COMENIUS UNIVERSITY IN BRATISLAVA
FACULTY OF MATHEMATICS, PHYSICS AND INFORMATICS

DYNAMIC ANALYSIS OF PANDEMIC MEASURES

Mária Holecyová Bratislava 2012

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DYNAMIC ANALYSIS OF PANDEMIC MEASURES

Master's Thesis

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Applied Mathematics, 1114
Economic and Financial Mathematics

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UNIVERZITA KOMENSKÉHO V BRATISLAVE
FAKULTA MATEMATIKY, FYZIKY A INFORMATIKY

DYNAMICKÁ ANALÝZA PROTIPANDEMICKÝCH OPATRENÍ

Diplomová práca

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Declaration

I declare on my honour that this thesis was written on my own, with the only help provided by my supervisor and the referred-to literature.

Bratislava, 24$^{\text{th}}$ April 2012 . . . . . .

Abstract

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Thesis Title:	Dynamic Analysis of Pandemic Measures
Institution:	Comenius University in Bratislava
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We present an analysis of pandemic measures that might be carried out during influenza epidemics, i.e. vaccination and implementation of face masks, in the population of Slovak Republic. At the beginning we provide a brief overview of current issues of mathematical epidemiology, the models and problems that they are used to solve. Thereafter we decide for the deterministic model that suits the behavior of influenza diseases and discuss its advantages and disadvantages comparing it with SIR model that is typically used in the literature. We apply the model to analyze the impact of vaccination and wearing masks on the spread of epidemics from the medical perspective as well as from the economic perspective using optimal control theory. And at the end, we derive a stochastic model of epidemics, we apply it to investigate the effect of pandemic measures, discuss the scope of its use and suggest how the theory of stochastic modeling could be extended in the future.

Keywords: pandemic measures, SIR model, vaccination, face masks, influenza, deterministic model of epidemics, optimal control theory, stochastic model of epidemics

Abstrakt

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V tejto práci predkladáme analýzu protipandemických opatrení (očkovanie a zavedenie rúšok), ktoré môžu byť vykonávané počas chrípkových epidémií a orientujeme sa na populáciu Slovenskej republiky. V úvode poskytujeme čitateľovi stručný prehľad aktuálnych otázok matematickej epidemiológie, modelov a problémov, ktoré sú pomocou nich riešené. Na základe toho si vyberáme taký deterministický model, ktorý najlepšie zodpovedá správaniu chrípkových ochorení a rozoberáme jeho výhody a nevýhody v porovnaní so SIR modelom, ktorý je tradične využívaný v literatúre. Model ďalej využívame na analýzu dopadu očkovania a nosenia rúšok na vývoj epidémie a to nielen z medicínskeho uhla pohľadu, ale aj z ekonomického hľadiska využitím teórie optimálneho riadenia. Na záver práce odvádzame stochastický model epidémie, pomocou ktorého opä sledujeme ť efekt protipandemických opatrení, zamýšľame sa nad rozsahom jeho využitia a prácu uzatvárame návrhom, akým novým výzvam by mala teória stochastického modelovania čeliť v budúcnosti.

Kľúčové slová: protipandemické opatrenia, SIR model, očkovania, rúška, chrípka, deterministický model epidémie, teória optimálneho riadenia, stochastický model epidémie

Contents

Preface

If people do not believe that mathematics is simple, it is only because they do not realize how complicated life is.
John Louis von Neumann

The symptoms of human influenza were clearly described by Hippocrates about 2,400 years ago [32], but despite our deep knowledge about its causes and behavior, flu epidemics are reappearing a year after year and typically there are between three and five million cases of severe illness and up to 500,000 deaths worldwide every year [42]. Three influenza pandemics occurred in the 20th century and killed tens of millions of people, with each of these pandemics being caused by the mutation. Often, these new strains appear when an existing influenza virus spreads to humans from other animal species, or when an existing human strain picks up new genes from a virus that usually infects birds or pigs.

Probably the most devastating influenza pandemic was caused by Spanish flu lasting from 1918 to 1919. It is estimated that 3 per cent of the world population died of the disease, and so it is sometimes called "the greatest medical holocaust in history". The latest influenza pandemic, swine influenza, occurred in 2009. It was not as lethal as Spanish flu, but still there are 1,632,258 confirmed cases and 19,633 deaths caused by the disease [20].

These numbers are alarming and rise concerns about our ability to control the disease if a new strain appear again. According to the World Health Organization (WHO), one of the biggest concerns for international health is an influenza pandemic [15]. The avian flu is a focus of pandemic preparedness, the conclusion of WHO is that a flu pandemic is inevitable [15]. And still there are influenza epidemics that we are more or less used to overcome every year by taking medications or vaccinating, but it is a serious threat for people with weaker immunity leading to more than half million deaths a year. How can we prepare for the epidemics? How can pandemic measures affect the spread of the disease? How does their impact change when they are implemented later, when the virus is already spreading?

We apply the theory of mathematical epidemiology to find at least partial answers

to these question. There are two main types of models, deterministic and stochastic, used to describe the course of the epidemics. And although one would probably expect that stochastic models rather than deterministic are used most as the nature of epidemics is basically stochastic, in the literature we can find much more deterministic analysis. Diekmann and Heesterbeek [18] note that epidemiological models provide only caricatural mathematical description of the mechanisms of transmission diseases. Although the theory is now centuries old and the models include numbers of factors affecting the transmission, it still does not provide the complex understanding of the phenomena. It it only a tool that can describe the principles of epidemics and help us to find the answers to questions we ask.

Introduction

According to Gani and Jerwood [19] epidemic modeling has three main aims:

- to understand better the mechanisms by which diseases spread,
- to predict the future course of the epidemic,
- to understand how we may control the spread of the epidemic.

In this thesis we deal with all the aims, analyzing impact of pandemic measures (vaccination and implementing face masks) on the spread of influenza epidemics in Slovakia. Firstly, we present a brief overview of mathematical epidemiology to understand the development of the theory and to decide how far can we go in order to describe the epidemics as rigorously as it is possible. Although we admit that the nature of virus transmission is stochastic, most of this thesis work with deterministic models, as it is considered a sufficient approximation and its main advantage is its simpler, but not necessarily simplistic analysis. We want to investigate the expected effect of the pandemic measures on epidemics, dealing with expected behavior of its spread that deterministic models illustrate.

In the second chapter, we decide for the deterministic model that suits the influenza and compare it to the SIR model typically used in the literature to analyze pandemic measures, e.g. Scherer and McLean [40]. We discuss its advantages and show the difference between the models both in the short term and in the long term.

Next chapter deals with vaccination. In its first part, we assume that vaccines are fully effective and in the second part, we assume their effectiveness to be only 70 per cent. In both cases, we do not look at the problem only from medical perspective, i.e. how vaccination can affect the spread of the disease, but also from economical perspective, i.e. how much we can save when we vaccinate the population.

The fourth chapter follows the methods derived in the previous chapter and analyze the impact of wearing face masks on the spread of the epidemics. We discuss the problem from medical perspective and economical point of view, as well. At the end of the chapter, we discuss the possibility of replacement of the vaccination by face masks. This is important when a new type of influenza appears and there are no efficient vaccines.

The purpose of the last chapter is to develop a stochastic model, discuss its use and study the instantaneous impact of pandemic measures on the probability that no more infective cases appear. The results can only indicate the principles of stochastic behavior and serve only to understand the basis of the nature of epidemics. We do not derive an effective tool to describe the stochasticity of epidemics. Therefore, we conclude the thesis suggesting some challenges that mathematical epidemiology should face in the future.

Chapter 1

Mathematical Epidemiology

This chapter serves as an introduction to mathematical epidemiology. We provide a brief history overview of mathematical approach in epidemiology from its very beginning. We also summarize current trends and describe the basic models that are widely used in the literature. The discussion about advantages and disadvantages of using stochastic model is included at the end of the chapter, suggesting that we should prefer deterministic model in our analysis as it is recommended in the case of larger populations.

1.1 History Overview

The mathematical study of diseases and their dissemination is at most just over three centuries old, dating from the first quantitative study of human diseases and deaths ensuing from them written by John Graunt [19]. However, the first study based on theoretical and mathematical approach to the effects of a disease, namely smallpox, can be be traced back to Daniel Bernoulli [10] almost a century later. In next years, only few works on mathematical epidemiology appeared, most of them based on Law of Mass Action (Boyle [11], Glasstone [22]). In 1854, John Snow demonstrated that cholera could be transmitted via drinking water applying statistical data of the infectious cases and after his discovery mathematical epidemiology had not recorded greater success for a long time. Hamer [24] was the first who foreshadowed the pragmatic 'mass action' principle for a deterministic epidemic model in discrete time. This principle, which incorporates the principle of homogeneous mixing, has been the basis of most subsequent developments in epidemic theory [19]. His idea was based on the equation

$$\triangle I(t) = \beta S(t) I(t)$$

where $S(t), I(t)$ are the number of susceptible individuals and infective individuals respectively at times $t = 0, 1, 2, ...$

The theory of mathematical epidemiology has become a real scientific challenge since the end of First World War, when Spanish influenza, the most serious pandemic in recent history, occured. It is estimated to be responsible for the deaths of over 50 million people.

Continuous time versions of epidemic equations derived by Hamer [24] were used by Ross [39] in 1916, and Ross and Hudson [38], but the form of equations most commonly used to characterize the typical general epidemic with the number of susceptibles $S(t)$, the number of infectives $I(t)$ and the number of removed (recovered) $R(t)$ is due to Kermack and McKendrick's study [28] in 1927.

$$\begin{aligned} \frac{dS(t)}{dt} &= -\beta S(t)I(t) \\ \frac{dI(t)}{dt} &= \beta S(t)I(t) - \alpha I(t) \\ \frac{dR(t)}{dt} &= \alpha I(t) \end{aligned} \tag{1.1}$$

where β is called transmission rate and α is removing (recovery) rate. The model is also called SIR model. McKendrick also derived one of the earliest of stochastic models [33], but Greenwood and Reed-Frost models have replaced it. SIR model (1.1) was later modified to stochastic continuous model, e.g. [34]. Finally, since 1957, the date of publication of Bailey's book *The Mathematical Theory of Epidemics* [3], that provided a great overview of epidemiological theory, the contributions to the subject of mathematical epidemiology have themselves behaved like an epidemic. Bailey's studies on malaria [5] and other infectious diseases [4] were accompanied by stochastic epidemic modelling provided by [9], [31] and others. The deterministic model was modified in several ways, adding mortality rates and more parameters to the dynamic system. The book by Gani and Jerwood [19] summarizes epidemiological modeling as it was till 1999. It presents a pillar for applications of epidemiological models. There has not remained much space for new inventions in the field of modeling, mainly deterministic modeling, therefore the newest studies are mostly aimed at applications of existing models, e.g. vaccination control tools [17], and at commenting and comparing the models [18].

1.2 Deterministic Models

Deterministic models currently used in literature are based on the Kermack and McKendrick ODE model (1.1). In these models, population sizes of susceptibles, infectives

and removals are assumed to be functions of discrete time $t = 0, 1, 2, ...$ or differentiable functions of continuous time $t > 0$. The evolution of epidemics is deterministic in the sense that no randomness is allowed. The results of a deterministic process are usually regarded as giving an approximation to the mean of a random process [19]. The deterministic model is an acceptable approximation of the stochastic one if the population is sufficiently large, however it is not exactly explained when the population is large enough [34]. Nevertheless, the SIR model (1.1) has proven useful in ascertaining gross factors affecting rate of growth and final size of epidemic [25]. The major significance of the model at the time of its first publication was a mathematical demonstration that even with a major outbreak of a disease satisfying the simple model, not all susceptibles would necessarily be infected.

The standard SIR model assume that demographic changes can be neglected, i.e. there are neither deaths nor births during the epidemics. This assumption was later excluded and a new SIR model with demographic changes derived [12].

$$\begin{aligned} \frac{dS(t)}{dt} &= -\beta S(t)I(t) + \mu(N - S(t)) \\ \frac{dI(t)}{dt} &= \beta S(t)I(t) - \alpha I(t) - \mu I(t) \\ \frac{dR(t)}{dt} &= \alpha I(t) - \mu R(t) \end{aligned} \tag{1.2}$$

where μ is mortality rate from causes unrelated to the infection. It is neccessary to include demographic changes when the epidemics lasts a long time.
Moreover, the SIR model is based on assumption that each infected individual can transmit the infection and later he recovers fully immune. When the infectious period is long, the assumption should be modified and a new parameter $E(t)$, number of infected but not infectious individuals at time t, should be introduced. The following differential equations represent this model:

$$\begin{aligned} \frac{dS(t)}{dt} &= -\beta S(t)I(t) + \mu(N - S(t)) \\ \frac{dE(t)}{dt} &= \beta S(t)I(t) - (\mu + \gamma)E(t) \\ \frac{dI(t)}{dt} &= \gamma E(t) - (\alpha + \mu)I(t) \\ \frac{dR(t)}{dt} &= \alpha I(t) - \mu R(t) \end{aligned} \tag{1.3}$$

where γ is the expected length of the latent period. [17] also added ω as the rate of loosing immunity. Another option is to simplify the model to SIS model (1.4) assuming

that a recovered individual can be infected again [2] or after some time, i.e. SIRS model (1.5) analyzed in [26].

$$\begin{aligned} \frac{dS(t)}{dt} &= -\beta S(t)I(t) + \mu(N - S(t)) + \alpha I(t) \\ \frac{dI(t)}{dt} &= \beta S(t)I(t) - (\mu + \alpha)I(t) \end{aligned} \tag{1.4}$$

$$\begin{aligned} \frac{dS(t)}{dt} &= -\beta S(t)I(t) + \mu(N - S(t)) + \rho R(t) \\ \frac{dI(t)}{dt} &= \beta S(t)I(t) - (\mu + \alpha)I(t) \\ \frac{dR(t)}{dt} &= \alpha I(t) - (\mu + \rho)R(t) \end{aligned} \tag{1.5}$$

where ρ is an average length of period during which an individual is immune.

There are also several diseases when an individual is born with a passive immunity from its mother [30]. To indicate this mathematically, an additional compartment $M(t)$ is added, which results in the following differential equations:

$$\begin{aligned} \frac{dM(t)}{dt} &= B - \delta S(t)M(t) + \mu M(t) \\ \frac{dS(t)}{dt} &= \delta S(t)M(t) - \beta S(t)I(t) + \mu S(t) \\ \frac{dE(t)}{dt} &= \beta S(t)I(t) - (\mu + \gamma)E(t) \\ \frac{dI(t)}{dt} &= \gamma E(t) - (\alpha + \mu)I(t) \\ \frac{dR(t)}{dt} &= \alpha I(t) - \mu R(t) \end{aligned} \tag{1.6}$$

Brunovsky and Kilianova [13] replaced expected length of infectious period by fixed length τ and derived the SIR model with following equations:

$$\begin{aligned} \frac{dS(t)}{dt} &= -\beta S(t)I(t) \\ \frac{dI(t)}{dt} &= \beta S(t)I(t) - \beta S(t-\tau)I(t-\tau) \\ \frac{dR(t)}{dt} &= \beta S(t-\tau)I(t-\tau) \end{aligned} \tag{1.7}$$

In order to provide a model that describes the disease behavior best, we can also use combinations of the models above. It is important to understand the basics of behavior of the epidemics we are about to analyze, using statistical data or medical theory before we decide for the model.

