Bull Math Biol (2014) 76:2073–2090
DOI 10.1007/s11538-014-9999-6

Society for Mathematical Biology

ORIGINAL ARTICLE

Vaccination Strategies for SIR Vector-Transmitted Diseases

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Received: 3 October 2013 / Accepted: 18 July 2014 / Published online: 8 August 2014

Abstract Vector-borne diseases are one of the major public health problems in the world with the fastest spreading rate. Control measures have been focused on vector control, with poor results in most cases. Vaccines should help to reduce the diseases incidence, but vaccination strategies should also be defined. In this work, we propose a vector-transmitted *SIR* disease model with age-structured population subject to a vaccination program. We find an expression for the age-dependent basic reproductive number R_0, and we show that the disease-free equilibrium is locally stable for $R_0 \leq 1$, and a unique endemic equilibrium exists for $R_0 > 1$. We apply the theoretical results to public data to evaluate vaccination strategies, immunization levels, and optimal age of vaccination for dengue disease.

Keywords Vector-borne disease · Age-dependent contact rate · Vaccination strategy · Optimal vaccination · Dengue

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1 Introduction

Vector-borne diseases are infections transmitted by the bite of infected arthropod species, such as mosquitoes, ticks, triatomine bugs, sandflies, and blackflies. According to World Health Organization, vector-borne diseases are responsible for 17 % of the estimated global burden of all infectious diseases (Townson et al. 2005). Only malaria, the most deadly vector-borne disease, caused an estimated of 300 millions of cases with 627,000 deaths in 2012, mostly African children under the age of five (World Health Organization 2009b). Dengue fever, together with associated dengue hemorrhagic fever (DHF), is the world's fastest growing vector-borne disease. It is estimated that dengue virus causes around 50–100 million cases every year (World Health Organization 2009a), with more than 500,000 reported cases with the severe form of the disease, dengue hemorrhagic fever (DHF), although other sources mention up to 390 million of cases (Bhatt et al. 2013). As dengue disease, yellow fever is a viral disease transmitted by Aedes mosquitoes, and found in tropical regions of Africa and the Americas. This disease can produce severe outbreaks, which can be prevented and controlled by mass vaccination campaigns. Other examples of vector-borne diseases with important impact are Chagas disease, West Nile virus disease, Chikungunya, among others.

Currently, the main aim of most programs is to reduce the densities of vector populations as much as possible and to maintain them at low levels. Control methods include the elimination or management of vector habitats, use of larvicides, use of biological agents, and the application of insecticides. However, all known control methods have limitations. For instance, indiscriminate use of insecticides rapidly produce resistance, besides to pollute the environment.

Biological control is based on the introduction of predators, parasites, or competitors in order to reduce the population of the target species. But although a biological control avoids chemical contamination of the environment, there may be operational limitations such as the cost and task of producing the control organisms on a large scale, and there is a potential risk that the control gets out of hand (World Health Organization 2009b). Thus, research on vaccines, environmentally safe insecticides, and alternative approaches to vector control are needed.

Commercial vaccines are available only for few vector-borne diseases, among them yellow fever, Japanese encephalitis, tickborne encephalitis, and plague, and they are not yet widely used. In general, the design of effective vaccines for major vector-borne diseases presents great challenges. For instance, in the case of malaria, some of the negative factors include the genetic complexity of the parasite. Another problem for malaria and Chagas disease is that the vaccines require a great amount of biological material (Zofou et al. 2014). The main problem for the development of a vaccine against dengue has been the existence of four different serotypes,[1] and the risk of dengue hemorrhagic fever (DHF) (Halstead et al. 2005). Due to these dengue-specific complexities, vaccine development focuses on the generation of a tetravalent vaccine aimed to provide long-term protection against all virus serotypes.

[1] Lately, there are claims about the discovery of a fifth serotype (ScienceInsider).

In spite of the difficulties mentioned above to elaborate effective vaccines for vector-borne diseases, significant progress has been made in recent years and, for instance, at the present several candidates are being developed for dengue disease (Guy et al. 2010).

Mathematical models have been an important tool to assess the efficacy of vaccination strategies, particularly for direct transmitted diseases, see Anderson and May (1994), Castillo-Chavez and Feng (1998), Dietz and Schenzle (1985), Gao and Hethcote (2006), Hadeler and Müeller (1993a), Hadeler and Müeller (1993b), Hethcote (1988) among others. Since no effective vaccine exists yet for some of the most common vector-transmitted diseases, few models have explicitly considered the potential impact of vaccination for such diseases. In Billings et al. (2008), an ODE model is given to evaluate the effects of single-strain vaccine campaigns on the dynamics of an epidemic multistrain model. More recently, in Coudeville and Garnett (2012) was proposed an age-structured, host-vector, and serotype-specific compartment model. Numerical simulations were done to design scenarios for the potential impact of a dengue disease vaccine on a population.

In this work, we formulate a mathematical model for vector-borne diseases with recovery, age-dependent infectivity, and vaccination. Our aim is to explore the impact of vaccines on the control of those diseases. We find an expression for the basic reproduction number, R_0, and we show that the disease can invade the population and a unique endemic steady state exists if $R_0 > 1$. As an application, we study the dengue incidence in Mexico. We apply the procedures discussed in Hadeler and Müeller (1993a), Hadeler and Müeller (1993b), Thieme (2003) to find possible optimal vaccine strategies for this disease. In particular, we found that vaccination between age two and three could be an optimal vaccination age in Mexico.

The paper is organized as follows. Formulation of the model is given in Sect. 2. The basic reproduction number R_0 and the net reproductive number $R_0(V)$ for a vaccination profile $V(a)$ are given in Sect. 3. Vaccination strategies applied to data of dengue disease in Mexico are presented in Sect. 4. Discussion of the results are given in Sect. 5. The mathematical details to prove the local stability of the infection-free steady state are presented in Appendix.

