



**HAL**  
open science

# Optimal individual strategies for influenza vaccines with imperfect efficacy and limited persistence

Francesco Salvarani, Gabriel Turinici

► **To cite this version:**

Francesco Salvarani, Gabriel Turinici. Optimal individual strategies for influenza vaccines with imperfect efficacy and limited persistence. 2016. hal-01302557v2

**HAL Id: hal-01302557**

**<https://hal.science/hal-01302557v2>**

Preprint submitted on 14 Oct 2016 (v2), last revised 30 Aug 2017 (v3)

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

# OPTIMAL INDIVIDUAL STRATEGIES FOR INFLUENZA VACCINES WITH IMPERFECT EFFICACY AND LIMITED PERSISTENCE

FRANCESCO SALVARANI AND GABRIEL TURINICI

**ABSTRACT.** We analyze a model of agent based vaccination campaign against influenza with imperfect vaccine efficacy and limited persistence. We prove the existence of a Nash equilibrium by Kakutani's fixed point theorem in the context of non-persistent immunity. Subsequently, we propose and test a novel numerical method to find the equilibrium. Various issues of the model are then discussed, among which the dependence of the optimal policy with respect to the imperfections of the vaccine and the best vaccination timing.

## 1. INTRODUCTION

Vaccination is a widely used epidemic control tool which may (and should) be analyzed from several perspectives, such as the design of fabrication techniques, the study of its action mechanisms, the analysis – at the individual level – of the medical issues of the vaccine, including its side effects, and the global impact on the epidemic spread of some carefully designed vaccination protocols.

Obviously, these different viewpoints are strictly interconnected: for example, the action mechanism of a vaccine determines its features and its protection effect against the target illness, and the public health strategies are consequence of the former two aspects.

When looking at vaccination policies, two approaches are possible.

The first one consists in supposing that a health authority can decide of a vaccination plan, which is then implemented. The plan optimizes the vaccination strategy as a function of the severity of the epidemic, its medical risks and the (economic and medical) costs associated with the vaccine.

This framework is suitable for compulsory vaccination or when the individuals fully adhere to the recommendations of the authority, and it has been the first historically considered one (see [32, 1, 44, 51, 20, 2, 38]).

However, this kind of studies is oriented to the best possible strategy for the population as a whole, and does not take into account the individual viewpoints. Indeed, when the vaccination is a choice – on a voluntary basis – or when there exist debates on the risks or costs of the vaccine, the previous approach is not valid anymore and the situation is better described by models which take into account the individual decision level.

In this second family of models, the agents decide for themselves whether the vaccination is suitable or not, but they cannot individually influence the epidemic propagation, which is given by the collective choice of all other persons.

---

*Date:* October 14, 2016.

*Key words and phrases.* Mean Field Games, SIR model, vaccination persistence, limited immunity, vaccine effectiveness, influenza.

The study of large populations of non-cooperative interacting individuals is a complicated problem, but it recently received a firm mathematical ground thanks to the *Mean Field Game* (MFG) theory, introduced in the literature by the pioneering works of Lasry and Lions [41, 40, 42] and of Huang, Malhamé and Caines [34, 33]. From the point of view of modeling, mean field game theory combines mean field theories, which are widely used in Physics and Mechanics, together with the notion of Nash equilibria in game theory.

One of the main goals of MFG is the study of the existence of equilibria for the whole population, namely a stable collection of individual strategies such that nobody has any incentive to change his own strategy.

Before the development of the MFG theory, some early works already were looking into this direction. We quote, for example, [26, 9, 31] which study the question of disease eradication, market equilibrium and externalities in relationship with vaccination. More recent contributions (see [5, 4, 52, 27, 50, 39]) treat the question of Nash equilibria for a large number of individuals in relation with an epidemic model. They investigated many aspects, such as the impact of the subjective perceptions and individual behaviors on the equilibrium (see, for example, [16, 15, 49]), the presence of several groups having distinct epidemic characteristics (see [30, 17, 13]), particular vaccination strategies or specific models about the available information at the individual level (see [10, 6, 24, 22, 23, 29, 56, 8, 21]).

In this article, we introduce and analyze a model for a non-compulsory vaccination campaign against influenza viruses, with imperfect vaccine efficacy and limited persistence. Our main purpose is the computation of the optimal individual strategy with the purpose of helping decision makers in designing efficient public health policies.

As the features of the target infectious disease heavily influence the dynamics of the epidemic spread, our model cannot be immediately generalized to the vaccination against other diseases. However, the global strategy can be easily modified, *mutatis mutandis*, for obtaining models adapted to other situations with a similar behavior (i.e. the vaccine is imperfect and the conferred immunity is not permanent).

We focus our attention on countries with temperate climates, which experience a marked seasonal influenza peak during the winter months [54]. Hence our time horizon will be of about one year.

Since influenza is a contagious disease, the major available tool against the spread of the illness is given by vaccination.

However, vaccination has no permanent effect. Indeed, as pointed out in [18], the protection against a virus, conferred by the corresponding vaccine to an individual, persists after some years and it is robust with respect to slight genetic mutations. But, because of the antigenic drift [12], sufficient changes can accumulate in the virus to allow influenza to reinfect the same host. The protection given by a previous vaccine can hence become useless. In order to overcome this phenomenon, the influenza vaccine content is annually reviewed. Note that vaccine mismatch is not taken into account in our study, because it would lead to introduce different questions, oriented to the modeling of the vaccine itself, rather than to the vaccination policies (which suppose, of course, that the annual release of the vaccine has a good efficacy).

We moreover suppose that the immunity conferred by the vaccine is time-dependent. Indeed, as pointed out in several studies, the estimated protection against infection, based on hemagglutination-inhibiting (HAI) antibody titers has a maximum 2-4 weeks after the vaccination, and it subsequently strictly decreases afterwards [58, 46]. In

particular, [46] estimates that there is a marked decline of the immunity some months after the vaccination. This behavior is taken into account in our analysis because it can be practically observed before reaching the time horizon of the problem.

The aforementioned features of the illness will be considered, in this article, as given data. Two main attributes of the vaccine are considered:

- the persistence, which is the duration of the immunity conferred by the vaccine; this can span from several months up to several years – see [18, 14, 3] and the literature therein;
- the vaccine efficacy (noted VE, an input in our model), which is the theoretical success rate (to be distinguished from the vaccine efficiency, which is the practical observed success and is the output of the model – see [57] for a presentation of the differences between the two). The VE can range from several percents to almost perfect efficacy – see the meta-analysis in [48] and also [47]; other references include [43] and [55].

Hence, our model is suitable for studying imperfect vaccines and takes into account not only the individual decision about the vaccination, but also the best timing of the vaccination if the individual decides to be vaccinated.

Since the best timing problem of a vaccination campaign is very actual and carefully studied by the health authorities, we hope that our model can give a contribution to better understanding the vaccination dynamics and to suggest efficient policies. In particular, our model forecasts that, in the non-cooperative setting, the individual behaviors are only partially in agreement with the suggestions of the World Health Organization (WHO), which encourages vaccination as soon as the vaccine of the corresponding seasonal influenza is available [19]: the agents tend to delay the vaccination in order to arrive at the peak of the epidemic with the best possible protection.

Because of the relatively short time horizon of the model, we do not consider any population dynamics, neither reinfection, since we suppose that antigenic drift is not very important on such small time scales [12].

From the mathematical point of view, in this article we work in a discrete setting and our model is described in terms of Markov chains. Since the time horizon of seasonal influenza has the order of magnitude of one year, this choice allows us to model the coarse graining of the real situation and makes this model more suitable for the applications. However, for the sake of completeness, we provide a continuous version of our model in the Appendix.

The individual vaccine model that we propose does not have, up to our knowledge, any explicit solution. Far from being a disadvantage, this situation prompted us into proposing a general numerical method to find the equilibrium; this is a second contribution of this work (see also [53] for some alternatives coming from the physics community for general Mean Field Games). The numerical method is adapted from general works in game theory (see Section 3) and is expected to give accurate results in any situation when an individual chooses the right timing to perform some action (here vaccination) with time-dependent costs. This procedure has been extensively tested on our model and performs in a satisfactory way.

The structure of the paper is the following: the model is presented in Section 2 and the theoretical result guaranteeing the existence of an equilibrium in Section 2.3. The numerical algorithm for finding the equilibrium is presented in Section 3 and the numerical results in Section 4.

The numerical simulations first describe a realistic situation for seasonal influenza dynamics. Subsequently, we test our model on two unrealistic cases (the duration of the immunity is of one or six months only), which show some striking behaviors of the population and which may help in understanding the strategic policies of the population.

Section 5 collects some considerations on the pertinence and validity of our approach and, finally, the Appendix describes the continuous version of the model.

## 2. THE MODEL

The model studies the dynamics of an epidemic in a population. In what follows we will suppose that

- the infection does not cause the death of the patient (as it is well known, the mortality associated to influenza does not induce significant modifications in the population structure [25]); moreover, by considering a time horizon of twelve months, we suppose that births and deaths, as well as age shifts, are non relevant;
- after the disease, the individuals who have been infected acquire permanent immunity (with respect to the time horizon of our model): this means that we will suppose the existence of a predominant virus strain, instead of considering a mixing of viruses and that reinfection is a rare phenomenon;
- the incubation period is short when compared to the time scale of the model;
- the individuals can be vaccinated. If the vaccine is successful, the protection of the vaccine is maximal (but possibly not total) after a time delay, it remains high during some period and then it decreases (see [46]);
- the evolution of the epidemic can be influenced by seasonality effects, as for influenza in temperated regions.

In what follows, we describe the model in pure mathematical terms, the quantification of the different parameters will be then discussed in Section 4.

We suppose that the time horizon  $T$  is finite, and that it can be discretized in  $(N + 1)$  ( $N \in \mathbb{N}$ ) time instants  $t_0 = 0$ ,  $t_1 = \Delta T$ ,  $t_2 = 2\Delta T, \dots, t_n = n\Delta T, \dots, t_N = T$ . The population is composed of

- *susceptible individuals*:  $S_n$  is the proportion of individuals in this class at time  $t_n$ ;
- *infected individuals*:  $I_n^\omega$  is the proportion of individuals in this class at time  $t_n$ , which have been infected at time  $t_{n-\omega}$ ; moreover we denote by  $I_n$  the sum of all  $I_n^\omega$ ;
- *recovered individuals* upon exiting the class of infected;
- *vaccinated individuals*:  $V_n^\theta$  is the proportion of individuals that vaccinated at time  $t_{n-\theta}$  and have not been infected since;
- *failed vaccinated individuals*:  $F_n$  is the proportion of individuals that vaccinated at same time  $t \leq t_n$ , whose vaccination failed and have not yet been infected since.

