

**Spread of Infectious Diseases:  
Impact on Demography,  
and the Eradication Effort in Models  
with Backward Bifurcation**

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**In the Name of Allah,  
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## Zusammenfassung

Trotz des großen Fortschritts in der Medizin, der zu der Entdeckung von sicheren und wirkungsvollen Medikamenten und Impfstoffen führte, sind ansteckende Krankheiten noch eine Hauptursache für Tod, Behinderung, soziale und ökonomische Belastung für Millionen von Menschen auf der Welt. Jährlich werden ca. 20% aller Todesfälle weltweit durch ansteckende Krankheiten verursacht. Folglich müssen die Auswirkungen dieser Infektionen auf die Demographie sowie der (minimale) Aufwand, der notwendig sind, um die jeweilige Infektionen auszurotten, untersucht werden. Da es nicht möglich ist, randomisierte Studien mit ganzen Bevölkerungen durchzuführen, benötigen wir mathematische Modelle, um unterschiedliche Kontrollstrategien zu evaluieren.

In dieser Arbeit konzentrieren wir uns auf Prävalenzmodelle (d.h. Modelle, in denen wir die Gesamtbevölkerung in Klassen unterteilen, wie etwa suzeptibel, latent, ansteckend und geheilt). Wir untersuchen zwei Hauptprobleme. Das erste ist Auswirkungen einer potenziell tödlichen Infektion auf die Demographie. Das zweite Problem bezieht sich auf Situationen, die durch Modelle mit rückwärtsgerichteter Bifurkation beschrieben werden. Hier interessierte die Reduktion der Kontaktrate, die mindestens notwendig ist, um die Infektion auszurotten. In den ersten zwei Kapiteln verallgemeinern wir das klassische epidemiologische SIR-Modell von Daniel Bernoulli für eine potentiell tödliche Infektion im Falle einer wachsenden Bevölkerung mit Altersstruktur. Die Gesamtbevölkerung wird in drei Klassen unterteilt, nämlich suzeptibel, ansteckend und immun. Anstatt der Standardannahme der differentiellen Sterblichkeit zu folgen, beschreiben wir die epidemiologischen und demographischen Prozesse hinsichtlich der Letalität (dem Anteil von angesteckten Individuen, die aufgrund der Infektion sterben). Der Fall altersunabhängiger Modellparameter wird in Kapitel 1 betrachtet, während die Analyse für den allgemeinen Fall in Kapitel 2 durchgeführt wird.

Ein zentrales Konzept in der mathematischen Epidemiologie ist die Basisreproduktionszahl, die durchschnittliche Zahl von Sekundärfällen, die durch einen infizierten Fall während der ansteckenden Periode in einer völlig suszeptiblen Bevölkerung erzeugt wird. Normalerweise, wenn  $R_0 > 1$ , dann persistiert die Infektion in einem endemischen Gleichgewicht. Wenn  $R_0 \leq 1$ , dann verschwindet die Infektion. Bei vielen klassischen Modellen liegt dieser Normalfall vor. In Modellen mit unterschiedlichen Bevölkerungsgruppen (geimpft/ nicht geimpft) tritt oft eine rückwärtsgerichtete Bifurkation auf. Dann persistiert die Infektion auch bei Werten  $R_0 < 1$  bis hin zu einem minimalen positiven Wert für die Kontaktrate. Folglich ist die Größe  $R_0$  als ein Kriterium für die Ausrottung nicht mehr sinnvoll und wir benötigen ein anderes Kriterium für die Ausrottung einer Infektion. In den Kapiteln 3, 4 und 5 untersuchen wir, nach unserer Kenntnis erstmalig, eine Methode zur Bestimmung der Extinktionsbedingungen für Modelle mit rückwärtsgerichteter Bifurkation.

In der vorliegenden Dissertation kommen wir zu den folgenden Schlussfolgerungen:

In dem Modell mit Letalität wird die Basisreproduktionszahl nicht durch die Letalität der Infektion beeinflusst, während in den Modellen mit differentieller Sterblichkeit sie umso kleiner wird, je mehr die differentielle Sterblichkeit durch die Infektion zunimmt. Die Rate des Bevölkerungswachstums sinkt monoton mit der Zunahme der Letalität, während sie sich im

Fälle des Modelles mit differentieller Sterblichkeit wieder erhöhen kann, nachdem sie ein Minimum erreicht hat. Die einfache Formel, wonach die Basisreproduktionszahl  $R_0$  dem Kehrwert der endemischen Prävalenz von Suszeptiblen  $\bar{x}$  entspricht, ist im Allgemeinen nicht mehr zutreffend. Im Grenzfall einer hohen Kontaktrate und einer kurzen Infektionsdauer existiert immer eine Letalität, bei der die betreffende Population stationär ist. Wenn jedoch die ansteckende Periode eine positive Dauer hat, existiert eine kritische Letalität, die notwendig ist, um das Populationswachstum zu stoppen, nur dann wenn  $R_0 \geq 1 + \frac{b}{\gamma} R_0(\mu)$ , wobei  $b$  die Geburtenrate,  $\gamma$  die Heilungsrate und  $R_0(\mu)$  die Basisreproduktionszahl im Falle einer stationären Bevölkerung ist. Das vorhandene Modell erlaubt es, die demographischen Auswirkungen einer potentiell tödlichen Infektion in Bezug auf die Verringerung der Lebenserwartung und der verringerten Wachstumsrate zu bestimmen. Die Analyse zeigt, dass die historischen Pocken-Epidemien das Bevölkerungswachstum kaum reduziert haben. Das Modell ist auf jede potentiell tödliche Infektion (z.B. Masern) in wachsenden Populationen anwendbar, bei welchen die Altersverteilung ungefähr gleich der stationären Verteilung ist.

In Modellen mit rückwärtsgerichteter Bifurkation ist die bisherige Basisreproduktionszahl nicht mehr sinnvoll. Das Verhältnis zwischen der tatsächlichen Kontaktrate und der kritischen Kontaktrate, bei der positive stationäre Zustände auftreten, kann als Reproduktionszahl interpretiert werden. In Modellen, in denen die Immunität wieder verloren geht, besteht die Möglichkeit, dass mehrfache stationäre Zustände auftreten. In dem verallgemeinerten SIS-Modell mit Impfung finden wir: je früher wir einen teilweise schützenden Impfstoff geben, desto geringer wird der Aufwand, die Infektion auszurotten.



## Preface

Despite the great progress in medicine which lead to the discovery of safe and effective drugs and vaccines, infectious diseases are still a major cause of death, disability and social and economic burden for millions of people around the world. Every year, about 20% of all deaths worldwide are caused by infectious diseases. As examples we mention malaria, HIV/AIDS, measles, tuberculosis, and influenza. Therefore, we need to know about the impact of these infections on demography and about the minimum efforts required to eliminate them. The World Health Organization pays much attention to control such infections. However, to control an infection we need to know the factors that affect the dynamics of the infection and how much effort is necessary to achieve a given reduction in incidence. Since it is not possible to perform randomized trials with whole populations, we need mathematical models to explore different control strategies.

Modeling infectious diseases has a long history in mathematical biology. However, recently it has had an increasing influence on the theory and practice of disease management and control [49]. Readers who are interested in the history of the mathematical theory of infectious diseases are referred to the book by Bailey [6].

The models differ from one infection to another. For instance, if we are speaking about macroparasitic infections we have to consider density models in which we take into account the number of parasites existing within the host. However, if we speak about microparasitic infections we consider prevalence models. For the latter, the total population is subdivided into categories (according to their epidemiological states) like susceptible, latent, infectious, recovered, etc. In this work we are interested in modeling viral and bacterial infections. Therefore, we consider prevalence models.

In this thesis we address two main problems. We study the impact of an immunizing potentially lethal infection on the demography and the effort required to get rid of the infection. In chapter 1 we generalize Daniel Bernoulli's epidemiological model for a potentially fatal infection to a growing population. It is an SIR epidemic model in which we consider the case fatality of the infection. We consider the model from two points of view: the differential mortality approach and the case fatality approach. To the knowledge of the author, the extensive studies of mathematical epidemiology focus on the differential mortality approach. By case fatality we mean the proportion of infected individuals who die due to the infection. We consider the case where model parameters are age-independent. However, in chapter 2 we consider the general case when model parameters are age-dependent and we apply our mathematical analysis to real data collected from The Hague and representing the case of smallpox spread in the eighteenth century. We come to the conclusion that smallpox was nowhere close to eliminate or even to stop the growth of the host population. Chapters 3, 4, and 5 are devoted to estimating the effort required to eradicate the infections in models with multiple stationary states. We introduce three different models and we found out for the first time an estimate of the minimum effort required to eradicate the infections represented by such models. The method we introduce to estimate this minimum effort is relevant to the whole class of models with backward bifurcation. The important thing is that if the immunity wanes, there is a possibility for multiple stationary states to occur.

The thesis is written in a way such that the reader who likes to start reading at the beginning of any chapter does not need to come back to the preceding one(s). Therefore, there will be some repetition at the beginning of some chapters. Every chapter has an introduction and a discussion. The thesis is concluded by a summary and the references.

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# 1 Effects of case fatality on demography

The classical epidemiological SIR model of Daniel Bernoulli for a potentially fatal infection is generalized for a growing population. The important feature is case fatality as opposed to differential mortality. The exponent of growth for the endemic state is determined and discussed in terms of case fatality, as well as the stable distribution with respect to age and susceptibility status. The question is discussed whether a growing population can be driven to a stationary state or even to extinction. Explicit expressions for survival functions and the distribution of infection states within an age cohort are given, and formulae for the life expectancy within an infected population. The formulae are discussed in terms of the model parameters as well as in terms of basic reproduction numbers. Particular attention is paid to the limiting case of high contact rate and quick recovery.

## 1.1 Introduction

We consider models for the spread of an infectious disease in a homogeneous population with age structure, here in the case of constant (with respect to age) parameters. We assume a homogeneous infection law (as opposed to mass action kinetics) and hence our models are homogeneous dynamical systems. Rather than following the by now standard approach of differential mortality ([9], [10], [34], [57] and [60]), we describe the epidemic and demographic phenomena in terms of case fatality. The parameter of case fatality gives the proportion of fatal (lethal) cases upon exit from the infected compartment.

Differential mortality and case fatality models are mathematically equivalent in the sense that there is a one-to-one correspondence between the two types of models. But the parameterization and the biological interpretation are different and hence the two types of models describe different types of diseases.

In the differential mortality view the effective recovery rate increases with increasing differential mortality. If the mortality of infected individuals increases then the basic reproduction number decreases since infected individuals are removed at a higher rate. In the case fatality view the exit rate from the infected compartment is constant, the basic reproduction number depends only on the exit rate and not on case fatality. The *a posteriori* differential mortality is the product of the exit rate and case fatality.

Case fatality models seem particularly suited for diseases like smallpox (as in Bernoulli's work) where infectivity is restricted to a few days and death will usually occur after the highly infectious period. Differential mortality models are suited for diseases with an infectious period lasting for many years like AIDS. A reduction of differential mortality by modern antiviral therapies may be associated with an increase of the reproduction number (Anderson et al.[3]).

In particular we are interested in the question whether a high case fatality or differential mortality can drive an exponentially growing population to a stationary situation. This problem is somewhat delicate since in the case of differential mortality very low and very high differential mortalities may not lead to a considerable decrease of the rate of growth. On the contrary, the rate of growth decreases monotonically with increasing case fatality.

Most research in modeling infectious diseases has been applied to stationary populations or

to the fictitious situation where the number of births is constant in spite of differential mortality (e.g. [1], [2], [4], [6], [48], [50], [59], [76]). May and Anderson [64] have studied an SIR epidemic model in a homogeneously mixing growing population in case of a non-lethal infection where the force of infection depends on age but not on time. Another study of epidemics in growing populations has been performed by Thieme [73]. He considered a potentially fatal infectious disease in a host population that would increase exponentially in the absence of the disease. Other examples of studies on populations with varying size are in Busenberg and van den Driessche [12], Diekmann and Kretzschmar [21], Martcheva and Castillo-Chavez [63], McLean [65], McLean and Anderson ([66], [67]), and Derrick and van den Driessche [17].

Daniel Bernoulli (1700-1782) was the first to apply mathematics in epidemiology. In the year 1760 he evaluated the potential effect of successful variolation against smallpox on life expectancy. For more details about his life and the origin of this work and its impact we refer to the paper by Dietz and Heesterbeek [22]. Bernoulli dealt with a static situation where the force of infection is constant throughout time and age. Dietz and Heesterbeek [22] generalized his approach by allowing both the force of infection and the case fatality (which is the proportion of infected individuals who die as a result of the infection) to depend on age. They considered the case of a stationary population taking into account an immunizing potentially lethal infection with very short infectious period and quick recovery. Here we extend their work to the case of a growing population with age structure (but constant parameters) and a potentially lethal immunizing infection with positive length of the infectious period. The case of age-dependent parameters is deferred to the next chapter.

The chapter is organized as follows. We first derive the general age-dependent case fatality model and then specialize to the case of constant coefficients (section 1.2). In section 1.3 we derive the corresponding system for proportions. In section 1.4 we present the differential mortality model, in section 1.5 we define reproduction numbers, and in section 1.6 we exhibit the parameter transformation which connects both models. In section 1.7 we investigate the demographic impact of differential mortality. In section 1.8 we discuss qualitative and quantitative features of the exponential solutions of the case fatality model, and section 1.9 we investigate the demographic impact of case fatality. We return to the age structure model in section 1.10 and compute age distributions, infected cohorts and life expectancy in 1.11.

## 1.2 The case fatality model

Consider a population structured by chronological age  $a$  which is subdivided into three classes: susceptible  $X$ , infected  $Y$ , and recovered  $Z$ . Let  $N = X + Y + Z$  denote the total population. The time variable is denoted by  $t$ . The model for disease transmission is based on the following assumptions:

- (1) The natural death rate (independent of the disease) is  $\mu(a)$  and the birth rate is  $b(a)$ .
- (2) The force of infection is  $\lambda(a, t)$ .

- (3) The susceptibility is  $s(a)$ .
- (4) The contact rate between susceptible and infected is  $\kappa$ .
- (5) The exit rate from the infected state is  $\gamma$ .
- (6) The case fatality is  $c(a)$ : Upon exit a fraction  $c(a)$  will die due to the disease and the remainder  $(1 - c(a))$  will become immune.

With these assumptions we have the following age-structured epidemic model:

$$\begin{aligned}
\frac{\partial X(a, t)}{\partial t} + \frac{\partial X(a, t)}{\partial a} &= -(\mu(a) + \lambda(a, t))X(a, t), \\
\frac{\partial Y(a, t)}{\partial t} + \frac{\partial Y(a, t)}{\partial a} &= \lambda(a, t)X(a, t) - (\gamma + \mu(a))Y(a, t), \\
\frac{\partial Z(a, t)}{\partial t} + \frac{\partial Z(a, t)}{\partial a} &= (1 - c(a))\gamma Y(a, t) - \mu(a)Z(a, t),
\end{aligned} \tag{1.1}$$

where the force of infection is

$$\lambda(a, t) = \frac{\kappa s(a) \int_0^\infty Y(a, t) da}{N(t)}, \tag{1.2}$$

and the total population size is

$$N(t) = \int_0^\infty (X(a, t) + Y(a, t) + Z(a, t)) da.$$

The boundary condition (birth law) is

$$\begin{aligned}
X(0, t) &= \int_0^\infty b(a)(X(a, t) + Y(a, t) + Z(a, t)) da, \\
Y(0, t) &= 0, \quad Z(0, t) = 0.
\end{aligned}$$

If all rates are constant then we can integrate over age, use the boundary conditions and obtain a system of ordinary differential equations for the variables  $\bar{X}(t) = \int_0^\infty X(a, t) da$ ,  $\bar{Y}(t) = \int_0^\infty Y(a, t) da$ ,  $\bar{Z}(t) = \int_0^\infty Z(a, t) da$ . We can also introduce the transmission rate  $\beta = \kappa s$ . We denote these variables by  $x, y, z$ . Then we obtain the system

$$\begin{aligned}
\dot{x} &= bN - \mu x - \frac{\beta}{N}xy \\
\dot{y} &= \frac{\beta}{N}xy - \mu y - \gamma y \\
\dot{z} &= (1 - c)\gamma y - \mu z,
\end{aligned} \tag{1.3}$$

where  $N = x + y + z$ . This is a homogeneous dynamical system. The typical “stationary” solution is not a stationary point but an exponential or “persistent” solution, i.e., a solution of

the form  $(x, y, z)^T e^{\rho t}$  where  $\rho$  is the rate of growth (or decay) and  $(x, y, z)^T$  is the stationary distribution of types. The rates of growth or “nonlinear eigenvalues”  $\rho$  can be found from a non-linear eigenvalue problem. We underline that these rates of growth do not say anything about the stability of the exponential solution considered. Stability is determined by associated linear eigenvalue problems, one for each persistent solution.

We shall see that (1.3) has a unique stable exponential solution with some rate of growth. We are interested in the question how this rate depends on the parameters of the system, in particular on case fatality.

The theory of finite-dimensional homogeneous systems has been worked out in detail in Haderer [39], its applications to SIR and SIRS models have been studied in Busenberg and Haderer [10]. Indeed, there is a close mathematical connection of our system (1.3) to the system studied in Busenberg and Haderer [10] which we can exploit while the interpretation of the parameters is quite different.

### 1.3 Scaling

Homogeneous systems can be reduced to standard systems in various ways, e.g. by projection to the triangle  $\{(x, y, z) \geq 0, x + y + z = 1\}$ , or to the triangle  $\mathcal{S} = \{(u, v) \geq 0, u + v \leq 1\}$  by putting  $u = x/N, v = y/N$  which leads to

$$\begin{aligned}\dot{u} &= b(1 - u) - (\beta - c\gamma)uv \\ \dot{v} &= \beta uv - (b + \gamma)v + c\gamma v^2.\end{aligned}\tag{1.4}$$

In this setting an exponential solution of system (1.3) corresponds to a stationary point of the system (1.4). The system (1.4) is particularly suited for the stability discussion, see Busenberg and Haderer [10], but not for the present goal of discussing rates of growth.

The triangle  $\mathcal{S}$  is positively invariant. The edge  $v = 0$  is an invariant set. Along  $u = 0$  we have  $\dot{u} = b$ , and for  $w = 1 - u - v$  we find

$$\dot{w} = -(b - \gamma v)w + \gamma v(1 - c)(1 - w).$$

Hence along the edge  $w = 0$  the vector field is pointing inward, except in the case  $c = 1$  when  $w = 0$  is an invariant set.

### 1.4 Epidemics and demography

The following system has been proposed and studied in Busenberg and Haderer [10]. Using the notation of that paper (to make comparison easy):

$$\begin{aligned}\dot{x} &= b_1x + b_2y + b_3z - \mu_1x - \beta xy/N + \gamma z \\ \dot{y} &= b_4y - \mu_2y + \beta xy/N - \alpha y \\ \dot{z} &= \alpha y - \mu_3z - \gamma z \\ N &= x + y + z.\end{aligned}\tag{1.5}$$



The parameters  $b_i$  are birth rates, in particular  $b_4$  is the rate of vertical transmission, the parameters  $\mu_i$  are mortalities,  $\alpha$  is the recovery rate, and  $\gamma$  is the rate of loss of immunity. For the birth and death rates it has been assumed that the inequalities

$$b_1 \geq b_3 \geq b_2 + b_4, \quad \mu_1 \leq \mu_3 \leq \mu_2$$

hold. These inequalities agree with the biological interpretation and, as it happens, also fit nicely into the analytical results. Since  $\mu_2 \geq \mu_1$ , the difference  $\delta = \mu_2 - \mu_1$  can be interpreted as a differential mortality.

For this model it has been shown in Busenberg and Haderer [10] that there are exactly two situations characterized by the quantity

$$\sigma = (\beta + b_4) - (b_1 - \mu_1) - (\mu_2 + \alpha). \quad (1.6)$$

The meaning of  $\sigma$  is that of a spectral bound. It is the difference between the infection rates and the washout rate and the exit rate from the infected compartment. It is an additive version of the basic reproduction number

$$R_0^{\text{homog}} = \frac{\beta + b_4}{(b_1 - \mu_1) + (\mu_2 + \alpha)} = \frac{\beta + b_4}{b_1 + \delta + \alpha} \quad (1.7)$$

for an exponentially growing (or decaying) population. The term  $b_1 - \mu_1$  in the denominator takes care of the washout effect caused by production of susceptible juveniles. The second expression on the right of (1.7) shows that the denominator is positive even in the case of a decaying population,  $b_1 - \mu_1 < 0$ .

i) If  $\sigma \leq 0$  then there is a unique (up to positive factors) “uninfected” exponential solution with rate  $\rho_0 = b_1 - \mu_1$  with an eigenvector  $(1, 0, 0)^T$  of susceptible individuals only. This solution is globally exponentially stable.

ii) If  $\sigma > 0$  then the uninfected solution is unstable. There is a unique (up to positive factors) “infected” exponential solution with rate  $\rho_1 \leq \rho_0$ . The eigenvector has all components positive. This solution is exponentially globally stable in the set of positive solutions.

For further reference we provide the characteristic polynomial of the non-linear eigenvalue problem for  $\rho_1$ . This polynomial has degree two (and not three, as one might expect),

$$\begin{aligned} p(\rho) = & (\rho + \mu_2 + \alpha - b_4)[\alpha(\bar{b}_1 - \bar{b}_3) + (\rho + \mu_3 + \gamma)(\bar{b}_1 - \bar{b}_2)] \\ & - \beta[\alpha(\rho - \bar{b}_3) + (\rho + \mu_3 + \gamma)(\rho - \bar{b}_2)] \end{aligned} \quad (1.8)$$

where

$$\bar{b}_1 = b_1 - \mu_1, \quad \bar{b}_2 = b_2 + b_4 - \mu_2, \quad \bar{b}_3 = b_3 - \mu_3.$$

In order to compare case fatality to differential mortality we consider a simplified version of (1.5),

$$\begin{aligned} b_1 = b_2 = b_3 = b, \quad b_4 = 0, \\ \mu_1 = \mu_3 = \mu, \quad \mu_2 = \mu + \delta, \end{aligned}$$

$$\gamma = 0.$$

Here  $\delta \geq 0$  is the differential mortality. Hence the model reads

$$\begin{aligned}\dot{x} &= bN - \mu x - \beta xy/N \\ \dot{y} &= \beta xy/N - (\alpha + \mu + \delta)y \\ \dot{z} &= \alpha y - \mu z.\end{aligned}\tag{1.9}$$

## 1.5 Reproduction numbers

The spectral bound  $\sigma$  is the decisive quantity for the existence of an infected exponential solution. One may wish to rephrase the conditions in terms of reproduction numbers instead. The reproduction number for (1.9) is, see (1.7),

$$R_0^{\text{homog}} = \frac{\beta}{(b - \mu) + \alpha + \mu + \delta} = \frac{\beta}{b + \alpha + \delta},\tag{1.10}$$

and for the case fatality model this expression becomes

$$R_0^{\text{homog}} = \frac{\beta}{\rho_0 + \mu + \gamma} = \frac{\beta}{(b - \mu) + \mu + \gamma} = \frac{\beta}{b + \gamma}.\tag{1.11}$$

In the static case  $b = \mu$  this expression becomes

$$R_0(\mu) = \frac{\beta}{\mu + \gamma}\tag{1.12}$$

which we henceforth call the epidemic reproduction number in a static population. We define the demographic reproduction number as

$$R_D = \frac{b}{\mu}.\tag{1.13}$$

In the case fatality model (1.3) one can let  $\beta$  and  $\gamma$  tend to infinity such that  $\beta/\gamma = R_0^\infty$  is fixed without affecting the case fatality. In the differential mortality model, letting  $\beta$  and  $\alpha$  tend to infinity and keeping the ratio constant at  $R_0^\infty$  will imply zero differential mortality.

## 1.6 Equivalence in parameter space

We observe that the systems (1.9) and (1.3) have essentially the same structure except for the parameters which have different ranges and different biological interpretations. However, there is a one-to-one correspondence

$$\begin{aligned}(c, \gamma) &\leftrightarrow (\delta, \alpha) \\ [0, 1] \times (0, \infty) &\leftrightarrow ([0, \infty) \times [0, \infty)) \setminus \{(0, 0)\}\end{aligned}\tag{1.14}$$

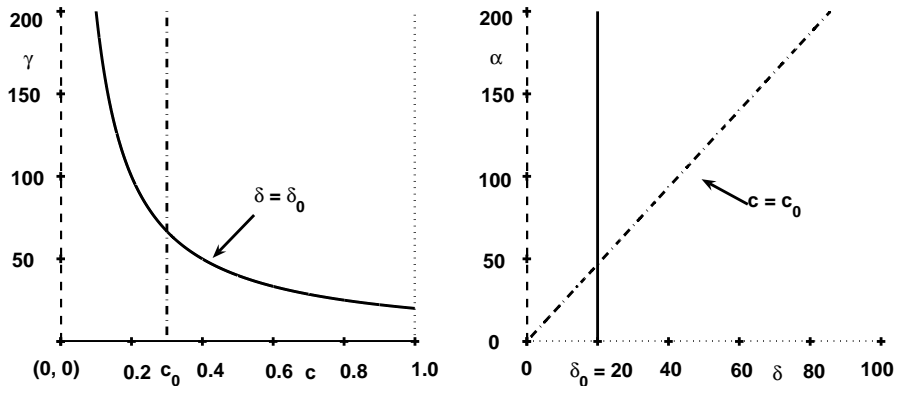


Figure 1.1: Transformation from the  $(c, \gamma)$ -plane to the  $(\delta, \alpha)$ -plane and vice versa. The coordinate axes  $\delta = 0$  and  $\alpha = 0$  in the  $(\delta, \alpha)$ -plane correspond to the lines  $c = 0$  and  $c = 1$  in the  $(c, \gamma)$ -plane, respectively. The vertical line  $\delta = \delta_0$  in the  $(\delta, \alpha)$ -plane corresponds to the hyperbola  $\gamma = \frac{\delta_0}{c}$ , denoted by  $\delta = \delta_0$  in the  $(c, \gamma)$ -plane. Finally, the line  $c = c_0$  in the  $(c, \gamma)$ -plane corresponds to a straight line through the origin  $\alpha = \delta(\frac{1}{c_0} - 1)$ , denoted by  $c = c_0$  in the  $(\delta, \alpha)$ -plane.

between the parameters which is explicitly given by the equations

$$\delta = c\gamma, \quad \alpha = (1 - c)\gamma, \quad (1.15)$$

$$\gamma = \alpha + \delta, \quad c = \delta/(\alpha + \delta). \quad (1.16)$$

In geometric terms, the mapping from  $(c, \gamma)$  to  $(\delta, \alpha)$  can be understood as follows (see Fig. 1.1). The feasible set for  $(c, \gamma)$  is the strip  $[0, 1] \times (0, \infty)$ . This strip is mapped onto the first orthant  $[0, \infty) \times [0, \infty)$  without the origin whereby the boundary  $c = 0$  becomes the axis  $\delta = 0$  and  $c = 1$  becomes  $\alpha = 0$ . The boundary  $0 \leq c \leq 1, \gamma = 0$  is contracted to the single point  $(0, 0)$ . Hence we have the following observation.

**Proposition 1.1.** *There is a one-to-one correspondence between case fatality and differential mortality models.*

In the case fatality setting the constant  $\gamma$  is the recovery rate from the infected compartment and  $c$  is the case fatality while  $1 - c$  is the proportion of recovering individuals who survive. Thus, we have formally written the differential mortality  $\delta = c\gamma$  as a product of exit rate and case fatality, and we have written the recovery rate  $\alpha = (1 - c)\gamma$  as a product of exit rate and the complement  $1 - c$  of case fatality. Although this substitution seems a mere way of different bookkeeping, it has far-reaching consequences in epidemiological terms.

Of course the interpretation of differential mortality and case fatality are different. With respect to differential mortality one takes the view that during the infected phase some individuals die because of the disease which would not have died due to natural causes. In case fatality one takes the view that individuals exit from the infected compartment at a rate  $\gamma$  (which has nothing to do with mortality) and at the moment of exiting it is decided whether the individual dies or enters the recovered compartment. Hence  $\delta$  is a rate and  $c$  is a probability.

The equivalence between the two models can be exploited insofar as the results of Busenberg and Haderer [10] carry over to the case fatality model. But the exceptional situation  $c = 1$ , which would correspond to  $\alpha = 0$ , must be treated separately.

## 1.7 Demographic effect of differential mortality

Now we consider the effect of differential mortality  $\delta$  on the rate  $\rho_1$  of the stable infected solution which we assume to exist for  $\delta = 0$ . The polynomial for  $\rho_1$  is, see (1.8),

$$p(\rho) = (\rho + \mu + \delta + \alpha)(\rho + \mu)\delta - \beta[\alpha(\rho + \mu - b) + (\rho + \mu)(\rho + \mu - b + \delta)], \quad (1.17)$$

and the parameter  $\sigma$  is now

$$\sigma(\delta) = \beta - (b - \mu) - (\mu + \delta + \alpha) = \beta - (b + \delta + \alpha).$$

By assumption  $\sigma(0) > 0$ . Of course we expect that large mortalities  $\delta$  drive the epidemic to extinction.

**Proposition 1.2.** *Suppose  $b - \mu > 0$  and  $\beta > b + \alpha > \mu + \alpha$ . For  $\delta = 0$  there is an unstable uninfected solution with positive rate  $\rho_0 = b - \mu > 0$  and a stable infected solution with rate  $\rho_1 = \rho_0$ . If  $\delta$  is slightly increased then  $\rho_1$  decreases (simply because more infected individuals die). However, if  $\delta$  is further increased up to the value  $\delta_{max} = \beta - b - \alpha > 0$  then the infected solution ceases to exist, i.e., it coalesces with the uninfected solution and again  $\rho_1 = \rho_0$ . Thus, if  $\delta$  increases from 0 to  $\delta_{max}$  then  $\rho_1$  decreases from  $\rho_0$  to lower values and then increases to  $\rho_0$  (Figure 1.2).*

Proof: For each value  $\rho$  the equation  $p(\rho) = 0$ , see (1.17), as an equation for  $\delta$ , is a quadratic equation, hence there are at most two roots  $\delta$ . Hence  $\rho_1$  as a function of  $\delta$  has a unique minimum.  $\square$

**Proposition 1.3.** *In the endemic situation the force of infection  $\lambda$  can be expressed in terms of  $\rho_1$  and the given parameters*

$$\lambda = \frac{\beta y}{N} = \frac{b\beta - (\mu + \rho_1)(\rho_1 + \mu + \gamma)}{\rho_1 + \mu + \gamma} = \frac{(\rho_1 + \mu)(\beta - (\rho_1 + \mu + \gamma))}{\rho_1 + \mu + \alpha}. \quad (1.18)$$

Proof: In (1.9) put  $\dot{x} = \rho x$  etc. and solve the linear system. Since the determinant vanishes by assumption, there are many equivalent expressions.  $\square$

We check whether  $\rho_1(\delta) = 0$  can be achieved for some  $\delta$ .

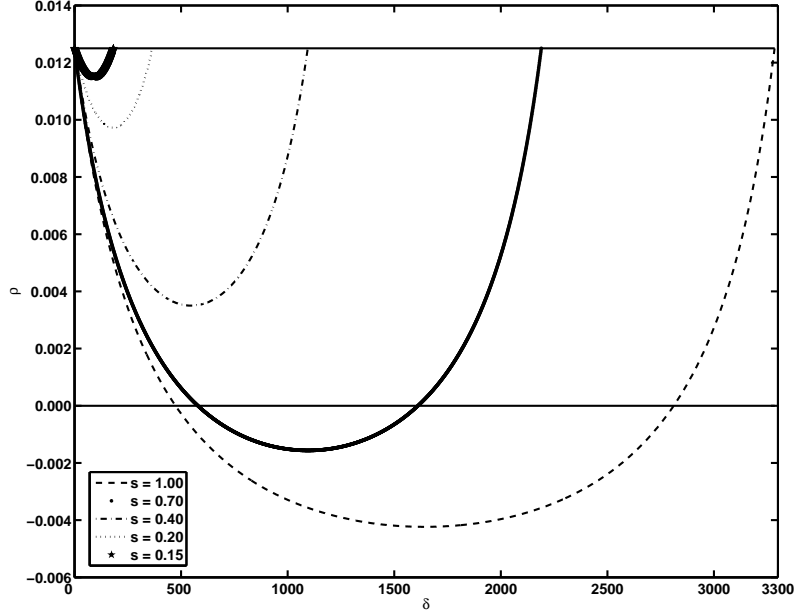


Figure 1.2: The growth rate  $\rho_1$  as a function of the differential mortality  $\delta$  with parameter values:  $b = 0.025$  per year,  $\mu = 0.0125$  per year,  $\alpha = 365$  per year, and  $\kappa = 3650$  per year, for several values of  $s$  ( $s = 0.15$ ,  $s = 0.20$ ,  $s = 0.40$ ,  $s = 0.70$ , and  $s = 1.00$ ),  $\beta = \kappa s$ . For  $\delta = 0$  per year, we have  $\rho_1 = \rho_0 = b - \mu$ . With increasing  $\delta$ , the rate  $\rho_1$  decreases until reaching a minimum and then it increases again till reaching  $\rho_0$  again when  $\delta = \delta_{max} = \beta - \alpha - b$ .

**Proposition 1.4.** *Very small and very large values of differential mortality do not noticeably reduce the rate of population growth. Zero growth, i.e.,  $\rho_1 = 0$ , can be achieved by an appropriate choice of  $\delta$  if and only if*

$$R_0(0) = \frac{\beta}{\alpha + \mu} > R_D \left( 1 + \sqrt{1 - \frac{1}{R_D}} \right)^2 \simeq 4R_D - 2, \quad (1.19)$$

*i.e., when the reproduction number in the absence of differential mortality is considerably higher than the demographic reproduction number.*

Proof: We put  $p(0) = 0$  and find that  $\delta$  must satisfy

$$\delta^2 + (\mu + \alpha - \beta)\delta + \beta(\alpha + \mu)(b/\mu - 1) = 0. \quad (1.20)$$

The necessary and sufficient condition for positive roots is

$$(\beta - \alpha - \mu)^2 \geq 4\beta(\alpha + \mu)\left(\frac{b}{\mu} - 1\right)$$

which is equivalent with (1.19).

If (1.19) is satisfied then the minimal  $\rho_1$  is negative (or zero in the case of equality), there are two values of  $\delta$  (which coalesce in the case of equality), both in the interval  $(0, \delta_{\max})$ , such that  $\rho_1 = 0$ .  $\square$

The condition (1.19) can be easily interpreted in terms of  $R_0$ . It says that reducing  $\rho_1$  to 0 is possible if  $R_0(0)$  is sufficiently large for given  $R_D$ .

## 1.8 Exponential solutions in the case fatality model

As shown in section 1.6, every case fatality model is equivalent to a differential mortality model for an appropriate choice of the parameters. Since the relation between the two models is non-trivial, it pays to reconsider the conditions for exponential solutions, even more so, as the limiting case  $c = 1$  is not covered by the results of Busenberg and Haderler [10], and that limiting case plays an important role in the present context.

The proportions of a normalized exponential solution of (1.3) with rate  $\rho$  satisfy

$$\begin{aligned}\rho x &= b - \mu x - \beta xy \\ \rho y &= \beta xy - \mu y - \gamma y \\ \rho z &= (1 - c)\gamma y - \mu z \\ 1 &= x + y + z.\end{aligned}\tag{1.21}$$

**Proposition 1.5.** *Suppose  $R_0^{\text{homog}} > 1$  and  $0 < c < 1$ . Then the following equations between the proportions  $x, y, z$  and the rate  $\rho = \rho_1$  hold.*

$$x = \frac{1}{\beta}(\mu + \gamma + \rho)\tag{1.22}$$

$$y = \frac{1}{c\gamma}(b - \mu - \rho)\tag{1.23}$$

$$y = \frac{b - (\mu + \rho)x}{\beta x}\tag{1.24}$$

$$(\rho + \mu)z = (1 - c)\gamma y\tag{1.25}$$

Proof: Add the first three equations and solve for  $y$

$$\rho = b - \mu - c\gamma y.\tag{1.26}$$

Divide the second equation by  $y$  and get (1.22). In (1.26) solve for  $y$  and get (1.23). In the first equation solve for  $y$  and get (1.24). In the third equation solve for  $z$ .  $\square$

Assume  $0 < c < 1$ . Introduce the expressions (1.22), (1.23), (1.25) into the fourth equation  $x + y + z = 1$ , rearrange terms, and get a quadratic equation for the rate  $\rho$ ,

$$\begin{aligned}p(\rho) &= (\rho + \mu + \gamma)(\rho + \mu)c\gamma \\ &\quad - \beta[(1 - c)\gamma(\rho + \mu - b) + (\rho + \mu)(\rho + \mu - b + c\gamma)].\end{aligned}\tag{1.27}$$

The solutions are always real and are given explicitly as

$$\rho_{\pm} = -\mu + \frac{1}{2} \left( \frac{\beta b}{\beta - c\gamma} - \gamma \right) \pm \frac{1}{2} \sqrt{\left( \frac{\beta b}{\beta - c\gamma} - \gamma \right)^2 + 4 \frac{\beta \gamma b}{\beta - c\gamma} (1 - c)}. \quad (1.28)$$

Notice that the expression  $\beta b/(\beta - c\gamma) - \gamma$  may be positive or negative. From (1.22), (1.23), (1.25) we see that any feasible exponential solution with  $z > 0$  must satisfy

$$-\mu < \rho \leq b - \mu. \quad (1.29)$$

An explicit check tells that it is always the larger solution  $\rho_+$  which satisfies these inequalities. Henceforth we call this solution  $\rho_1$ .

Now consider the limiting case  $c = 0$ . Then  $\rho_1 = \rho_+ = b - \mu$  is the rate of the infected solution, the proportions  $x, y, z$  can be obtained from (1.22), (1.24), (1.25) as

$$x = \frac{b + \gamma}{\beta} = \frac{1}{R_0}, \quad y = \frac{b}{b + \gamma} \left( 1 - \frac{1}{R_0} \right), \quad z = \frac{\gamma}{b} y.$$

### 1.8.1 The limiting case $c = 1$

The case  $c = 1$  is somewhat delicate. The formulas (1.22) through (1.25) are still valid, the equation (1.25) can be satisfied in two ways, with  $\rho = -\mu$  and also with  $z = 0$ , and both choices lead to feasible solutions. The formulas for the rates (1.28) simplify to

$$\begin{aligned} \rho_+ &= -\mu + \max\left(\frac{\beta b}{\beta - \gamma} - \gamma, 0\right) \\ \rho_- &= -\mu + \min\left(\frac{\beta b}{\beta - \gamma} - \gamma, 0\right). \end{aligned} \quad (1.30)$$

By simple algebra, applied to the system (1.21) with  $c = 1$ , we see that there are two infected exponential solutions (which need not be feasible, though)  $(x_i, y_i, z_i) \exp(\nu_i t)$ ,  $i = 1, 2$ , where

$$(x_1, y_1, z_1) = \left( \frac{b}{\beta - \gamma}, \frac{\beta - \gamma - b}{\beta - \gamma}, 0 \right), \quad \nu_1 = \frac{\beta b}{\beta - \gamma} - \gamma - \mu, \quad (1.31)$$

$$(x_2, y_2, z_2) = \left( \frac{\gamma}{\beta}, \frac{b}{\gamma}, \frac{\beta \gamma - \beta b - \gamma^2}{\beta \gamma} \right), \quad \nu_2 = -\mu. \quad (1.32)$$

The corresponding stationary points of the scaled system (1.4) with  $c = 1$  are  $(u_i, v_i) = (x_i, y_i)$ ,  $i = 1, 2$ . The Jacobian of (1.4), with  $c = 1$ , at an arbitrary point is

$$J = \begin{pmatrix} -b - (\beta - \gamma)v & -(\beta - \gamma)u \\ \beta v & \beta u - (b + \gamma) - 2\gamma v \end{pmatrix}.$$

Hence the Jacobian  $J_1$  at  $(u_1, v_1)$  is

$$J_1 = \begin{pmatrix} -(\beta - \gamma) & -b \\ \beta \frac{\beta - \gamma - b}{\beta - \gamma} & \beta \frac{b}{\beta - \gamma} - (b + \gamma) + 2\gamma \frac{\beta - \gamma - b}{\beta - \gamma} \end{pmatrix}.$$

The determinant is

$$\det J_1 = (\beta - \gamma - b) \left( \frac{\beta b}{\beta - \gamma} - \gamma \right) \quad (1.33)$$

We have  $\beta - \gamma - \mu > 0$  and

$$\frac{\beta b}{\beta - \gamma} - \gamma < 0 \iff b < \gamma \left( 1 - \frac{\gamma}{\beta} \right). \quad (1.34)$$

There are two scenarios.

**Scenario 1:** ( $b$  small)

$$b < \gamma \left( 1 - \frac{\gamma}{\beta} \right) < \beta \left( 1 - \frac{\gamma}{\beta} \right).$$

Then  $\beta b / (\beta - \gamma) - \gamma < 0$  and hence

$$\rho_+ = -\mu = \nu_2. \quad (1.35)$$

The point  $(u_2, v_2)$  is feasible, i.e., it is in the interior of the triangle  $\mathcal{S}$ . It is a local attractor, and it attracts all solutions with  $v(0) > 0$ ,  $u(0) + v(0) < 1$ . The corresponding exponential solution  $(x_2, y_2, z_2) \exp\{-\mu t\}$  is feasible and it attracts all solutions with  $y(0) > 0$ ,  $z(0) > 0$ .

The point  $(u_1, v_1)$  is sitting on the edge  $u + v = 1$ . It is a saddle point. Its stable manifold is the edge  $u + v = 1$ . The exponential solution to  $(u_1, v_1)$  has the rate  $\rho_- = \rho_1 < -\mu$ .

All populations which start with some immune individuals initially (no matter where these come from) approach the interior equilibrium. On the other hand, a population with no initial immune,  $z(0) = 0$ , arrives  $(u_1, v_1)$  and follows the exponential solution with rate  $\rho_-$ .

**Scenario 2:** ( $b$  large)

$$\gamma \left( 1 - \frac{\gamma}{\beta} \right) < b < \beta \left( 1 - \frac{\gamma}{\beta} \right).$$

Then  $\beta b / (\beta - \gamma) - \gamma < 0$  and hence

$$\rho_+ = \frac{\beta b}{\beta - \gamma} - \gamma - \mu = \nu_1 > -\mu. \quad (1.36)$$

Again the point  $(u_1, v_1)$  is sitting on the edge  $u + v = 1$  and it attracts the unstable manifold of  $(1, 0)$ . Furthermore it is a local attractor which attracts all trajectories in  $\mathcal{S}$  except the point  $(1, 0)$  itself. The point  $(u_2, v_2)$  is a saddle point which is not feasible. In terms of exponential solutions there is exactly one exponential solution with exponent  $-\mu$  and proportions  $(x_1, y_1, 0)$ .

