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Analysis of the Impact of Vaccination as Control Strategy of Dengue Transmission Dynamics Considering a Multi-Strain Model

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Abstract

Optimizing a strategy for Dengue control based on vaccination is very challenging, since the dynamics of Dengue can be influenced by the coexistence of more than one serotype (DENV-1, DENV-2, DENV-3 and DENV-4), allowing the appearance of heterologous infections. In addition, although the effect of cross-immunity lasts a short period, the real protective power of the immune response is still not entirely clear. The aim of this study is to develop an optimization model to control Dengue transmission considering a multi-strain model. In order to evaluate such optimization, the vaccination was considered the control strategy. The Dengue dynamics was modeled according to that one developed by [1]. This model considered a human population, which can be infected by two strains of Dengue virus (strain 1 and 2). Both strains are simultaneously present in the system and they determine 10 categories in human population: susceptible to strains 1 and 2 (x); primarily infected with strain 1 (y_1) or strain 2 (y_2); recovered from the first infection with strain 1 (z_1) or strain 2 (z_2); susceptible with a previous infection with strain 1 (x_1) or strain 2 (x_2); secondarily infected with strain 1, when the first infection was caused by strain 2 (y_{21}) or for second time infected with strain 2 when the first infection was caused by strain 1 (y_{12}); recovered from the secondary infection (z). Initially, with the purpose of understand the Dengue dynamics in such conditions, the model was simulated without the introduction of vaccination. Following, the vaccination was introduced in this model. Although the vaccination was distributed to whole population, the vaccination effects occurs only on individual of x_1 category (the vaccinated individuals from x_1 move to v_1 category). Once in this category, individuals can become infected due to vaccination, moving to y_2 category. Otherwise, they become successfully protected (v_2). Once the same individual cannot become infected by two different serotypes at the same time, there will be a competition between serotypes 1 and 2. However, the vaccination does not decrease the serotype 1 infected individuals, because there would be more susceptible individual's xx available to be infected by serotype 1. In other words, the serotype 1 would prevail in this population.

Keywords: Dengue; Mathematical Model; Optimal Control; Vaccine

Introduction

In the last years, the estimations of the number of dengue cases (symptomatic or not) have been three times higher than those of the World Health Organization (WHO). The increase on such estimations has occurred not only due to human and/or geographical changes [2,3]. This discrepancy in such estimations has occurred due to biases related to (i) diagnosis processes (failure or imprecision) and (ii) unreported dengue cases. Consequently, the evaluation of the efficacy of potential vaccines is impaired, since its real impact is masked by such biases [4-6]. Considering the difficulty of evaluating the real impact of vaccination and the optimal strategy of its application, an interesting alternative would be the use of mathematical models. The use of mathematical models has been

described in studies related to infectious diseases dynamics [7]. Regarding the evaluation of the dengue vaccine, the mathematical model can be a powerful tool to reach the optimization model for a strategy that considers the maximum between the reduction of the incidence of cases and the availability of resources. And, optimizing a strategy for dengue control based on vaccination is very challenging, since the dynamics of dengue can be influenced by the coexistence of more than one serotype (DENV-1, DENV-2, DENV-3 and DENV-4), allowing the appearance of heterologous infections. In addition, although the effect of cross-immunity lasts a short period, the real protective power of the immune response is still not entirely clear [8]. Similarly, the risk of heterologous infections and the uncertainty of the protective power of the immune response have also been reported in the studies about the impact of the dengue vaccine. As an example, it was observed that vaccination in seropositive individuals reduces the risk of hospitalization or symptomatology. However, all dengue vaccine models (produced by Sanofi®) applied to susceptible individuals have shown that they may increase the risk of dengue outbreaks [9,10].

