Chapter 9
Control Strategies

9.1 Introduction

Measures for prevention and control of infectious diseases include vaccination, treatment, quarantine, isolation, and prophylaxis.

Prophylaxis is the series of measures taken to prevent a specific infectious disease. These measures can be as simple as hand-washing with soap and water, or wearing protective gear, or taking a medication to prevent a disease. **Treatment** is the use of an agent, procedure, or regimen, such as a drug, or bed rest in an attempt to cure or mitigate a disease. Nowadays, for most infectious diseases, medications exist that can cure or lessen the impact of the diseases, while improving the life of the patients. Diseases for which medications can offer a cure include malaria and tuberculosis. Diseases for which medications offer relief but not a cure include HIV and genital herpes.

Vaccination is the process through which killed (inactivated) or weakened microorganisms are placed into the body. Our immune system recognizes vaccine agents as foreign. That triggers an immune response, and antibodies against them are developed. As a result, if the same types of microorganisms enter the body again, they will be destroyed much faster by the antibodies. Thus, an individual that is immunized is protected against the disease. If a large majority of people are vaccinated, it is much more difficult for an outbreak of disease to occur, let alone spread. This effect is called **herd immunity**.

Vaccination is one of the greatest achievements of public health. Vaccination has led to the complete eradication of smallpox worldwide, and a near eradication of polio. Table 9.1 gives the reduction of disease load in the United States as a result of widespread vaccination campaigns.

Vaccines do not guarantee complete protection from a disease. There remains the possibility that a vaccinated person may get the disease. Even if the host develops antibodies, some pathogens can mutate (the common cold and influenza viruses are highly efficient at this), and in any case, the immune system might still not be able

Table 9.1 Achievements of vaccination in the United States[a]

Disease	Baseline years	Cases/year	Cases in 1998	% Decrease
Smallpox	1900–1904	48,164	0	100
Diphtheria	1920–1922	175,885	1	100
Pertussis	1922–1925	147,271	6,279	95.7
Tetanus	1922–1926	1,314	34	97.4
Poliomyelitis	1951–1954	16,316	0	100
Measles	1958–1962	503,282	89	100
Mumps	1968	152,209	606	99.6
Rubella	1966–1968	47,745	345	99.3
Hib	1985	20,000	54+71	99.7

[a]**Source:** CDC, Morbidity and Mortality Weekly Report (MMWR) 48(12), 1999. *Achievements of Public Health, 1900–1999: Impact of Vaccines Universally Recommended for Children—US, 1990–1998*

to defeat the infection. The degree to which vaccinated individuals are protected against the disease is called *efficacy of the vaccine*.

Quarantine and **isolation** are two measures by which exposed or infectious individuals are removed from the population to prevent further spread of the infection. Quarantine is applied to seemingly healthy but potentially infected individuals, while isolation is applied to already infectious individuals. Isolation has been used and is being used to control many dangerous diseases. Quarantine is applied less often. It is one of the first response methods that can be used in an extreme emergency. Quarantine was implemented during the SARS epidemic of 2002–2003.

The reproduction number, computed for mathematical models involving control strategies, depends on the control strategies, and it is often called a *controlled reproduction number*.

9.2 Modeling Vaccination: Single-Strain Diseases

There are two points in which vaccination models can differ from one another. The first is that some models assume that vaccination is equivalent to going through the disease and treats vaccinated individuals as recovered individuals. Thus an SIR model can include vaccinated individuals without an additional class. Other models assume that vaccinated individuals have to be separated into a vaccinated class V. The second point of distinction is that some classes of models assume that individuals enter the system at a point of their life when they either get vaccinated or skip vaccination and enter the system as susceptibles. This is more or less accurate for school children. Other models allow for continuous vaccination of individuals while in the system.

9.2.1 A Model with Vaccination at Recruitment

Assume that we have a perfect vaccine, whereby everybody who is vaccinated is completely protected. Suppose we vaccinate at recruitment into the system a fraction p of individuals. So if μN is the recruitment term, a fraction $p\mu N$ goes directly into the recovered class, and a proportion $q\mu N$, where $q = 1 - p$, enters the susceptible class. Thus the SIR model with vaccination becomes

$$\frac{dS}{dt} = q\mu N - \beta SI - \mu S,$$
$$\frac{dI}{dt} = \beta SI - (\mu + \alpha)I, \tag{9.1}$$
$$\frac{dR}{dt} = p\mu N + \alpha I - \mu R.$$

The equation of the total population size here is $N'(t) = 0$, and the total population size is constant, $N = S_0 + I_0 + R_0$. The disease-free equilibrium, obtained from setting the derivatives equal to zero and $I = 0$, is given by $\mathscr{E}_0 = (qN, 0, pN)$. Thus, if

$$\mathscr{R}_0 = \frac{\beta N}{\alpha + \mu}$$

is the reproduction number in the absence of vaccination ($p = 0$), then $q\mathscr{R}_0$ is the reproduction number of the disease in the presence of vaccination. Consequently, vaccination has reduced the original reproduction number by the fraction q.

   Question: What fraction, p, of the population must be vaccinated so that the reproduction number of the disease is reduced below 1?

   To answer this question, we need $q\mathscr{R}_0 < 1$. Replacing q with $1 - p$ and solving the inequality for p, we obtain that $p > \hat{p}$, where

$$\hat{p} = 1 - \frac{1}{\mathscr{R}_0}.$$

Consequently, if a fraction $\hat{p}$ of the population is successfully vaccinated, then the disease will not spread in the population. In effect, the whole population will be protected. This is a manifestation of the herd immunity.

9.2.2 A Model with Continuous Vaccination

Most diseases for which vaccination is successful have a recovered (immune) stage. After all, vaccination works with the immune system more or less as the disease does, so if the disease does not provide immunity, how could vaccination? However, there are diseases for which it is justified to consider vaccination in addition to an SIS model, that is, a model where recovery brings the individual back to

the susceptible class. One such disease is tuberculosis, which imparts very short-lived immunity. Another situation occurs with bacterial infections with *Neisseria meningitidis* and *Streptococcus pneumoniae*. Both these bacteria can exist in the host without causing disease, a scenario, called *carriage*. Both carriers and infected (sick) people can transmit the microorganism, so from the point of view of disease transmission, they can be considered indistinguishable and modeled with one class. Carriage and disease impart immunity against the disease but probably not so much against carriage. Thus individuals who become completely pathogen-free can be counted as susceptible (at least for carriage). In both cases, there are vaccines, at least against some variants of the microorganisms, and an SIS model with vaccination may be appropriate.

9.2.2.1 An SIS Model with Vaccination

Let $V(t)$ denote the number of vaccinated individuals, and ψ the per capita vaccination rate. Vaccination is applied only to healthy individuals, so only susceptible individuals get vaccinated. In this model, we also take into account the fact that vaccines are rarely perfect, and some of the vaccinated individuals can become infected and infectious even though they have been vaccinated. That happens at a reduced transmission rate $\beta\delta$, where $0 \leq \delta \leq 1$ is the reduction coefficient. If $\delta = 0$, then vaccinated individuals cannot get infected, and the vaccine is perfect. This implies that the vaccine efficacy is $\varepsilon = 1$. If $\delta = 1$, then vaccinated individuals get infected just like susceptible individuals, and the vaccine plays no protective role. In that case, the vaccine efficacy is $\varepsilon = 0$.

We list the parameters and the variables in the Table 9.2.

Table 9.2 List of parameters, variables, and their meanings

Notation	Meaning
Λ	Birth/recruitment rate into the population
μ	Per capita natural death rate
β	Per capita transmission rate
γ	Per capita recovery rate
χ	Proportion of individuals who recover to the vaccinated class
$1 - \chi$	Proportion of individuals who recover to the susceptible class
ψ	Per capita vaccination rate
$\varepsilon = 1 - \delta$	Vaccine efficacy
$S(t)$	Number of susceptible individuals
$I(t)$	Number of infected individuals
$V(t)$	Number of vaccinated individuals

The model takes the form

$$\frac{dS}{dt} = \Lambda - \frac{\beta SI}{N} - (\mu + \psi)S + \chi\gamma I,$$
$$\frac{dI}{dt} = \frac{\beta SI}{N} + \frac{\beta\delta VI}{N} - (\mu + \gamma)I, \qquad (9.2)$$
$$\frac{dV}{dt} = \psi S - \frac{\beta\delta VI}{N} + (1-\chi)\gamma I - \mu V.$$

The flowchat of the model is given in Fig. 9.1.

The disease-free equilibrium is given by

$$\mathscr{E}_0 = \left(\frac{\Lambda}{\mu + \psi}, 0, \frac{\Lambda\psi}{\mu(\mu + \psi)} \right).$$

Since the equation of the total population is $N'(t) = \Lambda - \mu N$, the equilibrium total population size is $N = \frac{\Lambda}{\mu}$. Thus the proportions of susceptible and vaccinated in the disease-free population are given by

$$s^0 = \frac{\mu}{\mu + \psi}, \qquad v^0 = \frac{\psi}{\mu + \psi}.$$

9.2.2.2 The Reproduction Number and the Critical Vaccination Proportion

To compute the reproduction number, we compute the Jacobian at the disease-free equilibrium:
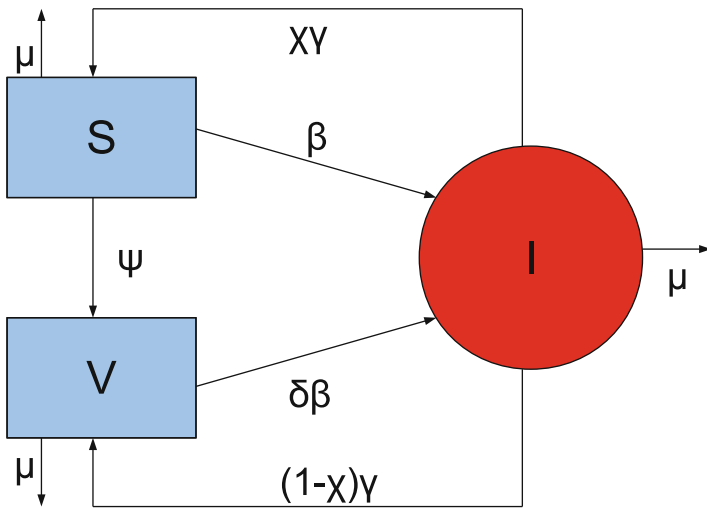

Fig. 9.1 Flowchart of the model with continuous vaccination with imperfect vaccine

$$\mathscr{J}(\mathscr{E}_0) = \begin{pmatrix} -(\mu + \psi) & -\beta s^0 + \chi\gamma & 0 \\ 0 & \beta s^0 + \beta\delta v^0 - (\mu + \gamma) & 0 \\ \psi & -\beta\delta v^0 + (1 - \chi)\gamma & -\mu \end{pmatrix}.$$

The Jacobian has two negative eigenvalues, $-\mu$ and $-(\mu + \psi)$. The third eigenvalue is given by $\beta s^0 + \beta\delta v^0 - (\mu + \gamma)$. Thus we define the reproduction number in the presence of vaccination as

$$\mathscr{R}(\psi) = \frac{\beta(\mu + \delta\psi)}{(\mu + \gamma)(\mu + \psi)}.$$

The reproduction number of the disease in the absence of vaccination is obtained by letting $\psi = 0$, and is given by

$$\mathscr{R}_0 = \frac{\beta}{\mu + \gamma}.$$

In interpreting the reproduction number, we notice that $\frac{\beta SI}{N}$ gives the number of secondary infections of susceptible individuals per unit of time. The number of secondary infections of susceptible individuals per unit of time for one infectious individual will be $\frac{\beta S}{N}$. The proportion of susceptibles in a disease-free population is $\frac{S}{N} = s^0 = \frac{\mu}{\mu + \psi}$. Since $\frac{1}{\mu + \gamma}$ is the time spent as an infectious individual, the first term in $\mathscr{R}(\psi)$, given by $\frac{\beta\mu}{(\mu + \gamma)(\mu + \psi)}$, gives the number of secondary infections of susceptible individuals that one infected individual can produce in a disease-free population. Similarly, $\frac{\beta\delta VI}{N}$ gives the number of secondary infections of vaccinated individuals per unit of time. The number of secondary infections of vaccinated individuals per unit of time for one infectious individual will be $\frac{\beta\delta V}{N}$. The proportion of vaccinated individuals in a disease-free population is $\frac{V}{N} = v^0 = \frac{\psi}{\mu + \psi}$. Since $\frac{1}{\mu + \gamma}$ is the time spent as an infectious individual, the second term in $\mathscr{R}(\psi)$, given by $\frac{\beta\delta\psi}{(\mu + \gamma)(\mu + \psi)}$, gives the number of secondary infections of vaccinated individuals that one infected individual can produce in a disease-free population.

