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Optimal Vaccination Strategies—for Whom?

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ABSTRACT

A SIRS model with vaccination is considered. The vaccination is assumed to have side effects (for simplicity, these side effects are modeled as a probability of becoming ill because of vaccination). It is the interest of the total population to minimize the prevalence of disease; hence, the vaccination rate that minimizes the prevalence will be determined. In Section 2, the individual is considered: an individual tries to minimize his or her own risk. This angle of approach results in a vaccination rate dependent on the prevalence of the disease. The bifurcations of this system are analyzed, and the optimal vaccination coverage for the individual is computed. This coverage is then compared with the optimal vaccination coverage for the total population: it is found that they disagree for some parameter sets.

1. INTRODUCTION

The usual approach to optimizing vaccination campaigns considers the interest of the total population. For example, the total costs incurred by the disease are minimized; total costs mean the social costs (caused by treatment, disablement, and so on) and the cost of the vaccination (including the vaccine, equipment, personnel, and so on) [1, 2]. Another idea is to reduce the reproduction number to 1 so that only a minimal number of vaccinations per time unit are required [3–5].

Individuals may have different interests. They try to reduce their own risk or the risk of their children. In general, vaccinations have some side effects. Often the risk of side effects is very low, though it cannot be neglected in mass vaccination programs. Thus, if the population is well vaccinated, an individual may refuse vaccination because the risk of side effects exceeds the risk of being infected. For example, in the years before the smallpox vaccination campaign in the United States was stopped, there were no cases of death due to the disease, but one out of 1 million vaccinated individuals died owing to problems resulting from vaccination damages—see, for example, Dietz [6].

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This problem was perhaps considered for the first time in the eighteenth century by d'Alembert [7], page 26: there was an old Turkish technique for immunization of individuals against smallpox, known as the inoculation. This technique contained many risks; because the mortality was about one out of 200, considerable interest centered on the question of whether the inoculation or exposure to natural smallpox was more dangerous. Fine and Clarkson [8] consider a phenomenological approach to the problem of side affects caused by vaccination. The function describing the effect of vaccination on the prevalence of the disease is simply defined ad hoc. They do not use a theoretical model to give a foundation for their choice of this function. Within this framework, they find situations where an individual refuses vaccination even though the vaccination is still meaningful because it continuous to decrease the prevalence of the disease.

In this paper, a SIRS model as the setting for investigation of side effects is considered. For simplicity, it is assumed that there is a certain probability of a vaccinated individual becoming infected because of the vaccination. This assumption is a crude simplification, because side effects are usually different in character from a natural infection: they are discovered earlier (which is why the increase of the prevalence due to side effects is low) and are in general less dangerous than the disease itself. Nevertheless, there is a conjecture that the attenuated vaccine for polio, for example, can remutate into the wild virus. The following model describes such behavior. Even in this simple model, the problem concerning the different aims of individuals and public health can be investigated.

2. BASIC MODEL

We consider a simple SIRS model with only three types of individuals: susceptibles, x; infectives, u; and immunes, w. The structure of the model is shown in Fig. 1. The disease can be transmitted only by a contact between a susceptible and an infective individual. Let $P = x + u + w$ be the total population size. The number of contacts is proportional to xu/P [9]. Thus the incidence is $\beta xu/P$, where the proportional factor β is the per contact transmission rate of infections. Infectives recover with a per capita rate α and become immune, and immunes lose their immunity with a per capita rate γ. The classical Kermack-McKendrick model does not incorporate population dynamics, because it is assumed that the time scale of the disease is much faster than that of population dynamics and thus, for short periods of time, the latter is irrelevant. However, the scope of the present article concentrates on middle- and long-term durations; therefore it is also important for births and deaths to be considered. The per capita

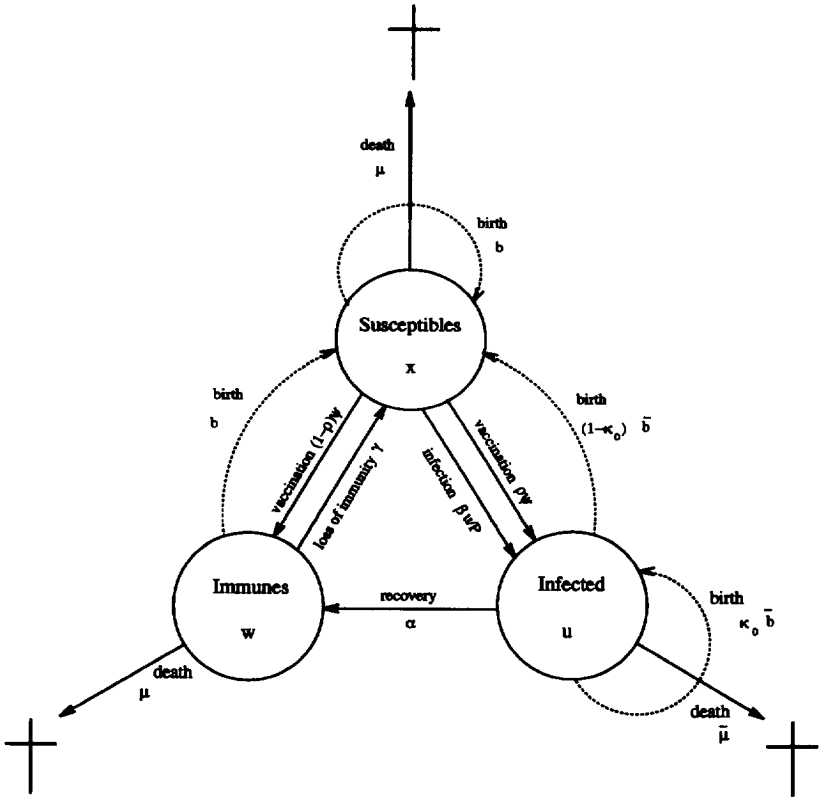

FIG. 1. The structure of the model.

mortality rate is μ and $\bar{\mu}$ for the susceptibles/immunes and infectives, respectively. The per capita birth rate for susceptibles and immunes is b and for infectives $\bar{b}$. There is vertical transmission; a fraction κ_0 of the offspring of infectives also are infected. Vaccination occurs with a per capita rate ψ. A fraction $1-\rho$ of these individuals become immune and a fraction ρ become diseased; thus ρ is the risk of side effects.

