Impact of Vaccination and Mobility on Disease Dynamics: A Two Patch Model for Measles

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Abstract

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Infectious diseases have played a major role in shaping humanity throughout history. Understanding the dynamics of infectious diseases is a critical aspect in the creation of public health policies when determining the best course of action to take when an epidemic takes hold of a society.

Since the introduction of vaccines, many deaths due to various diseases including measles, have been drastically reduced. In Canada, there is a recommended vaccine schedule for all residents of the country; however, vaccine practises and immunisation schedules can vary from location to location as well as vary from country to country, leading to discrepancies in vaccine coverage and herd immunities. In addition, some anti-vaccination movements have been noted to persuade individuals into refusing vaccines, even in historically well immunised locations. In order to investigate the effect of varying vaccine coverage, a two patch metapopulation model for measles incorporating a single dose vaccine is formulated and studied.

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Introduction

1.1 Measles

Vaccinations are a crucial part of modern medicine as they have played a critical role in decreasing the impact of various potentially deadly infectious diseases including (but not limited to) measles, mumps, rubella, diphtheria, pertussis and smallpox. Due to vaccination strategies implemented around the world, smallpox has been eradicated and morbidity rates have declined for many other diseases for which vaccines exist [13].

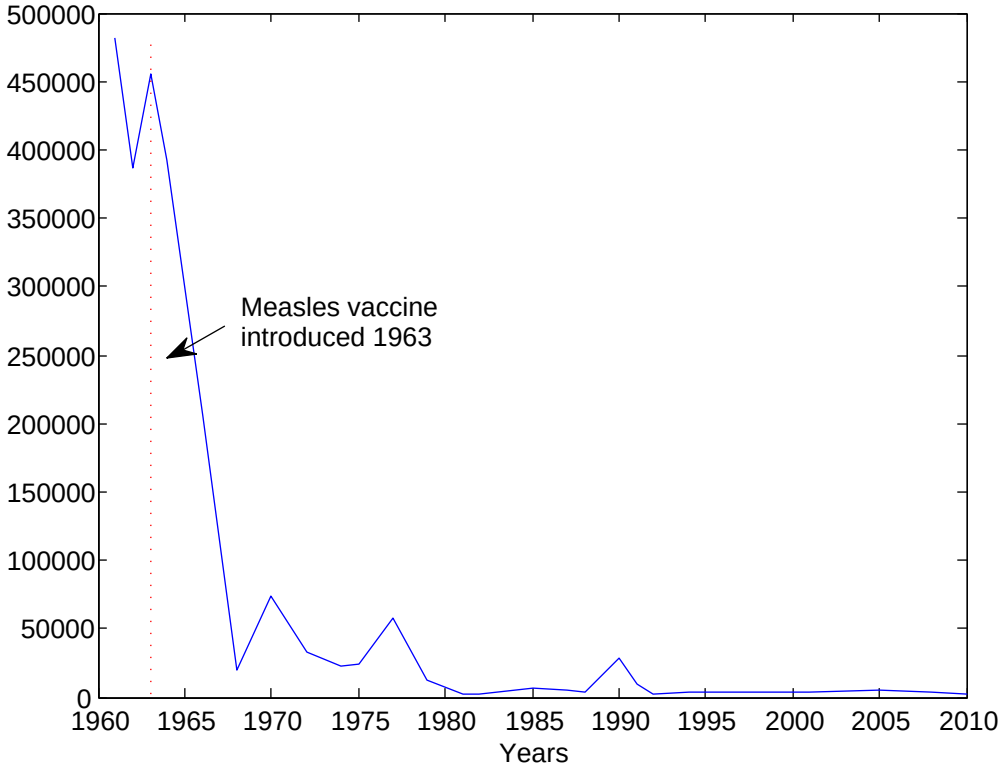

FIGURE 1.1: Measles incidence in the USA from 1961 - 2010. Data from US Centers for Disease Control and Prevention.

This thesis will focus on measles, a highly contagious viral disease that has the potential to be fatal, particularly in young children and adults over 20 years of age. It is estimated that the expected number of secondary infections from a single infectious individual in a wholly susceptible population is 18 [17], the mark of a highly transmissible disease. It remains one of the leading causes of death among children around the world, despite vaccinations being readily available, and it is estimated that there are 10 million cases of measles worldwide each year [24]. According to the World Health Organisation (WHO), measles caused approximately 114,900 deaths in 2014; however, this number is considerably lower than the 546,800 deaths caused by measles in the year 2000 [35].

Measles begins with a high fever, beginning 10 to 12 days after exposure to the virus and potentially lasting up to 7 days. After several days, a rash lasting 5 to 6 days begins and eventually spreads over the entire body. According to WHO, most measles-related

deaths are caused by complications of the disease including encephalitis, severe diarrhoea or pneumonia. Individuals prone to measles are likely to have a deficiency in vitamin A or have a weakened immune system. The WHO also notes that in populations lacking proper health care and nutrition, up to 10% of measles cases result in death.

The group of individuals most at risk for contracting measles are unvaccinated individuals. This is true in particular for individuals living in developing countries where measles is still prevalent. The virus is spread through droplets of nasal and throat secretions and can live up to 2 hours in air or on surfaces. Measles can be transmitted by an infected person 4 days prior to the eruption of the rash to 4 days after the rash begins. Since there are no antiviral treatments for measles, vaccination provides the best protection against the disease. The vaccine is safe, effective and inexpensive (it costs approximately one US dollar to immunise an individual). The measles vaccine is often combined with rubella and/or mumps vaccines (MMR), and provides the same level of protection as when administered alone while only slightly raising the cost.

According to the Public Health Agency of Canada [32], the routine childhood immunisation schedule recommends that children receive their first dose of the MMR vaccine at 12 to 15 months of age and the second dose at 18 months to 5 years of age (prior to beginning school). There are also vaccine schedules for individuals who were not previously immunised as infants; this schedule calls for the two doses of the vaccine to be administered at least 4 weeks apart. Measles is also a reportable disease in Canada and must be reported by health professionals to local public health departments. It is estimated that 15% of vaccinated individuals fail to develop immunity after a single dose, thus the protection for these individuals against contracting measles is provided by the successful immunisation of others within the same community. This concept is referred to as herd immunity [17].

1.2 Herd immunity

Herd immunity is a term used in public health to describe the fact that achieving a critical proportion of vaccinated individuals in a population can protect a community against a disease when an outbreak occurs. In other words, if a given threshold of individuals are immune to a disease, then the remaining susceptible individuals within a given population are protected. The main method used to induce herd immunity is vaccination. Herd immunity plays an important role in controlling the spread of measles, since humans are the only natural hosts of the disease. It is estimated that at least 90% of a population must have immunity to measles in order to maintain herd immunity [15]; however, even when this critical threshold is met, it does not seem to prevent annual epidemics in developing countries and there are also cases where outbreaks of measles still occur in developed countries [15].

1.3 Vaccination practises in Canada and around the world

Although herd immunity seems reliable, in reality there is the potential for vaccinations to wane or for individuals to choose not to vaccinate, thus decreasing the effectiveness of herd immunity. In Canada during 1990-1998, there was an outbreak of pertussis caused by the waning of a vaccine after mass immunisation took place during that time frame [22]. This outbreak was troubling as the people who contracted the disease were adults who had been immunised as children, indicating that the vaccine had most likely waned over time and these individuals were now able to potentially spread the disease to unvaccinated, young children [22].

