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A SIMPLE ANALYSIS OF VACCINATION STRATEGIES FOR RUBELLA

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Abstract. We consider an SEIR epidemic model with vertical transmission introduced by Li, Smith and Wang, [23], and apply optimal control theory to assess the effects of vaccination strategies on the model dynamics. The strategy is chosen to minimize the total number of infectious individuals and the cost associated with vaccination. We derive the optimality system and solve it numerically. The theoretical findings are then used to simulate a vaccination campaign for rubella in China.

1. **Introduction.** Among the very huge literature on epidemic models (see e.g. [1, 6, 9, 18]) an important role is played by studies concerning with infectious diseases that transmit through both horizontal and vertical modes, [8]. Roughly speaking, for humans and animal diseases, the horizontal transmission occurs through contacts with infectious hosts, which may be a direct physical contact or an indirect one, through e.g. biting insects. Vertical transmission, instead, occurs when the disease is transferred from parent to offspring. For example, an infectious mother may transmit the disease to her fetus by means of bodily fluid or breast milk. Examples of diseases that can be vertically transmitted include hepatitis B, herpes simplex, syphilis, rubella (german measles), Chagas disease (american trypanosomiasis) and HIV-AIDS.

Epidemic models including vertical transmission may be found in several papers, as e.g., [13, 26]. Here, we consider the following model introduced by Li, Smith and Wang, [23]:

$$\begin{cases} \dot{S} = b - kIS - pbE - qbI - bS \\ \dot{E} = kIS + pbE + qbI - (\epsilon + b)E \\ \dot{I} = \epsilon E - (\sigma + b)I \\ \dot{R} = \sigma I - bR. \end{cases} \tag{1}$$

In (1) the upper dot denotes the time derivative, the state variables are the fractions in which the host population is divided: the susceptibles (S), the exposed, i.e. infected but not yet infectious (E), the infectious (I), and the recovered (or immune) (R). The parameters (all positive constants) have the following meaning: b is the natural birth rate, which is assumed to be identical to the death rate, k is the contact rate, p is the fraction of the offspring from the exposed class that are born

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into the exposed class E, q is the fraction of the offspring from the infectious class that are born into the exposed class E, ϵ is the rate at which the exposed individuals become infectious, σ is the rate at which the infectious individuals recover.

The parameters p and q ($0 \leq p \leq 1$, $0 \leq q \leq 1$) represent the vertical transmission. The incidence term is assumed to be of bilinear mass-action form.

In [23] some qualitative properties of model (1) were found, including the stability properties of the equilibria. The model was extended in [25] to include also vaccination, which is represented by a linear transfer from susceptibles to removed compartments, with a constant vaccination rate.

In 2003, model (1) has been revisited by d'Onofrio, [12], who considered a periodically varying contact rate. He found a condition ensuring that the vaccine-induced disease-free solution is globally asymptotically stable.

In this paper, we use an optimal control approach to evaluate the effects of vaccination strategies on a community affected by a disease whose dynamics may be described by model (1).

As underlined in [15], optimal control theory, when applied to disease models, provides a powerful tool to get great insights into the best pathway to reduce disease burden. In particular, one can find the optimal response for a vaccination schedule that will minimize the disease burden while being mindful of the costs of the strategy.

Analytical and numerical results concerning with optimal control problems in mathematical epidemiology can be found in several papers, starting from the seventies. For example, applications of optimal control theory to simple SIR epidemic models can be found in [3, 29, 31, 34]. The great variety of epidemic models and problems that can be treated with optimal control theory (and the related literature) is described, briefly but effectively, in [2]. Recently, stimulated by new analytical and numerical findings, researchers found new impulses and interest to study the applications of optimal control theory to biology and epidemiology. A big contribution is given by Lenhart and her coworkers, [2, 21, 22]. Examples of recent applications of optimal control theory to epidemics can be found also in [4, 17, 20].

