OPTIMAL CONTROL OF VACCINATION AGAINST H1N1 FLU

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Abstract. *We introduce a mathematical model which describes the dynamics of the spread of H1N1 flu in a human population. The model is comprised of a system of ordinary differential equations that involve susceptible, exposed, infected and recovered/immune individuals. The distinguishing feature in the proposed model with respect to other models in the literature is that it takes into account the possibility of infection due to immunity loss over time. The acquired immunity comes from self-recovery of the flu or via vaccination. Furthermore, the proposed model strives to find an optimal vaccination strategy by means of an optimal control problem, solved by means of Pontryagin's Maximum Principle.*

Keywords: *Optimal Control, Mathematical Modeling, Pontryagin's Maximum Principle, H1N1 Flu, Vaccination*

1 INTRODUCTION

Epidemiological models are widely used to study the behavior of cyclic diseases, which return periodically over the years, such as the H1N1 flu. This form of disease spreads so rapidly that in 2009 it was classified as pandemic by the World Health Organization. Therefore, it is of the

utmost importance that models and tools that assist in the understanding of the dynamics and in the proposal of control mechanisms for the H1N1 flu are developed. This paper proposes a mathematical model based on differential equations and applies it to study the dynamics of the H1N1 flu. Moreover, we also propose an optimal control problem with a view at finding an optimal vaccination strategy over time, in such a way that contagion is kept to a minimum.

Problems involving differential equations find application in different areas of knowledge and require, as a result, a multidisciplinary approach that combines transport phenomena, control systems, numerical modeling and computing, among others. Such problems can be found in many fields, but we are particularly interested in the public health sector. In particular, we address the problem of simulating the spread of the H1N1 flu, while also elaborating a vaccination strategy aimed at minimizing contagion.

More specifically, this paper addresses a mathematical formulation comprising a set of ordinary differential equations based on the so-called Susceptible - Infected - Removed (SIR) model. This model, proposed by Kermack and McKendric (1927), is comprised of a non-linear system of equations that are common to each of the subgroups included in the model: the susceptible, which are individuals vulnerable to the disease; the infected, those that actually had a contact with it and may infect others; and the removed, which comprises two groups of individuals, those already recovered and considered immune to the disease thereafter and those who died from the disease. The proposed formulation considers the possibility of vaccination, which influences the dynamics of the disease by preventing contagion. The vaccination, however, may lose efficiency over time, occasioning the possibility of reinfection for vaccinated individuals. Such loss of efficiency is modeled by a parameter, which is varied in our experiments.

This paper also addresses the problem of generating an optimal vaccination strategy in terms of a cost functional, which takes into account both the number of infected people and the vaccination costs. This problem is modeled as an optimal control problem, and solved by an iterative procedure based on the gradient algorithm (Kirk, 1970).

2 THE VACCINATION

According to Yang (2001) the importance of the use of vaccination as a protection against disease may be based on two components: a decrease in the number of new cases (morbidity) and the low cost of the vaccine in relation to the treatment of disease (monetary). The goal is to induce a protection against the pathogen not only to save individuals against serious forms of the disease, but also to control the disease in the community.

Therefore, a thorough understanding of the effects of vaccination on the community requires more than pure biological knowledge. To attain it, one should consider the proper way of vaccinating people so that the chain of disease transmission is interrupted. In that context, mathematical models can be very useful, providing contributions to the understanding of the underlying dynamics. Such models describe the phenomenon of disease transmission and allow the generation of scenarios from different vaccination strategies, anticipating the effects of an eventual vaccination (Yang, 2001).

The vaccine production process for a novel flu strain requires at least 6 months for virus identification, vaccine invention, and then mass production using a long-standing egg-based technology (Larson and Teytelman, 2012). According to the Brazilian government, egg allergy

is the single counter indication of this manufacturing technology. In any case, in addition to side effects, there are other factors which are critical to the effectiveness of vaccination strategies. It is understood that the vaccine may fail in two levels. Firstly, it may not induce immunity in the individual, typically as a result of some failure in the manufacturing process or of some deficiency in the individual's immune system. Failure may also occur when the level of vaccination immunity is low, therefore resulting in immunity loss in a short time span (Yang, 2001). This illustrates the importance of incorporating the possibility of reinfection in a dynamic vaccination model.