1.3 Stochastic Models

While deterministic methods may be adequate to characterize the spread of an epidemic in a large population, they are not satisfactory for smaller populations, in particular those of household size [19]. The stochastic models most cited in the literature are Greenwood and Reed-Frost models [25] that differ only in the probability of a susceptible becoming infected at time t, $p(t)$. While in Greenwood model $p(t) = p$ is a constant not depending on the number of infectives, in Reed-Frost model it is supposed that the probability of a susceptible not becoming infected at time t is $1 - p(t) = (1-p)^{I(t)}$. Then the probability that there will be n new infective individuals in the population is binomially distributed,

$$P(I(t+1) - I(t) = n | S(t) = s, I(t) = i) = \binom{s}{n} p(t)^n (1 - p(t))^{s-n}.$$

The future generation of the dynamic system $S(t), I(t)$[1] depends only on the previous its generation, so we deal with Markov chain with conditional probabilities

$$P(Y(t+1) = n | S(t) = s, Y(t) = i) = \binom{s}{n} (1-p)^n p^{s-n} \tag{1.8}$$

for Greenwood model and

$$P(Y(t+1) = n | S(t) = s, Y(t) = i) = \binom{s}{n} (1 - (1-p)^i)^n \left((1-p)^i\right)^{s-n} \tag{1.9}$$

for Reed-Frost model, where $Y(t+1) = I(t) - I(t-1)$ the number of newly infected individuals at time t. Then $S(t+1) = S(t) - Y(t)$ and $S(t) + \sum_{j=0}^{t} Y(j) = N$, where N denotes the size of the population. The models are evidentally special cases of SIR model when the length of infectious period is deterministic.

Despite its apparent simplicity, the models are not readily analyzed for large populations due to computational difficulties. Although Ball and O'Neill [8] have managed to find the distribution of the final size, i.e. the total number of infected invidivuals during the epidemics, in the Reed-Frost model, Anderson and Britton show [2] that recursive formulas used to calculate it are numerically unstable and cannot be applied to obtain solutions when the number of susceptibles exceeds 50-100 individuals.
The main advantage of deterministic models is based on its simpler analysis, they can be more complex and yet still possible to be analyzed at least numerically. However, the de-

[1] $R(t)$ can be expressed as $N - I(t) - S(t)$ as the size of the population is consider constant N.

terministic process characterizes the epidemics as a mass action relying on the law of large numbers. Naturally, when we describe the spread of the disease we rather talk about the probability that one becomes infected than stating certainly whether the disease will be transmitted, as the nature of epidemic growth and spread is for the most part stochastic. Furthermore, probability of extinction cannot be analyzed in the deterministic model that describes only expected course of the epidemics not its deviations from expectations such as extinction. Anderson and Britton [2] provide even more detailed explanation claiming that stochastic models should be preferred when their analysis is possible, otherwise, deterministic models should be used. Since we consider a large population of about 5 million individuals, we decide to deal with deterministic model at first.

Chapter 2

Deterministic Model of Epidemics

In this chapter, we present notation and assumptions used throughout the thesis and derive a deterministic model of epidemics that is subjected to analysis and expanded in next chapters. The literature offers us various models that have been already deeply analyzed, but we focus on influenza epidemics and choose the model that suits the behavior of influenza best. Then, we compare our model to the one that is typically used in literature and discuss whether our choice makes a significant difference. We also define the reproduction number in order to precisely explain the difference between the models.

2.1 SIR model

The basic model that is typically used to analyze course of epidemics and have already been described in Chapter 1 *Mathematical Epidemiology* is called SIR model (1.1) and it is characterized by the system of differential equations. We derive our model from this one as the assumptions that it is based on, suite the case of influenza reasonably well.

This model is comes from following assumptions:

(i) *The population is closed.*
Populations are permanently changing: a part of individuals disappear by death or emigration and another part of them appear by birth or immigration. However, the time scale at which an influenza spreads though the population is often shorter than the time scale of demographic or migration process. Therefore we neglect all the changes within the population and consider it closed.

(ii) *The population is homogenous.*

Generally, individuals have different immunity against diseases depending on their physical condition, immune system, genetic influences etc. In our model, we assume that differences in their immunity are small and can be neglected, so the population is equally vulnerable to infection. Moreover, we assume that all the parameters used in the model have the same value for each individual.

(iii) *A recovered individual is absolutely immune to infection during the rest of the epidemics.*
We assume that we deal with microparasites; they trigger an autonomous process in the host which end up with either immunity or death. No individual can be infected more than once and we do not expect any death caused by the disease in the short time scale of influenza spread.

(iv) *Infectivity of infected individual does not vary in time.*
Although it is natural that at the beginning of infectious period a disease is strongest and can be transmitted easier, we assume that in the short time scale of infective period the transmissibility of disease does not change.

(v) *The number of contacts per time unit is deterministic.* We assume that each individual meet a constant number of different individuals and the transmission rate is directly proportional to the number of contacts.

(vi) *The length of the infectious period is random and has an exponential distribution.* The distribution has parameter α, i.e. the probability to be still infectious T units of time after infection is $e^{-\alpha T}$. So the increase in number of recovered individuals is a constant proportion of the number of infectives.

The last assumption is problematic, as influenza does not behave in such a way. The disease itself lasts from three to six days in average and it can be followed by fatigue for two or three weeks [29]. Therefore, we will change the (vi) assumption and assume that the average time during which an infected individual remains infective is fixed. Let us denote it by τ. We will mostly assume that $\tau = 4$. Hence, in general

$$\begin{aligned} I(t) &= S(t-\tau) - S(t) \\ R(t) &= N - S(t-\tau) \end{aligned} \tag{2.1}$$

The model we will consider is

$$\begin{aligned}\frac{dS(t)}{dt} &= -\beta S(t)I(t) = \beta S(t)(S(t-\tau) - S(t)) \\ \frac{dI(t)}{dt} &= \beta S(t)I(t) - \beta S(t-\tau)I(t-\tau) = \\ &= \beta S(t)(S(t-\tau) - S(t)) - \beta S(t-\tau)(S(t-2\tau) - S(t-\tau)) \\ \frac{dR(t)}{dt} &= \beta S(t-\tau)I(t-\tau) = \beta S(t-\tau)(S(t-2\tau) - S(t-\tau))\end{aligned} \tag{2.2}$$

As $S(t)$ can be expressed by its previous states, we can reduce the model to only first equation. Other variables can be derived from $S(t)$.

Following [18], we add three more parameters

N ... size of the population

k ... expected number of contacts of one individual per unit of time

π ... probability that an individual becomes infected after having met an infective one.

From the above assumptions and [13] we can find an expression for the transmission rate β. The instantaneous average number of infective individuals a susceptible one meets during an interval of unit length is $k\frac{I(t)}{N-1}$. We consider a large population, particularly 5 million population of Slovakia, so we can neglect the difference between N and $N-1$, and simplify the expression to $k\frac{I(t)}{N}$.
The probability of a susceptible becoming infected during a unit time period is the probability of becoming infected by one infected individual multiplied by the probability of meeting one infective individual, i.e. $\pi k\frac{I(t)}{N}$. Hence, the number of newly infected during a unit time period is $\pi k\frac{I(t)}{N}S(t)$. Denoting $\beta := \frac{\pi k}{N}$, we obtain (2.2).

2.2 Discretization of the Model

We decide to work with the model numerically by discretization

$$\begin{aligned}\frac{S(t+\triangle t) - S(t)}{\triangle t} &= \beta S(t)(S(t) - S(t-\tau)) \\ S(t+\triangle t) &= S(t) + \beta S(t)(S(t) - S(t-\tau))\triangle t.\end{aligned} \tag{2.3}$$

We divide the duration of epidemics by time unit $\triangle t = 1$ day, so we obtain

$$S(t+1) = S(t)(1 + \beta(S(t) - S(t-\tau))) \tag{2.4}$$

As we assume that $S(t) \geq 0 \ \forall t$, the sum $1 + \beta(S(t) - S(t-\tau))$ should always be positive. This is not true when $N < \pi k(S(t-\tau) - S(t))$. In that case, the spread of the disease is extremely strong and has the ability to infect more susceptibles than there are in the population. Then the model have to be modified to

$$S(i+1) = \max(0, S(t)(1 + \beta(S(t) - S(t-\tau))). \tag{2.5}$$

Despite this fact, we will use simpler formula (2.4) as we assume that the number of infectives during epidemics will not reach such a high level so that the whole population can be affected.

2.3 Reproduction Number

According to [18], we define the reproduction number R_0 as the expected number of effective contacts by one infected individual during an infectious period in virgin population (the population that is completely susceptible). Contact between an infected and susceptible individual is effective, when the disease is transmitted to a susceptible.

R_0 has a threshold value 1, i.e. if $R_0 > 1$, introduction of an infected individual to the completely susceptible population will result in epidemics, if $R_0 < 1$ the infection will die out soon. Generally, the larger the value of R_0, the harder it is to control the epidemics. From the assumptions including infectious period $\tau = 4$ days, we find

$$R_0 = \beta S(0) + \beta S(1) + \beta S(2) + \beta S(3)$$

where

$$\begin{aligned}
S(1) &= (1-\beta)S(0) \\
I(1) &= 1 + \beta S(0) \\
S(2) &= (1 - \beta I(1))S(1) = (1-\beta)S(0)(1 - \beta(1 + \beta S(0))) \\
I(2) &= 1 + \beta S(0) + \beta S(1)I(1) = (1 + \beta S(0))(1 + \beta(1-\beta)S(0)) \\
S(3) &= (1 - \beta I(2)) \\
S(3) &= (1-\beta)S(0)(1 - \beta(1 + \beta S(0)))(1 - \beta(1 + \beta S(0))(1 + \beta(1-\beta)S(0))).
\end{aligned}$$

As we assume that $\beta = \dfrac{k\pi}{N}$ is low for large N, we can neglect its higher powers. Using this approximation the value of R_0 will increase somewhat, as in fact we assume that the number of individuals getting infected by infectives other than the initial one is so small

that it can be neglected and so the initial one can infect more susceptibles.

Hence, in general

$$S(1) = (1-\beta)S(0)$$
$$S(2) = (1-\beta)^2 S(0)$$
$$\vdots$$
$$S(\tau-1) = (1-\beta)^{(\tau-1)} S(0)$$

For $\tau = 4$, the reproduction number $R_0 = S(0)(1-(1-\beta)^4)$ and generally $R_0 = S(0)(1-(1-\beta)^\tau)$. Brunovsky and Kilianova [13] neglected not only the part of population infected by individuals infected later as we did, but also changes in number of susceptibles at the beginning of epidemics. They derived $R^* = \beta S(0)\tau$. The Figure 2.3 shows the difference between our reproduction number R_0 and R^* depending on the length of infectious period. The difference is very low, but we do not neglect it because there is no need to simplify the formula; calculations are not much more complicated.

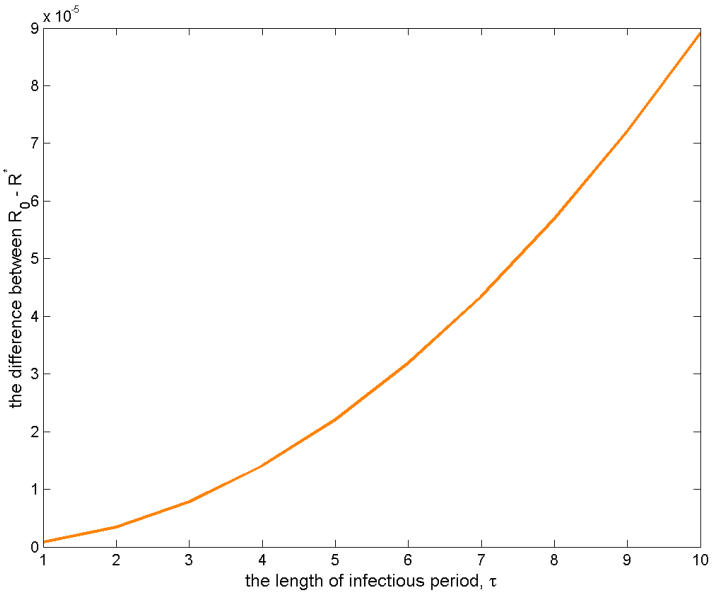

Figure 2.1: The difference between reproduction number R_0 and R^* for different lengths of infectious period τ

Figures 2.2 and 2.3 show the spread of the epidemics for reproduction number below and above 1. Although it is not clear from Figure 2.3 the number of infective individuals have not reached zero, it was only close to zero.

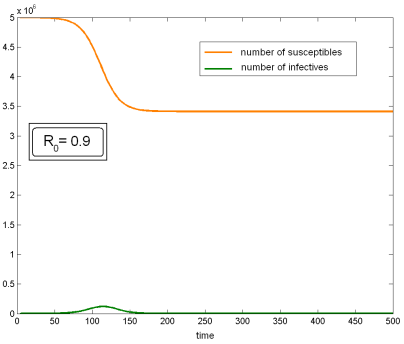

Figure 2.2: Reproduction number R_0 under its threshold value

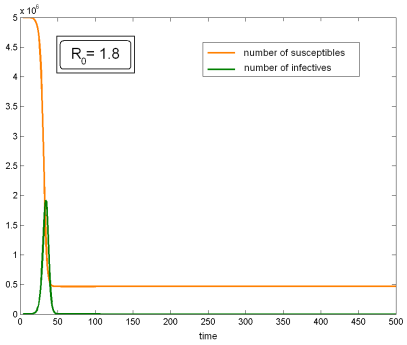

Figure 2.3: Reproduction number R_0 above its threshold value

2.4 Comparison of the Models

The model with exponential distribution is widely used in the mathematical epidemiology as it is relatively easily computable. Using the model with time delay may lead to complications because we have to remember τ previous states to compute the next one, and less standard functions with time delay generally require more complicated theory. Although the influenza behavior fits to the model with time delay, we ask whether the differences between models are so significant that we cannot simplify our problem by using ODR.

Figure 2.4 illustrates the difference between these approaches. If there are no new infected cases in the population, the number of infectives changes exponentially according to (1.1), while according to our assumptions and model (2.2) can reach zero in finite time.

