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Time heterogeneous programs of vaccination awareness: modeling and analysis

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Abstract We investigate the role of time heterogeneity of public health systems efforts in favoring the propensity of parents to vaccinate their newborns against a target childhood disease. The starting point of our investigation is the behavioral-epidemiology model proposed by d'Onofrio et al. (PLoS ONE 7:e45653, 2012), where the PHS effort was assumed to be constant. We also consider the co-presence of another layer of temporal heterogeneity: seasonality in the contact rate of the disease. We mainly assume that the effort is periodic with a 1-year period because of alternating working and holiday periods. We show that if the average effort is larger than a threshold, then the disease can be eliminated leading to an ideal equilibrium point with 100% of vaccinated newborns. A more realistic disease-free equilibrium can also be reached, under a condition that depends on the whole form of the time profile describing the PHS effort. We also generalize our disease elimination-related results to a wide class

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of time-heterogenous PHS efforts. Finally, we analytically show that if the disease elimination is not reached, then the disease remains uniformly persistent.

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1 Introduction

In the age of post-trust society [24], a significant development in mathematical epidemiology concerns the role of behavioral feedback as a determinant of disease spread and control. In turn, human behavior depends on the available information and rumors concerning the spread of an infectious disease. A new discipline, termed *behavioral epidemiology* has emerged, whose aim could be summarized as follows: introducing the 'human factor' into epidemic models. This is a Copernican revolution with respect to the statistical mechanics-based classical models [2,5,11,22,26], where i) individuals are modeled as interacting particles; and ii) contagion is modeled by means of the law of mass action. Classical representation most often fails when trying to represent the implementation of vaccination strategies in contemporary societies.

In this work we focus on behavior-dependent voluntary vaccination. Since vaccination is not mandatory, significant anti-vaccine groups have emerged and an increasing number of people are hesitant towards, or object to, vaccination [20,21,32,34]. Hesitancy and refusal of vaccination are based on pseudo-rational reasoning, mostly from the exaggerated perception of dangers associated with adverse-events of vaccines against diseases that are rare nowadays. This reasoning frequently ignores the fact that many of these disease *became* rare precisely because of mass vaccination [1,4]. Not surprisingly, outbreaks of infectious diseases are followed by an increased demand of vaccines, since propensity to vaccinate follows the incidence or prevalence of the target disease [3,6,13,25,27,29].

The dynamics of vaccine propensity is induced by the trade off between two opposite 'forces': the perceived vaccine-related risks (which decreases vaccination propensity [17,28]) and the actual disease-related risks (which increases vaccination propensity [3,27,29]).

If the vaccine propensity dynamics are very fast at population level, one can approximately assume that vaccine propensity is a phenomenological function of the available information on disease prevalence [12]. This is the approach used to build the susceptible-infectious-recovered (SIR)-like behavioral models introduced in [13,14], where two key results are obtained: i) disease elimination is a *mission impossible* since the proportion of parents that are not influenced by information and rumors needed to eliminate the disease must be equal or greater the elimination threshold for mandatory vaccination; and ii) significant recurrent epidemics are predicted in the case where the decision to vaccinate also depends on the past history of the disease. However, in many cases the dynamics can be far from instantaneous. As a consequence, vaccine propensity ought to be considered as a state variable.

A classical game-theoretic model of opinion dynamics between two opposite strategies in a given population is the *imitation game* (IG). An IG complementing SIR model has been adopted in [3], where the two above-mentioned strategies are '*to vaccinate*' and '*to not vaccinate*'. Namely, in [3] it has been assumed that the 'force' against the propensity to vaccinate is irrespective of any information on vaccine side-effects, whereas the one increasing vaccine propensity is an increasing function of disease prevalence.

In [12], an IG model has been proposed where the above mentioned 'force' depends on the information available on vaccine-induced side effects. Differently from [3, 12] showed that a huge disproportion between the perceived risks of disease and vaccination is necessary to be able to achieve high vaccination coverage. Furthermore, target-disease elimination is a 'mission impossible' in practice (although it remains theoretically possible).

A limitation of the pure IG-based approaches used in [3,12] is that they do not take into account the important actions enacted by *Public Health Systems* (PHS) to favor vaccination uptake. The existence of such actions is the basis of the model introduced in [16]. The main analytical result of [16] is that if the awareness campaigns enacted by a PHS are sufficiently intense, then disease elimination is possible.

The aim of this work is to go beyond an important limitation of [16], where PHS efforts have been assumed to be constant in time. On the contrary, many complex phenomena can lead to non-constant and periodic efforts. One of the most important effects is the yearly reduction of PHS effort during periods of work holidays, compounded with awareness campaigns being more intense during school terms.

Another important factor that can influence the dynamics of vaccine propensity, which will be taken into account in this work, is seasonality in the disease contact rate. This phenomenon, as is well known, can have a major impact on disease dynamics in absence of vaccination (see the review paper, [8], in this special issue). Note that seasonality in contact rate also impacts voluntary vaccination scenarios [15], even in the presence of PHS actions, as recently shown in [7].

2 A vaccination model with seasonality and periodic PHS intervention

In this section, starting from the model of voluntary vaccination under the PHS interventions proposed in [16], we consider periodic changes in such interventions and their impact on the stability of equilibrium points.

Let us consider the following generic SIR model with time-varying vaccination of newborns:

$$\dot{S} = \mu(1 - p(t)) - \mu S - \beta c(t) SI, \tag{1a}$$

$$\dot{I} = \beta c(t) SI - (\mu + \nu) I. \tag{1b}$$

Here the state variables represent the fractions of susceptible subjects (S) and infectious subjects (I) at time t. The parameters μ and ν are positive constants and represent, respectively, the inverse of life expectancy at birth and the rate of recovery from the disease. The transmission term is given by $\beta(t) = \beta\, c(t)$, where β is the (positive

constant) baseline transmission rate and $c(t)$ is a positive time periodic fluctuation function such that $\langle c(t)\rangle = 1$. This means that the fluctuation of the transmission can be seen as the result of fluctuations of the per capita contact rate of infectious individuals and/or the probability that a contact between a susceptible individual and an infectious individual results in transmission [26].