To understand the role of vaccination in the eradication of a disease, we must define two basic concepts in epidemiology. The first is called force of infection, which corresponds to a per capita disease incidence or incidence of new cases divided by the number of susceptible individuals in a population. The force of infection could determine not only the extent of spread but also the amount of the effort to combat the disease. The second concept is the most important parameter in epidemiology, the reproductive number R_0, defined as the average number of new infections caused by a typical infectious individual in a fully susceptible population. If $R_0 < 1$ the disease will be extinguished, while if $R_0 \geq 1$ the disease is endemic in state, its severity increasing with the value of R_0. The reproductive number can be determined depending on the strength of infection. For example, in the 2009 epidemic in Mexico, R_0 was estimated to range between 1.4 and 1.6 (Larson and Teytelman, 2012).

When vaccination is introduced in a population, a decrease in the force of infection is expected. Thus, susceptible individuals become immune without going through the infectious state. As a consequence, there is a decrease in secondary cases generated by infected individuals, thus reducing R_0. As vaccine-induced immunity weakens over time, it is necessary to consider also the possibility of reinfection. This paper introduces a SIR model that views vaccination as a mechanism of disease control, and studies its effect on influenza transmission. The model also accounts for reinfection, to emulate the effect of weakened immunity some time after vaccination.

3 THE MODEL

Influenza is a directly transmitted disease, i.e., its spread occurs following the contact of susceptible individuals (who have not had contact with the virus) and infected individuals (who have non-negligible concentration of virus in their bodies). The mathematical formulation consists of a set of ordinary differential equations that describe the so-called Susceptible - Infected - Removed (SIR) model. Considering only the temporal evolution, the model can be described by the equations:

$$\begin{aligned} \frac{dS}{dt} &= -\beta SI \\ \frac{dI}{dt} &= \beta SI - \gamma I \\ \frac{dR}{dt} &= \gamma I, \end{aligned} \tag{1}$$

where S is the number of susceptible individuals at time t, I is the number of infected individuals at time t , R is the number of removed individuals at time t, β is the infection rate, and γ is the removal rate. To solve the system we need initial values S_0, I_0 and R_0, at time t_0, for susceptible, infected and recovered individuals, respectively.

The compartmentalized model, widely used to study the transmission dynamics of infectious diseases, including H1N1 flu (Dias and Arruda, 2014; Dias, Arruda and Souza, 2015), assumes that an individual may successively visit stages of susceptibility, infection and recovery. It also assumes that immunity is permanent (for life). Normally, the model does not consider the latency period during which the virus replicates in the cells of the individual. That is, it does not consider infected but not infectious individuals. Additionally, the rates of birth and death are equal, which implies that the population is kept constant as time evolves. The model also has the limitation of considering that individuals are evenly spread in space. However, this assumption makes sense if one wishes to describe the spread of a disease in a population spatially distributed by means of differential equations.

In this study we consider two improvements in the SIR model given by Equation (1): firstly, we consider that part of the susceptible population has either been vaccinated or has already recovered from the infection and is partially protected from the complications arising from the disease. This effect will be introduced in Section 4 through a variable $u(t)$ that emulates the vaccination strength at any given time t, whose optimal levels will then be determined by means of an optimal control variable. Secondly, we consider that the vaccine has limited effect and that after a period of time there is a possibility of reinfection. The basic model, without vaccination, can be formulated as:

$$\begin{aligned}
\frac{dS}{dt} &= \alpha - \beta IS - \mu S \\
\frac{dE}{dt} &= \beta IS - kE - \mu E \\
\frac{dI}{dt} &= kE - \delta_1 I - \delta_2 I - \mu I \\
\frac{dR}{dt} &= \delta_2 I - \mu R,
\end{aligned} \tag{2}$$

where E is the number of exposed or latent individuals at time t , R is now the number of recovered individuals at time t. In (2), α is the rate of birth or immigration; β is the rate at which susceptible individuals become infected by those who are infectious; μ is the natural death rate; k is the rate at which the exposed individuals become infectious, δ_1 is the rate of disease-induced death; δ_2 is the rate of recovery from the disease. The dynamics of the proposed model is depicted in Figure 1.

Note that $S + E + I + R = N(t)$, where $N(t)$ is the total population considered. Note that $\frac{1}{k}$ is the average length of the latent period, and $\frac{1}{\delta_2}$ is the mean length of the infectious period before recovery (Lenhart and Workman, 2007).

