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# Vaccine demand driven by vaccine side effects: dynamic implications for SIR diseases.

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## Abstract

For infections for which the perceived risk of serious disease is steadily low, the *perceived risk of suffering some vaccine side effects* might become the driving force of the vaccine demand. We investigate the dynamics of SIR infections in homogeneously mixing populations where the vaccine uptake is a decreasing function of the current (or past) incidence, or prevalence, of vaccine side effects. We define an appropriate model where vaccine side-effects are modelled as functions of the age since vaccination.

It happens that the vaccine uptake follows its own dynamics independent of epidemiological variables. We show the conditions under which the vaccine uptake lands on a globally stable equilibrium, or steadily oscillates, and the implications of such behaviour for the dynamics of epidemiological variables. We finally report some unexpected scenarios caused by trends in vaccine side effects.

**Keywords:** Vaccine, side effects, rational exemption to vaccination, information, delay, stability, oscillations.

## 1 Introduction

The high degree of herd immunity allowed by sustained vaccination policies in many countries have gradually forced the perceived risk of infection from a wide spectrum of diseases to decline to negligible levels. The obvious drawback of this situation is that, despite the high degree of safety of current vaccines, the existence of any, however small, risks of vaccine side-effects (VSE) [32], necessarily yields, given the very large numbers of vaccines administered annually, a steady flow of VSE. According to the WHO definition VSE are a subset of the larger family of adverse events following immunisation: “Adverse events following immunization are defined as medical incidents that take place after an im-

munization, cause concern and are believed to be caused by immunization. Immunization can cause adverse events from the inherent properties of the vaccine (vaccine reaction), or some error in the immunization process (programme error). The event may also be totally unrelated to the immunization and only have a temporal association.” [34] For instance in the US approximately 30,000 reports of Vaccine Adverse Event Reporting System (VAERS) are notified each year, with 10–15% classified as serious, i.e. causing disability, hospitalization, life-threatening illness or death [7].

In such circumstances it is natural to expect that the perceived risk of experiencing a VSE will outweigh the perceived risk from infection [3, 4, 11]. A commonly brought example is Poliomyelitis

([33] and references therein). In western countries, thanks to intensive vaccination, Polio was brought under control already in the sixties and essentially eliminated, with the disappearance of wild polio cases, since 1995. As the probability of vaccine associated Poliomyelitis has remained essentially unchanged, mass vaccination programmes had nonetheless to face steady flows of serious VSE. For instance in Italy during 1979-1999 an average of one vaccine-induced Poliomyelitis cases per year was reported [19], three times more than natural Poliomyelitis cases observed in the same period. This would unavoidably suggest to the public, which is unaware of the complex issues of disease control, a much higher perceived risk of getting “vaccine induced Polio” compared to wild polio. In regimes of voluntary vaccination such situations might favour forms of vaccination free riding [28],[23]. Vaccination free riding results in the family’s decision not to vaccinate children after a seemingly rational comparison between the perceived risk of infection and the perceived risk of VSE. Vaccination free riding can take profit of the high degree of herd immunity existing in communities with high vaccine uptake [2, 3, 4, 11]. In our previous work [11, 12] we have described vaccination free-riding as “rational exemption”, in order to distinguish it from other forms of exemption observed in the history of vaccination, e.g. conscientious, religious, or philosophical [24].

An increasing number of papers is being devoted to the study of the implications of rational exemption for the dynamics and control of vaccine preventable diseases. Some of these works model vaccine uptake using explicit economic arguments [4, 23, 21] while other use more mathematically manageable phenomenological representations [11, 12]. As a rule all models based on homogeneous mixing, indicate that rational exemption might make eradication impossible. Exceptions to this rule seem to require more complex contact-network structures [21].

All previous studies have focused on the case where the driving force of the vaccine demand is represented by the time changes in the perceived risk of infection, measured for example through the current (or past) disease incidence. Also, in such studies the perceived risk of VSE does not play a role, or is just taken as constant ([4]).

In this paper we aim to investigate the opposite situation where the driving force of the vaccine demand is given by the time changes in the perceived risk of suffering a vaccine side effect. We feel this case is fundamentally more appropriate in the developed world than the alternative hypothesis that demand is driven by the disease incidence, especially for those common vaccine preventable infections which currently have very low or even zero incidence.

To this aim we study the dynamics of vaccine uptake for a homogeneously mixing vaccine preventable SIR disease [6] with vital dynamics and vaccination by a perfect vaccine under the following circumstances: a) vaccination is voluntary; b) the vaccine has a constant probability to generate severe, non-lethal, side effects; c) the perceived risk of suffering serious disease following infection is steadily low, so that the vaccine demand is essentially related, through a decreasing function, to the perceived risk  $M$  of suffering a vaccine associated side effect; d) the perceived risk  $M$  is evaluated from publicly available information on current, past, or even future (through expectations) trends of side effects caused, or attributed, to the vaccine. In particular, in order to evaluate the risk of VSE, parents are assumed to use the public information on the current, or past, reported incidence of VSE, or the prevalence of those who suffered side effects. For the sake of simplicity we avoid here the complexities related to VSE misreporting, and assume that the figures on VSE which are available to the public are those predicted by the model.

In order to properly incorporate the temporal association between vaccination and onset of VSE [34], we assume that the risk of occurrence of VSE is essentially related to the time elapsed since the moment of vaccination (i.e. the *age since vaccination*). This allows us to represent the vaccination dynamics by, respectively, an integro-differential equation for the prevalence of individuals who suffered side effects, and an integral equation for the corresponding incidence. These equations decouple from the other dynamic variables (i.e. susceptible and infective), with the noteworthy implication that the dynamics of VSE become the key determinant of the disease dynamics, through the influence that the time trajectories of the incidence, or prevalence, of VSE have on the actual vaccine uptake. Our key equations are then investigated both in general, and under specific assumption on the age risk of suffering a VSE. These investigations are carried out both for the case of current information and delayed information.

Our main results show that both modelling strategies lead to the existence of a unique epidemiologically meaningful steady state for the prevalence of VSE, and therefore to a unique equilibrium for the vaccine uptake. This steady state is proven to be globally stable (GAS) provided that the reaction of vaccine uptake to changing perceived risks of VSE a) is not too violent, and b) VSE occur without significant time-delays from the moment of vaccination. These general results hold for both the cases of current as well as lagged information, though in the latter case we need the further requirement that the average information delay is not too large. If requirements a) and b) are weakened sustained oscillations might arise. This result is not necessary but it depends on the specific patterns of onset of VSE. For example, under current information global stability always holds when the age-risk of VSE is constant, or when it is highly concentrated on the moment of vaccine administration. On the other hand, VSE arising with a fixed delay can yield sustained oscillations through Hopf bifurcations of the steady state. If finally, lagged instead of current information is used, the onset of oscillations is made easier. Similar results hold when vaccine uptake is a function of the incidence of VSE, although in this case oscillations are less common than under prevalence.

These dynamics of vaccine uptake act as an external forcing terms on the epidemiological variables (susceptible and infective). We supply some asymptotic results on the dynamics of epidemiological variables for the cases where the vaccine uptake is asymptotically constant, or it oscillates. Moreover in the final section we report the following noteworthy scenarios, illustrating the dynamic richness triggered by VSE: i) introduction of a new vaccine with transient (local) elimination of the disease but eventual long-term resurgence; ii) worsening of control conditions; iii) switches between control epochs; iv) steady (long-term) disease oscillations of the disease forced by steady oscillations in vaccine uptake. For example scenario i) occurs after the introduction of a new vaccine which allows a transient (local) elimination of the disease but can not prevent its long-term resurgence as a consequence of the susceptible build-up caused by the decline in vaccine uptake due to the gradual accumulation of VSE (which increase the perceived risk of VSE). Scenario ii) might naturally arises for diseases which are difficult to eliminate, as measles, for which the vaccine scare gradually increases due to the long time scales needed for elimination, which allow VSE to cumulate. Scenarios like i) and ii) had been predicted by the medical literature [8]. On the other hand scenario iii) is an yet unobserved phenomenon which could arise when long-period VSE-driven oscillations in vaccine uptake yield to epochs characterised by sharply different degrees of disease control. To the best of our knowledge no one attempted to obtain such scenarios as the output of a model with VSE-driven vaccination choice. The paper is organised as follows. In section 2 we introduce the mathematical model in its full generality, and derive the key equations for the prevalence and incidence of VSE. In section 3,4 we investigate the cases where the perceived risk of VSE is evaluated by, respectively, the prevalence and the incidence, of VSE. In section 5 we investigate how the dynamics of VSE affect epidemiological variables. Numerical simulations are reported in section 6. Concluding remarks follow.

## 2 Modelling the impact of information on vaccine side effects on vaccine uptake

Following ideas developed in d'Onofrio et al. [11, 13] we consider the following family of SIR models for a non-fatal disease in a constant homogeneously mixing population, with state-dependent vaccination coverage:

$$\begin{aligned} S'(t) &= \mu(1 - p(M(t))) - \mu S(t) - \beta(t)S(t)I(t) \\ I'(t) &= \beta(t)SI - (\mu + \nu)I \end{aligned} \quad (1)$$

$$\begin{aligned} R'(t) &= \nu I - \mu R \\ V_{tot}(t) &= 1 - S(t) - I(t) - R(t) \end{aligned} \quad (2)$$

where  $S$ ,  $I$ ,  $V_{tot}$  and  $R$ , denote the fractions of susceptible, infective, vaccinated and recovered individuals at time  $t$ ,  $\mu > 0$  represents the birth and death rate, which are assumed identical thereby ensuring the constancy of the population,  $\nu > 0$  the rate of recovery from infection,  $\beta(t) > 0$  the

transmission rate, which is assumed to be constant or bounded and periodically varying with minimal period  $\theta$  usually equal to one year [1],  $p$  the coverage for vaccination at birth. The vaccine is assumed to be 100% effective and providing lifelong immunity. As motivated in the introduction, the vaccination coverage  $p(M)$  is taken to be a positive decreasing function of the perceived risk  $M$  of suffering vaccine side effects:

$$p(M) \geq 0 \quad ; \quad p'(M) < 0$$

where the perceived risk  $M$  is assumed to be measured by individuals using publicly available information on either the current (or past) incidence of VSE, or the prevalence of individuals who suffered VSE. As clear from our assumptions the key dynamic variable becomes the vaccine uptake  $p$ . Therefore we will postpone further analysis of (1) to section 5, because our primary task will be the derivation of a dynamic equation for  $p$ . To this end we need appropriate dynamic equations for the incidence and prevalence of VSE. We distinguish between the cases of current and past information. Let us note first that the dynamics of current prevalence  $C(t)$  of VSE (for which it holds  $C(t) < V_{tot}(t)$ ) is determined by the balance between the outflow due to natural mortality (under the assumption that having experienced a VSE does not affect mortality) and the inflow  $H$  represented by the incidence of newly occurred VSE:

$$C'(t) = H(t) - \mu C, \quad (3)$$

In general if parents make their vaccination choices by using the current information only, we will have either  $M = F(C)$ , or  $M = F(H)$  where  $F$  is a continuous increasing function, owing to the intuition that the higher the numbers of publicly reported VSE the higher the risk perceived by the public. Here we assume, for the sake of simplicity, that  $F$  is the identity map, i.e. we take either  $M = C$ , or  $M = H$ .

To complete the specification of our model we need appropriate definitions for the time prevalence  $C$ , or the incidence  $H$ , of VSE. Consistently with the previous WHO definition, we assume that the actual risk to incur a VSE is a function of the time elapsed since vaccination. Our main modelling ingredient is therefore an appropriate modification of the age-since-vaccination density  $W(t, \tau)$ , introduced for other purposes by [17], and giving, at any time  $t$ , the distribution of vaccinated individuals who did not yet suffer VSE, according to the time  $\tau$  elapsed since vaccination. Letting  $\psi(\tau)$  to define the rate of occurrence of VSE for individuals having age of vaccination  $\tau$ ,  $W(t, \tau)$  obeys the balance PDE [17]:

$$\begin{aligned} \frac{\partial W}{\partial t} + \frac{\partial W}{\partial \tau} &= -\psi(\tau)W - \mu W \\ W(0, \tau) &= W_o(\tau) \\ W(t, 0) &= \mu p(M(t)) \end{aligned} \quad (4)$$

The PDE (4) states that vaccinated individuals of any age who did not yet suffer VSE, can be removed by the onset of a VSE, at the rate  $\psi(\tau)$ , or by mortality. The boundary condition  $W(t, 0) = \mu p(M(t))$  represents the per-capita incidence of new vaccinations per unit of time.