The quantity $p(t)$ in (1) represents the fraction at time t of the parents that are willing to vaccinate their children. We assume that the population of parents is proportional to the total (constant) population and that it may be divided into two mutually exclusive groups: parents who are pro-vaccine, and vaccinate their children (whose fraction is denoted by the above mentioned quantity $p(t)$), and parents that do not want to vaccinate their children (due to hesitancy or refusal), $A(t)$. Therefore $p(t) + A(t) = 1$ for all t.

Therefore, the imitation game is a double contagion of idea process [33]:

$$\dot{p} = -\alpha(p)pA + \theta(I)pA \tag{2a}$$

$$\dot{A} = \alpha(p)pA - \theta(I)pA \tag{2b}$$

Both the functions $\alpha(p)$ and $\theta(I)$ are, in general, assumed to be increasing and positive functions [16]. The action of PHS to promote awareness about the relevance of the vaccination leads to the passage from the non-vaccination group to the pro-vaccination one as follows:

$$\dot{p} = -\alpha(p)pA + \theta(I)pA + \tilde{\gamma}(t)A, \tag{3a}$$

$$\dot{A} = \alpha(p)pA - \theta(I)pA - \tilde{\gamma}(t)A, \tag{3b}$$

where $\tilde{\gamma}(t)$ is a positive function that summarizes the *efforts* taken by the public health agencies (such as information, education, availability of vaccination infrastructures and so on) in influencing perceptions regarding both vaccination and disease consequences.

As a special case, we consider:

$$\theta(I) = k\theta\, I \quad \alpha(p) = k\alpha\, p,$$

where θ and α are positive constant and k is a scale factor (useful in the practice, and to compare with [16], but not strictly necessary from a mathematical viewpoint) and

$$\gamma(t) = k\tilde{\gamma}(t).$$

Using $A = 1 - p$, from (1) and (3) we get the following system:

$$\dot{S} = \mu(1 - p(t) - S) - \beta c(t)SI \tag{4a}$$

$$\dot{I} = \beta c(t)SI - (\mu + \nu)I \tag{4b}$$

$$\dot{p} = k(1 - p)\left[(\theta\, I - \alpha\, p)p + \gamma(t)\right]. \tag{4c}$$

Model (4) has been investigated in the case of constant $\gamma(t)$ in [16], where it has been shown that if

$$\gamma > \alpha p_{cr}^2, \tag{5}$$

where

$$p_{cr} = 1 - \frac{1}{\mathcal{R}_0}, \tag{6}$$

is the eradication threshold for the SIR model with constant vaccination rate constant p.

Here we assume that the function $\gamma(t)$ is periodic with period T. In particular, we take $T = 1$ year, but other values of T can be considered, and we will briefly analyze them. Finally, we assume that $\beta(t)$ is either constant or one-year periodic.

The key epidemiological problem considered here is to characterize the PHS intervention modeled by $\gamma(t)$ in the fundamental case where it is able to eradicate the disease.

3 The disease-free scenario

In this section we will investigate the cases where the dynamics of the model is characterized by having $I(t) = 0$. This *scenario* can be spontaneous (i.e. the disease was never introduced in the target population but the PHS enact vaccinations campaigns to prevent future epidemics) or vaccine-induced. The latter case is, of course, the most interesting and in the following we will uniquely refer to it.

3.1 All vaccinators equilibrium

System (4) admits two disease-free equilibria. The first one is an *all vaccinators* equilibrium, where 100% of parents want to vaccinate their children. It is given by

$$E_1 = (0, 0, 1). \tag{7}$$

The stability of E_1 depends on the average value of $\gamma(t)$. The following theorem holds:

Theorem 1 *If*

$$\langle \gamma(t) \rangle > \alpha, \tag{8}$$

then E_1 is globally asymptotically stable. If

$$\langle \gamma(t) \rangle < \alpha, \tag{9}$$

then E_1 is unstable.

Proof Equation (4c) may be rewritten as follows:

$$\dot{p} = k(1 - p)\left[\theta\, Ip + \alpha(1 - p^2) + \gamma(t) - \alpha\right],$$

so that

$$\dot{p} \geq k(1-p)\left[\gamma(t)-\alpha\right]. \tag{10}$$

Therefore, one straightforwardly gets that if (8) holds, then $p(t) \to 1$, i.e. E_1 is GAS. On the other hand, linearizing around E_1, with $(S, I, p) = E_1 + (s, i, y)$, it follows that the linear dynamics of p is ruled by:

$$\dot{y} = (\alpha - \gamma(t))y. \tag{11}$$

Hence if (9) holds, then E_1 is unstable. □

In the following we assume that the inequality (9) holds, so that E_1 is unstable.

3.2 Mixed state equilibrium

The second equilibrium state is the disease-free state characterized by the absence of infectious subjects, $I = 0$. The disease-free state is a periodic vector function:

$$\eta(t) = (\sigma(t), 0, x(t)), \tag{12}$$

where $x(t)$ is the unique one-year periodic solution of the following scalar differential equation with a periodically varying parameter (SDEPVP):

$$\dot{x}(t) = k(1-x)\left[-\alpha\, x^2(t) + \gamma(t)\right], \tag{13}$$

with initial conditions (see discussion below)

$$x(0) = p(0),$$

and $\sigma(t)$ is the solution of the linear SDEPVP, depending on $x(t)$,

$$\dot{\sigma}(t) = \mu(1 - x(t) - \sigma(t)), \tag{14}$$

with initial condition $\sigma(0) = S(0)$ (see discussion below).

We note here that the solutions of scalar differential equations with periodic coefficients of period T are asymptotically periodic with the same period [18]. Thus $x(t)$ and, in turn, $\sigma(t)$ are asymptotically periodic with period T.
We now briefly investigate the properties $x(t)$ and then those of $\sigma(t)$.

Properties of $x(t)$.