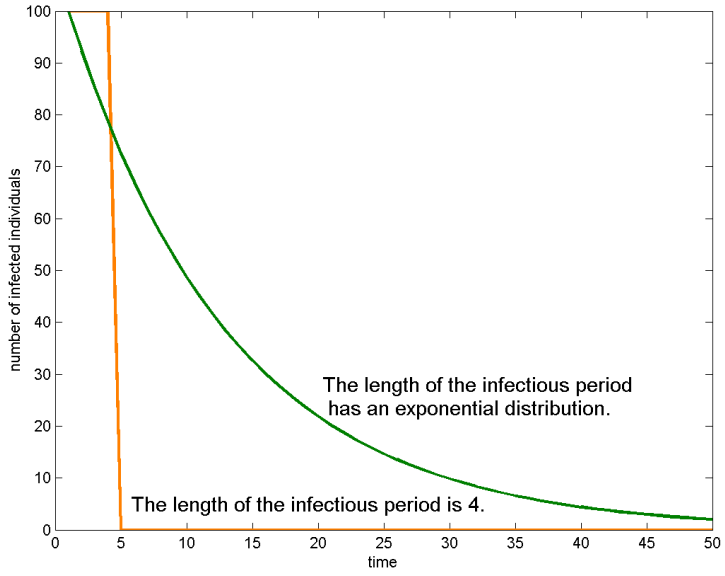

Figure 2.4: Decrease in number of infectives when no new infected individuals appear

In order to go deeper in analysis of the difference between the models, we have to calculate appropriate α, i.e. the parameter of exponential distribution in (1.1). We consider $\tau = 4$ as the average length of infectious period, so we find

$$\int_0^\infty te^{-\alpha t}dt = \frac{1}{\alpha} = 4.$$

Hence, $\alpha = \frac{1}{4}$ and generally $\alpha = \frac{1}{\tau}$ and the models to compare are

$$\begin{aligned} S_1(t+1) &= S_1(t) - \beta S_1(t)I(t) \\ I(t+1) &= I(t) + \beta S_2(t)I(t) - \frac{1}{\tau}I(t). \end{aligned} \tag{2.6}$$

and

$$S_2(t+1) = S_2(t)(1 + \beta(S_2(t) - S_2(t-\tau))) \tag{2.7}$$

And for the same input parameters, i.e. $N = 5.10^6$, $\tau = 4$, $I(0) = 1$, the development of epidemics does not differ much neither at the beginning of the epidemic season and nor at the end of the season as it is shown in the Figure 2.6. Naturally, in the long term there should not be big difference since we replaced exponential distribution by its expected value. And at the beginning, the epidemics does not spread quickly, so the differences are small. However, the differences always reach their relatively high peak between the beginning and the end of season. Since epidemic season does not last long, usually about 28 weeks in Slovakia, we cannot consider long term. If we were interested only in the final size of the epidemics and we consider longer term, the model with exponentially distributed infectious period would be acceptable as well. The crucial question would be: When is the term long enough?

In the long term, the difference yields to zero, but it does not go to zero neither with growing nor with decreasing reproduction number. The Figure 2.7 shows that after 1000 days, there is no difference in the number of susceptibles when reproduction number is lower than 1. This must be true because $R_0 < 1$ indicates that the epidemics has died out soon after its beginning and then $S(t)$ has not changed. Figure 2.6 showed that at the beginning of the epidemics, there are only very small differences. If $R_0 > 1$ the difference is growing and its peaks when R_0 is about 1.8.

We do not consider higher reproduction numbers because their transmission rate would be extremely high and it would lead to conflict with our assumption from section 2.2. *Discretization of the Model* that the number of infectives during epidemics will not reach such

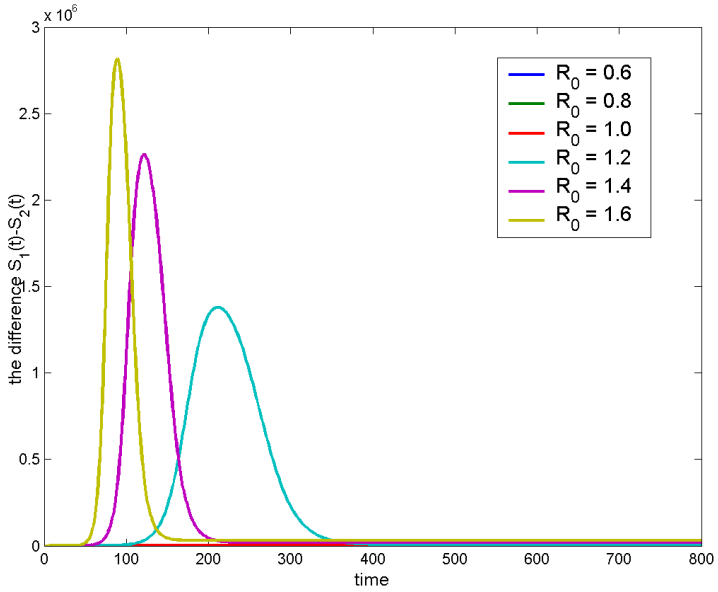

Figure 2.5: The difference between number of susceptibles in the model (2.6) and in the model (2.7)

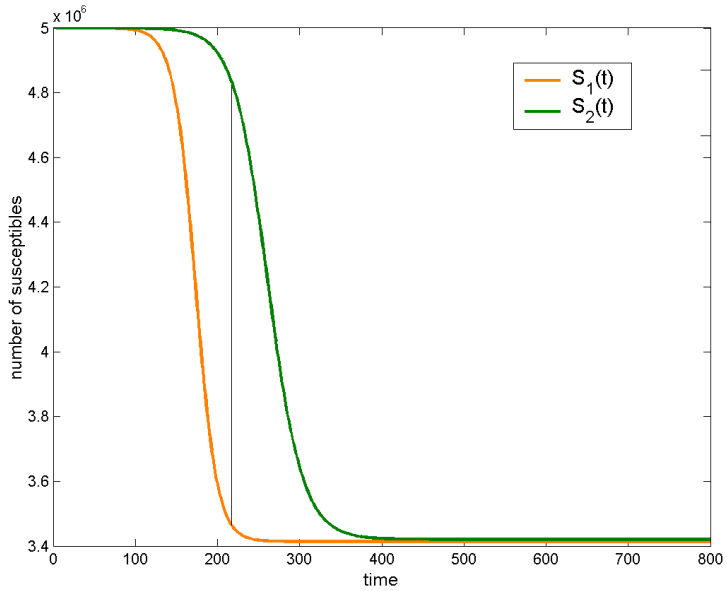

Figure 2.6: The number of susceptibles in the models. The black line shows the time, when the difference is highest.

a high level so that the whole population can be affected.

In next chapters, we will assume that reproduction number of influenza viruses $R_0 \in (1, 1.5)$ and following [13] we will mostly use the reproduction number $R_0 = 1.25$. We provide a detailed explanation in *Appendix*.

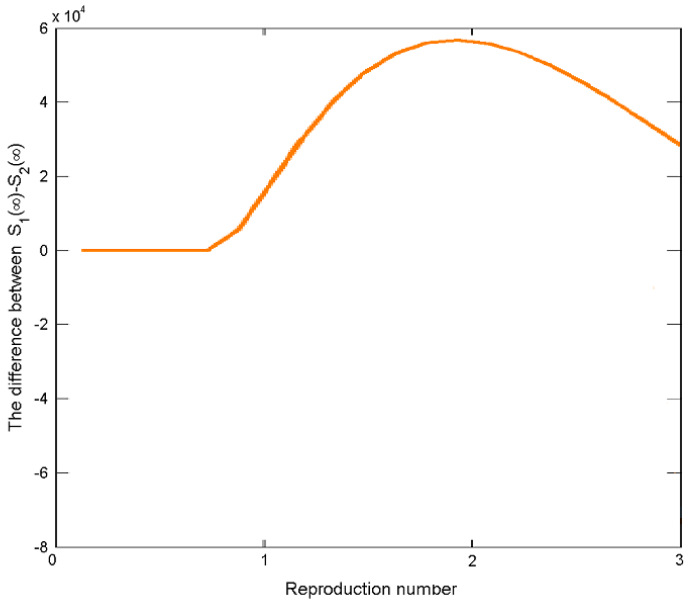

Figure 2.7: The difference between number of susceptibles in the model (2.6) and in the model (2.7) if we assume that the epidemic season ends after 1000 days

When we consider influenza with reproduction numbers below 1, we can use the model with exponential distribution of infectious period. When reproduction number increases, we should skip to the model with time delay that is more suitable for influenza and that differs to the previous model in the short term. If we are not interested in the development of the disease, only in its final size when the epidemic season is long enough, the models lead to the same results and we can prefer the model without time delay because it does not require so much memory. The longer the season is, the better. For reproduction numbers As the aim of this thesis is to analyze pandemic measures on the spread of the disease, we are not interested only in its final size, but also in its developlment. Therefore we decide to use only the model with time delay.

Chapter 3

Vaccination

Vaccination is the administration of antigenic material to stimulate the immune system of an individual and to develop adaptive immunity to a disease. The influenza vaccine is an annual vaccine to protect against the influenza viruses: type A subtype H3N2 virus strain, type A subtype H1N1 (seasonal) virus strain, and type B virus strain, the most common influenza viruses [16]. In large population, it is not possible to vaccinate everyone, at least not at once. However, if we vaccinate some higher proportion of the population, we can moderate the epidemics or even cause the epidemics dies out after vaccination is carried out.

Vaccination as the most efficient pandemic measure serves not only to control the epidemics, but consequently to save money. From the economical perspective, if vaccines are not too expensive and their efficiency is high enough, vaccination is beneficial as well. In this chapter, we will focus on the effect of vaccination when it is both fully and partially effective, asking how can we control the epidemics by vaccination and how can we benefit from that.

3.1 Vaccination with Full Efficiency

Following Brunovsky and Kilianova [13], we asses the effect of vaccination assuming that vaccination is fully effective, i.e. vaccinated individual is immune for the whole duration of the epidemics. We analyze the vaccination carried out before the epidemics starts, after it starts, and the case when it is carried out gradually.

3.1.1 Vaccination Before the Epidemics Starts

At first, we assume that vaccination is carried out shortly before or immediately at the beginning of the epidemics. In the previous chapter we derived reproduction number R_0 according to which we decide whether the epidemics dies out or spreads. When we vaccinate population before the epidemics starts, we change the reproduction number and so we may ask: What part of the population has to be vaccinated to prevent the epidemics, i.e. to achieve $R_0 < 1$?

Based on the previous subsection we have

$$R_0 = S(0)(1 - (1 - \beta)^4) = (N - V)(1 - (1 - \beta)^4),$$

where V denotes number of vaccinated individuals. Thus, threshold for vaccination is

$$V^* = N - \frac{1}{1 - (1 - \beta)^4}$$

In relative terms, this yields

$$v^* = \frac{V^*}{N} = 1 - \frac{1}{N(1 - (1 - \beta)^4)}$$

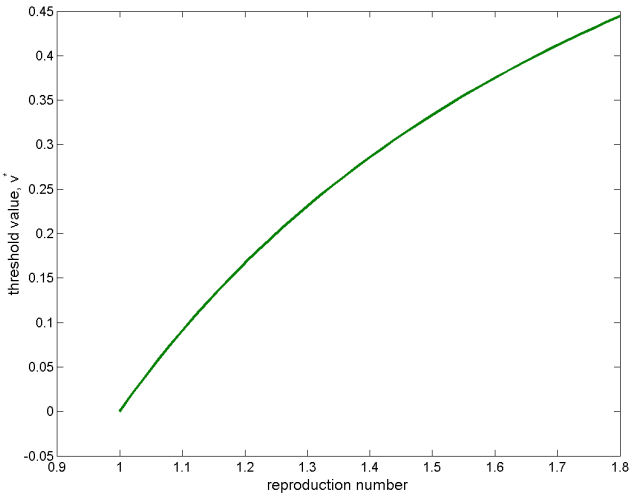

Figure 3.1: Vaccination threshold v^* for various transmission rates β

For example, if $R_0 = 1.25$, then it is sufficient to vaccinate 21 per cent of the population in order to avoid epidemics. As Brunovsky and Kilianova derived different reproduction number R^*, their result is not the same, optimal v^* does not depend on the size of population [13]. The same results can be found in Sherer and McLean [40]. However, the

optimal threshold v^* does not differ much as it is shown in Figure 3.2.

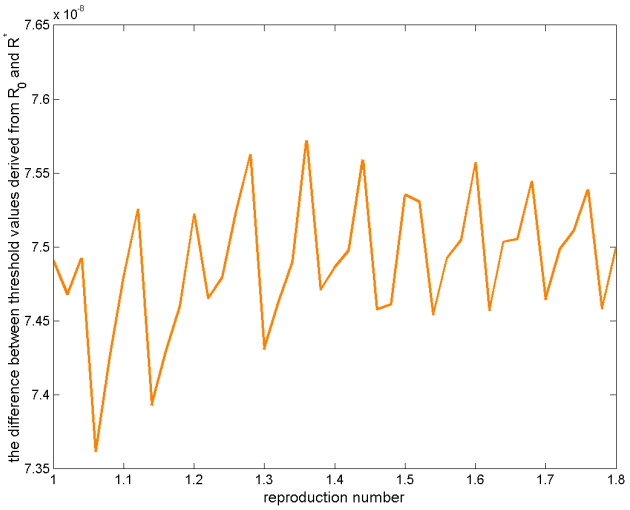

Figure 3.2: The difference in vaccination threshold v^* derived from R_0 and R^*

3.1.2 Vaccination After the Epidemics Starts

When a new type of disease appears, there are no vaccines and it takes some time to develop an effective antidote. This is a typical feature of influenza viruses, i.e. their ability to mutate to new types. Hence, the vaccination cannot be carried out shortly before the epidemics, but after some time. Let us denote it T. The new model is following

$$\begin{aligned} \forall t \neq T : S(t+1) &= S(t)(1-\beta I(t))) \\ I(t+1) &= I(t) + \beta S(t)I(t) - \beta S(t-\tau)I(t-\tau) \\ S(T+1) &= S(T)(1+\beta(S(T)-S(T-\tau))) - vS(T) \end{aligned} \tag{3.1}$$

First τ days after vaccination, we cannot use the equation (2.4) because $S(t-\tau)-S(t)$ would also include vaccinated part of the population.

The reproduction number will not help us in this case. At time T there is no virgin population, the number of recovered and infected individuals is non-zero. If it is not, the disease does not cause any harm to population and vaccination is not needed. The reproduction number is number of individuals infected after introduction of one infective. At time T, there are more infectives with different number of remaining infectious days. When a single infective enters the population, his contacts are maximum effective. Hence, if he is not able to infect at least one individual, others will not be able to do so neither and the epidemics will end soon. As the disease spreads, calculating reproduction number,

i.e. number of effective cases in the population when there are $I(T)$ infectives, clearly cannot be based on the same idea. R_0 has no sense in this case. We only know that if R_0 was lower than 1, the epidemics will die out even without vaccination.