Here, we choose the optimal strategy to minimize the total number of infectious individuals and the cost associated with vaccination. We derive the optimality system and solve it numerically. As stressed in [23], rubella is among the disease for which (1) is a good approximation. For this reason, inspired by paper [16], we will test our theoretical findings by simulating rubella vaccination strategies in China.

The paper is organized as follows: in Section 2 we recall the results obtained in [23] concerning with the qualitative properties of the solutions of model (1). In Section 3 the optimal control problem is introduced and the optimality conditions are derived. In Section 4 a simulation of rubella vaccination strategies in China is provided. Concluding remarks in Section 5, close the paper.

2. **Dynamical behavior.**

In this section we summarize some of the results obtained in [23], concerning with the dynamical behavior of (1). First of all, by using the relation $R = 1-S-E-I$, system (1) may be reduced to the following equivalent system:

$$\begin{cases} \dot{S} = b - kIS - pbE - qbI - bS \\ \dot{E} = kIS + pbE + qbI - (\epsilon + b)E \\ \dot{I} = \epsilon E - (\sigma + b)I, \end{cases} \tag{2}$$

which can be studied in the closed, positively invariant set:

$$\Gamma = \left\{(S, E, I) \in \mathbf{R}^3_+ : S + E + I \leq 1\right\}.$$

Introduce now the so called *basic reproductive number*:

$$R_0 = \frac{k\,\epsilon}{(b+\epsilon)(b+\sigma) - bp(b+\sigma) - bq\epsilon}. \tag{3}$$

System (2) admits the *disease-free* equilibrium $P_0 \equiv (1, 0, 0)$ on the boundary of Γ, and an *endemic* equilibrium $\overline{P} \equiv (\overline{S}, \overline{E}, \overline{I})$ in the interior of Γ, where:

$$\overline{S} = \frac{1}{R_0}; \quad \overline{I} = \frac{\epsilon\, b\,(R_0 - 1)}{(b+\epsilon)(b+\sigma)R_0}; \quad \overline{E} = \frac{b(R_0 - 1)}{(b+\epsilon)R_0}. \tag{4}$$

The following theorem may be established (see [23]):

Theorem 2.1. *If $R_0 \leq 1$, then P_0 is the only equilibrium and it is globally stable in Γ. If $R_0 > 1$, then P_0 is unstable and there exists a unique endemic equilibrium $\overline{P}$, and it is globally stable in the interior of Γ.*

Theorem 2.1 states that $R_0 = 1$ is a threshold for the system dynamics. If $R_0 \leq 1$, then the disease will be eradicated, whereas if $R_0 > 1$, then the disease will persist at the endemic equilibrium, for all initial state in the interior of the set Γ. The global stability result for the endemic equilibrium, contained in Theorem 2.1, has been obtained by using the so called *geometric approach* to stability due to Li and Muldowney (see e.g. [24]). Using such an approach, the same result has been proven for a more general system in [7], and derived for model (2) as a particular case.

3. **Optimal control problem and its analysis.** In this Section, we will introduce the intervention strategy by means of vaccination. Recent examples of optimal vaccination policy for struggling infectious diseases like influenza and west nile virus may be found in [4, 5]. Here we consider a vaccination campaign over a fixed time period, $[0, t_f]$. The vaccine drives the susceptibles individuals to the recovered class. So, we introduce the control function $u(t)$ and consider the modified system:

$$\begin{cases} \dot{S} = b - kIS - pbE - qbI - bS - u(t)S \\ \dot{E} = kIS + pbE + qbI - (\epsilon + b)E \\ \dot{I} = \epsilon E - (\sigma + b)I \\ \dot{R} = \sigma I - bR + u(t)S. \end{cases} \tag{5}$$

where $u(t)$ is a Lebesgue measurable function such that: $0 \leq u(t) \leq u_{max}$, for $t \in [0, t_f]$. The goal here is to minimize the total number of infectious individuals and the cost associated with vaccination during the vaccination campaign. Hence, the optimal control problem is to minimize the objective functional:

$$J(u) = \int_0^{t_f} \left[AI(t) + u^2(t)\right] dt, \tag{6}$$

subject to (5) and non negative initial data $S(0) = S_0$; $E(0) = E_0$, $I(0) = I_0$, $R(0) = \rho_0$.