In recent years, the anti-vaccination movement has skyrocketed. A plethora of websites and various literature is now at the fingertips of parents questioning whether to vaccinate their children [20]. The justifications for choosing not to vaccinate or to delay vaccination varies, but can include religious beliefs, fears of risks associated with vaccines and the disbelief in the effectiveness of vaccines [26]. In Southwest Alberta, Canada, a qualitative

study was conducted in order to investigate why individuals choose not to vaccinate. The sample included people of Dutch background, Hutterites and parents and practitioners who engage in alternative health practises [26]. The authors found that the main reason for individuals refusing or delaying immunisation included the belief that children were not at risk because diseases such as polio and diphtheria were only present in third-world countries. Religion also played a role in the decision making for Hutterites as they explained to the authors that the health status of a child was subject to God's will. This group also noted that countries in Europe had ceased vaccinations with no negative impact on their populations, attributing to their belief that the same would happen for their population [26]. In 2013, the Netherlands reported an outbreak of measles which occurred in communities where MMR vaccination rates were below 90%. Most of the cases were orthodox Protestants who were unvaccinated due to religious beliefs or critical attitudes toward vaccination. In order to help control the spread of the disease, measures were put in place to offer personal invitations to individuals residing in communities where MMR vaccination rates were below 90%, including those of orthodox Protestant faith. This vaccination campaign is unique to the Netherlands and has since helped to reduce the spread of measles with orthodox Protestant communities, as it is now estimated that only 15% of individuals from this group refuse vaccinations; much lower than the 92% it had been in the past [25].

1.4 Availability of health services in remote locations

Not only does the anti-vaccination movement have an impact on the resurgence of infectious diseases, but the health services and education available to individuals in remote locations can also contribute to the increasing number of outbreaks. In Manitoba, there are approximately 88,000 registered First Nations individuals residing on First Nations Communities (Reservations) and 63 First Nations Communities. Of those communities, 23 are not accessible by an all-weather road and this accounts for more than 74,000 individuals residing within remote reservations [31]. Some health care related issues faced by

individuals living in remote or rural communities include limited availability of health care services within the community due to infrastructure or other factors, scarcity of resources and varied enablement of health professionals to work at their full scope due to the lack of tools available in rural and northern areas [34]. Thus, many individuals from rural and remote communities must travel to larger urban areas in order to seek medical attention and health care; however, there are currently no studies investigating vaccine behaviours among individuals of Aboriginal descent within Canada [11].

Investigating studies which have been conducted in other rural communities around the world may help provide some insight into vaccination accessibility and practises in rural Canadian communities. In [30], the authors studied rural areas in Kenya and investigated whether spatial distancing from health care and socio-demographic status had an effect on the timeliness of immunisation administration. The authors conducted a vaccine coverage survey and found that travel time did not effect vaccine coverage or timeliness, when the maximum pedestrian and vehicular times to vaccine clinics was less than 3 hours and 2.5 hours, respectively. The authors also stated that although travel time did not have an effect on time-to-immunisation, other factors such as harvest season could impede travel and thus, reduce timely administration of immunisations.

A study was also done on immunisation practises of hard to reach populations in Papua New Guinea [43]. The authors of this paper conducted a household survey to collect information on the number of children aged 12 to 23 months who had been vaccinated according to the national immunisation schedule. Due to the geographical landscape of the country, some areas were more difficult for health care professionals to access or for individuals to travel from due to climate or terrain. Based on the survey, the authors concluded that late delivery of vaccinations was a problem throughout Papua New Guinea and that this was due to a mixture of lack of health care access, but also parental lack of knowledge of the benefits of immunisation as well as misconceptions around vaccinations. Therefore, due to the importance of timely vaccine administration in maintaining herd immunity and staving off potential epidemics, individuals residing

in remote communities may be required to travel to larger, urban centres in order to seek proper medical care.

1.5 Travel and the spread of disease

According to the Public Health Agency of Canada, outbreaks of measles, diphtheria, pertussis and other highly contagious but immunisable diseases in Canada are relatively rare compared to other countries in Europe and Africa due to high immunisation rates [32]. However, travel between countries in which measles is endemic or prevalent can have negative impacts in countries such as Canada and the United States. In 2011, Utah experienced an outbreak of measles when a teenager returned to Salt Lake City after travelling to Europe. The teenager was unvaccinated against measles and spread the disease to family members and fellow students. In 2011, there were 220 confirmed cases of measles in the United States, with 89% of those infections originating from unvaccinated individuals who had travelled abroad [12]. There was also a case in 2010 where a 23-month-old infected and contagious with measles travelled from Europe to the US. The US Centres for Disease Control and Prevention (CDC) did an investigation of the passengers who were on the same air plane as the child, and discovered that one other adult had become infected with measles as well. This was a concern since the adult was a chaperone to 270 students from Europe and Asia; continents where immunisation rates are not as high as North America [24].

1.6 Summary

Overall, it is clear that vaccinations and mobility play a role in the spread of infectious diseases, including measles. The focus of this thesis will be to use a mathematical model in order to investigate the effect varying vaccination rates as well as movement rates between two geographic locations of different size and socioeconomic status has on the transmission dynamics of measles. As mathematical definitions and notations are

needed in order to analyse the model, these are introduced in Chapter 2. The focus of Chapter 3 is to describe and define epidemiology and mathematical epidemiology terms and in Chapter 4, a mathematical epidemiology literature review is provided. Chapter 5 introduces the mathematical model which is the focus of this thesis and Chapter 6 provides mathematical analysis of the model presented in the previous chapter and provides an overview of the model. Chapter 7 includes numerical simulations and the final chapter provides some conclusions as well as ideas for future work.

Chapter 2

Mathematical Preliminaries

2.1 Ordinary Differential Equations

The use of mathematical models to investigate the dynamics of a disease dates as far back as the 1760s, when Daniel Bernoulli studied inoculation against smallpox [5]. In compartmental mathematical modelling, the independent variable is time t and the rates of transfer between compartments can be expressed as derivatives with respect to time of the sizes of the compartments. Thus, the model formulated in this thesis consists of differential equations, where interest lies in the qualitative nature of the model; that is, what is the behaviour of solutions as $t \to \infty$? When using differential equations to describe a model, it is assumed that the epidemic process is deterministic, meaning that the behaviour of the population is determined only by its history and the assumptions created to describe the model [45].

The following is based on material from [7, 16, 18, 37, 39].

2.1.1 First Order Differential Equations

It is important to understand ordinary differential equations (ODEs) as they are often used in mathematical modelling of populations and disease dynamics and will be used

throughout this thesis.

A simple model which shows that the constant rate (r) at which a population (P) is changing with respect to time (t) is given by the differential equation

$$\frac{dP}{dt} = rP.$$

In the above equation, which is often referred to as Malthusian growth, it is assumed that the rate of change of population size is directly proportional to the population size. However, this assumption leads to a solution

$$P(t) = P(0)e^{rt}$$

where $P(0)$ is the initial condition. Since it is not realistic to assume that a population can maintain exponential growth indefinitely, the model should be modified.

A more succinct model for population growth includes the assumption that the growth rate, which is the difference between reproduction and death rates, decreases with population size. The famous differential equation including the above assumption as well as competition amongst species used to describe the change in a population over time is the known as the **logistic growth equation**

$$\frac{dP}{dt} = r\left(1 - \frac{P}{K}\right)P, \tag{2.1}$$

where r and K are both constant, r is the growth rate and K represents the carrying capacity of the population.

2.1.2 Notations, Definitions and Theorems

A first order differential equation takes the form

$$\frac{d}{dt}x(t) = f(t, x(t)), \tag{2.2}$$

where $t \in \mathbb{R}$ is an independent variable, $x(t)$ is an unknown function and $f : \mathbb{R}^n \to \mathbb{R}$. If no ambiguity arises, then the dependence of $x(t)$ on t is often dropped; and $\frac{d}{dt}x$ is abbreviated x' such that (2.2) is denoted

$$x' = f(t, x). \tag{2.3}$$

If the vector field f does not depend explicitly on time, then (2.2) is said to be *autonomous* and takes the form

$$x' = f(x) \tag{2.4}$$

and the general solution is

$$x(t) = \int_{t_0}^{t} f(\tau)d\tau. \tag{2.5}$$

For $f_i : \mathbb{R}^n \to \mathbb{R}^n$ and $x_i \in \mathbb{R}^n$, a system of ordinary differential equations is defined when $n > 1$, otherwise the equation is scalar for $n = 1$.