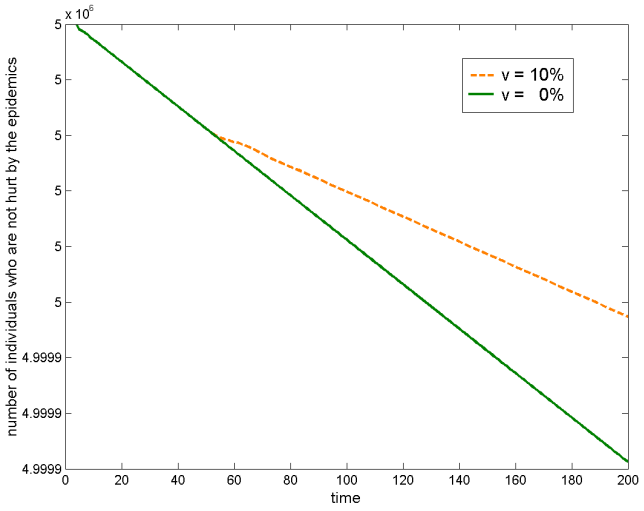

Figure 3.3: Number of susceptibles in non-vaccinated population and when 20% of susceptible population is vaccinated at time $T = 50$

As it is shown in Figure 3.3, vaccination of the population when the epidemics has been already spreading, can slow it down, but it does not affect transmission strength of the disease, i.e. $\beta I(t)$. The rest of the population will remain in danger as vaccination only reduces the number of susceptibles to the number that it would reach later. The crucial is fact that the final size of epidemics is not $S(0) - S_1(\infty)$, where $S_1(\infty)$ denotes the number of susceptibles at end of epidemics when vaccination is not carried out, but it is $S(0) - S_2(\infty) - V(T)$. Moreover, $S_2(\infty) > S_1(\infty)$, so the final size will be much smaller if we vaccinate.

The problem is described in diagrams (3.1.2),(3.5). When we vaccinate at time T, we exclude $vS(T)$ individuals from the dynamic process and only the rest of the susceptible population can become infective and later recovered. When we do not vaccinate, we can divide the susceptible population at time T to two parts, the second one includes the same number of susceptibles as it was vaccinated in the first case. It is still part of the dynamic system and moreover it contributes to higher $I(t)$, so the transmission strength of the disease, $\beta I(t)$, is higher.

When T is high, it would be difficult to vaccinate sufficiently high proportion of susceptible population to make the epidemics die out soon after vaccination. The reason is

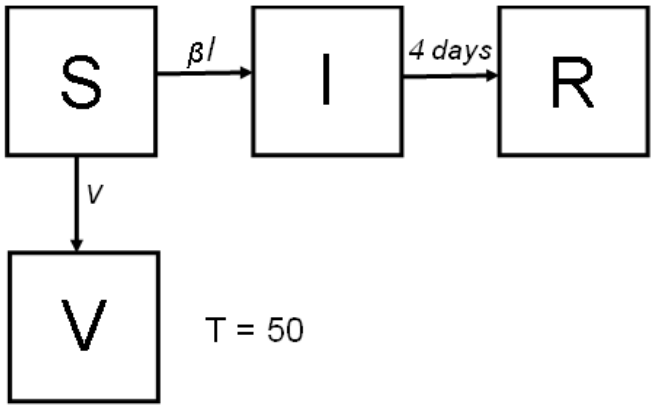

Figure 3.4: The effect of vaccination after epidemics starts

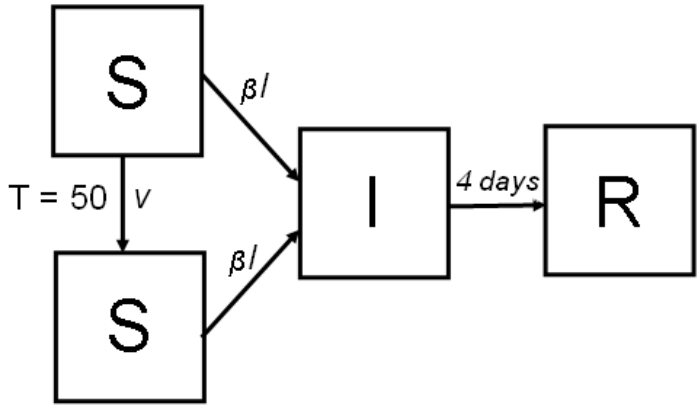

Figure 3.5: The dynamic system when vaccination is not carried out

based on high transmission strength of the disease. As the epidemics did not end soon after the beginning, reproduction number is higher than 1 and so transmission rate is high. Multiplied by increasing number of infectives, it is even higher and vaccination does not change it. It changes only number of susceptibles and so number of future infective cases. To eliminate such a strong transmission spread in the population we would need so many vaccines that probably it would not be possible to supply and employ so much medical personnel. We denote $N - S(\infty) - V(T)$ the final size of the epidemics when vaccination is carried out and $N - P(\infty)$ the final size when the population is not vaccinated. Then $S(\infty) + V(t) - P(\infty)$ is the number of individuals who escape from being infected if vaccination is carried out. Figure 3.6 shows, that the effect of vaccination decreases with growing T. When reproduction number is lower than 1, vaccination has no sense for higher T as in that time the spread has already ended. Reproduction numbers higher than 1 change the situation; when vaccination is carried out soon, it has strong effect on

the final size of the epidemics and it grows with increasing R_0. However, the time interval when vaccination can have significant effect on the final size is shorter for higher values of reproduction number.

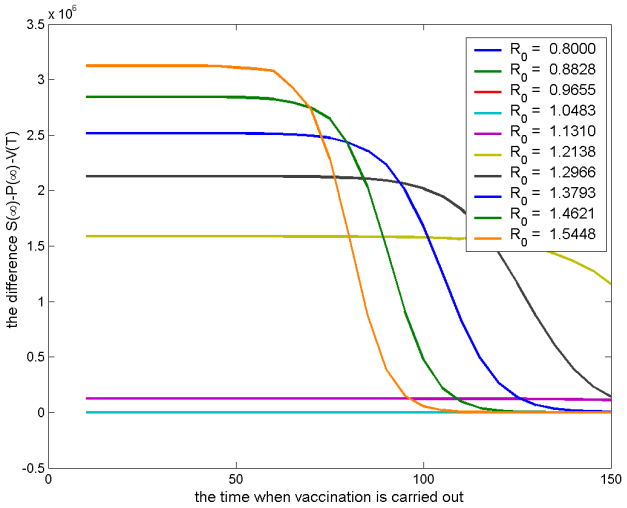

Figure 3.6: The absolute difference between $S(\infty) + V(T)$ and $P(\infty)$ depending on the time when vaccination is carried out

3.1.3 Gradual Vaccination

In fact, vaccination at once at a given time is not practically feasible because medical personnel, space and supply are limited. Therefore, we will assume that vaccination will be carried out gradually, i.e. $v(t)$ per cent of the remaining susceptible population will be vaccinated at time t. This yields to the model

$$\begin{aligned} S(t+1) &= S(t)(1 - v(t) - \beta I(t)) \\ I(t+1) &= I(t)(1 + \beta S(t)) - \beta S(t-\tau)I(t-\tau) \\ V(t+1) &= V(t) + v(t)S(t) = \sum_{k=0}^{t} v(k)S(k) \end{aligned} \tag{3.2}$$

Again, $I(t) \neq S(t-\tau) - S(t)$ since $S(t)$ decreases by vaccination as well. However, we can reduce the model (3.4) to equation of one variable by replacing $I(t) = S(t-\tau) - S(t) - v(t)S(t) - v(t-1)S(t-1) - \ldots - v(t-\tau)S(t-\tau)$. We obtain

$$S(t+1) = S(t)(1 - v(t) - \beta(S(t-\tau) - S(t) - v(t)S(t) - \ldots - v(t-\tau)S(t-\tau))) \tag{3.3}$$

If $v(t)$ is constant in time, the model can be simplified

$$S(t+1) = S(t)(1 - v - \beta(S(t-\tau) - S(t) - v\sum_{k=0}^{\tau} S(t-k)) \tag{3.4}$$

Let Q denote the maximum proportion of the population that can be vaccinated at once because of the limited vaccination requirements. As we have shown in the previous subsection, when we are vaccinating after after the epidemics starts, a relatively high level of vaccination is need to make it die out after the vaccination process, probably the number that could not be reached in the time scale of influenza epidemics and with Q limitation of vaccination. Therefore we will focus on vaccination from economic perspective.

Our goal now is to find optimal $v(t)$ not necessarily in order to force the epidemics spread to stop, but to minimize costs for medical treatment during the epidemic season, i.e. treatment costs for infected individuals and costs for vaccination.

It is an optimal control problem with boundaries in both state and control, with discrete time, with free end, given time, and state variables $X_1, X_2, ..., X_{\tau+1}$. We can easily derive objective function in both Lagrange and Bolza functional form.

$$\min_v \sum_{k=0}^{T} Av(k)S(k) + B\beta I(k)S(k)$$

or

$$\min_v A\sum_{k=0}^{T} v(k)S(k) + B\beta(N - S(T) - \sum_{k=0}^{T} v(k)S(k))$$

with following conditions

$$
\begin{aligned}
X_1(k+1) = S(k+1) &= S(k)(1 - v(k) - \beta(S(k-\tau) - S(k) - \\
&\quad - v(k)S(k) - \ldots - v(k-\tau)S(k-\tau))) \\
X_2(k+1) &= S(k) = X_1(k) \\
&\vdots \\
X_{\tau+1}(k+1) &= S(k-\tau+1) = X_{\tau-1}(k) \\
S(k) &\in \langle 0, N\rangle \quad \forall k = 0, 1, ..., T \\
v(k) &\in \langle 0, Q\rangle \quad \forall k = 0, 1, ..., T
\end{aligned} \tag{3.5}
$$

It is τ-dimensional problem, as we have to remember all τ previous states of $S(t)$ to calculate $S(t+1)$ and next. We could replace the vaccination rate $v(k)$ by number of susceptibles $V(k)$ with admissible interval $\langle 0, C\rangle$, where $C = constant \leq S(t) \quad \forall t$. But we assume that if we have vaccinated $V(k-1)$ individuals yeasterday, we are not able to vaccinate the same number today due to limited supply. The number of vaccinated individuals should depend on the vaccination carried out in the past, therefore we decided to limit the percentage of vaccinated population. We expect the solution showing that we should vaccinate the majority at the beginning of the epidemic season because at that time the susceptible population is biggest and so we can vaccinate the highest number of individuals.

Now we have to determine the parameters. Brunovsky et al.[14] analyzed the socio-economic impacts of several mitigation scenarios for Slovakia using following parameters

Vaccine price	7.83 Euro
Antibiotics	26.55 Euro
Complication treatment drugs	6.63 Euro
Hospitalization costs	445.7 Euro
Percentage of infected hospitalized	10%

Table 3.1: The parameters used in [14]

We use this information to decide the value of parameters in our problem.

Moreover, we will reduce the infectious period τ to one day, so that the problem is

Parameter	**Value**	**Explanation**
A	7.83 Euro	The price of one vaccine.
B	77.75 Euro	The average cost for one infected individual is sum of antibiotics' price, drugs' price and 10% of hospitalization costs.
Q	1%	We assume that not more than 1% of the susceptible population can be vaccinated at once.
N	5.10^6	The epidemics spreads in the Slovak population.
T	196	In Slovakia, epidemic season lasts about 28 weeks.
k	50	The average number of individuals that one meets is 50.
π	0.0125	The probability that a susceptible will be infected after meeting one infective is expected to be 0.0125, so that reproduction number is about 1.25.
β	$1,25.10^{-7}$	$\beta = \frac{k\pi}{N}$
$v(0)$	0	At the beginning, nobody is vaccinated.
$S(0)$	N	At the beginning, nobody is infective.
$S(1)$	$N-1$	We introduce one infective to the population.

Table 3.2: The parameters we use in optimal vaccination control problem

only 2-dimensional and it can be computed easier. The new problem is then

$$\begin{aligned}
&\min_{v} \sum_{k=0}^{196} 7.83v(k)S(k) + 77.75\beta S(k)(S(k-1) - S(k) - v(k)S(k) - v(k-1)S(k-1)) \\
&X_1(k+1) = S(k+1) = S(k)(1 - v(k) - \beta(S(k-1) - S(k) - v(k)S(k) - v(k-1)S(k-1))) \\
&X_2(k+1) = S(k) = X_1(k) \\
&S(k) \in \langle 0, 5.10^6 \rangle \quad \forall k = 0, 1, ..., 196 \\
&v(k) \in \langle 0, 0.01 \rangle \quad \forall k = 0, 1, ..., 196
\end{aligned} \tag{3.6}$$

We solve the problem by Bellman's principle of optimality that is described in Halicka et al. [23]. As there are too many admissible states for $S(k)$ and the solution would require long computation process, we divide its admissible interval to smaller parts, i.e. to 100 parts. The admissible interval for $v(k)$ is divided to 30 parts. This can lead to some inaccuracies in the results, but we still keep the problem complex and so our results can sufficiently uncover principles of optimal vaccination.

According to the solution, we should vaccinate at the beginning as much as possible till 18 days, because after that the effect of vaccination would not be strong enough to compensate its costs. Naturally, at the beginning of the epidemics we are able to vaccinate more, i.e. maximum 1 per cent of the susceptible population that is almost N and as

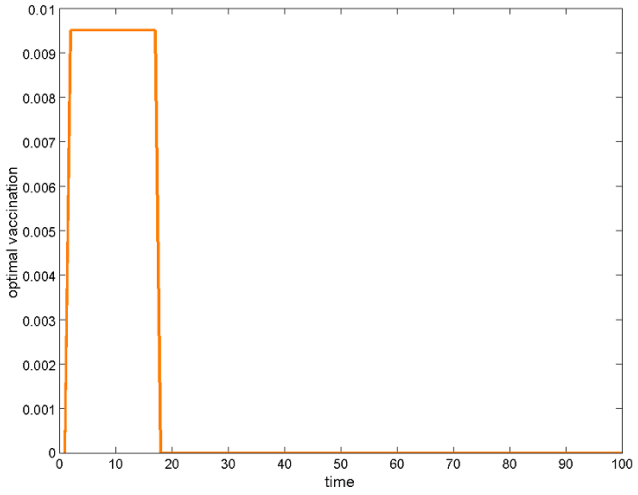

Figure 3.7: Optimal control $v(t)$

the time goes on, the number of susceptibles is decreasing, so we can vaccinate fewer individuals.

Figures 3.12, 3.13 show the development of epidemics when the optimal vaccination strategy is carried out and when it is not. Let denote the number of susceptibles when the vaccination is carried out $S(t)$, $V(t)$ the total number of vaccinated individuals at time t, and $U(t)$ the number of susceptibles when the vaccination is not carried out. The final size of the epidemics, the total number of individuals who became infected during the epidemics is then $S(0) - S(\infty) - V(\infty)$ and $U(0) - U(\infty)$. If we consider $T = 196$ the end of the epidemic season, then the difference between final sizes is 1,425,300 individuals. So if we vaccinate, we save $1.425.300B - V(\infty)A$ Euros. In this case, our savings are $1,0494.10^8$ Euros. We pay $4,4557.10^7$ Euros when we vaccinate and we pay $1,4949.10^8$ Euros for medical treatment when we do not vaccinate.

