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ROLE OF REPEAT INFECTION IN THE DYNAMICS OF A SIMPLE MODEL OF WANING AND BOOSTING IMMUNITY

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Some infectious diseases produce lifelong immunity while others only produce temporary immunity. In the case of short-lived immunity, the level of protection wanes over time and may be boosted upon re-exposure, via infection or vaccination. Previous work developed a simple model capturing waning and boosting immunity, known as the Susceptible-Infectious-Recovered-Waned-Susceptible (SIRWS) model, which exhibits rich dynamical behavior including supercritical and subcritical Hopf bifurcations among other structures. Here, we extend the bifurcation analyses of the SIRWS model to examine the influence of all parameters on these bifurcation structures. We show that the bistable region, involving both a stable fixed point and a stable limit cycle, exists only for a small region of biologically realistic parameter space. Furthermore, we contrast the SIRWS model with a modified version, where immune boosting may involve the occurrence of a secondary infection. Analysis of this extended model shows that oscillations and bistability, as found in the SIRWS model, depend on strong assumptions about infectivity and recovery rate from secondary infection. Understanding the dynamics of models of waning and boosting immunity is important for accurately assessing epidemiological data.

Keywords: Infectious Disease Dynamics; Waning Immunity; Boosting Immunity; Bifurcation Analysis; Hopf Bifurcation.

1. Introduction

Exposure to pathogenic agents typically induces an immune response that clears immediate infection and may provide future protection. For some infections, such as

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measles, this response is strongly protective and persists for long periods, perhaps even up to the lifetime of the host.[1,2] For other pathogens, such as the causative agent of pertussis, protection is only temporary and immunity to these pathogens wanes over time.[3,4] This transient immunity at the individual level can lead to the resurgence of disease in the population and complicated epidemiological dynamics such as multi-year outbreak oscillations.[5–8]

As complex infectious disease dynamics may have serious public health consequences, the underlying cause of these complexities has been the subject of much research both mathematically and in an applied context. Historically, compartmental models have played an important role in understanding the population dynamics of disease. In the classic Susceptible-Infectious-Recovered (SIR) model framework, individuals are classified into compartments based on their salient disease characteristics.[9] Codified through a coupled system of nonlinear ordinary differential equations (ODEs), this framework describes dynamics of the infection in the population.

An extension of the SIR framework adds a connection between the recovered class and susceptible class to represent the loss of immunity. The resulting system is known as the Susceptible-Infectious-Recovered-Susceptible (SIRS) model.[10] While the simple SIRS model is able to capture persistence of disease in a population, it is unable to reproduce oscillatory infection outbreaks.[10] However, when certain assumptions of the SIRS model are relaxed, such as through non-standard force of infection, oscillations in the level of infection in the population are possible.[11,12] Periodic behavior, however, can be recovered with simple models if both loss and regain of immunity are considered. Immunity against a pathogen may increase following re-exposure, and this *boosting* can be caused by either infection or vaccination. The resulting increase in immunity may occur with or without experiencing a secondary episode of the disease, i.e., potentially without visible symptoms or infectivity.

Describing waning immunity with compartmental models introduces new challenges. In particular, modelers must decide how to delineate and quantify levels of immunity.[10,13] Typically, these have been via discrete categories, although, more recently, immunity has been considered as a continuous parameter.[14–17] One exemplary model, the Susceptible-Infectious-Recovered-Waned-Susceptible (SIRWS) model incorporates waning and boosting immunity through the addition of a W compartment.[18] This compartment describes a waned state in which individuals are less immune than the recovered class, but more immune than the fully susceptible class. Initial analyses showed that the system exhibits three distinct dynamics depending on the degree of boosting — fixed points, limit cycles and bistability between the two.[18] Dafilis *et al.*[19] examined the influence of infectivity and natural mortality on the bifurcation structure of the SIRWS model and concluded that all three types of dynamical behavior are possible, but only if immune boosting is stronger than infection.

Other authors have extended the SIRWS model to explore additional questions such as the role of age structure, vaccination, seasonal forcing, strain dynamics, and more. Lavine *et al.*[18] examined the resurgence of pertussis by extending the SIRWS model to include age-structure and vaccination. They also performed a bifurcation analysis to determine the role of vaccination and immunity boosting on the structure of the system. Leung *et al.*[20] showed that the relative duration of vaccine-induced immunity and infection-induced immunity plays a significant role in determining epidemiological dynamics. Epidemiological patterns were found to be quite different when the duration of immunity varied widely between the two routes of infection, which is believed to be the case for pertussis.[4,21] Extensions in Dafilis *et al.*[22,23] considered seasonal forcing of disease transmission and found highly unpredictable behavior. Further work considered the interaction of similar pathogens[24] and demonstrated that much weaker boosting is necessary for periodic solutions in the context of cross-immunity. This highlights the interesting behavior when two phenomena that can cause oscillations — strain dynamics with cross-immunity[25,26] and waning/boosting of immunity[18] — are coupled. Recent work has examined the basic SIRWS model in more detail analytically, although open questions remain.[27]

In this paper, we extend the analyses of the SIRWS model. In particular, we determine an analytical condition for when the endemic equilibrium is stable. We also extend the numerical bifurcation analysis of the SIRWS model to all model parameters and determine the parameter regimes in which fixed points, limit cycles, and bistability occur. We show that the region of bistability is relatively small for biologically realistic parameters, despite its range mathematically. Furthermore, we introduce a modification of the SIRWS model that includes the potential for secondary infection en route to boosting of immunity. We compare the dynamics exhibited under the SIRWS and modified models to show that secondary infection must be very short or with extremely low infectivity to recover periodic behavior. Thus, nearly "silent" secondary infections are necessary for biologically realistic dynamics. This demonstrates a need for full understanding of the immune characteristics when evaluating the epidemiological course of infectious diseases.

The structure of the paper is as follows. In Sec. 2, we introduce the SIRWS model and our modification that includes secondary infection. In Sec. 3, we define an analytical condition for stability of the endemic equilibrium of the SIRWS model. In Sec. 4.1, we examine the bifurcation structure and dynamical properties of the SIRWS model, and in Sec. 4.2 those of the modified model. Finally, in Secs. 5 and 6, we place our results in a biological context and discuss the implications of our findings.

2. Model Formulation

In this section, we introduce the original SIRWS model and our extension that includes the possibility of immune boosting via secondary infection.

2.1. *SIRWS model*

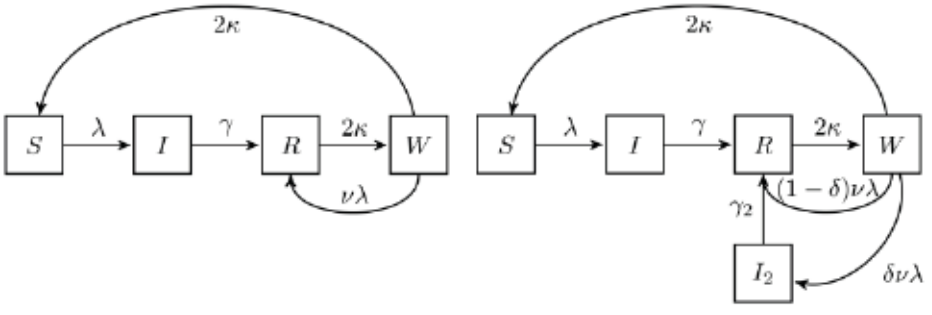
The classic SIRWS model describes the population of individuals in susceptible (S), infectious (I), recovered (R), and waned immune (W) compartments and is defined by the following system[18,24]:

$$\begin{aligned}
\frac{dS}{dt} &= \mu(1-S) - \lambda S + 2\kappa W, \\
\frac{dI}{dt} &= \lambda S - \gamma I - \mu I, \\
\frac{dR}{dt} &= \gamma I - 2\kappa R + \nu\lambda W - \mu R, \\
\frac{dW}{dt} &= 2\kappa R - 2\kappa W - \nu\lambda W - \mu W,
\end{aligned}$$

where $\lambda = \beta I$ is the force of infection, β is the infectivity, γ is the recovery rate, μ is the natural birth/death rate, κ is the immunity waning rate, and ν is the relative boost in immunity due to re-exposure. Parameter descriptions and baseline values are shown in Table 1. A flow diagram describing the movement of individuals through the population compartments is shown in Fig. 1(a).