The equations read

$$\frac{dx}{dt} = -\mu x + b(x+w) + (1-\kappa_0)\bar{b}u - \psi x + \gamma w - \beta\frac{u}{P}x, \quad (1)$$

$$\frac{du}{dt} = -\bar{\mu}u + \kappa_0\bar{b}u + \rho\psi x - \alpha u + \beta\frac{u}{P}x, \quad (2)$$

$$\frac{dw}{dt} = -\mu w + (1-\rho)\psi x - \gamma w + \alpha u, \quad (3)$$

$$P = x + u + w. \quad (4)$$

From the medical interpretation, the parameters satisfy

$$0 \leqslant \beta, \gamma, \alpha, \psi,$$
$$0 < \mu \leqslant \bar{\mu},$$
$$0 < \bar{b} \leqslant b,$$

and

$$0 \leqslant \kappa_0 \leqslant 1, \qquad 0 \leqslant \rho \leqslant 1.$$

Models resembling this are considered in [10–14]. For $\kappa_0 = 0$ and $\psi = 0$, this model is a special case of the work of Busenberg and Hadeler [10]. The result in this work says that there is no endemic state if $\beta < b - \bar{b} + \bar{\mu} - \mu + \alpha$. For $\kappa_0 > 0$, we get the threshold $\beta < b - \kappa_0 \bar{b} + \bar{\mu} - \mu + \alpha$. Because the vaccination has side effects, it does not make sense to vaccinate if the disease cannot invade the population. Thus we assume throughout the paper that

$$\beta > \beta_0 := b - \kappa_0 \bar{b} + \bar{\mu} - \mu + \alpha. \tag{5}$$

3. GLOBAL POINT OF VIEW

3.1. *DYNAMIC BEHAVIOR*

It is assumed that the government—or the public health authorities—are able to fix the vaccination rate ψ; this means the number of immunized individuals per time unit. We are interested in long-term predictions and considerations. We prove later that each trajectory of the system tends to an exponential solution. The total population as well as the number of infectives grow exponentially. Thus it makes no sense to consider the absolute number of infectives. One can also assume that the public health budget grows proportionally with the population. Hence the aim of the public health system is to reduce the *prevalence*, u/P, of the disease.

We transform the system:

$$\bar{x} := \frac{x}{P}, \qquad \bar{u} := \frac{u}{P}, \qquad \bar{w} := \frac{w}{P} = 1 - \bar{x} - \bar{u}.$$

Let $\delta = \bar{\mu} - \mu + b - \bar{b}$. The transformed system reads:

$$\frac{d\bar{x}}{dt} = -(b + \gamma + \psi)\bar{x} - \big(\gamma + b - (1 - \kappa_0)\bar{b}\big)\bar{u} - (\beta - \delta)\bar{x}\bar{u} + (b + \gamma), \tag{6}$$

$$\frac{d\bar{u}}{dt} = -\big(\delta + (1 - \kappa_0)\bar{b} + \alpha\big)\bar{u} + \rho\psi\bar{x} + \beta\bar{x}\bar{u} + \delta\bar{u}^2, \tag{7}$$

$$\frac{d\bar{w}}{dt} = -(b + \gamma)\bar{w} + \alpha\bar{u} + (1 - \rho)\psi\bar{x} + \delta\bar{w}\bar{u}, \tag{8}$$

$$1 = \bar{x} + \bar{u} + \bar{w}. \tag{9}$$

The system is essentially two-dimensional. We use $(\bar{x}, \bar{u})$ as coordinates. In the following discussion, the variables $\bar{x}, \bar{u}, \bar{w}$ are again named x, u, w. Because we use only the homogeneous coordinates, this renaming should not lead to confusion.

The behavior of this SIRS model for $\psi = 0$ is as follows. If the transmission rate, β, is low ($\beta < \beta_0$), then the disease dies out. Thus there is only one stationary point. In this point, there are no infective individuals. When β exceeds the threshold, β_0, the disease establishes itself in the population, the uninfected stationary point becomes unstable, and a stable infected stationary point appears. For $\psi > 0$, the situation is slightly different. Even in the uninfected situation, vaccination will produce some infectives. Thus the uninfected stationary point does not exist; there is only one stationary point, which is infected.

For a stationary point of Eq. (6), Eq. (7) holds:

$$0 = -(b+\gamma+\psi)x - \big(\gamma + b - (1-\kappa_0)\bar{b}\big)u - (\beta - \delta)xu + (b+\gamma), \tag{10}$$

$$0 = -\big(\delta + (1-\kappa_0)\bar{b} + \alpha\big)u + \rho\psi x + \beta x u + \delta u^2. \tag{11}$$

Eliminating x from these two equations yields a polynomial for u:

$$\begin{aligned} p(u) = {} & u^3\,\delta(\beta - \delta) \\ & - u^2\big[\beta\big(b+\gamma-(1-\kappa_0)\bar{b}\big) \\ & \quad + (\beta-\delta)\big(\delta + (1-\kappa_0)\bar{b} + \alpha\big) - \delta(b+\gamma+\psi)\big] \\ & - u\big[\rho\psi\big(b+\gamma-(1-\kappa_0)\bar{b}\big) \\ & \quad + (b+\gamma+\psi)\big(\delta + (1-\kappa_0)\bar{b} + \alpha\big) - \beta(b+\gamma)\big] \\ & + \rho\psi(b+\gamma). \end{aligned} \tag{12}$$

$p(u) = 0$ is necessary for a stationary point. Because $x + u + w = 1$ and $w \geq 0$ a feasible stationary point fulfills $x + u \leqslant 1$. Hence a feasible stationary point is in the compact set K [which is positive invariant with respect to Eqs. (6) and (7)]:

$$K := \{(x,u) \mid 0 \leqslant u \leqslant 1,\ 0 \leqslant x \leqslant 1-u\}.$$

In the proof of Result 1, it is shown that there is exactly one stationary point. Moreover, periodic orbits can be excluded.

RESULT 1

Assume condition (5). *In K there is exactly one stationary point for* $\psi > 0$. *The corresponding root* $u_0(\psi)$ *of the polynomial p is simple.*

Every trajectory of Eqs. (6) *and* (7) *in K approaches the unique stationary point.*

Proof. See Appendix A.1.

3.2. *BEST STRATEGY*

The goal is to find the best vaccination strategy in the sense of the public health system, which means a strategy minimizing $u_0(\psi)$. It turns out that, for a fixed parameter set, the prevalence depends monotonically on the vaccination rate ψ. For example, it is impossible for vaccination to be helpful for small vaccination rates and be detrimental for high rates.

There are two cases: if the risk due to vaccination is small (ρ is small), then obviously vaccination decreases the prevalence. In the second case, ρ is above some threshold ρ_0. Then the detrimental effect of vaccination dominates the positive effects and vaccination will increase the prevalence (Fig. 2). ρ_0 is the critical rate of side effects.

