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A two-age-classes dengue transmission model

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ABSTRACT

In this paper, we discuss a two-age-classes dengue transmission model with vaccination. The reason to divide the human population into two age classes is for practical purpose, as vaccination is usually concentrated in one age class. We assume that a constant rate of individuals in the child-class is vaccinated. We analyze a threshold number which is equivalent to the basic reproduction number. If there is an undeliberate vaccination to infectious children, which worsens their condition as the time span of being infectious increases, then paradoxically, vaccination can be counter productive. The paradox, stating that vaccination makes the basic reproduction number even bigger, can occur if the worsening effect is greater than a certain threshold, a function of the human demographic and epidemiological parameters, which is independent of the level of vaccination. However, if the worsening effect is to increase virulence so that one will develop symptoms, then the vaccination is always productive. In both situations, screening should take place before vaccination. In general, the presence of class division has obscured the known rule of thumb for vaccination.

1. Introduction

One of the most important public health programs in many tropical countries is the program to control or to eliminate dengue. This is because dengue is regarded as a very dangerous disease that may lead to death. The disease is caused by one of four known strains of flavivirus, namely DEN-1, DEN-2, DEN-3, and DEN-4. It is transmitted mainly by female *Aedes aegypti*, although it is also reported that *Aedes albopictus* can transmit the disease in some circumstances. The modes of transmission known in the literature are among others vertical transmission from the female adult mosquitoes to their young, mechanical transmission from a healthy mosquito that has just bitten an infectious human to a healthy human, and from an infectious mosquito to a healthy human. There are three stages of severity of an infected human: dengue fever (DF) comes with mild cold symptoms, dengue hemorrhagic fever (DHF) causes blood discharge from the vessel, and dengue shock syndrome (DSS) that may lead to death [20]. In the endeavor to eliminate the disease, some efforts have already been made in many countries, such as destroying the adult class of the mosquitoes with insecticides and stimulating predation of the larval class of the mosquitoes. Some other attempts are being investigated, such as modifying the age structure of the mosquitoes, e.g. by lowering their life expectancy genetically, introducing a transgenic mosquitoes population, e.g. by sterilizing male mosquitoes and developing a safe vaccine that can protect humans from the four known dengue viruses [6,21,27,33].

In the past, dengue has been recognized as a young children's disease. It attacks mostly children at the age of 3–6 years. However, it has been reported that nowadays there is a change in this trend. The predominant age to acquire dengue in Uttaradict Thailand has changed and increased by at least 2 years [35]. Other data showing the increase of the mean age at infection can be found in [32,46], in which the authors show that the mean age at infection in the city of Bandung Indonesia has increased from 19 years in the year 2003 to 25.5 years in the year 2004. The same figure also shows up in other part of Indonesia, in which among those who are infected, the population in the age class of 10–19 years accounted for the largest proportion of hospitalized DHF cases, followed by children 5–9 years and children of 4 years old [7]. Similar data from Singapore also show that the risk partly shifts from children to adults [34]. These changes in pattern have made the management of the disease even more difficult. In order to manage the disease, one needs to understand the dynamics of the spreading of the disease. Some health scientists have tried to obtain some insight in the transmission and elimination of the disease using mathematical modeling. Here, we mention for instance [41]. Many mathematical models have been devoted to address this issue since then, including the seminal work of [26]. In the following section we will review some mathematical models of dengue transmission.

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2. Review on mathematical models for dengue

Among the earliest mathematical models for the transmission of dengue are those developed in [12,17] which are closely related to the models for the transmission of malaria discussed in [4,11]. The authors in [17] discuss the model for two types of viruses by allowing temporary cross immunity and increased susceptibility to the second infection due to the first infection. They argue that there is competitive exclusion with the first strain of virus as the winner, if the susceptibility index of the first strain of the virus is greater than that of the second strain. Analytical stability results are established in case virulence is absence. The stability results for the virulence case are derived numerically. They also argue that age structure may increase the realism of the model. The author in [20] points out that age is among the risk factors that lead to the severity of dengue and indeed most of the patients having DHF are less than 15 years old. The data in [45] support the claims regarding the importance of age structure in the transmission of dengue.

Competitive exclusion or strain replacement, as shown in [17], is also observed in [25] as a result of excessive vaccination, in which the strain with a larger basic reproduction number outcompetes the strain with a smaller basic reproduction number. The authors in [9] have developed a two-strain dengue model, different from that of [17]. The authors in [9] assume that the viruses one after another. They argue that the susceptibles for the second infection are those individuals who have recovered from the first infection. They show that the condition needed for the system to be free from the disease, is that the vaccination level should be above a certain threshold. They also point out that controlling by reducing the number of mosquitoes is not sufficient, since it will only delay the time for the disease to outbreak. This is supported by [33].

The authors in [12] derive a threshold parameter for their model of dengue with one strain of virus. They have established a theorem concerning the global stability of the endemic equilibrium, concluding that if this threshold parameter is larger than one, then the endemic equilibrium is globally stable and otherwise it is unstable. They have generalized the model to include a variable human population in [13] and have included a secondary infection in [15]. Unlike the model discussed in [17], the model in [15] has a different formulation, namely with a variable host population and without virulence. They give sufficient conditions for coexistence of the two strains of viruses. They also consider mechanical and vertical transmission [14] and conclude that mechanical transmission has less impact than vertical transmission.

Although there are many papers on age-structured epidemic models, however, in modeling the spreading of dengue, most of the researchers have ignored this important age structure factor. Exceptions are [37,38]. The authors in [37] have generalized the model in [12] by separating the human population into age cohorts, and for each cohort by deriving a set of SIR equations. Disease free and endemic equilibria are found, but there is no stability analysis for these equilibria. Instead they have used the model to calculate the age-specific transmission rate for the DHF data in several places in Thailand. In [38], the authors have simplified their model to a two-age-classes model. They allow different transmission rates for the adult and the juvenile classes and assume that juveniles have a higher transmission rate. They have found disease free and endemic equilibria, and the condition for the local stability of the disease-free equilibrium in the general case. The stability condition for the endemic equilibrium has only been found for the special case, in which no infection occurs for the adult class. They also argue that the effect of age structure is to increase the period of fluctuation in both the susceptible and the infective populations in approaching the endemic equilibrium.