Vaccination with Progressive Price of Vaccination

In the problem (3.6), we did not take into account costs for the work of medical personnel in vaccination price. Moreover, when we vaccinate too much, we have to order extra supply and our costs rises. Therefore, we change the constant price, A, to progressive price depending on the number of vaccinated individuals. The new price is then

$$A(k) = A \exp\left\{\frac{30v(k)S(k)}{N}\right\}.$$

For smaller number of vaccinated susceptibles, it grows slightly and it goes up sharply

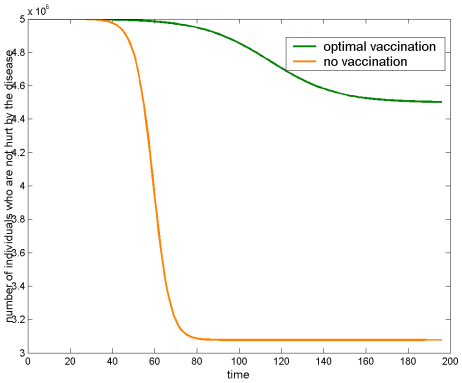

Figure 3.8: Number of individuals who are not hurt by the disease when optimal vaccination is carried out and when it is not

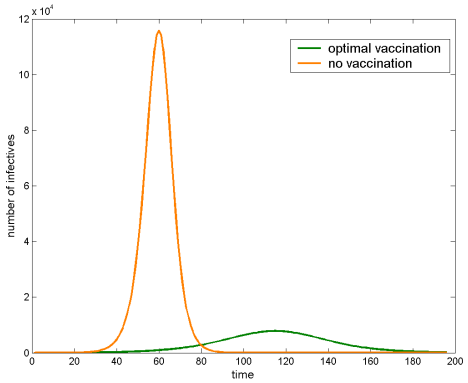

Figure 3.9: Number of infective individuals when optimal vaccination is carried out and when it is not

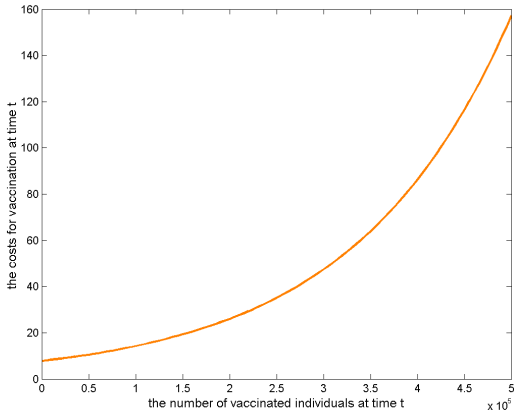

Figure 3.10: The vaccination price depending on the number of vaccinated individuals

with the increasing number of vaccinated individuals.

Progressive vaccination price did not change the optimal strategy, i.e. vaccinate at the beginning of the epidemics, but it changes the value of vaccination rate. We vaccinate less because the price rises with each new vaccinated individual and as the number of susceptibles is decreasing, we can vaccine a higher percentage of them for the same price as we paid at the beginning for the smaller percentage.

The difference in final size, i.e. in the total number of individuals who became infected during the season when optimal vaccination is carried out and when it is not, is lower than in the case of constant vaccine price because we vaccinate less. If we vaccinate, we save 1,000,730 individuals from becoming infected and so we pay $7.4136.10^7$ Euros less ($7.5359.10^7$ Euros if we vaccinate).

The optimal solution strongly depends on both reproduction number and vaccine price.

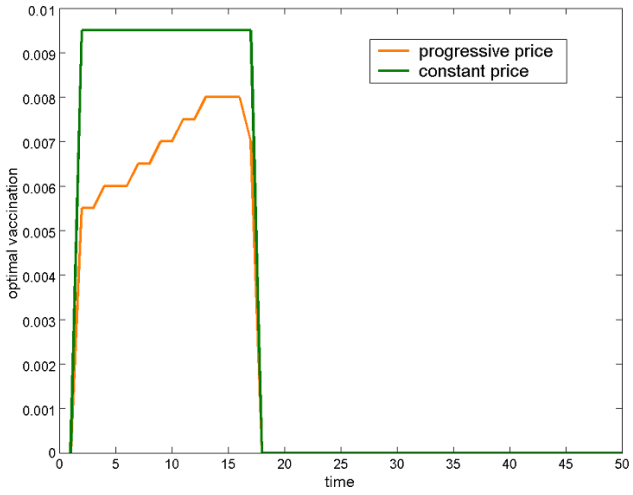

Figure 3.11: Optimal control $v(t)$ for problem with progressive and constant price of one vaccine

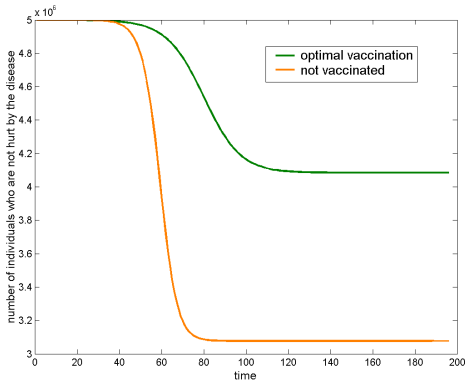

Figure 3.12: Number of individuals who are not hurt by the disease when optimal vaccination is carried out and when it is not

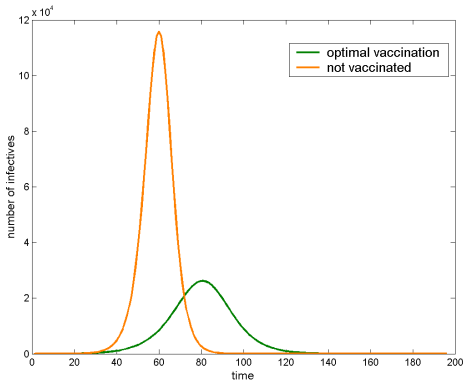

Figure 3.13: Number of infective individuals when optimal vaccination is carried out and when it is not

If $R_0 = 2$, we keep on vaccinating during the whole season and at the same vaccination level 0.033%, but at the beginning of the season we should vaccinate less than in the case of $R_0 = 1.2$. The reason is probably based on the threshold value of reproduction number. When it is more than 1, the epidemics does not die out. However, if it is still not so high and if we have sufficient measures to carry out, we can stop its spread after some time. For higher reproduction numbers and with limitations we set, this effect cannot be achieved, the vaccination is not so effective and it is not reasonable to vaccinate with a such effort because its costs will not be compensated in given time.

When $R_0 < 1$, population should be vaccinated only at the beginning as later the epidemics dies out and so it would not require high treatment costs if we did not vaccinate.

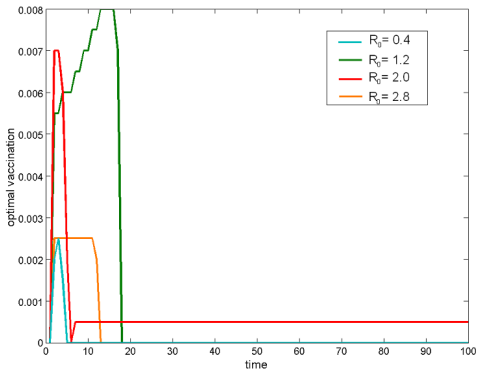

Figure 3.14: Number of susceptibles for various reproduction numbers

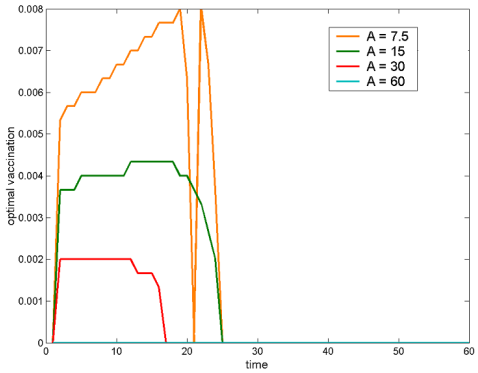

Figure 3.15: Number of susceptibles for various vaccine prices

Vaccination only speeds up the process. The vaccination control for $R_0 = 0.4$ is the smallest among considered, as the transmission strength of epidemics is low and there is much more susceptibles than in the models with higher reproduction number at the same time.

Another critical factor is price. The lower is the price of vaccine (or the higher is difference between treatment costs and vaccine costs), the later we should stop vaccinating. When the vaccine price is 60 Euro, the optimal solution is a vector of zeros, i.e. we do not vaccinate at all.

3.2 Vaccination With Partial Efficiency

Vaccines are not usually fully effective. A metastudy by Osterholm et all. [37] analyzed 31 prior studies on the effectiveness of influenza vaccination trials conducted between 1967 and 2011. The analysis found that flu shots were effective 67 percent of the time. The group most vulnerable to flu, the elderly, is also the least benefitted by the vaccine, with an average efficacy rate ranging from 40-50 per cent at age 65, and only 15-30 per cent past age 70 [35], while the populations that benefit the most from the vaccination were HIV-positive adults ages 18 to 55 (76 per cent), healthy adults ages 18 to 46 (approximately 70 per cent) and healthy children ages 6 to 24 months (66 per cent) [37]. Since we still consider the homogenous population, we neglect the different results within different groups in the population and we assume that our population is relatively young. We set the effectiveness of our vaccines is 70 per cent, and so the vaccination will decrease the probability of becoming infected after meeting one infective individual, i.e. from π to $p = 30\%\pi$.

3.2.1 Vaccination Before the Epidemics Starts

If we vaccinate v per cent of the population before the epidemics starts, the transmission rate for the vaccinated individuals will change from $\beta = \frac{k\pi}{N}$ to $\gamma = \frac{0.3\pi k}{N} = \frac{kp}{N} = 0.3\beta$. Hence, the model is

$$\begin{aligned} S(t+1) &= S(t) - \beta S(t)I(t) \\ V(t+1) &= V(t) - \gamma V(t)I(t) \\ I(t+1) &= I(t) + (\beta S(t) + \gamma V(t))I(t) - (\beta S(t-\tau) \\ &\quad + \gamma V(t-\tau))I(t-\tau) \\ &= S(t-\tau) + V(t-\tau) - S(t) - V(t) \\ R(t+1) &= R(t) + (\beta S(t-\tau) + \gamma V(t-\tau))I(t-\tau) \end{aligned} \tag{3.7}$$

where $S(0) = (1-v)N$ and $V(0) = vN$. The sum $S(t) + V(t)$ represent the part of population that has not been hurt by the disease till time t. The question we want to ask is how beneficial is to vaccinate vN individuals before the epidemics. To find the answer we should calculate

$$AvN + B\sum_{t=0}^{T}[\beta S_1(t) + \gamma V(t)]I_1(t) - B\sum_{t=0}^{T}\beta S_2(t)I_2(t) \tag{3.8}$$

where $S_1(t)$, $I_1(t)$ is number of susceptibles according to model (3.7) and $S_2(t)$, $I_2(t)$ is number of susceptibles according to model without vaccination (2.4). Using the data from the previous section, the equation and assuming that $v = 10\%$ is

$$7.83vN + 77.75\sum_{t=0}^{1}96[S_1(t) + 0.3V(t)]\beta I_1(t) - 77.75\sum_{t=0}^{1}96\beta S_2(t)(S_2(t-\tau) - S_2(t)) \tag{3.9}$$

In this case, the sum of costs for vaccination of 10 per cent of the population and costs for medical treatment of infected individuals during the whole season is 290.820.000 Euro and when the population is not vaccinated, the costs are 319.250.000 Euro, so we save 28.426.000 Euro.

Although we said, that there is no need to vaccinate the population when reproduction number $R_0 < 1$ because the epidemics dies out soon, from the financial perspective it can be reasonable. As the Figure 3.19 shows, when reproduction number is very low, vaccination leads to losses, but when $R_0 \approx 1$ it yields to highest benefits. The reason again is based on the strength of vaccination effect on the population. While 10 per cent

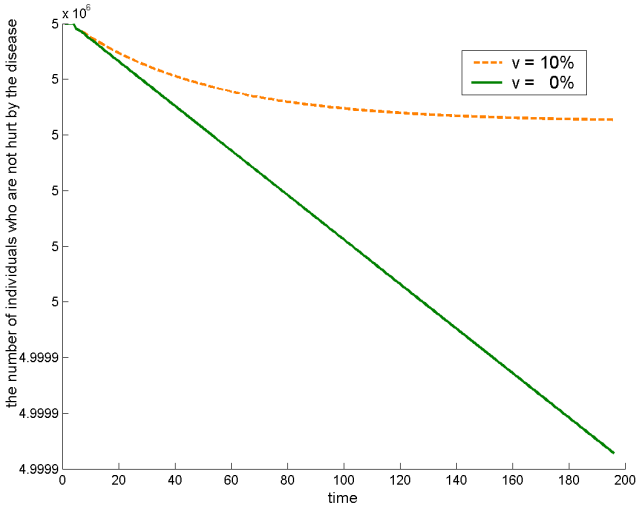

Figure 3.16: The number of individuals who are not hurt by the disease when vaccination is carried out with $v = 10$ per cent and when it is not.

vaccinated population is enough for the disease with reproduction number close to 1 to stop the spread of the epidemics in the given time and compensate the costs for such a high effort, it is not enough for the stronger diseases with higher reproduction number, i.e. in that case, the epidemics spreads, there is an increasing number of infectives and that results in higher treatment costs. When the disease has very low reproduction number, only few infectives appear during the season and costs for vaccination are higher than costs for their treatment.

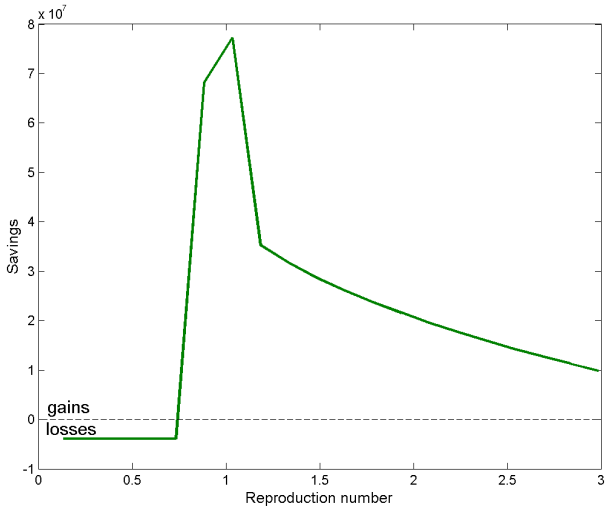

Figure 3.17: Savings resulting from vaccination with 70 per cent efficiency dependent on reproduction number, R_0, when 10 per cent of the population is vaccinated

The savings rise with the increasing vaccination rate v until its exceeds border, i.e.

there are too many vaccinated individuals which yields to high vaccination costs that are not appropriately compensated by its effect on the course of the epidemics. The Figure 3.18 shows that the border is quite high, about 60 per cent. In order to reach the border, we would need a great supply and we would have to hire huge number of new medical personnel, so its realization would be probably impossible. We can conclude that the more individuals are vaccinated before the epidemics, the better not only from medical perspective but from economical perspective as well. Moreover, when we focus on reproduction numbers $\in (0.9, 1.3)$ that characterize the standard influenza epidemics [13], we can see that the savings are highest.