Based on the above equation for  $W(t, \tau)$ , the fraction of vaccinated subjects at time  $t$  that did not suffer VSE is defined as:

$$V(t) = \int_0^{+\infty} W(t, \tau) d\tau. \quad (5)$$

whereas the relative incidence of VSE is given by:

$$H(t) = \int_0^{+\infty} \psi(\tau) W(t, \tau) d\tau, \quad (6)$$

After solving eq. (4) with standard methods (see the appendix), one has the following convolution relation for the incidence of VSE:

$$H(t) = f(t) + \mu \int_0^t p(M(t - \tau)) \psi(\tau) K_o(\tau) d\tau \quad (7)$$

By substituting into (3) we obtain the following relation for the prevalence of VSE:

$$C' = -\mu C + f(t) + \mu \int_0^t p(M(t-\tau)) \psi(\tau) K_0(\tau) d\tau \quad (8)$$

where the function  $f(t)$  depends on the initial age distribution of  $W$  and, for large  $t$ , tends to zero:  $f(t) \rightarrow 0$ ; moreover

$$K_0(\tau) = \exp\left(-\mu\tau - \int_0^\tau \psi(x) dx\right). \quad (9)$$

A detailed interpretation of the previous relations is postponed to next section. Note that both the equations governing the dynamics of  $C$  and  $H$  are independent of the epidemiological variables  $S, I$ , so one can first study the dynamics of  $C$  or  $H$ , and afterwards their influence on  $S$  and  $I$ . Note also that, both the model based on the incidence and that based on the prevalence become asymptotically autonomous since  $f(t) \rightarrow 0^+$ .

If instead parents also use past information  $M$  will be given by some convolution of the VSE history with some appropriate kernels  $L(\cdot)$ , e.g.

$$M(t) = \int_{-\infty}^t A(u) L(t-u) du, \quad (10)$$

where either  $A(t) = C(t)$  or  $A(t) = H(t)$ . The delaying kernel summarises how past information on VSE concur in determining the current perceived risk of suffering a vaccine side effect. In this paper we will only consider the most common delaying kernel, represented by the exponentially fading memory:  $L(x) = ae^{-ax}$  ( $x > 0, a > 0$ ), where the decay rate  $a$  is the reciprocal of the mean information delay  $D$ :  $a = 1/D$ . This kernel allows reduction of (10) to the ODE:

$$M' = a(F(A(t)) - M) \quad (11)$$

### 3 Dynamics of vaccine uptake when the perceived risk is evaluated by the prevalence of individuals who suffered VSE

If  $M = C$ , i.e. the perceived risk of VSE is evaluated by the current prevalence  $C$  of those who incurred VSE, the relation (3) takes the form of the following non-autonomous integro-differential equation:

$$C'(t) = -\mu C + f(t) + \mu \int_0^t p(C(t-\tau)) \psi(\tau) K_0(\tau) d\tau, \quad (12)$$

which is a nonlinear delay-differential equation with distributed delay [18] of the convolution form:

$$C'(t) = -\mu C + f(t) + \mu \text{Conv}(p(C(t)), K_D(t)) \quad (13)$$

with delaying kernel  $K_D(\tau) = \psi(\tau) K_0(\tau)$ . Having established the law governing the dynamics of  $C(t)$  one straightforwardly obtains the dynamics of vaccine uptake  $p(t)$  considered as a state variable:

$$p'(t) = \frac{1}{\pi_C(p)} (-\mu \pi_C(p) + f(t) + \mu \text{Conv}(p(t), K_D(t))), \quad (14)$$

where  $\pi_C(p)$  is the inverse of  $p(C)$ , and  $\pi_C'(p) < 0$ . The equation (14) has an intuitive interpretation: if the vaccine uptake  $p$  is a function of the prevalence of individuals who suffered some VSE in the past, then the dynamics of  $p$  depends uniquely on its current and past history, since past vaccinations are the only source of the current burden of people who experienced some VSE. A substantive consequence is then that under our hypotheses the burden of VSE becomes the unique determinant of vaccine uptake, and through this, the key determinant of infection dynamics. Note finally that the delaying kernel  $K_D$  depends on both the delay of onset of VSE after vaccine administration, and

the delay related to the subsequent individual survival, since we assume that VSE do never cause mortality.

However, although the interpretation of (14) is clear, the factor  $1/\pi'_C(p)$  makes a more detailed biological and biomathematical analysis less immediate respect to eq. (12). Therefore our mathematical analysis will focus first on the solutions of (12); once these will be known also the dynamics of vaccine uptake will be known through the relation  $p = p(C)$ .

The individual mechanisms governing the onset of vaccine associated side effects and, as a consequence, the shape of the risk function  $\psi(\tau)$  are still poorly understood. Moreover such phenomena are likely to be vaccine-specific, i.e. different vaccines could have different risk functions  $\psi(\tau)$ . The problem is further complicated under the multi-vaccine schedules adopted in many countries. Therefore we will first study (12) in the general case where the form of  $\psi(\tau)$  is left unspecified, in order to find general patterns for the endemic equilibria and their stability. Then in the next section we will consider the effects of some noteworthy forms of  $\psi(\tau)$ .

As for the mathematical analysis let us introduce the following useful quantity:

$$B_\psi(\mu) = \int_0^{+\infty} \psi(\tau) K_o(\tau) d\tau = \int_0^{+\infty} \exp(-\mu\tau) \exp\left(-\int_0^\tau \psi(z) dz\right) \psi(\tau) d\tau, \quad (15)$$

which represents the moment generating function with parameter  $(-\mu)$  (or the Laplace Transform calculated at the real  $\lambda = \mu$ ) of the age-density density of onset of VSE:

$$h(\tau) = \exp\left(-\int_0^\tau \psi(z) dz\right) \psi(\tau)$$

where  $\Psi(\tau) = \exp\left(-\int_0^\tau \psi(z) dz\right)$  is the corresponding survival function. Note that  $h(\tau)$  is a defective density since the cumulative lifetime probability  $1 - \Psi(\infty)$  to suffer some VSE is in most cases a small number. The function  $B_\psi(\mu)$  is a positive decreasing function such that  $B_\psi(0) = 1$ .

We start by observing that (12) always has a unique epidemiologically meaningful steady state, which fulfills:

$$C_\infty = B_\psi(\mu) p(C_\infty), \quad (16)$$

Note that  $C_\infty$  depends of  $\psi(\cdot)$ . Moreover  $C_\infty < \tilde{C}$  where  $\tilde{C}$  fulfills:  $\tilde{C} = p(\tilde{C})$ .

The local stability properties of  $C_\infty$  are determined by linearising at  $C_\infty$  and Laplace-transforming, which yields:

$$\lambda + \mu = \mu p'(C_\infty) B_\psi(\mu + \lambda), \quad (17)$$

The actual solutions of (17) depend on the actual form of  $\psi(\cdot)$  and we will deepen this issue in next section. However, the analysis of the general case yields the following simple and easily interpretable stability condition: if the absolute value of the derivative of  $p(C)$  at the equilibrium point  $C_\infty$  is not too large then the equilibrium is locally and globally stable:

**Proposition 3.1** *If the following constraint*

$$|p'(C_\infty)| B_\psi(\mu) < 1 \quad (18)$$

*holds then the equilibrium point  $C_\infty$  is locally and globally asymptotically stable.*

Therefore  $C_\infty$  is globally stable as far as the demand for vaccines  $p(C)$  is not too reactive to conditions of changing perceived risks of suffering VSE. More precisely, as far as  $p(C)$  is not too reactive to changing perceived risks of VSE the equilibrium is stable independently of the age mechanism through which VSE arise after vaccination. This agrees with our findings on different models of vaccinating behaviour [11, 12, 13].

However, as argued in previous work on prevalence-related vaccine uptake [23, 11, 13], we expect that in realistic circumstances the index  $M$  will embed not only the current but also some information on the past history of VSE. This case was important because, as shown in [23, 11, 13], the inclusion of delayed information was necessary to generate oscillations in simple SIR models with prevalence-related vaccination behaviour.



Thus, by treating  $M$  as a further state variable and by using (11) with  $A(t) = C(t)$ , we have that under an exponentially fading memory the single integro-differential equation (12) is replaced by the system:

$$C'(t) = -\mu C + f(t) + \mu \int_0^t p(M(t-\tau)) \psi(\tau) K_o(\tau) d\tau \quad (19)$$

$$M'(t) = a(C - M) \quad (20)$$

It is easy to check that (19)-(20) has the equilibrium point  $E_{CM} = (C_e, M_e) = (C_\infty, C_\infty)$ , where  $C_\infty$  is the solution of (16). The characteristic equation becomes:

$$\left(1 + \frac{\lambda}{a}\right) (\lambda + \mu) = \mu |p'(C_\infty)| B_\psi(\mu + \lambda) \quad (21)$$

One may show (see the appendix) that also in the present case with delayed information the condition (18) guarantees the global stability of the endemic equilibrium. The same interpretation therefore holds.

## 4 Impact of the side-effects rate $\psi(\tau)$ on vaccine uptake

We now investigate how specific noteworthy forms of the risk of side effects  $\psi(\tau)$  affect the dynamics of vaccine uptake  $p$  through a more detailed stability analysis of the equilibrium  $C_\infty$ . We focus on the onset of stable oscillations, either in absence or in presence of information delay, as represented by an exponentially fading memory. Letting  $\delta$  to denote Dirac's delta function, we shall consider the following (somewhat complementary) forms of  $\psi(\tau)$ :

- $\psi(\tau) = \bar{\psi}\delta(\tau)$ : "instantaneous" side effects, essentially occurring at the moment of vaccination;
- $\psi(\tau) = \bar{\psi} \quad \forall \tau > 0$ : the occurrence rate of VSE is independent of the age since vaccination;
- $\psi(\tau) = \bar{\psi}\delta(\tau - T)$ : VSE occur with a fixed delay  $T > 0$  after vaccination.

The following analysis will enable us to identify simple but biologically meaningful circumstances where (a) oscillations never occur, i.e. the equilibrium is stable independently of the form of the VSE generating mechanism and of the presence of information delays, (b) oscillations can only be triggered by information delay, c) oscillations arise as an endogenous property of the VSE generating mechanism, even in absence of information delays.

### 4.1 Instantaneous side effects

In this case, if  $M$  depends on current prevalence, equation (12) becomes:

$$C' = -\mu C + \mu \bar{\psi} \exp(-\bar{\psi}) p(C) \quad (22)$$

(with  $B_\psi(\mu) = \bar{\psi} \exp(-\bar{\psi})$ ), since the incidence  $H$  of VSE is proportional to the current vaccine uptake through the factor  $\bar{\psi} \exp(-\bar{\psi})$ , which represents the instantaneous probability of VSE per vaccination episode. It is immediate to see that the equilibrium  $C_\infty$  is globally attractive independently of the size of  $p'(C_\infty)$ .

If instead  $M$  depends on past prevalence, the system (19)-(20) becomes:

$$C'(t) = -\mu C + f(t) + \mu \bar{\psi} \exp(-\bar{\psi}) p(M) \quad (23)$$

$$M'(t) = a(C - M) \quad (24)$$

whose equilibrium  $(C_\infty, C_\infty)$  is, again, GAS independently of  $|p'(C_\infty)|$ . Therefore both for undelayed and delayed information the vaccine uptake  $p(t)$  will be characterized by the convergence to a steady state:  $p(C_\infty)$ .

## 4.2 Constant rate of appearance of side effects

If  $\psi(\tau)$  is constant and  $M$  depends on current prevalence, by recalling (6) and (5), we have  $H = \psi V$ . Moreover by integrating w.r.t.  $\tau$  eq. (4) over  $(0, \infty)$  we get the 2-dimensional ODE system:

$$\begin{aligned} V'(t) &= \mu p(C) - (\mu + \psi)V \\ C'(t) &= \psi V - \mu C \end{aligned} \quad (25)$$

for which  $B_\psi(\mu) = \psi/(\mu + \psi)$ . System (25) has a unique equilibrium point  $E_{VC} = (V_\infty, C_\infty)$  where  $V_\infty = (\mu/\psi)C_\infty$  and which is GAS independently of  $p'(C_\infty) = p'(C_\infty)$  (see appendix). Therefore, also in this case the vaccine uptake will approach the constant value  $p(C_\infty)$ .