Fluctuation in the vector population is likely. There is a mathematical model that considers this fluctuation for a closely related vector-borne disease, leishmaniasis, which is transmitted to human by female flies [2]. In this model the authors assume a periodic function as the recruitment function of the fly population. They also assume that the infective human population is structured by the time elapsed since the infection occurred. Their main conclusion is the formula for the basic reproduction number of a vector-borne disease with a periodic vector population. Another paper that takes fluctuation into account is [43], which also considers a periodic recruitment rate. However, the authors in [18,19] have argued that a cyclical epidemic in the case of dengue is most likely caused by the presence of multiple strains of viruses.

Another biological complication that arises in the literature regarding vector-borne diseases is the presence of multiple hosts. In this case the authors in [28] have studied the dynamics of African Horse Sickness, which is transmitted by biting midges *Culicoides imicola* among horses and donkeys, however, in the case of dengue, humans form the only main natural host. Transmission to other mammals is negligible. Other possibilities to make the model more realistic can be achieved by considering multiple vectors. The main vector of dengue in the urban area is *A. aegypti*, however, other species, such as *A. albopictus*, are also potential to transmit the disease, though they are less anthropophylic.

The previous mentioned papers mainly discuss the dynamics of the disease. There are also some studies emphasizing to find the formula for the basic reproduction number R_0 and to estimate it from available data. The simplest one is found in [29], where the dynamics in this paper is only given by the host without the vector. This work has been generalized in [8,16,30,31] to include the incubation time both for the vector and the host, and to include spatial heterogeneity. The authors in [18] have developed a technique to estimate the value of R_0 with strain-specific forces of infection. Recently there is a caveat in using the concept of R_0 as a guidance to control the transmission of a vector-borne disease. Despite the common use of the concept of R_0 in determining the strength of general infectious diseases and in controlling their transmission, the authors in [24,40] argue that R_0 can mislead and underestimate the effort to control a vector-borne disease, such as dengue. They have developed a new method that leads to the so called type reproduction number.

In this paper, we discuss a two-age-classes dengue transmission model with vaccination by comparing the basic reproduction number as a control to eliminate the disease. We divide the human population into two age classes: the child-class and the adult-class. The reason to divide the human population into two age classes is for practical purposes, as vaccination is usually concentrated in one age class, e.g. the school age class. A study in [42] shows that a pediatric dengue vaccination, that is a vaccination program which targets children, would be economically viable and highly cost-effective, once a perfect dengue vaccine is made. Apart from the inclusion of age classes, this model differs from a simple case of vaccination in [44], as here vaccination involves not only the newborns and there is an outflow of vaccinated individuals to the immune class in a linear effect form. This makes the model more realistic.

We also divide the human population into two subclasses, namely the subclass with asymptomatic infection and the subclass with symptomatic infection for the following reason. Several studies reveal that the majority of dengue infections were asymptomatic [5,22]. A study in [39] shows, using a longitudinal blood-test study on a cohort group in Bandung, Indonesia, an estimated asymptomatic infection rate of 56 cases per 1000 persons per year, while the number of reported incidence of symptomatic dengue infections is only 18 cases per 1000 persons per year. Even when there is no symptomatic case of dengue infection reported, they

conclude that the estimated asymptomatic infection rate is as high as eight cases per 1000 persons per year. This 'iceberg phenomenon' is typical in dengue infection, such as shown in [21,23,36]. This has led to the division of each age class into two subclasses, those with symptomatic infection and those with asymptomatic infection. Typical rates for each subclass, for example, are portrayed in [42]. To model this situation we use a discrete or compartmental SIR model with an addition of a symptomatic or severely infected class, which we assume is not contributing to the transmission of the disease, since individuals in this class are easily identified and most likely isolated by hospitalization.

Furthermore, we also assume that a constant rate of individuals in the child-class is vaccinated. This can be done in a relatively small and controllable population, e.g. in a district or town. However, since most of the infected children are asymptomatic, we cannot differentiate between the asymptomatic infected children and the healthy children as the target of vaccination. As a result, there will be a portion of the infectious children, that is vaccinated unintentionally. In this case, there is a possibility of a worsening effect, due to the presence of cross-reactive antibodies mechanism that enhances the severity of the infection [19]. This mechanism is complex and still not fully comprehended [18].

We devise two models, one assuming that the unintentional vaccination increases the infectious period. Another one assumes that unintentional vaccination leads to the development of symptoms. The results in this paper show that in the former case, vaccination can be counter productive, in the sense that it makes the basic reproduction number even bigger, if the worsening effect is greater than a certain threshold. However, in the later case, that is, if the worsening effect is to increase virulence so that the children will develop severe symptoms, then the vaccination is always productive.

3. Child-class vaccination with worsening effect on the sojourn time of infection

3.1. The mathematical model

Let us assume that the total population is divided into two age classes. The number of individuals in the child-class and the adults-class is denoted by N_1 and N_2, respectively. Let us also assume that the total number of individual in age class j at time t, i.e. $N_j(t)$, $j = 1, 2$, is composed of the number of susceptible individuals, $S_j(t)$, the number of asymptomatic infective individuals, $I_j(t)$, the number of symptomatic or severely infective individuals, $D_j(t)$, and the number of recovered or immune individual, $R_j(t)$. The constant recruitment rates for humans and mosquitoes are B and B_v, respectively. The natural death rates for humans and mosquitoes are μ and μ_v, respectively. The forces of infection for humans and mosquitoes are functions of the biting rate per mosquito b_i, and the probability of successful infection p_i in a human and p_v in a mosquito, respectively. The presence of the index i on the biting rate and the probability of successful infection indicates the age-dependence of the force of infection. A more general age-dependent force of infection is extensively explored in [1]. Once infected, a portion σ of the infected human enters the class of asymptomatically infectious individuals, while the remaining portion $1-\sigma$ enters the class of symptomatically infectious individuals. The human recovery rate is γ. We assume that the mosquitoes never recover once they are infected, since they have a much shorter life time compared to the life time of humans. In fact, the life time of the mosquitoes is almost the same as the viruses have. Hence, the total number of mosquitoes, $N_v(t)$, consists of the susceptible, $S_v(t)$, and the infectious, $I_v(t)$, individuals. Furthermore, there is an extrinsic incubation period τ_e and intrinsic incubation period τ_i experienced by infected mosquitoes and infected humans, respectively, before they become infectious. We assume that the rate of recruitment from the child-class to the adult-class in the human population is $\alpha = 1/T$, where T is the age at which an individual in the child-class goes into the adult-class (see also Appendix A).

