RESISTANCE MECHANISMS MATTER IN SIR MODELS

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ABSTRACT. We compare four SIR-style models describing behavioral or immunological disease resistance that may be both partial and temporary in parameter regions feasible for interpandemic influenza. For the models studied, backward bifurcations and bistability may occur in contexts where resistance is due to behavior change, but they do not occur when resistance originates from an immune response. Care must be exercised to ensure that modeling assumptions about resistance are consistent with the biological mechanisms under study.

1. **Introduction.** Resistance against an infectious disease is protection that reduces an individual's risk of contracting the disease, relative to some baseline susceptibility. Many public health policies for reducing the prevalence of infectious disease impede transmission by creating some form of resistance in the host population. Vaccination programs, on one hand, create immunological resistance by training our immune systems to identify a pathogen. Public education programs, on the other hand, create behavioral resistance by training us about preventive behaviors. In both cases, increases in resistance decrease transmission of the infectious agent.

At first pass, we may consider using similar models for both cases. For instance, Gomes et al. [1] use a model for immunological resistance (immunity) that is very similar to a model used by Hadeler and Castillo-Chavez [2] for behavioral resistance in sexually transmitted diseases. But the acquisition and persistence of these two forms of resistance have an important difference. Immunological resistance persists and is often enhanced by repeated infection [3]. Behavioral resistance, on the other hand, may be adopted and abandoned arbitrarily. People who adopt preventive behaviors but still get infected might revert to their original behavior because the preventive behavior did not avert their infection. This difference between behavioral resistance and immunological resistance can have important consequences for epidemiological dynamics.

In this paper, we compare four simple epidemic models that incorporate resistance. These models differ primarily in their bookkeeping of resistance. The comparison shows that if resistance is behavioral, backward bifurcations occur when reinfection causes a high rate of resistance loss. However, backward bifurcations do not occur when resistance is immunological, since reinfection strengthens immunological resistance. This qualitative difference in model predictions suggests that modelers should carefully specify the mechanisms of resistance particular to the problem at hand. We close with a discussion of an appropriate null model for immunological resistance and its application.
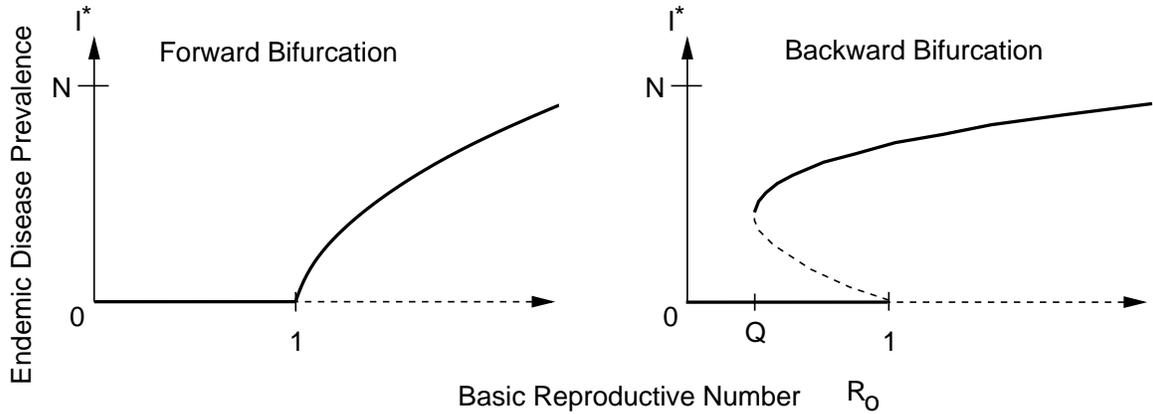
FIGURE 1. Illustrative bifurcation diagrams for forward (left) and backward (right) bifurcations in SIR models as functions of the basic reproductive number $\mathcal{R}_0$. The dotted lines represent locally unstable equilibria, while solid lines represent locally stable equilibria. In a forward bifurcation, there is always a single locally stable equilibrium. In a backward bifurcation, there exists a fold bifurcation at Q such that if $Q < \mathcal{R}_0 < 1$, locally stable endemic and disease-free equilibria coexist.