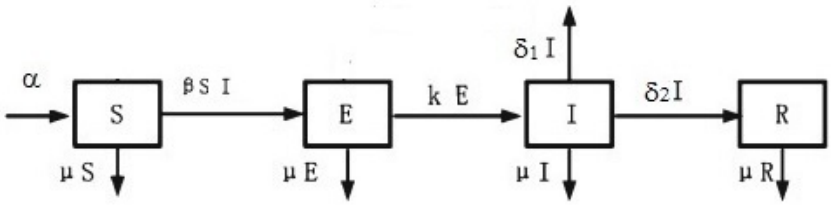

Figure 1: Transfer diagram of the influenza A (H1N1) epidemic model

As vaccine-induced immunity weakens over time, it is necessary to consider the rate of immunity loss π (Yang, 2001), where $\pi = 0$ means that one has perennial immunity. To take into account the possibility of reinfection, the model in Eq. (2) is modified to that in Eq. (3), illustrated in Figure 2:

$$\begin{aligned}
\frac{dS}{dt} &= \alpha + \pi R - \beta IS - \mu S \\
\frac{dE}{dt} &= \beta IS - kE - \mu E \\
\frac{dI}{dt} &= kE - \delta_1 I - \delta_2 I - \mu I \\
\frac{dR}{dt} &= \delta_2 I - \pi R - \mu R,
\end{aligned} \tag{3}$$

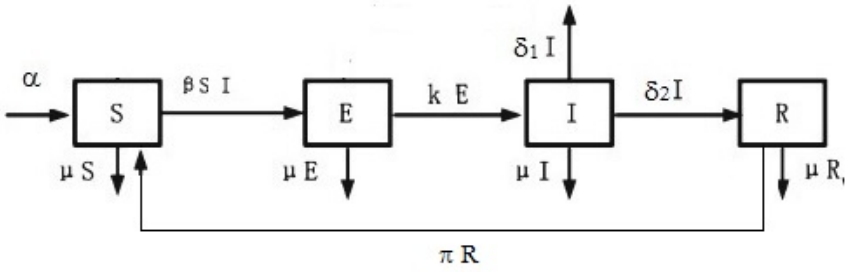

Figure 2: Transfer diagram of the influenza A (H1N1) epidemic model with reinfection.

4 THE OPTIMAL CONTROL PROBLEM

In this work we use an optimal control technique to find a vaccination schedule for the H1N1 flu. The purpose of this study is to minimize the number of infected individuals in population and the overall cost of vaccine during a fixed time period. Let the control variable

$0 \leq u(t) \leq 1$ represent the strength of the vaccination at time t. The optimal control problem is defined as:

$$J[u] = \text{Minimize} \int_0^T (I(t) + c\,u(t)^2)\,dt \tag{4}$$

Subject to:

$$\begin{aligned}
\tfrac{dS}{dt} &= \alpha + \pi R - \beta IS - \mu S - uS \\
\tfrac{dE}{dt} &= \beta IS - kE - \mu E \\
\tfrac{dI}{dt} &= kE - \delta_1 I - \delta_2 I - \mu I \\
\tfrac{dR}{dt} &= \delta_2 I - \pi R - \mu R + uS
\end{aligned} \tag{5}$$

The system is subject to initial conditions $S(0), E(0), I(0)$ and $R(0)$. Figure 2 shows the dynamics with the control of vaccination.

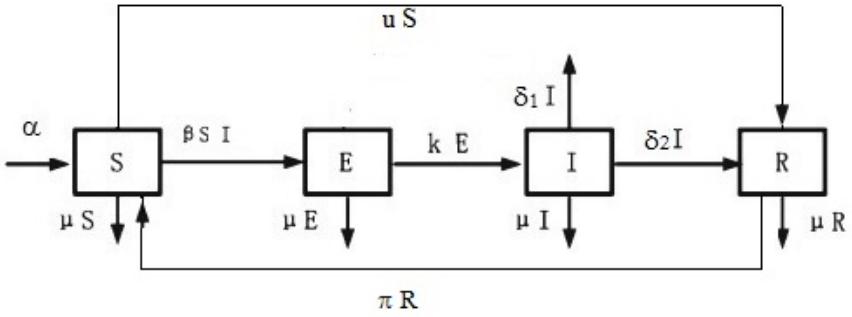

Figure 3: Transfer diagram of the influenza A (H1N1) epidemic model with the control of vaccination.

To solve the system of equations we make use of numerical methods. Such methods provide approximate solutions for problems that, in general, have no analytical solution or whose analytical solution is too hard to obtain. Derivative approximations are employed by the Finite Difference Method - FDM (Cunha, 2000).