2 Formulation of the Model

We assume a human population where the susceptible newborns are recruited at a constant rate B, and individuals die according to the rate $\mu(a)$. Further, the population is divided into susceptible, infected, and removed classes, where $s(a,t)$, $i(a,t)$, and $z(a,t)$ denote the densities of age a at time t in the respective class, and $n(a,t) = s(a,t) + i(a,t) + z(a,t)$ is the total population of age a at time t. The total human population at time t is equal to

$$N_h(t) = \int_0^\infty n(a,t)\mathrm{d}a.$$

The vector population is assumed constant, and it is denoted by N_v. We assume that vector population never recover from infection; therefore, we only consider the susceptible and infective for this population, where $s_v(t)$ and $i_v(t)$ are the proportion of individuals of each class, respectively.

Following Esteva and Vargas (1998), the rate of infection to an individual of age a, $\alpha_h(a,t)$, depends on the number of vector bites that an individual receives and on the probability, $\beta_h(a)$, that an infectious bite in an individual of age a gives rise to a new case. The average number of bites received by a human is given by $bm(t)$, where b is the vector biting rate, and $m(t) = \dfrac{N_v}{N_h(t)}$. Putting the above assumptions together, we obtain $\alpha_h(a,t) = bm(t)\beta_h(a)$. On the other hand, we assume that the infective rate per individual of age a to vectors is given by $\alpha_v(a) = b\beta_v(a)$, where $\beta_v(a)$ is the probability transmission from individuals of age a to vector.

For the human population, $\gamma(a)$ is the age-specific recovery rate, and $\mu(a)$ the age-specific mortality rate. The effective age-dependent immunization rate is given by $\sigma(a) = \nu\eta(a)$ where $\eta(a)$ is the age-dependent vaccination rate, and $0 \leq \nu \leq 1$ is the vaccine efficacy (we assume that this parameter is age independent). Finally, for the vector population, μ_v denotes the vector mortality rate.

According to the assumptions above, the dynamics of the disease transmission is governed by the following system of partial differential equations:

$$\begin{aligned}
\frac{\partial s(a,t)}{\partial a} + \frac{\partial s(a,t)}{\partial t} &= -\alpha_h(a,t)i_v(t)s(a,t) - (\sigma(a)+\mu(a))s(a,t)\\
\frac{\partial i(a,t)}{\partial a} + \frac{\partial i(a,t)}{\partial t} &= \alpha_h(a,t)i_v(t)s(a,t) - (\mu(a)+\gamma(a))i(a,t)\\
\frac{\partial z(a,t)}{\partial a} + \frac{\partial z(a,t)}{\partial t} &= \gamma(a)i(a,t) - \mu(a)z(a,t) + \sigma(a)s(a,t)\\
\frac{\mathrm{d}i_v}{\mathrm{d}t} &= \frac{1}{N_h(t)}\left(\int_0^\infty \alpha_v(a')i(a',t)\mathrm{d}a'\right)(1-i_v(t)) - \mu_v i_v(t)
\end{aligned} \tag{1}$$

with initial and boundary conditions given by

$$\begin{aligned}
&s(a,0) = s_0(a), \quad i(a,0) = i_0(a), \quad z(a,0) = z_0(a), \quad i_v(0) = i_{v_0}\\
&s(0,t) = B, \quad i(0,t) = 0, \quad z(0,t) = 0.
\end{aligned}$$

2.1 Age-Independent Model

Let $\lambda_v(t) = \frac{1}{N_h(t)}\int_0^\infty \alpha_v(a')i(a',t)\mathrm{d}a'$ the infection rate from humans to vectors. Assume $\mu(a)$, $\alpha_h(a,t)$, $\alpha_v(a)$, $\gamma(a)$, and $\sigma(a)$ independent of a. Adding the first three equations of system (1) and integrating with respect to a, we obtain that $N_h(t)$ satisfies

$$\frac{\mathrm{d}N_h(t)}{\mathrm{d}t} = B - \mu N_h(t), \tag{2}$$

and therefore $N_h(t) \to \dfrac{B}{\mu} \equiv \bar{N}_h$ when $t \to \infty$. In the limit, we obtain the following ODE system with constant coefficients for the number of individuals in each class at time t.

$$\begin{aligned}
\frac{\mathrm{d}S(t)}{\mathrm{d}t} &= B - \alpha_h S(t) i_v(t) - (\sigma + \mu) S(t) \\
\frac{\mathrm{d}I(t)}{\mathrm{d}t} &= \alpha_h S(t) i_v(t) - (\gamma + \mu) I(t) \\
\frac{\mathrm{d}Z(t)}{\mathrm{d}t} &= \gamma I(t) + \sigma S(t) - \mu Z(t) \\
\frac{\mathrm{d}i_v(t)}{\mathrm{d}t} &= \alpha_v \frac{I(t)}{\bar{N}_h}(1 - i_v(t)) - \mu_v i_v(t)
\end{aligned} \tag{3}$$

where

$$S(t) = \int_0^\infty s(a', t)\mathrm{d}a', \quad I(t) = \int_0^\infty i(a', t)\mathrm{d}a', \quad Z(t) = \int_0^\infty z(a', t)\mathrm{d}a'.$$

