Vaccination and Time Limited Immunization for SARS-CoV-2 Infection

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Abstract: The paper aims at a discussion of the effects of the containment measures against COVID-19 through the analysis of the reproduction number. Starting from a mathematical model in which several controls are considered, including the vaccination, and introducing also an hypotised limited duration of the immunity acquired both from vaccine and from healing from the illness, the steady state behaviour, both in the uncontrolled and in the controled cases is studied. The expressions for the basic reproduction number and the actual reproduction number under control actions are computed by means of the next generation matrix approach. This function is numerically investigated, showing some graphs which illustrate, qualitatively and quantitatively, in an intuitive way the positive effects of the controls and the negative contribution of the absence of a lifetime immunization from virus.

1 INTRODUCTION

Mathematical modelling of epidemics spread is a basic tool for prediction of different scenarios and for the definition of suitable control actions aiming at the virus containment.

Compartmental systems are usually adopted; since the pioneering work (Kermack and McKendrick, 1927), all of them consider at least the compartment of susceptible individuals S that can get infection, the infected ones I which can transmit the virus, and the recovered patients R healed from the illness (SIR model).

Richer descriptions include additional classes like, for example, the exposed patients E, if the virus has a significant incubation time, or people that lose immunity after infection C. Moreover, for the description of each specific infection, particular classes are included. Descriptions and discussions on epidemic modelling can be found in (Daley and Gani, 1999; Martcheva, 2015).

For the COVID-19, the more or less dangerousness of the evolution of the illness for different patients, going from asymptomatic ones to people requiring long stay in intensive care, and the variability of the death rate according to the age or the presence of comorbidities, motivated the introduction of additional compartments to take into account all these possible levels of infection and therapeutic needs. Despite the quite limited time since the beginning of this disease, the list of models introduced could be long. Among the first models designed specifically for the COVID-19 case there is (Tang et al., 2020), where the pre-symptomatic infectious (A), the hospitalized (H), the quarantined susceptible (Sq), the isolated exposed (Eq) and the isolated infected (Iq) compartments are considered. In (Di Giamberardino and Iacoviello, 2021) the quarantined compartment containing temporarily isolated individuals is added and the infected people are divided into symptomatic and asymptomatic ones, analysing the role of the latter. In (Gumel et al., 2021) the infected patients are divided into asymptomatic (Ia), symptomatic (Is), and hospitalized (Ih) classes. Sometimes the population is also divided into categories, often age based (Di Giamberardino et al., 2020), to analyse the effects of the epidemics on the different groups.

Models allow to study the actual spread dynamics, to predict its behaviour for different scenarios and to help in the designing of control laws or, at least, in supporting political and social decisions for epidemic containment. A compact description of the epidemic dangerousness, usually adopted for driving governments interventions, is the so called *basic reproduction number* $\mathcal{R}$, representing an important indicator commonly used for characterising the velocity of diffusion of one epidemic, so measuring its impact on

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the population in terms of rate of increment of infected individuals. It is defined as the number of individuals directly infected by one infective person assumed as the only infective subject in all the population (Diekmann et al., 1990; Dietz, 1993; Perasso, 2018; Zhao et al., 2020; Katul et al., 2020).

This definition is purely theoretical, since the estimation of such a quantity is performed when the disease is already present, the number of infective persons is much larger than one and some intervention policies are already adopted. So, there are statistical approaches to estimate $\mathcal{R}_0$ from data series of infected individuals (Dietz, 1993). The computation does not follow a unique approach, so there are several procedures for its computations which differ for statistical assumptions. In (Billah et al., 2020) such differences are presented and discussed. An estimation can also be computed on the basis of the model of the epidemics dynamics making use of the *next generation matrix* (Diekmann et al., 2010; van den Driessche, 2017; Perasso, 2018). The use of a model to compute the basic reproduction number can be helpful for the evaluation of the influence of the parameters to its value. Moreover, if the controls are considered too, a controlled reproduction number can be introduced to evaluate also their effects on the virus spread; this means that it is possible to establish a relationship, also in a quantitative way, between controls and reproduction number value, so supporting the evaluation of the effects of interventions (van den Driessche, 2017).

In the present work, the model proposed in (Di Giamberardino and Iacoviello, 2021) is considered as a validated starting point from which additional effects can be studied. In particular, in the present paper, the vaccination u_6 is introduced, being at present a relevant control action not sensibly present yet at time of (Di Giamberardino and Iacoviello, 2021). Moreover, based on the observation that the immunization produced by a vaccine seems to have a time limited duration, the lost of antibodies and then the possible reinfection is also considered (ρR), making the rate of vaccination an important issue to be faced. The analysis of the combined and contrasting effects of the modelled intervention actions and the end of the immunization is performed by means of the dependency of the basic reproduction number from such quantities. In Section 2 the model is introduced and briefly described while its equilibrium and stability characteristics are addressed in Section 3. In view of the analysis for the controlled case, the effects of the inputs on the equilibrium points and their stability are shown in Section 4. The influences of the controls on the reproduction number are studied and discussed in Section 5. Some concluding comments in Section 6 end the paper.

2 THE MATHEMATICAL MODEL

The mathematical model here adopted is the one introduced in (Di Giamberardino and Iacoviello, 2021), modified adding the vaccination control, denoted by u_6, and the limited time of immunity for healed and vaccinated individuals, introduced by means of a time constant ρ. Moreover, since the work is mainly focused on the analysis of the opposite effects of the vaccination and the lost of immunization with consequent possibility of reinfection, the model is simplified neglecting the quarantined class, also in view of the relatively low number of individuals in such a condition and, then, their negligible effect with respect of the vaccination process.

The scheme in Figure 1 describes the compartment model introduced. Solid lines/arrows denote the natural flux of the infection evolution, from the class S of susceptible to the class R of the recovered individuals, and from the recovered to the susceptible classes for the lost of immunity; this natural flux includes also the dotted arrows, representing the death people from all the classes. Dashed lines represent the control actions, whose description is provided below.

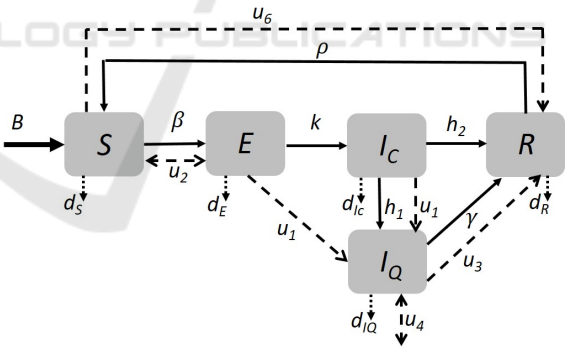

Figure 1: Block scheme of the compartmental model studied.