(i) First, we note that (13) may be rewritten as follows:

$$\frac{\dot{x}(t)}{k(1-x(t))} = -\alpha\, x^2(t) + \gamma(t). \tag{15}$$

The average values of both sides read

$$\frac{1}{k}\log(1-x(t))-\frac{1}{k}\log(1-x(t+T))=-\alpha\,\langle x^2(t)\rangle+\langle\gamma(t)\rangle, \tag{16}$$

asymptotically implying

$$\langle\gamma(t)\rangle=\alpha\,\langle x^2(t)\rangle. \tag{17}$$

This last condition means that if the effort provided by PHS, $\gamma(t)$, is able to eradicate the disease, then its average value is proportional to the *square* of the resulting steady state vaccination rate $x(t)$ at the eradication.

Now, let us rewrite the functions $\gamma(t)$ and $x(t)$ as Fourier series:

$$\gamma(t)=\Gamma_0+\sum_{h=1}^{+\infty}\Gamma_h\cos(h\omega t-\phi_h^{\gamma}) \tag{18}$$

$$x(t)=X_0+\sum_{h=1}^{+\infty}X_h\cos(h\omega t-\phi_h^{x}), \tag{19}$$

where $\omega=2\pi/T$.

As a consequence, the equality (17) can be written as

$$\Gamma_0=\alpha\left(X_0^2+\frac{1}{2}\sum_{h=1}^{+\infty}X_h^2\right). \tag{20}$$

(ii) Second, writing

$$\frac{\dot{x}}{k}=\gamma(t)-\alpha x^2-x\gamma(t)+\alpha x^3,$$

one gets

$$\langle\gamma x\rangle=\alpha\langle x^3\rangle,$$

and from

$$x^n\frac{\dot{x}}{k}=x^n(\gamma(t)-\alpha x^2-x\gamma(t)+\alpha x^3)$$

(with $n=1,2,3,\dots$) it follows that

$$\langle\gamma x^{n+1}\rangle=\alpha\langle x^{n+3}\rangle.$$

(iii) Third, from the following differential inequality:

$$\dot{p}\geq k(1-p)\left[(0-\alpha\,p)p+\gamma(t)\right], \tag{21}$$

it follows that if $x(0)=p(0)$ then

$$p(t)\geq x(t). \tag{22}$$

Properties of $\sigma(t)$.
(i) It is easy to show that

$$\langle \sigma(t) \rangle = 1 - \langle x(t) \rangle. \tag{23}$$

More in general, from (14) and (19) we get:

$$\sigma(t) = 1 - X_0 - \sum_{h=1}^{+\infty} \frac{\mu}{\sqrt{\mu^2 + \omega^2 h^2}} X_h \cos(h\omega t - \phi_h^x - \arg(\mu + i\omega h)). \tag{24}$$

Since in any case $\mu \ll 1/T < 2\pi/T$, it follows that for $h \geq 1$:

$$\frac{\mu}{\sqrt{\mu^2 + \omega^2 h^2}} \approx \frac{\mu}{\omega},$$
$$\arg(\mu + i\omega h) \approx \frac{\pi}{2},$$

implying that the Fourier coefficients $X_1, X_2, \ldots$ are strongly filtered and $\sigma(t)$ can be approximated as follows:

$$\sigma(t) \approx 1 - X_0 - \frac{\mu}{\omega} \sum_{h=1}^{+\infty} \frac{1}{h} X_h \sin(h\omega t - \phi_h^x). \tag{25}$$

(ii) Finally, from (4a) one has,

$$\dot{S}(t) \leq \mu(1 - p(t) - S(t)) \leq \mu(1 - x(t) - S(t)), \tag{26}$$

so that the following relationship between $S(t)$ and $\sigma(t)$ holds true provided that $\sigma(0) = S(0)$:

$$S(t) \leq \sigma(t). \tag{27}$$

3.3 Stability of the mixed state equilibrium

It is of interest to assess how the actions of the PHS (i.e. delivering vaccinations and the related effort to increase the vaccine uptake) must be planned to ensure that in case of introduction/re-introduction of the disease, it will not become endemic. Of course, the ideal case is the enactment of efforts such that the system reaches the all-vaccinators equilibrium we have studied in Sect. 3.1. However, the action of PHS has a cost, so that in many cases this is unfeasible. In such scenarios, it is important to guarantee that at least the mixed disease-free state is globally stable. In the practice, the global asymptotic stability (GAS) of an equilibrium state or point characterized by no infectious subjects is of interest. Indeed, GAS means that even if the disease is re-introduced in a population and a large epidemic breaks out it will any case become extinct and the disease will not become endemic.

Theorem 2 *If*

$$\mathcal{R}_0 \langle c(t)\sigma(t) \rangle < 1, \tag{28}$$

where $\mathcal{R}_0$ is the basic reproduction number of the SIR epidemic model with constant contact rate ($c(t) = 1$) and absence of vaccination, i.e.:

$$\mathcal{R}_0 = \frac{\beta}{\mu + \nu},$$

then the mixed state equilibrium $\eta(t)$ is globally asymptotically stable. If

$$\mathcal{R}_0 \langle c(t)\sigma(t)\rangle > 1 \tag{29}$$

then $\eta(t)$ is unstable.

Proof System (4) may be linearized around the mixed state equilibrium by setting:

$$(S(t), I(t), p(t)) = (\sigma(t), 0, x(t)) + (s(t), i(t), u(t)).$$

This yields, of course, a linear three dimensional system, where the differential equation for $i(t)$ does not depend on (s, u):

$$i'(t) = (\beta c(t)\sigma(t) - (\mu + \nu))\, i(t). \tag{30}$$

It easily follows that the LAS condition is (28). Indeed, one can write

$$\beta c(t)\sigma(t) = \beta \langle c(t)\sigma(t)\rangle + q(t),$$

where $q(t)$ are oscillating terms with zero mean value, and in turn

$$i(t) = i(0) \exp\left((\beta \langle c(t)\sigma(t)\rangle - (\mu + \nu))\, t + \int_0^t q(z)dz \right).$$