2.2. *Modified SIRWS model*

We extend the SIRWS model to include an additional compartment, I_2, for secondary infection. This revises the assumption that re-exposure to a pathogen boosts immunity back into the recovered state by instead allowing for a secondary infection



(a) SIRWS model (b) Modified SIRWS model

Fig. 1. Schematic representation of the standard and modified SIRWS models, ignoring demography. S, I, R, and W represent the susceptible, infected, recovered, and waned immune populations, respectively. The force of infection is given by λ, where in (a) $\lambda = \beta I$ and in (b) $\lambda = \beta(I + \alpha I_2)$. In both (a) and (b), β is the infectivity, γ is the recovery rate, κ is the waning rate, and ν is the relative boost in immunity upon re-exposure. In (b), I_2 is the class of individuals with secondary infection, α is the relative rate of infectivity, δ is the fraction of individuals that experience secondary infection, and γ_2 is the recovery rate of secondary infected individuals.

Table 1. Parameter descriptions and baseline values. The first five parameters appear in both original and modified SIRWS models, while the final three parameters only appear in the modified model. Parameter values for the SIRWS model are from Leung *et al.*[24] and new parameters are chosen to produce a scenario that recoups dynamics exhibited when using the original parameter set. y = year, p = person.

Symbol	Description	Value	Unit
μ	Birth and death rate	1/80	y^{-1}
γ	Recovery rate	17	y^{-1}
κ	Waning immunity rate	1/10	y^{-1}
ν	Immune boosting strength	1	—
β	Transmission rate	260	$p^{-1}y^{-1}$
α	Relative infectivity of secondary infection	1	—
γ_2	Recovery rate of secondary infection	17	y^{-1}
δ	Fraction of exposures that lead to secondary infection	0	—

of potentially diminished length and infectivity. A flow diagram describing the movement of individuals through the compartments is shown in Fig. 1(b).

The modified system of equations including secondary infection, I_2, is given by:

$$\begin{aligned}
\frac{dS}{dt} &= \mu(1-S) - \lambda S + 2\kappa W,\\
\frac{dI}{dt} &= \lambda S - \gamma I - \mu I,\\
\frac{dR}{dt} &= \gamma I + \gamma_2 I_2 + (1-\delta)\nu\lambda W - 2\kappa R - \mu R,\\
\frac{dW}{dt} &= 2\kappa R - 2\kappa W - \nu\lambda W - \mu W,\\
\frac{dI_2}{dt} &= \delta\nu\lambda W - \gamma_2 I_2 - \mu I_2,
\end{aligned}$$

where $\lambda = \beta(I + \alpha I_2)$ is the force of infection. β, γ, κ, μ, and ν are defined as in the SIRWS model (Table 1). Here, we introduce three new parameters: α, the relative infectivity of secondary infections to primary infections, δ, the fraction of exposures that lead to secondary infection, and γ_2, the recovery rate of secondary infections (Table 1). Note that for either $\delta = 0$, or $\alpha = 0$ with $\gamma_2 \to \infty$, we recover a model nearly identical to the original $SIRWS$ model. In the former case, this is because when $\delta = 0$ no individuals experience secondary infection. In the latter case, when $\alpha = 0$ the I_2 class acts as additional recovered class and as $\gamma_2 \to \infty$ individuals spend almost no time in the I_2 class before passing into the recovered class.

3. Analytical Results

In this section, we determine the equilibria of the SIRWS model and the modified SIRWS model. We also derive an analytical condition for the stability of the equilibria.

3.1. *SIRWS equilibria*

As the SIRWS model is a closed system, we only have three independent variables.

We choose to set $R = 1 - S - I - W$ and consider the following system:

$$\begin{aligned}\frac{dS}{dt} &= \mu(1-S) - \beta SI + 2\kappa W,\\ \frac{dI}{dt} &= \beta SI - \gamma I - \mu I,\\ \frac{dW}{dt} &= 2\kappa(1-S-I-W) - 2\kappa W - \nu\beta IW - \mu W.\end{aligned} \tag{3.1}$$

There are three equilibria: the trivial, disease-free equilibrium $(S^*, I^*, W^*) = (1, 0, 0)$, and a pair of endemic equilibria

$$\begin{aligned}S^* &= \frac{\gamma+\mu}{\beta},\\ I^* &= \frac{\mu(\beta-\gamma-\mu)}{\beta(\gamma+\mu)} + \frac{2\kappa W^*}{\gamma+\mu},\\ W^* &= \frac{-1}{4\beta\kappa\nu}(A \pm \sqrt{B}),\end{aligned}$$

where

$$A = ((2\kappa+\mu)^2 + \gamma(4\kappa+\mu)) + \mu\nu(\beta-\gamma-\mu),$$

$$B = (4\kappa^2 + 4\kappa\mu + \gamma(4\kappa+\mu-\mu\nu) + \mu(\mu+\beta\nu-\mu\nu))^2 + 16\gamma\kappa^2(\beta-\gamma-\mu)\nu.$$

Notice that S^* is the same for both endemic equilibria but I^* and W^* differ. For $\frac{\beta}{\gamma+\mu} > 1$, I^* and W^* are either both positive or both negative. Thus, the system exhibits two biologically relevant equilibria: the disease-free equilibrium and a positive endemic equilibrium.

3.2. *Stability of SIRWS equilibria*

Using our simplified system (3.1), we examine when each equilibrium is stable. We compute the Jacobian

$$J|_{(S^*,I^*,W^*)} = \begin{bmatrix} -\beta I^* - \mu & -\beta S^* & 2\kappa \\ \beta I^* & \beta S^* - \gamma - \mu & 0 \\ -2\kappa & -\nu\beta W^* - 2\kappa & -\nu\beta I^* - 4\kappa - \mu \end{bmatrix},$$

where (S^*, I^*, W^*) is the equilibrium point of interest, to determine its stability.

At the disease-free equilibrium, $(S^*, I^*, W^*) = (1, 0, 0)$, the Jacobian has eigenvalues $\lambda_1 = \beta - \gamma - \mu$, $\lambda_2 = -2\kappa - \mu$, and $\lambda_3 = -2\kappa - \mu$. For biologically realistic, non-negative parameters, the three eigenvalues are negative and the disease-free equilibrium is stable when $\beta < \gamma + \mu$ or $R_0 = \frac{\beta}{\gamma+\mu} < 1$.