To control the disease, we assume here that vaccination is only given to individuals in the child-class, with the rate q. However, we also assume that, since most of the infectious children are asymptomatic, we cannot differentiate between these asymptomatic infected children and the healthy children as the target of vaccination. As a result, a portion ω of the infectious children, who are vaccinated un-deliberately, will get worse by having a longer period of infection. Another possibility is that they develop symptoms and consequently move to the category D_1. Here we will consider the former case, while the latter will be discussed in a separate section. Assume that vaccine efficacy is s. Using these assumptions and notations, the dynamics of the human population is given by

$$\frac{dS_1(t)}{dt} = B - \alpha S_1(t) - \mu S_1(t) - b_1 p_1 I_v(t-\tau_i)\frac{S_1(t-\tau_i)}{N(t-\tau_i)} - sqS_1(t), \tag{1a}$$

$$\frac{dS_2(t)}{dt} = \alpha S_1(t) - \mu S_2(t) - b_2 p_2 I_v(t-\tau_i)\frac{S_2(t-\tau_i)}{N(t-\tau_i)}, \tag{1b}$$

$$\frac{dI_1(t)}{dt} = \sigma b_1 p_1 I_v(t-\tau_i)\frac{S_1(t-\tau_i)}{N(t-\tau_i)} - \mu I_1(t) - (\gamma - q\omega) I_1(t) - \alpha I_1(t), \tag{1c}$$

$$\frac{dI_2(t)}{dt} = \sigma b_2 p_2 I_v(t-\tau_i)\frac{S_2(t-\tau_i)}{N(t-\tau_i)} - \mu I_2(t) - \gamma I_2(t) + \alpha I_1(t), \tag{1d}$$

$$\frac{dD_1(t)}{dt} = [1-\sigma] b_1 p_1 I_v(t-\tau_i)\frac{S_1(t-\tau_i)}{N(t-\tau_i)} - \mu D_1(t) - \gamma_d D_1(t) - \alpha D_1(t), \tag{1e}$$

$$\frac{dD_2(t)}{dt} = [1-\sigma] b_2 p_2 I_v(t-\tau_i)\frac{S_2(t-\tau_i)}{N(t-\tau_i)} - \mu D_2(t) - \gamma_d D_2(t) + \alpha D_1(t), \tag{1f}$$

$$\frac{dR(t)}{dt} = sqS_1(t) + (\gamma - q\omega) I_1(t) + \gamma I_2(t) + \gamma_d D_1(t) + \gamma_d D_2(t) - \mu R(t). \tag{1g}$$

Meanwhile, the mosquito population dynamics is governed by

$$\frac{dS_v(t)}{dt} = B_v - [b_1 p_v I_1(t) + b_2 p_v I_2(t-\tau_e)]\frac{S_v(t-\tau_e)}{N(t-\tau_e)} e^{-\mu_v \tau_e} - \mu_v S_v(t), \tag{2a}$$

$$\frac{dI_v(t)}{dt} = [b_1 p_v I_1(t-\tau_e) + b_2 p_v I_2(t-\tau_e)]\frac{S_v(t-\tau_e)}{N(t-\tau_e)} e^{-\mu_v \tau_e} - \mu_v I_v(t). \tag{2b}$$

Note that the human and mosquito population densities at equilibrium are $N = \frac{B}{\mu}$ and $N_V = \frac{B_v}{\mu_v}$, respectively. In Appendix A we show the relationship between the two-age-classes model developed here and the more general age-structured model. In the next section we will discuss the basic reproduction number for dengue transmission in the two-age-classes model described by the system of Eqs. (1a)–(1g) and, (2a and 2b).

Rewriting the dynamics for the relative proportions using the new variables $\tilde{S}_1 = \frac{S_1}{N}$, $\tilde{S}_2 = \frac{S_2}{N}$, $\tilde{I}_1 = \frac{I_1}{N}$, $\tilde{I}_2 = \frac{I_2}{N}$, $\tilde{D}_1 = \frac{D_1}{N}$, $\tilde{D}_2 = \frac{D_2}{N}$, $\tilde{R} = \frac{R}{N}$, $\tilde{S}_v = \frac{S_v}{N_v}$, $\tilde{I}_v = \frac{I_v}{N_v}$, $\tilde{B} = \frac{B}{N}$, and $\tilde{B}_v = \frac{B_v}{N_v}$, we find at equilibrium the system of equations:

$$\widetilde{B} - \alpha\widetilde{S}_1 - \mu\widetilde{S}_1 - b_1p_1Q\widetilde{I}_v\widetilde{S}_1 - sq\widetilde{S}_1 = 0, \tag{3a}$$

$$\alpha\widetilde{S}_1 - \mu\widetilde{S}_2 - b_2p_2Q\widetilde{I}_v\widetilde{S}_2 = 0, \tag{3b}$$

$$\sigma b_1p_1Q\widetilde{I}_v\widetilde{S}_1 - \mu\widetilde{I}_1 - (\gamma - q\omega)\widetilde{I}_1 - \alpha\widetilde{I}_1 = 0, \tag{3c}$$

$$\sigma b_2p_2Q\widetilde{I}_v\widetilde{S}_2 - \mu\widetilde{I}_2 - \gamma\widetilde{I}_2 + \alpha\widetilde{I}_1 = 0, \tag{3d}$$

$$[1-\sigma]b_1p_1Q\widetilde{I}_v\widetilde{S}_1 - \mu\widetilde{D}_1 - \gamma_d\widetilde{D}_1 - \alpha\widetilde{D}_1 = 0, \tag{3e}$$

$$[1-\sigma]b_2p_2Q\widetilde{I}_v\widetilde{S}_2 - \mu\widetilde{D}_2 - \gamma_d\widetilde{D}_2 + \alpha\widetilde{D}_1 = 0, \tag{3f}$$