Thus, if (28) holds then $i(t) \to 0$.
Note that in case of constant contact rate (impying $c(t) = 1$), the LAS condition (28) becomes

$$\mathcal{R}_0 \langle \sigma(t)\rangle < 1,$$

which, in view of (23), reads as follows:

$$\mathcal{R}_0 (1 - \langle x(t)\rangle) < 1, \tag{31}$$

and, in turn, as:

$$\langle x(t)\rangle > p_{cr}, \tag{32}$$

where p_{cr} is the eradication threshold for SIR epidemic diseases with constant contact rate and constant vaccination rate, i.e.:

$$p_{cr} = 1 - \frac{1}{\mathcal{R}_0}.$$

Not surprisingly, the LAS condition (28) also guarantees the GAS of the periodic DFS. This easily follows from the following differential inequality:

$$\dot{I}(t) = I(t)(\beta c(t) S(t) - (\mu + \nu)) \leq I(t)(\beta c(t)\sigma(t) - (\mu + \nu)). \tag{33}$$

Finally, it is easy to check that the mixed state equilibrium is unstable under condition (29). □

Remark 1 From a purely mathematical point of view, it is of interest to study the borderline case $\mathcal{R}_0\langle c(t)\sigma(t)\rangle = 1$, which was not considered in the above analysis.

This case can be analyzed by taking into the account the state variable $V(t)$ describing the fraction of vaccinated people. The dynamics is described by the equation $\dot{V} = \mu(p(t) - V)$. In view of (22), it holds that $\dot{V} \geq \mu(x(t) - V)$. Therefore, $V(t) \geq W(t)$, where W is the solution of $\dot{W} = \mu(x(t) - W)$. Thus from (33) it follows:

$$\dot{I}(t) \leq I(t)(\beta c(t)(1 - I - W(t)) - (\mu + \nu)),$$

and therefore $I(t) \leq y(t)$, where $y(t)$ solves the following Riccati equation with periodic coefficients:

$$\dot{y} = y(t)\,(\beta c(t)(1 - W(t)) - (\mu + \nu)) - \beta c(t) y^2,$$

with initial condition $y(0) = I(0)$. In conclusion, in the borderline case, $\mathcal{R}_0\langle c(t)\sigma(t)\rangle = 1$ the DFS is GAS.

3.4 Differences with the case of constant PHS effort

In the case of constant PHS efforts, γ, the eradication condition is given by (5). Therefore one naively could think that for periodic PHS efforts the eradication condition might be $\langle\gamma\rangle > \alpha p_{cr}^2$. However, this is not the case as we have seen. In particular, in the case $c(t) = 1$, from (20) it follows that

$$X_0 = \sqrt{\frac{1}{\alpha}\Gamma_0 - \frac{1}{2}\sum_{h=1}^{+\infty} X_h^2}.$$

Thus, from (32) it follows that

$$\Gamma_0 > \alpha\left(p_{cr}^2 + \frac{1}{2}\sum_{h=1}^{+\infty} X_h^2\right). \tag{34}$$

The inequality (34) shows that the above conjecture is wrong, and in that in some cases, the average value Γ_0 has to be substantially larger than αp_{cr}^2. In other words, eradication of the disease depends on the whole function $\gamma(t)$ and not only on its average. Nevertheless, a rough, but sufficient, condition for eradication may be obtained by:

$$\gamma_{\min} > \alpha p_{cr}^2,$$

where $\gamma_{\min} = \min_{t\in[0,T]} \gamma$. This can be obtained, in view of (4c), from the differential inequality:

$$\dot{p} > k(1-p)(-\alpha p^2 + \gamma_{\min}),$$

and then proceeding along lines similar to those illustrated above.

We can also determine the effect of a $\gamma(t)$ whose average value is such that:

$$\langle \gamma(t) \rangle \in [\alpha p_{cr}^2, \alpha). \tag{35}$$

We remind the reader that in the scenario where $\gamma(t)$ and $\beta(t)$ are constant, the condition $\gamma \in [\alpha p_{cr}^2, \alpha)$ guarantees that $p(t)$ reaches and overcomes p_{cr} without 'coming back' to lower values. In the case of time-varying $\gamma(t)$ however, the condition (35) can only guarantee that $p(t)$ reaches the value p_{cr} at least once. Formally, if $p(0) < p_{cr}$, and condition (35) holds, then there exists a $\widehat{t}$, such that $p\left(\widehat{t}\right) = p_{cr}$. Indeed, rewriting equation (4c) as follows:

$$\dot{p} = k(1-p)\left[\theta\, Ip + \alpha(p_{cr}^2 - p^2) + \gamma(t) - \alpha p_{cr}^2\right],$$

as long as $p(t) < p_{cr}$, we obtain

$$\dot{p} \geq k(1-p)\left[\gamma(t) - \alpha p_{cr}^2\right],$$

easily confirming our claim.

One cannot guarantee, however, the impossibility of the reduction of $p(t)$ under p_{cr}. This is easily seen, for example by considering the case where k is sufficiently large to have a rapid response to the PHS action, and $\gamma(t)$ is null (or very small) for a sufficiently large time in $[0, T]$.

3.5 Solving the SDEPVP equation (13)

3.5.1 Small oscillations affecting a constant PHS effort

Let us suppose now that small oscillations affect a constant PHS effort,

$$\gamma(t) = \gamma_0 + \epsilon\Omega(t),$$

with $0 < \epsilon \ll 1$. Following the general methods of the theory of small forcing oscillations [23], we may rewrite the unknown function $x(t)$ as a series of powers of ϵ:

$$x(t) = x_0 + \sum_{q=1}^{+\infty} x_q(t)\epsilon^q.$$

Substituting this in (13) we obtain the infinite formally solvable system of the form

$$\begin{aligned} 0 &= f_0(x_0; \gamma_0), \\ \dot{x}_q(t) &= f_q(x_0, \ldots, x_q; \gamma_0, \Omega(t)), \quad q = 1, 2, \ldots . \end{aligned}$$

where the ODE for the q–th state variable is linear in $x_q(t)$. Thus one can solve first for x_0, and then for $x_1(t)$, up to a chosen index n. For example, if $n = 2$, one gets:

$$\begin{aligned} \alpha x_0^2 &= \gamma_0, \\ \dot{x}_1 &= k(1 - x_0)\Omega(t) - (2\alpha x_0(1 - x_0) + \Omega(t))\, x_1, \\ \dot{x}_2 &= 2\alpha x_0 x_1^2 - \alpha(1 - x_0)x_1 - 2\alpha x_0(1 - x_0)x_2, \end{aligned}$$