In (6) the parameter A is a *weight* parameter describing the comparative importance of the two terms in the functional. For example, an high value of A means that it is more important to reduce the disease burden than to reduce the vaccination costs.

The description of the intervention costs in the objective functional is a quite debated question in the literature. The dependence on the control may be linear or nonlinear. A pure linear cost in both the differential equations and the objective functional may drive to discontinuous optimal profiles, involving singular and bang-bang controls (i.e. the optimal control may only switch between the bounds of the control set), see e.g. [3, 29, 31]. It has been argued that finding the times at which the switching occurs is quite difficult, [19]. Furthermore, nonlinear description is preferable when a sudden change in epidemics control is not advisable, [33]. As a matter of fact, when the nonlinear description is adopted, it may be not completely clear which nonlinear form must be appropriately chosen (a typical example of similar dilemma is the transmission function in epidemic models). In this case, choosing the simplest form compatible with the mathematical requirements (existence, well-posedness of maximization problems, etc.) is a possible guideline. In this sense we consider a quadratic cost on the control, which is the simplest and widest used nonlinear representation of vaccination cost (see e.g. [2, 20, 21]). However it has been argued that other nonlinear functions might provide a better description of the actual vaccination cost, because of the increase of vaccination cost when most of the population is already removed (vaccinated or immune), [15].

The limitation on u reflects the idea that there are practical limitations on the maximum rate at which individuals who may be vaccinated in a given time period, [15] and we will assume $u_{max} = 0.9$.

Our problem may be addressed by using the Pontryagin's maximum principle, [30]. It is a constrained control problem, so we must minimize pointwise the Hamiltonian, [22]:

$$H(S, E, I, R, u, \lambda_1, \lambda_2, \lambda_3, \lambda_4, t) = AI(t) + u^2(t) + \sum_{i=1}^{4} \lambda_i f_i, \tag{7}$$

where f_i represents the right-hand size of the differential equation of the i-th variable and λ_i are the adjoint variables.
The adjoint equations are given by:

$$\begin{aligned}
\dot{\lambda}_1 &= -\frac{\partial H}{\partial S} = \lambda_1 (kI + b + u) - \lambda_2 kI - \lambda_4 u \\
\dot{\lambda}_2 &= -\frac{\partial H}{\partial E} = \lambda_1 pb - \lambda_2 (pb - \epsilon - b) - \lambda_3 \epsilon \\
\dot{\lambda}_3 &= -\frac{\partial H}{\partial I} = -A + \lambda_1 (kS + qb) - \lambda_2 (qb + kS) + \lambda_3 (\sigma + b) - \lambda_4 \sigma \\
\dot{\lambda}_4 &= -\frac{\partial H}{\partial R} = b\lambda_4.
\end{aligned} \tag{8}$$

The state variables are not assigned at the final time t_f so that we have the transversality equations:

$$\lambda_1(t_f) = \lambda_2(t_f) = \lambda_3(t_f) = \lambda_4(t_f) = 0. \tag{9}$$

In order to illustrate the characterization of the optimal control u^*, we consider the optimality condition:

$$\frac{\partial H}{\partial u} = 0,$$

at $u = u^*$, on the set $\{t \in [0, t_f] : 0 \leq u \leq 0.9\}$. That is:

$$u^*(t) = S^*(\lambda_1 - \lambda_4)/2,$$

Symbol	*Description*	*Value*
b	Natural birth rate	0.012 year^{-1}
ϵ	Progression rate from E to I	36.500 year^{-1}
σ	Progression rate from I to R	30.414 year^{-1}
p	Fraction of the offsprings from E born into E	0.65
q	Fraction of the offsprings from I born into E	0.65
k	Contact rate	527.59 ind^{-1} year^{-1}

TABLE 1. Description of the epidemiological parameters used in the simulations. See the text for details on the estimation.