The resulting dynamics is described by the equations

$$\begin{aligned}
\dot{S} &= B-\beta(1-u_2)SI_C-vu_6S+\rho R-d_SS\\
\dot{E} &= \beta(1-u_2)SI_C-au_1E-kE-d_EE\\
\dot{I}_C &= kE-au_1I_C-h_1I_C-h_2I_C-d_{I_C}I_C\\
\dot{I}_Q &= au_1(E+I_C)+h_1I_C\\
&\quad -(\gamma+\eta u_3)I_Q-d_{I_Q}(1-u_4)I_Q\\
\dot{R} &= h_2I_C+(\gamma+\eta u_3)I_Q+vu_6S-\rho R-d_RR
\end{aligned} \tag{1}$$

where all the state variables represent the number of individuals in the corresponding class. They are

- S the susceptible individuals;
- E the exposed ones, already infected but not yet infective since the virus is in its incubation period; the time constant for incubation condition is $1/k$
- I_C the infected patients without symptoms; they are infective and then are the responsible of the disease spread. They can remain asymptomatic for all the illness course till healing, with time rate h_2, or can start to have some symptoms, with rate h_1;
- I_Q the diagnosed infected patients which are isolated and then cannot transmit the virus even if infective. Patients in this class are the ones that can receive medical treatment both against the infection, u_3, like antivirals, monoclonal antibodies and so on, so increasing the recovering rate, and for reducing the secondary diseases or complications even to intensive care support, u_4, reducing the mortality;
- R the immune individuals which are supposed to be neither infected nor infectious, composed by the recovered patients, the ones healed spontaneously or after therapy, and the vaccinated individuals. They are protected from infection for a limited time period after which they return to be susceptible with a time rate ρ.

In the model are also present a constant rate of newborns B, the transmission rate β from which the epidemic spread depends, the spontaneous rate of healing of diagnosed patients γ, and the death rates d_*, possibly different for each class. Along with these parameters, in the model there are present the control u_2, which acts on the individual interactions by means of social restrictions, use of masks, till lock down periods, the input au_1 representing the effects of the tests for infection detection, and the vaccination rate vu_6. Note that vaccination affects susceptible individuals only since E and I_C, even if vaccinated, do not leave their classes because they do not change their infective status.

A short analysis of dynamical characteristics is provided in next Subsection 3 to show the differences with respect to the original model.

3 EQUILIBRIUM CONDITIONS

In the system analysis, the computation of the equilibrium points and the study of their stability is a preliminary step for understanding the qualitative behaviour of the dynamics. According to the classical approach, the uncontrolled system is considered ($u_i = 0, i = 1,2,\ldots,6$).

3.1 Equilibrium Points

The equilibrium points are obtained setting equal to zero the variations in (1). Then, the solutions of

$$\begin{aligned} B - \beta S^e I_C^e - d_S S^e + \rho R^e &= 0 && (2)\\ \beta S^e I_C^e - (k + d_E) E^e &= 0 && (3)\\ k E^e - (h_1 + h_2 + d_{I_C}) I_C^e &= 0 && (4)\\ h_1 I_C^e - \gamma I_Q^e - d_{I_Q} I_Q^e &= 0 && (5)\\ h_2 I_C^e + \gamma I_Q^e - d_R R^e - \rho R^e &= 0 && (6) \end{aligned}$$

must be computed. The system is a slight variation of the one considered in (Di Giamberardino and Iacoviello, 2021), but the presence of the reinfection term ρR plays a relevant role for changing the results. To find the solutions, from (4) the expression

$$E^e = \frac{m_1}{k} I_C^e \tag{7}$$

can be obtained, with $m_1 = h_1 + h_2 + d_{I_C}$; moreover, setting $m_2 = k + d_E$ and substituting (7) into (3), one gets

$$\left(\beta S^e - \frac{m_1 m_2}{k}\right) I_C^e = 0 \tag{8}$$

The solution $I_C^e = 0$ of (8), once substituted into (7) and evaluated (5), characterises the solution without infected individuals, and then the absence of infection. It corresponds to the so called *epidemic free* condition, corresponding to the equilibrium with all the infected classes empty. Computing the two remaining components the first equilibrium point P_1^e is obtained, whose expression is

$$\begin{aligned} P_1^e &= \begin{pmatrix} S_1^e & E_1^e & I_{C1}^e & I_{Q1}^e & R_1^e \end{pmatrix}^T \\ &= \begin{pmatrix} \frac{B}{d_S} & 0 & 0 & 0 & 0 \end{pmatrix}^T \end{aligned} \tag{9}$$

The second solution of (8) is

$$S^e = \frac{m_1 m_2}{\beta k} \tag{10}$$

Then, from (5) the relationship

$$I_Q^e = \frac{h_1}{(\gamma + d_{I_Q})} I_C^e \tag{11}$$

is obtained and, used in (6), one has

$$R^e = \frac{h_2(\gamma + d_{I_Q}) + \gamma h_1}{(d_R + \rho)(\gamma + d_{I_Q})} I_C^e \tag{12}$$

Making use of all such relationships in (2), the equation

$$B - d_S S^e - \left(\beta S^e - \rho \frac{h_2(\gamma + d_{I_Q}) + \gamma h_1}{(d_R + \rho)(\gamma + d_{I_Q})} \right) I^e_{C2} = 0 \tag{13}$$

is obtained, which, once solved, gives the values for the component $I^e_C \neq 0$ of the second equilibrium point. The non null number of infected individuals at the equilibrium, which means that in these conditions the epidemic is always present in the population, motivates the definition of *endemic* usually given to such a condition. Denoting by

$$P^e_2 = \begin{pmatrix} S^e_2 & E^e_2 & I^e_{C2} & I^e_{Q2} & R^e_2 \end{pmatrix}^T \tag{14}$$

the equilibrium point, S^e_2 corresponds to (10) and, from (13)

$$I^e_{C2} = \frac{B - d_S S^e_2}{\left(\beta S^e_2 - \rho \frac{h_2(\gamma + d_{I_Q}) + \gamma h_1}{(d_R + \rho)(\gamma + d_{I_Q})} \right)} \tag{15}$$