To calculate the basic reproductive number associated with model (3), we assume no vaccination and all of the population to be susceptible; therefore, the disease-free equilibrium is given by $(\bar{N}_h, 0, 0, 0)$. According to Diekmann and Heesterbeek (2000), Driessche and Watmough (2002) the basic reproductive number is given by the spectral ratio of the matrix

$$\begin{pmatrix} 0 & \frac{\alpha_h \bar{N}_h}{\mu_v} \\ \frac{\alpha_v}{(\gamma+\mu)\bar{N}_h} & 0 \end{pmatrix}$$

which is given by

$$R_0 = \sqrt{\frac{\alpha_h \alpha_v}{\mu_v(\gamma + \mu)}}. \tag{4}$$

If a fraction σ of the population is vaccinated per unit of time, the fraction of susceptibles in the absence of the disease becomes $S_\sigma = \dfrac{B}{\sigma + \mu}$; therefore, the number of secondary cases derived from a primary case is reduced to

$$R_0(\sigma) = \sqrt{\frac{\alpha_h \alpha_v S_\sigma}{\mu_v(\gamma + \mu)\bar{N}_h}}. \tag{5}$$

where $R_0(\sigma)$ denotes the *Net reproductive number*, which gives the number of secondary cases that an infected individual produces in a population that is vaccinated at

a per capita rate σ (Thieme 2003). Substituting S_σ and $\bar{N}_h$ in $R_0(\sigma)$, we obtain

$$R_0(\sigma) = \sqrt{\frac{\alpha_h \alpha_v B/(\sigma+\mu)}{\mu_v(\gamma+\mu)(B/\mu)}} = R_0\sqrt{\frac{\mu}{\sigma+\mu}}.$$

Then, the disease can be eradicated if $R_0(\sigma) \leq 1$ or

$$\sigma \geq \mu(R_0^2 - 1). \tag{6}$$

3 Steady State Age Model

In the previous section, vaccination policy was completely at random. However, the vaccination tests are done only in certain age groups depending upon the country (Guy et al. 2010). For this reason, it will be more realistic to consider an age-dependent vaccination scheme. We will consider the case when the steady state age distributions are reached as time approaches infinity, and therefore, the infection rate $\lambda_v(t)$ approaches a constant λ_v^*. As in the case with no age structure, we first assume no vaccination.

We notice that $n(a,t)$ satisfies the following PDE problem:

$$\frac{\partial n(a,t)}{\partial a} + \frac{\partial n(a,t)}{\partial t} = -\mu(a)N_h(a,t), \tag{7}$$

with $n(0,t) = B$, and $n(a,0) = n_0(a) = s_0(a) + i_0(a) + z_0(a)$.

Using the method of characteristics, we get:

$$n(a,t) = \begin{cases} n_0(a)e^{-\int_{a-t}^{a}\mu(a')\mathrm{d}a'} & a \geq t \\ Be^{-\int_0^a \mu(a')\mathrm{d}a'} & t > a. \end{cases}$$

As $t \to \infty$,

$$n(a,t) \to Be^{-\int_0^a \mu(a')\mathrm{d}a'} \equiv n^*(a),$$

and N_h approaches the constant value

$$B\int_0^\infty e^{-M(a)}\mathrm{d}a = N_h^*,$$

where $M(a) = \displaystyle\int_0^a \mu(a')\mathrm{d}a'$. In this case, $m = \dfrac{N_v}{N_h^*}$ is constant.

Assuming that the steady state distribution is reached, and (1) is independent of t, then we obtain the following system of linear differential equations for the independent

variable a

$$\begin{aligned}\frac{\mathrm{d}s^*(a)}{\mathrm{d}a} &= -\alpha_h(a)i_v^*s^*(a) - \mu(a)s^*(a)\\ \frac{\mathrm{d}i^*(a)}{\mathrm{d}a} &= \alpha_h(a)i_v^*s^*(a) - (\gamma(a)+\mu(a))i^*(a)\\ \frac{\mathrm{d}z^*(a)}{\mathrm{d}} &= \gamma(a)i^*(a) - \mu(a)z^*(a)\end{aligned} \tag{8}$$

where $s^*(0) = B$, $i^*(a) = 0$, $z^*(0) = 0$, and i_v^* denote the constant proportion of infected vectors given by

$$i_v^* = \frac{\dfrac{1}{N_h^*}\displaystyle\int_0^\infty \alpha_v(a')i^*(a')\mathrm{d}a'}{\dfrac{1}{N_h^*}\displaystyle\int_0^\infty \alpha_v(a')i^*(a')\mathrm{d}a' + \mu_v} = \frac{\lambda_v^*}{\lambda_v^* + \mu_v}. \tag{9}$$

Integrating (8), we obtain the following expressions for the steady state age distributions of the proportion of individuals in each class,

$$\begin{aligned}s^*(a) &= n^*(a)e^{-i_v^*\lambda_h(a)}\\ i^*(a) &= n^*(a)i_v^*\int_0^a \alpha_h(a')e^{-[i_v^*\lambda_h(a')+G(a)-G(a')]}\mathrm{d}a'\\ z^*(a) &= 1 - s^*(a) - i^*(a)\end{aligned} \tag{10}$$

where

$$\lambda_h(a) = \int_0^a \alpha_h(s)\mathrm{d}s, \tag{11}$$

and

$$G(a) = \int_0^a \gamma(s)\mathrm{d}s. \tag{12}$$

Substituting $i^*(a)$ and i_v^* in the expression (9), we obtain

$$\lambda_v^* = \int_0^\infty \frac{\alpha_v(a)}{N_h^*}n^*(a)\frac{\lambda_v^*}{\lambda_v^*+\mu_v}\int_0^a \alpha_h(a')e^{-[\frac{\lambda_v^*}{\lambda_v^*+\mu_v}\lambda_h(a')+G(a)-G(a')]}\mathrm{d}a'\mathrm{d}a. \tag{13}$$

From the above expression, either $\lambda_v^* = 0$ or λ_v^* satisfies the characteristic equation

$$1 = \int_0^\infty \frac{\alpha_v(a)}{N_h^*}n^*(a)\int_0^a \alpha_h(a')\frac{e^{-[\frac{\lambda_v^*}{\lambda_v^*+\mu_v}\lambda_h(a')]}}{\lambda_v^*+\mu_v}e^{-[G(a)-G(a')]}\mathrm{d}a'\mathrm{d}a. \tag{14}$$

Since

$$g(\lambda_v^*) = \frac{e^{-[\frac{\lambda_v^*}{\lambda_v^*+\mu_v}\lambda_h(a')]}\mu_v}{\lambda_v^*+\mu_v}$$

is a decreasing function of λ_v^*, with $g(0) = 1$, we conclude that (14) has a unique positive solution λ_v^* provided

$$R_0 = \int_0^\infty \frac{\alpha_v(a')}{N_h^*} i^*(a')\mathrm{d}a' n^*(a) e^{-G(a)} \int_0^a \frac{\alpha_h(a')}{\mu_v} e^{G(a')}\mathrm{d}a'\mathrm{d}a > 1. \tag{15}$$

is satisfied.