One can see that the reproduction number in the presence of vaccination is a decreasing function of the vaccination rate ψ. Thus, the higher the vaccination rate, the smaller the reproduction number. Furthermore,

$$\lim_{\psi \to \infty} \mathscr{R}(\psi) = \delta\mathscr{R}_0.$$

Thus, if the vaccine efficacy ε is not high enough (that is, δ is not small enough), then even if we vaccinate everybody, we may not be able to eradicate the disease. In other words, we cannot bring $\mathscr{R}(\psi)$ below 1, since the vaccinated individuals can become infected.

Question: What is the critical proportion of individuals that should be vaccinated if the vaccine is continuously applied and imperfect?

A critical vaccination proportion $\hat{p}_\varepsilon$ for the eradication of a disease with imperfect vaccination exists only if $\delta\mathscr{R}_0 < 1$, that is, if the vaccine efficacy satisfies

$$\varepsilon > \left(1 - \frac{1}{\mathscr{R}_0}\right). \tag{9.3}$$

If $\delta\mathscr{R}_0 < 1$, then there exists a critical vaccination level ψ^* such that $\mathscr{R}(\psi^*) = 1$. This critical vaccination level for eradication of the disease is given by

$$\psi^* = \frac{(\mathscr{R}_0 - 1)\mu}{1 - \delta\mathscr{R}_0}.$$

The proportion vaccinated in the population is given by $\psi/(\mu + \psi)$. We conclude that

> The critical proportion of the population that needs to be vaccinated with vaccine with efficacy ε is given by
>
> $$\hat{p}_\varepsilon = \frac{1}{\varepsilon}\left(1 - \frac{1}{\mathscr{R}_0}\right).$$
>
> In words, the critical proportion of the population that needs to be vaccinated with imperfect vaccine is the critical population that needs to be vaccinated with perfect vaccine divided by the vaccine efficacy.

We note that the formula above is an extension of the critical vaccination proportion to imperfect vaccines. If the vaccine is perfect, that is, if $\varepsilon = 1$, then we obtain the customary formula for the critical vaccination proportion for perfect vaccines.

Table 9.3 gives the estimates of $\mathscr{R}_0$ before the introduction of vaccination. Most data on the reproduction number before vaccination are from England, Wales, and the USA [10]. The table gives the critical vaccination fraction with perfect vaccines, vaccine efficacies of the most common vaccines used in the USA, and the critical vaccination fractions with imperfect vaccines. It can be seen from the table that the current vaccines are incapable of eliminating pertussis, and may be useful in eliminating polio and diphtheria if a sufficient proportion of the population is vaccinated. In fact, polio has been eliminated in the developed countries for which the reproduction number before vaccination and vaccine efficacies are most accurate.

9.2.2.3 Backward Bifurcation in the Imperfect Vaccination Model

The critical threshold above gives only the proportion that has to be vaccinated so that the reproduction number in the presence of vaccination is below one. However, imperfect vaccines have the disadvantage that they lead to backward bifurcation, and endemic equilibria exist and are stable even when the reproduction number in the presence of vaccination is below one. The main reason for the backward bifurcation is the fact that imperfect vaccination creates two classes of susceptible individuals with different susceptibilities—the naive susceptible and the vaccinated susceptible.

Table 9.3 Diseases and their eradication vaccination levels

Disease	$\mathscr{R}_0$	$\hat{p},\%$	Vaccine efficacy[a]	$\hat{p}_\varepsilon,\%$
Smallpox	3–5	67–80	0.75[b]	89–100
Measles	12–13	92	0.75–0.95	97–100
Mumps	4–7	75–86	0.75–0.95	79–100
Rubella	6–7	83–86	0.75–0.95	87–100
Chickenpox	9–10	89–90	0.8–0.95	94–100
Pertussis	13–17	92–94	0.8–0.9	–
Poliomyelitis	6	83	0.9–0.99	84–92
Diphtheria	4–6	75–83	0.87–0.96	78–95

[a]http://www.whale.to/vaccines/efficacy.html
[b]Vaccine efficacy never measured in clinical trials

To obtain a necessary and sufficient condition for backward bifurcation, we compute the endemic equilibria. First, we consider the equations for the proportions $(s = \frac{S}{N}, i = \frac{I}{N}, v = \frac{V}{N})$:

$$
\begin{aligned}
0 &= \mu - \beta si - (\mu + \psi)s + \chi\gamma i, \\
0 &= \beta si + \beta\delta vi - (\mu + \gamma)i, \\
0 &= \psi s - \beta\delta vi + (1 - \chi)\gamma i - \mu v.
\end{aligned}
\tag{9.4}
$$

Expressing s from the first equation and v from the third equation yields

$$
s = \frac{\mu + \chi\gamma i}{\beta i + \mu + \psi}, \qquad v = \frac{\psi s + (1 - \chi)\gamma i}{\beta\delta i + \mu},
$$

and substituting them in the second equation, we obtain a quadratic equation in i:

$$
\begin{aligned}
&\beta(\mu + \chi\gamma i)(\beta\delta i + \mu + \delta\psi) + \beta\delta(1 - \chi)\gamma i(\beta i + \mu + \psi) \\
&= (\mu + \gamma)(\beta\delta i + \mu)(\beta i + \mu + \psi).
\end{aligned}
\tag{9.5}
$$

If we think of β as a function of i, that is, $\beta(i)$, and we differentiate implicitly the above equation, we obtain for β' at the critical value $i = 0$ the following expression:

$$
\begin{aligned}
&\beta'(0) \\
&= \frac{\beta\{\delta(\mu + \gamma)(\mu + \psi) + \mu(\mu + \gamma) - \chi\gamma(\mu + \delta\psi) - \beta\delta\mu - \delta(1 - \chi)\gamma(\mu + \psi)\}}{\mu(\mu + \delta\psi)}.
\end{aligned}
$$

The bifurcation at the critical value $i = 0$ ($\mathscr{R}(\psi) = 1$) is backward if and only if $\beta'(0) < 0$, that is, if and only if the parameters satisfy the following condition:

$$
\begin{aligned}
\delta(\mu + \gamma)(\mu + \psi) + \mu(\mu + \gamma) &< \chi\gamma(\mu + \delta\psi) + \frac{(\mu + \gamma)(\mu + \psi)\delta\mu}{\mu + \delta\psi} \\
&\quad + \delta(1 - \chi)\gamma(\mu + \psi).
\end{aligned}
$$

To plot the dependence of i on $\mathscr{R}(\psi)$, we rewrite the equation for i as a quadratic equation in i, $Ai^2 + Bi + C = 0$, where after dividing by β in (9.5), the coefficients are
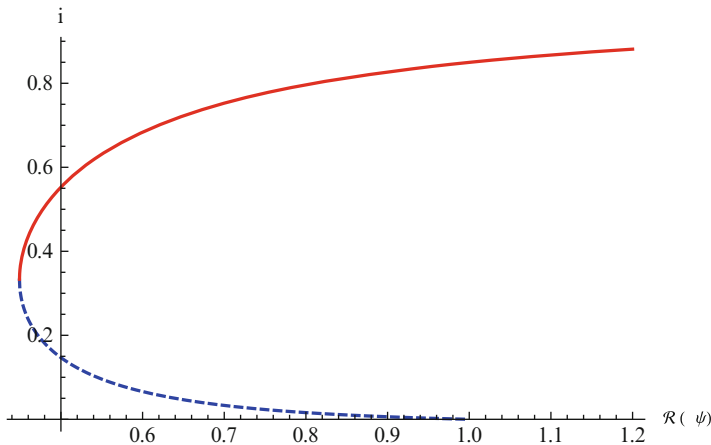
Fig. 9.2 The graph shows that the equilibrium value of i exhibits backward bifurcation as a function of the vaccine-dependent reproduction number. The parameters are taken as follows: $\mu = 0.01$, $\gamma = 3$, $\chi = 1$, $\delta = 0.1$, $\psi = 1$

$$A = \beta\delta\mu,$$
$$B = \mu(\mu+\gamma) + \delta(\mu+\gamma)(\mu+\psi) - \beta\mu\delta - (\mu+\delta\psi)\chi\gamma - \delta(1-\chi)\gamma(\mu+\psi),$$
$$C = \mu(\mu+\psi)(1-\mathscr{R}(\psi)).$$
$$(9.6)$$

We express these coefficients as functions of $\mathscr{R}(\psi)$ and eliminate β:

$$A = \mathscr{R}(\psi)\eta\delta\mu,$$
$$B = \mu(\mu+\gamma) + \delta(\mu+\gamma)(\mu+\psi) - \mathscr{R}(\psi)\eta\mu\delta - (\mu+\delta\psi)\chi\gamma - \delta(1-\chi)\gamma(\mu+\psi),$$
$$C = \mu(\mu+\psi)(1-\mathscr{R}(\psi)),$$
$$(9.7)$$

where $\eta = \frac{(\mu+\gamma)(\mu+\psi)}{(\mu+\delta\psi)}$. We illustrate the backward bifurcation in Fig. 9.2.

Imperfect vaccines lead to backward bifurcation. It is not hard to see that in the model above, backward bifurcation does not occur if the vaccine is perfect, $\delta = 0$. Also, if there is no vaccination $\psi = 0$, then backward bifurcation does not occur. In this case, it can be seen that if $\mathscr{R}_0 < 1$, the disease-free equilibrium is globally stable.

The presence of backward bifurcation means that in practice, if we vaccinate with imperfect vaccine, we may need to reduce the vaccine reproduction number not below one but below a much smaller value under which there are no endemic equilibria. Thus, it may appear that vaccinating with imperfect vaccine makes the task of controlling the disease harder rather than easier. However, it must be noted that at the same time, vaccination increases the parameter space of the remaining parameters where the vaccine-dependent reproduction number is below one, and

the disease-free equilibrium is locally stable. To illustrate this idea, assume that μ, ψ, and δ are given and fixed. Then in the absence of vaccination, the region in the (γ, β)-plane where the disease-free equilibrium is stable is given by $\mu + \gamma > \beta$, since there, $\mathscr{R}_0 < 1$. In the presence of vaccination, the region of local stability of the disease-free equilibrium is given by

$$\frac{\mu + \psi}{\mu + \delta \psi}(\mu + \gamma) > \beta,$$

which is a larger region, since the fraction $(\mu + \psi)/(\mu + \delta \psi)$ is greater than one.