In applications, it is important to determine a particular solution, rather than a general solution. To do this, initial conditions are needed.

Definition 2.1. (Initial Value Problem) A first order differential equation together with an initial condition,

$$x' = f(t, x) \tag{2.6a}$$

$$x(t_0) = x_0 \tag{2.6b}$$

is called an **initial value problem**. A solution of an initial value problem is a differentiable function $x(t)$ such that

1. $x'(t) = f(t, x(t))$ for all t in an interval containing t_0 where $x(t)$ is defined, and
2. $x(t_0) = x_0$.

Thus, the solution can be expressed in integral notation as

$$x(t) = x_0 + \int_{t_0}^{t} f(\tau, x(\tau))d\tau.$$

The system of ODEs analysed in this thesis is autonomous and takes the form $x' = f(x)$, with $x \in \mathbb{R}^8_+$ and $f : \mathbb{R}^8_+ \to \mathbb{R}^8_+$.

Definition 2.2. (Well-posededness). System (2.6) is well-posed if solutions exist, are unique, and for systems describing populations, solutions remain bounded and are non-negative for all non-negative initial conditions.

Theorem 2.3. *(Cauchy-Lipschitz) Consider the differential equation* (2.6) *with* $x \in \mathbb{R}^n$, *and suppose that* $f \in \mathbb{C}^1$. *Then there exists a unique solution of* (2.6) *that* $x(t_0) = x_0$, *where* $t_0 \in \mathbb{R}$ *and* $x_0 \in \mathbb{R}^n$, *defined on the largest interval* $t_0 \in I$ *on which* $f \in \mathbb{C}^1$.

Definition 2.4. (Equilibrium point) Consider equation (2.4). Then x^* is an equilibrium solution of (2.4) if $f(x^*) = 0$.

Definition 2.5. (Locally stable equilibrium point) An equilibrium solution, x^* of (2.4), is said to be locally stable if for all $\epsilon > 0$, we can find $\delta > 0$ (depending on ϵ) such that if $\Psi(t)$ is any solution of (2.4) having $||\Psi(t_0) - x^*|| < \delta$, then the solution $\Psi(t)$ exists $\forall$ $t \geq t_0$.

Definition (2.5) holds for any norm; however, for convenience the Euclidean norm can be used since this norm is the Euclidean distance which makes neighbourhoods spherical.

Definition 2.6. (Locally asymptotically stable equilibrium point) An equilibrium solution, x^* of (2.4), is said to be locally asymptotically stable if it is locally stable and if there exists a number $\delta_0 > 0$ such that if $\Psi(t)$ is any solution of (2.4) having $||\Psi(t_0) - x^*|| < \delta_0$, then $\lim_{t\to+\infty} \Psi(t) = x^*$.

Definition 2.7. (Globally asymptotically stable equilibrium point) An equilibrium solution, x^* of (2.4), is said to be globally asymptotically stable (with respect to $\Omega \subset \mathbb{R}^n$) if for all initial conditions in Ω, solutions approach x^* as $t \to \infty$.

An equilibrium solution is said to be **unstable** if it is not stable.

2.1.3 Linearisation

In order to study a nonlinear system of ODEs, it can be helpful to linearise the system. The Hartman-Grobman Theorem 2.9 allows approximation of a nonlinear system of ODEs about equilibria by a corresponding linear system. This system can be found by computing the system's Jacobian matrix at a given equilibrium point.

Theorem 2.3 implies that, for smooth functions $f : \mathbb{R}^n \to \mathbb{R}^n$, the solution $x(t) \in \mathbb{R}^n$ to the initial value problem is defined at least in some neighbourhood $t \in (-c, c)$ of $t = 0$ where $c > 0, c \in \mathbb{R}_+\backslash\{0\}$. Thus a local flow, $\phi_t : \mathbb{R}^n \to \mathbb{R}^n$, is defined by $\phi_t(x_0) = x(t, x_0)$.

When studying systems of ODEs, it is important to characterise the behaviour of solutions near a fixed point (often referred to as an equilibrium point) x^*. Studying the dynamics of nonlinear systems can be simplified when the system (2.6) is linearised at x^* such that

$$\xi' = Df(x^*)\xi \tag{2.7}$$

where $Df = [\partial f_i/\partial x_j]$ is said to be the Jacobian matrix of first partial derivatives of the function $f = (f_1(x_1, \ldots, x_n), f_2(x_1, \ldots, x_n), \ldots, f_n(x_1, \ldots, x_n))^T$.

Definition 2.8. A homeomorphism, or continuous transformation, is a one-to-one correspondence between points in two spaces and is continuous in both directions.

Theorem 2.9. *(Hartman-Grobman) If $Df(x_0)$ has no zero or purely imaginary eigenvalues then there is a continuous transformation, also known as a homeomorphism, h, defined on some neighbourhood U of x_0 in $\mathbb{R}^n$ locally taking orbits of the nonlinear flow ϕ_t of (2.6), to those of the linear flow $e^{tDf(x_0)}$ of (2.7). The homeomorphism preserves the sense of orbits and can also be chosen to preserve parameterization by time.*

2.2 Some useful results in matrix analysis

Let $\mathcal{M}_n \in \mathbb{C}^n$ be the set of all $n \times n$ square arrays

$$\begin{pmatrix} a_{11} & a_{21} & \ldots & a_{1n} \\ a_{21} & a_{22} & \ldots & a_{2n} \\ \vdots & \vdots & \ddots & \vdots \\ a_{n1} & a_{n2} & \ldots & a_{nn} \end{pmatrix},$$

where the entries in the matrix are denoted a_{ij} with the location of the entry being in the i^{th} row and j^{th} column.

Definition 2.10. The spectrum of a matrix $A = [a_{ij}] \in \mathcal{M}_n$, denoted $\sigma(A)$, is the set of all eigenvalues of A.

Definition 2.11. The spectral radius of a matrix $A = [a_{ij}] \in \mathcal{M}_n$, denoted $\rho(A)$, is the eigenvalue of A having maximum modulus.

Definition 2.12. A matrix $A = [a_{ij}] \in \mathcal{M}_n$ is said to be non-negative if all entries are ≥ 0.

Definition 2.13. A matrix $A = [a_{ij}] \in \mathcal{M}_n$ is said to be positive if all entries are strictly greater than 0.

Theorem 2.14. *Let $A = [a_{ij}] \in \mathcal{M}_n$ be non-negative. Then the spectral radius $\rho(A) = \max\{|\lambda|, \lambda \in \sigma(A)\}$ is bounded by the minimum and maximum of the column sums and the minimum and maximum of the row sums.*

Theorem 2.15. *If $A = [a_{ij}] \in \mathcal{M}_n$ is positive, then the geometric multiplicity of the spectral radius of A as an eigenvalue of A is 1.*

Definition 2.16. A matrix $A = [a_{ij}] \in \mathcal{M}_n$ is *diagonally dominant* if the absolute value of the diagonal entries is greater than or equal to the absolute sum of the off diagonal entries. The matrix A is *strictly diagonally dominant* if the absolute value of the diagonal entries is greater than the absolute sum of the off diagonal entries.

Theorem 2.17. *Let $A = [a_{ij}] \in \mathcal{M}_n$ be non-negative. Then the spectral radius is strictly positive if any main diagonal entry of A is positive.*

Definition 2.18. A matrix $A = [a_{ij}] \in M_n$ is reducible if there is a permutation matrix $P \in M_n$ such that

$$P^T AP = \begin{pmatrix} B & C \\ 0_{n-r,r} & D \end{pmatrix} \text{ and } 1 \leq r \leq n-1$$

where B and D are square matrices having size of at least 1.

Definition 2.19. A matrix $A = [a_{ij}] \in M_n$ is irreducible if it is not reducible.