If we let  $b$  run from small to large values (still less than  $\beta - \gamma$ ) then we move from scenario 1 to scenario 2. The point  $(u_2, v_2)$  moves through the edge  $u + v = 1$  at  $(u_1, v_1)$  and there is a transcritical bifurcation with exchange of stability.



### 1.8.2 The general case $c \leq 1$

**Proposition 1.6.** *In the case fatality model there is always the uninfected exponential solution with rate  $\rho_0 = b - \mu$ . If the basic reproduction number  $R_0^{\text{homog}} = \beta/(b + \gamma) > 1$  then there is an uninfected exponential solution with rate  $\rho_1 \in [-\mu, \rho_0]$  which is given by  $\rho_1 = \rho_+$  in (1.28) and in the limiting case  $c = 1$  also by (1.30). If  $c = 1$  and  $\rho_1 > -\mu$  then also  $\rho_-$  corresponds to a feasible uninfected solution.*

Finally we discuss the role of the second uninfected exponential solution which appears for  $c = 1$ . To understand the dynamic behaviour we return to the system (1.4) for  $R_0^{\text{homog}} > 1$  and  $c \in [0, 1]$ . There is always the uninfected stationary point  $u = 1, v = 0$ . If  $R_0^{\text{homog}} > 1$  then  $(1, 0)$  is unstable and there is the infected stationary state where  $u, v$  are given by (1.22). This point is stable. There is another stationary point corresponding to the rate  $\rho_-$  which for  $c < 1$  lies in the  $(u, v)$ -plane outside the triangle  $\mathcal{S}$ . This point is a saddle point with an unstable manifold entering the triangle through the edge  $u + v = 1$ . For  $c = 1$  and  $\rho_1 > -\mu$  this point moves onto the boundary of the triangle,  $(1 - v, v)$  with  $v = (\beta - b - \gamma)/(\beta - \gamma)$ . Hence in this case we have three stationary points, an attractor and two saddle points. The unstable manifold of the saddle point  $(1, 0)$  will leave  $(1, 0)$  in the direction of the other saddle point, and, after having approached that saddle point, it follows close to its unstable manifold towards the attractor. The important thing is that, while the second saddle point is not feasible for  $c < 1$ , the behaviour will be much the same if  $c$  is close to 1.

## 1.9 Demographic effect of case fatality

We ask whether for sufficiently large case fatality  $c$  the population can be driven to extinction, i.e., whether the rate  $\rho_1(c)$  of the infected solution can become negative.

We observe that  $\rho_1(c)$  is a decreasing function of  $c$ . The explicit expression (1.28) for  $\rho_1(c)$  may be defined for  $c > 1$  and give negative values for  $\rho_1(c)$ , but  $c$  is restricted to the interval  $[0, 1]$  and hence  $\rho_1(c) = 0$  may not be achieved. The exact conditions are given in the next proposition.

**Proposition 1.7.** *There are three cases:*

*i) If  $\beta b \leq (\beta - \gamma)\gamma$ , then  $\rho_1(1) = -\mu$ ,  $\rho_1(1) < -\mu$ , and  $\rho_1(c^*) = 0$  where*

$$c^* = \frac{1}{\gamma} \frac{\beta(b - \mu)(\mu + \gamma)}{\beta b - \mu(\mu + \gamma)} = \frac{R_0(0)(R_D - 1)}{R_D R_0(\mu) - 1} < 1. \quad (1.37)$$

*ii) If  $(\beta - \gamma)\gamma \leq \beta b < (\beta - \gamma)(\gamma + \mu)$ , then*

$$\rho_1(1) = \frac{\beta b}{\beta - \gamma} - \gamma - \mu > -\mu, \quad (1.38)$$

*$\rho_-(1) = -\mu$ , and  $\rho_1(c^*) = 0$  where  $c^*$  is given by (1.37).*

*iii) If  $(\beta - \gamma)(\gamma + \mu) < \beta b$ , then  $\rho_1(1)$  is given by (1.38),  $\rho_-(1) = -\mu$  and there is no  $c \in [0, 1]$  such that  $\rho_1(c) = 0$ .*

See figure 1.3 to understand more.

Proof: Use Proposition 1.6 and compute  $\rho_1(1)$ . □

The critical condition  $\beta b \leq (\beta - \gamma)(\gamma + \mu)$  can be written as

$$1 + \frac{b}{\gamma} R_0(\mu) \leq R_0. \quad (1.39)$$

Proposition 1.7 tells that there are rather different scenarios. These can be most easily explained in the case of high infectivity  $\beta$  and high case fatality  $c$ .

In scenario i) we have  $b < \gamma$ , the exit rate is larger than the renewal rate of the population. Then  $\rho_1(1) = -\mu$  and of course  $c^* < 1$ . This scenario would apply to human populations and fatal diseases. At the onset of the epidemic most individuals get infected, the population decays with the rate  $b - \mu - \gamma$ . Although the mean duration in the infectious state is small, disease-related mortality compensates any population growth. After this transition period there are essentially no births and the remaining susceptible decay with the natural mortality  $\mu$ . In this case unconditional asymptotic analysis is somewhat misleading. The asymptotic rate  $-\mu$  describes only the aftermath of the epidemic event. The phase plane analysis exhibiting a saddle-saddle connection shows that the main course of the epidemic event is characterized by the rate  $b - \mu - \gamma$ .

In scenario ii)  $\gamma < b < \gamma + \mu$ , we have  $\rho_1(1) = b - \mu - \gamma > -\mu$  and  $c^* < 1$ . If the birth rate is high, the population shows all the time the epidemic rate  $b - \mu - \gamma$  but this rate is negative due to high case fatality. This scenario would apply to a pest, i.e. an unwanted species that one tries to control by a fatal or nearly fatal disease.

In scenario iii)  $b > \mu + \gamma$ . The birth rate is so high that  $c^*$  does not exist (formally  $c^* > 1$ ), the population cannot be controlled by the disease, but its growth is slowed down to  $b - \mu - \gamma$ .

In the limit of high infectivity and short infectious period, (1.39) tells that  $\rho_1 = 0$  can be always achieved.

**Proposition 1.8.** *In the limiting case of high infectivity and short infectious period the critical case fatality is*

$$c^* = \frac{(\beta/\gamma)(b - \mu)}{(\beta/\gamma)b - \mu} = \frac{R_0(0)(R_D - 1)}{R_D R_0(0) - 1} = \frac{1 - \frac{1}{R_D}}{1 - \frac{1}{R_0 R_D}} < 1. \quad (1.40)$$

Proof: In this case the inequalities  $c^* < 1$  and  $R_0 > 1$  are equivalent. □

We discuss the expression (1.40). If  $R_0 < 1$ , there is no infection and in consequence,  $c^*$  is not defined. If  $R_0 = 1$ ,  $c^* = 1$  irrespective of the value of  $R_D$ . For fixed  $R_D$ ,  $c^*$  decreases in  $R_0$  very quickly and reaches an equilibrium. With the increase of the demographic reproduction number  $R_D$ , the stationary level of the critical case fatality as a function of  $R_0$  gets higher. This is shown in Figure 1.4.

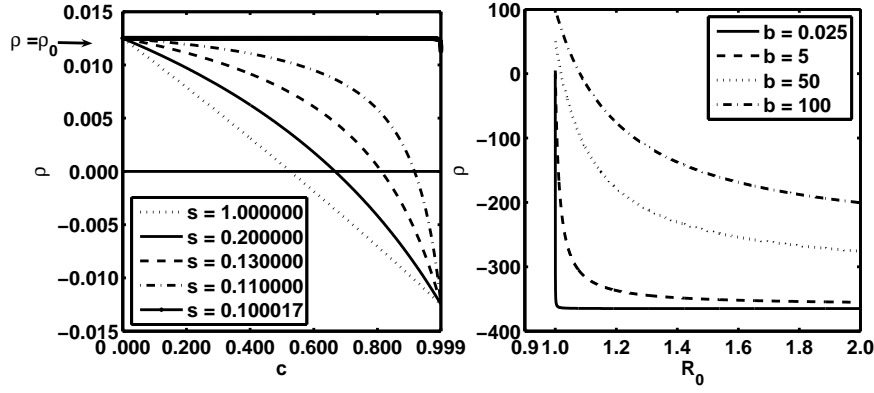


Figure 1.3: The growth rate  $\rho_1$  as a function of the case fatality  $c$  with parameter values:  $\mu = 0.0125$  per year,  $\gamma = 365$  per year,  $\kappa = 3650$  per year, and  $b = 0.025$  per year and for several values of  $s$  as shown in the graph. Here we set  $\beta = \kappa s$  where  $\kappa$  is the contact rate and  $s$  is the susceptibility. For  $c = 0$  we have  $\rho_1 = \rho_0 = b - \mu$ . With increasing  $c$ ,  $\rho_1$  decreases until reaching zero for  $c = c^*$ , the critical case fatality which is well defined if and only if  $b\beta > (\beta - \gamma)(\mu + \gamma)$ . For large susceptibility,  $s = 1$ , the dependence is almost linear, for smaller  $s$  it becomes markedly non-linear (see the left part of the figure which is true for  $0 \leq c < 1$ ). For  $c = 1$ , we produce the right part in which we draw  $\rho = -(\mu + \gamma) + \frac{\beta b}{\beta - \gamma}$  as a function of the basic reproduction number for the same  $\mu$  and  $\gamma$  values but for different values of  $b$  as shown on the figure. In the case  $1 \leq R_0 < \frac{1}{(1+b/\gamma)(1-b/(\mu+\gamma))}$ , the growth rate can not be driven to zero. This last condition can be written as  $\frac{I_p}{L_0} \frac{R_D}{(1-\frac{1}{R_0^\infty})} \leq 1$  where  $I_p = \frac{1}{\gamma + \mu}$  is the length of the infectious period,  $L_0 = \frac{1}{\mu}$  is the life expectancy at birth in the absence of infection,  $R_D = \frac{b}{\mu}$  is the demographic reproduction number, and  $R_0^\infty = \frac{\beta}{\gamma}$  is the basic reproduction number for a stationary population with ignored mortality. However, If  $1 \leq R_0 < \frac{1}{1-(b/\gamma)^2}$  the feasible solution is  $\rho_+$ . If  $R_0 = \frac{1}{1-(b/\gamma)^2}$ , both solutions  $\rho_+$  and  $\rho_-$  coincide. In the case  $R_0 > \frac{1}{1-(b/\gamma)^2}$ ,  $\rho_-$  leads to the feasible solution, whereas  $\rho_+$  does not. This means that the growth rate drawn in the right part is equal to  $\rho_-$  if  $R_0 \geq \frac{1}{1-(b/\gamma)^2}$ , and equals  $\rho_+$  if  $1 \leq R_0 \leq \frac{1}{1-(b/\gamma)^2}$ .

**Proposition 1.9.** *In terms of basic reproduction numbers the rate of the infected solution is given explicitly by*

$$\rho_1 = -\mu + \left(\frac{\gamma}{2}\right) \left( \sqrt{\left(1 - \frac{R_D}{(\gamma/\mu)(1-c/R_0)}\right)^2 + \frac{4R_D(1-c)}{(\gamma/\mu)(1-c/R_0)}} - \left(1 - \frac{R_D}{(\gamma/\mu)(1-c/R_0)}\right) \right) \quad (1.41)$$

whereby  $R_0 = R_0(0) = \beta/\gamma$ .

Proof: Explicit computation from (1.27). □

Of special interest is the case of high infectivity and short infectious period where  $\beta$  and  $\gamma$  are large.

**Proposition 1.10.** *Let the case fatality  $c$  be fixed. Consider the limiting case of high infectivity and short infectious period, with  $\beta/\gamma = R_0$  and large  $\gamma$ . Then the growth rate  $\rho_1$  is given by*

$$\rho_1 = b \frac{1-c}{1-\frac{c}{R_0}} - \mu + o\left(\frac{\mu}{\gamma}\right). \quad (1.42)$$

Proof: In (1.41) use  $\sqrt{1+1/\gamma} = 1 + \frac{1}{2\gamma} + o(1/\gamma)$  to expand the square root expressions, omitting  $1/\gamma^2$  terms, then cancel  $\gamma$  and collect terms.  $\square$

**Proposition 1.11.** *The force of infection  $\lambda$  can be expressed in terms of the rate of growth as*

$$\lambda = (\rho_1 + \mu) \frac{\beta - (\rho_1 + \mu + \gamma)}{\rho_1 + \mu + \gamma - c\gamma}. \quad (1.43)$$

*In the limit of high infectivity and fast recovery,  $\beta \rightarrow \infty$ ,  $\gamma \rightarrow \infty$ ,  $\beta/\gamma = R_0$ , this expression becomes*

$$\lambda = b \frac{R_0 - 1}{1 - \frac{c}{R_0}}. \quad (1.44)$$

Proof: (1.43) follows from (1.18) using (1.16), and then (1.44) follows immediately using (1.42) and the definition of  $R_0$ .  $\square$

Hence in this limiting case, the force of infection can be expressed in terms of the original parameters, independently of  $\rho_1$ . If the case fatality  $c$  runs from 0 to 1 then the force of infection *increases* from  $b(R_0 - 1)$  to  $bR_0$ .

Figure 1.4 shows the critical case fatality as a function of the basic reproduction number  $R_0$  for several values of the demographic reproduction number  $R_D$ , in the limiting case of high infectivity and quick recovery. We notice that when  $R_0$  is small, the critical case fatality is large and when  $R_0$  is large, the critical case fatality is small. If we let the basic reproduction number tend to infinity, the critical case fatality tends to  $1 - 1/R_D$ . We notice also that  $c^*$  increases as a function of  $R_D$ .

**Proposition 1.12.** *For small  $c$  the following expansion holds,*

$$\rho_1 = \rho_0 - \frac{b}{R_0} (R_0^{\text{homog}} - 1) + o(c). \quad (1.45)$$

Proof: By expansion of the square root and the denominators in (1.28).  $\square$

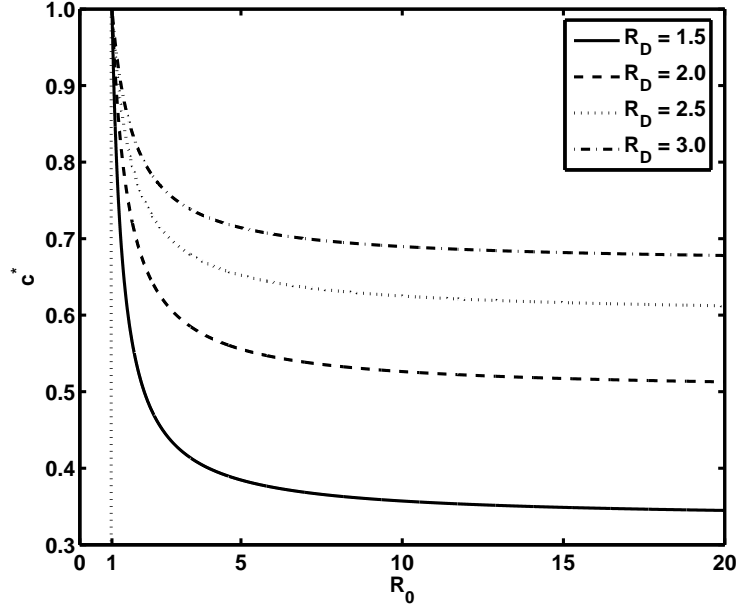


Figure 1.4: The limiting case of high infectivity and short infectious period: The critical case fatality  $c^*$  as a function of the basic reproduction number  $R_0$  for several values of the demographic reproduction number  $R_D$ .

## 1.10 Age distributions

We now derive the stationary age distribution of the infected exponential solution. Suppose that the age distributions can be written as the product of separated independent functions. i.e. let:  $X(a, t) = U(a)N(t)$ ,  $Y(a, t) = V(a)N(t)$ ,  $Z(a, t) = W(a)N(t)$  where  $N(t) = N_0 e^{\rho t}$ . Hence we have to solve the equations

$$\frac{dU(a)}{da} = -(\rho + \mu + \lambda)U(a) \quad (1.46)$$

$$\frac{dV(a)}{da} = -(\rho + \mu + \gamma)V(a) + \lambda U(a) \quad (1.47)$$

$$\frac{dW(a)}{da} = -(\rho + \mu)W(a) + (1 - c)\gamma V(a) \quad (1.48)$$

where  $\lambda$  is given by (1.18) and  $U(0) = 1$ ,  $V(0) = W(0) = 0$ .

**Proposition 1.13.** *The solution of the system of differential equations can be given as*

$$\begin{aligned} U(a) &= e^{-(\rho+\mu+\lambda)a} \\ V(a) &= \frac{\lambda}{\gamma - \lambda} \left( e^{-(\rho+\mu+\lambda)a} - e^{-(\rho+\mu+\gamma)a} \right) \\ W(a) &= \frac{1-c}{\gamma - \lambda} e^{-(\rho+\mu)a} \left( \gamma (1 - e^{-\lambda a}) - \lambda (1 - e^{-\gamma a}) \right) \end{aligned} \quad (1.49)$$

where  $\lambda$  is given by (1.18).

Proof: The proof is straightforward by successively integrating the equations for  $U$ ,  $V$  and finally for  $W$ .  $\square$

## 1.11 Infected cohorts and life expectancy

The survival function for an uninfected population is

$$p_0(a) = N(a)|_{\lambda=0} = e^{-\mu a}. \quad (1.50)$$

Now we are interested in survival in a population which follows the infected exponential solution. Let  $u(a)$ ,  $v(a)$ ,  $w(a)$  denote the probability that an individual survives age  $a$  and is susceptible, infected, recovered, respectively,

$$\begin{aligned} u(a) &= U(a)|_{\rho=0, U(0)=1} = e^{-(\mu+\lambda)a} \\ v(a) &= V(a)|_{\rho=0, U(0)=1} = \frac{\lambda}{\gamma - \lambda} \left( e^{-(\mu+\lambda)a} - e^{-(\mu+\gamma)a} \right) \\ w(a) &= W(a)|_{\rho=0, U(0)=1} = \frac{1-c}{\gamma - \lambda} e^{-\mu a} \left( \gamma (1 - e^{-\lambda a}) - \lambda (1 - e^{-\gamma a}) \right). \end{aligned} \quad (1.51)$$

Then the survival function in the presence of infection is:

$$l(a) = u(a) + v(a) + w(a). \quad (1.52)$$

By adding the expressions on the right hand side of (1.51) and simplifying we find the following formula.

**Proposition 1.14.** *The survival function in the presence of infection  $l(a)$  can be written as the product of two factors, one of them is the survival function in the absence of infection:*

$$l(a) = l_0(a) \left[ 1 - c + \frac{c}{\gamma - \lambda} (\gamma e^{-\lambda a} - \lambda e^{-\gamma a}) \right]. \quad (1.53)$$

Of particular interest are the proportions of susceptible, infected and recovered in a cohort at a given age  $a$ , i.e., the numbers  $\xi(a) = u(a)/l(a)$ ,  $\eta(a) = v(a)/l(a)$ ,  $\zeta(a) = w(a)/l(a)$ .

**Proposition 1.15.** *Let  $\lambda$  be the force of infection as given in Proposition 1.11. The proportion of infected in a cohort of age  $a$  is given by*

$$\eta(a) = \frac{\lambda(e^{-\lambda a} - e^{-\gamma a})}{(1-c)(\gamma - \lambda) + c(\gamma e^{-\lambda a} - \lambda e^{-\gamma a})}. \quad (1.54)$$

The life expectancy at birth in the absence of infection is

$$L_0 = \int_0^\infty l_0(a) da = \int_0^\infty e^{-\mu a} da = \frac{1}{\mu}. \quad (1.55)$$

**Proposition 1.16.** *The life expectancy at birth in the presence of infection is*

$$L = \frac{1}{\mu} \left( 1 - \frac{c\lambda\gamma}{(\mu + \gamma)(\mu + \lambda)} \right). \quad (1.56)$$

*In the limiting case of high infectivity and short infectious period*

$$L = \frac{1}{\mu} \left( 1 - \frac{c\lambda}{\mu + \lambda} \right) = \frac{1}{\mu} \left( 1 - \frac{cR_D(R_0 - 1)}{R_D(R_0 - 1) + 1 - \frac{c}{R_0}} \right). \quad (1.57)$$

Proof:

$$\begin{aligned} L &= \int_0^\infty l(a) da \\ &= \int_0^\infty e^{-\mu a} \left[ 1 - c + \frac{c}{\gamma - \lambda} (\gamma e^{-\lambda a} - \lambda e^{-\gamma a}) \right] da \\ &= \frac{1 - c}{\mu} + \frac{c}{\gamma - \lambda} \left( \frac{\gamma}{\mu + \lambda} - \frac{\lambda}{\mu + \gamma} \right) \end{aligned}$$

which is (1.56) after some algebra. Then take  $\gamma \rightarrow \infty$  and use (1.44) for  $\lambda$ .  $\square$

It is clear that, in the presence of infection, the life expectancy  $L$  decreases with increasing case fatality  $c$ . The following formula is not surprising in demographic terms but indicates the consistency of the model.

**Proposition 1.17.** *Suppose the critical case fatality  $c^*$  (at which the population becomes stationary) satisfies  $c^* < 1$ . Then the life expectancy at zero population growth is  $L = 1/b$ .*

Proof: Direct substitution of  $c = c^*$  from (1.43) in (1.57) and simplification gives the result.  $\square$

**Proposition 1.18.** *Assume  $R_0^{\text{homog}} > 1$  and the infected exponential solution. Then the proportion of susceptible  $\bar{x}$  satisfies*

$$\bar{x} = \frac{1}{R_0^{\text{homog}}} \frac{D_0}{D_1} \quad (1.58)$$

where  $D_i = 1/(\rho_i + \mu + \gamma)$ ,  $i = 0, 1$ .

Proof: Follows from (1.22).  $\square$

This formula generalizes the standard formula  $xR_0 = 1$  for the stationary case to exponentially growing or decaying populations.

**Proposition 1.19.** *Suppose the critical case fatality  $c^*$  (at which the population becomes stationary) satisfies  $c^* < 1$ . Then the gain in life expectancy is given by*

$$\frac{L_0}{L} = \frac{\bar{x}(R_0 - c^*)}{R_0\bar{x} - c^*}. \quad (1.59)$$

*In the limit of large  $\beta$  and  $\gamma$  this expression becomes*

$$\frac{L_0}{L} = \frac{1 - c^*\bar{x}}{1 - c^*}. \quad (1.60)$$

*The importance of this formula is that it contains parameters which can be estimated from real data.*

Proof: With  $c = c^*$  and  $\rho_1 = 0$  we have from (1.56)

$$L = L_0 \left( 1 - \frac{c^*\gamma\lambda}{(\mu + \gamma)(\mu + \lambda)} \right),$$

from (1.43)

$$\lambda = \mu \frac{\beta - (\mu + \gamma)}{\mu + \gamma - c^*\gamma}$$

and from (1.3), second equation, for the exponential solution,  $\bar{x} = (\mu + \gamma)/\beta$ , and hence

$$L = L_0 \left( 1 - \frac{c^*\gamma\mu \frac{\beta - (\mu + \gamma)}{\mu + \gamma - c^*\gamma}}{(\mu + \gamma) \left( \mu + \mu \frac{\beta - (\mu + \gamma)}{\mu + \gamma - c^*\gamma} \right)} \right)$$

and after simplification

$$L = L_0 \frac{\beta\bar{x} - c^*\gamma}{\bar{x}(\beta - c^*\gamma)}.$$

In the limit of large  $\beta, \gamma$  we have approximately  $\bar{x}R_0 = 1$ . □

## 1.12 Summary

We introduced an epidemiological model for a potentially lethal immunizing infection in a growing population. We treated the problem of infection induced mortality from two different points of view, the differential mortality and the case fatality approach.

The basic reproduction number in the case fatality model is  $R_0 = \beta/(\gamma + b)$  which is constant with respect to the case fatality, whereas in the differential mortality it is given by  $R_0 = \beta/(\alpha + \delta + b)$ . The latter decreases with the increase of the differential mortality. Therefore, the basic reproduction number  $R_0$  remains constant, with respect to the case fatality, in the case fatality model while it is affected by the differential mortality of the infection in the differential mortality model.



In the differential mortality model, the growth rate of the population decreases, with respect to the differential mortality, till reaching its minimum and then it increases again to reach its maximum when  $\delta = \delta_{max} = \beta - \alpha - b$ . However, in the case fatality model the situation is different. If  $c \in [0, 1)$ , then the growth rate decreases monotonically from its maximum at  $c = 0$ .

In the limiting case of high infectivity and short infectious period, formula  $c^* = \frac{1-(1/R_D)}{1-(1/R_0 R_D)} < 1$  says that the critical case fatality  $c^*$  required to drive the host population to its demographically stationary state exists for all  $R_0 \geq 1$ . If  $R_0 = 1$ , then  $c^* = 1$  irrespective of the values of other model parameters. However, for fixed demographic reproduction number,  $R_D$ , the critical  $c^*$  decreases quickly to reach an equilibrium with the increase of the basic reproduction number  $R_0$ . In the normal situation of finite contact and removal rates, the situation is a bit different. This situation is discussed in the context of proposition 1.7. The critical case fatality  $c^*$  exists under a certain constraint. If  $R_0 \geq 1 + \frac{b}{\gamma} R_0(\mu)$ , then  $c^* \in [0, 1]$  exists and is given by  $c^* = \frac{R_0(0)(R_D-1)}{R_D R_0(\mu)-1} < 1$  where  $R_0(\mu) = \beta/(\gamma + \mu)$  and  $R_0(0) = \beta/\gamma$ .

The formula  $\bar{x} = (1/R_0^{homog})(D_0/D_1)$  says that the basic reproduction number  $R_0$  is no longer being the inverse of the proportion of susceptible in the endemic equilibrium  $\bar{x}$ . The product  $R_0 \bar{x}$  equals the ratio between two times  $D_0 = 1/(\rho_0 + \mu + \gamma) = 1/(b + \gamma)$  and  $D_1 = 1/(\rho_1 + \mu + \gamma)$ . These two times we interpret as the discounted duration of the infectious period for a growing population with growth rate  $\rho_i$ , where  $i = 0, 1$ .

## 2 An immunizing potentially lethal infection in a growing population with age structure

### 2.1 Introduction

Epidemics in age-structured populations have been studied mathematically by many authors (e.g. [7], [8], [11], [25], [27], [30], and [47]), also including vertical transmission of infections (e.g. [26], [28], [29], [31], [32], [33], and [52]). For such models the analytic theory, i.e., existence and uniqueness of solutions, existence of stationary states and their stability, have been studied (e.g. [51], [77]). The main interest has been to determine the conditions for an outbreak or for the existence of an endemic equilibrium in a demographically stable population, (e.g., [13], [15], [16], and [58]). On the other hand, the impact of infections on population has usually not been the goal of mathematical investigations. Here we are mainly interested in the interrelation between population growth and endemic disease prevalence. We consider a homogeneous model for an age-structured population which allows exponentially growing populations. The infection is assumed to be potentially fatal. We assume that recovered individuals acquire immunity for the rest of their life. The growth rate, denoted by  $\rho$ , represents the rate at which the population grows (if  $\rho > 0$ ), decays (if  $\rho < 0$ ), or stays stationary (if  $\rho = 0$ ). If there is no infection, then the growth rate  $\rho$  has its largest possible value which we call the Malthusian parameter  $\rho_0$ . In the case where the infection is potentially fatal (positive case fatality), the growth rate stays below  $\rho_0$  and decreases with increasing case fatality. It can well be that the infection drives the growth rate  $\rho$  to zero or negative values. In the latter case the host population will go to extinction.

The traditional way to consider a fatal infection is to assume that infection victims die during the infectious periods. This concept is known as the differential mortality approach. It makes sense for infections with long infectious period. The differential mortality approach has been considered in age-structured epidemiological models (e.g. [42], [43], [70], [71]). In the case fatality approach, however, we assume that all infected individuals pass the infectious period and the victims die immediately after that period. By definition, case fatality is the proportion of infected individuals who die due to the infection.

An important and widely used concept in the theory of epidemics is the basic reproduction number, denoted by  $R_0$ . In words, it is the average number of secondary cases produced by a typical infected case, during its entire infectious period, when it is introduced into a totally susceptible population. In simple models, a way to evaluate  $R_0$  is to find the inverse of the proportion of susceptible individuals in the endemic equilibrium. However, in more complicated models such a simple relation does not hold. We will show that, for a growing population with age structure, this inverse has to be multiplied by some factor depending on average susceptibility and average discounted duration of the infectious period.

We remark that all models studied here are so-called separable models, i.e., it is assumed that the transmission rate is a product of an individual susceptibility of a susceptible individual and an infectivity which is a functional of the infected part of the population. The separability assumption is well established in epidemic modeling. In fact, there are few data that would justify more general transmission laws.

This chapter is organized as follows. We first introduce the model in section 2.2. We consider stable age distributions in the uninfected population in section 2.3. In sections 2.4 we present the endemic solutions and the equation from which we determine the rate of growth. The characteristic equations from which we determine the rate of growth corresponding to the positive infected solution are shown in section 2.5. The basic reproduction number as well as the demographic reproduction number are defined in section 2.6. To study the impact on demography we follow a cohort in section 2.7 and we study the relationship between the basic reproduction number, denoted by  $R_0$ , and the proportion of susceptible individuals in the endemic equilibrium, denoted by  $\bar{x}$ , in section 2.8. The impact of the infection on the life expectancy is presented in section 2.9. Since the infection is potentially lethal, we are interested in the minimal case fatality required to reduce the growth rate of the population to zero (section 2.10). In section 2.11 we present formulae for the average ages at infection for individuals who get infected as well as for those who die without getting infected. In section 2.12 we specify our analysis to the case of high infectivity (large number of contacts) and quick recovery (short infectious period). In section 2.13 we evaluate the life expectancy for individuals at any age. A numerical example with real data from The Hague representing the case of smallpox in the Eighteenth Century is introduced in section 2.14. Finally, we study the stability of the infection free equilibrium in section 2.15.

## 2.2 The model

In the previous chapter, we constructed our model which is a generalization of Daniel Bernoulli's epidemiological model to the case of growing populations. We studied the case where the model parameters are age-independent. In this chapter we generalize this study to the case of age-dependent model parameters. The model reads:

$$\begin{aligned}
\frac{\partial X(a, t)}{\partial t} + \frac{\partial X(a, t)}{\partial a} &= -(\mu(a) + \lambda(a, t))X(a, t) \\
\frac{\partial Y(a, t)}{\partial t} + \frac{\partial Y(a, t)}{\partial a} &= \lambda(a, t)X(a, t) - (\gamma + \mu(a))Y(a, t) \\
\frac{\partial Z(a, t)}{\partial t} + \frac{\partial Z(a, t)}{\partial a} &= (1 - c(a))\gamma Y(a, t) - \mu(a)Z(a, t)
\end{aligned} \tag{2.1}$$

where the force of infection is

$$\lambda(a, t) = \frac{\kappa s(a) \int_0^\infty Y(a, t) da}{N(t)}, \tag{2.2}$$

and total population size is

$$N(t) = \int_0^\infty (X(a, t) + Y(a, t) + Z(a, t)) da.$$

The boundary condition (birth law) is

$$\begin{aligned}
X(0, t) &= \int_0^\infty \beta(a) \left( X(a, t) + Y(a, t) + Z(a, t) \right) da, \\
Y(0, t) &= 0, \quad Z(0, t) = 0.
\end{aligned}$$

### 2.3 Stable age distribution (persistent solutions)

Persistent solutions are solutions that can be expressed as the product of two functions, one of them is an exponentially growing function of time and the other depends on the age. The latter is called the stable age distribution (a distribution in which the fraction of individuals in each class remains constant with respect to time). Assume that the age-specific per capita birth and death rates  $\beta(a)$  and  $\mu(a)$  are continuous on  $[0, \infty)$  and that  $\int_0^\infty \mu(a) da = \infty$ . Assume also that:

$$\begin{aligned}
X(a, t) &= X(a)P(t), & Y(a, t) &= Y(a)P(t), \\
Z(a, t) &= Z(a)P(t), & N(a, t) &= N(a)P(t),
\end{aligned} \tag{2.3}$$

where

$$N(a) = X(a) + Y(a) + Z(a).$$

$X(a)$ ,  $Y(a)$ , and  $Z(a)$  are respectively called the numbers of susceptible individuals, infected individuals, and recovered individuals of age  $a$ . Substituting from (2.3) into (2.2) gives:

$$\lambda(a, t) = \kappa s(a) \frac{\int_0^\infty Y(a) da}{\int_0^\infty N(a) da} = \lambda(a) \tag{2.4}$$

Substituting from (2.3) and (2.4) into (2.1) gives:

$$\begin{aligned}
\frac{dX(a)}{da} &= - \left[ \rho + \mu(a) + \lambda(a) \right] X(a) \\
\frac{dY(a)}{da} &= \lambda(a)X(a) - \left[ \rho + \gamma + \mu(a) \right] Y(a) \\
\frac{dZ(a)}{da} &= (1 - c(a))\gamma Y(a) - \left[ \rho + \mu(a) \right] Z(a) \\
\frac{dP(t)}{dt} &= \rho P(t),
\end{aligned} \tag{2.5}$$

where  $\rho$  is the demographic growth rate and

$$\begin{aligned}
X(0) &= \int_0^\infty \beta(a) \left[ X(a) + Y(a) + Z(a) \right] da \\
Y(0) &= Z(0) = 0
\end{aligned} \tag{2.6}$$

## 2.4 Endemic solutions

### 2.4.1 Infection free equilibrium (IFE)

The uninfected solution corresponds to  $\lambda(a) = 0$ . Thus the infection free equilibrium is given by  $(X(a), 0, 0)' \exp(\rho_0 t)$  where  $'$  represents vector transpose and  $\rho_0$  is the Malthusian parameter. It is the largest value of the rate of growth and is the unique real positive solution of the demographic characteristic equation:

$$1 = \int_0^{\infty} \beta(a) \exp(-(\rho_0 a + M(a))) da, \quad (2.7)$$

where

$$M(a) = \int_0^a \mu(\tau) d\tau \quad (2.8)$$

is the cumulative mortality.

### 2.4.2 Endemic equilibrium

The solution of system (2.5) is given by

$$\begin{aligned} X(a) &= X(0) \exp\left(-(\rho a + M(a) + \Lambda(a))\right), \\ Y(a) &= X(0) \exp\left(-(\rho a + M(a))\right) \int_0^a \lambda(\tau) \exp\left(-(\gamma(a - \tau) + \Lambda(\tau))\right) d\tau, \\ Z(a) &= X(0) \exp\left(-(\rho a + M(a))\right) \int_0^a (1 - c(\tau)) \int_0^{\tau} \gamma \lambda(\xi) \exp\left(-(\gamma(\tau - \xi) + \Lambda(\xi))\right) d\xi d\tau. \end{aligned} \quad (2.9)$$

where

$$\Lambda(a) = \int_0^a \lambda(\tau) d\tau. \quad (2.10)$$

is the cumulate force of infection.

It is clear from relation (2.4) that the force of infection  $\lambda(a)$  can be written as

$$\begin{aligned} \lambda(a) &= \bar{\lambda} s(a); \\ \bar{\lambda} &= \kappa \frac{\int_0^{\infty} Y(a) da}{\int_0^{\infty} N(a) da} = \kappa \bar{y} \end{aligned} \quad (2.11)$$

where  $\bar{y}$  is the endemic prevalence of infected population. In other words, it is the proportion of infected individuals in the population at equilibrium.

## 2.5 Characteristic equations

### Demographic equation

If we substitute from (2.9) into (2.6) and do some calculations, we get the demographic characteristic equation as

$$1 = \int_0^{\infty} \beta(a) \exp(-(\rho a + M(a))) \left( 1 - \gamma \bar{\lambda} \int_0^a c(\tau) \int_0^{\tau} s(\xi) \exp(-(\gamma(\tau - \xi) + \bar{\lambda} S(\xi))) d\xi d\tau \right) da \quad (2.12)$$

where

$$S(a) = \int_0^a s(\tau) d\tau \quad (2.13)$$

is the cumulate susceptibility.

### Epidemiologic equation

Substituting from (2.9) into (2.11) and performing some simple calculations we obtain the following epidemiologic characteristic equation

$$1 = \frac{\kappa \int_0^{\infty} \exp(-(\rho a + M(a))) \int_0^a s(\tau) \exp\left(-\left(\gamma(a - \tau) + \bar{\lambda} S(\tau)\right)\right) d\tau da}{\int_0^{\infty} \exp(-(\rho a + M(a))) \left( 1 - \gamma \bar{\lambda} \int_0^a c(\tau) \int_0^{\tau} s(\xi) \exp(-(\gamma(\tau - \xi) + \bar{\lambda} S(\xi))) d\xi d\tau \right) da} \quad (2.14)$$

Equations (2.12) and (2.14) form a nonlinear system for two unknowns  $\rho$  and  $\bar{\lambda}$ . An infected exponential solution exists if and only if the system (2.12), (2.14) has a real solution  $(\rho_1, \bar{\lambda})$  with positive  $\bar{\lambda}$ .

## 2.6 Reproduction numbers

### Demographic reproduction number $R_D$

The demographic reproduction number is the average number of children that a newborn is expected to beget in its entire life. It is given by:

$$R_D = \int_0^{\infty} \beta(a) \exp(-M(a)) da. \quad (2.15)$$

### Basic reproduction number $R_0$

One of the basic and fundamental questions in mathematical epidemiology is to know a threshold quantity from which we can predict whether an infection fades out or persists. This threshold quantity is known as the basic reproduction number/ratio. It is the average number of secondary cases produced by one infected case, during its infectious period, when it is introduced into a totally susceptible population. If  $R_0 \leq 1$  then the infection dies out, while if  $R_0 > 1$  then the infection persists. In the literature, there have been intensive studies to evaluate  $R_0$  (e.g. [18], [20], [23], [35], [38], [42], [45], [46]). For our model it is

$$R_0 = \frac{\kappa \int_0^\infty s(a) \exp(-(\rho_0 a + M(a))) \left( \int_a^\infty \exp \left( - \left[ (\rho_0 + \gamma)(a - \tau) + (M(\tau) - M(a)) \right] \right) d\tau \right) da}{\int_0^\infty \exp(-(\rho_0 a + M(a))) da}. \quad (2.16)$$

Proof: Define a function

$$F(\bar{\lambda}) = \frac{\kappa \int_0^\infty \exp(-(\rho a + M(a))) \int_0^a s(\tau) \exp(-\gamma(a - \tau) - \bar{\lambda} S(\tau)) d\tau da}{\int_0^\infty \exp(-\rho a - M(a)) (1 - \gamma \bar{\lambda} \int_0^a c(\tau) \int_0^\tau s(\xi) \exp(-\gamma(\tau - \xi) - \bar{\lambda} S(\xi)) d\xi d\tau) da} - 1.$$

In a totally susceptible population  $\bar{\lambda} = 0$  and  $\rho = \rho_0$ ; therefore

$$F(0) = \frac{\kappa \int_0^\infty \exp(-(\rho_0 a + M(a))) \int_0^a s(\tau) \exp(-\gamma(a - \tau)) d\tau da}{\int_0^\infty \exp(-\rho_0 a - M(a)) da} - 1 = 0.$$

If  $\bar{\lambda}$  increases to infinity, then  $F(\bar{\lambda})$  decreases to  $-1 < 0$ , whereas  $F(\bar{\lambda})$  increases to  $+\infty$  if  $\bar{\lambda}$  decreases to  $-\infty$ . Hence  $\bar{\lambda} = 0$  is a threshold condition. This threshold condition yields the basic reproduction number. Therefore,  $R_0 = 1$  and  $\rho = \rho_0$  at  $\bar{\lambda} = 0$ . This coincides with the definition of the basic reproduction number  $R_0$  which is the expected number of secondary cases produced by a typical infected individual during its entire infectious period, in a totally susceptible population. Thus

$$R_0 = \frac{\kappa \int_0^\infty \exp(-(\rho_0 a + M(a))) \int_0^a s(\tau) \exp(-\gamma(a - \tau)) d\tau da}{\int_0^\infty \exp(-\rho_0 a - M(a)) da}.$$

Interchanging the integration order in the numerator defines exactly relation (2.16).

Since we defined the basic reproduction number  $R_0$  from the epidemiologic characteristic equation, we define the demographic reproduction number from the demographic characteristic equation by setting  $R_D = 1$  when  $\bar{\lambda} = 0$  and  $\rho = 0$ .

□

## 2.7 Demography

Let  $u(a)$  denote the probability that an individual survives age  $a$  and is susceptible,  $v(a)$  denote the probability that an individual survives age  $a$  and is infected, and  $w(a)$  denote the probability that an individual survives age  $a$  and is immune. Then

$$\begin{aligned} u(a) &= X(a)|_{\rho=0, X(0)=1} = \exp(-(M(a) + \Lambda(a))), \\ v(a) &= Y(a)|_{\rho=0, X(0)=1} = \exp(-M(a)) \int_0^a \lambda(\tau) \exp(-(\gamma(a - \tau) + \Lambda(\tau))) d\tau, \\ w(a) &= Z(a)|_{\rho=0, X(0)=1} = \exp(-M(a)) \int_0^a \gamma(1 - c(\tau)) \int_0^\tau \lambda(\xi) \exp(-(\gamma(\tau - \xi) + \Lambda(\xi))) d\xi d\tau. \end{aligned} \quad (2.17)$$

Let  $l(a)$  denote the probability to survive age  $a$ . Then the survival function in the presence of infection is

$$l(a) = u(a) + v(a) + w(a). \quad (2.18)$$

The survival function in the absence of infection is

$$l_0(a) = l(a)|_{\lambda(a)=0} = \exp(-M(a)). \quad (2.19)$$

Equations (2.17 - 2.19) can be combined to give

$$l(a) = l_0(a) \left( 1 - \gamma \int_0^a c(\tau) \int_0^\tau \lambda(\xi) \exp(-(\gamma(\tau - \xi) + \Lambda(\xi))) d\xi d\tau \right). \quad (2.20)$$

## Prevalence

Assume that:

$x(a)$  denotes the probability to be susceptible at age  $a$  in a cohort (in other words, it is the proportion of susceptible individuals at age  $a$ ),

$y(a)$  denotes the probability to be infected at age  $a$  in a cohort,

$z(a)$  denotes the probability to be immune at age  $a$  in a cohort.

Hence

$$x(a) = \frac{u(a)}{l(a)}, y(a) = \frac{v(a)}{l(a)}, \text{ and } z(a) = \frac{w(a)}{l(a)}.$$

The proportion of susceptible, infected and recovered individuals, in the endemic equilibrium, in the total population are given by

$$\begin{aligned} \bar{x} &= \frac{\int_0^\infty X(a) da}{\int_0^\infty N(a) da}, \\ \bar{y} &= \frac{\int_0^\infty Y(a) da}{\int_0^\infty N(a) da}, \\ \bar{z} &= \frac{\int_0^\infty Z(a) da}{\int_0^\infty N(a) da} \end{aligned} \quad (2.21)$$

## 2.8 The relationship between the basic reproduction number $R_0$ and the proportion of susceptible individuals in the endemic equilibrium $\bar{x}$

The infectious period is the time period during which infected individuals are able to transmit an infection to any susceptible host or vector they contact. For a demographically stationary population, the duration of the infectious period is constant. However, for a growing population the number of individuals change during the infectious period and hence the duration of the infectious period has to be discounted.