The quantities  $\omega$  and  $\theta$  are counters. The first one measures the time lapse between the infection instant and the current instant,  $\omega = 0, 1, \dots, \Omega \in \mathbb{N}$ , whereas the second one measures the time lapse between the vaccination instant and the current instant,  $\theta = 0, 1, \dots, \Theta \in \mathbb{N}$ .

The upper bound  $\Theta$  indicates the maximal duration of the (possibly partial) immunity given by the vaccine. In the case of seasonal influenza  $\Theta$  is, in principle, greater than the time horizon of the problem. However, in order to make our model extensible also

to other situations, we decide to take into account the theoretical possibility to manage vaccines with very short persistency. For this reason, we consider also the class  $V^\Theta$ , which describes the vaccinated individuals that lost the immunity given by the vaccine. Since we suppose that they do not vaccinate twice, we need a specific class for describing them.

Similarly,  $\Omega$  is the maximum time before recovery, and it depends on the properties of the illness itself.

The equations of the model, which conserves the total number of individuals, have the following form:

$$S_{n+1} = (S_n - U_n) - \beta_{\Delta T}^n I_n (S_n - U_n) \quad (2.1)$$

$$I_{n+1}^0 = \beta_{\Delta T}^n \left[ F_n + S_n + \sum_{\theta=0}^{N-1} \alpha_\theta V_n^\theta \right] I_n \quad (2.2)$$

$$I_{n+1}^{\omega+1} = (1 - \gamma_{\Delta T}^\omega) I_n^\omega \quad \omega = 0, \dots, \Omega - 1 \quad (2.3)$$

$$V_{n+1}^0 = (1 - f) \cdot (1 - \beta_{\Delta T}^n I_n) U_n \quad (2.4)$$

$$V_{n+1}^{\theta+1} = (1 - \beta_{\Delta T}^n \alpha_\theta I_n) V_n^\theta, \quad \theta = 0, \dots, \Theta - 2 \quad (2.5)$$

$$V_{n+1}^\Theta = (1 - \beta_{\Delta T}^n \alpha_{\Theta-1} I_n) V_n^{\Theta-1} + (1 - \beta_{\Delta T}^n I_n) V_n^\Theta \quad (2.6)$$

$$F_{n+1} = f \cdot (1 - \beta_{\Delta T}^n I_n) U_n + F_n (1 - \beta_{\Delta T}^n I_n) \quad (2.7)$$

with initial conditions

$$S_0 = S_{0-}, \quad I_0^\omega = I_{0-}^\omega, \quad V_0^\theta = 0, \quad \forall \theta \geq 0, \quad F_0 = 0, \quad (2.8)$$

where

- $U$  describes the vaccination:  $U_n = u_n S_n$ , where  $u_n$  is the proportion of people vaccinated after time  $t_n$  and before  $t_{n+1}$ ; the admissible strategies correspond to  $u_n \in [0, 1]$ ;
- the vector  $\gamma = (\gamma^0, \dots, \gamma^\Omega) \in (\mathbb{R}_+)^{\Omega+1}$  describes how fast an infected individual recovers and depends on the duration of the illness itself. In particular, when  $\gamma^\omega = 0$ , there is no hope to recover at the next time instant; on the contrary, when  $\gamma^\omega = 1$ , the individual will recover with certainty in the next time slot.
- The function  $\beta(t)$  quantifies how infectious is a contact between an infected individual and susceptible one at time  $t$ . To take into account the length of the time interval  $\Delta T$ , we work with  $\beta_{\Delta T}^n := \beta(t_n) \cdot \Delta T$  and  $\gamma_{\Delta T}^\omega := \gamma^\omega \cdot \Delta T$ . In order to take into account the possible seasonality  $\beta(\cdot)$  is taken time-dependent, see Section 4 for an exemple.
- The vector  $\alpha_\theta$  are the time instants of a function  $A(\cdot)$  ( $\alpha_\theta = A(\theta \Delta T)$ ) with values in  $[0, 1]$ . This vector quantifies the protection given by the vaccine in terms of the probability of infection if vaccinated. It is known that this protection is not instantaneous, the immunity conferred by the vaccine being maximal after a latency period. As explained in the introduction, in the case of influenza vaccine, the protection is not complete, and the effects of the vaccine decrease with time.

In what follows, we suppose that there exists an upper bound  $\Theta > 0$  to the persistence of the vaccine (which can be, however, greater than the time horizon

of the model). In particular  $\alpha_\Theta = 1$ . Some possible candidates for the function  $A$  are shown in Figure 1.

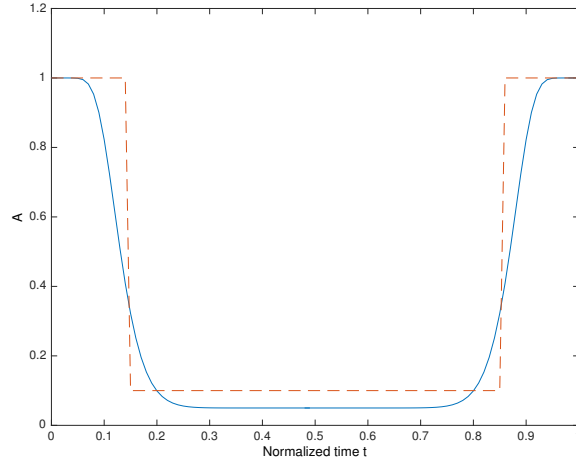


FIGURE 1. Two possible forms for the function  $A$ .

**2.1. The societal cost and individual cost.** Let  $r_I$  and  $r_V$  be the individual cost for the illness and the vaccination respectively. These costs are intended to be *global costs*. For example, they can be the monetary cost of the illness and of the vaccine, but they can also express the medical side-effects of the vaccine and the possible side-effects of the illness (see, for example, [45]).

We work under the meaningful assumption that  $r_I > r_V$  (although the alternative  $r_I \leq r_V$  may also give non-trivial problems in particular situations, see [38]).

The total societal cost associated to the vaccination strategy  $U$  is:

$$J(S_0, I_0, U) = r_I \sum_{n=0}^N I_n + r_V \sum_{n=0}^{N-1} U_n, \quad (2.9)$$

which has to be minimized (see [32, 1, 44, 51, 20, 38]) within the set of all admissible vaccination strategies  $U$ .

However this is not what the individuals do. They rather optimize an individual cost function. In order to define it, we have to consider the individual dynamics (see Figure 2 for an illustration). It takes the form of a controlled Markov chain with several states, *susceptible* ( $S$ ), *failed vaccination* ( $F$ ), *recovered* ( $R$ ), *infected* (indexed by the time counter  $\omega$ :  $I^0, \dots, I^\Omega$ ), and, finally, *vaccinated* states (indexed by the time counter  $\theta$ :  $V^0, \dots, V^\Theta$ ).

The Markov chain of the individual, denoted  $M_n$ , is described in terms of passage probabilities:

$$\begin{aligned}
\mathbb{P}(M_{n+1} = S | M_n = S) &= (1 - \lambda_n) (1 - \beta_{\Delta T}^n I_n) \\
\mathbb{P}(M_{n+1} = I^0 | M_n = S) &= \beta_{\Delta T}^n I_n \\
\mathbb{P}(M_{n+1} = V^0 | M_n = S) &= (1 - f) \cdot \lambda_n (1 - \beta_{\Delta T}^n I_n) \\
\mathbb{P}(M_{n+1} = F | M_n = S) &= f \cdot \lambda_n (1 - \beta_{\Delta T}^n I_n) \\
\mathbb{P}(M_{n+1} = R | M_n = I^\Omega) &= 1 \\
\mathbb{P}(M_{n+1} = R | M_n = I^\omega) &= \gamma_{\Delta T}^\omega, & \omega = 0, \dots, \Omega - 1 \\
\mathbb{P}(M_{n+1} = I^{\omega+1} | M_n = I^\omega) &= 1 - \gamma_{\Delta T}^\omega, & \omega = 0, \dots, \Omega - 1 \\
\mathbb{P}(M_{n+1} = I^0 | M_n = V^\theta) &= \alpha_\theta \beta_{\Delta T}^n I_n, & \theta = 0, \dots, \Theta - 1 \\
\mathbb{P}(M_{n+1} = V^{\theta+1} | M_n = V^\theta) &= 1 - \alpha_\theta \beta_{\Delta T}^n I_n, & \theta = 0, \dots, \Theta - 1 \\
\mathbb{P}(M_{n+1} = I^0 | M_n = V^\Theta) &= \beta_{\Delta T}^n I_n \\
\mathbb{P}(M_{n+1} = V^\Theta | M_n = V^\Theta) &= 1 - \beta_{\Delta T}^n I_n, \\
\mathbb{P}(M_{n+1} = I^0 | M_n = F) &= \beta_{\Delta T}^n I_n, \\
\mathbb{P}(M_{n+1} = F | M_n = F) &= 1 - \beta_{\Delta T}^n I_n.
\end{aligned} \tag{2.10}$$

The conditions  $\beta_{\Delta T}^n \leq 1$ ,  $\gamma_{\Delta T}^\omega \leq 1$ ,  $\lambda_n \geq 0$ ,  $\lambda_n \leq 1$  ensure the well-posedness of this definition.

The conditional rates  $\lambda_n$  are derived from a probability density  $\xi$  defined on  $\{t_0, \dots, t_{N-1}\} \cup \{\infty\}$ ; the value  $\xi_n$  is the probability that the individual vaccinates at time  $t_n$  (if it was not infected before  $t_n$ ). In practice, the agent chooses the probability distribution  $\xi$  before the dynamics starts. Then, he selects a random number  $n$  distributed with the aforementioned probability  $\xi$ , which means that before the beginning of the epidemic he knows the time  $t_n$  at which he will vaccinate (unless he is already infected by that time).

