A delayed SEIR-model of the Covid-19 pandemic

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Abstract

During the Covid-19 pandemic, mathematical models and the thought process behind them became more relevant for the common population then ever. Several restrictions was implemented based on predictions done by epidemiology models that not many people understood. As a soon to be teacher and mathematician I think it is important that people have some knowledge about mathematical models and why they are useful in cases like a pandemic. Therefore a SEIR model that hopefully is simple enough that it can be explained to and understood by non mathematicians, while taking vaccination and its efficacy into consideration and being somewhat realistic have been made and analysed in this thesis.
The vaccines against the Covid-19 virus does not work immediately after it have been taken, therefore a delay was added in the model to take that into consideration. With the delay added, a new analysis was done to see the impact it had on the models stability.
Several scenarios have been simulated both with the regular model and the delayed version to visualize how they affect the spread of the virus.
A sensitivity analysis have been performed to see which of the parameters in the model had the biggest impact on the infection peak. This knowledge can be used to explain why some of the control measures was implemented.
Finally a presentation and manuscript for explaining the model and the work done in this thesis to non-mathematicians have been made and will be presented at the end.

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Chapter 1

Introduction

1.1 Covid-19

Covid-19, also known as SARS-CoV-2 started as a epidemic in the Chinese city Wuhan in late 2019, before spreading rapidly around the world. March 11Th 2020 the World Health Organization, WHO, declared that the Corona virus was a pandemic due to how wide and fast the disease was spreading [1]. A pandemic can be called by WHO when a virus affects many countries and populations in addition to having a exponential growth [2]. At the end of 2021 there was over 5 million reported cases of people dying while infected world wide [3]. February 26Th 2020 the first case of Covid-19 was detected in Norway, and the country went into full lockdown 12Th of March after the virus had spread across the country [3]. Late 2020 a vaccine against the Corona virus was approved and the first vaccination dose in Norway was given 27Th December 2020. At the end of 2021 over 70% of the population in Norway had taken at least two doses of the vaccine [3]. During 2020 and 2021 several control measures was implemented, removed and then re-implemented with spikes in the infection rate coming in waves [3]. Eventually protests against the restrictions emerged around the world [4]. Was the protests a result of people getting tired of following rules they don't understand the reasoning behind, lack of knowledge, lack of trust, or something else? In an attempt of at least helping someone getting more understanding about the mathematical modelling that is behind some of the reasoning for the restrictions, we have made a simplified model that looks at a scenario were vaccination is the only control measure in play.

1.2 The basic reproduction number

The basic reproduction number, often shortened to R_0, is a metric used in epidemiology to estimate the number of secondary infections resulting from a infectious person roaming around in a completely susceptible population [5] [6]. The number represent how a disease potentially can spread within a population. If $R_0 > 1$ then each person will on average infect more than one person and the spread of the disease will increase. If instead $R_0 < 1$ then the number of new cases will decrease over time as each infected person will most likely on average transmit the virus to less then one other person [5]. With the reproduction number getting media attention throughout the pandemic and being a source of confusion, an investigation into R_0 will be part of this thesis.

1.3 Motivation

As a soon to be teacher and mathematician I want to spread knowledge and make people understand more about mathematical modeling with the hope that people will have the possibility to learn more about what models do and how they are used to make decisions regarding Covid and many other things in society. By making a epidemiology model that hopefully is understandable for most people, I can combine the teaching about mathematical modelling and spreading of information about the math behind something everyone can relate to, namely Covid restrictions.

1.4 Problem Statement

This thesis looks into developing a version of a SIR model that takes vaccination into consideration while being simple enough to explain to the common population. After the model is made, topics like stability, how much does the delay between getting the vaccine and it becoming effective matter, what happens if vaccination starts at a later date, and which parameter have the largest impact on the peak of the infection wave, will be investigated.

1.5 Objectives

The main objective in this thesis is to combined applied mathematics and the didactic knowledge of teaching students to make a model that takes vaccination into consideration while being understandable for non-mathematicians.

1.6 Contribution

Hopefully the work presented in this thesis will help people to understand some of the math behind the Covid restrictions, see the effect of only having vaccination as a control measure and understand why some of the restrictions was implemented. The thesis will also share some thoughts about presenting a mathematical model to non-mathematicians from the perspective of two teaching-students, that might help other academics in making their work easier understood by others.

1.7 Thesis outline

This thesis will look into developing and analyzing a SEIR-model that focuses on the Covid19 pandemic with vaccination and vaccine efficacy included. The main focus of the model is to make it simple enough for non-mathematicians to understand while making sure the models still can represent a real scenario.
The models limitation and assumptions as well as the problematic nature of the basic reproduction number will be discussed.
The model will be used to first theoretically analyse the effect of a delay between when

the vaccine is given and when it becomes effective, before running numerical simulations to get a visualization of the effect. Through simulations we will also look at how long some countries have before it is to late to start vaccination given a scenario with only 1 dose of vaccination and no other control measures.
A sensitivity analysis using the SAFE toolbox will be done to see which of the parameters in the model makes the biggest contribution on the infection peak.
Finally there will be a discussion about presenting the model SEIR-model first to academics, then based on feedback given, an adjusted presentation that hopefully work on the common population with a manuscript given at the end.
The work done in chapter 2, 3 and 7 and corresponding appendixes have been done in full cooperation with Maria Markhus Jacobsen [1] and will be almost identical to the matching chapters in her thesis.

[1] See Maria M. Jacobsen's master thesis titled: *A SEIR-model of the Covid-19 Pandemic; Developed, Optimized and Explained.* UiB, June2022

Chapter 2

Modelling

2.1 SIR- and SEIR-models

2.1.1 SIR

A popular mathematical model in epidemiology is the SIR-model. It is a model made up of differential equations that each denote changes within different groups in a population as time goes on. It is used for simulating, analyzing, and predicting how a pandemic or epidemic will develop, and can be used as a tool for e.g. governments to handle outbreaks.
While developing a SIR-model one first identifies the initial set of dependent variables, and denote the size of the different groups of people in the population, divided into number of susceptible, $S(t)$, infected $I(t)$, and recovered, $R(t)$ individuals as time, t, progresses [7]. It is assumed that a recovered individual has immunity and can not go back to being susceptible. Recovered can also mean removed, in that people who die from the disease being studied also falls into this category [8].
Visually these transitions can be presented in a flowchart as in figure 2.1, where S, I and R denotes the susceptible, infected and recovered individuals in a population, respectively.

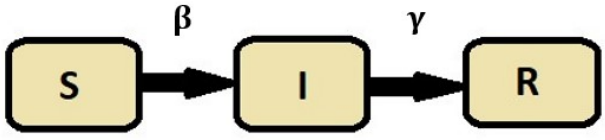


Figure 2.1: Flowchart of a SIR-model, where S, I and R denotes the susceptible, infected and recovered individuals in a population, respectively.

Certain parameter-values are needed to describe the rate of which individuals transition from S to I and from I to R. For this purpose β is used as the parameter describing the effective transmission rate that transfer individuals from S to I, and γ is the recovery-rate, describing the rate of which individuals go from being infected to being recovered. See figure 2.1.

A set of dependent variables denote the *change* in variables S, I and R in that they describe how quickly individuals in a population move from one box to the next. These changes are described by differential equations. These are the equations that make up the model itself. A basic SIR-model could look like this:

$$\begin{aligned} \frac{dS}{dt} &= -\beta SI \\ \frac{dI}{dT} &= \beta SI - \gamma I \\ \frac{dR}{dt} &= \gamma I \end{aligned} \tag{2.1}$$

The first equation describes how many susceptible individuals are in contact with infected individuals and consequently get infected and then leaves the susceptible-compartment. The second equation correspondingly increase by the susceptible individuals get infected, and also decrease as those who are infected recover (or die). The final equation describes the amount of individuals who have recovered (or died) from the disease being studied [8].
One of several properties of model 2.1 is that the total population, N, is conserved. Since the equations $\frac{dS}{dt}$ and $\frac{dI}{dt}$ does not depend on R, one can write

$$R = N - S - I. \tag{2.2}$$

This also helps make the later analysis of the model easier, as it is sufficient to consider the equations not depending on R while constructing e.g. the Jacobian matrix [9].

2.1.2 SEIR

The SIR-model can be expanded in numerous ways, where one of the most common is to add a compartment, E, which denotes those individuals that have been exposed to the disease but have not yet reached an infectious state. One can also add rates of natural births and deaths in a population, here denoted by μ, see fig. 2.2.

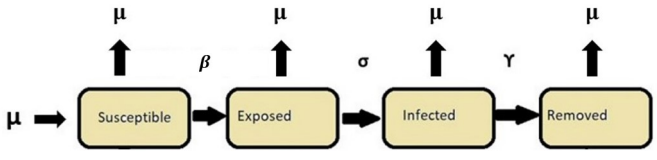


Figure 2.2: Flowchart of a SIR-model, where S, E, I and R denotes the susceptible, exposed, infected and recovered individuals in a population, respectively.

Inspired by how Osman and Adu constructed a similar model for their work on Malaria transmission, we propose an example of what a general SEIR-model can look

like [10]:

$$\begin{aligned} \frac{dS}{dt} &= \mu - \beta SI - \mu S \\ \frac{dE}{dT} &= \beta SI - \sigma E - \mu E \\ \frac{dI}{dt} &= \sigma E - \gamma I - \mu I \\ \frac{dR}{dt} &= \gamma I - \mu R \end{aligned} \tag{2.3}$$

Where μ, β, σ and γ represent the natural birth-/death rate, transmission rate, incubation rate and recovery rate, respectively.
To find the basic reproduction number R_0 for this model we use the Next Generation Method [11]. To use this method, we first need to find the disease-free equilibrium point of the system, then find the corresponding *next generation matrix* and finish by calculating the *spectral radius* of that matrix. The next generation matrix is denoted by FV^{-1}, so we first need to find both F and V. F is the infection ratio, in other words, the ratio in which new infection enters different compartments. In the model in eq. 2.3 new infection can originate from $\frac{dS}{dt}$ and $\frac{dR}{dt}$ as these are what is called *non infection categories*. From $\frac{dS}{dt}$ infection is only generated by the term βSI, so we have $F_1 = \beta SI$. From $\frac{dR}{dt}$ no new infection is generated, so $F_2 = 0$. As compartments $\frac{dE}{dt}$ and $\frac{dI}{dt}$ are the ones that pass infection through the population, we consider these dimensions when constructing the F-matrix containing partial derivatives. F will then be

$$F = \begin{bmatrix} \frac{\delta F_1}{\delta E} & \frac{\delta F_1}{\delta I} \\ \\ \frac{\delta F_2}{\delta E} & \frac{\delta F_2}{\delta I} \end{bmatrix}$$

with respect to the disease-free equilibrium point. This point exists prior to infection entering the system, thus when $(S,E,I) = (1,0,0)$.
This makes:

$$F = \begin{bmatrix} 0 & \beta \\ \\ 0 & 0 \end{bmatrix}.$$

V is the ratio of which the infectious part of the population transfers from one compartment to another. For V we have $V_1 = (\mu + \sigma)E$, the transfer rate in E and $V_2 = -\sigma E + (\mu + \gamma)I$ which is the transfer rate in I. We can now calculate

$$V = \begin{bmatrix} \frac{\delta V_1}{\delta E} & \frac{\delta V_1}{\delta I} \\ \\ \frac{\delta V_2}{\delta E} & \frac{\delta V_2}{\delta I} \end{bmatrix} = \begin{bmatrix} \mu + \sigma & 0 \\ -\sigma & \mu + \gamma \end{bmatrix}.$$

Now we get V^{-1} and from this, finally FV^{-1}:

$$V^{-1} = \frac{1}{(\mu + \sigma)(\mu + \gamma)} \begin{bmatrix} \mu + \gamma & 0 \\ \sigma & \mu + \sigma \end{bmatrix}$$

$$FV^{-1} = \begin{bmatrix} \frac{\beta\sigma}{(\mu+\sigma)(\mu+\gamma)} & \frac{\beta(\mu+\sigma)}{(\mu+\sigma)(\mu+\gamma)} \\ 0 & 0 \end{bmatrix}$$

The spectral radius of a square matrix is the eigenvalue with largest absolute real value, which in this case gives us the following basic reproduction number:

$$R_0 = \frac{\beta\sigma}{(\mu+\sigma)(\mu+\gamma)} \tag{2.4}$$

[11], [12], [13].

SEIR-model including vaccines

In this thesis we developed a SEIR-model to be used on the Covid-19-pandemic. Several expansions and versions of the SIR-model were visited before we concluded on the model below:

$$\begin{aligned} \frac{dS}{dt} &= \mu - \beta SI(x(1-\varepsilon)+(1-x)) - x\varepsilon S - \mu S \\ \frac{dE}{dT} &= \beta SI(x(1-\varepsilon)+(1-x)) - \sigma E - \mu E \\ \frac{dI}{dt} &= \sigma E - \gamma I - \mu I \\ \frac{dR}{dt} &= \gamma I + xeS - \mu R \end{aligned} \tag{2.5}$$

Where as before μ, β, σ and γ represent the natural birth-/death rate, transmission rate, incubation rate and recovery rate, respectively. The two new parameters are x which is the vaccination rate, and ε which is the vaccine efficiency. The various stages of the development of this model is explained in Appendix A.

Using the next generation method on this model we get the following R_0:

$$R_0 = \frac{\beta\mu\sigma(1-x\varepsilon)}{(\gamma+\mu)(\sigma+\mu)(x\varepsilon+\mu)}.$$

To verify that this represents an appropriate R_0, we can set the vaccination rate to zero. We then get the same expression of R_0 as for the general SEIR-model, found in eq. 2.3, confirming potential legitimacy of our model.

2.1.3 Limitations and assumptions

A model of any phenomena is just that; a model. It is an attempt of representing natural occurrences as well as possible, but a model will never be completely accurate or predictive. As the purpose of this paper is partly to represent a model of the Covid-19 pandemic in a relatively understandable way a lot of assumptions and simplifications have been applied, making the model even less accurate and predictive. The model is still useful as an illustrative and descriptive tool, but a lot of other factors that affect the

actual situation have not been considered. The final results will hence most likely not reflect the actual current situation.
Below follows a short summary of several factors that have not been taken into considerations when developing the model of this paper:

- Quarantine and isolation: Quarantine and isolation are measures put in place to limit spread of infection. Quarantining restricts movement of exposed individuals as they wait to see if they are in fact infected, and isolation separates infected people from individuals who are not sick [14]. Both measures have been largely used all over the world during the Covid-19 pandemic, but are not included in our model. The result of this is that the spread of infection simulated by the model spreads much faster than it would in the real world. According to our model infected people would interact with susceptible people at the same rate as in usual everyday life, which largely is not the case. If so desired quarantine and isolation could be included by changing parameters, but we decided to not take it into consideration.

- Reinfection: Already prior to any notable variants of the Coronavirus, the topic of reinfection was discussed. Mainly immunity was assumed post undergone infection, but a handful of cases of reinfections had been reported as of December 2020 [15]. One specific case presented a middle-aged man with asymptomatic infection who after a period of testing negative got infected a second time which suggests a strong possibility of reinfection [15]. This paper's model does assume complete immunity after undergone infection. This leads to a simulation where the pandemic ends faster than it would in real life as the recovered-compartment would actually grow slower than it does in the model. This could be included in our model by adding a link from the recovered-compartment back to the susceptible-compartment, but we decided to leave it out for simplicity.

- Early vaccinations: As mentioned earlier, Norway was put under lockdown on March 12th 2020. From data provided by the Norwegian Institute of Public Health (FHI) and Pandemisenteret one can see that the first doses of the vaccine however were not administered until week 50 of 2020 when 8 doses were given. It was not before well into 2021 that mass-vaccination was underway. In our model vaccinations are administered from day 1, simulating earlier higher levels of immunity than were actually the case. This results in a simulation where more individuals count as recovered or immune earlier than in reality.

- Constant vaccination rate and efficacy: Our model assumes a constant vaccination rate. After prolonged periods of vaccination the unvaccinated part of the population would get smaller and consequently the vaccination rate would decrease. Another aspect of vaccination rate is vaccine hesitancy which also potentially limits the vaccination rate [16]. This leads to the recovered-compartment growing faster in the model than it would in real life as we assume a prolonged, high daily vaccine rate.
  The vaccine efficacy is also held constant in the model. In reality some studies have identified waning effectiveness within a time period following vaccination [17]. In the model it is assumed that a portion of vaccinated individuals gains

complete lasting immunity, when in reality vaccinated individuals would go back to being susceptible after the duration of the vaccines' effectiveness has passed.

- Several doses: In addition to assuming vaccines were already distributed from the beginning of the pandemic, the model also only takes one dose and the corresponding efficacy into consideration. In the real world several doses provide increased immunity in addition to this vaccines do not necessarily prevent infection, but protect against severe illness, hospitalization and death.

- Multiple strains: As the pandemic has progressed several variants of the Covid-19-virus have developed. These have among other things led to increased probability of reinfections by different variants, varying effectiveness of the vaccines and varying transmission rate [18]. The consequence of this is a pandemic that lasts for a longer time than what the model in this thesis displays. Because of all assumptions and simplifications made the model only goes through one wave of infection before it settles at an endemic equilibrium point, when in reality it will develop somewhat differently and several waves of infection occur.

- Parameters: The beta, β, used in this thesis assumes that every individual in the population interact with each other at the same rate. This is not the case, as people's living situation differs, geographical differences play a big role, people change their behaviour during difficult times, different occupations sometimes require people to interact with many/few people, etc. All of this play a role on the average transmission rate of the virus in society, but it is hard to include every sociocultural difference into one parameter. A similar characteristic goes for the other parameters as well, as individuals of e.g. varying age and health status might exhibit different rates of both incubation and recovery.

- Compartments: For simplicity reasons our model only contains four compartments; susceptible, exposed, infected, and recovered. It is possible however to include a multitude of various compartments describing the different states individuals can be in, depending on how complex and accurate of a model one seek to work with. [11] and [19] provide examples of more complex compartmental models developed for the Covid-19 pandemic.

2.2 A comment on the R_0-number

At this point, the only thing that has been mentioned about the R_0-number is a short introduction to the concept. However, while it may seem simple and practical to calculate a number that can act as an indicator of severity, R_0 is flawed [6] [20]. Initially the concept was introduced in demography to count offspring, but has since been adopted and adapted by epidemiology [6]. Numerous variations have been proposed. However these are not identical which makes the applicability of the concept challenging. Simply interpreting a given value of R_0 requires sublime understanding of the structures, inputs and interactions of the model used for generating the number [6]. Many researchers, let alone the general population, have no training when it comes to such complicated mathematical techniques, which inevitably increases the risk that R_0 is misinterpreted, misapplied and misrepresented [6].

There are several ways to calculate the R_0-number, such as e.g. *The Survival Function*, *The Jacobian*, *Constant term of the Characteristic Polynomial*, *The Next-Generation Method*, *The Graph-Theoretic Method* and *Existence of the Endemic Equilibrium*, and mostly these do not agree with each other. See Li et.al for a brief explanation of each [20].
Consequently the method one chooses to calculate the R_0-number for a given disease will give a different number than what a different method would. Only intricate knowledge of the method used would let oneself understand what the R_0-number really means.

2.2.1 Factors used in calculation

R_0 are often estimated based on three main factors: the duration of contagiousness, likelihood of infection per contact and contact rate, along other parameters [6]. The general situation related to a disease may also inspire a various range of parameters to include in the calculation of R_0. Because of this, the applicability of a disease is often strictly limited to the region it was calculated [6]. In addition to factors related to the disease itself, population density, social integration, even weather, will affect the contact rate, meaning that R_0 is not only a function of the biological characteristics of a pathogen but also of human behaviors [6]. This largely varies, e.g. studies have shown that more than 20 different values for R_0 was reported for measles across different periods and places [6].

2.2.2 Vaccines and the basic reproduction number

Vaccines have proven to be efficient when it comes to mitigating outbreaks by reducing the amount of people that is susceptible to a disease but does not directly affect the basic reproduction number [6]. This might seem contradictory but R_0 is a indication of contagiousness in a completely susceptible population, meaning that the R_0-number would not apply in an immune population. Vaccines reduces the value of the *effective reproductive number* that does not assume complete susceptibility in a population. If vaccines are used to mitigate outbreaks, the R_0-number is not a good metric to include [6].

2.2.3 Problems with R_0

The three main properties of the basic reproduction number are [20]:

- An endemic infection persists only if $R_0 > 1$.
- R_0 is a measure of the control efforts required to eliminate infection.
- Pathogens evolve to maximize their value of R_0.

However, as proved by Roberts [21], all of these properties can be false.
The first statement fails if there is a backwards bifurcation. This occurs when there exist

multiple stable equilibrium points even when $R_0 < 1$ [20]. The second property can fail because control measures differ between different groups of hosts in the population. R_0 is determined by averaging across all hosts of the pathogen, and as different control efforts are required among groups at different levels of risk R_0 does not describe a universal indicator of required efforts [20]. The third property can be false if there are two pathogens that coexist in a stable steady state, but their separate steady states are unstable. The order of which the pathogens establish in a population matters but the pathogen with the largest R_0-number will not necessarily exclude the other [20].

Why R_0 then?

R_0 has a big role in disease modelling but is indeed complicated [20]. As we have seen it almost never calculates consistently and does not even satisfy its most fundamental properties. Different diseases can't be compared unless the same method has been used. Even still, it is what we've got. The concept itself can be understood across several different modelling specialized fields, and terms regarding the calculation of the basic reproduction number has intuitive appeal [20]. What is needed is a simple, accurate measure that non-mathematicians can understand [20].