According to Health Ministry/Minister's Office (MH/MO) Ordinance no. 204 (2016 February 17th), the reporting cases of dengue fever is compulsory in Brazil. Such data are available at Brazilian Health System Data (DATASUS) [11] and the most recent data refers to 2017 year. The Ministry of Health is the first authority concerning to public health and medical processes. According to such data, the number of cases has been increasing over time. Therefore, those data are a good reference to understand the epidemiological scenery about dengue in Brazil. This fact is directly related to consequences in terms of epidemiology and economy. In simple words, infected people are sources of infection and they reduce the workforce, and also increase the public costs due to medicines and treatments. Although this is a simple way to think about this problem (other variables may interfere too), it illustrates the impact of dengue in the society. In addition to the increase of cases, studies have been carried out in order to develop a vaccine which (1) is effective and safe for dengue, (2) provides immunity against the 4 serotypes and (3) is durable. Although the best animal model is the rhesus monkey, there still are some details that make the correlation between clinical research findings and the respective conduct in humans harder [12,13]. Considering this context, the development of a mathematical model in order to study the impact of vaccination emerges as an alternative to the ethical question (since the use of living beings for experimentation would be avoided) and to estimate quantitative indexes for the impact of the vaccine in the epidemiological, social and economic approaches [6].

The aim of this study is to develop an optimization model to control dengue transmission considering a multi-strain model. In order to evaluate such optimization, the vaccination was considered the control strategy. Here, the vaccine model produced by Sanofi® (which is recommended by World Health Organization) was taken as reference to the simulations. Therefore, it is expected to evaluate the epidemiologic impact of dengue vaccination as preventive control strategy.

The Model

Firstly, the mathematical model presented in this project is an adaptation of that one proposed by Santos in her doctoral thesis [1], and also added some conceptions from [14-16]. Thus, in this project, it is considered:

I. A human population, which is constant over time, is divided into ten classes: (i) susceptible to strains 1 and 2 (x); (ii) primarily infected with strain 1 (y_1) or strain 2 (y_2); (iii) recovered from the first infection with strain 1 (z_1) or strain 2 (z_2); (iv) susceptible with a previous infection with strain 1 (x_1x_1) or strain 2 (x_2); (v) secondarily infected with strain 1, when the first infection was caused by strain 2 (y_{21}) or for second time infected with strain 2 when the first infection was caused by strain 1 (y_{12}); (vi) recovered from the secondary infection (z);

II. Individuals from x_1 can be vaccinated and move to v_1 category. Once in this category, individuals can become infected due to vaccination, moving to y_2 category. Otherwise, they become successfully protected, v_2;

III. The infection by one serotype confers life-long immunity to that serotype;

IV. The human population is homogeneously in contact with two strains of dengue fever;

The complete system of ordinary differential equations for the two-strain epidemiological system is given by system (1) and the dynamics is described as follows. Susceptible individuals to both strains (x) can get the first infection (no matter if it is strain 1 or 2) with (i) infection rate $\beta(t)$, when the infection is acquired via an individual in his first infection; or (ii) infection rate $\phi\beta(t)$, when the infection is acquired via an individual in his second infection. Next, those infected individuals (y_1 or y_2) recover from this first infection with a recovery rate $\gamma\gamma$. Although such recovered individuals (z_1 or z_2) acquire full and life-long immunity against the strain that they were exposed to, this recovering process presents a short period of temporary cross-immunity α against the

other strain, becoming a "new" susceptible (x_1 or x_2) to a second infection with a different strain after the ending of such period α. The susceptible individuals x_1 or x_2 acquire the secondary infection and become infected y_{12} or y_{21}, respectively, in a same process as described to the first infection case. Then, with recovery rate $\gamma\gamma$, the individuals x_{12} or x_{21} recover and become immune against all strains (z).

No epidemiological asymmetry between strains is assumed, i.e. infections with strain 1 followed by strain 2 or vice versa contribute in the same way to the force of infection. Here, the only relevant difference concerning disease transmissibility is that the force of infection varies accordingly to the number of previous infections the hosts have experienced. In a primary infection, the individuals transmit the disease with a force of infection $\beta(t)y_i$, $i = 1, 2$. On the other hand, in a secondary infection, the transmission is given with a force of infection $\phi\beta(t)y_j$, $i = 21, 12$, where ϕ can be larger or smaller than 1, i.e. increasing or decreasing the transmission rate. The flowchart is presented in (Figure 1) and the parameter values are given in (Table 1).