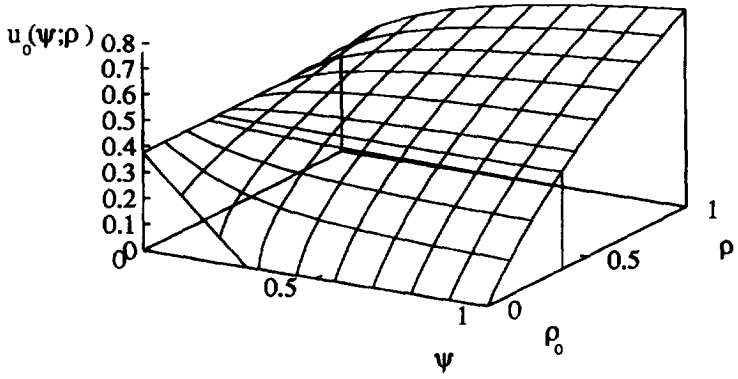

FIG. 2. The dependence of the prevalence, $u_0(\psi; \rho)$, in equilibrium on the vaccination rate, ψ, and the proportion of vaccine side effects, ρ. There is a threshold ρ_0 for ρ. Below this threshold, vaccination decreases the prevalence of the disease; above it, the prevalence is increased. Parameter values are $\delta = 0$, $\beta = 0.8$, $b = 0.5$, $\bar{b} = 0.5$, $\kappa_0 = 0$, $\alpha = 0$, $\gamma = 0$.

RESULT 2

Let

$$\rho_0 = u_0(0)\frac{(1-u_0(0))\delta + (1-\kappa_0)\bar{b} + \alpha}{b+\gamma-(b+\gamma-(1-\kappa_0)\bar{b})u_0(0)}.$$

We have $0 < \rho_0 < 1$. *If* $\rho < \rho_0$ *then vaccination decreases equilibrium prevalence. If* $\rho > \rho_0$ *then vaccination increases equilibrium prevalence.*

Proof. See Appendix A.2.

Thus the public health authorities vaccinate as much as possible if $\rho_0 > \rho$ and do not vaccinate at all for $\rho_0 < \rho$. For $\rho = \rho_0$ vaccination does not change the equilibrium prevalence but causes costs; hence there will be no vaccination.

An infinite vaccination rate is equivalent to a population where no susceptibles exist. Each individual is immune or diseased. Of course, in practice, for logistic reasons, it is not possible to reach this state exactly but—at least if γ is small—approximately.

What does the corresponding prevalence look like? If $\psi = 0$ it is just $u_0(0)$. If ψ becomes large, then the vaccination determines the prevalence and the natural infection no longer has an effect on the behavior of the disease. Thus the prevalence settles on a value that does not depend on β we get (proof in Remark 1, Appendix A.2)

$$u_\infty(\rho) := \lim_{\psi\to\infty} u_0(\psi) = \frac{1}{2\delta}\Big[\delta + (1-\kappa_0)\bar{b} + \alpha + \rho\big(b+\gamma-(1-\kappa_0)\bar{b}\big) - \sqrt{\big\{\delta + (1-\kappa_0)\bar{b} + \alpha + \rho\big(b+\gamma-(1-\kappa_0)\bar{b}\big)\big\}^2 - 4\rho(b+\gamma)\delta}\Big].$$

Hence the prevalence corresponding to the best vaccination coverage in the sense of the public health system is

$$u_{pub}(\rho) = \begin{cases} u_\infty(\rho) & \text{for } \rho < \rho_0 \\ u_0(0) & \text{for } \rho \geqslant \rho_0. \end{cases}$$

4. INDIVIDUAL POINT OF VIEW

4.1. *DYNAMIC BEHAVIOR*

Assume that an individual does not care for the global aspects of vaccination—the "selfish" strategy is to reduce his or her own risk. Thus the rate of vaccination is dependent on the risk of falling ill.

Because this risk is a function of the prevalence, we get

$$\psi = \psi(u).$$

In regard to the medical interpretation, we suppose that $\psi(u)$ is continuous and nondecreasing in u. Moreover, $\psi(0) = 0$. An alternative interpretation of the parameters shows that this system is equivalent to SIRS models with a general prevalence-dependent incidence. Let $\beta = 0$ and $\rho = 1$. Then there is no "natural" infection, but every vaccination leads to an infection. Thus the term $\psi(u)x$ can be interpreted as a general prevalence-dependent incidence. Hence it is no coincidence that the results we get here have some similarity with the results that have been proved for such models [15–19]: for example, the existence of periodic orbits, more than one equilibrium, and so on.

We let $\psi = \psi(u)$. Modifying Eqs. (6) and (7) yields

$$\frac{dx}{dt} = -(b + \gamma + \psi(u))x - (\gamma + b - (1 - \kappa_0)\bar{b})u - (\beta - \delta)xu + (b + \gamma), \tag{13}$$

$$\frac{du}{dt} = -(\delta + (1 - \kappa_0)\bar{b} + \alpha)u + \rho\psi(u)x + \beta xu + \delta u^2. \tag{14}$$

We now show that this system has positive stationary solutions. The proof uses a fixed-point argument. Let

$$T(u) := u_0[\psi(u)].$$

A stationary solution corresponds to a fixed point of T in the interval $[0,1]$. If $u = 0$ then $\psi(u) = 0$ and thus $T(u) = u_0(0) > 0$. For $u = 1$, $\psi(1) \geqslant 0$ stands, and therefore $T(u) = u_0[\psi(1)] < 1$. Moreover, T is continuous. Thus there is at least one $\tilde{u}_0$ with $T(\tilde{u}_0) = \tilde{u}_0$. We distinguish two cases: $\rho \leqslant \rho_0$ and $\rho > \rho_0$ (note that the case $\rho = \rho_0$ can be equally treated as $\rho < \rho_0$).

Case 1. $\rho \leqslant \rho_0$

Thus $u_0(\psi)$ is nonincreasing in ψ, and therefore $T(u)$ also is nonincreasing in u. Hence there is exactly one fixed point U. Let the corresponding stationary point be (X, U). An analysis of the stability of this stationary point yields Result 3 [here $J_0(U)$ is the Jacobian of the system of Eqs. (13) and (14) at the point (X, U) with a constant vaccination rate $\psi(u) \equiv \psi(U)$]. To formulate the result in terms of bifurcations, we introduce a bifurcation parameter τ: let $\psi_\tau(u) = \tau\psi(u) + (1 - \tau)\psi(U)$, $\tau \in [0,1]$. For $\tau = 0$ the vaccination rate $\psi_\tau(u)$ is constant; and, for $\tau = 1$ we have $\psi_\tau(u) = \psi(u)$.