4.1 Solving the Optimal Control Problem

To solve Problem (4), we make use of the so-called Pontryagin's Maximum Principle (Fleming & Rishel, 1975). This principle makes use of Lagrange multipliers in finite dimensional spaces (Leitão, 2001), and establishes a set of necessary optimality conditions. To derive these conditions, we firstly write]the Hamiltonian of the controlled system in (5):

$$H = I(t) + cu(t)^2 + w_1[\alpha + \pi R - \beta IS - \mu S - uS] + +w_2[\beta IS - kE - \mu_E] \\ +w_3[kE - \delta_1 I - \delta_2 I - \mu I] + +w_4[\delta_2 I - \pi R - \mu R + uS] + vu, \quad (6)$$

where w_i, $i = 1 \ldots, 4$, are called adjoint or co-state variables determining the adjoint system. Variable v is a penalty multiplier or slack variable, introduced to make sure that $u^* \geq 0$. In order for that to hold, it suffices that $v(t)u^\star(t) = 0$, $\forall t \geq 0$. Optimal control theory yields that the optimal control variable $u^\star$ maximizes the Hamiltonian over all feasible control actions u at all times. This implies the necessary condition:

$$\frac{\partial H}{\partial u^\star} = 0.$$

By solving the expression above, one finds that the optimal control problem is characterized by:

$$u^\star = max\{0, \tfrac{S(w_1 - w_4)}{2c}\} \quad (7)$$

For the co-state variables, the maximum principle states that: $\frac{\partial w}{\partial t} = -\frac{\partial H}{\partial x}$. That generate the adjoint system:

$$\begin{cases} \frac{dw_1}{dt} = w_1(\beta I + \mu + u) - w_2\beta I - w_4 u \\ \frac{dw_2}{dt} = w_2(k + \mu) - w_3 k \\ \frac{dw_3}{dt} = -1 + w_1\beta S - w_2\beta S + w_3(\delta_1 + \delta_2 + \mu) - w_4\delta_2 \\ \frac{dw_4}{dt} = -w_1\pi + w_4(\pi + \mu) \end{cases} \quad (8)$$

The Transversality Conditions (Fleming & Rishel, 1975) lead to the final conditions for the adjoint system:

$$w_i(T) = 0; \quad i = 1, \ldots, 4. \quad (9)$$

The optimal solution is then characterized by the state system (5), the adjoint system (8), the optimal control variables (7), the initial conditions of the system and the transversality conditions (9) of the co-state variables.

5 NUMERICAL SOLUTION

Note that the optimal control variable in (7) depends on the co-state variables at the optimal trajectory. Hence, since the optimal trajectory is not known a priori, u^* cannot be determined analytically. In this paper, we make use of numerical methods to solve the optimality conditions. In particular, we employ the finite difference method to find the optimal trajectories for a 150-day period.

In solving the problem we seek to optimal controls that simultaneously solve the initial value problem described by the state system and the final value problem described by the adjoint system. In this work, the optimal control trajectories are iteratively obtained by employing a classical specialized gradient algorithm (Kirk, 1970). We analyze the effect of vaccination with the following initial values: $S(0) = 1000$; $E(0) = 0$; $I(0) = 50$ and $R(0) = 0$. Table 1 presents the values of the parameters adopted.

Table 1: Parameters (Zhou and Guo, 2012).

Parameter	Nomenclature	Value
Rate of birth or immigration	α	15/day
Rate at which susceptible individuals become infected	β	0.00018
Natural death	μ	0.0000548/day
Reduction due to development of clinical symptoms	k	0.2/day
Rate of disease-induced death	δ_1	0.001/day
Rate of recovery from the disease	δ_2	0.14/day
Rate of loss of immunity	π	0.01
Time	T	150 days