The expression of the left-hand side of (15) is interpreted as the average number of secondary cases one infectious individual produces in a population if it is introduced in a disease-free population. Hence, R_0 is the basic reproduction number. When $R_0 > 1$, λ_v^* is positive, and i_v^*, $s^*(a)$, $i^*(a)$, $z^*(a)$ given by Eqs. (9) and (10) correspond to an endemic steady state age distribution, meanwhile, if $R_0 < 1$, $\lambda_v^* = 0$, and Eqs. (9), (10) correspond to the disease-free steady state age distributions with no infected and recovered individuals. In Appendix, we prove the stability of the disease-free steady state age distribution for some kind of perturbations.

3.1 Vaccination

In the following, we are interested in the effect of vaccination on the threshold condition (15). Given the age dependent per capita vaccination rate $\sigma(a)$, the steady demographic proportion of susceptibles in the absence of the disease is given by

$$s_\sigma^*(a) = n^*(a)V(a) \tag{16}$$

where

$$V(a) = e^{-\int_0^a \sigma(\alpha)d\alpha} \tag{17}$$

is the fraction of individuals still not being vaccinated at age a. Using the same arguments as for the basic reproduction number, we obtain that the net reproductive number $R_0(V)$ associated with the vaccination profile $V(a)$ is given by

$$R_0(V) = \int_0^\infty \frac{\alpha_v(a)}{N_h^*} n^*(a) e^{-G(a)} \int_0^a \frac{\alpha_h(a')}{\mu_v} V(a') e^{G(a')}\mathrm{d}a'\mathrm{d}a \tag{18}$$

It is clear that $R_0(V) \leq R_0$. Changing the order of integration, and a' by a, $R_0(V)$ becomes

$$R_0(V) = \int_0^\infty \Phi(a)V(a)\mathrm{d}a, \tag{19}$$

where

$$\Phi(a) = \frac{\alpha_h(a)}{\mu_v} e^{G(a)} \int_a^\infty \frac{\alpha_v(a')}{N_h^*} n^*(a') e^{-G(a')}\mathrm{d}a'. \tag{20}$$

Now, we want a vaccination strategy to get mass immunity. If cost of vaccination is not considered, it is enough to find V such that $R_0(V) < 1$. In the following, we will assume that human mortality (μ), recovery rate (γ), and transmission rate from

Table 1 Demographic and epidemiological parameters

Parameter	Meaning	Value	Sources
N_h^*	Human population	112, 336, 538	Instituto Nacional de Estadística (2014)
B	Recruitment birth rate	$0.019 \times N_h^*$	Instituto Nacional de Estadística (2014)
μ	Human mortality	$0.00004\ \text{days}^{-1}$	
μ_v	Vector mortality	$0.06\ \text{days}^{-1}$	Pinho et al. (2010)
b	Mosquito biting rate	$0.5\ \text{day}^{-1}$	Gubler (1986)
β_v	Human–vector transmission	0.75	Newton and Reiter (1992)
$\beta_h = 0.0244ae^{-0.0625a}$	Vector–human transmission		Estimated from Fig. 1
$1/\gamma$	Average infection period	8 days	Gubler (1986)

humans to vectors (α_v) are age independent with values given in Table 1. In this case, $\Phi(a)$ adopts the form

$$\Phi(a) = \frac{\alpha_v B}{\mu_v(\mu_h + \gamma)N_h^*}\alpha_h(a)e^{-\mu a}. \tag{21}$$

4 Application to Dengue Disease

In this section, we apply the model developed previously to the age distribution of dengue in Mexico during 2013 (SINAVE 2014). These data are shown in Fig. 1.

As was said in the Introduction, several candidates for a dengue vaccine are being developed, in particular a tetravalent vaccine composed of four recombinant live attenuated vaccines (Guy et al. 2010). Clinical trials were conducted in the USA, the Philippines, Mexico, and Australia among other countries, in a three dose regimen over 12 months to evaluate vaccine reactions, viremia induction, and antibody response. Reported results indicate that the majority of the adverse symptoms were from mild to moderate, and transitory. In the trial done to Mexican children aged 2–5 years, the found seropositivity was from 88 to 100 % (Guy et al. 2010). However, we should mention that in Sabchareon et al. (2012), it is shown that, despite the levels of protection against the four serotypes combined, protection against serotype 2 was small (efficacy of 9.2 %).

We normalize data given in Fig. 1 with respect to the total number of cases, and we fit a function of the form

$$f(a) = kae^{-da}, \tag{22}$$

with $k = 0.0244$, and $d = 0.0625$ (see Fig. 2). The data were normalized in order to interpret $f(a)$ as the age-specific probability of becoming infected through vector bites, $\beta_h(a)$. Therefore, the infection rate $\alpha_h(a) = mbf(a)$, where b is the biting rate, and m is the quotient of vectors to humans, defined in Sect. 2.1.