Interpretation of R_0

As mentioned earlier we used the Next Generation Method to calculate the basic reproduction number that characterize the pandemic simulated by our model [12]. This number was calculated to be:

$$R_0 = \frac{\beta\mu\sigma(1-x\varepsilon)}{(\gamma+\mu)(\sigma+\mu)(x\varepsilon+\mu)}.$$

In this case R_0 includes vaccination rate and efficacy which goes against the definition of R_0 as it includes a control measure that makes part of the population immune to the disease. As an R_0 describe how infectious a disease or virus is in a completely susceptible population, it will by definition no longer be applicable in this situation. We did however not ignore this fact when working on this thesis and started calculating the basic reproduction number. During our research we discovered several articles that implement the Next Generation Method and claim an R_0-number, see [11] and [22]. Confidently leaning on work already done we decided to move forward with the method.
At a later point, with a desire to keep true to the definition of R_0, which we have already seen is such a complicated metric, we do admit it is not directly relevant in this situation. However, R_0 and the Next Generation Method can aid in expressing R_{eff} and R_v which are other important epidemiological metrics.
R_{eff} is called the effective reproductive number and allows for including immunity in a population. This can be expressed as

$$R_{eff} = R_0 S,$$

where S is the susceptible portion of the population [22]. R_{eff} aids in categorizing the spread of disease in a partial susceptible population [22].
Using the Next Generation Method to calculate R_0 on a system including vaccines does

not truly find R_0, but rather what is called the *vaccination reproduction number*: R_v [12]. This number can in certain cases provide insight into how large portion of a population must be vaccinated in order to obtain herd immunity [12].
As we include vaccines in our model 2.5 we assume we obtain R_v through the Next Generation Method, and not the true R_0.

By abuse of notation we will continue to use the notation R_0 when referring to the reproduction number.

2.3 Analyzing Equilibrium Points and Stability

The equilibrium points of the model in eq. 2.5 is found by setting $\frac{dS}{dt} = \frac{dE}{dt} = \frac{dI}{dt} = \frac{dR}{dt} = 0$. As neither $\frac{dS}{dt}$, $\frac{dE}{dt}$ nor $\frac{dI}{dt}$ depend on R we can expand on equation 2.2 to get:

$$R = 1 - S - E - I,$$

where 1 is the normalized N and hence S, E, I and R represent proportions of the population belonging to the respective compartments. This allows us, without loss of generality, to only consider (S^*, E^*, I^*) when stating the equilibrium points. Our system has two equilibrium points:

$$(S_1^*, E_1^*, I_1^*) = \left(\frac{\mu}{x\varepsilon + \mu}, 0, 0\right)$$

and

$$(S_2^*, E_2^*, I_2^*) = \left(\frac{\mu}{R_0(x\varepsilon+\mu)}, \frac{(\gamma+\mu)(R_0-1)(x\varepsilon+\mu)}{\sigma\beta(1-x\varepsilon)}, \frac{(R_0-1)(x\varepsilon+\mu)}{\beta(1-x\varepsilon)}\right),$$

where

$$R_0 = \frac{\beta\mu\sigma(1-x\varepsilon)}{(\gamma+\mu)(\sigma+\mu)(x\varepsilon+\mu)}.$$

(S_1^*, E_1^*, I_1^*) represents a disease free environment of 2.5 as both $I_1^* = 0$ and $E_1^* = 0$, indicating that infection has not yet entered the system. As S_1^* includes vaccination parameters the model represents a situation where vaccination occurs in a disease free environment, which can be interpreted as a precautionary measure. R_1^* in this case is $\frac{x\varepsilon}{x\varepsilon+\mu}$.
As we consider a normalized population, $(0,0,0) \leq (S,E,I) \leq (1,1,1)$ must be true. As we study (S_2^*, E_2^*, I_2^*) we see that for this to hold R_0 must be > 1 and infection persists. Then, by definition (S_2^*, E_2^*, I_2^*) is an endemic equilibrium point.

Categorizing equilibrium points

In order to classify the disease free equilibrium point, (S_1^*, E_1^*, I_1^*), we do a linear analysis by constructing a Jacobian matrix:

$$\mathcal{J}(S_1^*, E_1^*, I_1^*) = \begin{bmatrix} -\mu - x\varepsilon & 0 & -\frac{\beta\mu}{x\varepsilon+\mu}(x(1-\varepsilon)+(1-x)) \\ 0 & -\sigma-\mu & \frac{\beta\mu}{x\varepsilon+\mu}(x(1-\varepsilon)+(1-x)) \\ 0 & \sigma & -\gamma-\mu \end{bmatrix}.$$

From this we get the characteristic polynomial:

$$p(\lambda) = det(J - \lambda I) = -(\mu + x\varepsilon + \lambda)\left((\mu + \sigma + \lambda)(\gamma + \mu + \lambda) - \frac{\beta\sigma\mu(1-x\varepsilon)}{\mu + x\varepsilon}\right).$$

From which we get three roots, $\lambda_1, \lambda_2, \lambda_3$:

$$\lambda_1 = -\mu - x\varepsilon.$$

λ_2 and λ_3 are the roots of $(\mu + \sigma + \lambda)(\gamma + \mu + \lambda) - \frac{\beta\sigma\mu(1-x\varepsilon)}{\mu + x\varepsilon}$,
which can be written as:

$$\lambda^2 + \lambda(\sigma + \gamma + 2\mu) + \sigma\mu + \sigma\gamma + \mu^2 + \mu\gamma - \frac{\sigma\beta\mu(1-x\varepsilon)}{x\varepsilon + \mu}.$$

Using Zabczyk's theorem [23] (see appendix A, section A.1.2, theorem iv.) we get the constants:

$$a = \sigma + \gamma + 2\mu > 0$$

and

$$b = \sigma\mu + \sigma\gamma + \mu^2 + \mu\gamma - \frac{\sigma\beta\mu(1-x\varepsilon)}{x\varepsilon + \mu}.$$

Using that $R_0 = \frac{\beta\mu\sigma(1-x\varepsilon)}{(\gamma+\mu)(\sigma+\mu)(x\varepsilon+\mu)}$, we can rewrite b as:

$$b = (\gamma + \mu)(\sigma + \mu) - R_0(\gamma + \mu)(\sigma + \mu) = (1 - R_0)(\gamma + \mu)(\sigma + \mu),$$

from which we get that R_0 must be < 1 for the polynomial to be stable.

The endemic equilibrium point S_2^*, E_2^*, I_2^* is:

$$\left(\frac{\mu}{R_0(x\varepsilon + \mu)}, \frac{(\gamma + \mu)(R_0 - 1)(x\varepsilon + \mu)}{\sigma\beta(1 - x\varepsilon)}, \frac{(R_0 - 1)(x\varepsilon + \mu)}{\beta(1 - x\varepsilon)}\right).$$

Which gives us the following Jacobi matrix:

$$\mathcal{J}(S_2^*, E_2^*, I_2^*) = \begin{bmatrix} -\mu - x\varepsilon - (R_0 - 1)(x\varepsilon + \mu) & 0 & -\frac{\beta\mu(1-x\varepsilon)}{R_0(x\varepsilon+\mu)} \\ (R_0 - 1)(x\varepsilon + \mu) & -\sigma - \mu & \frac{\beta\mu(1-x\varepsilon)}{R_0(x\varepsilon+\mu)} \\ 0 & \sigma & -\gamma - \mu \end{bmatrix}$$

With the characteristic equation

$$det(J - \lambda I) = [(1 - R_0)(x\varepsilon + \mu) - x\varepsilon - \mu - \lambda][(-\sigma - \mu - \lambda)(-\gamma - \mu - \lambda) - \frac{\sigma\beta\mu(1 - x\varepsilon)}{R_0(x\varepsilon + \mu)}]$$

$$+(1 - R_0)(x\varepsilon + \mu)\frac{\sigma\beta\mu(1 - x\varepsilon)}{R_0(x\varepsilon + \mu)} = 0.$$

We need the equation on the following form to be able to use Zabczyk's theorem (see Appendix A, section A.1.2, theorem iv.):

$$\lambda^3 + a\lambda^2 + b\lambda + c.$$

To get there, we need to do some substantial calculations. These are presented in more detail in appendix C. Following these calculations we are able to express $det(J-\lambda I)$ as such:

$$\lambda^3+\lambda^2(2\mu+\gamma+\sigma+R_0(x\varepsilon+\mu))$$
$$+\lambda(R_0(xe+\mu)(2\mu+\gamma+\sigma))+(R_0-1)(\gamma+\mu)(\sigma+\mu)(x\varepsilon+\mu)=0.$$

The following conditions must fulfilled:

$$a=2\mu+\gamma+\sigma+R_0(x\varepsilon+\mu)>0,$$

$$b=R_0(x\varepsilon+\mu)(2\mu+\gamma+\sigma)>0,$$
$$c=(R_0-1)(\gamma+\mu)(\sigma+\mu)(x\varepsilon+\mu)>0.$$

We see that a, b and c are all positive for $R_0>1$, but theorem iv. also require ab $>$ c. We get:

$$ab-c=(2\mu+\gamma+\sigma)(R_0(x\varepsilon+\mu)(2\mu+\gamma+\sigma))+R_0^2(x\varepsilon+\mu)^2(2\mu+\gamma+\sigma)$$
$$-(R_0-1)(\gamma+\mu)(\sigma+\mu)(x\varepsilon+\mu),$$

which can be rewritten as

$$R_0^2(x\varepsilon+\mu)(2\mu+\gamma+\sigma)+R_0(3\mu^2+3\mu\sigma+3\mu\gamma+\sigma^2+\sigma\gamma+\gamma^2)+\gamma\sigma+\gamma\mu+\mu\sigma+\mu^2$$

From which we see that $ab>c$. All conditions are fulfilled and we conclude that the endemic equilibrium point is stable for $R_0>1$.

Chapter 3

Numerical Results

In this chapter we explain how we obtained the desired parameter values. We also provide simulations run on the model in eq. 2.5 with parameters from different countries and compare the results.

Reaching out to FHI

Ultimately we wanted to run simulations using Norwegian parameter values. In order to do this we reached out to FHI [1] and Pandemisenteret [2] at UiB in Bergen to get as accurate estimates of the parameters included in the model as possible. The following was requested:

- β: the product of contact rate and transmissibility. We realize these values have varied throughout the pandemic but we would like an estimate from early on in the pandemic before intrusive measures were put in place.
- σ: describes the incubation period. We would like the average incubation period of the virus.
- γ: describes how long an individual is infectious for.
- x: describes the rate of vaccination. What proportion of the population gets vaccinated daily (estimated from the time of mass vaccination)?
- ε: describes the efficacy of the vaccine. We treat efficacy as the percentage of the vaccinated individuals that is considered immune to the virus (estimate from early on in the vaccination process).

Using numbers provided by reports done by FHI [3] we get $\sigma = 0.25$ and $\gamma = 0.157$. Using raw data provided by FHI of how many have received their first vaccination dose each week since the beginning of vaccination, we calculate x to be 0.002. We arrived at

[1] FHI Webpage: https://www.fhi.no/en/

[2] Pandemic Center Webpage: https://www.uib.no/en/pandemic

[3] 2020.05.04 Corona Report used for parameters σ and γ: https://www.fhi.no/en/id/infectious-diseases/coronavirus/coronavirus-modelling-at-the-niph-fhi/

this by averaging the number of weekly vaccinated individuals through the entire vaccination period, but excluding the earlier weeks as a negligible number of vaccines were distributed at that time. From Polack's research on vaccine safety and efficacy, we get $\varepsilon = 0.52$ [24]. Birth- and death rate, μ, was determined by first dividing the number of births in Norway in 2021 by 365 days [25]. The resulting number was again divided by Norway's total population as of January 1st 2022 [26]. All of this is listed in table 3.1:

Table 3.1: Norwegian parameter values gathered from various sources.

σ: 0.25 per day
γ: 0.157 per day
x: 0.002 per day
ε: 0.52
μ: 2.829×10^{-5}

Still, a few parameters were lacking for us to run a simulation. While working to obtain these we continued to explore data found from other parts of the world.

3.1 USA

We study parameter values from Wintachai & Prathom's paper on stability analysis done in USA and India [27]. As that paper uses different parameter values to describe birth- and death rate and our model assumes they are the same we will only be using their estimate of birth rate. In that paper $E(0)$ and $I(0)$ are combined into one number when identifying initial values. In our simulation we divide this number by 2 to obtain separate initial values. The paper does not include values of vaccination rate and vaccine efficacy, x and ε, so we use the values listed in table 3.1.
Combining this we get the parameter values for USA collected in table 3.2.

Table 3.2: Parameter Values from USA.

Transmission rate	β	0.462
Recovery rate	γ	0.0696 per day
Incubation rate	σ	0.0870 per day
Birth-/ death rate	μ	3.178×10^{-5} per day
Vaccine rate	x	0.002 per day
Vaccine efficacy	ε	0.52
Initial values	S0, E0+I0, R0	0.97286, 0.00905, 0.01809

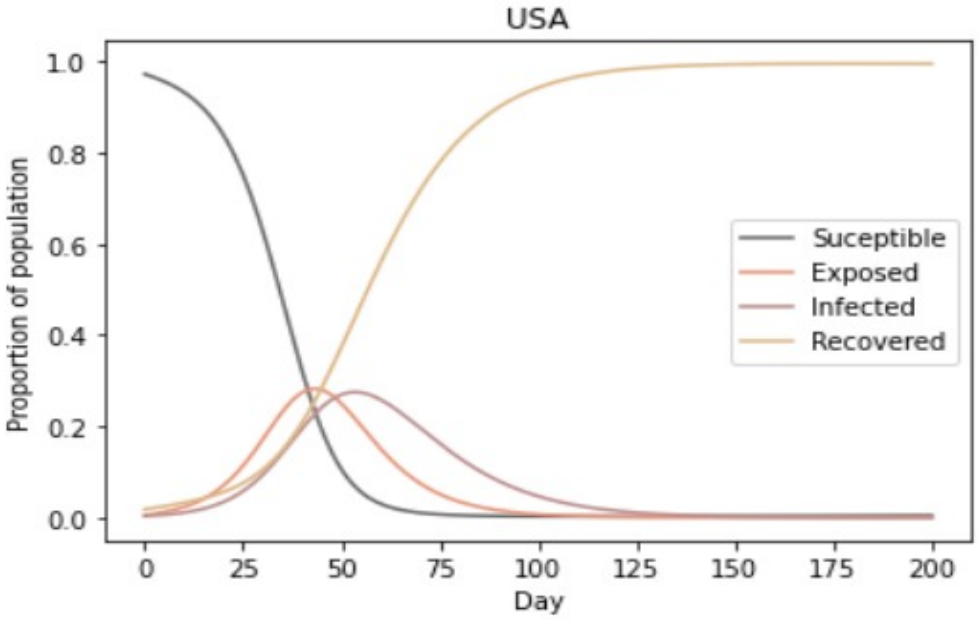


Figure 3.1: Simulation using data from USA, table 3.2.

Running a simulation of the model with the values from USA in table 3.2 we get the graphs in figure 3.1. Peak of infection occurs on day 53 with 27.5% of the population being infected at the same time.

3.2 India

We still look to Wintachai's paper and its parameter values identified for the situation in India [27]. Using these as well as x and ε from table 3.1 we get the values presented in table 3.3.

Table 3.3: Parameter Values from India.

Transmission rate	β	0.32
Recovery rate	γ	0.0686 per day
Incubation rate	σ	0.0870 per day
Birth-/ death rate	μ	4.893×10^{-5} per day
Vaccine rate	x	0.002 per day
Vaccine efficacy	ε	0.52
Initial values	S0, E0+I0, R0	0.994, 3.813×10^{-4}, 5.569×10^{-3}

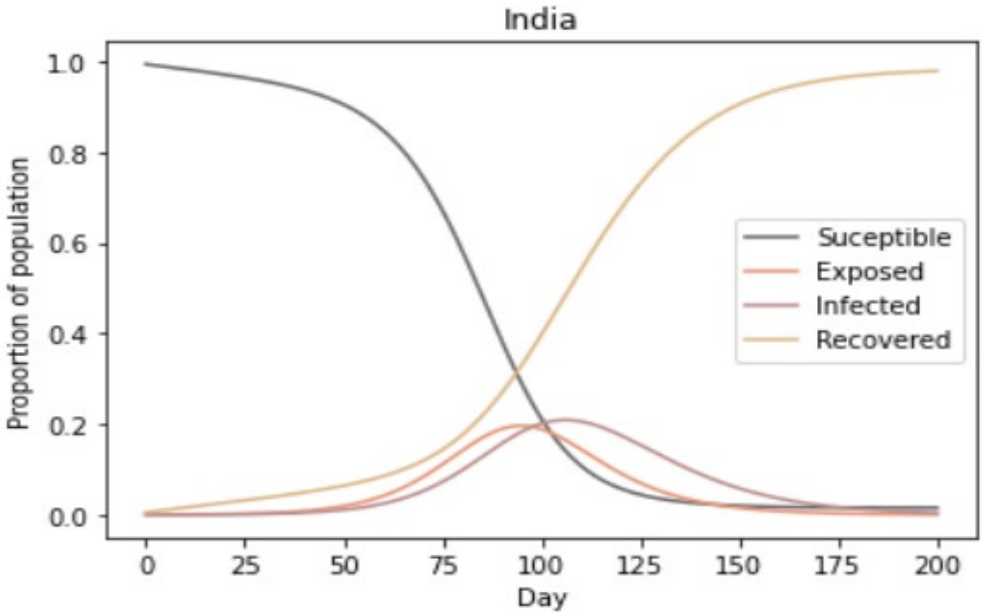


Figure 3.2: Simulation using data from India, table tab 3.3.

Running a simulation of the model with the values from India in table 3.3 we get figure 3.2. Here the peak of infection occurs on day 106 with 20.9% of the population being infected at the same time. Comparing the graphs from figure 3.1 and 3.2, we clearly see a difference in when the peak of infection occurs and how extensive it is.

The main difference between the data from USA and India are the respective values of the parameter β and the initial values. Running test-simulations where only the initial values are exchanged we can conclude that the results are sensitive to both β and the initial values as this leads to changes in both height and time of the peak of infection, see figure 3.3.

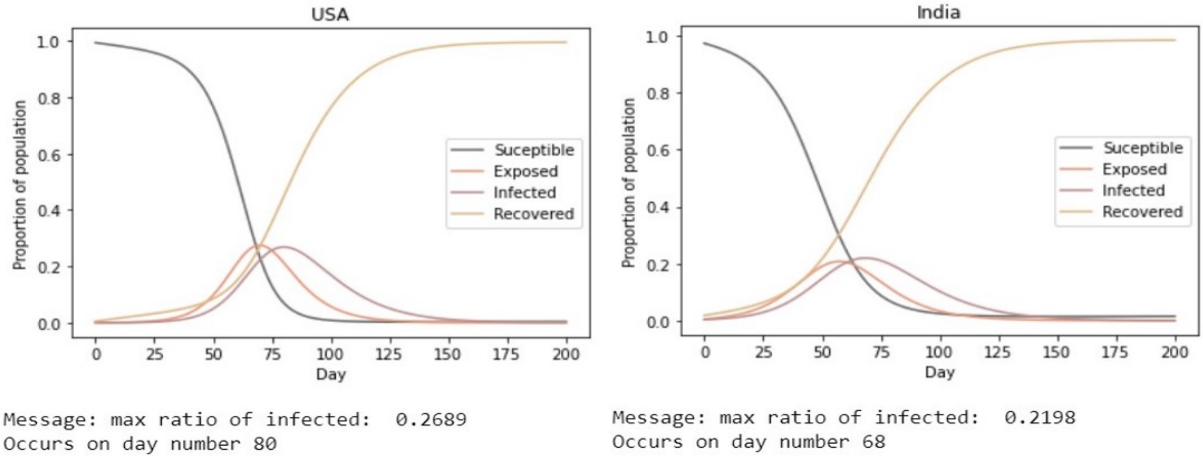


Figure 3.3: Initial conditions in table 3.2 and 3.3 exchanged.

3.3 Norway

Now we want to run a simulation using the parameters from Norway. As we were unable to obtain specifically Norwegian values for every parameter, we use the same β and initial values as in table 3.3. All parameters used when running a simulation from Norway are presented in the table below.

Table 3.4: Norwegian parameter values gathered from various sources.

Transmission rate	β	0.32
Recovery rate	γ	0.157 per day
Incubation rate	σ	0.25 per day
Birth-/ death rate	μ	2.829×10^{-5} per day
Vaccine rate	x	0.002 per day
Vaccine efficacy	ε	0.52
Initial values	S0, E0+I0, R0	0.994, 3.813×10^{-4}, 5.569×10^{-3}

This lets us run the following simulation:

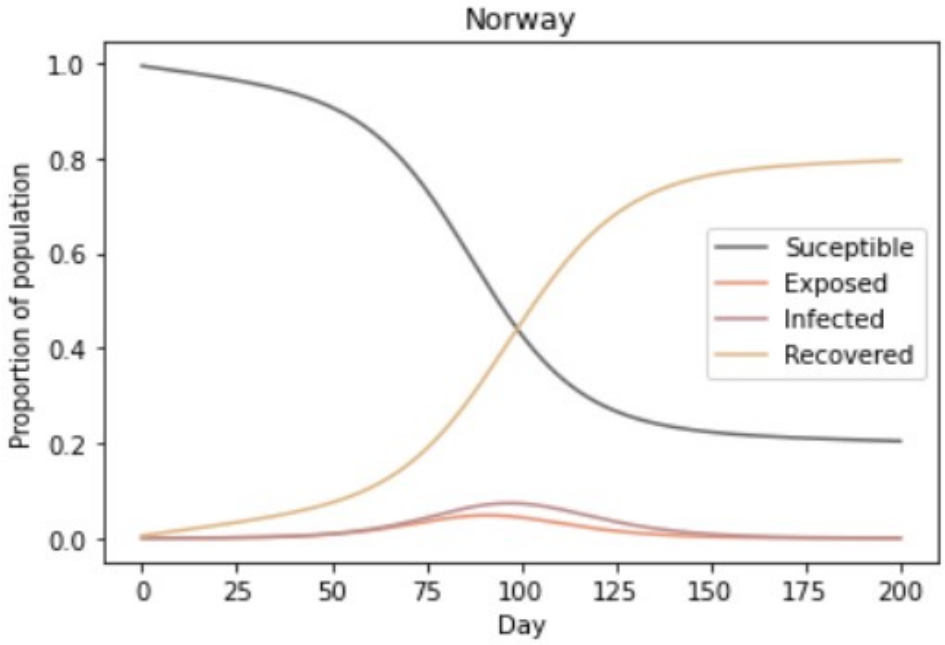


Figure 3.4: Simulation using data from Norway, table 3.4.

