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A MODEL OF VARICELLA-ZOSTER REACTIVATION

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Abstract. Mathematical models have been used to study the dynamic interaction of many infectious diseases with the host's immune system. In this paper, we study Varicella Zoster Virus, which is responsible for chicken pox (varicella), and after a long period of latency, herpes zoster (shingles). After developing the model and demonstrating that is exhibits the type of periodic behavior necessary for long term latency and reactivation, we examine the implications of the model for vaccine booster programs aimed at preventing herpes zoster.

1. **Introduction.** Varicella-Zoster Virus, or VZV, is an α-herpesvirus which causes varicella (chickenpox) as a result of acute primary infection. Prior to 1995, there was no vaccination program in the United States, and as a result approximately 98% of Americans were infected with VZV [3]. Following this initial infection, the virus is established and persists in the sensory ganglia, clusters of nerve cells which form the junctions between the spine and the peripheral nerves [4]. It is conjectured that reactivations of the virus from this latent site are common, but are generally controlled by the host immune system, and may even serve to boost immunity [6, 10], as does exposure to other individuals with acute varicella [5, 12].

As the host ages, however, the immune system declines, and the likelihood of a symptomatic recurrence, in the form of herpes zoster (shingles), grows. Herpes zoster typically presents as a rash, localized to a single dermatome, the area of skin covered by one spinal nerve. The rash is generally accompanied by pain in the affected area, and in a minority of cases, this pain persists for six months or more, a condition called post-herpetic neuralgia [7].

According the the Centers for Disease Control and Prevention, in a cohort of latently infected individuals living to age 85, 50% suffer from herpes zoster in their lifetimes, while in the general population, this number is approximately 33% [3], although other sources put have lower estimates of 20-30% [13] or even 10-20% [11].

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The likelihood of developing herpes zoster increases sharply between the ages of 50 and 60 [3].

A live-attenuate vaccine against varicella zoster virus exists, and since 1995 a program of universal vaccination of children has been in effect in the United States. Those vaccinated can still become latently infected with virus, and can develop herpes zoster later in life, though initial studies indicate that the prevalence of herpes zoster in these patients might be lowered [2]. Because of the location of the latent infection in neurons, which are immuno-priveleged and extremely long-lived, the latent VZV infection is never cleared, and a vaccine booster is necessary to ensure continued protection as the immune system weakens with age. A stronger version of the varicella vaccine, based on the Oka strain, can be administered in older patients to boost VZV-specific immunity and prevent or delay the onset of herpes zoster [8, 9].

The goal of this paper is to develop a mathematical model for the dynamics of VZV infection through primary, latent and reactivation stages. We use this model to isolate parameters which determine the course and outcome of infection. We also aim to provide a guideline for the design of vaccine protocols that would predict the best times for booster administration in terms of preventing or delaying herpes zoster reactivation.

2. **Model description.**

After initial infection, a high level of VZV-specific antibody is produced and maintained in the host. As a result, free virus is very rare, most transmission is achieved cell to cell [1], and a zoster rash rarely appears in more than one dermatome simultaneously. We model the interaction between the population of infected epithelial cells of a particular dermatome, x, and the immune cells, y, which are VZV-specific CD8+ T cells. The dynamics of our model are governed by the following system of ordinary differential equations.

$$dx/dt = rx(K - x)(x - \alpha) + s - cxy \tag{1}$$

$$dy/dt = pxy - dy. \tag{2}$$

In the absence of the cellular immune response, the growth rate of the infected cell population is governed by two processes. Firstly, there is a constant source, s, of infection from the site of latency. During primary infection, VZV establishes itself in sensory neurons, a long-lived population of cells which are protected from the immune system. Neurons do not express MHC class I, rendering the CD8+ T-cells inefficacious and making immune clearance of the latent infection impossible. Evidence of this constant source of infection is provided by the recovery of VZV-specific T cell populations following bone marrow transplants [14]. Many of these patients experience measurable reactivation of VZV shortly after transplantation, while they are immunocompromised, and the VZV-specific immune response is reconstituted. Both of these observations indicate a baseline viremia from the site of latency.

The second process governing the infected cell population is a strong Allee effect. When the number of infected cells is very low, there is lower recruitment and higher mortality, as there is a greater chance that the infected cells will be cleared before the virus can be spread. Infected cells may be cleared by circulating natural killer (NK) cells or simply be lost to natural cell death before infection can be spread to another cell [4]. The threshold α is the minimum number of cells needed to overcome this hurdle.