The stability of the endemic equilibrium is more complicated, and has not been analytically shown to our knowledge, although it has been examined extensively numerically.[18–20,22–24,27] In line with unpublished work,[27] we examine the characteristic polynomial of the Jacobian evaluated at the endemic equilibrium expressed as $x^3 + a_2x^2 + a_1x + a_0$ where

$$\begin{aligned}
a_2 &= \beta(1+\nu)I^* + 2(2\kappa+\mu),\\
a_1 &= \beta^2\nu(I^*)^2 + \beta\big(\gamma + 4\kappa + \mu(2+\nu)\big)I^* + (2\kappa+\mu)^2,\\
a_0 &= \beta I^*(4\kappa^2 + 4\kappa\mu + \mu^2 + 2\beta\kappa\nu W^* + \beta\mu\nu I^* + \gamma(\beta\nu I^* + 4\kappa + \mu)).
\end{aligned}$$

Employing the Routh–Hurwitz criterion,[28–30] we require that $a_2 > 0$, $a_0 > 0$, and $a_2a_1 > a_0$. For any solution where I^* and W^* exist, i.e., are real and positive given biologically realistic, non-negative parameters, then all the coefficients are clearly positive. Rearranging the last condition we see

$$\begin{aligned}
a_2a_1 - a_0 = &-\beta I^*(\gamma(\nu\beta I^* + 4\kappa + \mu) + \beta\mu\nu I^* + 2\beta\kappa\nu W^* + 4\kappa^2 + 4\kappa\mu + \mu^2)\\
&+ (\beta(1+\nu)I^* + 2(2\kappa+\mu))((2\kappa+\mu)^2 + \beta^2\nu I^*\\
&+ \beta I^*(\gamma + 4\kappa + \mu(2+\nu))),
\end{aligned}$$

which can achieve both positive and negative values depending on the parameters. It can be shown numerically that loss of stability of the positive endemic equilibrium requires $\nu > 1$. Furthermore, in Leung,[27] the author examines the limits of ν and shows that as $\nu \to 0$, SIRS dynamics are recovered, and when $\nu \to \infty$, SIR dynamics are recovered.

3.3. *Modified SIRWS equilibria*

As the modified SIRWS model is a closed system, it contains only four independent variables. Thus, we set $R = 1 - S - I - W - I_2$ and consider the following system:

$$\begin{aligned}
\frac{dS}{dt} &= \mu(1-S) - \lambda S + 2\kappa W,\\
\frac{dI}{dt} &= \lambda S - \gamma I - \mu I,\\
\frac{dW}{dt} &= 2\kappa(1 - S - I - W - I_2) - 2\kappa W - \nu\lambda W - \mu W,\\
\frac{dI_2}{dt} &= \delta\nu\lambda W - \gamma_2 I_2 - \mu I_2,
\end{aligned} \tag{3.2}$$

where $\lambda = \beta(I + \alpha I_2)$ is the force of infection. There are three equilibria: the trivial, disease-free equilibrium $(S^*, I^*, W^*, I_2^*) = (1, 0, 0, 0)$, and a pair of endemic

equilibria

$$S^* = \frac{\gamma+\mu}{\beta} - \alpha\gamma\nu W^*,$$

$$I^* = \frac{\mu(\beta-\gamma-\mu)}{\beta(\gamma+\mu)} + \frac{(2\kappa+\alpha\delta\mu\nu)W^*}{\gamma+\mu},$$

$$I_2^* = \frac{\delta\nu W^*}{\gamma+\mu-\alpha\beta\delta\nu W^*}\left(\frac{\mu(\beta-\gamma-\mu)}{\beta(\gamma+\mu)} + \frac{(2\kappa+\alpha\delta\mu\nu)\beta W^*}{\gamma+\mu}\right),$$

$$W^* = \frac{-1}{C}\left(A \pm \sqrt{B}\right),$$

where

$$\begin{aligned}
A &= 4\beta\gamma^2\kappa + 4\beta\gamma\kappa^2 + \beta\gamma^2\mu + 8\beta\gamma\kappa\mu + 4\beta\kappa^2\mu + 2\beta\gamma\mu^2 + 4\beta\kappa\mu^2 + \beta\mu^3 + 2\alpha\beta^2 \\
&\quad \times\gamma\delta\kappa\nu - 4\alpha\beta\gamma^2\delta\kappa\nu + \beta^2\gamma\mu\nu - \beta\gamma^2\mu\nu + 2\beta^2\delta\kappa\mu\nu - 2\beta\gamma\delta\kappa\mu\nu - 4\alpha\beta\gamma\delta\kappa\mu\nu \\
&\quad + \beta^2\mu^2\nu - 2\beta\gamma\mu^2\nu - 2\beta\delta\kappa\mu^2\nu - \beta\mu^3\nu, \\
B &= \beta^2[-8\gamma\kappa(\gamma+\mu)(\gamma+\mu-\beta)\nu(-4(\alpha-1)\delta\kappa^2 + 2\kappa\mu - 4\alpha\delta\kappa\mu + \alpha\gamma\delta\mu(\nu-1) \\
&\quad + \alpha\delta\mu^2(\nu-1) + 2\alpha\delta^2\kappa\mu\nu + 2\gamma\kappa(1-2\alpha\delta+\alpha^2\delta^2\nu)) \\
&\quad + (\gamma^2(\mu-\mu\nu+\kappa(4-4\alpha\delta\nu)) + \mu(4\kappa^2 + \mu(\mu+\beta\nu-\mu\nu) + \kappa(4\mu+2\beta\delta\nu \\
&\quad - 2\delta\mu\nu)) + \gamma(4\kappa^2 - 2\mu^2(\nu-1) + 2\alpha\beta\delta\kappa\nu + \beta\mu\nu - 2\kappa\mu(\delta(\nu+2\alpha\nu)-4)))^2], \\
C &= 2\beta^2\nu(-4(\alpha-1) + \delta\kappa^2 + 2\kappa\mu - 4\alpha\delta\kappa\mu + \alpha\gamma\delta\mu(\nu-1) \\
&\quad + \alpha\delta\mu^2(\nu-1) + 2\alpha\delta^2\kappa\mu\nu + 2\gamma\kappa(1-2\alpha\delta+\alpha^2\delta^2\nu).
\end{aligned}$$

3.4. *Stability of modified SIRWS equilibria*

Using our simplified system (3.2), we examine when the equilibria are stable. We compute the Jacobian

$$J = \begin{bmatrix}
-\beta(I^*+\alpha I_2^*) - \mu & -\beta S^* & 2\kappa & -\alpha\beta S^* \\
\beta(I^*+\alpha I_2^*) & \beta S^* - \gamma - \mu & 0 & \alpha\beta S^* \\
-2\kappa & -\nu\beta W^* - 2\kappa & -\nu\beta(I^*+\alpha I_2^*) - 4\kappa - \mu & -\nu\alpha\beta W^* - 2\kappa \\
0 & \nu\delta\beta W^* & \nu\delta\beta(I^*+\alpha I_2^*) & \alpha\beta\delta\nu W^* - \gamma - \mu
\end{bmatrix}$$

at (S^*, I^*, W^*, I_2^*) to determine the stability of an equilibrium.