**Definition 2.1.** *The discounted duration of the infectious period for an individual of age  $a$  in a growing population with growth rate  $\rho_0$  is*

$$D_0(a) = \int_a^\infty \exp \left( - \left[ (\rho_0 + \gamma)(\tau - a) + (M(\tau) - M(a)) \right] \right) d\tau. \quad (2.22)$$

**Definition 2.2.** *The discounted duration of the infectious period for an individual of age  $a$  in a growing population with growth rate  $\rho_1$  is*

$$D_c(a) = \int_a^\infty \exp \left( - \left[ (\rho_1 + \gamma)(\tau - a) + (M(\tau) - M(a)) \right] \right) d\tau. \quad (2.23)$$

**Definition 2.3.** *The average discounted duration of the infectious period for an individual of age  $a$  in a growing population with growth rate  $\rho_0$  is*

$$\bar{D}_0 = \frac{\int_0^\infty D_0(a) \exp(-(\rho_0 a + M(a))) da}{\int_0^\infty \exp(-(\rho_0 a + M(a))) da}. \quad (2.24)$$

**Definition 2.4.** *The average discounted duration of the infectious period for an individual of age  $a$  in a totally susceptible growing population with growth rate  $\rho_1$  is*

$$\bar{D}_\lambda = \frac{\int_0^\infty D_c(a) \exp(-(\rho_1 a + M(a) + \Lambda(a))) da}{\int_0^\infty \exp(-(\rho_1 a + M(a) + \Lambda(a))) da}. \quad (2.25)$$

**Definition 2.5.** *The average susceptibility for individuals in a growing population with growth rate  $\rho_0$  is*

$$\bar{s}_0 = \frac{\int_0^\infty s(a) \exp(-(\rho_0 a + M(a))) D_0(a) da}{\int_0^\infty \exp(-(\rho_0 a + M(a))) D_0(a) da}. \quad (2.26)$$

**Definition 2.6.** *The average susceptibility for individuals in a totally susceptible growing population with growth rate  $\rho_1$  is*

$$\bar{s}_\lambda = \frac{\int_0^\infty s(a) \exp(-(\rho_1 a + M(a) + \Lambda(a))) D_c(a) da}{\int_0^\infty \exp(-(\rho_1 a + M(a) + \Lambda(a))) D_c(a) da}. \quad (2.27)$$

**Proposition 2.1.** *In case of potentially fatal infection and of age-dependent susceptibility and death rate, the basic reproduction number  $R_0$  does not equal the inverse of the proportion of susceptible individuals in the endemic equilibrium  $\bar{x}$ , whereas for constant susceptibility and death rate and for nonfatal infection  $\bar{x}R_0 = 1$ , i.e.,*

$$R_0 \bar{x} = \frac{\bar{s}_0 \bar{D}_0}{\bar{s}_\lambda \bar{D}_\lambda} \quad (2.28)$$

*If the susceptibility  $s(a)$  is constant, then  $\bar{s}_0 = \bar{s}_\lambda$ . Also if  $\mu(a)$  is constant, then both  $D_0(a)$  and  $D_c(a)$  are constants. They are equal only in case of the absence of case fatality (since  $\rho_1 = \rho_0$ ). Thus  $R_0 \bar{x} = 1$  only if the case fatality vanishes and both the susceptibility and the death rate are age-independent.*

**Proof:** The proportion of susceptible in the endemic equilibrium,  $\bar{x}$ , is given by

$$\bar{x} = \frac{\int_0^\infty \exp(-(\rho_1 a + M(a) + \Lambda(a))) da}{\int_0^\infty \exp(-(\rho_1 a + M(a))) (1 - \gamma \int_0^a c(\tau) \int_0^\tau \lambda(\xi) \exp(-(\gamma(\tau - \xi) + \Lambda(\xi))) d\xi d\tau) da}$$

and by (2.14)

$$\bar{x} = \frac{\int_0^\infty \exp(-(\rho_1 a + M(a) + \Lambda(a))) da}{\kappa \int_0^\infty \exp(-(\rho_1 a + M(a))) \int_0^a s(\tau) \exp(-(\gamma(a - \tau) + \Lambda(\tau))) d\tau da}.$$

On the other hand and since

$$R_0 = \frac{\kappa \int_0^\infty \exp(-(\rho_0 a + M(a))) \int_0^a s(\tau) \exp(-\gamma(a - \tau)) d\tau da}{\int_0^\infty \exp(-\rho_0 a - M(a)) da},$$

then

$$\begin{aligned} R_0 \bar{x} &= \frac{(\int_0^\infty \exp(-(\rho_0 a + M(a))) \int_0^a s(\tau) \exp(-\gamma(a - \tau)) d\tau da) (\int_0^\infty \exp(-(\rho_1 a + M(a) + \Lambda(a))) da)}{(\int_0^\infty \exp(-\rho_0 a - M(a)) da) (\int_0^\infty \exp(-(\rho_1 a + M(a))) \int_0^a s(\tau) \exp(-(\gamma(a - \tau) + \Lambda(\tau))) d\tau da)} \\ &= \frac{\int_0^\infty s(a) \exp(-(\rho_0 a + M(a))) \left( \int_a^\infty \exp(-((\rho_0 + \gamma)(\tau - a) + (M(\tau) - M(a)))) d\tau \right) da}{\int_0^\infty \exp(-(\rho_0 a + M(a))) da} \\ &\quad \cdot \frac{\int_0^\infty \exp(-(\rho_1 a + M(a) + \Lambda(a))) da}{\int_0^\infty s(a) \exp(-(\rho_1 a + M(a) + \Lambda(a))) \left( \int_a^\infty \exp(-((\rho_1 + \gamma)(\tau - a) + (M(\tau) - M(a)))) d\tau \right) da} \end{aligned} \quad (2.29)$$

$$\begin{aligned} &= \frac{\int_0^\infty s(a) \exp(-(\rho_0 a + M(a))) D_0(a) da}{\int_0^\infty \exp(-(\rho_0 a + M(a))) da} \cdot \frac{\int_0^\infty \exp(-(\rho_1 a + M(a) + \Lambda(a))) da}{\int_0^\infty s(a) \exp(-(\rho_1 a + M(a) + \Lambda(a))) D_c(a) da} \\ &= \frac{\int_0^\infty s(a) \exp(-(\rho_0 a + M(a))) D_0(a) da}{\int_0^\infty \exp(-(\rho_0 a + M(a))) D_0(a) da} \cdot \frac{\int_0^\infty D_0(a) \exp(-(\rho_0 a + M(a))) da}{\int_0^\infty \exp(-(\rho_0 a + M(a))) da} \\ &\quad \cdot \frac{\int_0^\infty \exp(-(\rho_1 a + M(a) + \Lambda(a))) da}{\int_0^\infty D_c(a) \exp(-(\rho_1 a + M(a) + \Lambda(a))) da} \cdot \frac{\int_0^\infty \exp(-(\rho_1 a + M(a) + \Lambda(a))) D_c(a) da}{\int_0^\infty s(a) \exp(-(\rho_1 a + M(a) + \Lambda(a))) D_c(a) da} \\ &= \bar{s}_0 \cdot \bar{D}_0 \cdot \frac{1}{\bar{D}_\lambda} \cdot \frac{1}{\bar{s}_\lambda} \\ &= \frac{\bar{s}_0 \bar{D}_0}{\bar{s}_\lambda \bar{D}_\lambda} \\ &\neq 1 \end{aligned}$$

in general.

□

**Definition 2.7.** *The discounted duration of the infectious period for an individual of age  $a$  in a population with zero growth rate is*

$$D(a) = \int_a^\infty \exp(-(\gamma(\tau - a) + (M(\tau) - M(a))))d\tau. \quad (2.30)$$

**Definition 2.8.** *The average discounted duration of the infectious period for an individual of age  $a$  in a population with zero growth rate is*

$$\bar{D}_0^0 = \frac{\int_0^\infty D(a) \exp(-M(a))da}{\int_0^\infty \exp(-M(a))da}. \quad (2.31)$$

**Definition 2.9.** *The average discounted duration of the infectious period for an individual of age  $a$  in a totally susceptible population with zero growth rate is*

$$\bar{D}_\lambda^0 = \frac{\int_0^\infty D(a) \exp(-(M(a) + \Lambda(a)))da}{\int_0^\infty \exp(-(M(a) + \Lambda(a)))da}. \quad (2.32)$$

**Definition 2.10.** *The average susceptibility for individuals in a population with zero growth rate is*

$$\bar{s}_0^0 = \frac{\int_0^\infty s(a) \exp(-M(a))D(a)da}{\int_0^\infty \exp(-M(a))D(a)da}. \quad (2.33)$$

**Definition 2.11.** *The average susceptibility for individuals in a totally susceptible population with zero growth rate is*

$$\bar{s}_\lambda^0 = \frac{\int_0^\infty s(a) \exp(-(M(a) + \Lambda(a)))D(a)da}{\int_0^\infty \exp(-(M(a) + \Lambda(a)))D(a)da}. \quad (2.34)$$

**Corollary:** In case of a demographically stationary population, the basic reproduction number  $R_0$  is not the inverse of the proportion of susceptible individuals in the endemic equilibrium  $\bar{x}$  in general.

proof: For a population with zero growth rate we have

$$\begin{aligned} R_0 \bar{x} &= \frac{\int_0^\infty s(a) \exp(-M(a))D(a)da}{\int_0^\infty \exp(-M(a))da} \cdot \frac{\int_0^\infty \exp(-(M(a) + \Lambda(a)))da}{\int_0^\infty s(a) \exp(-(M(a) + \Lambda(a)))D(a)da} \\ &= \frac{\int_0^\infty s(a) \exp(-M(a))D(a)da}{\int_0^\infty \exp(-M(a))D(a)da} \cdot \frac{\int_0^\infty D(a) \exp(-M(a))da}{\int_0^\infty \exp(-M(a))da} \\ &\quad \cdot \frac{\int_0^\infty \exp(-(M(a) + \Lambda(a)))da}{\int_0^\infty D(a) \exp(-(M(a) + \Lambda(a)))da} \cdot \frac{\int_0^\infty \exp(-(M(a) + \Lambda(a)))D(a)da}{\int_0^\infty s(a) \exp(-(M(a) + \Lambda(a)))D(a)da} \\ &= \bar{s}_0^0 \cdot \bar{D}_0^0 \cdot \frac{1}{\bar{D}_\lambda^0} \cdot \frac{1}{\bar{s}_\lambda^0} \\ &= \frac{\bar{s}_0^0}{\bar{s}_\lambda^0} \cdot \frac{\bar{D}_0^0}{\bar{D}_\lambda^0} \\ &\neq 1 \end{aligned}$$

in general.

## 2.9 The impact on the life expectancy

**Definition 2.12.** *The life expectancy at birth in the absence of infection is*

$$L_0 = \int_0^\infty l_0(a) da = \int_0^\infty \exp(-M(a)) da. \quad (2.35)$$

**Definition 2.13.** *The expected time spent in the susceptible state (i.e., the duration of the lifetime in the susceptible state) is*

$$L_u = \int_0^\infty \exp(-(M(a) + \Lambda(a))) da. \quad (2.36)$$

**Definition 2.14.** *The expected time of life spent in the infected state is*

$$L_v = \int_0^\infty \lambda(a) \exp(-(M(a) + \Lambda(a))) \int_a^\infty \exp(-(\gamma(\tau - a) + (M(\tau) - M(a)))) d\tau da. \quad (2.37)$$

**Definition 2.15.** *The expected time of life at birth in the presence of infection in a population with zero growth rate is*

$$\begin{aligned} L &= \int_0^\infty l(a) da \\ &= \int_0^\infty \exp(-M(a)) \left( 1 - \gamma \int_0^a c(\tau) \int_0^\tau \lambda(\xi) \exp\left(-\left(\gamma(\tau - \xi) + \Lambda(\xi)\right)\right) d\xi d\tau \right) da. \end{aligned} \quad (2.38)$$

**Definition 2.16.** *The expected time of life at birth in the presence of infection in a growing population with growth rate  $\rho_1$  is*

$$L_1 = \int_0^\infty \exp\left(-\left(\rho_1 a + M(a)\right)\right) \left( 1 - \gamma \int_0^a c(\tau) \int_0^\tau \lambda(\xi) \exp\left(-\left(\gamma(\tau - \xi) + \Lambda(\xi)\right)\right) d\xi d\tau \right) da. \quad (2.39)$$

**Proposition 2.2.** *The gain in life expectancy of eradicating the infection is given by*

$$\frac{L_0}{L} = \frac{1}{1 - \bar{c}} \left( 1 - \left( \frac{L_u}{L} + \frac{L_v}{L} \right) \bar{c} \right) \quad (2.40)$$

where

$$\bar{c} = \frac{\int_0^\infty c(a) \left( \exp(-\gamma a) \int_0^a \lambda(\xi) \exp(\gamma\xi - \Lambda(\xi)) d\xi \right) \left( \int_a^\infty \exp(-M(\tau)) d\tau \right) da}{\int_0^\infty \left( \exp(-\gamma a) \int_0^a \lambda(\xi) \exp(\gamma\xi - \Lambda(\xi)) d\xi \right) \left( \int_a^\infty \exp(-M(\tau)) d\tau \right) da}$$

is an average case fatality.

**Proof:** The survival function in the absence of infection is

$$l_0(a) = \exp(-M(a)),$$

whereas the survival function in the presence of infection is

$$\begin{aligned} l(a) &= \exp(-M(a)) \left( 1 - \gamma \int_0^a c(\tau) \exp(-\gamma\tau) \int_0^\tau \lambda(\xi) \exp(\gamma\xi - \Lambda(\xi)) d\xi d\tau \right) \\ &= l_0(a) \left( 1 - \gamma \int_0^a c(\tau) \exp(-\gamma\tau) \int_0^\tau \lambda(\xi) \exp(\gamma\xi - \Lambda(\xi)) d\xi d\tau \right) \\ &= l_0(a) - \gamma \exp(-M(a)) \int_0^a c(\tau) \exp(-\gamma\tau) \int_0^\tau \lambda(\xi) \exp(\gamma\xi - \Lambda(\xi)) d\xi d\tau. \end{aligned}$$

Hence the life expectancy at birth in the presence of infection is

$$\begin{aligned} L(a) &= \int_0^\infty l(a) da \\ &= \int_0^\infty l_0(a) da - \int_0^\infty \gamma \exp(-M(a)) \int_0^a c(\tau) \exp(-\gamma\tau) \int_0^\tau \lambda(\xi) \exp(\gamma\xi - \Lambda(\xi)) d\xi d\tau da \\ &= L_0 - term_1, \end{aligned}$$

where

$$\begin{aligned} term_1 &= \int_0^\infty \gamma \exp(-M(a)) \int_0^a c(\tau) \exp(-\gamma\tau) \int_0^\tau \lambda(\xi) \exp(\gamma\xi - \Lambda(\xi)) d\xi d\tau da \\ &= \gamma \int_0^\infty c(\tau) \exp(-\gamma\tau) \left( \int_0^\tau \lambda(\xi) \exp(\gamma\xi - \Lambda(\xi)) d\xi \right) \left( \int_\tau^\infty \exp(-M(a)) da \right) d\tau \\ &= \gamma \bar{c} \int_0^\infty \left( \exp(-\gamma a) \int_0^a \lambda(\xi) \exp(\gamma\xi - \Lambda(\xi)) d\xi \right) \left( \int_a^\infty \exp(-M(\tau)) d\tau \right) da, \end{aligned}$$

where

$$\bar{c} = \frac{\int_0^\infty c(a) \left( \exp(-\gamma a) \int_0^a \lambda(\xi) \exp(\gamma\xi - \Lambda(\xi)) d\xi \right) \left( \int_a^\infty \exp(-M(\tau)) d\tau \right) da}{\int_0^\infty \left( \exp(-\gamma a) \int_0^a \lambda(\xi) \exp(\gamma\xi - \Lambda(\xi)) d\xi \right) \left( \int_a^\infty \exp(-M(\tau)) d\tau \right) da}$$

is an average case fatality. Therefore,

$$\begin{aligned}
term_1 &= \gamma \bar{c} \int_0^\infty \exp(-M(a)) \left[ \int_0^a \exp(-\gamma\tau) \int_0^\tau \lambda(\xi) \exp(\gamma\xi - \Lambda(\xi)) d\xi d\tau \right] da \\
&= \gamma \bar{c} \int_0^\infty \exp(-M(a)) \left[ \int_0^a \lambda(\xi) \exp(\gamma\xi - \Lambda(\xi)) \int_\xi^a \exp(-\gamma\tau) d\tau d\xi \right] da \\
&= \bar{c} \int_0^\infty \exp(-M(a)) \left[ \int_0^a \lambda(\tau) \left[ \exp(-\Lambda(\tau)) - \exp(-(\gamma(a - \tau) + \Lambda(\tau))) \right] d\tau \right] da \\
&= \bar{c} \int_0^\infty \exp(-M(a)) \left[ 1 - \exp(-\Lambda(a)) - \int_0^a \lambda(\tau) \exp(-(\gamma(a - \tau) + \Lambda(\tau))) d\tau \right] da \\
&= \bar{c}(L_0 - L_u) \\
&\quad - \bar{c} \int_0^\infty \lambda(a) \exp(-(M(a) + \Lambda(a))) \int_a^\infty \exp(-(\gamma(\tau - a) + (M(\tau) - M(a)))) d\tau da \\
&= \bar{c}(L_0 - L_u) - \bar{c}L_v \\
&= \bar{c}L_0 - \bar{c}(L_u + L_v).
\end{aligned}$$

Hence

$$L = L_0 - term_1 = (1 - \bar{c})L_0 + \bar{c}(L_u + L_v).$$

I.e.,

$$\frac{L_0}{L} = \frac{1}{1 - \bar{c}} \left( 1 - \left( \frac{L_u}{L} + \frac{L_v}{L} \right) \bar{c} \right)$$

□

Formula (2.40) shows that the life expectancy at birth in the absence of infection depends on quantities that can be estimated. If we know  $\bar{c}$ ,  $L_u$ ,  $L_v$ , and  $L$  we can predict the gain in the expected time of life at birth if the infection is eradicated. This is the question that Daniel Bernoulli tried to answer.

**Proposition 2.3.** *The proportion of susceptible in the endemic equilibrium  $\bar{x}$  can be written as*

$$\bar{x} = \frac{P_D}{\hat{c}\hat{\lambda}L_1} \quad (2.41)$$

where

$$\hat{c} = \frac{\int_0^\infty c(a)\lambda(a) \exp(-(\rho_1 a + M(a) + \Lambda(a))) da}{\int_0^\infty \lambda(a) \exp(-(\rho_1 a + M(a) + \Lambda(a))) da}$$

is an average case fatality,

$$\hat{\lambda} = \frac{\int_0^\infty \lambda(a) \exp(-(\rho_1 a + M(a) + \Lambda(a))) da}{\int_0^\infty \exp(-(\rho_1 a + M(a) + \Lambda(a))) da}$$

is an average force of infection, and

$$P_D = \int_0^\infty c(a)\lambda(a) \exp(-(\rho_1 a + M(a) + \Lambda(a)))da$$

is the lifetime risk of the infection.

## 2.10 Stationary population

In this section we discuss the effect of the case fatality on the growth of the population. We look for the existence of sufficiently large case fatality such that the rate of growth of the population is driven to zero. First we discuss the situation when the case fatality does not depend on age. This means that all infected individuals have the same risk to die due the infection. Thereon, we consider the case of age-dependent case fatality. In other words, infected individuals have different risks to die due to the infection.

**Constant case fatality**  $c(a) = c_1$ :

In this case the characteristic equations read

$$\begin{aligned} 1 &= \int_0^\infty \beta(a) \exp(-M(a)) \left( 1 - \gamma \bar{\lambda}_1 c_1 \int_0^a \int_0^\tau s(\xi) \exp(-(\gamma(\tau - \xi) + \bar{\lambda}_1 S(\xi))) d\xi d\tau \right) da \\ 1 &= \frac{\kappa \int_0^\infty \exp(-M(a)) \int_0^a s(\tau) \exp\left(-\left(\gamma(a - \tau) + \bar{\lambda}_1 S(\tau)\right)\right) d\tau da}{\int_0^\infty \exp(-M(a)) \left( 1 - \gamma \bar{\lambda}_1 c_1 \int_0^a \int_0^\tau s(\xi) \exp(-(\gamma(\tau - \xi) + \bar{\lambda}_1 S(\xi))) d\xi d\tau \right) da}, \end{aligned} \quad (2.42)$$

The system (2.42) can be written as

$$\begin{aligned} R_D - 1 &= c_1(R_D - (p_{susc} + p_{inf})) = c_1(R_D - 1 + p_{rec}) \\ L_0 &= \frac{\kappa}{\bar{\lambda}_1} L_{v_0} + c_1(L_0 - L_{u_0} - L_{v_0}), \end{aligned} \quad (2.43)$$

where

$$p_{susc} = \int_0^\infty \beta(a) \exp(-M(a) + \Lambda(a)) da$$

is the number of newborns from susceptible parents,

$$p_{inf} = \int_0^\infty \beta(a) \exp(-M(a) + \Lambda(a)) \int_0^a \lambda(\tau) \exp(-\gamma(a - \tau) + (\Lambda(a) - \Lambda(\tau))) d\tau da$$

is the number of newborns from infected parents, and

$$p_{rec} = 1 - (p_{susc} + p_{inf})$$

is the number of newborns from recovered parents, and

$$\begin{aligned} L_{u_0} &= \int_0^\infty \exp(-(M(a) + \Lambda_1(a))) da, \\ L_{v_0} &= \int_0^\infty \lambda(a) \exp(-(M(a) + \Lambda_1(a))) \int_a^\infty \exp(-(\gamma(\tau - a) + (M(\tau) - M(a)))) d\tau da, \\ \Lambda_1(a) &= \bar{\lambda}_1 \int_0^a s(\tau) d\tau. \end{aligned}$$

Hence the critical case fatality required to reduce the growth rate of the population to zero is

$$\begin{aligned} c_1^* &= \frac{R_D - 1}{R_D - 1 + p_{rec}} \\ &= \frac{L_0 - (\kappa/\bar{\lambda}_1)L_{v_0}}{L_0 - (L_{u_0} + L_{v_0})}, \end{aligned} \quad (2.44)$$

where  $\bar{\lambda}_1$  is the real positive solution of the nonlinear equation

$$L_0 p_{rec} = (R_D - 1) \left( \frac{\kappa}{\bar{\lambda}_1} L_{v_0} - (L_{u_0} + L_{v_0}) \right). \quad (2.45)$$

Notice that if the nonlinear equation (2.45) does not have a real positive solution, then there is no case fatality sufficient to stop the growth of the population. However, if there is a positive real solution to (2.45) but  $c_1^* \notin (0, 1]$ , then the growth of the population cannot be reduced to zero.

### Age-dependent case fatality $c(a)$ :

To study the effect of age-dependent case fatality we assume that  $c(a) = qc_0(a)$  where  $c_0(a)$  is a non-negative continuous function not identically zero. The task now is to try to evaluate how much we can raise this parameter  $q$  such that the population goes to extinction or even to its demographic stationary. Whence the characteristic equations read:

$$\begin{aligned} 1 &= \int_0^\infty \beta(a) \exp(-M(a)) \left[ 1 - q\gamma\bar{\lambda}_0 \int_0^a c_0(\tau) \int_0^\tau s(\xi) \exp(-(\gamma(\tau - \xi) + \bar{\lambda}_0 S(\xi))) d\xi d\tau \right] da \\ 1 &= \frac{\kappa \int_0^\infty \exp(-M(a)) \int_0^a s(\tau) \exp \left[ - \left( \gamma(a - \tau) + \bar{\lambda}_0 S(\tau) \right) \right] d\tau da}{\int_0^\infty \exp(-M(a)) \left[ 1 - q\gamma\bar{\lambda}_0 \int_0^a c_0(\tau) \int_0^\tau s(\xi) \exp(-(\gamma(\tau - \xi) + \bar{\lambda}_0 S(\xi))) d\xi d\tau \right] da}, \end{aligned} \quad (2.46)$$



System (2.46) consists of two nonlinear equations in two unknowns, one of them is the parameter scaling of the case fatality,  $q$ , and the other is the critical value of  $\bar{\lambda}$  which we call here  $\bar{\lambda}_0$  and the null refers to a zero growth rate. This system can be written as

$$\begin{aligned} R_D - 1 &= q\bar{B}(\bar{\lambda}_0)\bar{c}_0(\bar{\lambda}_0)(L_0 - (L_u(\bar{\lambda}_0) + L_v(\bar{\lambda}_0))), \\ L_0 - \frac{\kappa}{\bar{\lambda}_0}L_v(\bar{\lambda}_0) &= q\bar{c}_0(\bar{\lambda}_0) \left[ L_0 - (L_u(\bar{\lambda}_0) + L_v(\bar{\lambda}_0)) \right], \end{aligned} \quad (2.47)$$

where

$$\bar{B}(\bar{\lambda}_0) = \frac{\int_0^\infty \beta(a) \exp(-M(a)) \int_0^a c_0(\tau) \int_0^\tau \lambda_0(\xi) \exp(-(\gamma(\tau - \xi) + \Lambda_0(\xi))) d\xi d\tau da}{\int_0^\infty \exp(-M(a)) \int_0^a c_0(\tau) \int_0^\tau \lambda_0(\xi) \exp(-(\gamma(\tau - \xi) + \Lambda_0(\xi))) d\xi d\tau da}$$

is an average birth rate. It depends on the force of infection and the case fatality. However, since the case fatality appears in both the numerator and denominator, the parameter  $q$  cancels and hence the average birth rate depends only on one unknown that is  $\bar{\lambda}_0$  which appears in the form of the force of infection. The notation

$$\lambda_0(\xi) = \bar{\lambda}_0 s(\xi)$$

denotes the force of infection corresponding to the case of stationary population. Also

$$\Lambda_0(\xi) = \bar{\lambda}_0 S(\xi)$$

denotes the cumulative force of infection corresponding to a stationary population, and

$$\bar{c}_0(\bar{\lambda}_0) = \frac{\int_0^\infty c_0(a) \left( \exp(-\gamma a) \int_0^a \lambda_0(\xi) \exp(\gamma\xi - \Lambda_0(\xi)) d\xi \right) \left( \int_a^\infty \exp(-M(\tau)) d\tau \right) da}{\int_0^\infty \left( \exp(-\gamma a) \int_0^a \lambda_0(\xi) \exp(\gamma\xi - \Lambda_0(\xi)) d\xi \right) \left( \int_a^\infty \exp(-M(\tau)) d\tau \right) da}$$

is an average of the rescaled case fatality  $c_0(a)$ . Hence the extension in the rescaled parameter  $q$  required to get a stationary population is given by

$$\begin{aligned} q &= \frac{R_D - 1}{\bar{B}(\bar{\lambda}_0)\bar{c}(\bar{\lambda}_0)(L_0 - (L_u(\bar{\lambda}_0) + L_v(\bar{\lambda}_0)))} \\ &= \frac{L_0 - (\kappa/\bar{\lambda}_0)L_v(\bar{\lambda}_0)}{\bar{c}(\bar{\lambda}_0)(L_0 - (L_u(\bar{\lambda}_0) + L_v(\bar{\lambda}_0)))} \end{aligned} \quad (2.48)$$

and therefore the average case fatality required to drive the population to its stationary is given by

$$\begin{aligned} \bar{c}^*(\bar{\lambda}_0) &= \frac{R_D - 1}{\bar{B}(\bar{\lambda}_0)(L_0 - (L_u(\bar{\lambda}_0) + L_v(\bar{\lambda}_0)))} \\ &= \frac{L_0 - (\kappa/\bar{\lambda}_0)L_v(\bar{\lambda}_0)}{(L_0 - (L_u(\bar{\lambda}_0) + L_v(\bar{\lambda}_0)))} \end{aligned} \quad (2.49)$$

where  $\bar{\lambda}_0$  is the real positive solution of the nonlinear equation

$$R_D - 1 = \bar{B}(\bar{\lambda}_0) \left( L_0 - \frac{\kappa}{\bar{\lambda}_0} L_v(\bar{\lambda}_0) \right). \quad (2.50)$$

The left hand side of (2.50) depends neither on the rescaling parameter  $q$  nor on  $\bar{\lambda}_0$ . However, the right hand side contains only  $\bar{\lambda}_0$  but not  $q$ . Therefore, the equation has only one unknown. This equation can be rewritten as

$$R_D - 1 = \bar{B}(\bar{\lambda}_0) (L_0 - L(q, \bar{\lambda}_0)). \quad (2.51)$$

This is because  $\bar{\lambda} = \kappa \bar{y}$  in general. And for a demographically stationary population, the proportion of susceptible individuals in the endemic equilibrium is the ratio between the expected time of life spent in the infected state  $L_v$  and the life expectancy at birth in the presence of infection  $L$ .

Therefore, to find out the required rise in the case fatality to drive the population to its stationary we have first to solve equation (2.50) with respect to  $\bar{\lambda}_0$  and then substitute in (2.48) to get  $q$ . Thereon, we evaluate the new case fatality  $c^*(a) = qc_0(a)$ . There may be two nonfeasible cases in addition to a feasible one. Either equation (2.50) has no real positive solution or it may have but  $qc_0(a)$  is not in the interval  $(0, 1]$ . If this happens, then there is no feasible extension in the case fatality to stop the growth of the population. In other words, the population can not be contained. Whence a suitable extension means a real positive solution of (2.50) such that  $c^*(a) = qc_0(a) \in (0, 1]$  for all age classes.

## 2.11 Average ages

The average age at infection for individuals who get infected in a growing population is

$$\bar{A}_\lambda = \frac{\int_0^\infty a \lambda(a) \exp(-(\rho_1 a + M(a) + \Lambda(a))) da}{\int_0^\infty \lambda(a) \exp(-(\rho_1 a + M(a) + \Lambda(a))) da} \quad (2.52)$$

The average age at which susceptible individuals die is

$$\bar{A}_\mu = \frac{\int_0^\infty a \mu(a) \exp(-(\rho_1 a + M(a) + \Lambda(a))) da}{\int_0^\infty \mu(a) \exp(-(\rho_1 a + M(a) + \Lambda(a))) da} \quad (2.53)$$

## 2.12 The limiting case of high infectivity and quick recovery

In the case of high infectivity (large  $\kappa$ ) and quick recovery (large  $\gamma$ ), the ratio  $\frac{\kappa}{\gamma}$  is kept constant. This constant we denote by  $R$ . Hence the system (2.5) reads

$$\begin{aligned} \frac{dX(a)}{da} &= - \left( \rho + \mu(a) + \lambda(a) \right) X(a), \\ \frac{dZ(a)}{da} &= -(\rho + \mu(a))Z(a) + (1 - c(a))\lambda(a)X(a), \\ \frac{dP(t)}{dt} &= \rho P(t), \end{aligned} \quad (2.54)$$

where

$$\begin{aligned} X(0) &= \int_0^\infty \beta(a) \left( X(a) + Z(a) \right) da \\ Z(0) &= 0. \end{aligned}$$

### Endemic equilibrium

The solution of the system (2.54) reads

$$\begin{aligned} X(a) &= X(0) \exp \left( -(\tilde{\rho}a + M(a) + \tilde{\Lambda}(a)) \right), \\ Z(a) &= X(0) \exp(-\tilde{\rho}a + M(a)) \int_0^a (1 - c(\tau)) \tilde{\lambda}(\tau) \exp(-\tilde{\Lambda}(\tau)) da, \end{aligned} \quad (2.55)$$

where

$$\begin{aligned} \tilde{\lambda}(a) &= \tilde{\lambda}_1 s(a), \\ \tilde{\Lambda}(a) &= \int_0^a \tilde{\lambda}(\tau) d\tau = \tilde{\lambda}_1 S(a), \\ S(a) &= \int_0^a s(\tau) d\tau, \end{aligned} \quad (2.56)$$

and  $(\tilde{\rho}, \tilde{\lambda}_1)$  is the solution of the nonlinear system of characteristic equations

$$\begin{aligned} 1 &= \int_0^\infty \beta(a) \exp(-(\tilde{\rho}a + M(a))) \left( 1 - \tilde{\lambda}_1 \int_0^a c(\tau) s(\tau) \exp(-\tilde{\lambda}_1 S(\tau)) d\tau \right) da, \\ 1 &= R \frac{\int_0^\infty s(a) \exp \left( -(\tilde{\rho}a + M(a) + \tilde{\lambda}_1 S(a)) \right) da}{\int_0^\infty \exp \left( -(\tilde{\rho}a + M(a)) \right) \left( 1 - \tilde{\lambda}_1 \int_0^a c(\tau) s(\tau) \exp(-\tilde{\lambda}_1 S(\tau)) d\tau \right) da}. \end{aligned} \quad (2.57)$$

The basic reproduction number in the limiting case is

$$R_0 = R \frac{\int_0^\infty s(a) \exp(-(\rho_0 a + M(a))) da}{\int_0^\infty \exp(-(\rho_0 a + M(a))) da} = R \tilde{s}_0. \quad (2.58)$$

The remaining proportion of susceptible in the limiting case is

$$\tilde{x} = \frac{\int_0^\infty \exp \left( -(\tilde{\rho}a + M(a) + \tilde{\lambda}_1 S(a)) \right) da}{\int_0^\infty \exp \left( -(\tilde{\rho}a + M(a)) \right) \left( 1 - \tilde{\lambda}_1 \int_0^a c(\tau) s(\tau) \exp(-\tilde{\lambda}_1 S(\tau)) d\tau \right) da}. \quad (2.59)$$

The relationship between the basic reproduction number and the proportion of susceptible individuals, in the endemic equilibrium, in the limiting case is

$$R_0 \tilde{x} = \frac{\tilde{s}_0}{\tilde{s}_\lambda}, \quad (2.60)$$

where

$$\tilde{s}_0 = \frac{\int_0^\infty s(a) \exp(-(\rho_0 a + M(a))) da}{\int_0^\infty \exp(-(\rho_0 a + M(a))) da} \quad (2.61)$$

$$\tilde{s}_\lambda = \frac{\int_0^\infty s(a) \exp(-(\tilde{\rho} a + M(a) + \tilde{\lambda}_1 S(a))) da}{\int_0^\infty \exp(-(\tilde{\rho} a + M(a) + \tilde{\lambda}_1 S(a))) da} \quad (2.62)$$

is an average susceptibility for individuals in a growing population, in the limiting case of high infectivity and quick recovery, in the presence of infection. A relation similar to that in (2.40) can be derived and written in the form

$$\frac{L_0^\ell}{L^\ell} = \frac{1}{1 - \tilde{c}} \left( 1 - \frac{\tilde{r}}{\tilde{r}_1} \tilde{c} \tilde{x} \right), \quad (2.63)$$

where

$$\tilde{c} = \frac{\int_0^\infty c(a) \tilde{\lambda}(a) \exp(-M(a) + \tilde{\Lambda}(a)) \left( \int_a^\infty \exp(-M(\tau) - M(a)) d\tau \right) da}{\int_0^\infty \tilde{\lambda}(a) \exp(-M(a) + \tilde{\Lambda}(a)) \left( \int_a^\infty \exp(-M(\tau) - M(a)) d\tau \right) da},$$

$$\tilde{r} = \frac{\int_0^\infty \exp(-(\tilde{\rho} a + M(a))) \left( 1 - \tilde{\lambda}_1 \int_0^a c(\tau) s(\tau) \exp(-\tilde{\lambda}_1 S(\tau)) d\tau \right) da}{\int_0^\infty \exp(-M(a)) \left( 1 - \tilde{\lambda}_1 \int_0^a c(\tau) s(\tau) \exp(-\tilde{\lambda}_1 S(\tau)) d\tau \right) da}.$$

Relation (2.63) is the gain in life expectancy in the limiting case of large contact rate and quick recovery.

If we assume a constant case fatality, we find that the minimal case fatality required to drive the growth rate of the population to zero is given by

$$\begin{aligned} \tilde{c}_1^* &= \frac{R_D - 1}{R_D - 1 + \tilde{p}_{rec}} \\ &= \frac{L_0 - R\tilde{P}_I/\tilde{\lambda}_0}{L_0 - L_u} \end{aligned} \quad (2.64)$$

where

$$\tilde{p}_{rec} = 1 - \int_0^\infty \beta(a) \exp(-M(a) + \tilde{\Lambda}(a)) da$$

is the number of newborns from recovered parents in the limiting case,

$$\tilde{P}_I = \int_0^\infty \tilde{\lambda}(a) \exp(-M(a) + \tilde{\Lambda}(a)) da$$

is the proportion of a cohort which gets infected in the limiting case, and  $\tilde{\lambda}_0$  is the positive real solution of the nonlinear equation

$$0 = (R_D - 1)(\tilde{\lambda}_0 L_u - R\tilde{P}_I) + \tilde{p}_{rec}(\tilde{\lambda}_0 L_0 - R\tilde{P}_I).$$

However, if we assume that case fatality depends on age,  $c(a) = qc_0(a)$ , then the extension in the case fatality required to stop the growth of the population is

$$\begin{aligned}\tilde{q}^* &= \frac{R_D - 1}{\tilde{B}\tilde{c}_0(L_0 - L_u)} \\ &= \frac{L_0 - \tilde{P}_I R / \tilde{\lambda}_0^*}{\tilde{c}_0(L_0 - L_u)}\end{aligned}\quad (2.65)$$

and the average case fatality required to drive the population growth rate to zero, in the limiting case, is

$$\tilde{c}^* = \tilde{q}^* \tilde{c}_0 = \frac{R_D - 1}{\tilde{B}(L_0 - L_u)} = \frac{L_0 - \tilde{P}_I R / \tilde{\lambda}_0^*}{(L_0 - L_u)},$$

where

$$\begin{aligned}\tilde{B} &= \frac{\int_0^\infty \beta(a) \exp(-M(a)) \int_0^a c_0(\tau) \tilde{\lambda}(\tau) \exp(-\tilde{\Lambda}(\tau)) d\tau da}{\int_0^\infty \exp(-M(a)) \int_0^a c_0(\tau) \tilde{\lambda}(\tau) \exp(-\tilde{\Lambda}(\tau)) d\tau da}, \\ \tilde{c}_0 &= \frac{\int_0^\infty c_0(a) \tilde{\lambda}(a) \exp\left(-M(a) + \tilde{\Lambda}(a)\right) \int_a^\infty \exp\left(-M(\tau) - M(a)\right) d\tau da}{\int_0^\infty \tilde{\lambda}(a) \exp\left(-M(a) + \tilde{\Lambda}(a)\right) \int_a^\infty \exp\left(-M(\tau) - M(a)\right) d\tau da},\end{aligned}$$

and  $\tilde{\lambda}_0^*$  is the real positive solution of the nonlinear equation

$$R_D - 1 = \tilde{B}(L_0 - \tilde{P}_I R / \tilde{\lambda}_0^*). \quad (2.66)$$

### 2.13 The life expectancy of individuals at any age $a$

To predict the average lifetime of an individual aged  $a$ , we follow a cohort. Assume that  $x(a)$ , and  $y(a)$  are the proportions of susceptible and infected of age  $a$  at the initial time. Assume also that  $U_a(\tau)$ ,  $V_a(\tau)$ , and  $W_a(\tau)$  are the probabilities that an individual of age  $a$  survives up to age  $\tau$  and is susceptible, infected, and immune respectively. Therefore,

$$\begin{aligned}U_a(\tau) &= x(a) \exp\left(-((M(\tau) - M(a)) + (\Lambda(\tau) - \Lambda(a)))\right), \\ V_a(\tau) &= \exp\left[-\gamma(\tau - a) - (M(\tau) - M(a))\right] \left(y(a) \right. \\ &\quad \left. + x(a) \int_a^\tau \lambda(\xi) \exp(\gamma(\xi - a) - (\Lambda(\xi) - \Lambda(a))) d\xi\right) \\ W_a(\tau) &= 1 - U_a(\tau) - V_a(\tau) \\ &= \exp\left[-(M(\tau) - M(a))\right] \left(1 - x(a) - y(a) + \gamma \int_a^\tau (1 - c(\xi)) \exp(-\gamma(\xi - a)) \left(y(a) \right. \right. \\ &\quad \left. \left. + x(a) \int_a^\xi \lambda(\eta) \exp\left[\gamma(\eta - a) - (\Lambda(\eta) - \Lambda(a))\right] d\eta\right) d\xi\right).\end{aligned}\quad (2.67)$$

The survival function of a cohort aged  $a$  which will survive up to age  $\tau$  in the presence of infection is

$$l_a(\tau) = \exp\left(- (M(\tau) - M(a))\right) \left(1 - \gamma \int_a^\tau c(\xi) \exp(-\gamma(\xi - a)) \left(y(a) + x(a) \int_a^\xi \lambda(\eta) \exp\left[\gamma(\eta - a) - (\Lambda(\eta) - \Lambda(a))\right] d\eta\right) d\xi\right). \quad (2.68)$$

The survival function for a cohort of age  $a$  which will survive up to age  $\tau$  in the absence of infection is

$$l_a^0(\tau) = \exp\left(- (M(\tau) - M(a))\right). \quad (2.69)$$

The life expectancy of an individual at age  $a$  in the absence of infection is

$$L_0(a) = \int_a^\infty \exp\left(- (M(\tau) - M(a))\right) d\tau. \quad (2.70)$$

The life expectancy of an individual at age  $a$  in the presence of infection is

$$\begin{aligned} L(a) &= L_0(a) - \gamma y(a) \int_a^\infty \exp\left(- (M(\tau) - M(a))\right) \int_a^\tau c(\xi) \exp(-\gamma(\xi - a)) d\xi d\tau \\ &\quad - \gamma x(a) \int_a^\infty \exp\left(- (M(\tau) - M(a))\right) \int_a^\tau c(\xi) \exp(-\gamma(\xi - a)) \\ &\quad \left(\int_a^\xi \lambda(\eta) \exp\left[\gamma(\eta - a) - (\Lambda(\eta) - \Lambda(a))\right] d\eta\right) d\xi d\tau. \end{aligned} \quad (2.71)$$

The proportions of susceptible and infected individuals of age  $a$  are given by

$$\begin{aligned} x(a) &= \frac{u(a)}{l(a)} = \frac{\exp(-\Lambda(a))}{1 - \gamma \int_0^a \lambda(\xi) \exp(-\Lambda(\xi)) \int_\xi^a c(\tau) \exp(-\gamma(\tau - \xi)) d\tau d\xi}, \\ y(a) &= \frac{v(a)}{l(a)} = \frac{\int_0^a \lambda(\tau) \exp(-\gamma(a - \tau) - \Lambda(\tau)) d\tau}{1 - \gamma \int_0^a \lambda(\xi) \exp(-\Lambda(\xi)) \int_\xi^a c(\tau) \exp(-\gamma(\tau - \xi)) d\tau d\xi}. \end{aligned} \quad (2.72)$$

## 2.14 A numerical example

In the following we apply our model to the case of smallpox spread in the Eighteenth Century. The data are obtained from The Hague. We estimated the parameters  $\mu(a)$ ,  $c(a)$ , and  $\lambda(a)$  from the data and we will publish the curve fitting problem somewhere else. The fitted parameters are

$$\begin{aligned} \mu(a) &= \mu_0 \exp(\alpha_0 a) + \mu_1 \delta a^{\delta-1} \exp\left(-\left(\delta_0 + \mu_1 a^\delta\right)\right) + \frac{\mu_2}{\sigma \sqrt{2\pi}} \exp\left(-\frac{1}{2} \left(\frac{1}{\sigma} \ln \frac{a}{A_1}\right)^2\right), \\ c(a) &= d_0 \exp(-\alpha_2 a) + d_1 \left(1 - \exp(-\alpha_3 a)\right)^2, \\ \lambda(a) &= \begin{cases} \lambda_0 a & \text{if } a \leq A, \\ \lambda_0 A \left(\frac{A}{a}\right) & \text{if } a \geq A. \end{cases} \end{aligned}$$

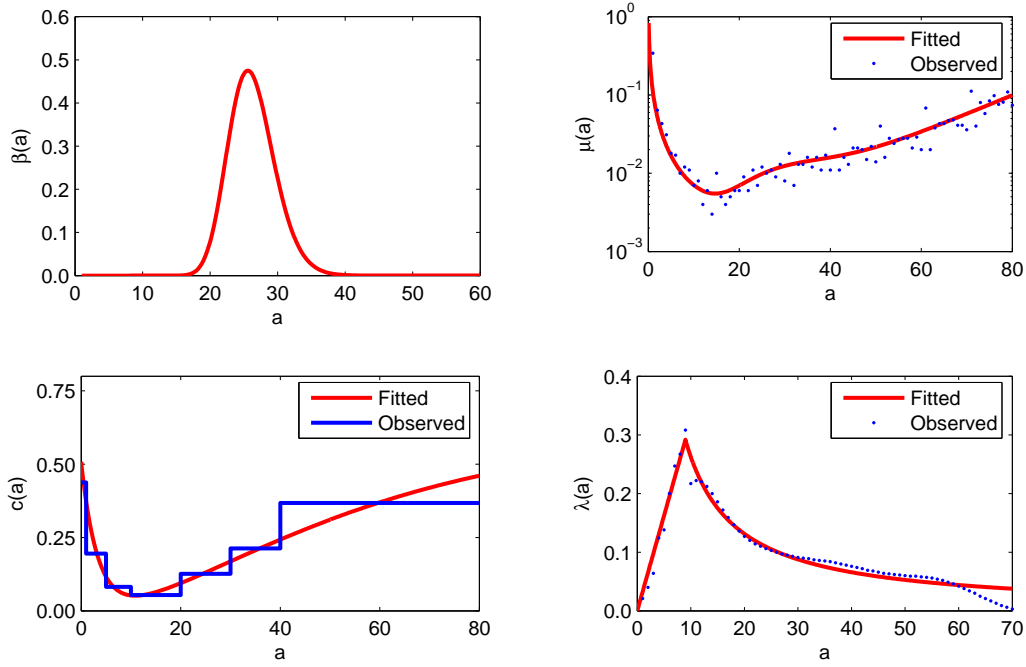


Figure 2.1: Age specific model parameters.

where

$$\begin{aligned} \mu_0 = 0.0012, \quad \alpha_0 = 0.0552, \quad \mu_1 = 1.0963, \quad \delta = 0.4146, \quad \delta_0 = 0.3223, \quad \mu_2 = 0.0049, \\ \sigma = 0.3373, \quad A_1 = 32.5314, \quad d_0 = 0.5083, \quad \alpha_2 = 0.3097, \quad d_1 = 0.6262, \quad \alpha_3 = 0.0244, \\ \lambda_0 = 0.0324, \quad \text{and } A = 9. \end{aligned}$$

We consider the per capita age specific birth rate

$$\beta(a) = \frac{\beta_0}{a\sigma\sqrt{2\pi}} \exp\left(-\left(\frac{\ln a - \bar{\mu}}{\sigma\sqrt{2}}\right)^2\right)$$

where  $\beta_0 = 4$ ,  $\bar{\mu} = 3.26$ , and  $\sigma = 0.13$ . The graphs of the previous four age specific functions are shown in figure 2.1. We assume the recovery rate  $\gamma = 52$  per year which means that the length of the infectious period is of about one week. We assume also that the number of contacts an infected individual can perform with susceptible individuals is  $\kappa = 500$  per year. Using the previous functions we got the following results

- 1) The growth rate of the population is  $\rho_1 = 0.0177$  per year.
- 2) The parameter  $\bar{\lambda} = 0.3199$  per year. Therefore the age specific susceptibility is  $s(a) = \frac{1}{\bar{\lambda}}\lambda(a)$  and is shown in figure 2.2.
- 3) The largest possible growth rate (Malthusian) is  $\rho_0 = 0.0220$  per year.
- 4) The basic reproduction number is  $R_0 = 8.63$ , whereas the demographic reproduction number is  $R_D = 1.77$ .