2. **Analysis.** In the classic compartmental Kermack–McKendrick model with population turnover, a population is subdivided into susceptible (S), infected (I), and recovered and resistant (R) classes [4]. A standard-incidence formulation, where β is the transmission rate, γ is the recovery rate, and μ is the population turnover rate, gives the model equations

$$\frac{dS}{dt} = \mu N - \beta \frac{I}{N} S - \mu S, \tag{1a}$$

$$\frac{dI}{dt} = \beta \frac{I}{N} S - \gamma I - \mu I, \tag{1b}$$

$$\frac{dR}{dt} = \gamma I - \mu R, \tag{1c}$$

with the total population size $N = S + I + R$. In this model, the birth rate exactly offsets the natural mortality rate. Since there is no disease-induced mortality, the population's size never changes and is determined by the initial conditions. Thus, N is not a dynamic variable and, without loss of generality, the reader may assume $N = 1$.

System (1) has two stationary solutions: a disease-free solution where

$$S(t) = N, \quad I(t) = 0, \quad R(t) = 0, \tag{2}$$

and an endemic solution where

$$S(t) = N \frac{\mu + \gamma}{\beta}, \quad I(t) = N \frac{\mu}{\beta} \left(\frac{\beta}{\mu + \gamma} - 1 \right), \quad R(t) = N \frac{\gamma}{\beta} \left(\frac{\beta}{\mu + \gamma} - 1 \right). \tag{3}$$

The two stationary solutions exchange stability depending on the value of the basic reproduction number $\mathcal{R}_0$, the expected number of times a single infectious individual will transmit the disease in an otherwise disease-free population. $\mathcal{R}_0$ can be calculated using standard methods [5]. For System (1),

$$\mathcal{R}_0 = \frac{\beta}{\mu + \gamma}. \tag{4}$$

A transcritical bifurcation in the stationary solutions occurs at $\mathcal{R}_0 = 1$ (see Figure 1). If $\mathcal{R}_0 < 1$, no biologically meaningful endemic stationary solution exists, and the disease-free stationary solution is a global attractor. But if $\mathcal{R}_0 > 1$, the endemic solution exists and is a global attractor, while the disease-free solution is a saddle point [6]. This is referred to as a forward bifurcation because in the neighborhood of the bifurcation point, the endemic disease prevalence is an increasing function of $\mathcal{R}_0$.

44   For some epidemic processes, there may be two endemic equilibria that coexist when $\mathcal{R}_0 < 1$ (see Figure 1). These endemic equilibria compose the two branches of a fold bifurcation: typically one that is
46   locally stable, and one that is locally unstable. For example, for $\mathcal{R}_0$ slightly less than 1, there are two endemic stationary solutions to System (5) (see Figure 2), which we will introduce shortly. If $\mathcal{R}_0$ decreases
48   further below 1, the two endemic solutions collide and annihilate each other in a fold bifurcation, leaving the disease-free solution as the only stationary solution. For mathematical methods to identify backward
50   bifurcations, see Dushoff et al. [7], Huang et al. [8], and van den Driessche and Watmough [5]. Backward bifurcations may appear in multigroup models [9, 10], standard-incidence models with strong demographic
52   effects [11], and diseases with synergistic interactions [12], but have also been identified in some models with behavioral resistance [2].
54   We will now study the dynamics of an infectious disease against which individuals can acquire resistance that is only temporary and only partially protective. For the moment, we will intentionally leave
56   the exact nature of this resistance vague, and define the resistance only in terms of individuals moving to and from the resistant class R. Individuals in the resistant class have a reduced risk: they become infected
58   at a fraction σ of the rate of susceptible individuals. Susceptible individuals directly acquire resistance at rate ν, presumably through some public health intervention, but resistant individuals revert to the
60   susceptible class at rate a. Of those individuals recovering from infection, the fraction $1 - f$ enter the resistant class and the fraction f enter the susceptible class. Applying these generalizations directly to
62   System (1) gives

$$\frac{dS}{dt} = \mu N - \beta S \frac{I}{N} + f\gamma I + aR - \nu S - \mu S, \tag{5a}$$

$$\frac{dI}{dt} = \beta(S + \sigma R)\frac{I}{N} - \gamma I - \mu I, \tag{5b}$$

$$\frac{dR}{dt} = -\sigma\beta R \frac{I}{N} + (1 - f)\gamma I - aR + \nu S - \mu R. \tag{5c}$$