RESULT 3

Let $\rho \leqslant \rho_0$. Then there is exactly one stationary point (X,U). This point is locally stable, if

$$\psi'(U) \leqslant -\frac{\operatorname{tr}[J_0(U)]}{\rho X}.$$

At $\tau_0\psi'(U) = -\operatorname{tr}[J_0(U)]/(\rho X)$, generically a Hopf bifurcation occurs. Other local bifurcations are not possible.

Proof. See Appendix A.3.

Case 2. $\rho > \rho_0$

In this case, it cannot be excluded that $T(u)$ has more than one fixed point. Hence, in general, the system of Eqs. (13) and (14) has more than one stationary point. Let (X,U) be a stationary point. Again, we investigate the stability and possible bifurcations of this stationary point in terms of τ.

RESULT 4

Let $\rho > \rho_0$. Then, in general, there is more than one stationary point. Let (X,U) be such a stationary point. This point is locally stable if

$$\psi'(U) < \min\left\{-\frac{\operatorname{tr}[J_0(U)]}{\rho X}, \frac{1}{u_0'[\psi(U)]}\right\}.$$

At $\tau\psi'(U) = -\operatorname{tr}[J_0(U)]/(\rho X)$ and $\tau\psi'(U) < 1/u_0'[\psi(U)]$, generically a Hopf bifurcation and, at $\tau\psi'(U) = 1/u_0'[\psi(U)]$, generically a saddle-node bifurcation occurs.

Proof. See Appendix A.4.

Thus bifurcations are possible for

$$\psi'(U) = -\frac{\operatorname{tr}[J_0(U)]}{\rho X} =: \psi'_{\text{Hopf}}(\rho), \qquad \det[J_0(U)] \geqslant 0,$$

or

$$\psi'(U) = \frac{1}{u_0'[\psi(U)]} = \frac{-p'(U)}{q(U)} =: \psi'_{\text{saddle node}}(\rho).$$

The latter condition implies a saddle-node bifurcation, whereas the first corresponds to a Hopf bifurcation. The function $\psi'_{\text{Hopf}}(\rho)$ has a pole at $\rho = 0$, whereas $\psi'_{\text{saddle node}}(\rho)$ has a pole at $\rho = \rho_0$. Thus there are Hopf

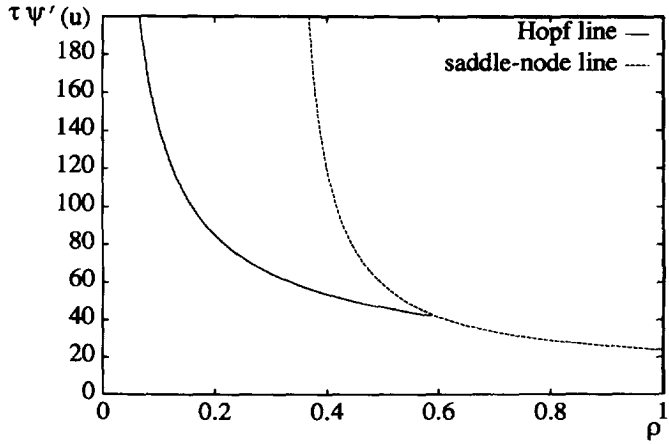

FIG. 3. A typical diagram for the bifurcation lines. The Hopf line has a pole at zero, whereas the saddle-node line has a pole at ρ_0. For some parameter values, the graphs of both bifurcation conditions intersect. At this point, a Takens-Bogdanov bifurcation happens. With other parameter values, the Hopf and the saddle-node lines are distinct for all $\rho \in [0,1]$. Parameter values; $\delta = 0$, $\beta = 2$, $b = 1$, $\bar{b} = 1$, $\mu = 1$, $\gamma = 1$, $\kappa_0 = 0.4$, $\alpha = 0.3$, ψ(stationary point) = 2.

and saddle-node bifurcations for $\rho > \rho_0$. For some sets of parameters, both bifurcation lines intersect (Fig. 3). Then we have a Takens-Bogdanov bifurcation—see, for example, Guckenheimer and Holmes [20], page 364. This shows that the dynamic behavior of the system is much more complicated for $\rho > \rho_0$ than for $\rho \leqslant \rho_0$.

4.2. *IDEAL SELFISH STRATEGY*

The aim is to compare the ideal vaccination rate in the sense of the public health system with the ideal strategy in the view of an individual. Thus the individuals are assumed to be "strictly selfish": If a person recognizes that the risk of infection is greater than the risk of side effects, then the person wants to be vaccinated immediately. Conversely, if the risk of side effects is greater than the risk of infection, the person refuses vaccination. For simplicity, we exclude loss of immunity ($\gamma = 0$). Then the risk of falling ill because of vaccination is

$$r_{\text{vaccination}} = \rho.$$

Let the prevalence be a constant u. For a susceptible individual, there are two possibilities: he or she can get the disease before dying or can

stay uninfected until death. The mortality rate for a susceptible individual is μ, and the rate of infection is βu. Thus the probability for a nonvaccinated individual to fall ill during his or her life is

$$r_{\text{infection}} = \frac{\beta u}{\beta u + \mu}.$$

Therefore an individual wants to be vaccinated immediately if $r_{\text{vaccination}} < r_{\text{infection}}$ and does not want to be vaccinated at all if $r_{\text{vaccination}} > r_{\text{infection}}$. A level for the prevalence that balances both risks is

$$u_{\text{crit}} = \frac{\rho\mu}{\beta(1-\rho)}.$$

Thus the optimal vaccination rate $\psi(u)$ is zero for $u \leqslant u_{\text{crit}}$ and ∞ otherwise.

A stationary point corresponding to this vaccination rate is biologically relevant if and only if it is stable, because, apart from the trajectory that always sits at the equilibrium point, no trajectory stays in a neighborhood of an unstable point. Instability corresponds to a high derivative of ψ at the stationary point. This is the case if $u_{\text{crit}} \in [u_0(0), u_\infty]$. Moreover, there then can be more than one stationary point. For simplicity, we do not consider parameter sets with $u_{\text{crit}} \in [u_0(0), u_\infty]$. Then there is only one (locally stable) stationary point.

Let u_{ind} be the prevalence in the stationary point. We distinguish two cases.

Case 1. $\max\{u_0(0), u_\infty\} < u_{\text{crit}}$

Because $u \in [\min\{u_0(0), u_\infty\}, \max\{u_0(0), u_\infty\}]$ we have $u < u_{\text{crit}}$ and hence $\psi(u) = 0$. Thus, in this case, $u_{\text{ind}} = u_0(0)$.

