months respectively, so that if primary infections are free of risk the optimal age sur-
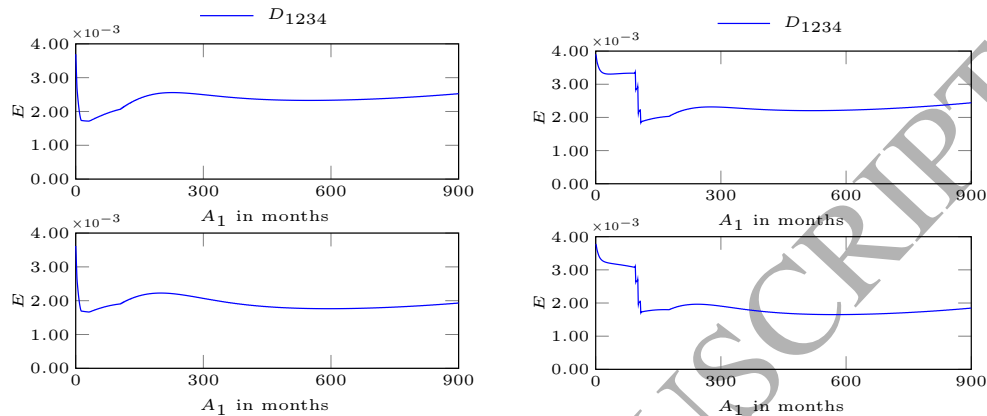
(a) Top: The optimal vaccination age A_1 is 31, 106, 31 and 22 months for DENv123, DENv124, DENv134 and DENv234 respectively. Bottom: The optimal vaccination age A_1 is 643, 636, 31 and 13 months for DENv123, DENv124, DENv134 and DENv234 respectively.

(b) Top: The optimal vaccination age A_1 is 575, 176, 109 and 109 months for DENv123, DENv124, DENv134 and DENv234 respectively. Bottom: The optimal vaccination age A_1 is 636, 616, 108 and 109 months for DENv123, DENv134 and DENv234 respectively.

Figure 8: The lifetime expected risk E for endemic areas with three serotypes in circulation given as a function of vaccination age A_1 in months which corresponds to the age at which the first of three doses is given. **(a)** shows the risk for constant vaccine efficacies, while **(b)** shows vaccine efficacies depending on the age groups <9 years and $\geq$ 9 years as shown in Table 3. The graphs at the top show results for each infection having the risk function given by equation (17), while the ones at the bottom assume $R(a) = 0$ for a primary infection. DENvijk denotes the co-circulation of serotypes i, j and k.

passes the maximum guideline age. For three and four coexisting serotypes and constant efficacy many optimal vaccination ages are below 9 years, while the remaining ones are at least 46 years. Even if efficacy is based on age-groups there are combinations where the optimal age is outwith the currently licensed age-range of 9-45 years. Limiting the age-range to the license again results in the expected shift of vaccination age to approximately 9 years in most cases in which the optimal age was found below this value. An exception to this is seen when the vaccine efficacy is constant for the combination of DENv1, 2 and 3 if a primary infection is considered risky and if it is risk-free for all four serotypes and DENv1, 3 and 4 co-circulating, in those cases the optimal vaccination age increases from 31 to 538 or 539 months with the lifetime expected risk increasing between 6 and 37% as given in Table 6. In the remaining cases the increase from the minimal lifetime expected risk ranges from 22 to 49% for constant efficacy and from 0.2 to 1.3% for age-dependent efficacy. Therefore it can again be said that if efficacy is age-dependent the age-range for which Dengvaxia is licensed makes it possible to achieve near
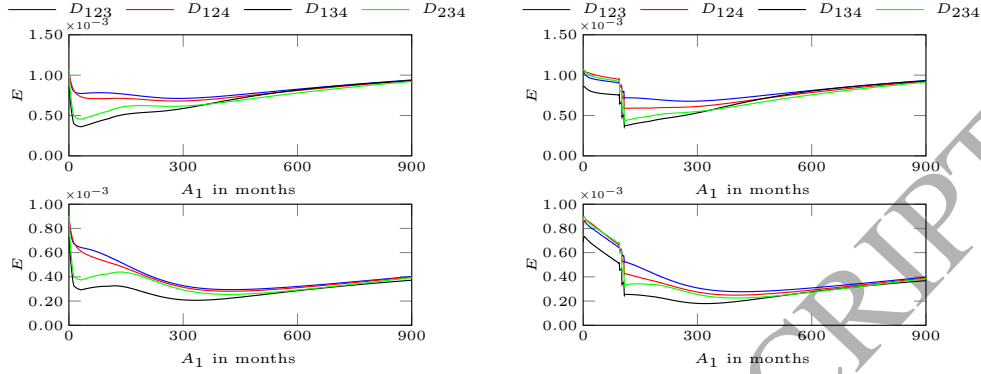
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optimal lifetime expected risk.