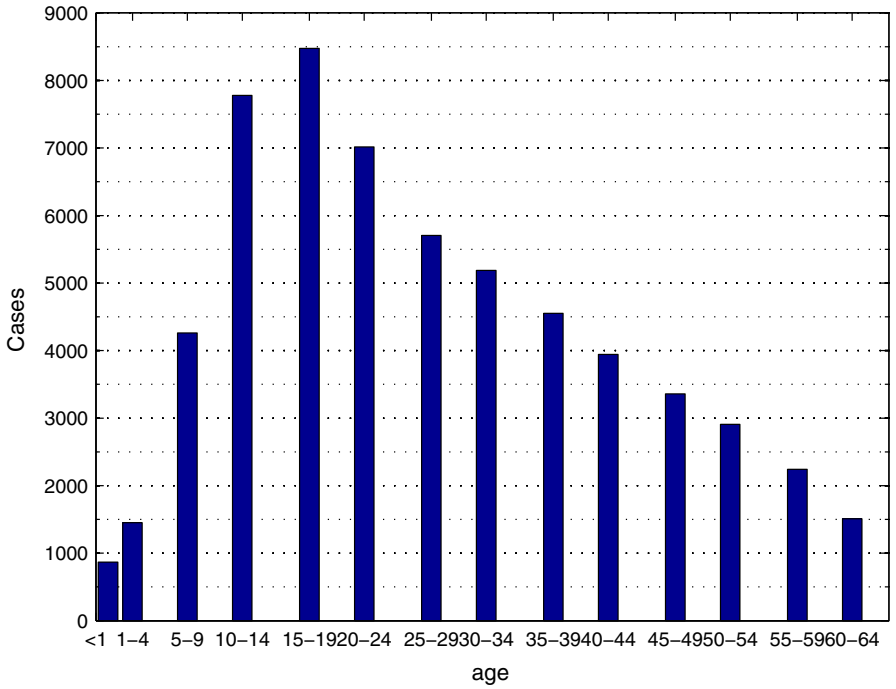

Fig. 1 Distribution of dengue cases by age groups, Mexico, 2013. Data taken from SINAVE (2014)

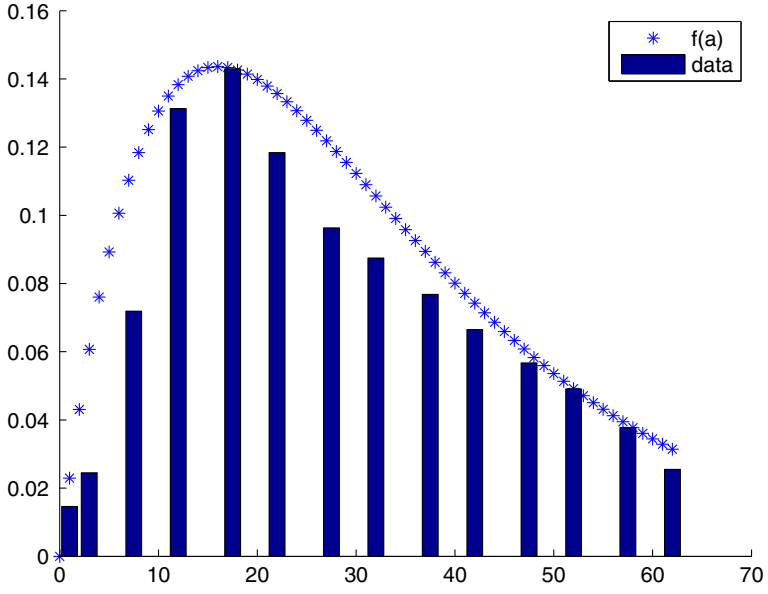

Fig. 2 Adjusted function $f(a) = 0.0244ae^{-0.0625a}$ of the proportion of dengue infections by age group with respect to the total number of cases. Data taken from SINAVE (2014)

Substituting α_h and the parameter values of Table 1 in the expression for $R_0(V)$ given in (19), we obtain

$$R_0(V) = \int_0^\infty V(a)\Phi(a)\mathrm{d}a = 0.014m\int_0^\infty ae^{-[\sigma(a)+0.06254a]}\mathrm{d}a.$$

Since we want the infected proportion to decrease, we need $R_0(V) \leq 1$; therefore, $\sigma(a)$ must satisfy

$$\int_0^\infty ae^{-[\sigma(a)+0.06254a]}\mathrm{d}a \leq \frac{71.43}{m}. \tag{23}$$

By definition, $V(a)$ is a non-increasing function that takes values in the interval [0,1] and represents the fraction of individuals not yet immunized at age a. Then, inequality (23) gives a condition for the fraction of not immunized individuals that should be satisfied in order to get mass immunity. Observe that this condition is inversely proportional to m, and therefore, if the quotient of vectors to humans increases, the fraction of immunized individuals $\sigma(a)$ should increase as it is expected.

4.1 Optimal Vaccination Strategies

This section is based upon the work of Thieme (2003). We apply his results to the data of dengue disease in Mexico.

The goal of a vaccination campaign is to reduce as much as possible the disease prevalence considering the limitations of the health budget. In designing an optimal vaccination policy, the cost of vaccination should be balanced with the degree of protection of the population. Here, we will assume that increasing the protection of the population is proportional to decreasing the net reproductive number.

Two optimization problems can be considered: a) find a vaccination strategy $V(a)$ that minimizes the cost $C(V)$ of vaccination restricted to $R_0(V) \leq \rho$, and b) find a vaccination strategy $V(a)$ that minimizes $R_0(V)$ restricted to $C(V) \leq c$. Here, we will focus on the second problem; that is, minimizing the net reproductive number, and consequently, maximizing the protection of the population.