There is also a limit to the number of target cells available. The parameter K provides an upper bound on size the infected cell population can achieve. The actual Allee threshold and carrying capacity of the system are altered slightly by the presence of the source term s, but we may think of α as the baseline Allee threshold and K as the baseline carrying capacity. In the absence of the immune response, the number of infected cells can either grow logistically to include all available susceptible cells, or if the initial level of infection is too small, the population will be unable to expand. As is the case with a logistic differential equation, the natural death of infected cells is incorporated into this term.

The rate of removal of infected cells by the immune system is proportional both to the number of infected cells present and the number of immune cells ($-cxy$). Similarly, we assume relatively simple dynamics for the immune response. When immune cells recognize an infection in the form of an antigen peptide on the surface of an antigen presenting cell, they start to proliferate at a rate p. In our model, we consider the amount of antigen presentation to be proportional to the number of infected cells. Therefore, the proliferation term will be given by a mass action term, pxy.

3. **Analysis.**

We now proceed to prove the positivity and boundedness of solutions to the system (1,2) and explore the existence, location and stability of steady state solutions.

3.1. **Positivity and boundedness.**

Lemma 3.1. *If $x(0)$ and $y(0)$ are positive, then $x(t)$ and $y(t)$ are positive and bounded for all $t > 0$.*

Proof. We begin with positivity. When $x(t) = 0$, $dx/dt = s > 0$, so $x(t)$ must remain positive for all $t > 0$. Since Equation (2) is proportional to y, it is clear that $y(t)$ remains positive for all $t > 0$.

Define the function $h(x) = rx(K - x)(x - \alpha)$. Since $h(x)$ is a degree three polynomial with negative lead coefficient, there exists an x_M such that $h(x_M) = 0$ and $f(x) - s < 0$ for all $x > x_M$. From the positivity of $x(t)$ and $y(t)$ it follows that $dx/dt < h(x) + s - cxy < 0$ for all $x > x_M$. If $x(0) < x_M$, then $x(t) \leq x_M$ for all $t > 0$, and if $x(0) > x_M$, $x(t) < x(0)$ for all $t > 0$. Thus $x(t)$ is bounded by $\max\{x(0), x_M\}$.

To prove the boundedness of $y(t)$, we define the new variable $z = x + (c/p)y$. Given that x is known to be bounded and both x and y are positive, z is positive and y is bounded if and only if z is as well. The differential equation describing z is

$$\begin{aligned} dz/dt &= dx/dt - (c/p)dy/dt = h(x) + s - (dc/p)y \\ &= h(x) + dx - dz \end{aligned}$$

The value of $x(t)$ is known to be bounded by $\max\{x(0), x_M\}$, and it follows that $h(x) + dx$ is bounded by some $M > 0$ as well. We have $dz/dt < M - dz$, from which it follows that z is bounded, as desired. □

3.2. **Steady states.**

To find the location of steady states, we set the right hand sides of equations (1) and (2) equal to 0. We will take equation (2) first. There are two possible solutions, $\bar{x} = d/p$ and $\bar{y} = 0$. When $\bar{x} = d/p$, we have

$$\bar{y} = (r\bar{x}(K - \bar{x})(\bar{x} - \alpha) + s)/c\bar{x}.$$

This steady state exists so long as $s > f(d/p)$, where $f(x) = rx(x - K)(x - \alpha)$.

Steady State	Conditions for Existence	Biological Significance
$(x_1, 0)$	$s < \tilde{s}$	Latent Infection
$(x_2, 0)$	$s < \tilde{s}$	Threshold
$(x_3, 0)$	always exists	Immune Failure, Unchecked Infection
(x_4, y_4)	$s > f(d/p)$	Chronic Infection

TABLE 1. Conditions for the existence of the steady states of the system (1, 2). When the steady states $(x_1, 0)$ and $(x_2, 0)$ exist, they satisfy $x_1 < x_2 < \alpha < K < x_3$.

If $\bar{y} = 0$, then the equation (1) is solved when

$$f(\bar{x}) = s. \tag{3}$$

As f is a cubic, and s is a positive constant, there are two possibilities for equation (3). For small values of s, there are three solutions, and for larger values of s there is only one solution.