There is a mapping between  $\lambda = (\lambda_n)_{n=0}^{N-1}$  and  $\xi$  defined by:

$$\xi_\infty = \prod_{n=0}^{N-1} (1 - \lambda_n), \quad \xi_n = \lambda_n \prod_{k=0}^{n-1} (1 - \lambda_k), \quad n \leq N - 1 \tag{2.11}$$

$$\forall n \leq N - 1 : \lambda_n = \begin{cases} \frac{\xi_n}{\xi_n + \dots + \xi_\infty}, & \text{if } \xi_n + \dots + \xi_\infty > 0 \\ 0, & \text{otherwise} \end{cases}. \tag{2.12}$$

The cost of a vaccination strategy depends on  $\xi$  (see [39] for a similar situation). The individual incurs the cost  $r_I$  upon arriving in class  $I^0$  and the cost  $r_V$  upon arriving in class  $V^0$ . The cost for an individual will have three components:

- the cost  $r_I$  of being infected before vaccination;
- the cost  $r_V$  of vaccination plus a possible cost of being infected while immunity is still building or after the persistence period;



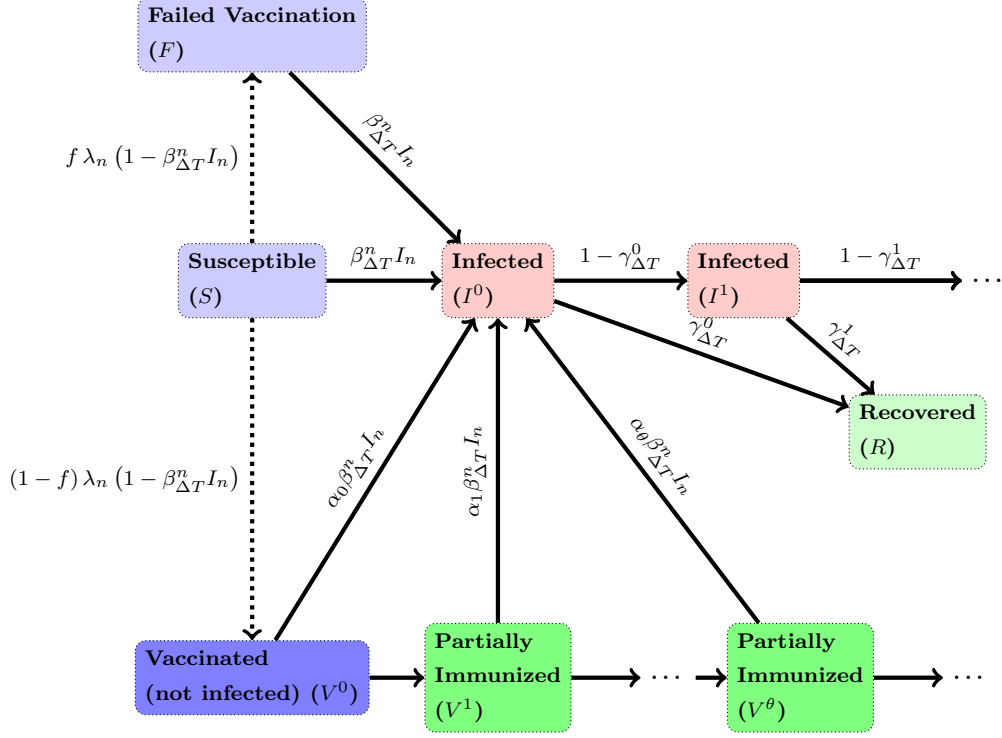


FIGURE 2. Individual model.

- the cost  $r_V$  of failed vaccination plus a possible cost of being infected.

Note that an individual may incur both costs if he vaccinates and, moreover, if he is infected. For an individual starting at  $M_0 = S$ , the total cost is:

$$\begin{aligned}
 J_{indi}(\xi; U) &= r_V \mathbb{P} \left( \bigcup_{n < N} \{M_{n+1} = V^0, M_n \neq V^0\} \middle| M_0 = S \right) \\
 &+ r_V \mathbb{P} \left( \bigcup_{n < N} \{M_{n+1} = F, M_n \neq F\} \middle| M_0 = S \right) \\
 &+ r_I \mathbb{P} \left( \bigcup_{n < N} \{M_{n+1} = I^0, M_n \neq I^0\} \middle| M_0 = S \right). \tag{2.13}
 \end{aligned}$$

This form for  $J_{indi}(\xi; U)$  is impractical and has to be made more explicit. One possibility is to sum over the first passages from  $S$  to  $I^0$ ,  $V^0$  or  $F$ . The following quantities are useful for general  $n$ :

- the probability  $\varphi_n^{V,I}$  of infection (at time  $t_{n+1}$  or later) of an individual that vaccinated in the interval  $[t_n, t_{n+1}]$ , given by the formula:

$$\varphi_n^{V,I} = 1 - \prod_{k=n}^{\ominus} \left( 1 - \beta_{\Delta T}^k \alpha_{k-n-1} I_k \right), \tag{2.14}$$

where we introduce the coefficient  $\alpha_{-1} = 1$ ;

- the conditional probability of being infected (strictly) before  $t_{n+1}$  (of a person that did not vaccinate)

$$\varphi_n^I = \mathbb{P} \left[ \bigcup_{k=0}^n \{M_k = I\} \middle| M_0 = S, M_k \neq V^0, M_k \neq F, k \leq n \right],$$

given by the formula:

$$\varphi_n^I = 1 - \prod_{k=0}^n \left(1 - \beta_{\Delta T}^k I_k\right). \quad (2.15)$$

Note that the probability of being infected after the time  $n$  is

$$1 - \frac{1 - \varphi_\infty^I}{1 - \varphi_n^I} = \frac{\varphi_\infty^I - \varphi_n^I}{1 - \varphi_n^I},$$

where

$$\varphi_\infty^I = 1 - \prod_{k=0}^N \left(1 - \beta_{\Delta T}^k I_k\right).$$

Then, after elementary computations:

$$J_{indi}(\xi; U) = r_I \varphi_\infty^I \xi_\infty + \sum_{n=0}^{N-1} \left[ r_I \varphi_n^I + (1 - \varphi_n^I)(r_V + (1 - f)r_I \varphi_n^{V,I}) + r_I f(\varphi_\infty^I - \varphi_n^I) \right] \xi_n. \quad (2.16)$$

The individual cannot change  $U_n$  neither  $S_n$ ,  $I_n^\omega$  nor  $V_n^\theta$ . He can only choose his vaccination strategy  $\xi$ . Denote

$$g_n^U = \begin{cases} r_I \varphi_n^I + (1 - \varphi_n^I)(r_V + (1 - f)r_I \varphi_n^{V,I}) + r_I f(\varphi_\infty^I - \varphi_n^I), & \text{for } n \leq N - 1 \\ r_I \varphi_\infty^I & \text{for } n = N. \end{cases} \quad (2.17)$$

If we denote the Euclidean scalar product between two vectors  $X, Y \in \mathbb{R}^{N+1}$  by

$$\langle X, Y \rangle := \sum_{k=1}^{N+1} X_k Y_k, \quad (2.18)$$

then  $J_{indi}(\xi; U) = \langle \xi, g^U \rangle$ , where  $g^U$  and  $\xi$  are seen as vectors in  $\mathbb{R}^{N+1}$ . It is to be minimized under the constraint  $\xi_0 + \dots + \xi_{N-1} + \xi_\infty = 1$ . Then any probability distribution  $\xi$  with support in  $\{n \mid g_n^U \leq g_k^U, k = 0, \dots, N\}$  attains the minimum.

Now, for a given individual policy  $\xi$  one can ask whether the equations (2.1)-(2.8) are obtained when *all* individuals follow this vaccination policy and in this case what is the compatibility relationship between  $\xi$  and  $U$ . Supposing identical initial conditions  $S_0$ - and  $I_0$ -, the compatibility relation between the two dynamics is:

$$U_n = \lambda_n S_n, \quad (2.19)$$

i.e.  $\lambda_n = u_n$ , see the discussion after formula (2.8).

**2.2. Failed vaccination.** A simplified model can be proposed to tackle the possibility of vaccination failure. Note that, for  $n \leq N - 1$ ,

$$g_n^U = r_I f \varphi_\infty^I + (1 - f)[r_I \varphi_n^I + (1 - \varphi_n^I)(r_V/(1 - f) + r_I \varphi_n^{V,I})].$$

Therefore, since the term  $r_I f \varphi_\infty^I$  does not depend on  $n$  and  $(1 - f)$  is an overall factor, the cost has exactly the same minimum as that of a model without the class  $F$  when we replace  $r_V$  by  $r_V/(1 - f)$ . Therefore, when the efficacy  $1 - f$  of the vaccine is not 100%, this can be treated by considering that the cost of the vaccine is multiplied by  $(1 - f)^{-1}$ . See Section 4 for some numerical illustrations.

Note however that this is a first order approximation as, in practice, the quantities  $\varphi_n^{V,I}$  depend on the precise values of  $I_n^\omega$  and a different model with different classes will change those values.

**2.3. Equilibrium.** Consider now the following mapping: for any given probability law  $\eta$  on  $\{t_0, \dots, t_{N-1}\} \cup \{\infty\}$  define  $\lambda$  by (2.12) (using  $\eta_n$  instead of  $\xi_n$ ),  $U_n, S_n, I_n$  recursively by the relations (2.1)-(2.5) and (2.19). Denote  $\mathcal{C}_\eta = g^U$ .

Let  $\mathcal{J}(\eta)$  be the ensemble containing all optimal individual strategies  $\xi$  that minimize the cost  $\langle \xi, \mathcal{C}_\eta \rangle$ .

The goal of this subsection is to deduce the existence of an equilibrium of the system, i.e. a common strategy which is a Nash equilibrium when it is used by all agents of the population. The following result holds.

**Theorem 2.1.** *There exists at least one law  $\eta$  such that  $\eta \in \mathcal{J}(\eta)$  (i.e., an equilibrium).*

*Proof.* We use Kakutani's fixed point theorem (see [36, page 457]) for the function  $\mathcal{J}(\cdot)$  defined on the simplex

$$\Sigma_{N+1} = \{(x_0, \dots, x_N) \in \mathbb{R}^{N+1} | x_k \geq 0, x_0 + \dots + x_N = 1\}. \quad (2.20)$$

Recall that the assumptions of the theorem are the following:

- (1) for any  $\eta \in \Sigma_{N+1}$ , the set  $\mathcal{J}(\eta)$  is non-void, closed and convex; this property is trivially verified in our setting.
- (2) the mapping  $\mathcal{J}(\cdot)$  is upper semi-continuous, or, stated otherwise, it has the closed graph property.