Versions of this model have been studied by Hadeler and van den Driessche [10], Kribs-Zaleta and
64   Velasco-Hernandez [13], and Gomes et al. [14]. Some features are similar to those of System (1). The basic reproduction number is the expected number of new transmissions to susceptible individuals plus the
66   expected number of new transmissions to vaccinated individuals over the course of an infection, or

$$\mathcal{R}_0 = \left(\frac{\beta}{\mu + \gamma}\right)\left(\frac{\mu + a}{\mu + a + \nu}\right) + \left(\frac{\sigma\beta}{\mu + \gamma}\right)\left(\frac{\nu}{\mu + a + \nu}\right). \tag{6}$$

The disease-free stationary solution

$$S(t) = N\frac{\mu + a}{\mu + \nu + a}, \ I(t) = 0, \ R(t) = N\frac{\nu}{\mu + \nu + a} \tag{7}$$

68   is locally stable for $\mathcal{R}_0 < 1$, and locally unstable for $\mathcal{R}_0 > 1$. But unlike System (1), the bifurcation at $\mathcal{R}_0 = 1$ is a backward bifurcation [2] if

$$1 + \frac{(a + \sigma\nu)^2 + \mu\nu\sigma(1 + \sigma) + 2a\mu + \mu^2}{\gamma(1 - \sigma)(a + \mu)} < \left(1 + \frac{\sigma\nu}{a + \mu}\right)f. \tag{8}$$

70   This condition is derived using Huang's method [8]. In general, $0 \le f \le 1$, so there are situations where no choice of f can satisfy Equation (8). For instance, if $\sigma = 0$ or $\sigma = 1$, Equation (8) can not be satisfied. But
72   there is a subset of parameter space where Equation (8) is satisfied. For instance, for the parameter values in Table 1, which are motivated by interpandemic influenza, the bifurcation is backward when $f > 0.82$.
74   This was an exceptionally interesting result when first discovered by Hadeler and Castillo-Chavez [2]. It showed that backward bifurcations can occur in very simple models. Yet the mathematical analysis has not
76   provided us with a satisfactory biological explanation of *why* System (5) can exhibit a backward bifurcation while System (1) can not.
78   Suppose we take a closer look at the construction of System (5). While System (5) is an obvious generalization of System (1) under the conditions we have described, there is an equally reasonable
80   alternative. If we subdivide the infected population into a class of individuals who were previously susceptible (I_S) and a class of individuals who were previously resistant (I_R) and assume reinfection can

TABLE 1. Model parameters motivated by inter-pandemic influenza. The infectivity β corresponds to a basic reproductive number of approximately $R_0 = 4$ in the absence of vaccination.

Parameter	Estimate	Reference
Infectious period, $1/\gamma$	6 days	Dushoff et al. [15]
Immune period, $1/a$	6 years	Dushoff et al. [15]
Population turnover period, $1/\mu$	77.9 years	Miniño et al. [16]
Infectivity, β	570 year^{-1} person^{-1}	Dushoff et al. [15]
Vaccination rate, ν	1/3 year^{-1}	CDC [17]
Vaccine effectiveness, $1 - \sigma$	0.88	Wilde et al. [18]
Infection-acquired-immunity uptake, $1 - f$	Unknown	

not directly cause a loss of resistance,

$$\frac{dS}{dt} = \mu N - \beta S \frac{I_S + I_R}{N} + f\gamma I_S + aR - \nu S - \mu S, \tag{9a}$$

$$\frac{dI_S}{dt} = \beta S \frac{I_S + I_R}{N} - \gamma I_S - \mu I_S, \tag{9b}$$

$$\frac{dI_R}{dt} = \sigma \beta R \frac{I_S + I_R}{N} - \gamma I_R - \mu I_R, \tag{9c}$$

$$\frac{dR}{dt} = -\sigma \beta R \frac{I_S + I_R}{N} + (1 - f)\gamma I_S + \gamma I_R - aR + \nu S - \mu R, \tag{9d}$$

with

$$S + I_S + I_R + R = N. \tag{9e}$$

Just as in System (5), individuals can acquire and lose resistance, become sick, recover, and die. The basic reproductive number of System (9) is still given by Equation (6), and the dynamics of both systems are driven by many of the same properties. But there is a subtle difference. In System (5), recovering individuals may enter the susceptible or resistant classes independent of their past history. In System (9), infected individuals who were previously resistant can never return directly to the susceptible class. This difference turns out to be crucial. From (8), we see that the backward bifurcation only occurs when a large fraction f of recovered individuals return to the susceptible compartment. In System (9), the condition for a backward bifurcation is

$$1 + \frac{(a + \sigma\nu)^2 + \mu\nu\sigma(1 + \sigma) + 2a\mu + \mu^2}{\gamma(1 - \sigma)(a + \mu)} < f. \tag{10}$$

Since $f \leq 1$, Equation (10) can not be satisfied, no matter what fraction of infected susceptible individuals return to the susceptible compartment. Thus, a backward bifurcation is impossible in System (9).