Case 2. $u_{\text{crit}} < \min\{u_0(0), u_\infty\}$

Hence $u_{\text{crit}} < u$ and therefore $\psi(u) = \infty$. We get, in Case 2, $u_{\text{ind}} = u_\infty$.

Hence the prevalence corresponding to the "strictly selfish" vaccination strategy is

$$u_{\text{ind}} = \begin{cases} u_\infty & \text{for } \dfrac{\rho\mu}{\beta(1-\rho)} < \min\{u_0(0), u_\infty\} \\ u_0(0) & \text{for } \dfrac{\rho\mu}{\beta(1-\rho)} > \max\{u_0(0), u_\infty\}. \end{cases}$$

5. COMPARISON

Within a wide range of parameter values, the best public and the best individual vaccination coverage coincide (Fig. 4). u_{pub} jumps from $u_0(0)$ to u_∞ at $\rho = \rho_0$ while the jump of u_{ind} occurs for ρ in the interval

$$[\underline{\rho}, \bar{\rho}] := \left\{ \rho \middle| u_0(0) < \frac{\rho\mu}{\beta(1-\rho)} < u_\infty \text{ or } u_\infty < \frac{\rho\mu}{\beta(1-\rho)} < u_0(0) \right\}.$$

Thus the two vaccination coverages are the same only if $\rho_0 \in [\underline{\rho}, \bar{\rho}]$. There are two situations in which the best global strategy is different from the best individual strategy (see Fig. 4). In the first situation, the individuals want to be vaccinated while vaccination increases the prevalence: The risk of disease (at a vaccination level of zero) is greater than the risk of side effects $[u_0(0) < u_{\text{crit}}]$ while vaccination increases the prevalence ($\rho > \rho_0$). In the second scenario, the individuals refuse vaccination while vaccination decreases the prevalence: This happens if, with maximal vaccination coverage, the risk of infection by transmission is lower than the risk of infection by vaccination ($u_\infty > u_{\text{crit}}$) while vaccination decreases the prevalence ($\rho < \rho_0$). Realistic parameter estimation for ρ, ρ_0 is outside the scope of the present work because parameter estimation requires sophisticated statistical methods.

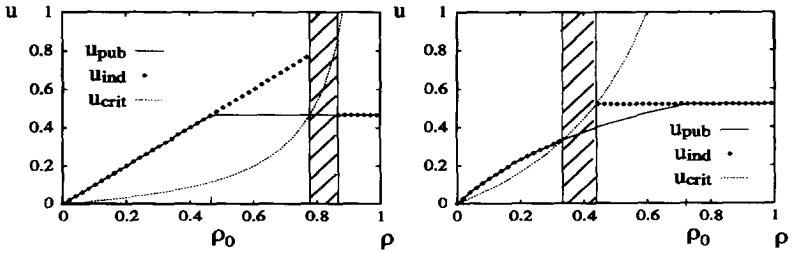

FIG. 4. The equilibrium prevalence corresponding to the best public and the best individual vaccination strategy for two different sets of parameters. The function u_{crit} denotes the level of prevalence where the risk of infection and the risk of side effects are the same. Within the hatched region, it is $u_{\text{crit}} \in [u_0(0), u_\infty]$, and thus this region is not considered. (*Left*) There is a range of risk, wherein the best public strategy is not to vaccinate, whereas the best individual strategy would be to vaccinate. (Parameter values: $\kappa_0 = 0$, $b = 0.8$, $\bar{b} = 0.8$, $\mu = 0.2$, $\delta = 0$, $\beta = 1.5$, $\alpha = \gamma = 0$.) (*Right*) There also is a range of risk, wherein the best public strategy is to vaccinate, whereas the best individual strategy would be not to vaccinate. (Parameter values: $\kappa_0 = 1$, $b = 0.3$, $\bar{b} = 0.3$, $\mu = 1$, $\delta = 0$, $\beta = 1.5$, $\alpha = \gamma = 0$.)

At this point, the mathematical analysis must stop. There are no mathematical tools for evaluating the two contradicting vaccination strategies. The reasons for the contradicting "best" vaccination coverages are the different aims of population and individuals. What mathematics *can* do is to describe such effects and investigate scenarios to work out the difficulties. The decision itself is a social and political one.

6. DISCUSSION

In the first part, we analyzed a SIRS model with a vaccination that may produce side effects. The vaccination rate was assumed to be constant. If the vaccination rate is not zero and there is a positive risk of side effects (positive possibility of the vaccination producing diseased cases), then the behavior of the model is slightly different from that of a usual SIRS model: there is no uninfected stationary solution (because vaccination in a totally uninfected population produces some infectives immediately) but exactly one infected stationary solution. This solution is asymptotically globally stable. The prevalence at this stationary solution depends monotonically on the vaccination rate: if the risk of side effects ρ is below some threshold ρ_0, then vaccination decreases prevalence; otherwise, vaccination increases prevalence. The optimal vaccination coverage for the population (the coverage that minimizes prevalence) was determined.

In the second part, the point of view of an individual was considered. Therefore the vaccination rate was assumed to depend on prevalence. This assumption yields a SIRS model that has had similarities to models with nonlinear incidence functions. The (local) bifurcations were determined. The possible bifurcations are Hopf, saddle-node, and (possibly singular) Takens-Bogdanov bifurcations. It is well known that the last also implies global bifurcations (e.g., the bifurcation of two nested periodic orbits). This gives some hope that (using the known tools for the Takens-Bogdanov bifurcations in two dimensions) the behavior of the systems with nonlinear vaccination or incidence rate can be classified, although they show global bifurcations. The optimal vaccination rate for the individuals of the population (the coverage that minimizes the risk for the individuals) was determined.

In part three, the two optimal vaccination rates were compared. For the most part, they agree. Nevertheless, some situations do exist where a conflict occurs between the interest of the population and that of single individuals.

Until now, not much attention has been paid to the problem of comparing and evaluating different types of optimization approaches. Such considerations are necessary for the design of general accepted vaccination guidelines.