$$
\begin{aligned}
\dot{x}(t) &= \mu\big(1 - x(t)\big) - \beta(t)(\phi y_{21}(t) + y_1(t) + \rho)x(t) - \beta(t)(\phi y_{12}(t) + y_2(t) + \rho)x(t)\\
\dot{y_1}(t) &= \beta(t)(\phi y_{21}(t) + y_1(t) + \rho)x(t) - (\gamma + \mu)y_1(t)\\
\dot{y_2}(t) &= \beta(t)(\phi y_{12}(t) + y_2(t) + \rho)x(t) - (\gamma + \mu)y_2(t) + \psi v_1(t)\\
\dot{z_1}(t) &= \gamma y_1(t) - (\alpha + \mu)z_1(t)\\
\dot{z_2}(t) &= \gamma y_2(t) - (\alpha + \mu)z_2(t)\\
\dot{x_1}(t) &= \alpha z_1(t) - \beta(t)(\phi y_{12}(t) + y_2(t) + \rho)x_1(t) - (\upsilon + \mu)x_1(t)\\
\dot{x_2}(t) &= \alpha z_2(t) - \beta(t)(\phi y_{21}(t) + y_1(t) + \rho)x_2(t) - \mu x_2(t)\\
\dot{x_2}(t) &= \alpha z_2(t) - \beta(t)(\phi y_{21}(t) + y_1(t) + \rho)x_2(t) - \mu x_2(t)\\
\dot{y_{12}}(t) &= \beta(t)(\phi y_{12}(t) + y_2(t) + \rho)x_1(t) - (\gamma + \mu)y_{12}(t)\\
\dot{y_{21}}(t) &= \beta(t)(\phi y_{21}(t) + y_1(t) + \rho)x_2(t) - (\gamma + \mu)y_{21}(t)\\
\dot{z}(t) &= \gamma y_{12}(t) + \gamma y_{21}(t) - \mu z(t)\\
\dot{v_1}(t) &= \upsilon x_1(t) - \psi v_1(t) - \tau^{-1}v_1(t) - \mu v_1(t)\\
\dot{v_2}(t) &= \tau^{-1}v_1(t) - \mu v_2(t)\dot{v_2}(t) = \tau^{-1}v_1(t) - \mu v_2(t)
\end{aligned}
\qquad (1)
$$

The process of model analysis and results interpretation will be similar to that one developed by [14,16,26,27].

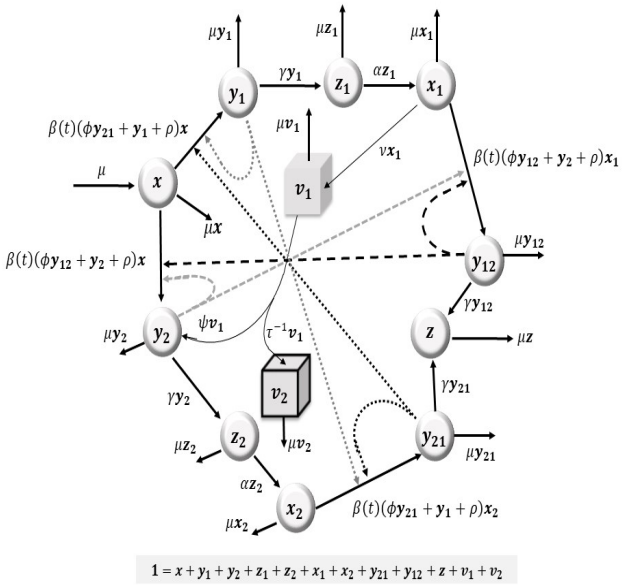

Figure 1: Compartment model and flowchart. The non-continuous line indicates the influence of a category on the indicated flux. For instance, $y_1\,y_1$ influences on the transition of x to y_1 and x_2 to y_{21}.

Parameter	Biological meaning	Value	Unit	Source
μ	Natural mortality rate	3.67×10^{-5}	day^{-1}	(Brazilian Institute of Geography and Statistics, 2013) [17]
γ	Recovery rate	1.43×10^{-1}	day^{-1}	(Halstead, 1990) [18]
$\beta(t)$	Infection rate	2.85×10^{-1}	$(human \times day)^{-1}$	(Fergurson, et al., 1999)[19]
α	Temporary cross-immunity rate	5.48×10^{-5}	day^{-1}	(Matheus, et al., 2005) [20]
ϕ	Ratio of secondary infections contributing to force of infection	$\in [0, 3]$	dimensionless	(Aguiar, et al., 2008)[21]
ρ	Import parameter	0 to 10^{-10}	dimensionless	(Nagao & Koelle, 2008)[22]
υ	Vaccination rate	variable	day^{-1}	-
ψ	Infection rate to $y_2 y_2$ due to vaccination	variable	day^{-1}	-
τ	Interval between vaccine doses	1.82×10^{2}	day	(World Health Organization, 2017) [23,24]
η	Proportion of reported cases	5.0×10^{-2}	dimensionless	Silva et al. (2016) [25]

Table 1: Parameters and their biological meaning adapted from [1].