9.3 Vaccination and Genetic Diversity of Microorganisms

When a pathogen is represented by several variants, they may not all be included in the vaccine. The strains that are included in the vaccine are called *vaccine strains*. The number of strains included in the vaccine is called vaccine *valency*. For instance, the flu vaccine is trivalent, that is, it contains three strains.

The immunity that a vaccine creates is specific to those strains that are included in the vaccine. The vaccine may provide partial immunity, or no immunity at all, to strains that are not included in the vaccine. That makes impossible the eradication of diseases whose causative agents mutate and that are represented by multiple variants.

Biologists report an increase of genetic diversity after the introduction of vaccination [142]. In terms of modeling, this says that vaccination should cause coexistence of pathogen variants, in other words, vaccination is a coexistence mechanism. To see this, we consider the model above with two strains. We assume that one of the strains is a vaccine strain with respect to which the vaccine is perfect. With respect to the other strain, the vaccine offers only partial protection. The model with two strains and vaccination becomes

$$
\begin{aligned}
\frac{dS}{dt} &= \Lambda - \frac{\beta_1 SI}{N} - \frac{\beta_2 SJ}{N} - (\mu + \psi)S + \chi \gamma I + \alpha J, \\
\frac{dI}{dt} &= \frac{\beta_1 SI}{N} + \frac{\beta_1 \delta VI}{N} - (\mu + \gamma)I, \\
\frac{dJ}{dt} &= \frac{\beta_2 SJ}{N} - (\mu + \alpha)J, \\
\frac{dV}{dt} &= \psi S - \frac{\beta_1 \delta VI}{N} + (1 - \chi)\gamma I - \mu V,
\end{aligned}
\tag{9.8}
$$

where $I(t)$ is the number infected with the first strain, and $J(t)$ is the number infected with the second strain. The parameter α is the per capita recovery rate from the second strain. Recovered individuals from the second strain go to the susceptible class, because only susceptible individuals can become infected with the second strain. The second strain is assumed to be the vaccine strain. The reproduction number of

the first strain is as before:

$$\mathscr{R}_1(\psi) = \frac{\beta_1(\mu + \delta\psi)}{(\mu + \gamma)(\mu + \psi)}.$$

The reproduction number of the second strain is

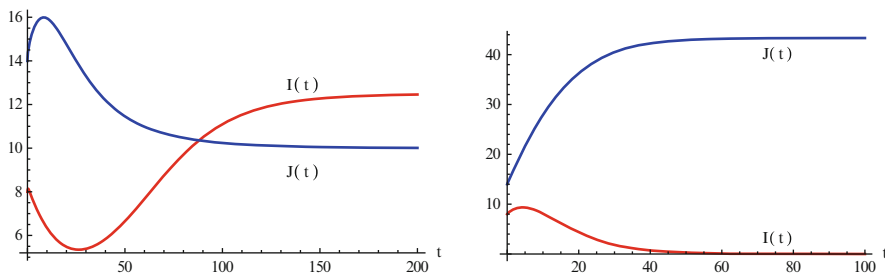$$\mathscr{R}_2(\psi) = \frac{\beta_2\mu}{(\mu + \alpha)(\mu + \psi)}.$$

Fig. 9.3 The *left figure* illustrates that the number infected with strain one, $I(t)$, and the number infected with strain two, $J(t)$, may tend toward a coexistence equilibrium when $\psi = 0.5$. The *right figure* illustrates that if $\psi = 0$, strain two eliminates strain one. The remaining parameters used for these figures are $\beta_1 = 6$, $\beta_2 = 4.5$, $\gamma = 0.8$, $\alpha = 0.5$, $\mu = 0.1$, $\chi = 1.0$, $\delta = 0.04$, $\Lambda = 5$. The corresponding reproduction numbers are given by $\mathscr{R}_1(\psi) = 1.333$ and $\mathscr{R}_2(\psi) = 1.25$. The reproduction numbers in the absence of vaccination are $\mathscr{R}_1 = 6.66667$ and $\mathscr{R}_2 = 7.5$

Proving the existence of a unique coexistence equilibrium is possible but not trivial. So to see the coexistence, we do a simulation. Figure 9.3 illustrates the coexistence.

Question: What causes the coexistence? We can answer this question by examining the parts for the model that cause the coexistence. In particular, we examine the equations for the coexistence equilibrium:

$$\begin{aligned}
0 &= \mu - \beta_1 si - \beta_2 sj - (\mu + \psi)s + \chi\gamma i + \alpha j,\\
0 &= \beta_1 si + \beta_1 \delta vi - (\mu + \gamma)i,\\
0 &= \beta_2 sj - (\mu + \alpha)j,\\
0 &= \psi s - \beta_1 \delta vi + (1 - \chi)\gamma i - \mu v,
\end{aligned} \qquad (9.9)$$

where as before, s, i, j, v denote the proportions. If $\delta = 0$, then from the second and third equations, we have

$$s = \frac{\mu + \gamma}{\beta_1}, \qquad s = \frac{\mu + \alpha}{\beta_2}.$$

Clearly these two expressions for s are equal in very special cases, but not in general. So coexistence does not occur. Thus a necessary condition for coexistence is the imperfection of the vaccine. If there is no vaccination, that is, $\psi = 0$ and $\chi = 1$ (no recovery to the vaccinated class), then $v = 0$, and s must satisfy the same two expressions. So coexistence does not occur. Thus vaccination, and particularly vaccine imperfections, are the cause of coexistence.

When a disease is caused by a pathogen of multiple variants, not all of them are included in a vaccine (for various reasons). Vaccination is carried out under several scenarios:

1. Vaccination is carried against the dominant subtype. For instance, *Haemophilus influenzae* is represented by six serotypes: a, b, c, d, e, f, but before vaccination was instituted, serotype b caused most disease. Vaccination is now carried out against serotype b.
2. Vaccination is carried out against several strains that account for most cases. For instance, *Streptococcus pneumoniae* is represented by more than 90 serotypes, but only 23 of the most common ones are included in the polysaccharide vaccine.
3. When possible, vaccination is carried out against all subtypes (possibly one by one). For instance, poliomyelitis (caused by poliovirus, PV) is represented by three serotypes. Vaccination against each one is necessary, but polio has been nearly eradicated.

When vaccination is carried out against only one or more but not all of the pathogen variants, what is observed is decline in the number of disease cases caused by those variants included in the vaccine. At the same time, disease cases caused by other pathogen variants not included in the vaccine rise. This phenomenon is called *strain (serotype) replacement* (Table 9.4). The main mechanism by which serotype replacement occurs is that the vaccine has *differential effectiveness*: it is very effective with respect to some strains, and very little effective, or not effective at all, with respect to other strains. Thus vaccinated individuals are removed from the susceptible pool of the vaccine strains but effectively added to the susceptible pool of the nonvaccine strains, since the vaccine strains can no longer infect them.

That differential effectiveness of the vaccine leads to strain replacement can be seen from model (9.8). We illustrate this in Fig. 9.4. We note that the overall prevalence before vaccination is greater than the prevalence after vaccination. Thus replacement cannot completely "erase" what is being gained from vaccination. However, strain replacement is undesirable, because it still takes from what could have been gained.

Since differential effectiveness of the vaccine leads to replacement, vaccine developers have tried to make vaccines less differentially effective. One way to

Table 9.4 Reported increases in nonvaccine strains after vaccination [109]

| Disease	Vaccine	Increase in	Region
H. influenzae	Hib	Nontype b	Alaska
	Hib	Type f	m. states, US
	conj. Hib	Type a	Brazil
	conj. Hib	Noncapsulated	UK
S. pneumoniae	PCV-7	NVT	Finland
	PCV-7	NVT (carriage)	US
	PCV-7	Serogroups 15 and 33	US PMPSG, US
	PCV-7	NVT (AOM)	Pittsburgh
	PPV-23	12F*, 7F, 22F, 7C	Alaska
N. meningitidis	A-C vaccine	Serogroup B	Austria
	A-C vaccine	Serogroup B	Europe
	A-C vaccine	Serogroup B	Cuba
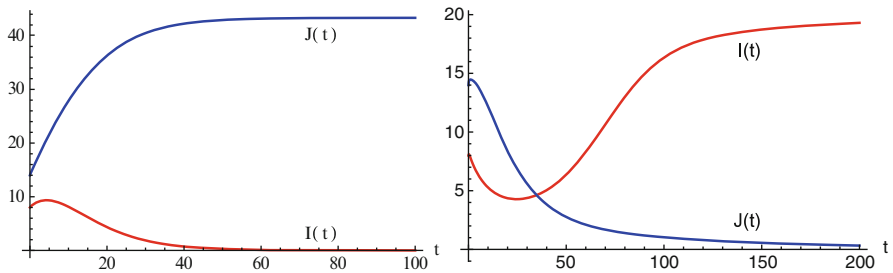
Fig. 9.4 The *left figure* illustrates that the number infected with strain one $I(t)$ tends to zero and the number infected with strain two $J(t)$ tends toward an endemic equilibrium when $\psi = 0$. The *right figure* illustrates that if $\psi = 0.7$, then strain one eliminates strain two. The remaining parameters used for these figures are $\beta_1 = 6$, $\beta_2 = 4.5$, $\gamma = 0.8$, $\alpha = 0.5$, $\mu = 0.1$, $\chi = 1.0$, $\delta = 0.04$, $\Lambda = 5$. The corresponding reproduction numbers are given by $\mathscr{R}_1(\psi) = 1.06667$ and $\mathscr{R}_2(\psi) = 0.9375$. The reproduction numbers in the absence of vaccination are $\mathscr{R}_1 = 6.66667$ and $\mathscr{R}_2 = 7.5$

do that is to include (if possible) more strains in the vaccine. That has been the case with pneumococcal polysaccharide vaccine, which originally contained very few serotypes of *Streptococcus pneumoniae* but now contains 23. That is still many fewer than the 90 serotypes that exist. A new approach is to target surface proteins that are common in all 90 serotypes.

Question: Suppose we can produce a vaccine that is perfect with respect to all strains. Will we eliminate strain replacement?