Thus, the only hypothesis left to check is the closed graph property of  $\mathcal{J}(\cdot)$ . Let  $\eta^\ell$  be a sequence of points in  $\Sigma_{N+1}$  (i.e., probability laws on  $\{t_0, \dots, t_{N-1}\} \cup \{\infty\}$ ) converging to  $\eta$  and  $\xi^\ell \in \mathcal{J}(\eta^\ell)$  converging to  $\xi$ . We have to prove that  $\xi \in \mathcal{J}(\eta)$ .

We denote by  $S^\ell, U^\ell, I^\ell, g^{U^\ell}$  (respectively  $S, U, I, g^U$ ) the dynamics corresponding to  $\eta^\ell$  (respectively  $\eta$ ).

Let  $Z$  be the first index such that  $\eta_Z + \dots + \eta_\infty = 0$ . We consider the non-trivial case when  $Z > 1$ .

Consider  $\lambda^\ell$  (respectively  $\lambda$ ) the rates associated to  $\eta^\ell$  (respectively  $\eta$ ) by the formula (2.12). In particular  $\eta_{Z-1} > 0$  and  $\lambda_{Z-1}^\ell = 1$ .

Although  $\eta^\ell \rightarrow \eta$  as  $\ell \rightarrow \infty$  we do not have that  $\lambda^\ell \rightarrow \lambda$ , but we have instead that  $\lambda_n^\ell \rightarrow \lambda_n$  for all  $n < Z$ . In particular  $\lambda_n^\ell S_n^\ell \rightarrow \lambda_n S_n$  for all  $n < Z$ . On the other hand, since  $\lambda_{Z-1} = 1$  we have  $S_Z = S_{Z-1}(1 - \lambda_{Z-1})(1 - \beta_{\Delta T}^n I_{Z-1}) = 0$  and  $\lambda_{Z-1}^\ell \rightarrow 1$  implies  $S_Z^\ell \rightarrow 0$ ; furthermore,  $S^\ell$  being monotonically decreasing we also have  $S_n^\ell \rightarrow 0$  for any  $n \geq Z$ . Since all rates  $\lambda^\ell$  are bounded by 1 we obtain thus that  $\lambda_n^\ell S_n^\ell \rightarrow 0 = \lambda_n S_n$  for all  $n \geq Z$  and thus ultimately  $\lambda_n^\ell S_n^\ell \rightarrow \lambda_n S_n$  for all  $n \leq N$ . This, combined with the formulas (2.1)-(2.8) and (2.19) show that  $U^\ell \rightarrow U, S^\ell \rightarrow S, I^\ell \rightarrow I$  as  $\ell \rightarrow \infty$ . Thus we also have  $\mathcal{C}_{\eta^\ell} \rightarrow \mathcal{C}_\eta$ ; therefore the limit of any converging sequence of minimas of  $\mathcal{C}_{\eta^\ell}$  is also a minima of  $\mathcal{C}_\eta$  which, given its definition, proves the closed graph property of  $\mathcal{J}(\cdot)$ .  $\square$

**Remark 2.2.** *The theorem reduces the existence of the equilibrium to the study of the mapping  $\eta \mapsto \mathcal{C}_\eta$ . This mapping has a well-defined meaning for a large class of vaccination games because the variable  $\xi$  is nothing else than the (mixed) individual strategy and the vector  $\mathcal{C}_\xi$  collects the cost of pure strategies of the individual (given*

the overall epidemic propagation dynamics). We expect that this methodology can be generalized to other situations.

**Remark 2.3.** *The result does not say anything about the uniqueness of the fixed point. In the Mean Field Game framework, uniqueness results usually from convexity considerations (see e.g., [41, 40, 34]) and it is not mandatory, see [37] for a situation where there is no uniqueness. Although this setting is not convex, in all numerical simulations we pursued, a unique solution was always found.*

### 3. FINDING THE EQUILIBRIUM

The result of the Section 2.3 guarantees the existence of at least one equilibrium. But, it does not prescribe a constructive method to find it.

For arbitrary strategy  $\xi$ , introduce the quantity  $E(\xi)$  defined as follows: consider a situation when all individuals use the strategy  $\xi$ . If the individual follows himself the strategy  $\xi$  the expected cost is the average, with respect to the probability distribution  $\xi$ , of costs  $\mathcal{C}_\xi$ . By using the Euclidian scalar product (2.18) the cost can be written as  $\langle \xi, \mathcal{C}_\xi \rangle$ . But the individual can also choose some other strategies to minimize his cost. For instance if  $\mathcal{C}_\xi$  reaches its minimum at the  $k$ -th component, the best cost is obtained with a strategy that vaccinates at time  $t_k$  with certainty. When the minimum is not unique, the general value of the lowest cost that the individual can reach is  $\min_{\eta \in \Sigma_{N+1}} \langle \eta, \mathcal{C}_\xi \rangle$  where  $\Sigma_{N+1}$  is the space of all possible strategies. The mismatch between the cost of “following the others” and the “lowest possible cost” is denoted with  $E(\xi)$ . It represents the maximum gain obtained by an individual if he changes unilaterally his strategy (and everybody else remaining with the strategy  $\xi$ ). In mathematical terms:

$$E(\xi) = \langle \xi, \mathcal{C}_\xi \rangle - \min_{\eta \in \Sigma_{N+1}} \langle \eta, \mathcal{C}_\xi \rangle. \quad (3.1)$$

Note that  $E(\cdot) \geq 0$  and that an equilibrium corresponds to a  $\xi$  such that  $\langle \xi, \mathcal{C}_\xi \rangle \leq \langle \eta, \mathcal{C}_\xi \rangle$  for any other strategy  $\eta \in \Sigma_{N+1}$ , which means  $E(\xi) = 0$ . The equilibrium can be rephrased as finding a strategy  $\xi$  such that the mapping  $\xi \mapsto E(\xi)$  is minimized.

A natural idea is then to try to minimize  $E(\cdot)$  over  $\Sigma_{N+1}$ . But, this intuitive approach is not always the better because, in order to be efficient, minimization of  $E(\cdot)$  requires to compute, for instance, some gradient of  $\mathcal{C}_\xi$  with respect to  $\xi$ , which could make the computations complicated.

Another idea is simpler and intuitively more appealing: the equilibrium will be found by successive approximations in a way that mimics a real-life repeated game (see also [28] for additional considerations). Consider a strategy candidate  $\xi_k$  obtained at the iteration  $k$  and construct the cost  $\mathcal{C}_{\xi_k}$  obtained if everybody uses the strategy  $\xi_k$ . An individual of this population will test whether  $\xi_k$  is optimal, i.e. if it is a minimum of  $E(\cdot)$ . If this is the case then the equilibrium is  $\xi_k$ ; otherwise the individual will adjust its strategy  $\xi_k$  by exploring a strategy  $\xi_{k+1}$ , which is not too far from  $\xi_k$  but that goes towards the lowest possible cost  $\min_{\eta \in \Sigma_{N+1}} \langle \eta, \mathcal{C}_{\xi_k} \rangle$ . In practice (with ideas close to the general framework of gradient flows, see [35] for an entry point to this literature), one can choose  $\xi_{k+1}$  to be a minimizer of a weighted sum containing both *desiderata*, which can be expressed in mathematical terms:

$$\xi_{k+1} \text{ is a minimizer over } \Sigma_{N+1} \text{ of } \eta \mapsto \frac{\text{dist}(\eta, \xi_k)^2}{2\tau} + \langle \eta, \mathcal{C}_{\xi_k} \rangle, \quad (3.2)$$

where  $\text{dist}(\cdot, \cdot)$  is some suitable distance in  $\Sigma_{N+1}$ . Then the procedure is iterated till convergence. This idea is similar to the paradigms of “Best Reply” (see [7]) and “fictitious

play” for which some proofs of convergence exist under specific hypotheses (see [11]). The term  $1/2\tau$  weights the relative importance of staying close to  $\xi_k$  with respect to optimizing the cost. In particular  $\tau$  can be interpreted as a pseudo-time counting the number of infinitesimal adjustments required to converge to the equilibrium. Note also that, when  $\tau \rightarrow 0$ , the distance  $dist$  is the Euclidian distance and  $\Sigma_{N+1}$  is the whole  $\mathbb{R}^{N+1}$ , the strategy  $\xi$  can be seen as the time-indexed solution of the differential equation

$$\frac{d}{d\tau}\xi(\tau) = \mathcal{C}_{\xi(\tau)}.$$

In order to keep the presentation as simple as possible, we used as distance in (3.2) the standard euclidian distance on  $\mathbb{R}^{N+1}$  although in principle other distances (such as the 2-Wasserstein distance) may perform better.

In practice, the algorithm applied is the following:

**Step 1** Choose a step  $\tau > 0$  and a starting distribution  $\xi_1$ .

Set iteration count  $k = 1$ .

**Step 2** Compute  $\xi_{k+1}$  as in formula (3.2).

**Step 3** If  $E(\xi_{k+1})$  is smaller than a given tolerance then stop and exit, otherwise set  $k \rightarrow k + 1$  and go back to Step 1.

In practice **Step 2** is computed with a quadratic programming routine (`quadprog` in `Matlab/Gnu Octave`) that can accommodate linear constraints.

**Remark 3.1.** *The procedure proposed above can be extended in a straightforward manner to any 'rational individual' vaccination model, by replacing the vector  $\mathcal{C}_{\xi}$  by a time-dependent function  $c(\cdot)$ , where  $c(t)$  is the cost of the pure strategy consisting in vaccinating at the time  $t$  under the assumption that everybody follows the strategy  $\xi$ .*

#### 4. NUMERICAL RESULTS

In order to test the model, we simulated the situation of an epidemic with several sets of parameters, such as long or short persistence, as indicated below.

**4.1. Preliminary tests.** We first tested the procedure for a situation when the analytic result is known (see [27, 39]): we used the parameters in [39, Figure 5] and obtained that the optimum individual strategy is a mixed strategy with  $\xi_0 = 33\%$  probability to vaccinate at  $t = 0$  and  $\xi_{\infty} = 67\%$  probability to not vaccinate at all; its cost is 0.5067; this compares favorably with the analytic result which is a mixed strategy with  $\xi_0 = 34\%$ ,  $\xi_{\infty} = 66\%$  and a cost 0.5.

