

Effects of quarantine in six endemic models for infectious diseases

Herbert Hethcote^{a,*}, Ma Zhien^b, Liao Shengbing^b

^a *Department of Mathematics, University of Iowa, 14 MacLean Hall, Iowa City, IA 52242-1419, USA*

^b *Department of Mathematics, Xi'an Jiaotong University, Xi'an, Shaan'xi 710049, People's Republic of China*

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Abstract

Thresholds, equilibria, and their stability are found for SIQS and SIQR epidemiology models with three forms of the incidence. For most of these models, the endemic equilibrium is asymptotically stable, but for the SIQR model with the quarantine-adjusted incidence, the endemic equilibrium is an unstable spiral for some parameter values and periodic solutions arise by Hopf bifurcation. The Hopf bifurcation surface and stable periodic solutions are found numerically.

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1. Introduction

One intervention procedure to control the spread of infectious diseases is to isolate some infectives, in order to reduce transmissions of the infection to susceptibles. Isolation may have been the first infection control method, since biblical passages refer to the ostracism of lepers, and plague sufferers were often isolated. The word quarantine originally corresponded to a period of forty days, which is the length of time that arriving ships suspected of plague infection were constrained from intercourse with the shore in Mediterranean ports in the 15–19th centuries [1]. The word quarantine has evolved to mean forced isolation or stoppage of interactions with others. Over the centuries quarantine has been used to reduce the transmission of human diseases such as leprosy, plague, cholera, typhus, yellow fever, smallpox, diphtheria, tuberculosis, measles,

* Corresponding author. Tel.: +1-319 335 0790; fax: +1-319 335 0627.

E-mail address: herbert-hethcote@uiowa.edu (H. Hethcote).

mumps, ebola and lassa fever. Quarantine has also been used for animal diseases such as rinderpest, foot and mouth, psittacosis, Newcastle disease and rabies.

An epidemic is an outbreak of a disease over a short time period; a disease is said to be endemic if it persists in a population over a long period of time. In order to study the effects of quarantine on endemic infectious diseases, we look at six modifications of standard SIS and SIR endemic models that include a new class Q of quarantined individuals, who have been removed and isolated either voluntarily or coercively from the infectious class. For some milder diseases, quarantined people could be people who choose to stay home from school or work because they are sick. For other more severe diseases, quarantined people could be those who are forced into isolation. It is assumed that these quarantined individuals do not mix with others, so that they do not infect susceptibles. In these models susceptibles in the S class become infected and move to the infectious class I . In the three SIQS models for infections that do not confer immunity, susceptibles become infected and then some infected individuals remain in the I class for their entire infectious period before they return to the susceptible class, while other infected individuals are transferred into a quarantined class Q and remain there until they are no longer infectious, at which time they return to the susceptible class. In the three SIQR models for infections that confer permanent immunity, susceptibles become infected and then some infected individuals stay in the I class while they are infectious and then move to the removed class R upon recovery. Other infected individuals are transferred into the quarantine class Q while they are infectious, and then move into the removed class R . The models here have a variable total population size, because they have recruitment into the susceptible class by births or immigration and they have both natural and disease-related deaths [2]. In these models we identify the basic reproduction numbers that are the thresholds, find the disease-free and endemic equilibria, and determine their stability.

The incidence is the infection rate of susceptible individuals through their contacts with infectives. Let $S(t)$ be the number of susceptibles at time t , $I(t)$ be the number of infectives, $Q(t)$ be the number of quarantined individuals, and $N(t)$ be the total population size. In the three models with a removed or recovered class of permanently immune people, let $R(t)$ be the number of removed people. If β is the average number of adequate contacts (i.e. contacts sufficient for transmission) of a person per unit time, then I/N is the infectious fraction, $\beta I/N$ is the average number of contacts with infectives per unit time of one susceptible, and $(\beta I/N)S$ is the number of new cases per unit time due to the S susceptibles. Because it is formulated from the basic principles above, this form $\beta SI/N$ is called the standard incidence [2,3]. The simple mass action law βSI with β as a mass action coefficient is sometimes used for the incidence, but in this case the average number of adequate contacts per person per unit time is βN . Data [4, p. 157] [5, p. 306] suggest that the standard incidence is more realistic for human diseases than the simple mass action incidence. This result is consistent with the concept that people are infected through their daily encounters and the patterns of daily encounters are largely independent of community size within a given country (e.g. schools in a country have similar class sizes). For more information about the differences in models using these two forms of the incidence, see [3,6–10].

Four of the models in this paper use either the standard incidence $(\beta I/N)S$ or the simple mass action incidence βSI in SIQS and SIQR models. Using the simple mass action incidence βSI , the contacts βQ with the quarantined (but still infectious) people are lost, so that the total contact rate is $\beta(S + I + R) = \beta(N - Q)$, which is less than βN if the number Q of quarantined people is

positive. Similarly, with the standard incidence $(\beta I/N)S$, the contacts $\beta Q/N$ with the quarantined fraction Q/N are lost and do not occur. Thus the total contacts of a susceptible using this form of the incidence are $\beta(S + I + R)/N = \beta(N - Q)/N < \beta$, so that the total number of contacts per day is reduced by the quarantine process. This scenario would be plausible if a quarantined child misses school, so that the classmates have fewer contacts on that day. It would also be plausible if a quarantined employee misses work and is not replaced, so that the other employees have fewer contacts. But this scenario would not be plausible if a quarantined teacher misses work and is replaced by a substitute teacher, so that the school children have the usual number of contacts. It would also not be plausible if the quarantined employee who misses work is replaced by another person, so that the other employees at that work location have the usual number of contacts. Thus if the quarantined person such as a teacher, bus driver, waiter, etc. is replaced by another person, then the people who would normally contact the quarantined person would be contacting someone else in the population. In this second scenario, the average number of adequate contacts per day would still be β , but these contacts would occur within the population of size $N - Q$. Thus the denominator N in the standard incidence is replaced by $N - Q$, so that $I/(N - Q)$ is the infectious fraction of the circulating population, and $\beta I/(N - Q)$ is the average number of contacts with infectives per unit time of one susceptible. In this paper, the incidence given by $\beta SI/(N - Q)$ is called the quarantine-adjusted incidence. The total contacts of a susceptible using this form of the incidence are $\beta(S + I + R)/(N - Q) = \beta(N - Q)/(N - Q) = \beta$, so that the total number of contacts per day is maintained at β during the quarantine process. In this paper, we also consider SIQS and SIQR models with the quarantine-adjusted incidence.

The SIQS models with the simple mass action incidence, the standard incidence, and the quarantine-adjusted incidence are considered in Sections 2–4. The SIQR models with these same three incidence forms are considered in Sections 5–7. The first five models have endemic equilibria that are asymptotically stable, but the SIQR model with the quarantine-adjusted incidence in Section 7 can have an endemic equilibria that is a stable or unstable spiral, so that periodic solutions can occur by Hopf bifurcation.

The standard SIS and SIR endemic models in a homogeneously mixing population have been described in papers and books [2,3,5,11,12]. Because oscillations with periods of one or a few years are observed for many infectious diseases, it is of interest to study possible mechanisms for periodic solutions in epidemiology models. See [13] for a survey of mechanisms that can lead to periodicity in epidemiological models. Feng and Thieme [14] considered an SIQR model with a quarantine class, that is a special case of our SIQR model with quarantine-adjusted incidence in Section 7. They found that the introduction of a quarantine class is a new mechanism that can lead to periodic solutions. They investigated these periodic solutions and considered diseases where this mechanism might explain observed oscillations. Feng and Thieme [15,16] considered very general endemic models that include SEIQR models with arbitrarily distributed periods of infection including quarantine, and with a general form for the incidence term that includes the three forms above. In their models all individuals must go through the quarantine class Q . They proved extinction and persistence results, found minimum quarantine periods in order to make the endemic equilibrium unstable, and applied their results to scarlet fever data. For an SIQR endemic model, Wu and Feng [17] showed that an epidemic approximation near $R_0 = 1$ can have a homoclinic bifurcation, so that some perturbation of the original model might also have a homoclinic bifurcation.

One purpose of this paper is to examine and compare formulations of models with a quarantine class. Another purpose is to determine if periodic solutions also occur in similar SIQS and SIQR models. These models generalize the models of Feng and Thieme by allowing some infected individuals to follow the usual recovery route and others to be detoured through the quarantine class. Many aspects of the SIQR model with the quarantine-adjusted incidence seem consistent with the sustained oscillations that are observed in actual disease incidences. However, we did not find a parameter set and corresponding periodic solution that match every aspect of the observed data. This situation and the main results in this paper are discussed in Section 8.