In order to be an admissible value for the equilibrium point, I^e_{C2} must be non negative. The resulting conditions are

$$\begin{cases} B - d_S \frac{m_1 m_2}{\beta k} > 0 \\ \frac{m_1 m_2}{k} - \rho \frac{h_2(\gamma + d_{I_Q}) + \gamma h_1}{(d_R + \rho)(\gamma + d_{I_Q})} > 0 \end{cases} \tag{16}$$

or

$$\begin{cases} B - d_S \frac{m_1 m_2}{\beta k} < 0 \\ \frac{m_1 m_2}{k} - \rho \frac{h_2(\gamma + d_{I_Q}) + \gamma h_1}{(d_R + \rho)(\gamma + d_{I_Q})} < 0 \end{cases} \tag{17}$$

The first can be written as

$$\begin{cases} \frac{m_1 m_2}{k} < \frac{\beta B}{d_S} \\ \frac{m_1 m_2}{k} > \rho \frac{h_2(\gamma + d_{I_Q}) + \gamma h_1}{(d_R + \rho)(\gamma + d_{I_Q})} \end{cases} \tag{18}$$

and it is satisfied if and only if

$$\rho \frac{h_2(\gamma + d_{I_Q}) + \gamma h_1}{(d_R + \rho)(\gamma + d_{I_Q})} < \frac{m_1 m_2}{k} < \frac{\beta B}{d_S} \tag{19}$$

while the second holds if and only if

$$\begin{cases} \frac{m_1 m_2}{k} > \frac{\beta B}{d_S} \\ \frac{m_1 m_2}{k} < \rho \frac{h_2(\gamma + d_{I_Q}) + \gamma h_1}{(d_R + \rho)(\gamma + d_{I_Q})} \end{cases} \tag{20}$$

that is

$$\frac{\beta B}{d_S} < \frac{m_1 m_2}{k} < \rho \frac{h_2(\gamma + d_{I_Q}) + \gamma h_1}{(d_R + \rho)(\gamma + d_{I_Q})} \tag{21}$$

It must be noted that in this case, the presence of the reinfection factor ρ affects the existence of the endemic equilibrium point, introducing one distinction from the case discussed in (Di Giamberardino and Iacoviello, 2021). Clearly, if $\rho = 0$, the conditions reduce to one only, the same as in (Di Giamberardino and Iacoviello, 2021)

$$B - d_S S^e = B - d_S \frac{m_1 m_2}{\beta k} > 0 \tag{22}$$

3.2 Stability Analysis

The local stability of the two equilibrium points previously found is now studied. The Jacobian for the given dynamics in the uncontrolled case, evaluated in the equilibrium point P^e_1 is

$$J(P^e_1) = \left(\begin{array}{c|cc} -d_S & J_{1,2} & \\ \hline 0 & A_{1,1} & 0 \\ & A_{2,1} & A_{2,2} \end{array} \right) \tag{23}$$

with

$$A_{1,1} = \begin{pmatrix} -m_2 & \beta S^e_1 \\ k & -m_1 \end{pmatrix} \tag{24}$$

$$A_{2,2} = \begin{pmatrix} -(\gamma + d_{I_Q}) & 0 \\ \gamma & -(\rho + d_R) \end{pmatrix} \tag{25}$$

The eigenvalues

$$\lambda_1 = -d_S, \qquad \lambda_2 = -\gamma + d_{I_Q} \tag{26}$$

$$\lambda_3 = -(\rho + d_R) \tag{27}$$

are directly obtained thanks to the structure of the matrix (23), and are all real negative. The remaining two, the ones of matrix $A_{1,1}$, are the solutions of the characteristic equation

$$\lambda^2 + (m_1 + m_2)\lambda + (m_1 m_2 - k\beta S^e_1) = 0 \tag{28}$$

For the Descartes' rule of signs, they have a negative real part if and only if

$$m_1 m_2 - k\beta S^e_1 > 0 \tag{29}$$

Then, the fulfilment of condition (29) implies the local asymptotic stability of the equilibrium point P^e_1.

As far as P^e_2 is concerned, the Jacobian evaluated in such a point assumes the expression

$$J(P^e_2) = \begin{pmatrix} -\beta I^e_{C2} - d_S & 0 & -\beta S^e_2 & 0 & \rho \\ \beta I^e_{C2} & -m_2 & \beta S^e_2 & 0 & 0 \\ 0 & k & -m_1 & 0 & 0 \\ 0 & 0 & h_1 & -(\gamma + d_{I_Q}) & 0 \\ 0 & 0 & h_2 & \gamma & -(\rho + d_R) \end{pmatrix} \tag{30}$$

Its characteristic equation is given by

$$p(\lambda) = \lambda^5 + C_4\lambda^4 + C_3\lambda^3 + C_2\lambda^2 + C_1\lambda + C_0 = 0 \tag{31}$$

with

$$C_4 = \beta I^e_{C2} + d_S + m_1 + m_2 + \rho + d_R + \gamma + d_{I_Q}$$

$$C_3 = (\beta I^e_{C2} + d_S)(m_1 + m_2 + \gamma + d_{I_Q} + \rho + d_R) + (\gamma + d_{I_Q} + \rho + d_R)(m_1 + m_2) + (\gamma + d_{I_Q})(\rho + d_R)$$

$$C_2 = (\rho + d_R + \gamma + d_{I_Q})(\beta I^e_C + d_S)(m_1 + m_2) + (\beta I^e_C + d_S + m_1 + m_2)(\rho + d_R)(\gamma + d_{I_Q}) + \beta I^e_{C2} m_1 m_2$$

$$C_1 = \beta I^e_{C2} m_1 m_2 (\gamma + d_{I_Q} + \rho + d_R) - k h_2 \rho \beta I^e_{C2} + (m_1 + m_2)(\beta I^e_{C2} + d_S)(\gamma + d_{I_Q})(\rho + d_R)$$

$$C_0 = \beta I^e_{C2} m_1 m_2 (\gamma + d_{I_Q})(\rho + d_R) - \rho k \beta I^e_{C2} \left(h_1 \gamma + h_2 (\gamma + d_{I_Q})\right)$$