At the disease-free equilibrium, $(S^*, I^*, W^*, I_2^*) = (1, 0, 0, 0)$, the Jacobian has eigenvalues $\lambda_1 = \beta - \gamma - \mu$, $\lambda_2 = -2\kappa - \mu$, $\lambda_3 = -2\kappa - \mu$, and $\lambda_4 = \gamma - \mu$. For biologically realistic, non-negative parameters, the four eigenvalues are negative and the disease-free equilibrium is stable when $\beta < \gamma + \mu$ or $R_0 = \frac{\beta}{\gamma+\mu} < 1$. This is an identical condition as seen for the classic SIRWS model. As system (3.2) is four

dimensional, an analytical solution for the stability of the endemic equilibria is not tractable. We can however, consider the eigenvalues of the Jacobian numerically to determine stability.

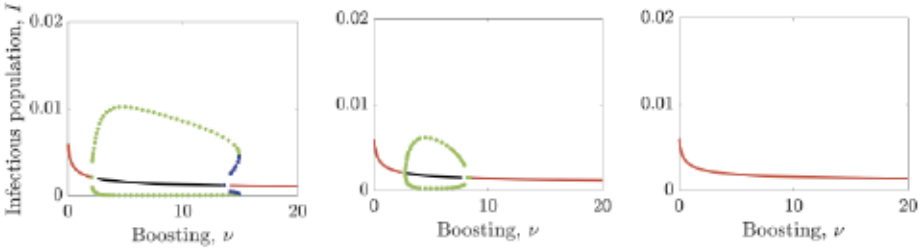
4. Numerical Bifurcation Results

Models that include both waning and boosting immunity, such as the SIRWS model and our modified version, produce a rich set of dynamical behavior. Depending on the degree of immune boosting (ν) they may exhibit fixed points, limit cycles, or regions of bistability characterized by a stable limit cycle and a stable fixed point separated by an unstable limit cycle. Previous work demonstrated that values of ν greater than one allow for the existence of oscillatory behavior when using a standard set of parameters in the SIRWS model (Table 1).[19,27] Here, we perform a full two-parameter bifurcation analysis to examine the effect of each of the parameters on the capability of ν to produce oscillations. We also include multiple series of one-parameter bifurcation diagrams to demonstrate the influence of κ, γ, α, and δ on the amplitude of outbreak oscillations for a range of boosting strengths (ν). Bifurcation analysis was performed with Runge–Kutta integration in XPP 8.0 and continuation in XPPAUT[31] with data processing in MATLAB. Details of all numerical conditions for continuation are available upon request.

Previous analysis of the SIRWS model[18,19,27] (reviewed here for clarity) determined the progression of dynamics as ν is increased under the standard model parameterization (Table 1). For small ν, the system exhibits a stable fixed point that decreases as ν increases. When $\nu \approx 2.06$, a supercritical Hopf occurs, producing a stable limit cycle and flipping the stability of the fixed point (Fig. 2(a)). Continued increase of ν causes the amplitude of the limit cycle to rise sharply followed by a gradual decline as ν approaches 13.61. At $\nu \approx 13.61$ a subcritical Hopf occurs, replacing the unstable fixed-point with a region of bistability. In the bistable region, the fixed point regains stability and is separated from the stable limit cycle by an unstable limit cycle. With further increases of ν, the unstable limit cycle grows in amplitude to meet the shrinking stable limit cycle in a saddle node of limit cycles (Bautin point), leaving only a stable equilibrium for $\nu > 14.94$.

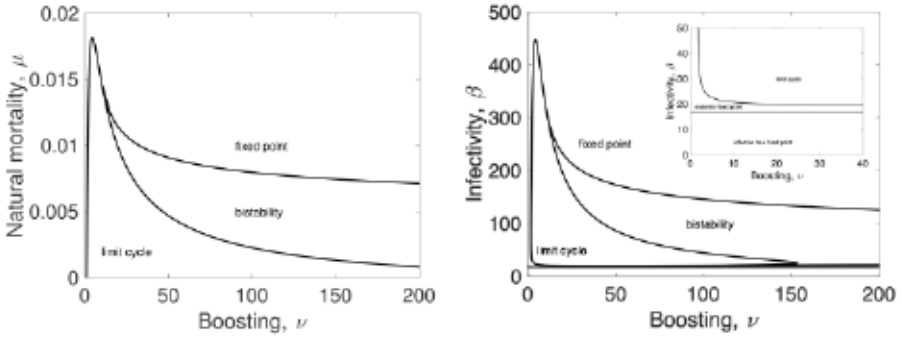
This one-parameter bifurcation structure of the infectious population, I, with respect to ν in which the system transitions from a stable fixed point, to a stable limit cycle, to a bistable regime, and back to a fixed point is observed for a range of parameter values. Parameters outside this range produce either a system that exhibits only fixed points (Fig. 2(c)), or a system in which the subcritical Hopf bifurcation is replaced with a supercritical Hopf bifurcation such that bistability is absent and amplitude of the stable limit cycle changes continuously with ν (Fig. 2(b)).

Curves in the two-parameter bifurcation diagrams represent four types of bifurcation points: supercritical Hopf, subcritical Hopf, saddle node of limit cycles, and transcritical bifurcations (Fig. 3). The supercritical and subcritical Hopf curves are

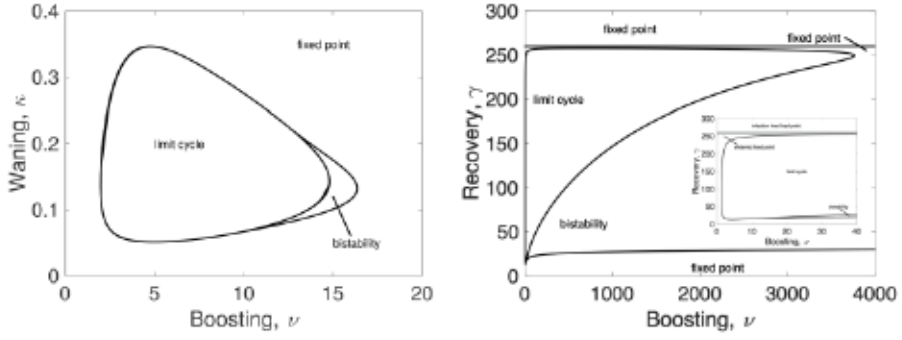


(a) $\mu = 0.0125$ (b) $\mu = 0.016$ (c) $\mu = 0.02$

Fig. 2. One-parameter bifurcation structure of the SIRWS model using the baseline parameter values and varying mortality. (a) For standard parameter, $\mu = 0.0125$, the system produces four dynamic regimes: a stable fixed point regime ($\nu < 2.06$), a stable limit cycle regime ($2.06 < \nu < 13.61$), a bistable regime ($13.61 < \nu < 14.94$), and a second fixed point regime ($\nu > 14.94$). (b) For $\mu = 0.016$ the right subcritical Hopf bifurcation in (a) is replaced by a supercritical Hopf bifurcation. (c) For $\mu = 0.02$, the system exhibits only a stable fixed point. Values of ν at the bifurcation points are approximations. All parameters are at values from Table 1 unless otherwise indicated.



(a) Boosting versus Mortality (b) Boosting versus Infectivity



(c) Boosting versus Waning (d) Boosting versus Recovery

Fig. 3. Two-parameter bifurcation diagrams of SIRWS model with boosting immunity as (a) natural mortality, (b) infectivity, (c) waning immunity, and (d) recovery rate vary. The different dynamical regimes — fixed point, limit cycle, or bistability — are labeled. Insets to panels (b) and (d) show zoomed in portions of the full bifurcation diagram. All parameters are at values from Table 1 unless otherwise indicated.

joined by the saddle node of limit cycles at a generalized Hopf point (also known as a Bautin point). This phenomenon was noted in Dafilis *et al.*[19] Two such generalized Hopf points are found when varying κ, β, and γ as the curves come together, closing the region of bistability. In the case of κ (Fig. 3(c)), the region is quite small, while for β and γ it extends to large levels boosting, i.e., $\nu > 1000$ (Figs. 3(b) and 3(d)).