**4.2. Equilibrium with waning immunity and imperfect efficacy.** The numerical values used in this simulations are the following: total simulation time  $T = 1$  (one year), number of time instants:  $N = 365 \times 3$  (three times a day); recovery rate  $\gamma^{\omega} = \gamma = 365/3.2$  (mean recovery time 3.2 days,  $\Omega = 20$ ), reproduction number  $R_0 = 1.35$ , thus  $\beta = \gamma R_0$ ; initial proportion of susceptibles  $S_0 = 0.94$  and infected  $I_0 = 2.0 \times 10^{-6}$ ; relative costs  $r_I = 1$ ,  $r_V = 0.005$ . To take into account the seasonality of  $\beta(t)$  we set  $\beta_{min} = \gamma/S_0$  and  $\beta(t) = \beta$  for  $t \leq t_2^{\beta} := 1/2$  (6 months) and then  $\beta(t) = \beta_{min}$  for  $t > t_2^{\beta} = 1/2$ ; these parameters model an epidemic having a duration of 6 months.

We set vaccine efficacy to  $f = 50\%$ ; the persistence of the vaccine is related to the waning of the immunity. Although very few studies are available to date to make precise the waning immunity dynamics, it is generally accepted that the immunity is rising and

reaching a peak after some weeks (here we took 3 weeks) and declines then in a timescale of the order of months (see also [14]). For instance the study in [46] found a significant decay (20% to 50%) over a period of 9 months. As we will see, even if the immunity is not completely lost by the end of the season, this decay influences the equilibrium. With our notations, the function  $A(t)$  was taken to be

$$A(t) = 1 - c_1 t^{c_2} e^{-c_3 t}, \quad (4.1)$$

with constants  $c_1, c_2, c_3$  set such that the minimum value (zero) is reached in  $t = 3/52$  while 9 months after, i.e., at  $t = 3/52 + 9/12$  the value is either  $Im_1 = 1/10$  (which corresponds to 9/10 immunity still active 9 months after the peak) or  $Im_2 = 1/3$  (which corresponds to 2/3 immunity still active 9 months after the peak).

First the 'ideal' case of perfect immunity is considered (results not shown here); the equilibrium is a policy when people vaccinate at  $t = 0$  (10% of them).

Then the equilibrium for  $Im_1$  was computed and is shown in Figure 3. Note that the vaccination peak is delayed by one month, even if the decay in the immunity is relatively moderate (immunity is still at 90% after 9 months).

Finally, a different situation when immunity falls to 66% is presented in Figure 4; here the vaccination is delayed with approximately two months.

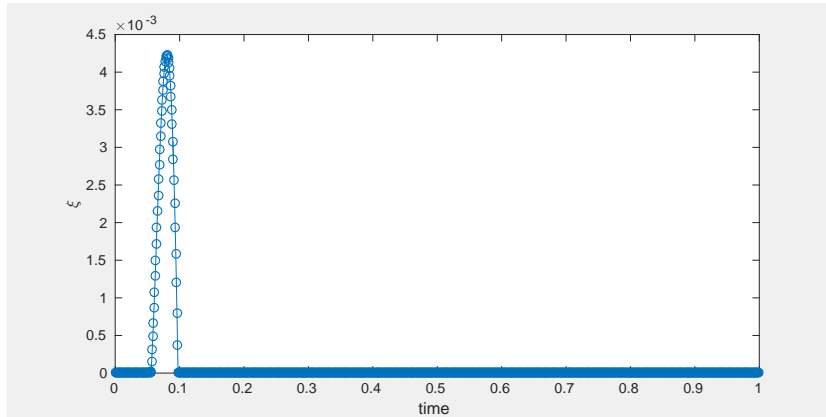


FIGURE 3. The optimal converged strategy  $\xi^{MFG}$  at times  $\{t_0, \dots, t_{N-1}\}$  for subsection 4.2, case  $Im_1$ . The weight of the non-vaccinating pure strategy (i.e., corresponding to time  $t = \infty$ ) is 88%; this means that 12% of the population vaccinates.

**4.3. Robustness with respect to parameters.** We investigate in this subsection the robustness of the numerical results with respect to various choices of parameters. Of interests are especially the persistence and efficacy, as detailed below.

**4.3.1. Short persistence, large efficacy.** To define the persistence of the vaccine we set  $t_1 = 5/365, t_2 = 1/12$  (one month,  $\Theta = 93$ ) and  $A(t) = 1 - \mathbb{1}_{[t_1, t_2]}$ . The vaccine efficacy is set to 100%, i.e., we suppose a failure rate  $f = 0$ . The step is  $\tau = 0.1$  and we performed 1000 iterations.

The results are displayed in Figures 5, 6 and 7. A good quality equilibrium is found: the incentive to change the strategy, as measured by the function  $E(\xi)$ , is more than two orders of magnitude lower at the solution than at the initial guess. The cost of the solution  $\langle \xi^{MFG}, \mathcal{C}_{\xi^{MFG}} \rangle$  is 0.0237.

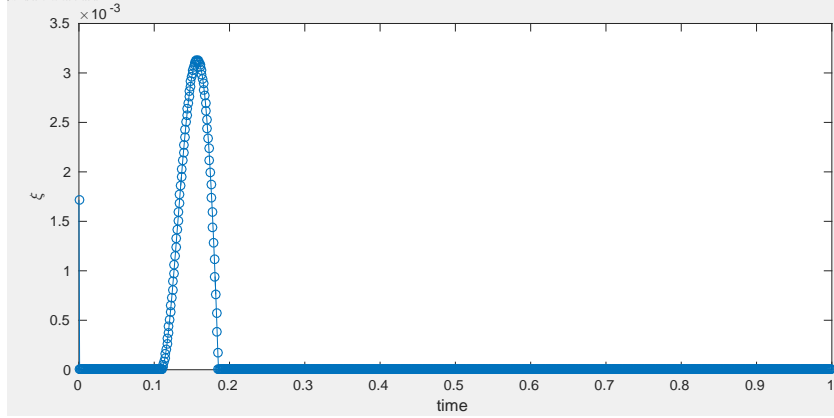


FIGURE 4. The optimal converged strategy  $\xi^{MFG}$  at times  $\{t_0, \dots, t_{N-1}\}$  for subsection 4.2, case  $Im_2$ . Here 15% of the population vaccinates.

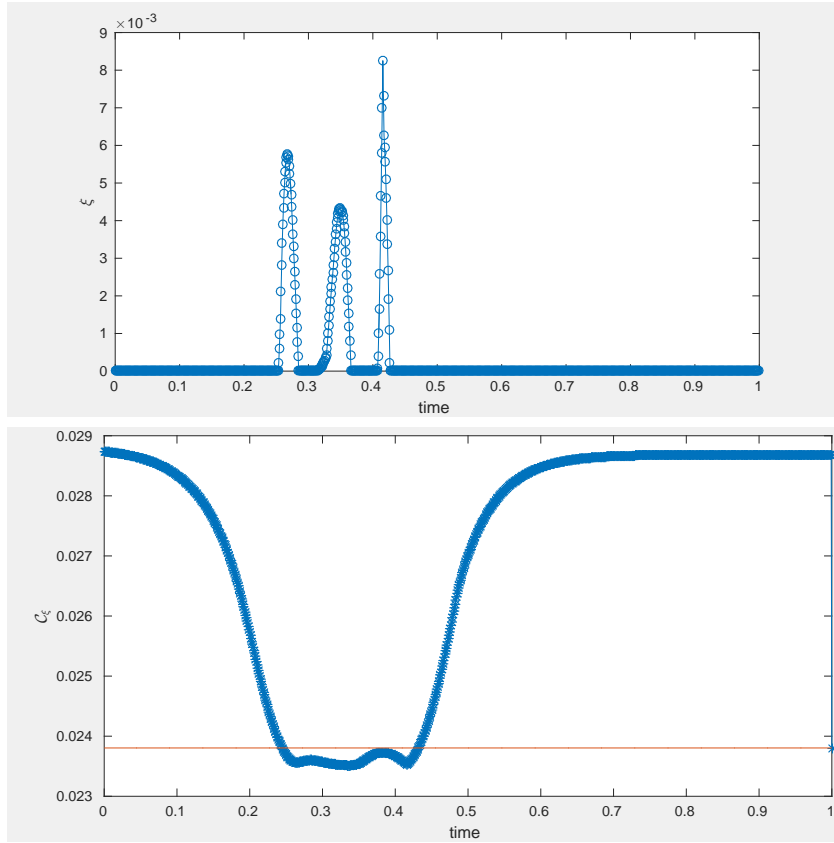


FIGURE 5. Results for Subsection 4.3.1. Top: the optimal converged strategy  $\xi^{MFG}$  at times  $\{t_0, \dots, t_{N-1}\}$ . The weight of the non-vaccinating pure strategy (i.e., corresponding to time  $t = \infty$ ) is 68%. Bottom: the corresponding cost  $\mathcal{C}_{\xi^{MFG}}$ . The red line corresponds to the cost of the non-vaccinating pure strategy  $(\mathcal{C}_{\xi^{MFG}})_{N+1}$ .

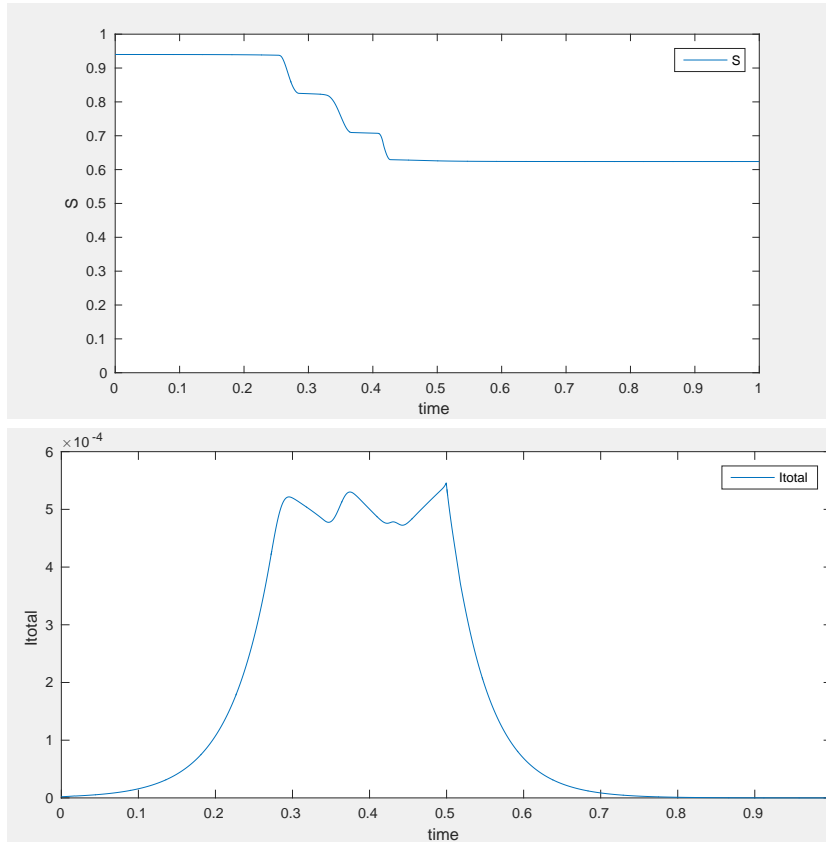


FIGURE 6. Results of Subsection 4.3.1. Top: the evolution of the susceptible class  $S_n$ ; bottom: the (total) infected class  $I_n$ .