The Reported Cases

In Brazil, reporting cases of Dengue fever is compulsory (Ordinance MH/MO no. 204 (2016 February 17th)). Thus, we can assume:

- An infected human should look for medical treatment when he/she will become clinically ill;
- Only a fraction of those humans that are clinically ill will be reported to sanitary authorities. The remaining fraction (I) will not look for medical help, even if the clinical symptoms and signs appear; or (II) will not be correctly reported in the hospitals. Now, the equations related to infected categories in system (1) are:

$$\begin{aligned} \dot{y_1}(t) &= \beta(t)(\phi y_{21}(t) + y_1(t) + \rho)x(t) - (\gamma + \mu)y_1(t) \\ \dot{y_2}(t) &= \beta(t)(\phi y_{12}(t) + y_2(t) + \rho)x(t) - (\gamma + \mu)y_2(t) + \psi v_1(t) \\ \dot{y_{12}}(t) &= \beta(t)(\phi y_{12}(t) + y_2(t) + \rho)x_1(t) - (\gamma + \mu)y_{12}(t) \\ \dot{y_{21}}(t) &= \beta(t)(\phi y_{21}(t) + y_1(t) + \rho)x_2(t) - (\gamma + \mu)y_{21}(t) \end{aligned} \quad (2)$$

The terms that include $\beta(t)$ from (2) mean the rate of humans who become clinically ill per day. Thus, per day, those amounts of humans are eligible to look for medical help. However, only a fraction $(1 - \eta)$ of those clinically ill humans will be correctly reported to sanitary authorities. Therefore, the daily rate of reported human cases $R(t)$ is defined by (3):

$$
\begin{aligned}
R_1(t) &= \eta\beta(t)(\phi y_{21}(t) + y_1(t) + \rho)x(t) \\
R_2(t) &= \eta\beta(t)(\phi y_{12}(t) + y_2(t) + \rho)x(t) \\
R_{12}(t) &= \eta\beta(t)(\phi y_{12}(t) + y_2(t) + \rho)x_1(t) \\
R_{21}(t) &= \eta\,\beta(t)(\phi y_{21}(t) + y_1(t) + \rho)x_2(t) \\
R(t) &= R_1(t) + R_2(t) + R_{12}(t) + R_{21}(t)
\end{aligned} \qquad (3)
$$

Where $R_i(t)$ (with $i = 1, 2, 12, 21$) means the daily rate of reported human cases specific of each category of the model purposed.

The data provided by Brazilian Ministery of Health represents the reported cases per year. Thus, since time scale considered in this work is day, it was estimated an average of human reported cases per day for each year (dividing the total from each year by 365). Finally, model considers a normalized population (all population is constant). As a last step, we have to divide each rate of human reported cases per day by the official population size of Brazil. The estimated population size of Brazil is available on Brazilian Institute of Geography and Statistics (BIGS) website [17]. In order to fit and compare the model output to real data, it was also calculated a normalized average of reported cases per day from each 365 days of simulation. This simulation was run considering 50 years and the obtained curve was fitted by simple handling along the time-axis (for instance, we could assume the initial day $t_0 = 1 t_0 = 1$ as the first day of 1980 or 1990, depending on how best the simulated curve fits on the real data). Thus, we could obtain the yearly average of reported human cases per day and compare it to the real yearly average provided by Brazilian Ministry of Health (Table 2).