The following theorem on limiting systems [18] will be useful in our mathematical analyses. In a typical application we show that one or more dependent variables approach limiting values and then analyze the asymptotically autonomous limiting system.

Lemma 1. *Consider the following two systems*

$$\frac{dx}{dt} = f(t, x), \frac{dy}{dt} = g(y),$$

where $x, y \in \mathbb{R}^n$, f and g are continuous, satisfy a local Lipschitz condition in any compact set $X \in \mathbb{R}^n$, and $f(t, x) \rightarrow g(x)$ as $t \rightarrow +\infty$, so that the second system is the limit system for the first system. Let $\Phi(t, t_0, x_0)$ and $\varphi(t, t_0, y_0)$ be solutions of these systems, respectively. Suppose that $e \in X$ is a locally asymptotically stable equilibrium of the limit system and its attractive region is

$$W(e) = \{y \in X | \varphi(t, t_0, y) \rightarrow e, t \rightarrow +\infty\}.$$

Let W_Φ be the omega limit set of $\Phi(t, t_0, x_0)$. If $W_\Phi \cap W(e) \neq \emptyset$, then $\lim_{t \rightarrow +\infty} \Phi(t, t_0, x_0) = e$.

2. The SIQS model with simple mass action incidence

The total population $N(t)$ is divided into three compartments with $N(t) = S(t) + I(t) + Q(t)$, where S is the number of individuals in the susceptible class, I is the number of individuals who are infectious but not quarantined, and Q is the number of individuals who are quarantined. The latent period, in which the person is infected but not yet infectious, is neglected, and it is assumed that an infection does not confer immunity. This model is called an SIQS model since one typical pathway is through S , then I , then Q , and then back to S , as shown in Fig. 1.

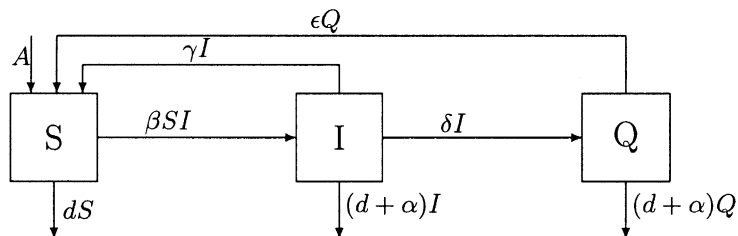


Fig. 1. The general transfer diagram for the SIQS model.

The differential equations for this SIQS model are:

$$\begin{aligned} S'(t) &= A - \beta SI - dS + \gamma I + \varepsilon Q, \\ I'(t) &= [\beta S - (\gamma + \delta + d + \alpha)]I, \\ Q'(t) &= \delta I - (\varepsilon + d + \alpha)Q, \end{aligned} \tag{1}$$

where parameters A , d and β are positive constants, and γ , δ , ε and α are non-negative constants. The constant A is the recruitment rate of susceptibles corresponding to births and immigration, d is the per capita natural mortality rate, $\beta(S + I + R)$ is the average number of adequate contacts (with those who are not quarantined) per person per unit time, δ is the rate constant for individuals leaving the infective compartment I for the quarantine compartment Q , α is the disease-related death rate constant in compartments I and Q , and γ and ε are the rates at which individuals recover and return to susceptible compartment S from compartments I and Q , respectively.

The total population size $N(t)$ is variable with $N'(t) = A - dN - \alpha(I + Q)$. In the absence of disease, the population size N approaches the carrying capacity A/d . The differential equation for N implies that solutions of (1) starting in the positive orthant R_+^3 either approach, enter, or remain in the subset of R_+^3 defined by

$$D = \{(S, I, Q) | S \geq 0, I \geq 0, Q \geq 0, S + I + Q \leq A/d\}.$$

Thus it suffices to consider solutions in the region D . Solutions of the initial value problem starting in D and defined by (1) exist and are unique on a maximal interval [19]. Since solutions remain bounded in the positively invariant region D , the maximal interval is $[0, \infty)$. Thus the initial value problem is well posed both mathematically and epidemiologically.

The system (1) always has the disease-free equilibrium $P_0 = (A/d, 0, 0)$. Define the quarantine reproduction number as

$$R_q = \frac{\beta(A/d)}{\gamma + \delta + d + \alpha},$$

which is product of the contact rate coefficient β , the number A/d of susceptibles at the disease-free equilibrium, and the average residence time $1/(\gamma + \delta + d + \alpha)$ in the infective class I . Thus R_q is the average number of secondary infections in a completely susceptible population when one infective enters the population in the situation where the average infectious period is decreased by the quarantining of some infectives. Note that we use the name ‘quarantine reproduction number’ for the threshold quantity above, because we think of the quarantine process as an intervention strategy that is used to reduce or control the disease. The basic reproduction number would be $R_0 = \beta(A/d)/(\gamma + d + \alpha)$ for the SIS model without quarantine ($\delta = 0$). If $R_q > 1$, then D also contains a unique positive, endemic equilibrium $P^* = (S^*, I^*, Q^*)$, where

$$S^* = \frac{A/d}{R_q}, \quad I^* = \frac{A(1 - 1/R_q)}{(d + \alpha)[1 + \delta/(\varepsilon + d + \alpha)]}, \quad Q^* = \frac{\delta I^*}{\varepsilon + d + \alpha}.$$

Note that

$$N^* = S^* + I^* + Q^* = \frac{A}{d} - \frac{A\alpha(1 - 1/R_q)}{d(d + \alpha)}.$$

Thus when the disease-related death rate constant α is positive, then the total population N^* at the endemic equilibrium P^* is less than the disease-free carrying capacity A/d . The following theorem describes the behavior of solutions of (1) in the region D .

Theorem 2. *Consider system (1). If $R_q \leq 1$, then D is an asymptotic stability region for the disease-free equilibrium P_0 . If $R_q > 1$, then the region $D - \{(S, I, Q) | I = 0\}$ is an asymptotic stability region for the endemic equilibrium P^* .*

Proof. Analysis of the Jacobian matrix of the system at equilibrium P_0 shows that it is locally asymptotically stable if $R_q < 1$ and is unstable if $R_q > 1$. In order to prove the global stability when $R_q \leq 1$, consider the Liapunov function $V = I$ with the Liapunov derivative

$$V' = [\beta S - (\gamma + \delta + d + \alpha)]I \leq [\beta A/d - (\gamma + \delta + d + \alpha)]I \leq 0,$$

since $S \leq A/d$. By the Liapunov–Lasalle theorem [19, p. 296], solutions in D approach the largest positively invariant subset of the set where $V' = 0$, which is the set where $I = 0$. In this set, $Q'(t) = -(\varepsilon + d + \alpha)Q$, so that $Q \rightarrow 0$ as $t \rightarrow \infty$. Thus $S'(t) = A - dS + \varepsilon Q$ is asymptotically equivalent to $S'(t) = A - dS$, so that $S \rightarrow A/d$. Thus all solutions in the set where $I = 0$ go to the disease-free equilibrium P_0 . By Lemma 1, all solutions in D must also approach P_0 .