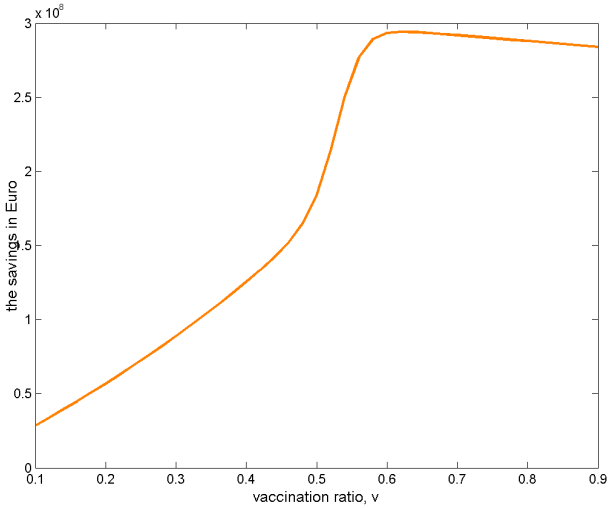

Figure 3.18: Savings resulting from vaccination with 70 per cent efficiency dependent on vaccination ratio, v

3.2.2 Gradual Vaccination

Similarly to the previous section, we assume that the vaccination is carried out gradually, $v(t)$ per cent of the susceptible population at time t, but the vaccination is only partially effective.

This yields to a new model

$$\begin{aligned} S(t+1) &= S(t) - \beta S(t)I(t) - v(t)S(t) \\ V(t+1) &= V(t) - \gamma V(t)I(t) + v(t)S(t) \\ I(t+1) &= I(t) - (\beta S(t) + \gamma V(t))I(t) - (\beta S(t-\tau) + \gamma V(t-\tau))I(t-\tau) \\ R(t+1) &= R(t) + (\beta S(t-\tau) + \gamma V(t-\tau))I(t-\tau) \end{aligned} \tag{3.10}$$

Our goal is to find optimal vaccination strategy that minimizes costs for medical treatment. Again, we use the same parameters as in the Table 3.1.3, we just add one more parameter $V(0) = 0$, i.e. at the beginning we do not vaccinate. The problem is optimal control problem with boundaries in both state and control, with free end and given time.The problem is now 4-dimensional as we need to calculate states of $V(t)$ as well and generally for τ it is $2(\tau + 1)$-dimensional problem.

$$
\begin{aligned}
&\min_{v} \sum_{k=0}^{196} 7.83v(k)S(k) + 77.75\beta S(k)(S(k-1) + V(k-1) - S(k) - V(k)) \\
&X_1(k+1) = S(k+1) = S(k)(1 - v(k) - \beta(S(k-1) + V(k-1) - S(k) - V(k))) \\
&X_2(k+1) = S(k) = X_1(k) \\
&Y_1(k+1) = V(k+1) = V(k)(1 - \gamma(S(k-1) + V(k-1) - S(k) - V(k))) + v(k)S(k) \\
&Y_2(k+1) = V(k) = Y_1(k) \\
&S(k) \in \langle 0, 5.10^6 \rangle \quad \forall k = 0, 1, ..., 196 \\
&V(k) \in \langle 0, 5.10^6 \rangle \quad \forall k = 0, 1, ..., 196 \\
&v(k) \in \langle 0, 0.01 \rangle \quad \forall k = 0, 1, ..., 196
\end{aligned}
\tag{3.11}
$$

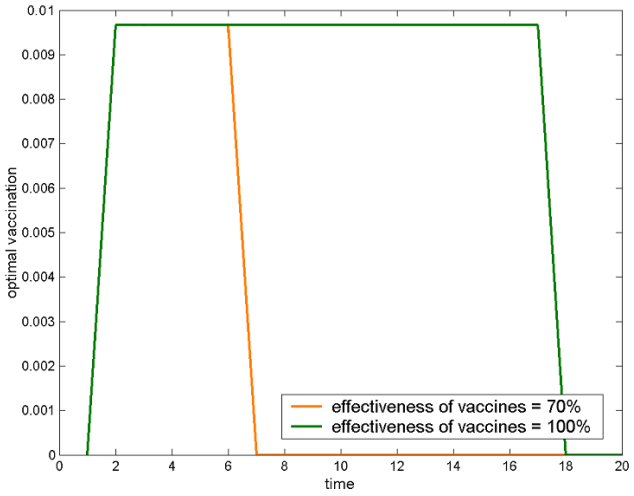

Figure 3.19: Optimal vaccination when vaccines are 70 per cent effective

The optimal solution has not changed much. At the beginning, we should vaccinate as much as possible, but we should stop vaccinating sooner than in the case of full efficiency. The effect of 70% effective vaccination for the same price sooner loses an ability to compensate its costs and therefore we vaccinate shorter time. In both cases, the fully

and partially efficient vaccines, the optimal solution with constant prices is on the boundaries of its interval as Hamiltonian function of the problem is linear in $v(t)$. Only when special conditions are satisfied, it can reach values in its admissible interval. Our results slightly deviate from the boundary of 0.01 due to the inaccuracies resulting from numerical solution, but still suggest that we should vaccinate as much as possible at the beginning.

Chapter 4

Wearing Face Masks

In this chapter, we analyze the impact of wearing face masks on the spread of influenza. We focus on N95 respirator that is currently the most common of the seven types of particulate filtering face piece respirators [36]. There is a number of studies that have analyzed the effectiveness of face masks against nanoparticles in the size range of viruses [6], [7]. They showed that it is effective at almost 95%. However, it is not so effective in real. These studies provide data on the actual protection of masks against nanoparticles, it does not take into consideration that a mask will not be completely sealed on an individual, and that he will not always be wearing the mask, e.g. when he eats.

The study by Aiello et al. [1] evaluates the effectiveness of hygiene and face masks in preventing influenza from spreading. The study conducted a randomized cluster intervention trial among students living in dorm housing. The students were randomly separated into two intervention groups, one wearing masks and practicing hand hygiene, one just wearing masks, and also in a control group. The study found that the group wearing face masks and practising hand hygiene was 35–51% better protected against influenza. Therefore we assume that wearing masks is 40% effective in protection against the disease and it decreases the probability of becoming infected when an infective individual is met from π to $p = 0.6\pi$. This yields to almost the same problem as we have already analyzed in the section 3.2. *Vaccination with Partial Efficiency.*

$$
\begin{aligned}
S(t+1) &= S(t) - \beta S(t)I(t) \\
W(t+1) &= W(t) - \gamma W(t)I(t) \\
I(t+1) &= I(t) + (\beta S(t) + \gamma W(t))I(t) - (\beta S(t-\tau) + \gamma W(t-\tau))I(t-\tau) \\
&= S(t-\tau) + W(t-\tau) - S(t) - W(t) \\
R(t+1) &= R(t) + (\beta S(t-\tau) + \gamma V(t-\tau))I(t-\tau)
\end{aligned} \tag{4.1}
$$

where $W(t)$ is number of individuals wearing face masks and $\gamma = 0.6\beta$. We assume that $W(0) = wN$ and when an individual who wears face mask gets infected, he stops using masks. The Figures 4.7, 4.8 show the impact of wearing face masks on the spread of epidemics if $R_0 = 1.25$, $w = 80\%$, $T = 196$. The difference between $S_1(t)$, i.e. number of susceptibles when nobody wears face masks, and $S_2(t)$, i.e. number of susceptibles when 80% of the population is wearing masks, is in fact very low. The efficiency of masks is too low to have a stronger impact on the spread of epidemics during such a short time. The difference increases with time, so in the longer term wearing masks would be more crucial.

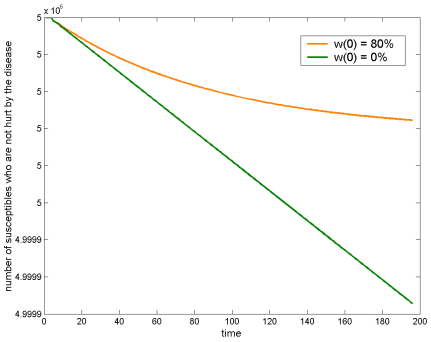

Figure 4.1: Number of susceptibles when 80% of the population wear face masks of 40% effectivess and when nobody wears them

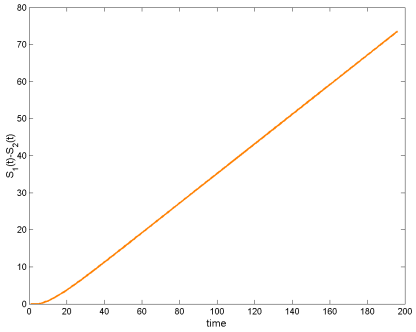

Figure 4.2: The difference between the number of susceptibles when 80% of the population wear face masks and when nobody wears them

People do not wear face masks right after the epidemics starts, it has to spread a while and after some T days, they start wearing them. The Figure 4.3 shows that masks' impact on the development of epidemics in the case of $R_0 = 1.25$ does not depend on T significantly.

For the same input parameters, the number of susceptibles wearing masks at the beginning has not significant impact on the final size of epidemics. The spread of the disease is in the case of R_0 mild and so implementation of masks with only 40% efficiency

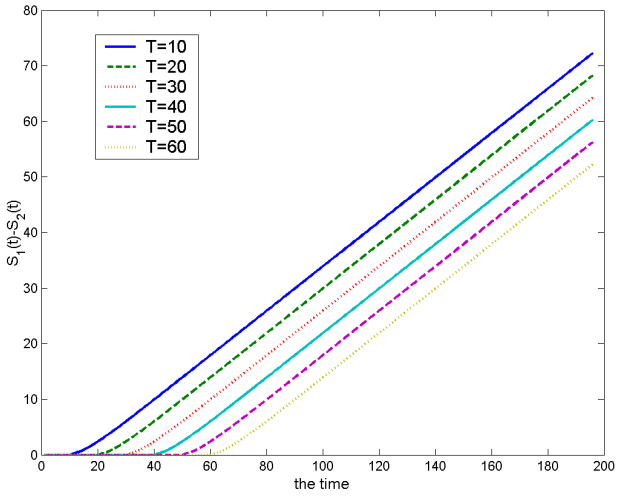

Figure 4.3: Sensitivity of the impact of wearing masks to the time when masks are implemented to the population

leads to only slight improvement.

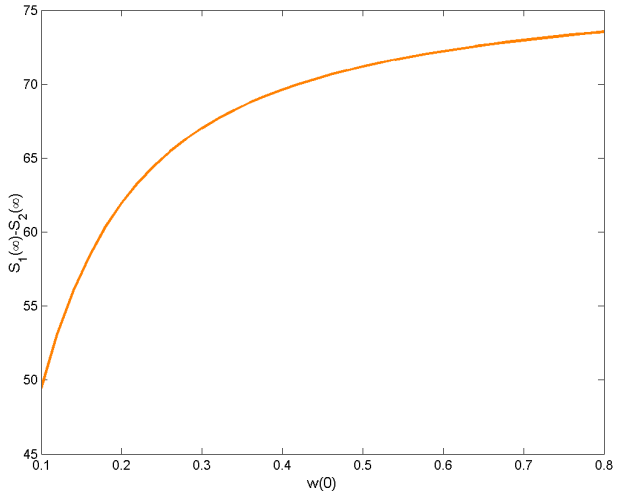

Figure 4.4: Number of susceptibles for various $w(0)$, i.e. the proportion of the population that wears masks at the beginning of the epidemics

Is this improvement worth of buying masks? Now, we solve the problem from economical perspective. The price for pack of 20 respirators costs 8.45 Euro, the price of one respirator is then approximately 0.42 Euro. Respirator should be changed at least every day, therefore those who wear face masks and do not get infected during the whole season pay $0.42T$ Euro. For $T = 196$, the costs for wearing masks and not getting infected are 141.12 Euro. We again assume that the price of medical treatment is 77.75 Euro, i.e. 55% of the price of wearing masks. Can the efficiency of the face masks compensate such high

expenses? Individually, it is reasonable to pay 77.75 Euro with probability lower than 1, i.e. the probability of becoming infected during the season, rather than paying 141.12 Euro for sure. However, when we solve the problem looking at the population as a whole and minimizing common costs, it could be beneficial to implement masks and so lower the spread of the epidemics.
The price the population pays during the season is

$$77.75 \sum_{t=0}^{T} [\beta S(t) + \gamma W(t)] I_1(t) + 0.42 W(t) \tag{4.2}$$

We compare the costs with the situation when we do not implement masks and the Figure 4.9 shows our results for various $w(0)$ and for the same parameters as we used before.

We lose when we implement face masks to the population. The more individuals wear face masks, the worse the loss. As it was already said, the impact of wearing masks is very small so it cannot compensate its high costs.

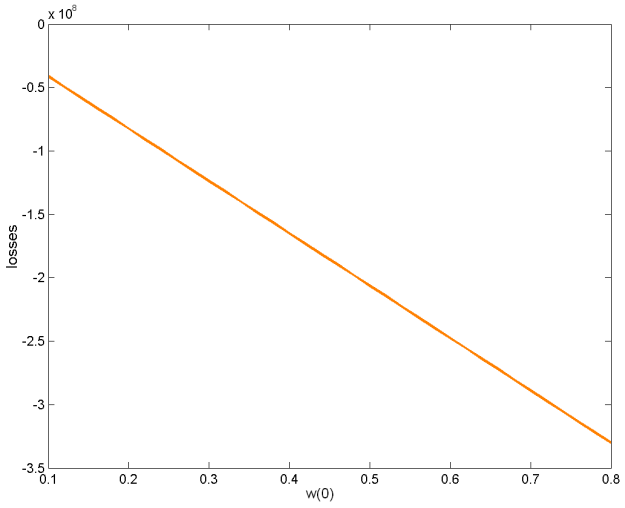

Figure 4.5: Losses resulting from implementation of face masks to the population for various $w(0)$

However, the situation changes with higher reproduction numbers. When the disease is stronger, the spread of the disease is fast and we are willing to pay more to slow it down. The costs are compensated by the impact of wearing masks. Highest gains are reached for the diseases with reproduction number $\in (2, 2.5)$ when the face masks can significantly slow down the epidemics. In the case of stronger diseases, their efficiency is

too low to affect the spread so much. Disease with such reproduction numbers would be disastrous for the population as in the very short term, the whole population would get infected.