Year	Total of reported cases (Brazilian Ministry of Health, 2018)	Day average	Total Brazilian population (BIGS, 2013)	Normalized day average	Log (Normalized day average)
2000	506	1.39	173448346	7.99E-09	-8.1
2001	1938	5.31	175885229	3.02E-08	-7.52
2002	3786	10.37	178276128	5.82E-08	-7.24
2003	1285	3.52	180619108	1.95E-08	-7.71
2004	859	2.35	182911487	1.29E-08	-7.89
2005	1185	3.25	185150806	1.75E-08	-7.76
2006	1425	3.9	187335137	2.08E-08	-7.68
2007	1453	3.98	189462755	2.10E-08	-7.68
2008	1073	2.94	191532439	1.53E-08	-7.81
2009	1376	3.77	193543969	1.95E-08	-7.71
2010	2978	8.16	195497797	4.17E-08	-7.38
2011	3129	8.57	197397018	4.34E-08	-7.36
2012	2853	7.82	199242462	3.92E-08	-7.41
2013	2928	8.02	201032714	3.99E-08	-7.4
2014	2742	7.51	202768562	3.70E-08	-7.43
2015	4720	12.93	204450649	6.33E-08	-7.2
2016	1475741	4043.13	206081432	1.96E-05	-4.71
2017	24742	677.87	20766092	3.26E-06	-5.49

Table 2: Human reported cases in Brazil: average of the normalized rate per day for each year.

Numerical Simulation

In order to analyze the dynamics of our model, we simulated the set of equations from (1) considering the parameters on Table 1. It was focused on human reported rate, since the real data can be used as reference (Figure 2) illustrate the reported human cases rate and the trend indicated by the simulation (yearly average).

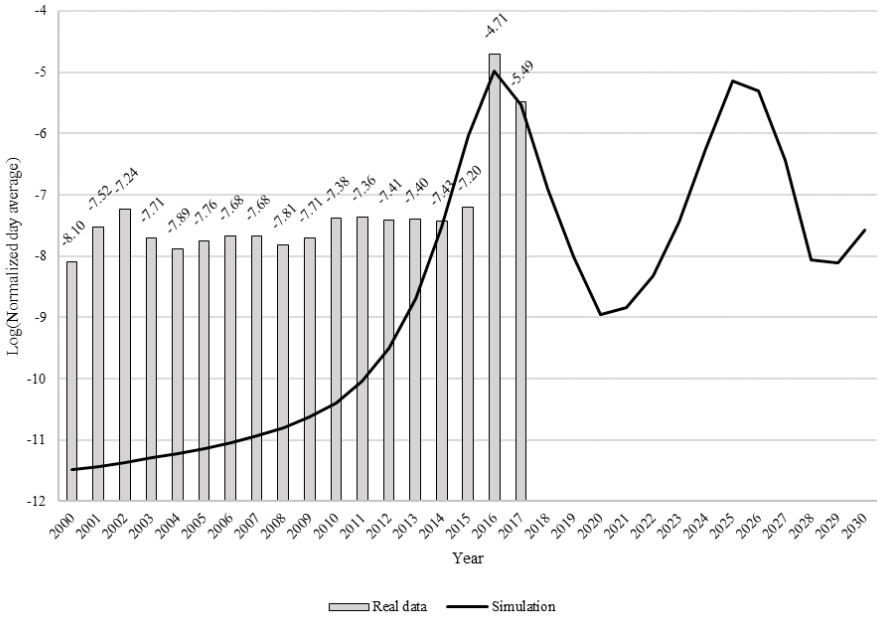

Figure 2: Dynamics of reported human cases rate. The available real data are from 2000 to 2017 (bars) and our model was fitted for the same period (line). Observe that the real data has increased over time and reaches a peak in 2016. Source: Brazilian Ministry of Health (SINAN) and BIGE.

For the evaluation of the impact of vaccination, it was supposed that the vaccination campaign would start by 2018. Then, a vaccination rate $\upsilon = 0.1$/day is introduced in the model. For simplicity, it is considered that the vaccine is homogenously distributed in the population and, therefore, all individuals has the same probability to be vaccinated. The (Figure 3) presents the dynamics of Dengue fever when the vaccination is introduced, considering the sum of all categories and the contribution of each category.