The differences in the bifurcations of Systems (5) and (9) can be seen in Figures 2 and 3. By comparing these two models of partial and temporary resistance, we discover that the backward bifurcation of System (5) is a property of the exact nature of resistance (hence, our original vagueness). If resistance corresponds to an acquired antibody response that repeated infection reinforces, System (9) is more appropriate and we have only a forward bifurcation. But if resistance corresponds to a change in behavior that individuals may abandon when it fails to prevent infection, then System (5) is more appropriate, and backward bifurcations are a possibility.

A complete exploration of the bifurcation direction can be undertaken by allowing different classes of infection to enter the susceptible and resistant classes at different rates. Hadeler and van den Driessche

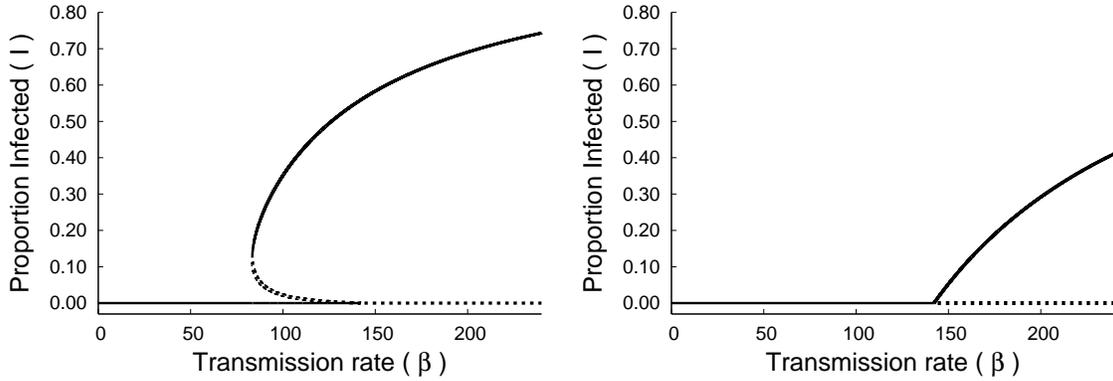FIGURE 2. Bifurcation plots for the equilibrium infection prevalence as functions of transmission rate β. Solid lines denote locally stable branches while dotted lines denote unstable branches. System (5) (left) has a subinterval of transmission rates for which there are two simultaneously stable equilibria. System (9) (right) exhibits a classic forward bifurcation with a unique locally stable equilibrium for all transmission rates. The parameter values from Table 1 with $N = 1$ and $f = 1$ were used in both plots.
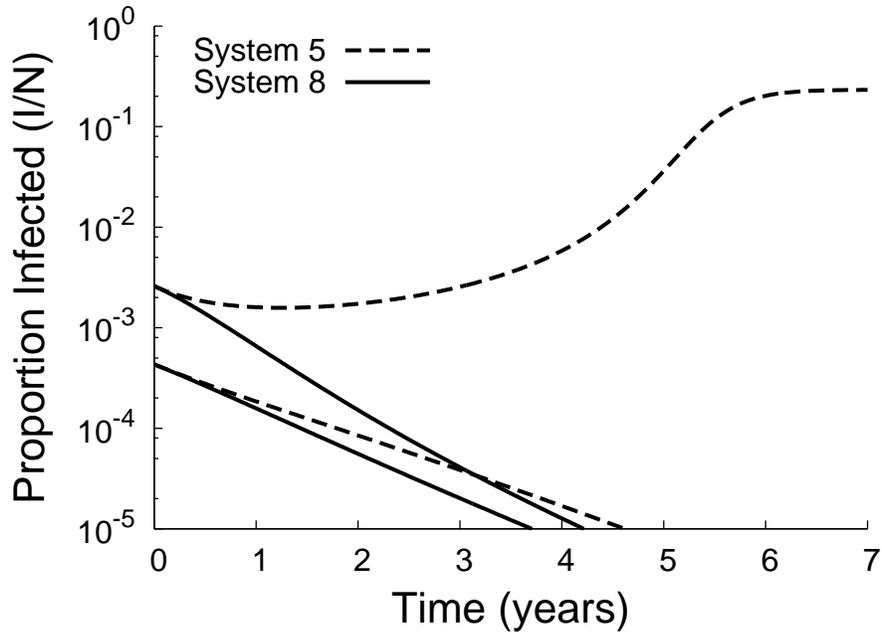