Note that, in case of current information, the two somewhat opposite cases, i.e. instantaneous versus constant rate onset of VSE, show a similar global behaviour for the vaccine uptake. On the other hand in case of delayed information the pattern is different because, as we now demonstrate, oscillations, which were excluded for instantaneous VSE, can occur in the constant rate case. In this case one obtains from (19)-(20) the 3-dimensional system:

$$\begin{aligned} V'(t) &= \mu p(M) - (\mu + \psi)V \\ C'(t) &= \psi V - \mu C, \\ M'(t) &= a(C - M) \end{aligned} \quad (26)$$

having the unique equilibrium:

$$EQ_{VCM} = (V_\infty, C_\infty, M_\infty) = \left( \frac{\mu}{\mu + \psi} p(C_\infty), C_\infty, C_\infty \right).$$

By taking  $a$  as bifurcation parameter and linearizing at  $EQ_{VCM}$  one easily obtains (see the appendix) that if the following condition is fulfilled:

$$\mu\psi|p'(C_\infty)| < (2\mu + \psi)^2 + 2(2\mu + \psi)\sqrt{\mu(\mu + \psi)} \quad (27)$$

then there is an interval  $(a_1, a_2)$ , with  $a_1 > 0$ , such that if either  $a < a_1$  or  $a > a_2$  the equilibrium is locally stable, whereas if  $a \in (a_1, a_2)$ , the equilibrium is unstable. Both  $a = a_1$  and  $a = a_2$  are Hopf bifurcations points. Moreover for  $a \in (a_1, a_2)$  the orbits are Yakubovitch oscillatory [29, 30, 31], i.e., i.e. there exists two real numbers  $\pi^-$  and  $\pi^+ > \pi^-$  such that:

$$\liminf_{t \rightarrow +\infty} C(t) = \pi^-$$

and

$$\limsup_{t \rightarrow +\infty} C(t) = \pi^+.$$

To sum up, in the case of VSE arising at constant rate, the inclusion of the information delay can yield sustained oscillations in the vaccine uptake  $p(t)$ , whereas global attractiveness of the equilibrium  $p_\infty$  was prevailing when only current information was considered. This confirms the destabilising role played by the information delay. It is interesting to note from (27) that, consistently with the findings in [11, 12, 13], the onset of oscillations also requires, besides the above described delay pattern, a high sensitiveness of the vaccine uptake to changing perceived risk at equilibrium. If this occurs then there is a whole window  $(D_2 = 1/a_2, D_1 = 1/a_1)$  of values of the average information delay  $D = 1/a$ , yielding steady oscillations.

The onset of Yakubovitch oscillations [29, 30, 31] is important since, **stricto sensu**, the Hopf bifurcation theorem only gives informations on the behaviour of a system for values of the bifurcation parameter that are close to the Hopf bifurcation threshold, and of course near the equilibrium point. On the contrary, Yakubovitch oscillations are a global property. Moreover, although their mathematical nature is not defined (they might be periodic, quasi-periodic or also chaotic), this uncertain mathematical classification is less important from the epidemiological point of view.

### 4.3 Side effects appearing with a constant delay

If VSE appear with a fixed delay after vaccination:  $\psi(\tau) = \bar{\psi}\delta(\tau - T)$ , we get the following delay-differential equation:

$$C'(t) = \begin{cases} -\mu C + f(t) & \text{if } 0 < t < T \\ -\mu C + f(t) + \mu\bar{\psi} \exp(-\mu T - \bar{\psi}) p(C(t - T)) & \text{if } t \geq T \end{cases} \quad (28)$$

Here  $B_\psi(\mu) = \bar{\psi} \exp(-\mu T - \bar{\psi})$ , and the level of the unique steady state  $C_\infty$  is a decreasing function of  $T$ :

$$\frac{d}{dT}C_\infty(T) = \frac{-\mu P(C_\infty)\mu\bar{\psi} \exp(-\mu T - \bar{\psi})}{1 - P'(C_\infty)\mu\bar{\psi} \exp(-\mu T - \bar{\psi})} < 0$$

The interesting new is that oscillations are possible even in the case of current information. In particular  $T$  is a natural candidate as a bifurcation parameter.

The following result holds:

**Proposition 4.1** *If  $G(T) < 1$  then EQ is GAS. If  $G(T) > 1$ , let us denote as  $T_0, T_1, \dots$  the solution of the equation:*

$$\left(\mu\sqrt{G(T)^2 - 1}\right) T = \arccos\left(-\frac{1}{G(T)}\right) + 2k\pi, \quad k = 0, 1, \dots \quad (29)$$

If

$$\mu G'(T_0) \left(\mu T_0 G(T_0) + \frac{1}{G(T_0)}\right) + \omega^2(T_0) > 0 \quad (30)$$

then EQ is LAS for  $T < T_0$ , it is unstable for  $T > T_0$  and at  $T = T_0$  there is a Hopf bifurcation. Moreover, in the interval of instability the solutions are oscillatory in the sense of Yakubovitch

The epidemiological interpretation of the above result is that if VSE arise with a fixed time delay after vaccination, then the steady state  $C_\infty$  is stable for small delays, whatever be the extent of the reaction by the public, in terms of vaccine uptake, to changing perceived risks of VSE. However for highly reactive  $p(C)$  functions  $C_\infty$  may be destabilised in presence of longer delays, yielding sustained oscillations of vaccine uptake *without the need for information delays*. The intuition underlying this result, compared to the previous ones, is that there is a genuine positive delay due to the age-since-vaccination structure (and not to the information delay which is absent), confirming once more the typically destabilising role of time lags. It is also of interest to compare this case with the one of VSE arising at constant rate: when VSE arise at constant rate, and therefore with an exponential delay, oscillations can not occur. Oscillations insted occur when a fixed delay is considered.

As for Yakubovitch oscillations, at the best of our knowledge Yakubovitch-type theorems have only been demonstrated for ODE and DDE with constant lag. In the previous section we gave an example of application to a system endowed of a simple delay kernel allowing reduction to finite dimensional system. However, we conjecture that they might be also applied to a general model with distributed delays with a unique equilibrium and bounded orbits, as in our general case.

In case of delayed information the model reads:

$$C'(t) = \begin{cases} -\mu C + f(t) & \text{if } 0 < t < T \\ -\mu C + f(t) + \mu\bar{\psi} \exp(-\mu T - \bar{\psi}) p(M(t - T)) & \text{if } t \geq T \end{cases} \quad (31)$$

$$M' = a(C - M) \quad (32)$$

Assuming  $a$  as a bifurcation parameter, and that in absence of information delay the lag in the occurrence of side effects,  $T$ , is such that to guarantee the local stability of the equilibrium and proceeding as in section one may show that (see the appendix) that for  $G(T) > 1$ :

- If  $a > a_1$  then EQ is LAS;

- If  $a < a_1$   $EQ$  is unstable, and afterwards there is another series of stability switches, and at  $a_1$  there is a Hopf bifurcation;
- Moreover, from the boundedness of the solutions of system (31)-(32) it follows that in the instability interval the system undergoes Yakubovitch oscillations.

## 5 Dynamics of vaccine uptake when the perceived risk is evaluated by the incidence of VSE

The case where the perceived risk of VSE is measured through the (current or past) incidence of VSE will be studied here quite concisely, since there are many similarities with the results of the previous sections.

If the current incidence is used, then we get the following nonlinear integral equation in the incidence:

$$H(t) = f(t) + \mu \int_0^t p(H(t-\tau)) \psi(\tau) K_o(\tau) d\tau, \quad (33)$$

The interpretation of (34) is that the incidence of VSE at any time  $t$  is the sum of two components: the component due to VSE occurred in individuals vaccinated after time zero according to the schedule  $p$ , and the component  $f(t)$  due to VSE arisen in individuals who already get vaccinated at  $t = 0$ . As we did in the prevalence case we can derive an equivalent nonlinear integral equation for vaccine uptake taken as the state variable of the form:

$$\chi(p(t)) = f(t) + \mu \int_0^t p(t-\tau) \psi(\tau) K_o(\tau) d\tau, \quad (34)$$

Again, however, the analysis of (34) seems to us less straightforward than (33) on which we will focus in subsequent analyses. Similarly to the prevalence case it happens that there is a unique positive equilibrium  $H_\infty = \mu p(H_\infty) B(\mu; \psi(\cdot))$  i.e. in terms of vaccine uptake:

$$\chi(p_\infty) = \mu p_\infty B(\mu; \psi(\cdot)) \quad (35)$$

and it holds that the condition:

$$\mu |p'(H_\infty)| B(\mu; \psi(\cdot)) < 1 \quad (36)$$

guarantees the local and global stability of the equilibrium.

When the past incidence of VSE is considered, we obtain, under the assumption of exponentially fading memory, the system

$$H(t) = f(t) + \mu \int_0^t p(M(t-\tau)) \psi(\tau) K_o(\tau) d\tau \quad (37)$$

$$M'(t) = a(H - M) \quad (38)$$

Again a unique equilibrium  $(H_e, M_e) = (H_\infty, H_\infty)$  exists. Moreover, also here condition (36) implies the global stability of the equilibrium.

As it is easy to verify, the incidence  $H(t)$ , both in the current information case (33) and in the delayed information case (37)-(38), globally tends to the steady state  $H_\infty$ , for both instantaneous and constant rate side effects, independently on the steepness of  $p$  at equilibrium. Therefore in all such cases the vaccine uptake globally converges to the steady state  $p(H_\infty)$ .

In particular, the result concerning the case of constant rate under delayed information is of interest as it remarkably differs from the corresponding case where the perceived risk is evaluated from the delayed prevalence of side effects. In the present  $H$ -case oscillations can not arise, whereas they were possible under sufficiently long patterns of delay in the  $C$ -case. The explanation is that the two types of information are by no means equivalent in that in the  $C$ -case a twofold delaying mechanism is included, i.e. the information delay in the prevalence of VSE, and the past history of incidence

included in the definition of the prevalence of VSE.

In case of VSE occurring with a fixed delay (i.e.  $\psi(\tau) = \bar{\psi}\delta(\tau - T)$ ) and the information is undelayed then it holds

$$H(t) = \begin{cases} f(t), & \text{if } 0 < t < T; \\ f(t) + \mu\bar{\psi}\exp(-\bar{\psi} - \mu T)p(H(t - T)), & \text{if } t > T; \end{cases} \quad (39)$$

The stability analysis of the unique equilibrium  $H_\infty$  yields (see the appendix) that if a condition  $G(T) < 1$  holds then the equilibrium of (39) is GAS, while if  $G(T) > 1$  the equilibrium is unstable. For example, in case of linearly decreasing  $p(M) = p_o - \Theta M$  it holds:  $G(T) = \mu\Theta\bar{\psi}\exp(-\bar{\psi} - \mu T)$  so that if  $G(0) < 1$  the equilibrium is GAS for all  $T > 0$ ; otherwise the zone of GAS is given by

$$T > T^* = \frac{1}{\mu} \log(\mu\Theta\bar{\psi}\exp(-\bar{\psi}))$$

In case of delayed information with mean delay  $D = 1/a$  the dynamics of  $H$  is governed, for  $t > T$ , by the scalar delay differential equation:

$$M' = a(f(t) + \mu\bar{\psi}\exp(-\bar{\psi} - \mu T)p(M(t - T)) - M) \quad (40)$$

Again, if  $G(T) < 1$  then the equilibrium is GAS. On the other hand, if  $G(T) > 1$ , we have that *i)* for pairs  $(T, a)$  lying below the curve  $\gamma_0(T, a) = 0$ , where  $\gamma_0(T, a)$  is defined as follows:

$$\gamma_0(T, a) = -aT\sqrt{G^2(T) - 1} + \pi - Atn\sqrt{G^2(T) - 1} \quad (41)$$

then the equilibrium is LAS; *ii)* pairs  $(T, a)$  lying on the locus  $\gamma_0(T, a) = 0$  are Hopf bifurcation points; *iii)* for pairs  $(T, a)$  lying above the curve  $\gamma_0(T, a) = 0$  the equilibrium is unstable and the solutions undergo Yakubovitch oscillations.