The answer is expected to be affirmative if differential effectiveness is the mechanism behind strain replacement. Although such perfect vaccines do not yet exist, we can address this question with mathematical models. Consider the model of superinfection. We add vaccination with a perfect vaccine to this model. Thus, the model becomes

$$\frac{dS}{dt} = \Lambda - \beta_1 \frac{SI}{N} - \beta_2 \frac{SJ}{N} - (\mu + \psi)S + \gamma_1 I + \gamma_2 J,$$
$$\frac{dI}{dt} = \beta_1 \frac{SI}{N} + \beta_1 \delta \frac{IJ}{N} - (\mu + \gamma_1)I,$$
$$\frac{dJ}{dt} = \beta_2 \frac{SJ}{N} - \beta_1 \delta \frac{IJ}{N} - (\mu + \gamma_2)J,$$ (9.10)
$$\frac{dV}{dt} = \psi S - \mu V,$$

where $N = S + I + J + V$ is the total population. Notice that vaccinated individuals cannot become infected with any of the strains. It turns out, however, that strain replacement still occurs. We illustrate this in Fig. 9.5. What is causing it? If the vaccine is not "differentially effective," how does it differentiate between the strains? In what follows, we address these questions.
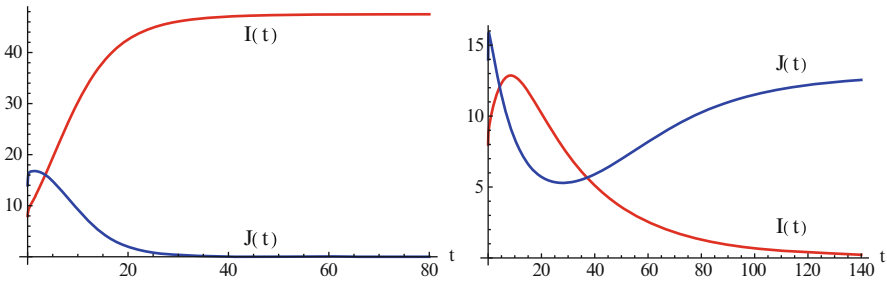

Fig. 9.5 The *left figure* illustrates that the number infected with strain one, $I(t)$, tends to a nonzero equilibrium, and the number infected with strain two, $J(t)$, tends to zero when $\psi = 0$. The *right figure* illustrates that if $\psi = 1.75$, then strain two eliminates strain one. The remaining parameters used for these figures are $\beta_1 = 12$, $\beta_2 = 15$, $\gamma_1 = 0.5$, $\gamma_2 = 0.5$, $\mu = 0.1$, $\delta = 0.03$, $\Lambda = 5$

The reproduction numbers of the two strains are given by

$$\mathcal{R}_i(\psi) = \frac{\beta_i \mu}{(\mu + \gamma_i)(\mu + \psi)}, \qquad i = 1, 2.$$

Note that they are both decreasing functions of the vaccination rate ψ. In addition, they do not depend on superinfection, and particularly on the coefficient of reduction or enhancement δ, since superinfection does not lead to infection of susceptible individuals.

The corresponding invasion reproduction numbers, however, are not independent of the superinfection process, since they measure the number of secondary infections one strain-i infected individual will produce in a population in which strain j is at equilibrium. To compute the invasion numbers, we first compute the two dominance equilibria. The dominance equilibrium of strain one is given by $\mathcal{E}_1 = (s, i, 0, v)$ with

$$\mathcal{E}_1 = \left(\frac{1}{\mathcal{R}_1}, 1 - \frac{1}{\mathcal{R}_1(\psi)}, 0, \frac{\psi}{\mu} \frac{1}{\mathcal{R}_1} \right),$$

where $\mathscr{R}_i = \mathscr{R}_i(0)$. The dominance equilibrium of strain two is given by $\mathscr{E}_2 = (s, 0, j, v)$ with

$$\mathscr{E}_2 = \left(\frac{1}{\mathscr{R}_2}, 0, 1 - \frac{1}{\mathscr{R}_2(\psi)}, \frac{\psi}{\mu} \frac{1}{\mathscr{R}_2} \right).$$

The invasion reproduction number of strain one is obtained from differentiating the right-hand side of the equation for I with respect to I (to get the respective diagonal entry in the Jacobian). We get $\beta_1 s + \beta_1 \delta j - (\mu + \gamma_1)$. We substitute s and j from $\mathscr{E}_2$. Therefore, the invasion reproduction number of the first strain is given by

$$\hat{\mathscr{R}}_1 = \frac{\mathscr{R}_1}{\mathscr{R}_2} + \delta \mathscr{R}_1 \left(1 - \frac{1}{\mathscr{R}_2(\psi)} \right).$$

An important observation here is that as the vaccination rate ψ increases, $\hat{\mathscr{R}}_1$ decreases. Thus, vaccination decreases the invasion capabilities of the first strain.

To obtain the invasion reproduction number of strain two, we differentiate the right-hand side of the equation for J with respect to J (to get the respective diagonal
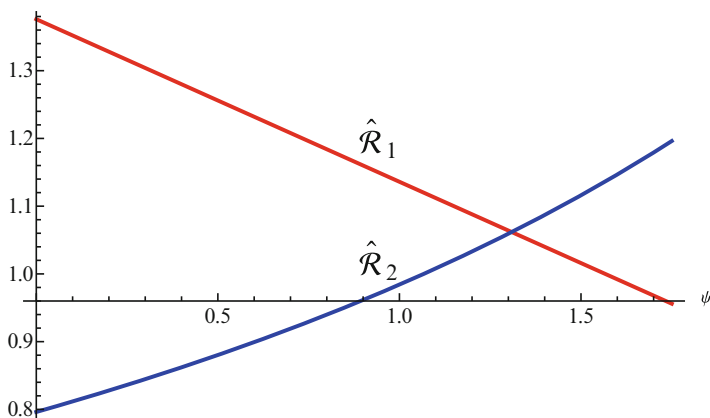

Fig. 9.6 The graph shows the invasion reproduction numbers $\hat{\mathscr{R}}_1$ and $\hat{\mathscr{R}}_2$ as functions of ψ. Clearly, $\hat{\mathscr{R}}_1$ is a decreasing function of ψ. In contrast, $\hat{\mathscr{R}}_2$ is an increasing function of ψ. The parameters are taken as follows: $\beta_1 = 12$, $\beta_2 = 15$, $\mu = 0.1$, $\gamma_1 = 0.5$, $\gamma_2 = 0.5$, $\delta = 0.03$

entry in the Jacobian). We get $\beta_2 s - \beta_1 \delta i - (\mu + \gamma_2)$. We substitute s and i from $\mathscr{E}_1$. Therefore, the invasion reproduction number of the second strain is given by

$$\hat{\mathscr{R}}_2 = \frac{(\mu + \gamma_2) \frac{\mathscr{R}_2}{\mathscr{R}_1}}{(\mu + \gamma_2) + (\mu + \gamma_1) \mathscr{R}_1 \delta \left(1 - \frac{1}{\mathscr{R}_1(\psi)} \right)}.$$

In contrast, the invasion reproduction number of the second strain is an increasing function of the vaccination rate. Hence, vaccination increases the invasion capabilities of the second strain. The reason for this effect is that when the two strains coexist, increasing the vaccination rate decreases the number of those infected with strain 1. That, in turn, reduces the superinfections, which take away from

the infections with the second strain. This produces an overall effect of increase in infections with the second strain.

We illustrate the trend with increasing ψ in the two invasion reproduction numbers in Fig. 9.6. Figure 9.6 also shows that there is a vaccination level ψ_1^* such that for $\psi < \psi_1^*$, the following conditions are satisfied: $\hat{\mathscr{R}}_2 < 1$ and $\hat{\mathscr{R}}_1 > 1$ (while $\mathscr{R}_1(\psi) > 1$ and $\mathscr{R}_2(\psi) > 1$). In this case, strain one, which can invade the equilibrium of strain two, dominates, since strain two cannot invade the equilibrium of strain one. Then there is a vaccination level ψ_2^* such that for $\psi_1^* < \psi < \psi_2^*$, the following conditions are satisfied: $\hat{\mathscr{R}}_2 > 1$ and $\hat{\mathscr{R}}_1 > 1$. In this case, both strains can invade each other's equilibrium, and therefore, they coexist. For vaccination levels $\psi > \psi_2^*$, the following conditions are satisfied: $\hat{\mathscr{R}}_2 > 1$ and $\hat{\mathscr{R}}_1 < 1$. In this case, strain two, which can invade the equilibrium of strain one, dominates, since strain one cannot invade the equilibrium of strain two. Thus, replacement of strain one, which dominated without vaccination, has occurred. The replacing strain is strain two.

9.4 Modeling Quarantine and Isolation

Quarantine and isolation are typically modeled by introducing separate classes into the model. Isolation is more often employed as a control strategy in epidemic models than quarantine. Isolated infected individuals move to a separate class Q. A simple extension of the SIR model with isolation will take the form

$$
\begin{aligned}
\frac{dS}{dt} &= \Lambda - \beta \frac{SI}{N-Q} - \mu S, \\
\frac{dI}{dt} &= \beta \frac{SI}{N-Q} - (\mu + \sigma + r_2)I, \\
\frac{dQ}{dt} &= \sigma I - (\mu + r_1)Q, \\
\frac{dR}{dt} &= r_2 I + r_1 Q - \mu R.
\end{aligned}
\tag{9.11}
$$

We note here that in standard incidence, the total active population is $N - Q$.

Epidemic models with isolation have been considered with respect to different diseases. Isolation has been found to destabilize the dynamics and lead to oscillations [61, 73] (see Chap. 7). As a result, isolation has been suggested as a potential intrinsic mechanism responsible for the recurrent outbreaks of childhood diseases [61].

The controlled reproduction number of model (9.11) is given by
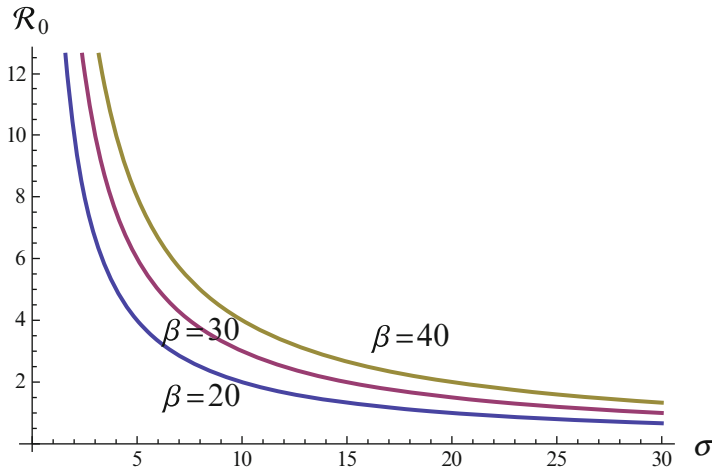
$$
\mathscr{R}_c = \frac{\beta}{\mu + \sigma + r_2}.
$$

Fig. 9.7 The figure shows the controlled reproduction number as a decreasing, concave up, function of σ for several values of β. The smaller the β, the steeper the decline in $\mathscr{R}_c$

The reproduction number is a decreasing function of the isolation rate σ. The critical isolation rate that gives $\mathscr{R}_0 = 1$ is given by $\sigma^* = \beta - \mu - r_2$. The reproduction number as a function of σ is plotted in Fig. 9.7.

The disease prevalence at equilibrium is given by

$$I^* = \frac{\Lambda \mathscr{R}_c (\mathscr{R}_c - 1)}{\beta (\mathscr{R}_c - 1) + \mu (1 + p) \mathscr{R}_c},$$

where

$$p = \left(\frac{r_2}{\mu} + \frac{r_1 \sigma}{\mu (\mu + r_1)} \right).$$

The prevalence is also a decreasing function of σ, at least when $\mathscr{R}_c > 1$. However, Fig. 9.8 suggests that the nonzero endemic equilibrium exists even if $\mathscr{R}_c < 1$. It can be shown that this equilibrium is unstable and that for $\mathscr{R}_c < 1$ the disease-free equilibrium is globally stable.