$$sq\widetilde{S}_1 + (\gamma - q\omega)\widetilde{I}_1 + \gamma\widetilde{I}_2 + \gamma_d\widetilde{D}_1 + \gamma_d\widetilde{D}_2 - \mu\widetilde{R} = 0, \tag{3g}$$

with $Q = \frac{N_v}{N}$ is a person index measuring the average mosquitoes per person. Similar equilibrium equations for the mosquitoes dynamics are given by

$$\widetilde{B}_v - \left[b_1p_v\widetilde{I}_1 + b_2p_v\widetilde{I}_2\right]\widetilde{S}_v e^{-\mu_v\tau_e} - \mu_v\widetilde{S}_v = 0, \tag{4a}$$

$$\left[b_1p_v\widetilde{I}_1 + b_2p_v\widetilde{I}_2\right]\widetilde{S}_v e^{-\mu_v\tau_e} - \mu_v\widetilde{I}_v = 0. \tag{4b}$$

The total population of humans and mosquitoes at equilibrium are normalized to one. In the following section we derive the basic reproduction number for transmission of the disease, which will be used extensively in the discussion throughout the remaining of the paper.

3.2. The basic reproduction number

The basic reproduction number R_0 is given by $\lim_{n\to\infty}\|K^n\|^{1/n}$. Alternatively, R_0 is the dominant eigenvalue of K. Here $K = (k_{ij})$ is the next generation matrix, where k_{ij} is the expected number of newly generated infected individuals with index i, caused by an infective individual from the population with index j (see [10]). In our model, i and j are elements of the set $\{1, 2, V\}$. Hence, the next generation matrix for the system above is given by

$$K = \begin{pmatrix} 0 & 0 & \frac{\sigma b_1p_1Q}{\mu_v}\widetilde{S}_1^* \\ \frac{\alpha}{\alpha+\mu+\gamma-q\omega} & 0 & \frac{\sigma b_2p_2Q}{\mu_v}\widetilde{S}_2^* \\ \frac{e^{-\mu_v\tau_e}b_1p_v}{\mu+\gamma-q\omega}\widetilde{S}_v^* & \frac{e^{-\mu_v\tau_e}b_2p_v}{\mu+\gamma}\widetilde{S}_v^* & 0 \end{pmatrix}. \tag{5}$$

The basic reproduction number $\overline{R}_q$ for the system is the largest eigenvalue of this matrix where $\widetilde{S}_1^* = \frac{B}{\alpha+\mu+sq}$, $\widetilde{S}_2^* = \frac{\alpha}{\mu}\frac{B}{\alpha+\mu+sq}$, and $\widetilde{S}_v^* = \frac{B_v}{\mu_v}$ are the steady state population sizes in the absence of infection. The characteristic polynomial for K is given by

$$\begin{aligned} F(\lambda) = {} & \mu_V^2B(\mu+\gamma-\alpha)(\alpha+\mu+\gamma-q\omega)(\alpha+\mu+sq)\lambda^3 \\ & - p_VB_V\mu M\sigma\Big(p_1b_1^2\mu^2 + b_2^2p_2\alpha\mu - \mu b_1^2p_1\alpha + \mu b_1^2p_1\gamma \\ & + b_2^2p_2\alpha\gamma + b_2^2p_2\alpha^2 - b_2^2p_2\alpha q\omega\Big)\lambda - p_VB_V\mu^2M\alpha p_1b_2\sigma b_1, \end{aligned} \tag{6}$$

where $M = e^{-\mu_V\tau_e}$. The eigen value of K may not be found explicitly. Note that $F + p_VB_V\mu^2M\alpha p_1b_2\sigma b_1$ is antisymmetrical with respect to $\lambda = 0$. The largest eigen value λ_0 occurs in the interval $(0, \infty)$, hence $\lambda_0 > 1$ if and only if $F(1) < 0$. Here we find a threshold parameter

$$R_q = \sqrt{\frac{\sigma p_Ve^{-\mu_V\tau_e}Q}{(\alpha+\mu+sq)\mu_V}\left(\frac{\mu b_1^2p_1}{(\alpha+\gamma+\mu-q\omega)} + \frac{\alpha b_2^2p_2}{(\gamma+\mu)} + \frac{\alpha\mu b_1b_2p_1}{(\alpha+\gamma+\mu-q\omega)(\gamma+\mu)}\right)}. \tag{7}$$

This threshold is different from the reproduction number $\widetilde{R}_q$, but both give the equivalent condition $R_q > 1 \iff \widetilde{R}_q > 1$. For the remaining of the paper we will use the threshold number R_q as the basis of the analysis. Note that the notation R_q denotes the effective threshold number and R_0 is reserved to the threshold number in the absence of vaccination. The condition $R_q = 1$ is related to the bifurcation parameter for the non-endemic equilibrium at which it becomes unstable when $R_q > 1$ and the endemic equilibrium appears.

Note that the effect of biting rate is quadratic implying that reducing the biting rate, for example by using insect repellent, is among the most effective way in decreasing the reproduction number. Numerical examples in Fig. 1 show that the reduction of the biting rate has a more significant effect than the reduction of the vector abundance does in reducing the basic reproduction number. This is reasonable, since its effect to the reproduction number is quadratic. Meanwhile, the effect of the vector abundance is only linear. It is also worth to note that the presence of the extrinsic time delay τ_e also decreases the value of the repro-