Theorem 2.20. *(Perron-Frobenius). Let $A = [a_{ij}] \in M_n$ be irreducible and non-negative, and suppose that $n \geq 2$. Then*

(a) $\rho(A) > 0$

(b) $\rho(A)$ is an algebraically simple eigenvalue of A

(c) there is a unique real vector $x = [x_i]$ such that $Ax = \rho(A)x$ and $x_1 + \ldots + x_n = 1$; this vector is positive

(d) there is a unique real vector $y = [y_i]$ *such that* $y^T A = \rho(A)y^T$ *and* $x_1y_1 + \ldots + x_ny_n = 1$*; this vector is positive*

2.3 Lyapunov Functions

The material in this section has been taken from [46].

The method of Lyapunov functions is often used to determine the stability of equilibrium points when an equilibrium point is nonhyperbolic, and more specifically, to determine global stability of an equilibrium point.

Recall that local asymptotic stability implies that we begin in a specified neighbourhood of the equilibrium point. However, with the use of Lyapunov functions, it is possible to make this result more precise by determining stability of the equilibrium point in $\mathbb{R}^n$.

Theorem 2.21. *Consider the following vector field*

$$x' = f(x), \qquad x \in \mathbb{R}^n. \tag{2.8}$$

Let x^* *be a fixed point of* (2.8) *and let* $V : U \to \mathbb{R}$ *be a* $\mathcal{C}^1$ *function defined on some neighbourhood* U *of* x^* *such that*

i) $V(x^*) = 0$ *and* $V(x) > 0$ *if* $x \neq x^*$.

ii) $V'(x) \leq 0$ *in* $U - \{x^*\}$.

Then x^* *is stable. Moreover, if*

iii) $V'(x) < 0$ *in* $U - \{x^*\}$ *(strict Lyapunov function)*

then x^* *is asymptotically stable.*

Furthermore, if U can be chosen to be all of $\mathbb{R}^n$ in Theorem 2.21, then the fixed point, x^* is said to be **globally stable** if (i) and (ii) hold and **globally asymptotically stable** if (i) and (iii) hold.

Chapter 3

Epidemiological and Mathematical Epidemiology Preliminaries

The focus of this chapter is to define public health terms which are relevant to the model studied in this thesis. It is important to note that terms used in public health have specific meanings and may differ from general definitions. The following material has been adapted from [38, 48].

3.1 Epidemiological terms and definitions

The definition of health has varied over time, but the underlying message of health promotion and disease prevention is present across the board. In 1984, The World Health Organisation defined health as

> [**Health**] is the extent to which an individual or group is able on the one hand to realise aspirations and satisfy needs, and, on the other hand, to change and cope with the environment. Health is therefore seen as a resource for

> everyday life, not the objective of living; it is a positive concept emphasising social and personal resources as well as physical capacities.

When investigating the dynamics of a disease within a Canadian population, it is important to consider what health means to Canadians. In 1986, [9] proposed a definition for health, highlighting that "health recognises freedom of choice and emphasises the role of individuals and communities in defining what health means." From this definition, 'freedom of choice' may been seen as freedom to choose whether or not to vaccinate, which has an effect on the health of communities under consideration.

Population is generally defined as the number of people in given geographic or political area. When studying the dynamics of a disease within a population, it is important to make a distinction between *de facto* (individuals actually present in a location at the time of counting) and *de jure* (individuals who usually belong to a specific area, but are momentarily absent) in order to decide who should be included in the total population in question. Since the movement of individuals from one geographic location to another plays a role in the spread of diseases, the model presented in this thesis will consider individuals present within a region at the time of study.

The term **population health** can be seen as a "conceptual framework for thinking about why some people are healthier than others and the policy development, research agenda, and resource allocation that flow from this." On the other hand, **public health** refers to organised efforts by a community and the government to provide services and programs in order to prevent disease and promote health. Examples of these efforts can include immunisation programs or education focused around healthy lifestyle choices for families.

Epidemic, endemic and pandemic differ in meaning. An **epidemic** is usually short-lived and affects a given geographical region and specific population. A **pandemic** is an epidemic, but on a larger scale. According to the Dictionary of Epidemiology, a pandemic is defined as an "epidemic occurring worldwide, or over a very wide area, crossing international boundaries and usually affecting a large number of people". Examples of

diseases considered pandemic are Black Death, which occurred in the mid-fourteenth century and severe acute respiratory syndrome (SARS), a more modern example which spread to over two dozen countries in 2003. On the other hand, a disease is said to be **endemic** if it is constantly present in an area or population and the level at which it persists can be thought of as a 'baseline' to measure an epidemic against.

Two common measures when describing population health are **incidence** and **prevalence**, which are often misconstrued. In general, incidence refers to the number of new cases of a disease, whereas prevalence describes the number of individuals afflicted by a disease. Incidence can be thought of as 'change' and 'new' cases, whereas prevalence can be thought of as 'status' of 'existing' cases. In addition, incidence can be further broken down into **cumulative incidence** and **incidence rate**. Cumulative incidence is defined as the number of individuals who experience the onset of a health-related event during a specified time interval. This time interval is usually the same for all individuals in the group of interest; however, may vary from person to person without reference to age. On the other hand, incidence rate is defined as the number of new cases divided by the sum of the individual person-times as risk (infection period). In general, incidence rate is the rate at which new events occur in a population.

Epidemiology is defined as "the study of the distribution and determinants of health-related states or events in specified populations, and the application of this study to control health problems" [38]. In general, epidemiology is the study of epidemics, including not only those caused by infectious diseases, but also those caused by drugs, diet and environmental hazards. The focus of this thesis is mathematical epidemiology which is the study of epidemics using mathematical models, and in addition, only infectious diseases are considered.

3.2 Mathematical epidemiology

Contagious and infectious diseases such as measles, chicken pox, HIV and malaria have been a fact of life for hundreds of years. With years of research, we are now able to identify the mechanism of transmission for most diseases. The purpose of mathematical modelling is to use collected data along with a sound mathematical model to aid in the creation of public health policies in the case of epidemics. This section will provide an introduction to mathematical modelling as well as some techniques used to analyse the model.

The following is based on material in [45].

3.2.1 Compartmental and deterministic model overview

Compartmental modelling refers to grouping a population into various compartments in order to study the dynamics of disease transmission. In order to formulate a sound model, assumptions are made about the nature of movement from one compartment to another. For example, a population can be divided into three classes labelled S, I and R. Here, $S(t)$ is defined as the number of susceptible individuals at time t, $I(t)$ denotes the number of individuals who are infected and infectious and thus, are able to spread the disease to susceptible individuals. The final compartment, $R(t)$, denotes the number of removed individuals at time t and individuals are considered removed due to isolation, recovery, immunisation, natural immunity or death due to disease. A model divided into these three compartments is referred to as an SIR model. The following subsection will describe this model in more detail.

3.2.2 SIR Model

In 1927, W.O. Kermack and A.G. McKendrick [21] published a paper describing epidemic models with the use of mathematics. In this paper, the authors consider equations which

arise when time is divided into intervals and assume that infections occur at the exact moment of passing from one time interval to the next. They then formulate a rather complex model with various parameters, including rate of removal and rate of infectivity as functions of the time intervals. The model that has been made famous from this paper is the special case in which the rate of removal and rate of infectivity are constant. This model has become known as the Kermack-McKendrick model and takes the form

$$S' = -\beta SI \tag{3.1a}$$

$$I' = \beta SI - \gamma I \tag{3.1b}$$

$$R' = \gamma I, \tag{3.1c}$$

where S represents the number of susceptible individuals at time t, I represents the number of infected individuals at time t and R represents the number of removed individuals at time t.