A necessary condition for having all the roots with negative real part is that all the coefficients C_i are positive. From the non negativeness of the parameters, it is possible to see that $C_4 > 0$, $C_3 > 0$ and $C_2 > 0$. Also $C_1 > 0$ because, recalling the expressions for m_1 and m_2, after some manipulations it is possible to get the expression

$$C_1 = \beta I^e_{C2} m_1 m_2 (\gamma + d_{I_Q} + d_R) + \rho \beta I^e_{C2} \left((h_1 + h_2 + d_{I_C}) d_E + (h_1 + d_{I_C}) k\right) + (m_1 + m_2)(\beta I^e_{C2} + d_S)(\gamma + d_{I_Q})(\rho + d_R)$$

As far as C_0 is concerned, its positiveness is guaranteed if and only if

$$\frac{m_1 m_2}{k} - \rho \frac{h_2(\gamma + d_{I_Q}) + \gamma h_1}{(d_R + \rho)(\gamma + d_{I_Q})} > 0 \tag{32}$$

since simple computations allows to write

$$C_0 = \beta k I^e_{C2} (\gamma + d_{I_Q})(\rho + d_R) \times \tag{33}$$

$$\left(\frac{m_1 m_2}{k} - \rho \frac{\left(h_1 \gamma + h_2 (\gamma + d_{I_Q})\right)}{(\gamma + d_{I_Q})(\rho + d_R)} \right) \tag{34}$$

The necessary and sufficient conditions for the polynomial to have roots with negative real part can be obtained making use of the Rooth–Hurwitz criterion. It requires the fulfilment of the following conditions

$$C_4 > 0 \tag{35}$$

$$C_6 = C_3 C_4 - C_2 > 0 \tag{36}$$

$$C_8 = C_2 C_6 - C_4 C_7 > 0 \tag{37}$$

$$C_9 = C_7 (C_2 C_6 - C_4 C_7) - C_0 C_6 > 0 \tag{38}$$

where

$$C_7 = C_1 C_4 - C_0; \tag{39}$$

Once again, the presence of the reinfection term makes the computations much more long and difficult with respect to the case in (Di Giamberardino and Iacoviello, 2021). Since they are not so meaningful as for the epidemic free equilibrium, the computations are not here explicitly performed.

The consistence of the present conditions can be verified noticing that, setting $\rho = 0$, the polynomial (31) can be written as

$$p(\lambda) = (\rho + d_R)(\gamma + d_{I_Q}) p_2(\lambda) \tag{40}$$

where

$$p_2(\lambda) = \lambda^3 + \tilde{C}_2 \lambda^3 + \tilde{C}_1 \lambda + \tilde{C}_0 \tag{41}$$

with

$$\tilde{C}_2 = \beta I^e_{C2} + d_S + m_1 + m_2 \tag{42}$$

$$\tilde{C}_1 = (m_1 + m_2) \beta I^e_{C2} \tag{43}$$

$$\tilde{C}_0 = m_1 m_2 \beta I^e_{C2} \tag{44}$$

and it is possible to verify that the Rooth–Hurwitz conditions $C_0 > 0$, $C_2 > 0$ and $C_1 C_2 - C_0$ are satisfied provided that $I^e_{C2} 0$ is admissible, i.e. condition (16) or (17) hold.

3.3 The Basic Reproduction Number $\mathcal{R}_0$

Starting from the model (1), the basic reproduction number is here computed making use of the *next generation matrix* (Diekmann et al., 2010).

This approach, in the present case, brings to the following steps. The part of the dynamics directly involved in the contagious or in the secondary infections is the one which characterises the state variables

$$Z = \begin{pmatrix} E & I_C & I_Q \end{pmatrix}^T \tag{45}$$

The corresponding part of the dynamics must be partitioned into the part $\mathcal{F}$ which describes the first infection, that is the transmission from one infected to a susceptible individual

$$\mathcal{F} = \begin{pmatrix} \beta S I_C & 0 & 0 \end{pmatrix}^T \tag{46}$$

and the part $-\mathcal{V}$ which describes the disease propagation

$$\mathcal{V} = \begin{pmatrix} m_2 E \\ -kE + m_1 I_C \\ -h_1 I_C + (\gamma + d_{I_Q}) I_Q \end{pmatrix} \tag{47}$$

The following matrices can be computed

$$F = \left. \frac{\partial \mathcal{F}}{\partial Z} \right|_{P^e_1} = \left(\begin{array}{cc|c} 0 & \beta S & 0 \\ 0 & 0 & 0 \\ \hline 0 & 0 & 0 \end{array} \right) \tag{48}$$

$$V = \left. \frac{\partial \mathcal{V}}{\partial Z} \right|_{P^e_1} = \left(\begin{array}{cc|c} m_2 & 0 & 0 \\ -k & m_1 & 0 \\ \hline 0 & -h_1 & (\gamma + d_{I_Q}) \end{array} \right) \tag{49}$$

The estimation of $\mathcal{R}_0$ is then given by the eigenvector with the greatest modulus of the matrix FV^{-1}. Then,

$$V^{-1} = \begin{pmatrix} \frac{1}{m_2} & 0 & 0 \\ \frac{k}{m_1 m_2} & \frac{1}{m_1} & 0 \\ * & * & \frac{1}{\gamma + d_{I_Q}} \end{pmatrix} \tag{50}$$

$$FV^{-1} = \begin{pmatrix} \frac{k \beta S^{e1}}{m_1 m_2} & \frac{\beta S^{e1}}{m_1} & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix} \tag{51}$$

and the basic reproduction number is given by

$$\mathcal{R}_0 = \frac{k \beta S^{e1}}{m_1 m_2} = \frac{k \beta B}{m_1 m_2 d_S} \tag{52}$$

4 ANALYSIS FOR THE CASE OF CONSTANT CONTROLS

The classical stability analysis performed in the previous Section can be enriched including the possibility of having non null controls, making the equilibrium points and their stability conditions a function of the inputs. This analysis can be very important since once the relationships between the actions performed and the epidemic evolution are quantitatively defined, it is possible to analyse different scenarios according to social and political choices of intervention. For sake of length and complexity in the expressions involved, the analysis is mainly focused on the epidemic free equilibrium existence and stability, since it is the desired condition to which the evolution is intended to be driven, and also because of its relationship with the important parameter $\mathcal{R}_0$.