Local stability analysis at the endemic equilibrium P^* when $R_q > 1$ shows that it is locally asymptotically stable by the Routh–Hurwitz criteria. In order to prove the global stability when $R_q > 1$, first note that the system (1) is equivalent to the following system involving N, I and Q and the endemic equilibrium values N^*, I^* and Q^* .

$$\begin{aligned} N' &= -d(N - N^*) - \alpha(I - I^*) - \alpha(Q - Q^*), \\ I' &= [\beta(N - N^*) - \beta(I - I^*) - \beta(Q - Q^*)]I, \\ Q' &= \delta(I - I^*) - (\varepsilon + d + \alpha)(Q - Q^*) \end{aligned}$$

Consider the Liapunov function

$$\begin{aligned} V &= \frac{(\delta + \varepsilon + 2d + \alpha)}{\beta} \left[I - I^* - I^* \ln \frac{I}{I^*} \right] + \frac{1}{2} \left\{ \frac{(\varepsilon + 2d)(N - N^*)^2}{\alpha} + [(N - N^*) - (Q - Q^*)]^2 \right. \\ &\quad \left. + \frac{(\varepsilon + 2d)(Q - Q^*)^2}{\delta} \right\}, \end{aligned}$$

which is a positive definite function in the region $D - \{(S, I, Q) | I = 0\}$. The Liapunov derivative is

$$\begin{aligned} V' &= -(\delta + \varepsilon + 2d + \alpha)(I - I^*)^2 - \frac{d(\varepsilon + 2d + \alpha)}{\alpha}(N - N^*)^2 \\ &\quad - \left[\frac{(\varepsilon + 2d)(\varepsilon + d + \alpha)}{\delta} + (\varepsilon + d) \right] (Q - Q^*)^2. \end{aligned}$$

Because V' is negative definite, the Liapunov theorem [19] implies that the endemic equilibrium is globally asymptotically stable in the region $D - \{(S, I, Q) | I = 0\}$. \square

3. The SIQS model with the standard incidence

We now consider the SIQS model with the standard incidence $\beta SI/N$ described in Section 1. The transfer diagram for this SIQS model is similar to that in Fig. 1, except that the simple mass action incidence βSI is replaced by the standard incidence $\beta SI/(S + I + Q)$. Hence the new SIQS model is

$$\begin{aligned} S'(t) &= A - \beta SI/(S + I + Q) - dS + \gamma I + \varepsilon Q, \\ I'(t) &= [\beta S/(S + I + Q) - (\gamma + \delta + d + \alpha)]I, \\ Q'(t) &= \delta I - (\varepsilon + d + \alpha)Q, \end{aligned} \tag{2}$$

This model uses the same variables and parameters as the model in the previous section; the only difference is the form of the incidence. The total population size $N(t)$ still satisfies $N'(t) = A - dN - \alpha(I + Q)$, so that in the absence of disease, the population size N approaches the carrying capacity A/d . Moreover, it suffices to consider solutions of (2) starting in the set D defined in the previous section and the initial value problem is well posed in D .

The system (2) has the disease-free equilibrium $P_0 = (A/d, 0, 0)$ as in the previous SIQS model, but the quarantine reproduction number is now

$$R_q = \frac{\beta}{\gamma + \delta + d + \alpha}, \tag{3}$$

which is product of the daily contact rate β per person and the average residence time $1/(\gamma + \delta + d + \alpha)$ in the infective class I . If $R_q > 1$, then D also contains a unique positive, endemic equilibrium $P^* = (S^*, I^*, Q^*)$, where

$$\begin{aligned} S^* &= \frac{I^*(\delta + \varepsilon + d + \alpha)}{(R_q - 1)(\varepsilon + d + \alpha)}, & I^* &= \frac{A(R_q - 1)(\varepsilon + d + \alpha)}{(\delta + \varepsilon + d + \alpha)[d + (R_q - 1)(d + \alpha)]}, \\ Q^* &= \frac{\delta I^*}{\varepsilon + d + \alpha}, & \text{and } N^* = S^* + I^* + Q^* &= \frac{AR_q}{d + (R_q - 1)(d + \alpha)}. \end{aligned}$$

When the disease-related death rate constant α is positive, the total population N^* at the endemic equilibrium P^* is less than the disease-free carrying capacity A/d . We expect that the global stability result in the theorem below when $R_q > 1$ and $\alpha = 0$ is also true when $\alpha > 0$, but we did not find a proof.

Theorem 3. *Consider system (2). If $R_q \leq 1$, then D is an asymptotic stability region for the disease-free equilibrium P_0 . If $R_q > 1$, then the equilibrium P_0 is unstable, the disease is uniformly persistent, and the endemic equilibrium P^* is locally asymptotically stable. Moreover, if $R_q > 1$ and $\alpha = 0$ (so there are no disease-related deaths), then the region $D - \{S, I, Q | I = 0\}$ is an asymptotic stability region for the endemic equilibrium P^* .*

Proof. A local analysis at the disease-free equilibrium P_0 shows that it is locally asymptotically stable if $R_q < 1$ and is unstable if $R_q > 1$. When $R_q \leq 1$, the Liapunov function $V = I$ is used as in the previous section to show that all solutions of (2) starting in D approach P_0 .

The system (2) is defined to be uniformly persistent if $\liminf_{t \rightarrow \infty} I(t) \geq c$ for some $c > 0$ for all initial points such that $I(0) > 0$. The local stability analysis shows that the equilibrium P_0 is

unstable if $R_q > 1$ with a repulsive direction into D , so that the disease is uniformly persistent by Theorem 4.5 in [20]. A Maple computer algebra program has been used to show that the Routh–Hurwitz criteria are satisfied, so that the endemic equilibrium P^* is locally asymptotically stable.

In order to prove the global stability when $R_q > 1$ and $\alpha = 0$, first note that $N' = A - dN$, so that $N \rightarrow A/d$ as $t \rightarrow \infty$. The limit system for (2) is

$$\begin{aligned} N' &= 0, \\ I' &= [\beta(A/d - I - Q)/(A/d) - (\gamma + \delta + d)]I, \\ Q' &= \delta I - (d + \varepsilon)Q \end{aligned} \tag{4}$$

with $N = A/d$. In the two-dimensional IQ first quadrant region with $I + Q \leq A/d$, the equilibrium $(0, 0)$ is a saddle that is attractive along $I = 0$ and has a repulsive direction into the region. The other equilibrium (I^*, Q^*) in the region is locally asymptotically stable. Using Dulac’s criteria with multiplier $1/I$, we have

$$\frac{\partial}{\partial I} [\beta(A/d - I - Q)/(A/d) - \gamma - \delta - d] + \frac{\partial}{\partial Q} [\delta - (\varepsilon + d)Q/I] = -\beta/(A/d) - (\varepsilon + d)/I < 0,$$

so that there are no periodic solutions in the region. Thus by the Poincaré–Bendixson theory, all solutions starting in the first quadrant region with $I > 0$ and $I + Q \leq A/d$ approach (I^*, Q^*) as $t \rightarrow \infty$. Thus P^* is a globally asymptotically stable equilibrium for the limit system (4). By Lemma 1, all solutions starting in the region $D - \{S, I, Q | I = 0\}$ of the original system (2) approach the endemic equilibrium P^* as $t \rightarrow \infty$. \square

4. The SIQS model with the quarantine-adjusted incidence

We now consider the SIQS model with the quarantine-adjusted incidence described in Section 1. Here the denominator N in the standard incidence $\beta SI/N$ has been replaced by the actively mixing population $N - Q = S + I$ to get the quarantine-adjusted incidence $\beta SI/(S + I)$. The transfer diagram for this SIQS model is similar to that in Fig. 1, except that the simple mass action incidence βSI is replaced by $\beta SI/(S + I)$. Hence the new SIQS model is

$$\begin{aligned} S'(t) &= A - \beta SI/(S + I) - dS + \gamma I + \varepsilon Q, \\ I'(t) &= [\beta S/(S + I) - (\gamma + \delta + d + \alpha)]I, \\ Q'(t) &= \delta I - (\varepsilon + d + \alpha)Q. \end{aligned} \tag{5}$$

This model uses the same variables and parameters as the models in the previous sections; the only difference is the form of the incidence. The total population size $N(t)$ still satisfies $N'(t) = A - dN - \alpha(I + Q)$, so that in the absence of disease, the population size N approaches the carrying capacity A/d . As in the previous models, it suffices to consider solutions of (5) starting in the set D defined in Section 2 and the initial value problem is well posed in D .

The system (5) has the same disease-free equilibrium $P_0 = (A/d, 0, 0)$ as in the previous SIQS models, and the quarantine reproduction number R_q is still given by (3) in the previous section. If $R_q > 1$, then D also contains a unique positive, endemic equilibrium P^* with coordinates

$$S^* = \frac{I^*}{R_q - 1}, \quad I^* = \frac{A}{\frac{d}{1-1/R_q} + \alpha + \frac{\delta(\alpha+d)}{\varepsilon+d+\alpha}}, \quad Q^* = \frac{\delta I^*}{\varepsilon + d + \alpha}.$$

For this model,

$$N^* = S^* + I^* + Q^* = \frac{A \left(\frac{1}{1-1/R_q} + \frac{\delta}{\varepsilon+d+\alpha} \right)}{\frac{d}{1-1/R_q} + \alpha + \frac{\delta(\alpha+d)}{\varepsilon+d+\alpha}}.$$

The proof of the theorem below is omitted, because it is analogous to the proof in the previous section.