(a) Top: The optimal vaccination age A_1 is 31 months. Bottom: The optimal vaccination age A_1 is 31 months.

(b) Top: The optimal vaccination age A_1 is 109 months. Bottom: The optimal vaccination age A_1 is 575 months.
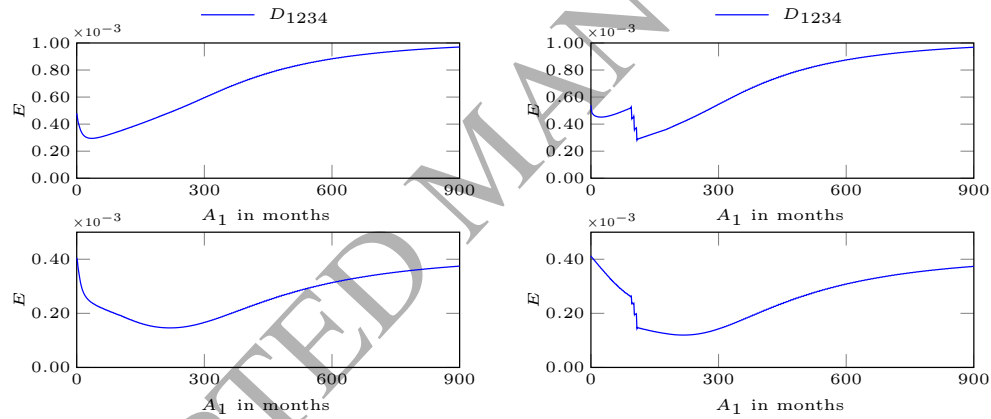
Figure 9: The lifetime expected risk E for endemic areas with all four serotypes in circulation given as a function of vaccination age A_1 in months which corresponds to the age at which the first of three doses is given. **(a)** shows the risk for constant vaccine efficacies, while **(b)** shows vaccine efficacies depending on the age groups <9 years and ≥ 9 years as shown in Table 3. The graphs at the top show results for each infection having the risk function given by equation (17), while the ones at the bottom assume $R_i(a) = 0$ for a primary infection.

Lastly we want to incorporate no subsequent symptomatic infection after a secondary infection when the Dengue risk function is lethality. The results for this are shown in Figure 10 for both three and four co-circulating serotypes. These results are particularly interesting for the case of a risk-free primary infection. By assuming asymptomatic third and fourth Dengue infections and risk-free primary infections the lifetime expected risk is entirely based on secondary infections so that these results may be considered the most realistic if the risk is considered to be the risk of death. First we consider constant efficacy, when for combinations where both DENv3 and DENv4 are in existence the optimal vaccination ages are fairly low if primary infections are risk-free, i.e. 31 months for three serotypes and 36 months for four. These are the only combinations if tertiary and quaternary infections are asymptomatic that lead to optimal vaccination ages outwith the range of 9-45 years and restricting the age to this range leads to vaccination ages of 109 months and an increase of approximately 20 to 30%. For combinations of DENv1, 2 and 3 DENv1, 2 and 4 the optimal ages are 288 and 280 months

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(a) Top: The optimal vaccination age A_1 is 288, 280, 31 and 31 months for DENv123, DENv124, DENv134 and DENv234 respectively. Bottom: The optimal vaccination age A_1 is 428, 423, 334 and 423 months for DENv123, DENv124, DENv134 and DENv234 respectively.

(b) Top: The optimal vaccination age A_1 is 278 months for DENv123 and 109 months for DENv124, DENv134 and DENv234 respectively. Bottom: The optimal vaccination age A_1 is 417, 400, 319 and 400 months for DENv123, DENv124, DENv134 and DENv234 respectively.