For example, if we consider a linear  $p(M)$  function, we may have two different scenarios: in the first the equilibrium is GAS for all  $T > 0$ , i.e. the stability region in the  $(T, a)$  parameter space is  $\mathbb{R}_+^2$ ; in the other scenario the equilibrium is always stable in the region  $(T^*, +\infty) \cdot \mathbb{R}_+$ , while for  $T \in (0, T^*)$  stability occurs for

$$a < q(T) := \frac{\pi - Atn\sqrt{G^2(T) - 1}}{T\sqrt{G^2(T) - 1}},$$

where  $q(T)$  has two vertical asymptotes at  $T = 0$  and at  $T = T^*$ . Thus, in the region  $T \in (0, T^*)$  the information delay is a stabilising force for a system that, in absence of lag, is unstable. In figure (1) the bifurcation locus  $\gamma_0(T, a) = 0$  is shown for  $\mu = 0.02 \text{ years}^{-1}$ ,  $\bar{\psi} = 1$  and  $\Theta = 50000$ .

## 6 Dynamics of $(S, I)$

Here we analyse how the dynamics of the full epidemiological system (1) are affected by the behaviour of the vaccine coverage  $p(t)$ . As we have seen in the previous sections, for large times either  $p$  (globally or locally) tends to an equilibrium  $p_\infty$  or it undergoes Yakubovitch oscillations of, in principle, general nature.

In the case where the coverage stabilizes to  $p_\infty$ , the (1) becomes asymptotically autonomous and equivalent to a SIR model under constant vaccination at a rate  $p^* = p_\infty$ . Therefore if

$$p_\infty \geq p_c = 1 - \frac{1}{R_0}$$

where  $R_0 = \beta/(\mu + \nu)$  is the basic reproduction number (BRN), and  $p_c$  denotes the critical vaccine uptake, then the disease free equilibrium  $DfE = (1 - p_\infty, 0)$  is GAS, otherwise it is unstable and the unique endemic state  $EE = (\frac{1}{R_0}, \frac{\mu}{\mu + \nu} (1 - p_\infty - \frac{1}{R_0}))$  is GAS. In case of periodically varying contact rate the same formula holds provided that one use the average BRN:  $R_0^{av} = \langle \beta(t) \rangle / (\mu + \nu)$ . A scenario of special interest is when  $p(t)$  undergoes Yakubovitch oscillations, which we have shown

to occur under a variety of circumstances in the previous sections.

As a consequence, we are dealing with a nonlinear non-autonomous dynamical system with known small oscillating forcing term  $F(t) = \mu p(t)$ :

$$x' = Q(x; t) - F(t)e_1, \quad (42)$$

where  $x = (S, I)^{Tr}$ ,  $e_1 = (1, 0)^{Tr}$  and  $Q(x, t) = (\mu(1 - x_1) - \beta(t)x_1x_2, x_2(\beta(t)x_1 - (\mu + \nu)))^{Tr}$ . In principle, the solutions of (42) may undergo nonlinear resonances and chaos. Note that the force  $F(t)$  itself might be chaotic, so that it might also happen that  $x(t)$  could “filter” it.

Now, considering for example the case of constant  $\beta$ , such oscillations in vaccine uptake might for a while lie above the critical coverage  $p_c = 1 - 1/R_0$  (we expect this to occur when the perceived risk of vaccine associated side effects is low), but the opposite might occur during phases of vaccine scare. Thus it is important to consider the possibility of disease-free asymptotic behaviour in response to general oscillatory behaviour of the vaccine coverage  $p(t)$ . We term a disease-free solution (DFS) one for which:

$$DFS = (X_1^*(t), 0), \quad (43)$$

where  $X_1^*(t)$  is the solution of the following linear differential equation:

$$X_1' = \mu(1 - p(t) - X_1). \quad (44)$$

Observe that from

$$S' \leq \mu(1 - p_{MAX} - S),$$

where  $p_{MAX}$  is the maximum attained by  $p(t)$  in its in principle known oscillations, and using standard procedures one gets that if  $p_{MAX} > p_c$  then DFS is globally stable, which is biologically trivial since this case means that the vaccine coverage is constantly over the critical value  $p_c$ . Linearizing at DFS one gets  $i' = i(\beta X_1^*(t) - (\mu + \nu))$  and considering that it must be  $X_1' > \mu(1 - p_{min} - X_1)$  implying that, for large times,  $X_1^*(t) > 1 - p_{min}$ , one also gets that if  $p_{min} < p_c$  then DFS is unstable. Indeed this means that  $p(t)$  is constantly under the threshold  $p_c$ .

More in general, if  $p(t)$  is known by using appropriate averages one may find conditions for the global stability of the DFS.

The previous results suggests to what extent departures from the critical coverage might be allowed during epochs of high (oscillating) perceived risk of VSE without compromising the target of elimination. This sub-critical disease-free asymptotic behaviour is a phenomenon of special interest for situations where elimination has been achieved but the vaccine scare generates oscillations in vaccination coverage which will in its turn build up cohorts of less vaccinated individuals. Such oscillations could then create the conditions for epidemics of various sizes as a consequence of stochastic reintroduction of the infection through e.g. immigration. The size of these stochastically reintroduced epidemics would critically depend on the patterns of oscillations in the perceived risk.

## 7 Simulations

We report two numerical investigations dealing with two main sub-cases discussed in the paper, i.e. the case of VSE arising at constant rate, and the fixed-delay case. In both examples we focus on the case where the perceived risk of VSE is measured by the (current or delayed) prevalence of individuals with VSE. In the first simulation we present a sample of noteworthy transient and long-term scenarios showing how disease control is affected when the vaccine uptake is mainly affected by the perceived risk of VSE. As a rule we will see that the dependency of the vaccine demand on VSE weakens the conditions for control but with a rich variety of dynamic patterns. In the second simulation we give some simple insight on the mechanisms underlying the appearance of VSE-induced oscillations in vaccine uptake.

## 7.1 Simulation 1: side effects occurring at constant rate

We compare system (25), which does not include the information delay, with the corresponding delayed system (26). This case offers predictions which, though perhaps inaccurate in quantitative terms, since it assumes that everyone who is vaccinated is exposed to VSE with a risk which is independent of the age since vaccination, are nonetheless very rich in qualitative terms. Note that (26) collapses into (25) when we let the average information delay go to zero ( $a \rightarrow \infty$ ). Note further that the discriminant  $\Delta$  of the linearised system of (25) is given by  $\Delta = \psi(\psi + 4\mu p'(C_\infty))$  suggesting that solutions to (25) will be stable but oscillatory when, comparatively, the rate  $\psi$  of onset of VSE is small, and the absolute slope  $p'(C_\infty)$  of the vaccination response at equilibrium is large. The corresponding pseudo-period of the linearised oscillation will be given by  $4\pi/\sqrt{-\Delta}$ , and the dumping rate is proportional to  $(2\mu + \psi)$ . The following functional form was adopted for the  $p(M)$  function:

$$p(M) = p_0 + (1 - p_0 - \varepsilon) \cdot p_1(M)$$

where

$$p_1(M) = p_{\min} + \frac{(p_{\max} - p_{\min})}{1 + \exp(-\sigma(M - M^*))}$$

This formulation corresponds to the epidemiologically founded idea that the population is divided into three groups, say groups 1,2,3, having different vaccination lifestyles. The first group, having relative size  $p_0$ , always vaccinates independently of the perceived risk ( $M$ ) of VSE; the second one (having size  $\varepsilon$ ) never vaccinates independently of  $M$ ; finally group 3, having relative size  $(1 - p_0 - \varepsilon)$ , vaccinates accordingly to the perceived risk of VSE summarised by the function  $p_1(M)$ . The latter function is S-shaped and decreasing in  $M$ , taking the value  $p_{\max}$  for  $M = 0$  and approaching  $p_{\min}$  for large  $M$  (here we set for simplicity  $p_{\max} = 1, p_{\min} = 0$ ). The inflection point  $M^*$  represents the average “societal tolerance” of VSE, nearby which most change in vaccinating behaviour as a consequence of changing perceived risk of VSE, will occur. Finally  $\sigma$  can be taken as the speed of behaviour change in that increasing values of  $\sigma$  correspond to increasingly violent responses by the public to changing perceived risks of VSE. Overall, the shape of  $p(M)$  corresponds to the epidemiological intuition that as far as the perceived risk of VSE is small then  $p(M)$  is high (i.e. roughly equal to  $(1 - \varepsilon)$ ) because individuals of group 3 have no reason to change their propensity to vaccinate, while if  $M$  becomes large the propensity to vaccinate of group 3 will fall dramatically, even up to zero, thereby making the community vaccine uptake close to  $p_0$ . We note that though  $M$  is a bounded function, so that arbitrarily large values of  $M$  can not be considered, suitable choices of parameters  $(\sigma, M^*)$  allow to capture all possibly relevant vaccinating behaviour discussed here.

As regards the disease dynamics we consider the following benchmark parameter constellation mimicking measles in developed countries:  $\mu = (1/L)$ , where  $L = 75$  years (so  $\mu = 3.65 \times 10^{-5}$  days $^{-1}$ ) is the life expectancy of the population,  $v = 1/D$ , where  $D = 7$  days is the average duration of the infective period,  $R_0 = 15$ , implying an average daily transmission rate  $\beta = 2.143$  days $^{-1}$ , and a critical coverage  $p_{crit} = 1 - 1/R_0 = 0.93$ . Finally, as regards the rate  $\psi$  of onset of VSE we preferred, for illustrative purposes, to let it to vary in order to consider different scenarios, rather than to stick to the few, possibly biased, estimates available in the literature.

Fig. 2 shows the dependency of the equilibrium  $C_\infty$ , which is the unique solution of the equation  $p(C) = r_\psi(C)$ , where  $r_\psi(C) = \frac{\mu + \psi}{\psi}C$ , on: (a) the rate  $\psi$  of onset of VSE, (b) the shape of the  $p$  function, for three distinct values of  $\psi$ :  $\psi_{low}$ ,  $\psi_{medium}$ ,  $\psi_{high}$  ( $\psi_{low} = \mu/10$ ,  $\psi_{medium} = \mu/5$ ,  $\psi_{high} = \mu/2$ ). As the ratio  $\psi/(\psi + \mu)$  represent the lifetime probability to suffer a VSE, for example  $\psi_{low}$  would imply an (about) 9% lifetime probability of VSE. The  $p(C)$  function is drawn for  $p_0 = 0.8$ ,  $\varepsilon = 0.02$ ,  $M^* = 0.145$  and for two distinct values of  $\sigma$  ( $\sigma_{low} = 10$ ,  $\sigma_{high} = 100$ ). The critical coverage  $p_{crit}$  is also added for sake of completeness.

The whole asymptotic dynamics of the system (25) and of the related epidemiological variable is therefore easily predicted by Fig. 2. Consider for example the case  $\sigma = 100$ . Then: (a) for the “low” rate of onset of VSE  $\psi_{low}$ , the steady state  $C_\infty$  occurs in the high-flat part of  $p(C)$  yielding a low value of  $C_\infty$ , i.e. a low perceived risk of VSE at equilibrium, which does not cause a substantial decline in coverage; the equilibrium coverage  $p(C_\infty)$  remains in excess of the critical one, thereby allowing

elimination; the convergence to the equilibrium uptake is monotonic since  $C_\infty$  occurs in the flat part of  $p(C)$ ; (b) for  $\psi = \psi_{high}$  the equilibrium  $C_\infty$  occurs in the low-flat part of  $p(C)$ . This yields a high value of  $C_\infty$ , i.e. a high perceived risk of VSE at equilibrium, and a substantial decline in the equilibrium coverage, little in excess of  $p_0$ , and therefore largely below the critical level. This allows the endemic persistence of the disease, with dynamics which do not differ from those of the SIR model with vaccine uptake set at the level of  $p_0$ ; (c) finally, for  $\psi = \psi_{medium}$ , the steady state  $C_\infty$  occurs in the steep part of the  $p(C)$  curve, again yielding an equilibrium coverage  $p(C_\infty)$  below the critical level so that the long term outcome is still disease persistence. The interesting new is that in this case the convergence to  $C_\infty$  is oscillatory, thereby causing an oscillatory forcing to the epidemiological system. In this case ( $\sigma = 100$ ) the linear pseudo-period is too large ( $\vartheta = 155$  years) to have epidemiological significance, which does not prevent other parameter constellations to yield more interesting results.<sup>1</sup> The dynamics of the vaccination variables of (25) yield however several interesting possibilities as regards the actual patterns of the epidemiological variables ( $S, I$ ). We consider first the standard transient situation where a new vaccine is introduced at the (slightly perturbed) pre-vaccination endemic state of the SIR model:

$$S(0) = S_{SIR} = \frac{1}{R_0}, I(0) = I_{SIR} = \frac{\mu}{\mu + v} \left(1 - \frac{1}{R_0}\right).$$

Initial conditions for  $V, C$  are in this case:  $V(0) = 0, C(0) = 0$ . After time zero VSE start to cumulate, i.e. the  $C(t)$  function monotonically increases in the first epochs after vaccine introduction, thereby increasing the degree of vaccine scare. The actual impact of this process on the disease dynamics depends on the interplay of the various parameters relating to VSE and the public's response. We report a sample of various interesting transient post-vaccination scenarios.