Lemma 3.2. *Let*

$$\tilde{x} = \left[K + \alpha - \sqrt{K^2 - K\alpha + \alpha^2}\right]/3,$$

and

$$\tilde{s} = f(\tilde{x}).$$

Equation (3) has three distinct solutions for $0 < s < \tilde{s}$*, and one solution for* $s > \tilde{s}$*.*

Proof. For $s = 0$, there are three solutions, 0, α, and K. The transition from three solutions to one occurs when s is equal to the relative minimum value of f. To locate the critical points of f, we calculate

$$f'(x) = 3rx^2 - 2r(K + \alpha)x + rK\alpha = 0.$$

The relative minimum of f occurs at the lesser of the two solutions of this quadratic, i.e. at

$$\tilde{x} = \left[K + \alpha - \sqrt{K^2 - K\alpha + \alpha^2}\right]/3.$$

The value of s at this critical point is $\tilde{s} = f(\tilde{x})$. □

The conditions for existence of steady states is summarized in Table 1. When these conditions are combined, it is possible to have one, two, three or four steady states. We will refer to the steady state $(x_1, 0)$ as latent infection, since the the virus exists at an extremely low level, and is maintained at this low level without triggering an immune response. When the latent steady state is stable, no reemergence from this low level of infection occurs. $(x_2, 0)$ is a threshold state. Whenever it exists, it is unstable, so it will never be directly observed, but plays a role in determining the dynamics of the system. $(x_3, 0)$ is a full infection state. The infection achieves the highest possible level, and the immune reaction is not present. Finally, the steady state (x_4, y_4) represents chronic infection, as both the infection and immune response are maintained at nonzero levels.

3.3. **Stability conditions.** Next we will examine the conditions for the stability of these steady states. The Jacobian for the system (1,2) at a steady state $(\bar{x}, \bar{y})$ is

$$\mathcal{J} = \begin{pmatrix} -f'(\bar{x}) - c\bar{y} & -c\bar{x} \\ p\bar{y} & p\bar{x} - d \end{pmatrix} \tag{4}$$

For the steady states $(x_i, 0)$, $i = 1, 2, 3$, this becomes

$$\begin{pmatrix} -f'(x_i) & -cx_i \\ 0 & px_i - d \end{pmatrix},$$

and the eigenvalues are $\lambda_1 = -f'(x_i)$ and $\lambda_2 = px_i - d$.

For $(x_1, 0)$, $f'(x_1) > 0$, so the first eigenvalue is negative. Thus, $(x_1, 0)$ is a stable node if $x_1 < d/p$ and is a saddle if $x_1 > d/p$. For $(x_2, 0)$, $f'(x_2) < 0$, so λ_1 is always positive. Thus, $(x_2, 0)$ is a saddle is $x_2 < d/p$ and is an unstable node if $x_2 > d/p$. For the third steady state, $(x_3, 0)$, $f'(x_3) > 0$, so the steady state is a stable node if $x_3 < d/p$ and a saddle if $x_3 > d/p$.

The Jacobian of the fourth steady state (x_4, y_4) has the form

$$\mathcal{J}_4 = \begin{pmatrix} -f'(x_4) - cy_4 & -\frac{cd}{p} \\ py_4 & 0 \end{pmatrix},$$

and the conditions for stability are contained in the following result.

Lemma 3.3. *Let $g(x) = x^2(K + \alpha - 2x)$. The steady state (x_4, y_4) is stable for $s > g(d/p)$ and unstable for $s < g(d/p)$.*

Proof. For (x_4, y_4) to be stable, we need $\det \mathcal{J}_4 > 0$ and $\mathrm{tr}\mathcal{J}_4 < 0$. The determinant of $\mathcal{J}_4$ is cdy_4, which is positive, so the stability of the steady steady is determined by the trace of $\mathcal{J}_4$.

$$\begin{aligned} \mathrm{tr}(\mathcal{J}_4) &= -f'(x_4) - cy_4 \\ &= r\left(-3x_4^2 + 2(K+\alpha)x_4 - K\alpha - [x_4(K - x_4)(x_4 - \alpha) + s]/x_4\right) \\ (x_4/r)\mathrm{tr}(\mathcal{J}_4) &= -3x_4^3 + 2(K+\alpha)x_4^2 - K\alpha x_4 - x_4(-x_4^2 + (K+\alpha)x_4 - K\alpha) - s \\ &= -2x_4^3 + (K+\alpha)x_4^2 - s \end{aligned}$$

The trace is negative if $-2x_4^3 + (K + \alpha)x_4^2 - s < 0$, i.e. if $s > g(x_4) = g(d/p)$. In this case, the steady state is stable. Conversely, the steady state is unstable if $s < g(x_4) = g(d/p)$. □

We can use the information about the existence and location of the steady states to create a diagram of the possible behaviors of the system as a function of the two key parameters, s and d/p.