Let $c(a)$ be the cost associated with one vaccination at age a. Such cost depends on several factors, cost of vaccine, rate of vaccination, accessibility to the age class, among others. Recalling that $s_\sigma^* = Be^{-M(a)}V(a)$ represents the susceptible population of age a under a vaccination scheme given by σ, then the total cost of a vaccination program is given by

$$C = \int_0^\infty c(a)\sigma(a)s_\sigma^*(a)\mathrm{d}a. \tag{24}$$

Since $\dot{V}(a) = -\sigma(a)V(a)$, where $\cdot = d/\mathrm{d}a$, the cost function can be written in the form:

$$C = -\int_0^\infty c(a)Be^{-M(a)}\dot{V}(a)\mathrm{d}a. \tag{25}$$

The *vaccination distribution*, $W(a)$, represents the probability of being vaccinated up to age a:

$$W(a) = 1 - V(a). \tag{26}$$

$W(a)$ is a non-decreasing function that takes values between 0 and 1, and $W(0) = 0$. When all individuals are vaccinated at one age, $\bar{a} \geq 0$, $W(a)$ adopts the form

$$W_{\bar{a}}(a) = \begin{cases} 0 & 0 \leq a < \bar{a} \\ 1 & a > \bar{a}, \end{cases} \tag{27}$$

and for $0 \leq q \leq 1$, $qW_{\bar{a}}$ represents a vaccination schedule where a fraction q of individuals of age $\bar{a}$ is vaccinated.

Taking $du = \Phi \mathrm{d}a$ and $v = V$ in (19), $R_0(V)$ becomes

$$R_0(V) = \int_0^\infty \Phi(a)\mathrm{d}a + \int_0^\infty \left(\int_a^\infty \Phi(a')\mathrm{d}a'\right)\dot{V}(a)\mathrm{d}a.$$

Therefore, in terms of W, the net reproductive number and the cost function become:

$$\begin{aligned} R_0(W) &= h_1(0) - \int_0^\infty h_1(a)\dot{W}(a)\mathrm{d}a \\ C(W) &= \int_0^\infty h_2(a)\dot{W}(a)\mathrm{d}a. \end{aligned} \tag{28}$$

with

$$\begin{aligned} h_1(a) &= \int_a^\infty \Phi(a')\mathrm{d}a' \\ h_2(a) &= c(a)Be^{-M(a)} \end{aligned} \tag{29}$$

The functions h_1 and h_2 satisfy

$$\frac{h_1(a)}{h_2(a)} \leq r \times \frac{L(a)}{c(a)} \tag{30}$$

where $L(a) = \dfrac{\int_0^\infty e^{-M(a')}\mathrm{d}a'}{e^{-M(a)}}$ is the expected remaining life at age a.

We will assume that everybody is vaccinated at the same age (one-age strategy). We want to minimize $R_0(V)$ with the cost constraint $C(w) \leq c$. If newborns can be vaccinated, and the cost of immunizing everybody at birth is less than c, it is better to adopt a vaccination distribution W_0 with $W(0) = 0$, and $W(a) > 0$ for $a > 0$.

If $C(W_0) > c$, the problem is not trivial, and in this case, minimizing $R_0(W)$ is equivalent to maximizing

$$\int_0^\infty h_1(a)\dot{W}(a)a = \int_0^l \frac{h_1(a)}{h_2(a)} h_2(a)\dot{W}(a)\mathrm{d}a \tag{31}$$

where l is the maximum lifetime. Assuming $L(a)/c(a) \to 0$, it is proved that for a one-age strategy concentrated at age $\bar{a}$, $qW_{\bar{a}}$, the maximum is obtained vaccinating at age a^* where h_1/h_2 attains its maximum. Furthermore, if $C(W_{a^*}) \geq c$, then the one-age strategy concentrated at age a^* is optimal. In this case, the percentage of people vaccinated is chosen such that $q = c/C(W_{a^*})$. If $C(W_{a^*}) < c$, a better strategy can be obtained combining it with vaccination at age 0, and, in fact, optimal strategies are one-age strategies where everybody is vaccinated when reaching the same specific age $a \leq a^*$, or two-age strategies where at the second vaccination age, h_1/h_2 takes its maximum, and all the individuals that have not been vaccinated at the first age are vaccinated at the second age (see Hadeler and Müeller 1993a, b).

Next, we apply the above concepts to dengue data in Mexico. Let assume that Φ is given by (21) with parameters values in Tables 1 and 2. Then,

$$\begin{aligned} h_1(a) &= \int_a^\infty bmka' e^{-(d-\gamma)a'} \left(\int_{a'}^\infty \frac{\alpha_v}{N_h^*} B e^{-(\mu+\gamma)a''} \mathrm{d}a'' \right) \mathrm{d}a' \\ &= \bar{K} B \left((d+\mu)a + 1\right) e^{-(d+\mu)a}, \end{aligned}$$

where $\bar{K} = \dfrac{bmk\alpha_v}{N_h^*(\mu+\gamma)(d+\mu)^2}$. Therefore,

$$\frac{h_1}{h_2} = \frac{\bar{K}\left((d+\mu)a + 1\right) e^{-\mathrm{d}a}}{c(a)}. \tag{32}$$

Suppose $c(a)$ is a constant equal to $c_o \geq c$, the optimal strategy is to vaccinate at the age where $h_1(a)$ attains its maximum value $a^* = \dfrac{\mu}{d(d+\mu)}$. For $1/\mu = 70$ years, and $d = 0.0625 = 1/16$ years, $a^* = 2.9$, which implies that the maximum protection against the disease is obtained vaccinating between 2 and 3 years of age. In this case, the proportion of individuals to vaccinate is $q = c/c_0$.

It is interesting to observe from Fig. 1 that the maximum incidence of dengue is around 16 years of age, but the optimal age of vaccination is around 3 years of age. If, for instance, the maximum incidence was at 25 years old, the optimal age would be around 6–7 years old. According to the above example, if vaccination cost is age independent, the optimal schedule depends on the maximum age incidence.