To design a model with quarantine and isolation, we need to express in terms of equations the events that happen in reality. Susceptible individuals S come into a contact with infectious I and exposed E individuals and move to the exposed class E. At the same time, the contacts of infectious individuals are traced. Some of the traced individuals happen to be susceptible, and others happen to be exposed. Traced susceptible individuals move to the quarantine class Q_1 at a rate ρ. Traced exposed individuals move to the quarantine class at a rate ρ. Quarantined individuals either show no symptoms and after the end of the quarantine return to the susceptible class, or they become sick and move to the isolated class Q_2:
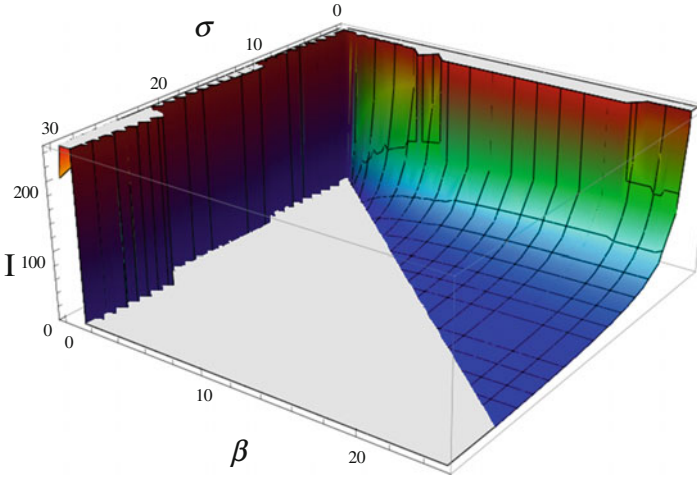
Fig. 9.8 The figure shows the prevalence as a decreasing, concave up function of σ and an increasing function of β. The smaller the β, the steeper the decline in prevalence

$$
\begin{aligned}
\frac{dS}{dt} &= \Lambda - \beta \frac{S(I+qE)}{N-Q} - \rho S - \mu S + \eta_1 Q_1, \\
\frac{dE}{dt} &= \beta \frac{S(I+qE)}{N-Q} - \rho E - (\mu + \gamma)E, \\
\frac{dQ_1}{dt} &= \rho S + \rho E - (\mu + \eta_1 + \eta_2)Q_1, \\
\frac{dI}{dt} &= \gamma E - (\mu + \sigma + r_2)I, \\
\frac{dQ_2}{dt} &= \sigma I + \eta_2 Q_1 - (\mu + r_1)Q_2, \\
\frac{dR}{dt} &= r_2 I + r_1 Q_2 - \mu R.
\end{aligned}
\tag{9.12}
$$

Quarantined and isolated individuals do not participate in the total active population, so the total active population in the denominator of the standard incidence is given by $N - Q_1 - Q_2 = N - Q$, where $Q = Q_1 + Q_2$. Infectious and isolated individuals recover and move to the recovered class R. The meaning and the values of the parameters are given in Table 9.5.

The controlled reproduction number is given by

$$
\mathscr{R}_c = \frac{\beta \gamma}{(\gamma + \rho + \mu)(r_2 + \sigma + \mu)} + \frac{q\beta}{\gamma + \rho + \mu}.
$$

In interpreting the controlled reproduction number, we notice that the first term is the number of secondary infections generated by the infectious individuals, and the

Table 9.5 Parameter meanings and parameter values [120]

Parameter	Parameter meaning	Value
Λ	Recruitment rate	240 people/day
β	Transmission rate	0.25 per day
ρ	Quarantine rate	1/10 per day
μ	Natural death rate	1/(70*365) per day
γ	Rate of developing symptoms	1/6 per day
σ	Isolation rate	1/5 per day
η_1	Rate of return to susceptible class	1/10 per day
η_2	Rate of progression to infectiousness	1/6.5 per day
r_1	Recovery rate for isolated individuals	1/20 per day
r_2	Recovery rate for infectious individuals	1/25 per day
q	Reduction of infectivity of exposed individuals	0.8 (variable)

second term is the number of secondary infections generated by exposed individuals; $\gamma/(\gamma + \rho + \mu)$ is the proportion of exposed individuals who move to the infectious class.

We plot the region $\mathscr{R}_c > 1$ for two values of $q = 0.5$ and $q = 0.8$ in Fig. 9.9. The region for $q = 0.8$ is larger and asymmetric. We plot the point with coordinates given in Table 9.5 in red. That point belongs to the region $\mathscr{R}_c > 1$; hence for the quarantine and isolation rates in Table 9.5, the disease will not be eradicated. We would like to compute the values of quarantine and isolation rates that will represent the smallest change from the values in Table 9.5 but will lead to eradication of the disease. For that reason, we compute the point on the curve $\mathscr{R}_c = 1$ that is closest to the red point. To do that, let the black point have coordinates (x, y). The square of the distance between the two points is given by

$$(x - 0.1)^2 + (y - 0.2)^2,$$

where $(0.1, 0.2)$ are the coordinates of the red point. Furthermore, we replace ρ with x and σ with y in $\mathscr{R}_c$. From the equation $\mathscr{R}_c = 1$, we express σ (or y) as a function of ρ (or x): $y = f(x)$. Substituting y in the distance formula, we obtain the square of the distance as a function of x:

$$(x - 0.1)^2 + (f(x) - 0.2)^2.$$

To minimize that function, we differentiate with respect to x and set the derivative to zero. This leads to the equation

$$(x - 0.1) + (f(x) - 0.2)f'(x) = 0.$$

In the case $q = 0.5$, the black point has coordinates $(0.12214, 0.214265)$; in the case of $q = 0.8$, the black point has coordinates $(0.180881, 0.242281)$. From these coordinates, we need to see how we need to change the quarantine and isolation
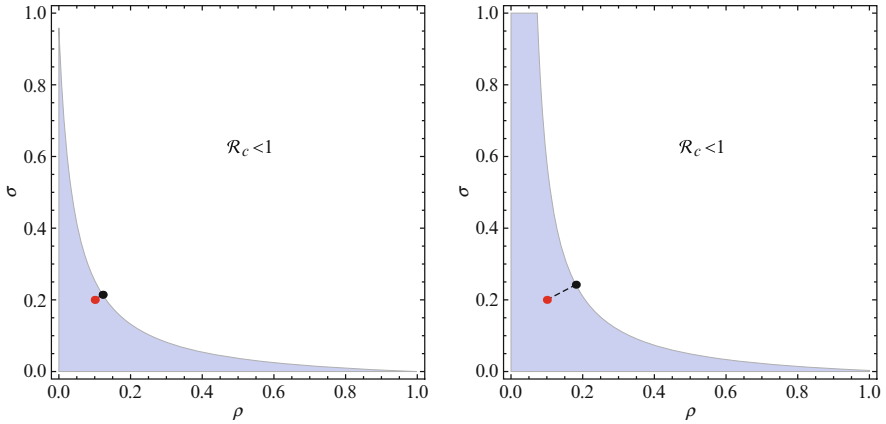
Fig. 9.9 Both figures illustrate the region $\mathcal{R}_c > 1$, the epidemic situation with a *red point*, and the closest point on the curve $\mathcal{R}_c = 1$ in *black*. The *left figure* does so for $q = 0.5$, while the *right figure* gives the same scenario for $q = 0.8$

rates to achieve elimination. The optimal new periods for quarantine and isolation are given by $1/c$, where c is a coordinate of a black point. These optimal periods that will lead to elimination are listed in Table 9.6.

Table 9.6 Optimal periods for quarantine and isolation

Strategy	$q = 0.5$	$q = 0.8$
$1/\rho$	8.19 days	5.53 days
$1/\sigma$	4.67 days	4.13 days

This table suggests that in the case $q = 0.8$, the contact tracing and quarantining should improve dramatically from 10 days to 5.5 days, while isolation should improve from 5 days to 4 days, in order for the disease to be eliminated.

9.5 Optimal Control Strategies

In previous sections, we considered control strategies to be constant in time, but in reality, control strategies are variable in time. The mathematical theory used to derive optimal control strategies that vary in time is called *optimal control theory*. In this section, we introduce the basic principles and illustrate them with examples.

9.5.1 Basic Theory of Optimal Control

Optimal control is applied to differential equation models in normal form. Here we will be concerned with ordinary differential equation models. We consider a system of ODEs

$$
\begin{aligned}
\mathbf{x}'(t) &= \mathbf{f}(\mathbf{x}(t)), \\
\mathbf{x}(0) &= \mathbf{x}_0,
\end{aligned}
\tag{9.13}
$$

where the given initial condition is $\mathbf{x}_0 \in \mathbb{R}^n$, and $\mathbf{f} : \mathbb{R}^n \to \mathbb{R}^n$. The unknown vector is $\mathbf{x} : [0, \infty) \to \mathbb{R}^n$.

Now we generalize the setup and suppose that the right-hand side depends on a parameter $\mathbf{u} : [0, \infty) \to A$, where $A \subset \mathbb{R}^m$, that is allowed to depend on time $u(t)$. Thus the system above becomes

$$
\begin{aligned}
\mathbf{x}'(t) &= \mathbf{f}(\mathbf{x}(t), \mathbf{u}(t)), \\
\mathbf{x}(0) &= \mathbf{x}_0, \\
\mathbf{x}(T) &\quad \text{free.}
\end{aligned}
\tag{9.14}
$$

The variable $\mathbf{u}(t)$ is called *control*, and in the presence of the control, the solution $\mathbf{x}(t)$ depends on the control. The trajectory that corresponds to the control $\mathbf{u}(t)$ is called a corresponding *response* of the system.

To make this presentation more specific, we recast some of the models for vaccination and isolation from this chapter in the framework of control. For instance, in model (9.2), the "control" is the vaccination, given by the vaccination rate ψ. Hence, the right-hand side of (9.2) depends on the dependent variables and the control parameter ψ. Now we let ψ vary with time, and we replace it with $u(t)$. We obtain the following problem with control:

$$
\begin{aligned}
\frac{dS}{dt} &= \Lambda - \frac{\beta SI}{N} - (\mu + u(t))S + \chi \gamma I, \\
\frac{dI}{dt} &= \frac{\beta SI}{N} + \frac{\beta \delta VI}{N} - (\mu + \gamma)I, \\
\frac{dV}{dt} &= u(t)S - \frac{\beta \delta VI}{N} + (1 - \chi)\gamma I - \mu V.
\end{aligned}
\tag{9.15}
$$

Here the control is given by $u : [0, \infty) \to \mathbb{R}_+$.

We introduce the set of *admissible controls*

$$
\mathscr{A} = \{\mathbf{u}(t) \in L^1(0, T) | \mathbf{u}(t) \in A\}.
$$

As posed, problem (9.14) does not have a solution, since the control may be arbitrary. We need to find the best control in some sense. For disease-control models, we need to find the control in such a way that we minimize the prevalence and/or minimize the cost of controlling the disease. To make this more specific, we define a *payoff functional*:

$$\mathscr{C}[\mathbf{u}] := \int_0^T g(\mathbf{x}(t), \mathbf{u}(t))dt, \tag{9.16}$$

where $\mathbf{x}(t)$ solves (9.14) for the specified control $\mathbf{u}(t)$. The function $g : \mathbb{R}^n \times A \to \mathbb{R}$ is given. The terminal time T is given as well. The function g is called the *running payoff*. We need to solve the following optimal control problem: find a control $\mathbf{u}^*(t)$ that minimizes the payoff functional, that is,

$$\mathscr{C}[\mathbf{u}^*] = \min_{u \in \mathscr{A}} \mathscr{C}[u].$$

If such a control $\mathbf{u}^*(t)$ exists, it is called an *optimal control*. The optimal control together with the corresponding solution gives the optimal control pair $(\mathbf{x}^*, \mathbf{u}^*)$.