APPENDIX A. PROOF OF THE RESULTS

A.1. *PROOF OF RESULT* 1

Step 1. *Existence and Uniqueness of the Feasible Stationary Point*

Let u_0 be a root of p. Let x_0 be determined by Eq. (10). Hence (x_0, u_0) is a stationary point of Eqs. (6) and (7). Because x, u, and w are positive and $x + u + w \leqslant 1$, we are interested only in stationary points of the invariant compact set

$$K := \{(x,u) | 0 \leqslant u \leqslant 1,\ 0 \leqslant x \leqslant 1-u\}.$$

Thus any root u leading to a feasible stationary point satisfies [using Eq. (10) and condition (5)]

$$u + x = u + \frac{b + \gamma - \left[\gamma + b - (1-\kappa_0)\bar{b}\right]u}{b + \psi + \gamma + (\beta - \delta)u} \leqslant 1 \quad \Leftrightarrow \quad p_1(u) \leqslant 0$$

with

$$p_1(u) = (\beta - \delta)u^2 + \left[\psi + (1-\kappa_0)\bar{b} - (\beta - \delta)\right]u - \psi. \qquad (15)$$

Because $p_1(0) = -\psi < 0 < (1-\kappa_0)\bar{b} = p_1(1)$, there is a constant $u^* \in (0,1)$, such that each root u_0 of p with $u_0 \in (0, u^*)$ corresponds to a feasible stationary point $(x_0, u_0) \in K$. The next step is to show that there is exactly one stationary point in K; that is, that $p(u)$ has exactly one root in $(0, u^*)$. We prove $p(u^*) < 0$. u^* satisfies $p_1(u^*) = 0$. Thus

$$\delta(\beta - \delta)u^{*3} = \delta\left[(\beta - \delta) - \psi - (1-\kappa_0)\bar{b}\right]u^{*2} + \delta\psi u^*.$$

Replace the third-order term in $p(u^*)$:

$$\begin{aligned} p(u^*) = &-u^{*2}(\beta - \delta)(\alpha + b + \gamma) \\ &- u^*\Big\{\rho\psi\left[b + \gamma - (1-\kappa_0)\bar{b}\right] \\ &\qquad + (b+\gamma)\left[\delta - \beta + (1-\kappa_0)\bar{b} + \alpha\right] + \psi\left[\alpha + (1-\kappa_0)\bar{b}\right]\Big\} \\ &+ \rho\psi(b+\gamma). \end{aligned}$$

Similarly, replacing the second-order term leads to

$$\begin{aligned} p(u^*) &= -\Big\{-(1-\rho)\psi\left[b + \gamma - (1-\kappa_0)\bar{b}\right] \\ &\qquad + \left[\beta - \delta + b + \gamma - (1-\kappa_0)\bar{b}\right]\alpha\Big\}u^* \\ &\quad -(1-\rho)\psi(b+\gamma) - \psi\alpha \\ &= Au^* + B. \end{aligned}$$

Because $B < 0$ and, using Eq. (5), $A + B < 0$ and $u^* \in (0,1)$, $p(u^*) < 0$. Furthermore, $p(0) = \rho\psi(b+\gamma) > 0$ holds. Thus there is at least one root of p in the interval $(0, u^*)$. Moreover, from $p(0) > 0$ and $p(u) \to -\infty$ for $u \to -\infty$ one can conclude that p has at least one root in $(-\infty, 0)$. Similarly, there is a root in (u^*, ∞). Because degree$(p) = 3$, there are at most three real roots. Hence exactly one simple root is located in $(0, u^*)$.

Step 2. The ω-Limit Set of K Is the Unique Stationary Point in K

Because K is a two-dimensional positive invariant compact set that contains only one stationary point, the ω-limit set can contain only periodic orbits and this stationary point. Now periodic orbits are excluded: it is useful not to consider the coordinates x, u but $\xi := x/w$, $\eta := u/w$. The corresponding system of differential equation reads

$$\dot{\xi} = \xi(b+\gamma-\psi) - (1-\rho)\psi\xi^2 + (1-\kappa_0)\bar{b}\eta - \alpha\xi\eta - \beta\frac{\xi\eta}{1+\xi+\eta} + (b+\gamma),$$

$$\dot{\eta} = -\left(\bar{\mu} - \mu + \alpha - \kappa_0\bar{b} - \gamma\right)\eta - \alpha\eta^2 + \rho\psi\xi + \beta\frac{\xi\eta}{1+\xi+\eta} - (1-\rho)\psi\xi\eta.$$

Dividing these differential equations by $\xi\eta$ and rescaling time, we obtain

$$\dot{\xi} = f(\xi, \eta), \qquad \dot{\eta} = g(\xi, \eta)$$

with

$$f(\xi,\eta) := (b+\gamma-\psi)\frac{1}{\eta} - (1-\rho)\psi\frac{\xi}{\eta} + (1-\kappa_0)\bar{b}\frac{1}{\xi} - \alpha - \beta\frac{1}{1+\xi+\eta} + (b+\gamma)\frac{1}{\xi\eta},$$

$$g(\xi,\eta) := -\left(\bar{\mu} - \mu + \alpha - \kappa_0\bar{b} - \gamma\right)\frac{1}{\xi} - \alpha\frac{\eta}{\xi} + \rho\psi\frac{1}{\eta} + \beta\frac{1}{1+\xi+\eta} - (1-\rho)\psi.$$

The divergence of this system is

$$\frac{\partial f}{\partial \xi} + \frac{\partial g}{\partial \eta} = -(1-\rho)\psi\frac{1}{\eta} - (1-\kappa_0)\bar{b}\frac{1}{\xi^2} - (b+\gamma)\frac{1}{\xi^2\eta} - \alpha\frac{1}{\xi} - \rho\psi\frac{1}{\eta^2} < 0. \tag{16}$$

From the negative criterion of Bendixson, it follows that there are no periodic orbits.

A.2. PROOF OF RESULT 2

We determine the sign of $u_0'(\psi)$. From $p[u(\psi);\psi] \equiv 0$ we conclude

$$u_0'(\psi) = -\left[p'(u)|_{u_0(\psi)}\right]^{-1}\frac{\partial}{\partial\psi}p[u_0(\psi);\psi].$$

Let

$$\begin{aligned} q(u) &:= \frac{\partial}{\partial\psi}p(u;\psi) \\ &= \delta u^2 - \left\{\delta + (1-\kappa_0)\bar{b} + \alpha + \rho\left[b+\gamma-(1-\kappa_0)\bar{b}\right]\right\}u \\ &\quad + \rho(b+\gamma), \\ f(\psi) &:= \left|p'(u)|_{u_0(\psi)}\right|^{-1}. \end{aligned}$$