In this simulation the peak of infection occurs on day 97 with 7.39% of the population being infected. This is much lower than what we saw in simulations using parameters from USA and India. We see significant differences between the parameters γ and σ as the Norwegian values for these are much higher. With large values of γ and σ individuals would move from exposed to infected and from infected to removed rather quickly. This can lead to a situation where exposed individuals get infected and then recover before they have had much time to spread the disease. As we see in the simulation in figure 3.4 a large portion of the population end up in the recovered-compartment, either through infection or vaccination, without the peak of infection ever getting as high

as high as the simulations done for USA and India.
This is not how reality looked in Norway where peak of infection occurred around 2 years after the first case of Covid was confirmed and as of May 24th 2022 more than 1.4 million cases of Covid have been reported in Norway [28].
This substantial inaccuracy is due to the many limitations of this model, some of which are presented in section 2.1.3.

Chapter 4

Time delay

4.1 DDE

In recent times time delay have been included in epidemic models, mainly to account for latent periods [29]. Several articles focus on the time between exposure and becoming infectious, often called the incubation time [29] [30] [31]. By including a time delay in the term that represents people getting infected, they make the model more realistic by preventing those who get exposed from instantaneously moving to the infectious category [29]. An interesting effect of the time delay is that it can change the qualitative behavior of the model e.g. destabilize an equilibrium point [29].
When adding a time delay τ to a ordinary differential equation (ODE) it becomes a delayed differential equation (DDE). The difference between them is that the derivatives of the DDE for any time t, depends on the solution at prior times [32]. Because of that, to solve a DDE we need to define how the dynamical system behaves when $t - \tau < t_0$, with t_0 being the starting time of the system. To describe the behavior of the system in the interval before t_0 an initial history function is used to specify the values of the solution set at that interval [32]. It is important to note that the time delay is not necessarily constant, but can also be state-dependant [32]. A DDE with constant time delay look like this:

$$\frac{d\mathbf{x}}{dt} = \mathbf{f}(\mathbf{x}(t), \mathbf{x}(t-\tau_1), \mathbf{x}(t-\tau_2), ..., \mathbf{x}(t-\tau_n)), \tag{4.1}$$

where $\mathbf{x} \in \mathbb{R}^n$ and the delays τ_i are positive constants [32].

The method to determine the stability of equilibrium points of DDEs is similarly to the one for ODEs, we can look at the characteristic equation of the equilibrium point [32]. For a DDE on the form of equation (4.1) the characteristic equation is given by

$$|\mathbf{J}_0 + e^{-\lambda\tau_1}\mathbf{J}_{\tau_1} + ... + e^{-\lambda\tau_n}\mathbf{J}_{\tau_n} - \lambda\mathbf{I}| = 0, \tag{4.2}$$

where λ is an eigenvalue of the Jacobian matrix and J_{τ_i} is the Jacobian matrix of the corresponding $\mathbf{x}(t-\tau_i)$ [32]. Expanding out the determinant leads to polynomials which include some terms in $e^{-\lambda\tau_i}$ and these are called quasi-polynomials [32]. An example of a polynomial on this form that might be easier to understand is:

$$\lambda^3 + p_1\lambda^2 + p_2\lambda + p3 + (q_1\lambda^2 + q_2\lambda + q_3)e^{-\lambda\tau} = 0. \tag{4.3}$$

In the same way as with ODEs, the critical point is stable if all solutions of equation (4.1) have negative real part, otherwise it is unstable or in some cases non-hyperbolic [32]. Equations with quasi-polynomials commonly have infinitely many roots in the complex plane, which often makes it impossible to find all the roots [33]. Even with infinite roots it is usually possible to classify a equilibrium point analytically [33]. A way to classify the equilibrium points of a equation on the form of 4.2 is presented by Tipsri and Chinviriyasit in the article "The effect of time delay on the dynamics of an SEIR model with nonlinear incidence" [29]. Through five lemmas they show a way to check the stability of the equilibrium points. I will present a summary of the parts needed for this thesis, for a better overview and proofs, see [29].

Lemma 1 *For a equation on the form of 4.2, for all τ, all roots have no positive real parts, if $p_i > 0$, i=1,2,3 and $p_1p_2 - p_3 > 0$ [29].*

It is not enough to show that the roots have no positive real parts, since they can still be purely imaginary. Therefore $\lambda = i\omega(\lambda > 0)$ must be investigated.
$\lambda = i\omega, (\omega > 0)$ is a root of 4.2 if and only if ω satisfies

$$-\omega^3 i - p_1\omega^2 + p_2 i\omega + p_3 + (-q_1\omega^2 + q_2 i\omega + q_3)(cos\omega\tau - isin\omega\tau) = 0. \quad (4.4)$$

Separating the real and the imaginary parts, then squaring and adding them together we get

$$z^3 + pz^2 + qz + r = 0 \quad (4.5)$$

where $z = \omega^2$, $p = p_1^2 - 2p_2 - q_1^2$, $q = p_2^2 - 2p_1p_3 + 2q_1q_3 - q_2^2$ and $r = p_3^2 - q_3^2$.
From here we can look at another relevant lemma from the article.

Lemma 2 *For a equation on the form 4.2 with $p_i > 0$, i=1,2,3 and $p_1p_2 - p_3 > 0$, the following results are claimed:*
a) all roots of 4.2 have negative real parts for $\tau \geq 0$ if

$$r \geq 0, \;\; p \geq 0 \;\; and \;\; q > 0$$

or

$$r \geq 0 \;\; and \;\; p^2 - 3q \leq 0$$

b) all roots of 4.2 have negative real parts for some positive value τ if

$$r < 0$$

[29].

As mentioned earlier, the critical point is stable if all solutions of the equation have negative real part. This result will be used later in this chapter.

4.2 Reason for using time delay and the model change

After getting the first dose of the COVID-19 vaccine, it is estimated that it takes between 12 and 21 days to become well protected against serious illness from the disease

[34] [24]. To take that into account, a time delay is added to the successful vaccination term $S(t)x\varepsilon$. Then the model becomes:

$$\begin{aligned} \frac{dS}{dt} &= \mu - \beta S(t)I(t)(1-x\varepsilon) - x\varepsilon S(t-\tau) - \mu S(t) \\ \frac{dE}{dT} &= \beta S(t)I(t)(1-x\varepsilon) - \sigma E(t) - \mu E(t) \\ \frac{dI}{dt} &= \sigma E(t) - \gamma I(t) - \mu I(t) \\ \frac{dR}{dt} &= \gamma I(t) + x\varepsilon S(t-\tau) - \mu R(t) \end{aligned} \tag{4.6}$$

In both $\frac{dS}{dt}$ and $\frac{dR}{dt}$ we now have $S(t-\tau)$, which makes it so that the ones who are successfully vaccinated at time t, are only moved from S to R after a time t + τ.

The equilibrium points of the new system is the same as for the system with zero delay. This is because by definition, all nearby trajectories will approach the stable equilibrium point asymptotically as $t- > \infty$, so the delay will not have an affect on the equilibrium points [29]. In the same way as in chapter 2, $\frac{dR}{dt}$ can be ignored when looking at stability since R=1-S-E-I.

4.3 Analysis of the time delay model

4.3.1 Disease free equilibrium point

As we found earlier the disease free equilibrium point is:

$$(S_1^*, E_1^*, I_1^*) = \left(\frac{\mu}{x\varepsilon+\mu}, 0, 0\right)$$

Notice that if we set $x = 0$, we get $S = 1$ which makes sense since without any infectious people in the population, no one gets exposed. As mentioned in chapter 2, $R_1^* = \frac{x\varepsilon}{x\varepsilon+\mu}$, so the only movement between compartments at this point is from S to R through successful vaccination. With this equilibrium point we get the following Jacobian matrix:

$$\mathcal{J}(S_1^*, E_1^*, I_1^*) = \begin{bmatrix} -\mu - e^{-\lambda\tau}x\varepsilon & 0 & -\frac{\beta\mu}{x\varepsilon+\mu}(1-x\varepsilon) \\ 0 & -\sigma-\mu & \frac{\beta\mu}{x\varepsilon+\mu}(1-x\varepsilon) \\ 0 & \sigma & -\gamma-\mu \end{bmatrix}.$$

From the Jacobi matrix we can find the characteristic equation:

$$p(\lambda) = (-\mu - e^{-\lambda\tau}x\varepsilon - \lambda)$$

$$\left((-\mu-\sigma-\lambda)(-\gamma-\mu-\lambda) - \frac{\beta\sigma\mu(1-x\varepsilon)}{\mu+x\varepsilon}\right) = 0$$

Since $R_0 = \frac{\beta\mu\sigma(1-x\varepsilon)}{(\gamma+\mu)(\sigma+\mu)(x\varepsilon+\mu)}$ we can write $\frac{\beta\mu\sigma(1-x\varepsilon)}{(x\varepsilon+\mu)} = R_0(\gamma+\mu)(\sigma+\mu)$, and with some work we get:

$$p(\lambda) = \lambda^3 + \lambda^2(3\mu+\sigma+\gamma)$$

$$+\lambda(\sigma\mu+\mu\gamma+\mu^2+(1-R_0)(\gamma+\mu)(\sigma+\mu))+(1-R_0)\mu(\gamma+\mu)(\sigma+\mu)$$
$$+[x\varepsilon\lambda^2+x\varepsilon(2\mu+\sigma+\gamma)\lambda+(1-R_0)(\gamma+\mu)(\sigma+\mu)]e^{-\lambda\tau}=0$$

We want to use Lemma 2 by Tipsri and Chinviriyasit [29]. To use it we first need to have the equation on the same form as equation (4.2). Rewriting the characteristic equation we get

$$\lambda^3+p_1\lambda^2+p_2\lambda+p3+(q_1\lambda^2+q_2\lambda)e^{-\lambda\tau}=0,$$

where

$$p_1=3\mu+\sigma+\gamma,$$
$$p_2=\sigma\mu+\mu\gamma+\mu^2+(1-R_0)(\gamma+\mu)(\sigma+\mu),$$
$$p_3=(1-R_0)\mu(\gamma+\mu)(\sigma+\mu),$$
$$q_1=x\varepsilon,$$
$$q_2=x\varepsilon(2\mu+\sigma+\gamma),$$
$$q_3=(1-R_0)(\gamma+\mu)(\sigma+\mu).$$

To use Lemma 2 we need to show that $p_i>0$, i=1,2,3 and $p_1p_2-p_3>0$. p_1, p_2 and p_3 are all clearly positive for $R_0<1$. In the case of $p_1p_2-p_3$, we get

$$p_1p_2-p_3=(3\mu+\sigma+\gamma)(\sigma\mu+\mu\gamma+\mu^2)+(1-R_0)(\gamma+\mu)(\sigma+\mu)(2\mu+\sigma+\mu)$$

Which is also positive for $R_0<1$. With the requirements satisfied, we want to look at the values of r, p and q from equation (4.5). If we now can show that $r\geq 0,\ \ p\geq 0\ \ and\ \ q>0$, then the equilibrium point is stable. We start with r:

$$r=p_3^2-q_3^2=(1-R_0)^2(\gamma+\mu)^2(\sigma+\mu)^2(\mu^2-1)$$

Since we are working with a normalized system, where 1 is the whole population, μ the parameter for birth- and death rate will never be 1 or higher in any realistic scenario. Therefore we conclude that $r<0$. By Lemma 2 the roots of the characteristic equation have negative real parts for some positive value τ. This makes the disease free equilibrium point conditionally stable [29].

4.3.2 Endemic equilibrium point

As we found earlier, the endemic equilibrium point is

$$(S_2^*,E_2^*,I_2^*)=\left(\frac{\mu}{R_0(x\varepsilon+\mu)},\frac{(\gamma+\mu)(R_0-1)(x\varepsilon+\mu)}{\sigma\beta(1-x\varepsilon)},\frac{(R_0-1)(x\varepsilon+\mu)}{\beta(1-x\varepsilon)}\right).$$

Which gives us the following Jacobi matrix

$$\mathcal{J}(S_2^*,E_2^*,I_2^*)=\begin{bmatrix}-\mu-e^{-\lambda\tau}x\varepsilon-(R_0-1)(x\varepsilon+\mu) & 0 & -\frac{\beta\mu(1-x\varepsilon)}{R_0(x\varepsilon+\mu)}\\ (R_0-1)(x\varepsilon+\mu) & -\sigma-\mu & \frac{\beta\mu(1-x\varepsilon)}{R_0(x\varepsilon+\mu)}\\ 0 & \sigma & -\gamma-\mu\end{bmatrix}.$$

With the characteristic equation

$$-\lambda^3-\lambda^2(-(1-R_0)(x\varepsilon+\mu)+e^{-\lambda\tau}x\varepsilon+3\mu+\sigma+\gamma)$$

$$-\lambda[-(2\mu+\sigma+\gamma)(1-R_0)(x\varepsilon+\mu)+(2\mu+\sigma+\gamma)(e^{-\lambda\tau}x\varepsilon+\mu)+$$

$$(\gamma+\mu)(\sigma+\mu)-\frac{\sigma\beta\mu(1-x\varepsilon)}{R_0(x\varepsilon+\mu)}]$$

$$+(1-R_0)(x\varepsilon+\mu)(\gamma+\mu)(\sigma+\mu)-(e^{-\lambda\tau}x\varepsilon+\mu)(\gamma+\mu)(\sigma+\mu)+$$

$$(e^{-\lambda\tau}x\varepsilon+\mu)\frac{\sigma\beta\mu(1-x\varepsilon)}{R_0(x\varepsilon+\mu)}=0$$

Since $R_0=\frac{\beta\mu\sigma(1-x\varepsilon)}{(\gamma+\mu)(\sigma+\mu)(x\varepsilon+\mu)}$ we can write $\frac{\beta\mu\sigma(1-x\varepsilon)}{R_0(x\varepsilon+\mu)}=(\gamma+\mu)(\sigma+\mu)$. Using that and multiplying with -1 we get

$$\lambda^3+\lambda^2[e^{-\lambda\tau}x\varepsilon+3\mu+\sigma+\gamma-(1-R_0)(x\varepsilon+\mu)]+$$

$$\lambda[(2\mu+\sigma\gamma)(e^{-\lambda\tau}x\varepsilon+\mu)-(2\mu+\sigma+\gamma)(1-R_0)(x\varepsilon+\mu)]$$
$$-(1-R_0)(x\varepsilon+\mu)(\gamma+\mu)(\sigma+\mu).$$

Setting $\tau=0$ we get the same characteristic equation as for the no delay model. Then the endemic equilibrium point is locally asymptotically stable as showed in chapter 2. For $\tau>0$ we want to again use Lemma 2 by Tipsri and Chinviriyasit [29]. To use it we first need to have the equation on the same form as equation (4.2). Rewriting the characteristic equation we get

$$\lambda^3+p_1\lambda^2+p_2\lambda+p3+(q_1\lambda^2+q_2\lambda)e^{-\lambda\tau}=0,$$

where

$$p_1=3\mu+\sigma+\gamma+(R_0-1)(x\varepsilon+\mu),$$
$$p_2=(2\mu+\sigma\gamma)(\mu+(R_0-1)(x\varepsilon+\mu)),$$
$$p_3=(R_0-1)(x\varepsilon+\mu)(\gamma+\mu)(\sigma+\mu),$$
$$q_1=x\varepsilon,$$
$$q_2=x\varepsilon(2\mu+\sigma+\gamma).$$

We need to satisfy the conditions for using Lemma 2, namely that $p_i>0$, i=1,2,3 and $p_1p_2-p_3>0$. p_1, p_2 and p_3 are all clearly positive for $R_0>1$. In the case of $p_1p_2-p_3$, we get

$$(6\mu^2+5\mu\sigma+5\mu\gamma+\sigma\gamma+\gamma^2+\sigma^2)(R_0-1)(x\varepsilon+\mu)+\mu\sigma\gamma+(2\mu+\sigma+\gamma)(R_0-1)^2(x\varepsilon+\mu)^2,$$

which again clearly is positive for $R_0>1$. With the requirements satisfied, we want to look at the values of r, p and q from equation (4.5). If we now can show that $r\geq 0,\ p\geq 0\ \textit{and}\ q>0$, then the equilibrium point is stable. We start with the easiest, namely r.

$$r=p_3^2-q_3^2$$

Since $q_3 = 0$ in our case, $r \geq = 0$.
Moving on to p we have

$$p = p_1^2 - 2p_2 - q_1^2.$$

Setting in for p_1,p_2 and q_1 we get

$$p = (3\mu + \sigma + \gamma + (R_0 - 1)(x\varepsilon + \mu))^2 - 2[(2\mu + \sigma + \gamma)(\mu + (R_0 - 1)(x\varepsilon + \mu))] - (x\varepsilon)^2.$$

With some work this can be proven to be non negative. Now we only need

$$q = p_2^2 - 2p_1p_3 - q_2^2 > 0.$$

Setting in for p_1,p_2,p_3 and q_2 we get

$$\begin{gathered} q = [(2\mu + \sigma + \gamma)(\mu + (R_0 - 1)(x\varepsilon + \mu))]^2 \\ -2[3\mu + \sigma + \gamma + (R_0 - 1)(x\varepsilon + \mu)](R_0 - 1)(x\varepsilon + \mu)(\gamma + \mu)(\sigma + \mu) \\ -(x\varepsilon)^2(2\mu + \sigma + \gamma)^2 \\ = (2\mu + \sigma + \gamma)^2[\mu^2 + 2\mu(R_0 - 1)(x\varepsilon + \mu) + (R_0 - 1)^2(x\varepsilon + \mu)^2] \\ -(6\mu + 2\sigma + 2\gamma)(R_0 - 1)(x\varepsilon + \mu)(\sigma\gamma + \mu\gamma + \mu\sigma + \mu^2) \\ -(x\varepsilon)^2(2\mu + \sigma + \gamma)^2. \end{gathered}$$

The equation ends up becoming very tedious and difficult to say anything about, the alternative $p^2 - 3q$ even more so. Without the last requirement in place we cant prove that all the roots have negative real value, but Lemma 1 gives us that the roots does not have any positive real roots. That means that the roots either have a negative real value or they are purely imaginary. A purely imaginary root in a linear system means we have stable center at the equilibrium point. So the endemic equilibrium point is stable in the linearized system. The problem is that the non-linear system could still be unstable, since the stable center could change when the system goes back to non-linear.

4.4 Endemic equilibrium point stability using specific parameter values

Since it was problematic to prove stability for the endemic equilibrium point of the delayed SEIR-model in a general way, I will now look at specific cases using the parameter values from USA, India and Norway. From all the graphs later on in section 5.2 we can clearly see that with the given data R_0 should be greater than 1 and we should end up with a stable endemic equilibrium point. To show stability, I will continue the attempt in using Lemma 2 from the article by Tipsri and Chinviriyasit (2015) [29]. p_1, p_2, p_3, r and p have all been shown theoretically to be non negative for all non negative parameter values and $R_0 > 1$, so the focus will be on testing for $q > 0$ and the alternative $p^2 - 3q \leq 0$.

Let us start with the values from USA in table (3.2). If we insert those values into

$$q = [(2\mu + \sigma + \gamma)(\mu + (R_0 - 1)(x\varepsilon + \mu))]^2$$

$$-2[3\mu+\sigma+\gamma+(R_0-1)(x\varepsilon+\mu)](R_0-1)(x\varepsilon+\mu)(\gamma+\mu)(\sigma+\mu)$$
$$-(x\varepsilon)^2(2\mu+\sigma+\gamma)^2,$$

we get $q = 3.22 * 10^{-5}$. The result shows that $q > 0$, but before we can celebrate we need to check that R_0 actually is greater then 1 with these values. As a reminder

$$R_0 = \frac{\beta\mu\sigma(1-x\varepsilon)}{(\gamma+\mu)(\sigma+\mu)(x\varepsilon+\mu)}.$$

Here we get that $R_0 = 0.199$ which is by far lower then the limit 1. With $R_0 < 1$ the endemic equilibrium point

$$\left(\frac{\mu}{R_0(x\varepsilon+\mu)}, \frac{(\gamma+\mu)(R_0-1)(x\varepsilon+\mu)}{\sigma\beta(1-x\varepsilon)}, \frac{(R_0-1)(x\varepsilon+\mu)}{\beta(1-x\varepsilon)}\right)$$

have negative values for E and I which makes the point non-existing. The same problem shows up using data from India in table(3.3) and from Norway in table(3.1) with R_0 values of 0.209 and 0.0539 respectively. Based on the discussion around the reproduction number we had in chapter 2, we should not have an pandemic outbreak with these values, but based on the simulation we clearly do. Another strange fact is that India have a higher R_0 value then USA, but in the simulations USA have a much faster way to the peak and a higher peak overall which should indicate a higher reproduction number. As mentioned in chapter 2 there is many ways to calculate the reproduction number and there are several versions of the reproduction number e.g. R_0, R_v and R_{eff}. Based on the vast differences between the theoretical analysis and the numerical simulations, something seems off with the reproduction number used in this thesis.

Giving the lemma another chance we insert values for the parameters into the equation for q, but keep R_0 as a variable and solve for R_0. For q to be positive we need R_0 values as presented in the table below.