and, taking into account the bounds on u^*, the characterization is:

$$u^* = \begin{cases} 0 & \text{if } S^*(\lambda_1 - \lambda_4) < 0 \\ S^*(\lambda_1 - \lambda_4)/2 & \text{if } 0 \leq S^*(\lambda_1 - \lambda_4) \leq 1.8 \\ 0.9 & \text{if } S^*(\lambda_1 - \lambda_4) > 1.8. \end{cases}$$

which, in short form, may be written:

$$u^*(t) = \min\left(\max\left(0, S^*(\lambda_1 - \lambda_4)/2\right), 0.9\right).$$

The existence and the uniqueness of the optimal control, for small t_f, is standard and follows from the boundedness of the state and adjoint variables, the lipschitzianity of the right sides of the ODEs (see, e.g., [21]). The convexity of the objective functional in u ensures that it is a minimizing problem.

We may summarize our result in the following:

Theorem 3.1. *There exists an optimal control $u^*(t)$ and the corresponding solution, $S^*(t)$, $E^*(t)$, $I^*(t)$, $R^*(t)$, and H^*, that minimizes (6) subject to (5), $0 \leq u \leq 0.9$ and the initial conditions. Furthermore, there exist adjoint functions $\lambda_i(t)$, $i = 1, 2, 3, 4$, that are solutions of (8) with transversality conditions (9).*

4. A simulation of rubella vaccination strategies.

4.1. Estimation of epidemiological parameters.

In a recent paper, [16], Gao and Hethcote considered an age structured model to evaluate the dynamics of rubella over time in China, under various scenarios of vaccination or non-vaccination. We will estimate our epidemiological parameters by using data from their paper (unless otherwise stated). In this way we test our theoretical findings on the same case study in China.

• *Natural birth rate, b*: the crude birth rate for China in 2007 was 12.10 per 1,000 people per year, [10]. The crude death rate was 6.93 per 1,000 people per year, resulting in a natural growth rate of 5.17 per 1,000 people per year. However, here we assume that both birth and death rate have the same value, altough this hypothesis is not strictly necessary for our analysis. We do that for two main reasons: first, this is a specific assumption on which the original model is based, [23]. Then, we will consider a quite short vaccination campaign (3 years) so that the total population may be considered to be approximately constant. We take $b = 0.012$ per year.

• *Rate at which the exposed individuals become infectious, ϵ*: the mean residence time for the exposed (latent) class, i.e. the time from exposure to infectiousness, is $1/\epsilon$=10 days. So we take $\epsilon = 365/10 = 36.5$ per year.

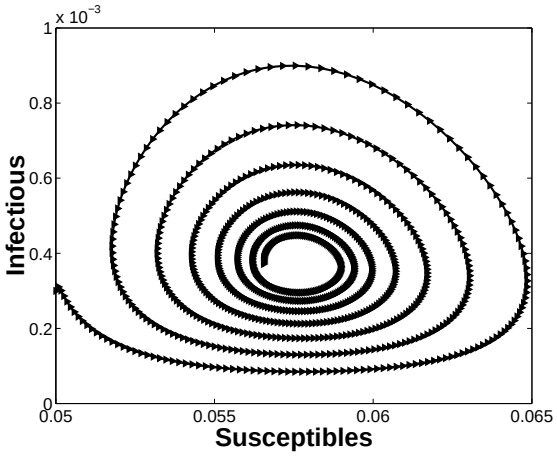

FIGURE 1. Without vaccination, solutions of model (5) converge to the endemic state (10), in agreement with Theorem 2.1. Here the convergence is depicted in the $S - I$ plane. The equilibrium is a stable focus. The simulation is performed with parameter values given in Table 1 and initial data $S_0 = 5 \cdot 10^{-2}$, $E_0 = 3 \cdot 10^{-4}$, $I_0 = 3 \cdot 10^{-4}$, $\rho_0 = 0.9494$.