Theorem 4. Consider system (5). If $R_q \leq 1$, then D is an asymptotic stability region for the disease-free equilibrium P_0 . If $R_q > 1$, then the equilibrium P_0 is unstable, the disease is uniformly persistent, and the endemic equilibrium P^* is locally asymptotically stable. Moreover, if $R_q > 1$ and $\alpha = 0$ (so there are no disease-related deaths), then the region $D - \{(S, I, Q) | I = 0\}$ is an asymptotic stability region for the endemic equilibrium P^* .

5. The SIQR model with simple mass action incidence

Assume that infection confers permanent immunity, so that individuals can move from the I and Q classes to the R class, where $R(t)$ is the number of individuals with permanent immunity and $N(t) = S(t) + I(t) + Q(t) + R(t)$. In this SIQR model, the flow is from the S class to the I class, and then either directly to the R class or to the Q class and then to the R class as shown in Fig. 2.

This SIQR model with simple mass action incidence is

$$\begin{aligned} S'(t) &= A - \beta SI - dS, \\ I'(t) &= [\beta S - (\gamma + \delta + d + \alpha_1)]I, \\ Q'(t) &= \delta I - (d + \alpha_2 + \varepsilon)Q, \\ R'(t) &= \gamma I + \varepsilon Q - dR, \end{aligned} \tag{6}$$

where δ and ε are the removal rate constants from group I and Q respectively, and α_1 and α_2 represent the extra disease-related death rate constants in classes I and Q , respectively. The other parameters are the same as in the previous models.

The total population size $N(t)$ satisfies $N'(t) = A - dN - \alpha_1 I - \alpha_2 Q$, so that the population size N approaches the carrying capacity A/d when there is no disease. As in the previous models, the differential equation for N implies that solutions of (6) starting in the positive orthant R_4^+ either approach, enter, or remain in the subset

$$D = \{(S, I, Q, R) | S \geq 0, I \geq 0, Q \geq 0, R \geq 0, S + I + Q + R \leq A/d\}.$$

Thus it suffices to consider solutions in the region D . As before, the initial value problem is well posed both mathematically and epidemiologically in D .

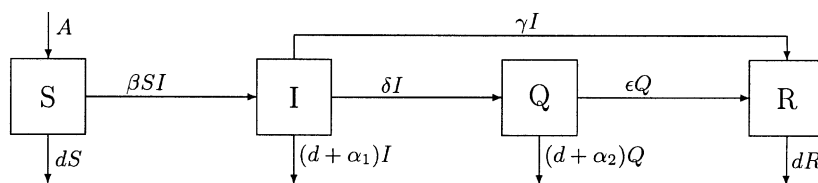


Fig. 2. The transfer diagram for the SIQR model with simple mass action incidence.

The system (6) always has the disease-free equilibrium $P_0 = (A/d, 0, 0, 0)$. Here the quarantine reproduction number is

$$R_q = \frac{\beta(A/d)}{\gamma + \delta + d + \alpha_1}.$$

If $R_q > 1$, then D also contains a unique positive, endemic equilibrium $P^* = (S^*, I^*, Q^*, R^*)$, where

$$S^* = \frac{A/d}{R_q}, \quad I^* = \frac{d(R_q - 1)}{\beta}, \quad Q^* = \frac{\delta d(R_q - 1)}{\beta(\varepsilon + d + \alpha_2)}, \quad R^* = \left[\gamma + \frac{\varepsilon \delta}{\varepsilon + d + \alpha_2} \right] \frac{R_q - 1}{\beta}.$$

Note that

$$N^* = S^* + I^* + Q^* + R^* = \frac{A/d}{R_q} + \left[d + \gamma + \frac{\delta(\varepsilon + d)}{\varepsilon + d + \alpha_2} \right] \frac{R_q - 1}{\beta}.$$

The following theorem describes the behavior of solutions of (6) in the region D .

Theorem 5. *Consider system (6). If $R_q \leq 1$, then D is an asymptotic stability region for the disease-free equilibrium P_0 . If $R_q > 1$, then the region $D - \{(S, I, Q, R) | I = 0\}$ is an asymptotic stability region for the endemic equilibrium P^* .*

Proof. Linear analysis of the system at equilibrium P_0 shows that it is locally asymptotically stable if $R_q < 1$ and is unstable if $R_q > 1$. In order to prove the global stability when $R_q \leq 1$, consider the Liapunov function $V = I$ with the Liapunov derivative

$$V' = [\beta S - (\gamma + \delta + d + \alpha_1)]I \leq [\beta A/d - (\gamma + \delta + d + \alpha_1)]I \leq 0,$$

since $S \leq A/d$. As in the previous proofs, the Liapunov–Lasalle theorem [19, p. 296] implies that solutions in D approach the largest positively invariant subset of the set where $V' = 0$, which is the set where $I = 0$. In this set, $Q'(t) = -(d + \alpha_2 + \varepsilon)Q$, and $S'(t) = A - dS$, so that $Q \rightarrow 0$ and $S \rightarrow A/d$ as $t \rightarrow \infty$. Hence the differential equation for R is asymptotically equivalent to $R'(t) = -dR$, so that $R \rightarrow 0$ as $t \rightarrow \infty$. Thus all solutions in the set $I = 0$ go to the disease-free equilibrium P_0 . By Lemma 1, all solutions in D must also approach P_0 .

Note that for $R_q > 1$, we could prove persistence and locally asymptotic stability of the endemic equilibrium P^* by the Routh–Hurwitz criteria, but these are not necessary for this model since we prove global stability by using a Liapunov function. Consider the SI subsystem of model (6) which is independent of the Q and R variables. The Liapunov function

$$V = S^* \int_{S^*}^S \frac{\beta u - (\gamma + \delta + d + \alpha_1)}{u} du + \int_{I^*}^I \frac{\beta S^* u + dS^* - A}{u} du$$

is positive definite for $(S - S^*)^2 + (I - I^*)^2 > 0$ and goes to infinity as $S \rightarrow \infty$ or $I \rightarrow \infty$. Using $\gamma + \delta + d + \alpha_1 = \beta S^*$, the Liapunov derivative is

$$\begin{aligned} V' &= S^*(\beta S - \beta S^*)(A - \beta SI - dS)/S + (\beta S^* I + dS^* - A)(\beta S - \beta S^*) \\ &= -A(S - S^*)(\beta S - \beta S^*)/S = -A\beta(S - S^*)^2/S \leq 0. \end{aligned}$$

Note that $V' = 0$ on the set where $S = S^*$. Because $S' \neq 0$ on $S = S^*$ unless $I = I^*$, the largest positively invariant subset is the equilibrium (S^*, I^*) , so that the Liapunov–Lasalle theorem [19, p. 296] implies that (S^*, I^*) is globally stable in R_+^2 and $\lim_{t \rightarrow \infty} I(t) = I^*$.

From the third equation in (6) we can formally solve to obtain

$$Q(t) = \left[Q_0 + \int_{t_0}^t \delta I(\tau) e^{(\varepsilon+d+\alpha_2)(\tau-t_0)} d\tau \right] / e^{(\varepsilon+d+\alpha_2)(t-t_0)}$$

By L'Hospital's rule we obtain $\lim_{t \rightarrow \infty} Q(t) = \lim_{t \rightarrow \infty} \delta I(t) / (\varepsilon + d + \alpha_2) = \delta I^* / (\varepsilon + d + \alpha_2) = Q^*$. Similarly, solving for R using the fourth equation in (6) and using L'Hospital's rule, we obtain $\lim_{t \rightarrow \infty} R(t) = [\alpha I^* + \varepsilon Q^*] / d = R^*$. An application of Lemma 1 shows that the endemic equilibrium P^* of model (6) is globally asymptotically stable in the region $D - \{(S, I, Q, R) | I = 0\}$. \square

6. The SIQR model with the standard incidence

The transfer diagram for this SIQR model is similar to that in Fig. 2, except that the simple mass action incidence βSI is replaced by standard incidence $\beta SI/N$, where $N = S + I + Q + R$. This SIQR model is

$$\begin{aligned} S'(t) &= A - \beta SI/N - dS, \\ I'(t) &= [\beta S/N - (\gamma + \delta + d + \alpha_1)]I, \\ Q'(t) &= \delta I - (\varepsilon + d + \alpha_2)Q, \\ R'(t) &= \gamma I + \varepsilon Q - dR, \end{aligned} \tag{7}$$

where the parameters are the same as in the SIQR model in Section 5. As in the previous model, the differential equation for $N(t)$ is $N'(t) = A - dN - \alpha_1 I - \alpha_2 Q$, so that N approaches the carrying capacity A/d when there is no disease. As in the previous models, it suffices to consider solutions of (7) in the region D defined in the previous section.