Table 4.1: R_0 values needed for q to be positive

Data from	R_0 value needed
USA	$R_0 < 0.987$ or $R_0 > 142.138$
India	$R_0 < 0.987$ or $R_0 > 139.900$
Norway	$R_0 < 0.995$ or $R_0 > 344.159$

From table 4.1 we see that R_0 either needs to be below the threshold 1 or absurdly high. Again the results seems off and the strategy with using specific parameter values did not give us any more information.

Chapter 5

Numerical results with different types of delay

With the parameter values from USA, India and Norway available we can run some simulations to see the behavior of both the regular no delay model in eq.2.5 and the delayed model in eq.4.6. Using Matlab I will look at two simulations, one with a delay in vaccination start on the regular model, and one with different values for τ in the delayed model, to see how much of an impact those delays have on the infection peak I_{max}.

5.1 Delayed vaccination start

In this section we will look at the difference between having the vaccine ready immediately, and at a later time. By running the no delay model with data from various countries with different parameter values, and setting the vaccination rate x to zero for the first days, we can see how the threshold for when it is too late for the vaccination to start and still have an effect, changes. Each graph will contain 3 curves; infection with vaccine ready immediately, infection with vaccine ready at a later stage, and infection with no vaccine available.

5.1.1 USA data

Using the USA data from table 3.2 we get the following graphs

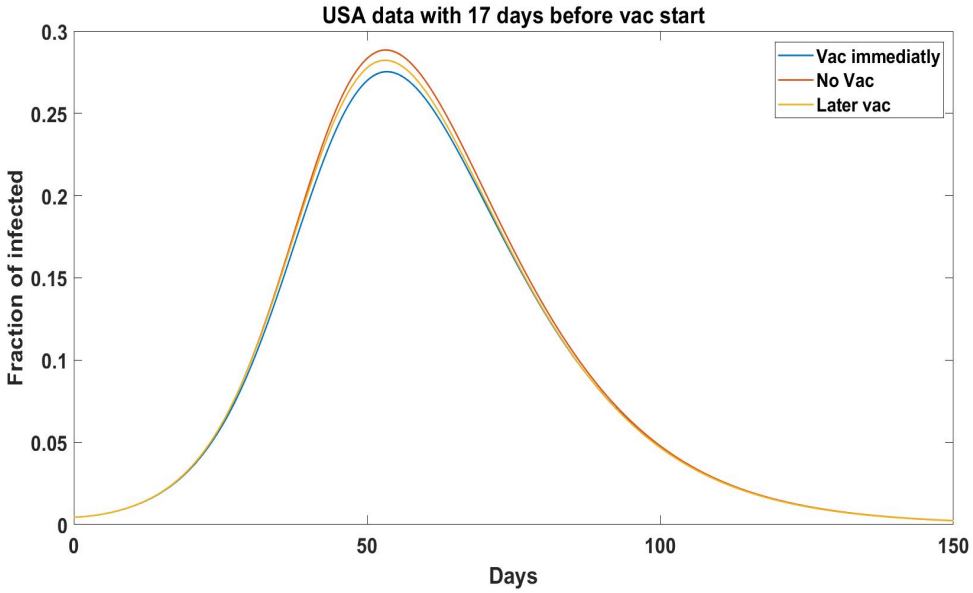


Figure 5.1: USA data, table3.2, with vaccination starting after 17 days

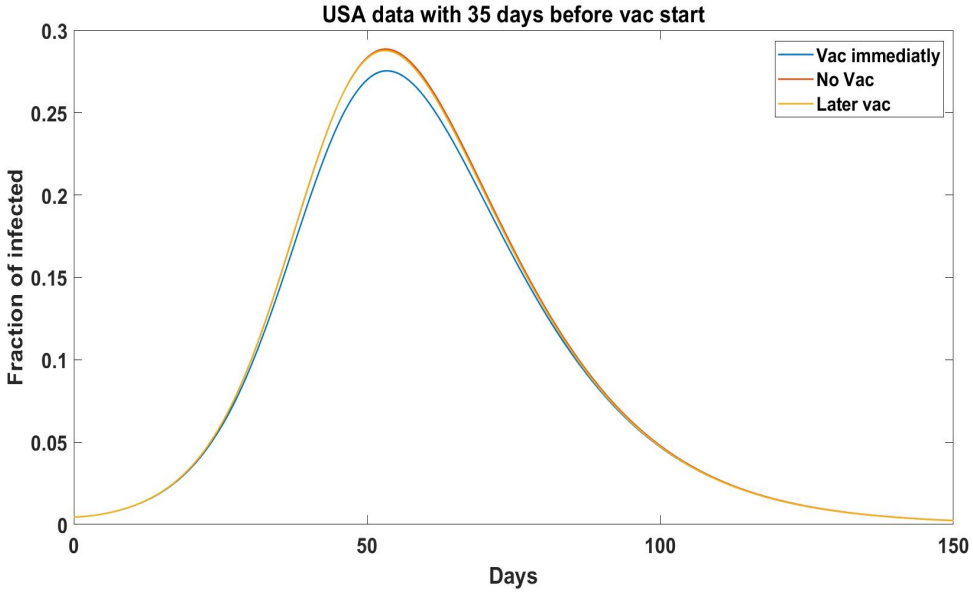


Figure 5.2: USA data, table3.2, with vaccination starting after 35 days

We can see from figure 5.1 and 5.2 that the effect of vaccination to lower the peak of the infection loses half of its value after only 17 days and almost all value after 35 days.
Both the time limit and the height of I_{max} might seem extreme, but we have to take into consideration that in this model, with these parameters, there is no mandatory quarantine, no social distancing, and people are continuously infectious for 14 days. So the values might be plausible and show a scenario of what could have happened if the only countermeasure to the pandemic was 1 dose of vaccination.

5.1.2 India data

The data from India, given in table 3.3 have both a lower transmission rate and fewer infectious at the start then the data from USA. This gives the vaccination program more time to work with, as seen in the simulations.

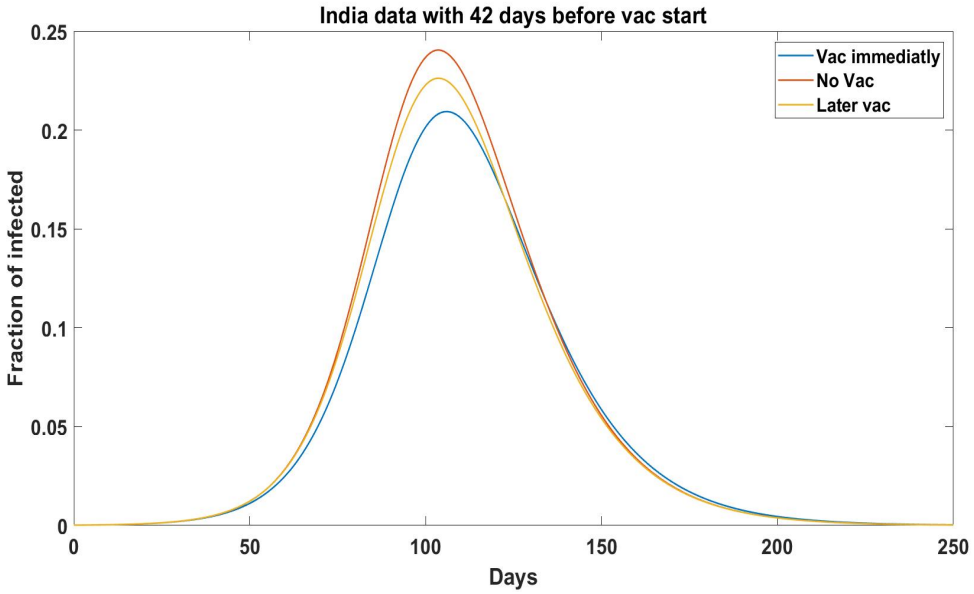


Figure 5.3: India data, table3.3, with vaccination starting after 42 days

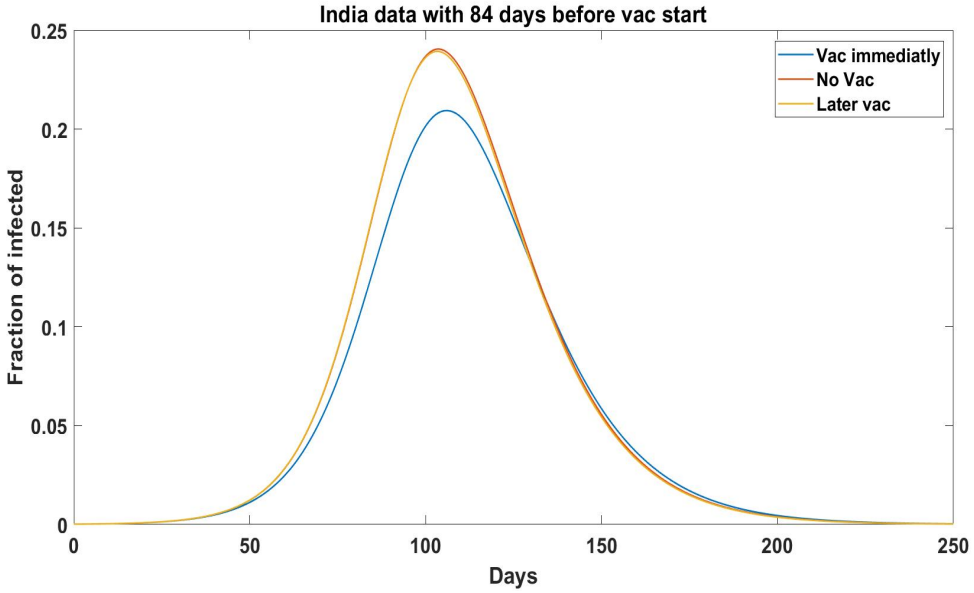


Figure 5.4: India data, table3.3, with vaccination starting after 84 days

We can see from these graphs that the effect of vaccination to lower the peak of the infection curve loses half of its value after 42 days and almost all value after 84 days.

5.1.3 Data from Norway

As mentioned in chapter 3, both σ and γ presented by FHI, shown in table 3.1, is under half of what was presented in the article by Wintachai and Prathom (2021) [27]. The data from Norway is a bit lacking, therefore to make simulations possible, the values from table 3.4 have been used.

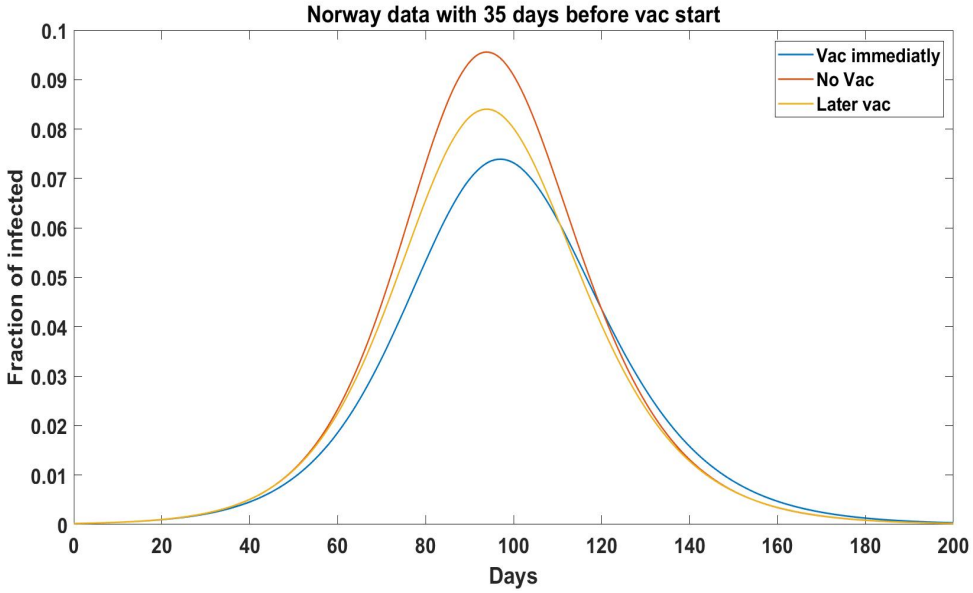


Figure 5.5: Data from Norway, table3.4, with vaccination starting after 35 days

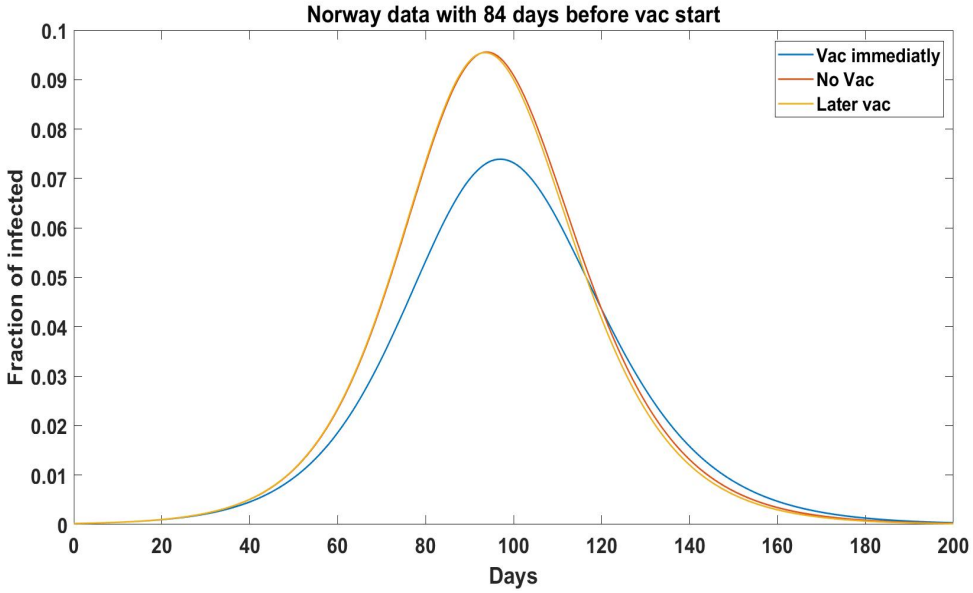


Figure 5.6: Data from Norway, table3.4, with vaccination starting after 84 days

We can see from figure 5.5 and 5.6 that half of the vaccination effect is lost if the vaccination starts at day 35 of the pandemic, while if it starts at day 84 the vaccination does not matter anymore.

5.1.4 Comparing the countries

Table 5.1: I_{max} with different vaccination start using data from USA, India and Norway

Vaccination start	I_{max} in Norway	I_{max} in USA	I_{max} in India
Day 1	7.39%	27.34%	20.94%
Day 35	8.41%	28.21%	22.62%
Day 84	9.54%	28.77%	23.90%
No vac	9.56%	28.80%	24.05%

With USA having a much higher and earlier peak of infection, they also have a lot less time to start their vaccination program. The infection wave in Norway is fairly low compared to both India and USA. The biggest differences between the three data sets is the values of γ, σ and β. Later in the thesis there will be a sensitivity analysis to see which of the parameters have the biggest impact on I_{max}.

5.2 Delay before vaccine is effective

The simulations in this section will look at the effect of the delay between when the vaccine is taken and when it becomes effective.

5.2.1 USA data

Using the parameter and initial values in table 3.2 and $\tau = 21$, we get a infection curve as presented in the graph in figure 5.7.

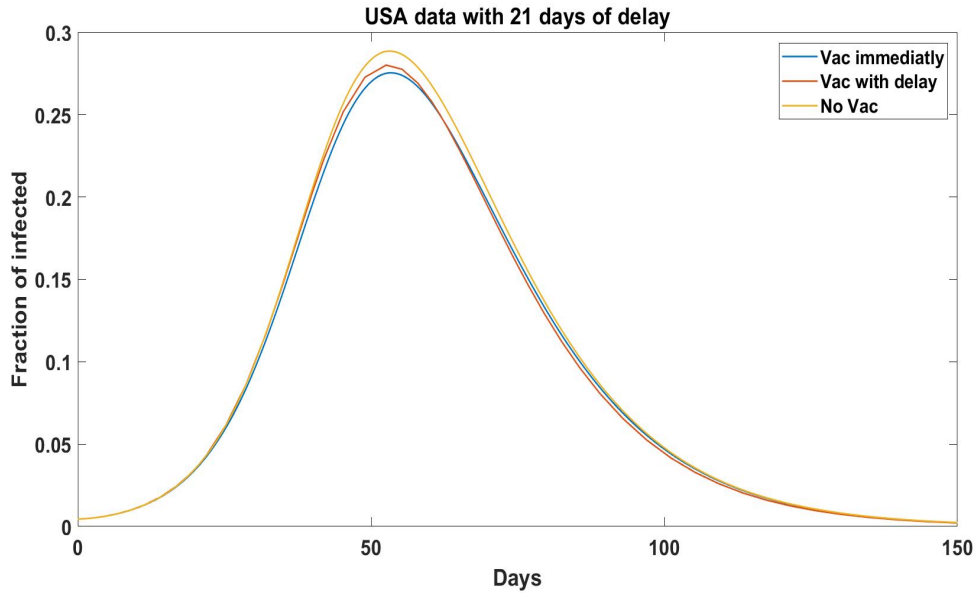


Figure 5.7: USA data, table3.2, with 21 days of delay on the orange line. Blue line is with no delay and yellow is for no vaccination

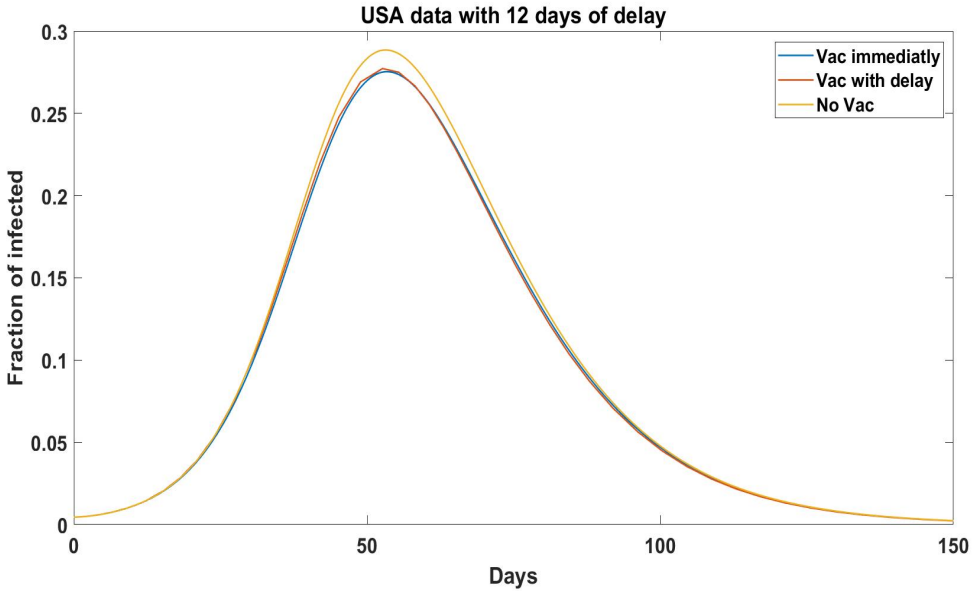


Figure 5.8: USA data, table3.2, with 12 days of delay on the orange line. Blue line is with no delay and yellow is for no vaccination

Without a delay before the vaccine starts to work, the number of infected at the same time peaks at 27.54% of the population, while with the delay, it peaks at 28.01% If we reduce τ to 12 days instead, the peak goes down to 27.72% as showed in figure 5.8. The no vaccination peak is the same as in section 5.1, 28.85%.

5.2.2 India data

Using the parameter and initial values presented in table 3.3 and $\tau = 21$, we get a infection curve as presented in figure 5.9.