- (a) *Elimination and eventual disease reemergence.* This scenario is illustrated in Fig. 3, where the parameters are:  $p_0 = 0.80, \varepsilon = 0.02, \psi = 2.5\mu, M^* = 0.145, \sigma = 10$ . Here model (25) converges to its steady state in a non-oscillatory way (Fig. 3, left). In particular the vaccination programme satisfies  $p(t) > p_c$  for a period of time long enough to allow elimination in the short-term. This occurs because in this phase the accumulation of VSE is slow enough so that elimination occurs before the perceived risk of VSE (measured through  $C$ ) has increased enough to significantly affect vaccine uptake. However the disease eventually re-emerges. Indeed, the effective reproduction number  $R_E(t) = R_0 S(t)$ , which continued to decline for about 20 year after the initiation of the programme, re-starts to steadily increase after that date (Fig. 3, right). This is the consequence of the gradual accumulation of VSE which gradually enflame  $C$  and therefore the perceived risk of VSE, therefore reducing vaccine uptake, which in turn yields a steady build up in the susceptible fraction. By assuming that the disease is not globally eradicated (so that the local vaccination policy is continued), a stochastic reintroduction of a single infective individual at (about)  $t = 55$  years causes a large epidemic outbreak first, and then the endemic re-emergence of the disease, since the vaccine uptake in the long term does not significantly exceed 80%, i.e. largely below the critical level. Note that the disease re-emergence occurs with a gradual decrease in the inter-epidemic period, that in the long-term will land on a value which are characteristic of the classical SIR model with 80% vaccination at birth.
- (b) *Worsening of control conditions.* This scenario is illustrated in Fig. 4, where the parameters are:  $p_0 = 0.80, \varepsilon = 0.08, \psi = 2.5\mu, M^* = .145, \sigma = 10$ . In this case  $C$  and  $p(C)$  still converge without oscillations. Since  $\varepsilon$  is large initial elimination can not occur. Nonetheless the disease is initially brought to high levels of control (with long inter-epidemic oscillations) because vaccine uptake is initially high because the perceived risk of VSE is initially very low, still due to the low accumulation of VSE. However in the long term the slow but continued accumulation of VSE make vaccine uptake much lower so that the disease progressively switches to a different dynamic pattern by restoring shorter period inter-epidemic oscillations. This situation, which

<sup>1</sup>Finally, less interesting things occur when  $p(C)$  lies always above or always below the critical uptake: in the former case the disease is always eliminated independently of the public responses to perceived risks of VSE, while in the latter the disease will always persist.



had been predicted in the medical literature [8], is a potential danger faced by developed countries especially in the case of diseases difficult to eliminate, and for which the perceived risk of serious disease is steadily small.

- (c) *Switches in control epochs.* This scenario is illustrated in Fig. 5, where the parameters are:  $p_0 = 0.80$ ,  $\varepsilon=0.08$ ,  $\psi = \mu/5$ ,  $M^* = .145$ ,  $\sigma = 20000$ . Under this parameter constellation system (25) exhibits damped oscillations, triggered by the large  $\sigma$  value. After the initial adjustment phase during which the prevalence of VSE cumulate toward its steady-state, the vaccination variables ( $V, C, p(C)$ ) initiate to show pronounced waves (Fig. 5, left). These waves are triggered by the shape of  $p(M)$  but are a natural outcome of the vaccination system, where epochs of vaccine scare diminish vaccine uptake which subsequently reduces the prevalence of individuals with VSE, thereby stimulating an increase in vaccine uptake. These long-period waves (the pseudo-period of linear oscillations close to the equilibrium is in this case about 40 years) force the epidemiological variables to oscillate in the form of sequences of “vaccination epochs”, nicely depicted in Fig. 5 (right). Epochs of low vaccine uptake are characterised by comparatively shorter inter-epidemic oscillations which are however gradually replaced over time by new epochs of higher vaccine uptake with longer inter-epidemic period, and so on.

The dynamics of the delayed system (26) are richer, thereby forcing richer dynamics in the epidemiological variable. As the mathematical analysis suggests, we expect that as far as the speed of behaviour change  $\sigma$  is small then the unique equilibrium of (26) is locally (and globally) *stable independently of the delay*. In this case the dynamics of the delayed system remain similar to those of its non-delayed counterpart. When however, other things being equal,  $\sigma$  exceeds a critical value  $\sigma_{crit}$ , and provided the steady state lies in the steep portion of  $p(C)$ , then the presence of the information delay allows the onset of asymptotically steady oscillations through Hopf bifurcation of the steady state. Fig. 6 shows the regions of values of the mean information delay  $D$  yielding to local stability vs local instability computed through the Routh-Hurwitz stability condition, for two distinct values of  $\sigma$ . Note that: i) higher values of  $\sigma$  yield a wider instability region, and ii) for large  $\sigma$  values essentially any, however small, information delays are likely to yield steady oscillations.

The onset of (asymptotically) stable oscillations in the vaccination system ( $V, C$ ) supplies an asymptotically periodic forcing to the system of epidemiological variables ( $S, I$ ). In particular since a long-transient is necessary in order that the stable limit cycle of the vaccination system ( $V, C$ ) to materialise, a long and complex oscillatory transient occurs also in the ( $S, I$ ) system. To illustrate the asymptotic effect of the vaccination dynamics for the epidemiological system we therefore focus only on long-term behaviour.

For example (see Fig. 7, where:  $p_0 = 0.80$ ,  $\varepsilon=0.05$ ,  $\psi = \mu/5$ ,  $M^* = .145$ ,  $\sigma = 45000$ ,  $D = 220$  days. Note that this is a parametric constellation corresponding to a unstable equilibrium) an average information delay of about 7 months yield a nice stable limit cycle in vaccine uptake, with a period of about 28 years (Fig 7 left). These oscillations trigger stable oscillations with the same period in ( $S, I$ ) (Fig. 6 right). In particular the very steep shape of  $p(C)$  causes the vaccine uptake to bounce between its affordable minimum and maximum, so that the effective reproduction number shows oscillations of considerable amplitude. Further stretching of critical parameters, such as  $\sigma$ , are able to increase the amplitude of oscillations in the ( $V, C$ ) variables, yielding even richer oscillation patterns in the epidemiological ones ( $S, I$ ), seemingly through period doubling and chaos (not reported here). Nonetheless it is to be pointed out that such oscillations are characterised by minima of the infective proportion during the low phases of such oscillations which become smaller and smaller, therefore questioning the validity of the deterministic framework.

## 7.2 Simulation 2: side effects arising with a fixed delay

Here we consider system (28) under the following piecewise linear vaccine uptake function:

$$p(C) = \max\left(1 - \frac{C}{C^*}, 0\right) \quad (45)$$

implying that the vaccine uptake is maximal when the perceived risk of VSE is zero, but it approaches zero as  $C$  approaches a value  $C^* > 0$ , and it remains zero thereafter. The constant  $C^*$  can be taken to represent the maximal level of VSE the community is capable to tolerate. The previous formulation is rather “extremal” but it has the advantage of being simple, thereby making transparent the mechanisms leading to oscillations. The equilibrium equation here takes the simple form

$$C_\infty = \bar{\psi} \exp(-\bar{\psi}) \exp(-\mu T) p(C_\infty)$$

which is easily solved as:

$$C_\infty = \frac{\bar{\psi} \exp(-\bar{\psi}) \exp(-\mu T)}{\bar{\psi} \exp(-\bar{\psi}) \exp(-\mu T) + C^*} C^*$$

In particular the  $A(T)$  quantity which appears in the characteristic equation sharply simplifies since  $p(C)$  has a constant derivative:

$$A(T) = \frac{\mu \bar{\psi} \exp(-\bar{\psi}) \exp(-\mu T)}{C^*}$$

This allows to simplify for essentially all cases of practical interest the equation (29) determining the bifurcating delays. In fact the term  $\exp(-\mu T) = \exp(-T/L)$  (where  $L$  is the life expectancy of the human host) is essentially equal to unit in the most important case of short-delay VSE (the case where the causal link to the vaccine can be meaningfully established), e.g.  $T$  of the order of days or at most a few weeks ( $T/L$  has the order  $10^{-5} - 10^{-4}$ ) and still gives an excellent approximation for  $T$  of the order of a few years. The latter case is not of little relevance since it potentially deals with the situation where vaccines are perceived by the public as a possible cause underlying the long-term onset of allergic or of auto-immune diseases. Here the issue of causal imputation is of course a complex one, but nonetheless the problem can not be ignored since what really matters is the public’s perception that a causal link might exist. As regards the current medical literature, there seems to be little evidence that vaccines cause allergic diseases ([5],[15],[25]), but on the other hand the possibility that vaccines might be responsible of auto-immune diseases is an accepted hypothesis ([20]). Be things as they may, the possibility that time series of incidence of auto-immune and/or allergic diseases enter the “information set” on which anti-vaccinators base their decisions is a concrete one, largely documented in the official documents and sites of anti-vaccination groups.

In all these cases we can take

$$A(T) \approx \frac{\mu \bar{\psi} \exp(-\bar{\psi})}{C^*} = A$$

so that equation (29) simplifies to

$$\left( \sqrt{A^2 - \mu^2} \right) T = \arccos\left(-\frac{\mu}{A}\right) + 2k\pi, \quad k = 0, 1, \dots$$

In particular the first switch from stability to instability, which is the most relevant for practical purposes, occurs for

$$T_{H,1} = \frac{\text{Arc cos}(-C^*/\psi \exp(-\psi))}{\sqrt{(\psi \exp(-\psi)/C^*)^2 - 1^2}}$$

It is thus easy to see that for fastly occurring VSE the first bifurcating delay  $T_{H,1}$  (provided it is meaningful) is, as expected, an increasing function of  $C^*$ : indeed as  $C^*$  increases, the slope of the  $p(C)$  function decreases, thereby requiring longer average information delays to destabilise the equilibrium. A possible shape of the bifurcation locus in the  $(C^*, T)$  plane is depicted in Fig. 8 (in log scale) for two distinct values of the rate  $\psi$  of onset of VSE. The graph indicates an exponential relation between  $T_{H,1}$  for relatively large  $C^*$ , and, other things being equal, that the bifurcating delay  $T_{H,1}$  is decreasing in  $\psi$ . Overall this indicates that for values of the delay  $T$  of onset of VSE of the order of a few days, as are those specified in the protocols for identification of vaccination as the causal factor of VSE, the onset of “VSE induced” oscillations requires a combination of unlikely high rates  $\psi$  of onset

of VSE, and a very low “societal” tolerance ( $C^*$ ) to VSE. For example for  $C^* = 10^{-4}$ , a meaningful bifurcating delay of 11 days would require values of  $\psi$  close to 1 (implying that on average 67% of vaccinated individuals incur some VSE), whereas the more reasonable value  $\psi = 0.05$  (implying that on average 5% of vaccinated individuals incur some VSE), already yields a bifurcating delay around 3 months. Things would be different if vaccines could be identified as responsible of long-term side effects, as it would be the case for the onset of allergic or auto-immune diseases long after vaccination. In this case the average delay  $T$  would take large values, say several years, therefore allowing the onset of oscillations for less stressed values of  $\psi$  and  $C^*$ . This seems to suggest that reactions by the public to VSE are more likely to induce oscillations in vaccine uptake when long delays occur between the moment of vaccination and the onset of the presumed VSE, as it might occur for the scare that vaccines cause allergic diseases, or when further delaying factors, as information delays (not considered here), are included.