whose formal solution is:

$$\begin{aligned} x_0 &= \sqrt{\frac{\gamma_0}{\alpha}}, \\ x_1(t) &= e^{(-2\alpha x_0(1-x_0)t - W(t))} \int_0^t e^{(2\alpha x_0(1-x_0)z + W(z))} k(1 - x_0)\Omega(z)dz, \\ x_2(t) &= \int_0^t e^{-2\alpha x_0(1-x_0)(t-z)} \left(2\alpha x_0 x_1^2(z) - \alpha(1 - x_0)x_1(z)\right) dz, \end{aligned}$$

where

$$W(t) = \int_0^t \Omega(s)ds.$$

The above solution is quite complex to be analyzed, even in the simple case $\Omega(t) = \cos(\omega t - \phi)$.

3.5.2 The case of piecewise-constant effort $\gamma(t)$

The differential equation for $x(t)$ can be *semi-analytically* solved in the important case where $\gamma(t)$ is piecewise constant. From the public health viewpoint this case is of great interest because, in practice due to logistic limitations, the effort of the PHS cannot vary in a continuous manner, but it remains constant for more or less long periods of time [9]. An idealized case would be, for example, a two-valued $\gamma(t)$ assuming a low value during the holidays and a larger value during the work terms.

For the sake of the simplicity, let us consider the basic case of a single holiday term, yielding

$$\gamma(t) = \begin{cases} \alpha x_U^2 & \text{if } t \in [0, T_1) \\ \alpha x_L^2 & \text{if } t \in (T_1, T) \end{cases}, \tag{36}$$

where

$$0 \leq x_L < x_U.$$

We also set $x_L < 1$, otherwise we are in the trivial case where the steady state solution is $\tilde{x}(t) = 1$ and $x(t) \to 1$ for $t \to +\infty$.

In $[0, T_1)$ we have to solve the following differential equation:

$$\frac{\dot{x}(t)}{(1-x)(x_U+x)(x_U-x)} = \alpha k,$$

with initial condition $x(0) = a$, whose solution is of the form:

$$\Psi(x) = \Psi(a)\, e^{\alpha k t},$$

so that

$$x(t) = \Psi^{-1}\left(\Psi(a) e^{\alpha k t}\right).$$

Defining

$$h = x(T_1) = \Psi^{-1}\left(\Psi(a)\, e^{\alpha k T_1}\right),$$

then in (T_1, T) we have to solve:

$$\frac{\dot{x}(t)}{(1-x)(x_L+x)(x_L-x)} = \alpha k,$$

together with $x(T_1) = h$, whose solution is of the form:

$$\widetilde{\Psi}(x) = \widetilde{\Psi}(h)\, e^{\alpha k (t-T_1)},$$

and hence

$$x(t) = \widetilde{\Psi}^{-1}\left(\widetilde{\Psi}(h)\, e^{\alpha k (t-T_1)}\right).$$

As far as the two functions $\Psi(x)$ and $\widetilde{\Psi}(x)$ are concerned, defining

$$G(x, x_q) = |1-x|^{\frac{1}{x_q^2-1}} \, |x_q + x|^{\frac{1}{2x_q(x_q+1)}} \, |x_q - x|^{\frac{1}{2x_q(x_q-1)}},$$

one has

$$\Psi(x) = G(x, x_H); \quad \widetilde{\Psi}(x) = G(x, x_L).$$

Since we are interested in finding the periodic solution for $x(t)$, then a is not known and it is the solution of the following equation

$$a = x(T),$$

that is,

$$a = \widetilde{\Psi}^{-1}\left(\widetilde{\Psi}(h(a))\, e^{\alpha k (T-T_1)}\right),$$

where $h(a)$ reminds us that $h = x(T_1)$ depends on a.

Of course, in the analysis above, one has to take into the account whether x_L or x_U or both lie in $[0, 1]$, because their position determines the signs of the moduli in the utility function $G(x, x_q)$. For example, we have already mentioned that if $x_L \geq 1$ then $x(t) \to 1$ for $t \to +\infty$.

4 Time-heterogeneous contact rates: going beyond the periodicity

We assumed that the PHS effort is periodic with a one year period. An effort planned over an integer number of years, or over a number of seasons greater that four, does not change our third result. In the purely theoretical case where the period T is an irrational number of years, and $c(t)$ remains one year periodic, then the eradication condition must be modified as follows:

$$\mathcal{R}_0 \left(\lim_{T \to +\infty} \frac{1}{T} \int_0^T c(t)\sigma(t)dt \right) < 1. \tag{37}$$

In reality, following the lines of the works by Thieme on non-behavioral epidemic models with general time-varying parameters [30,31], we can consider very general time-heterogeneous PHS efforts, $\gamma(t)$, and contact rates. Namely, defining for a real positive function $f(t)$ its generalized mean:

$$GenAvg(f(.)) = \lim_{t \to +\infty} \frac{1}{t} \int_0^t f(z)dz, \tag{38}$$

it holds that:

Theorem 3 *If*

$$GenAvg(\gamma(.)) > \alpha, \tag{39}$$

then E_1 is globally asymptotically stable. If

$$GenAvg(\gamma(.)) < \alpha, \tag{40}$$

then E_1 is unstable.

and:

Theorem 4 *If*

$$\mathcal{R}_0\, GenAvg(c(.)\sigma(.)) < 1, \tag{41}$$

then the mixed state equilibrium $\eta(t)$ is globally asymptotically stable. If

$$\mathcal{R}_0\, GenAvg(c(.)\sigma(.)) > 1 \tag{42}$$

then $\eta(t)$ is unstable.

The proofs of the above theorems are very similar to the proofs of the corresponding Theorems 1 and 2. For example, to proof the instability condition (40), one gets the linearized equation (11), whose solution can be written as follows:

$$y(t) = y(0) \exp\left(t \left(\alpha - \frac{1}{t} \int_0^t \gamma(z)dz \right) \right).$$

As a consequence, if (40) holds, then $y(t) \to +\infty$, i.e., E_1 is unstable.