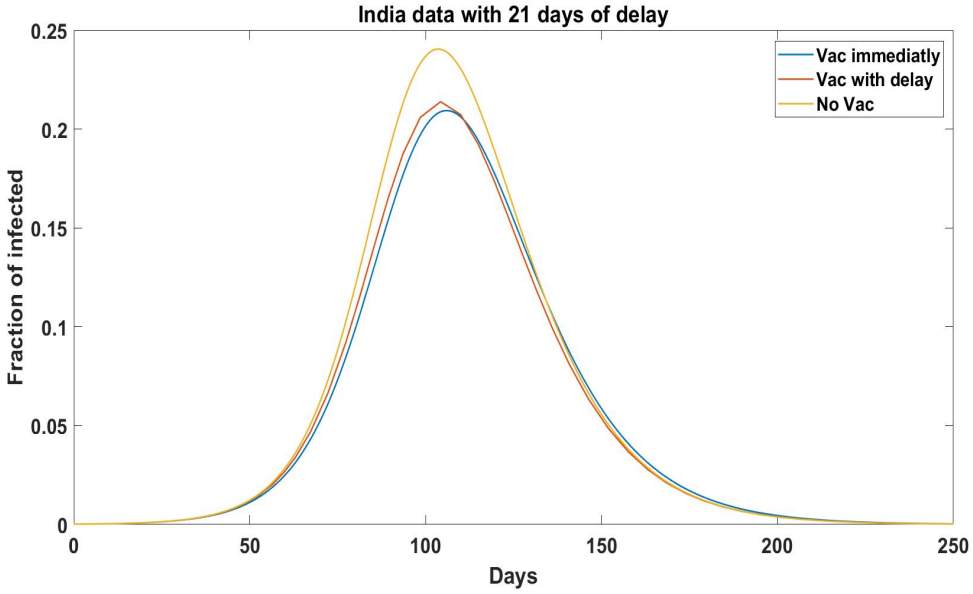


Figure 5.9: India data, table3.3, with 21 days of delay on the orange line. Blue line is with no delay and yellow is for no vaccination

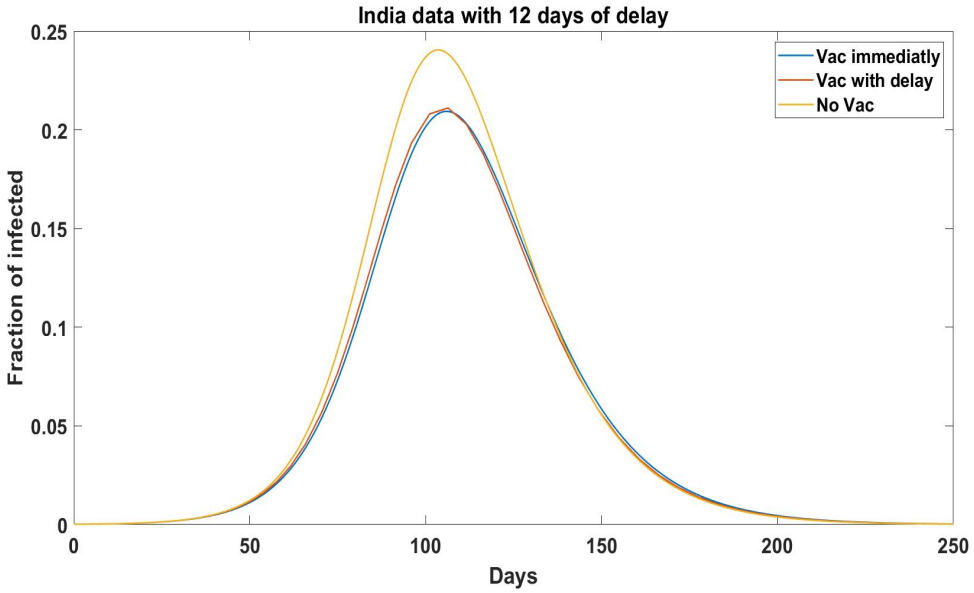


Figure 5.10: India data, table3.3, with 12 days of delay on the orange line. Blue line is with no delay and yellow is for no vaccination

Without a delay before the vaccine starts to work, the number of infected at the same time peaks at 20.94% of the population, while with the delay it peaks at 21.38% If we reduce τ to 12 days instead, see figure 5.10, the peak goes down to 21.11%, which might not sound that much but with a population of 1.38 billion people, a reduction of 0.3 % is 4140000 less infected. As previous the no vaccination peak is 24.05%

5.2.3 Data from Norway

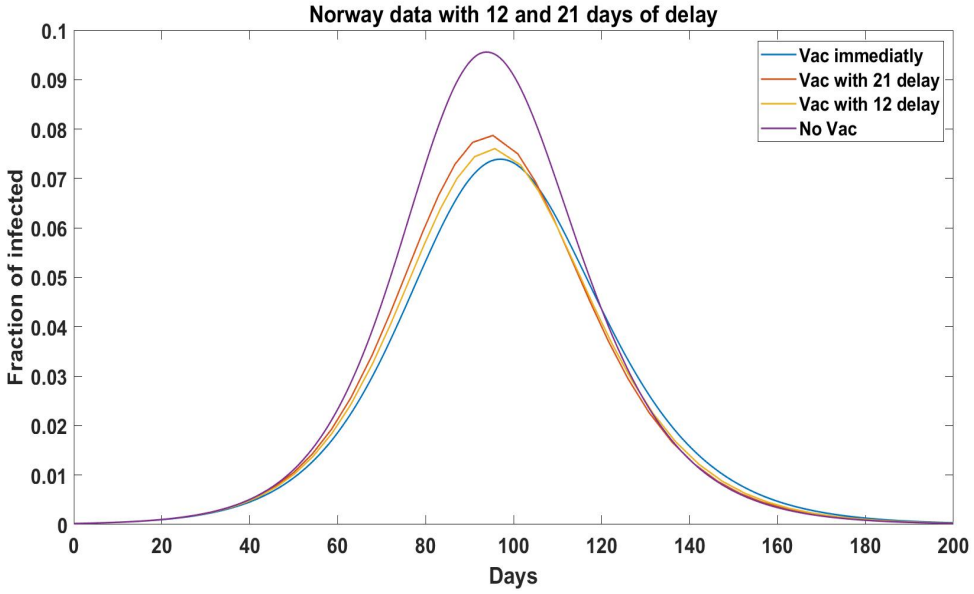


Figure 5.11: Data from Norway, table3.4, with 21 days of delay on the orange line, 12 days of delay on the yellow line. Blue line is with no delay and purple is for no vaccination

Given that the simulations with Norwegian data have a much lower infectious peak compared to India and USA, the effect of the delay, showed in figure 5.11, is easier to see.

5.2.4 Comparing the countries

Table 5.2: I_{max} in Norway, USA and India with different values on τ

Vaccination delay	I_{max} in Norway	I_{max} in USA	I_{max} in India
None	7.39%	27.54%	20.94%
12 days	7.63%	27.72%	21.11%
21 days	7.89%	28.01%	21.38%
No vac	9.56%	28.85%	24.05%

From the simulations done by data from USA, India and Norway, we can see that percentage wise the delay before the vaccine have an effect have a small impact on I_{max}. But it is important to note that with a large population, even small percentages is a lot of people.

Chapter 6

Sensitivity analysis

A sensitivity analysis can be used to investigate how much the output of a model is affected by variance in a input parameter [35]. As mentioned earlier, the basic reproduction number R_0, describes how many new cases an infected individual will cause in a population of completely susceptible individuals. Therefore in an attempt to flatten the infectious curve, it makes sense to find the optimal way to reduce R_0 or I_{max}. A way to find out the relative importance of the different factors in R_0 is to carry out a sensitivity analysis [36]. Sensitivity analysis can be classified into two categories, local and global sensitivity analysis. We will first look at a local analysis, before we do a global one.

6.1 Local sensitivity analysis

One of the several ways to do an sensitivity analysis is by taking the derivative of the model output with respect to the input variation. Sometimes this process is normalized using the standard deviation of the output and input values, or by using the values around where the derivative is calculated [37]. Since we are measuring the sensitivity over a small area or a fixed point where the derivation is taken, this version of sensitivity analysis is called local. The local sensitivity index measure the effect of a individual parameter at the time by keeping the others fixed [37] .
One of the methods to calculate the local sensitivity index is called the normalized forward sensitivity index. If the output is a differentiably function of the parameter, we can use the following formula:

$$\Gamma_p^u = \frac{\delta u}{\delta p}\frac{p}{u} =$$

where u is the variable, that depends differentiably on the parameter p [36].
We apply the formula to all the parameters to check their sensitivity index.

$$\Gamma_\beta^{R_0} = \frac{\delta R_0}{\delta \beta}\frac{\beta}{R_0} =$$

$$\frac{\mu\sigma(1-x\varepsilon)}{(\gamma+\mu)(\sigma+\mu)(x\varepsilon+\mu)}\frac{(\gamma+\mu)(\sigma+\mu)(x\varepsilon+\mu)}{\mu\sigma(1-x\varepsilon)} = 1$$

$$\Gamma_{\mu}^{R_0} = \frac{\delta R_0}{\delta \mu}\frac{\mu}{R_0} = \frac{(x\varepsilon - 1)(x\varepsilon(\mu^2 - \gamma\sigma) + \mu^2(\gamma + \sigma + 2\mu))}{(\gamma+\mu)(\sigma+\mu)(x\varepsilon+\mu)}$$

$$\Gamma_{\sigma}^{R_0} = \frac{\delta R_0}{\delta \sigma}\frac{\sigma}{R_0} = \frac{\mu}{\sigma+\mu}$$

$$\Gamma_{x}^{R_0} = \frac{\delta R_0}{\delta x}\frac{x}{R_0} = \frac{-x\varepsilon(\mu+1)}{x\varepsilon+\mu}$$

$$\Gamma_{\varepsilon}^{R_0} = \frac{\delta R_0}{\delta \varepsilon}\frac{x}{R_0} = \frac{-x\varepsilon(\mu+1)}{x\varepsilon+\mu}$$

$$\Gamma_{\gamma}^{R_0} = \frac{\delta R_0}{\delta \gamma}\frac{\gamma}{R_0} = \frac{-\gamma}{\gamma+\mu}$$

We see that the sensitivity index of R_0 with respect to β does not change with the parameter values, while the rest of them do. Therefore to find the rest of the index values we need to put in some parameter values.

Table 6.1: Local sensitivity index of R_0 with data from USA, India and Norway

Parameter	India	USA	Norway
β	1	1	1
γ	-0.9993	-0.9995	-0.9998
μ	0.9528	0.9685	0.9720
σ	$5,624 \times 10^{-4}$	$3,653 \times 10^{-4}$	$4,139 \times 10^{-4}$
x	-0.9551	-0.9704	-0.9734
ε	-0.9551	-0.9704	-0.9734

From table 6.1 we can see that the effective transmission rate, β have the biggest impact on R_0, with the rest except the incubation time σ close behind. Inserting the different data from India, USA and Norway have little impact on the local sensitivity index of the parameters. Based on this analysis, implementing control measures against any parameter except σ will have almost the same effect on the reproduction number.

6.2 Global sensitivity analysis

Global sensitivity analysis, often shorted to GSA, looks at the resulting uncertainty in the output, from the whole range of values in the input parameter [35] . This type of analysis can help modelers identify which of the components in the model that have a high influence and which is non-influential. If a non-influential parameter is found, it can be removed and the model will be less complex [38]. Within GSA there is three

categories: moment independent model, non-parameter techniques and lastly, variance based method [39]. Variance based sensitivity analysis (VBSA) looks at the output sensitivity as the proportion of output variance that comes from the variation in each of the uncertain input factors [38]. One way to do a VBSA is by calculating the Sobol indices, the first order sensitivity index S_i can be found with the following formula:

$$S_i = \frac{V_i}{V(Y)}.$$

Here V(Y) is the total variance in the output Y, and V_i is the amount of variance a parameter contributes to the total variance [40]. By setting an input value to a fixed spot, the first order sensitivity index will tell you how much the total variance in the output changes by removing the uncertainty around that input value. We can also find the total sensitivity index

$$S_{Ti} = 1 - \frac{V_{\sim i}}{V(Y)}$$

which shows how much of the total variance in the output will remain as long as the input parameter we are looking at, remains unknown [40]. $V_{\sim i}$ is the total output variance caused by all other parameters than the one we are looking at.
Under the moment independent category, there is the moment independent indices, which is indices that does not depend on the shape of the distribution since it does not use a specific moment of the output distribution to characterise uncertainty [41]. Since these methods looks at the Probability Density Function (PDF) of the model output, instead of only the variance, they are at times called density based methods [41]. A method called PAWN tries to calculate the density-based sensitivity indices in a effective way.

6.2.1 PAWN method

Instead of using the PDF to derive the density-based sensitivity indices, PAWN chooses to characterise the output distribution by the Cumulative Distribution Function (CDF) [41]. A CDF $F_X(x)$ describes the probability that a random variable X with a given probability distribution will be found at a value less or equal to x [42]. The creators of the PAWN method, Pianosi and Wagener claims that the method have several benefits. The method gives the possibility to look at just a specific region of the output distribution instead of the entire range of variation of the output. It requires no computing cost to approximate the empirical CDFs from a data sample and the approximation does not need any tuning parameter, which makes the method easier to implement and ease the application of convergence analysis and bootstrapping [41]. PAWN uses the Kolmogorov-Smirnov (KS) statistic as a measure of distance between conditional and unconditional CDFs. The use of KS statistic makes the sensitivity index of PAWN an absolute measure, since it goes between 0 and 1 regardless of the range of variation of the model output y. The KS statistic also makes it possible to determine inputs that are non-influential [41]. The formula for the KS statistic is the following

$$KS(x_i) = \max_y |F_y(y) - F_{y|x_i}(y)|$$

where $F_y(y)$ is the unconditional cumulative distribution function of the output y and $F_{y|x_i}(y)$ is the conditional cumulative distribution function with x_i fixed [41]. Since the KS statistic depends on the value that x_i is fixed at, the PAWN index T_i study a statistic over all possible values of x_i [41].

$$T_i = \underset{x_i}{stat}[KS(x_i)].$$

T_i is a number between 0 and 1, and the lower value it have, the less influential is x_i. If T_i is zero, then the parameter have no influence over the output [41]. For further reading about the method, I highly recommend reading the articles about PAWN by Pianosi and Wagener [41], [38].

6.2.2 Elementary Effect Test

In 1991 Max D. Morris made a parameter screening method that uses a factorial sampling strategy to find which parameters that can be fixed at any value within their range without the variance of the model outcome getting affected [43]. The method called Elementary Effect Test, often shortened to EET is an average of derivatives over the space of factors [44]. In the book The Primer [44], Saltelli defines the EET in the following way;
Consider a model with k independent input factors $X_i, i = 1,2,...,k$, which varies across p levels. The input space is the discretized p-level grid Ω. For a given values of $\mathbf{X}$, the elementary effect of the ith input factor is defined as

$$EE_i = \frac{[Y(X_1, X_2, ...X_{i-1}, X_i + \Delta, X_{i+1}, ...X_k) - Y(\mathbf{X})]}{\Delta}$$

where p is the number if levels, Δ is a value in 1/(p-1),...,1-1/(p-1), $\mathbf{X}$=$(X_1, X_2, ...X_k$ is any selected value in Ω such that the transformed point ($\mathbf{X}$+$e_i\Delta$) is still in Ω for each index i=1,...,k, and e_i is a vector of zeros but with a unit as its ith component [44].
The mean value μ and the standard deviation σ of the distribution that is obtained by randomly sampling different $\mathbf{X}$ from Ω are the sensitivity measures proposed by Morris [45]. The overall influence a factor have on the output is assessed by μ, while σ measures the combining higher order effects of the factor [45]. If μ is high for a factor X_i, it means that the elementary effect values for X_i is significantly impacted by the values of the other factors [45]. On the other hand, low μ means that the effect of X_i is almost independent of the values of the other factors [45]. Instead of μ it is possible to use μ^*, which estimates the mean of the distribution of the absolute values of the elementary effects [45]. The absolute values of the EE_i, computed at r different grid points for each factor, are averaged

$$\mu_i{}^* = \frac{1}{r}\sum_{j=1}^{r} |EE_i{}^j|$$

and the factors are ranked according to the obtained mean $\mu_i{}^*$ [44].

6.2.3 SAFE Toolbox

To use the methods mentioned above, numerical methods are required. SAFE (Sensitivity Analysis For Everybody) is a Matlab/Octave toolbox designed to do GSA. It includes several established GSA methods and have numerous visualisation tools for investigation and communication of GSA results [46]. In this thesis the SAFE toolbox will be used to perform global sensitivity analysis with the PAWN method, Elementary Effect test and Sobol method.

6.2.4 Analysis using the SAFE Toolbox

PAWN method

By doing some changes in the very useful examples given by the toolbox, the PAWN method was implemented on the DDE model with the seven parameters; effective transmission rate β, birth- and death rate μ, incubation time σ, recovery rate γ, vaccination rate x, vaccine efficacy ε and the time delay τ. The toolbox gives several informative figure, but the focus will be on the three given below.

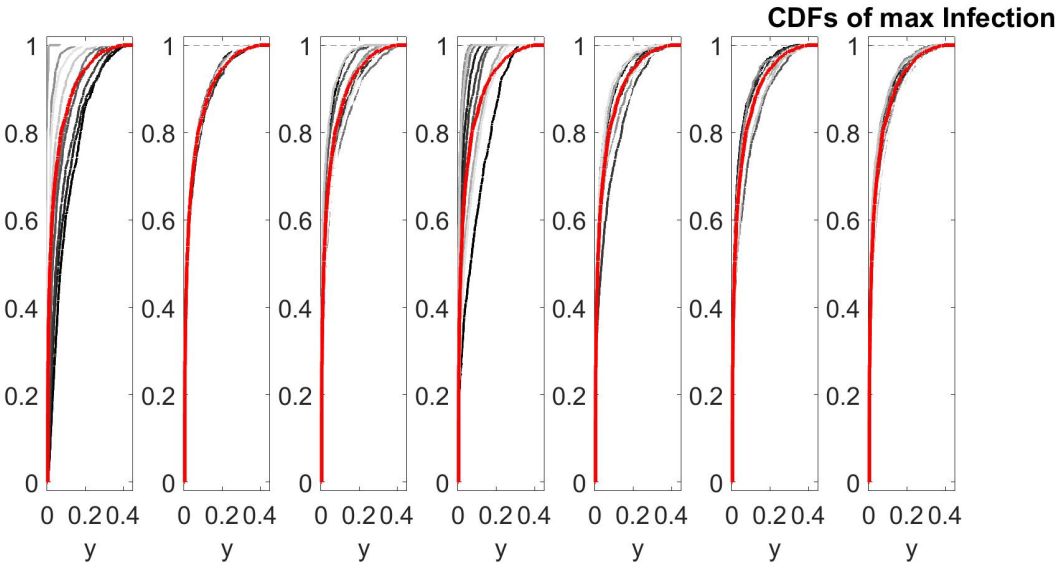


Figure 6.1: CDF from PAWN, from left to right the boxes shows the CDF for β, μ, σ, γ, x, ε, τ

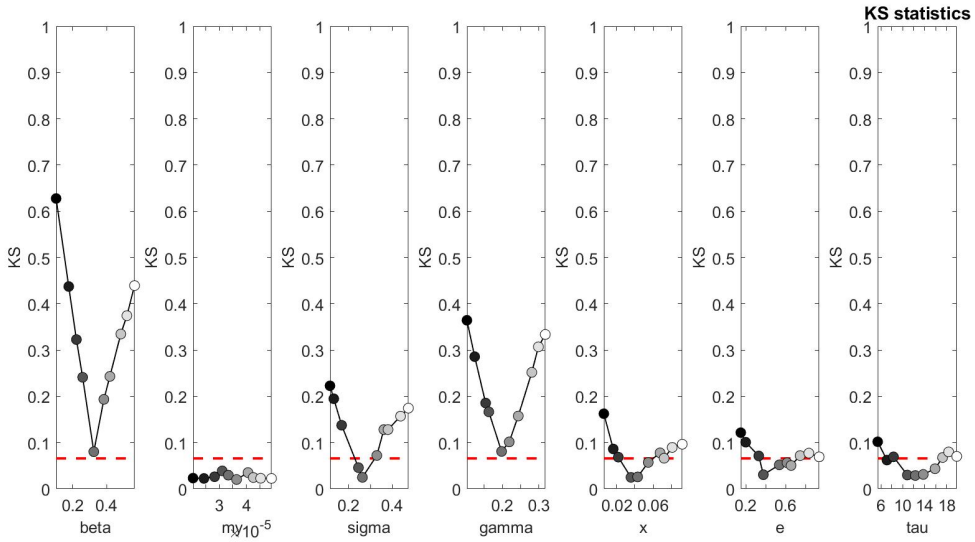


Figure 6.2: KS statistic from PAWN

In figure 6.1 we see the cumulative distribution function, with the empirical unconditional output distribution as the red line, and grey lines as the conditional ones. The distance between the red line and the grey lines indicate how much influence x_i have on the output. If they coincides then x_i have no influence on y. From the figure we can see that β and γ have more outliers then the rest. The same result can be seen in figure 6.2, which shows the Kolmogorov-Smirnov statistic at different conditional values of x_i. The dashed red line is the critical values of the KS statistic at confidence level of 0.05 [41]. From the results of figure 6.1 and 6.2 we get the PAWN index as shown in figure 6.3.

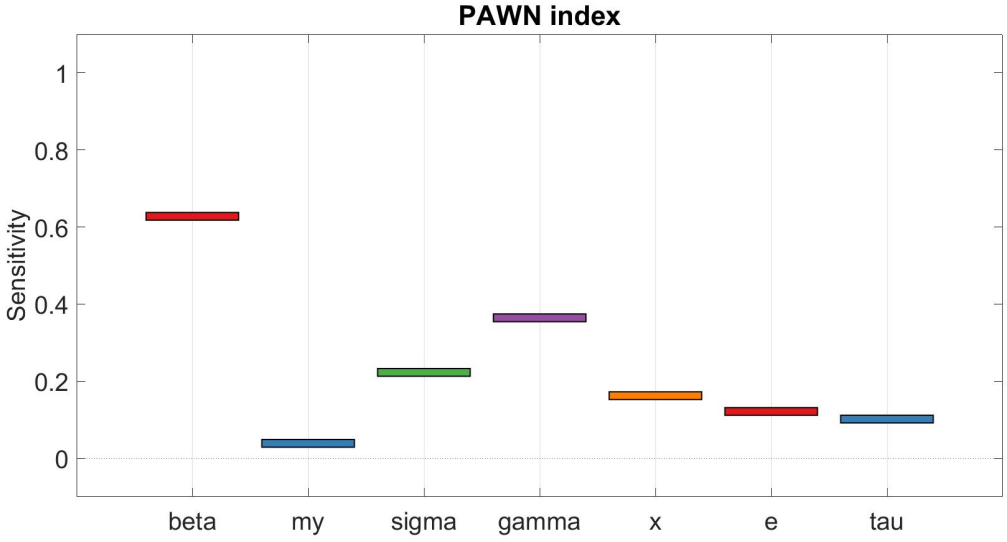


Figure 6.3: PAWN index

Here it is clear that β have by far the biggest impact on the output, followed by γ, with the rest except μ having similar sensitivity index.

EET

Similarly to the implementation of the PAWN method, the elementary effect test was implemented by doing some changes to an example in the SAFE toolbox. To generate samples for the EET, the SAFE toolbox uses Latin Hyperbole Sampling (LHS). To create a sample size N, LHS takes the parameter of each variable $x_1, x_2, ..., x_n$ and divides it into N non-overlapping intervals on the basis of equal probability size $1/N$ [47]. The N samples for each variable is then randomly selected one at the time and again randomly placed into a tuple with a sample from each of the other variables [47]. In the end we end up with a set of Nn-tuples that is the Latin hypercube sample [47]. Running the code gives figure 6.4 and table 6.2.