The first question that must be addressed is whether an optimal control pair $(\mathbf{x}^*(t), \mathbf{u}^*(t))$ exists. The question of existence is settled by the following theorem [143]:

Theorem 9.1 (Filippov–Cesari Existence Theorem). *For all $(t, \mathbf{x}) \in \mathbb{R}^{n+1}$, define the set*

$$N(t, \mathbf{x}) = \{(g(\mathbf{x}, \mathbf{u}) + \xi, \mathbf{f}(\mathbf{x}, \mathbf{u})) : \xi \leq 0, \mathbf{u} \in A\}.$$

Suppose that

1. *$N(t, \mathbf{x})$ is convex for every $(t, \mathbf{x})$.*
2. *A is compact.*
3. *There exists a constant $K > 0$ such that $\|\mathbf{x}(t)\| \leq K$ for all $t \in (0, T)$ and all admissible pairs $(\mathbf{x}, \mathbf{u})$.*

Then there exists an optimal pair $(\mathbf{x}^*(t), \mathbf{u}^*(t))$, where $\mathbf{u}^*(t) \in \mathscr{A}$.

If a solution exists, it can be found with Pontryagin's minimum principle [143]. First, one introduces a time-varying Lagrange multiplier vector $\lambda(t)$, whose elements are called the *adjoint variables* of the system. Next, the Hamiltonian H is defined for all $t \in [0, T]$ by

$$H(\mathbf{x}(t), \mathbf{u}(t), \lambda(t)) = g(\mathbf{x}(t), \mathbf{u}(t)) + \sum_{i=1}^n \lambda_i(t) f_i(\mathbf{x}(t), \mathbf{u}(t)). \tag{9.17}$$

The Pontryagin minimum principle is as follows.

Theorem 9.2 (Pontryagin's Minimum Principle). *For the optimality of control $\mathbf{u}^*(t)$ and corresponding trajectory $\mathbf{x}^*(t)$ with $t \in [0, T]$, it is necessary that there exist a nonzero adjoint vector function $\lambda^*(t)$ that is a solution to the adjoint system*

$$\begin{aligned} \lambda'(t) &= -\frac{\partial H(\mathbf{x}(t), \mathbf{u}(t), \lambda(t))}{\partial x} \\ \lambda(T) &= 0, \end{aligned} \tag{9.18}$$

so that

$$H(\mathbf{x}^*(t), \mathbf{u}^*(t), \lambda^*(t)) = \min_{\mathbf{u} \in \mathscr{A}} H(\mathbf{x}^*(t), \mathbf{u}(t), \lambda^*(t)).$$

Thus, the necessary conditions for optimizing the Hamiltonian are [117]:

$$\frac{\partial H}{\partial u} = 0 \Longrightarrow g_u + \sum_{i=1}^{n} \lambda_i(t)(f_i)_u = 0, \quad \text{optimality equation,}$$

$$\lambda_i'(t) = -\frac{\partial H(\mathbf{x}(t), \mathbf{u}(t), \lambda(t))}{\partial x_i} \Longrightarrow \lambda_i'(t) = -g_{x_i} - \sum_{i=1}^{n} \lambda_i(t)(f_i)_{x_i}, \text{ adjoint equation,}$$

$$\lambda(T) = 0, \quad \text{transversality condition.}$$

(9.19)

We note that for minimization, we must also have

$$\frac{\partial^2 H}{\partial u^2} \geq 0 \quad \text{at} \quad \mathbf{u}^*.$$

The following theorem gives sufficient conditions for the existence and uniqueness of the optimal pair [143]:

Theorem 9.3 (Mangasarian Theorem). *Suppose*

1. *A is convex.*
2. *The partial derivative $\partial g/\partial u_j$ and $\partial f_i/\partial u_j$ all exist and are continuous.*
3. *The pair $(\mathbf{x}^*(t), \mathbf{u}^*(t))$ satisfies all conditions of the Pontryagin minimum principle.*
4. *$H(t, \mathbf{x}, \mathbf{u})$ is concave down in $(\mathbf{x}, \mathbf{u})$ for all $t \in [0, T]$.*

Then the pair $(\mathbf{x}^*(t), \mathbf{u}^*(t))$ solves the problem. If $H(t, \mathbf{x}, \mathbf{u})$ is strictly concave down in $(\mathbf{x}, \mathbf{u})$, then the solution is unique.

There are several excellent books that introduce optimal control theory applied to biological systems [13, 94]. We illustrate the application of the existence theorem and Pontryagin's minimum principle to finding the optimal control in the next subsection.

9.5.2 Examples

In this subsection we consider two examples of application of optimal control to epidemic models. The first example is an SIS model with treatment.

9.5.2.1 SIS Model with Treatment

The model assumes constant total population size N. In this case, the susceptible individuals can be represented as $S = N - I$, and the 2×2 system can be reduced to a single equation:

$$\begin{aligned} I'(t) &= \beta(N - I)I - (\mu + \gamma)I - u(t)I, \\ I(0) &= I_0, \\ I(T) &\quad \text{free,} \end{aligned}$$

(9.20)

where β is the transmission rate, μ is the natural death rate, and γ is the natural recovery rate without treatment. The term $u(t)I$ models the additional recovery rate due to treatment. The set of admissible controls is

$$\mathscr{A} = \{u(t) \in L^1(0,T) | 0 \le u(t) \le U_{\max}\},$$

where $U_{\max} < \infty$ is a positive constant. We are applying optimal control theory to determine the "best" treatment regime that will minimize the prevalence and the cost of applying the treatment. In particular, we seek a control u^* that minimizes the payoff functional

$$\mathscr{C}[u^*] = \min_{u \in \mathscr{A}} \int_0^T (w_1 I(t) + u^2(t)) dt, \qquad (9.21)$$

where w_1 is a constant cost of minimizing prevalence, and u^2 requires us to minimize the treatment, and also the cost of applying it. We assume that the cost of treatment is nonlinear and takes a quadratic form.

We first prove the existence of an optimal control pair. We use the Filippov–Cesari theorem.

Proposition 9.1. *The optimal control problem (9.20)–(9.21) has a solution.*

Proof. Let $N(t,\mathbf{x})$ be defined as in Theorem 9.1. Let $y_1, y_2 \in N(t,\mathbf{x})$. To show that $N(t,\mathbf{x})$ is convex for each $(t,\mathbf{x})$, we will show that the line connecting y_1 and y_2 lies entirely in $N(t,\mathbf{x})$. Hence, we have to show that

$$\alpha y_1 + (1-\alpha) y_2 \in N(t,\mathbf{x}) \quad \text{for every } \alpha \in [0,1].$$

The fact that $y_i \in N(t,\mathbf{x})$ implies that there exist $\xi_1, \xi_2 \le 0$ and control vectors $\mathbf{u}_1(t), \mathbf{u}_2(t) \in A$ such that

$$y_i = \{g(\mathbf{x}, \mathbf{u}_i) + \xi_i, \mathbf{f}(\mathbf{x}, \mathbf{u}_i)\} \quad \text{for} \quad i = 1, 2.$$

Then, we have

$$\begin{aligned}
\alpha(g(\mathbf{x}, \mathbf{u}_1) + \xi_1) &+ (1-\alpha)(g(\mathbf{x}, \mathbf{u}_2) + \xi_2) \\
&= \alpha(w_1 I(t) + u_1^2(t)) + (1-\alpha)(w_1 I(t) + u_2^2(t)) + \alpha\xi_1 + (1-\alpha)\xi_2 \\
&= w_1 I(t) + \alpha u_1^2 + (1-\alpha)u_2^2 + \alpha\xi_1 + (1-\alpha)\xi_2. \qquad (9.22)
\end{aligned}$$

Letting $u_3 = \sqrt{\alpha u_1^2 + (1-\alpha)u_2^2}$, we notice that $u_3 \in A$. Furthermore, letting $\xi_3 = \alpha\xi_1 + (1-\alpha)\xi_2$, we notice that $\xi_3 \le 0$. Thus, the first component of the convex combination belongs to $N(t,\mathbf{x})$. Next, we check the second component:

$$\begin{aligned}
\alpha(f(\mathbf{x}, \mathbf{u}_1) &+ (1-\alpha)f(\mathbf{x}, \mathbf{u}_2) \\
&= \alpha(\beta(N-I)I - (\mu+\gamma)I - u_1(t)I) + (1-\alpha)(\beta(N-I)I - (\mu+\gamma)I - u_2(t)I) \\
&= \beta(N-I)I - (\mu+\gamma)I - (\alpha u_1(t) + (1-\alpha)u_2)I. \qquad (9.23)
\end{aligned}$$

Letting $u_4 = \alpha u_1(t) + (1 - \alpha)u_2$, we notice that $u_4 \in A$. We conclude that the convex combination $\alpha y_1 + (1 - \alpha)y_2$ is in $N(t, \mathbf{x})$. Clearly, A is compact. Next, we show that the solution of (9.20) is bounded. Indeed,

$$I'(t) \leq \beta(N - I)I.$$

We have that $I(t) \leq \sup_t \hat{I}$, where $\hat{I}$ is the solution of the equation $\hat{I}'(t) = \beta(N - \hat{I})\hat{I}$. Thus, $\sup_t I(t) \leq \max\{I_0, N\}$. If $I_0 \leq N$, then $\max_t\{I(t)\} \leq N$. This concludes the proof. $\square$

To apply Pontryagin's minimum principle, we define the Hamiltonian:

$$H(I(t), u(t), \lambda(t)) = w_1 I(t) + u^2(t) + \lambda(t)(\beta(N - I(t))I(t) - (\mu + \gamma)I(t) - u(t)I(t)).$$

Posing the necessary conditions from Pontryagin's principle, we have first that u^* must be a critical point of the Hamiltonian, that is, we must have $\partial H/\partial u = 0$. This leads to the following condition on the optimal control: $2u - \lambda(t)I(t) = 0$. Hence, we have

$$u^*(t) = \frac{\lambda(t)I(t)}{2}.$$

Next, we check that the critical point is indeed a minimum: $\partial^2 H/\partial u^2 = 2 > 0$. The adjoint system is given by

$$\begin{aligned} \lambda'(t) &= -w_1 - \lambda(t)(\beta(N - I(t)) - \beta I(t) - (\mu + \gamma) - u(t)), \\ \lambda(T) &= 0. \end{aligned} \tag{9.24}$$

Since u^* must belong to $\mathscr{A}$, we must have

$$u^*(t) = \min\left\{U_{\max}, \max\left\{0, \frac{\lambda(t)I(t)}{2}\right\}\right\}. \tag{9.25}$$

To find the optimal control and the prevalence that corresponds to it, we must solve the system

$$\begin{aligned} I'(t) &= \beta(N - I)I - (\mu + \gamma)I - u^*(t)I, \\ I(0) &= I_0, \\ \lambda'(t) &= -w_1 - \lambda(t)(\beta(N - I(t)) - \beta I(t) - (\mu + \gamma) - u^*(t)), \\ \lambda(T) &= 0, \end{aligned} \tag{9.26}$$

where u^* is given by (9.25). System (9.26) cannot be solved by hand, and numerical methods must be used. Both Mathematica and Matlab can be used. Mathematica's NDSolve can take in boundary conditions, and system (9.26) can be directly input into it. The optimal control and the respective solution are plotted in Fig. 9.10.