FIGURE 3. Dynamics for Systems (5) and (9) with $\mathcal{R}_0 < 1$ for two different initial conditions. For System (9), neither initial condition leads to endemic disease. But for System (5), the larger initial infection load leads to endemic infection, while infection dies out when the initial infection load is smaller. Parameter values are as in Table 1, except $\beta = 140$, $N = 1$, and $f = 0.9$. The initial conditions are perturbations from the disease-free equilibrium, $S_0 = \frac{\alpha+\mu}{\alpha+\mu+\nu}(N - I_0) \approx 0.35(1 - I_0)$ and $R_0 = \frac{\nu}{\alpha+\mu+\nu}(N - I_0) \approx 0.65(1 - I_0)$. The value of I at the unstable equilibrium is about 8.6×10^{-4} and I_0 was chosen to be half and three times this value.

[10] study a generalized class of models that includes

$$\frac{dS}{dt} = \mu N - \beta S \frac{I_S + I_R}{N} + f_S \gamma I_S + f_R \gamma I_R + aR - \nu S - \mu S, \tag{11a}$$

$$\frac{dI_S}{dt} = \beta S \frac{I_S + I_R}{N} - \gamma I_S - \mu I_S, \tag{11b}$$

$$\frac{dI_R}{dt} = \sigma \beta R \frac{I_S + I_R}{N} - \gamma I_R - \mu I_R, \tag{11c}$$

$$\frac{dR}{dt} = -\sigma \beta R \frac{I_S + I_R}{N} + (1 - f_S) \gamma I_S + (1 - f_R) \gamma I_R - aR + \nu S - \mu R. \tag{11d}$$

104 In this model, a proportion of individuals who recover from infection are resistant to reinfection and this
proportion depends on whether the individual was susceptible $(1 - f_S)$ or resistant $(1 - f_R)$ at the time of
106 infection. If $f_S = f_R$ then the proportion who become resistant is independent of their state prior to
becoming infected and System (11) reduces to System (5). If, instead, all of the individuals who were
108 resistant when they became infected return to the resistant class after infection, then $f_R = 0$ and
System (11) reduces to System (9).
110   We can define the population's average resistance as

$$1 - \frac{S + \sigma R}{N}. \tag{12}$$

At the disease-free equilibrium, the average resistance is

$$\frac{(1 - \sigma)\nu}{\mu + a + \nu}. \tag{13}$$

112 Near the bifurcation point $\mathcal{R}_0 = 1$, change in the average resistance can be understood in terms of center
manifold theory [19]. The dominant direction of change in the state variables in the neighborhood of the
114 disease-free equilibrium is in the approximate direction of the right eigenvector of the Jacobian of
System (11) corresponding to the bifurcating eigenvalue. When $\mathcal{R}_0 = 1$, the eigenvector of the bifurcating
116 eigenvalue is

$$\begin{bmatrix} \nu f_r \gamma \sigma - \sigma \nu a - (a + \mu)(1 - f_s)\gamma - (a + \mu)^2 \\ (\mu + a)(\mu + a + \nu) \\ \sigma \nu (\mu + a + \nu) \\ (a + \mu)[(1 - f_s)\gamma - \nu] - \nu \mu \sigma - \nu f_r \gamma \sigma - \nu^2 \sigma \end{bmatrix}. \tag{14}$$