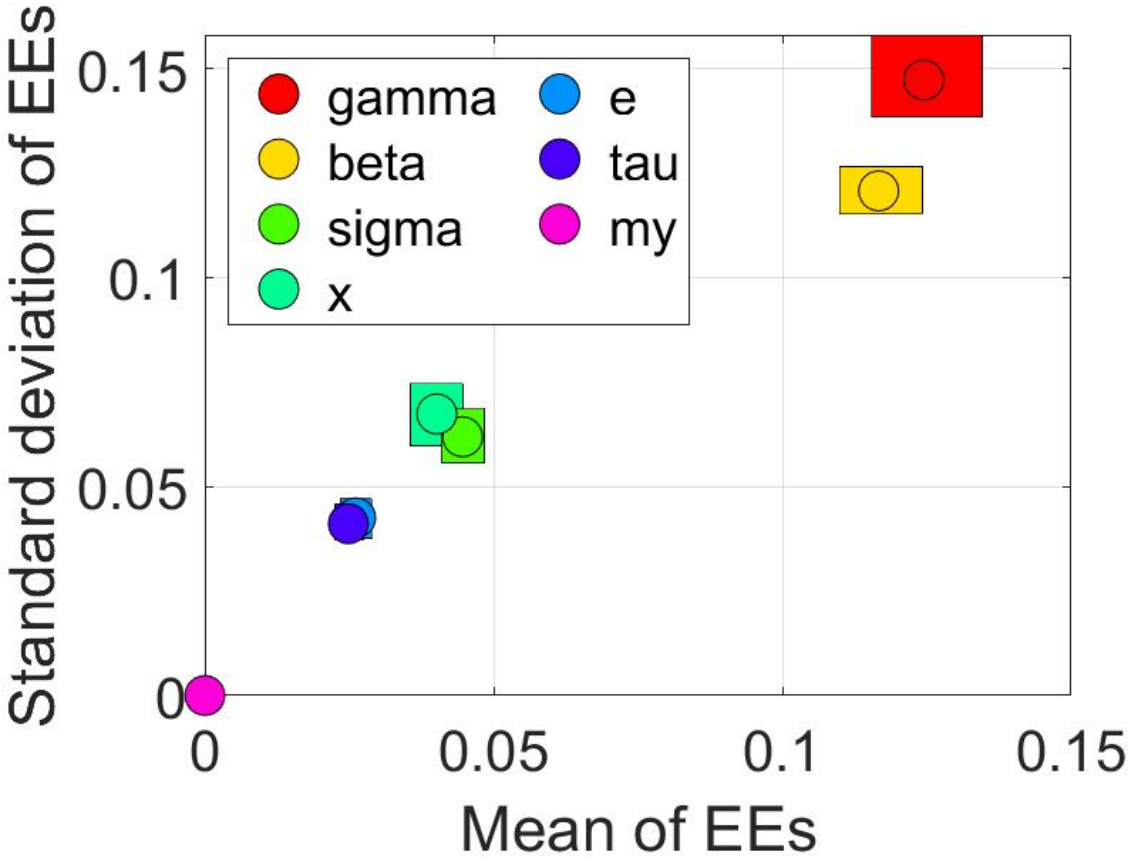


Figure 6.4: EET index

The elementary effect test gives us that γ is the parameter that have the largest impact on the output, with β close behind. Likewise as with PAWN the other parameters are close to each other in the middle, with μ having the lowest impact.

6.2.5 Sobol method

The SAFE toolbox can also calculate the Sobol indices. Running a simulation with the delayed SEIR model in eq.4.6 gives the result seen in figure 6.5. The main effect is what was earlier referred to as the first order sensitivity index.

Table 6.2: Mean value and standard deviation of elementary effect

Parameters	Mean EE	STD EE
β	0.117	0.121
μ	0.000	0.000
σ	0.045	0.062
γ	0.124	0.147
x	0.040	0.067
e	0.026	0.043
τ	0.025	0.041

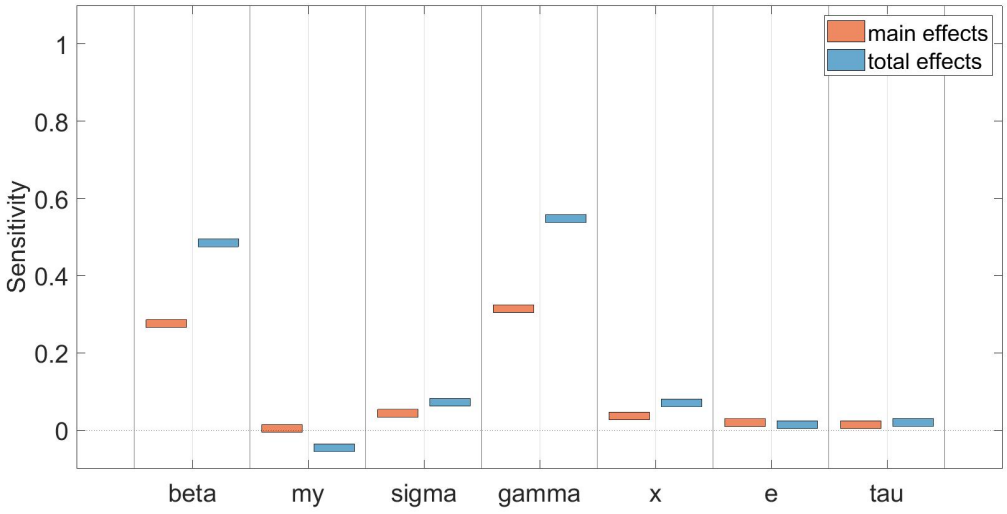


Figure 6.5: Main and total effect of the parameters using the Sobol method

Here we can see that the Sobol indices agrees with the result from the Elementary Effect test, placing γ as the parameter with the biggest impact on I_{max}, with β right below. As with the other GSA methods, the rest of the parameters have little impact on the output.

The three methods agrees that β and γ are the parameters with the largest impact on the output, but disagree on their order. PAWN places β much higher then γ, while EET and Sobol have γ just above β. Inserting control measures against one or both of them seems to be the best way to lower I_{max}.

Chapter 7

Presenting mathematical models

By: Eirik Vivelid Stokke and Maria Markhus Jacobsen

7.1 Explaining mathematical models to non-mathematicians

To model a real life problem, one often have to make some difficult decisions about what to include and exclude in the model. As a result the mathematical model will only be uniquely determined by the situation in the most simple cases [48].
The main task of a mathematical model, if not the only task, is to describe or represent a real situation. Sometimes models are even used in an attempt to predict the future. It's important to note that a mathematical model is based on a hypothetical situation and will therefore never be an exact reflection of what it tries to represent. One of the challenges with mathematical models is to figure out to which degree they match reality [49]. Even though there is uncertainty around models, a famous quote by George E. P. Box: *All model are wrong, but some are useful*, should be taken into account. Many models are close enough to reality that they can provide valuable information. Therefore many decisions are based on the information given from models. One example is when airline companies use an "overbooking model" to figure out how they can most likely in the long run profit from overbooking their planes [49]. The conclusion of the example is one of the core properties of a mathematical model: that we can gain valuable insight into different hypothetical situations, but also that "most likely" and "guaranteed" are not the same thing [49]. During the Covid-19-pandemic FHI have used mathematical models to look at other hypothetical situations.

For anyone other than an expert modeller, the transition between the real world and mathematical models can be difficult to grasp [50]. Mathematical modelling involves several challenging processes, like deciding how to mathematise real-world problems, decide which aspects of the real world are relevant or not, and also using techniques to test the model against reality [50]. Studies have shown that the context is relevant to how well young students understand the link between reality and models. This understanding could also impact student's experiences with models in university [50].
In a commentary form 1989, John Durant, Geoffrey Evans and Geoffrey Thomas explore the public interest in and knowledge of science [51]. Through surveys in both the

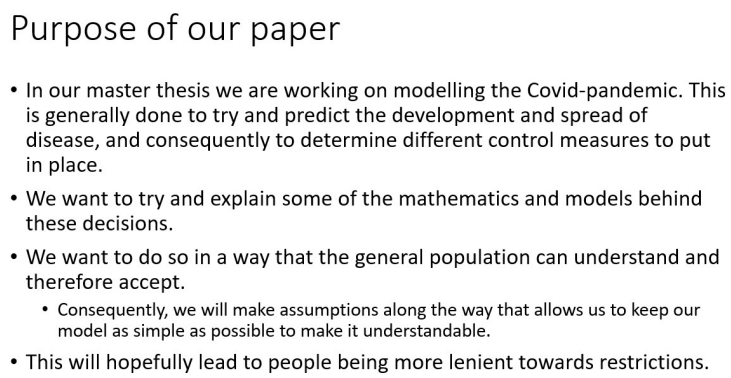
US and the UK they discovered that the public reports high levels of interest for scientific topic, but that the scientific knowledge was not necessarily corresponding. They identified relationships between education, gender, age, etc. and knowledge of science, as well as a strong association between interest and understanding [51].

7.2 Preparing for the presentation

During the work on this thesis an opportunity arose to present our model and findings to an interdisciplinary audience from both social and natural sciences at Pandemisenteret[1]. In this context there would be master students, PhD students, professors and other academic staff from various specialties. We were invited to hold a presentation about what we have been working on with this thesis. As one aspect of this thesis is to be able to present the SEIR-model and its implications to the public in an understandable way, this was a great opportunity to test just that.
As chapter 2, 3 and 7 are joint work between the authors, we cooperated on presenting these, after which we presented our separate projects. Here, my separate work is done on delay and sensitivity analysis.
Remembering how difficult mathematical modelling is to non-mathematicians and about the public's difficulties with scientific understanding, we had to prepare a well thought-out explanation and some accompanying presentation slides that summarizes what we wanted to convey.

7.2.1 Presentation slides and reflections prior to presentation

Here we present the slides that would be part of the presentation and corresponding reflections done and plans made during our preparations prior to the presentation.



When getting new and difficult stuff presented it can occasionally be hard to find motivation to be invested in learning. Knowing why one has to learn the material can often help with this. As the pandemic and its consequent restrictions are something that affects almost everyone, it will hopefully easy to understand why it can be useful to gain some knowledge into this.

[1] Pandemisenteret Webpage: https://www.uib.no/en/pandemic

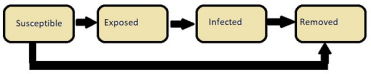
Therefore the presentation will start with a transparent statement about how we want to promote understanding of the reasoning behind the restrictions to provide some motivation for following them.

Mathematical models

- "All models are wrong, but some are useful." (George E.P. Box)
- A model is just that; a model. It is an attempt to illustrate and/or predict a phenomenon.
- It is not an exact representation of reality. Still, it can be very helpful.
  - A model can never take every factor into account, it can still give somewhat of a picture of a situation and its development. This makes it our best shot at making the best possible decisions.
- In our work we have tried to model a very specific scenario; the spread of the COVID-19-virus with vaccines as the only control measure.
- SEIR-model

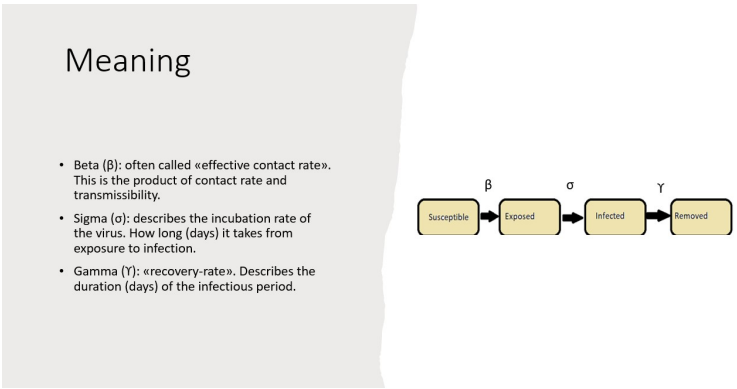
At first it is important that we introduce the concept of a model and challenges regarding accuracy. When large sets of data are available model can get potentially more accurate, but during the pandemic every day have brought new discoveries. Models have been made, but only based on what little knowledge was available. With no way of knowing how infectious if was, how it spread, etc., a lot of assumptions had to be made and one had to rely on the models we had developed for other epidemics and we must explain this.

SEIR-model

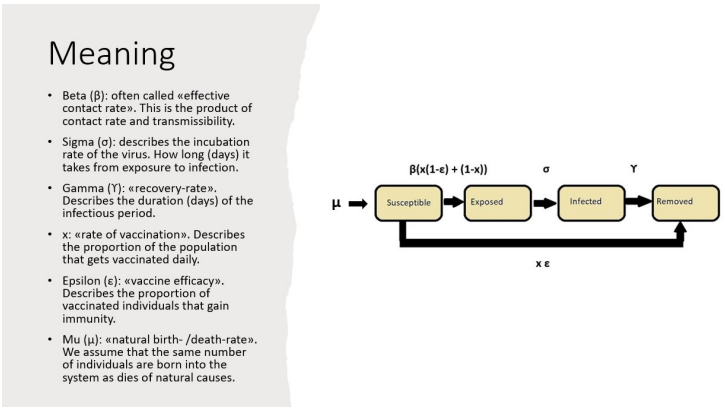


- We divide the population into four groups: susceptible, exposed, infectious and recovered/removed (immune).
  - Susceptible: Healthy individuals that might get infected.
  - Exposed: Individuals that have been exposed to the virus but are not yet infected/infectious.
  - Infected: individuals that are infected and might infect others.
  - Removed: Individuals that have been through infection and have gained immunity through recovery. Vaccines can also provide immunity and allow susceptible individuals to move directly to the "removed-box."
- Mathematical equations describe at which rates people move from one box to the next.
- The model illustrates how large proportion of the population belong to the different boxes at any given time.

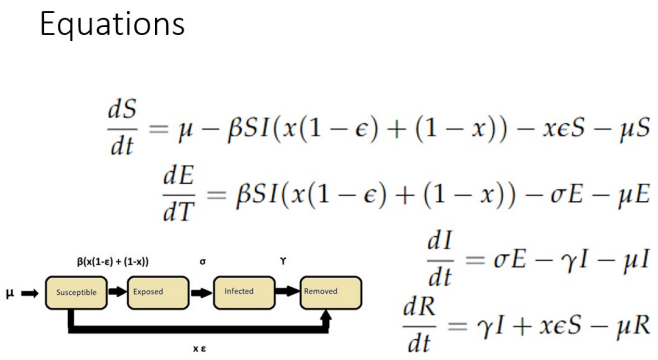
Then the SEIR-model will be introduced. It will be important to use visual components like the box-diagram, as it can help illustrate how the model works. The audience will with high probability have personal experiences with the virus which will be helpful, as context is important for understanding models. An extremely large proportion of the worlds population is now familiar with how the virus spreads. This will set a clear context for the models relevance and hence the audiences understanding. As the pandemic has greatly affected the everyday life of the population, one can also assume that interest will be high.



To make it easier for the audience and avoid too much new information at once, we will present the most general parameters first (β, σ, γ). We will first describe what each parameter means and what they represent. The flowchart will be presented to make it easier to follow where the parameters come in to play in the model.



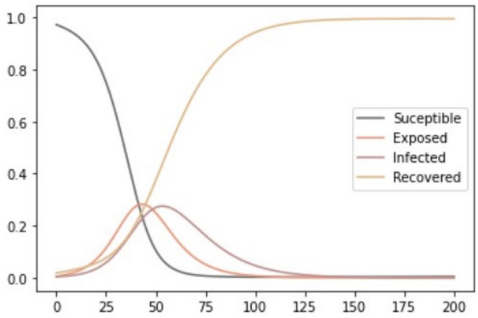
Then we add the remaining three parameters (x, ε, and μ) so the complete flow between the boxes can be visualized before the equations are presented. We will first explain the vaccination term, as it will make the resulting expansion in the beta term more understandable. We will avoid the term "normalized" as it is not necessarily a word everyone know the meaning of. Instead we will say that we look at a "proportion" of the population.



This slide with the four equations might initially seem intimidating, but we will try to explain one equation at the time and show how a term that is subtracted from one

equation, is added to the next. Then we must explain that these terms denote individuals that "change" groups. We will also use the flowchart from the previous slide to show where each term comes from. By teaching the audience the thought process behind the system of equations, they will hopefully have a stronger foundation for understanding more complex models. A possibility to make this easier to follow could be to show the equations in a standard SEIR-model first and then show where the extra parameters come in.

Simulation



Here we will show the audience an example of a simulation that uses the model combined with parameters from USA. We will start with explaining the x-axis and y-axis, since a graph without axis does not make sense, and again mention that 1 means the whole population. With this simulation the audience will be able to see that as the susceptible portion of the population decreases, the recovered portion increases, and that the infected curve follows the exposed curve with a little delay.

The basic reproduction number

- This kind of model and parameters are often what is used when calculating the R-number we hear so much about.
  - Main property: pandemic is increasing when R>1 and decreasing when R<1
- Problems with the R0/R/Rt/Reff-number:
  - Many different methods of calculation.
  - Depends on many different factors, like rate of transmission, duration of contagiousness, environment, population density, etc.
  - Even the main properties of the R-number can under certain circumstances fail.
  - Be careful to make strong claims.
- In our thesis: the basic reproduction number describes the rate of contagiousness in a completely susceptible population.
  - Making it applicable initially in a pandemic – which gives an indication of severity.

The reproduction number might be the hardest thing to explain in a simple way, if one goes further than the easiest property. We decide it will be sufficient to explain *why* it is such a difficult topic and complicated entity. Then we will explain how it has been used for this specific thesis, which is always important when talking about the R-number. The R-number can be calculated in many different ways and contain a lot of different factors. It will be important to explain this fact to the audience, but we will not demonstrate the mathematics behind it as that is hard to comprehend for even experienced mathematicians.

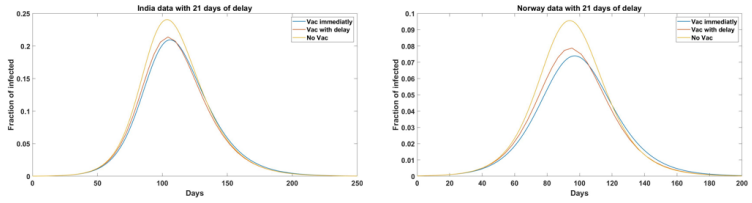
7.3 My specific project

DDE (Delayed Differential Equations)

- Estimated that it takes between 12 and 21 days to become well protected against serious illness from the disease after first dose.
- Added a delay on the vaccination term in the model
- This means that those who are vaccinated are not removed from the S-category immediately

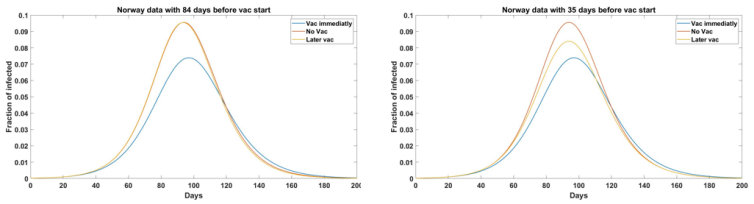
I will start with explaining the reason for adding a delay and what a delay means for the movement between the boxes. I will not show how that changes the equations as it is not necessary to understand and might cause confusion when time and τ is added.

Numerical analysis with the added delay



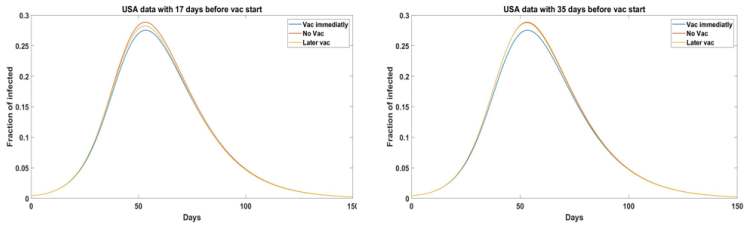
In this slide the audience will get to see the effect of the delay and how it compares to scenarios without the delay or without the vaccine. By showing three different scenarios, it is easier for the audience to see exactly how the delay have an impact.

Later vaccination start in Norway



Instead of a delay before the vaccine is effective, I add a delay before the vaccination starts. The point of this graph is to see how little time there is to start vaccination in a scenario where there is no other control measures.

Later vaccination start USA



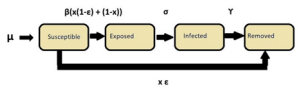
Same as in the previous slide, but with data from USA instead, to show the audience how different values decide how much time the country have before it is too late to start the vaccination.

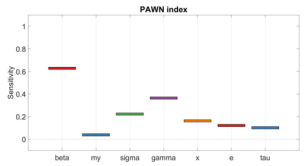
Sensitivity analysis

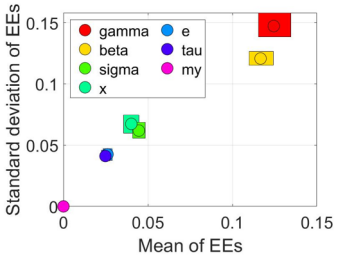
- How do we flatten the infected curve?
- Trying to find out the relative importance of the different parameters
- Global sensitivity analysis

Now that the audience have seen how large the infection curve is, they might be more interested in ways to deal with it. So now I present the results from a sensitivity analysis. The math behind it is complex and is not necessary to understand at this level.

Results from SAFE toolbox







Since I dont show the audience the math behind it, they will just have to accept the results shown in the figures. Moving from explaining the whole process to just showing

the result is something that should have been avoided, but in this case, it is hard to see a better solution. The result is important for showing the audience why some of the control measures during the pandemic was implemented.

7.4 Presenting our findings to non-mathematicians

7.4.1 Feedback after presenting to non-mathematicians

The following feedback was requested:

- We would like to know how understandable the presentation is as one of the main ideas behind our thesis is to be able to convey this information to people without a mathematical background.
- What is easy to understand?
- Are there any terms that should have been explained more in depth?
- Do we loose you? Where?