The system (7) always has the disease-free equilibrium $P_0 = (A/d, 0, 0, 0)$. For this SIQR model, the quarantine reproduction number is

$$R_q = \frac{\beta}{\gamma + \delta + d + \alpha_1}. \tag{8}$$

If $R_q > 1$, then D also contains a unique positive, endemic equilibrium $P^* = (S^*, I^*, Q^*, R^*)$, where

$$\begin{aligned} S^* &= \frac{(A/d)[(\gamma + d)(\varepsilon + d + \alpha_2) + \delta(\varepsilon + d)]}{(\varepsilon + d + \alpha_2)[R_q(\gamma + \delta + d + \alpha_1) - \alpha_1] - \alpha_2 \delta}, \\ I^* &= \frac{A(R_q - 1)(\varepsilon + d + \alpha_2)}{(\varepsilon + d + \alpha_2)[R_q(\gamma + \delta + d + \alpha_1) - \alpha_1] - \alpha_2 \delta}, \\ Q^* &= \frac{\delta A(R_q - 1)}{(\varepsilon + d + \alpha_2)[R_q(\gamma + \delta + d + \alpha_1) - \alpha_1] - \alpha_2 \delta}, \\ R^* &= \frac{(A/d)(R_q - 1)[\gamma(\varepsilon + d + \alpha_2) + \varepsilon \delta]}{(\varepsilon + d + \alpha_2)[R_q(\gamma + \delta + d + \alpha_1) - \alpha_1] - \alpha_2 \delta}, \\ N^* &= S^* + I^* + Q^* + R^* = \frac{(A/d)R_q[(\gamma + d)(\varepsilon + d + \alpha_2) + \delta(\varepsilon + d)]}{(\varepsilon + d + \alpha_2)[R_q(\gamma + \delta + d + \alpha_1) - \alpha_1] - \alpha_2 \delta}. \end{aligned} \tag{9}$$

The following theorem describes the behavior of solutions of (7) in the region D .

Theorem 6. Consider system (7). If $R_q \leq 1$, then D is an asymptotic stability region for the disease-free equilibrium P_0 . If $R_q > 1$, then the equilibrium P_0 is unstable, the disease is uniformly persistent, and the unique endemic equilibrium P^* with coordinates given by (9) is locally asymptotically stable. Moreover, if $R_q > 1$ and $\alpha_1 = \alpha_2 = 0$ (so there are no disease-related deaths), then the region $D - \{(S, I, Q, R) | I = 0\}$ is an asymptotic stability region for the endemic equilibrium P^* .

Proof. Linear analysis of the system at equilibrium P_0 shows that it is locally asymptotically stable if $R_q < 1$ and is unstable if $R_q > 1$. The proof of global stability when $R_q < 1$ uses the Liapunov function $V = I$ and is analogous with the proofs in the previous sections. The local stability analysis shows that the equilibrium P_0 is unstable if $R_q > 1$ with a repulsive direction into D , so that the disease is uniformly persistent by Theorem 4.5 in [20]. Using a Maple computer algebra program, we find that the Routh–Hurwitz criteria at the endemic equilibrium are satisfied, so that the endemic equilibrium P^* given by (9) is locally asymptotically stable.

In order to prove the global stability when $R_q > 1$ and $\alpha_1 = \alpha_2 = 0$, first note that $N' = A - dN$, so that $N \rightarrow A/d$ as $t \rightarrow \infty$. The limit system for (7) is

$$\begin{aligned} S'(t) &= A - d\beta SI/A - dS, \\ I'(t) &= [d\beta S/A - (\gamma + \delta + d + \alpha_1)]I, \\ Q'(t) &= \delta I - (\varepsilon + d + \alpha_2)Q, \\ R'(t) &= \gamma I + \varepsilon Q - dR \end{aligned} \tag{10}$$

with $N = A/d$. The first two equations are independent of Q and R . In the two dimensional SI first quadrant region with $S + I \leq A/d$, the equilibrium $(0, 0)$ is a saddle that is attractive along $I = 0$ and has a repulsive direction into the region. The other equilibrium (S^*, I^*) in the region is locally asymptotically stable. Using Dulac's criteria with multiplier $1/I$, we have

$$\frac{\partial}{\partial S} [A/I - d\beta S/A - dS/I] + \frac{\partial}{\partial I} [d\beta S/A - (\gamma + \delta + d + \alpha_1)] = -\beta d/A - d/I < 0,$$

so that there are no periodic solutions in the region. Thus by the Poincaré–Bendixson theory, all solutions starting in the first quadrant region with $I > 0$ and $S + I \leq A/d$ approach (S^*, I^*) as $t \rightarrow \infty$. In this case the differential equation for Q has the limiting equation $Q'(t) = \delta I^* - (\varepsilon + d + \alpha_2)Q$, so that $Q \rightarrow Q^*$ by Lemma 1. Similarly, the differential equation for R has the limiting equation $R'(t) = -\gamma I^* + \varepsilon Q^* - dR$, so that $R \rightarrow R^*$ by Lemma 1. Thus P^* is a globally asymptotically stable equilibrium for the limit system (10). Hence by Lemma 1 all solutions starting in the region $D - \{(S, I, Q, R) | I = 0\}$ of the original system (7) approach the endemic equilibrium P^* as $t \rightarrow \infty$. \square

7. The SIQR model with quarantine-adjusted incidence

The transfer diagram for this SIQR model is similar to that in Fig. 2, except that the simple mass action incidence βSI is replaced by quarantine-adjusted incidence $\beta SI/(S + I + R)$. This model generalizes the SIQR model of Feng and Thieme [14] in two important ways; it has some individuals going directly from the I class to the R class without going through the quarantine class and it includes disease-related deaths. This SIQR model is

$$\begin{aligned}
 S'(t) &= A - \beta SI / (S + I + R) - dS, \\
 I'(t) &= [\beta S / (S + I + R) - (\gamma + \delta + d + \alpha_1)]I, \\
 Q'(t) &= \delta I - (\varepsilon + d + \alpha_2)Q, \\
 R'(t) &= \gamma I + \varepsilon Q - dR,
 \end{aligned}
 \tag{11}$$

where the parameters are the same as in the SIQR model in Section 5. As in the two previous models, we consider solutions of (11) in the region D defined in Section 5.

The system (11) always has the disease-free equilibrium $P_0 = (A/d, 0, 0, 0)$. For this SIQR model the quarantine reproduction number R_q is still given by (8). If $R_q > 1$, then D also contains a unique positive, endemic equilibrium $P^* = (S^*, I^*, Q^*, R^*)$, where

$$\begin{aligned}
 S^* &= \frac{(A/d)[(\gamma + d)(\varepsilon + d + \alpha_2) + \varepsilon\delta]}{(\varepsilon + d + \alpha_2)[R_q(\gamma + \delta + d + \alpha_1) - \delta - \alpha_1] + \varepsilon\delta}, \\
 I^* &= \frac{A(R_q - 1)(\varepsilon + d + \alpha_2)}{(\varepsilon + d + \alpha_2)[R_q(\gamma + \delta + d + \alpha_1) - \delta - \alpha_1] + \varepsilon\delta}, \\
 Q^* &= \frac{\delta A(R_q - 1)}{(\varepsilon + d + \alpha_2)[R_q(\gamma + \delta + d + \alpha_1) - \delta - \alpha_1] + \varepsilon\delta}, \\
 R^* &= \frac{(A/d)(R_q - 1)[\gamma(\varepsilon + d + \alpha_2) + \varepsilon\delta]}{(\varepsilon + d + \alpha_2)[R_q(\gamma + \delta + d + \alpha_1) - \delta - \alpha_1] + \varepsilon\delta}, \\
 N^* &= S^* + I^* + Q^* + R^* = \frac{(A/d)\{R_q[(\gamma + d)(\varepsilon + d + \alpha_2) + \delta(\varepsilon + d)] - d\delta\}}{(\varepsilon + d + \alpha_2)[R_q(\gamma + \delta + d + \alpha_1) - \delta - \alpha_1] + \varepsilon\delta}.
 \end{aligned}
 \tag{12}$$

The following theorem describes the behavior of solutions of (11) in the region D . The interesting aspect of this SIQR model is that Hopf bifurcation can occur for $R_q > 1$.