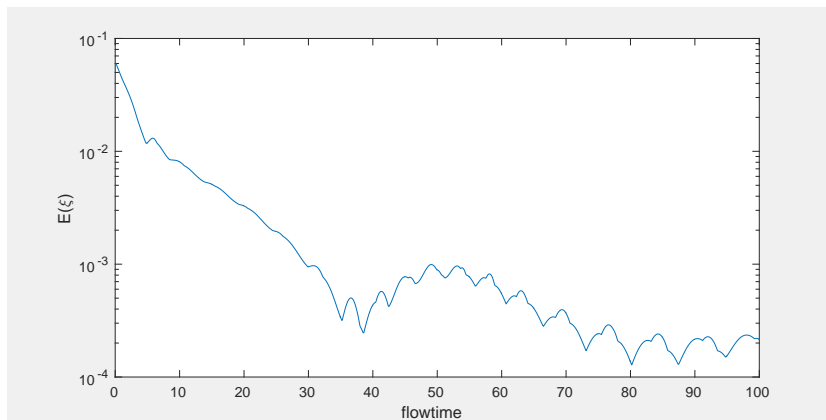


FIGURE 7. The decrease of the incentive to change strategy  $E(\xi_k)$ . Note that  $E(\xi_k)$  does not decrease monotonically. In fact, there is no reason to expect such a behavior, since we are not minimizing  $E(\cdot)$  in a monotonic fashion.



The solution is a strategy  $\xi^{MFG}$  supported at several time instants between 0.25 and 0.43 and also having 68% of the mass at the non-vaccinating time  $t = \infty$ . Note that the cost is adapted accordingly, reaching its minimum at all points in the support of the solution  $\xi^{MFG}$ . Generally the vaccination occurs when  $I_n$  has large values, except at the end of the epidemic (time 0.5) when people expect the epidemic to end and estimate that their infection probability is low; the individuals have a strategic behavior, in coherence with the model. This can be compared with the model in [6] where the vaccination rate is supposed proportional with the number of people infected. The two models agree in a majority of time instants except the end of the epidemic. This behavior has been observed across a wide range of vaccination persistence times and initial conditions (the results are not shown here). It is remarkably to see that a simple model such as in [6] has such a considerable applicability.

It should be mentioned that the solution  $\xi^{MFG}$ , with cost 0.0237, is *not* the solution that minimizes the average cost across individuals (see also equation (2.9)) which is  $M(\xi) = \langle \xi, \mathcal{C}_\xi \rangle$ : for instance the strategy  $\xi^{min}$  that vaccinates with certainty at time  $t = 0.0$  (unless infected by that time) has  $M(\xi^{min}) = 0.005$ . This result is not surprising and often appears in such contexts (see [39]). When  $M(\xi^{MFG}) > M(\xi^{min})$  the game is said to have a positive *cost of anarchy*. It can be intuitively explained as follows: suppose that everybody uses the strategy  $\xi^{min}$ . The cost of an individual with strategy  $\eta$  will be  $\langle \eta, \mathcal{C}_{\xi^{min}} \rangle$  and it turns out that there exists some  $\eta_1$  with  $\langle \eta_1, \mathcal{C}_{\xi^{min}} \rangle < \langle \xi^{min}, \mathcal{C}_{\xi^{min}} \rangle$ . For instance here  $\eta_1$  can be a pure non-vaccinator strategy whose cost is very low  $8.0 \cdot 10^{-6}$ . Therefore any individual with current strategy  $\xi^{min}$  has an incentive to change his strategy (and use  $\eta_1$ ) by hoping that everybody else remains with the strategy  $\xi^{min}$ . This does not happen and everybody slides towards  $\eta_1$  and so on until the Nash equilibrium  $\xi^{MFG}$  is found. In the process the cost of *everybody* will increase and this is the price to pay for equilibrium.

**4.3.2. Long persistence, 100% efficacy.** The parameters are identical as in Subsection 4.3.1, except the vaccine persistence time  $t_2$  which is set now to 6 months  $t_2 = 1/2$  ( $\Theta = 549$ ). The convergence is quickly attained (100 iterations) and the results are displayed in Figure 8. Although fewer people vaccinate (only 9% here, to compare with 32% in Subsection 4.3.1), the fact that vaccine persistence is higher improves the outcome. The equilibrium cost becomes 0.005, almost one order of magnitude lower than in the previous test.

**4.3.3. Long persistence, smaller efficacy.** In this Subsection, we test a situation when the vaccine efficacy is only 50%. All other inputs are as in Subsection 4.3.2. The result, not shown here because very similar to those described in the previous tests, has however several differences:

- the probability of the non-vaccinating strategy is now 86% (i.e. 14% of people vaccinate);
- the cost of the optimal strategy is 0.0101.

Therefore the equilibrium shifts towards a bigger fraction of the population that vaccinate (in order to compensate lower vaccine efficacy). However, the overall number of protected people is lower (50% of 14% being smaller than 100% of 9%) which results in a larger overall equilibrium cost (about twice larger). We tested other settings and these conclusions were consistently obtained: the introduction of imperfect vaccines (here lower efficacy) generates overall lower coverage rates and larger costs.

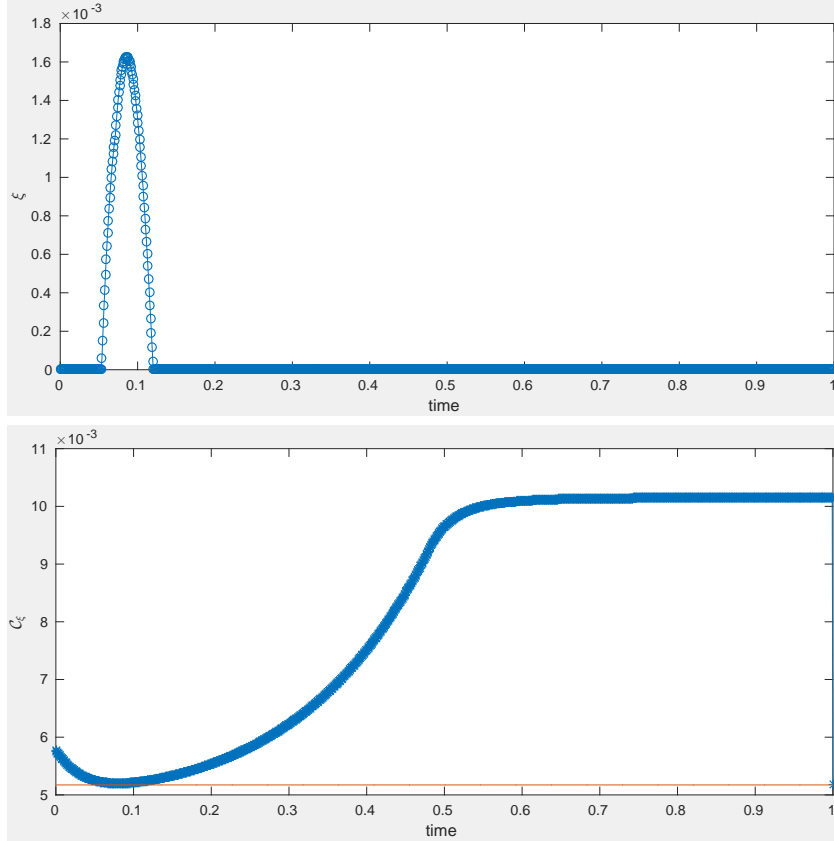


FIGURE 8. Results of Subsection 4.3.2. Top: the optimal converged strategy  $\xi^{MFG}$ . The weight of the non-vaccinating pure strategy (i.e., corresponding to time  $t = \infty$ ) is 91%. Bottom: the corresponding cost  $\mathcal{C}_{\xi^{MFG}}$ . The thin horizontal line corresponds to the cost of the non-vaccinating pure strategy  $(\mathcal{C}_{\xi^{MFG}})_{N+1}$ .

We also compared this result with result obtained by setting the cost  $r_V \rightarrow r_V/(1 - f) = 0.01$ ,  $f \rightarrow 0$ . In this case the cost is 0.0103 (with 6.6% vaccinators) which is very similar and confirms the qualitative analysis of Subsection 2.2.

**4.4. Effects of the failed vaccination rate on the vaccination strategy.** We analyze in this subsection the effects of the failed vaccination rate on the overall vaccination policy. The numerical value of the vaccination cost is  $r_V = 0.025$ , whereas the other parameters are the same as in Subsection 4.3.3. The results are presented in Table 1.

When the failure rate  $f$  is small, the vaccination rate  $(1 - \xi_\infty)$  is increasing with  $f$ . However, when the failure rate  $f$  is larger than a given value (in our numerical simulations, when  $f \geq 0.60$ ), the vaccination rate decreases as  $f$  increases.

When the failure rate is small, the individuals tend to vaccinate more to compensate the decrease in efficacy and therefore to contribute to and profit from the group protection. However, after a given threshold, the construction of a group protection is too expensive, and therefore the individuals are oriented to avoid vaccination (if  $f = 0.85$ , the vaccination rate  $(1 - \xi_\infty)$  is zero; in this case, the probability of being infected is 14.38%).

Failed vaccination rate $f$	Vaccination rate $1 - \xi_\infty$
0.00	5.04%
0.25	5.94%
0.50	7.02%
0.55	7.20%
0.60	7.29%
0.65	7.23%
0.75	5.74%
0.80	2.93%
0.85	0.00%

TABLE 1. Results for the Subsection 4.4. Individual vaccination policy with respect to the failed vaccination rate of the vaccine.