4.1. *SIRWS model*

While the SIRWS model can exhibit all of the dynamics described above, the bistable region, in which a stable limit cycle and stable fixed point coexist, is observed primarily in biologically unrealistic parameter space. Interestingly, for some parameters, such as waning immunity (κ), the range of values that produces bistability is quite small, in regards to changes in both ν and κ (Fig. 3(c)). While for other parameters, such as μ, β and γ, the range of values is wide (Figs. 3(a), 3b and 3(d)). It is important to note, however, that large bistable regions occur at quite large values of immune boosting (ν), that is, a value hundreds to thousands of times more effective than the initial infection. Biologically, there is no evidence of immune boosting of this magnitude.

4.1.1. *Waning immunity*

Changes in the waning rate, κ, produce a qualitatively different two-parameter bifurcation diagram from that seen when comparing natural mortality, μ, and immune boosting, ν. While limit cycles and bistability persist as μ decreases (Fig. 3(a)), bistability is lost if the average length of immunity ($1/\kappa$) moves outside a range of 7–20 years (Figs. 3(c) and 4, left). Similarly, limit cycles are lost if the average length of immunity moves outside a range of five to thirty-five years.

Both small increases and decreases in κ maintain the capacity for bistability, as long as the average time of immunity lasts from approximately 7 to 20 years (Figs. 3(c) and 4, left column). The loss and appearance of limit cycles induced by changes in κ occur via supercritical Hopf bifurcations (Figs. 3(c) and 4, left). Surprisingly, unlike for changes other model parameters, intermediate levels of boosting ($\nu > 17$) abrogate oscillatory behavior for any level of waning immunity. Additionally, for very short (<5 years) or very long (>35 years) periods of immunity, oscillatory behavior is not possible.

It is, however, important to note that the influence of κ on the system is not restricted to the presence or absence of limit cycles. It also plays a role in determining the effect of immune boosting, ν, on the level of the infected individuals in the stable-steady state (Fig. 4, left column, top and bottom panels). When immunity lasts a long time, i.e., κ is small, the equilibrium level of the infectious population is low for all levels of boosting (ν). When immunity only lasts a short period, i.e., κ is large, the equilibrium level of the infectious population is highly dependent on the value of ν, with lower ν values associated with high levels of infection (Fig. 4, left column, top and bottom panels).

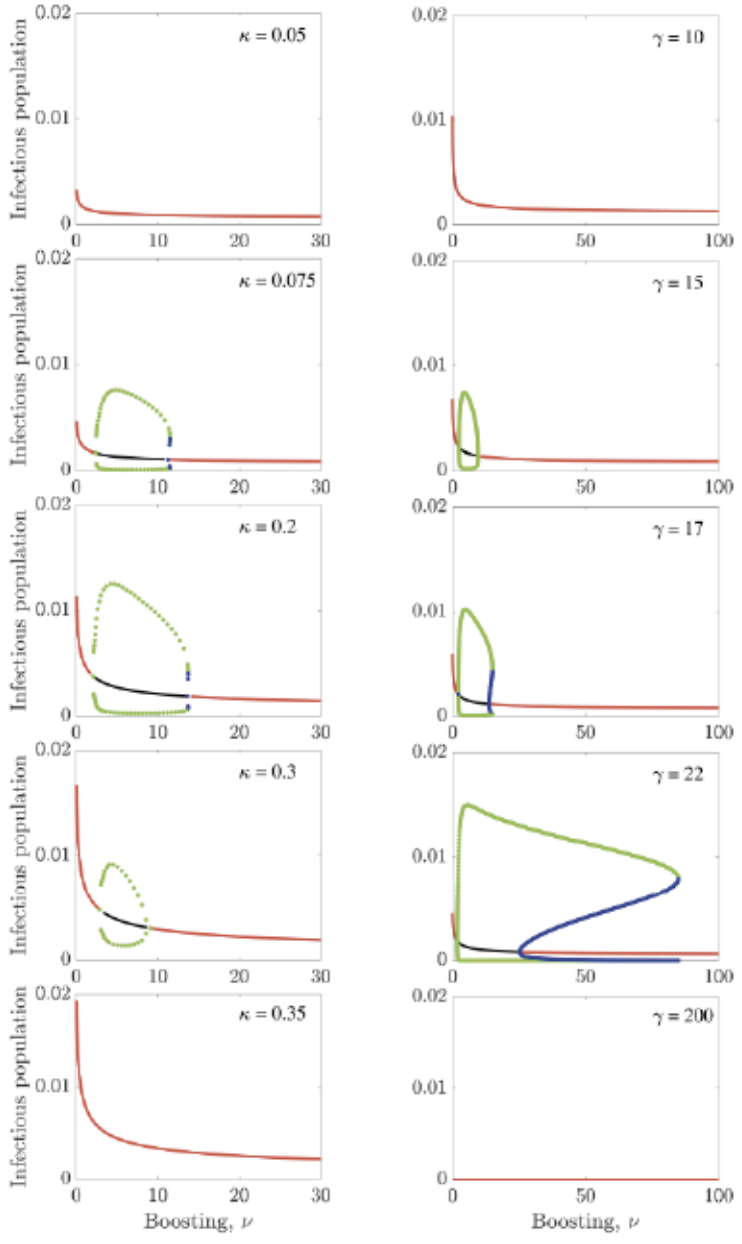


Fig. 4. One-parameter bifurcation diagram of infectious population with respect to immune boosting as waning immunity and recovery rates vary. Long term behavior: stable fixed point (red line), unstable fixed point (black line), stable limit cycle (green dots), unstable limit cycles (blue dots). In the left column, waning immunity, κ, increases from top to bottom. In the right column recovery rate, γ, increases from top to bottom. All parameters are at values from Table 1 unless otherwise indicated.

4.1.2. *Recovery rate*

The recovery rate, γ, differs from other parameters by several orders of magnitude, with the infectious period on the order of weeks rather than years. For $\gamma = 17$, the system exhibits the same dynamic regions discussed above. As γ decreases, the bistable region is abruptly lost, followed by the disappearance of oscillatory behavior, leaving only a single fixed point that is highly sensitive to levels of boosting, ν (Fig. 4, right column top panel). Interestingly, this pattern, where the level of the infectious population is sensitive to ν at low γ and insensitive to ν at high γ is the inverse of pattern observed when varying the waning immunity rate, κ (Fig. 4, top and bottom panels). Biologically, low values of γ are unlikely, as they indicate an infectious period much longer than what is currently estimated.