To compute the equilibrium points, the system

$$B-\beta_u SI_C-c_1S+\rho R=0 \quad (53)$$
$$\beta_u SI_C-c_2E=0 \quad (54)$$
$$kE-c_3I_C=0 \quad (55)$$
$$au_1(E+I_C)+h_1I_C-c_4I_Q=0 \quad (56)$$
$$h_2I_C+(\gamma+\eta u_3)I_Q+vu_6S-(\rho+d_R)R=0 \quad (57)$$

with

$$\beta_u=\beta(1-u_2) \quad (58)$$

$$c_1 = vu_6+d_S \quad (59)$$
$$c_2 = au_1+m_2 \quad (60)$$
$$c_3 = au_1+m_1 \quad (61)$$
$$c_4 = ((\gamma+\eta u_3)+d_{I_Q}(1-u_4)) \quad (62)$$

must be solved. It is the same as (2)–(6) with all the controls present. From (55), one has

$$E=\frac{c_3}{k}I_C \quad (63)$$

that, used in (54), gives

$$\left(\beta_u S-\frac{c_2c_3}{k}\right)I_C=0 \quad (64)$$

From this equation the two roots

$$I_C=0 \qquad S=\frac{c_2c_3}{k\beta_u} \quad (65)$$

are obtained. Making use of the first one, for (63) one gets $E=0$. With the null values for E and I_C, the remaining equations to be solved are

$$B-c_1S+\rho R = 0 \quad (66)$$
$$-c_4I_Q = 0 \quad (67)$$
$$(\gamma+\eta u_3)I_Q+vu_6S-(\rho+d_R)R = 0 \quad (68)$$

from which the value $I_Q=0$ is obtained. As a consequence, the relationship

$$R=\frac{vu_6}{(\rho+d_R)}S \quad (69)$$

holds and, by substitution, the equation

$$B-\left(c_1S-\rho\frac{vu_6}{(\rho+d_R)}\right)S=0 \quad (70)$$

is obtained. Once solved, all the components of the equilibrium point, here denoted by P_u^{e1}, are computed. One has

$$S_u^{e1}=\frac{B}{\left(c_1-\rho\frac{vu_6}{(\rho+d_R)}\right)} \quad (71)$$

which can be rewritten as

$$S_u^{e1}=\frac{B}{\frac{d_R}{(\rho+d_R)}vu_6+d_S} \quad (72)$$

which, by (69), yields

$$R_u^{e1}=\frac{Bvu_6}{d_Rvu_6+d_S(\rho+d_R)} \quad (73)$$

so getting the first equilibrium point

$$P_u^{e1}=\left(\frac{B}{\frac{d_R}{(\rho+d_R)}vu_6+d_S} \quad 0 \quad 0 \quad 0 \quad \frac{Bvu_6}{d_Rvu_6+d_S(\rho+d_R)}\right) \quad (74)$$

Also for the controlled case, the point P_u^{e1}, characterised by the absence of infected individuals ($I_{Cu}^{e1}=0$, $E_u^{e1}=0$ and $I_{Qu}^{e1}=0$), can be denoted as *epidemic free equilibrium*.

For the second solution, with S_u^{e2} as in (65), from (56) one gets

$$I_Q=\left(au_1\frac{c_3+k}{c_4k}+\frac{h_1}{c_4}\right)I_C \quad (75)$$

while, from (53) and (57), the linear system

$$\Sigma\begin{pmatrix}I_C\\R\end{pmatrix}=\chi \quad (76)$$

with

$$\Sigma=\begin{pmatrix}\frac{c_2c_3}{k} & -\rho\\ -h_2-(\gamma+\eta u_3)\left(au_1\frac{c_3+k}{c_4k}+\frac{h_1}{c_4}\right) & (\rho+d_R)\end{pmatrix} \quad (77)$$

and

$$\chi=\begin{pmatrix}B-\frac{c_1c_2c_3}{k\beta_u}\\ vu_6\frac{c_2c_3}{k\beta_u}\end{pmatrix} \quad (78)$$

can be written. Provided that Σ is not singular, it can be solved and the so obtained values I_{Cu}^{e2} and R_u^{e2} can be substituted into the other relations of the equilibrium components; the second point P_u^{e2} is then obtained. Also for this point, like for P^{e2} the admissibility is given by the satisfaction of constraints on the non negativity of the solution.

4.1 Stability of the Epidemic Free Equilibrium Point

The Jacobian evaluated in P_u^{e1} has the expression

$$J(P_u^{e1}) = \begin{pmatrix} -c_1 & 0 & -\beta_u S_u^{e1} & 0 & \rho \\ 0 & -c_2 & \beta_u S_u^{e1} & 0 & 0 \\ 0 & k & -c_3 & 0 & 0 \\ 0 & au_1 & au_1+h_1 & -c_4 & 0 \\ vu_6 & 0 & h_2 & (\gamma+\eta u_3) & -(\rho+d_R) \end{pmatrix} \quad (79)$$

The computation of the characteristic equation is simplified by the structure, yielding to

$$p(\lambda) = p_1(\lambda)p_2(\lambda)p_3(\lambda) = 0 \quad (80)$$

with

$$\begin{aligned} p_1(\lambda) &= \lambda^2 + (\rho + d_R + c_1)\lambda + (\rho + d_R)c_1 - \rho v u_6 \\ p_2(\lambda) &= -(c_4 + \lambda) \\ p_3(\lambda) &= \lambda^2 + (c_2 + c_3)\lambda + c_2 c_3 - k\beta_u S_u^{e1} \end{aligned}$$

All the roots have negative real part once

$$\begin{aligned} (\rho + d_R)c_1 - \rho v u_6 > 0 \\ c_2 c_3 - k\beta_u S_u^{e1} > 0 \end{aligned} \quad (81)$$

The first condition is always satisfied since, making use of the expression of c_1, it is equivalent to

$$\rho d_S + d_R(vu_6 + d_S) > 0 \quad (82)$$

while the second one holds if and only if

$$(au_1 + m_2)(au_1 + m_1) - k\beta_u S_u^{e1} > 0 \quad (83)$$

which is the straightforward generalization of (29). Putting in evidence the dependencies on the controls, one has

$$(au_1 + m_2)(au_1 + m_1) - \frac{Bk\beta(1-u_2)}{\frac{d_R}{(\rho+d_R)}vu_6 + d_S} > 0 \quad (84)$$

and it is interesting to observe that the presence of the inputs u_1, u_2 and u_6, can help to satisfy this condition for suitable choices of control actions.