Model (3.1) includes the following assumptions:

- a susceptible individual makes contact sufficient to contract the disease from a infected individual at a rate of βN per unit time. This is referred to as **mass action incidence**;
- infective individuals leave the infected class at a rate of γI per unit time;
- there is no entry into or exit from the population

Since R does not play a role in the dynamics of S nor I, and R does not depend on S or I, equation (3.1c) can be removed and therefore (3.1) is reduced to an SI model

$$S' = -\beta SI \tag{3.2a}$$

$$I' = (\beta S - \gamma)I. \tag{3.2b}$$

The system is analysed by studying the behaviour of its solutions using a qualitative approach. It can be observed that $S(t)$ and $I(t)$ must remain non-negative, otherwise the model would not make sense. It can also be noted that $S' < 0 \ \forall \ t$ and $I' > 0$ if and only if $S < \frac{\gamma}{\beta}$. Considering the initial condition $S(0) < \frac{\gamma}{\beta}$, then I will decrease to 0 indicating no epidemic. On the other hand, if $S(0) > \frac{\gamma}{\beta}$, then I will first increase (indicating an epidemic) before decreasing. This leads to the quantity $\frac{\beta S(0)}{\gamma}$, which is referred to as the **basic reproduction number**.

3.2.3 The Basic Reproduction Number, Disease Free Equilibrium and Endemic Equilibrium

The basic reproduction number is a critical component of modelling and is one of the main considerations when investigating the severity of an infectious disease.

Definition 3.1. [45] The **basic reproduction number**, denoted $\mathcal{R}_0$, is the number of expected secondary infections caused by a single infectious individual introduced into a wholly susceptible population.

Definition 3.2. A **disease free equilibrium** (denoted DFE) is the equilibrium solution to a system of ordinary differential equations in which there are no infected or infectious individuals.

Definition 3.3. An **endemic equilibrium point** (denoted EEP) is the equilibrium solution to a system of ordinary differential equations in which there are infected and infectious individuals present.

3.2.4 Next generation method for calculating $\mathcal{R}_0$

The next generation method is useful in computing $\mathcal{R}_0$ when a disease is modelled using a system of ordinary differential equations. This method was developed by van den Driessche and Watmough [44] and is summarised below.

Given a system of ODEs along with non-negative initial conditions which take the form

$$x_i' = f_i(x) = \mathcal{F}_i(x) - \mathcal{V}_i(x), \quad \text{for} \quad i = 1, ..., n \tag{3.3}$$

where $\mathcal{F}_i(x)$ is the rate of new infections into compartment i, $\mathcal{V}_i^+(x)$ is the rate of transfer of individuals into compartment i by all other means, $\mathcal{V}_i^-(x)$ is the rate of transfer of individuals out of compartment i, and $\mathcal{V}_i = \mathcal{V}_i^-(x) - \mathcal{V}_i^+(x)$.

The set of all disease free states, $\mathbf{X}_s$, can be defined as

$$\mathbf{X}_s = \{x \geq 0 \mid x_i = 0, i = 1, \ldots, m\}.$$

The functions must also satisfy the conditions (A1) to (A5) below.

Since $\mathcal{F}_i$,$\mathcal{V}_i^-$, $\mathcal{V}_i^+$ represent the transfer of individuals, they are all nonnegative. Thus,

(A1) if $x \geq 0$, then $\mathcal{F}_i$,$\mathcal{V}_i^-$, $\mathcal{V}_i^+ \geq 0$ for $i = 1, \ldots, n$.

If a compartment is empty, there can be no movement of individuals out of the compartment by any means, thus,

(A2) if $x_i = 0$, then $\mathcal{V}_i^- = 0$.

This holds since for each nonnegative initial condition, there is a unique, nonnegative solution [46].

(A3) in the uninfected compartments, the incidence of infection is 0. Thus, $\mathcal{F}_i = 0$ if $i > m$.

(A4) to ensure the disease free space in invariant, assume that a population initially free of disease will remain free of disease. Thus, $x \in X_s$ then $\mathcal{F}_i(x) = 0$ and $\mathcal{V}_i^+(x) = 0$ for $i = 1, \ldots, m$.

The final condition is based on the assumption that if a population remains near a DFE (denoted by x_0), then th population will return to the DFE according to the linearized system

$$x = Df(x_0)(x - x_0)$$

where $Df(x_0)$ is the Jacobian matrix evaluated at the DFE. The authors then state their attention is focused on systems in which the DFE is table in the absence of new infection. Hence,

(A5) If $\mathcal{F}(x) = 0$, then all eigenvalues of $Df(x_0)$ have negative real parts.

The conditions above allow the matrix $Df(x_0)$ to be partitioned as seen in the theorem below.

Theorem 3.4. *If x^* is a DFE of (3.3), then the derivatives of $D\mathcal{F}(x_0)$ and $D\mathcal{V}(x_0)$ are partitioned as*

$$D\mathcal{F}(x_0) = \begin{pmatrix} F & 0 \\ 0 & 0 \end{pmatrix} \text{ and } D\mathcal{V}(x_0) = \begin{pmatrix} V & 0 \\ J_3 & J_4 \end{pmatrix},$$

where F and V are the $m \times m$ matrices defined by

$$F = \left[\frac{\partial \mathcal{F}_i}{\partial x_j}(x_0)\right] \text{ and } V = \left[\frac{\partial \mathcal{V}_i}{\partial x_j}(x_0)\right] \text{ with } 1 \leq i, j \leq m.$$

Furthermore, F is non-negative, V is a non-singular M-matrix and all eigenvalues of J_4 have positive real part.

Theorem 3.5. *(Reproduction Number) The reproduction number, $\mathcal{R}_0$, is the spectral radius of FV^{-1}.*

Theorem 3.6. *(Local Stability of DFE) The disease free equilibrium (DFE) is said to be locally asymptotically stable if $\mathcal{R}_0 < 1$ and unstable if $\mathcal{R}_0 > 1$.*

Example 3.7. Given an SIR model with demography, we can compute the DFE and use the next generation method to determine $\mathcal{R}_0$ and the stability. Here, assume b denotes births and that individuals are only born into the susceptible class and d denotes death.

$$\begin{aligned} S' &= b - \beta SI - dS \\ I' &= \beta SI - \gamma I - dI \\ R' &= \gamma I - dR \end{aligned}$$

Thus, the DFE can be calculated by setting $I = 0$ resulting in

$$DFE = \left(\frac{b}{d}, 0, 0\right).$$

Using the next generation method seen in Theorem 3.4, the matrices F and V are of size 1×1 and are as follows:

$$\mathcal{F} = \begin{pmatrix} \beta SI \end{pmatrix} \qquad \text{and} \qquad \mathcal{V} = \begin{pmatrix} \gamma I + dI \end{pmatrix}.$$

Taking the derivative of both $\mathcal{F}$ and $\mathcal{V}$ with respect to I and evaluating at the DFE yields

$$F = \beta\frac{b}{d} \qquad and \qquad V = \gamma + d.$$

Thus, the reproduction number is the spectral radius of FV^{-1}. Since the matrices are 1×1

$$\mathcal{R}_0 = \frac{\beta b}{d(\gamma + d)}.$$

In addition, the DFE is locally asymptotically stable if $\mathcal{R}_0 < 1$ and unstable if $\mathcal{R}_0 > 1$.

Chapter 4

Mathematical Modelling of Measles with Mobility and Vaccination

The study of the movement of individuals between geographic locations as well as the impact of vaccines on infectious diseases using mathematical modelling can be seen throughout the literature. Models which involve the movement of individuals between geographic locations are referred to as *metapopulation models*. In these models, individuals in populations are grouped by geographic location and the groupings are often referred to as patches. Each patch has their own dynamics but these dynamics can vary due to the connectivity of the patches and movement of individuals [10]. In this thesis, each individual within a patch will be grouped according to the stage of the disease in which they are in and two geographic locations will be linked via travel in order to study the effect travel has on the spread of measles in which vaccinations are available.