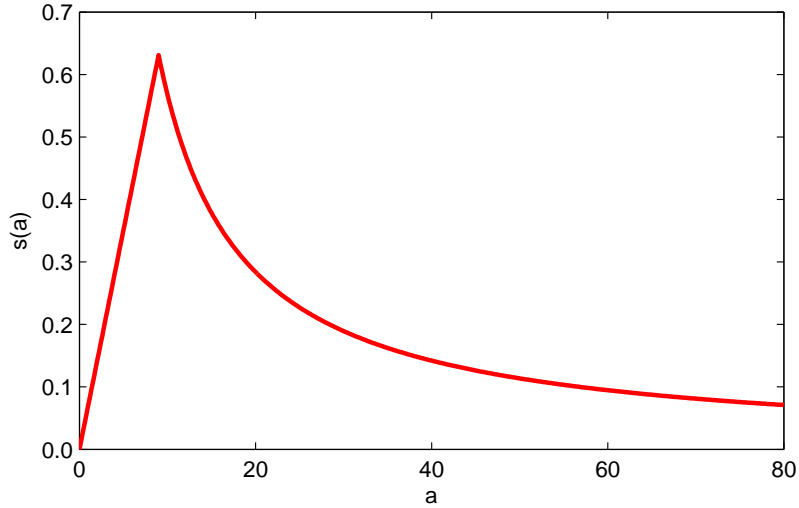


Figure 2.2: The age specific susceptibility  $s(a)$ .

- 5) The proportions of susceptible and infected individuals in the endemic equilibrium are  $\bar{x} = 0.2295$  and  $\bar{y} = 0.0006$ . The age distribution of the population classes (susceptible  $X(a)$ , infected  $Y(a)$ , and recovered  $Z(a)$ ) as well as the total population  $N(a)$  is shown in figure 2.3
- 6) The life expectancy at birth in the absence of infection  $L_0$  and in the presence of infection  $L$  are respectively  $L_0 = 28.483$  years and  $L = 25.89$  years.
- 7) A graph explaining the life expectancies at any age in the absence  $L_0(a)$  as well as in the presence  $L(a)$  of infection is shown in figure 2.4.
- 8) Now we evaluate the quantities in relation (2.28). The average susceptibility for individuals in a totally susceptible growing population is  $\bar{s}_0 = 0.904$ , whereas that in the presence of infection is  $\bar{s}_\lambda = 0.402$ . The average discounted duration of the infectious period for an individual of age  $a$  in a growing population with growth rate  $\rho_0 = 0.0220$  ( $\rho_1 = 0.0177$ ) per year is  $\bar{D}_0 = 0.0192$  ( $\bar{D}_\lambda = 0.0218$ ) years. I.e.,  $\bar{D}_0 = 7.008$  ( $\bar{D}_\lambda = 7.957$ ) days.
- 9) The duration of the lifetime in the susceptible state is  $L_u = 3.881$  years, whereas the expected time of life spent in the infected state is  $L_v = 0.0114$  years (i.e., about 4.161 days).
- 10) If we assume a constant case fatality, then the case fatality required to drive the population to stationary is  $c_1^* = 0.5040$ .
- 11) If we consider an age-specific case fatality and we parameterize the existent case fatality in to write it in the form  $c^*(a) = qc_0(a)$  where  $q$  is the parameter to be determined and  $c_0(a) = \exp(-\alpha_2 a) + \frac{d_1}{d_0} \left(1 - \exp(-\alpha_3 a)\right)^2$ . Then  $q = 2.1222$ . Figure (2.5) shows the critical age specific case fatality required to stop the growth of the population. It is clear



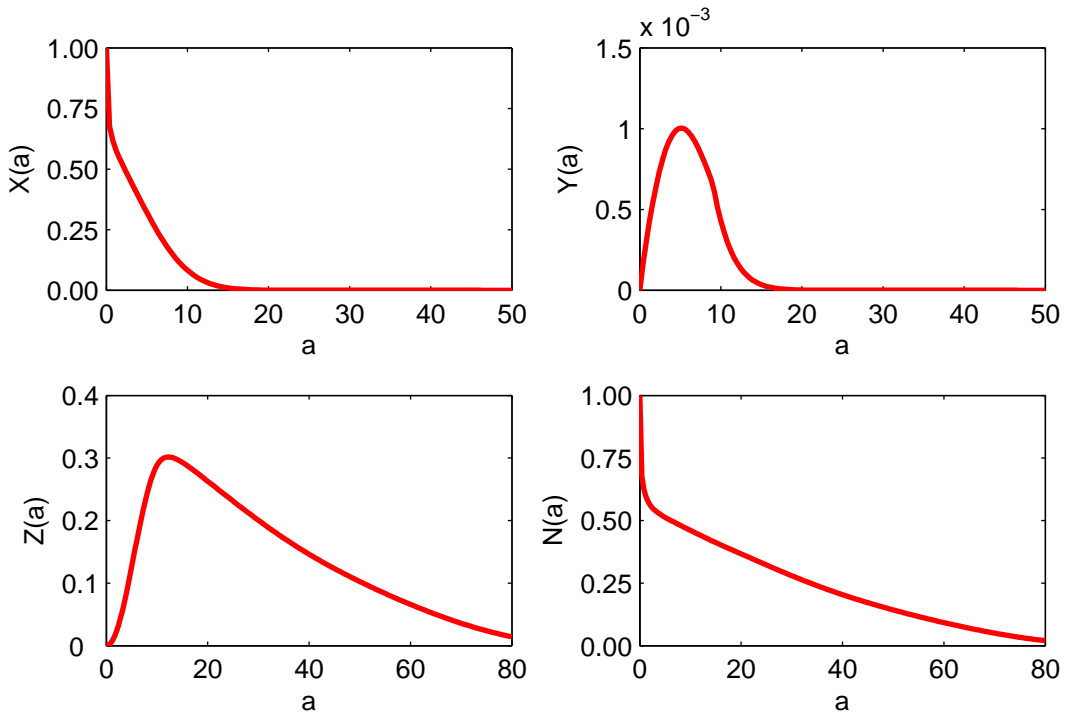


Figure 2.3: The age distribution.

that  $c^*(a) > 1$  which is nonfeasible because  $c(a) \in [0, 1]$  for all ages  $a \in [0, \infty)$ . Therefore, the smallpox was not able to eradicate or even to stop the growth of the population.

- 12) The average age at infection for individuals who get infected in a growing population is  $\bar{A}_\lambda = 6.003$  years, whereas the average age of individuals who die without getting infected is  $\bar{A}_\mu = 4.4703$  years.
- 13) The proportion of immunes at any age for different values of case fatality is shown in figure 2.6.

## 2.15 Stability

Let us now turn to study the problem of stability of the equilibria. Since the variable  $Z(a, t)$  does not appear in the first two equations of (2.1), we consider instead the model

$$\begin{aligned}
 \frac{\partial X(a, t)}{\partial t} + \frac{\partial X(a, t)}{\partial a} &= -(\mu(a) + \lambda(a, t))X(a, t), \\
 \frac{\partial Y(a, t)}{\partial t} + \frac{\partial Y(a, t)}{\partial a} &= -(\gamma + \mu(a))Y(a, t) + \lambda(a, t), \\
 \frac{\partial N(a, t)}{\partial t} + \frac{\partial N(a, t)}{\partial a} &= -\mu(a)N(a, t) - c(a)\gamma Y(a, t),
 \end{aligned} \tag{2.73}$$

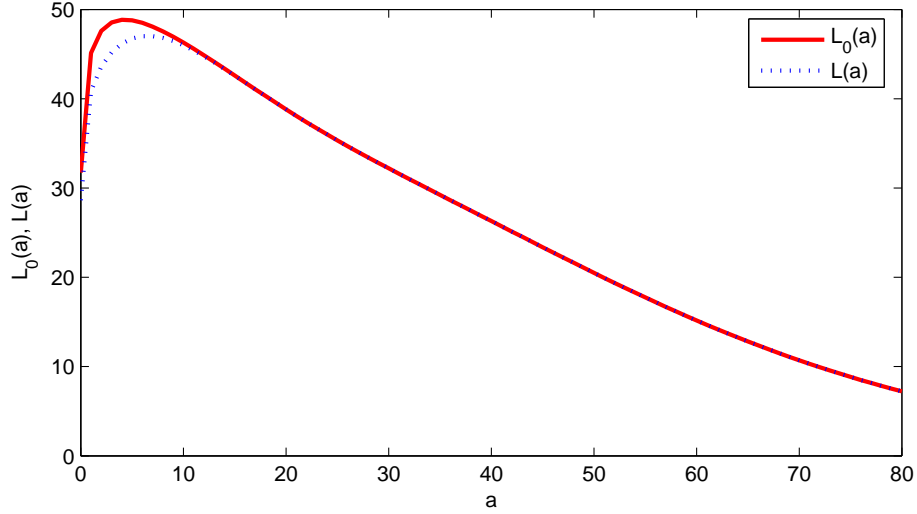


Figure 2.4: The life expectancies at any age. The solid line represents the life expectancy at any age in the absence of smallpox  $L_0(a)$ , whereas the dotted curve represents the expected time of life at any age  $a$  in the presence of smallpox  $L(a)$ .

with boundary conditions

$$\begin{aligned} X(0, t) &= N(0, t) = \int_0^\infty \beta(a)N(a, t)da, \\ Y(0, t) &= 0, \end{aligned} \tag{2.74}$$

where

$$\lambda(a, t) = \kappa s(a) \frac{\int_0^\infty Y(a, t)da}{\int_0^\infty N(a, t)da}. \tag{2.75}$$

This model has the endemic equilibria: The infection free equilibrium (IFE)

$$(X(a, t), Y(a, t), Z(a, t))' = (N_0(a), 0, N_0(a))' \exp(\rho_0 t)$$

where  $\rho_0$  is the largest value of the growth rate (the Malthus parameter) and is the solution of equation (2.7) and

$$N_0(a) = N(0) \exp\left(-(\rho_0 a + M(a))\right).$$

The endemic equilibrium

$$(X(a), Y(a), N(a))' \exp(\rho_1 t)$$

where  $\rho_1$  as well as the parameter  $\bar{\lambda}$  is determined from the system (2.12 - 2.14) and  $X(a)$ ,  $Y(a)$ , and  $N(a)$  are determined from (2.9). The variable  $N(a)$  does not, however, appear in (2.9) but it is the summation of all three components. I.e.,  $N(a) = X(a) + Y(a) + Z(a)$ .

### Linearization:

To study the stability of the equilibria, we introduce small perturbations about the endemic

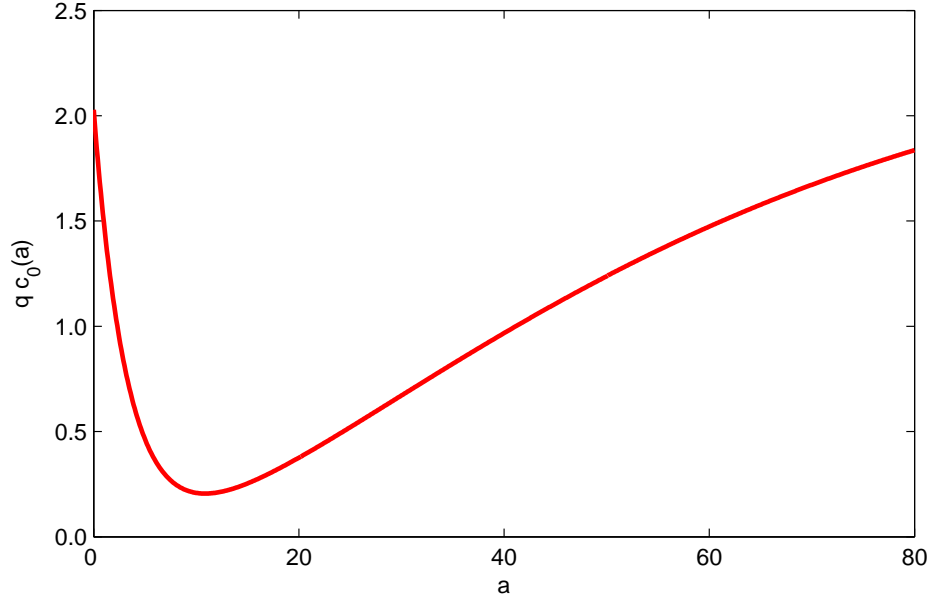


Figure 2.5: This figure shows the age-specific case fatality required to drive the population to its demographic stationary. We parameterize the actual case fatality (the fitted one from the data) and try to write it as the product of an age-independent parameter called  $q$  and an age-dependent function called  $c_0(a)$ . The parameter  $q$  is the unknown, whereas  $c_0(a)$  is given. Then we solve to get  $q$  and the required case fatality would be  $c^*(a) = qc_0(a)$ . We notice that  $c^*(a) \not\leq 1$  for all  $a \in [0, \infty)$ . Therefore there is no feasible age-dependent case fatality to stop the growth of the population. In other words, smallpox was not able to eliminate or even to stop the growth of the population.

states. First we consider a general equilibrium solution and somewhere later in the text we will specify the equations to each equilibrium solution. Let

$$\begin{aligned}
 X(a, t) &= X(a) \exp(\rho t) + \epsilon_1(a, t), \\
 Y(a, t) &= Y(a) \exp(\rho t) + \epsilon_2(a, t), \\
 N(a, t) &= N(a) \exp(\rho t) + \epsilon(a, t).
 \end{aligned} \tag{2.76}$$

Substituting from (2.76) into (2.75), and performing some calculations give

$$\lambda(a, t) = \kappa s(a) \frac{1}{\bar{N}} \left( \bar{Y} + \exp(-\rho t) \int_0^\infty \epsilon_2(a, t) da - \frac{\bar{Y} \exp(-\rho t)}{\bar{N}} \int_0^\infty \epsilon(a, t) da + O(\epsilon^2) \right), \tag{2.77}$$

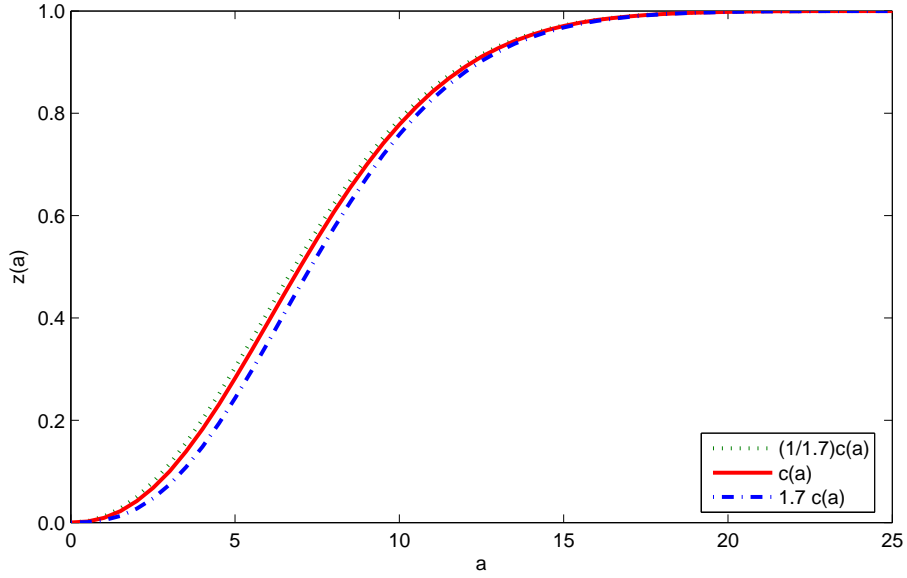


Figure 2.6: The proportion of immunes at any age for three different levels of the case fatality. The solid line represents the case if we consider the case fatality as defined before. The dashed-dotted line corresponds to the case of 1.7 times the case fatality and this line is below the solid one. The line above the solid one and is dotted represents the case if we consider only  $1/(1.7)$  times the case fatality. With the increase of the level of the case fatality, the proportion of immunes at any age decreases.

where

$$\begin{aligned}
 \bar{X} &= \int_0^{\infty} X(a) da, \\
 \bar{Y} &= \int_0^{\infty} Y(a) da, \\
 \bar{N} &= \int_0^{\infty} N(a) da.
 \end{aligned} \tag{2.78}$$

The perturbation  $\epsilon$  is small such that quantities  $O(\epsilon^2)$  can be neglected. Therefore,

$$\begin{aligned}
 &\lambda(a, t)X(a, t) \\
 = &\frac{\kappa s(a)}{\bar{N}} \left( \bar{Y} X(a) \exp(\rho t) + X(a) \int_0^{\infty} \epsilon_2(a, t) da - \frac{\bar{Y}}{\bar{N}} X(a) \int_0^{\infty} \epsilon(a, t) da + \bar{Y} \epsilon_1(a, t) \right).
 \end{aligned} \tag{2.79}$$

Now we use (2.76 - 2.79) in (2.73) and (2.74) and the assumption that  $(X(a), Y(a), N(a))' \exp(\rho t)$  is an equilibrium solution to get

$$\begin{aligned}
\frac{\partial \epsilon_1(a, t)}{\partial a} + \frac{\partial \epsilon_1(a, t)}{\partial t} &= -\mu(a)\epsilon_1(a, t) \\
&\quad - \frac{\kappa s(a)}{\bar{N}} \left( X(a) \int_0^\infty \epsilon_2(a, t) da - \frac{\bar{Y}}{\bar{N}} X(a) \int_0^\infty \epsilon(a, t) da + \bar{Y} \epsilon_1(a, t) \right), \\
\frac{\partial \epsilon_2(a, t)}{\partial a} + \frac{\partial \epsilon_2(a, t)}{\partial t} &= -(\gamma + \mu(a))\epsilon_2(a, t) \\
&\quad + \frac{\kappa s(a)}{\bar{N}} \left( X(a) \int_0^\infty \epsilon_2(a, t) da - \frac{\bar{Y}}{\bar{N}} X(a) \int_0^\infty \epsilon(a, t) da + \bar{Y} \epsilon_1(a, t) \right), \\
\frac{\partial \epsilon(a, t)}{\partial a} + \frac{\partial \epsilon(a, t)}{\partial t} &= -\mu(a)\epsilon(a, t) - c(a)\gamma\epsilon_2(a, t).
\end{aligned} \tag{2.80}$$

with boundary conditions

$$\begin{aligned}
\epsilon_1(0, t) &= \epsilon(0, t) = \int_0^\infty \beta(a)\epsilon(a, t) da, \\
\epsilon_2(0, t) &= 0.
\end{aligned} \tag{2.81}$$

We are looking for solutions of the form

$$\begin{aligned}
\epsilon_1(a, t) &= \epsilon_1(a) \exp(\sigma t), \\
\epsilon_2(0, t) &= \epsilon_2(a) \exp(\sigma t), \\
\epsilon(a, t) &= \epsilon(a) \exp(\sigma t).
\end{aligned} \tag{2.82}$$

Therefore by using (2.82) in (2.80) and (2.81), we get

$$\begin{aligned}
\sigma \epsilon_1(a) + \frac{d\epsilon_1(a)}{da} &= -\mu(a)\epsilon_1(a) - \frac{\kappa s(a)}{\bar{N}} \left( X(a)\bar{\epsilon}_2 - \frac{\bar{Y}}{\bar{N}} X(a)\bar{\epsilon} + \bar{Y} \epsilon_1(a) \right), \\
\sigma \epsilon_2(a) + \frac{d\epsilon_2(a)}{da} &= -(\gamma + \mu(a))\epsilon_2(a) + \frac{\kappa s(a)}{\bar{N}} \left( X(a)\bar{\epsilon}_2 - \frac{\bar{Y}}{\bar{N}} X(a)\bar{\epsilon} + \bar{Y} \epsilon_1(a) \right), \\
\sigma \epsilon(a) + \frac{d\epsilon(a)}{da} &= -\mu(a)\epsilon(a) - c(a)\gamma\epsilon_2(a),
\end{aligned} \tag{2.83}$$

with boundary conditions

$$\begin{aligned}
\epsilon_1(0) &= \epsilon(0) = \int_0^\infty \beta(a)\epsilon(a) da, \\
\epsilon_2(0) &= 0,
\end{aligned} \tag{2.84}$$

where

$$\begin{aligned}
\bar{\epsilon}_1 &= \int_0^\infty \epsilon_1(a) da, \\
\bar{\epsilon}_2 &= \int_0^\infty \epsilon_2(a) da, \\
\bar{\epsilon} &= \int_0^\infty \epsilon(a) da.
\end{aligned} \tag{2.85}$$

Model (2.83 - 2.84) is general. In other words, it applies to any equilibrium solution of the main model (2.1 - 2.2).

**Stability of the IFE**  $(N_0(a), 0, N_0(a))' \exp(\rho_0 t)$ :

For the infection free equilibrium, model (2.83) reads

$$\begin{aligned}\frac{d\epsilon_1(a)}{da} &= -(\sigma + \mu(a))\epsilon_1(a) - \frac{\kappa s(a)}{\bar{N}_0} N_0(a) \bar{\epsilon}_2, \\ \frac{d\epsilon_2(a)}{da} &= -(\sigma + \gamma + \mu(a))\epsilon_2(a) + \frac{\kappa s(a)}{\bar{N}_0} N_0(a) \bar{\epsilon}_2, \\ \frac{d\epsilon(a)}{da} &= -(\sigma + \mu(a))\epsilon(a) - c(a)\gamma\epsilon_2(a),\end{aligned}\tag{2.86}$$

with boundary conditions in (2.84) and where

$$\bar{N}_0 = \int_0^\infty N_0(a) da = N(0) \int_0^\infty \exp\left(-(\rho_0 a + M(a))\right) da.\tag{2.87}$$

The solution of the system (2.86) is

$$\begin{aligned}\epsilon_1(a) &= \left( \epsilon_1(0) - \bar{\epsilon}_2 \frac{\kappa N(0)}{\bar{N}_0} \int_0^a s(\tau) \exp((\sigma - \rho_0)\tau) d\tau \right) \exp\left(-(\sigma a + M(a))\right), \\ \epsilon_2(a) &= \left( \bar{\epsilon}_2 \frac{\kappa N(0)}{\bar{N}_0} \int_0^a s(\tau) \exp((\sigma - \rho_0 + \gamma)\tau) d\tau \right) \exp\left(-((\sigma + \gamma)a + M(a))\right), \\ \epsilon(a) &= \left( -\bar{\epsilon}_2 \gamma \frac{\kappa N(0)}{\bar{N}_0} \int_0^a c(\tau) \exp(-\gamma\tau) \int_0^\tau s(\xi) \exp((\sigma - \rho_0 + \gamma)\xi) d\xi d\tau \right. \\ &\quad \left. + \epsilon_1(0) \right) \exp\left(-(\sigma a + M(a))\right),\end{aligned}\tag{2.88}$$

where

$$\begin{aligned}\epsilon_1(0) &= \int_0^\infty \beta(a) \exp\left(-(\sigma a + M(a))\right) \left( \epsilon_1(0) \right. \\ &\quad \left. - \bar{\epsilon}_2 \gamma \frac{\kappa N(0)}{\bar{N}_0} \int_0^a c(\tau) \exp(-\gamma\tau) \int_0^\tau s(\xi) \exp((\sigma - \rho_0 + \gamma)\xi) d\xi d\tau \right) da.\end{aligned}\tag{2.89}$$

Integrating all sides in (2.88) over all ages from 0 to  $\infty$  and taking into account relation (2.89) give

$$\begin{aligned}
0 &= \epsilon_1(0) \int_0^\infty \exp(-(\sigma a + M(a))) da - \bar{\epsilon}_1 - \\
&\quad \bar{\epsilon}_2 \frac{\kappa N(0)}{\bar{N}_0} \int_0^\infty \exp(-(\sigma a + M(a))) \int_0^a s(\tau) \exp((\sigma - \rho_0)\tau) d\tau da, \\
0 &= \bar{\epsilon}_2 \left( -1 + \frac{\kappa N(0)}{\bar{N}_0} \int_0^\infty \exp(-((\sigma + \gamma)a + M(a))) \int_0^a s(\tau) \exp((\sigma - \rho_0 + \gamma)\tau) d\tau da \right), \\
0 &= \epsilon_1(0) \int_0^\infty \exp(-(\sigma a + M(a))) da - \bar{\epsilon} - \\
&\quad \bar{\epsilon}_2 \gamma \frac{\kappa N(0)}{\bar{N}_0} \int_0^\infty \exp(-(\sigma a + M(a))) \int_0^a c(\tau) \exp(-\gamma\tau) \int_0^\tau s(\xi) \exp((\sigma - \rho_0 + \gamma)\xi) d\xi d\tau da, \\
0 &= \epsilon_1(0) \left( -1 + \int_0^\infty \beta(a) \exp(-(\sigma a + M(a))) da \right) - \\
&\quad \bar{\epsilon}_2 \gamma \frac{\kappa N(0)}{\bar{N}_0} \int_0^\infty \beta(a) \exp(-(\sigma a + M(a))) \int_0^a c(\tau) \exp(-\gamma\tau) \int_0^\tau s(\xi) \exp((\sigma - \rho_0 + \gamma)\xi) d\xi d\tau da.
\end{aligned} \tag{2.90}$$

This is a homogeneous algebraic system of the fourth degree. It can be written in matrix form as

$$\begin{pmatrix} A_{11}(\sigma) & -1 & -A_{13}(\sigma) & 0 \\ 0 & 0 & A_{23}(\sigma) & 0 \\ A_{31}(\sigma) & 0 & -A_{33}(\sigma) & -1 \\ A_{41}(\sigma) & 0 & -A_{43}(\sigma) & 0 \end{pmatrix} \begin{pmatrix} \epsilon_1(0) \\ \bar{\epsilon}_1 \\ \bar{\epsilon}_2 \\ \bar{\epsilon} \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \\ 0 \\ 0 \end{pmatrix}, \tag{2.91}$$

where

$$\begin{aligned}
A_{11}(\sigma) &= \int_0^\infty \exp(-(\sigma a + M(a))) da, \\
A_{13}(\sigma) &= \frac{\kappa N(0)}{\bar{N}_0} \int_0^\infty \exp(-(\sigma a + M(a))) \int_0^a s(\tau) \exp((\sigma - \rho_0)\tau) d\tau da, \\
A_{23}(\sigma) &= -1 + \frac{\kappa N(0)}{\bar{N}_0} \int_0^\infty \exp(-((\sigma + \gamma)a + M(a))) \int_0^a s(\tau) \exp((\sigma - \rho_0 + \gamma)\tau) d\tau da, \\
A_{31}(\sigma) &= \int_0^\infty \exp(-(\sigma a + M(a))) da, \\
A_{33}(\sigma) &= \gamma \frac{\kappa N(0)}{\bar{N}_0} \cdot \\
&\quad \int_0^\infty \exp(-(\sigma a + M(a))) \int_0^a c(\tau) \exp(-\gamma\tau) \int_0^\tau s(\xi) \exp((\sigma - \rho_0 + \gamma)\xi) d\xi d\tau da,
\end{aligned} \tag{2.92}$$

$$\begin{aligned}
A_{41}(\sigma) &= -1 + \int_0^\infty \beta(a) \exp(-(\sigma a + M(a))) da, \\
A_{43}(\sigma) &= \gamma \frac{\kappa N(0)}{\bar{N}_0} \cdot \\
&\quad \int_0^\infty \beta(a) \exp(-(\sigma a + M(a))) \int_0^a c(\tau) \exp(-\gamma\tau) \int_0^\tau s(\xi) \exp((\sigma - \rho_0 + \gamma)\xi) d\xi d\tau da.
\end{aligned}$$

This system has a nontrivial solution if and only if

$$A_{23}(\sigma)A_{41}(\sigma) = 0.$$

Therefore, either  $A_{41}(\sigma) = 0$  or  $A_{23}(\sigma) = 0$ . I.e., either

$$\int_0^\infty \beta(a) \exp(-(\sigma a + M(a))) da = 1 \quad (2.93)$$

or

$$\frac{\kappa N(0)}{\bar{N}_0} \int_0^\infty \exp(-((\sigma + \gamma)a + M(a))) \int_0^a s(\tau) \exp((\sigma - \rho_0 + \gamma)\tau) d\tau da = 1. \quad (2.94)$$

Equation (2.93) has an infinite number of solutions. Comparing with equation (2.7), we observe that the real solution is  $\sigma = \rho_0$  whereas the remaining set consists of conjugate complex roots. From (2.87) and (2.16), we get

$$\kappa \frac{N(0)}{\bar{N}_0} = \frac{R_0}{\int_0^\infty \exp(-(\rho_0 a + M(a))) \int_0^a s(\tau) \exp(-\gamma(a - \tau)) d\tau da}. \quad (2.95)$$

Using (2.94) and (2.95), we get

$$\begin{aligned}
R_0 \int_0^\infty \exp(-(\rho_0 a + M(a))) \int_0^a s(\tau) \exp(-(\sigma - \rho_0 + \gamma)(a - \tau)) d\tau da = \\
\int_0^\infty \exp(-(\rho_0 a + M(a))) \int_0^a s(\tau) \exp(-\gamma(a - \tau)) d\tau da.
\end{aligned} \quad (2.96)$$

Assume that  $\sigma^R$  and  $\sigma^I$  are the real and imaginary parts of  $\sigma$ . Then equation (2.96) leads to

$$\begin{aligned}
R_0 \int_0^\infty \exp(-(\rho_0 a + M(a))) \int_0^a s(\tau) \exp(-(\sigma^R - \rho_0 + \gamma)(a - \tau)) \cos(\sigma^I(a - \tau)) d\tau da = \\
\int_0^\infty \exp(-(\rho_0 a + M(a))) \int_0^a s(\tau) \exp(-\gamma(a - \tau)) d\tau da.
\end{aligned} \quad (2.97)$$

Equation (2.97) is a nonlinear equation in the variable  $\sigma$ . The right hand side is constant, whereas the left hand side is the multiplication of both the basic reproduction number  $R_0$  and a function in  $\sigma$ . There are two cases:

case 1: If  $Re(\sigma) = \sigma^R = \rho_0$ , then equation (2.97) says  $R_0 = 1$ .

Case 2: If  $Re(\sigma) = \sigma^R \neq \rho_0$ . Assume that  $Re(\sigma) < \rho_0$ , then

$$\begin{aligned}
\int_0^\infty \exp(-(\rho_0 a + M(a))) \int_0^a s(\tau) \exp(-(\sigma^R - \rho_0 + \gamma)(a - \tau)) \cos(\sigma^I(a - \tau)) d\tau da > \\
\int_0^\infty \exp(-(\rho_0 a + M(a))) \int_0^a s(\tau) \exp(-\gamma(a - \tau)) d\tau da.
\end{aligned}$$



Therefore,  $R_0 < 1$  since the right hand side in (2.97) is constant. Whence  $R_0 < 1$  if and only if  $Re(\sigma) < \rho_0$ . According to the theory of homogeneous evolution equations, the condition of stability is  $Re(\sigma) < \rho_0$ . Thereon, the infection free equilibrium is locally asymptotically exponentially stable if and only if  $R_0 < 1$ .

## 2.16 Summary

In this chapter we presented an SIR epidemic model for a potentially lethal infection. Rather than following the standard approach by considering a demographically stationary population and the so-called differential mortality approach, we considered a population which grows exponentially and we considered the case fatality approach. In section (2.5) we introduced the by now called demographic characteristic equation from which we determine the rate of growth. If the infection is not fatal, this rate of growth has its largest value being called the Malthusian parameter. With the increase of the case fatality, the rate of growth decreases nonlinearly. The possibility to drive the rate of growth to zero and hence the host population to extinction has been discussed in section (2.10). The importance of the relations in section (2.10) is that they show the requirements on the case fatality to pull down the growth rate to zero in both cases if the case fatality is constant and if it is age-dependent. In a numerical example, section (2.14), which represents the case of smallpox in Europe in the Eighteenth Century we found out that smallpox was nowhere able to eradicate or even to stop the growth of the host population.

Section (2.8) presents the relationship between the basic reproduction number  $R_0$  and the proportion of susceptible individuals in the endemic equilibrium,  $\bar{x}$ . If both the susceptibility and the per capita death rate are age-independent and in addition is the population demographically stationary, then the basic reproduction number is the inverse of the proportion of susceptible individuals in the endemic equilibrium. Equation (2.28) says that the product  $R_0\bar{x} \neq 1$  in general but it equals the product of two ratios. One of them is the ratio between two averages of susceptibilities, in the absence  $\bar{s}_0$  and in the presence  $\bar{s}_\lambda$  of the infection. The other ratio is that between two average discounts in the duration of the infectious period for an individual of age  $a$  in a growing population with growth rate  $\rho_0$  for  $\bar{D}_0$  and  $\rho_1$  for  $\bar{D}_\lambda$ . Even if we have a demographically stationary population but age-dependent model parameters, the product  $R_0\bar{x} \neq 1$  in general (see the corollary in section (2.8)). In the numerical example we have  $\bar{s}_0 = 0.904$ ,  $\bar{s}_\lambda = 0.402$ ,  $\bar{D}_0 = 0.0192$  years,  $\bar{D}_\lambda = 0.0218$  years,  $R_0 = 8.63$ , and  $\bar{x} = 0.2295$ . We notice that  $R_0\bar{x} = 1.98 = \frac{\bar{s}_0}{\bar{s}_\lambda} \frac{\bar{D}_0}{\bar{D}_\lambda}$ .

Formula (2.40) in section (2.9) explains the gain in the life expectancy. It contains five quantities (the life expectancies at birth in the absence  $L_0$  and presence  $L$  of infection, the duration of the lifetime spent in the susceptible state  $L_u$  and in the infected state  $L_v$ , and an average case fatality  $\bar{c}$ ). We can find one of them if we know the rest. These quantities are all measurable in the sense that they can be estimated from the data. In the numerical example we evaluated the life expectancies at birth in the absence of infection  $L_0 = 28.483$  years and in the presence of infection  $L = 25.89$  years. The expected duration of the lifetime spent in the susceptible and infected states are  $L_u = 3.881$  years and  $L_v = 0.0114$  years, respectively. Hence we can estimate the average case fatality using (2.40) to be  $\bar{c} = (L_0 - L)/(L_0 - L_u - L_v) = 0.105$ . The remaining proportions of susceptible and infected individuals are  $\bar{x} = 0.2295$ , and  $\bar{y} = 0.0006$ .

The expected time an individual of any age  $a$  will live is shown in section (2.13).

Finally, the proportion of immunes at any age  $a$  changes if we change the case fatality. If we consider a case fatality which is the product of a parameter and the present case fatality, the proportion of immunes at any age increases or decreases according to the value of the parameter. if the parameter is larger than one, the proportion of immunes at any age extends , whereas if the parameter is less than one, the proportion shrinks. This is shown in figure 2.6.

### 3 The minimum effort required to eradicate infections in models with backward bifurcation

We study an epidemiological model which assumes that the susceptibility after a primary infection is  $r$  times the susceptibility before a primary infection. For  $r = 0$  ( $r = 1$ ) this is the SIR (SIS) model. For  $r > 1 + \mu/\alpha$  this model shows backward bifurcations, where  $\mu$  is the death rate and  $\alpha$  is the recovery rate. We show for the first time that for such models we can give an expression for the minimum effort required to eradicate the infection if we concentrate on control measures affecting the transmission rate constant  $\beta$ . This eradication effort is explicitly expressed in terms of  $\alpha$ ,  $r$ , and  $\mu$ . As in models without backward bifurcation it can be interpreted as a reproduction number, but not necessarily as the basic reproduction number. We define the relevant reproduction numbers for this purpose. The eradication effort can be estimated from the endemic steady state. The classical basic reproduction number  $R_0$  is smaller than the eradication effort for  $r > 1 + \mu/\alpha$  and equal to the effort for smaller values of  $r$ . The method we present is relevant to the whole class of compartmental models with backward bifurcation.

#### 3.1 Introduction

We analyze a special case of a model which K. P. Hadeler proposed together with Carlos Castillo-Chavez [40] for studying the effect of behaviour changes for the control of a sexually transmitted disease. This model is of the SIS type, i.e. individuals return to the susceptible state after each infection. Hadeler and Castillo-Chavez distinguish primary susceptible and "educated" or "vaccinated" susceptible which differ by their susceptibility. They showed that this model can have backward bifurcations for certain parameter values. This backward bifurcation phenomenon (the appearance of multiple infective stationary states) has recently been studied in several epidemic models, e.g. [37], [44], [54], [55], [56], [68], [69], [74], and [75]. In all those cases there exist, for certain values of the parameters, three endemic steady states, two of which are stable and one is unstable. The basis of our model is a special case of the model of Hadeler and Castillo-Chavez when there is no direct transfer of primary susceptible to the state of "educated" susceptible ( $\psi = 0$  in their notation) and all recovered individuals enter the class of "educated" susceptible ( $\gamma = 1$  in their notation). The "educated" susceptible can be interpreted as "immunized" susceptible because they can only reach this state after having experienced at least one infection. We drop this terminology as used by Hadeler and Castillo-Chavez for the rest of our paper.

Our model comprises a whole family of infectious disease models which contains on one end the SIR model (i.e. individuals have zero susceptibility after the first and only infection, i.e. they are fully immune). The key parameter of our model is the ratio  $r$  of the susceptibility after a primary infection and the susceptibility before a primary infection. For the SIR model,  $r = 0$ . For the SIS model we have  $r = 1$ . We shall provide a lower bound of  $r$  for which backward bifurcations are possible. When they occur, then  $r > 1$ , i.e. after a primary infection the susceptibility is higher than before. This could be interpreted as immuno-suppression, which may be relevant for some infections like pertussis where backward bifurcations have been studied in

a slightly more complicated model by van Boven et al [74].

We describe the model and its steady states in Section 2. In Section 3 we determine the minimum eradication effort and show how this can be obtained from the stable endemic equilibrium. Since for models without backward bifurcation the minimum eradication effort is identical to the basic reproduction number  $R_0$  [20], we investigate to what extent this result still holds true for this model with backward bifurcation. We shall distinguish an episode reproduction number from the effective reproduction number (Section 4). In Section 5 we determine for which initial conditions the minimum eradication effort can be interpreted as a reproduction number. In Section 6 we shall discuss the applicability of our approach to models with backward bifurcation.