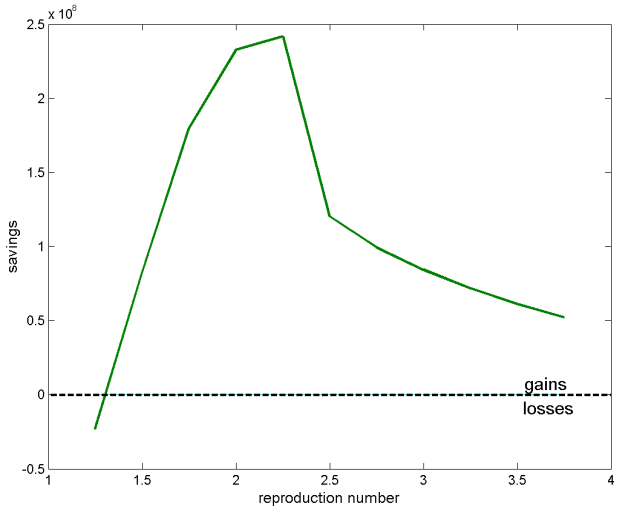

Figure 4.6: Savings resulting from implementation of face masks to the 80% of the population at the beginning of the epidemics for various R_0

Only a small increase in the reproduction number lead to significant difference. If we keep $R_0 = 1.25$, even the highest efficiency of face masks will not lead to gains. However, if $R_0 = 1.5$ we always gain from implementation of masks to 80% of the population.

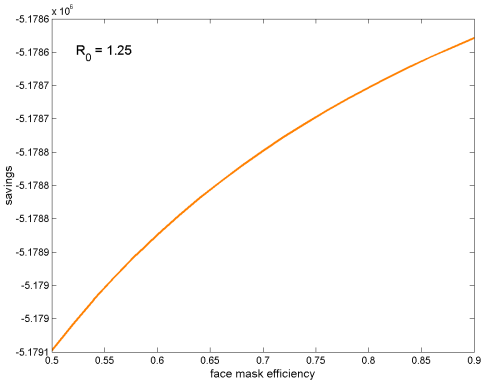

Figure 4.7: Savings depending on the price of face masks for reproduction number 1.25

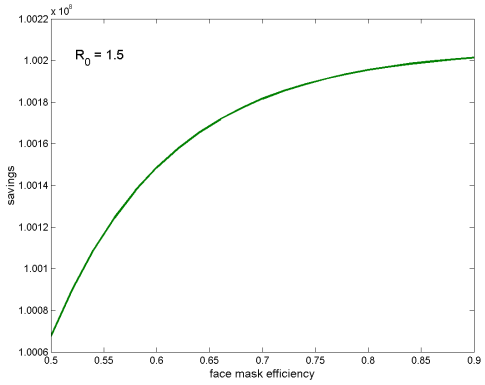

Figure 4.8: Savings depending on the price of face masks for reproduction number 1.5

When reproduction number is 1.25, wearing face masks leads to losses, so they would rather not be implemented. However, when reproduction number increases, face masks have stronger impact on the epidemics and their implementation may lead to gains.

Moreover, their impact is comparable to the impact of vaccination. We set $R_0 = 1.5$ and we compare the effect of vaccinating 10 per cent of the population by the vaccine of constant price 7.83 to the effect of wearing masks with 40 per cent efficiency. We can see in the Figure 4.9 that we need to implement masks to about 18 per cent of the population to reach the same final size as in the case of vaccination. This might be important when a new disease occurs and there is no vaccines yet. Wearing masks can lead to the same final size of the epidemics, but its costs would be higher. In this case, the vaccination costs are $4,2919.10^6$ Euro and face masks costs are $2,304.10^7$ Euro, it is $18,7481.10^6$ Euro more.

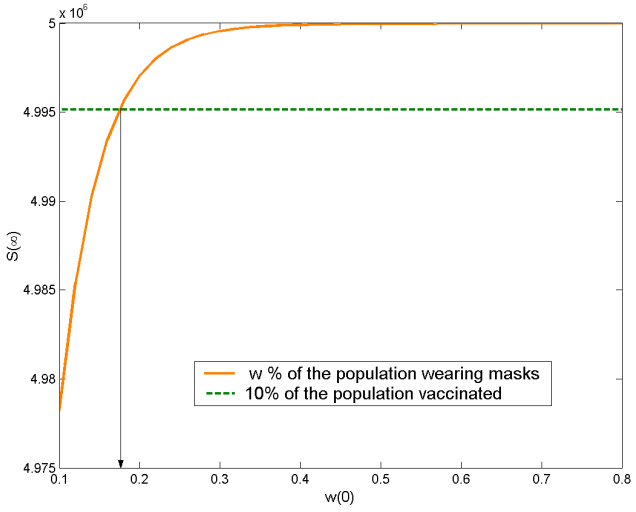

Figure 4.9: Savings resulting from implementation of face masks to the 80% of the population at the beginning of the epidemics for various R_0

The impact of wearing masks strongly depends on the reproduction number. We have shown that if $R_0 = 1.25$ using masks will not lead to improvement that is worth of its costs. However, only slight increase in the reproduction number leads to absolutely different results and the implementation of face masks may lead to high gains.
Furthermore, wearing face masks can have the same impact as vaccination. When a new type of influenza appears, implementation face masks to about 18 per cent of the population lead to the same final size of epidemics as vaccination of 10% of population by vaccines with 70% efficiency. We still assume that the epidemics season lasts 28 weeks that would not be probably true in the case of new type of virus. However, we represented universal method that lead to the conclusion that wearing masks can compensate vaccination in given conditions.

In conclusion, implementation of masks is beneficial only for stronger diseases. The

higher efficiency they have, the better. Vaccination is typically more efficient and cheaper way to prevent the disease, but when there is no effective antidote yet, vaccination can be sufficiently substituted by wearing masks.

Chapter 5

Stochastic Model of Epidemics

In this chapter, we deal with stochastic nature of epidemics. According to Isham [8], the simple stochastic models may be useful for understanding underlying principles and according to Nasel [34] they should not be replaced by deterministic approximation when population is not sufficiently large, i.e. in the case of households [21]. In the Chapter 1 *Mathematical Epidemiology*, we discussed the advantages and disadvantages of using stochastic model and concluded that if it can be analyzed, it should be preferred to deterministic model. However, Anderson and Britton showed [2] that when number of susceptibles is about 50 and more, the equations of existing stochastic models are numerically unstable and therefore we are not able to use the models for the population of 5 million individuals. However, stochastic modeling has several advantages, i.e. the nature of epidemics is stochastic, deterministic model in fact works only with expected course of the epidemics, so it cannot include deviations from the expected processes, e.g. extinction, some cases of stochastic processes does not satisfy the law of large numbers, i.e. when only a small proportion of the population gets infected. Due to these reasons we decide to deal with stochastic process of epidemics as well and derive a new stochastic model based on the deterministic model used throughout the thesis and the existing stochastic models and discuss its possible use.

In the literature we can find two classical discrete time stochastic models, both of the so called chain-binomial type. These are the Greenwood model and the Reed-Frost model, which was proposed in 1928 in biostatistics lectures at Johns Hopkins, not published by the proponents but subsequently referred to. Both models are described in Chapter 1 *Mathematical Epidemiology*.
In the Greenwood model, probability that one infective becomes infected at time t is constant, while in Reed-Frost it depends on the number of infectives in the population.

The models were later modified in several ways, e.g. [34] where models are transformed to continuous time SIR, SIS and SIRS model and [25] that made it adaptable for different diseases.

We keep the notation and assumptions of Chapter 2 *Deterministic Model of Epidemics*, including the length of infectious period being fixed to τ days. According to Reed-Frost model, we assume that the probability of an individual becoming infected at time t varies in time and depends on the number of infectives in the population.

If one meets k different individuals at time t, the probability of meeting i infectives has an hypergeometric distribution, i.e. $p^*(t) \sim Hg(N-1, I(t), k)$.

$$p_i(t) = \frac{\binom{I(t)}{i}\binom{N-I(t)-1}{k-i}}{\binom{N-1}{k}}. \tag{5.1}$$

In the the deterministic model, we could replace $N-1$ by N as we considered large population. In stochastic model we keep $N-1$ because it is basically used for smaller populations.

And the probability of a susceptible becoming infected after meeting i infectives is $q_i = 1 - P(\text{not becoming infected after meeting } i \text{ individuals})$, so that

$$p_i^* = 1 - (1-\pi)^i. \tag{5.2}$$

Summing the products of (5.1), (5.2) over i leads to probability that a susceptible individual becomes infected at time t

$$p_1(t) = \sum_{i=1}^{\min k, I(t)} q_i p_i(t) = \sum_{i=1}^{\min k, I(t)} (1-(1-\pi))^i \frac{\binom{I(t)}{i}\binom{N-I(t)-1}{k-i}}{\binom{N-1}{k}} \tag{5.3}$$

In [27] the same probability is expressed by the formula

$$p(t) = 1 - \left(1 - \pi\frac{I(t)}{N-1}\right)^k, \tag{5.4}$$

clearly assuming that one individual meets k individuals in unit time who are not necessarily different.

Figure 5.1 and Figure 5.2 depict the difference between these approaches when $\pi = 0.06$ and $N = 200$. It is small and it is increasing with growing $I(t)$. The population is big enough so that we can assume that if one meets k individuals at time t, the probability

he meets one individual more than once can be neglected. Therefore we are indifferent to the approaches and decide for (5.4) as it does not require so complicated calculations that may result in non-exact values after computation.

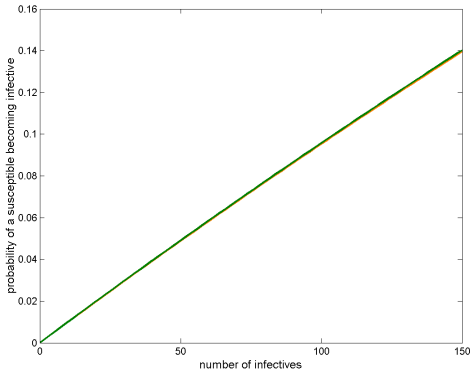

Figure 5.1: Probabilities of a susceptible becoming infected at time t when there is $I(t)$ infectives in the population

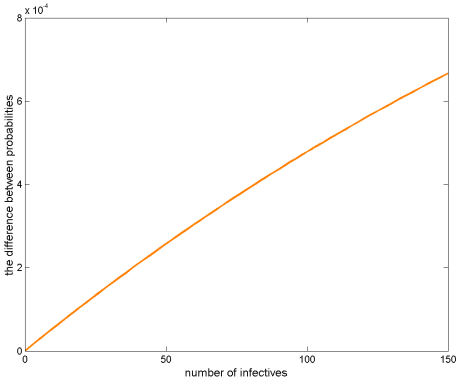

Figure 5.2: The difference between probabilities of a susceptible becoming infected at time t depending on $I(t)$

The probability that n susceptibles do not become infected at time t when there is $I(t) = S(t-\tau) - S(t)$ infected individuals, is binomially distributed, i.e. $P(S(t) - S(t+1) = n) \sim bin(1 - p(t))$, hence

$$P(S(t) - S(t+1) = n | S(t) = i, I(t) = j)) = \binom{i}{n}(1 - p(t))^n p(t)^{i-n} =$$
$$= \binom{i}{n}\left(1 - \left(1 - \left(1 - \pi\frac{j}{N-1}\right)^k\right)\right)^n \left(1 - \left(1 - \pi\frac{j}{N-1}\right)^k\right)^{i-n} \tag{5.5}$$

5.1 τ-dimensional Markov chain

To calculate future states, we need to remember all the states of number of susceptibles from $t - \tau$ to t . So we define vector $U(t) = (S(t), S(t-1), ..., S(t-\tau))$. We can express conditional probabilities

$$\begin{aligned} &P(U(t+1) = \mathbf{j} | U(t) = \mathbf{i}, U(t-1) = \mathbf{i}_1, ..., U(0) = \mathbf{i}_t) \\ &\quad = P(S(t+1) = j_0, S(t) = j_1, ..., S(t-\tau+1) = j_\tau | S(t) = i_0, S(t-1) = i_1, ... \\ &\quad ..., S(t-\tau) = i_\tau) = p_{i_0 i_1 ... i_\tau}^{j_0 j_1 ... j_\tau}(t) = P(U(t+1) = \mathbf{j} | U(t) = \mathbf{i}) \end{aligned} \tag{5.6}$$

So that $U(t)$ is τ-dimensional Markov chain with conditional probabilities $p_{\mathbf{i}}^{\mathbf{j}}(t)$. The number of susceptibles is non-increasing function of time, so it applies

$$p_{\mathbf{i}}^{\mathbf{j}}(t) = p_{i_0 i_1 \dots i_\tau}^{j_0 j_1 \dots j_\tau}(t) = \begin{cases} \binom{i_0}{j_0}(1-p(t))^{j_0} p(t)^{i_0 - j_0} & \text{if} j_0 \leq i_0 = j_1 \leq i_1 = j_2 \leq \dots \leq i_\tau \\ 0 & \text{otherwise,} \end{cases} \tag{5.7}$$

where $p(t) = 1 - \left(1 - \pi \frac{i_\tau - i_0}{N-1}\right)^k$.

The chain is homogenous, as $p_{i_0 i_1 \dots i_\tau}^{j_0 j_1 \dots j_\tau}(t+T) = p_{i_0 i_1 \dots i_\tau}^{j_0 j_1 \dots j_\tau}(t) \quad \forall T \quad \in N_0$, so we can use notation $p_{i_0 i_1 \dots i_\tau}^{j_0 j_1 \dots j_\tau}$. Now, we can express absolute probabilities $p_{j_0 j_1 \dots j_\tau}(t+1) = P(S(t+1+\tau) = j_0, S(t+\tau) = j_1, \dots, S(t+1) = j_\tau)$.

$$p_{j_0 j_1 \dots j_\tau (t+1)} = \sum_{i_0} \sum_{i_1} \dots \sum_{i_\tau} p_{i_0 i_1 \dots i_\tau}^{j_0 j_1 \dots j_\tau} p_{i_0 i_1 \dots i_\tau}(t) \tag{5.8}$$

or in the form of matrices

$$\mathbf{p}(t+1) = \mathbf{p}(t)\mathbf{P}, \tag{5.9}$$

where we define transition matrix $\mathbf{P} = \{p_{i_0 i_1 \dots i_\tau}^{j_0 j_1 \dots j_\tau}\}_{j_0 \leq i_0 = j_1 \leq i_1 = j_2 \leq \dots \leq i_\tau = 0}^{N}$. Then we obtain $\mathbf{p}(t+\tau) = \mathbf{p}(0)\mathbf{P}^t$.

The size of matrix is huge, $S_1 \times S_2 \times \dots \times S_\tau \quad \times S_1 \times S_2 \times \dots \times S_\tau$. We have to calculate the number of variations with repetition where $i_0 \leq i_1 \leq \dots \leq i_m$ to determine S_m. It is an arithmetic progression with common difference of m and the initial term 1. Then the size is

$$(N+1) \times \frac{(N+1)(N+2)}{2} \times \frac{(2N+2)(N+1)}{2} \times \dots \times \frac{(\tau N+2)(N+1)}{2} \times$$

$$\times \quad (N+1) \times \frac{(N+1)(N+2)}{2} \times \frac{(2N+2)(N+1)}{2} \times \dots \times \frac{(\tau N+2)(N+1)}{2}$$

If we assume that $\tau = 1$, and simplify our problem to second order Markov chain, the transition matrix

$$\mathbf{P} = \{p_{i_0 i_1}^{n}\}_{n \leq i_0 \leq i_1 = 0}^{N}$$

is of size $(N+1) \times \frac{(N+1)(N+2)}{2} \quad \times (N+1) \times \frac{(N+1)(N+2)}{2}$ and it is clearly not feasible to work with such a big matrix for large N. We did not manage to derive the model that would allow us to determine the stochastic behavior of the epidemics and its final size in the Slovak population.