Matlab requires use of numerical methods to solve the system of differential equations. The forward–backward sweep method [94] is often employed in this case. It combines the forward application of a fourth-order Runge–Kutta method
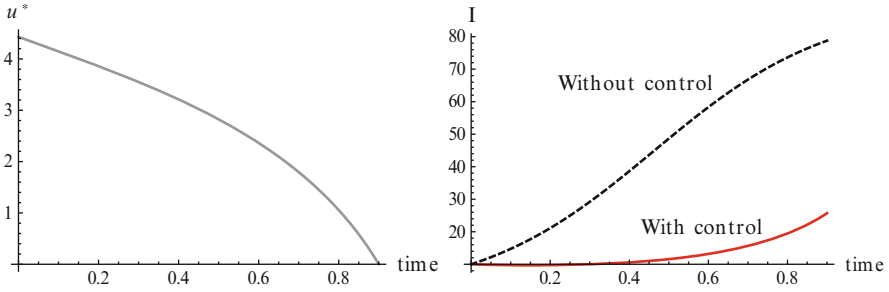
Fig. 9.10 The *left figure* shows the optimal control $u^*(t)$. The *right figure* shows the controlled prevalence $I^*(t)$ and the original prevalence $I(t)$

for the original system with the backward application of a fourth-order Runge–Kutta method for the adjoint system. The Matlab code for system (9.26) is included in the appendix.

9.5.2.2 Two-Strain Model with Vaccination

The second model is the model with two strains and vaccination given in Eq. (9.10). The control $u(t)$ replaces the vaccination rate ψ. The model with control becomes

$$
\begin{aligned}
\frac{dS}{dt} &= \Lambda - \beta_1 \frac{SI}{N} - \beta_2 \frac{SJ}{N} - (\mu + u(t))S + \gamma_1 I + \gamma_2 J, \\
\frac{dI}{dt} &= \beta_1 \frac{SI}{N} + \beta_1 \delta \frac{IJ}{N} - (\mu + \gamma_1)I, \\
\frac{dJ}{dt} &= \beta_2 \frac{SJ}{N} - \beta_1 \delta \frac{IJ}{N} - (\mu + \gamma_2)J, \\
\frac{dV}{dt} &= u(t)S - \mu V.
\end{aligned}
\tag{9.27}
$$

The set of admissible controls is

$$
\mathscr{A} = \{u(t) \in L^1(0,T) | 0 \le u(t) \le U_{\max}\}.
$$

We are applying optimal control theory to determine the "best" vaccination regime that will minimize the the prevalence and the cost of applying the vaccination. In particular, we seek a control u^* that minimizes the payoff functional

$$
\mathscr{C}[u^*] = \min_{u \in \mathscr{A}} \int_0^T (w_1 I(t) + w_2 J(t) + w_3 uS(t) + u^2(t))dt,
$$

where w_1, w_2 are constant costs of minimizing prevalence, and the term uS intends to minimize the number of vaccines used with constant weight w_3. Finally, u^2 requires us to minimize the vaccination rate, and also the cost of vaccination. We assume that the cost of vaccination is nonlinear and takes a quadratic form.

To apply Pontryagin's minimum principle, we define the Hamiltonian:

$$H = w_1 I + w_2 J + w_3 uS + u^2 + \lambda_S \left(\Lambda - \beta_1 \frac{SI}{N} - \beta_2 \frac{SJ}{N} - (\mu + u(t))S + \gamma_1 I + \gamma_2 J \right)$$
$$+ \lambda_I \left(\beta_1 \frac{SI}{N} + \beta_1 \delta \frac{IJ}{N} - (\mu + \gamma_1)I \right)$$
$$+ \lambda_J \left(\beta_2 \frac{SJ}{N} - \beta_1 \delta \frac{IJ}{N} - (\mu + \gamma_2)J \right) + \lambda_V (uS - \mu V).$$

$$(9.28)$$

Again, applying the necessary conditions from Pontryagin's principle, we have first that u^* must be a critical point of the Hamiltonian, that is, we must have $\partial H / \partial u = 0$. This leads to the following condition on the optimal control: $2u - \lambda_S(t)S(t) + \lambda_V(t)S(t) + w_3 S(t) = 0$. This leads to the following expression for the control:

$$u^*(t) = \frac{(\lambda_S(t) - \lambda_V(t) - w_3)S(t)}{2}.$$

Next, we check that critical point is indeed a minimum: $\partial^2 H / \partial u^2 = 2 > 0$. The adjoint system is given by

$$\lambda_S'(t) = -w_3 u - \lambda_S \left(\beta_1 \frac{I}{N} + \beta_1 \frac{SI}{N^2} - \beta_2 \frac{J}{N} + \beta_2 \frac{SJ}{N^2} - (\mu + u) \right)$$
$$- \lambda_I \left(\beta_1 \frac{I}{N} - \beta_1 \frac{SI}{N^2} - \beta_1 \delta \frac{IJ}{N^2} \right)$$
$$- \lambda_J \left(\beta_2 \frac{J}{N} - \beta_2 \frac{SJ}{N^2} + \beta_1 \delta \frac{IJ}{N^2} \right) - \lambda_V u$$
$$\lambda_I'(t) = -w_1 - \lambda_S \left(\beta_1 \frac{S}{N} + \beta_1 \frac{SI}{N^2} + \beta_2 \frac{SJ}{N^2} + \gamma_1 \right)$$
$$\lambda_I \left(\beta_1 \frac{S}{N} - \beta_1 \frac{SI}{N^2} + \beta_1 \delta \frac{J}{N} - \beta_1 \delta \frac{IJ}{N^2} - (\mu + \gamma_1) \right)$$
$$\lambda_J \left(-\beta_2 \frac{IJ}{N^2} - \beta_1 \delta \frac{J}{N} + \beta_1 \delta \frac{IJ}{N^2} \right)$$
$$\lambda_J'(t) = -w_2 - \lambda_S \left(\beta_1 \frac{SI}{N^2} - \beta_2 \frac{S}{N} + \beta_2 \frac{SJ}{N^2} + \gamma_2 \right)$$
$$- \lambda_I \left(-\beta_1 \frac{SI}{N^2} + \beta_1 \delta \frac{I}{N} - \beta_1 \delta \frac{IJ}{N^2} \right)$$
$$- \lambda_J \left(\beta_2 \frac{S}{N} - \beta_2 \frac{SJ}{N^2} - \beta_1 \delta \frac{I}{N} + \beta_1 \delta \frac{IJ}{N^2} - (\mu + \gamma_2) \right)$$
$$\lambda_V'(t) = \mu \lambda_V$$
$$\lambda(T) = 0; \quad \lambda_I(T) = 0; \quad \lambda_J(T) = 0; \quad \lambda_V(T) = 0.$$

$$(9.29)$$

From the equation for λ_V and its boundary condition, we see that $\lambda_V = 0$. Hence, the optimal control is characterized by the following formula:

$$u^*(t) = \min\left\{U_{\max}, \max\left\{0, \frac{(\lambda_S(t) - w_3)S(t)}{2}\right\}\right\}.$$

The optimal control and the solution with and without control are plotted in Fig. 9.11. We note that in the case $w_3 \neq 0$, the control is zero for some of the control interval.
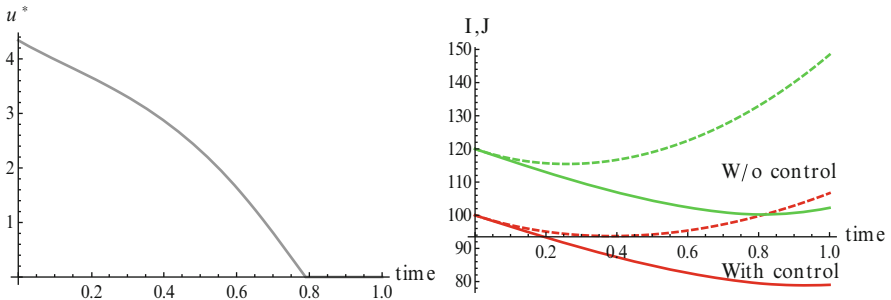

Fig. 9.11 The *left figure* shows the optimal control $u^*(t)$. The *right figure* shows the controlled prevalence $I^*(t)$ and $J^*(t)$ and the original prevalences $I(t)$ and $J(t)$ in *dashed*. Parameters are $\beta_1 = 12; \beta_2 = 15; \gamma_1 = 0.5; \gamma_2 = 0.5; \mu = 0.1; \delta = 0.03; \Lambda = 500; w_1 = 1; w_2 = 1; w_3 = 0.01$

Appendix

In this appendix we include the Matlab code that executes the forward–backward sweep for system (9.26) [94].

```matlab
function ocmodel1
% This function computes the optimal control
%   and the corresponding solution using forward-backward ...
        sweep
clc;
clear all;


test = -1;


Δ = 0.001;      %set tolerance
N = 100;        %number of subdivisions
h = 1/N;        %step
t = 0:h:1;      % t-variable mesh
```

```
15
16  u = zeros(1,length(t));        %initialization
17  x = zeros(1,length(t));
18  lam = zeros(1,length(t));
19
20  x(1) = 10;        %initial value assigned to x(0)
21
22  beta = 0.05;      %parameters
23  mu = 0.01;
24  gamma = 0.5;
25  P = 100;
26  w1 = 1;
27
28
29  while (test<0)     % while the tolerance is reached, repeat
30      oldu = u;
31      oldx = x;
32      oldlam = lam;
33
34      for i=1:N      %loop that solve the forward ...
            differential equation
35          k1 = beta*(P-x(i))*x(i)  -(mu + gamma)*x(i) - ...
                u(i)*x(i);
36          k2 = beta*(P-x(i)-0.5*k1*h)*(x(i)+0.5*k1*h) - ...
                (mu+gamma)*(x(i)+0.5*k1*h)...
37                          -0.5*(u(i)+u(i+1))*(x(i)+0.5*k1*h);
38          k3 = beta*(P-x(i)-0.5*k2*h)*(x(i)+0.5*k2*h) - ...
                (mu+gamma)*(x(i)+0.5*k2*h)...
39                          -0.5*(u(i)+u(i+1))*(x(i)+0.5*k2*h);
40          k4 = beta*(P-x(i)-k3*h)*(x(i)+k3*h) - ...
                (mu+gamma)*(x(i)+k3*h)...
41                          -u(i+1)*(x(i)+k3*h);
42
43          x(i+1) = x(i) + (h/6)*(k1+2*k2+2*k3+k4);
44
45      end
46
47      for i=1:N      %loop that solves the backward ...
            differential equation of the adjoint system
48          j = N + 2 -i;
49          k1 = ...
                -w1-lam(j)*(beta*(P-x(j))-beta*x(j)-(mu+gamma) ...
                - u(j));
50          k2 = ...
                -w1-(lam(j)-0.5*k1*h)*(beta*(P-x(j)+0.5*k1*h) ...
                -(mu+gamma) -0.5*(u(j)+u(j-1)));
51          k3 = ...
                -w1-(lam(j)-0.5*k2*h)*(beta*(P-x(j)+0.5*k2*h) ...
                -(mu+gamma) -0.5*(u(j)+u(j-1)));
52          k4 = -w1 -(lam(j)-k3*h)*(beta*(P-x(j)+k3*h) ...
                -(mu+gamma) - u(j-1));
53
54          lam(j-1) = lam(j) - (h/6)*(k1+2*k2+2*k3+k4);
55
```

```
56        end

57

58        u1 = min(100,max(0,lam.*x/2));
59        u = 0.5*(u1 + oldu);

60

61        temp1 = Δ*sum(abs(u))  - sum(abs(oldu - u));
62        temp2 = Δ*sum(abs(x))  - sum(abs(oldx - x));
63        temp3 = Δ*sum(abs(lam)) - sum(abs(oldlam -lam));

64

65        test = min(temp1,min(temp2,temp3));

66

67  end

68

69  figure(1)              %plotting
70  plot(t,u)

71

72

73  figure(2)
74  plot(t,x)

75

76  end
```

Problems

9.1. Consider the model with perfect vaccination

$$\frac{dS}{dt} = \Lambda - \beta SI - (\mu + \psi)S,$$
$$\frac{dI}{dt} = \beta SI - (\mu + \gamma)I, \qquad (9.30)$$
$$\frac{dV}{dt} = \psi S - \mu V + \gamma I.$$

(a) Compute the reproduction number and investigate the stability of the disease-free equilibrium.
(b) Compute the endemic equilibrium. Does backward bifurcation occur?
(c) Determine the stability of the endemic equilibrium.
(d) Compute the fraction of the population p_c that needs to be vaccinated to eradicate the disease.