### 3.2 The model and its equilibria

Consider a demographically stationary population structured into three classes of individuals according to their epidemiological status. The first class is that of susceptible without past infections  $S_0(t)$ , *i.e.* individuals who never were infected and may contract the infection (to be referred to as naive individuals); the second class is that of infectious individuals  $I(t)$ ; and the third class is that of susceptible with at least one past infection  $S_1(t)$ , to be referred to as recovered. We model in terms of fractions and assume that the total size is equal to one,  $S_0 + I + S_1 = 1$ .

Assume that individuals are born naive with per capita birth rate  $\mu$ . Naive individuals can either die with per capita death rate  $\mu$  or they get infected with linear incidence rate  $\beta I = r_0 \kappa I$  where  $\kappa$  is the per capita contact rate and  $r_0$  is the probability of success of contacts between infected and naive individuals and hence  $\beta$  is the successful contact rate between  $S_0$  and  $I$ . Infected individuals can either die with per capita death rate  $\mu$  or recover with per capita rate  $\alpha$ . Recovered individuals can either die with per capita death rate  $\mu$  or get infected again with linear incidence rate  $\tilde{\beta} I = r_1 \kappa I$ , where  $r_1$  is the probability of success of contacts between  $I$  and  $S_1$  and hence  $\tilde{\beta}$  is the successful contact rate between infected and recovered individuals. Define  $r = \frac{r_1}{r_0}$  as the ratio of transmission probabilities. Hence the successful contact rate between infected and recovered individuals is  $r\beta$ . These assumptions lead to the following system of ordinary differential equations:

$$\begin{aligned} \frac{dS_0}{dt} &= \mu - (\mu + \beta I)S_0, \\ \frac{dI}{dt} &= (\beta S_0 + \tilde{\beta} S_1)I - (\alpha + \mu)I, \\ \frac{dS_1}{dt} &= \alpha I - (\mu + \tilde{\beta} I)S_1, \end{aligned} \tag{3.1}$$

or equivalently:

$$\begin{aligned}
\frac{dS_0}{dt} &= \mu - (\mu + \beta I)S_0, \\
\frac{dI}{dt} &= \beta(S_0 + rS_1)I - (\alpha + \mu)I, \\
\frac{dS_1}{dt} &= \alpha I - (\mu + r\beta I)S_1.
\end{aligned} \tag{3.2}$$

When  $r = 0$ , the model is an SIR model; when  $r = 1$ , the model becomes an SIS model. For system (3.2) we have

$$R_0 = \frac{\beta}{\alpha + \mu}.$$

Note that  $r$  plays no role in  $R_0$  since in the invasion phase in a homogeneously mixing population, the probability that a recovered individual comes into contact again with an infectious individual is neglected.

### 3.2.1 SIR model

When  $r = 0$ , the dynamical system (3.2) is written as:

$$\begin{aligned}
\frac{dS_0}{dt} &= \mu - (\mu + \beta I)S_0, \\
\frac{dI}{dt} &= \beta S_0 I - (\alpha + \mu)I, \\
\frac{dS_1}{dt} &= \alpha I - \mu S_1,
\end{aligned} \tag{3.3}$$

which is the well-known SIR model with two steady states [19]:

- (1) The infection-free equilibrium (IFE)  $(1, 0, 0)$ , which is globally asymptotically stable if and only if  $\beta \leq \alpha + \mu$ , *i.e.* when  $R_0 \leq 1$ .
- (2) The endemic equilibrium (EE)  $(1/R_0, \frac{\mu}{\alpha + \mu}(1 - 1/R_0), \frac{\alpha}{\alpha + \mu}(1 - 1/R_0))$ , which is unique and is globally asymptotically stable if and only if  $R_0 > 1$  (*i.e.*, in the set of solutions with  $\bar{I} > 0$ ).

### 3.2.2 SIS model

When  $r = 1$ , the dynamical system (3.2) is written as:

$$\begin{aligned}
\frac{dS_0}{dt} &= \mu - (\mu + \beta I)S_0, \\
\frac{dI}{dt} &= \beta(S_0 + S_1)I - (\alpha + \mu)I, \\
\frac{dS_1}{dt} &= \alpha I - (\mu + \beta I)S_1.
\end{aligned} \tag{3.4}$$

Equations (3.4) represent an SIS model with the following steady states [19]:

- (1) The infection-free equilibrium  $(1, 0, 0)$ , which is globally asymptotically stable if and only if  $R_0 \leq 1$ .
- (2) The endemic equilibrium  $(\frac{\mu}{\mu+\beta(1-1/R_0)}, 1-1/R_0, \frac{\alpha(1-1/R_0)}{\mu+\beta(1-1/R_0)})$ , which is unique and is globally asymptotically stable if and only if  $R_0 > 1$ .

### 3.2.3 Forward bifurcations

If  $0 < r < 1 + \frac{\mu}{\alpha}$ , then the dynamical system (3.2) has the following endemic states:

- (1) The infection-free equilibrium  $(1, 0, 0)$ , which is globally asymptotically stable if and only if  $R_0 < 1$ .
- (2) The endemic equilibrium  $(\bar{S}_0, \bar{I}, \bar{S}_1)$ , which is unique and is globally asymptotically stable if and only if  $R_0 > 1$ , where:

$$\begin{aligned}\bar{I} &= \frac{1}{2} \left( \left( 1 - \frac{1}{rR_0} - \frac{\mu}{(\alpha + \mu)R_0} \right) + \sqrt{\left( 1 - \frac{1}{rR_0} - \frac{\mu}{(\alpha + \mu)R_0} \right)^2 + \frac{4\mu(1 - \frac{1}{R_0})}{(\alpha + \mu)rR_0}} \right), \\ \bar{S}_0 &= \frac{\mu}{\mu + \alpha\bar{I}}, \\ \bar{S}_1 &= \frac{\alpha\bar{I}}{\mu + \alpha\bar{I}}.\end{aligned}\tag{3.5}$$

For  $R_0 > 1/r$  and  $\alpha \gg \mu$ , the endemic equilibrium for  $I$  is approximately equal to  $1 - 1/(rR_0)$ . Although the endemic level  $\bar{I}$  increases monotonically with  $R_0$ , there are two inflection points close to  $R_0 = 1/r$ . Both the point with the minimal and the maximal slope are close to each other (Figure (3.1a)).

### 3.2.4 Backward bifurcation model

For  $r > 1 + \mu/\alpha$ , the model (3.2) exhibits a backward bifurcation. Apart from the infection-free equilibrium  $(S_0, I, S_1) = (1, 0, 0)$  there can exist a single unique endemic steady state or two positive steady states depending on the solutions to a quadratic equation. The endemic steady state values for  $S_0$  and  $S_1$  are as given above in (3.5), where  $\bar{I} \in [0, 1]$  is the solution of the quadratic equation:

$$f(I) = r\beta^2 I^2 + (r\mu - (r\beta - (\alpha + \mu)))\beta I + \mu(\alpha + \mu - \beta) = 0.\tag{3.6}$$

This equation has one or two feasible (*i.e.* positive, real) solutions, depending on the values of the parameters. As seen in the previous subsection, there is one solution, given in (3.5), for

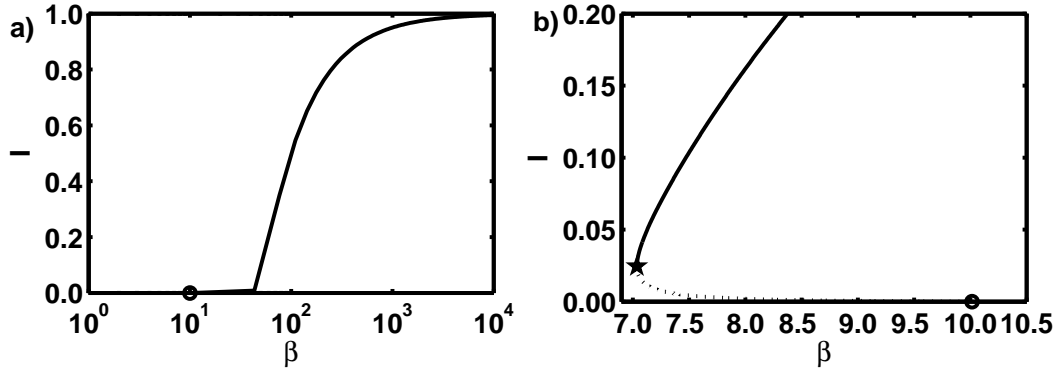


Figure 3.1: This figure shows the endemic prevalence  $I$  as a function of the contact rate  $\beta$  for two values of  $r$  ( $r = 0.2$  part (a),  $r = 1.5$  part (b),  $\alpha = 10$  per year and  $\mu = 0.015$  per year). For  $r$  between 0 and  $1 + \mu/\alpha$ , there are two inflection points close to  $R_0 = 1/r$ . For  $R_0 > 1/r$ , the endemic equilibrium is close to  $1 - 1/(rR_0)$  (a). For  $r > 1 + \mu/\alpha$ , there are three equilibrium points between  $R_0 = R_0^*$  and  $R_0 = 1$  (b).

the case when  $R_0 > 1$  and arbitrary  $r > 0$ . For  $R_0 < 1$  the situation is more complicated. For  $r > 1 + \mu/\alpha$  there is a region of values for  $R_0 < 1$  where there are two feasible solutions:

$$\bar{I}^\pm = \frac{1}{2} \left( \left( 1 - \frac{1}{rR_0} - \frac{\mu}{(\alpha + \mu)R_0} \right) \pm \sqrt{\left( 1 - \frac{1}{rR_0} - \frac{\mu}{(\alpha + \mu)R_0} \right)^2 + \frac{4\mu(1 - \frac{1}{R_0})}{(\alpha + \mu)rR_0}} \right). \quad (3.7)$$

### 3.2.5 The critical contact rate $\beta^*$

We denote the two endemic steady states by  $E^+$  and  $E^-$ . We now refer to Figure 3.1b for additional notation for the situation  $r > 1 + \mu/\alpha$ . On the vertical axis we give the  $I$ -component of  $E^+$  and  $E^-$ . On the horizontal axis we vary the contact rate  $\beta$ . In other words, on the horizontal axis we vary  $R_0$ , but we assume that all ingredients of  $R_0$  other than  $\beta$  are constant. When moving from  $R_0 > 1$  to  $R_0 < 1$  we only decrease  $\beta$ . The effect is that the corresponding values for the  $I$ -component of  $E^+$  and  $E^-$  will come closer together. At the turning point [72] of the bifurcating branch the steady states coincide in a point  $E^*$ , with  $I$ -component  $I^+ = I^- =: I^*$ . The value of  $\beta$  and  $R_0$  for which that happens will be denoted by  $\beta^*$  and  $R_0^*$ , respectively. It is a straightforward calculation from (3.7) to obtain that at the turning point

$$\begin{aligned} \beta^* &= \frac{\left( \sqrt{\mu(r-1)} + \sqrt{\alpha} \right)^2}{r} & \text{for } r \geq 1 + \frac{\mu}{\alpha} \\ R_0^* &= \frac{\beta^*}{\alpha + \mu}, \\ I^* &= \frac{r\beta^* - r\mu - (\alpha + \mu)}{2r\beta^*}. \end{aligned} \quad (3.8)$$

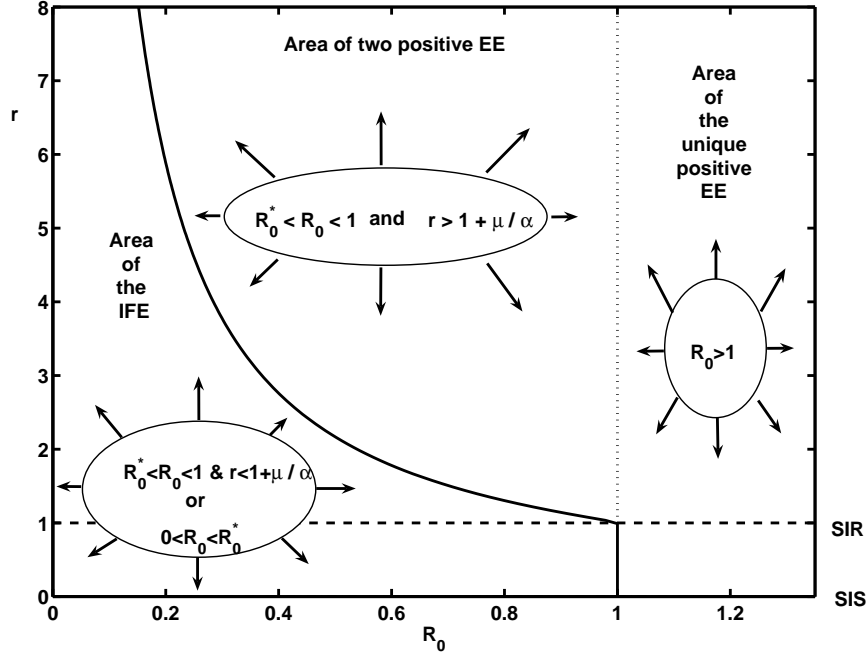


Figure 3.2: Bifurcation diagram in the  $(R_0, r)$ -plane showing the partition of the plane according to the number of the endemic equilibrium points ( $\alpha = 10$  per year and  $\mu = 0.015$  per year).

When we reduce  $r$  from a value slightly above  $1 + \mu/\alpha$  the bifurcating curve will shift down and to the right and for  $r = 1 + \mu/\alpha$  the turning point coincides with the intersection with the horizontal axis, *i.e.*  $\beta = \alpha + \mu$  which is equivalent to  $R_0 = 1$ , and the curve of steady state solutions for  $I$  will be forward bifurcating from that intersection. There is only one positive endemic steady state. For all values of  $r \leq 1 + \mu/\alpha$  this will be the case and therefore  $\beta^* = \alpha + \mu$  in that region. On the other hand, if we increase  $r$  from a value slightly above  $1 + \mu/\alpha$  the bifurcating curve will shift down and to the left and if  $r$  tends to  $\infty$  the turning point coincides with the horizontal axis when  $\beta = \mu$  which is equivalent to very small  $R_0$ , may be very close to zero and therefore there is only a forward bifurcating curve. The following Proposition summarizes the behaviour. Figure 3.2 shows the partition of the  $(R_0, r)$ -plane with the same information about the steady states.

**Proposition 3.1.**

*For:*

- (a)  $R_0 > 1$ , a unique positive endemic equilibrium exists in addition to the infection-free equilibrium,
- (b)  $R_0^* < R_0 < 1$  and  $r > 1 + \mu/\alpha$  two positive endemic equilibria exist in addition to the IFE,
- (c)  $0 < R_0 < R_0^*$  or  $(R_0^* < R_0 < 1$  and  $r < 1 + \mu/\alpha)$ , there is only the IFE.



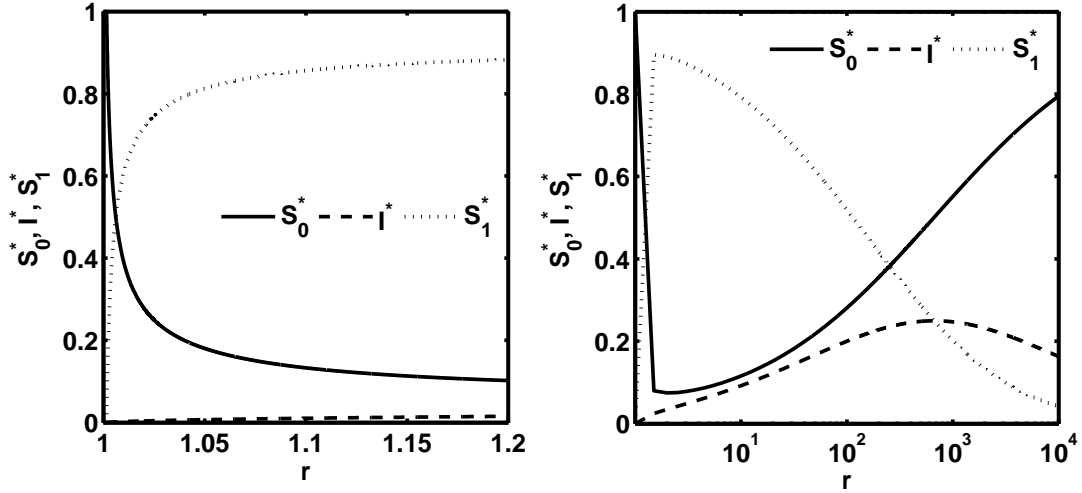


Figure 3.3: The dependence of the components of the point  $E^*$  on the ratio  $r$  for parameter values  $\alpha = 10$  per year, and  $\mu = 0.015$  per year. The left picture is a "zoom in" of the right one.

**Proof:**

From (3.6), one can simply evaluate:

$$\begin{aligned} f(1) &= \beta(r\mu + \alpha) + \mu(\alpha + \mu), \\ f(0) &= \mu(\alpha + \mu)(1 - R_0), \\ f'(0) &= \beta(r\mu + \alpha + \mu - r\beta). \end{aligned}$$

It is easy to check that  $f'(I^*) = 0$  where  $I^* = \frac{r\beta - r\mu - (\alpha + \mu)}{2r\beta} > 0$  iff  $\beta > \mu + (\alpha + \mu)/r$ .

It is clear that  $f(1) > 0$ ,  $f(0)$  can be positive or negative depending on the value of the basic reproduction number  $R_0$ , and  $f'(0)$  can be positive or negative according to the relation between the parameters. If  $f(0) > 0$ ,  $f'(0) < 0$  and  $f(I^*) < 0$ , there are two positive endemic equilibria in addition to the infection-free equilibrium. If  $f(0) < 0$  and  $f'(0) > 0$ , then there is a unique positive endemic state in addition to the infection-free equilibrium. Otherwise, there is only the infection-free equilibrium. It is easy to check that:

$$f(0) > 0 \text{ if and only if } R_0 < 1.$$

$$f'(0) < 0 \text{ if and only if } R_0 > \frac{\mu}{(\alpha + \mu)} + \frac{1}{r}.$$

$$f(I^*) < 0 \text{ if and only if } R_0 > R_0^*.$$

Combining the conditions together finishes the proof.

□

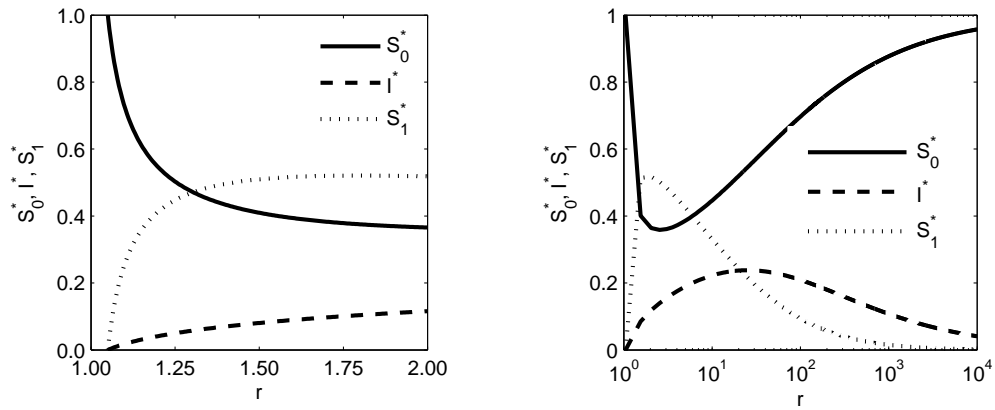


Figure 3.4: The dependence of the components of the point  $E^*$  on the ratio  $r$  for parameter values  $\alpha = 10$  per year, and  $\mu = 0.5$  per year. The left picture is a "zoom in" of the right one.

For  $r > 1 + \mu/\alpha$ , we have computed the turning point where the two positive endemic states merge by  $E^* = (S_0^*, I^*, S_1^*)$  where

$$\begin{aligned}
 S_0^* &= \frac{1}{1 + \sqrt{\frac{\alpha}{\mu(r-1)}}} \left( \frac{r}{r-1} \right) \\
 I^* &= \frac{1}{1 + \sqrt{\frac{\alpha}{\mu(r-1)}}} \left( 1 - S_0^* \right) \\
 S_1^* &= \frac{\sqrt{\frac{\alpha}{\mu(r-1)}}}{1 + \sqrt{\frac{\alpha}{\mu(r-1)}}} \left( 1 - S_0^* \right)
 \end{aligned}$$

Figures 3.3 and 3.4 show how these coordinates depend on  $r$ . At the beginning,  $S_0^*$  (continuous line) starts with value one and it decreases till reaching a minimum when  $r = 2 \left( 1 + \frac{\mu}{\alpha} + \sqrt{\frac{\mu}{\alpha} \left( 1 + \frac{\mu}{\alpha} \right)} \right)$  and then it increases and approaches one again when  $r$  tends to infinity. On the other hand, both  $I^*$  (dashed line) and  $S_1^*$  (dotted line) start with zero and they increase until reaching their maximum when  $r = 1 + \frac{\alpha}{\mu} \left( 1 + 2\frac{\mu}{\alpha} \right)^2$  and  $r = \frac{1}{2} \left( 3 + \frac{9\mu}{4\alpha} + \sqrt{\frac{9\mu}{4\alpha} \left( 2 + \frac{9\mu}{4\alpha} \right)} \right)$ , respectively. After that, they decrease and approach zero again when  $r$  tends to infinity.

In summary the critical contact rate  $\beta^*$  is the contact rate at which positive endemic equilibria starts to appear. Therefore,

$$\beta^* = \begin{cases} \alpha + \mu & \text{for } r \leq 1 + \frac{\mu}{\alpha}, \\ \frac{(\sqrt{\mu(r-1)} + \sqrt{\alpha})^2}{r} & \text{for } r \geq 1 + \frac{\mu}{\alpha}, \end{cases} \quad (3.9)$$

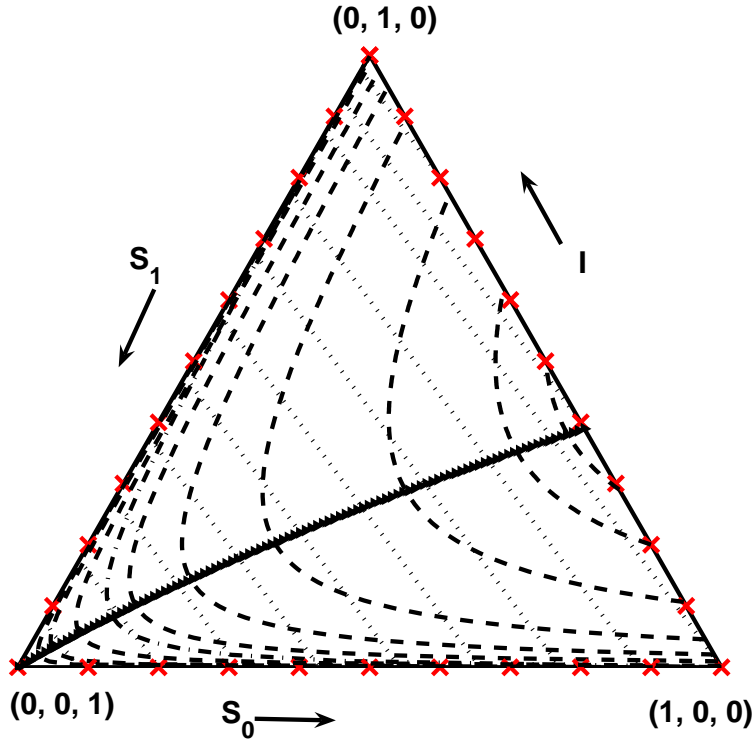


Figure 3.5: This figure shows the contour lines for both the episode (straight lines) and the case (hyperbolic lines) reproduction number in a ternary plot for model's parameters ( $\alpha = 10$  per year,  $\mu = 0.015$  per year,  $\beta = 1.8$  per year, and  $r = 8$ ). The marked line indicates the maximum case reproduction number for fixed  $S_1$ . Notice that the  $S_0$ ,  $I$ , and  $S_1$  axes increase counter clockwise.

### 3.3 The minimum effort $\mathcal{R}$ required to eradicate an infection

In the last section we saw that a reduction of the contact rate  $\beta$  below its critical value  $\beta^*$  would reduce the equilibrium prevalence to zero, for the region of values for  $r$ , where our system exhibits a backward bifurcation. For the region  $r < 1 + \frac{\mu}{\alpha}$  we found that  $\beta^* = \alpha + \mu$ , so also there  $\beta^*$  is the value of  $\beta$  separating between the existence of the zero and endemic steady state. Given this one could define a measure for the control effort required to eradicate an infection in such a system when starting from a situation where the contact rate has the value  $\beta$  and we concentrate our control effort on reducing contacts. Can we find a measure that indicates minimum effort needed and express this in terms of measurable steady state fractions? We denote the measure of eradication effort by

$$\mathcal{R} := \frac{\beta}{\beta^*},$$

where  $\beta^*$  is given by (3.9).

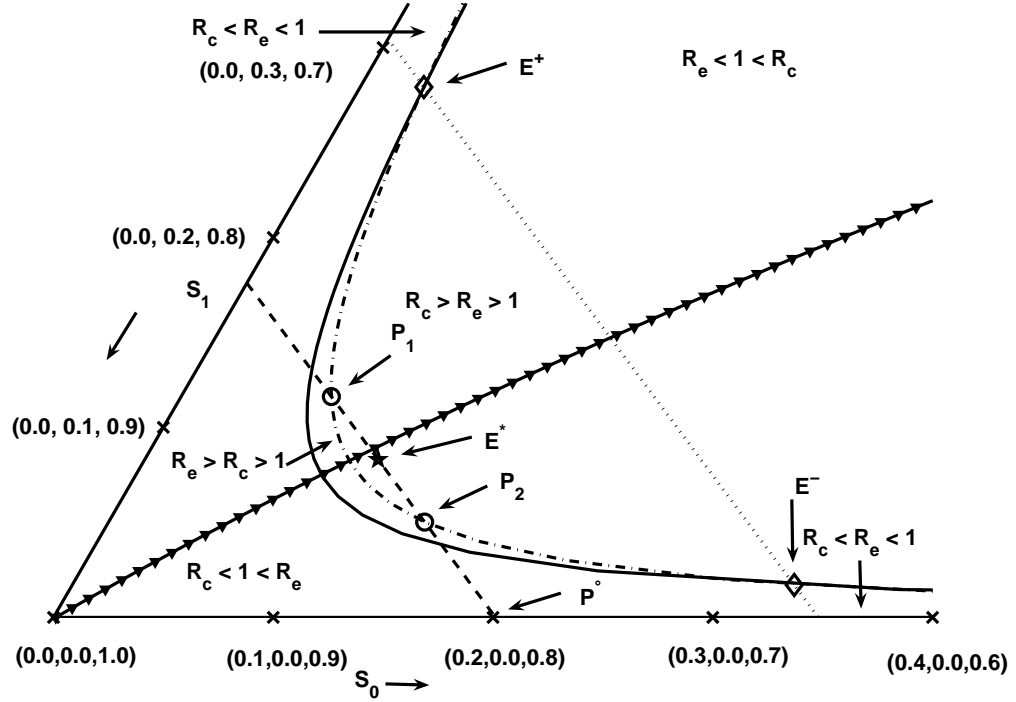


Figure 3.6: Barycentric plot for the episode and the case reproduction numbers in the case of backward bifurcation with two endemic equilibria  $E^+$  (stable) and  $E^-$  (unstable). The straight dotted line through these points is the contour line  $R_e = 1$ . The continuous hyperbola through these points is the contour line  $R_c = 1$ . The dashed dotted line is the contour line where  $R_e = R_c$ . The dashed line through  $E^*$  is the contour line  $R_e = \frac{\beta}{\beta^*}$ . This line hits the axis  $I = 0$  in the point  $P^\circ$ . This line intersects the line  $R_e = R_c$  at the points  $P_1$  and  $P_2$  where both reproduction numbers are equal to the eradication effort. The line with arrow heads indicates the maximum  $R_c$  for fixed  $S_1$ . The contour lines divide the triangle into areas where the inserted inequalities are valid.

**Proposition 3.2.**

The ratio between the contact rate,  $\beta$ , and the critical contact rate,  $\beta^*$ , at equilibrium is given by:

$$\mathcal{R} = \frac{\beta}{\beta^*} = \begin{cases} \frac{1}{\bar{S}_0 + r\bar{S}_1} & \text{for } r \leq 1 + \frac{\mu}{\alpha}, \\ \frac{1}{\left(\sqrt{\frac{\bar{S}_0}{1-\bar{S}_0}}\bar{I}(1-\frac{1}{r}) + \sqrt{\bar{S}_1(1+\frac{1}{r}\frac{\bar{S}_0}{1-\bar{S}_0})}\right)^2} & \text{for } r \geq 1 + \frac{\mu}{\alpha}, \end{cases} \quad (3.10)$$

where the ratio  $r$  is determined from the relation

$$r = \frac{\bar{S}_0}{1 - \bar{S}_0} \left( \frac{\alpha \bar{I}}{\mu \bar{S}_1} - 1 \right). \quad (3.11)$$

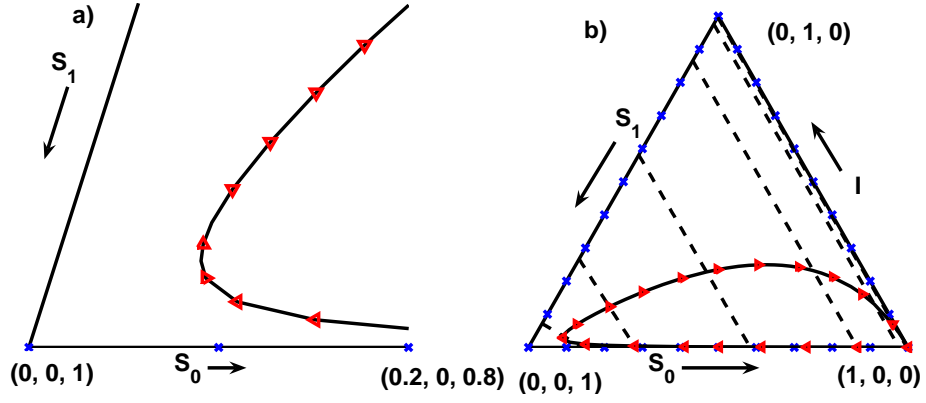


Figure 3.7: This figure shows the curve in the triangle on which the point  $E^*$  lies for values of  $r \geq 1 + \frac{\mu}{\alpha}$  and the isoclines  $R_e = \frac{\beta}{\beta^*}$  for values of  $r = 2, 20, 200, 2000, 20000,$  and  $200000$ . In Fig. 3.7(b), we have the whole curve. At  $r = 1 + \frac{\mu}{\alpha}$ ,  $E^*$  coincides with the IFE. When  $r$  increases, the point  $E^*$  moves clockwise on a closed curve until reaching the IFE again when  $r$  tends to infinity. The behaviour is as follows: First  $S_0$  decreases while  $S_1$  increases till reaching the corner in the left and then it turns to the right with an increase of  $S_0$  accompanied by a decrease in  $S_1$ . An explanation to the left corner is shown in Fig. 3.7(a). This is done for values of  $r$ , clockwise from the right bottom, located at head arrows 1.08, 1.2, 1.45, 2, 3.5, 5.5, 8.5, and 12.5 respectively.

**Proof:**

At equilibrium, one can find:

$$\begin{aligned} \mu &= \beta \bar{I} \frac{\bar{S}_0}{1 - \bar{S}_0}, \\ \alpha &= \beta \left( \bar{S}_0 + r(1 - \bar{S}_0 - \bar{I}) - \bar{I} \frac{\bar{S}_0}{1 - \bar{S}_0} \right). \end{aligned}$$

Substituting these expressions into the relation

$$\beta^* = \begin{cases} \alpha + \mu & \text{for } r \leq 1 + \frac{\mu}{\alpha}, \\ \frac{(\sqrt{\mu(r-1)} + \sqrt{\alpha})^2}{r} & \text{for } r \geq 1 + \frac{\mu}{\alpha}, \end{cases}$$

and performing some simple calculations finish the proof of (3.10). To derive (3.11), we find at equilibrium

$$\begin{aligned} \beta \bar{I} &= \frac{\mu(1 - \bar{S}_0)}{\bar{S}_0}, \\ r \bar{S}_1 &= \frac{\alpha \bar{I} - \mu \bar{S}_1}{\beta \bar{I}}. \end{aligned}$$

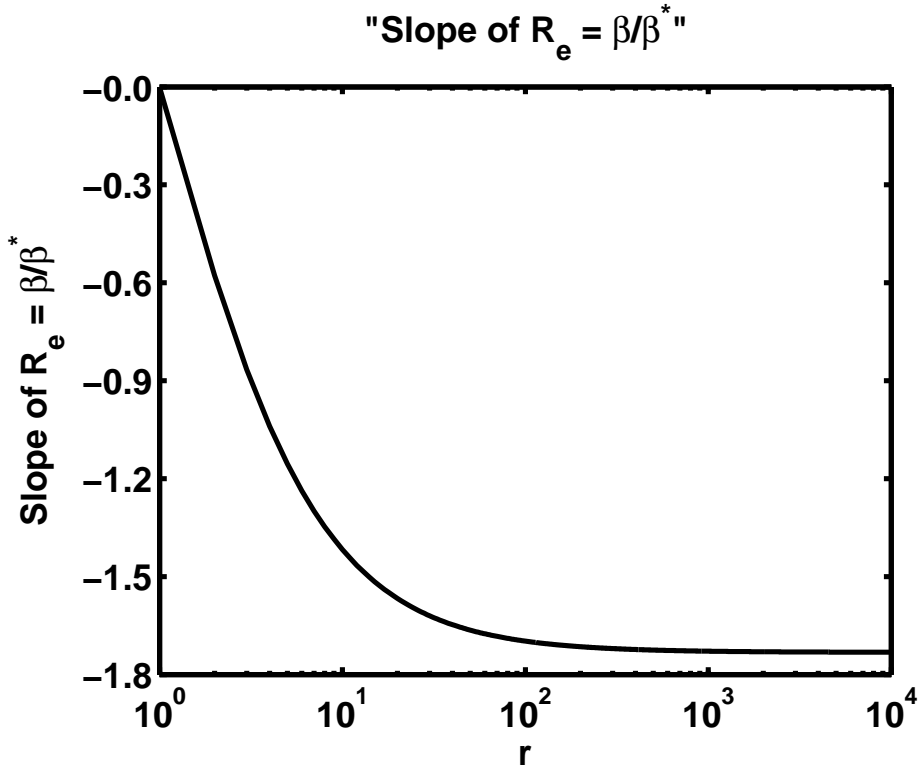


Figure 3.8: This figure shows the slope of the isoclines  $R_e = \frac{\beta}{\beta^*}$  for parameter values of  $\alpha = 10$  and  $\mu = 0.015$ . It starts with zero and decreases till reaching some equilibrium. When  $r$  tends to infinity, it asymptotically approaches  $-\sqrt{3}$ .

Hence,

$$\begin{aligned} r &= \alpha \frac{\bar{I}}{\bar{S}_1} - \mu \frac{\bar{S}_0}{\mu(1 - \bar{S}_0)}, \\ &= \frac{\bar{S}_0}{1 - \bar{S}_0} \left( \frac{\alpha \bar{I}}{\mu \bar{S}_1} - 1 \right). \end{aligned}$$

□

Note that for the SIR ( $r = 0$ ) and SIS ( $r = 1$ ) models, the control effort  $\mathcal{R} = R_0 = \frac{1}{\bar{S}}$  and we recover the well-known identity according to which the product of the basic reproduction number and the equilibrium proportion of susceptible equals one (where  $\bar{S}$  is  $\bar{S}_0$  or  $\bar{S}_0 + \bar{S}_1$ , as appropriate). For other values of  $r < 1 + \frac{\mu}{\alpha}$ , the equilibrium proportion of susceptible  $\bar{S}_0$  and  $\bar{S}_1$  are weighted according to their relative susceptibility  $r$ . For  $r > 1 + \frac{\mu}{\alpha}$  the corresponding formula is more complicated but it can still be given in an explicit form (3.10).

If we know the equilibrium solution,  $(\bar{S}_0, \bar{I}, \bar{S}_1)$ , in addition to the model parameters  $\alpha$  and  $\mu$ , we can evaluate  $r$  from (3.11) and then use (3.10) to evaluate the effort required to eradicate the infection. The equilibrium proportions of the three epidemiological states can be estimated from a cross sectional survey. The death rate  $\mu$  is obtained from demographic observations and

the recovery rate  $\alpha$  is estimated from the duration of the infectious period of infected cases.

The question arises whether the expression for control effort can be interpreted as a reproduction number like in the case of the SIR and SIS model. This problem will be addressed in the following sections. We can define two reproduction numbers: the episode reproduction number and the case reproduction number. The first reproduction number determines how many secondary infectious episodes are generated during one infectious episode. It depends on both  $S_0$  and  $S_1$ . The case reproduction number asks how many new cases are generated by one case throughout life. It only depends on  $S_0$  and on the prevalence of infection which determines the duration of all infectious periods throughout life of a newly infected individual. If the population is completely susceptible (*i.e.*  $(S_0, I, S_1) = (1, 0, 0)$ ), then both reproduction numbers are identical and equal to  $R_0$ . We will regard these numbers in a broader setting, however, where we want to express the "reproductive capacity" of an infected individual in a population with arbitrary characteristics  $(S_0, I, S_1)$ . One often sees the term "effective" reproduction number for such a quantity. We give two different names since the quantities defined are in general not equal. We note that, since the population composition is not fixed for their definition, all these reproduction numbers are in fact functions, in contrast to  $R_0$ . To emphasize their biological interpretation and dimension we stick, however, to the term "numbers" for all quantities.

The ratio of the control effort  $\mathcal{R}$  and the basic reproduction number will play a role in the following sections. We therefore give it explicitly for easy reference

$$\begin{aligned} \frac{\mathcal{R}}{R_0} &= \frac{r(\alpha + \mu)}{\left(\sqrt{\mu(r-1)} + \sqrt{\alpha}\right)^2} \\ &= \frac{\bar{S}_0 + r\bar{S}_1}{\left(\sqrt{\frac{\bar{S}_0}{1-\bar{S}_0}}\bar{T}\left(1 - \frac{1}{r}\right) + \sqrt{\bar{S}_1}\left(1 + \frac{1}{r}\frac{\bar{S}_0}{1-\bar{S}_0}\right)\right)^2} \end{aligned} \quad (3.12)$$

where  $r$  is given by (3.11).  $\frac{\mathcal{R}}{R_0}$  is always larger than one.

### 3.4 The episode reproduction number $R_e$ and the case reproduction number $R_c$

The episode reproduction number, denoted by  $R_e$ , is defined as the average number of secondary episodes (infectious periods) produced by one episode (infectious period) when the sub-populations are given by the fractions  $(S_0, I, S_1)$ . In the simple case of our model system, it is the product of three quantities:

$$R_e = \frac{\beta (S_0 + rS_1)}{(\alpha + \mu)} \quad (3.13)$$

One can see immediately from the differential equation for  $I$  in (3.2) that  $R_e = 1$  in steady state. Also, when the population consists of naive individuals only we see that  $R_e = R_0$ .

The case reproduction number, denoted by  $R_c$ , is the expected number of secondary cases produced by one infected case throughout life. It is the product of three quantities: the successful contact rate, the proportion of individuals who have never got infected, and the total time of life spent in the infectious state  $T(I)$ . Hence:

(I) For the SIR model we have

$$R_c = \frac{\beta S_0}{\alpha + \mu}. \quad (3.14)$$

(II) For the SIS model we get

$$R_c = \frac{\beta S_0(\mu + \beta I)}{\mu(\alpha + \mu + \beta I)}. \quad (3.15)$$

(III) In general we have

$$\begin{aligned} R_c &= \beta S_0 T(I), \\ T(I) &= \frac{\mu + r\beta I}{\mu(\alpha + \mu + r\beta I)}. \end{aligned} \quad (3.16)$$

To evaluate  $T(I)$  we follow a newly infected individual  $i$ . An infected individual  $i$  can either die with per capita death rate  $\mu$  or recover without immunity to become recovered individual  $s_1$  with per capita recovery rate  $\alpha$ . Such recovered individuals can either die with per capita death rate  $\mu$  or become infected again with force of infection  $r\beta I$  where  $I$  is the proportion of infected in the whole population. The dynamics of the newly infected individual is then described by the simple model:

$$\begin{aligned} \frac{di}{dt} &= r\beta I s_1 - (\alpha + \mu)i, \\ \frac{ds_1}{dt} &= \alpha i - (\mu + r\beta I)s_1, \end{aligned} \quad (3.17)$$

with initial conditions:

$$\begin{aligned} i(0) &= 1, \\ s_1(0) &= 0. \end{aligned} \quad (3.18)$$

Applying Laplace transformation, we can evaluate the total time spent in the infected state as

$$T(I) = \int_0^\infty i(\tau) d\tau = \frac{\mu + r\beta I}{\mu(\alpha + \mu + r\beta I)}.$$

An alternative way of expressing the above calculation is to describe the dynamics of state changes for the newly infected individual by a Markov transition matrix as in [19]. For the system described above there are two states  $I$  and  $S_1$ , and the transition matrix is given by

$$G = \begin{pmatrix} -(\alpha + \mu) & r\beta I \\ \alpha & -(\mu + r\beta I) \end{pmatrix}.$$

The expected time spent in state 1 ( $I$ ) is then given by



"Ternary plot in case of one stable IFE"  
 $\alpha = 10, \mu = 0.015, \beta = 3.5, r = 2$

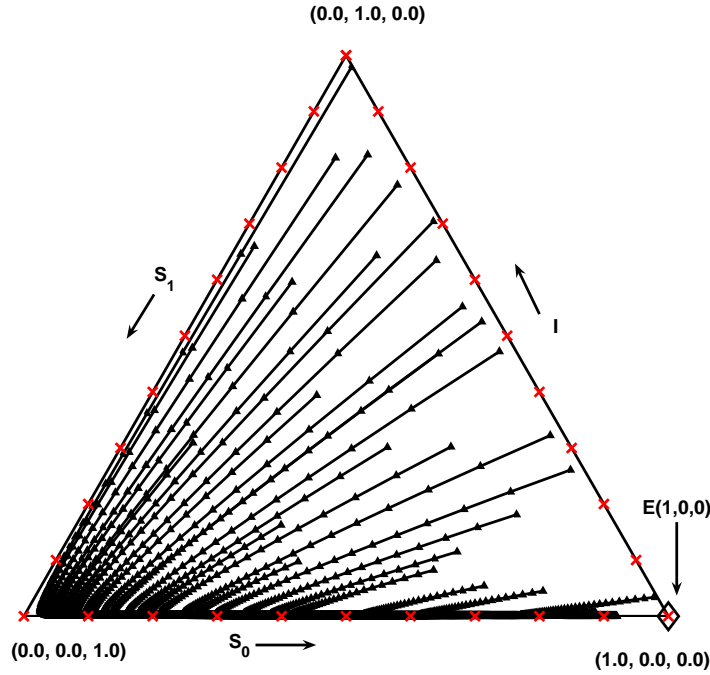


Figure 3.9: This figure shows the trajectories in the triangle for the parameter values given at the top.

$$T(I) = - \begin{pmatrix} 1 & 0 \end{pmatrix} G^{-1} \begin{pmatrix} 1 \\ 0 \end{pmatrix}.$$

By rearranging the equations of system (3.2) at steady state, one can easily see that the case reproduction number,  $R_c$  has the following properties:  $R_c = 1$  at equilibrium; in case the population consists of naive individuals only,  $R_c = R_0$ .