5.2 The Effect of Pandemic Measures on Stochastic Model

In order to analyze the stochastic model and the instantaneous effect of pandemic measures, we do not have to necessarily focus on the final size of the epidemics that require a lot of calculations, we can use the probability that no more infectives appear as it is done in [25].

We use following parameters

τ	4	the infectious period is fixed to 4 days
π	0.006	the probability of a susceptible becoming infected after meeting one infective
k	50	number of contacts remains 50
N_1	180	we assume the small population of 180 individuals
N_2	5.10^6	we also assume the large population of 5.10^6 individuals

Table 5.1: The values of parameters used in stochastic model of epidemics

In our model the probability of no new infected cases at time t is

$$P(\text{nobody gets infected}|S(t)=i, I(t)=j) = (1-p(t))^{i\tau} = \left(1-\pi\frac{j}{N-1}\right)^{ki\tau} \quad (5.10)$$

When we vaccinate the population or implement face masks, the probability that one gets infected after meeting one infective individual, i.e. π, decreases. The impact of the measures depends on effectiveness of vaccines or face masks. Let denote their effectiveness α. Then the probability of becoming infected after meeting one infective is $(1-\alpha)\pi$.

We also assume that 5 per cent of the population is recovered and 5 per cent, hence we calculate

$$P(\text{nobody gets infected}|S(t)=0.9N, I(t)=j) = (1-p(t))^{0.9N\tau} = \left(1-\pi\frac{j}{N-1}\right)^{0.9Nk\tau} \quad (5.11)$$

When we consider only small populations there are not limitations on supply and we can assume that everyone can be vaccinated at once and everyone can wear face masks.

Figure 5.3 shows that we are able to maximize the probability that there will not be more infective cases to almost 1 when the measure we carry out is 90 per cent to 100 per cent effective.

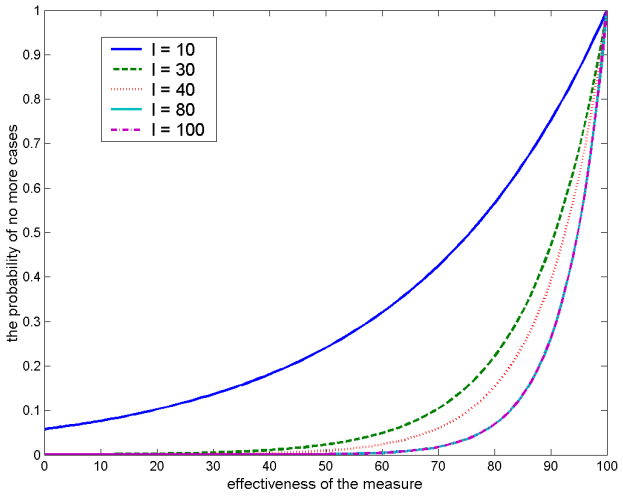

Figure 5.3: The probability that no more infectives appear depending on the effectiveness of the pandemic measure for various numbers of infectives in the population when the population is small and $\tau = 4$

However, as argued in the chapters 3 *Vaccination* and 4 *Wearing Face Masks*, the effectiveness is typically no more than 70 per cent. In this case, the probability can be risen significantly only when the number of infectives is low, i.e. at the beginning of the epidemics. In this case, as the probability of no more infected cases is almost one, the epidemics is about to die out soon after the measures have been carried out. When we carry out the pandemic measures later with the same efficiency, we are only able to moderate the epidemics.
Interestingly, for higher numbers of infectives, the probability does not vary so much and effectiveness lower than 60 per cent has no noticeable effect. If we wanted to affect the epidemics, we would have to use highly effective pandemic measures or just minimize the number of contacts, i.e. if we consider the population of students and teachers in a school, an effective measure would be flu vacations.

For longer infectious periods, the probability is again very low and only highly-effective measures can affect the epidemics significantly. The period can be influenced by better medicaments. Figure 5.7 shows that although there is 10 infectives in the population the measures are only able to moderate the epidemics in the case of long infectious period.

When we investigate the impact of pandemic measures on the probability that no more infective cases appear and changes the size of the population to large number N_2, we find out that the measures has not such effect. It is clear from the equation (5.11) that the probability depends on N, the larger it is, the smaller is the probability. Moreover,

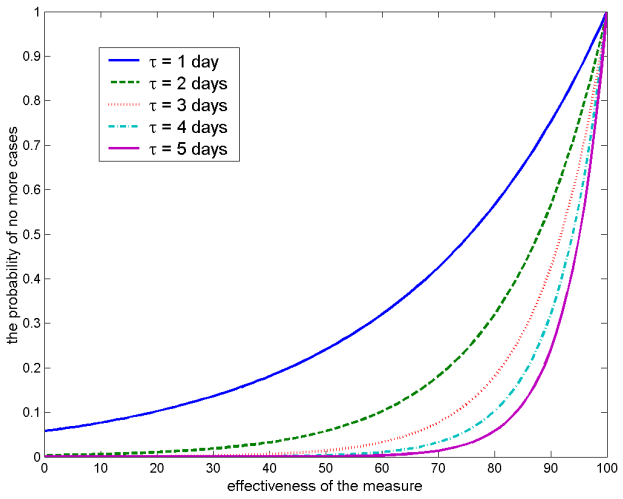

Figure 5.4: The probability that no more infectives appear depending on the effectiveness of the pandemic measure for various lengths of infectious period when the population is small and $I(t) = 5\%N$

Figures 5.5 and 5.6 shows that the 70 per cent efficient measures almost do not affect the probability, even when the whole population is vaccinated. Changing the proportion of vaccinated population would lead to even smaller impact. When there is 5 per cent of the population infectious, the impact of measures is so small that it does not vary with growing infectious period.

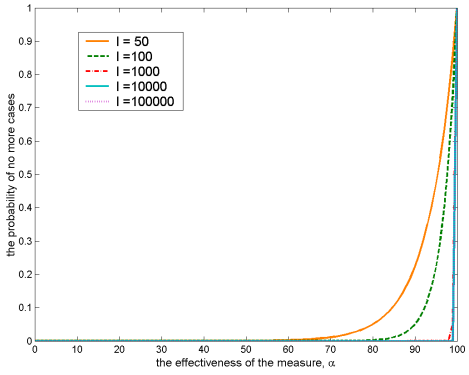

Figure 5.5: The probability that no more infectives appear depending on the effectiveness of the pandemic measure for various numbers of infectives when the population is large and $\tau = 4$

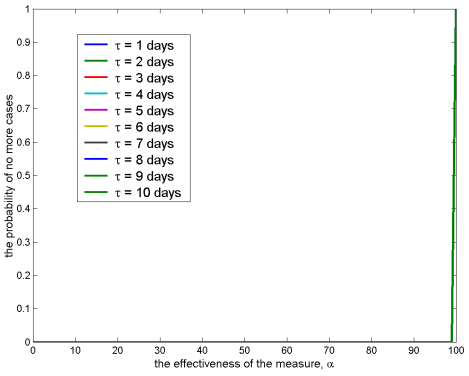

Figure 5.6: The probability that no more infectives appear depending on the effectiveness of the pandemic measure for various lengths of infectious period, when the population is large and $I(t) = 5\%N$

When the size of the population exceeds 10,000, the difference of probabilities of no more cases is very small. In this case, if 5% of the population is infected, vaccination or

face masks have a significant impact only if they are almost fully efficient. In the Chapter 3 *Vaccination* we investigated the fully efficient vaccination of 20% of the population and according to Figure 3.3 it has instantaneous effect, but also very small. In the long term, it yields to significant difference in comparison to the non-vaccinated population. Therefore, we assume that even small instantaneous impact on the probability of no more cases may lead to significant difference in the long term and we can not conclude that a pandemic measure with available efficiency about 70% cannot significantly affect the spread of the disease.

However, for smaller population it can lead to a sooner termination of the epidemics, while in the case of larger population, its impact does not vary as much as in the case of smaller population and can only moderate the spread of the disease. So the effect of the measures depends on N. In the section 3.1.1 *Vaccination Before the Epidemics Starts*, we calculated the threshold value v^*, the optimal vaccination rate so that $R_0 < 1$ and we avoid the epidemics, we derived the formula depending on N. The approach by Brunovsky and Kilianova [13] and others, leads to formula independent to N that is not in accordance with results from this chapter.

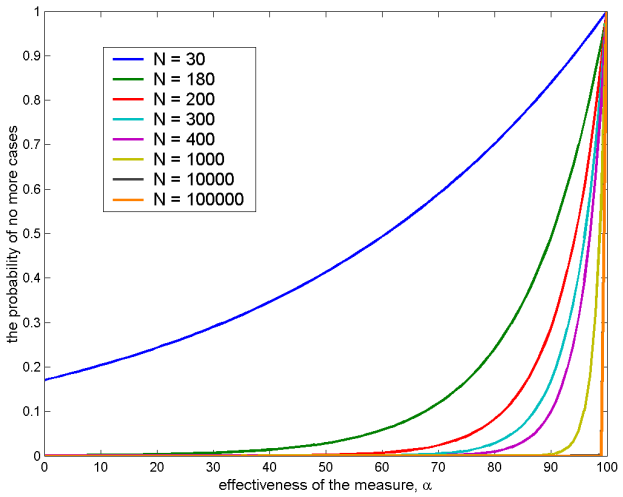

Figure 5.7: The probability that no more infectives appear depending on the effectiveness of the pandemic measure for sizes of the population $I(t) = 5\%N$ and $\tau = 4$

In order to analyze the impact of pandemic measures in the long term, we would have to use some of the stochastic models and calculate the distribution of final size of the epidemics. The model however should not be too simple in order to make it computable, as it could lose its realistic value. In [8] a method is derived only for smaller populations but not for larger, so there is still a lot of space for new findings. The stochastic model that could be used even for larger population should become a new challenge in the field

of mathematical epidemiology.

The stochastic model we present in this chapter requires a huge memory, but it can be still used in smaller populations such as households or classes in the school instead of traditional the Reed-Frost or the Greenwood model.

Conclusion

We analyzed the effect of pandemic measures on the spread of epidemics in Slovak republic, mostly for epidemics with reproduction number 1.25. We decided to use deterministic SIR model based on the assumption that the length of infectious period is fixed and we discussed the difference that it makes in comparison to the traditional SIR model with exponential distribution of the length of infectious period. When we consider weak diseases with reproduction number less than 1, there is no difference and we should prefer traditional model mainly because it does not require so much memory. In the long term, the models yield the same results, so if we are not interested in the development of the epidemics, only in its final size, we can use a traditional SIR model. Otherwise, we prefer the time delay model, especially in the case of influenza epidemics because within the interval of influenza pandemics and with the typical length of their duration the difference between the models is most significant.

In the next chapter we investigated the effect of vaccination, when it is fully, and when it is partially efficient. We derived a formula for threshold value of vaccination rate, saying what proportion of the population should be vaccinated before the epidemics starts in order to avoid its outbreak. Our formula depends on the size of the population, while the formula used in several resources is independent to the size of the population. However, our findings in the last chapter suggest, that the effect of vaccination varies with growing number of individuals in the population, so our formula can offer more precise threshold values.

We also found out that it would be difficult to make the epidemics die out after the vaccination process if it is carried out when the disease is already spreading. Supply of vaccines and medical personnel are limited and when the disease is strong, i.e. it has large reproduction number or there are a lot of infectives in the population, vaccination can only moderate the spread. It still makes a sense, even when it can not cause the epidemics die out, because there is still difference in the final size of epidemics when vaccination is carried out and when it is not. Hence, vaccination can lead to financial benefits even in the case when it can not stop the spread. We solved the optimal control problem of

vaccination asking how should we vaccinate gradually during the epidemics when there are limitations to supply in order to minimize our costs for medical treatment and vaccination. The solutions were based on the same idea - to vaccinate at the beginning as much as possible and after given time units to let the epidemics spread without vaccination because the costs for vaccination would not be compensated by its effect on the development of epidemics. When the reproduction number is near 1 and limitations not so strict, we can stop the spread after some time and in this case, our benefits are highest. It is also the case of reproduction number of typical influenza epidemics. Vaccination does not necessarily lead to benefits when reproduction number is lower than 1 as it can only speed up the extinction process of the epidemics.

In next chapter, we deal with implementation of wearing face masks. Neither its economical nor its practical effect is as high as the effect of vaccination, but they have one main advantage; they are always available. If a new type of virus mutates and there is no antidote yet, we can implement face masks to the part of population achieving the effect comparable to the effect when some smaller proportion of the population is vaccinated. However, when the disease has reproduction number 1.25, implementation of wearing masks lead to financial losses and therefore we do not recommend it during the typical influenza epidemics.

We also derived a stochastic model of the epidemics, but it is not computable for large populations. We could only observe the impact of pandemic measures on the probability that no more infective cases appear and that helped us to understand some principles of epidemic behavior. Surely, if there is a stochastic model that can be applied to large population, it would uncover more principles, we would be able to calculate the probability of extinction of the population etc. Therefore, the epidemiological modeling should fill this gap in the future, setting this as a prior challenge.

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Appendix

Brunovsky and Kilianova [13] define the attacked rate $\alpha = \dfrac{S(0) - S(\infty)}{S(0)}$, where $S(0)$ is the initial number of susceptibles and $S(\infty)$ is the number of susceptibles having avoided the disease transmission. The difference $S(0) - S(\infty)$ is the final size of the epidemics. And they analyze the development of influenza for $\alpha \in \langle 0.15, 0.5 \rangle$.

An implicit formula for the final size of epidemics is derived in [18] and it reads

$$\ln S(\infty) - \ln S_0 = A(S(\infty) - S_0) \tag{5.12}$$

Keeping the definition $\beta = \dfrac{k\pi}{N}$, we can express β from the equation (5.13)

$$\beta = \frac{1}{\tau(S(0) - S(\infty))} \ln \frac{S(0)}{\tau S(\infty)} = \frac{1}{\tau(S(0) - S(\infty))} \ln \frac{1}{1-\alpha} = \frac{1}{\tau \alpha S(0)} \ln(1-\alpha) \tag{5.13}$$

Then using the simplistic formula for reproduction number derived in [13], $R_0 = \beta S(0)\tau$, we obtain $R_0 = -\dfrac{1}{\alpha} \ln(1-\alpha)$. Therefore, if the disease is characterized by the attack rate $\alpha \in \langle 0.15, 0.5 \rangle$, then its reproduction number is $\alpha \in \langle 1.08, 1.38 \rangle$. We assume that the average reproduction number of influenza is then 1.25.