In contrast, shortening the infectious period, i.e., increasing γ, as may be the result of treatment, leads to wide regions of oscillatory behavior. With increasing γ, the region with only a stable limit cycle grows to encompass larger and larger ν (Fig. 3(d)). Similarly, the bistable region includes extremely large ν values as γ increases. Indeed, the bistable region stretches to values of boosting as wide as $\nu \approx 10^6$ before abruptly disappearing. Although numerically difficult to obtain, we expect that the region of bistability closes with a generalized Hopf point, near $\nu \approx 3700$ and $\gamma \approx 260$. However, we are not able to confirm this with numerical continuation of the Hopf curve and thus omit this line from Fig. 3(d). Above the regions of oscillations and bistability, as γ increases, there is a small region where the endemic equilibrium is stable (Fig. 3(d), inset). For very fast recovery, e.g., $\gamma = 200$, akin to an infectious period of about 1.5 days, the system undergoes a transcritical bifurcation and the infection-free state becomes stable (Fig. 4, bottom right panel). In other words, with very short infectious periods, the disease can no longer persist.

4.1.3. *Infectivity*

Bifurcation analysis of infectivity, β, with immune boosting, ν, produces a bifurcation diagram of similar structure to that of μ and ν for large values of β (Fig. 3(b)). Currently estimated at $\beta = 260$ (Table 1), if infectivity were higher than considered, there would be a progressive loss of bistability followed by loss of oscillations with the size of the infectious population at equilibrium highly dependent on assumptions on boosting (not shown). However, parallels between qualitative similarities of β and μ diverge for very small β. In this case, instead of a continuous increase in the width of the oscillatory region, near $\beta \approx 20$ the distance between Hopf bifurcation points continuously but abruptly decreases until both points disappear. (Fig. 3(b), inset). When $\beta \approx 17$, the system exhibits another change in dynamics (Fig. 3(b), inset). Here the stable positive infection fixed point loses stability and the disease becomes extinct. In this case, the level of infectivity is not large enough to sustain disease transmission. Decreases in β could be thought to be due to non-pharmaceutical

interventions such as social distancing or isolation. Interestingly, decreases in β show the possibility of bistability for intermediate values of boosting. Decreases in infectivity do not elicit the same dynamical behaviors as decreases in the infectious period, γ, where bistability rapidly becomes possible only for very large levels of boosting.

4.2. *Modified SIRWS*

The modified SIRWS model includes potential boosting of immunity through secondary infection. Not all individuals experience active secondary infection for boosting of immunity. The fraction of individuals experiencing active secondary infection is given by δ; relative infectivity of individuals with a secondary infection is determined by α; and the recovery rate of secondary infection is tuned by γ_2. Individuals infected for a second time may recover faster ($\gamma_2 > \gamma$) or may contribute less to transmission ($\alpha < 1$) than individuals infected for the first time.

4.2.1. *Role of relative infectivity of secondary infections*

We begin with the assumption that secondary infections and primary infections are equally infectious, both in infectivity ($\alpha = 1$) and length of infection ($\gamma_2 = \gamma$), and that all individuals experience secondary infection ($\delta = 1$). In this case, only the stable fixed point is observed and the secondary infection class contains more individuals than the primary infection class. (Fig. 5, top panels).

The equilibrium level of infection in the population is highly dependent on the strength of boosting, with lower values of ν producing higher levels of primary infection but lower levels of secondary infection (Fig. 5). The equilibrium level of secondary infection in the population is largely unchanged as the relative infectivity, α, decreases (Fig. 5, right column, top to bottom), while the level of primary infection significantly drops (Fig. 5, left column, top to bottom). As the equilibrium level of secondary infection in the population is generally two to five times higher than primary infection, the level of total infectious individuals does not appreciably decrease (Fig. 5). Increases in ν, apart from very small values, have limited influence on the equilibrium level of secondary infection (Fig. 5, right column).

The initial assumption of our modified model that both primary and secondary infection exhibit the same infectivity, i.e., $\alpha = 1$, strays considerably from the idea behind the original SIRWS model, where boosting of immunity does not require the occurrence of an infection. If we shift this assumption to the opposite extreme, and consider the case where individuals in the I_2 class are not at all infectious, i.e., $\alpha = 0$, we recover behavior nearly identical to the standard SIRWS model (Fig. 6(a)). In other words, the system exhibits a supercritical Hopf for low ν values, a subcritical Hopf for intermediate ν values, and a saddle node of limit cycles so that only a single stable equilibrium remains for large ν. The recovery of the SIRWS model bifurcation structure at $\alpha = 0$ is due to the fact that I_2 individuals do not

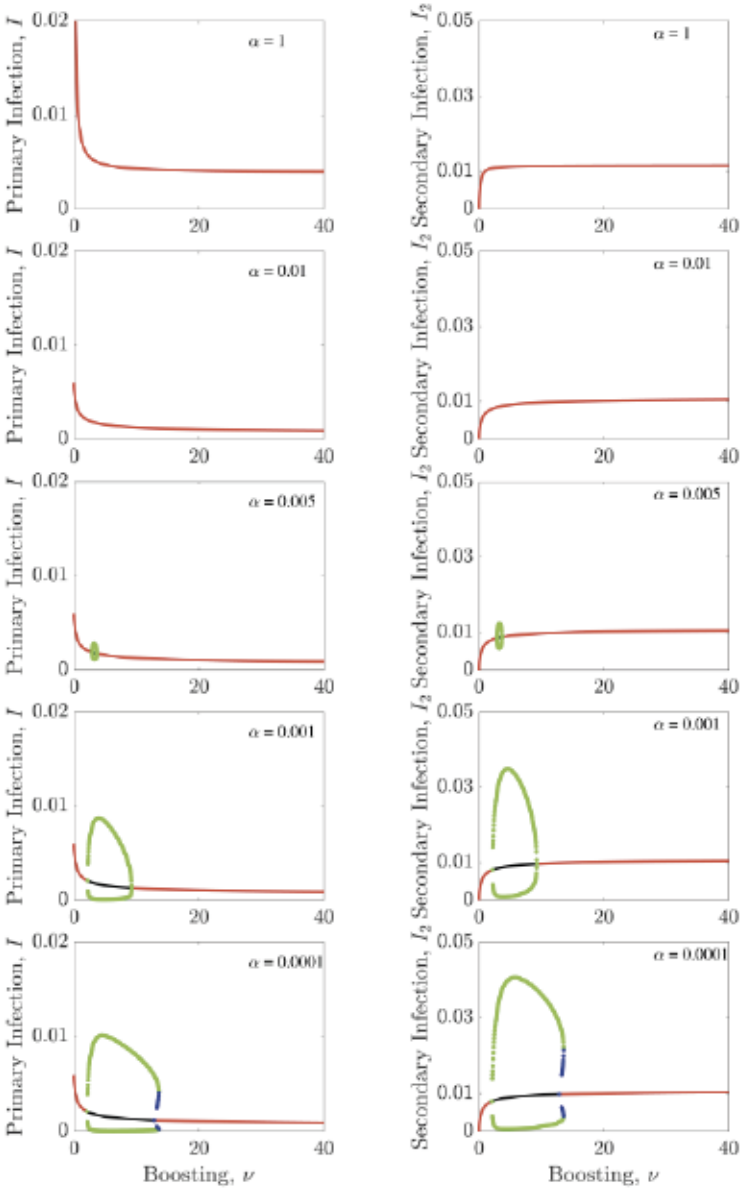


Fig. 5. One-parameter bifurcation diagrams of infectious population with respect to immune boosting as relative infectivity varies. The left column is primary infection and the right column is secondary infection with relative infectivity from top to bottom: $\alpha = 1.0$, 0.01, 0.005, 0.001, and 0.0001. Here, the probability of secondary infection (δ) is 1. Long term behavior: stable fixed point (red line), unstable fixed point (black line), stable limit cycle (green dots), unstable limit cycles (blue dots). Note that the y-axis scales are different for primary infection (left column) and secondary infection (right column). All parameters are at values from Table 1 unless otherwise indicated.

contribute to onward infection. The I_2 class merely acts as a delay between the W and R classes.