• *Rate at which the infectious individuals recover, σ*: the mean residence time in the infectious class for rubella, i.e. the average infectious period, is $1/\sigma$=12 days. So we take $\sigma = 365/12 = 30.417$ per year.
• *Fractions p and q of the offspring from the exposed and infectious class that are born into the Exposed class E*: the risk of congenital defects varies with the gestational age at which maternal infection occurs. It has been reported to be 90% when maternal infection/exposure occurs before 11 weeks of gestation, 33% at 11-12 weeks, 11% at 13-14 weeks, 24% at 15-16 weeks, and 0% after 16 weeks, [14, 28]. According to this report, in [11] it is estimated the risk of congenital rubella syndrome (CRS) after infection in the first sixteen weeks of pregnancy to be 65%, and zero after infection later in pregnancy.

Here, the age is not taken into account. Furthermore, we do not distinguish between CRS cases coming from exposed and infected mothers. Hence, we take $p = q = 0.65$.
• *Contact rate, k*: In [16] several values for the rubella force of infection are reported for different age groups. The average for people between 0 and 50 years is 0.196 per year. In (5) the force of infection is modelled as a linear term kI, where k is the contact rate. Hence, at the endemic state, taking into account of (4), it is:

$$k\,\frac{\epsilon\, b\,(R_0 - 1)}{(b+\epsilon)(b+\sigma)R_0} = 0.196,$$

i.e., in view of (3),

$$k = 0.196\frac{(b+\epsilon)(b+\sigma)}{\epsilon b} + \frac{[(b+\epsilon)(b+\sigma) - bp(b+\sigma) - bq\epsilon]}{\epsilon}.$$

The values above for b, ϵ, σ, p, q, drive to $k = 527.59$ per individual per year (and, consequently, $R_0 = 17.34$).

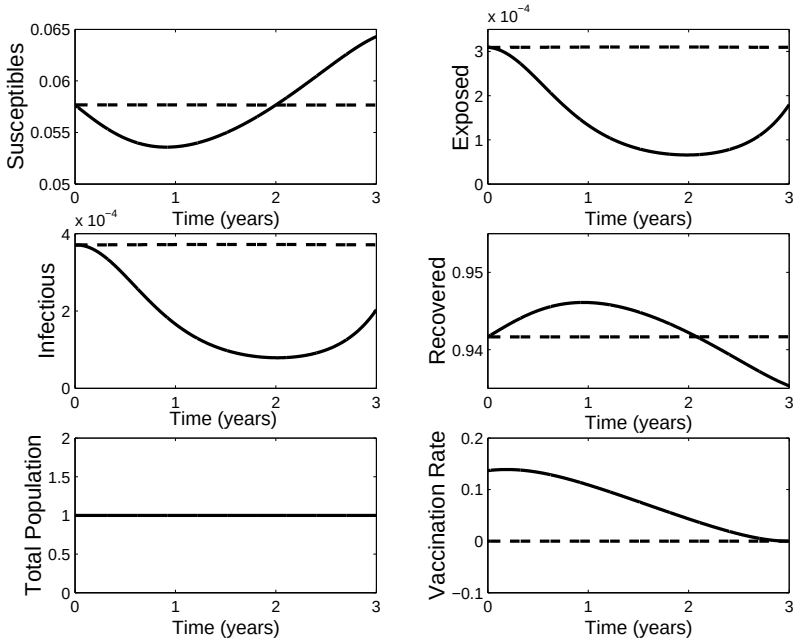

FIGURE 2. The solid lines represent the dynamics of model (5) with $A = 100$. The dashed lines correspond to the equilibrium solution in absence of control, i. e. the endemic equilibrium of model (1). The others parameter values are given in Table 1. The initial data are: $S_0 = 5.767 \cdot 10^{-2}$, $E_0 = 3.1 \cdot 10^{-4}$, $I_0 = 3.7 \cdot 10^{-4}$, $\rho_0 = 0.94165$.