5 Uniform persistence

From the epidemic point of view, the antisymmetric case of GAS is uniform persistence. Indeed in such a case, showing that the system is uniformly persistent means showing that the disease remains endemic in a non-constant fashion.

5.1 Invariant region

Lemma 1 *Any solution of* (4) *starting in the region*

$$\Omega = \{(S, I, p) \in \mathbf{R}^3_+ : 0 \leq S + I \leq 1, \quad 0 \leq p \leq 1\}, \tag{43}$$

does not leave it by crossing one of its boundaries. In other words, Ω is a positively invariant set for (4)*. Further, it holds that*

$$\limsup_{t\to\infty} (S(t) + I(t) - \sigma(t)) = 0$$

Proof Set $N = S + I$ and $y = N - \sigma(t)$. Then:

$$\dot{y} = -\mu y - \mu(p - x) - \nu I$$

Since $p(t) \geq x(t)$ and $I \geq 0$, it follows that $\limsup_{t\to\infty} y(t) = \limsup_{t\to\infty} (N - \sigma) = 0$. □

We know that the all-vaccinators equilibrium $E_1 = (0, 0, 1)$ is unstable if $\langle \gamma(t) \rangle < \alpha$. On the other hand, it is easy to check that the plane $p(t) = 1$ is a stable manifold for E_1. Therefore, for any triple $x_0 = (S_0, I_0, p_0)$ in the interior of Ω, it is not possible that $p(t, x_0) \to 1$ for $t \to \infty$. Therefore, there exists a time $\tilde{t} > 0$ such that any solution of (4) starting in the interior of Ω will be confined in the region

$$\Omega = \{(S, I, p) \in \mathbf{R}^2_+ : 0 \leq S + I \leq 1, \quad 0 \leq p \leq \tilde{p}\}. \tag{44}$$

where

$$\tilde{p} = \sup_{(t,x_0)\in(\tilde{t},+\infty)\times\mathring{\Omega}} p(t, x_0) < 1.$$

5.2 Uniform persistence

The SIp model (4) admits the locally asymptotically stable disease-free solution (7) under condition (28). Here we show that (4) is uniformly persistent under the reversed condition (29).

Let X_0 and ∂X_0 be subsets of a complete metric space X with metric d, such that $X_0 \cap \partial X_0 = \emptyset$ and $X_0 \cup \partial X_0 = X$. Let X_0 be open and positively invariant for a periodic semiflow $Q(t)$, and ∂X_0 be a closed subset. Recall the following definition

([35], Def. 3.1.1, p. 64): A T-periodic semiflow $Q(t)$ is said to be *uniformly persistent* with respect to $(X_0, \partial X_0)$, if there exists $\eta > 0$ such that for any $x \in X_0$, $\liminf_{t\to+\infty} d(Q(t)(x_0), \partial X_0) \geq \eta$.

In our case, we begin by taking

$$X = \{(S, I, p) \in \mathbf{R}^2_+ \times [0, \tilde{p}]\}, \quad X_0 = \{(S, I, p) \in X : I > 0\},$$

and denote

$$\partial X_0 := X \backslash X_0 = \{(S, I, p) \in X : I = 0\}. \tag{45}$$

Then, we introduce the Poincaré map:

$$P : x_0 \in X \to u(T, x_0) \in X.$$

where $u(t, x_0)$ is the unique solution of the system (4) corresponding to initial data $x_0 = (S_0, I_0, p_0) \in X$.

Given the disease-free solution (7), set

$$E := \eta(0) = (\sigma(0),\ 0,\ x(0))\,.$$

Denote with $\|\cdot\|$ a norm in $\mathbf{R}^3$. We first prove the following result:

Lemma 2 *If (29) is satisfied, then there exists $\delta^* > 0$ such that, for any $x_0 \in X_0$,*

$$\limsup_{n\to+\infty} d\left(P^n(x_0), E\right) \geq \delta^*. \tag{46}$$

Proof Condition (29) may be written as

$$\frac{1}{T}\int_0^T \beta c(t)\sigma(t)dt > (\mu + \nu)\,.$$

Then, there exists an $\epsilon > 0$ such that

$$\frac{1}{T}\int_0^T (1-\epsilon)\beta c(t)\sigma(t)dt > (\mu + \nu)\,. \tag{47}$$

Take $\delta < \epsilon$. By continuity of the flow of (7) with respect to the initial data, there exists $\delta^* := \delta^*(\delta) > 0$ such that for all $x_0 \in X_0$ with $\| x_0 - E \| \leq \delta^*$, it holds that

$$\| u(t, x_0) - u(t, E) \| < \delta, \quad \forall t \in [0, T].$$

Now we show (46). Assume on the contrary that

$$\limsup_{n\to+\infty} d\left(P^n(x_0), E\right) < \delta^*,$$

for some $x_0 \in X_0$. Without loss of generality, we assume that, for any $n > 0$,

$$d\left(P^n(x_0), E\right) < \delta^*, \tag{48}$$

and therefore

$$\| u(t, P^n(x_0)) - u(t, E) \| < \delta^*, \quad \forall t \in [0, T].$$

By the propriety of composition of semiflows it follows that

$$u(t + nT, x_0) = Q(t + nT)(x_0) = Q(t)Q(nT)(x_0) = Q(t)(P^n(x_0)),$$

and therefore

$$u(t + nT, x_0) = u(t, P^n(x_0)).$$

Furthermore, for any $t \geq 0$ let $t = nT + t'$, where $t' \in [0, T]$ and $n = \left[\frac{t}{T}\right]$ (the greatest integer less than or equal to t/T).

It follows that

$$\| u(t, x_0) - u(t, E) \| = \| u(t', P^n(x_0)) - u(t', E) \| < \delta, \quad \forall t \geq 0. \tag{49}$$

where the inequality comes from (48).