5 THE REPRODUCTION NUMBER $\mathcal{R}_u$

The reproduction number in presence of the control actions is here considered. The aim is to show how the expression of the basic reproduction number found in Subsection 3.3 can be enriched by the controls, and to establish a relationship between this parameter and the choices for the intervention. Since *basic* is referred to the intrinsic characterization of the epidemics, that is at the beginning of the infection and without any containment action yet, once the controls are considered, the term *controlled* is here introduced and the corresponding quantity is denoted by $\mathcal{R}_u$. For its computation, the restricted state space is the same as in Subsection 3.3

$$Z = \begin{pmatrix} E & I_C & I_Q \end{pmatrix}^T \quad (85)$$

while the dynamics are taken from (1) including the inputs

$$\mathcal{F} = \begin{pmatrix} \beta_u S I_C & 0 & 0 \end{pmatrix}^T \quad (86)$$

$$\mathcal{V} = \begin{pmatrix} c_2 E \\ -kE + c_3 I_C \\ -au_1(E + I_C) - h_1 I_C + c_4 I_Q \end{pmatrix} \quad (87)$$

The computation of $\mathcal{R}_u$ requires the matrices

$$F = \left(\begin{array}{cc|c} 0 & \beta_u S & 0 \\ 0 & 0 & 0 \\ \hline 0 & 0 & 0 \end{array}\right) \quad (88)$$

$$V = \left(\begin{array}{cc|c} c_2 & 0 & 0 \\ -k & c_3 & 0 \\ \hline -au_1 & -(au_1 + h_1) & c_4 \end{array}\right) \quad (89)$$

$$V^{-1} = \begin{pmatrix} \frac{1}{c_2} & 0 & 0 \\ \frac{k}{c_2 c_3} & \frac{1}{c_3} & 0 \\ * & * & \frac{1}{c_4} \end{pmatrix} \quad (90)$$

so that $\mathcal{R}_0$ can be obtained as the spectral radius of

$$FV^{-1} = \begin{pmatrix} \frac{k\beta_u S_u^{e1}}{c_2 c_3} & \frac{\beta_u S}{c_3} & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix} \quad (91)$$

Thanks to the structure of the matrix FV^{-1}, it is easy to find

$$\mathcal{R}_u = \frac{k\beta_u S_u^{e1}}{c_2 c_3} = \quad (92)$$

$$= \frac{k\beta(1-u_2)B}{(au_1 + m_1)(au_1 + m_2)(d_S + vu_6 \frac{d_R}{(\rho+d_R)})} \quad (93)$$

which corresponds to (84) with u_1, u_2 and u_6 present.

Since the amplitude $\mathcal{R}_u$ characterises the velocity of the epidemic spread, with condition $\mathcal{R}_u < 1$ which implies the containment of the virus, making the number of infected individuals going to zero asymptotically, the effects of the controls on the fulfilment of such a condition are now investigated.

It is possible to put in evidence three independent factors which contribute to the definition of $\mathcal{R}_u$

$$\phi_1(u_1) = \frac{k}{(au_1 + m_1)(au_1 + m_2)} \quad (94)$$

$$\phi_2(u_2) = \beta(1 - u_2) \quad (95)$$

$$\phi_3(\rho;u_6) = \frac{B}{(d_S + vu_6 \frac{d_R}{(\rho+d_R)})} = S_u^{e1} \qquad (96)$$

each of them depending on one different input separately.

$\phi_1(u_1)$ shows the contribution to the reproduction number of the test campaign u_1. It is worth to note that au_1 denotes the rate of testing, while the effect, in terms of positive or negative results, as well as its cost, depend on the number of effective infected individuals. In fact, if $au_1(E+I_C)$ is the contribution of the tests to isolate infected individuals, the corresponding cost is proportional to $au_1(S+E+I_C)$, since tests are performed for all the candidate population.

$\phi_2(u_2)$ describes the contribution given by the reduction of the contacts, acting with social distancing up to lockdown policies, represented by u_2; its high effect on virus spread containment is well known and in fact it is mainly adopted as the first intervention for epidemic containment.

$\phi_3(\rho;u_6)$ is the term which takes into account the presence of the vaccination input u_6 and, at the same time, the possible reinfection rate ρ. The strict connection between the two effects is clearly due to their contribution to the dynamics: they represent two opposite fluxes from susceptible to recovered individuals.

The quantification of the effect of each control to the reproduction number is given by (93); it is clear that all them contribute to its reduction.

5.1 Numerical Results

Numerical evaluation of the contributions of the controls on $\mathcal{R}_u$ are reported in the Figures below. The values of parameters are chosen making reference to the Italian situation so to use the same values as the ones defined in (Di Giamberardino and Iacoviello, 2021). The parameters appearing in expression (93) are reported in Table 1

Table 1: Numerical values of the parameters present in expression (93).

Parameter	B	β	k
Value	1180	$2.5 \cdot 10^{-8}$	1/7
Parameter	h_1	h_2	
Value	0.3	$1/150$	
Parameter	$d_S = d_E = d_R$	d_{I_C}	
Value	$2 \cdot 10^{-5}$	$2 \cdot 10^{-5}$	

Note that the normalization process adopted in the numerical analysis performed in the sequel makes the results independent from the parameters in the first line of Table 1.

In Figures 2, 3 and 4 the dependence of each factor ϕ_i from the control is depicted, normalised with respect to their maximum values. Each of them corresponds to a variation of $\mathcal{R}_u$ with the other controls set to zero. As expected, the greater is the control, the smaller is the corresponding factor. More in particular, in Figure 2 the contribution of u_1 is written in terms of the number of tests per day which correspond to the value of au_1. A more immediate representation of control u_6 in Figure (4) is also performed, reporting in the abscissas the corresponding time required to vaccinate the entire population: it corresponds to the inverse of the vaccination rate vu_6; these conversion makes easier a direct comparison with the duration of immunization, which characterizes the different curves depicted.

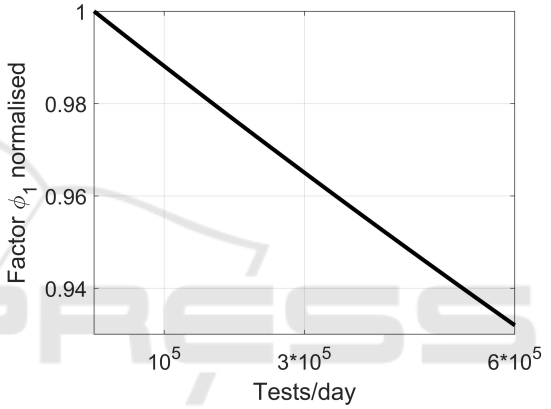

Figure 2: Contribution of u_1, expressed as number of tests per day, to ϕ_1.