We now study the system's dynamics in terms of the quantities defined. In order to show the isoclines of  $R_e$  in the unit simplex we use so-called ternary plots. This graphical tool (also known as De Finetti diagram) is quite common in genetics for the representation of the relative frequencies of three genotypes ([41] and [53]). Figure 3.5 shows the contour lines for the episode reproduction number  $R_e$  (straight lines) and the case reproduction number  $R_c$  (hyperbolic lines) for values of model's parameters in the area in which there are two positive endemic equilibria in addition to the IFE. Along the axis  $S_0 = 0$ ,  $R_e$  increases linearly with  $S_1$  for  $r > 1$  with a maximum value equal to  $\frac{r\beta}{\alpha+\mu}$  for  $S_1 = 1$  and a minimum value equal to zero for  $I = 1$ . Isoclines are parallel straight lines in a ternary plot, whose slopes depend on  $r$ .

We are particularly interested in the isocline passing through the point  $E^* = (S_0^*, I^*, S_1^*)$ ,

"Ternary plot in case of unique positive EE"

" $\alpha = 10, \mu = 0.015, \beta = 14, r = 2$ "

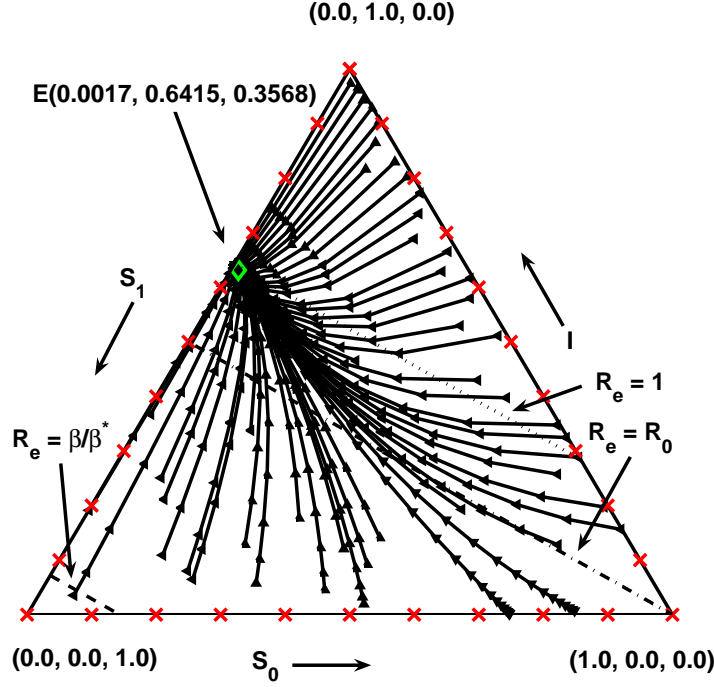


Figure 3.10: This figure shows the ternary plot with model parameters defining a unique positive endemic equilibrium. Here we notice that the positive stationary solution is the global attractor. The dotted straight line passing through the equilibrium point corresponds to  $R_e = 1$ .

see Fig. 3.6. Along this line,  $R_e = \frac{\beta}{\beta^*}$ . It intersects the line  $I = 0$  in the point with coordinates:

$$P^\circ = (S_0^\circ, I^\circ, S_1^\circ) = \frac{1}{r-1} \left( r - \frac{\mathcal{R}}{R_0}, 0, \frac{\mathcal{R}}{R_0} - 1 \right).$$

It also intersects with the isocline  $R_e = R_c$  in two points  $P_1$  and  $P_2$ . The coordinates of the points ( $P_1$  and  $P_2$ ) of intersection between the lines  $R_e = \frac{\beta}{\beta^*}$  and  $R_e = R_c$  are

$$\begin{aligned} I_{1,2} &= \frac{1}{2} \left( 1 - \frac{\mu + \mathcal{R}(\alpha + r\mu)}{\mathcal{R}(\sqrt{\alpha} + \sqrt{\mu(r-1)})^2} \right) \\ &\pm \sqrt{\frac{1}{4} \left( 1 - \frac{\mu + \mathcal{R}(\alpha + r\mu)}{\mathcal{R}(\sqrt{\alpha} + \sqrt{\mu(r-1)})^2} \right)^2 - \frac{\mu}{\mathcal{R}(\sqrt{\alpha} + \sqrt{\mu(r-1)})^2} \left( \frac{\mathcal{R}}{R_0} - 1 \right)}, \\ S_{01,2} &= \frac{1}{r-1} \left( r(1 - I_{1,2}) - \frac{\mathcal{R}}{R_0} \right), \\ S_{11,2} &= \frac{1}{r-1} \left( -(1 - I_{1,2}) + \frac{\mathcal{R}}{R_0} \right). \end{aligned} \quad (3.19)$$

The isocline which connects the two equilibria,  $E^-$  and  $E^+$ , corresponds to an  $R_e$  value of 1. The location of the point  $E^*$  in the triangle and the slope of isocline  $R_e = \frac{\beta}{\beta^*}$  for all possible

"Ternary plot in case of two stable equilibria"  
 $\alpha = 10, \mu = 0.015, \beta = 2, r = 7$

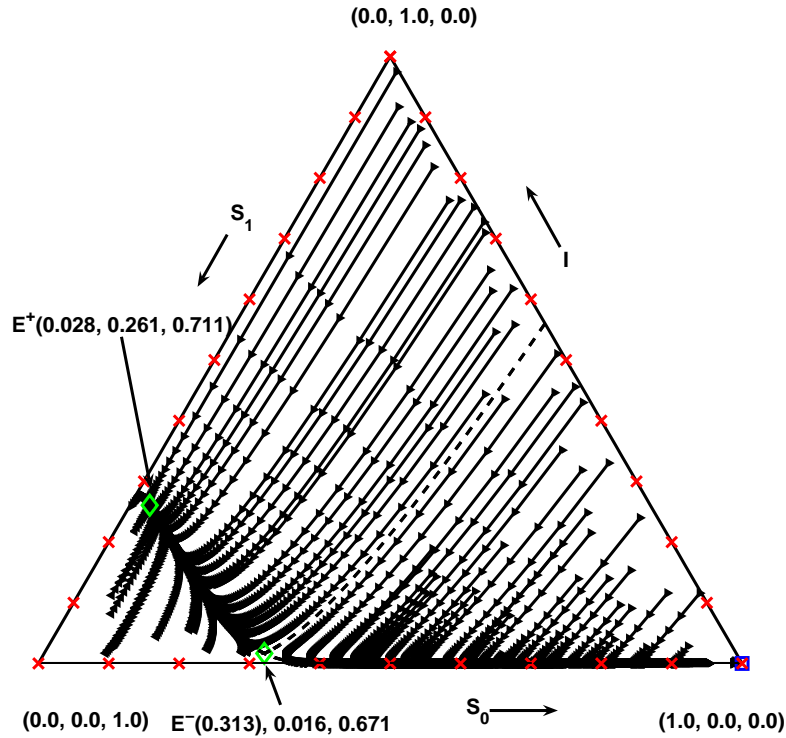


Figure 3.11: This figure shows the trajectories when there are two stable equilibria  $E^+$  and the IFE with an unstable one  $E^-$  in between. The broken line indicates the separatrix which separates the domains of attraction of the two stable equilibria.

values of  $r$  are shown in the Fig. 3.7 and Fig. 3.8 respectively.

From the last discussion we deduce that the episode reproduction number  $R_e$  is increasing in  $S_1$  for all  $1 < r$ .

### 3.5 Transient behaviour

Since analytical solutions of model (3.2) are impossible, numerical simulations have been performed. Fig. 3.9 shows the trajectories in a ternary plot when only the infection free equilibrium  $S_0 = 1$  is stable. If we begin the calculations at a random position within the ternary triangle first  $I$  and  $S_0$  decrease, whereas  $S_1$  increases up to a maximum value depending on the initial values until  $I$  approaches zero. Subsequently,  $S_1$  decreases again and  $S_0$  eventually increases to reach 1.

In this case we find that the episode reproduction number  $R_e$  is always less than one, as a consequence we get a monotonic decrease of the prevalence  $I$  while in the case of a unique endemic equilibrium in addition to the IFE, the behaviour of the trajectories is more varied.

The initial  $R_e$  can be less than or bigger than one. If  $R_e > 1$  we get a monotonic increase until reaching the equilibrium. This increase can be uniform in speed or it can be composed of a fast and slow component (weak growth followed by a strong one). On the other hand, if, however,  $R_e < 1$  we get either a uniform decrease until reaching the equilibrium or an initial decrease followed by a sudden increase (Fig. 3.10).

If we solve the system with random initial conditions in the ternary triangle with parameter values for which there are two endemic equilibria in addition to the IFE (Fig. 3.11), we get a combination of the previous types of behaviour. The separatrix (broken line) divides between the domains of attraction of the IFE and the stable positive endemic equilibrium. It passes through the unstable endemic equilibrium. The isocline  $R_e = 1$  is a straight line passing through the two positive endemic states. In the domain of attraction of the IFE, the trajectories behave exactly like the solutions in Fig. 3.9. In the other part of the triangle we have two patterns (above and below  $R_e = 1$ ). Below the line  $R_e = 1$ , both  $S_0$  and  $I$  initially increase while  $S_1$  decreases till reaching the line  $R_e = 1$  and suddenly  $S_0$  decreases. Above the line  $R_e = 1$ , both  $I$  and  $S_0$  decrease while  $S_1$  increases until reaching the line  $R_e = 1$  and then  $I$  increases to reach the equilibrium. We see that  $R_e$  plays an important role in the dynamics.

The important thing to notice is that for given initial prevalence  $I$  we can reach both of the stable equilibria. This makes the initial conditions useless in evaluating the eradication effort in the presence of backward bifurcations. This is in contrast to the situation in the case without such bifurcations.

Since  $\alpha$  and  $\mu$  are the removal and birth/death rate respectively, we fix them in all calculations (the length of the infectious period " $1/(\alpha + \mu)$ " is fixed). Hence the variability can occur with respect to both  $r$  and  $\beta$ . We considered three different points of  $(\beta, r)$  namely  $(3.5, 2)$ ,  $(14, 2)$  and  $(2, 7)$ . They belong to the three areas in the  $(R_0, r)$ -plane in figure 3.2 and are representative for the different behaviour of the solutions in the three areas of the  $(R_0, r)$ -plane.

The importance of using ternary triangles here is that we can immediately see the dynamics of the three components simultaneously and the local and global attractors. In Fig. 3.9 for example we notice that if we start anywhere, then a sudden decrease in both  $S_0$  and  $I$  accompanied by a sudden increase in  $S_1$  occurs and then  $S_0$  increases again with a decrease in  $S_1$  where  $I$  seems to be very close to zero. However, in Fig. 3.10 we notice that if we start anywhere, then there are three types of behaviour depending on the value of the episode reproduction number  $R_e$ . If  $R_e < 1$ , then both  $S_0$  and  $I$  decrease while  $S_1$  increases till reaching the global attractor. If  $1 < R_e < R_0$ , then both  $I$  and  $S_1$  increase while  $S_0$  decreases till reaching the global attractor. If  $R_0 < R_e$ , then  $I$  always increases while both  $S_0$  and  $S_1$  change to reach the equilibrium. Finally, Fig. 3.11 shows a behaviour which combines the previous two types of behaviour.

### 3.6 Discussion

Several authors noted before that for models with backward bifurcation, the basic reproduction number can no longer be used as an indicator of the eradication effort ([5], [14], [24], [36], [37], [54], [55], [56], [69], [74], and [75]). In the present chapter, we provide for the first time a

method to determine the eradication effort for models with backward bifurcation. It can be estimated from the composition of the population at the endemic equilibrium. We generalize the notion of the basic reproduction number for an arbitrary composition of the population in order to determine those initial conditions at which the episode reproduction number equals the eradication effort. In all models without backward bifurcation, the basic reproduction number is evaluated at the infection free equilibrium (i.e. at the IFE the episode reproduction number coincides with the basic reproduction number). At this point,  $R_0$  represents the maximum reproduction number. In the present model with backward bifurcation the generalization of the basic reproduction number is not unique because it is ambiguous what one should call a new case: each time someone gets infected with the agent or only the infections of naive susceptible without infection history for that agent. In the infection free equilibrium both concepts (the episode reproduction number  $R_e$  and the case reproduction number  $R_c$ ) are indistinguishable from the basic reproduction number  $R_0$ . We have seen, however, that for a model with backward bifurcation the two concepts ( $R_e$  and  $R_c$ ) are only identical along a hyperbolic curve. Outside this curve, they behave in opposite directions: for increasing proportion of susceptible with previous infections the episode reproduction number increases whereas the case reproduction number decreases. It therefore does not help to take the maximum of the two reproduction numbers like in the models without backward bifurcation, because these maxima occur at opposite ends of the proportion of susceptible with primary infections. One cannot even take the maximum of the reproduction numbers where both concepts agree with each other, because then the eradication effort would be overestimated. There are exactly two compositions of the population where both concepts agree with each other and with the eradication effort. They are connected by a straight line which goes through the critical composition of the population which yields the smallest positive endemic level if we decrease the contact rate. Since epidemics do not start in general in these states, this insight is only of theoretical use. If  $R_0 < 1$ , then one infective introduced into a large fully susceptible population without past infections would not trigger an epidemic at all. In order to reach a positive equilibrium, either the initial proportion of susceptible with past infections would have to be above a certain threshold or the initial number of infectives would have to be sufficiently high. In practice, one usually does not know the state of the population at the beginning of an epidemic. By the time, epidemiologists arrive to study the epidemic it is too late to determine the initial state.

Formula (3.11) defines the relative susceptibility  $r$  in terms of the three equilibrium proportions  $\bar{S}_0$ ,  $\bar{S}_1$  and  $\bar{I}$  and the model parameters  $\mu$  and  $\alpha$ . If we know these five quantities we can estimate  $r$  and then we substitute in equation (3.10) to get the necessary eradication effort  $\mathcal{R}$ . The importance of this formula is that it does not depend on the contact rate  $\beta$ . Hence we conclude that the new formula (3.10) is relevant for stable endemic states.

Our approach is applicable to the whole class of compartmental models with backward bifurcation. It has been applied successfully to simple and complicated models like those in [37], [40], [44], [68], and [74].

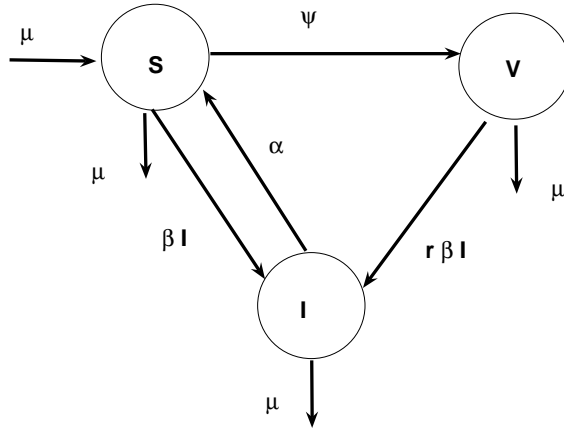


Figure 4.1: Compartmental diagram for the model.

## 4 A simple SIS endemic model with vaccination and backward bifurcation

In this chapter, I would like to introduce a more general, but still simple, model in which one sees the backward bifurcation phenomenon. It is a simple SIS model with vaccination leading to incomplete immunity. The aim of the vaccination is to immunize the organism. In other words, the body of the organism acquires some protection through vaccination against certain diseases. There are two types of vaccinations, passive vaccination and active vaccination. In a passive vaccination, the body receives antibodies against a specific disease. Passive vaccination can be applied if there is an immediate threat of becoming infected, or, on the public health level, of an epidemic. In the latter case, campaigns work extensively to vaccinate the population. In an active vaccination, we inject antigens in the form of attenuated or killed germs or parts of it into the body immediately after birth. In this way, the body produces the antibodies actively. Therefore, the body gets a specific and long-lasting protection. I will consider the two cases when we immediately vaccinate after birth and when there is some delay until getting vaccinated and the difference I would like to discuss.

### Passive vaccination Problem

#### 4.1 Construction of the model

We subdivide the total population into three categories. The first is that of susceptible  $S$ , individuals being able to contract the infection. The second is that of vaccinated  $V$ , individuals who were susceptible and received a vaccine. The last is that of infected  $I$ , individuals being able to transmit the infection to others. Individuals are supposed to be born susceptible with birth rate  $\mu$ . Susceptible individuals can either die with death rate  $\mu$ , be vaccinated with

vaccination rate  $\psi$  but with imperfect vaccine, or be infected with force of infection  $\beta I$  deduced from a law similar to that of mass action in chemistry, where  $\beta$  is the successful contact rate between  $S$  and  $I$  individuals and is the product of two quantities (the number of contacts per unit of time and the probability of success of a contact). Vaccinated individuals can either die with death rate  $\mu$  or be infected with force of infection  $r\beta I$ , different from the previous one, where  $r$  denotes the relative susceptibility of individuals in the compartment  $V$  to those in the compartment  $S$  and is the ratio between the probability of successful contact between individuals in  $V$  and  $I$  to the probability of successful contact between individuals in  $S$  and  $I$ . If  $r < 1$ , the vaccine gives partial protection. If it is bigger than one, this can be interpreted as immunosuppression. Infected individuals can either die with per capita death rate  $\mu$  or recover without immunity to be susceptible again with removal rate  $\alpha$ . This is shown in figure 4.1.

## 4.2 The model

The mathematical representation of the model is

$$\begin{aligned}\dot{S} &= \mu(S + V + I) + \alpha I - (\beta I + \psi + \mu) S, \\ \dot{V} &= \psi S - (r\beta I + \mu) V, \\ \dot{I} &= \beta(S + rV)I - (\alpha + \mu)I, \\ 1 &= S + V + I,\end{aligned}\tag{4.1}$$

where the dot means derivative with respect to time. If  $r = 0$ , the model is reduced to an SIS with perfect vaccination. If  $0 < r < 1$ , the vaccine gives partial protection. The case  $r > 1$  corresponds to immuno-suppression.

## 4.3 Stationary states

The importance of mathematically modeling a biological phenomenon is that it allows to predict the behaviour of compartments after long time such that the trajectory has reached the global attractor. In many concrete examples it reaches a stationary point. Therefore we first discuss stationary points by setting the time derivatives equal to zero which gives the system of equations

$$\begin{aligned}0 &= \mu + \alpha\bar{I} - (\beta\bar{I} + \psi + \mu)\bar{S}, \\ 0 &= \psi\bar{S} - (r\beta\bar{I} + \mu)\bar{V}, \\ 0 &= \beta(\bar{S} + r\bar{V})\bar{I} - (\alpha + \mu)\bar{I} \\ 1 &= \bar{S} + \bar{V} + \bar{I}.\end{aligned}\tag{4.2}$$

The uninfected solution is given by

$$(\bar{S}, \bar{V}, \bar{I}) = \left( \frac{\mu}{\mu + \psi}, \frac{\psi}{\mu + \psi}, 0 \right).$$

## 4.4 Reproduction numbers

### The basic reproduction number $R_0$

The basic reproduction number is the expected number of secondary cases produced by one case when it is introduced into a totally susceptible population. Mathematically it is

$$R_0 = \frac{\beta}{\alpha + \mu} \left( \frac{\mu}{\mu + \psi} + r \frac{\psi}{\mu + \psi} \right). \quad (4.3)$$

It is the product of three quantities: The successful contact rate between susceptible individuals and infected, the length of the infectious period, and a third quantity representing the sum of two terms. One of these two is the proportion of susceptible in an infection free population and the other is the relative susceptibility of vaccinated to susceptible times the endemic proportion of vaccinated individuals in a population which is free from the infection. Another way to interpret the basic reproduction number in (4.3) is to explain it as the sum of two reproduction numbers. One is the basic reproduction number for a population consisting entirely of susceptible and the other is the basic reproduction number for an entirely vaccinated population. A third way to interpret  $R_0$  is to say, it is the ratio between the successful contact rate  $\beta$  and the zero successful contact rate, say  $\beta_0$ , where  $\beta_0$  means the successful contact rate when the endemic prevalence of infected falls down to be zero. This will be explained later on.

### The episode reproduction number $R_e$

The episode reproduction number is the expected number of secondary episodes produced by one episode when the sub-populations are given by the fractions  $(S, V, I)$ . It is given by

$$R_e = \frac{\beta}{\alpha + \mu} (S + rV) \quad (4.4)$$

From the third equation in (4.1) we notice that the episode reproduction equals one in the steady state. If  $R_e > 1$ , then  $I$  initially increases while if  $R_e < 1$  it initially decreases. When the population is totally susceptible, the basic reproduction number coincides with the episode reproduction number.

## 4.5 Bifurcation equation

We want a simple characterization of the infected stationary solutions. In (4.2) we assume  $I \neq 0$  and we eliminate the variables  $S$  and  $V$ . Then we arrive at a scalar equation for the variable  $\bar{I}$

$$0 = F(\beta, \bar{I}) = r\beta^2\bar{I}^2 + (\mu + r(\alpha + \mu + \psi - \beta))\beta\bar{I} + (\mu + \psi)(\mu + \alpha) - \beta(\mu + r\psi) \quad (4.5)$$

which can be seen as a bifurcation equation. Once a solution  $\bar{I} > 0$  of this equation has been obtained, we find positive  $V$  and  $S$  from the other equations. Hence we have a one-to-one correspondence between the positive solutions of (4.5) and the infected stationary points.



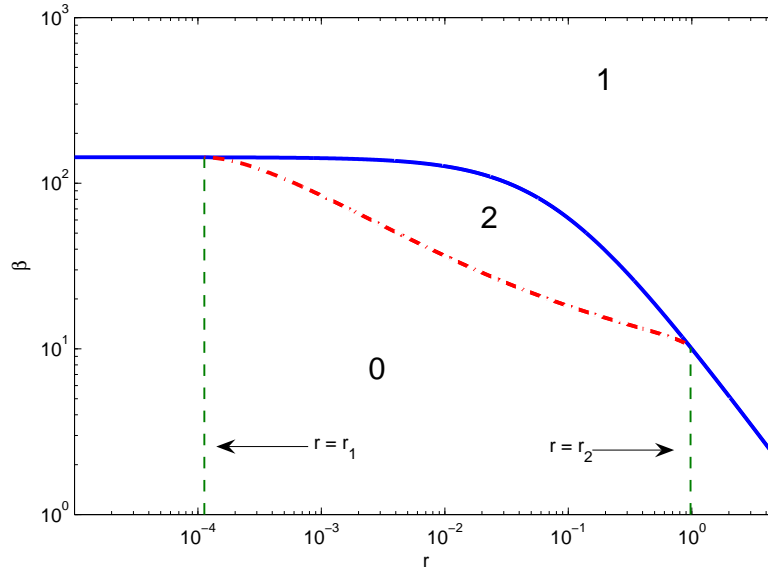


Figure 4.2: The  $(r, \beta)$ -plane is subdivided into three regions according to the number of positive endemic equilibria in addition to the infection free equilibrium (IFE) a region has. The dashed dotted line separates between nonexistence and existence of positive stationary states. We see here three regions. Each one has a number representing the number of positive equilibrium points. If  $\beta > \beta_0$  (i.e. above the solid curve), there is a unique endemic equilibrium in addition to the IFE. In this region, the latter is not stable whereas the first is globally asymptotically stable. In the region denoted by 2, there are two positive stationary solutions in addition to the IFE. Both the IFE and the bigger positive endemic equilibrium are locally asymptotically stable while the third, lying in between, is unstable. The unstable one is sometimes called the breakpoint. Plotting has been performed with parameter values  $\alpha = 10$  per year,  $\mu = 0.015$  per year, and  $\psi = 0.2$  per year.

We keep the parameters  $\mu, \alpha, \psi$  and  $r$  fixed and discuss the equation in terms of  $\beta$  and  $\bar{I}$ . Eventually we are interested in the solutions  $\bar{I}$  for a given value of  $\beta$  and in the global dependence of  $\bar{I}$  depending on  $\beta$ .

The function  $F$  is a polynomial of order four in two variables  $\beta$  and  $\bar{I}$ . Now we describe qualitative features of the null set. For fixed  $\beta$ , the polynomial is quadratic in  $\bar{I}$  and hence there are at most two solutions  $\bar{I}$ . For fixed  $\bar{I}$ , the polynomial is quadratic in  $\beta$  and hence there are at most two solutions  $\beta$ . For  $\beta = 0$  there are no solutions. For large  $\beta$ , i.e.,  $|\beta| \rightarrow \infty$ , the asymptotes are  $\bar{I} \sim 0$  and  $\bar{I} \sim 1$ . For  $\bar{I} = 0$ , the only solution is positive,  $\beta = \beta_0$ .

Hence the curve described by  $F(\beta, \bar{I}) = 0$  has at least two branches, one in  $\beta > 0$  and one in  $\beta < 0$ . There are only two branches because otherwise there would be more than two solutions for some given  $\bar{I}$ . The negative branch looks like a hairpin in  $0 < \bar{I} < 1$  with asymptotes 0 and 1, the positive branch is another hairpin which is asymptotic to 1 from below and also asymptotic to 0 from below. It crosses the  $\beta$  axis at  $\bar{I} = 0$ ,  $\beta = \beta_0$  where  $\beta_0$  is the zero contact rate.

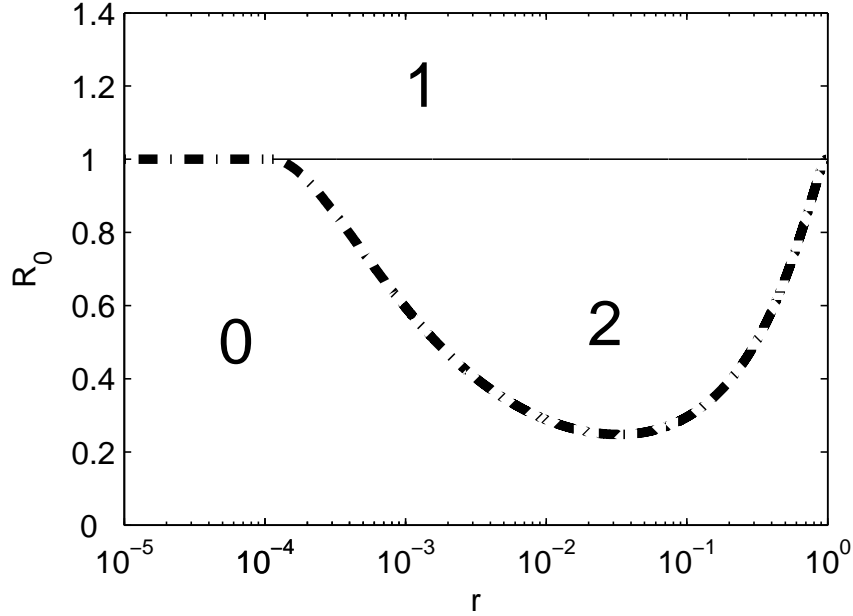


Figure 4.3: The  $(r, R_0)$ -plane is subdivided into three regions according to the number of positive endemic equilibria in addition to the infection free equilibrium (IFE) a region has. The dashed dotted line separates between nonexistence and existence of positive stationary states. We see here three regions. Each one has a number representing the number of positive equilibrium points. If  $R_0 > 1$ , there is a unique endemic equilibrium in addition to the IFE. In this region, the latter is not stable whereas the first is globally asymptotically stable. In the region denoted by 2, there are two positive stationary solutions in addition to the IFE. Both the IFE and the bigger positive endemic equilibrium are locally asymptotically stable while the third, lying in between, is unstable. The unstable one is sometimes called the breakpoint. Plotting has been performed with parameter values  $\alpha = 10$  per year,  $\mu = 0.015$  per year, and  $\psi = 0.2$  per year.

**Definition 4.1. Zero contact rate  $\beta_0$**

The zero contact rate  $\beta_0$  is the value of the contact rate at which the prevalence of infected is zero. This is determined by solving (4.5) with respect to  $\beta$  when  $\bar{I} = 0$ . Therefore

$$\beta_0 = \frac{(\alpha + \mu)(\psi + \mu)}{(r\psi + \mu)}. \tag{4.6}$$

Of course only the positive branch is of interest with respect to the epidemiological problem.

**4.6 Direction of bifurcation**

At  $\beta = \beta_0$ ,  $\bar{I} = 0$  we compute the direction of bifurcation:

$$\frac{d\bar{I}}{d\beta} = -\frac{F_\beta}{F_{\bar{I}}}$$

whereby

$$\begin{aligned} F_\beta|_{(\beta_0,0)} &= -(\mu + r\psi) < 0, \\ F_{\bar{I}}|_{(\beta_0,0)} &= \beta_0[\mu + r(\mu + \alpha + \psi) - r\beta_0]. \end{aligned}$$

Using the definition of  $\beta_0$ , we thus find

$$\frac{d\bar{I}}{d\beta} = \frac{(\mu + r\psi)^2}{\beta_0} \frac{1}{\mu^2 + r\psi(\mu - \alpha) + r^2\psi(\mu + \alpha + \psi)}.$$

Hence we have a forward bifurcation if

$$\mu^2 + r\psi(\mu - \alpha) + r^2\psi(\mu + \alpha + \psi) > 0 \quad (4.7)$$

and a backward bifurcation if

$$\mu^2 + r\psi(\mu - \alpha) + r^2\psi(\mu + \alpha + \psi) < 0. \quad (4.8)$$

This condition for a backward bifurcation is not very transparent in terms of the original epidemiological parameters. It is obvious that the condition can be met provided  $r \in (0, 1)$ , the other parameters being fixed, for large  $\alpha$ . We show the following proposition.

**Proposition 4.1.** *The condition (4.8) for backward bifurcation is equivalent with the following set of inequalities:*

$$\alpha > 3\mu, \quad (4.9)$$

$$\psi > \psi_c = \frac{4\mu^2}{\alpha - 3\mu}, \quad (4.10)$$

$$r_1 < r < r_2, \quad (4.11)$$

where

$$r_{1,2} = \frac{\psi(\alpha + \mu) \mp \sqrt{\psi^2(\alpha - \mu)^2 - 4\mu^2\psi(\alpha + \mu + \psi)}}{2\psi(\alpha + \mu + \psi)}. \quad (4.12)$$

The inequalities (4.9), (4.10) ensure that  $0 < r_1 < r_2 < 1$ .

**Proof:** Define

$$\phi(r) = r^2\psi(\mu + \alpha + \psi) + r\psi(\mu - \alpha) + \mu^2.$$

Then  $\phi(0) > 0$ ,  $\phi(1) > 0$ ,  $\phi'(0) < 0$ ,  $\phi'(1) > 0$ . Hence the minimum of  $\phi$  is in  $(0, 1)$ . Hence it is sufficient to check whether  $\phi$  is definite. The function  $\phi$  is negative for some  $r$  if

$$4(\mu + \alpha + \psi)\mu^2 < \psi(\alpha - \mu)^2.$$

The rest of the proof is elementary. □

## 4.7 The critical contact rate

Once we have a backward bifurcation, the turning point of (the positive part of) the curve of infected solutions in the  $(\beta, I)$ -plane has a positive  $I$  coordinate. We want to determine the corresponding value of  $\beta$  which we call  $\beta^*$ . For given  $\beta$ , the quadratic equation  $F(\beta, I) = 0$  has two solutions

$$\begin{aligned} \bar{I} &= -\frac{1}{2\beta r}(\mu + r(\mu + \alpha + \psi) - r\beta) \\ &\pm \sqrt{\left[\frac{1}{2\beta r}(\mu + r(\mu + \alpha + \psi) - r\beta)\right]^2 - \frac{(\mu + \alpha)(\mu + \psi)}{r\beta^2} + \frac{\mu + r\psi}{r\beta}}. \end{aligned}$$

At  $\beta = \beta^*$  the two solutions coalesce, the radicand vanishes. From this condition we obtain  $\beta^*$  as

$$\beta^* = \frac{1}{r} \left( \left( \sqrt{(1-r)\psi} + \sqrt{r(\alpha + \mu)} \right)^2 - (\mu + \psi) \right). \quad (4.13)$$

The other root of the quadratic equation corresponds to the negative branch. This formula gives the turning point of the positive branch independent of the direction of bifurcation. In the case of a forward bifurcation the value  $I$  at the turning point is negative and hence  $\beta^* > \beta_0$  has no biological meaning. However, in the case of a backward bifurcation we have  $\beta^* < \beta_0$  and the corresponding value  $I^*$  is positive. In this case  $\beta^*$  is the minimal contact rate for which there are infected stationary solutions.

Now it makes sense to extend the definition to comprise both cases and put

$$\beta^* = \begin{cases} \frac{1}{r} \left( \left( \sqrt{(1-r)\psi} + \sqrt{r(\alpha + \mu)} \right)^2 - (\mu + \psi) \right) & ; \quad r_1 \leq r \leq r_2, \psi_c \leq \psi, \alpha + \mu > 4\mu, \\ \beta_0 & ; \quad \text{otherwise.} \end{cases} \quad (4.14)$$

We try to interpret these formulae in epidemiological terms. The condition  $4\mu < \alpha + \mu$  or equivalently  $\frac{1}{\alpha + \mu} < \frac{1}{4\mu}$  means that the length of the infectious period has to be less than one fourth (a quarter of) the life expectancy at birth in the absence of infection. Whereas  $\psi_c < \psi$  or equivalently  $\frac{1}{\psi} < \frac{1}{\psi_c}$  means that the average age of getting vaccinated,  $\frac{1}{\psi}$ , has to be less than the product of the life expectancy at birth in the absence of infection,  $\frac{1}{\mu}$ , and another quantity representing the difference between one fourth the ratio of the life expectancy at birth in the absence of infection to the length of the infectious period,  $\frac{\alpha + \mu}{4\mu}$ , and 1. The inequality  $r_1 < r < r_2$  means that the relative susceptibility of vaccinated individuals lies in an interval  $(r_1, r_2) \subset (0, 1)$ . A relative susceptibility  $r \in (0, 1)$  means that the vaccine gives some protection against the infection, however multiple stationary states exist. Hence, larger effort than reducing  $R_0$  to values slightly less than zero is required to eradicate the infection.

**Definition 4.2.** *The critical basic reproduction number  $R_0^*$ : The critical basic reproduction number is the basic reproduction number evaluated at the turning point, i.e., we replace  $\beta$*

by  $\beta^*$ . Therefore,

$$R_0^* = \frac{\beta^*}{\alpha + \mu} \left( \frac{\mu}{\mu + \psi} + r \frac{\psi}{\mu + \psi} \right). \quad (4.15)$$

**Proposition 4.2.**

Assume that  $\beta^*$  is well defined, then the  $(r, R_0)$ -plane is partitioned as follows:

If  $0 \leq R_0 < R_0^*$ , there is only the infection free equilibrium which is globally asymptotically stable in this area,

If  $R_0^* < R_0 < 1$ , there are two positive endemic equilibria in addition to the infection free equilibrium. The larger of them and the IFE are locally asymptotically stable, whereas the lower, lying in between, is unstable. If  $R_0 = R_0^*$ , then the two positive equilibria coincide. The point corresponding to this is called the turning point.

If  $R_0 \geq 1$ , there is a unique positive endemic equilibrium in addition to the IFE. The IFE is locally asymptotically unstable, whereas the positive one is globally asymptotically stable. If  $R_0 = 1$ , the lower positive endemic equilibrium is reduced to the IFE.

Figure 4.2 shows the partition of the  $(r, \beta)$ -plane according to the number of positive stationary states. Although  $r$  and  $R_0$  are not independent, we draw Figure 4.3 to explain the area below  $R_0 = 1$  which has positive stationary states. I.e., reducing  $R_0$  below one is not sufficient to eliminate the infection.

### 4.8 The turning point

The turning point in our notation corresponds to the point in the  $(\beta, \bar{I})$ -plane at which both positive endemic states coincide. Therefore, the proportions of the three states at this point are  $S^*$ ,  $V^*$ , and  $I^*$  where

$$\begin{aligned} S^* &= \left( \frac{r}{1-r} \right) \left( \frac{(1-r)(\alpha + \mu) - \sqrt{r(1-r)\psi(\alpha + \mu)}}{r(\alpha + \mu) - (\mu + r\psi) + 2\sqrt{r(1-r)\psi(\alpha + \mu)}} \right) \\ V^* &= \left( 2(1-r) + \frac{r(\alpha + \mu) - (\mu + r\psi)}{\sqrt{r(1-r)\psi(\alpha + \mu)}} \right)^{-1} \\ I^* &= \frac{-(\mu + r\psi) + \sqrt{r(1-r)\psi(\alpha + \mu)}}{r(\alpha + \mu) - (\mu + r\psi) + 2\sqrt{r(1-r)\psi(\alpha + \mu)}} \end{aligned} \quad (4.16)$$

As a function of the relative susceptibility,  $r$ , the critical prevalence of infected,  $I^*$ , starts with zero prevalence for all  $r \in [0, r_1]$  and then it increases to reach a maximum at  $r = r_I^{max}$  where

$$r_I^{max} = \frac{\mu \left( \sqrt{\mu(\alpha + \mu)} + \sqrt{\mu(\alpha + \mu) - \psi(\alpha + \psi + 2\mu)} \right)^2 + \mu\psi(2(\alpha + \psi) + 5\mu)}{4\mu^2(\alpha + \mu) + \psi(\alpha + \psi + 3\mu)^2} \quad (4.17)$$

then it decreases again to zero when  $r = r_2$ . On the other hand, the critical proportion of vaccinated individuals starts with level  $\frac{\psi}{\mu + \psi}$  at  $r = r_1$  and it decreases to reach a minimum at

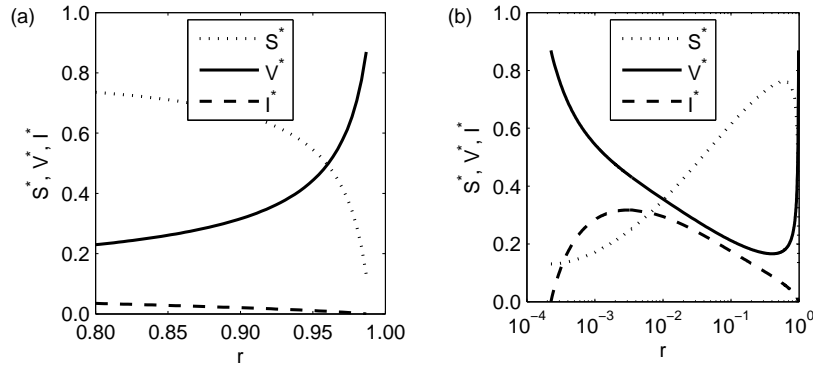


Figure 4.4: In this figure we show the components of the turning point as functions of the relative in susceptibility of individuals in compartment  $V$  to those in compartment  $S$ . Let us stick ourselves to the interval  $[r_1, r_2]$  in which there is a possibility to get multiple stationary solutions. At  $r = r_1$ , the prevalence of infected at the turning point,  $I^*$ , is zero while the proportion of susceptible and vaccinated are respectively  $\frac{\mu}{\mu+\psi}$  and  $\frac{\psi}{\mu+\psi}$ , i.e., a totally susceptible population. With the increase of the relative susceptibility  $r$ , the prevalence of infected increases till reaching a maximum at  $r = r_I^{max}$  and then it decreases again to reach zero when  $r = r_2$ . However, the proportion of susceptible at the turning point,  $S^*$ , increases slowly till reaching a maximum at  $r = r_S^{max}$  and then it decreases again to reach  $\frac{\mu}{\mu+\psi}$  when  $r = r_2$  whereas the proportion of vaccinated at the turning point decreases to reach a minimum at  $r = r_V^{min}$  and then it increases again to reach  $\frac{\psi}{\mu+\psi}$  when  $r = r_2$ . This is explained in the part (b) of the current figure. The right part is an enlarged part of the figure (a). Calculations have been performed with parameter values  $\alpha = 10$  per year,  $\mu = 0.015$  per year, and  $\psi = 0.1$  per year.

$r = r_V^{min}$ , where  $r_V^{min}$  is the feasible solution of the nonlinear algebraic equation

$$4r(1-r)\sqrt{r(1-r)\psi(\alpha+\mu)} - \mu(1-r) - r(\alpha-\psi) = 0.$$

By the feasible solution, I mean a value of  $r \in (r_1, r_2)$ . In a similar way, one can evaluate the relative susceptibility corresponding to  $\frac{dS^*}{dr} = 0$  and notice that the solution of this algebraic equation is exactly the value of  $r \in (r_1, r_2)$  at which the critical proportion of susceptible has its maximum. An explanation of this is shown in figure 4.4.

In figure 4.5 we show how this point, the turning point, behaves in a ternary plot. The ternary plot is presented by this triangle with  $S, I$ , and  $V$  as its vertices. They are set in a counterclockwise direction as shown on the figure. We notice that the turning point moves on a closed path. It starts its trip when  $r = r_1$  at a point on the horizontal. This position on the horizontal corresponds to the infection free equilibrium and is denoted by  $E_0$ . As  $r$  increases from  $r_1$  on, both  $I^*$  and  $S^*$  increase whereas  $V^*$  decreases until  $I^*$  reaches a maximum. After that, both  $I^*$  and  $V^*$  decrease whereas  $S^*$  continues to increase until  $S^*$  reaches a maximum and  $V^*$  reaches a minimum. After that,  $V^*$  increases again and both  $S^*$  and  $I^*$  decrease again to reach their levels in the infection free equilibrium at  $r = r_2$ . Therefore, the trip starts and ends at the infection free equilibrium.

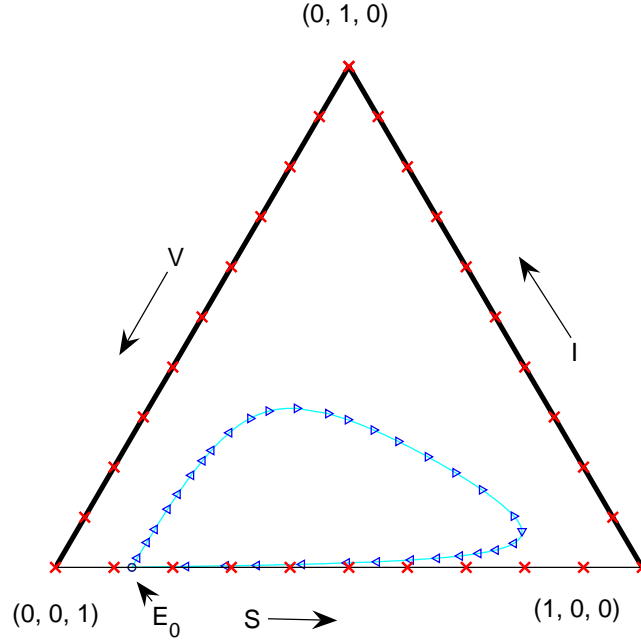


Figure 4.5: The turning point is drawn in the ternary plot for several values of the relative susceptibility  $r$  in the interval  $[r_1, r_2]$ . The turning point moves on a closed curve starting the trip from the point  $E_0$  representing the initial free equilibrium when  $r = r_1$ . With the increase of  $r$ , it moves clock wisely on the closed curve. This movement is described as follows. First  $V^*$  decreases while both  $S^*$  and  $I^*$  increase whereinto  $I^*$  reaches a maximum at  $r = r_I^{max}$ . Then,  $S^*$  continues to increase whereas both  $I^*$  and  $V^*$  decrease until  $S^*$  reaches a maximum at  $r = r_S^{max}$ . After that,  $V^*$  increases while both  $S^*$  and  $I^*$  decrease until  $V^*$  reaches its maximum again with maximum  $\frac{\psi}{\mu+\psi}$ . This occurs when  $r = r_2$  at which the turning point coincides with the infection free equilibrium. Calculations have been performed with parameter values  $\alpha = 10$  per year,  $\mu = 0.015$  per year, and  $\psi = 0.1$  per year.