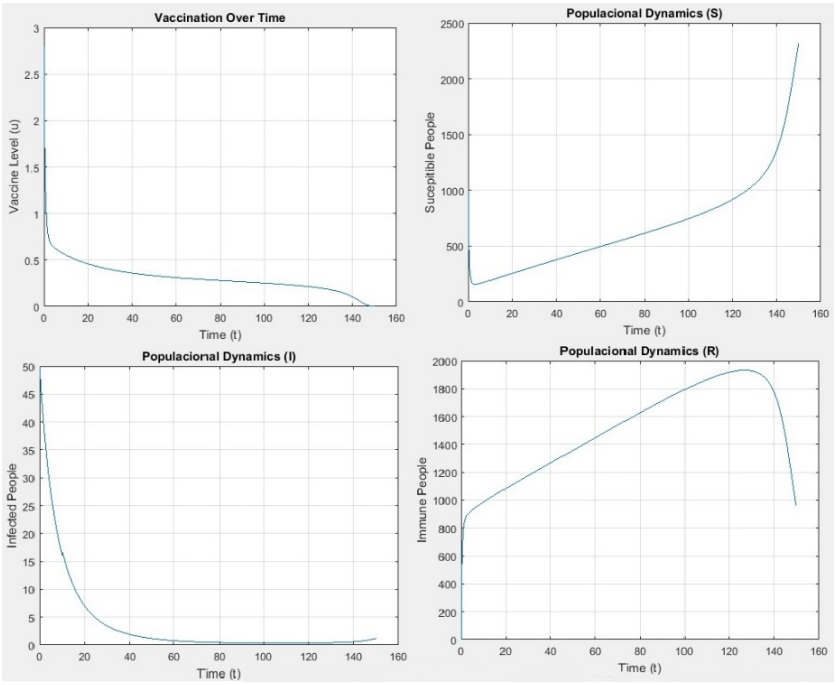

Figure 4: Numerical Experiments with $c = 1$ and $\pi = 0.1$.

Figure 4 shows the results for the experiment with $c = 1$ and $\pi = 0.1$. With a low vaccination cost and a high reinfection rate, the optimal control strategy prescribes the vaccination of large portion of the population. Note that the number of infected individuals decreases steeply.

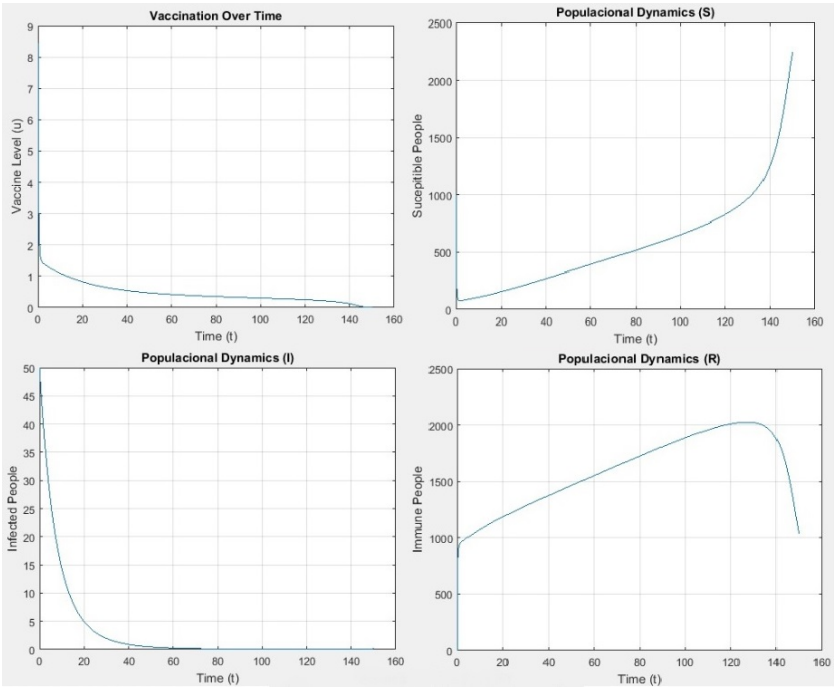

Figure 5: Numerical Experiments with $c = 10$ and $\pi = 0.1$.