Theorem 7. *Consider system (11). If $R_q \leq 1$, then D is an asymptotic stability region for the disease-free equilibrium P_0 . If $R_q > 1$, then the equilibrium P_0 is unstable, the disease is uniformly persistent, and there is a unique endemic equilibrium P^* with coordinates given by (12). This endemic equilibrium P^* is usually locally asymptotically stable, but Hopf bifurcation can occur for some parameter values, so that P^* is sometimes an unstable spiral and periodic solutions around P^* can occur.*

Proof. Linear analysis of the system at equilibrium P_0 shows that it is locally asymptotically stable if $R_q < 1$ and is unstable if $R_q > 1$. The proof of global stability when $R_q \leq 1$ uses the Liapunov function $V = I$ and is analogous with the proofs in the previous sections. The local stability analysis shows that the equilibrium P_0 is unstable if $R_q > 1$ with a repulsive direction into D , so that the disease is uniformly persistent by Theorem 4.5 in [20].

The Jacobian at the endemic equilibrium is

$$J(P^*) = \begin{bmatrix} C - B - d & C - K & 0 & C \\ B - C & -C & 0 & -C \\ 0 & \delta & -D & 0 \\ 0 & \gamma & \varepsilon & -d \end{bmatrix},$$

where $K = \gamma + \delta + d + \alpha_1$, $D = \varepsilon + d + \alpha_2$,

$$B = \frac{KI^*}{S^*} = \frac{Kd(R_q - 1)D}{(\gamma + d)D + \varepsilon\delta},$$

and

$$C = \frac{KI^*}{S^* + I^* + R^*} = \frac{Kd(R_q - 1)D}{R_q[(\gamma + d)D + \varepsilon\delta]} = \frac{B}{R_q}.$$

The characteristic equation at the endemic equilibrium is a fourth degree polynomial given by $P_4(z) = z^4 + c_1z^3 + c_2z^2 + c_3z + c_4 = 0$, where the coefficients are

$$\begin{aligned} c_1 &= 2d + B + D, \\ c_2 &= (B - C)(d + D + K) + C(2d + \gamma + D) + 2dD + d^2, \\ c_3 &= d^2D + (B - C)(dD + dK + KD) + C(d^2 + d\gamma + 2dD + \gamma D + \delta\varepsilon), \\ c_4 &= d[(B - C)KD + C(dD + \gamma D + \delta\varepsilon)], \end{aligned}$$

Since $B > C > 0$, all of the coefficients c_i are positive. The Routh–Hurwitz criteria that are necessary and sufficient for the local asymptotic stability of the endemic equilibrium are that the coefficients are positive and the Hurwitz determinants H_i are all positive [21]. For a fourth degree polynomial the Hurwitz determinant criteria are $H_1 = c_1 > 0$, $H_2 = c_1c_2 - c_3 > 0$, $H_3 = c_1c_2c_3 - c_1^2c_4 - c_3^2 > 0$, and $H_4 = c_4H_3 > 0$. Using a Maple computer algebra program, we find that

$$\begin{aligned} H_2 &= -\delta\varepsilon C + 2d(d + D)^2 + CD^2 + 4dC(d + D) + C(2dC + CD + \gamma d + \gamma C) \\ &\quad + (B - C)[CK + 3Cd + 2CD + \gamma C + 4Dd + Kd + D^2 + 3d^2] + (B - C)^2[K + d + D] \\ H_3 &= [\delta\varepsilon C + 2d(dC + dD + CD) + 2d^3 + (B - C)(d + D)(d + K) + \gamma C(d + D)] \\ &\quad \times [(B - C)^2(D + K) + (B - C)(D^2 + 2dD + 2CD + dC + dK + CK + \gamma C) \\ &\quad + C(d + D)^2 + (C^2 + dD)(d + D) + \gamma C(d + C) - \delta\varepsilon C]. \end{aligned}$$

Note that the first factor in H_3 is always positive, but the second factor has one negative term $-\delta\varepsilon C$, so that H_3 may not be positive for all parameter values. Thus the Routh–Hurwitz criteria may not be satisfied.

The Hopf bifurcation theorem states that under certain conditions a branch of periodic solutions splits off from an equilibrium when the real part of a complex conjugate pair of eigenvalues changes sign as the parameters change [22, pp. 150–156]. The differential equation $\mathbf{x}' = f(\mathbf{x}, \mu)$ with $\mathbf{x} \in R^n$, $\mu \in R$, smooth f , and an equilibrium point given by $\mathbf{x} = \mathbf{x}_0(\mu)$ is said to have a Hopf bifurcation at $\mu = \mu_0$ if the equilibrium \mathbf{x}_0 bifurcates into a ‘small amplitude’ periodic solution as μ passes through μ_0 . The conditions for a Hopf bifurcation are (1) the Jacobian $A(\mu) = D_{\mathbf{x}}f(\mathbf{x}_0(\mu), \mu)$, has a pair of complex conjugate eigenvalues $\alpha(\mu) \pm i\beta(\mu)$, (2) for some value $\mu = \mu_0$, $\alpha(\mu_0) = 0$, $\beta(\mu_0) > 0$, $\alpha'(\mu_0) \neq 0$, and (3) the remaining eigenvalues of $A(\mu_0)$ have non-zero real parts. Let $P_n(z) = z^n + c_1(\mu)z^{n-1} + \dots + c_n(\mu) = 0$ be the characteristic equation at the equilibrium $\mathbf{x} = \mathbf{x}_0$ and let $H_n(\mu)$ be the n dimensional Hurwitz determinant.

The following lemma gives criteria that guarantee that the first two conditions for Hopf bifurcation are satisfied [23,24].

Lemma 8. *If $H_{n-1}(\mu_0) = 0$, $H_{n-2}(\mu_0) \neq 0$, $H_{n-3}(\mu_0) \neq 0$, $c_j(\mu_0) > 0$, for $j = 1, \dots, n$, and $(dH_{n-1}/d\mu)(\mu_0) \neq 0$, then the first two conditions for the existence of a Hopf bifurcation are satisfied.*

For the case considered here with $n = 4$, all of the coefficients are positive and $H_1 > 0$. We look for Hopf bifurcation by seeking a surface in parameter space where the second factor (call it factor H_3) in H_3 is zero, so that the complex conjugate pair of eigenvalues are pure imaginary. Although H_2 has a negative term, we can solve for $\delta\varepsilon C$ by equating factor H_3 to zero, and then substitute this expression into H_2 using Maple to show that $H_2 > 0$ for parameter values on the bifurcation surface. The Hopf bifurcation surface given by factor $H_3 = 0$ depends on the seven parameters d , α_1 , α_2 , ε , γ , δ and R_q , and is intractable analytically. However, we can examine this surface numerically. A contour plot of the Hopf bifurcation surface factor $H_3 = 0$ with $A = d = 0.00027473$, $\alpha_1 = 0$, $\alpha_2 = 0$, $\gamma = 0.5$, and $\delta = 1, 2$ and 4 is shown in Fig. 3, where the contours are functions of R_q and ε . Note that the curves in Fig. 3 are cross-sections of the Hopf bifurcation surface in the hyperplane when the five parameters d , α_1 , α_2 , γ and δ are fixed.