9.2. Consider the model with perfect vaccination

$$\frac{dS}{dt} = (1 - p)\pi - \beta SI - \mu S,$$
$$\frac{dI}{dt} = \beta SI - (\mu + \gamma)I, \qquad (9.31)$$
$$\frac{dV}{dt} = p\pi - \mu V + \gamma I,$$

where π is the recruitment rate.

(a) Compute the reproduction number and investigate the stability of the disease-free equilibrium.
(b) Compute the endemic equilibrium.
(c) Determine the stability of the endemic equilibrium.
(d) Compute the fraction of the population p_c that needs to be vaccinated to eradicate the disease.

9.3. Consider the model with perfect vaccination

$$
\begin{aligned}
\frac{dS}{dt} &= (1-p)\pi - \beta SI - \mu S, \\
\frac{dI}{dt} &= \beta SI + \delta \beta VI - (\mu + \gamma)I, \\
\frac{dV}{dt} &= p\pi - \delta \beta VI - \mu V + \gamma I,
\end{aligned}
\tag{9.32}
$$

where π is the recruitment rate.

(a) Compute the reproduction number and investigate the stability of the disease-free equilibrium.
(b) Compute the endemic equilibrium.
(c) Compute the fraction of the population p_c that needs to be vaccinated to eradicate the disease.

9.4. Consider the model with imperfect vaccination

$$
\begin{aligned}
\frac{dS}{dt} &= \Lambda - \beta SI - (\mu + \psi)S, \\
\frac{dI}{dt} &= \beta SI + \sigma \beta VI - (\mu + \gamma)I, \\
\frac{dV}{dt} &= \psi S - \sigma \beta VI - \mu V + \gamma I.
\end{aligned}
\tag{9.33}
$$

(a) Compute the reproduction number and investigate the stability of the disease-free equilibrium.
(b) Compute the equation for the endemic equilibria. Derive the condition for backward bifurcation to occur.
(c) Simulate the model and show that even if $\mathscr{R}_0(\psi) < 1$, the solution may converge to an endemic equilibrium.
(d) Consider the model

$$
\begin{aligned}
\frac{dS}{dt} &= \Lambda - \beta(1 - \eta H(t - \tau_1) + \eta H(t - \tau_2))SI - (\mu + \psi)S, \\
\frac{dI}{dt} &= \beta(1 - \eta H(t - \tau_1) + \eta H(t - \tau_2))SI \\
&\quad + \sigma \beta(1 - \eta H(t - \tau_1) + \eta H(t - \tau_2))VI - (\mu + \gamma)I, \\
\frac{dV}{dt} &= \psi S - \sigma \beta(1 - \eta H(t - \tau_1) + \eta H(t - \tau_2))VI - \mu V + \gamma I,
\end{aligned}
\tag{9.34}
$$

where $H(t-\tau)$ is the Heaviside function. The added term $(1 - \eta H(t - \tau_1) + \eta H(t - \tau_2))$ models temporary control measures such as movement restriction, which are adopted at time τ_1 and lifted at time τ_2. Show that with the parameters from part (c), after the lifting of the control measures, the solution may converge to the disease-free equilibrium.

9.5. Vaccine Strain in the Case of Mutation

Consider the following model with mutation:

$$
\begin{aligned}
S' &= \Lambda - \frac{\beta_1 SI}{N} - \frac{\beta_2 SJ}{N} - \mu S, \\
I' &= \frac{\beta_1 SI}{N} - (\mu + \alpha_1 + m)I, \\
J' &= \frac{\beta_2 SJ}{N} - (\mu + \alpha_2)J + mI.
\end{aligned}
\tag{9.35}
$$

Assume $\mathscr{R}_2 < 1$. A vaccine is being designed, but it may include only one of the strains. In that case, the vaccine will be perfect with respect to the vaccine strain and not effective at all with respect to the other. Which of the strains should be the vaccine strain so that the vaccine eliminates both strains?

9.6. Asymptomatic Spread of Avian Influenza

Consider the following model of avian influenza with vaccination and asymptomatic stage:

$$
\begin{aligned}
\frac{dS}{dt} &= \Lambda - \beta S(I + qA) - (\mu + \psi)S, \\
\frac{dI}{dt} &= \beta S(I + qA) - (\mu + v)I, \\
\frac{dV}{dt} &= \psi S - \eta V(I + qA) - \mu V + \gamma A, \\
\frac{dA}{dt} &= \eta V(I + qA) - (\mu + \gamma)A,
\end{aligned}
\tag{9.36}
$$

where A are the asymptomatic individuals infected with avian influenza after imperfect vaccination, and V are the vaccinated individuals.

(a) Compute the disease-free equilibrium and the reproduction number $\mathscr{R}_0(\psi)$. Determine the stability of the disease-free equilibrium based on the reproduction number.

(b) Is the reproduction number an increasing, decreasing, or nonmonotone function of ψ. What is the epidemiological significance of your observation?

9.7. Backward Bifurcation with Perfect Vaccination

Consider the following model of vaccination in a disease with vertical transmission:

$$\frac{dS}{dt} = (1-p)\pi + (r_1 S + r_2 \eta I)\left(1 - \frac{S+I}{K}\right) - \beta SI - \mu S,$$

$$\frac{dI}{dt} = r_2(1-\eta)I\left(1 - \frac{S+I}{K}\right) + \beta SI - (\mu + \alpha)I, \qquad (9.37)$$

$$\frac{dV}{dt} = p\pi - \mu V,$$

where the vaccine is applied at the entry point to the population, and a fraction p is being vaccinated; r_1 and r_2 are the reproduction rates of susceptible and infected individuals respectively, η is the fraction of the progeny of infected individuals that are susceptible.

(a) Compute the disease-free equilibrium and the reproduction number $\mathcal{R}_0(p)$. Determine the stability of the disease-free equilibrium based on the reproduction number.

(b) Derive an equation for the endemic equilibrium. Show that backward bifurcation may occur, even though the vaccine is perfect.

9.8. Saturating Treatment Rates and Vaccination

Consider a model of two strains with saturated per capita treatment rate:

$$S' = \Lambda - \frac{\beta_1 SI}{N} - \frac{\beta_2 SJ}{N} - (\mu + \psi)S,$$

$$I' = \frac{\beta_1 SI}{N} - \mu I - \frac{\alpha_1 I^2}{A+I+J},$$

$$J' = \frac{\beta_2 SJ}{N} - \mu J - \frac{\alpha_2 J^2}{B+I+J}, \qquad (9.38)$$

$$V' = \psi S - \mu V.$$

(a) Compute the disease-free equilibrium and the reproduction numbers of the two strains.

(b) Show that there is a unique dominance equilibrium corresponding to each strain. Investigate the stability of the dominance equilibria and define the two invasion numbers.

(c) How does the vaccination rate ψ affect the invasion numbers?

9.9. Saturating Incidence

Consider a model of two strains with saturated incidence and perfect vaccination:

$$S' = \Lambda - \frac{\beta_1 SI}{1+a_1 N} - \frac{\beta_2 SJ}{1+a_2 N} - (\mu + \psi)S,$$

$$I' = \frac{\beta_1 SI}{1+a_1 N} - (\mu + \alpha_1)I,$$

$$J' = \frac{\beta_2 SJ}{1+a_2 N} - (\mu + \alpha_2)J, \qquad (9.39)$$

$$V' = \psi S - \mu V.$$

(a) Compute the disease-free equilibrium and the reproduction numbers of the two strains.

(b) Compute the two dominance equilibria. Investigate their stability and define the two invasion numbers.
(c) How does vaccination rate ψ affect the invasion numbers?

9.10. Cross-Immunity

Consider a model of two strains with cross-immunity and vaccination:

$$
\begin{aligned}
S' &= \Lambda - \beta_1 \frac{S(I_1 + J_1)}{A} - \beta_2 \frac{S(I_2 + J_2)}{A} - (\mu + \psi)S, \\
I_1' &= \beta_1 \frac{S(I_1 + J_1)}{A} - (\mu + \alpha_1 + \delta_1)I_1, \\
Q_1' &= \delta_1 I_1 - (\mu + \gamma_1)Q_1, \\
R_1' &= \alpha_1 I_1 + \gamma_1 Q_1 - \sigma_2 \beta_2 \frac{R_1(I_2 + J_2)}{A} - \mu R_1, \\
J_1' &= \sigma_1 \beta_1 \frac{R_2(I_1 + J_1)}{A} - (\mu + \alpha_1)J_1, \\
I_2' &= \beta_2 \frac{S(I_2 + J_2)}{A} - (\mu + \alpha_2 + \delta_2)I_2, \\
Q_2' &= \delta_2 I_2 - (\mu + \gamma_2)Q_2, \\
R_2' &= \alpha_2 I_2 + \gamma_2 Q_2 - \delta_1 \beta_1 \frac{(I_1 + J)I_2}{A} - \mu R_2, \\
J_2' &= \sigma_2 \beta_2 \frac{R_1(I_2 + J_2)}{A} - (\mu + \alpha_2)J_2, \\
W' &= \alpha_1 J_1 + \alpha_2 J_2 - \mu W, \\
V' &= \psi S - \mu S.
\end{aligned}
\tag{9.40}
$$

(a) Compute the disease-free equilibrium and the reproduction numbers of the two strains.
(b) Compute the two dominance equilibria.
(c) Use the next-generation approach to compute the two invasion numbers.
(d) Are the invasion numbers increasing, decreasing, or nonmonotone functions of ψ? What are the epidemiological consequences of this observation?

9.11. Optimal Control

Create an optimal control analogue of model (9.8).

(a) Prove that the optimal control problem has a solution.
(b) Derive the equations for application of Pontryagin's minimum principle.
(c) Write a Matlab code to find the optimal control solution and the optimal control.

9.12. Optimal Control

Create an optimal control analogue of model (9.11).

(a) Prove that the optimal control problem has a solution.
(b) Derive the equations for application of Pontryagin's minimum principle.
(c) Write a Matlab code to find the optimal control solution and the optimal control.