Recall that for all $t \geq 0$, $u(t, x_0)$ is the solution $(S(t), I(t), p(t))$ of (4) with initial condition x_0. Therefore from (49), it follows:

$$|S(t) - \sigma(t)| < \delta,$$

and therefore

$$S(t) > \sigma(t) - \delta > \sigma(t) - \epsilon, \quad \forall t \geq 0.$$

This last condition implies the following differential inequality:

$$\dot{I} > \beta c(t)\sigma(t)(1 - \epsilon)I - (\mu + \nu)I. \tag{50}$$

Given the comparison equation:

$$\dot{\overline{I}} = \beta c(t)\sigma(t)(1 - \epsilon)\overline{I} - (\mu + \nu)\overline{I}, \tag{51}$$

for any nonnegative initial condition $I(0)$ of (51), since from (47) it follows that

$$\int_0^T (1 - \epsilon)\beta c(t)\sigma(t)dt > \int_0^T (\mu + \nu)\, dt.$$

We have $\overline{I}(t) \to \infty$ for $t \to \infty$ and therefore also $I(t) \to \infty$ for $t \to \infty$, which is a contradiction since I is bounded. Therefore (46) holds. □

Now we can state the uniform persistence result, checking that the requirements of the *strong repellers* theorem (assumptions (A1) and (A2) in the Appendix) are satisfied.

Theorem 5 *If (29) is satisfied, then there exists $\eta > 0$ such that every solution $x(t) = (S(t), I(t), p(t))$ of model (4) with initial condition $x_0 = (S_0, I_0, p_0) \in X_0$ satisfies:*

$$\liminf_{t \to +\infty} I(t) \geq \eta. \tag{52}$$

Proof First of all, we prove that the Poincaré map defined above is uniformly persistent with respect to $(X_0, \partial X_0)$. Consider the set:

$$M_\partial = \{x_0 \in \partial X_0 : P^n(x_0) \in \partial X_0, \forall n \in \mathbf{N}\}.$$

From (45) we have that $\{(S, 0, p) : S \geq 0, 0 \leq p \leq \tilde{p}\} \subset M_\partial$.

Then, any solution starting in ∂X_0 satisfies $S(t) > 0$, $I(t) = 0$, $0 \leq p \leq \tilde{p}$ for all $t > \tilde{t}$. This implies that

$$M_\partial = \{(S, 0, p) : S \geq 0, 0 \leq p \leq \tilde{p}\},$$

and

$$E := \eta(0) = (\sigma(0),\ 0,\ x(0))$$

is the only one fixed point of P in M_∂ and $\{E\}$. Recalling that

$$W^S(E) = \{x_0 \in X : \lim_{n \to +\infty} \| P^n(x_0) - E \| = 0\},$$

from Lemma 2 it follows that

$$W^S(E) \cap X_0 = \emptyset.$$

Furthermore, it is easy to check that the orbits in M_∂ approaches E_2. Finally, the existence of the region (43) ensures that P has a global attractor, i.e. a positively invariant set which attracts all the positive orbits in X. This proves that if (29) is satisfied, all the conditions required by Theorem 1.3.1 (and Remark 1.3.1) in [35] are satisfied. Therefore, P is uniformly persistent with respect to $(X_0, \partial X_0)$.

Finally, from Lemma (1), P is compact and point dissipative[1]; therefore from Theorem 3.1.1 in [35], it follows that there exists $\eta > 0$ such that,

$$\liminf_{t \to +\infty} d(Q(t)(x_0), \partial X_0) \geq \eta, \quad \forall x_0 \in X_0,$$

which implies (52). □

[1] We recall that a continuous map $T : X \to X$ is said to be *point dissipative* if there is a bounded set $B \subset X$ with the property that, for any $x \in X$, there is an integer $N(x)$ such that $T^n x \in B$ for $n > N(x)$ (see [19]).

6 Conclusions

In this work, we showed that if the average PHS effort overcomes a given threshold (roughly speaking, the relative impact of the fear of side effects compared to the fear of the disease itself), then a highly idealized equilibrium where all people get vaccinated is globally asymptotically stable. More realistically, it is possible to reach a GAS equilibrium state where there are no infectious but the fraction of newborns' parents who vaccinate their babies is periodically fluctuating. The stability properties of this disease-free state depend on the whole function $\gamma(t)$ in a non-trivial manner (or if one prefers, on its whole Fourier spectrum) and not only on its average value (i.e., the spectral value at frequency 0).

We also briefly showed that similar properties hold for a wide class of general time-heterogeneous efforts (also when the contact rate has a generalized temporal pattern). We equally focused on the opposite side of the impacts of the PHS intervention, i.e. the very frequent cases where disease elimination is not successful — namely, we provided an analytical study of uniform persistence of the disease.

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A Strong repellers theorem

We recall here the strong repellers theorem, as in [35] (Theorem 1.3.1 and Remark 1.3.1). Let $f : X \to X$ be a continuous map with precompact positive orbits, and $X_0 \cup X$ an open set. Define $\partial X_0 := X_0 := X \backslash X_0$, and $M_\partial := \{x \in \partial X_0 : f^n(x) \in \partial X_0, n \geq 0\}$.

Now, assume that the following assumptions holds true:

(A1) $f(X_0) \subset X_0$, and f has a global attractor A;
(A2) There exists a finite sequence $M = \{M_1, \ldots, M_k\}$ of disjoint, compact, and isolated invariant sets in ∂X_0 such that:

(i) $\Omega(M_\partial) := \cup_{x \in M_\partial} \omega(x) \subset \cup_{i=1}^{k} M_i$;
(ii) no subset of M forms a cycle in ∂X_0;
(iii) M_i is isolated in X; and
(iv) $W^s(M_1) \cap X_0 = \emptyset$ for each $1 \leq i \leq k$.

Then there exists $\delta > 0$ such that for any compact internally chain transitive set L with $L \not\subset M_i$, for all $1 \leq i \leq k$, it follows that $\inf_{x \in L} d(x, \partial X_0) > \delta$.