## 5. DISCUSSION

We analyzed in this work the vaccination equilibrium in a context of rational individual vaccination choices; the situation is modeled as a Nash equilibrium with an infinity of players. A specific focus of our work is the presence of imperfect vaccine. We presented a theoretical approach (existence of an equilibrium via the Kakutani fixed point theorem) and a numerical algorithm (similar to a gradient flow). Both approaches have the advantage to use rather weak assumptions on the structure of the model. For this reason, we hope that our study will be useful in other situations.

In the simulations dealing with an influenza epidemic, we remark that the long-term behavior of the vaccine-induced immunity influences the best timing for the individuals. Indeed, when the protection of the vaccine against influenza does not decrease within the time horizon of the problem, the individuals vaccinate as soon as possible (in agreement with the recommendation given by WHO [19]). However, if the vaccine efficacy decreases, the behavior of the population changes and delays the vaccination for optimizing the vaccine protection around the peak of the epidemic.

In addition the previous simulations show that the imperfections of the vaccine increase the overall cost. But the obtained equilibrium is such that the increased vaccination rate does not compensate the lower efficacy (or persistence) of the vaccine.

When the failure rate is below a given threshold, the cost for building a group protection is advantageous with respect to the infection cost. In this case, a higher vaccination rate can be optimal to compensate an increase in the failure rate. However, this individual policy is far from the societal level optimal strategy, which would consist in a global optimization of the vaccination policy.

Several assumptions in this work may motivate further studies:

- a general question is whether the individuals choose their vaccination strategies beforehand; for instance, Fine and Clarkson (see [26]) argue that the individuals will rather respond to the prevalence; see also [6] where the vaccination rate is dependent on the number of people infected. However the “learning” of an equilibrium is a topic in itself in game theory (we refer to the monograph [28] for general considerations). In our specific setting, an encouraging factor is that the “game” is played several times (once each season) and as such a learning mechanism is at work. Moreover the individuals have appropriate feedbacks (through general news for instance) on both the history of the epidemic and

the vaccination dynamics, as well as – more importantly – projections for the upcoming season (for example, data on the potential severity of the epidemic and the expected dynamics of vaccination). But, of course, the setting presented here remains ideal and the interpretability of the results is dependent on our hypotheses. A model that can detect to which extent the individuals adhere to this assumption would be more versatile.

- the individuals are supposed perfectly aware of the past, present and future epidemic dynamics: a model with limited information may be more realistic;
- the individuals are identical. In particular the cost of the illness is exactly the same, irrespective of age: considering several age groups may prove interesting especially if their strategies are different;
- the geographical heterogeneity in the propagation of the epidemic is neglected: travels and intra/inter-community contacts may be important for the epidemic propagation.

#### APPENDIX

In this appendix, we will give the continuous version of the discrete model studied in this article. The population is composed of *susceptible individuals* (described by a function  $S = S(t)$ ), *infected individuals* (described by a function  $I = I(t)$ ), *recovered individuals* (upon exiting the class of infected) and *vaccinated individuals* (described by a distribution of density  $V = V(t, \theta)$ ), where  $t \in \mathbb{R}$  is a continuous time variable and  $\theta$  is a continuous counter that measures the time lapse between the vaccination instant and  $t$ . Finally,  $F = F(t)$  is the class of *failed vaccination individuals*.

The equations of the continuous form, which conserves the total number of individuals, are the following:

$$S'(t) = -\beta S(t)I(t) - U'(t) \quad (5.1)$$

$$I'(t) = \beta \left[ S(t) + F(t) + \int_0^{+\infty} A(\theta)V(t, \theta)d\theta \right] I(t) - \gamma I(t) \quad (5.2)$$

$$\partial_t V(t, \theta) + \partial_\theta V(t, \theta) = -\beta A(\theta)V(t, \theta)I(t) \quad (5.3)$$

$$F'(t) = fU'(t) - \beta F(t)I(t). \quad (5.4)$$

The model is supplemented with the initial and boundary conditions

$$\begin{aligned} S(0) = S_{0-}, I(0) = I_{0-}, \forall t \geq 0 : S(t) \geq 0, F(0^-) = 0, \\ V(0^-, \theta) = 0, \forall \theta \geq 0, V(t, 0) = (1 - f)U'(t), \end{aligned} \quad (5.5)$$

where

- $U : [0, \infty[ \rightarrow [0, 1]$  describes the vaccination:  $U(t)$  is the fraction of people that have vaccinated by time  $t$ . Note that in general  $U(t)$  is not necessarily derivable and in fact neither continuous. When  $U(t)$  is discontinuous this means that the vaccination of a non-negligible part of the population can be instantaneous. In this case  $U'(t)$  is a positive measure (for instance a Dirac mass; we refer to [39] for a more detailed discussion). The mathematical object  $U(t)$  is a cumulative distribution defined on  $[0, \infty[ \cup \{\infty\}$  and  $U'(t)$  is a probability density on  $[0, \infty[ \cup \{\infty\}$  with the convention that vaccination at  $t = \infty$  means in fact no vaccination and this occurs with probability  $1 - U(\infty)$ . Moreover there can be no vaccination once  $S$  reached the value zero. Thus  $U$  is required to be zero once  $S$  is zero. This is a restriction on the set of admissible vaccination schedules  $U$ .

- the non-negative constants  $\beta$ ,  $\gamma$ ,  $f$  and the function  $A$  describe the model as in the discrete time dynamics.
- $V(t, \theta)$  describes the fraction of people at time  $t$ , vaccinated at time  $t - \theta$ , that have not been infected since vaccination. It is a positive measure like  $U'(t)$ .

Note that, by looking at equation (5.3) and by ignoring any regularity issues, it is easy to recognize that the function

$$V(t, \theta) := (1 - f)U'(t - \theta) \exp \left[ - \int_{t-\theta}^t \beta I(\tau) A(\tau - t + \theta) d\tau \right], \quad (5.6)$$

is a solution of (5.3)-(5.5). Likewise  $F(t) = f \int_0^t U'(t - \theta) \exp \left[ - \int_{t-\theta}^t \beta I(\tau) d\tau \right] d\theta$ . Thus, the continuous model reduces to the simpler form:

$$\begin{aligned} S'(t) &= -\beta S(t)I(t) - U'(t) \\ \frac{I'(t)}{I(t)} &= \beta \left[ S(t) + \int_0^{+\infty} U'(t - \theta) \left( f e^{-\int_{t-\theta}^t \beta I(\tau) d\tau} + (1-f)A(\theta) e^{-\int_{t-\theta}^t \beta I(\tau) A(\tau - t + \theta) d\tau} \right) d\theta \right] - \gamma. \end{aligned}$$

#### ACKNOWLEDGEMENTS

G.T. acknowledges support from the Agence Nationale de la Recherche (ANR), projects *EMAQS* ANR-2011-BS01-017-01 and *CINE-PARA*. F.S has been supported by the ANR projects *Kimega* (ANR-14-ACHN-0030-01) and *Kibord* (ANR-13-BS01-0004).

#### REFERENCES

- [1] Andris Abakuks. Optimal immunisation policies for epidemics. *Advances in Appl. Probability*, 6:494–511, 1974.
- [2] Nicolas Bacaër. *A short history of mathematical population dynamics*. Springer-Verlag London, Ltd., London, 2011.
- [3] Yunhua Bai, Nianmin Shi, Qiang Lu, Liqing Yang, Zhaoyun Wang, Li Li, HuiXia Han, Dongyi Zheng, FengJi Luo, Zheng Zhang, and Xing Ai. Immunological persistence of a seasonal influenza vaccine in people more than 3years old. *Human Vaccines & Immunotherapeutics*, 11(7):1648–1653, 2015. PMID: 26083828.
- [4] Chris T. Bauch and David J. D. Earn. Vaccination and the theory of games. *Proc. Natl. Acad. Sci. USA*, 101(36):13391–13394 (electronic), 2004.
- [5] Chris T. Bauch, Alison P. Galvani, and David J. D. Earn. Group interest versus self-interest in smallpox vaccination policy. *Proceedings of the National Academy of Sciences*, 100(18):10564–10567, 2003.
- [6] C.T. Bauch. Imitation dynamics predict vaccinating behaviour. *Proc Biol Sci*, 272(1573):1669–1675, 2005.
- [7] Adrien Blanchet and Guillaume Carlier. From Nash to Cournot-Nash equilibria via the Monge-Kantorovich problem. *Philos. Trans. R. Soc. Lond. Ser. A Math. Phys. Eng. Sci.*, 372(2028):20130398, 11, 2014.
- [8] Romulus Breban, Raffaele Vardavas, and Sally Blower. Mean-field analysis of an inductive reasoning game: Application to influenza vaccination. *Phys. Rev. E*, 76:031127, Sep 2007.
- [9] Dagobert L. Brito, Eytan Sheshinski, and Michael D. Intriligator. Externalities and compulsory vaccinations. *Journal of Public Economics*, 45(1):69 – 90, 1991.
- [10] Bruno Buonomo, Alberto d’Onofrio, and Deborah Lacitignola. Global stability of an {SIR} epidemic model with information dependent vaccination. *Mathematical Biosciences*, 216(1):9 – 16, 2008.
- [11] P. Cardaliaguet and S. Hadikhanloo. Learning in Mean Field Games: the Fictitious Play. *ArXiv e-prints*, July 2015. no. 1507.06280, to appear in COCV.
- [12] Fabrice Carrat and Antoine Flahault. Influenza vaccine: the challenge of antigenic drift. *Vaccine*, 25(39):6852–6862, 2007.
- [13] Frederick H. Chen. A susceptible-infected epidemic model with voluntary vaccinations. *Journal of Mathematical Biology*, 53(2):253–272, 2006.