Because we already know that $p'[u_0(\psi)] < 0$, the equation for $u_0'(\psi)$ reads

$$u_0'(\psi) = f(\psi)q[u_0(\psi)]. \tag{17}$$

This equation can be interpreted as a differential equation for u_0 with time ψ. Because $f(\psi) > 0$, this differential equation is (up to a rescaling of the time ψ) an autonomous equation. Hence u_0' cannot change sign. This means that all vaccination rates ψ will either lower prevalence or increase prevalence. The question whether vaccination has any advantage can be answered by inspecting the sign of $u_0'(\psi)$ for $\psi = 0$. The quantity $u_0(0)$ is the only root of p in the interval $(0, u^*)$. For $\psi = 0$, p is a quadratic polynomial in u multiplied by u; that is, $u_0(0)$ can be explicitly computed (although it is not worth doing it). However, it is of interest to find a criterion that determines whether vaccination increases or decreases the prevalence. The critical case is obviously $u_0'(0) = 0$; that is, $q[u_0(0)] = 0$. In this equation, one can solve for ρ and obtain a critical threshold ρ_0 for ρ,

$$q[u_0(0)] = 0 \quad \Leftrightarrow \quad \rho = \rho_0,$$

with ρ_0 defined by

$$\rho_0 := u_0(0)\frac{[1-u_0(0)]\delta+(1-\kappa_0)\bar{b}+\alpha}{b+\gamma-[b+\gamma-(1-\kappa_0)\bar{b}]u_0(0)}.$$

We now show $0<\rho_0<1$. The inequality $0<\rho_0$ is obvious from $u_0(0)<1$. We prove the inequality $\rho_0 \leqslant 1$. To do so, we consider $\rho=1$ and show that, if vaccination is certain to lead to illness, it cannot decrease the prevalence. Let $v=u_0(0)$. v is the positive root of Eq. (12) for $\psi=0$:

$$0=v^2\delta(\beta-\delta)-v[(\beta-\delta)(\delta+\alpha+b+\gamma)-(1-\kappa_0)\bar{b}\delta] + (b+\gamma)[\beta-\beta_0] =: \tilde{p}(v). \tag{18}$$

We can estimate v. For $v=0$, $\tilde{p}(v)=(b+\gamma)(\beta-\beta_0)>0$ and, for $v=(b+\gamma)/\delta$,

$$\tilde{p}\left(\frac{(b+\gamma)}{\delta}\right) = -\left\{(\beta-\beta_0)+\left[(1-\kappa_0)\bar{b}+\alpha\right]\right\}\left(1+\frac{\alpha}{\delta}\right)(b+\gamma) + \left[(\beta-\beta_0)+(1-\kappa_0)\bar{b}\right](b+\gamma)<0,$$

and hence $v<(b+\gamma)/\delta$. Furthermore, we have for $\rho=1$ that

$$q(v)=\delta v^2-(\delta+\alpha+b+\gamma)v+(b+\gamma).$$

Using Eq. (18) to eliminate the quadratic term, we get

$$q(v)=\frac{[(1-\kappa_0)\bar{b}+\alpha](b+\gamma)-(1-\kappa_0)\bar{b}\delta v}{\beta-\delta}.$$

The latter expression is positive for $v\in[0,(b+\gamma)/\delta]$, and thus vaccination increases the prevalence for $\rho=1$. Hence, $\rho_0<1$. ■

Remark 1

The function $\psi \mapsto u_0(\psi)$ has a limit for $\psi\to\infty$. Within this limit, everyone who enters the class of susceptibles is vaccinated immediately. All infections are caused by the side effects of vaccination; there is no natural transmission of infection any more. Let $u_\infty(\rho) := \lim_{\psi\to\infty} u_0(\psi;\rho)$. Dividing Eq. (12) by ψ and letting $\psi\to\infty$ one gets

$q(u_\infty) = 0$. The roots of q are

$$u_{+/-} = \frac{1}{2\delta}\Big(\delta + (1-\kappa_0)\bar{b} + \alpha + \rho\big[b + \gamma - (1-\kappa_0)\bar{b}\big] \pm \sqrt{\Big\{\delta + (1-\kappa_0)\bar{b} + \alpha + \rho\big[b+\gamma-(1-\kappa_0)\bar{b}\big]\Big\}^2 - 4\rho(b+\gamma)\delta}\Big).$$

An elementary computation shows that $0 < u_- < 1 < u_+$; that is, $u_\infty(\rho) = u_-$. Later on, we will need the monotonicity of $u_\infty(\rho)$ in ρ. Differentiating $q[u_\infty(\rho); \rho] \equiv 0$ with respect to ρ yields

$$0 = \big[b + \gamma - (1-\kappa_0)\bar{b}\big]u_\infty(\rho) + (b+\gamma) + q'(u_\infty;\rho)u'_\infty(\rho).$$

Because the polynomial q is of degree 2, $q(u;\rho) \to \infty$ for $u \to \infty$, and u_∞ is the smaller root of q, it is $q'(u_\infty;\rho) < 0$. Thus it follows that

$$u'_\infty(\rho) > 0.$$

Remark 2

Let J_0 be the Jacobian of this system at the stationary point. We can obtain from Result 1 that $\operatorname{tr}(J_0) \leqslant 0$ and $\det(J_0) \geqslant 0$. In the proofs for Results 3 and 4, we need the strict inequalities. To avoid lengthy computations, only the idea of the proofs will be given.

$\operatorname{tr}(J_0) < 0$. In the proof for Result 1, step 2, we considered a transformed system. For this system, the trace of the Jacobian at the stationary point is strictly negative. Thus the distance of a solution to the stationary point asymptotically behaves like $e^{-\epsilon t}$, $\epsilon > 0$. If we transform the system back to the original one, ϵ may change its magnitude but can never become nonnegative. Thus, also in the original system, a trajectory tends asymptotically to the stationary point with a distance behavior like $e^{-\epsilon' t}$, and therefore $\operatorname{tr}(J_0) < 0$.

$\det(J_0) > 0$. Rewrite the system of Eqs. (6) and (7) as

$$x' = f(x,u),$$
$$u' = g(x,u).$$

We have $\det(J_0) = f_x g_u - g_x f_u$. We know that (x_0, u_0) is the unique stationary point. Moreover, $f_x(x_0,u_0) \neq 0$. Thus we can use the implicit function theorem. There is a function $h(u)$ with $h(u_0) = x_0$ and $f[h(u),u] \equiv 0$. Equation (12) is identical with $g[h(u),u] = 0$ up to a

nonsingular transformation. We know that the root u_0 is simple; that is, at the point, u_0 holds:

$$0 \neq \frac{d}{du} g[h(u), u] = g_x h' + g_u = g_x \left(-\frac{f_u}{f_x} \right) + g_u$$

$$\Rightarrow \quad 0 \neq -g_x f_u + g_u f_x = \det(J_0).$$

Because the determinant cannot be negative, it is strictly positive.