Our modeling effort concentrates on Region I, in which there are two steady states, both of which are unstable. We shall show that when the parameters of the model are in this region, solutions to the system of differential equations demonstrate the recurrence of widespread infection after a long period of latency. This describes the long latency period of VZV infection in the sensory ganglia, and the reemergence of infection as herpes zoster at a much later time.

The model demonstrates a wide range of possible dynamics, however, depending on the combination of the parameters s and d/p (Figure 2). In Regions II and III, the steady state (x_4, y_4) is stable, and all solutions approach it in the long run. This is a chronic infection, in which the immune system recognizes and fights the infection, but cannot eliminate it.

In Region IV, the chronic steady state does not exist, and the only stable solution is the latency steady state, $(x_1, 0)$. The number of infected cells (x) is nonzero. We call this a region of latent infection, since the long term level of infection is small $(x_1 < \alpha)$ and maintained at this level without immune system interference.

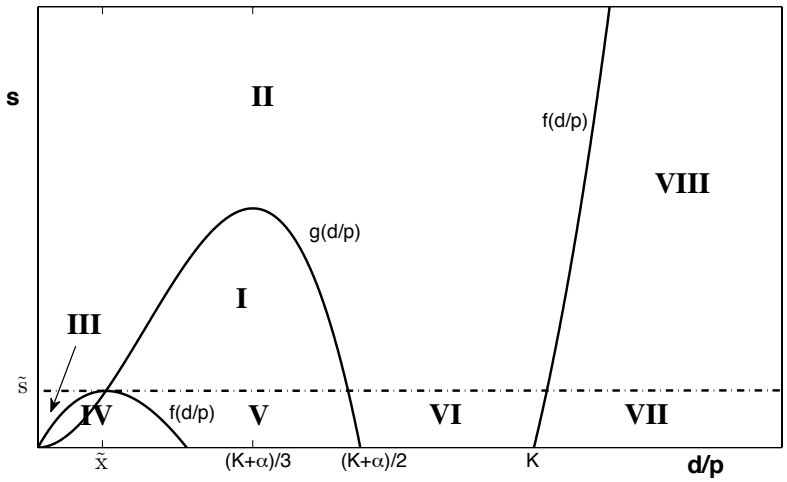

FIGURE 1. Bifurcation diagram of the system (1,2). The region is divided by the curves $s = f(d/p)$ and $s = g(d/p)$ and the line $s = \tilde{s}$

In Region V, $(x_1, 0)$ continues to be the only stable solution. The chronic infection steady state (x_4, y_4) exists, but is unstable. When the initial immune level is small, solutions demonstrate a spike in infection followed by immune containment and convergence to the latent infection state $(x_1, 0)$. This is what one expects in a case of primary infection followed by immune control. If the initial immune level is sufficiently large, the spike is avoided, so the infection becomes latent and remains in that state.

In Regions VI and VII, there are two stable steady states, and the dynamics are bistable. Which solution will be approached in the long run depends on the initial conditions. In Region VI, the two possible outcomes are latent and chronic infection (x_4, y_4). We will refer to this as the bistable chronic state.

In Region VII, the chronic infection steady states does not exist, and the possible outcomes are latency and full infection (the steady state $(x_3, 0)$). In the latter case, the infection is established at the highest level possible, i.e. x reaches its carrying capacity, while the immune response is exhausted. We will refer to this situation as bistable immune failure.

Finally, in Region VIII, the only stable outcome is the third steady state $(x_3, 0)$. In this situation, the immune response disappears in the long run, and the virus is established at its carrying capacity. The parameter conditions for these region are listed in Table 2, along with the stable solutions in each.