4.2 Age-Independent Vaccination Strategy

When costs of the immunization campaign are not the most important restriction, and vaccination can be done at any age, the vaccination rate, σ, can be considered constant

in order to give a rough estimation of the proportion that has to be immunized to achieve herd immunity. In this case, $V(a) = e^{-\sigma a}$, and after integration (23) becomes

$$\frac{1}{(\sigma + 0.062544)^2} \leq \frac{71.43}{m},$$

or

$$\sigma \geq \frac{\sqrt{m} - 0.53}{8.45}. \tag{33}$$

Recall that $\sigma = \nu\eta$ where η is the vaccination rate, and $0 \leq \nu \leq 1$ is the vaccine efficacy. For dengue disease, it is estimated that vaccine efficacy against the four serotypes is between 88 and 100 %; therefore, if $\nu = 0.88$, immunity can be achieved if the vaccination rate

$$\eta \geq \frac{\sqrt{m} - 0.53}{8.45 \times \nu} = \frac{\sqrt{m} - 0.53}{7.44}.$$

On the other side, the fraction of individuals that have not been immunized are given by $\int_0^\infty V(a)\mathrm{d}a = \frac{1}{\sigma}$, and therefore, $1 - \frac{1}{\sigma}$ represents the fraction of immunized ones. Thus, from condition (33), we obtain in this example that the fraction of individuals that have to be immunized in order to get mass immunity is

$$1 - \frac{1}{\sigma} \geq 1 - \frac{7.44}{\sqrt{m} - 0.53}, \tag{34}$$

In the hypothetical case $m = 100$, we obtain that at least 78 % of the population should be immunized.

5 Conclusions

The model and methods described in this work can be employed to obtain estimates of the degree of vaccination required to get herd immunity against a vector-borne disease. Assuming age-independent infection, the approximate values for the fraction σ of individuals that should be vaccinated to eradicate transmission may be derived from the relation $\sigma \geq \mu(R_0^2 - 1)$, where R_0 is the basic reproductive number. However, the severity of the infection is in general age dependent and has an effect on the immunization for the control of the disease, and therefore, there should be an optimal age to immunize. For this reason, our main interest is the introduction of age structure in R_0, and in the vaccination strategies. For this end, we formulate an age-structured model which allowed us to find an age-dependent expression for R_0. Besides, we prove local stability of the disease-free equilibrium, as well as the existence of a unique endemic equilibrium. We analyze the dynamics of the disease under a vaccination scheme in terms of the net reproductive number $R_0(V)$, and we obtain conditions over the vaccination rate to eradicate the infection.

We applied these theoretical results to dengue data in Mexico. We assumed that age-infective rate $\alpha_h(a)$ is proportional to the age-dependent dengue prevalence, and

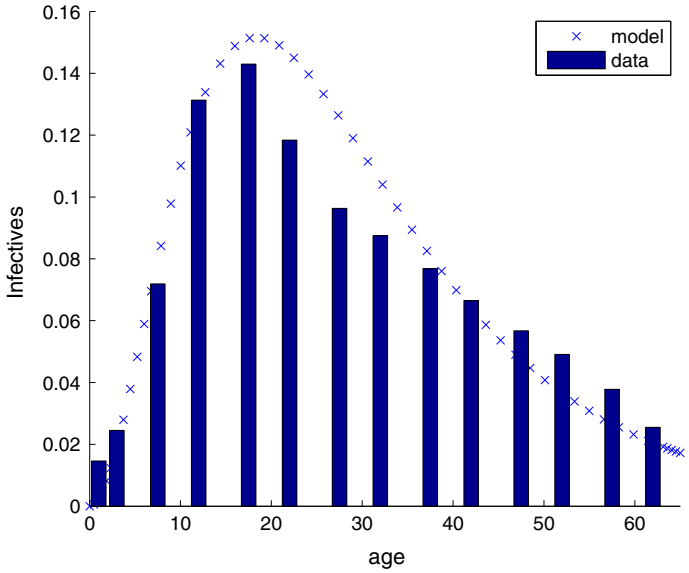

Fig. 3 Comparison between the numerical simulation of model (10) and the proportions of infected individuals of age a with respect to the reported infections. In this simulation, $m = 1$, and the other parameters are as in Table 1. Initial conditions in the simulation are $s(0) = 0.6, i(0) = 0, z(0) = 0$. The number of reported infected individuals in 2013 was 61,871. Data taken from SINAVE (2014)

we found that the proportion of individuals to be vaccinated depends on the vector density. The results were compared with data from Mexico, and we obtained a good agreement as can be seen in Fig. 3, which shows a comparison between the numerical simulation of the system of Eq. (10) and the proportions of infected individual of age a. Further, we applied cost-related vaccination strategies to the same example, and we obtained that under a one-age vaccination scheme, the optimal age of vaccination is between 2 and 3 years of age. In general, our model predicts that if vaccination cost is independent of the age, early vaccination is an optimal strategy. Finally, we gave a rough estimation of the proportion to be immunized to achieve herd immunity considering a vaccination rate independent of age.

Acknowledgments This work was supported by Grant IN-112713 of PAPIIT-UNAM. Acknowledgments to Germán González Santos, Ana Cecilia Pérez and Ramiro Chávez for technical support.