The responses, although not completely compatible with what was requested, can be summarized as follows:

What is worth doing? Do we just avoid the inevitable? Vaccines change the game.
The participant reflected on how at the start of a pandemic there is a discussion of what measures are worth implementing. This because if you flatten the initial curve the next wave will become bigger as a result. The vaccines change the game by making a part of the population immune or protected against serious illness given enough time. Then we move from discussing how much of the curve is worth flattening, to how do we can give the vaccines enough time to work.

Will the unfairness be part of the modelling?
The context for the question was that the less fortunate part of the population lives in smaller homes and often with more people together. As a result the contact rate would generally be higher for this part of the population. However, in the simplified model in our thesis we have used the same β for the whole population. To take into account scenarios like economical situations we would need to split the model into several variants that looks at small areas at the time. We would also need a large amount of data to figure out the specific β in each area. In an ideal situation this is something that the model should include as it matters for accuracy, but with our limited amount of time and resources, this has not been considered.

Making models understandable is good. Modelling is a tool to ***either*** *make people change behavior* ***or*** *as an explanation of reality. To my understanding you guys are aiming for the first one. There is a fine line between simplifying the model so that its understandable, and making it so simple that it loses all relevance because it is too far away from reality.*

The model does not consider the change in human behavior as a result of large infection numbers. With a higher risk of getting infected, many people will naturally avoid large crowds and stay more at home, and as a result the contact rate will go down. While this is true, it would require greater access to data than we've had.

How is your model suppose to help? Many of those who are sceptical to vaccines and control measures already do not listen to the experts, so why would they listen to you? Is the lack of trust the problem? It is indeed difficult for us to say if the problem is trust or something else entirely. From our math-teacher-perspective the hope is that an explanation of models and the process around epidemiological modelling will give some understanding that causes some changes in attitude towards the measures implemented. The goal is not to argue with conspiracy theorists, but rather provide some knowledge and insight for those who want to do what they can but are getting tired of following restrictions they do not understand the reasoning behind.

Other comments were largely concerned about details regarding vaccines and the consequences of simplifying the model as much as we have. A discussion on what could and should be included or not in an epidemiological model and how this would affect its relevance is something that serves as a great teaching tool and should be encouraged. This is simply a sign that the listeners are engaged in what is being presented and understands aspects of both the relevance and limitations of the model, which is the essence of what we seek to teach.

It generally seemed like the audience understood the mathematics and models that was presented. Rather than questioning what had been said, they even had questions and input regarding aspects of the thesis itself. Some of the feedback received have already been addressed in the section concerning limitations of the model, see 2.1.3.

7.4.2 What should be done differently?

Given the feedback on the different aspects of reality that is not included in our model, it would possibly be beneficial to dedicate more time to reflect on the consequences of this. Perhaps after presenting our simple model and explaining thoroughly the mathematical modelling concepts behind it we can assume the audience understands the material well enough that it is safe to discuss how, potentially, one could expand the model further. As a lot of feedback addressed the sociocultural differences and social aspects of reality, it seems including reflections on this will help engage the listeners. Some specific examples of this might also be helpful as long as we take the time to explain all additional pieces of information.
Based on this one could argue that our model is perhaps too simple for an engaged audience. Still, we have to remember that the purpose of the model is to illustrate a simplified, very specific scenario for teaching-purposes, not necessarily to develop a replication of the reality at hand. We wish to provide some knowledge of what models are, how they work, and what they are used for. Because our model is so simple, ex-

plaining and teaching is more easily achieved. Again taking the time to go through the assumptions made during the development of the model and what scenario this model specifically illustrates seems important if we want the audience to accept the current model and understand how is can be expanded on to closer resemble what health-care executives use when making decisions about control measures.

Potential sources of error regarding the feedback we received is presented below.

Sources of error

Even though most of the audience were non-mathematicians, they are highly educated individuals. This opens the possibility that their understanding was higher than it would be among the general population as this group of people are all very well trained in critical and analytical thinking.

We have to trust that the feedback was genuine. However there is a possibility that some people might not be comfortable admitting that something is difficult to understand, and hence saying that the presentation was understandable regardless of what their personal perception was.

Interest is important for understanding. This presentation was held at a interdisciplinary space started to learn from the Covid-19 pandemic from each other, so it's safe to assume that interest was high. Understanding might have been higher in this space than it would be elsewhere where attendees do not actively seek to learn from the pandemic.

Considering our experience with the presentation, the feedback from the audience and potential sources of error, we utilized the slides used for the presentation, and developed a manuscript of how a presentation of the same material ideally could be held for the general, non-mathematical, non-academic population. This manuscript is presented in its entirety in Appendix B.

Chapter 8

Conclusions and Future Work

After trying different extensions of the SIR-model, we settled on a SEIR-model that included parameters for vaccination rate and vaccine efficacy. After finding the basic reproduction number with the Next Generation method, the model was then checked for stability, with and without a delay in the successful vaccination term $S(t)x\varepsilon$. To get a clear view of the models behavior, graphs from numerical simulations with parameter values from India, USA and Norway was discussed. Following the numerical analysis, a local and global sensitivity analysis was implemented to see how much the variance in parameter values changed the output, which in this case was R_0 for the local and I_{max} for the global sensitivity analysis. From the GSA it was clear that β and γ had the largest impact on the infection peak. Finally we discussed our thoughts about presenting the model to non-mathematicians and the feedback we got when we tried to present it to a interdisciplinary academic group related to Pandemisenteret at UiB.
In a scenario with one dose of vaccination being the only counter measure it is clear that the pandemic will run rampant with a large percent of the population being infected at the same time. To give the vaccine enough time to work, implementing more control measures to lower the effective contact rate β and the recovery rate γ seems to make the most sense based on the results from our model.
Calculating and using R_0 correctly according to the the definition have proven to be difficult. With the Next Generation method, a method that works on SEIR-models, we got a result that includes vaccination which makes some people immune, while the definition of R_0 requires a completely susceptible population. A different method might have given a better result. Showing stability of the equilibrium points in the delay model ended up being difficult as well. The simulations strongly indicated that they should be stable, but for the endemic equilibrium point I only managed to prove stability for the linearized system. Trying to do it numerically instead ended up as another clash with the the reproduction number. There is still much confusion around R_0 and its use, and even published articles [11], [52] uses it in a way that seems to go against its definition.

In an attempt of making the model understandable for non-mathematicians the list of limitations became long and it might have lost too much contact with the real world. A suggestion for future work is to test our presentation of the model on non-academics and if it works, see if a more complex model could be made understandable as well. A model that reflects the real situation better while still being presentable could arguably

motivate people more to attempt to understand it. On the other hand, the model presented by FHI [1] [53] is not that more complex than the one presented in this thesis. By understanding our SEIR-model, people would have come a long way to understand the main epidemic model used in Norway.

[1] https://www.fhi.no/en/id/infectious-diseases/coronavirus/coronavirus-modelling-at-the-niph-fhi/

Appendix A

Stages of Development of our Covid Model

A.1 Developing the Vaccination Model

A.1.1 SIRV

We wanted our model to show how individuals move between belonging to the susceptible, exposed, infectious or removed (recovered or dead) groups of the population, as well as how vaccination affects this development. Our starting point was a general SIR-model, like system (1), to which we added a vaccination-compartment. Birth- and death-rates were left out for simplicity. We constructed this model inspired by Ghostine, Gharamti, Hassrouny, and Hoteits work with modelling the Covid-19 pandemic in Saudi-Arabia [54]. Their model contains several compartments we decided to leave out of our model for simplicity, but we were inspired when it came to describing how individuals move to and from the vaccinated-compartment. As the vaccines are not completely efficient, we also added the vaccine-inefficacy-parameter which moved individuals from the vaccinated-compartment to the infectious-compartment. The flow with corresponding parameters is illustrated in the flowchart in figure A.1.

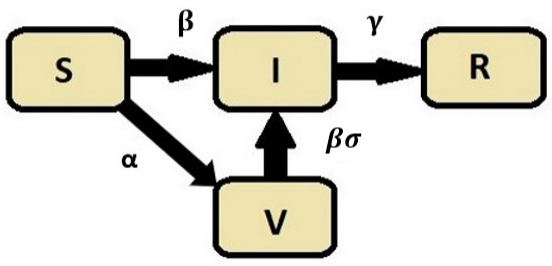


Figure A.1: Flowchart of the SIRV-model.

This results in the SIRV-model as presented in system A.1.

$$\begin{aligned} \frac{dS}{dt} &= -\beta SI - \alpha S \\ \frac{dI}{dT} &= \beta SI - \gamma I + \sigma\beta VI \\ \frac{dR}{dt} &= \gamma I \\ \frac{dV}{dt} &= \alpha S - \sigma\beta VI \end{aligned} \tag{A.1}$$

Where the parameters $\beta, \alpha, \gamma, \sigma$ symbolize the transmission rate, vaccination rate, the recovery rate, and the vaccine inefficacy, respectively.

Since natural birth- and death rate are ignored, we consider the size of the population as a fixed number N, so that $S+I+R+V=N$. Viewing the variables S, I, R and V as respective proportions of the population we get that $\frac{S}{N}+\frac{I}{N}+\frac{R}{N}+\frac{V}{N}=1$. Occasionally it will make sense to change the numbers of the variables when normalizing so that $\frac{S}{N}=s,\ +\frac{I}{N}=i,\ \frac{R}{N}=r,\ \frac{V}{N}=v$ and $s+i+r+v=1$, but we will keep using upper case letters and keep in mind that we consider a normalized population. Noting that change in susceptibles, infectious and vaccinated is not dependent on the "removed" group we see that it is adequate to consider the change in S, I and V when finding critical points as we can simply put R as $R=1-S-I-V$.

This model has a critical point in $(0,0,\frac{\gamma}{\sigma\beta})$. Intuitively, this point represents what is called the endemic equilibrium point where there is no susceptible or infected individuals left in a population because everyone has gained immunity either through vaccination or recovery. The Jacobian matrix corresponding to this point is:

$$\mathcal{J}(0,0,\frac{\gamma}{\sigma\beta}) = \begin{bmatrix} -\alpha & 0 & 0 \\ 0 & 0 & 0 \\ \alpha & -\gamma & 0 \end{bmatrix}$$

Now, our goal is to classify the critical point by first computing and analyzing the characteristic polynomial $p(\lambda)=\det(\mathcal{J}(0,0,\frac{\gamma}{\sigma\beta})-\lambda I)$ [55]. From $p(\lambda)=0$ we find the eigenvalues, λ, of the matrix. As the entire right row is made up of zeroes, one of the eigenvalues will be $\lambda=0$. When we venture on to finding eigenvectors from $p(\lambda)=0$ this eigenvalue will leave us with the original Jacobian matrix. This matrix is singular, as $\Delta=0$ [56]. Consequently there is no unique solution to $\mathcal{J}-\lambda I=0$. Therefore, we cannot find the corresponding eigenvector and our analysis comes to a halt.

We also notice that our model has only one equilibrium point which is an endemic point. The fact that the model is lacking a disease-free equilibrium point is a large red flag. However, we will try to manipulate our equations to work out these issues.
In order to find a solution to our problems, we started by searching for a different way

to express the vaccination rate α. One approach was to view the vaccination-rate as a function of the number of infected and vaccinated, like such: $\alpha = f(I,V)$, changing the term describing the vaccinated individuals from αS to $f(I,V)S$. The new system now looked like this:

$$\begin{aligned} \frac{dS}{dt} &= -\beta SI - f(I,V)S \\ \frac{dI}{dT} &= \beta SI - \gamma I + \sigma\beta VI \\ \frac{dR}{dt} &= \gamma I \\ \frac{dV}{dt} &= f(I,V)S - \sigma\beta VI \end{aligned} \tag{A.2}$$

In order to calculate the disease-free equilibrium point of this model, we put $I = 0$. However, we quickly notice that regardless of what $f(I,V)$ is, in this case the model doesn't tell us anything about either S or V. The endemic equilibrium point is the same, and brings the same problems, as for model in eq.A.1.
After several variations of the SIRV-model we concluded that including a vaccination-compartment was incompatible with the way we wanted to analyze our model, as when e.g. calculating the basic reproduction number of this model using the Next Generation Method proved impractical.

A.1.2 SEIR

We decided to pivot to a standard SEIR-model, like system 2.3, that we could expand on to represent what we needed to model. This model has a disease-free equilibrium point when both I and E is zero. We get the Jacobian matrix:

$$\mathcal{J}(1,0,0) = \begin{bmatrix} -\mu & 0 & -\beta \\ 0 & -\sigma-\mu & \beta \\ 0 & \sigma & -\gamma-\mu \end{bmatrix}$$

When categorizing the stability of equilibrium points we will use a variation of the Routh-Hurwitz Stability Criterion presented as a theorem by Zabczyk in his book *Mathematical Control Theory: An Introduction* [57] [23]. This is presented as follows:

Polynomials with real coefficients:

i. $\lambda + a$,

ii. $\lambda^2 + a\lambda + b$,

iii. $\lambda^3 + a\lambda^2 + b\lambda + c$,

iv. $\lambda^4 + a\lambda^3 + b\lambda^2 + c\lambda + d$

are stable if and only if, respectively:

i. $a > 0$,

ii. $a > 0, b > 0$,

iii. $a > 0, b > 0, c > 0$ and $ab > c$,

iv. $a > 0, b > 0, c > 0, d > 0$ and $abc > c^2 + a^2 d$.

[23]
For system 2.3, the characteristic polynomial can be written as:

$$p(\lambda) = -(\mu+\lambda)\left((\sigma+\mu+\lambda)(\gamma+\mu+\lambda) - \sigma\beta\right),$$

making $\lambda_1 = -\mu$, and we can use Zabczyk's theorem on the remaining part:

$$(\sigma+\mu+\lambda)(\gamma+\mu+\lambda) - \sigma\beta.$$

This can be rewritten as:

$$\lambda^2 + \lambda(2\mu+\sigma+\gamma) + \sigma\mu + \sigma\gamma + \mu\gamma + \mu^2 - \sigma\beta.$$

From this we get that

$$a = 2\mu + \sigma + \gamma > 0.$$

Using $R_0 = \frac{\beta\sigma}{(\mu+\sigma)(\mu+\gamma)}$ we get

$$b = (\mu+\sigma)(\mu+\gamma) - R_0(\mu+\sigma)(\mu+\gamma) = (1-R_0)(\mu+\sigma)(\mu+\gamma),$$

from which we get that R_0 must be < 1 for the polynomial to be stable, which is consistent with traditional properties of R_0 [6].

A.1.3 Further expansion

In order to expand on the SEIR-model we used Meng, Cai, Si, and Duan as our inspiration [11]. In their work with their model, instead of adding vaccination as a compartment, they establish coefficients representing rates of vaccination and vaccine efficiency and use these as a means to move individuals from susceptibles to exposed and removed. They also introduce a coefficient that denotes the natural birth- and death rate.
First we tried including vaccination rates, but not natural birth- and death rates as our system is closed. We made it so that some vaccinated individuals gain immunity and move from the susceptible-compartment to recovered. We also wanted to take vaccine-efficacy into consideration, and adding a parameter denoting this allowed us to do this. This is illustrated in figure A.2.

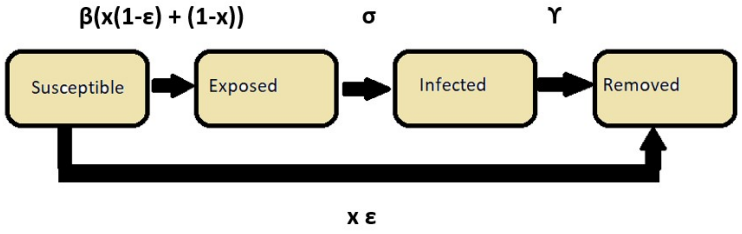


Figure A.2: Flowchart of a SEIR-model with vaccine-parameter.

The new system of equations now looks like this:

$$\begin{aligned} \frac{dS}{dt} &= -\beta SI(x(1-\varepsilon)) + (1-x) - x\varepsilon S \\ \frac{dE}{dT} &= \beta SI(x(1-\varepsilon)) + (1-x) - \sigma E \\ \frac{dI}{dt} &= \sigma E - \gamma I \\ \frac{dR}{dt} &= \gamma I + x\varepsilon S \end{aligned} \tag{A.3}$$

Where β, σ, γ, x, and ε are transmission rate, incubation rate, recovery rate, vaccination rate and vaccine efficiency, respectively. This model has a disease-free equilibrium point when S, E, and I are zero. $S = 0$ is found from $-\beta SI(x(1-\varepsilon)+(1-x)) - x\varepsilon S = 0$ which becomes $-x\varepsilon S = 0$ when $I = 0$. This implies that $S = 0$ but if we think about it intuitively we could say that in a disease-free environment there would be no vaccination, so we can put $x = 0$ instead. This still leaves us with the Jacobian:

$$\mathcal{J}(S,0,0) = \begin{bmatrix} 0 & 0 & -\beta S \\ 0 & -\sigma & \beta S \\ 0 & \sigma & -\gamma \end{bmatrix}$$

And we end with the same problem as for the model in eq.(A.1).

We then chose to add a parameter of birth- and death rate to this system. Assuming that birth- and death rate is the same, we get the flowchart in figure A.3:

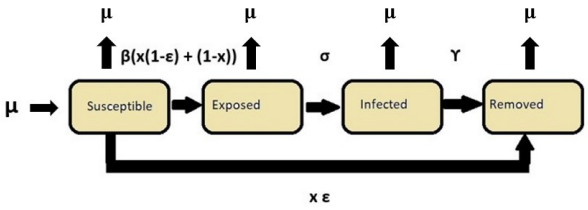


Figure A.3: Flowchart of the final SEIR-model with vaccine-parameter.

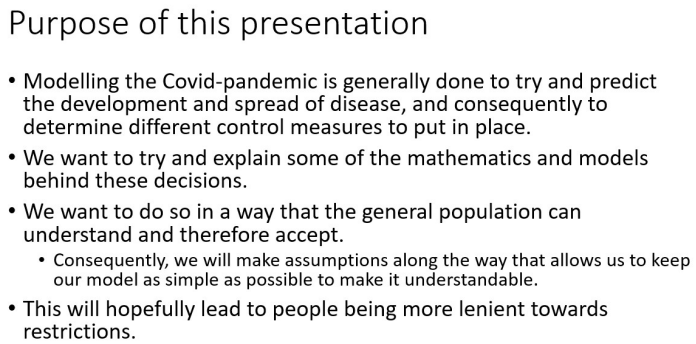
And the final system of equations:

$$\begin{aligned} \frac{dS}{dt} &= \mu - \beta SI(x(1-\varepsilon)+(1-x)) - x\varepsilon S - \mu S \\ \frac{dE}{dT} &= \beta SI(x(1-\varepsilon)+(1-x)) - \sigma E - \mu E \\ \frac{dI}{dt} &= \sigma E - \gamma I - \mu I \\ \frac{dR}{dt} &= \gamma I + xeS - \mu R \end{aligned} \tag{A.4}$$

Where μ, β, σ, γ, x, and ε are the birth-/death-rate, transmission rate, incubation rate, recovery rate, vaccination rate and vaccine efficiency, respectively.

Appendix B

Manuscript



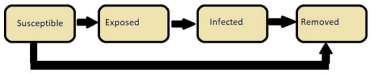
The purpose of this presentation is to try and make the mathematics behind the pandemic a little more understandable. Restrictions and frustration are just some of the many things we've all had to deal with through the past couple of years. Especially during a lockdown or during times with varying levels of infection when health-executives and governments announce more and more strict control measures, one can feel helpless and hopeless if what is being done doesn't make any sense.
Our hope is that knowledge and understanding can help ease some of the hopelessness and frustration and aid in motivation for keeping with the restrictions.
We will demonstrate how mathematical models used in epidemiology work, and develop our own model for a specific scenario. Our model will be much simpler than what the actual situation is like, but the goal is to show how models help us predict possible outcomes and consequently to make decisions about control measures.

Mathematical models

- "All models are wrong, but some are useful." (George E.P. Box)
- A model is just that; a model. It is an attempt to illustrate and/or predict a phenomenon.
- It is not an exact representation of reality. Still, it can be very helpful.
  - A model can never take every factor into account, it can still give somewhat of a picture of a situation and its development. This makes it our best shot at making the best possible decisions.
- In our work we have tried to model a very specific scenario; the spread of the COVID-19-virus with vaccines as the only control measure.
- SEIR-model

The quote by George E.P. Box encompasses very well what a model can be, as it is just that: a model. It is an attempt at illustrating a phenomenon, but it will never be able to replicate reality exactly. The world is unpredictable and there are countless factors coming into play in different situations, which makes it impossible to make a completely accurately prediction.
Some models CAN get close enough to reality and those models can be very helpful. A somewhat realistic prediction can help us prepare for what will happen. SEIR-models are a class of mathematical models used in epidemiology. This is the kind of model we have been developing and working with on our master project.