If we consider intermediate values of relative infectivity, α, we see that both the existence of a bistable region and the level of infection at the equilibrium depend on α. At $\alpha = 0.0001$, the bifurcation structure is similar to the $\alpha = 0$ case, exhibiting the two Hopf bifurcation points and the Bautin point (Fig. 5, bottom panel). But, if α is increased to 0.001, the Bautin point disappears and the bistable region is lost so that only the Hopf bifurcation points remain. Further increase in α to $\alpha \approx 0.005$ causes a complete loss of oscillatory behavior so that only the stable fixed point remains. Importantly, when $\alpha = 0.005$, a primary infection is assumed to be 200 times more infectious than a secondary infection, while when $\alpha = 0.0001$, a primary infection is 10,000 times more infectious. Thus understanding the true contribution of secondary infection is important for determining the type of dynamics expected.

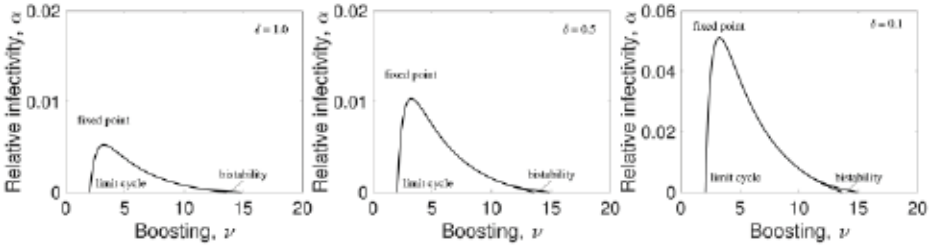
4.2.2. *Role of probability of secondary infection on dynamic regimes*

The standard SIRWS model assumes that individuals with partial immunity can be boosted back to full immunity following exposure to infectious individuals. Our revised model includes the possibility of secondary infection, and shows that if values of relative infectivity, α, are small bifurcation analysis produces similar dynamics regimes to the SIRWS model (Fig. 6(a)).

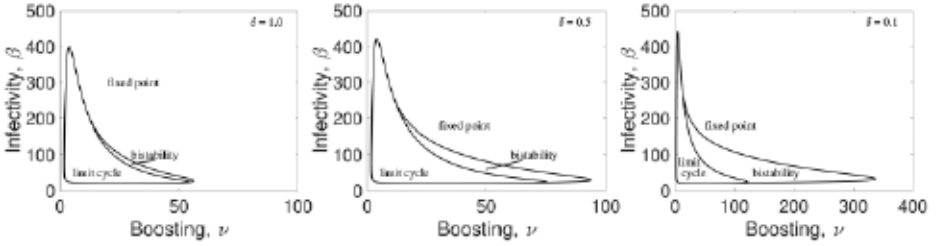
The range of relative infectivity, α, for which oscillations and bistability are present grows as the fraction of individuals experiencing a second infection, δ, shrinks. Thus, when the fraction of individuals acquiring full immunity through a secondary infection is low, oscillations and bistability are possible even if those individuals experiencing the second infection are highly infectious. This relationship between relative infectivity, α, and fraction of individuals experiencing secondary infections, δ, is symmetric, in that oscillations are also present for a large range of δ when α is low (not shown).

The effect of the fraction of individuals experiencing secondary infection, δ, on the β versus ν bifurcation structures is more nuanced. When all boosting results in secondary infection ($\delta = 1$), oscillations can occur for significant portion of (β–ν) parameter space; however, bistability is only observed for a very narrow region (Fig. 6(b)). As the fraction of individuals experiencing secondary infection decreases the region of bistability grows. Further decreases in δ lead to further expansion of the bistable region while the limit cycle region only increases slightly. Thus, when secondary infection is unlikely, i.e., δ is low, the standard parameter set sits well within the limit cycle regime.

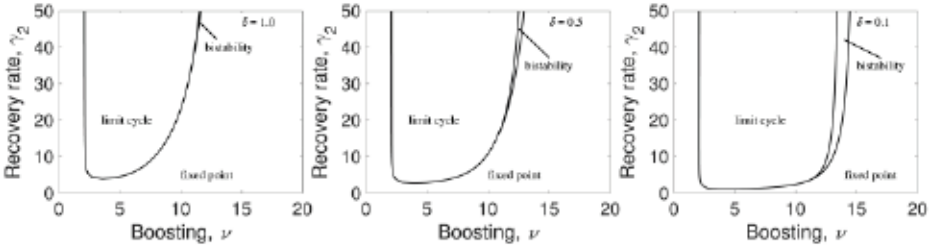
A similar pattern is observed for the influence of fraction of individuals experiencing secondary infection, δ, on the γ_2 versus ν bifurcation structure. When secondary infection is likely, i.e., δ is large, bistability is only possible for a narrow region (Fig. 6(c)). The region of bistability grows as the fraction of individuals



(a) Boosting versus Relative infectivity



(b) Boosting versus Infectivity



(c) Boosting versus Recovery

Fig. 6. Two-parameter bifurcation diagrams of modified SIRWS model with respect to boosting immunity as (a) relative infectivity, (b) infectivity, and (c) secondary recovery rate vary. From left to right the fraction of individuals experiencing secondary infection, δ, decreases: 1.0, 0.5 0.1, as indicated in the upper right hand corner of each panel. For (b) and (c), the relative infectivity is fixed at $\alpha = 0.001$. The different dynamical regimes — fixed point, limit cycle or bistability — are labeled. Note that the y-axis scale in the third panel of (a) and the x-axis scale in the third panel of (b) are wider than in other panels. All parameters are at values from Table 1 unless otherwise indicated.

experiencing secondary infection decreases. In contrast to observations with β, the region of bistability only grows slightly with decreasing δ, but an expansion of the limit cycle region is apparent, especially for low recovery rate values. This indicates that extended infectious periods can still create oscillations. Additionally, regardless of the relative infectivity of secondary infections to primary infections, we can still recover behavior analogous to the standard SIRWS model, but for large γ_2 (Fig. 6(c)). It appears that the system asymptotes to the bifurcation structure

observed in the SIRWS model as $\gamma_2 \to \infty$, which indicates boosting directly into the recovered class.