#### 4.9 The eradication effort $\mathcal{R}$

We claim that  $\mathcal{R} = \frac{\beta}{\beta^*}$  can be interpreted as a reproduction number. For this purpose, we consider the episode reproduction number and evaluate it at the turning point. Therefore, we need to evaluate  $R_e(\beta, S^*, V^*)$ . Since

$$\begin{aligned}
 S^* + rV^* &= \frac{r(\alpha + \mu)}{\left(\sqrt{(1-r)\psi} + \sqrt{r(\alpha + \mu)}\right)^2 - (\mu + \psi)} \\
 &= \frac{\alpha + \mu}{\beta^*}
 \end{aligned} \tag{4.18}$$

Hence,

$$\mathcal{R} = R_e(\beta, S^*, V^*) = \frac{\beta}{\beta^*} \tag{4.19}$$

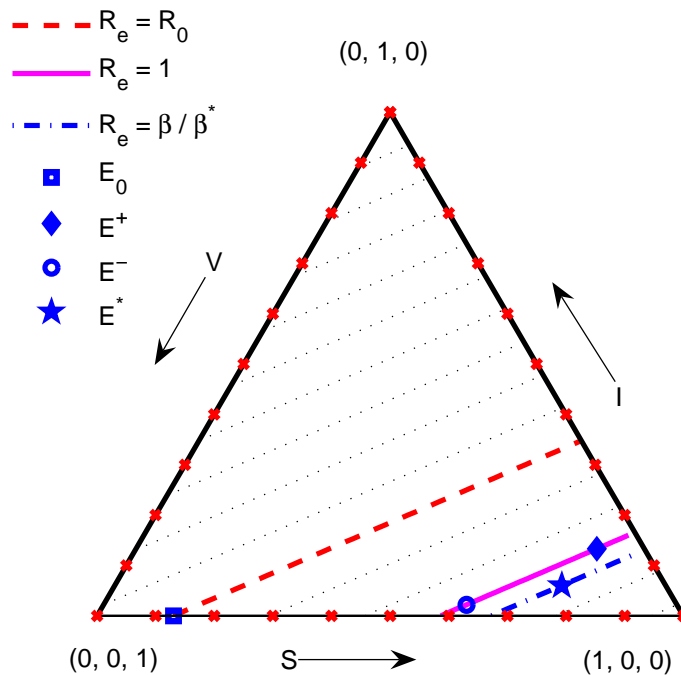


Figure 4.6: The compartments  $S, I$ , and  $V$  are represented here in terms of a ternary plot. They are set in a counterclockwise direction. Here we show the contour lines for the episode reproduction number  $R_e$  when it equals some constant times the basic reproduction number  $R_0$ . We notice that the contour lines are straight lines with slope  $\frac{(1-r)\sqrt{3}}{1+r}$ . If  $r < 1$ , then the contour lines tangent to the right as in this figure. This is the case of interest now. The dashed line corresponds to an  $R_e = R_0$ . This line passes through the IFE. The continuous line corresponds to an  $R_e = 1$  and passes through the two positive endemic equilibria. The dashed dotted line corresponds to an  $R_e = \frac{\beta}{\beta^*}$  and passes through the turning point (The point at which both positive stationary states coincide). Calculations have been performed with parameter values  $\beta = 13$  per year,  $r = 0.6$ ,  $\alpha = 10$  per year,  $\mu = 0.015$  per year, and  $\psi = 0.1$  per year.

An explanation of this is shown in figure 4.6. There, we draw the contour lines for the episode reproduction number in the ternary plot. The contour lines correspond to an  $R_e$  equal to a constant times the basic reproduction number  $R_0$ . Therefore, they are all parallel and their tangent is  $\frac{(1-r)\sqrt{3}}{1+r}$ . These contour lines are represented by the straight dotted lines. The first but high line corresponds to an  $R_e = 0.1R_0$ . Then we continue increasing the constant by step 0.1. The dashed line corresponds to an  $R_e = R_0$  and it passes through the infection free equilibrium,  $E_0$ . The continuous contour line corresponds to an  $R_e = 1$  and it passes through the two positive equilibria,  $E^+$  and  $E^-$ . The dashed dotted line represents the contour line for an  $R_e = \mathcal{R} = \frac{\beta}{\beta^*}$  and it goes through the point corresponding to the turning point,  $E^*$ .

**Proposition 4.3.** *The ratio between the contact rate  $\beta$  and the critical contact rate  $\beta^*$  at*



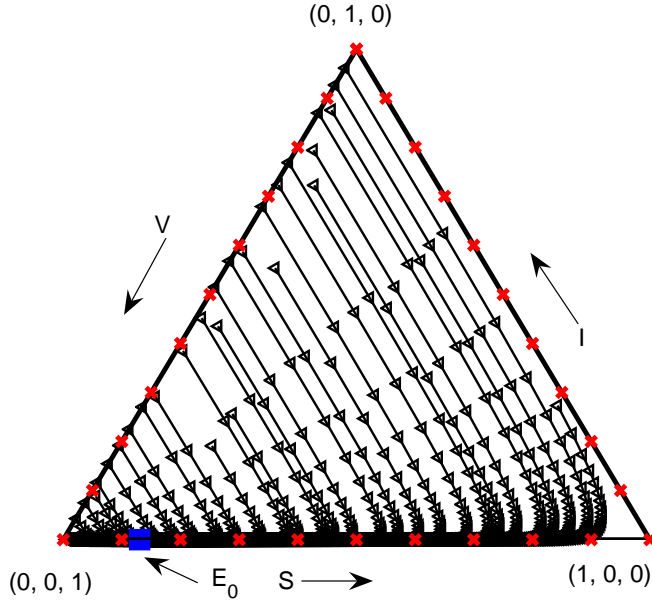


Figure 4.7: This figure shows the trajectories in the ternary plot for parameter values corresponding to the area in which the infection free equilibrium is globally asymptotically stable. If we start anywhere, a sudden decrease in the prevalence of infected accompanied by a sudden increase in the proportion of susceptible occurs. Thereon, an increase in the proportion of vaccinated accompanied by a decrease in the proportion of susceptible occurs. Calculations have been performed for parameter values  $R_0 = 0.1$  ( $\beta = 28.33$  per year),  $r = 0.01$ ,  $\alpha = 10$ , per year  $\mu = 0.015$  per year, and  $\psi = 0.1$  per year.

*equilibrium is given by*

$$\frac{\beta}{\beta^*} = \begin{cases} \frac{1}{\bar{S} + r\bar{V}} \left( \frac{r(\alpha + \mu)}{(\sqrt{(1-r)\psi} + \sqrt{r(\alpha + \mu)})^2 - (\mu + \psi)} \right) & ; r_1 \leq r \leq r_2, \psi_c \leq \psi, \alpha + \mu > 4\mu, \\ \frac{1}{\bar{S} + r\bar{V}} \left( \frac{\mu}{\mu + \psi} + r \frac{\psi}{\mu + \psi} \right) & ; \textit{otherwise} \end{cases} \quad (4.20)$$

*where the ratio  $r$  is determined from the relation*

$$r = \frac{\bar{S}}{\bar{V}} \left( \frac{(\mu + \alpha)\bar{I}}{(\mu + \alpha)\bar{I} - \psi\bar{S} + \mu\bar{V}} - 1 \right). \quad (4.21)$$

The importance of (4.20) is that it does not explicitly depend on the contact rate  $\beta$ . If we know the composition of the population at equilibrium in addition to the life expectancy at birth in the absence of infection  $1/\mu$ , the length of the infectious period  $1/(\alpha + \mu)$ , and the average age of getting vaccinated  $1/\psi$ , then we can use (4.21) to determine the relative susceptibility  $r$  and hence by (4.20) we estimate the eradication effort  $\mathcal{R} = \beta/\beta^*$ .

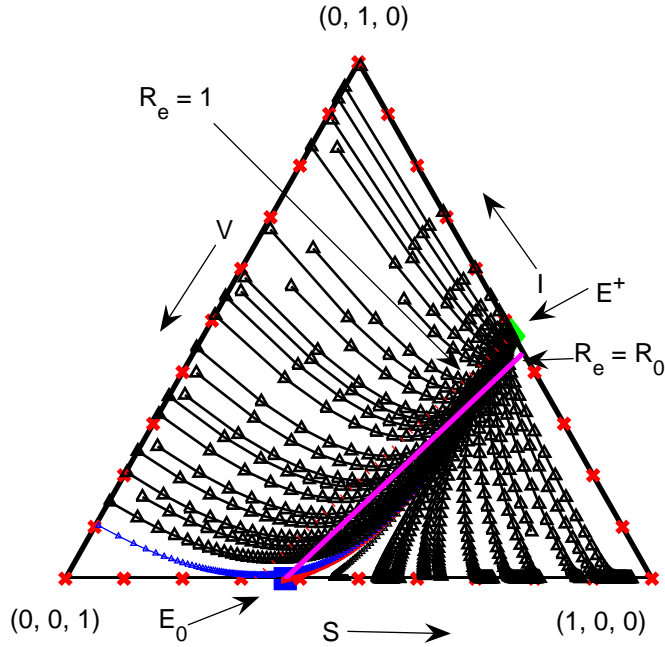


Figure 4.8: Here we show the trajectories for parameter values  $\beta = 19$  per year,  $r = 0.3$ ,  $\alpha = 10$  per year,  $\mu = 0.015$  per year, and  $\psi = 0.025$  per year. These values correspond to the area in which there is a unique positive endemic state in addition to the IFE. If  $R_e < R_0$ , a sudden increase in the proportion of susceptible accompanied by sudden decrease in both the prevalence of infected and that of vaccinated. Thereon, a decrease in the proportion of vaccinated individuals and increase in the other two proportions occurs to get to the equilibrium. However, if  $R_e > R_0$ , a decrease in the proportion of susceptible accompanied with an increase in the proportion of vaccinated occurs. After that, both the proportions of susceptible and infected increase, whereas the proportion of vaccinated individuals declines. All solutions approach the endemic state which is globally asymptotically stable in this area. Therefore  $E^+$  is the attractor.

#### 4.10 Transient behaviour

Since analytical solutions to model (4.1) are impossible, numerical simulations have been performed. Figure (4.7) shows the trajectories in the ternary plot for parameter values corresponding to the area in which the infection free equilibrium is globally asymptotically stable. A description of the behaviour is mentioned in the legend of the figure.

If we solve the system (4.1) with parameter values for which there is a unique endemic equilibrium in addition to the infection free equilibrium, we get a dramatic behaviour. The prevalence of infected can initially decrease and then increase again to reach the equilibrium or it can uniformly increase to reach the equilibrium. This is shown and explained in figure 4.8.

Figure (4.9) shows the trajectories with parameter values for which there are two positive stationary states in addition to the IFE. The higher stationary state, denoted by  $E^+$ , as well as the infection free equilibrium, denoted by  $E_0$ , is locally asymptotically stable whereas the

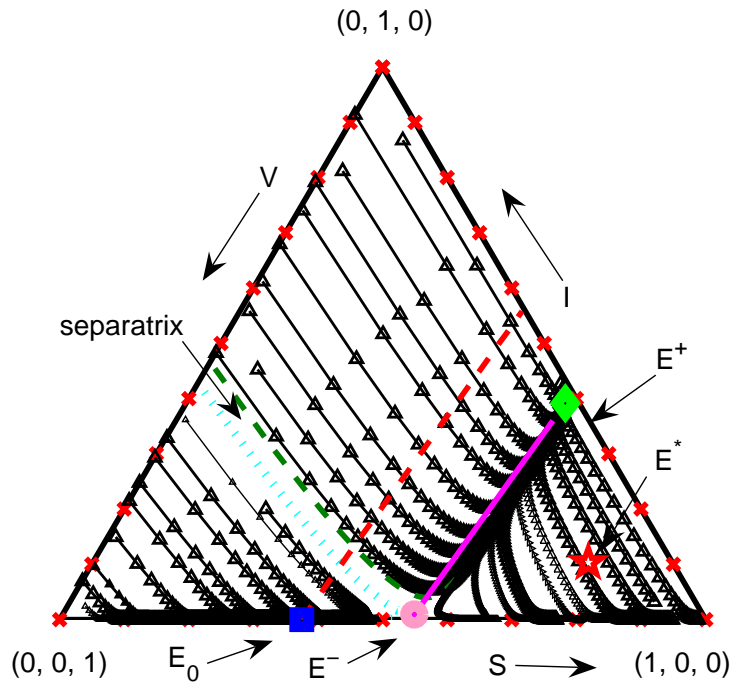


Figure 4.9: This figure shows the trajectories when there are two positive stationary solutions in addition to the infection free equilibrium.

lower positive stationary state, denoted by  $E^-$ , is unstable. The dashed straight line going through the IFE  $E_0$  represents the contour line for  $R_e = R_0$ . However, the continuous straight line passing through both the positive equilibria,  $E^+$  and  $E^-$ , represents the line for an  $R_e = 1$ . The point denoted by  $E^*$  represents the turning point and is represented by this star in the right corner. The dotted line coming down from the left and passing through the unstable equilibrium,  $E^-$ , represents the separatrix. By the separatrix we mean the line separating the domain of attraction of both the stable states,  $E_0$  and  $E^+$ . If we are in the domain of attraction of the IFE, an increase in the proportion of susceptible occurs whereas a sudden decrease in the prevalence of infected occurs until it reaches zero. After that, there are two cases. Either it reaches zero on the left of  $E_0$  (in this case, the proportion of susceptible increases while the proportion of vaccinated increases to reach the IFE) or it reaches zero on the right of  $E_0$  (in this case, a decrease in the proportion of susceptible accompanied by an increase in the proportion of vaccinated individuals occurs). On the other hand, if we start somewhere in the domain of attraction of the stable positive endemic state, there are two cases. Either  $R_e < 1$  (in this case, the proportion of susceptible increases to reach some level while both the proportions of vaccinated and infected decrease. The decline in the infected is much faster. After that, the prevalence of infected increases until reaching the locally asymptotically stable equilibrium  $E^+$ ), or  $R_e > 1$  (in this case, an increase in both proportions of infected and vaccinated individuals occurs whereas the proportion of susceptible declines till some level. Then, the proportion of vaccinated individuals declines, while both proportions of susceptible and infected occur till reaching the stable equilibrium). Calculations have been performed with

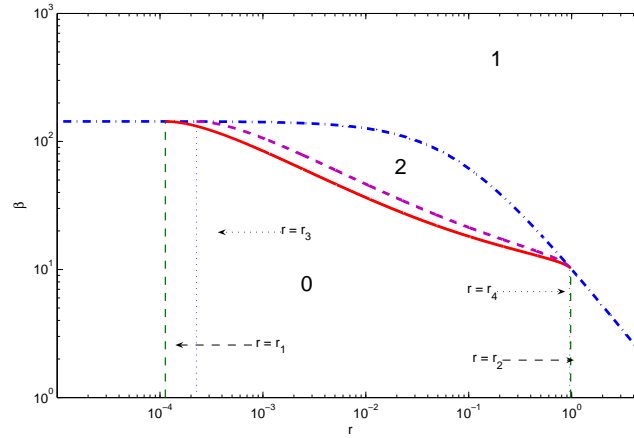


Figure 4.10: The bifurcation diagram in the  $(r, \beta)$ -plane for both cases, linear and nonlinear incidence. Simulations have been performed with parameter values  $\alpha = 10$  per year,  $\mu = 0.015$  per year, and  $\psi = 0.2$  per year. The plane is subdivided into three areas according to the number of positive endemic states an area has. If  $\beta > \beta_0$  (area above the dashed-dotted line), There is a unique endemic state in addition to the IFE. The first is globally asymptotically stable whereas the later is unstable in this area. If  $\beta < \beta_0$  (area below the horizontal dashed-dotted line), we have an area which is subdivided into two areas. One of them has two positive stationary states and the other has no positive endemic state in addition to the IFE. Both the IFE and the higher positive stationary state are locally asymptotically stable, whereas the lower positive one lies in between and is unstable. The bounds of the one containing two are as follows: from the left and right we respectively have  $r = r_1$  and  $r = r_2$ , from above we have  $\beta = \beta_0$ , and from down we have a curve denoted by  $\beta^*$  (the dashed (nonlinear incidence) or the continuous (linear incidence)). The area in which there are multiple stationary states shrinks if we consider nonlinear incidence.  $r_1$  gets bigger (to coincide with  $r_3$ ) while  $r_2$  gets smaller (to coincide with  $r_4$ ), and  $\beta^*$  gets higher whereas  $\beta_0$  is fixed. The rest of the area below  $\beta = \beta_0$  represents the area in which there is no positive stationary state but the IFE is globally asymptotically stable.

parameter values  $\beta = 17$  per year,  $r = 0.1$ ,  $\alpha = 10$  per year,  $\mu = 0.015$  per year, and  $\psi = 0.025$  per year.

#### 4.11 Effect of nonlinear incidence

In this section we would like to look at the problem from another point of view. We would like to investigate how the results change with nonlinear incidence of the infection and try to compare this with the linear one. Liu et al. [61, 62] proposed models that incorporate nonlinear incidence rates of the form  $\frac{\kappa I^l}{(1+\alpha I^h)}$  with positive parameters  $\kappa, l, \alpha$ , and  $h$ . Here we assume that  $l = h = \alpha = 1$ . Thus the force of infection affecting susceptible is  $\frac{\kappa I}{1+I}$ . In our notation, it is  $\frac{\beta I}{1+I}$  where  $\beta = r_s \kappa_1$ .  $\kappa_1$  represents the number of contacts per unit of time that an infected individual makes with susceptible, and  $r_s$  represents the probability of success that a contact leads to infection. Thus  $\beta$  is the successful contact rate between infected and susceptible.

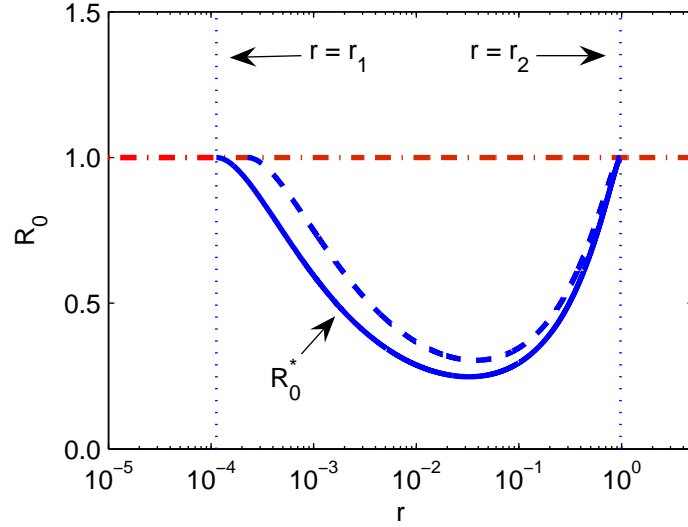


Figure 4.11: The bifurcation diagram in the  $(r, R_0)$ -plane for both cases, linear and nonlinear incidence. Simulations have been performed with parameter values  $\alpha = 10$  per year,  $\mu = 0.015$  per year, and  $\psi = 0.2$  per year. The plane is subdivided into three areas according to the number of positive endemic state an area has. If  $R_0 > 1$  (area above the horizontal dashed-dotted line), There is a unique endemic state in addition to the IFE. The first is globally asymptotically stable whereas the later is unstable in this area. If  $R_0 < 1$  (area below the horizontal dashed-dotted line), we have an area which is subdivided into two areas. One of them has two positive stationary states and the other has no positive endemic state in addition to the IFE. Both the IFE and the higher positive stationary state are locally asymptotically stable, whereas the lower positive one lies in between and is unstable. The bounds of the one containing two are as follows: from the left and right we respectively have  $r = r_1$  and  $r = r_2$ , from above we have  $R_0 = 1$ , and from down we have a curve denoted by  $R_0^*$  (the dashed (nonlinear incidence) or the continuous (linear incidence)). The area in which there multiple stationary states shrinks if we consider nonlinear incidence.  $r_1$  gets bigger while  $r_2$  gets smaller, and  $R_0^*$  gets higher whereas  $R_0$  is fixed. The rest of the area below  $R_0 = 1$  represents the area in which there is no positive stationary state but the IFE is globally asymptotically stable.

### The model

The model reads

$$\begin{aligned}
 \dot{S} &= \mu - \left( \beta \frac{I}{1+I} + \psi + \mu \right) S + \alpha I, \\
 \dot{V} &= \psi S - \left( r \beta \frac{I}{1+I} + \mu \right) V, \\
 \dot{I} &= (S + rV) \beta \frac{I}{1+I} - (\alpha + \mu) I \\
 1 &= S + V + I.
 \end{aligned} \tag{4.22}$$

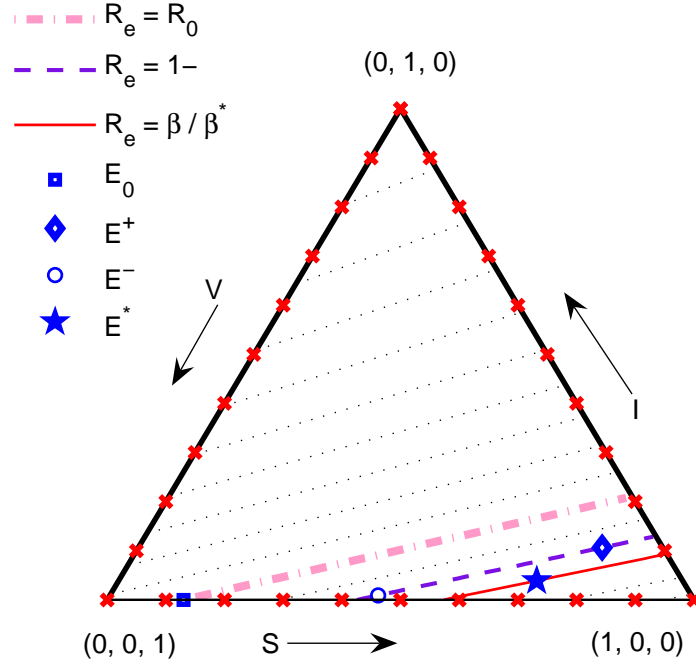


Figure 4.12: The ternary plot shows the contour lines for the episode reproduction number, the contour lines for  $R_e = R_0$ ,  $R_e = 1$ , and  $R_e = \mathcal{R} = \frac{\beta}{\beta^*}$  the equilibria ( $E_0$ ,  $E^-$ , and  $E^+$ ), and the point corresponding to the turning point ( $E^*$ ). All contour lines are parallel and have the same tangent  $\frac{(1-r)\sqrt{3}}{1+r}$ . The contour line  $R_e = \mathcal{R} = \frac{\beta}{\beta^*}$  goes through the point  $E^*$ . Calculations have been done with parameter values  $\alpha = 10$  per year,  $\mu = 0.015$  per year,  $\beta = 13$  per year,  $r = 0.6$ ,  $\psi = 0.1$  per year.

The infection free equilibrium remains the same, whereas the bifurcation equation reads

$$\begin{aligned}
 0 = F(I) &= ((\psi + \mu)(\alpha + \mu + r\beta) + \beta(\mu + r(\alpha + \beta))) I^2 \\
 &+ (2(\psi + \mu)(\alpha + \mu) + r\beta(\alpha + \mu - r\beta)) I \\
 &+ (\psi + \mu)(\alpha + \mu) - \beta(\mu + r\psi)
 \end{aligned} \tag{4.23}$$

Both the zero contact rate  $\beta_0$  and the basic reproduction number  $R_0$  remain the same, whereas the episode reproduction number reads

$$R_e = \frac{\beta(S + rV)}{(\alpha + \mu)(1 + I)} \tag{4.24}$$

The critical contact rate  $\beta_1^*$  turns out to be

$$\beta^* = \begin{cases} \frac{1}{r} \left( \left( \sqrt{r(\alpha + \mu)} + \sqrt{2(1-r)\psi} \right)^2 - 2(\psi + \mu) \right) & ; \quad r_3 \leq r \leq r_4, \psi_{cn} \leq \psi, \alpha + \mu > 8\mu, \\ \beta_0 & ; \quad \text{otherwise} \end{cases} \tag{4.25}$$

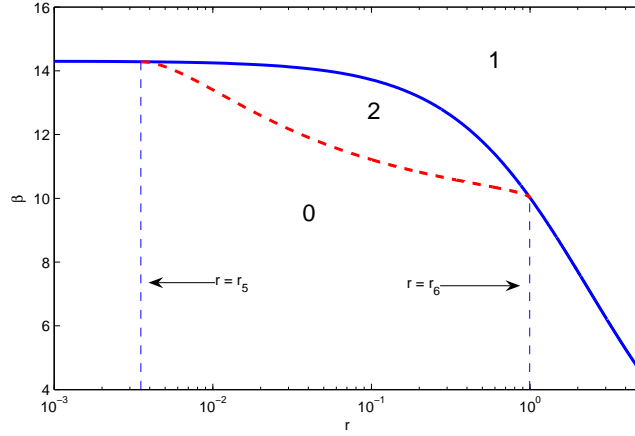


Figure 4.13: Bifurcation diagram for the model if we consider active vaccination (i.e., we vaccinate immediately after birth). There are two main areas (either  $\beta > \beta_0$ , this corresponds to the area in which there is a unique endemic equilibrium in addition to the infection free equilibrium, or  $\beta < \beta_0$  (this area is subdivided into two areas, one with two positive steady states and the other without)). The numbers 0, 2, and 1 on the figure represent the number of positive stationary states in the corresponding areas. Simulations have been performed With parameter values  $\alpha = 10$  per year,  $\mu = 0.015$  per year, and  $p = 0.3$ .

where

$$\begin{aligned} \frac{\psi_{cn}}{\mu} &= \left(-1 + \frac{\alpha + \mu}{8\mu}\right)^{-1} \\ r_{3,4} &= \frac{1}{2} \left(1 + \frac{2\psi}{\alpha + \mu}\right)^{-1} \left( \left(1 - \frac{4\mu}{\alpha + \mu}\right) \mp \sqrt{1 - \frac{8\mu}{\alpha + \mu} \left(1 + \frac{\mu}{\psi}\right)} \right) \end{aligned} \quad (4.26)$$

The first condition,  $\alpha + \mu > 8\mu$  means that the length of the infectious period must be less than one eighth the life expectancy at birth in the absence of infection, whereas the condition  $\psi > \psi_{cn}$  or equivalently,  $\frac{\mu}{\psi} < \frac{\mu}{\psi_{cn}}$  means that the proportion of the life expectancy at birth in the absence of infection spent until getting vaccinated is less than minus one plus one eighth the ratio between the life expectancy at birth in the absence of infection and the length of the infectious period.

The bifurcation diagram is explained in figures 4.11 and 4.10. Details are given in the legends.

If we substitute the components of the turning point in the formula for the episode reproduction number defined in (4.24), we get that  $R_e = \mathcal{R} = \frac{\beta}{\beta^*}$ . The contour lines for the episode reproduction number, the stationary states, the line  $R_e = R_0$ , the line  $R_e = 1$ , the point corresponding to the turning point, and the line  $R_e = \frac{\beta}{\beta^*}$  are shown in figure 4.12.

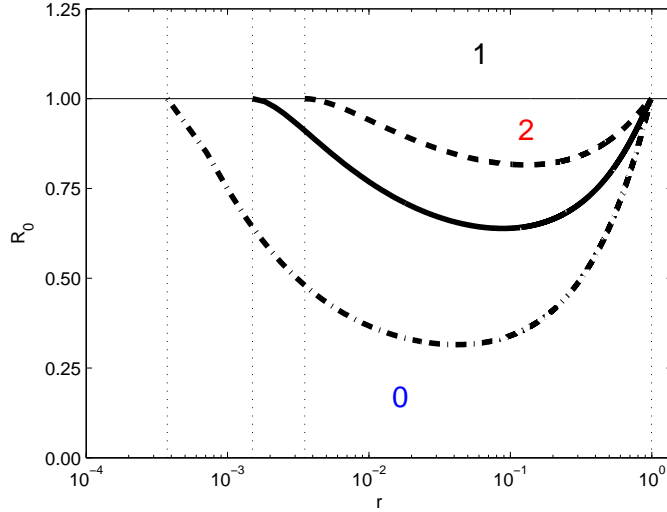


Figure 4.14: Bifurcation diagram for the model if we consider active vaccination (i.e., we vaccinate immediately after birth). There are two main areas (either  $R_0 > 1$ , this corresponds to the area in which there is a unique endemic equilibrium in addition to the infection free equilibrium, or  $R_0 < 1$  (this area is subdivided into two areas, one with two positive steady states and the other without)). The numbers 0, 2, and 1 on the figure represent the number of positive stationary states in the corresponding areas. Simulations have been performed With parameter values  $\alpha = 10$  per year,  $\mu = 0.015$  per year, and three times for  $p$ .  $p = 0.3$  (the dashed),  $p = 0.5$  (the continuous), and  $p = 0.8$  (the dashed-dotted). We notice that the area of multiple stationary states extends with the increase of the proportion of children being vaccinated immediately after birth.

## 4.12 Active vaccination problem

Here, we assume that the vaccination will be given immediately after birth to a proportion  $p$  of the newborns. Therefore, the model reads:

$$\begin{aligned}\dot{S} &= (1-p)\mu - (\mu + \beta I)S + \alpha I, \\ \dot{V} &= p\mu - (\mu + r\beta I)V, \\ \dot{I} &= \beta(S + rV)I - (\alpha + \mu)I.\end{aligned}\tag{4.27}$$

The infection free equilibrium is  $E_0 = (1-p, p, 0)$ .

The bifurcation equation is

$$0 = F(I) = r(\beta I)^2 + (\mu + r(\alpha + \mu - \beta))\beta I + \mu(\alpha + \mu - (1-p + rp)\beta).\tag{4.28}$$

The zero contact rate is

$$\beta_0 = \frac{\alpha + \mu}{1-p + rp}\tag{4.29}$$

whereas the basic reproduction number is

$$R_0 = \frac{\beta}{\beta_0} = \frac{\beta((1-p) + rp)}{\alpha + \mu}.\tag{4.30}$$



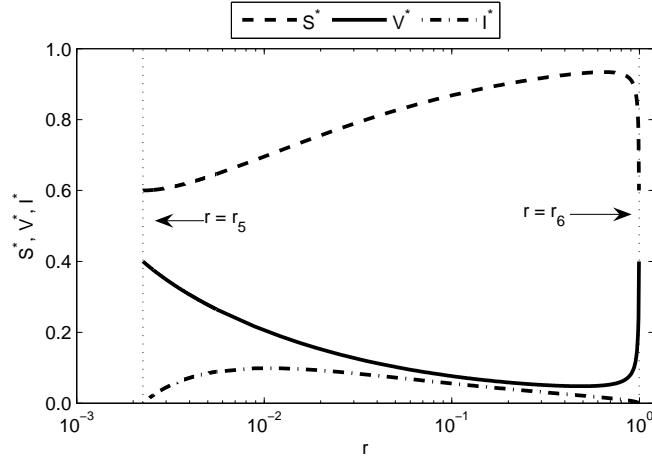


Figure 4.15: The coordinates corresponding to the components of the turning point as functions of the relative susceptibility of vaccinated individuals to susceptible. The critical prevalence of infected  $I^*$  starts at zero when  $r = r_5$  and initially increases till reaching a maximum when  $r = r_I^{max2}$  and then it decreases again to reach zero when  $r = r_6$ . However, while the critical proportion of susceptible  $S^*$  increases from  $(1-p)$  at  $r = r_5$ , the critical proportion of vaccinated individuals  $V^*$  decreases from  $p$  until  $S^*$  reaches a maximum at which  $V^*$  reaches its minimum and thereon  $S^*(V^*)$  decreases (increases) to reach again the level corresponding to the IFE at  $r = r_6$ . Simulations have been performed with parameter values  $\alpha = 10$  per year,  $\mu = 0.015$  per year,  $p = 0.4$ .

The critical contact rate is

$$\beta^* = \begin{cases} \frac{1}{r} \left( \sqrt{(1-r)p\mu} + \sqrt{r\alpha - (1-p)(1-r)\mu} \right)^2 & ; \quad 0 < r_5 \leq r \leq r_6 < 1, p > p_c, \\ \beta_0 & ; \quad \text{otherwise} \end{cases} \quad (4.31)$$

where

$$\begin{aligned} p_c &= 4 \left( \frac{\mu}{\alpha + \mu} \right) \left( 1 + \frac{\mu}{\alpha + \mu} \right)^{-2} \\ r_{5,6} &= \frac{1}{2} \left( \left( 1 - \frac{\mu}{\alpha + \mu} \right) \mp \sqrt{\left( 1 + \frac{\mu}{\alpha + \mu} \right)^2 - \frac{4}{p} \frac{\mu}{\alpha + \mu}} \right). \end{aligned} \quad (4.32)$$

This means that the vaccination ratio,  $p$ , has to be greater than a critical ratio,  $p_c$ . This critical vaccination ratio depends mainly on the ratio between the length of the infectious period to the life expectancy at birth in the absence of infection.

The bifurcation diagram is shown in figures 4.13 and 4.14. Details are given in the legends. The critical contact rate depends on the vaccination ratio,  $p$ . Extending the vaccination ratio extends the area in which multiple endemic equilibria exist.

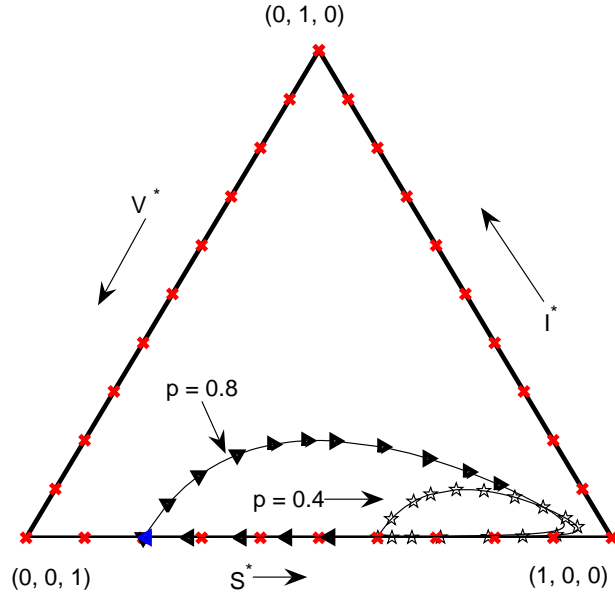


Figure 4.16: The representation of the turning point in the ternary plot for  $\alpha = 10$  per year,  $\mu = 0.015$  per year, and two values of  $p$  ( $p = 0.4$  and  $p = 0.8$ ) and for  $r_5 \leq r \leq r_6$ . The turning point moves on a closed curve. The trip starts at the infection free equilibrium when  $r = r_5$  in a clockwise direction and ends at the infection free equilibrium when  $r = r_6$ . An initial but quick increase in the critical prevalence of infected  $I^*$  occurs, while a slower increase (decrease) in the critical proportion of susceptible  $S^*$  (vaccinated individuals  $V^*$ ) occurs. This quick increase in  $I^*$  happens till it reaches a maximum when  $r = r_I^{max2}$ . Then,  $I^*$  starts to decrease while  $S^*$  ( $V^*$ ) continues to increase (decrease) until reaching a maximum (minimum). Thereon,  $S^*$  ( $V^*$ ) decreases (increases) again while  $I^*$  continues to decrease until reaching the position corresponding to the infection free equilibrium. In the figure we see two closed curves, each of them corresponds to a value of the proportion of immediately vaccinated children after birth. The one within corresponds to  $p = 0.4$  while the outer one corresponds to  $p = 0.8$ . This means that the closed path extends with the extension in the proportion of vaccinated individuals.

The coordinates of the point corresponding to the turning point are

$$\begin{aligned}
 I_1^* &= \frac{1}{2} \left( 1 - \frac{\mu + r(\alpha + \mu)}{\left( \sqrt{(1-r)p\mu} + \sqrt{r\alpha - (1-p)(1-r)\mu} \right)^2} \right) \\
 S_1^* &= \frac{r}{2(1-r)} \left( 1 + \frac{\alpha + (1-r)(\alpha + \mu)}{\left( \sqrt{(1-r)p\mu} + \sqrt{r\alpha - (1-p)(1-r)\mu} \right)^2} \right) \\
 V_1^* &= 1 - (S^* + I^*)
 \end{aligned} \tag{4.33}$$

As functions of the relative susceptibility  $r$ , the components corresponding to the turning point are shown in figure 4.15. A ternary plot containing the correspondence to the turning

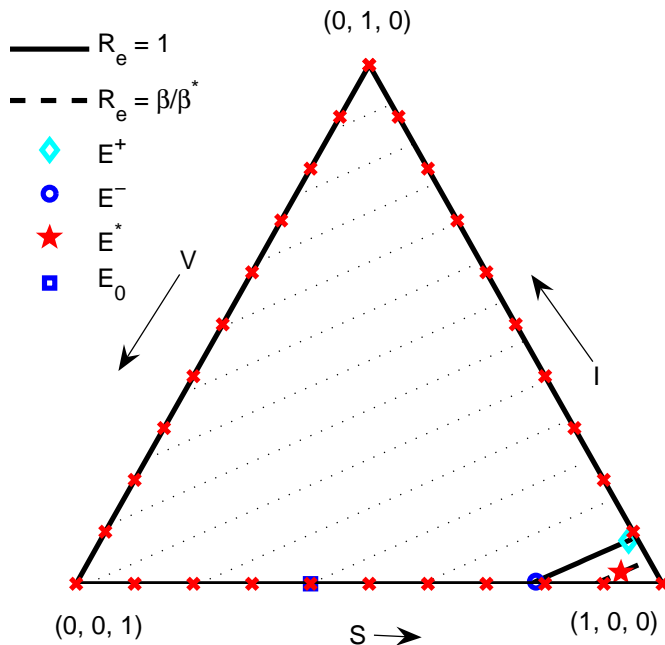


Figure 4.17: The contour lines for the episode reproduction number in the ternary plot. They are all parallel and have the same tangent  $\frac{(1-r)\sqrt{3}}{1+r}$ . The line  $R_e = 1$  goes through the two positive equilibria,  $E^-$  and  $E^+$ . The line  $R_e = R_0$  goes through the infection free equilibrium,  $E_0$ . The line  $R_e = \frac{\beta}{\beta^*}$  goes through the point corresponding to the turning point,  $E^*$ . Simulations have been performed with parameter values  $\beta = 11$  per year,  $r = 0.6$ ,  $\alpha = 10$  per year,  $\mu = 0.015$  per year, and  $p = 0.6$ .

point for values of  $r \in [r_5, r_6]$  is shown in figure 4.16.

The episode reproduction number,  $R_e$ , is

$$R_e(\beta, S, V) = \frac{\beta(S + rV)}{\alpha + \mu} \quad (4.34)$$

We notice that

$$R_e(\beta, S_1^*, V_1^*) = \frac{\beta}{\beta^*} \quad (4.35)$$

Figure (4.17) shows the contour lines for the episode reproduction number and the equilibria. It also shows that the contour line  $R_e = \frac{\beta}{\beta^*}$  goes through the point corresponding to the turning point. Hence,  $\mathcal{R} = \frac{\beta}{\beta^*}$  is a reproduction number.

### 4.13 Discussion and conclusion

In this chapter we introduced a simple SIS epidemic model with vaccination which gives partial immunity against the infection. However, we considered the model in three different cases. In the first two cases we consider linear incidence deduced from a law similar to that of mass action and nonlinear incidence of Holling-type II both with vaccination given sometime after birth. In

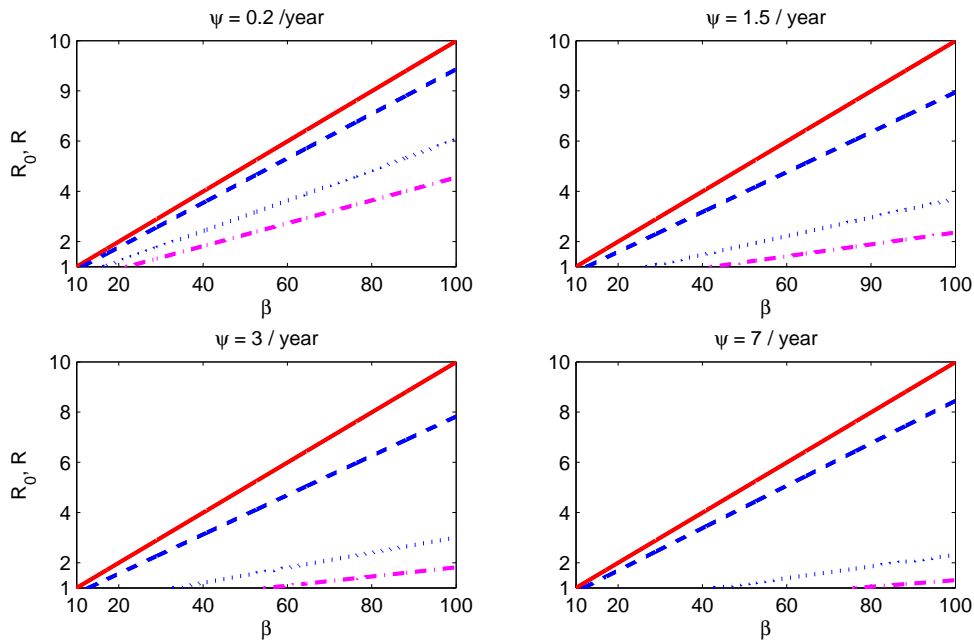


Figure 4.18: This figure consists of four parts with different values of the vaccination rate  $\psi$ . Each part shows the minimum effort required to eradicate the infection  $\mathcal{R}$  for different values of the relative susceptibility  $r$  in each part and the basic reproduction number for the model if we consider no vaccination. Simulations have been done for parameter values  $\alpha = 10$  per year,  $\mu = 0.015$  per year, and different values for the relative susceptibility  $r$ .  $r = 0.0490$  (the dashed dotted line),  $r = 0.1467$  (the dotted line), and  $r = 0.7819$  for the broken (dashed) line. The solid line in each part of the figure represents the basic reproduction number if we consider no vaccination  $R_{00} = \beta/(\alpha + \mu)$ . The remaining three lines in each part represent the minimum effort  $\mathcal{R}$  for the different values of  $r$ . With the increase of the vaccination rate  $\psi$ , the minimum effort decreases. On the contrary, the minimum effort increases with increase of  $r$ . We notice that the minimum effort  $\mathcal{R}$  is always less than the basic reproduction number if we consider no vaccination.

the third case we consider linear incidence but the vaccination is given immediately after birth for a proportion  $p$  of the newborns. The first thing that I would like to discuss is the problem of vaccination. If we do not vaccinate, then there is no backward bifurcation. Therefore the effort required to eliminate the infection is simply to reduce the basic reproduction number in case of no vaccination  $R_0 = \beta/(\alpha + \mu)$  to values slightly less than one. However if we consider the model with vaccination, the basic reproduction number differs. Let us stick now to the first model in this chapter which considers linear incidence with delayed vaccination and is defined in system (4.1) and similar discussion is correct for the remaining two models in the chapter. For this model the basic reproduction number is given by formula (4.3) and the model ensures the existence of multiple stationary states. However if we reduce  $R_0$  in (4.3) to values slightly less than one, the infection can not be eradicated. Therefore, we need to estimate another quantity which achieves our goal. This is what we introduced in (4.19) and it is bigger than

$R_0$  in (4.3). However this new but big quantity is still smaller than the basic reproduction number for a model with no vaccination  $R_0 = \beta/(\alpha + \mu)$ . In figure 4.18 we draw both  $R_0$  and  $\mathcal{R}$  in different cases. First of all the figure has four parts corresponding to four different values of the vaccination rate  $\psi$  as explained in each part. Then each part has a solid straight line representing  $R_{00}$  and three other lines corresponding to  $\mathcal{R}$  for three different values of the relative susceptibility  $r$ . We notice that  $\mathcal{R}$  is always less than  $R_{00}$  and with increasing  $\psi$ ,  $\mathcal{R}$  decreases.