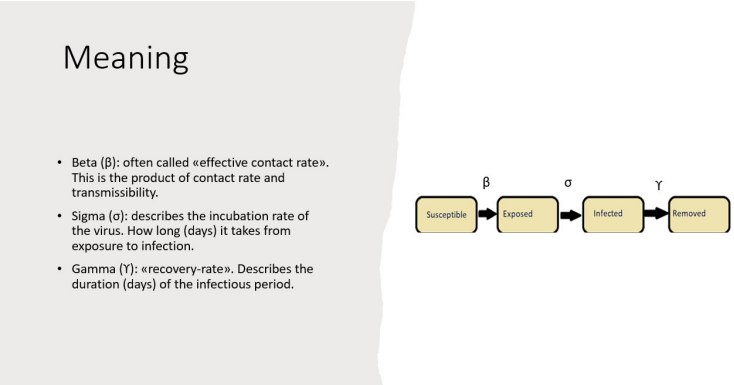
SEIR-model



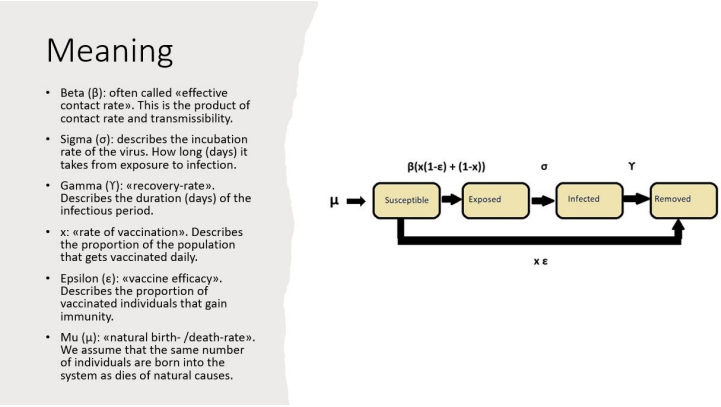
- We divide the population into four groups: susceptible, exposed, infectious and recovered/removed (immune).
  - Susceptible: Healthy individuals that might get infected.
  - Exposed: Individuals that have been exposed to the virus but are not yet infected/infectious.
  - Infected: individuals that are infected and might infect others.
  - Removed: Individuals that have been through infection and have gained immunity through recovery. Vaccines can also provide immunity and allow susceptible individuals to move directly to the "removed-box."
- Mathematical equations describe at which rates people move from one box to the next.
- The model illustrates how large proportion of the population belong to the different boxes at any given time.

These boxes illustrate how the coronavirus travels through the population. First we have to imagine that we divide the population into four categories; susceptible, exposed, infected, and recovered (or removed).
At the beginning of the pandemic, we are all in the susceptible category as the virus has not started spreading and none of us have been exposed yet. Then as time progresses, the virus starts moving. When a person gets exposed to an infected individual it moves to the exposed category. Then after the incubation period this person tests positive and moves to the infected box. Finally, when the person has recovered it moves to the recovered category. We all know that with the different variants one can get reinfected, but for simplicity in our work we have assumed that one gains complete immunity after having had Covid.
In our thesis we have also included vaccines. The arrow at the bottom illustrates those who get vaccinated and then gains immunity and can then count as recovered without having gone through the disease. In reality there are several doses, varying vaccine

efficacy from variant to variant and the fact that the (current) vaccine protects mainly against severe disease and not from infection itself. Again, for simplicity, we assume that some portion of the vaccinated individuals gain immunity, and the rest are unlucky enough to still be susceptible to getting the virus.
In the model itself there are mathematical equations that describe at which rates people move from one box to the next.
We can then illustrate how large proportion of the population belong to the different boxes at any given time.



To describe the change between the boxes, we need some parameters. We start by looking at the three most used. For someone to move from susceptible to exposed they need to come into contact with someone that is infectious. To measure this scenario we use beta, often called effective contact rate. This is the product of contact rate and transmissibility. Then those who are exposed move to the infected box after an incubation period. For this process we use sigma for the incubation rate. Lastly after being sick, you move to the removed box. We use gamma as the recovery rate, which is an average of how many days people are infectious.



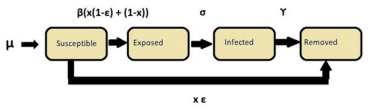
Here we have added three more parameters as we take take birth/death and vaccination into account. Mu is the rate of birth and natural death, which we assume is the same for simplicity. The only way the susceptible-box gets more members is through birth, and we might lose someone in any of the boxes if they die. Here we only look at death from natural causes. If someone dies from the diseases they are still moved to the removed-box. Then for vaccination we have two parameters; x for the rate of which people are vaccinated daily, and epsilon for the vaccine efficacy. Since the vaccine is

not 100% effective, we have chosen to look at a scenario were you either gain immunity or the vaccine has no effect on you. The arrow that moves from susceptible directly to removed symbolises those who are successfully vaccinated, denoted by the rate x times epsilon. Where we on the last slide only had beta, we now see some more terms. We look proportions of the population and therefore use 1 if we speak of the whole population. This means that 1-x describes the portions of the population who are not yet vaccinated. Then similarly those who are vaccinated but did not gain immunity is described by x(1-epsilon).

Equations

$$\frac{dS}{dt} = \mu - \beta SI(x(1-\epsilon) + (1-x)) - x\epsilon S - \mu S$$

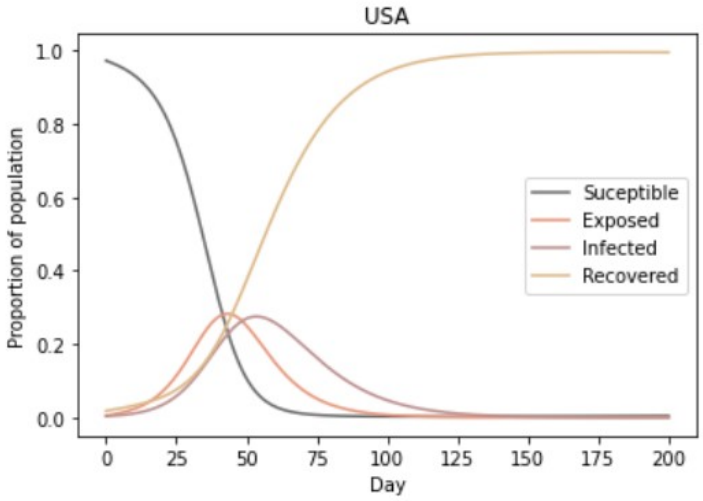
$$\frac{dE}{dT} = \beta SI(x(1-\epsilon) + (1-x)) - \sigma E - \mu E$$



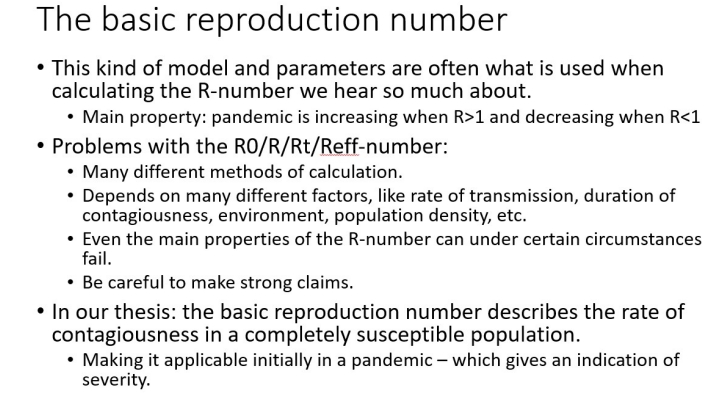
$$\frac{dI}{dt} = \sigma E - \gamma I - \mu I$$

$$\frac{dR}{dt} = \gamma I + x\epsilon S - \mu R$$

Now to make use if these parameters and describe the movement in and out of each box, we have four equations, where dS/dt means the change in the susceptible population per time, which is per day on this case. If the terms are positive it describes movement into the box, while negative terms describe movement out of the box. We can start with the first equation. As we saw in the last slide, mu is for newborns entering the susceptible population. Then we have this big "scary" term that describes those who get exposed to the virus. We see this term between the susceptible and exposed-box. In the term we also see S and I because it matters how many people are moving around and how many infectious individuals are out there that they can come into contact with. Then we have x epsilon S denoting those who get successfully vaccinated. The S is added because we need to take into account how many people can get the vaccine. Then at the end we have mu S for those who dies of natural causes. In the second equation we recognise the first term as those who have become exposed to the virus and have moved from the susceptible-box. Sigma E is for those who are finished with the incubation period. And finally mu E denote those who dies of natural causes. Then again in the third equation we see the sigma E term again, as it describes those who moves from exposed to infected. Then we have gamma I for those who have recovered and are no longer infectious. Then as always, we have the term describing natural death. In the final equation describes the movement in and out of the removed category, we again see the gamma I term. We also have those who got vaccinated and moved from susceptible directly to removed, and finally those who dies of natural causes while in the removed category.

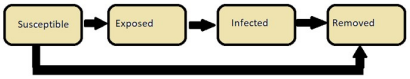


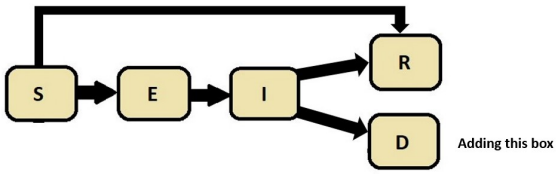
To see the model in action, we here have a simulation with data from 2020 in USA. As mentioned earlier, this simulation has vaccination as the only control measure, so there is no quarantine, no social distancing, people dont stay at home when they are sick, but moves freely around and infect others. On the x-axis we have number of days into the pandemic and on the y-axis, we have the proportion of the people in each the categories. In this specific scenario we get an infection peak at over 25% of the population, which is extremely high. We will look at some more simulations later.



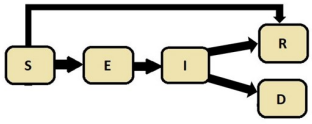
I will now talk a little bit about the R-number that we have heard so much about in the news. Quickly explained the basic reproduction number is defined as the number of new cases an infected individual will cause in a population of completely susceptible individuals.
We can quickly identify one problem; it is confusing. In the media we hear about one R (at least that was my impression), but when reading articles for our thesis we have discovered that there are several different variations of R-numbers. All of these deal with roughly the same thing, but there are differences to each of them.
In our thesis we have been using the basic reproduction number, R0, and have seen that there are many different methods of calculation and that the number can vary depending on the disease and population it describes. A lot of different factors are considered when calculation R0, like factors regarding the disease, for example the infectiousness

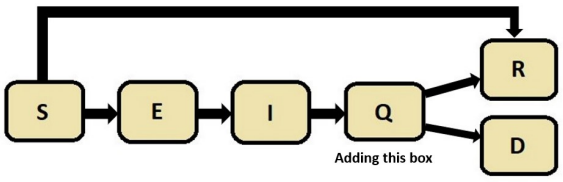
and duration of contagiousness, as well as factors regarding the community, for example the environment and population density.
The R0 used in this paper is supposed to describe the infectiousness in a general population where there is no immunity. As we include vaccines and assume that they do provide immunity, our R0 will not be applicable. Generally it can be used as an indication of expected spread initially in the pandemic.



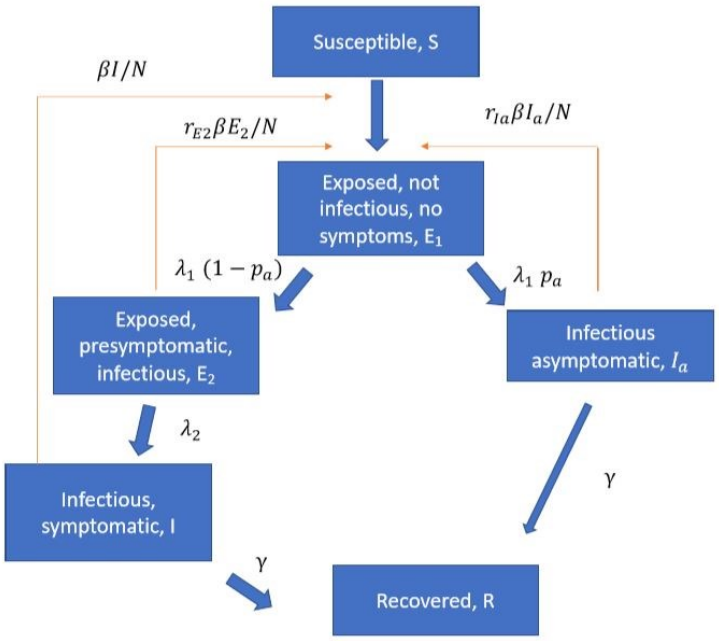


Before we move on I would just like to present a couple examples of ways to expand on this model. If we seek to make the model more realistic we have to include more aspects of reality. In our model we have a removed-box that includes both those who have gained immunity through recovering from the virus as well as those who die from it. In reality one would absolutely not put these individuals in the same category. Here you see an example of a flowchart where we separate these individuals into two different compartments by adding a box that will include those who sadly dies from the disease, which we will call a SEIRD-model. In this case everyone is a susceptible individual initially, before they eventually gain immunity through vaccination or get exposed to the virus. Following exposure comes infection, as we have already seen. But in this example we rightfully differentiate between what happens next; one either recovers and gains immunity or one passes away.





To complicate things even further we can add another box to the model that includes infected individuals that are in quarantine. In this scenario we assume that shortly after an individual gets infected it is placed in quarantine, where he or she cannot infect any more individuals. The flowchart follows the same order as in the SEIRD-model, only following infection we add a "quarantine"-compartment. Now infected individuals are "safely" isolated while they wait to either recover or die. We can call this version a SEIQRD-model. Both in this and the SEIRD-model different parameters and equations will describe how quickly individuals move from one compartment to the next, as we have already seen for the SEIR-model. As we add compartments to the model it gets more and more complicated, but we also see that it includes various aspects of the Covid-reality we actually recognize.



Different goals and uses require different models. Now we have learned so much that we can take a quick look at the actual model used by FHI in Norway [1]*. Instead of adding compartments describing individuals who pass away or are in quarantine, FHIs needs require them to rather include compartments that differentiate between symptomatic and asymptomatic exposed and infected individuals.*

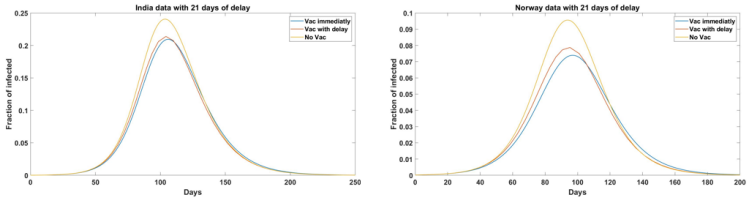
[1] Picture taken from FHI/NIPH article (May 26th 2022): De Blasio, B. F. et.al. *Coronavirus modelling at the NIPH*. From https://www.fhi.no/en/id/infectious-diseases/coronavirus/coronavirus-modelling-at-the-niph-fhi/.

DDE (Delayed Differential Equations)

- Estimated that it takes between 12 and 21 days to become well protected against serious illness from the disease after first dose.
- Added a delay on the vaccination term in the model
- This means that those who are vaccinated are not removed from the S-category immediately

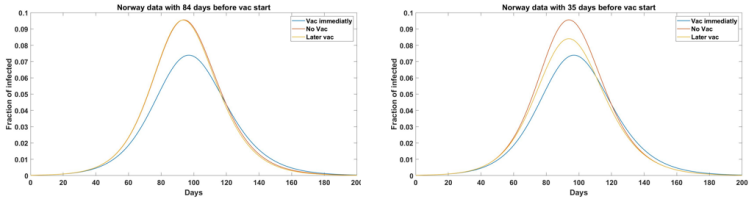
Different research report that it takes 12 to 21 days from the vaccine is given, to it is effective. To take that into account I have added a delay in the successful vaccination term. This makes it so that those who are successfully vaccinated are not move to the removed box immediately but will remain in the susceptible box for a certain amount of time. While they are there, they can still get infected. The math behind this is not so important to understand, but we can look at some simulation to see the effect of the delay.

Numerical analysis with the added delay



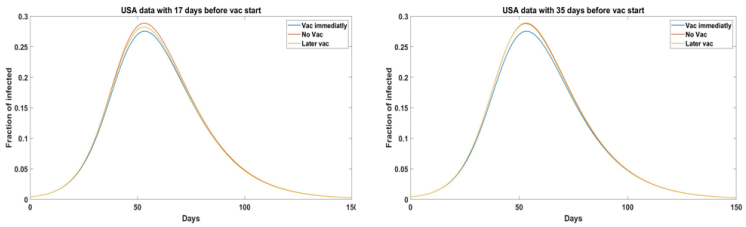
On the left side we have a simulation done with data from India. Here we only look at the fraction of infected since thats what matters. The blue line shows the outcome of the vaccine working immediately, the orange shows the effect of the delay, while the yellow line is for the case of no vaccination. We see a clear difference between immediately vaccine and no vaccine, but the delay seems like it doesnt matter a lot. The difference is only 0.5% but with India having a population of 1.38 billion people, that is 6.9 million people, so it matters a lot. On the right side, we have the same graphs, but with data from Norway. Here we see that infection peak is a lot smaller, but the delay still affects the peak with 0.5%.

Later vaccination start in Norway



Now what if instead of a delay between the dose it set, to it working, we add a delay before vaccination starts. We rarely have a vaccine ready at day one, so here we can see how long we have before it is to late to start the vaccination. Again, this is in a scenario where we have no other control measures. With the Norwegian data, we can see that using vaccination to lower the peak of infection, loses half of its value if the vaccination starts 35 days later, and the vaccine will have no effect if the start is after 84 days. This is on a scenario where the peak hits after roughly 100 days. Let us look at the same scenario with data from USA.

Later vaccination start USA



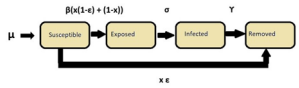
Here we see the peak hits after 50-60 days, so the vaccine loses half of its effect if it only starts 17 days later, and the whole effect after only 35 days. We can see in these scenarios that the pandemic happens so fast, that the vaccination does not have enough time to make a difference. Therefore, we need to flatten the curve with some other control measure to give the vaccine room to work with.

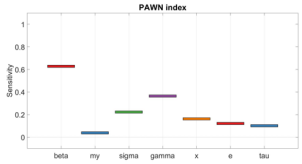
Sensitivity analysis

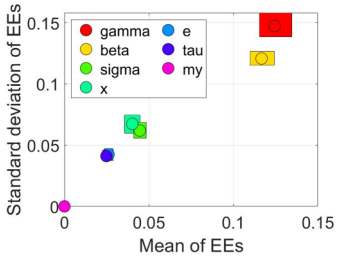
- How do we flatten the infected curve?
- Trying to find out the relative importance of the different parameters
- Global sensitivity analysis

So how do we flatten the curve? I have done a sensitivity analysis to find out which of the parameters makes the biggest difference on the infection peak. The math behind it includes a lot of statistic, so we will here rather focus on what the analysis tells us.

Results from SAFE toolbox







A couple of mathematicians have made a software called SAFE toolbox design to do sensitivity analysis. Using this software, I have done an analysis with two different methods called PAWN and Elementary effect. On the left side we have the result of the PAWN method. On the x-axis we have the parameters and on the y-axis the sensitivity. The sensitivity is a measure of how much the parameter affect the outcome, which is the infection peak. High sensitivity means that the parameter has a large effect. Here we can clearly see that beta, the effective contact rate matters the most, followed by the recovery rate gamma. On the right side we have the Elementary Effect Test, here it is gamma that matters the most, closely followed by beta. Even though the methods have different outcome, they agree that reducing beta and/or gamma is the way to reduce the infection peak. Based on this analysis, control measures like social distancing to reduce the number of contacts, and quarantine to indirectly reduce gamma, by removing those who are infectious from the rest of the population, seems to make the most sense.

Appendix C

Calculations done in chapter 3

In order to get

$$det(J-\lambda I) = [(1-R_0)(x\varepsilon+\mu)-x\varepsilon-\mu-\lambda][(-\sigma-\mu-\lambda)(-\gamma-\mu-\lambda)-\frac{\sigma\beta\mu(1-x\varepsilon)}{R_0(x\varepsilon+\mu)}]$$

$$+(1-R_0)(x\varepsilon+\mu)\frac{\sigma\beta\mu(1-x\varepsilon)}{R_0(x\varepsilon+\mu)} = 0$$

on the form of: $\lambda^3 + a\lambda^2 + b\lambda + c$, the following calculations were made:

$$(1-R_0)(x\varepsilon+\mu)(-\sigma-\mu-\lambda)(-\gamma-\mu-\lambda) - (1-R_0)(x\varepsilon+\mu)\frac{\sigma\beta\mu(1-x\varepsilon)}{R_0(x\varepsilon+\mu)}$$

$$-(x\varepsilon+\mu+\lambda)(-\sigma-\mu-\lambda)(-\gamma-\mu-\lambda)+$$

$$(x\varepsilon+\mu+\lambda)\frac{\sigma\beta\mu(1-x\varepsilon)}{R_0(x\varepsilon+\mu)} + \frac{\sigma\beta\mu(1-x\varepsilon)(1-R_0)}{R_0} = 0$$

This is rewritten as:

$$-\lambda^3 - \lambda^2(2\mu+\sigma\gamma-(1-R_0)(x\varepsilon+\mu)+x\varepsilon+\mu)$$

$$-\lambda[\mu^2+\sigma\gamma+\sigma\mu+\mu\gamma-(1-R_0)(x\varepsilon+\mu)(\sigma+2\mu+\gamma)+$$

$$(x\varepsilon+\mu)(\sigma+\gamma+2\mu) - \frac{\sigma\beta\mu(1-x\varepsilon)(1-R_0)}{R_0(x\varepsilon+\mu)}]$$

$$+(1-R_0)(x\varepsilon+\mu)(\gamma+\mu)(\sigma+\mu) - (x\varepsilon+\mu)(\gamma+\mu)(\sigma+\mu)+$$

$$\frac{\sigma\beta\mu(1-x\varepsilon)(1-R_0)}{R_0} = 0$$

Since $R_0 = \frac{\beta\mu\sigma(1-x\varepsilon)}{(\gamma+\mu)(\sigma+\mu)(xe+\mu)}$ we can write $\frac{\beta\mu\sigma(1-x\varepsilon)}{R_0(xe+\mu)} = (\gamma+\mu)(\sigma+\mu)$ Using that and multiplying with -1 we get

$$\lambda^3 + \lambda^2(2\mu+\gamma+\sigma+R_0(x\varepsilon+\mu))$$

$$+\lambda(R_0(xe+\mu)(2\mu+\gamma+\sigma)) + (R_0-1)(\gamma+\mu)(\sigma+\mu)(x\varepsilon+\mu) = 0$$

and we can identify the constants a, b and c.

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