(c) Top: The optimal vaccination age A_1 is 36 months. Bottom: The optimal vaccination age A_1 is 219 months.

(d) Top: The optimal vaccination age A_1 is 109 months. Bottom: The optimal vaccination age A_1 is 215 months.

Figure 10: The lifetime expected risk E for endemic areas with three or four serotypes in circulation given as a function of vaccination age A_1 in months which corresponds to the age at which the first of three doses is given. It is assumed that secondary infections lead to permanent cross-immunity for all other serotypes so that $R_{ijk}(a) = 0$ for three and $R_{ijkl}(a) = 0$ and $R_{ijk\bar{l}}(a) = 0$ for fourth infections. **(a)** and **(c)** show the risk for constant vaccine efficacies for three and four serotypes, while **(b)** and **(d)** show vaccine efficacies depending on the age groups <9 years and $\geq$ 9 years as shown in Table 3. The graphs at the top show results for each primary and secondary infection having the risk function given by equation (17). The ones at the bottom assume $R_i(a) = 0$ for a primary infection.

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respectively for risky primary infections. The assumption of risk-free primary infections leads to an increase in optimal age to between 334 and 428 months for three serotypes and 219 months for four serotypes. Similar results are obtained for age-dependent efficacy where the optimal vaccination ages for risk-free primary infections are 109 months for all combinations apart from DENv1, 2 and 3, which requires vaccination at 278 months. For risk-free primary infections the ages again increase to between 319 and 417 months for three and to 215 months for four serotypes. So the current vaccination guidelines are reasonable if vaccination aims to limit the risk of death due to Dengue and secondary infections are the main cause for serious cases of Dengue independently of whether efficacy is age-dependent or not.

7. Discussion

In this paper we have studied a mathematical model to find the optimal vaccination age for Dengue vaccination in Brazil. We used data from the Brazilian Health Ministry to calculate R_0 for each of the four Dengue serotypes and then adapted the method of Hethcote [1] to find the optimal vaccination age. The vaccine has differing efficacies for each serotype. We started off with the situation where there was just one serotype in circulation and then moved on to the optimal vaccination ages for multiple serotypes. The optimal vaccination ages were found for both constant vaccine effectiveness across all ages and when the vaccine efficacy depends on the age at which each dose is given. For the case where multiple serotypes were present the calculations were done first for the first infection being risky and secondly for only subsequent infections being risky (to model Dengue Antibody Enhancement). Note that the model is intended to estimate the optimal age to vaccinate in the routine vaccination calendar. No catch-up campaigns were considered.

As one commonly accepted theory is that any Dengue infections after the second one do not cause serious effects due possibly to partial immunity the calculations were then repeated excluding these infections. All of these calculations were done twice, first with the risk function being hospitalisation and secondly when it is mortality. The assumption that a second infection with Dengue is more risky than a first infection is commonly made. One theory is that a first infection provides some immunity, but that if immunity fails resulting in a secondary infection, the risk is higher. Burattini et al. [47] claim that hospitalisation risk is almost the same for those who have

Table 6: Vaccination ages A_1 in months for the initial of three doses optimal under the age-constraints of the current Dengvaxia license and the percentage increase $\delta^\%_E$ of the lifetime expected risk E compared to its minimum. Only results for constant efficacy are shown in the case of the risk of Dengue being hospitalisation since all optimal vaccination ages for the age-dependent efficacy cases adhere to the license restriction, Table 4 shows the optimal ages in this case. Note that the highest possible age for the first dose was set as 539 months since this leads to all three doses being given before an individual reaches age 46 years. The lifetime expected risk for the first dose for only DENv3, only DENv4 and the combination of those two existing and constant efficacy increases from 0 therefore the corresponding percentage is denoted as ∞. − denotes the cases where the minimal lifetime expected risk is reached between the ages of 9 and 45 years, the minimal lifetime expected risks are given in Tables 4 and 5 for hospitalisation and lethality respectively.