4.1 Motivation

4.1.1 Mathematical modelling of metapopulations

Since the year 2000, two infamous examples of diseases which spread due to travel of infectious individuals are severe acute respiratory syndrome (SARS) in 2003 and H1N1 influenza in 2009. SARS began in Foshan, a city southwest of Guangzhou in Guangdong province of China, and spread to other areas in China, including Heyuan and Zhongshan in Guangdong, as well as around the world due to travel of infectious individuals [14]. Approximately six years later in April 2009, the CDC confirmed two cases of H1N1 in southern California, and by June 2009, there were 30,000 cases of H1N1 influenza confirmed across 74 countries, again due to travel of infected individuals [41].

Investigating the effect travel has on the spread of infectious diseases using mathematical modelling can be critical to the creation of public health policies and can aid in reducing an epidemic. In [4], the authors formulate a Susceptible-Infectious-Susceptible (SIS) model with mobility between n cities and compute the reproduction number in order to determine the disease dynamics. With the use of mathematical and computational analysis, the authors concluded that if a system is at an equilibrium and one city is at the disease-free equilibrium, then all cities with access to that city are also at the disease-free equilibrium. They also found that when the system is at an equilibrium and one city has an endemic disease level, then all cities with access to this city are also at an endemic level. However, the most important point made in this paper is that the application of the next generation matrix method (seen in section 3.2.4) can be used to determine the basic reproduction number in a model with mobility.

Another example in which metapopulations are studied is in [19]. In this paper, the authors present a stochastic metapopulation model in which the patches in the model are fully coupled. The main focus of this paper is disease transmission within animal populations (for example, foot and mouth and avian flu); however, could easily be extended to diseases affecting human populations. The authors consider within-patch

dynamics and use a Susceptible-Infectious-Recovered (SIR) model to classify individuals within each patch. The authors then examine the effect of three different movement rates (low, peak and high) between patches and concluded that there are three cases of disease behaviour. With the use of simulations, the first case shows that, in general, low levels of travel between patches does not induce an outbreak of disease. The second case shows that when the movement rate peaks, there is usually one epidemic outbreak followed by the disease dying out and finally, when movement rates are at their highest, there could be several consecutive epidemics and the infection could persist at an endemic level.

Nonlinear incidence functions in a multi-city epidemic model is considered in [28]. The authors study an SIR model with travel between multiple cities and also investigate the effect of pulse vaccination control strategies on the transmission of an infectious disease. The authors conclude by stating threshold conditions which guarantee disease eradication in the multi-city SIR model and the multi-city model with disease control strategies (including vaccinations); however, they did not investigate the stability of an endemic equilibrium.

An SIR metapopulation model and the effect of varying population size is the focus of [2]. The authors created an SIR model with travel between a large urban city with many smaller satellite cities and the model also employs different incidence functions in the patches (see subsection 5.2 for more information on incidence functions), with the urban city having proportional incidence and the smaller satellite cities having mass action incidence. The authors then calculate individual and coupled reproduction numbers and investigate the dynamics of disease transmission as well as what effect travel can have on the coupled reproduction number. In the end, it was found that lower connectivity between the large city and satellite city can have an impact on the value of the coupled reproduction number.

The effect of media induced social distancing on the spread of disease in a metapopulation model is considered in [42]. In this paper, the authors are interested in determining what effect ample media coverage can have on the transmission of a disease when two patches

are linked by travel. They formulated a two-patch SIS model with standard incidence; however, they also include the assumption that reporting by media is an increasing function of the number of present infectious cases in a patch, and thus, the contact rate between susceptible and infectious individuals is a decreasing function. The authors then define the contact rate to be a non-linear function of the infectious individuals, compute the basic reproduction number and run simulations in order to investigate the effect of different parameters. In the end, the authors conclude that media coverage does not have an effect on reducing the reproduction number if it is larger than one, but if the reproduction number has already been lowered to a number below one based on other means, then increased media coverage of a disease can help to lead to extinction of the epidemic by influencing individuals to reduce unnecessary travel.

4.1.2 Mathematical models with vaccination

The use of vaccinations and their efficacy to control the spread of infectious disease is apparent in the literature. In [47], the authors study a Susceptible-Infectious-Recovered-Vaccinated (SIRV) model with varying population through demography. In this paper, the authors state that a proportion of the susceptible population is vaccinated at a given rate, but can still become infected due to imperfect or waning vaccines. A modified vaccination rate is derived, which is described as an increasing function of the infection rate, vaccination waning rate and the vaccine efficacy parameter. The authors prove global asymptotic stability of the disease-free equilibrium using real analysis instead of a suitable Lyapunov function and concluded that a disease will die out when the actual vaccination rate is greater than the modified vaccination rate but will become endemic if the opposite is true.

In [1], the authors develop an SVIR model in which vaccinated individuals are considered separately from recovered individuals due to imperfect or waning vaccines. In the model, standard incidence for the transmission of the disease is used and demography is included. The main disease under consideration in this paper is pertussis, but the model

could be extended to other diseases with similar vaccination schedules and transmission characteristics. The authors analyse the model and determine an endemic equilibria exists only for a basic reproduction number greater than one and two cases related to bifurcation occur depending on increasing vaccine efficacy above a critical threshold. In the first case, increasing vaccine efficacy above the stated critical value leads to classical forward bifurcation to a unique endemic equilibria and in the second case, backward bifurcation is present when an increase in vaccine efficacy above the given threshold leads to the existence of two equilibria. The authors also compute a new reproduction number which they refer to as $\mathcal{R}_{vac}$ in which the basic reproduction number is modified by vaccination. Using this modified reproduction number, the authors analyse stability of the disease free equilibrium and conclude with three cases: one where no endemic equilibria exists, the second in which a unique endemic equilibrium exists and the third, two distinct endemic equilibria exist.

In addition to studying the effects vaccine efficacy, the effect varying vaccine schedules can have an impact on disease spread. In [29], the authors consider two strategies for immunising a population; continuous vaccination and pulse vaccination. In the continuous vaccination strategy, an SVIR model with demography is studied and the disease-free equilibrium, endemic equilibrium and basic reproduction number are computed. In the pulse vaccination strategy, it is assumed that the vaccination process is discontinuous or seasonal and is therefore best modelled with impulsive differential equations. With impulsive differential equations, the global behaviours of solutions become more difficult to analyse, but the authors note that based on the reproduction number, all positive solutions will tend to the disease free equilibrium when the reproduction number is less than one and the disease will remain at endemic levels if the reproduction number is greater than one.

4.1.3 Vaccinations and economic impact

Another factor considered when studying the use of vaccines to control disease spread is optimal cost-benefit strategies. Since vaccines can be used to reduce the spread of disease not only preventatively, but also during the outbreak of an epidemic, the feasible economics and costs associated with vaccine strategies should be considered. In [23], the authors combine epidemiological and economic modelling in order to determine the best disease control strategies while minimising cost. The authors examine three strategies: treat all individuals (global treatment), treat a local neighbourhood of individuals (local treatment) or treat no individuals (however, these individuals can be treated for symptoms, but are not treated to control the spread of disease). The authors studied an SIR model and included the assumption that asymptomatic individuals could transmit the given disease. After analysis of the model and simulations, the authors concluded that in some cases, refraining from treatment might be the most cost-effective strategy while controlling the spread of a disease. They also noted that the application of the local treatment strategy does not depend strongly on the cost of treatment, however, the decision of whether to treat locally or globally does depend on cost.

4.1.4 Limited vaccine availability

Studies investigating the impact of vaccinations within rural areas can be found in the literature. In [40], the authors built a face-to-face contact network based on the surveys of participants and with the use of a Susceptible-Latent-Infected-Recovered (SLIR) model, the authors were able to simulate a stochastic SLIR Poisson process. In this model, the authors assumed that when an individual entered the latent class, that individual is infected but not yet infectious. The authors wanted to determine the best immunisation strategy to employ when there are limited vaccines available. Various geographic locations were identified in the rural town in which individuals were more likely to have high levels of contact with other individuals (for example, restaurants) and thus, were more likely to spread disease or become infected. The authors concluded that when

vaccines are limited, the optimal immunisation strategy is to target subpopulations who were identified as frequenting critical locations with high contact rates.