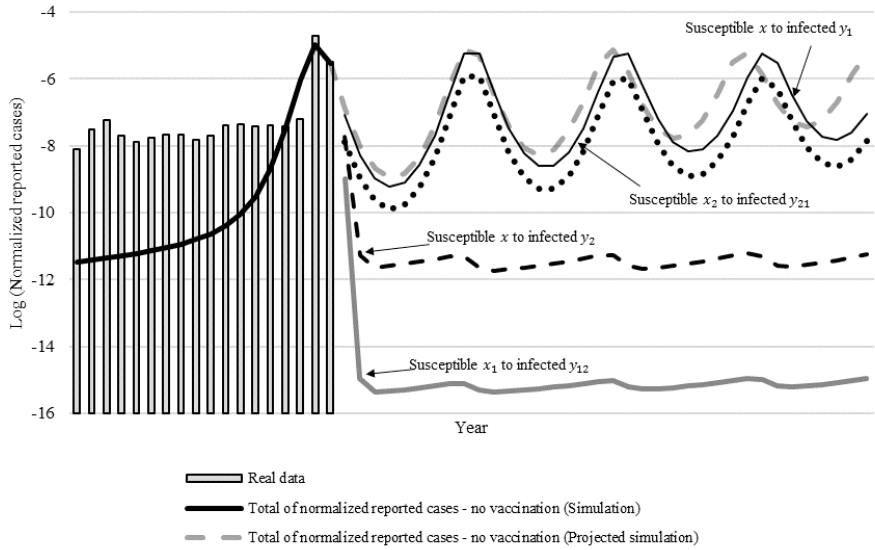

Figure 3: Impact of vaccination on dynamics of reported human cases rate. The graph represents a scenery where the vaccination starts in 2018 (the simulation estimated that the average density of total reported cases per day was around 2.94×10^{-6}/day in 2017). After 2018, the graph presents two categories of curves. One of them refers to the curve of projected simulation. The other one refers to the curves of each category of infected individuals.

Some comments can be introduced about the dynamics presented in Figure 3. Note that, for a vaccination rate of $v = 0.1$ /day, the curves related only to categories y_2 and y_{12} decreased. On the other hand, although the curves related to y_1 and y_{21} keep the oscillation patterns, they had their period increased in comparison to the curve of the projected simulation. Another point to be mentioned is that a soft and gradual decay on the amplitude of the y_1 and y_{21} curves can be observed. In short, while there is a decrease of reported cases related to categories y_2 and y_{12}, there is a desynchronization among the projected simulation, y_1 and y_{21} curves (causing a delay of y_1 and y_{21} curves in respect to the projected simulation's one).

Analysis of Vaccination Impact

Considering the evaluation of the efficacy and cost-effectiveness of a dengue vaccination ($v = 0.1$/day), a simple criterion was adopted. This criterion refers to the amount of vaccinated individuals necessary to avoid one human to become clinically ill. Thus, it was calculated the ratio total of vaccinated individuals/total of saved humans (Eq. 4).

$$\Im_v(t_f) = \frac{T_v(t_f)}{\mathcal{T}^v_{saved}(t_f)} \quad (4)$$

where $\Im_v$ means the ratio of total vaccinated individuals/ total saved humans, T_v is the total of vaccinated individuals, $\mathcal{T}^v_{saved}$ means the total of saved humans, and t_f is the final time. For simplicity, it is assumed that the vaccine is distributed to all Brazilian individuals. In other words, all categories presented in the mathematical model would be eligible to be vaccinated (although the biological effects would happen only to individuals of x_1).

In the case of $\mathcal{T}^v_{saved}$, it was estimated considering the difference between the results from the sceneries with and without the inclusion of the vaccination (Figure 4). If the total of normalized reported cases per day $R(t)$ is considered, the respective $\mathcal{T}^v_{saved}$ can be written as follows (Eq. 5).

$$\mathcal{T}^v_{saved}(t_f) = \int_{t_0}^{t_f} \left(R(t) - R^v(t)\right) dt \quad (5)$$

where $R^v(t)$ means the normalized reported cases per day if the vaccination is introduced. Thus, Eq. 5 means the amount of cases that is avoided. (Figure 4) presents the result of this ratio over time.

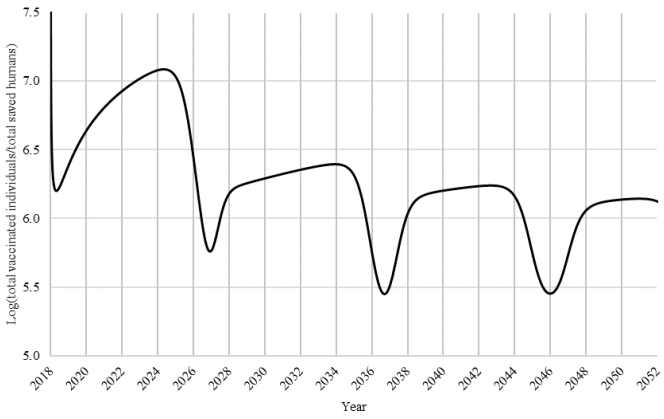

Figure 4: Result of the simulations of expression (4) over time, according to each strategy.