Fig. 9 reports, for the sake of completeness, the convergence to a stable limit cycle fluctuating around  $C^*$  of the key variable  $C$  (other parameter values are:  $\psi = 0.1$ ,  $C^* = 10^{-4}$ , so that  $T_{H,1} = 47$ days) and  $T = 540$  days, i.e. a delay of 1.5 years mimicking the scare of vaccine induced allergic, or auto-immune, diseases. The inter-epidemic is around 30 years. These oscillations cause the vaccine uptake, and therefore also the epidemiological variables, to oscillate. These oscillations can be shown to be very small because  $p(C)$  shows small amplitude oscillations (between 0 and 0.05), which little affect the epidemiological oscillations. This is an obvious consequence of the peculiar choice (45) of the vaccine uptake function.

Finally, in the case of delayed information obeying an exponentially fading memory, our numerical calculations show that not in all cases the information delay is able to destabilize the equilibrium state. For example, let us assume, as above that  $\psi = 0.1$  and  $C^* = 10^{-4}$ , implying a Hopf bifurcation at  $T = 47$  days. If  $T = 32$  then there is the onset of oscillations at  $D_H \approx 95$ days (where  $N_z > 0$ ) and the stability is lost at  $D \approx 1410$  days (where  $N_z < 0$ ); for  $T = 40$  days the Hopf bifurcation occurs at  $D_H \approx 11$ days, whereas the stability is recovered at the unrealistically high value  $D \approx 8850$ days. However, if  $T = 30$  the equilibrium remains stable.

## 8 Discussion

The paper has investigated a variety of models for the dynamic implications of vaccination choices in contexts where vaccination is voluntary, and the perceived risk of serious disease is steadily low, so that the only endogenous determinant of vaccination choices is given by the trend in the perceived risk of experiencing some vaccine side effect. At the best of our knowledge, compared to the large number of works on prevalence driven vaccine demand, this is the first paper focusing on VSE as the main determinant of vaccine uptake. We have considered two main cases, i.e. the case where the perceived risk of VSE is evaluated from the publicly available information on the prevalence of individuals who suffered some VSE, and the case where the perceived risk of VSE is evaluated from the incidence of VSE.

An interesting consequence of our modelling choice is that the vaccination sub-system, which determines the perceived risk of VSE and the vaccine uptake, decouples from the epidemiological sub-system. As regards the vaccination sub-system we have demonstrated, both in general and for selected epidemiologically relevant sub-cases, the conditions under which the dynamics of vaccine uptake lands on a globally stable steady state, rather than in stable oscillations, of vaccine uptake. Unlike previous results on epidemiological models with prevalence-driven vaccination [23, 11, 13], where information lags were necessary to trigger oscillations, in the present case steady oscillations can arise also when current information only is used to evaluate the perceived risk (of VSE). The explanation is that the appropriate modelling of vaccine side effects required the introduction of an age mechanism, e.g. another type of lag, to describe the onset of VSE.

The actual dynamics of VSE then act as an external forcing for the dynamics of the epidemiological sub-system. This leads to the interesting scenarios for disease control discussed in the simulations. In particular we have also considered the case of VSE arising with long time-delays. Though in this case the problem of the correct causal imputation of a given disease condition to a vaccination occurred

several years prior to the disease onset is probably hopeless, we feel nonetheless this case well represents the case of the scare that vaccines can cause allergic or auto-immune disease, which is a main argument by anti-vaccinators.

The type of modelling adopted here, and the related predictions, seem to be of interest for all situations where the (immediate or long-term) consequences of the disease are perceived as minor. Such situations do not only arise as a consequence of high degrees of control through vaccination, but also at sub-optimal degrees of control for diseases which are perceived by the public to be of little dangerousness, despite circulation is still significant. An example of such situation could be Varicella, for which the introduction of the vaccine is still under debate. We feel Varicella is a disease currently perceived as minor by parents, which are usually unaware of the protecting role of vaccination against zoster. We guess so that the introduction of a (voluntary) vaccination programme against varicella could in some cases yield largely sub-optimal coverages, so that the social alarm caused by episodes of vaccine associated side effects, from the varicella one but also from other vaccines, could become a main driving force of disease dynamics.

Though there is little direct empirical evidence that trends and fluctuations in incidence of VSE actually affect individuals' vaccination choices, the possibility that vaccine success in controlling disease would ultimately yield the incidence of VSE to override disease incidence was forecasted long time ago ([8]). Moreover there is a wide evidence indicating that the scare of the lack of vaccine safety is a major argument behind vaccine refusal. A good example here is represented by the persistency of the MMR- autism scare over time, which has caused a persistent decline largely below the critical threshold in MMR vaccine uptake in the UK ([14],[26],[27]). We feel that this should not necessarily be interpreted as an isolated rumour, but perhaps as a persistent phenomenon where families are carefully monitoring the incidence of autism cases over time, and taking it into account in their decision function.

In perspective we feel that appropriate studies of the vaccine demand should abandon the “reductionist” approach (i.e. focusing on a single disease at time) used by standard epidemiological modelling, to better investigate how patterns of VSE from some vaccines could affect vaccine uptake from other (or all) vaccines as well. Future work should improve the present model by including vaccination choices in a behavioural, rather than phenomenological, manner (according to e.g. [4]). Stochastic extension of the model would allow better predictions for all the circumstances where the disease becomes sub-critical as a consequence of fluctuations in vaccine uptake. Spatial extensions would allow to better take into account the social alert caused by VSE at the various local scales, e.g. the possibility that mild VSE create rumours that are likely to have some importance only in the local network of contacts (e.g. the child who suffered from VSE, his/her family, and neighbours), while episodes of severe VSE typically receive large amplifications by media, being thereby communicated to the whole population.

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## Appendix

### A Proofs of propositions and of statements

#### A.1 Mathematical derivation of the main model

The solution of (4) is:

$$W(t, \tau) = \begin{cases} \mu p(M(t - \tau)) K_o(\tau), & \text{if } 0 < \tau < t \\ W_o(\tau - t) \frac{K_o(\tau)}{K_o(\tau - t)}, & \text{otherwise.} \end{cases} \quad (46)$$

where  $K_o(\tau)$  is given by (9). Thus since:

$$H(t) = \int_0^t \psi(\tau)W(t, \tau)d\tau + \int_t^{+\infty} \psi(\tau)W(t, \tau)d\tau$$

and after defining the function:

$$f(t) = \exp(-\mu t) \int_t^{+\infty} W_o(\tau - t) \exp\left(-\int_{\tau-t}^{\tau} \psi(\tau)d\tau\right) d\tau \Rightarrow \lim_{t \rightarrow +\infty} f(t) = 0^+$$

we immediately get the main relation (7).

## A.2 Main propositions

**Proof of proposition 3.1.** Let it  $\lambda$  be a solution of (17) such that  $\Re(\lambda) \geq 0$ . Thus, taking the moduli of both l.h.s and l.h.s. of (17) one, respectively, obtains that:

$$|l.h.s.| = |\lambda + \mu| > \mu$$

(which follows from  $\Re(\lambda) \geq 0$ ) and:

$$|r.h.s.| = \mu |p'(C_\infty)| \left| \int_0^{+\infty} \text{Exp}(-\lambda u) \psi(u) \text{Exp}(-\mu u - \Psi(u)) du \right| < \mu |p'(C_\infty)| B_\psi(\mu).$$

As a consequence if (18) holds then  $|r.h.s.| < \mu$ . As a consequence, due to the contradiction, (17) cannot have solution with non-negative real part, and the equilibrium is locally stable.

The proof on global stability is essentially based method of contracting rectangles (in our case: intervals) [6, 22], and in it we shall use the function  $g(z) = B_\psi(\mu)P(z)$ . Since  $p(C)$  is decreasing, it is  $p(C(t)) \leq p(0)$  and as a consequence:

$$C' \leq -\mu C + f(t) + \mu p(0) \int_0^t \psi(\tau)K_o(\tau)d\tau,$$

which implies that:

$$\varlimsup_{t \rightarrow +\infty} C(t) \leq g(0),$$

i.e. the interval  $J_0 = [0, g(0)]$  is attractive. Thus, we may consider initial conditions lying in  $J_0$ . For them it is:

$$C' \geq -\mu C + f(t) + \mu p(g(0)) \int_0^t \psi(\tau)K_o(\tau)d\tau,$$

implying:

$$\varliminf_{t \rightarrow +\infty} C(t) \geq g^{(2)}(0),$$

thus the interval  $J_1 = [g^{(2)}(0), g(0)]$  is positively invariant and attractive. Proceeding in this way, after  $k$  'steps' we obtain that the interval

$$J_k = [g^{(k+1)}(0), g^{(k)}(0)]$$

is attractive. These intervals tend to the degenerate interval  $[C_\infty, C_\infty]^2$  provided that the discrete dynamical system :

$$y_{k+1} = g(y_k) \tag{47}$$

has  $C_{inf ty}$  as globally asymptotically stable equilibrium. Now, setting  $y_{2k} = u_k$  where

$$u_{k+1} = g^{(2)}(u_k), u_0 = y_0$$

and  $y_{2k+1} = v_k$  where

$$v_{k+1} = g^{(2)}(v_k), v_0 = g(y_0),$$

we have that the behaviour of (47) depends on the behaviour of the discrete dynamical system induced by the map  $g^{(2)}(z)$ . This map is monotone increasing since it is the composition of two strictly decreasing maps, thus the well known condition that its derivative at the equilibrium point is less than one:

$$\frac{d}{dz}g^{(2)}(z)|_{z=C_\infty} < 1$$

idest

$$(g'(C_\infty))^2 < 1$$

guarantees the global asymptotic convergence to  $C_\infty$ . As a consequence, condition (18) implies the global asymptotic stability of the equilibrium solution of (8)

◇

In the case of delayed information, it holds that:

**Proposition A.1** *Condition 18 guarantees the Local and Global Asymptotic Stability of the equilibrium solution of (19)-(20).*

**Proof** Let it  $\lambda$  be a solution of (21) such that  $\Re(\lambda) \geq 0$ . Thus, calculating the modulus l.h.s. of (21) it yields that:

$$|l.h.s.| = |1 + \frac{\lambda}{a}| |\lambda + \mu| > \mu$$

(as it is straightforward to verify). Thus, proceeding as in proposition 3.1 we may easily demonstrate our claim.

Similarly, also the proof of the global stability is an extension of the proof of proposition 3.1. Indeed, that proof was based on a sequence of contracting intervals determined by a sequence of differential inequalities. Also here we shall use the function:  $g(z) = B_\psi(\mu)p(z)$ . Since  $p(M)$  is decreasing, it is  $p(C(t)) \leq p(0)$  and as a consequence:

$$C' \leq -\mu C + \mu p(0) \int_0^t \psi(\tau) K_o(\tau) d\tau < -\mu C + \mu p(0) \int_0^t \psi(\tau) K_o(\tau) d\tau,$$

which implies that:

$$\lim_{t \rightarrow +\infty} C(t) \leq g(0).$$

and that the interval  $J_0 = [0, g(0)]$  is such that positively invariant and attractive for  $C(t)$  and, thanks to the inequalities:

$$-aM \leq M' \leq a(g(0) - M),$$

also for  $M(t)$ . Summarizing the rectangle:

$$A_0 = J_0 \times J_0$$

is attractive for  $(M, C)$ . Thus, we may consider initial conditions lying in  $A_0$ . For them it is:

$$C' > -\mu C + f(t) + \mu p(g(0)) \int_0^t \psi(\tau) K_o(\tau) d\tau$$

and easily we may show that the rectangle  $A_1 = [g^{(2)}(0), g(0)] \times [g^{(2)}(0), g(0)]$  is positively invariant and attractive. Proceeding in this way, after  $k$  'steps' we obtain that the rectangle

$$A_k = [g^{(k+1)}(0), g^{(k)}(0)] \times [g^{(k+1)}(0), g^{(k)}(0)]$$

is positively attractive. Thus, proceeding as in the other proof, we may show that this sequence of rectangles tends towards the point  $(C_\infty, C_\infty)$  (= towards a degenerate rectangle).