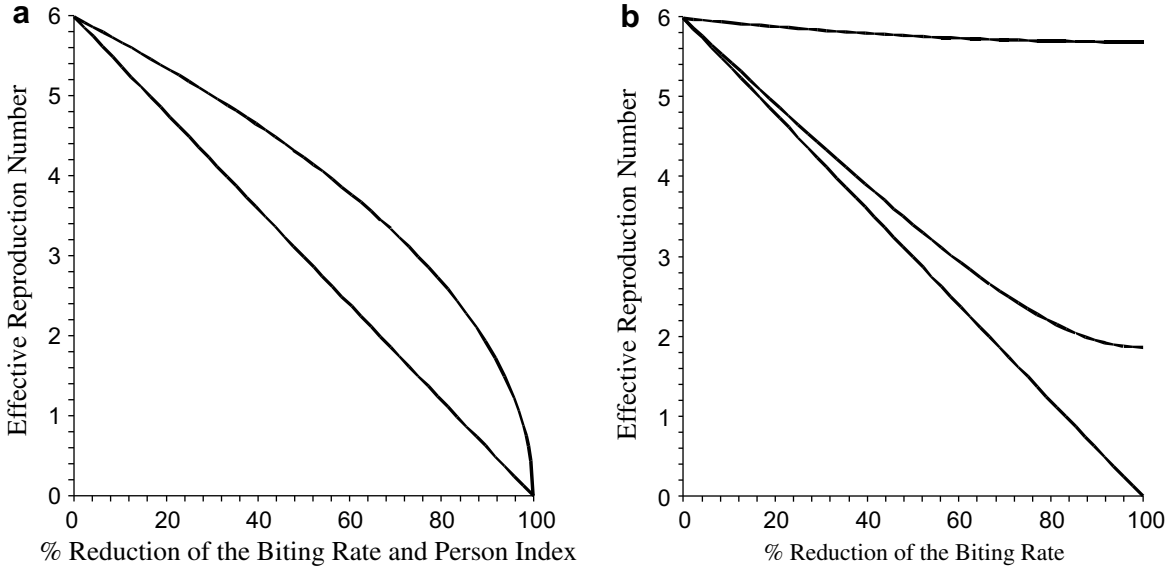

Fig. 1. (a) The effective reproduction number R_q as the biting rate reduces (lower curve) and the person index Q, i.e. the ratio of the mosquito and human densities, reduces (upper curve) to certain percentages. The parameter values used in this figure are $Q = 2$, $\omega = 0.1$, $\mu = 1/65/365$, $\mu_v = 1/14$, $\gamma = 1/14$,$\sigma = 0.5$, $s = 0.5$, $p_1 = 0.2$, $p_2 = 0.1$, $p_V = 0.5$, $b_1 = 1$, $b_2 = 2$, $\tau_e = 0$, and $\alpha = 1/14/365$. The figure shows that the reduction of the biting rate is more significant than the reduction of the person index in reducing the basic reproduction number. This is because the effect of the biting rate is quadratic, while the effect of the person index is linear. (b) The effective reproduction number R_q as the biting rate in the adult-class reduces (upper curve), if it reduces in the child-class (middle curve), and if it reduces in both classes (lower curve) to certain percentages. Reducing the biting rate in the child-class is more significant than it is to reduce the adult-class, since in this case, the probability of getting infected in the child-class is higher than in the adult-class.

duction number. This is one of the arguments why some scientists try to reduce the life span of adult mosquitoes, genetically or by some other means, in the attempt to control dengue.

Another way to eliminate dengue is by means of vaccination. The dengue vaccine is being developed, it is not readily available yet for practical uses. We have already remarked various negative effects of vaccination, such as the prolongation of infectious period. Most of the infectious children are asymptomatic and hence we cannot differentiate between the asymptomatic infectious children and the healthy children as the target of vaccination. As a result, there will be a portion of the infectious children, that is vaccinated unintentionally. Considering the effective reproduction number above, if we are sure that all vaccination are correctly given to the susceptible children, then the effective reproduction number is lower than the basic reproduction number. Otherwise, if every vaccination is unintentionally given to the asymptomatic infectious children, the opposite will happen. In between, there is a trade off regarding the effect of vaccination coverage q to the basic reproduction number R_0. The following section discusses this issue in greater detail.

3.3. The effectiveness and ineffectiveness of vaccination

To compare the effectiveness of the vaccination, in terms of reducing the basic reproduction number we do as follows: first, let us assume $\alpha = 0$, which is the case of a single age class, and let P denotes the ratio of the effective reproduction number after vaccination, R_q, and the basic reproduction number before vaccination, R_0. Then we have the identity

$$P = \sqrt{\frac{\mu(\gamma+\mu)}{(\mu+sq)(\gamma+\mu-q\omega)}}. \tag{8}$$

Obviously, if $s = 1$ and $\omega = 0$, then $P < 1$, while if $s = 0$ and $\omega = 1$, then $P > 1$. We also notice that if there is no vaccination, $q = 0$, then there is no effect, indicated by $P = 1$. In general, observe that P will be less than one, that is the reproduction number in the presence of vaccination is smaller than the reproduction number in the absence vaccination, if and only if

$$\omega < \frac{s(\gamma+\mu)}{sq+\mu} = \omega^*. \tag{9}$$

In this case, ω^* is called the threshold for the ineffective vaccination to occur. If $\omega > \omega^*$ then, instead of having a lower reproduction number, vaccination results in a higher reproduction number. Note that the value of ω^* depends on the vaccination coverage constant q. We conclude that the vaccination is effective, in terms of decreasing the basic reproduction number, if and only if the worsening effect ω is small enough compared to the vaccine efficacy s so that inequality (9) holds. As an illustration, Fig. 2 shows the ratio of the effective and the basic reproduction numbers, as a function of the vaccination coverage q, with a small value of worsening effect (Fig. 2(a)) and with a large value of the worsening effect (Fig. 2(b)).

Note that the inequality can be rewritten as $sq < \frac{s(\gamma+\mu)-\mu\omega}{\omega}$. In an extreme situation, when $s < \frac{\mu}{(\gamma+\mu)}\omega$, vaccination can never reduce the basic reproduction number. In other words, no matter how big the effort taken for vaccination is, in terms of the portion of children being vaccinated, the basic reproduction number will increase. This can be viewed as another form of the ineffectiveness of the vaccination. The occurrence is independent of the vaccination coverage q. The last expression can be rewritten as $\frac{s}{\omega} < \frac{\mu}{(\gamma+\mu)}$, which shows the ratio of vaccine efficacy and the worsening effect must be less than the ratio of the effective infectious period $1/(\gamma+\mu)$ and the life expectancy $1/\mu$.