4. **Periodic solutions and herpes zoster.** When parameters of the model are chosen so that $(s, d/p)$ lies in Region I of Figure 1, we have shown that the system has two unstable steady states, labeled $(x_3, 0)$ and (x_4, y_4). We will now show that in this case a periodic solution always exists. In order to do so, we will apply the Poincaré-Bendixson Theorem. We must show that there is a region Ω in the xy plane such that any solution with an initial point in Ω remains in Ω for all future time.

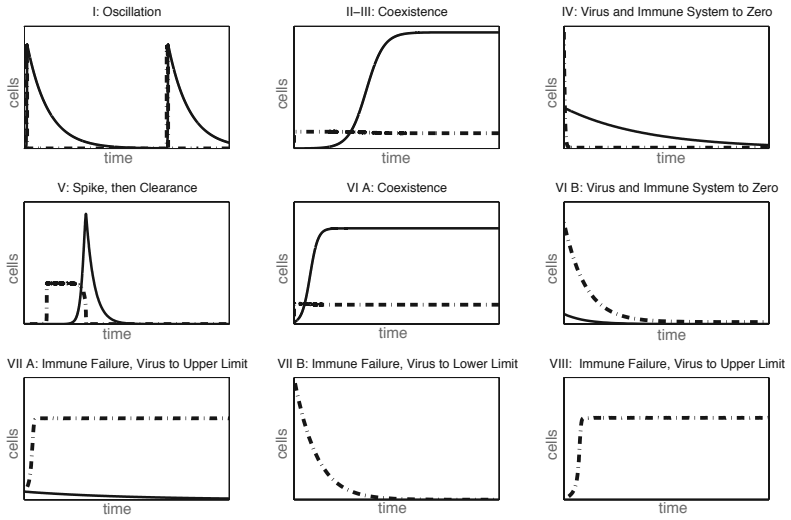

FIGURE 2. Samples of the course of infection (dashed line) and immune reaction (solid line) in the regions delineated in Figure 1. The oscillations in Region I demonstrate how latent virus can reemerge as the immune system gradually weakens over time. Chronic infection is demonstrated in Regions II, III, and VI, while permanent latent infection is observed in Region IV. In Region V, a large primary infection is followed by permanent latency. In Regions VII and VIII, the immune response is inefficient, and the infection establishes at a high level, if the initial inoculum us sufficient.

Region	Condition	Stable Solutions
I	$f(d/p) < \tilde{s} < s < g(d/p)$	stable limit cycle
II	$s > \max\{\tilde{s}, g(d/p), f(d/p)\}$	(x_4, y_4) stable
III	$0 < g(d/p) < f(d/p) < s < \tilde{s}$	(x_4, y_4) stable
IV	$d/p < K, s < \tilde{s} < f(d/p)$	$(x_1, 0)$ stable (x_4, y_4) does not exist
V	$f(d/p) < s < \tilde{s} < g(d/p)$	$(x_1, 0)$ stable, (x_4, y_4) unstable.
VI	$d/p > (K + \alpha)/3$ and $\max\{f(d/p), g(d/p)\} < s < \tilde{s}$	$(x_1, 0)$ and (x_4, y_4) both stable
VII	$d/p > K, s < \tilde{s}$	$(x_1, 0)$ and $(x_3, 0)$ both stable
VIII	$d/p > K, \tilde{s} < s < f(d/p)$	$(x_3, 0)$ stable

TABLE 2. Parameter conditions for stability conditions of equations (1,2). $f(x) = rx(x - K)(x - \alpha)$ and $g(x) = x^2(K + \alpha - 2x)$.

The trapping region Ω is illustrated in Figure (3). Two segments of Ω will be provided by the x and y axes. A third segment is the vertical line connecting the points $(x_3, 0)$ and (x_3, Δ), where Δ is a positive number defined below. The fourth piece of the boundary, will be a line with a negative slope m, extending from the

point (x_3, Δ). The formula for this line has the form

$$y = m(x - x_3) + \Delta, \tag{5}$$

where $x_4 \leq x \leq x_3$. We choose Δ so that for $y \geq \Delta$ and $x_4 \leq x \leq x_3$,

$$\frac{dx}{dt} < -2p\left(x_3 - x_4\right)^2,$$

and define

$$m = -\Delta/(x_3 - x_4).$$

The final segment of the boundary connects the line segment just described to the y axis. In particular, this would be the horizontal line $y = m(x_4 - x_3) + \Delta = 2\Delta$.