4.2.3. *Influence of secondary infection probability δ on the amplitude of infection oscillations*

The modified SIRWS model is capable of producing stable limit cycles for a range of δ, i.e., fraction of individuals experiencing secondary infection, as infectivity, β, and immune boosting, ν, are varied (Fig. 6(b)). In fact, the fraction of individuals experiencing secondary infection has limited influence on the (β, ν) coordinates of

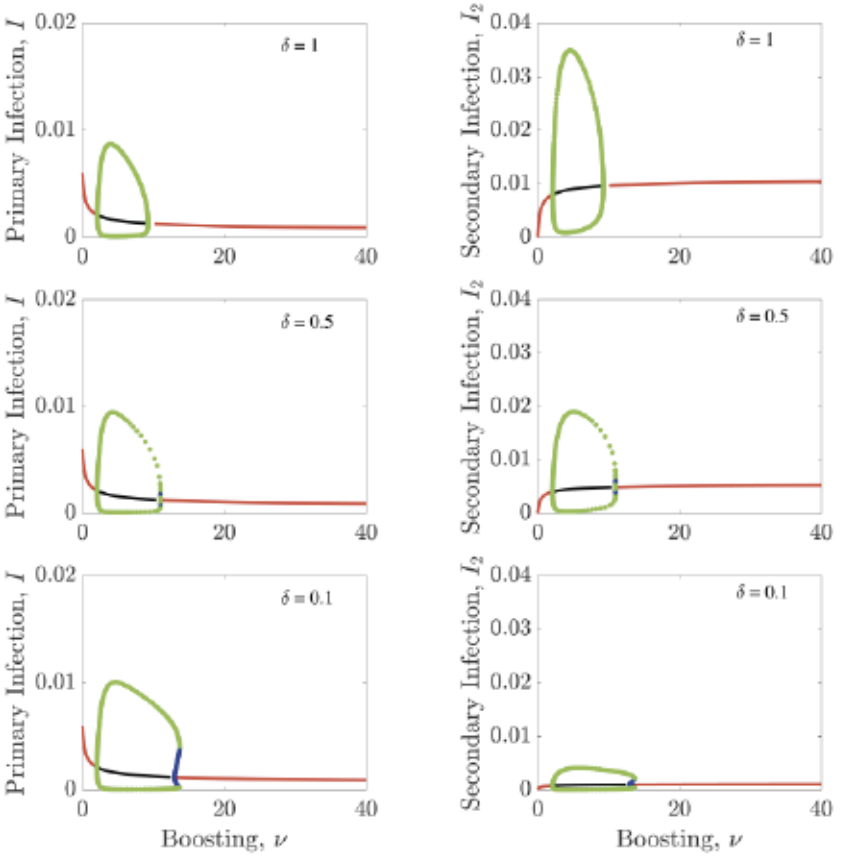


Fig. 7. One-parameter bifurcation diagram of infectious population with respect to immune boosting as the fraction of individuals experiencing secondary infections for immune boosting varies. A fixed relative infectivity, $\alpha = 0.001$, is assumed. The left column is primary infection, I, and the right column is secondary infection, I_2. From top to bottom the fraction of individuals experiencing secondary infection with boosting, δ, ranges 1.0, 0.5, 0.1. Long term behavior: stable fixed point (red line), unstable fixed point (black line), stable limit cycle (green dots), unstable limit cycles (blue dots). Note that the y-axis scale for I_2 is double that for I. All parameters are at values from Table 1 unless otherwise indicated.

the Hopf bifurcation points when $\alpha = 0.001$. However, while these boundaries of the stable limit cycle regime in (β, ν)-space are relatively constant as δ varies, δ does influence the amplitude of oscillations in the infectious population (Fig. 7). Indeed, one-parameter bifurcation analysis of the primary infectious population, I, versus immune boosting, ν, shows that the amplitude of oscillations at the left Hopf bifurcation point is relatively fixed while the amplitude at the right Hopf bifurcation point and at intermediate values of ν increases as δ decreases (Fig. 7, left). In contrast, δ influences the amplitude of the stable I_2 limit cycles across the relevant ν domain. Thus, while the probability of secondary infection does not influence combinations of infectivity and boosting (β, ν) required to produce limit cycles, it does determine the magnitude of outbreaks within the oscillatory regime.

5. Discussion

In this paper, we examine waning and boosting immunity in the context of simple ODE models. We compare the classic SIRWS model with an extension in which boosting of immunity may involve secondary infection. Analytically, we extend the understanding of dynamics of the SIRWS model by deriving a condition for the stability of the endemic equilibrium. We also calculate the endemic equilibrium for our extended model. Numerically, we provide full two-parameter bifurcation curves for each parameter paired with the boosting of immunity for both models. Finally, we show how biological assumptions about the manner of boosting immunity — direct or via secondary infection — affect our understanding of possible disease dynamics.

The presence of bistability is important for understanding the role of both the intervention against infection and the importation of infection. In the former case, if the population currently harbors low but persistent levels of infection, large-scale, nearly instantaneous changes, such as mass drug administration, may shift the level of infection in the population low enough to enter an oscillatory regime. This would result in epidemic-like disease expansion with increased burden of infection. In the latter case, the arrival of infected travelers could raise the infection level out of the basin of attraction of the fixed point, causing large oscillations. Each of these scenarios could vastly change the observed burden of infection, particularly over short time periods.

As different rates of waning immunity (κ) suggest qualitatively different dynamical regimes, detailed information of the biology of a disease is essential to understand epidemiological patterns. Immunity that persists for an intermediate length of time ($\sim$5 to 35 years) is necessary for the appearance of oscillatory behavior (Fig. 6(c)). While this range is wide, it is still substantially shorter than the average life span, indicating the potential for re-infection. Furthermore, in the case of pertussis, there is considerable debate of the length of protection,[3] with thoughts that the length of immunity may vary by route: natural infection versus vaccination.[4,18,21]

At times the dynamical structures found in our one-parameter bifurcation diagrams are situated very close together. In Fig. 4 ($\gamma = 22$), the lower branches of the

unstable and stable limit cycles are nearly indistinguishable and just above zero. Although separate in the deterministic system, a stochastic version would likely result in behavior settling to the stable fixed point. In other words, if a trajectory oscillated toward the lower bound of the stable limit cycle any small stochastic perturbation would throw it into the basin of attraction for the unstable cycle such that the trajectory would be driven toward the stable fixed point. While mathematically we observe oscillations in the deterministic system, the oscillatory nature of the system is, perhaps, practically lost at some point. Similarly, as the lower branch of many of the limit cycles sits just above zero, it is possible that stochastic perturbations would result in extinction rather than a return to a high level of infection.

Our analyses indicate that policy-relevant changes will impact the dynamics in non-intuitive ways. While large decreases in infectivity (β) or large increases in recovery rate (γ) both lead to extinction of the disease, the dynamics to get there differ. As seen in Fig. 3, the region of bistability is much broader with changes in recovery rate, but does not appear unless under high levels of boosting. In addition, changes to disease characteristics, such as the length of immunity generated following infection (κ), lead to a stable fixed point when immunity is both very short and very long. A more complete understanding of the expected dynamical changes with interventions such as drugs, which would speed up recovery rate, or social distancing, which would reduce infectivity, will enhance our ability to monitor and respond to infectious disease outbreaks.

The SIRWS model exhibits rich dynamical behavior, for which the details of transitions are, as yet, not fully understood. Here, we have focused on broad regimes of behavior exhibited when varying each of the model parameters. The bifurcation structure of the system demonstrates the parameter regimes in which limit cycles arise as well as the amplitude of these oscillations. We have not, however, explored the period of the oscillations. A short discussion of the influence of boosting on oscillation periods can be found in Dafilis *et al.*[19] As the period indicates when we expect to see large peaks in transmission, an understanding of these dynamics would assist in policy recommendations. Furthermore, we have considered variation in combinations of two parameters, but always centered around a standard parameter set (Table 1). The bifurcation structure away from this parameter regime is, as yet, undetermined.

6. Conclusion

Despite its simplicity, the SIRWS model of waning and boosting immunity demonstrates rich dynamical behavior. It is a foundation for policy-relevant models of waning and boosting immunity, and a complete understanding of the details of the dynamics and their biological underpinning will be essential to help guide recommendations for combating the spread of infectious diseases, such as pertussis.

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