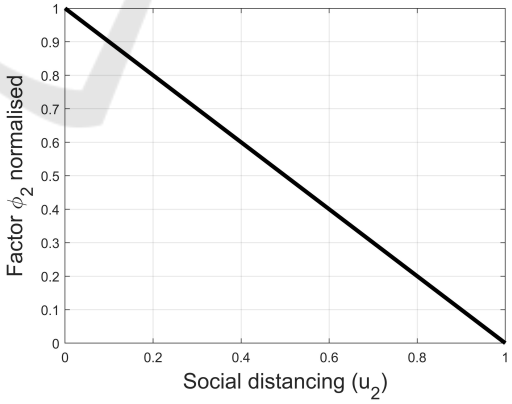

Figure 3: Dependency of ϕ_2 from the social distancing u_2.

The strong relationship between the time for people vaccination and the length of immunization can be appreciated in Figure 5 from which it is evident that the increasing benefits from higher vaccination speed are reduced by the presence of possible reinfection due to a lost of immunity.

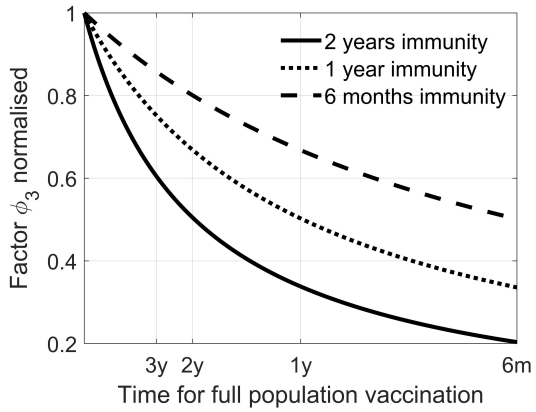

Figure 4: Contribution of u_6, expressed as the expected time to vaccinate all the population to ϕ_1; three curves are reported for different immunization times.

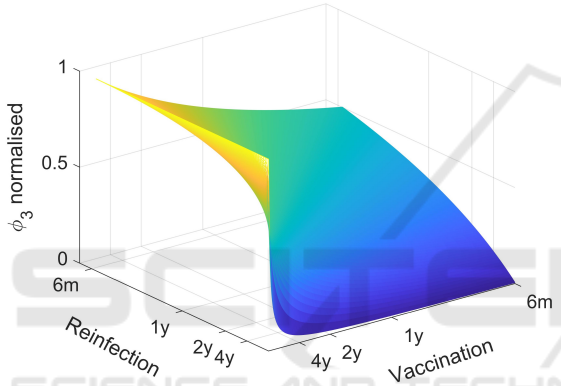

Figure 5: Dependence of ϕ_3 from vaccination and reinfection times.

A comparison between the contributions of the controls to the reduction of $\mathcal{R}_u$, which can help in the choice of type and intensity of the actions to apply, can be evidenced from Figures 6, 7 and 8; the normalised reduction of the reproduction number is reported under the action of two inputs at the same time. From Figures 6 and 7 the low contribution of the test campaign to the reduction of the spread can be evidenced, at least with the rates considered. This result is also contained in Figure 2, where a reduction of $\mathcal{R}_u$ (ϕ_1) of less than 7%, under $6 \cdot 10^5$ tests/day, is depicted.

Figures 6 and 8 show the sensible effect of a reduction of social contacts, as expected, strongly improved by the combined action of vaccination (Figure 8). Unfortunately, a reduction of the benefits of vaccination, under the hypothesis of a possible lost of immunity after a certain time, is well represented in Figures 7 and 8. In case of lifetime immunization, even a quite low vaccination rate produces a strong contribu-

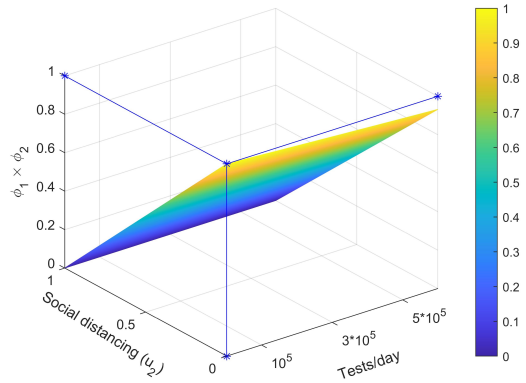

Figure 6: Combined effect of u_1 and u_2 to the spread reduction.

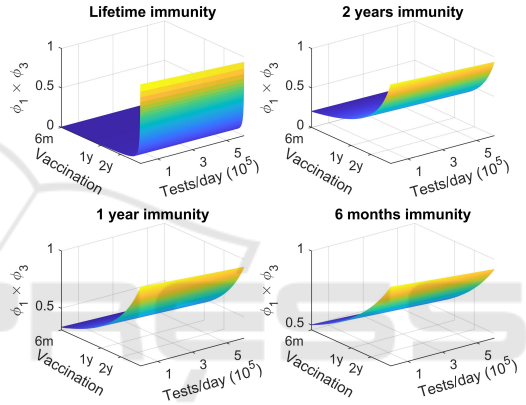

Figure 7: Combined effects of u_1 and u_6 to the spread reduction.

tion, only comparable with very high constraints on social contacts. In presence of a limited time of immunization, the vaccination loses its great effectiveness, becoming important its rate of execution with respect to the one of reinfection.

In addition, it can be useful to study the contribution of the controls to the variation of the reproduction number: it can represent an useful indication about the most effective lines of intervention to produce a larger variation of $\mathcal{R}_u$. One then can study the relative variation of $\mathcal{R}_u$ w.r.t. the controls. Starting from

$$d\mathcal{R}_u = \frac{\partial \mathcal{R}_u}{\partial \phi_1}\frac{\partial \phi_1}{\partial u_1}du_1 + \frac{\partial \mathcal{R}_u}{\partial \phi_2}\frac{\partial \phi_2}{\partial u_2}du_2 + \frac{\partial \mathcal{R}_u}{\partial \phi_3}\frac{\partial \phi_1}{\partial u_6}du_6 \quad (97)$$

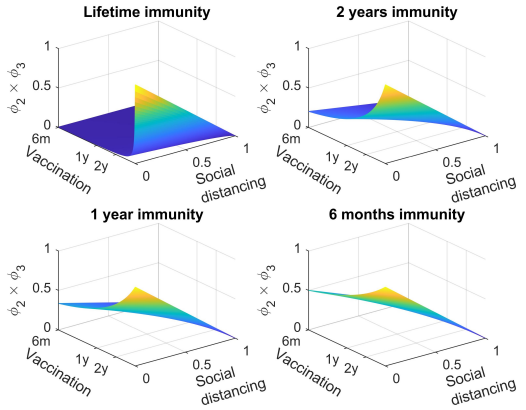

Figure 8: Combined effects of u_2 and u_6 to the spread reduction.