A.3. PROOF OF RESULT 3

Because $\rho \leqslant \rho_0$, $u_0(\psi)$ is nonincreasing in ψ; that is, $T(u)$ is nonincreasing in u. Hence there is exactly one fixed point U. Let the corresponding stationary point be (X, U).

In the following discussion, the stability of this fixed point will be analyzed. Here the results of Section 3 will be used. Fix $\theta \in [0,1]$ and consider $\psi \equiv \psi(\theta)$. This yilds a system with a constant vaccination rate $\psi(\theta)$ that depends on a parameter θ. This system was analyzed in Section three. On the other hand, we have the system with $\psi = \psi(u)$ which will be discussed now.

Rewrite the system of Eqs. (13) and (14) as $dx/dt = f[x, u, \psi(u)]$, $du/dt = g[x, u, \psi(u)]$. The Jacobian of this system at (X, U) is

$$J = \begin{pmatrix} f_x[X, U, \psi(U)] & f_u[X, U, \psi(U)] + f_\psi[X, U, \psi(U)]\psi'(U) \\ g_x[X, U, \psi(U)] & g_u[X, U, \psi(U)] + g_\psi[X, U, \psi(U)]\psi'(U) \end{pmatrix}. \tag{19}$$

Thus

$$\operatorname{tr}(J) = f_x + g_u + g_\psi \psi'(U),$$

$$\det(J) = (f_x g_u - g_x f_u) + \psi'(U)(f_x g_\psi - g_x f_\psi).$$

Let J_0 be the Jacobian of Eqs. (13) and (14) with constant vaccination rate $\psi(u) \equiv \psi(U)$. The determinant and trace of J read

$$\operatorname{tr}(J) = \operatorname{tr}(J_0) + \rho X \psi'(U),$$

$$\det(J) = \det(J_0) + \psi'(U)(f_x g_\psi - g_x f_\psi).$$

To replace the term $\psi'(U)(f_x g_\psi - g_x f_\psi)$, consider the case that the vaccination rate ψ is constant $\psi(\theta)$ with $\theta \in [0,1]$. Then there is a unique stationary point $(\chi_0(\theta), \vartheta_0(\theta))$ of the system of Eq. (13) and

(14). Thus $(\chi_0(\theta), \vartheta_0(\theta))$ is determined by $f[\chi_0(\theta), \vartheta_0(\theta), \psi(\theta)] = 0$, $g[\chi_0(\theta), \vartheta_0(\theta), \psi(\theta)] = 0$. Differentaiting these equations with respect to θ leads to

$$f_x \chi_0'(\theta) + f_u \vartheta_0'(\theta) + f_\psi \psi'(\theta) = 0, \tag{20}$$

$$g_x \chi_0'(\theta) + g_u \vartheta_0'(\theta) + g_\psi \psi'(\theta) = 0. \tag{21}$$

From Eqs. (20) and (21), it follows that $\psi'(\theta)(f_x g_\psi - g_x f_\psi) = -(f_x g_u - g_x f_u)\vartheta_0'(\theta)$. Identifying θ with U and $\vartheta_0(\theta)$ with $u_0[\psi(U)]$, we obtain

$$\psi'(U)(f_x g_\psi - g_x f_\psi) = -\det(J_0)\frac{du_0(\psi)}{d\psi}\frac{d\psi(U)}{dU}.$$

Now, for all $\tau \in [0,1]$ we have $\psi_\tau(U_0) \equiv \psi(U_0)$. Thus (X_0, U_0) is a stationary point of the system independent of τ. If $\tau = 0$, (X_0, U_0) is stable and the only stationary point. Let J_τ be the Jacobian of the system at the point (X_0, U_0) with vaccination rate $\psi_\tau(u)$. We obtain the equations

$$\operatorname{tr}(J_\tau) = \operatorname{tr}(J_0) + \tau\rho X_0 \psi'(U_0),$$

$$\det(J_\tau) = \det(J_0)\{1 - u_0'[\psi_\tau(U)]\tau\psi'[U_0]\}.$$

We have from Remark 2 in the proof of Result 2 that $\operatorname{tr}(J_0) < 0$ and $\det(J_0) > 0$. Because $\rho \leqslant \rho_0$, we know already that $T'(U) \leqslant 0$ and thus $\det(J) > 0$. Hence only a Hopf bifurcation can take place. For a Hopf bifurcation to occur it is necessary that the eigenvalues $\lambda_{+/-}(\tau)$ of the Jacobian are imaginary for $\tau = \tau_0 \in (0,1)$ and $(d/d\tau)re(\lambda_{+/-})|_{\tau=\tau_0} \neq 0$. Moreover, some conditions for nonsingularity must be fulfilled—see Theorem 3.4.2 in Guckenheimer and Holmes [20]. The first condition implies $\psi_{\tau_0}'(U_0) = -\operatorname{tr}(J_0)/\rho X_0$. The second condition corresponds with $\rho X_0 \psi'(U_0) \neq 0$, which is trivially fulfilled. The nonsingularity of the bifurcation is generically fulfilled. Thus Hopf bifurcation occurs for

$$\tau_0 \psi'(U) = -\frac{\operatorname{tr}(J_0)}{\rho X}. \qquad \blacksquare$$

A.4. PROOF OF RESULT 4

For $\rho > \rho_0$, it cannot be excluded that $T(u)$ has more than one fixed point; that is, in general the system of Eqs. (13) and (14) has more than one stationary point.

Let (X_0, U_0) be a stationary point. Again, we want to investigate the stability and possible bifurcations of this stationary point. As before, we

define $\psi_\tau(u) = \tau\psi(u) + (1-\tau)\psi(U_0)$, $\tau \in [0,1]$. A Hopf bifurcation generically occurs for

$$\psi'_{\tau_0}(U_0) = -\frac{\operatorname{tr}(J_0)}{\rho X_0} =: \psi'_{\text{Hopf}}(\rho), \qquad \det(J_\tau) \geqslant 0.$$

For a saddle-node bifurcation, necessary conditions are that $\det(J_\tau) = 0$, transversality of the eigenvalues (which is fulfilled similarly to the proof of Result 3), and some nonsingularity conditions (which are generic); see Theorem 3.4.1 in Guckenheimer and Holmes [20]. Hence, generically a saddle-node bifurcation occurs for

$$\psi'_{\tau_0}(U_0) = \frac{1}{u'_0[\psi(U_0)]} = \frac{-p'(U_0)}{q(U_0)} =: \psi'_{\text{saddle node}}(\rho). \qquad \blacksquare$$

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