Mathematical Biosciences 247 (2014) 1–12

Contents lists available at ScienceDirect

Mathematical Biosciences

journal homepage: www.elsevier.com/locate/mbs

Vaccination models and optimal control strategies to dengue

Helena Sofia Rodrigues [a,b,c], M. Teresa T. Monteiro [b,d], Delfim F.M. Torres [a,e,*]

[a] CIDMA — Center for Research and Development in Mathematics and Applications, University of Aveiro, Campus Universitário de Santiago, 3810-193 Aveiro, Portugal
[b] ALGORITMI Research Centre, University of Minho, Campus de Azurém, 4800-058 Guimarães, Portugal
[c] School of Business Studies, Viana do Castelo Polytechnic Institute, Avenida Miguel Dantas, 4930-678 Valença, Portugal
[d] Department of Production and Systems, University of Minho, Campus de Gualtar, 4710-057 Braga, Portugal
[e] Department of Mathematics, University of Aveiro, Campus Universitário de Santiago, 3810-193 Aveiro, Portugal

ARTICLE INFO

Article history:
Received 8 November 2012
Received in revised form 21 May 2013
Accepted 14 October 2013
Available online 24 October 2013

Keywords:
Dengue
Vaccine
SVIR model
Optimal control

ABSTRACT

As the development of a dengue vaccine is ongoing, we simulate an hypothetical vaccine as an extra protection to the population. In a first phase, the vaccination process is studied as a new compartment in the model, and different ways of distributing the vaccines investigated: pediatric and random mass vaccines, with distinct levels of efficacy and durability. In a second step, the vaccination is seen as a control variable in the epidemiological process. In both cases, epidemic and endemic scenarios are included in order to analyze distinct outbreak realities.

1. Introduction

Since 1760, when the Swiss mathematician Daniel Bernoulli published a study on the impact of immunization with cowpox, the process of protecting individuals from infection by immunization has become a routine, with historical success in reducing both mortality and morbidity [1]. The impact of vaccination may be regarded not only as an individual protective measure, but also as a collective one. While direct individual protection is the major focus of a mass vaccination program, the effects on population also contribute indirectly to other individual protection through herd immunity, providing protection for unprotected individuals [2]. This means that when we have a large neighborhood of vaccinated people, a susceptible individual has a lower probability in coming into contact with the infection, being more difficult for diseases to spread, which decreases the relief of health facilities and can break the chain of infection.

Dengue is a vector-borne disease that transcends international borders. It is transmitted to humans through mosquito bite, mainly the *Aedes aegypti*. In this process the female mosquito acquires the virus while feeding on the blood of an infected person. The blood is necessary to feed their eggs. Larvae hatch when water inundates the eggs as a result of rains or an addition of water by people. When the larva has acquired enough energy and size, metamorphosis is done, changing the larva into pupa. The newly formed adult emerges from the water after breaking the pupal skin. This process could lasts between 8 to 10 days [3]. Vector control remains the only available strategy against dengue. Despite integrated vector control with community participation, along with active disease surveillance and insecticides, there are only a few examples of successful dengue prevention and control on a national scale [4]. Besides, the levels of resistance of *A. aegypti* to insecticides has increased, which implies shorter intervals between treatments, and only few insecticide products are available in the market due to the high costs for development and registration and low returns [5].

Dengue vaccines have been under development since the 1940s, but due to the limited appreciation of global disease burden and the potential markets for dengue vaccines, industry interest languished throughout the 20th century. However, in recent years, the development of dengue vaccines has dramatically accelerated with the increase in dengue infections, as well as the prevalence of all four circulating serotypes. Faster development of a vaccine became a serious concern [6]. Economic analysis are conducted to guide public support for vaccine development in both industrialized and developing countries, including a previous cost-effectiveness study of dengue [7–9]. The authors of these works compared the cost of the disease burden with the possibility of making a vaccination campaign; they suggest that there is a potential economic benefit associated with promising dengue interventions, such as dengue vaccines and vector control innovations,

* Corresponding author at: CIDMA — Center for Research and Development in Mathematics and Applications, University of Aveiro, Campus Universitário de Santiago, 3810-193 Aveiro, Portugal. Tel.: +351 234370668.
E-mail addresses: sofiarodrigues@esce.ipvc.pt (H.S. Rodrigues), tm@dps.uminho.pt (M. Teresa T. Monteiro), delfim@ua.pt (D.F.M. Torres).

0025-5564/$ - see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.mbs.2013.10.006

when compared to the cost associated to the disease treatments. Constructing a successful vaccine for dengue has been challenging: the knowledge of disease pathogenesis is insufficient and in addition the vaccine must protect simultaneously against all serotypes in order to not increase the level of dengue haemorrhagic fever [10].

Currently, the features of a dengue vaccine are mostly unknown. Therefore, in this paper we opt to present a set of simulations with different efficacy and different ways of distributing the vaccine. We have also explored the vaccination process under two different perspectives. In Section 2 a new compartment in the model is used and several kinds of vaccines are considered. In Section 3, a second perspective is studied using the vaccination process as a disease control in the mathematical formulation. In that case the theory of optimal control is applied. Both methods assume a continuous vaccination strategy.

2. Vaccine as a new compartment in the model

The interaction human–mosquito is detailed in a previous work by the authors [11]. See also [12]. The notation used in our mathematical model includes four epidemiological states for humans:

$S_h(t)$- susceptible (individuals who can contract the disease);
$V_h(t)$- vaccinated (individuals who were vaccinated and are now immune);
$I_h(t)$- infected (individuals who are capable of transmitting the disease);
$R_h(t)$- resistant (individuals who have acquired immunity).