and computing the three contributions

$$\frac{\partial \phi_1}{\partial u_1} = -\phi_1 \left(\frac{1}{(u_1 + \frac{m_1}{a})} + \frac{1}{(u_1 + \frac{m_2}{a})} \right) \quad (98)$$

$$\frac{\partial \phi_2}{\partial u_2} = -\beta = -\phi_2 \frac{1}{1-u_2} \quad (99)$$

$$\frac{\partial \phi_3}{\partial u_6} = -\phi_3 \frac{v \frac{d_R}{(\rho + d_R)}}{(d_S + v u_6 \frac{d_R}{(\rho + d_R)})} - \phi_3 \frac{1}{(d_S \left(1 + \frac{\rho}{d_R}\right) + v u_6)} \quad (100)$$

it is possible to write

$$\frac{d\mathcal{R}_u}{\mathcal{R}_u} = -\left(\frac{1}{(u_1 + \frac{m_1}{a})} + \frac{1}{(u_1 + \frac{m_2}{a})} \right) du_1 - \frac{du_2}{1-u_2} - \frac{du_6}{(d_S \frac{(\rho + d_R)}{v d_R} + u_6)} \quad (101)$$

The contribution of each control to the variation of $\mathcal{R}_u$ is depicted in Figures 9–11. The graphs confirm the previous results: the test campaign contributes to a limited reduction of the reproduction number of about 3.5 % almost independently from the rate of tests performed, according to Figure 9. Differently, policies to reduce the physical interactions between people have a large impact on virus spread reduction, with an increasing contribution as their intensity increase, as depicted in Figure 10 along with the particular of the initial shape. It must be considered that $u_2 = 1$ corresponds to the unrealistic total isolation of each person. The opposite behaviour can be observed in Figure 11 for the vaccination: the higher is its rate, the smaller is the relative reduction of $\mathcal{R}_u$; the reduction decreases also in presence of reinfection and according to the time of immunity presence.

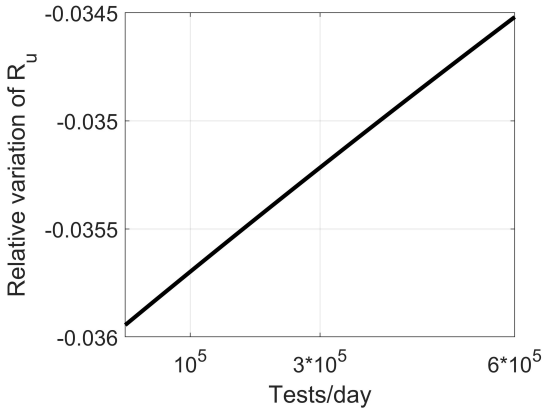

Figure 9: Relative variation of R_u due to changes of u_1.

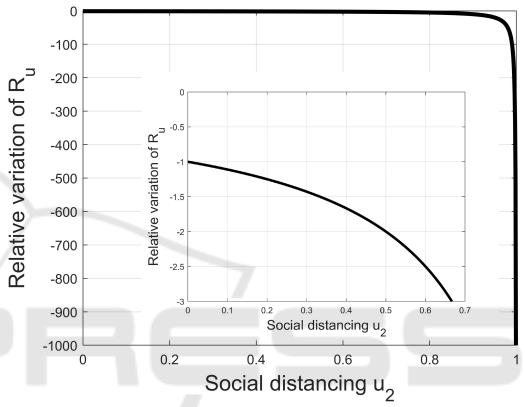

Figure 10: Relative variation of R_u due to changes of u_2.

6 CONCLUSIONS

In the present paper a model of COVID-19 is considered introducing also the vaccination as a control input and, at the same time, the possibility of lost of immunity, according to the present knowledge on the

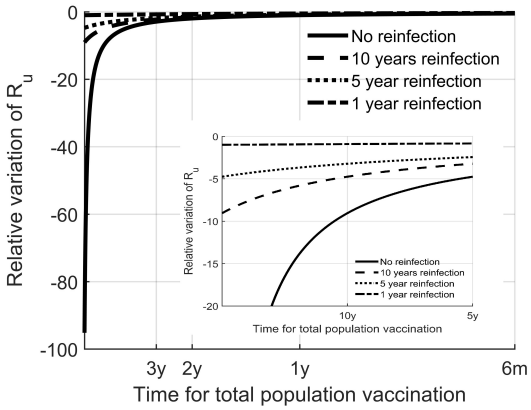

Figure 11: Relative variation of R_u due to changes of u_6 for diffferent time of reinfection.

effects of the available vaccines and the clinical evolution of people previously infected and healed.

An analysis of steady state behaviour of the model is performed, both in the classical uncontrolled case and, in view of the subsequent study, under the hypothesis of non zero constant control.

All the computations aimed at the determination of an expression for the reproduction number under constant control actions, to be used for analysing the impact of the controls and the reinfection on the virus spread.

Along with the expected result that social distancing measurements are effective actions, with an increasing relative increment as the level of restriction increases, the relative small contribution of the test campaign is observed.

The new result obtained is related to the effect of the vaccination on the epidemic containment and, possibly, extinction. The high impact against the virus spread is proved, but once the possibility that the immunization given by the vaccine has a limited duration is considered, the real effectiveness of the vaccine reduces, and depends on the rate of people vaccination with respect to the rate of immunity lost. On the basis of the computation performed, if the time of vaccination of the entire population is the same as the immunity duration, the reproduction number is halved w.r.t. its original value, despite intuitively it could seem that, under the same rates, the population should be, at steady state, completely vaccinated. For a disease with $\mathcal{R}_0 \simeq 3.6$ as given for Italy, reduction factor must be smaller than $\frac{1}{3.6} = 0.277$: with the vaccine as the only intervention measurement, a vaccination rate four times the reinfection one is necessary (Figure 4). An alternative solution could be represented by keeping social restrictions at the minimum level for which an additional reduction factor is present (Figures 3 and 8). These results suggest to maintain socially acceptable but non null contact limitations, even if infection trends are satisfactory, and to speed up the vaccination until levels of immunised individual is fully compatible with a herd immunity status.

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