Next, we look into a more general case, $\alpha \neq 0$. Here we have

$$P = \sqrt{\frac{(\alpha+\mu)(\alpha+\gamma+\mu)}{(\alpha+\mu+sq)(\alpha+\gamma+\mu-q\omega)}\left(1-\frac{\alpha p_2 b_2^2 q\omega}{\left(p_1 b_1^2\mu+p_2 b_2^2\alpha\right)(\gamma+\mu)+\alpha\left(b_1 b_2 p_1\mu+b_2^2 p_2\alpha\right)}\right)}, \tag{10}$$

which clearly reduces to Eq. (8) when $\alpha = 0$. Using a similar argument as above, there would be a threshold ω_α^* dividing the case where the vaccination helps or worsens. Vaccination is effective if only if

$$\omega < \frac{s\left(c_3\alpha^3+c_2\alpha^2+c_1\alpha+b_1^2 p_1\mu(\mu+\gamma)^2\right)}{d_2\alpha^2+d_1\alpha+b_1^2 p_1\mu(\mu+\gamma)(\mu+qs)} = \omega_\alpha^*, \tag{11}$$

where $c_3 = b_2^2 p_2$, $c_2 = b_2(2b_2 p_2\gamma + 2b_2\mu p_2 + b_1 p_1\mu)$, $c_1 = (\mu+\gamma)(b_2^2 p_2\gamma + b_1^2 p_1\mu + b_2\mu p_1 b_1 + \mu b_2^2 p_2)$, $d_2 = b_2(qsp_2 b_2 + b_1 p_1\mu)$ and $d_1 = (qsb_2^2 p_2\gamma + p_1 b_1^2\mu^2 + qs\mu b_2^2 p_2 + qsb_2\mu p_1 b_1 + \mu b_1^2 p_1\gamma + b_2\mu^2 p_1 b_1)$. Again, when $\alpha = 0$, identity (11) reduces to ω^* in (9) and it can also

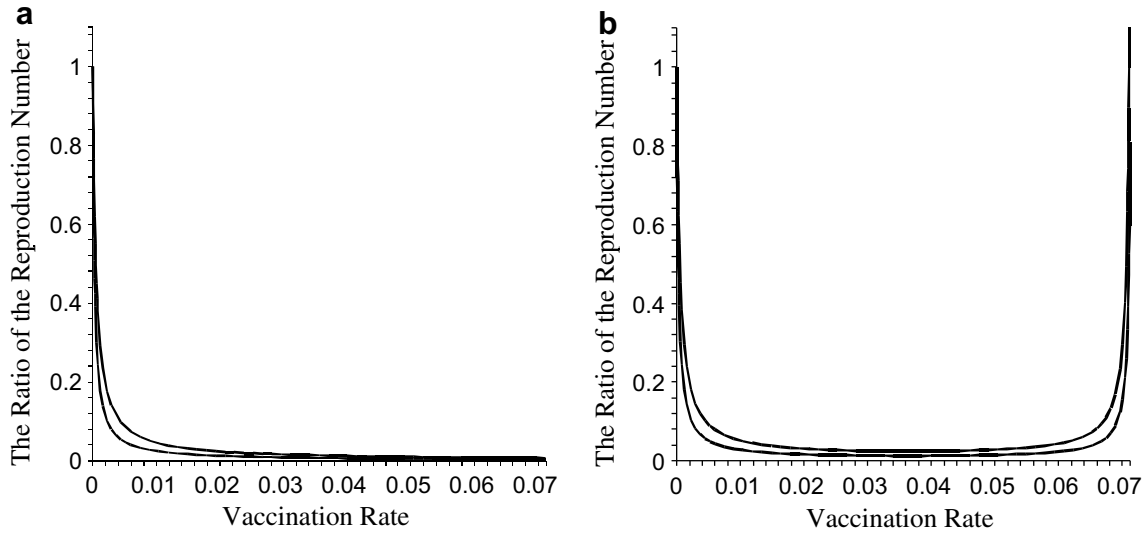

Fig. 2. (a) The value of P, the ratio of the effective and basic reproduction numbers, as a function of the vaccination coverage q with a small worsening effect $\omega = 0.1$. The upper curve for a low value of the vaccine efficacy, $s = 0.50$, and the lower curve for a high value of the vaccine efficacy, $s = 0.95$. In both cases $P < 1$ if $q > 0$. (b) The value of P as a function of the vaccination coverage q with a high worsening effect $\omega = 1$. The upper curve for a low value of the vaccine efficacy, $s = 0.50$, and the lower curve for a high value of the vaccine efficacy, $s = 0.95$. In both cases $P > 1$ for $q > 0$ large enough.

be written as $\omega < \frac{s(\alpha+\gamma+\mu)X}{sqX+(\alpha+\mu)Y}$, where $X = b_2^2 p_2 \alpha\gamma + b_2\alpha\mu p_1 b_1 + p_1 b_1^2 \mu^2 + b_2^2 p_2 \alpha^2 + \mu b_2^2 p_2 \alpha + \mu b_1^2 p_1 \gamma$ and $Y = b_1 p_1 \mu(b_1\gamma + b_1\mu + b_2\alpha)$. As in the previous case, no vaccination coverage succeeds in reducing the basic reproduction number if $\frac{s(Y+b^2 p_2 \mu\alpha)}{\omega Y} < \frac{(\alpha+\mu)}{(\alpha+\gamma+\mu)}$, or if the ratio between vaccine efficacy and the worsening effect is too small. Fig. 2 shows the value of P as a function of vaccination coverage q. It reveals that for a small worsening effect ω, P is always less than one (Fig. 2(a)). However, when the worsening effect ω is sufficiently high (Fig. 2(b)), $P > 1$ for sufficiently large vaccination coverage q. The effective reproduction numbers for both cases are illustrated in Fig. 3. It is worth to note, although theoretically vaccination ineffectiveness may occur, practically for most of the realistic parameters of the model, the ω-region for this ineffectiveness to occur is very small, as indicated by the numerical example in Fig. 4.