It is assumed that the total human population (N_h) is constant, so, $N_h = S_h + V_h + I_h + R_h$. The compartment V_h represents the group of human population that is vaccinated, in order to distinguish the resistance obtained through vaccination and the one achieved by disease recovery. There are also three other state variables, related to the mosquitoes:

$A_m(t)$- aquatic phase (includes the eggs, larva and pupa stages);
$S_m(t)$- susceptible (mosquitoes able to contract the disease);
$I_m(t)$- infected (mosquitoes capable of transmitting the disease to humans).

Similarly to the human population, it is assumed that the total adult mosquito population is constant, which means $N_m = S_m + I_m$. There is no resistant phase in mosquitoes due to its short lifespan and the fact that the coefficient of disease transmission is considered fixed. Another assumption is the susceptibility of the humans and mosquitoes when they born. The parameters of the model are:

N_h- total population;
B- average number of bites on humans by mosquitoes, per day;
β_{mh}- transmission probability from I_m (per bite);
β_{hm}- transmission probability from I_h (per bite);
$1/\mu_h$- average lifespan of humans (in days);
$1/\eta_h$- mean viremic period (in days);
$1/\mu_m$- average lifespan of adult mosquitoes (in days);
φ- number of eggs at each deposit per capita (per day);
$1/\mu_A$- natural mortality of larvae (per day);
η_A- maturation rate from larvae to adult (per day);
m- female mosquitoes per human;
k- number of larvae per human.

Two forms of random vaccination are possible. The most common to reduce the prevalence of an endemic disease is pediatric vaccination; the alternative being random vaccination of the entire population in an outbreak. In both cases, the vaccination can be considered perfect, conferring 100% protection along all life, or imperfect. This last case can be due to the difficulty of producing an effective vaccine, the heterogeneity of the population or even the lifespan of the vaccine.

2.1. Perfect pediatric vaccine

For many potentially human infections, such as measles, mumps, rubella, whooping cough, polio, there has been much focus on vaccinating newborns or very young infants. Dengue can be a serious candidate for this type of vaccination. In the *SVIR* model, a continuous vaccination strategy is considered, where a proportion of the newborn p (where $0 \leqslant p \leqslant 1$), was by default vaccinated. This model also assumes that the permanent immunity acquired through vaccination is the same as the natural immunity obtained from infected individuals eliminating the disease naturally. The population remains constant, i.e., $N_h = S_h + V_h + I_h + R_h$. The model is represented in Fig. 1. The mathematical formulation is:

$$\begin{cases} \frac{dS_h}{dt}(t) = (1-p)\mu_h N_h - \left(B\beta_{mh}\frac{I_m(t)}{N_h} + \mu_h\right)S_h(t) \\ \frac{dV_h}{dt}(t) = p\mu_h N_h - \mu_h V_h(t) \\ \frac{dI_h}{dt}(t) = B\beta_{mh}\frac{I_m(t)}{N_h}S_h(t) - (\eta_h + \mu_h)I_h(t) \\ \frac{dR_h}{dt}(t) = \eta_h I_h(t) - \mu_h R_h(t) \\ \frac{dA_m}{dt}(t) = \varphi\left(1 - \frac{A_m(t)}{kN_h}\right)(S_m(t) + I_m(t)) - (\eta_A + \mu_A)A_m(t) \\ \frac{dS_m}{dt}(t) = \eta_A A_m(t) - \left(B\beta_{hm}\frac{I_h(t)}{N_h} + \mu_m\right)S_m(t) \\ \frac{dI_m}{dt}(t) = B\beta_{hm}\frac{I_h(t)}{N_h}S_m(t) - \mu_m I_m(t). \end{cases} \quad (1)$$

We are assuming that the vaccine is perfect, which means that it confers life-long protection. The nontrivial disease-free equilibrium for system (1) is given by

$$S_h = (1-p)N_h, \quad V_h = pN_h, \quad I_h = 0, \quad R_h = 0,$$
$$A_m = \left(1 - \frac{\eta_A + \mu_A}{\varphi\,\eta_A}\mu_m\right)kN_h, \quad S_m = \frac{\eta_A}{\mu_m}A_m, \quad I_m = 0.$$

As a first step, we determine the basic reproduction number without vaccination ($p = 0$).

Theorem 2.1. *Without vaccination, the basic reproduction number $\mathcal{R}_0$, associated to the differential system (1), is given by*

$$\mathcal{R}_0 = \sqrt{\frac{kB^2\beta_{hm}\beta_{mh}(-\eta_A\mu_m - \mu_A\mu_m + \varphi\eta_A)}{\varphi(\eta_h + \mu_h)\mu_m^2}}. \quad (2)$$

Proof. The proof is similar to the one presented in [13]. □

We do all the simulations in two scenarios: an epidemic and an endemic situation. The following values for the parameters of the differential system and initial conditions were used (Tables 1 and 2). These values are based on previous works [11,13]. A small number of initial infected individuals ($I_{h0} = 10$) is considered, to simulate an early action by the health authorities. We recall that dengue is endemic when it occurs several times in a year, and is not related with the initial value of infected individuals. Moreover, a small initial value of infected individuals in an endemic scenario is in agreement with [14]. In our work the same initial value of I_h for both epidemic and endemic scenarios is important in order to compare the development of the disease.

Two main differences between an epidemic episode and an endemic situation were found. Firstly, in the endemic situation there