	risk of hospitalisation				risk of death							
	constant efficacy				constant efficacy				efficacy based on age-groups			
	1st infection risky		1st infection risk-free		1st infection risky		1st infection risk-free		1st infection risky		1st infection risk-free	
	A_1	$\delta^\%_E$	A_1	$\delta^\%_E$	A_1	$\delta^\%_E$	A_1	$\delta^\%_E$	A_1	$\delta^\%_E$	A_1	$\delta^\%_E$
DENv1	109	46.6	122	—	538	0.029	539	3.54	538	0.002	539	3.62
DENv2	109	23.7	109	30.5	539	1.64	538	8.69	539	1.53	538	1.45
DENv3	108	∞	109	1.26	108	∞	109	2.77	108	—	176	—
DENv4	109	∞	109	22.5	109	∞	539	39.3	108	—	109	1.88
DENv12	109	34.0	122	1.07	539	0.649	539	8.49	539	0.515	176	—
DENv13	109	93.1	109	∞	519	35.2	538	∞	109	—	108	—
DENv14	109	48.5	109	8.68	109	2.14	109	1.37	176	—	108	—
DENv23	109	66.2	109	0.437	109	39.4	539	1.22	109	—	539	1.25
DENv24	109	24.9	109	23.3	109	3.12	109	436.8	176	—	539	0.813
DENv34	109	∞	109	18.7	109	∞	109	40.2	108	—	108	—
DENv123	109	56.2	109	6.77	539	10.4	539	6.36	539	0.074	539	0.163
DENv124	109	34.8	109	0.437	109	0.946	539	1.22	176	—	539	—
DENv134	109	95.0	109	23.3	109	48.5	538	436.8	109	—	108	—
DENv234	109	67.8	109	18.7	109	41.2	109	40.2	109	—	109	—
DENv1234	109	57.1	109	6.77	109	22.1	539	6.36	539	—	539	—
DENv123	109	84.5	122	—	288	—	428	—	278	—	417	—
DENv124	109	62.2	122	—	280	—	423	—	400	—	400	—
DENv134	109	154	109	10.1	109	29.6	334	—	319	—	319	—
DENv234	109	103	109	8.57	109	23.9	423	—	400	—	400	—
DENv1234	109	199	109	5.69	109	20.9	219	—	215	—	215	—

(Side annotations: the first fifteen rows are labelled *symptomatic*; the final five rows are labelled *asymptomatic* and *3rd and 4th infections*.)

or have not had a recorded secondary infection. This does not necessarily contradict a second infection being more risky as primary infections are often asymptomatic.

On the other hand there seems substantial evidence in the literature that vaccination with Dengvaxia increases hospitalisation risk on Dengue infection relative to seronegative individuals [28], particularly for children. For the Dengvaxia trials, in Asian sites in year three, the Dengue hospitalisation rate was significantly higher among vaccinated children aged less than or equal to five years of age (20 of 2,029 [0.99%]) than among controls (2 of 1,005 [0.2%]) with a relative risk of 4.95 ($p = 0.3$) [30, 50]. This is discussed further by Halstead [26]. Moreover during year three of the Dengvaxia trials there was an overall efficacy against hospitalisation of 16.7% but a relative risk of hospitalisation of 1.6 amongst children younger than nine years of age [30]. Halstead [27] discusses possible ways to improve the trial design and to estimate vaccine efficacy taking into account that vaccination of seronegatives increases their risk on subsequent infection.

It was found that for some serotype combinations the optimal age at vaccination lay outside the range for which Dengvaxia is currently licensed, whenever this was the case the resulting minimal lifetime expected risk was compared with that found for ages between 9 and 45 years, a summary of which is shown in Table 6. Tables 4 and 5 give an overview of the achieved minimal lifetime expected risk with the corresponding optimal vaccination ages for the risk of hospitalisation and death respectively. The optimal vaccination age to reduce the risk of hospitalisation was commonly found to be below 9 years for constant efficacy especially when primary infections were considered risky. For efficacy based on age-groups the optimal vaccination age was always found to be within the range of the license. When considering lethality the results were often above 45 years, but for constant efficacy there were also cases with optimal ages below 9 years. The much higher vaccination ages found for the risk of death in comparison to those for hospitalisation are due to the high increase in risk at old compared to young ages. The maximum risk for children is approximately 0.18 at 6 years for hospitalisation and 0.0011 at 5 years for lethality, while for 75 year-olds the risk of hospitalisation is only 0.14 and that of death is 0.0047, more than four times the maximum risk for children. It is therefore essential for the vaccination programme not to increase the average age of infections to high values in the case of the risk being death which can be avoided by vaccinating after the current average age of infection.