The values above are summarized in Table 1. With this choice, according to Theorem 2.1, in absence of vaccination the disease will reach the endemic equilibrium $\overline{P} \equiv (\overline{S}, \overline{E}, \overline{I})$, where:

$$\overline{S} \approx 0.05767; \quad \overline{E} \approx 3.08 \cdot 10^{-4}; \quad \overline{I} \approx 3.70 \cdot 10^{-4}, \tag{10}$$

and $\overline{R} = 1 - \overline{S} - \overline{E} - \overline{I} \approx 0.94165$. This endemic equilibrium will be reached whatever be the initial state of the system.

4.2. **Numerical settings.** The optimality system is numerically solved by using the so called forward-backward sweep method, described in detail in [22]. The process begin with an initial guess on the control variable. Then, the state equations are solved simultaneously forward in time, and next the adjoint equations are simultaneously solved backward in time. The control is updated by inserting the new values of states and adjoints into its characterization, and the process is repeated until convergence occurs. As in [22], the solver used for the state and adjoint systems is a Runge-Kutta fourth order procedure. A MATLAB code, [27], has been built to perform the simulations. The code is similar to the one used in [22] for a generic SEIR epidemic model.

4.3. **Discussion.** Our first simulation is depicted in Figure 1. It is shown that, according to Theorem 2.1, without vaccination, solutions of model (5) converge to the endemic state (10). The convergence is depicted in the $S - I$ plane and it can be seen that the equilibrium is a stable focus. In other words, the state variables

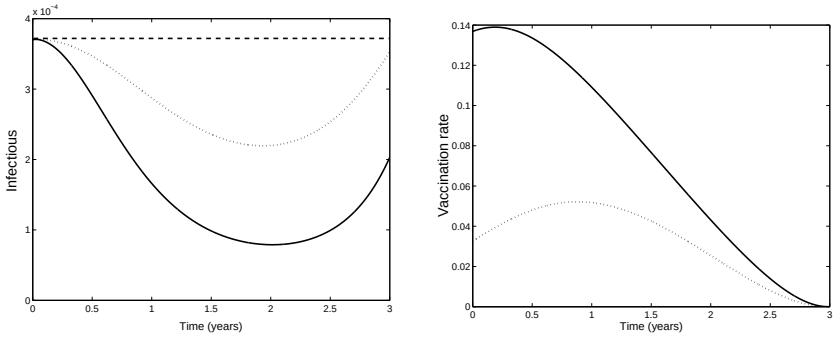

FIGURE 3. Infectious (on the left) and Vaccination rate (on the right) versus time. The solid lines correspond to the case $A = 100$, the dotted line to the case $A = 30$. The straight line in the left picture is the equilibrium solution. The others parameter values are given in Table 1. The initial data are: $S_0 = 5.767 \cdot 10^{-2}$, $E_0 = 3.1 \cdot 10^{-4}$, $I_0 = 3.7 \cdot 10^{-4}$, $\rho_0 = 0.94165$.

approach the endemic state through dumped oscillations. The simulation is performed with parameter values given in Table 1 and generic initial data (specified in the caption of Figure 1).

According to World Health Organization data statistics, [35], the reported cases of rubella in China are increasing in the last years. There were 24,015 reported cases in 2004, that jumped to 74,746 in 2007 and 120,354 in 2008. According to (5), with parameter values given in Table 1, the cases will increase until the endemic state (10) will be reached, which corresponds to $I^* \approx 3.70 \cdot 10^{-4}$, that is to say, taking into account of a total population of $1.3 \cdot 10^9$ individuals, that 481,000 infected individuals are expected at the endemic state.

We test the optimal vaccination strategy at the endemic state in order to emphasize the effects of optimal vaccination on system dynamics. Hence, in the second simulation, model (5) is considered with a non negative vaccination term, which is the control variable. The optimal control problem is to minimize the total number of infectious individuals and the cost associated with vaccination.
The results for a three-years campaign are shown in Figure 2.