- [14] M.L. Clements and B.R. Murphy. Development and persistence of local and systemic antibody responses in adults given live attenuated or inactivated influenza a virus vaccine. *Journal of Clinical Microbiology*, 23(1):66–72, 1986.
- [15] Claudia T. Codeço, Paula M. Luz, Flavio Coelho, Alison P Galvani, and Claudio Struchiner. Vaccinating in disease-free regions: a vaccine model with application to yellow fever. *Journal of The Royal Society Interface*, 4(17):1119–1125, 2007.
- [16] Flávio Codeço Coelho and Claudia T. Codeço. Dynamic modeling of vaccinating behavior as a function of individual beliefs. *PLoS Comput Biol*, 5(7):e1000425, 07 2009.
- [17] Monica-Gabriela Cojocar. Dynamic equilibria of group vaccination strategies in a heterogeneous population. *Journal of Global Optimization*, 40(1-3):51–63, 2008.
- [18] Robert B Couch and Julius A Kasel. Immunity to influenza in man. *Annual Reviews in Microbiology*, 37(1):529–549, 1983.
- [19] Nancy Cox. Influenza seasonality: timing and formulation of vaccines. *Bulletin of the World Health Organization*, 92(5):311–311, 2014.
- [20] O. Diekmann and J.A.P. Heesterbeek. *Mathematical epidemiology of infectious diseases. Model building, analysis and interpretation*. Wiley Series in Mathematical and Computational Biology. Chichester: Wiley., 1999.
- [21] Josu Doncel, Nicolas Gast, and Bruno Gaujal. Mean-Field Games with Explicit Interactions. working paper or preprint, February 2016.
- [22] Alberto d’Onofrio, Piero Manfredi, and Ernesto Salinelli. Vaccinating behaviour, information, and the dynamics of SIR vaccine preventable diseases. *Theoretical Population Biology*, 71(3):301 – 317, 2007.
- [23] Alberto d’Onofrio, Piero Manfredi, and Ernesto Salinelli. Fatal SIR diseases and rational exemption to vaccination. *Mathematical Medicine and Biology*, 25(4):337–357, 2008.
- [24] Paulo Doutor, Paula Rodrigues, Maria do Céu Soares, and Fabio A. C. C. Chalub. Optimal vaccination strategies and rational behaviour in seasonal epidemics. *Journal of Mathematical Biology*, pages 1–29, 2016.
- [25] Jonathan Dushoff, Joshua B Plotkin, Cecile Viboud, David JD Earn, and Lone Simonsen. Mortality due to influenza in the united states: an annualized regression approach using multiple-cause mortality data. *American journal of epidemiology*, 163(2):181–187, 2006.
- [26] Paul E. M Fine and Jacqueline A Clarkson. Individual versus public priorities in the determination of optimal vaccination policies. *American Journal of Epidemiology*, 124(6):1012–1020, 1986.
- [27] Peter J. Francis. Optimal tax/subsidy combinations for the flu season. *Journal of Economic Dynamics and Control*, 28(10):2037 – 2054, 2004.
- [28] Drew Fudenberg and David K. Levine. *The theory of learning in games*, volume 2 of *MIT Press Series on Economic Learning and Social Evolution*. MIT Press, Cambridge, MA, 1998.
- [29] Sebastian Funk, Marcel Salathé, and Vincent A. A. Jansen. Modelling the influence of human behaviour on the spread of infectious diseases: a review. *Journal of The Royal Society Interface*, 7(50):1247–1256, 2010.
- [30] Alison P. Galvani, Timothy C. Reluga, and Gretchen B. Chapman. Long-standing influenza vaccination policy is in accord with individual self-interest but not with the utilitarian optimum. *Proceedings of the National Academy of Sciences*, 104(13):5692–5697, 2007.
- [31] Pierre-Yves Geoffard and Tomas Philipson. Disease eradication: Private versus public vaccination. *The American Economic Review*, 87(1):pp. 222–230, 1997.
- [32] Herbert W. Hethcote and Paul Waltman. Optimal vaccination schedules in a deterministic epidemic model. *Mathematical Biosciences*, 18(3-4):365–381, December 1973.
- [33] Minyi Huang, Roland P. Malhamé, and Peter E. Caines. Nash equilibria for large-population linear stochastic systems of weakly coupled agents. In Elkébir Boukas and Roland P. Malhamé, editors, *Analysis, Control and Optimization of Complex Dynamic Systems*, pages 215–252. Springer US, 2005.
- [34] Minyi Huang, Roland P. Malhamé, and Peter E. Caines. Large population stochastic dynamic games: closed-loop mckean-vlasov systems and the Nash certainty equivalence principle. *Commun. Inf. Syst.*, 6(3):221–252, 2006.
- [35] Richard Jordan, David Kinderlehrer, and Felix Otto. The variational formulation of the Fokker-Planck equation. *SIAM J. Math. Anal.*, 29(1):1–17, 1998.
- [36] Shizuo Kakutani. A generalization of brouwers fixed point theorem. *Duke Math. J.*, 8(3):457–459, 09 1941.

- [37] Aime Lachapelle, Julien Salomon, and Gabriel Turinici. Computation of mean field equilibria in economics. *Math. Models Methods Appl. Sci.*, 20(4):567–588, 2010.
- [38] Laetitia Laguzet and Gabriel Turinici. Global optimal vaccination in the SIR model: Properties of the value function and application to cost-effectiveness analysis. *Mathematical Biosciences*, 263:180–197, 2015.
- [39] Laetitia Laguzet and Gabriel Turinici. Individual vaccination as Nash equilibrium in a SIR model with application to the 2009–2010 influenza A (H1N1) epidemic in France. *Bulletin of Mathematical Biology*, 77(10):1955–1984, 2015.
- [40] Jean-Michel Lasry and Pierre-Louis Lions. Jeux à champ moyen. I: Le cas stationnaire. *C. R., Math., Acad. Sci. Paris*, 343(9):619–625, 2006.
- [41] Jean-Michel Lasry and Pierre-Louis Lions. Jeux à champ moyen. II: Horizon fini et contrôle optimal. *C. R., Math., Acad. Sci. Paris*, 343(10):679–684, 2006.
- [42] Jean-Michel Lasry and Pierre-Louis Lions. Mean field games. *Japanese Journal of Mathematics*, 2(1):229–260, 2007.
- [43] Arnold S. Monto, Suzanne E. Ohmit, Joshua G. Petrie, Emileigh Johnson, Rachel Truscon, Esther Teich, Judy Rotthoff, Matthew Boulton, and John C. Victor. Comparative efficacy of inactivated and live attenuated influenza vaccines. *New England Journal of Medicine*, 361(13):1260–1267, 2009. PMID: 19776407.
- [44] R. Morton and K. H. Wickwire. On the optimal control of a deterministic epidemic. *Advances in Appl. Probability*, 6:622–635, 1974.
- [45] Johannes Müller. Optimal vaccination strategies for whom? *Mathematical biosciences*, 139(2):133–154, 1997.
- [46] Sophia Ng, Vicky J. Fang, Dennis K. M. Ip, Kwok-Hung Chan, Gabriel M. Leung, J. S. Malik Peiris, and Benjamin J. Cowling. Estimation of the association between antibody titers and protection against confirmed influenza virus infection in children. *Journal of Infectious Diseases*, 208(8):1320–1324, 2013.
- [47] Kristin L. Nichol, April Lind, Karen L. Margolis, Maureen Murdoch, Rodney McFadden, Meri Hauge, Sanne Magnan, and Mari Drake. The effectiveness of vaccination against influenza in healthy, working adults. *New England Journal of Medicine*, 333(14):889–893, 1995. PMID: 7666874.
- [48] Michael T Osterholm, Nicholas S Kelley, Alfred Sommer, and Edward A Belongia. Efficacy and effectiveness of influenza vaccines: a systematic review and meta-analysis. *The Lancet Infectious Diseases*, 12(1):36–44, 2012.
- [49] Timothy C. Reluga, Chris T. Bauch, and Alison P. Galvani. Evolving public perceptions and stability in vaccine uptake. *Math. Biosci.*, 204(2):185–198, 2006.
- [50] Timothy C. Reluga and Alison P. Galvani. A general approach for population games with application to vaccination. *Mathematical Biosciences*, 230(2):67–78, 2011.
- [51] Suresh P. Sethi and Preston W. Staats. Optimal control of some simple deterministic epidemic models. *J. Oper. Res. Soc.*, 29(2):129–136, 1978.
- [52] Eunha Shim, Gretchen B. Chapman, Jeffrey P. Townsend, and Alison P. Galvani. The influence of altruism on influenza vaccination decisions. *Journal of The Royal Society Interface*, 9(74):2234–2243, September 2012.
- [53] Igor Swiecicki, Thierry Gobron, and Denis Ullmo. Schrödinger approach to mean field games. *Phys. Rev. Lett.*, 116:128701, Mar 2016.
- [54] James D Tamerius, Jeffrey Shaman, Wladimir J Alonso, Kimberly Bloom-Feshbach, Christopher K Uejio, Andrew Comrie, and Cécile Viboud. Environmental predictors of seasonal influenza epidemics across temperate and tropical climates. *PLoS Pathog*, 9(3):e1003194, 2013.
- [55] John J. Treanor, H. Keipp Talbot, Suzanne E. Ohmit, Laura A. Coleman, Mark G. Thompson, Po-Yung Cheng, Joshua G. Petrie, Geraldine Lofthus, Jennifer K. Meece, John V. Williams, LaShondra Berman, Caroline Breese Hall, Arnold S. Monto, Marie R. Griffin, Edward Belongia, David K. Shay, and for the US Flu-VE Network. Effectiveness of seasonal influenza vaccines in the United States during a season with circulation of all three vaccine strains. *Clinical Infectious Diseases*, 55(7):951–959, 2012.
- [56] Raffaele Vardavas, Romulus Breban, and Sally Blower. Can influenza epidemics be prevented by voluntary vaccination? *PLoS Comput Biol*, 3(5):e85, 05 2007.
- [57] Geoffrey A. Weinberg and Peter G. Szilagyi. Vaccine epidemiology: Efficacy, effectiveness, and the translational research roadmap. *Journal of Infectious Diseases*, 201(11):1607–1610, 2010.

- [58] Xiahong Zhao, Vicky J Fang, Suzanne E Ohmit, Arnold S Monto, Alex R Cook, and Benjamin J Cowling. Quantifying protection against influenza virus infection measured by hemagglutination-inhibition assays in vaccine trials. *Epidemiology*, 27(1):143, 2016.

F.S.: UNIVERSITÉ PARIS-DAUPHINE, PSL RESEARCH UNIVERSITY, CNRS UMR 7534, CEREMADE, 75016 PARIS, FRANCE & UNIVERSITÀ DEGLI STUDI DI PAVIA, DIPARTIMENTO DI MATEMATICA, 27100 PAVIA, ITALY

*E-mail address:* `francesco.salvarani@unipv.it`

G.T.: UNIVERSITÉ PARIS-DAUPHINE, PSL RESEARCH UNIVERSITY, CNRS UMR 7534, CEREMADE, 75016 PARIS, FRANCE & INSTITUT UNIVERSITAIRE DE FRANCE

*E-mail address:* `gabriel.turinici@dauphine.fr`