3.4. The critical level of vaccination

The next important question is to what extent the vaccination effort is needed to eliminate the disease. Here we will assume that $\omega < \omega^*_\alpha$, so that vaccination is effective. Note that in Eq. (7), the second term in the right hand side is the adult contribution to the basic reproduction number. In what follows we will assume that

$$\sqrt{\frac{\sigma p_V e^{-\mu_V \tau_e} Q}{(\alpha+\mu)\mu_V}\left(\frac{\alpha b_2^2 p_2}{\gamma+\mu}\right)} < 1, \tag{12}$$

that is, the presence of adults alone cannot sustain the presence of the disease. So it is plausible that vaccination is addressed to the child-class. To eliminate the disease we require that a condition that R_q^2 in Eq. (7) to be less than one. It is easy to show that if $\omega = 0$, the condition is equivalent to

$$q > \left(R_0^2 - 1\right)\frac{(\alpha+\mu)}{s}. \tag{13}$$

However, if $\omega \neq 0$ then the condition is more complicated and takes form as $q > (R_0^2 - 1)\frac{(\alpha+\mu+\gamma)(\mu+\gamma)}{(\alpha A b_2^2 p_2 - (\gamma+\mu))\omega}$, where $A = \frac{\sigma p_V e^{-\mu_V}\tau_e Q}{(\alpha+\mu+sq)\mu_V}$. The last inequality is a general rule for vaccinating the child-class such that the effective reproduction number is less than one, when there is a worsening effect of vaccination. Note that in a special case, when $\alpha = 0$ and there is no worsening effect of vaccination, from inequality (13) we have $\frac{sq}{\mu} > R_0^2 - 1$. This can be regarded as vaccinating the whole population without distinction between adults and children with vaccination coverage q. In this case the known rule of thumb for vaccination is recovered, except for the presence of the square [9].

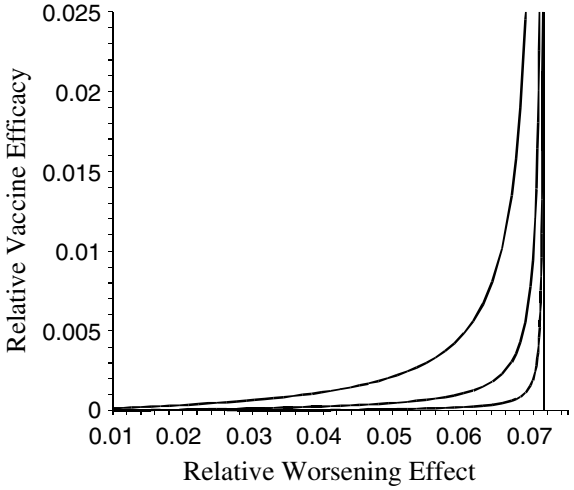

Fig. 4. The figure shows the graph of the relative vaccine efficacy qs as a function of the relative worsening effect $q\omega$. Other parameters are given, i.e. $\mu = 1/65/365$, $\gamma = 1/14$, $p_1 = 0.2$, $p_2 = 0.1$, $b_1 = 2$, $b_2 = 0.5$. The region where the vaccination is counter productive is below the curve, where $qs < q\omega$. This area is relatively small compared to all possible realistic combination of qs and $q\omega$ parameters. The value of α is zero for the lowest curve. The middle and the upper curves have a medium and high value of α, respectively.

4. Child-class vaccination with worsening effect on the disease virulence

In the previous section we have assumed that as a result of undeliberate vaccination of infected children, a portion ω of them will be infectious during a longer period of time. Another possibility is that they develop severe symptoms due to increased viru-

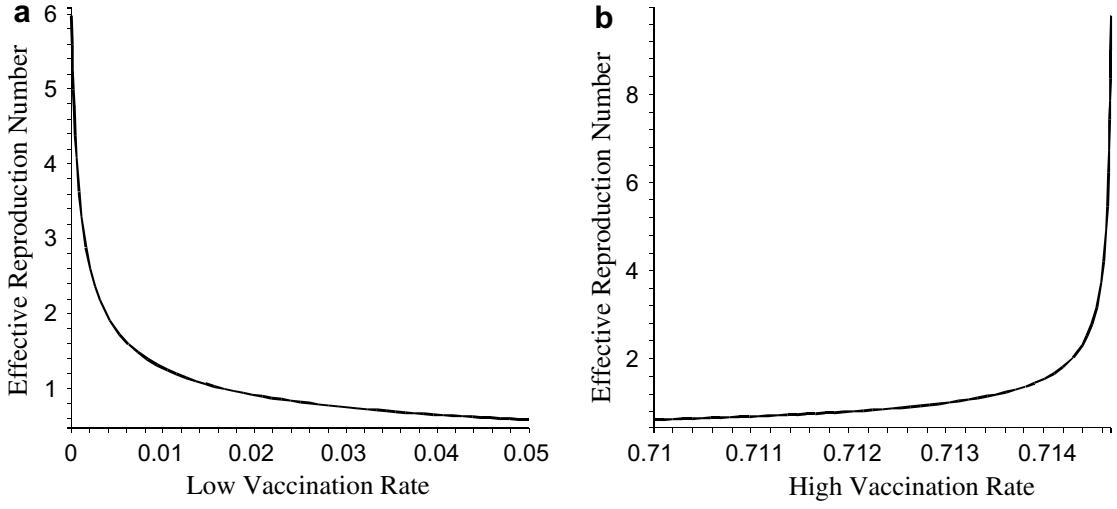

Fig. 3. (a) The effective reproduction number R_q when the vaccination rate is low and reveals that low vaccination rates generate effective reproduction numbers that are lower than the basic reproduction number before vaccination. (b) The effective reproduction number R_q when the vaccination rate is very high which may yield a higher effective reproduction number compared to the basic reproduction number R_0. The parameter values used are the same as in Fig. 1.

lence, and that they move to the category of D_1 as a consequence. Basically the equations are the same except the term $q\omega I_1(t)$ in Eq. (1c) has the opposite sign to express an outflow into the class D_1. Doing so will give the effective reproduction number

$$R_q = \sqrt{\frac{\sigma p_v e^{-\mu_V \tau_e} Q}{(\alpha+\mu+sq)\mu_V}\left(\frac{\mu b_1^2 p_1}{(\gamma+\mu+\alpha+q\omega)}+\frac{\alpha b_2^2 p_2}{(\gamma+\mu)}\right)}. \tag{14}$$

Unlike in the previous model, here the vaccination is always effective since

$$\frac{R_q}{R_0} = \sqrt{\frac{(\alpha+\mu)}{(\alpha+\mu+sq)}\frac{(\gamma+\mu+\alpha)}{(\gamma+\mu+\alpha+q\omega)}\frac{b_1^2 p_1\mu(\gamma+\mu)+b_2^2 p_2\alpha(\gamma+\mu+\alpha+q\omega)}{b_1^2 p_1\mu(\gamma+\mu)+b_2^2 p_2\alpha(\gamma+\mu+\alpha)}}, \tag{15}$$

which is obviously always less than 1. In this case the critical level of vaccination is similar to inequality (13) with the opposite sign of $q\omega$ terms.