As part of the numerical calculations, we have verified transversality by showing that $dH_3/d\varepsilon \neq 0$ on these cross-sections of the Hopf surface; that is, the real parts of the complex conjugate pair of eigenvalues do change sign as the Hopf bifurcation surface is crossed. Thus the first two conditions for Hopf bifurcation are satisfied by Lemma 8. Zero is not a root and the pure imaginary roots $\pm i\omega$ are not repeated roots, since $P'_4(i\omega) = 0$ leads to a contradiction when the

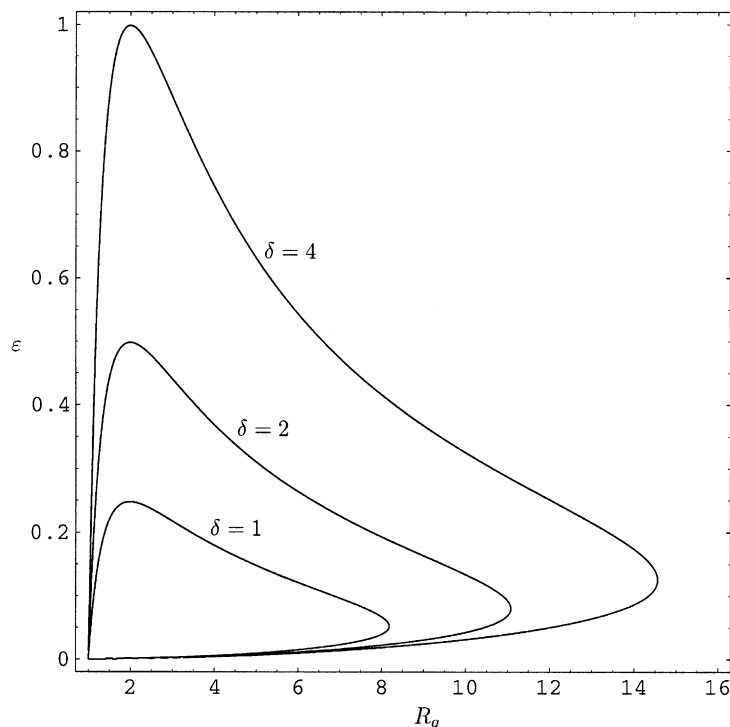


Fig. 3. The cross-section of the Hopf bifurcation surface is shown in the $R_q\varepsilon$ plane when the parameters are $A = d = 0.00027473$, $\alpha_1 = 0$, $\alpha_2 = 0$, $\gamma = 0.5$, and $\delta = 1, 2$, and 4 . Note that these curves change only imperceptibly when γ ranges from 0.1 to 2 .

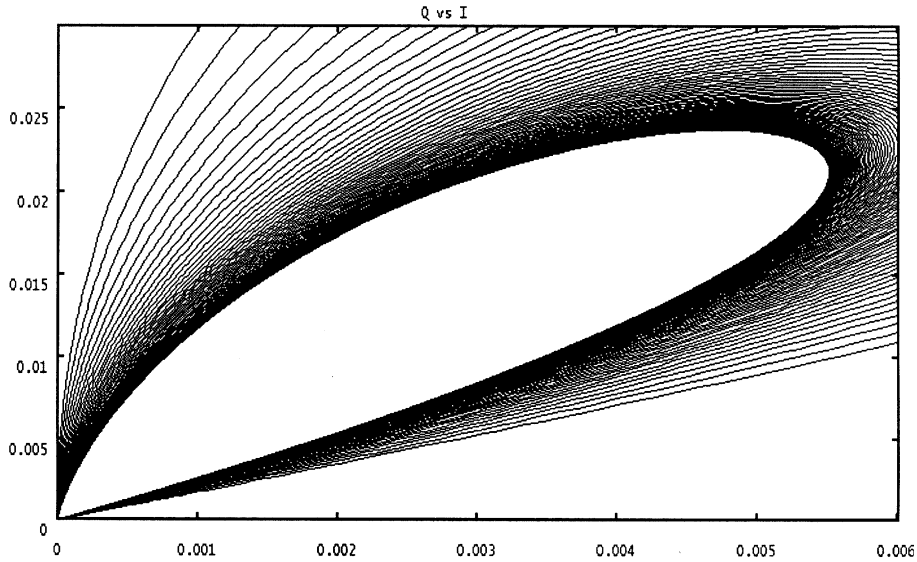


Fig. 4. This WINPP plot shows solutions spiraling into a stable periodic solution for parameter values $A = d = 0.00027473$, $\alpha_1 = 0$, $\alpha_2 = 0$, $\delta = 2$, $\gamma = 0.5$, $R_q = 2.5$, and $\varepsilon = 0.4$. Here the unstable endemic equilibrium is in the lower left corner with coordinate values $I = 0.000065942$, $Q = 0.00032949$, $S = 0.39987$, and $R = 0.59974$, and eigenvalues -0.401 , -0.000275 , $0.0000641 \pm i0.0321$.

expressions for the coefficients are substituted. Thus condition (3) for Hopf bifurcation is also satisfied, so that we have shown that Hopf bifurcation does occur. ■

The existence of attracting periodic solutions of the system (11) for parameter values inside the Hopf curves in Fig. 3 has been confirmed by finding some of them numerically using WINPP (a differential equations package distributed free by Bard Ermentrout at the University of Pittsburgh). The Hopf bifurcation curves in Fig. 3 were verified using LOCBIF, which is embedded in WINPP. Moreover, the stability calculations in LOCBIF showed that the Hopf bifurcation near these curves is always supercritical; that is, stable periodic solutions occur around the unstable spiral endemic equilibria corresponding to points inside the bifurcation curve. Fig. 4 shows the stable periodic solution around the unstable endemic equilibrium P^* for the parameter values $A = d = 0.00027473$, $\alpha_1 = 0$, $\alpha_2 = 0$, $\delta = 2$, $\gamma = 0.5$, $R_q = 2.5$, and $\varepsilon = 0.4$, corresponding to a point inside the $\delta = 2$ Hopf bifurcation curve in Fig. 3. Substituting $z = i\omega$ into $P_4(z) = 0$ yields $\omega = \sqrt{c_3/c_1}$, so that the oscillation frequencies of the bifurcating periodic solutions near a point on the Hopf bifurcation surface are approximately equal to this ω . With the parameter values above, the approximate period given by $2\pi/\omega = 2\pi\sqrt{c_1/c_3}$ is 3.8 years.

8. Discussion

As described in Section 1, the occurrence of sustained oscillations in the observed incidence of some infectious diseases has led to an interest in identifying possible mechanisms for periodic solutions in epidemiology models. Here we have shown that the SIQS models with three different

forms for the incidence have endemic equilibria that are asymptotically stable, so that periodic solutions do not arise by Hopf bifurcation. Similarly, the SIQR models with the simple mass action and standard incidence have asymptotically stable endemic equilibria, so they do not have periodic solutions appearing by Hopf bifurcation. But the SIQR model with the quarantine-adjusted incidence in Section 7 can have endemic equilibria that are unstable spirals for some parameter values, so that periodic solutions can occur by Hopf bifurcation. Thus it appears that periodic solutions only arise in these endemic models with quarantine when there is an immune class R and the quarantine-adjusted incidence is used.

Periodic solutions have been found in previous endemic models with the simple mass action incidence in which the number of contacts between susceptibles and infectives is βN , and the population size N is strongly influenced by the prevalence of the disease [9,10,13,25,26]. The reason for the periodic solutions in these endemic models is that the number of contacts between susceptibles and infectives is changed by the prevalence of the disease. Here the number of contacts is influenced by the size of the quarantine class Q . In Section 1, we found that the total number of contacts is $\beta(N - Q)$ for the simple mass action incidence, $\beta(1 - Q/N)$ for the standard incidence, and β for the quarantine-adjusted incidence. In this last case, this maintenance of the contacts among those who are not quarantined gives more contacts of susceptibles with infectives. This increase in contacts is strong enough in the SIQR model in Section 7 to cause periodic solutions.

The six endemic models in this paper have a recruitment-death demographic structure with a constant A corresponding to recruitment of susceptibles through births or immigration and a death rate dN proportional to the population size N , so that in the absence of disease, $N' = A - dN$ and $N(t) \rightarrow A/d$ as $t \rightarrow \infty$. In the birth–death model with a natural birth rate bN and a natural death rate dN , the differential equation in the absence of disease is $N' = (b - d)N$. Because it gives exponential growth or decay of the population when $b \neq d$, it is often called the exponential demographic model [2]. Each of the six endemic models in this paper has an analogous model with an exponential demographic structure. Periodic solutions around endemic equilibria were not found in the SIRS models with exponential demographic structure and the standard incidence or the simple mass action incidence [7], so it is unlikely that there are periodic solutions in the analogous SIQR models. Because the population size can be growing or decaying in endemic models with exponential demographic structure, one often looks at the differential equations for the fractions of the population in the epidemiologic classes, in which cases the reproduction number threshold condition determines whether the infective fraction goes to zero or remains positive. For the analog of the SIQR model with quarantine-adjusted incidence in Section 7, we found that the Jacobian at the endemic equilibrium for the fraction differential equations is formally the same as that in Section 7. Thus Hopf bifurcation to a periodic solution can also occur in the SIQR model with quarantine-adjusted incidence and exponential demographic structure.