Near the disease-free equilibrium, the slow time-scale dynamics are along a center manifold tangent to this
118 eigenvector. (Note that there also exists a second eigenvector with eigenvalue 0 corresponding to the
invariance of the population's size, which is not the vector of interest.) We can show, given the eigenvector
120 in Equation (14), that at the bifurcation point the average resistance given by Equation (12) is locally
decreasing in the direction of the eigenvector if and only if

$$1 + \frac{(a + \sigma \nu)^2 + \mu \nu \sigma(1 + \sigma) + 2a\mu + \mu^2}{\gamma(1 - \sigma)(a + \mu)} < f_S + \frac{\sigma \nu}{a + \mu} f_R. \tag{15}$$

122 This is exactly the backward bifurcation condition calculated using Huang's method [8]. Thus, System (11)
has a backward bifurcation if and only if small perturbations away from the disease-free steady state at the
124 bifurcation point lead to a decrease in the average resistance of the population.
By taking $f_S = f_R = 1$ and solving for a, we find that a necessary condition (see Figure 4) for a
126 backward bifurcation is

$$0 < \frac{a}{\gamma} < \sqrt{\sigma(1 - \sigma)\left(1 + \frac{\mu}{\gamma}\right)\frac{\nu}{\gamma}} - \sigma\frac{\nu}{\gamma} - \frac{\mu}{\gamma}. \tag{16}$$

Equation (16) indicates that backward bifurcations in this family of models with temporary and partial
128 resistance can occur only when resistance confers an intermediate level of protection from future infection,
population turnover is slow, resistance wanes slowly, and the resistance-acquisition rate ν is of intermediate
130 value. As the resistance-acquisition rate is increased from 0, the backward bifurcation can appear and then
disappear. This has important consequences for public policy design, since the resistance-acquisition rate is
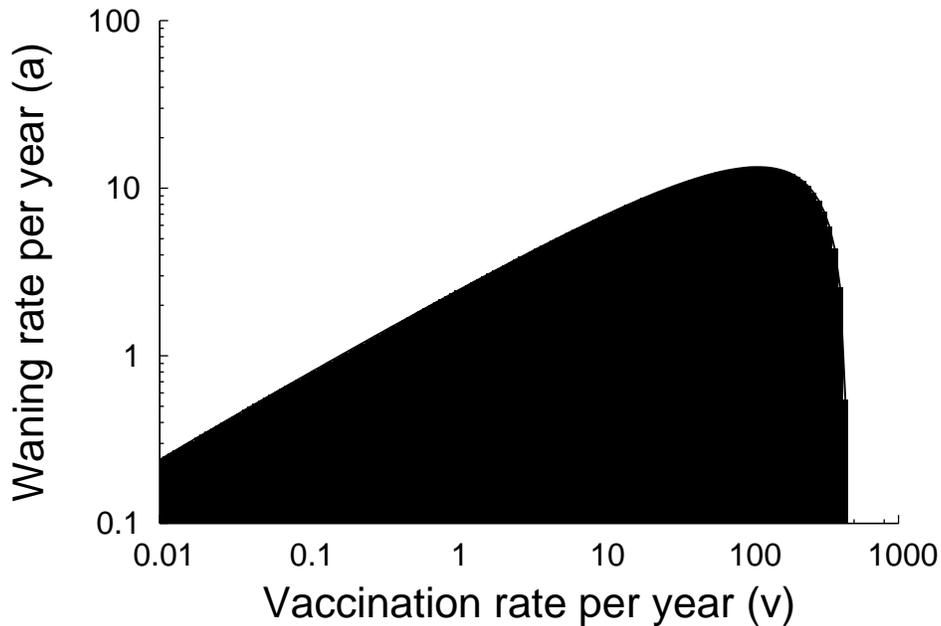132 easily controlled by public health programs.

FIGURE 4. A plot of the subset of (a, v)-parameter space for which backward bifurcations are possible, as determined by Equation (16). The shaded region includes a large part of the feasible ranges of the vaccination and waning rates. Parameters γ, μ, and σ have the values given in Table 1.

3. **Discussion.** When backward bifurcations occur in Systems (5) and (11) at the $\mathcal{R}_0 = 1$ threshold, the dynamics progress through a feedback process. If $\mathcal{R}_0 = 1$, the presence of a small number of infections has a net effect of slightly *reducing* the population's average resistance. This reduction in resistance leads to a slightly greater infection rate, and in turn, a further reduction in resistance. This self-amplifying feedback process grows rapidly as the population's resistance exhibits a partial collapse. This contrasts with the case of a forward bifurcation, where an increase in prevalence leads to a compensatory increase in resistance.