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All scenarios that required optimal vaccination at ages below 9 or above 45 years were investigated further by limiting the vaccination to start between 108 and 539 months. The optimal vaccination ages under these restrictions were always found to decrease to 538 or 539 months in cases that required vaccination above this age to achieve the minimal lifetime expected risk. If vaccination was found to be optimal below 9 years the restrictions led to optimal ages of 108 or 109 months for hospitalisation, for lethality there were some cases where the age increased to above 500 months. The effect of the age restriction on the lifetime expected risk varied significantly for all cases with increases from the minimum value between 0.002% and almost 200% (Table 6). For serotypes DENv3 and 4 separately as well as combined the risk both of hospitalisation and lethality could be reduced to zero at young ages, which was no longer the case under the age-restriction. The increase was generally higher for hospitalisation.

In our simulations we used the risk of hospitalisation and death as substitutes for the more severe reactions to Dengue such as DHF and DSS which are considered most probable in secondary infections [51]. In almost all cases the optimal vaccination age was higher for risk-free primary infections than for the corresponding simulations with risky ones. This is to be expected since vaccination is unnecessary prior to a primary infection if this infection carries no risk for the infected. The exceptions to this led to very young ages in either case. Further the efficacy study by Hadinegoro et al. [30] implies that the assumption of a constant efficacy may be an oversimplification so that an age-dependent efficacy reflects the actual conditions more accurately. Our simulations showed that in most cases the optimal vaccination age is significantly higher if the efficacy is based on age-groups rather than constant. This is because the efficacy found for vaccination at age 9 or above is much higher for each serotype than if vaccines are administered to younger children so that in most cases simulated optimal vaccination could only be achieved with this higher efficacy. Taking these more realistic scenarios of age-dependent efficacy and risk-free primary infections every optimal vaccination age for the hospitalisation risk was within 9-45 years. The reduction of the risk of death was found to be optimal for vaccination ages that in some cases were above 45 years. However, the optimal vaccination ages varied significantly for the number of co-circulating serotypes as well as for the specific serotype combinations. The lowest optimal vaccination age for age-dependent efficacy was found to be 108 months; this was found for several scenarios, e.g. for the only serotype in circulation being DENv4 and with

the risk being mortality. The highest age found with efficacy based on age-groups was 728 months which was found to minimise the risk of death for a combination of DENv1 and DENv2 when a primary infection was free of risk.

We also considered third and fourth infections to be asymptomatic as this is a common theory and have found that in many of the scenarios there is little difference in the optimal vaccination age in comparison to symptomatic tertiary and quaternary infections for hospitalisation risk. However if lethality is considered asymptomaticity resulted in optimal vaccination ages that were within the age range of 9-45 years for almost all serotype combinations.

Our results therefore demonstrate that we must think about the main objective of the vaccine as well as the serotypes which are in circulation in a region where Dengue is endemic before specific vaccination campaigns can be considered. It is probable that the higher efficacy of Dengvaxia in individuals older than 9 years is more dependent on the occurrence of previous infections than on the increasing age per se ([25, 26, 28, 52]). This would mean that the vaccine efficacy is poor and a little better only in the case of previous Dengue infection. If this is true then the assumptions of equal efficacy within all age classes are the most accurate ones. Especially serotype combinations including DENv2 resulted in higher lifetime expected risk so that the exact efficacy is important. Moreover the results presented were obtained for a constant death rate μ_H which is widely accepted in epidemiological modelling as an approximation but does not adequately describe population dynamics in developed countries so that the optimal vaccination ages are indications only.

Additionally one could easily use our methods to propose optimal vaccination strategies other than the ones for which Dengvaxia is currently licensed. For example the first vaccination could be given at early ages and then a booster dose at older ages.

Note that this work differs from previous work in that we have included the survival probability in the risk function. We believe that this gives a biologically more accurate risk function. Note also that the work assumes that the spread of different Dengue serotypes are independent. It is commonly believed that infection with one serotype provides permanent immunity to that serotype but temporary immunity to other serotypes. It would be most accurate to model this explicitly but as the period of cross-protection is relatively short the current model may provide a realistic approximation. As Dengvaxia is currently undergoing Phase IV trials Dengue vaccination and

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the appropriate age at which to do it is a real practical problem and determination of the effects of different vaccination programs is vital and urgently needed.

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