The SIQR model with quarantine-adjusted incidence in Section 7 allows infectives to follow either the usual route directly to the removed class R upon recovery or to enter the quarantine class Q before going to the removed class R . This seems more realistic than the similar SIQR model of Feng and Thieme [14], in which all infectives must pass through the quarantine class Q before going to the removed class R . Feng and Thieme observed that periodic solutions do not occur for small and large values of the mean quarantine time. We can see this phenomenon occurs in our SIQR model with quarantine-adjusted incidence by noting that periodic solutions occur for

parameter values inside the Hopf bifurcation curve in Fig. 3. Thus for fixed R_q and δ in Fig. 3, periodic solutions occur for intermediate values of ε , but they do not occur for small and large values of ε , corresponding to large and small values of the mean quarantine period $1/\varepsilon$.

In the usual SIS and SIR endemic models without quarantine, decreasing the average infectious period $1/\gamma$ decreases the endemic infectious fraction. If $1/\gamma$ is decreased enough, then the basic reproduction number R_0 is reduced below 1, so that the disease dies out. The quarantine process is another method for reducing the average infectious period by isolating some infectives, so that they do not transmit the infection. In the SIQS and SIQR models with quarantine, we can see that both the effective infectious period $1/(\gamma + \delta + d + \alpha)$ and R_q decrease as the quarantine rate constant δ increases.

Feng and Thieme [14] observed that the quarantine reproduction number R_q in their SIQR model was independent of the mean residence time in the quarantine class Q . This independence also occurs in the six models in this paper, since the mean time in Q is $1/\varepsilon$, and the expressions for R_q do not involve the parameter ε . It is not surprising that the average length $1/\varepsilon$ of the quarantine period does not affect the threshold quantity R_q , since the models assume that people in the quarantine class Q do not infect others and people are not infectious when they move out of the quarantine class. However, all of the quarantine reproduction numbers R_q do depend on the parameter δ , which governs the transfer rate out of the infectious class into the quarantine class. For example, if $\delta = \gamma$, then transfer out of the infectious class I to the quarantine class Q and removed class R are equally frequent. If $\delta = 2\gamma$, then transfer out of I to Q is twice as frequent as transfer to R . A positive rate constant δ for transfer out of I by quarantine does decrease the quarantine reproduction number R_q , so that it is less than its value without quarantine. Hence the use of quarantine to control a disease not only decreases the endemic infective class size when R_q remains above 1, but also makes it easier to obtain $R_q \leq 1$ leading to disease extinction.

The periodic behavior of some solutions in the SIQR model with the quarantine-adjusted incidence suggests that quarantine might be a factor contributing to the observed sustained oscillations in some directly transmitted viral diseases such as measles, rubella, mumps, and chickenpox, which have periods between 1 and 5 years [5, p. 129]. Hence we examine whether this possibility is plausible. Note that values of the quarantine reproduction number R_q inside the Hopf bifurcation curves in Fig. 3 are between 1 and 14.6, which are consistent with estimated values between 2 and 18 of the basic reproduction number R_0 for directly transmitted diseases [5, p. 70]. Observed infectious periods for directly transmitted diseases are in the 1–3 week range [5, p. 31]. The parameter values $A = d = 0.00027473$, $\alpha_1 = 0$, $\alpha_2 = 0$, $\gamma = 0.5$, and $\delta = 1, 2$ and 4 used in Section 7 for Fig. 3 are plausible, since they correspond to an average lifetime $1/d$ of 3640 weeks which is 70 years, an average infectious period $1/\delta$ before quarantine of 0.25 to 1 week, an average infectious period $1/\gamma$ before going to the removed class of 2 weeks, and no excess disease-related deaths. Note that the Hopf bifurcation curves in Fig. 3 are almost independent of the value of γ in the range 0.1–2, but are strongly dependent on the value of δ .

From a practical point of view, it is likely that the quarantine period $1/\varepsilon$ would be chosen to be at least as large as the average infectious period $1/\gamma$, so that $\varepsilon \leq \gamma$. For example, if the mean infectious period $1/\gamma$ is 2 weeks, then the mean quarantine time $1/\varepsilon$ would probably be at least 2 weeks, so $\varepsilon \leq 0.5$. The Hopf bifurcation curves in Fig. 3 have ε values inside the curves, which are consistent with $\varepsilon \leq 0.5$. For example, if we choose $\delta = 2$, and $\varepsilon = 0.4$, corresponding to an average infectious period $1/\delta$ before quarantine of 0.5 week and a mean quarantine time $1/\varepsilon$ of 2.5 weeks,

then the quarantine reproduction number R_q is between 1.4 and 3.5 inside the Hopf bifurcation curve and the corresponding approximate periods of oscillation calculated from $2\pi\sqrt{c_1/c_3}$ are between about 7.3 and 2.9 years. If we change ε to 0.2, corresponding to a mean quarantine time of 5 weeks, then the quarantine reproduction number R_q is between 1.15 and 7.9 inside the Hopf bifurcation curve and the corresponding approximate periods of oscillation are between about 11.9 and 1.8 years. These values of R_q and the approximate periods of oscillation between 2 and 5 years are consistent with the observed values cited above.

Thus the parameter values in the previous two paragraphs at which periodic solutions occur in the SIQR model with quarantine-adjusted incidence are plausible and the periods of the periodic solutions arising by Hopf bifurcation are in the range of the observed sustained oscillations in disease incidences. However, in Fig. 4 the value of the equilibrium infectious fraction $I^* = 0.0000659$ is small and the minimum infectious fraction in the limit cycle is about 10^{-45} , which is an unrealistically low infectious fraction. Thus the parameters used in Fig. 4 are plausible, but the minimum value on the limit cycle is not realistic. For parameter values similar to those used for scarlet fever in Feng and Thieme [14], let $A = d = 0.00027473$, $\alpha_1 = 0$, $\alpha_2 = 0$, $\delta = 3$, $\gamma = 0.3$, $R_q = 7$, and $\varepsilon = 0.3$, corresponding to an average infectious period $1/\delta$ before quarantine of $1/3$ week, a mean infectious period $1/\gamma$ of 3.33 weeks, and a mean quarantine time $1/\varepsilon$ of 3.33 weeks. In this case the approximate period is 1.64 years and $I^* = 0.0000714$, but the minimum value of I on the periodic solution is about 6×10^{-9} , which is still unrealistically low. One could imagine that the periodic solutions correspond to local extinction and reintroduction in a stochastic analog of this SIQR model, but the reintroductions would occur erratically, so that this interpretation seems unsatisfactory.

For other parameter values the infectious fractions at the equilibrium and on the periodic solution are more realistic. For example, if $A = d = 0.00027473$, $\alpha_1 = 0$, $\alpha_2 = 0$, $\delta = 0.1$, $\gamma = 0.1$, $R_q = 2$, and $\varepsilon = 0.022$, then the equilibrium infectious fraction of $I^* = 0.000688$ is an order of magnitude larger and the maximum and minimum values of I in the limit cycle are about 0.001 and 0.0005. In order for the minimum value on this periodic solution to be at least one person, the population size would have to be at least 2000, and to justify the use of a deterministic model without probabilistic effects, the population size would need to be about 10^5 , so that the minimum size on the limit cycle would be about 50 people. The model assumptions including homogeneous mixing are plausible in a population of 100 000 people, so that the minimum value of the limit cycle is realistic. But the parameter values in this example are less plausible, since the mean infectious periods $1/\gamma$ and $1/\delta$ before removal and quarantine are both 10 weeks, and the mean quarantine time $1/\varepsilon$ is 45.5 weeks. The mean infectious period $1/\gamma$ is longer than the average times observed for many diseases, and the mean quarantine time seems unrealistically long. Moreover, the approximate period of 16.5 years given by $2\pi\sqrt{c_1/c_3}$ in the limit cycle is larger than observed periods. After examining many parameter sets and the corresponding periodic solutions, we have found that as one aspect becomes more realistic, another becomes less realistic. Thus we have not been able to find a parameter set that matches every feature of the observed data. Hence the quarantine mechanism in the SIQR model in Section 7 may not be a possible explanation for the observed oscillations in disease incidences. However, as Feng and Thieme pointed out in [16, p. 986], the quarantine process could contribute to sustained oscillations in diseases by combining with other factors such as seasonal variation in the contact rates, stochastic effects, and density-dependent demographics.

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