But the existence of a feedback process alone cannot distinguish forward and backward bifurcations. Whether a positive perturbation in the number of infected individuals leads to a self-amplifying feedback loop or to compensatory feedback depends on the details of the system. Self-amplifying feedback describes the dynamics only *when* the system is given a sufficiently large perturbation to switch basins of attraction. For values of $\mathcal{R}_0$ below 1, a small initial perturbation in the number of infections does not lead to a self-amplifying feedback in resistance reduction. Thus, the presence of a feedback loop by itself is not sufficient to identify backward bifurcations. In addition, it is not clear that this feedback mechanism applies to other backward bifurcations (e.g., Corbett et al. [11]). Providing a biological interpretation of the condition of Huang et al. [8] remains an important open problem in mathematical epidemiology.

Behavioral resistance can have almost arbitrary structure, so it is difficult to state anything general about how it affects bifurcation structure. On the other hand, biology suggests to us that the structure of immunological resistance usually satisfies certain monotonicity conditions, and that these monotonicity conditions preclude backward bifurcations in the absence of additional dynamic effects. First, the greater the resistance, the less chance of infection. Second, the greater the resistance, the faster the recovery if infection does occur. Third, exposure to disease or vaccine increases resistance. Fourth, resistance wanes sequentially, such that stronger resistance always lasts longer than weaker resistance. We refer to these four conditions as the immunological-resistance conditions (IRCs).

The IRCs can be formulated mathematically in several ways. As one example, we could consider an ordinary differential equation model without demographic effects, where the susceptible and infected

populations are subdivided among $j = 1 \ldots n$ compartments, S_j and I_j respectively, each with resistance $1 - \sigma_j$:

$$\frac{dS_j}{dt} = w_{j+1}S_{j+1} - w_j S_j - \beta \left(\sum_{j=1}^{n} I_j \right) \sigma_j S_j - \nu S_j + \gamma_{j-1}I_{j-1} + \nu S_{j-1}, \tag{17a}$$

$$\frac{dI_j}{dt} = \beta \left(\sum_{j=1}^{n} I_j \right) \sigma_j S_j - \gamma_j I_j. \tag{17b}$$

Here, w_j is the waning rate of resistance, ν is the vaccination rate, β is the infection rate, and γ_j is the recovery rate. The IRCs require that for all $i < j$, the susceptibilities $\sigma_i \geq \sigma_j$ and the recovery rates $\gamma_i \leq \gamma_j$. The third and fourth conditions are built into the structure of Equation (17). We also take $w_0 = w_{n+1} = \gamma_0 = S_0 = 0$. There also exist more general formulations of the IRCs.

Several models that exhibit backward bifurcations violate these conditions. The model studied in Arino et al. [20] violates the IRCs, as the authors note, because natural resistance provides greater protection than vaccination but lasts for a shorter time. Lipsitch and Murray [21] point out that the tuberculosis model of Feng et al. [22] exhibits backward bifurcations only when the parameter values violate the IRCs. Systems (5) and (11) can violate our IRCs because infection can result in a loss of resistance. Systems (1) and (9) satisfy the IRCs and admit only forward bifurcations. These examples show that the IRCs can play an important role in a model's bifurcation structure. Unless there is specific biological evidence to the contrary, we suggest that the IRCs should be adopted as the null model for immunological resistance. We also conjecture that models like System (17) do not exhibit backward bifurcations for biologically feasible parameter values.

Our comparative study illustrates the importance of the sometimes subtle bookkeeping issues associated with resistance mechanisms in epidemiological models. In situations where repeated infection is expected to stimulate resistance, extra state variables may be needed to adequately track the resistance state of individuals. In models where the resistance state after infection is independent of the resistance state before infection, extra state variables are not needed. In the models we considered, vaccination can occur at any time. Equivalent results can be derived for models like those studied in Gomes et al. [1], where vaccination occurs when new individuals enter the population, either through birth or immigration.

The subtly different models presented here have qualitatively different bifurcation structures with important epidemiological interpretations. If a backward bifurcation is present, reducing the basic reproduction number below 1 is necessary but may not suffice to eradicate an endemic disease. Eradication may require significantly greater investment than that needed to prevent reintroduction. We conclude that the bookkeeping of resistance history should be carefully constructed to encapsulate the specifics of the epidemiology and immunology under study.

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