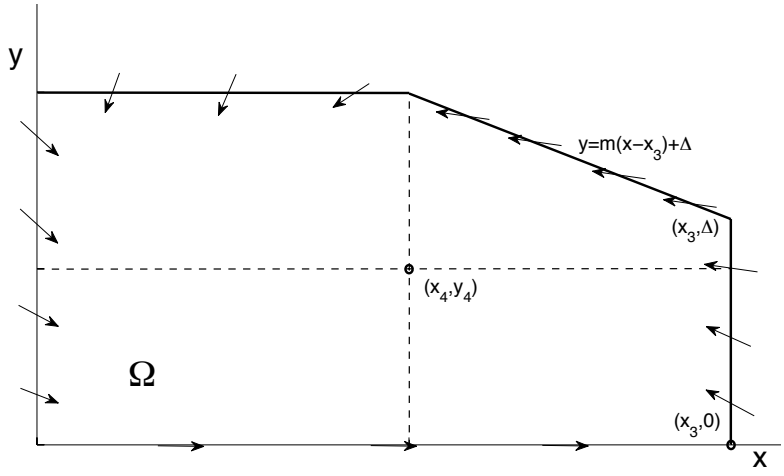

FIGURE 3. The trapping region Ω in the xy plane. Any solution with initial conditions in Ω will remain in Ω for all future time.

We must now show that along the boundary of Ω, no solution can cross from the interior to the exterior. At each point in the xy-plane, the differential equations (1,2) generate a direction vector, which gives the slope of the tangent line of the solution passing through that point. To show that Ω is a trapping region, we need to show that along the boundary these vectors point inward.

Along the y-axis, $dx/dt = s$ and $dy/dt = -dy$, so all vectors point downward and right, and hence to the interior. Along the x-axis, dy/dt is constantly 0, and, due to the uniqueness of solutions to the system of differential equations, no solution which has an initial point off of the axis can ever reach it.

Along the right-hand boundary $x = x_3$, $dx/dt = -cxy < 0$, while $dy/dt = y(px_3 - d) > 0$, so vectors point upward and to the left, toward the interior. Likewise, on the upper, horizontal boundary, dx/dt is negative since $y > y_4$, and $dy/dt < 0$, since $x < d/p$. Thus the vectors point downward and left, toward the interior.

Finally, we look along the upper right boundary, for which x is between $x_4 = d/p$ and x_3. At any point on this line segment, $dx/dt < 0$, since Δ has been chosen such that $dx/dt < -2p\left(x_3 - x_4\right)^2 < 0$. Also, $dy/dt > 0$ at points on this line segment,

since $dy/dt = (px - d)y > (px_4 - d)y = 0$. It remains to show that the slopes, dy/dx, of the vectors along the line $y = m(x - x_3) + \Delta$ are greater than m.

$$\begin{aligned}\frac{dy}{dx} &= \frac{dy/dt}{dx/dt} = \frac{y(px-d)}{dx/dt} > \frac{y(px_3-d)}{-2p\left(x_3-x_4\right)^2} \\ &= -\frac{y}{2\left(x_3-x_4\right)} = -\frac{m(x-x_3)+\Delta}{2\left(x_3-x_4\right)} \\ &> -\frac{m\left(x_4-x_3\right)+\Delta}{2\left(x_3-x_4\right)} = -\frac{\Delta+\Delta}{2\left(x_3-x_4\right)} = m\end{aligned}$$

So any disease trajectory that enters the region Ω cannot leave again, and this region contains a periodic solution. This periodic solution represents the course of a disease that permanently cycles from low level latent infection maintained over a long period of time, followed by rapid, spontaneous reemergence of infection. This is the course of events that leads to reactivation of a latent VZV infection to cause herpes zoster. Figure 4 illustrates this periodic behavior, and that the periodic solution is stable, so any other trajectory follows the same course of recurrence after a brief initial transition period.