◇

### A.3 The delayed prevalence case: side effects occurring at a constant rate

Concerning the oscillation result of subsection (4.2), by linearising system (26) at its equilibrium point one gets the characteristic equation:

$$\lambda^3 + (2\mu + \psi + a)\lambda^2 + (a\mu + (\mu + \psi)(\mu + a))\lambda + a\mu(\mu + \psi(1 + |p'(C_\infty)|)) = 0 \quad (48)$$

Since the coefficients are positive the unique requirement for local stability is the Routh-Hurwitz condition, leading to the condition (27). The claim on the Yakubovitch oscillatory easily follows by *i*) the boundedness of  $C(t)$  (remember that  $C(t) < V_{tot}(t) < 1$ ); *ii*) the instability of EQ. The properties *i*) and *ii*) allow applying the Yakubovitch-Efimov-Fradkov theorems [29, 30, 31].

### A.4 The prevalence case: side effects occurring with a constant delay

**Proof of proposition 4.1.** y linearising and applying the Laplace transform, we obtain the characteristic equation:

$$\lambda + \mu = -A(T) \exp(-\lambda T) \quad (49)$$

where

$$A(T) = |p'(C_\infty(T))| \mu \bar{\psi} \exp(-\bar{\psi} - \mu T). \quad (50)$$

It easy to show that (49) has, for small  $T < 1$  or two negative real solutions, one near  $-\mu - A(0)$  and the other very large. Therefore in both cases instability can only occur through a Hopf bifurcation. In particular, consistently with the previous example, the case  $T = 0$  is a stable one, and bifurcations, if any, must occur for higher delays. Let us look therefore for Hopf bifurcation points, searching purely imaginary solutions  $\lambda = j\omega$  of the characteristic equation, leading to the following pair of equations:

$$\begin{aligned} \cos(\omega T) &= \frac{-1}{G(T)} \\ \sin(\omega T) &= \frac{\omega}{\mu G(T)} \end{aligned} \quad (51)$$

Note that GAS condition implies  $\cos(\omega T) < -1$ . From (51) we immediately get:

$$\omega(T) = \pm \mu \sqrt{G(T)^2 - 1}$$

Observe that since for  $T = 0$  the DDE reduces to an ODE with a unique and GAS equilibrium point, for continuity this fact implies that  $G(T) > 1$  implies the existence of a threshold  $T^*$  where the inequality is not fulfilled and where the equilibrium point  $C_\infty(T)$  is locally stable.

The bifurcation values are, then, determined by the eq. (29). The proof of the stability switch follows by the considerations exposed before the statement of this proposition, and, in particular, condition (30) is simply the non-zero speed condition:

$$\frac{d\lambda}{dT} \Big|_{\lambda=i\omega_H(T_0)} \neq 0$$

◇

Moreover, by including the information delay, we observe that a candidate Hopf point  $\lambda = i\omega$  has to solve:

$$\left(1 + \left(\frac{\omega}{a}\right)^2\right)(\mu^2 + \omega^2) = \mu^2 G^2(T). \quad (52)$$

Of course, if  $G(T) < 1$  eq. (52) has no solutions, whereas if  $G(T) > 1$  there is the following solution:

$$\omega_H^2(a) = \frac{-\mu^2 - a^2 + \sqrt{4a^2\mu^2G^2 + (a^2 - \mu^2)^2}}{2} \quad (53)$$

and it may be shown that the non-zero speed condition:

$$\Re \left( \frac{d\lambda}{da} \Big|_{\lambda=i\omega_H} \right) = \frac{\mu(\mu+a)(G-1) - \omega_H^2}{(\mu+a)^2 + \omega_H^2} > 0$$

is fulfilled since also the numerator is positive, as

$$2\mu(\mu+a)(G-1) + (a^2 + \mu^2) > +\sqrt{4a^2\mu^2G^2 + (a^2 - \mu^2)^2}.$$

The bifurcation values  $D_1, D_2, \dots$ , for  $D = a^{-1}$  are obtained by setting  $\lambda = i\omega_H(a)$ , yielding:

$$T\omega_H(a) = \text{Arg} \left( \frac{a\omega_H^2(a) - \mu + i(a\mu + 1)\omega_H(a)}{A(T)} \right), \quad (54)$$

### A.5 The incidence case: instantaneous side effects

In presence of vaccination choices based on current information, instantaneous side effects yields the equation:

$$H(t) = f(t) + \mu\bar{\psi}\exp(-\bar{\psi})p(H(t)),$$

for which it is trivial to show that  $H(t) \rightarrow H_\infty$  globally.

When vaccination choices are based on past information according to an exponentially fading memory, one yields the simple scalar ODE:  $M'(t) = a(\mu\bar{\psi}p(M) - M)$ , whose unique equilibrium is GAS.

### A.6 The incidence case: side effects occurring at constant rate

In the case  $\psi(\tau) = \psi$  it holds  $H(t) = \psi V$ . In turn,  $V$  obeys the ODE:

$$V' = \mu p(\psi V) - (\mu + \psi)V,$$

which has a unique GAS equilibrium given by:  $(\mu + \psi)V_\infty = \mu p(\psi V_\infty)$ .

In case of delayed information, we get the following 2-dimensional ODE system

$$\begin{aligned} M' &= a(\psi V - M) \\ V' &= \mu p(M) - (\mu + \psi)V \end{aligned} \quad (55)$$

whose unique equilibrium is GAS.

### A.7 The incidence case: side effects occurring after a constant delay

When vaccination choices are based on current information, the characteristic equation reads as:

$$\lambda = \frac{1}{T} \ln(G(T)) + i\pi.$$

where:

$$G(T) = \mu |p'(H_\infty)| \bar{\psi} \exp(-\bar{\psi} - \mu T). \quad (56)$$

which quickly leads to the results reported in the main text.

When vaccination choices are based on past information according to an exponentially fading memory the characteristic equation becomes:

$$1 + \frac{\lambda}{a} = -A(T) \exp(-\lambda T) \quad (57)$$



where  $A(T) = \mu G(T)$ , and  $G(T)$  was defined above. If  $G(T) < 1$  then the equilibrium is GAS. On the contrary if  $G(T) > \text{Max}(1, 1/a)$  then the Hopf bifurcation points lie on the curves  $\gamma_k(T, a) = 0$  where  $\gamma_k(T, a)$  is defined as follows

$$\gamma_k(T, a) = -aT\sqrt{G^2(T) - 1} + \pi - Atn\sqrt{G^2(T) - 1} + 2k\pi \quad (58)$$

Therefore if the point  $(T, a)$  lies below the curve  $\gamma_0(T, a) = 0$  then the equilibrium is LAS, while if  $(T, a)$  lies above the curve, then the equilibrium is unstable. This is readily seen by choosing  $a$  as bifurcation parameter and calculating the nonzero speed condition at the Hopf point, which reads:

$$\text{Re} \left( \frac{d\lambda}{da} \Big|_{\lambda=i\omega_H} \right) = \frac{aT (G^2(T) - 1)}{|1 - aG(T)E^{-i\omega_H}|} > 0 \quad (59)$$

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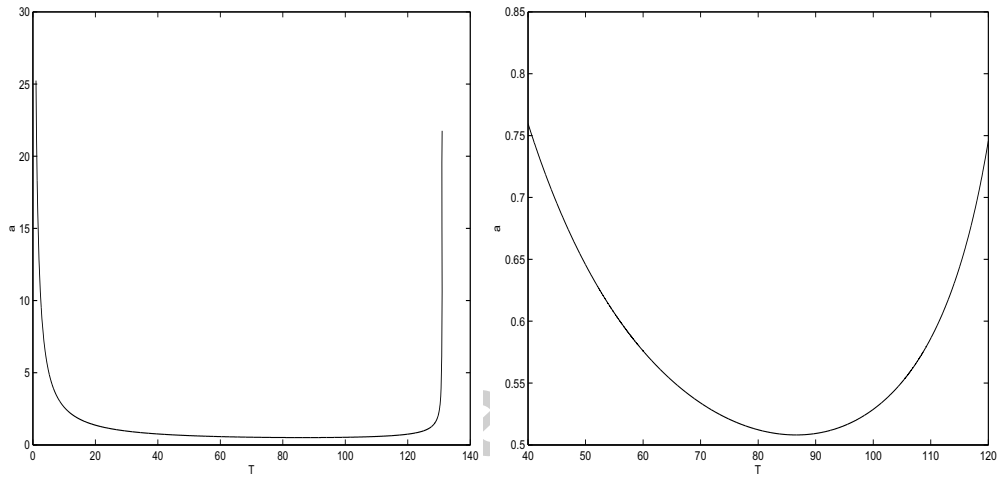


Figure 1: Perceived risk evaluated by the delayed incidence of VSE. VSE arising with a fixed delay. Curve  $\gamma_0(T, a) = 0$  with  $\mu = 0.02, \text{ years}^{-1}$ ,  $\bar{\psi} = 1$  and  $\Theta = 50000$ . Left sub-figure: plot for  $0 < T < T^+ \approx 131$ ; right sub-figure : plot for  $40 < T < 120$ .

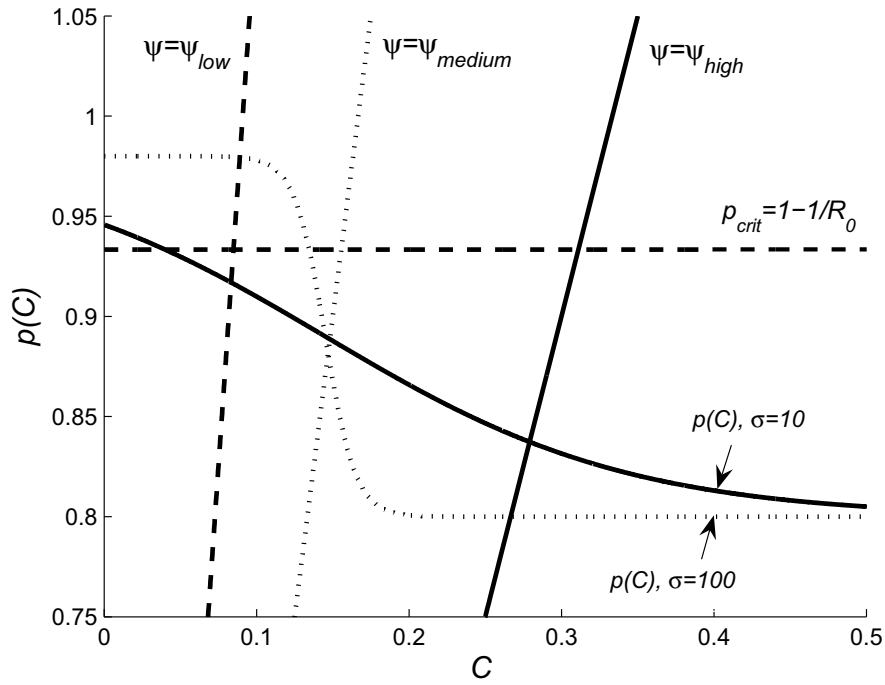


Figure 2: Model (25): graphic solution of the equation for equilibria  $p(C) = r_\psi(C)$ , where  $r_\psi(C) = \frac{\mu + \psi}{\psi}C$ . The line  $r(C)$  is drawn for three distinct values of  $\psi$ :  $\psi_{low} = \mu/10$ ,  $\psi_{medium} = \mu/5$ ,  $\psi_{high} = \mu/2$ . The  $p(C)$  function is drawn for  $\sigma_{low} = 10$  and  $\sigma_{high} = 100$ , and its other parameters are:  $p_0 = 0.8$ ,  $\varepsilon = 0.02$ ,  $M^* = 0.145$ .