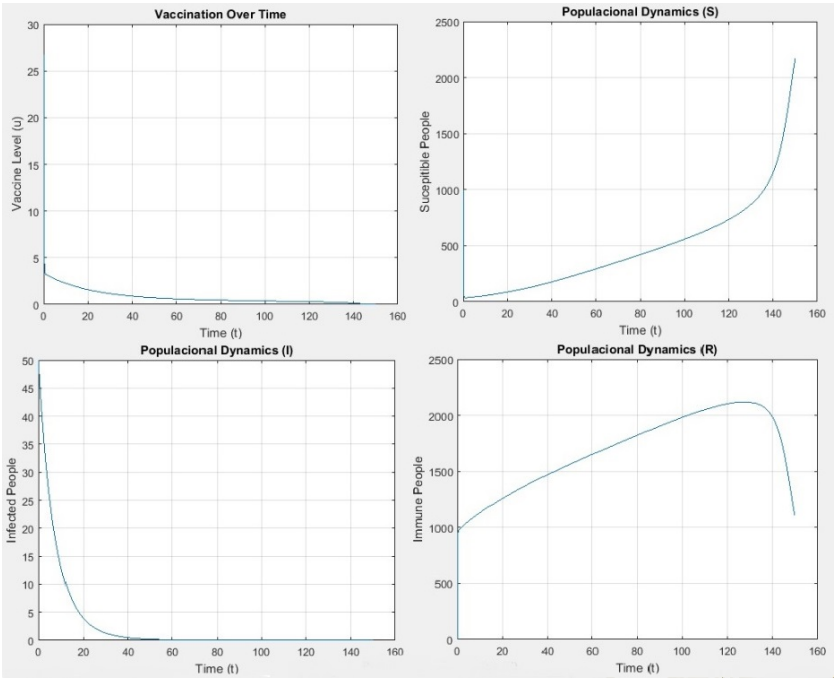

Figure 6: Numerical Experiments with $c = 1$ and $\pi = 0.01$.

Increasing the cost of vaccination (see Figure 5, with $c = 10$ and $\pi = 0.1$), one observes the same behavior but with a smaller number of vaccinated individuals. The same experiment is repeated with a lower reinfection rate $\pi = 0.01$, and the results are reported in Figure 6, with $c = 1$ and Figure 7, with $c = 10$. We observe a similar behavior, with only slight numerical variation.

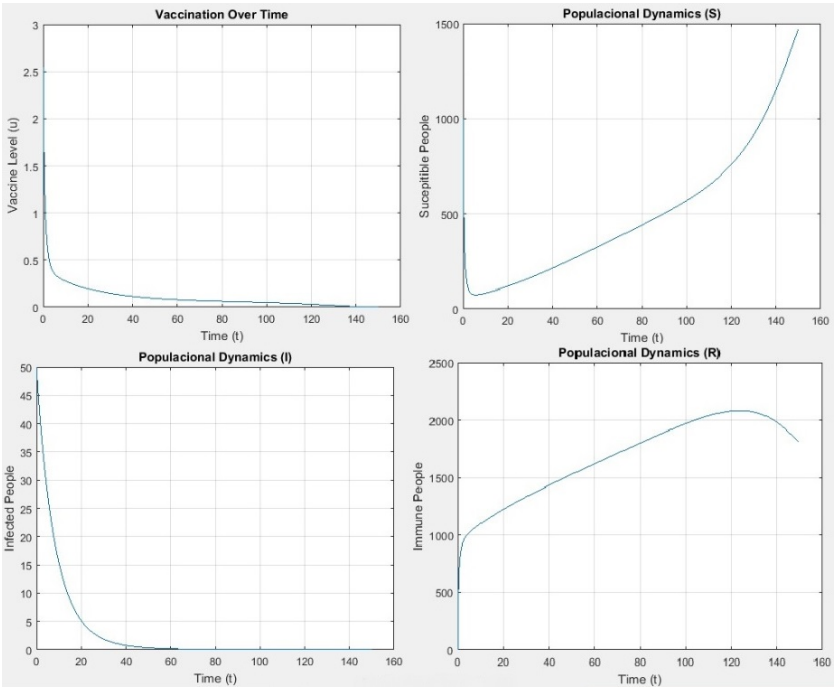

Figure 7: Numerical Experiments with $c = 10$ and $\pi = 0.01$.

The results of numerical experiments are consistent and suggest that the proposed model indeed represents the dynamics of the disease.

6 CONCLUSIONS

It is known that naturally created immunity for infection and immunity induced by vaccination are not permanent. They reduce over time causing a significant impact on immunization programs. We employ a model that takes into account the immunity loss over time.

Vaccines can be used to control or eradicate a disease. If the goal is the eradication, it is necessary to know the period that the vaccine protects the individual immunized. Thus, eradication strategies based on vaccination will only be effective if the protection time is long enough. Specifically regarding Influenza, that poses a great challenge.

We proposed an optimal control problem to retrieve an optimal vaccination for a prescribed period, taking into account the immunity loss that leads to reinfection. The obtained results are promising and suggest that the model is sound.

Future research includes the analysis of equilibrium and stability of the proposed model. In addition, we intend to evaluate the correlation between reinfection and virus mutation.

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