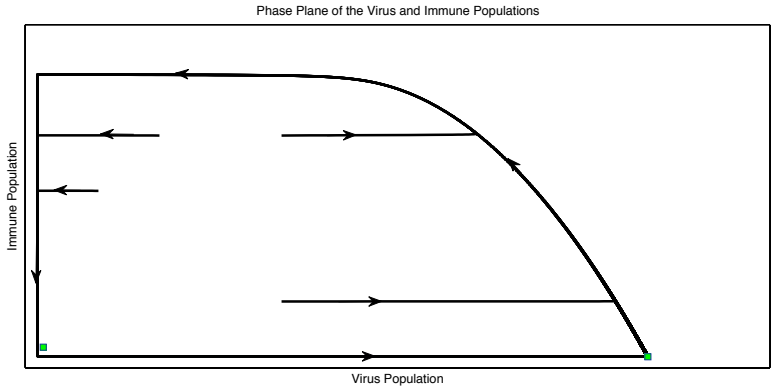

FIGURE 4. When s and d/p are chosen from Region I, a periodic solution of the system of equations (1,2), represented by a closed loop, exists and is rapidly approached by other solutions. So, independently of initial conditions, the host will eventually develop herpes zoster

In the parameter region in which periodic solutions exist (Region I), the choice of initial conditions determines only the transient behavior of the solution (Figure 5). As all trajectories quickly approach the periodic solution (Figure 4), we will assume initial conditions along the stable periodic solution when modeling the phenomenon of VZV reactivation. It is also interesting to note the effect on the model of reintroducing a large amount of infection can reset the phase of the periodic solution. During the long, slow decline of the immune response, small perturbations to the number of infected cells relax back to the current trajectory, but large changes in x, representing large rightward shifts in the phase plane given in Figure 4 would lead to reactivation of the infection and immune response, resetting the phase of the cycle. This could represent subclinical cases of reinfection or reactivation.

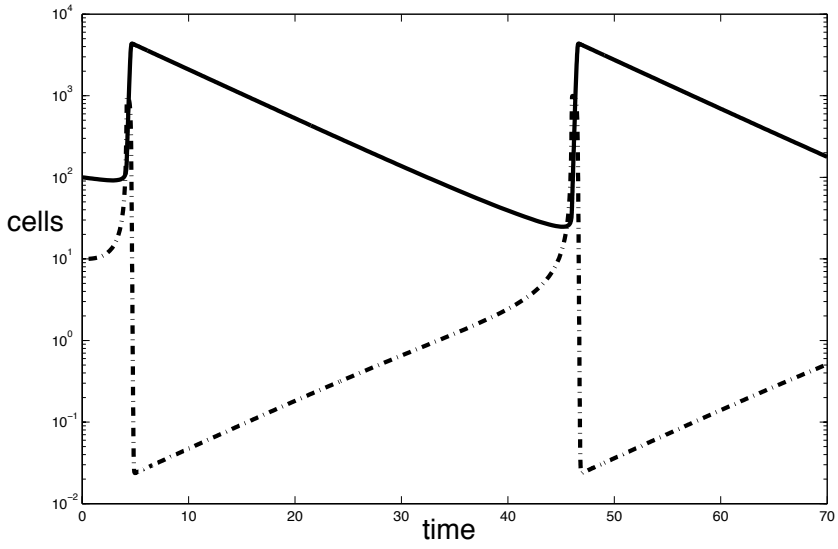

FIGURE 5. A sample trajectory for parameters in Region I. After an initial transient, the stable periodic solution is reached. The chosen parameters are $r = 0.0001$, $K = 1000$, $\alpha = s = 1$, $c = p = 0.01$, and $d = 0.1386$, with initial conditions $x(0) = 10$ and $y(0) = 100$.

5. **Herpes zoster prevention.** The reemergence of VZV infection from latency as herpes zoster is associated with extreme pain, which can sometimes persists for months. A number of factors are likely to increase the incidence of this disease. The population of the United States is aging, and the prevalence of zoster increases significantly with age. Furthermore, universal vaccination of children decreases the contact of latently infected host with active chickenpox cases, so a source of immune boosting is lost. Next, we will use our model to predict ways prevent the emergence of herpes zoster.

In the bifurcation diagram (Figure 1), there is a minimum value ($\tilde{s}$) which must be achieved by s in order for a reactivation from latency to occur. If s can be lowered below this minimum value, then the dynamics of the system would be altered in a fundamental way. Biologically, this would mean finding a way to lower the rate at which new infected cells are generated by infection from the site of latency. Since the live-attenuated virus vaccine does establish a latent infection and can lead to herpes zoster, the model suggests that a modification of the vaccine strain that could affect this specific aspect of the viral life cycle could eliminate the threat of herpes zoster. It is important to notice that the infectivity of latently infected cells would not have to be reduced to zero, but only to below the threshold $\tilde{s}$ in order to achieve this result.