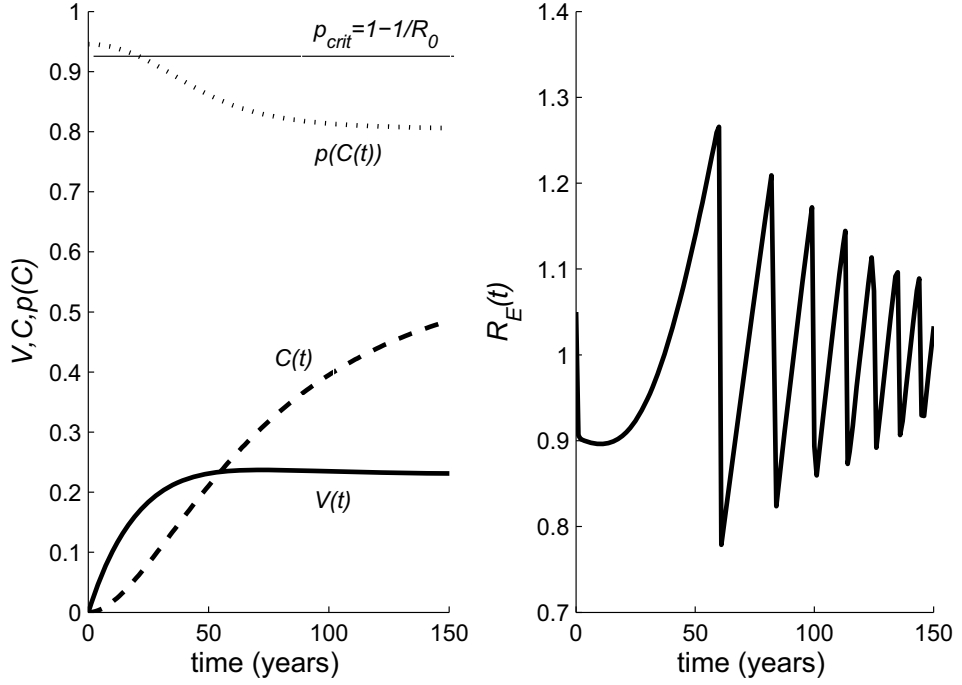


Figure 3: Model (25). The disease re-emergence scenario due to declining uptake caused by the increase in the prevalence of VSE and stochastic reintroduction of one infective individual at time  $t = 55$ ; (left) time evolution of  $V, C, p(C)$ ; (right) time evolution of the effective reproduction rate  $R_E = R_0 S$  (parameters:  $\psi = 2.5\mu$ ,  $\varepsilon = 0.02$ ,  $M^* = 0.145$ ;  $\sigma = 10$ ).

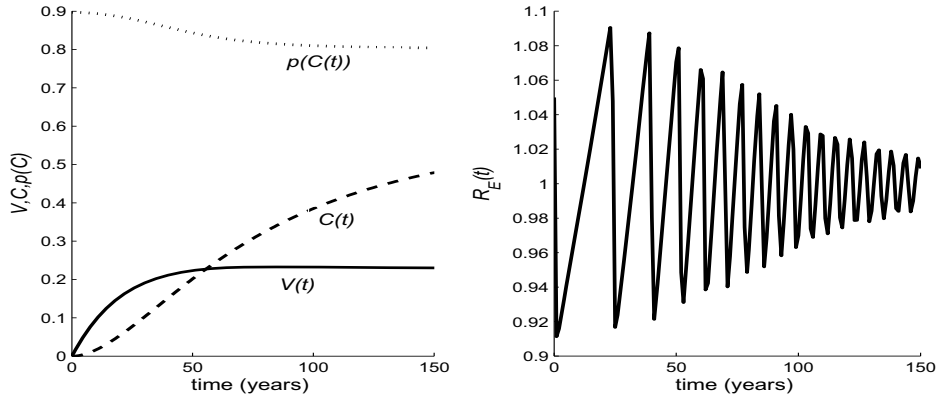


Figure 4: Model (25). The worsening control conditions scenario with long-term contraction of the inter-epidemic period as a consequence of gradual growth in the perceived risk of side effects. (left) time evolution of  $V, C, p(C)$ ; (right) time evolution of the effective reproduction rate  $R_E = R_0 S$  (parameters  $p_0 = 0.80$ ,  $\varepsilon = 0.08$ ,  $\psi = 2.5\mu$ ,  $M^* = .145$ ,  $\sigma = 10$ ).

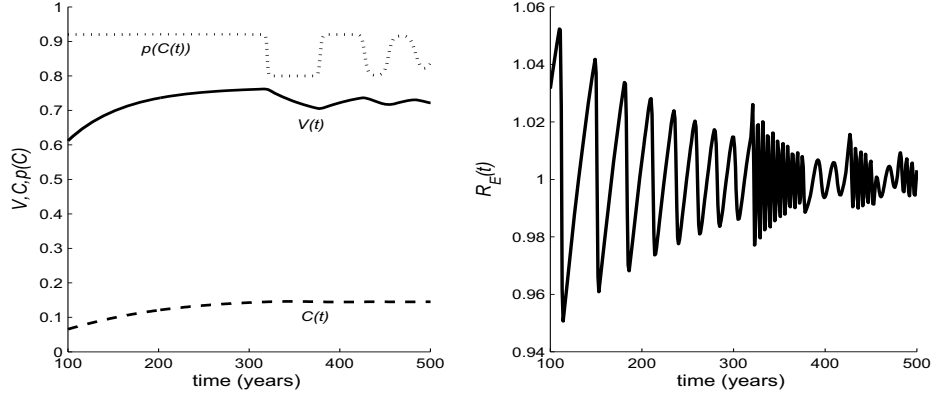


Figure 5: Model (25). The epochs switch scenario. (left) time evolution of  $V, C, p(C)$ ; (right) time evolution of the effective reproduction rate  $R_E = R_0 S$  (parameters  $p_0 = 0.80$ ,  $\varepsilon = 0.08$ ,  $\psi = \mu/5$ ,  $M^* = .145$ ,  $\sigma = 20000$ ).

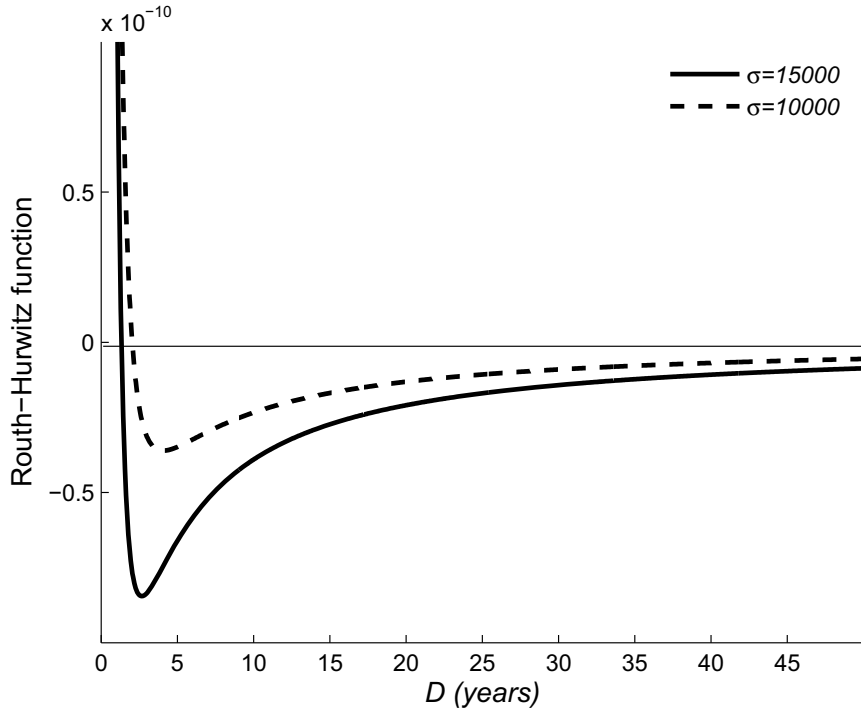


Figure 6: Model (26). Values of the mean information delay  $D$  yielding local asymptotic stability (where the Routh-Hurwitz function is positive) vs local instability (where the function is negative) of the equilibrium, for  $D \leq 45$  years and for two values of  $\sigma$ . Other parameters:  $p_0 = 0.80$ ,  $\varepsilon = 0.08$ ,  $\psi = \mu/5$ ,  $M^* = 0.145$ .

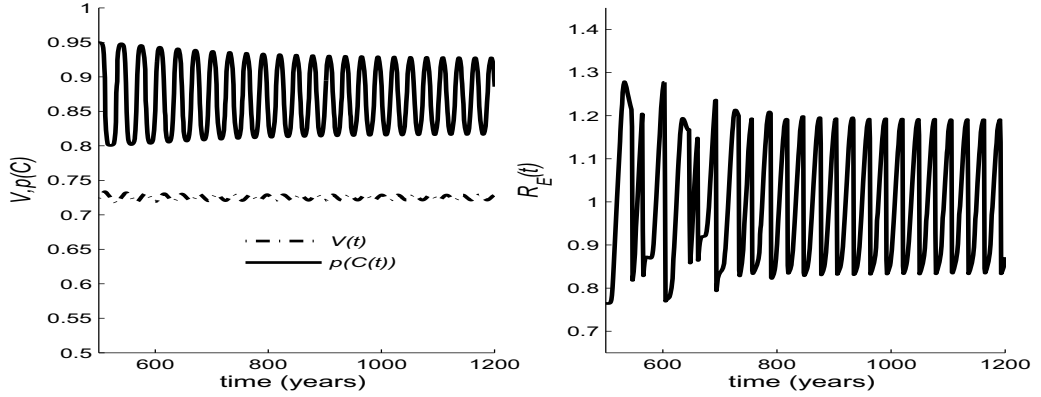


Figure 7: Model (26). The steady long-term oscillations of vaccine uptake (left) force asymptotically steady oscillations of epidemiological variables (parameters  $p_0 = 0.80$ ,  $\varepsilon=0.08$ ,  $\psi = \mu/5$ ,  $M^* = .145$ ,  $\sigma = 45000$ ,  $D = 220$  days).

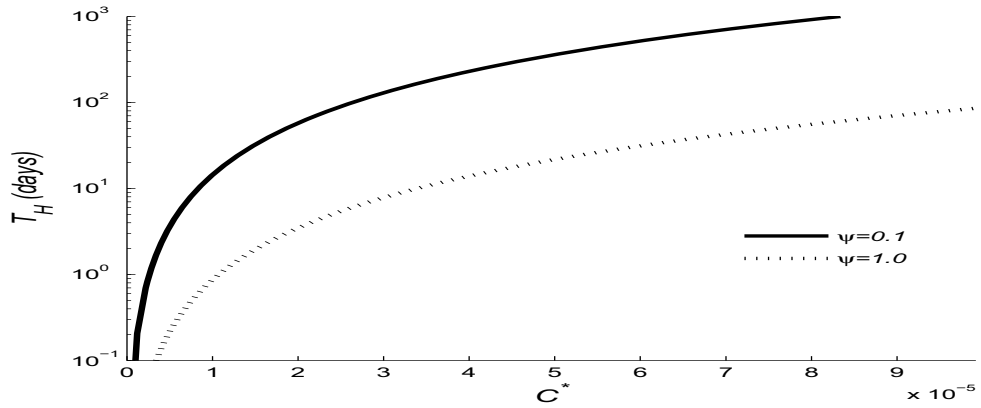


Figure 8: Model Model (28) with fixed delay to VSE. Shape of the bifurcation locus in the  $(C^*, T)$  plane (log-scale), for distinct  $\psi$  values.

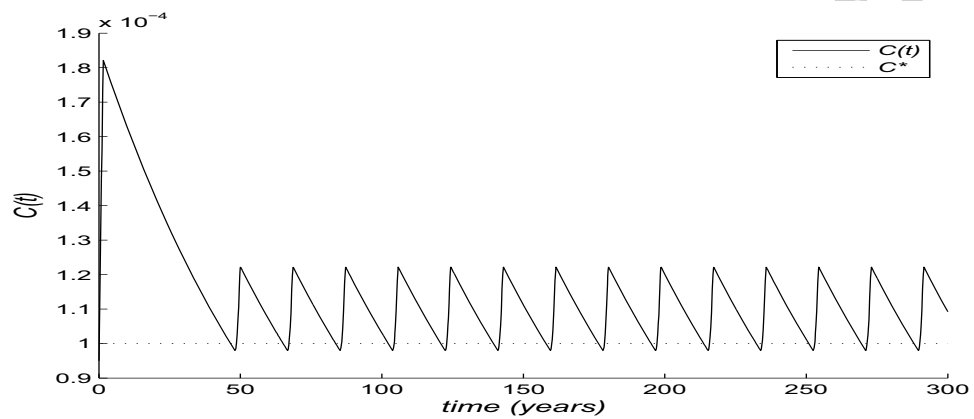


Figure 9: Model (28) with fixed delay to VSE. Convergence toward a limit cycle of the key-variable  $C$  ( $C^* = 0.0001$ ,  $\psi = 0.1$ ;  $T = 540$  days).