The second thing I would like to discuss is the area in which multiple stationary states are possible. Figure (4.11) shows simply that the area in which backward bifurcation is possible shrinks under the effect of nonlinear incidence. This means that if we neglect the nonlinearity, then we are on the safe side but we simply give more effort.

If we vaccinate immediately after birth, then backward bifurcation is possible to occur under some conditions as explained in section (4.12).

For all cases, we deduce that  $\mathcal{R} = \beta/\beta^*$  is interpreted as a reproduction number.

Therefore we conclude that the earlier the administration of the vaccination is, the smaller the eradication effort is. Also, the more the efficiency of the vaccine (i.e., the less the value of  $r$ ), the less the eradication effort of the infection.

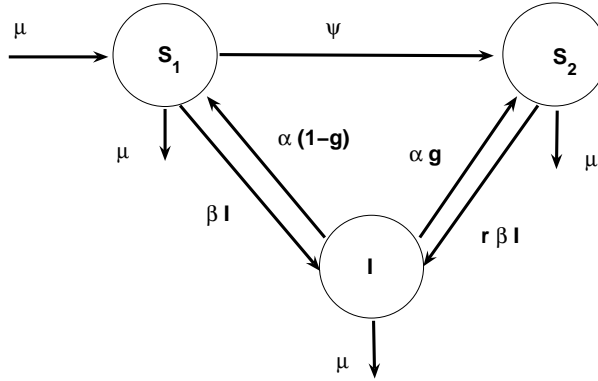


Figure 5.1: Compartmental diagram for the model.

## 5 A core group model for disease transmission revisited

In this chapter, I would like to reformulate the model of Hadeler and Castillo-Chavez in 1995 and study it.

### 5.1 Construction of the model

The total population is subdivided into three categories: Susceptible of type one  $S_1$ , susceptible of type two  $S_2$ , and infected. Infected individuals are those being able to transmit the infection. However, to recognize susceptible we perform a test for the level of antibodies. Individuals with normal range levels are categorized to the susceptible of type one compartment, whereas the rest are categorized to the compartment of type two susceptible. We assume here a demographically stationary population. Individuals are supposed to be born susceptible of type one with birth rate  $\mu$ . Individuals of type one can either die with death rate  $\mu$ , be vaccinated (with imperfect vaccine) with vaccination rate  $\psi$  to be susceptible of type two, or get infected with force of infection  $\beta I$  deduced from the mass action law, where  $\beta$  is the successful contact rate between infected and type one susceptible and it is the product of the number of type one susceptible partners to an infected individual and the transmission probability (the susceptibility to the infection). Susceptible of type two can either die with death rate  $\mu$ , or get infected with force of infection  $r\beta I$  different from the previous one. The parameter  $r$  is of course dimensionless and is the relative susceptibility of type two susceptible to type one susceptible (mathematically, it is the ratio between the susceptibility of type two susceptible and that of type one susceptible). If  $r < 1$ , then individuals in the  $S_2$  compartment are partially protected against the infection, whereas if  $r > 1$ , then this corresponds to an immuno-suppression. Infected individuals can either die with death rate  $\mu$  or be removed with removal rate  $\alpha$ . A proportion  $g$  of the removed individuals will be transferred to the type two susceptible compartment, whereas the rest will be transferred to the compartment of type one susceptible. Therefore, the parameter  $g$  here represents the probability that a removed individual from the compartment of infected indi-

	Notes	$g = 0$	$g = 0, \psi = 0$	$g = 1$	$g = 1, \psi = 0$
$r = 0$	No backward bifurcation (BB) at all	SIS with vaccination	SIS without vaccination, no BB at all	SIR with vaccination, no BB at all	SIR without vaccination, no BB at all
$r = 1$	No BB at all	SIS with useless vaccination, no BB	Traditinal SIS, no BB at all	SIVI with useless vaccination, no BB at all	Usual SIS, no BB at all
$0 < r < 1$	There is BB iff $g < g_1 < 1$ & $\psi > \psi_2 > 0$	SVIS, yes for BB	SIS, no BB at all	SIVI with vaccination, no BB at all	SIVI without vaccination, no BB at all
$1 < r$	There is BB for all $g \in [0, 1]$ and some conditions on $\psi$	No BB at all	No BB at all	yes for BB	yes for BB

Table 1: This table explains the connection to other models as special cases of the model under consideration.

viduals will be transferred to the compartment of type two susceptible. This is shown in figure 5.1.

## 5.2 The model

The mathematical representation of the model is

$$\begin{aligned}
\dot{S}_1 &= \mu - (\beta I + \psi + \mu) S_1 + (1 - g)\alpha I, \\
\dot{S}_2 &= \psi S_1 - (r\beta I + \mu) S_2 + g\alpha I, \\
\dot{I} &= (S_1 + rS_2)\beta I - (\alpha + \mu)I, \\
1 &= S_1 + S_2 + I,
\end{aligned} \tag{5.1}$$

where the dot means derivative with respect to time. If  $0 < r < 1$ , the individuals in the  $S_2$  compartment are partially protected. If  $r > 1$ , their immune system is suppressed.

### 5.3 Connection to other models

The model can be connected to other models depending on the values of the parameters  $g, r,$  and  $\psi$ . Table (1) shows some connections to other cases.

### 5.4 Equilibrium

The stationary states are obtained by putting the derivatives, with respect to time, in the left hand side of (5.1) equal zero. Therefore,

$$\begin{aligned}
 0 &= \mu - (\beta\bar{I} + \psi + \mu) \bar{S}_1 + (1 - g)\alpha\bar{I}, \\
 0 &= \psi\bar{S}_1 - (r\beta\bar{I} + \mu) \bar{S}_2 + g\alpha\bar{I}, \\
 0 &= (\bar{S}_1 + r\bar{S}_2) \beta\bar{I} - (\alpha + \mu)\bar{I}, \\
 1 &= \bar{S}_1 + \bar{S}_2 + \bar{I}.
 \end{aligned} \tag{5.2}$$

#### The infection free equilibrium

The equilibrium solution corresponding to a totally susceptible population is given by  $(S_1^\circ, S_2^\circ, I^\circ) = (\frac{\mu}{\mu+\psi}, \frac{\psi}{\mu+\psi}, 0)$ .

### 5.5 Reproduction numbers

#### The basic reproduction number $R_0$

It is defined as the expected number of secondary cases produced by one infected case introduced into a totally susceptible (free infection) population. Therefore,

$$\begin{aligned}
 R_0 &= \left( \frac{\beta}{\alpha + \mu} \frac{\mu}{\mu + \psi} + \frac{\beta}{\alpha + \mu} \frac{r\psi}{\mu + \psi} \right) \\
 &= \frac{\beta}{\alpha + \mu} \left( \frac{\mu}{\mu + \psi} + r \frac{\psi}{\mu + \psi} \right) \\
 &= \frac{\beta}{(\alpha + \mu)(\psi + \mu) / (\mu + r\psi)}.
 \end{aligned} \tag{5.3}$$

So, the basic reproduction number can be interpreted in three ways. It is the summation of two reproduction numbers, one of them is the basic reproduction number for a population consisting entirely of susceptible of type one, whereas the other is the basic reproduction number for a population consisting entirely of all susceptible of type two. Another interpretation is, it is the product of three quantities: the successful contact rate between susceptible of type one and infected, the length of the infectious period, and a quantity representing the summation of the endemic proportion of susceptible of type one if there is no infection and the product of the relative susceptibility,  $r$ , and the endemic proportion of susceptible of type two if there is no infection. The third relation represents the ratio between the successful contact rate to the zero contact rate between infected and susceptible of type one.



## The episode reproduction number, $R_e$

Usually, reducing the value of the basic reproduction number,  $R_0$ , to slightly less than one or even to one, forces the infection to go to extinction. This is true if we have only forward bifurcation. However, in some models (like the current one) the backward bifurcation phenomenon exists. This means that even if we reduce the value of the basic reproduction number to slightly less than one, the infection can be established. Therefore, the basic reproduction number is no longer meaningful and we have to find another concept. We introduce here the so-called, episode reproduction number. It is defined as the expected number of episodes produced by one episode and is given mathematically by

$$R_e(\beta, S_1, S_2) = \frac{\beta}{\alpha + \mu}(S_1 + rS_2). \quad (5.4)$$

It is defined as the successful contact rate  $\beta$  times the length of the infectious period times the sum of the proportion of susceptible of type one and the relative susceptibility  $r$  times the proportion of susceptible of type two.

## 5.6 The endemic equilibria

Assume that  $I \neq 0$ , then we can get

$$\begin{aligned} \bar{S}_1 &= \frac{\mu + (1 - g)\alpha\bar{I}}{\mu + \psi + \beta\bar{I}}, \\ \bar{S}_2 &= 1 - \bar{S}_1 - \bar{I}. \end{aligned} \quad (5.5)$$

where  $\bar{I} \in [0, 1]$  is the endemic prevalence of infected and is determined from the following equation

$$\begin{aligned} 0 = F(\bar{I}) &= r(\beta\bar{I})^2 + (\mu + g\alpha + (\mu + \psi + (1 - g)\alpha - \beta)r)\beta\bar{I} \\ &+ (\alpha + \mu)(\psi + \mu) - \beta(\mu + r\psi). \end{aligned} \quad (5.6)$$

We notice that

$$F(1) = (\alpha + \mu)(\psi + \mu) + ((g + (1 - g)r)\alpha + r\mu)\beta$$

is always positive, whereas

$$F(0) = (\alpha + \mu)(\psi + \mu) - (\mu + r\psi)\beta$$

can be positive or negative depending on the parameter values. Therefore, there is a possibility to get multiple stationary states. Conditions on the parameter values to assure the existence of multiple stationary states will be clarified in the diagnostic section.

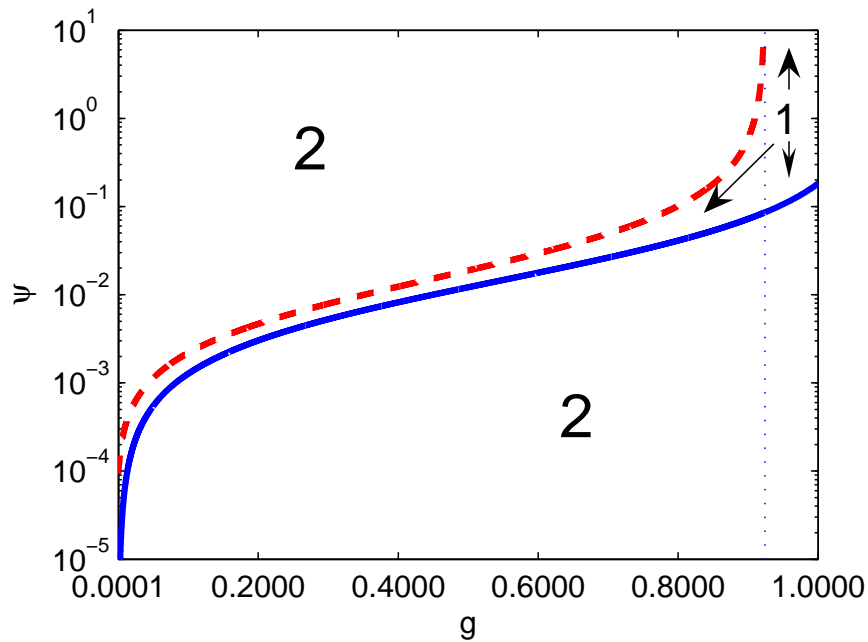


Figure 5.2: Bifurcation diagram in the  $(g, \psi)$ -plane. The vertical straight dotted line corresponds to the line  $g = g_c$ . However, the solid curve corresponds to  $\psi_1(g)$  and the dashed line corresponds to  $\psi_2(g)$ . Above the dashed curve as well as below the solid one there is a possibility for multiple stationary states to exist, whereas in between forward bifurcation phenomenon exists. Above the dashed curve, it holds  $0 < r_1 < r < r_2 < 1$ , while  $1 < r_1 < r < r_2$  in the area below the solid one.

## 5.7 Identification of thresholds

I would like to start this section by introducing some definitions.

**The zero contact rate  $\beta_0$ :** It is the value of the contact rate at which the prevalence of infected is zero (it is the value of  $\beta$  corresponding to the bifurcation point in the  $(\beta, \bar{I})$ -plane), in other words it is the value of the contact rate at which the basic reproduction number is equal to one. We also may define it as the value of the contact rate at which the infection free equilibrium changes its stability status.

**The critical contact rate:** It is the value of the contact rate at which positive stationary states start to appear. This means that below this value, the infection free equilibrium is globally asymptotically stable whereas above it, positive endemic states exist. In other words, it is the value of the contact rate corresponding to the point in the  $(\beta, \bar{I})$ -plane separating between nonexistence and existence of positive endemic equilibria. If there is no backward bifurcation, then the critical contact rate coincides with the zero contact rate  $\beta_0$ . Otherwise, it is less than the zero contact rate ( $\beta^* < \beta_0$ ). Therefore, the critical contact rate in the case there is backward bifurcation is given by

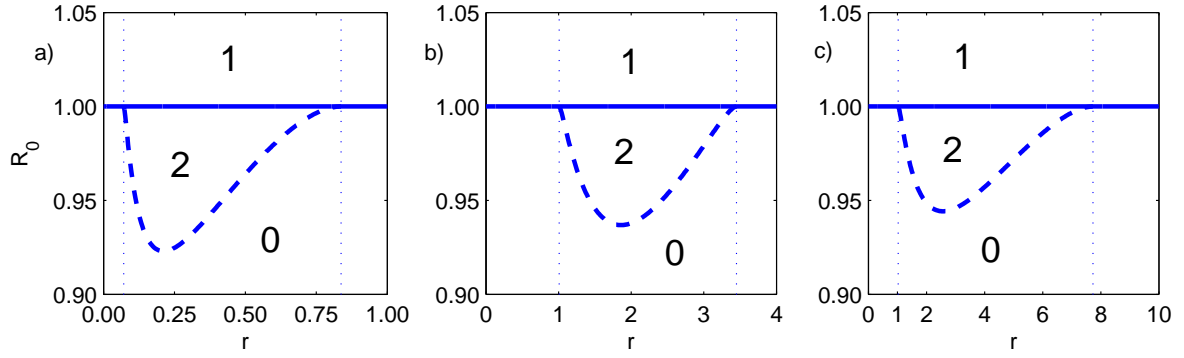


Figure 5.3: Bifurcation diagram in the  $(r, R_0)$ -plane. Calculations are done here for parameter values  $\alpha = 10$  per year,  $\mu = 0.015$  per year, and the pair  $(g, \psi)$  differs from part to part. In the three parts a), b), and c), we have, respectively,  $g = 0.7, 0.7$ , and  $0.96$ , whereas  $\psi = 0.5$  per year,  $0.01$  per year, and  $0.04$  per year. The plane is subdivided into three regions according to the number of positive endemic states, in addition to the trivial equilibrium. The numbers 0, 1, and 2 denote the number of positive equilibria in the correspondent regions. Here we consider three cases. In part a), we consider the case if  $g < g_c$  and  $\psi$  is taken above the dashed curve in figure 5.2, whereas part b) corresponds to  $g < g_c$  and  $\psi$  below the solid curve. However, part c) corresponds to  $g > g_c$  and  $\psi$  below the solid curve. The broken curve represents the critical basic reproduction number  $R_0^*$ , whereas the horizontal solid line represents  $R_0 = 1$ . The two vertical dotted lines represent  $r = r_1$  on the left, and  $r = r_2$  on the right. In part a) we have  $0 < r_1 < r_2 < 1$ , This corresponds to the area above the broken curve in figure 5.2. However, in the remaining two parts b) and c), we have  $1 < r_1 < r_2$  where the calculations are performed for values of  $g$  and  $\psi$  from the area below the solid curve in figure 5.2.

$$\beta^* = \frac{(g\alpha - \mu) + r(\mu + (1 - g)\alpha - \psi) + 2\sqrt{(1 - r)(r\psi(\mu + (1 - g)\alpha) - g\mu\alpha)}}{r}. \quad (5.7)$$

In the case there is backward bifurcation, The critical contact rate  $\beta^*$  is well defined if and only if  $r_1 \leq r \leq r_2$ ,  $\frac{\mu}{\mu + \alpha} < \frac{1}{4}$ , and some conditions on both  $g$  and  $\psi$  where

$$\begin{aligned} r_{1,2} &= \frac{b \mp \sqrt{b^2 - 4ac}}{2a}; \\ a &= (\mu + \psi + (1 - g)\alpha)\psi, \\ b &= g\mu\alpha + ((1 - g)\alpha - \mu)\psi, \\ c &= \mu(\mu + g\alpha). \end{aligned} \quad (5.8)$$

The condition  $\frac{\mu}{\mu + \alpha} < \frac{1}{4}$  means that the ratio of the expected time of life, at birth in the absence of infection, spent in the infectious state for an episode must be less than four. The conditions on the parameters  $g$  and  $\psi$  determine the bifurcation in the  $(g, \psi)$ -plane. To show them, we

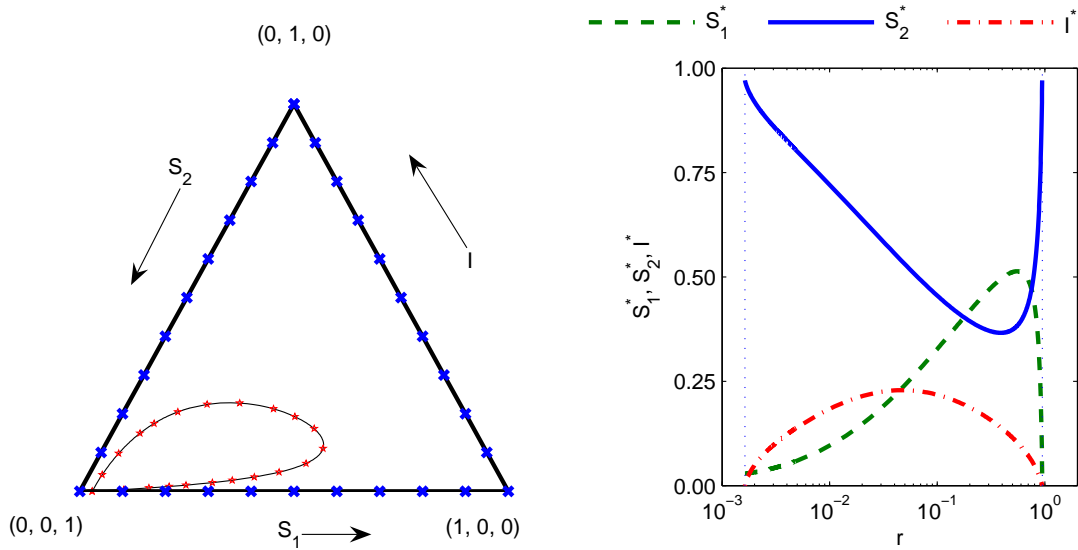


Figure 5.4: This figure shows the components of the point corresponding to the turning point as functions of the relative susceptibility  $r \in [r_1, r_2]$ . Calculations have been done with parameter values:  $\alpha = 10$  per year,  $\mu = 0.015$  per year,  $g = 0.05$ , and  $\psi = 0.5$  per year. These values correspond to the area in figure 5.2 above the broken line. When  $r = r_1$ , the components corresponding to the turning point coincide with the coordinates of the infection free equilibrium. Then as functions of the relative susceptibility  $r$ , both the critical proportions of type one susceptible  $S_1^*$  and infected  $I^*$  increase while the critical proportion of type two susceptible  $S_2^*$  decrease until  $I^*$  reaches a maximum. Thereby,  $I^*$  decrease,  $S_2^*$  continues to decrease while  $S_1^*$  continues to increase until  $S_2^*$  reaches a minimum at which  $S_1^*$  reaches a maximum. Then,  $I^*$  continues to decrease,  $S_2^*$  increases, whereas  $S_1^*$  decreases until all components coincide again with the components of the infection free equilibrium  $E_0$ . This coincidence occurs when  $r = r_2$  (see the right part). Thus the point corresponding to the turning point moves on a closed curve (the left part) in a clockwise direction. It starts the trip, from the very left and moves to the right, at  $r = r_1$  with coordinates typical to that of  $E_0$  and ends the trip at  $r = r_2$  with the same coordinates of  $E_0$ .

define the following quantities:

$$\begin{aligned}
 g_c &= \left(1 - \frac{\mu}{\mu + \alpha}\right)^{-1} \left(1 - 2\sqrt{\frac{\mu}{\mu + \alpha}}\right), \\
 \psi_c &= \frac{\mu g_c^2 \alpha^2}{2((\alpha + \mu)(g_c \alpha + 2\mu) - g_c^2 \alpha^2)} \\
 &= \left(\frac{1}{\mu + \alpha} \left(1 - \frac{\mu}{\mu + \alpha}\right)\right)^{-1} \left(\sqrt{\frac{\mu}{\mu + \alpha}} \left(1 + \sqrt{\frac{\mu}{\mu + \alpha}}\right) - 4\frac{\mu}{\mu + \alpha} \left(1 - \frac{\mu}{\mu + \alpha}\right)\right),
 \end{aligned} \tag{5.9}$$

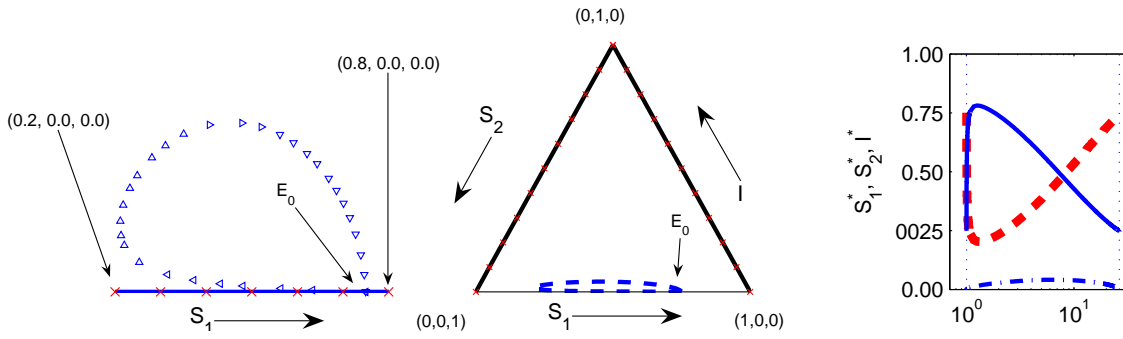


Figure 5.5: The dynamics of the point corresponding to the turning point. Calculations have been done with parameter values:  $\alpha = 10$  per year,  $\mu = 0.015$  per year,  $g = 0.9$ , and  $\psi = 0.005$  per year. These values correspond to the area below the solid line and on the left of the vertical dotted line in figure 5.2. The point corresponding to the turning point moves on a closed curve in a clockwise direction (the first two parts from the left). It starts the trip from the very right at  $r = r_1$  and moves to the left on a closed path until returning again to starting point when  $r = r_2$ . The start and end points coincide of course with the infection free equilibrium  $E_0$ . The dynamical behaviour is shown in the very right part of the figure. The dashed line corresponds to the critical proportion of type one susceptible  $S_1^*$ , the solid line represents the curve of the critical proportion of susceptible of type two  $S_2^*$ , whereas the dashed dotted line represents the critical prevalence of infected  $I^*$ . At  $r = r_1$ , then  $I^* = 0$ ,  $S_1^* = \frac{\mu}{\psi + \mu}$ , whereas  $S_2^* = \frac{\psi}{\psi + \mu}$ . As functions of the relative susceptibility  $r$ , both  $I^*$  and  $S_2^*$  increase while  $S_1^*$  decreases until  $S_1^*$  reaches a minimum at which  $S_2^*$  has its maximum. Then,  $I^*$  continues to decrease while both  $S_1^*$  and  $S_2^*$  change their behaviour from decrease to increase and vice versa. This happens till  $I^*$  reaches a maximum. After that,  $I^*$  decreases till reaching zero at  $r = r_2$  while both  $S_1^*$  and  $S_2^*$  continue with the same behaviour till reaching their starting values again when  $r = r_2$ .

$$\begin{aligned}
\psi_{1,2} &= \frac{\mu (-g^2\alpha^2 + (\alpha + \mu)(\sqrt{g\alpha + \mu} \mp \sqrt{\mu})^2)}{(\mu + (1 - g)\alpha)^2 - 4\mu(\alpha + \mu)} \\
&= \mu \left( \left( 1 - g + \frac{g\mu}{\alpha + \mu} \right)^2 - 4\frac{\mu}{\mu + \alpha} \right)^{-1} \left( \left( \sqrt{g + \frac{(1 - g)\mu}{\mu + \alpha}} \mp \sqrt{\frac{\mu}{\mu + \alpha}} \right)^2 - \right. \\
&\quad \left. g^2 \left( 1 - \frac{\mu}{\mu + \alpha} \right)^2 \right).
\end{aligned}$$

We notice that: if  $g = 0$  then  $\psi_1 = 0$  whereas  $\psi_2 = \mu \left( \frac{4\mu}{\mu + \alpha} \right) \left( 1 - 4\frac{\mu}{\mu + \alpha} \right)^{-1}$ . However, if  $g = 1$  then  $\psi_1$  is no longer defined, whereas

$$\psi_2 = (\mu + \alpha) \left( 1 + 2\frac{\mu}{\mu + \alpha} \right)^{-1} \left( -\frac{\mu}{\mu + \alpha} \left( 1 + \frac{\mu}{\mu + \alpha} \right) + 2\sqrt{\frac{\mu}{\mu + \alpha}} \right).$$

Therefore, the bifurcation analysis in the  $(g, \psi)$ -plane is determined as follows:

- 1) If  $g = 0$ , then multiple stationary states exist if and only if  $\psi > \mu \left( \frac{4\mu}{\mu + \alpha} \right) \left( 1 - 4\frac{\mu}{\mu + \alpha} \right)^{-1}$ ,

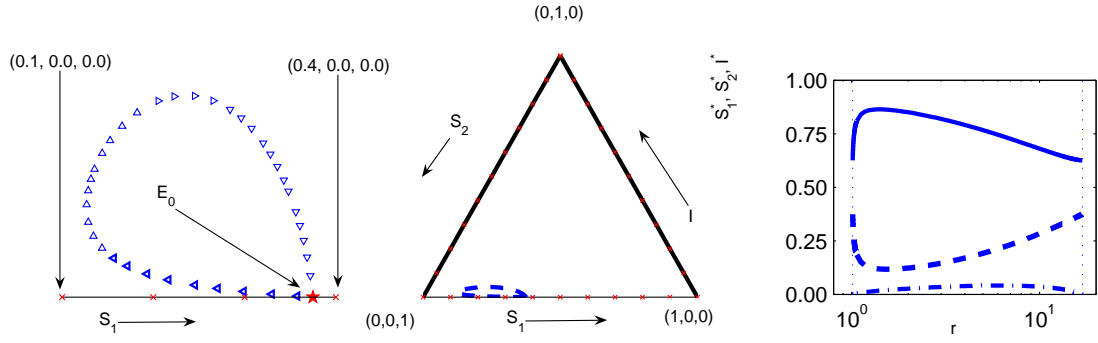


Figure 5.6: The behaviour of the point corresponding to the turning point in both the plane (the very right part) and the ternary plot (the two parts on the left) for several values of  $r \in [r_1, r_2]$ . Calculations have been performed with parameter values:  $\alpha = 10$  per year,  $\mu = 0.015$  per year,  $g = 0.97$ , and  $\psi = 0.025$  per year. These values correspond to the area below the solid curve and on the right of the dotted vertical straight line in figure 5.2. The point corresponding to the turning point  $E^*$  moves on a closed curve (see the two parts on the left of the figure) in the triangle with  $S_1$ ,  $I$ , and  $S_2$  as the three sides. At  $r = r_1$ , the components of  $E^*$  coincide with the components of the infection free equilibrium  $E_0$ . Then the point  $E^*$  moves from the very right to the left in a clockwise direction on a closed curve and it reaches the initial point  $E_0$  again when  $r = r_2$ . To explain the behaviour of each component, we consider the plane shown in the right part of the figure. As functions of  $r$ , the proportion  $I^*$  (the dashed dotted curve) starts with zero at  $r = r_1$ , whereas  $S_1^*$  (the dashed curve) and  $S_2^*$  (the solid curve) start respectively with the values  $\frac{\mu}{\mu+\psi}$  and  $\frac{\psi}{\mu+\psi}$ . Then  $I^*$  and  $S_2^*$  increase while  $S_1^*$  decreases till  $S_1^*$  reaches a minimum at which  $S_2^*$  reaches its maximum. Then,  $I^*$  continues to increase whereas both  $S_1^*$  and  $S_2^*$  exchange their behaviour (decrease to increase and vice versa). This occurs until  $I^*$  reaches its maximum. After that,  $I^*$  decreases while the other two components continue with the same behaviour until the three components coincide with their initial values when  $r = r_2$ . What is clear is that for parameter values corresponding to the area below the solid line in figure 5.2, the point  $E_0$  in the ternary is always at the very right and the point corresponding to the turning point  $E^*$  moves first to the left and then it returns to reach the starting point again when  $r = r_2$ .

- 2) If  $0 < g < g_c$ , then multiple stationary states exist if and only if either  $\psi < \psi_1$  or  $\psi > \psi_2$ ,
- 3) If  $g = g_c$ , then there are multiple stationary states if and only if  $\psi < \psi_c$ ,
- 4) If  $g_c < g \leq 1$ , then multiple equilibria exist if and only if  $\psi < \psi_2$ .

This is shown in figure 5.2.

**The critical basic reproduction number  $R_0^*$ :** It is the basic reproduction number evaluated at the point at which both positive equilibria coincide, i.e., we replace  $\beta$  by  $\beta^*$  in the  $R_0$  relation. Therefore,

$$R_0^* = \frac{\beta^*}{\alpha + \mu} \left( \frac{\mu}{\mu + \psi} + r \frac{\psi}{\mu + \psi} \right). \quad (5.10)$$

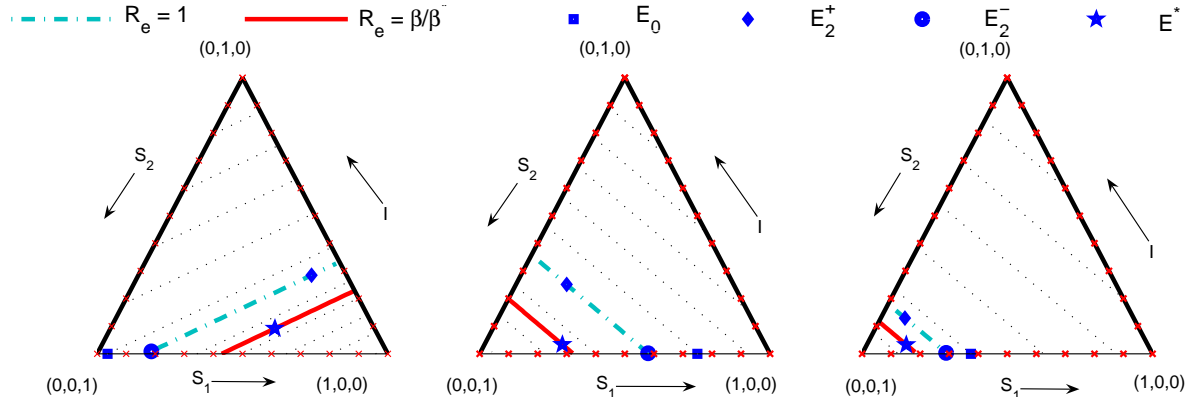


Figure 5.7: The contour lines for the episode reproduction number in three cases. The left part corresponds to the case if we take parameter values from the area above the broken curve in figure 5.2, whereas the middle part corresponds to an area below the solid curve but on the left of the vertical dotted straight line in figure 5.2, and the right part corresponds to the area below the solid curve but on the right of the dotted vertical straight line in the figure (5.2). Calculations have been done with parameter values:  $\beta = 15, 6, 4.7$  per year,  $r = 0.6, 2.6, 2.6$ ,  $\alpha = 10$  per year,  $\mu = 0.015$  per year,  $\psi = 0.4, 0.005, 0.025$  per year, and  $g = 0.025, 0.9, 0.97$  respectively for the three parts of the figure from left to right. Whereas the contour line  $R_e = 1$  goes always through the two positive equilibria  $E_2^+$  and  $E_2^-$ , the contour line  $R_e = R_0$  goes through the infection free equilibrium  $E_0$ , and the contour line  $R_e = \beta/\beta^*$  passes through the point  $E^*$  which corresponds to the turning point. In the left part, the episode reproduction number increases from left to right, whereas in the other two parts of the figure  $R_e$  increases from right to left. This is because  $r < 1$  in the first case, while  $r > 1$  in the other two cases.

Assume now that the pair  $(g, \psi)$  is chosen such that multiple stationary states exist, then in the  $(r, R_0)$ -plane there are multiple stationary states if and only if  $R_0^* < R_0 < 1$  and  $r_1 < r < r_2$ . If  $R_0 > 1$ , then a unique positive endemic state exists in addition to the infection free equilibrium. Otherwise, no positive stationary state exists and the infection free equilibrium is globally asymptotically stable. This is shown in figure 5.3.

## 5.8 The turning point

The turning point is the point in the  $(\beta, \bar{I})$ -plane at which both positive equilibria coincide. In other words, it is the point separating between nonexistence and existence of multiple positive stationary states. Therefore, the components corresponding to the turning point are  $S_1^*, S_2^*$ ,

and  $I^*$  where

$$\begin{aligned}
I^* &= \frac{-(\mu + r\psi) + \sqrt{(1-r)((\alpha + \mu)r\psi - g\alpha(\mu + r\psi))}}{-(\mu + r\psi) + (1-r)g\alpha + r(\alpha + \mu) + 2\sqrt{(1-r)((\alpha + \mu)r\psi - g\alpha(\mu + r\psi))}}, \\
S_1^* &= \frac{\alpha + \mu - r\beta^*(1 - I^*)}{(1-r)\beta^*}, \\
&= \frac{r}{1-r} \left( \frac{(1-r)(\mu + (1-g)\alpha) + \sqrt{(1-r)((\alpha + \mu)r\psi - g\alpha(\mu + r\psi))}}{-(\mu + r\psi) + g\alpha + r(\mu + (1-g)\alpha) + 2\sqrt{(1-r)((\alpha + \mu)r\psi - g\alpha(\mu + r\psi))}} \right), \\
S_2^* &= 1 - S_1^* - I^*.
\end{aligned} \tag{5.11}$$

Numerical calculations which show the movement of the point  $E^*$  in the ternary plot and the behaviour of the coordinates  $S_1^*, S_2^*$  and  $I^*$  with parameter values corresponding to the areas in the  $(g, \psi)$ -plane and several values of  $r \in [r_1, r_2]$  are shown in figures 5.4, 5.5, and 5.6.

## 5.9 The eradication effort $\mathcal{R}$

Here we introduce a new concept called the minimum effort required to eradicate the infection. If the model shows a backward bifurcation phenomenon, then we claim that the effort is just the ratio between the contact rate  $\beta$  and the critical contact rate  $\beta^*$ . However, if the model shows only forward bifurcation, then the effort is the basic reproduction number  $R_0$  which is the ratio between the contact rate  $\beta$  and the zero contact rate  $\beta_0$ . To analytically evaluate this effort, we come to the definition of the episode reproduction number in formula (5.4). Then we get  $\mathcal{R} = R_e(\beta, S_1^*, S_2^*) = \frac{\beta}{\beta^*}$ . However, the basic reproduction number is  $R_0 = R_e(\beta, S_1^o, S_2^o) = \frac{\beta}{\beta_0}$ . Numerical calculations to show the contour lines for the episode reproduction number  $R_e$  in the ternary plot for the three areas in figure 5.2 are shown in figure 5.7. The contour line  $R_e = 1$  goes through both the stable and unstable positive equilibria  $E_2^+$  and  $E_2^-$ , respectively, whereas the contour lines  $R_e = 1$  and  $R_e = \mathcal{R} = \frac{\beta}{\beta^*}$  go, respectively, through the infection free equilibrium  $E_0$  and the point corresponding to the turning point  $E^*$ .

## 5.10 Summary

The current model is a model of SIS type. What we wanted to stress here is the applicability of our approach, the minimum eradication effort, which we had introduced in the chapter 3. For fixed  $g$  and variable  $\psi$ , there is always a possibility for the occurrence of multiple stationary states. The same is done if we fix  $\psi$  and let  $g$  vary. However, if we choose the pair  $(g, \psi)$  to be in the area denoted by 2 in figure 5.2, there is always the backward bifurcation phenomenon. Any way, this says for any imperfect vaccination there is a possibility of multiple stationary states.



## 6 Summary

Despite the great progress in medicine which lead to the discovery of safe and effective drugs and vaccines, infectious diseases are still a major cause of death, disability and social and economic burden for millions of people around the world. Every year, about 20% of all deaths are caused by infectious diseases. Therefore, we need to know about the impact of these infections on demography and about the minimum efforts required to eliminate them. Since it is not possible to perform randomized trials with whole populations, we need mathematical models to explore different control strategies.

In this work, we concentrate on prevalence models (i.e., models in which we subdivide the total population into disjoint classes like susceptible, latent, infectious, and recovered). We address two main problems, namely the impact of an immunising potentially lethal infection on demography and the minimum effort required to eradicate infections in models with backward bifurcation.

In the first two chapters we generalize the classical epidemiological SIR model of Daniel Bernoulli for a potentially fatal infection to a growing population with age structure. The total population is subdivided into three classes, namely susceptible, infected, and immune. Rather than following the by now standard approach of differential mortality, we describe the epidemic and demographic phenomena in terms of case fatality (the proportion of infected individuals who die due to the infection). Individuals are assumed to be born susceptible with per capita age-specific birth rate  $\beta(a)$  where  $a$  denotes the age of the mother. All individuals are assumed to die with per capita age-specific infection-free death rate  $\mu(a)$ . Susceptible individuals will either get infected with force of infection  $\lambda(a, t)$ , where  $t$  denotes time, or die with per capita death rate  $\mu(a)$ . Infected individuals will either recover with life-long immunity with per capita rate  $(1 - c(a))\gamma$ , where  $c(a)$  is the case fatality and  $\gamma$  is the exit rate from the infected state, or die with rate  $\mu(a) + \gamma c(a)$ . Immune individuals will die with per capita rate  $\mu(a)$ . The case of age-independent model parameters is considered in chapter one, while the analysis for the general case of age structure has been performed in chapter two.

An important concept in mathematical epidemiology is the basic reproduction number. It is the average number of secondary cases produced by an infected case, during the infectious period, introduced in a totally susceptible population. Usually, if  $R_0 > 1$  then the infection persists. If  $R_0 \leq 1$  then the infection dies out. However, in models with backward bifurcation we find that, even if  $R_0$  is reduced to values slightly less than one, the infection does not go to extinction. Therefore  $R_0$  is no longer meaningful and we need another quantity. In chapters 3, 4, and 5, we study the necessary effort required to eradicate infections in three models with backward bifurcation. To our best knowledge, we provide, for the first time, a method to determine the eradication effort (if we concentrate on control measures affecting the transmission rate) for models with backward bifurcation.

From the thesis we come to the following conclusions: In the case fatality model, the basic reproduction number is not affected by the case fatality of the infection, while in the differential mortality models it gets smaller with increasing differential mortality. The rate of growth of the population declines monotonically with the increase of the case fatality while it can increase after reaching a minimum in case of the differential mortality model. The simple formula that

the basic reproduction number  $R_0$  equals the inverse of the endemic proportion of susceptible  $\bar{x}$  is no longer true in general. However, the product  $R_0\bar{x}$  is the ratio between the times available to make successful contacts during the infectious period in the absence and presence of the infection, respectively. In the limiting case of high infectivity and short infectious period, there is always a feasible case fatality being able to drive the host population to extinction. However, when the infectious period has a positive duration then the critical case fatality required to stop the growth of the population exists only if the basic reproduction number  $R_0$  satisfies  $R_0 \geq 1 + \frac{b}{\gamma}R_0(\mu)$  where  $b$  is the birth rate,  $\gamma$  is the removal rate, and  $R_0(\mu)$  is the basic reproduction number in case of a static population.

The present model allows to determine the demographic impact of a potentially lethal infection in terms of the reduction in life expectancy and the reduced growth rate. The present analysis suggests that smallpox was nowhere near to stop population growth. The present model is applicable to any potentially lethal immunizing infection (e.g. measles) in growing populations whose age-distribution is close to the stationary distribution.

In models with the backward bifurcation phenomenon, the basic reproduction number is no longer meaningful. The ratio between the actual contact rate and the critical contact rate at which positive stationary states start to appear can be interpreted as a reproduction number. For models in which the immunity wanes, there is a possibility for multiple stationary states to occur. In the simple SIS endemic model with vaccination, the earlier we give a partially protective vaccine, the less the effort to eradicate the infection.

## 7 References

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## Curriculum Vitae

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### Education

1980 - 1986	Primary school in Nawasa Elgheet - Aga - DK - Egypt.
1986 - 1989	Preparatory school in Nawasa Elgheet - Aga - DK - Egypt.
1989 - 1992	Secondary school in Aga - DK - Egypt.
1992 - 1996	BSc in Mathematics with grade "Excellent with honour degree", Faculty of Science - Mansoura University - Egypt.
1996 - 1997	Preparatory courses for MSc in mathematics, Faculty of Science - Mansoura University - Egypt.
1998 - 1999	MSc in applied mathematics "Biomathematics" for the thesis entitled "Some Mathematical Studies for Hepatitis B", Mansoura University, Egypt.
1996 - 1999	Demonstrator in Applied Mathematics, Faculty of Science - Mansoura University - Egypt.
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