Another question for herpes zoster prevention is the timing of the administration of a vaccine booster against VZV. Currently, the FDA recommends vaccination for patients aged 60, since after this age the incidence of zoster is significantly higher

than before [3]. Our model suggests a way of evaluating the timing of this vaccine in order to maximize its effectiveness.

Let h be the minimum level of VZV-specific immune cells that is considered protective against zoster. After the immune peak following primary infection, the number of infected cells is essentially 0, and the dynamics of the immune population is governed by $dy/dt \approx -dy$, so if y_m is the peak immune cell population, $y(t) = y_m \exp(-dt)$, where t is the time after the primary infection. The time it takes the immune population to fall below h is $\tilde{t} = (1/d)\ln(y_m/h)$, which we will refer to as the protection time. Now suppose the booster has the effect of increasing the immune cell population by a fixed amount B. The resulting increase in the protection time is dependent on the time T at which the booster is administered. Both T and $\tilde{t}$ are measured in years after primary infection. For $T < \tilde{t}$, the new protection time is

$$T + (1/d)\left[\ln(y_m e^{-dT} + B) - \ln h\right], \tag{6}$$

which is an increasing function of T. This suggests that the booster should be delayed for as long as is practicable.

The goal of the vaccine booster, however, is not to protect for the longest time possible, but to protect for the lifetime of the patient and as effectively as possible. The earlier the booster can be administered with assurance that it will remain protective for the rest of the patient's life, the more benefit it will provide. If the goal of vaccine administration is to guarantee protective levels of immunity through the next L years, and the current level of VZV-specific immune cells is known to be C, then the ideal time to administer the vaccine is the minimum of

$$T_1 = (1/d)\ln(C/h) \tag{7}$$

and

$$T_2 = (1/d)\left[\ln(he^{dL} - C) - \ln B\right]. \tag{8}$$

T_1 represents the time at which protective immunity will disappear in the absence of a vaccine booster, while T_2 is the time at which vaccine administration will ensure coverage through time L.

The immune level needed at the current time to guarantee coverage through a time L years in the future is he^{dL}. If $he^{dL} < C$, then no booster will be necessary. If $he^{dL} - C < B$, immediate administration of the booster would provide the required protection. Finally, if $he^{dL} - C > B$, then the vaccine should be administered at time $T = \min\{T_1, T_2\}$. If $T_1 < T_2$, further boosters will be needed to maintain protective immunity through time L.

The preceding calculations demonstrate how a mathematical model of virus-host interactions might be used to guide individualized decisions about the timing of zoster vaccine administration. Many improvements, however, are needed before such calculations can be or practical use. Longitudinal data on the rate at which cellular immunity to VZV wanes and on the strength of the booster effect of the vaccine are needed to properly estimate parameter values and improve upon the model itself.

6. **Conclusion.** We have developed a simple mathematical model based on the known biology of varicella-zoster virus infection, including the latent infection of neurons and the VZV-specific immune response. We have shown that this model explains the long latency period of the infection, and its spontaneous reactivation as a result of declining specific immunity with age. Mathematically, this course

of reactivation is represented by a limit cycle. Cycling behavior can only occur when the levels of viral production from the site of latency (the parameter s) and reactivity of the specific immune cells (d/p) lie within a defined set of values.

Based on this model, we can make predictions about means of preventing the reemergence of infection, which causes herpes zoster. In particular, the model can be used to make predictions about the ideal timing of the administration of vaccine boosters intended to prevent herpes zoster. As more information about the effects of this booster on patients becomes available, the model can serve as a platform for converting this patient data into recommendations about booster timing.

Finally, we have also seen that this mathematical model of infection and immunity demonstrates a wide variety of possible dynamic behaviors. As Figure 2 illustrates, by choosing two parameters appropriately, the model can be used to simulate many different possible biologically relevant courses of infection, including acute infection followed by clearance and chronic infection. This indicates that this model may be useful not only for the study of varicella-zoster virus, but also of other infectious diseases which have quite different natural histories.

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