4.1.5 Summary

In this thesis, a two-patch model will be analysed. One patch will represent a large city, such as Winnipeg, whereas the other patch will represent a small community or town such as a Hutterite colony or First Nations Reservation. Both the uncoupled and coupled systems will be considered. In the province of Manitoba, there are many isolated communities in which vaccine schedules may not be adhered to due to lack of convenient access to proper medical care or religious reasons. Thus, individuals travelling to a larger city to seek medical care may be carriers of disease or highly susceptible to certain diseases. Some interesting questions to investigate include

1. Using a similar model as seen in [47], how long does it take to eradicate disease in each patch when vaccination is present compared to the case where vaccination is not present as in a traditional SIR model?

2. Coverage and herd immunity in each uncoupled patch are considered. What critical threshold of individuals must be vaccinated in order to achieve herd immunity?

3. What happens to the reproduction numbers of each patch when the efficacy of a vaccine in the relative patch fluctuates?

4. How many cases of disease are averted due to the introduction of a single dose vaccine into each uncoupled patch?

5. Based on the work in [4], how do the travel rates between the large, urban city and small, rural community effect the coupled reproduction number? What public health policies regarding travel can be concluded? What happens to the coupled reproduction number when one travel rate is much greater than the other?

6. Although vaccine efficacy is fairly standard, it may be interesting to investigate what the effect on the global reproduction number with vaccination is when one patch has a 0% or very low vaccine efficacy.

7. How is the coupled reproduction number influenced by the individual reproduction numbers? Which individual reproduction number seems to drive the global reproduction number?

Part II

Deterministic metapopulation model for measles

Chapter 5

The Model

5.1 Model overview

The model analysed in this thesis is an autonomous, compartmental SVIR model. Here, a two patch model is considered. The patch with subscript w represents a large city, whereas the patch with subscript r represents a small town. Let S, V, I, and R denote the numbers of susceptible, vaccinated, infected and recovered individuals within a population, respectively. Individuals in the S class are assumed to be completely susceptible to a given disease. It is also assumed that individuals in V have begun a vaccination schedule and thus, have partial immunity to a given disease such as measles. Individuals in I are considered infected and may be symptomatic or asymptomatic, but regardless, are also assumed infectious and thus, able to spread the disease. Individuals in the R class are considered removed from the population, either due to recovery and subsequent immunity or a form of natural immunity.

Demographics are also included in the model. Each patch will have its own associated birth rate represented by b_w and b_r; however, the death rate will be the same in each patch, represented by d. It is also important to note that death due to disease or death due to other means is indistinguishable in this model. The rate of disease transmission is denoted by β and will differ in each patch. Next, let γ be the recovery rate. This will

be the same within each patch as the recovery for a given disease is based on an average regardless of location. The recruitment from the susceptible class to the vaccinated class is represented by α and the efficacy of vaccines will be denoted $1-\sigma$, thus, it is assumed that a proportion of vaccinated individuals will become infected. Note that $\sigma \in [0,1]$.

Each patch will be analysed individually (uncoupled systems) and also linked with mobility (coupled system). Here, it is assumed that all individuals regardless of health status, travel at the same rate between the two patches. It will also be assumed that the rate of travel from the small town to the large city is proportionally higher than travel from the large city to the small town. In order to analyse the system, initial conditions are needed. All initial conditions are assumed to be nonnegative and take the form $(S(0), V(0), I(0), R(0))$.

5.2 Incidence functions

The type of incidence used in modelling can vary depending on assumptions. In mass-action incidence, which takes the form βSI, it is assumed that new infections are generated through homogeneous mixing [45]. Generally, this type of incidence is appropriate for small populations, but is unrealistic for larger populations. Another type of incidence is proportional incidence (also known as standard-incidence) in which the mass-action incidence is divided over the entire population, thus $\beta\frac{SI}{N}$. This type of incidence may be more appropriate when modelling a larger population as it is unlikely that all susceptible individuals will come into contact with all infected individuals over a given time period, but rather a proportion of individuals will come into contact with one another. Both of these types of incidence depend linearly on the number of currently infected individuals within a population, however, neither of these may be realistic when considering a larger density of infected individuals decreases their per capita infectivity or in cases where an individual must come into contact with an infected individual on multiple occasions in order for transmission to occur [45]. A more realistic incidence function for the aforementioned population may by one which takes the form $\beta\frac{I^pS^q}{N}$, where $p > 1$

corresponds to synergistic effects amongst pathogens where a viral concentrations must exceed a critical level for transmission to occur, or could also apply to vector-borne diseases where a disease vector (such as a mosquito) must attack multiple infected hosts in order to increase its level of infectivity to a level suitable for transmission [45]. In [27], the authors use this type of incidence function in an SIRS model and found that if the initial number of infected individuals is larger than a given threshold, the infection will increase rapidly and then either die out or persist in the population at a stable constant level or with stable periodic oscillation.

In this thesis, mass-action incidence will be used in the small town as it is more likely that in a small population, individuals will come into contact with all other individuals. On the other hand, proportional-incidence is used in the large city as it is more likely that individuals in this population will remain in specific locations in the city and only come into contact with a proportion of individuals.

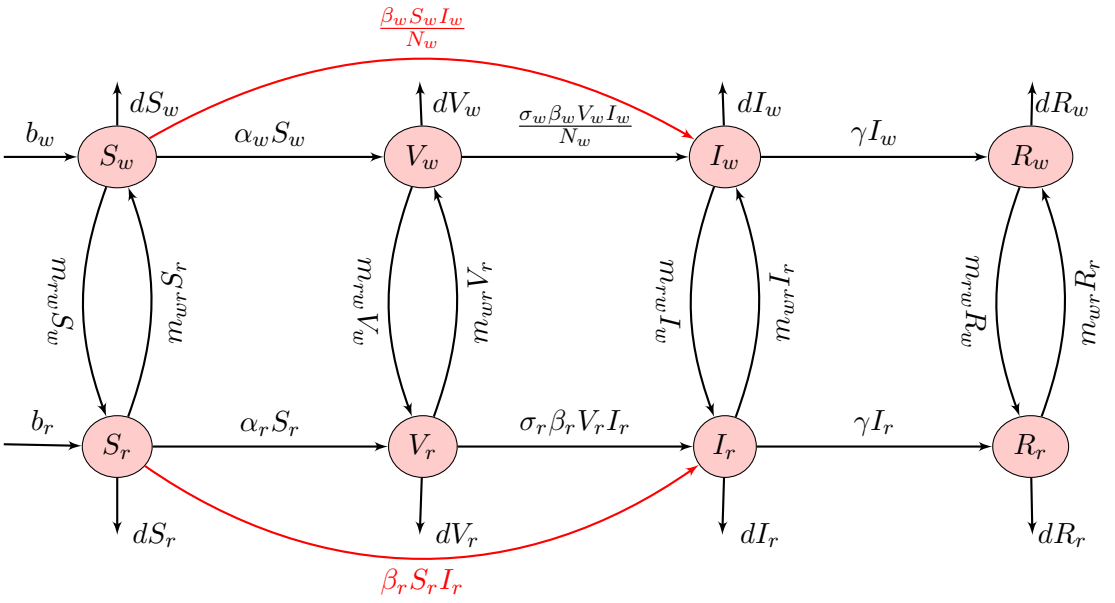

FIGURE 5.1: Flow diagram for a coupled SVIR model.