We first note that the vaccination rate is at the highest possible value in the first stage of vaccination campaign. This result is in agreement with the remark made in [15], where a similar optimal vaccination policy was observed for several different epidemic model with SIR and SEIR structure. The authors found that regardless of the disease structure, vaccinate at the highest possible rate as early as possible is essential for controlling an epidemic. We also remark that the optimal control profile depicted in Figure 2 is similar to that observed in [2] for an SIR metapopulation model.

According to the optimal strategy, the infectious can be reduced up to 75% around the second year of campaign (see the infectious graph in Figure 2). At the end of campaign, infectious and exposed both show an increasing trend, due to the immission of new susceptibles. However they are more or less the half of those who were at the beginning. This result can be helpful to plan periodic vaccination campaigns.

We used relatively big value of the balancing factor A, to empasize how the relative cost of vaccination plays a relevant role in the vaccination strategy. By reducing the parameter A, we observe that the maximum vaccination rate shifts on the right in the optimal control profile (Figure 3, right). Hence, if the vaccination cost is relatively high, a gradual increase of the vaccination rate is suggested. Of course, higher is the priority of cost reduction, lower is the efficacy of the campaign on disease burden (Figure 3, left).

5. **Conclusions.** In this note, the SEIR epidemic model with vertical transmission introduced by Li, Smith and Wang, [23], and analysed in [12, 23, 25], is applied to epidemic spread of rubella in China. To our knowledge, this model has never been tested before with real data. We perform the optimal control approach described in [22] and test our theoretical findings to simulate simple scenarios for rubella vaccination strategies.

Our application is somewhat inspired by the simulations of rubella vaccination strategies by Gao and Hethcote, [16] and we use some of their epidemiological parameter values. Our first result is that in absence of vaccination a strong increase of total rubella cases in China, up to 225%, is predicted by model (5). On the other hand, in [16] it has been observed that an unsufficient vaccination campaign may drive the total CRS incidence in China to be more than twice the current level. Furthermore, Gao and Hethcote find that routine vaccination coverage of over 80% of 1-year old children may sensibly reduce the CRS cases and eliminate rubella in fifty years. Moreover, a mass vaccinations combined with routine vaccinations may help to accelerate the eradication of rubella. Taking into account of chinese total population of $1.3{\cdot}10^9$ individuals, and that the percentage of 1-years old children in 2000 was 0.01 (chinese age distribution in F! igure 2 in [16]), we can estimate that at least $10.4{\cdot}10^6$ vaccinations are needed to obtain the eradication predicted in [16]. Here, in the case $A = 100$, we get a maximum initial vaccination rate of 0.137 (approximately, see Figure 3) with a suceptibles endemic level of 0.05767, so that at least $10.27{\cdot}10^6$ vaccinations are required at the beginning of the campaign, if it starts when the infection is at its endemic state. This result is comparable with the one obtained in [16]. However the comparison with the studies done in [16] cannot go further. In fact, Gao and Hethcote have considered an age structured model and the analysis is extended for a larger time span. Model (5) does not consider age groups, however the optimal control approach can give a qualitative insight on short term vaccination strategies. In particular, we have seen how optimal strategies may be scheduled over a three years campaign, to reduce the disease burden when it is at its endemic state.

There are several directions to improve our analysis. First of all, the model introduced in [23], used here, does not take into account of population subcompartments, which are of big importance for diseases like rubella (pregnant women, childrens, etc.). This reduce the accuracy of our results but they are still readable, at least qualitatively. Furthermore, in the optimal strategy may be also important to consider treatment explicitly. Indeed, as shown in [15], treatment may be a valuable resource in decreasing the infectious so that, in turn, it may have a great effect on vaccination strategies. Even if this aspect is not relevant for rubella, because there is no specific treatment and cure generally consists of rest and medication for symptoms, a two-controls problem may be a further way to investigate model (1) when it is applied to other vertically transmitted diseases. Finally, the inclusion of

seasonality may be appropriate for this model. For example, several diseases are driven by the seasonally changing contact rate between children which increases sharply at the beginning of each school year, and strongly controls the ensuing disease transmission, [32]. These aspects will be considered in forthcoming works.

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