Here, the result presented in Figure 4 deserve for some clarification. As described before, (Figure 4) informs how many vaccines were needing to avoid one reported case over time. For example, considering 2 years after the introduction of the vaccination (2020 year), Figure 4 indicates that it was necessary around 10^6 to 10^7 vaccines to avoid one reported case. On the other hand, in 2046 it was need close to $10^{5.5}$ vaccines. It is important to highlight that the presently size of Brazil population is of the order of magnitude of 10^8 inhabitants.

Discussion

In this work, the impact of Dengue vaccination was evaluated considering a mathematical model adapted from [1], which in turn evaluated the Dengue fever dynamics based on a multi-strain model. Here, the parameters values were modified to day time scale and their values were changed according to Brazilian scenery. The study presented here provided a new approach for impact of Dengue vaccine. Since Dengue fever is caused by 4 serotypes, the usual mathematical models that consider the Dengue transmission by a generic virus cannot be the best option. Due to this fact, a multi-strain model was adapted to evaluate the Dengue dynamics and the impact of vaccination on it. To the best of our knowledge, the work presented here is one of the first in which evaluated by mathematical modeling the impact of Dengue vaccination considering a multi-strain model. Also, considering that such vaccine has a short period of cross-immunity and the possibility of vaccinated individuals become serotype 2 infected, the mathematical modeling of this phenomena was very useful to aid in the comprehension of this dynamics. The results

presented in Figure 3 indicates how the Dengue dynamics would be modified if the vaccine described by World Health Organization is introduced. It is important to highlight that the immunization effect of such vaccine is valid only to individuals from category x_1 (the individuals who had previously been infected by Dengue virus serotype 1). In terms of strategic interpretation, the vaccination aims to "isolate" the individuals of the population from the virus. This is exactly the idea of vaccination in the model presented in this study. As the same individual cannot become infected by two different serotypes at the same time, there will be a competition between serotypes 1 and 2. However, the vaccination does not decrease the serotype 1 infected individuals, because there would be more susceptible individuals x available to be infected by serotype 1. In other words, the serotype 1 would prevail in this population. Even though there it is considered a proportion of vaccination fail ($\psi = 0.5$/day), it was not enough to keep the density of serotype 2 infected individuals unaltered. The planning of good vaccination strategy also should consider how effective the vaccination is. The results presented in (Figure 4) illustrates the effort that should be done to avoid one case over time. Although the oscillation pattern, the ratio $\Im_v(t_f)$ (total of vaccinated individuals/total of saved humans) corresponds to the pattern presented in (Figure 3) and it trends to decrease over time. In short, when the ratio is high, the amount of reported cases is low and vice-versa. Here, it is important to remind that the vaccination rate was considered constant in the mathematical model ($\upsilon = 0.1$/day). This partially explain the results observed in (Figure 4).

Finally, it should be noted that in multi-strain models like the current one [28] showed that the strain which is only directly transmitted can invade the endemic state of the strain with mixed transmission. The endemic state of the first strain, however, is neutrally stable to invasion by the second strain.

The study presented here provided a general approach about how the Dengue dynamics can change when the vaccine is introduced. In addition, it also helps to understand how the densities of each infected category are modified over time. Since the vaccinated individual x_1 can become serotype 2 infected y_2 due to vaccine failure, the results of this mathematical model can be very helpful to future vaccination strategy plans. As upcoming works, the optimal value for vaccination rate υ should be estimated. In this present study, the main scope was to understand the Dengue dynamics in a multi-strain model and the changes that occur when a vaccine is introduced [29-31]. Because of this, a simple vaccination rate $\upsilon = 0.1$/day was adopted for numerical simulations and it was considered good enough. In practical terms, any conclusion regarding to Dengue vaccination strategies should be better supported if it is justified by economical argumentation. Therefore, the evaluation of a vaccination rate based not only epidemiological approaches, but also on economical restrictions, should be considered.

Acknowledgments

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