6 Appendix: Stability Analysis

We proceed with the stability analysis of the steady state age distributions given by model (8). For this end, we take a perturbation of the steady states

$$\begin{aligned} s(a,t) &= s^*(a) + \psi(a,t) \\ i(a,t) &= i^*(a) + \eta(a,t) \\ i_v(t) &= i_v^* + \theta(t) \end{aligned} \tag{35}$$

Substituting the variables above in (1) and neglecting terms of order bigger than two, we obtain the following PDE system for ψ, η, and θ:

$$\begin{aligned}\frac{d\psi}{\mathrm{d}a}+\frac{d\psi}{\mathrm{d}t}&=-\alpha_h(a)(\psi(a,t)i_v^*+s^*(a)\theta(t))-\mu_a\psi(a,t)\\ \frac{\mathrm{d}\eta}{\mathrm{d}a}+\frac{\mathrm{d}\eta}{\mathrm{d}t}&=\alpha_h(a)(\psi(a,t)i_v^*+s^*(a)\theta(t))-(\gamma(a)+\mu(a))\eta(a,t)\\ \frac{d\theta}{\mathrm{d}t}&=\int_0^\infty\frac{\alpha_v(a')}{N_h^*}[\eta(a',t)(1-i_v^*)-i^*(a')\theta(t)]\mathrm{d}a'-\mu_v\theta(t)\end{aligned}\tag{36}$$

with the initial and boundary conditions

$$\begin{aligned}&\psi(a,0)=s_0(a)-s^*(a),\ \eta(a,0)=i_0(a)-i^*(a),\ \theta(0)=i_{v_0}-i_v^*,\\ &\psi(0,t)=\eta(0,t)=0.\end{aligned}$$

Following Castillo-Chavez et al. (1989), we restrict to perturbations in separable form given by

$$\begin{aligned}\psi(a,t)&=\bar{\psi}(a)e^{pt}\\ \eta(a,t)&=\bar{\eta}(a)e^{pt}\\ \theta(a,t)&=\bar{\theta}e^{pt}\end{aligned}\tag{37}$$

with $\bar{\theta}$ constant. If real part of p is less than zero, then the perturbations given in (37) will approach zero as t goes to infinity. Substituting them in system (36), we obtain after some manipulations that

$$\begin{aligned}\bar{\psi}(a)&=-\bar{\theta}Be^{-[\frac{\lambda_v^*}{\lambda_v^*+\mu_v}\lambda_h(a)+M(a)]}\int_0^a\alpha_h(a')e^{-p(a-a')}\mathrm{d}a'\\ \bar{\eta}(a)&=\bar{\theta}Be^{-(G(a)+M(a))}\int_0^a\alpha_h(a')e^{-[\frac{\lambda_v^*}{\lambda_v^*+\mu_v}\lambda_h(a')-G(a')+p(a-a')]}\\ &\quad\times\left(1-\frac{\lambda_v^*}{\lambda_v^*+\mu_v}\int_0^{a'}\alpha_h(a'')e^{-p(a'-a'')}\mathrm{d}a''\right)\mathrm{d}a'\\ \bar{\theta}&=\frac{\mu_v}{(p+\mu_v+\lambda_v^*)(\mu_v+\lambda_v^*)}\int_0^\infty\frac{\alpha_v}{N_h^*}\bar{\eta}(a)\mathrm{d}a\end{aligned}\tag{38}$$

Assuming $\bar{\theta}\neq 0$, and substituting $\bar{\eta}(a)$ into the equation for $\bar{\theta}$, we obtain that p is solution of the following characteristic equation:

$$\begin{aligned}1=&\frac{\mu_v^2}{(p+\mu_v+\lambda_v^*)(\mu_v+\lambda_v^*)}\\ &\times\int_0^\infty\frac{\alpha_v(a)}{N_h^*}Be^{-(M(a)+G(a))}\left[\int_0^a\frac{\alpha_h(a')}{\mu_v}e^{-[\frac{\lambda_v^*}{\lambda_v^*+\mu_v}\lambda_h(a')-G(a')]}\right.\end{aligned}$$

$$\times\left(e^{-p(a-a')}-\frac{\lambda_v^*}{\mu_v+\lambda_v^*}\int_0^{a'}\alpha_h(a'')e^{-p(a-a'')}\mathrm{d}a''\right)\mathrm{d}a'\Bigg]\mathrm{d}a. \quad (39)$$

We have two cases, $\lambda_v^*=0$, and $\lambda_v^*\neq 0$. In the first one, the steady state age distribution is the trivial one, and the inequality

$$R_0=\int_0^\infty\frac{\alpha_v(a)}{N_h^*}Be^{-[M(a)+G(a)]}\int_0^a\frac{\alpha_h(a')}{\mu_v}e^{G(a')}\mathrm{d}a'\mathrm{d}a\leq 1 \quad (40)$$

holds. On the other hand, the characteristic Eq. (39) becomes

$$1=\frac{1}{p+\mu_v}\int_0^\infty\frac{\alpha_v(a)}{N_h^*}Be^{-(M(a)+G(a))}\left(\int_0^a\alpha_h(a')e^{G(a')-p(a-a')}\mathrm{d}a'\right)\mathrm{d}a. \quad (41)$$

It is clear from equations above that (40) has only a real root $p\leq 0$, and $p=0$ only at the threshold. Now, if $p=q+si$ is a complex root, then substituting it in (40), we obtain that the real part that satisfies the equation

$$1=\frac{q+\mu_v}{(q+\mu_v)^2+s^2} \quad (42)$$
$$\times\int_0^\infty\frac{\alpha_v(a)}{N_h^*}Be^{-(M(a)+G(a))}\left(\int_0^a\alpha_h(a-r)e^{G(a-r)-qr}\cos(sr)dr\right)\mathrm{d}a,$$

where $r=a-a'$. Since $\cos(sr)\leq 1$, and $\frac{q+\mu_v}{(q+\mu_v)^2+s^2}<\frac{1}{q+\mu_v}$, it follows that

$$\frac{1}{q+\mu_v}\int_0^\infty\frac{\alpha_v(a)}{N_h^*}Be^{-(M(a)+G(a))}\left(\int_0^a\alpha_h(a-r)e^{G(a-r)-qr}dr\right)\mathrm{d}a>1, \quad (43)$$

and comparing this result with Eq. (40), we conclude that $q<p\leq 0$. Therefore, if $R_0<1$, the trivial disease-free steady state age distribution is locally asymptotically stable for perturbations of the form (37). If $R_0>1$, then (41) has a unique positive root, and the disease-free steady state age distribution becomes unstable.

For $\lambda^*>0$, $R_0>1$, and the endemic steady state distribution emerges.

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