References

1. Anderson, R.M.: The impact of vaccination on the epidemiology of infectious diseases. In: Bloom, B.R., Lambert, P.-H. (eds.) The Vaccine Book, 2nd edn, pp. 3–31. Elsevier B. V, Amsterdam (2016)
2. Anderson, R.M., May, R.M.: Infectious Diseases of Humans. Dynamics and Control. Oxford University Press, Oxford (1991)

3. Bauch, C.T.: Imitation dynamics predict vaccinating behaviour. Proc. R. Soc. B **272**, 1669–1675 (2005)
4. Bloom, B.R., Lambert, P.-H. (eds.): The Vaccine Book, 2nd edn. Elsevier B. V, Amsterdam (2016)
5. Brauer, F., van den Driessche, P., Wu, J.: Mathematical Epidemiology. Lecture Notes in Mathematics. Mathematical Biosciences Subseries, vol. 1945. Springer, Berlin (2008)
6. Buonomo, B., d'Onofrio, A., Lacitignola, D.: Modeling of pseudo-rational exemption to vaccination for SEIR diseases. J. Math. Anal. Appl. **404**, 385–398 (2013)
7. Buonomo, B., Carbone, G., d'Onofrio, A.: Effect of seasonality on the dynamics of an imitation-based vaccination model with public health intervention. Math. Biosci. Eng. **15**, 299–321 (2018)
8. Buonomo, B., Chitnis, N., d'Onofrio, A.: Seasonality in epidemic models: a literature review. Ric. Mat. (2018). https://doi.org/10.1007/s11587-017-0348-6
9. Buonomo, B., d'Onofrio, A., Manfredi, P.: Optimal time-profiles of public health intervention to shape voluntary vaccination for childhood diseases. (Submitted)
10. Caminade, C., Kovats, S., Rocklov, J., Tompkins, A.M., Morse, A.P., Colón-González, F.J., Stenlund, H., Martens, P., Lloyd, S.J.: Impact of climate change on global malaria distribution. Proc. Nat. Acad. Sci. USA **111**, 3286–3291 (2014)
11. Capasso, V.: Mathematical Structures of Epidemic Systems. Springer, Berlin (1993)
12. d'Onofrio, A., Manfredi, P., Poletti, P.: The impact of vaccine side effects on the natural history of immunization programmes: an imitation-game approach. J. Theor. Biol. **273**, 63–71 (2011)
13. d'Onofrio, A., Manfredi, P., Salinelli, E.: Vaccinating behaviour, information, and the dynamics of SIR vaccine preventable diseases. Theor. Popul. Biol. **71**, 301–317 (2007)
14. d'Onofrio, A., Manfredi, P., Salinelli, E.: Fatal SIR diseases and rational exemption to vaccination. Math. Med. Biol. **25**, 337–357 (2008)
15. d'Onofrio, A., Manfredi, P., Salinelli, E.: Vaccinating behaviour and the dynamics of vaccine preventable infections. In: Manfredi, P., d'Onofrio, A., et al. (eds.) Modeling the Interplay Between Human Behavior and the Spread of Infectious Diseases, pp. 267–287. Springer, New York (2013)
16. d'Onofrio, A., Manfredi, P., Poletti, P.: The interplay of public intervention and private choices in determining the outcome of vaccination programmes. PLoS One **7**, e45653 (2012)
17. Elliman, D., Bedford, H.: MMR: Where are we now? Arch. Dis. Childh. **92**, 1055–1057 (2007)
18. Hale, J.K.: Ordinary Differential Equations. Dover Publications, Mineola (1997)
19. Hale, J.K., Lopes, O.: Fixed point theorems and dissipative processes. J. Differ. Equ. **13**, 391–402 (1973)
20. Kata, A.: A postmodern Pandora's box: anti-vaccination misinformation on the Internet. Vaccine **28**, 1709–1716 (2010)
21. Kata, A.: Anti-vaccine activists, Web 2.0, and the postmodern paradigm-an overview of tactics and tropes used online by the anti-vaccination movement. Vaccine **30**, 3778–3789 (2012)
22. Keeling, M.J., Rohani, P.: Modeling Infectious Diseases in Humans and Animals. Princeton University Press, Princeton (2008)
23. Landau, L.D., Lifshitz, E.M.: Mechanics. Pergamon Press, Oxford (1976)
24. L-fstedt, R.: Risk Management in Post-Trust Societies. Palgrave Macmillan, New York (2005)
25. Manfredi, P., d'Onofrio, A. (eds.): Modeling the Interplay Between Human Behavior and the Spread of Infectious Diseases. Springer, New York (2013)
26. Martcheva, M.: An Introduction to Mathematical Epidemiology. Texts in Applied Mathematics, vol. 61. Springer, New York (2015)
27. Miller, E., Gay, N.J.: Epidemiological determinants of pertussis. Dev. Biol. Stand. **89**, 15–23 (1997)
28. Napier, G., Lee, D., Robertson, C., Lawson, A., Pollock, K.G.: A model to estimate the impact of changes in MMR vaccine uptake on inequalities in measles susceptibility in Scotland. Stat. Methods Med. Res. **25**, 1185–1200 (2016)
29. Philipson, T.: Private Vaccination and Public Health an empirical examination for U.S. Measles. J. Hum. Res. **31**, 611–630 (1996)
30. Thieme, H.: Uniform weak implies uniform strong persistence for non-autonomous semiflows. Proc. Am. Math. Soc. **127**(8), 2395–2403 (1999)
31. Thieme, H.R.: Uniform persistence and permanence for non-autonomous semiflows in population biology. Math. Biosci. **166**(2), 173–201 (2000)
32. van Lier, A., van de Kassteele, J., de Hoogh, P., Drijfhout, I., de Melker, H.: Vaccine uptake determinants in The Netherlands. Eur. J. Public Health **24**, 304–309 (2013)
33. Wang, Z., Bauch, C.T., Bhattacharyya, S., d'Onofrio, A., Manfredi, P., Perc, M., Perra, N., Salathe, M., Zhao, D.: Statistical physics of vaccination. Phys. Rep. **664**, 1–113 (2016)

34. Wolfe, R.M., Sharp, L.K.: Anti-vaccinationists past and present. Br. Med. J. **325**, 430 (2002)
35. Zhao, X.Q.: Dynamical Systems in Population Biology. CMS Books in Mathematics, vol. 16. Springer, New York (2003)