In the previous model (Section 3) we have assumed a scenario in which a health manager does not realize the presence of the infectious classes I_j. We call this as an ignorant scenario of a vaccination program. In this case the vaccination effort is set at a level of coverage q and enforced to the 'assumed' susceptible part of the population, which is $S_1 + I_1$ instead of S_1. This may result in wasting vaccination effort besides, in some circumstances, creates an ineffective vaccination if the model in Section 3 is believed to be true. Although in terms of reducing the basic reproduction number, the model in Section 4 predicts that vaccination is always effective, ethically, we should avoid the chance of vaccinating asymptomatic infected individuals that may lead to more severe symptom for them.

We can consider another scenario, where the manager realizes the presence of the asymptomatic infectious classes I_j, but still cannot identify to which class an individual belongs. In this case, a portion p of vaccination is given after screening to ensure that the vaccine is given to individuals of the true susceptible child-class. The remaining portion is given randomly to presumably susceptible individuals with successful probability of finding the truly susceptible is r. In this scenario, the effective reproduction number in Eq. (7) changes. As a result the measure of vaccination effectiveness also changes. For example, if $\alpha = 0$, it is given by

$$P = \sqrt{\frac{\mu(\gamma+\mu)}{(\mu+(p+(1-p)r)sq)(\gamma+\mu-(1-p)(1-r)q\omega)}}. \tag{16}$$

Clearly if p tends to one, then P is always less than one. Furthermore, the condition for avoiding the ineffectiveness of the vaccination in inequality (9) also changes into

$$\omega < (\mu+\gamma)s\frac{p+r(1-p)}{(1-p)(1-r)(sq(r(1-p)+p)+\mu)}, \tag{17}$$

which always holds if p is sufficiently close to one. These suggest that screening is necessary to gain an effective vaccination program. Furthermore, screening can also save the unnecessary effort of vaccinating infectious children.

5. Concluding remarks

We have discussed a two-age-classes dengue transmission model and assumed that a negative effect of vaccination might occur. If there is an undeliberate vaccination of asymptomatic infectious children that effectively enlarges the infectious period, then a paradox of vaccination might occur. The paradox, stating that vaccination makes the basic reproduction number bigger, might occur if the worsening effect is greater than a certain threshold. The threshold is a function of the human demographic and epidemiological parameters, which might be independent of the level of vaccination. Although the region of the realistic parameters in which the vaccination might happen is regarded as a small region, still this paradox must be avoided. It can be avoided, for example, by screening the target population before vaccination. However, if the worsening effect increases virulence so that one will develop symptoms, then the vaccination always helps in reducing the basic reproduction number. Further work can be done by explicitly modeling the mechanism of the second and third infections via the introduction of multiple strains of viruses. Severe infection can be modeled as a result of certain combinations of consecutive infections by different strains of viruses [39]. Improvement of the model can also be accomplished by considering a different age distribution in the child-class.

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Appendix A

Without loss of generality, let us concentrate on the susceptible child-class. The analogous partial differential equation for Eq. (1a) is given by:

$$\frac{\partial s_1(t,a)}{\mathrm{d}t}+\frac{\partial s_1(t,a)}{\mathrm{d}a} = -\mu s_1(t,a) - b_1 p_1 I_v(t)\frac{s_1(t,a)}{N} - q s_1(t,a), \tag{A.1}$$

with

$$s_1(t,0) = B. \tag{A.2}$$

Suppose that T is the final age of the child-class, and let us assume that $s_1(t,T) = s_2(t,T)$ or in the other words the starting age of the adult-class is the final age of the child-class. Let

$$S_1(t) = \int_0^T s_1(t,a)\,\mathrm{d}a. \tag{A.3}$$

The integration of Eq. (A.1) with the respect to age along the interval $[0,T]$ gives

$$\frac{\mathrm{d}S_1(t)}{\mathrm{d}t} = B - s_1(t,T) - \mu S_1(t) - b_1 p_1 I_v(t)\frac{S_1(t)}{N} - q S_1(t). \tag{A.4}$$

Hence Eq. (1a) is obtained if we have the relation $s_1(t,T) = \alpha S_1(t)$. This relation can be obtained for a certain choice of α. Note that from A.3, and using the Mean Value Theorem, there exists $T^* \in (0,T)$ such that

$$S_1(t) = \int_0^T s_1(t,a)\mathrm{d}a = T s_1(t,T^*). \tag{A.5}$$

Moreover, by the Taylor expansion for a fixed t yields

$$s_1(t,T^*) = s_1(t,T) + s_1'(t,T)(T^*-T) + \frac{1}{2}T^2 s_1''(t,T_1)\left(\frac{T^*}{T}-1\right)^2, \tag{A.6}$$

for some $T^* < T_1 < T$. We consider a type of population distribution $s(t,a)$ in which for any $t > 0$, $\frac{\mathrm{d}s(t,T)}{\mathrm{d}a} = 0$ and $|\frac{\mathrm{d}^2 s(t,T)}{\mathrm{d}a^2}| << 1$ for some $T > 0$. This assumption represents a real condition in some region

(see [3]) where the population distribution is slowly increasing from the new born age to the transition age T reaching its maximum at T, and relatively flat around T. Hence, if we choose T such that $s_1'(t,T)=0$ and assuming that $|s_1''(t,T_1)| \ll \frac{2}{T^2}$, then from (A.6) we have $s_1(t,T^*) \approx s_1(t,T)$. Consequently, by choosing $\alpha = \frac{1}{T}$ the required relation is obtained.

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