The above assumptions lead to the following system of differential equations. This system represents the coupled system. In order to analyse the uncoupled systems, simply remove all of the travel terms.

$$S'_w = b_w - \alpha_w S_w - \frac{\beta_w S_w I_w}{N_w} + m_{wr} S_r - m_{rw} S_w - d S_w \tag{5.1a}$$

$$V'_w = \alpha_w S_w - \frac{\sigma_w \beta_w V_w I_w}{N_w} + m_{wr} V_r - m_{rw} V_w - d V_w \tag{5.1b}$$

$$I'_w = \frac{\beta_w S_w I_w}{N_w} + \frac{\sigma_w \beta_w V_w I_w}{N_w} - \gamma I_w - m_{rw} I_w + m_{wr} I_r - d I_w \tag{5.1c}$$

$$R'_w = \gamma I_w - m_{rw} R_w + m_{wr} R_r - d R_w \tag{5.1d}$$

$$S'_r = b_r - \alpha_r S_r - \beta_r S_r I_r - m_{wr} S_r + m_{rw} S_w - d S_r \tag{5.1e}$$

$$V'_r = \alpha_r S_r - \sigma_r \beta_r V_r I_r - m_{wr} V_r + m_{rw} V_w - d V_r \tag{5.1f}$$

$$I'_r = \beta_r S_r I_r + \sigma_r \beta_r V_r I_r - \gamma I_r + m_{rw} I_w - m_{wr} I_r - d I_r \tag{5.1g}$$

$$R'_r = \gamma I_r + m_{rw} R_w - m_{wr} R_r - d R_r \tag{5.1h}$$

Also, the total populations of each patch are

$$N_w = S_w + V_w + I_w + R_w$$

$$N_r = S_r + V_r + I_r + R_r,$$

and the total population for the metapopulation model is

$$N = N_w + N_r.$$

The definitions of parameters are summarised in Table 5.1.

Parameter	Definition
β_w	disease transmission rate in large city (per capita)
β_r	disease transmission rate in small town (per capita/ per contact)
b_w	birth rate in large city
b_r	birth rate in small town
α_w	vaccination rate in large city
α_r	vaccination rate in small town
$1 - \sigma_w$	vaccine efficacy in large city
$1 - \sigma_r$	vaccine efficacy in small town
m_{rw}	movement of individuals from large city to small town
m_{wr}	movement of individuals from small town to large city
d	death rate
γ	recovery rate

Table 5.1: Definition of parameters

Chapter 6

Mathematical Considerations

This chapter focuses on the analysis of System 5.1 presented in Chapter 5. Both the coupled and uncoupled patches will be analysed throughout this chapter.

Where needed in the rest of this chapter, the system will be written as

$$x' = f(x), \tag{6.1}$$

where $x(t) = (S_w(t), V_w(t), I_w(t), R_w(t), S_r(t), V_r(t), I_r(t), R_r(t))^T \in \mathbb{R}^8_+ \backslash \{0\}$.

6.1 Well-Posedness

6.1.1 Existence and uniqueness

Proposition 6.1. *(Existence and uniqueness). Consider system (5.1) with non-negative initial conditions. Then solutions to system (5.1) exist and are unique for all $t \geq 0$.*

Proof. System 5.1 is written in form $\frac{d}{dt}x = f(x)$. The components of f are denoted by f_i for $i = \{1, 2, 3, 4, 5, 6, 7, 8\}$.

The vector field f consists of sums of terms written in terms of $S_w, V_w, I_w, R_w, S_r, V_r, I_r$ and R_r. Thus, f_i are continuous functions on $R_+^8 \backslash \{0\}$ and $\frac{df_i}{dS_w}$ $\frac{df_i}{dV_w}$ $\frac{df_i}{dI_w}$ $\frac{df_i}{dR_w}$ $\frac{df_i}{dS_r}$ $\frac{df_i}{dV_r}$ $\frac{df_i}{dI_r}$ $\frac{df_i}{dR_r}$ exist, which implies that f_i are differentiable functions $\forall i$. The total population of the large city, $N_w(t)$ converges and is strictly positive. This can be seen in Section 6.1.3. By Definition 2.1, a unique solution exists to the initial value problem $\frac{d}{dt}x = f(x)$ for any initial condition

$$x(0) \in \mathbb{R}_+^8 \backslash \{0\}. \quad \square$$

6.1.2 Non-negativity of solutions

Proposition 6.2. *Given non-negative initial conditions to System 5.1, $x(t)$ is non-negative $\forall t \geq 0$.*

Proof. Assume that initial conditions are non-negative. Setting $S_w = 0$ and $S_r = 0$ in (5.1a) gives

$$S_w' = b_w > 0.$$

This conclusion holds $\forall t \geq 0$, indicating that the total susceptible population remains positive for all time.

Now set $V_w = 0$ and $V_r = 0$ in (5.1b). This gives

$$V_w' = \alpha_w S_w$$

The sign of V_w' depends on the sign of S_w; however S_w was positive, so $V_w' \geq 0$, indicating $V_w(t)$ is also non-negative $\forall t \geq 0$.
Now set $I_w = 0$ and $I_r = 0$ in (5.1c). This gives

$$I_w' = 0,$$

which is clearly non-negative, so $I_w(t)$ is also non-negative $\forall t \geq 0$.

Next set $R_w = 0$ and $R_r = 0$ in (5.1d), which gives

$$R_w' = \gamma I_w.$$

Since $I_w(t)$ was non-negative $\forall t \geq 0$, this implies $R_w(t)$ is also non-negative $\forall t \geq 0$.

The same will apply equations (5.1e) to (5.1h) of system (5.1). Hence, the system has non-negative solutions when given non-negative initial conditions. □

6.1.3 Positivity and boundedness of the total population

Lemma 6.3. *The total population, $N(t)$, is positive and bounded.*

Summing all equations of (5.1) gives the evolution of the total population $N(t)$,

$$N'(t) = b - dN$$

where $b = b_w + b_r$. Integrating with respect to t using integrating factors method, gives

$$N(t) = \frac{b}{d} + e^{-dt}K,$$

where K is a constant. To solve for K, use the initial condition $N(0) = N_0$

$$N(0) = \frac{b}{d} + K = N_0.$$

Thus,

$$K = N_0 - \frac{b}{d}.$$

Since e^{-dt} is a decreasing function and goes to 0 as $t \to \infty$, it reaches a maximum when $t = 0$. The maximum of $e^{-dt} = 1$. Therefore, $N(t) = \frac{b}{d} + e^{-dt}(N_0 - \frac{b}{d}) < N_0$, showing the total population size is bounded.

Finally, System (5.1) is well posed in a biological sense since solutions exist and are unique, remain non-negative for initial conditions greater than zero $\forall t \geq 0$ and the total population size is bounded.

6.2 Convergence of total population in the patches

It can be shown that the population in each patch converges when travel terms are introduced. Here, assume that all individuals travel at the same rate regardless of health status.

Summing equations (5.1a) to (5.1d) yields

$$N_w' = b_w - dN_w + m_{wr}N_r - m_{rw}N_w$$

and summing equations (5.1e) to (5.1h) yields

$$N_r' = b_r - dN_r - m_{wr}N_r + m_{rw}N_w.$$

Next, rewrite the system in vector form so it is easier to analyse:

$$\begin{pmatrix} N_w' \\ N_r' \end{pmatrix} = \begin{pmatrix} b_w \\ b_r \end{pmatrix} - d \begin{pmatrix} N_w \\ N_r \end{pmatrix} + \mathcal{M} \begin{pmatrix} N_w \\ N_r \end{pmatrix},$$

where $\mathcal{M}$ is the movement matrix

$$\mathcal{M} = \begin{pmatrix} -m_{rw} & m_{wr} \\ m_{rw} & -m_{wr} \end{pmatrix}. \tag{6.2}$$

The movement matrix $\mathcal{M}$ is clearly singular. The following useful lemma is given in [2].

Lemma 6.4. *Let $c \in \mathcal{R}_+ \backslash \{0\}$. The matrix $\mathcal{M}$ (6.2) has the following properties.*

1) $-\mathcal{M}$ is a singular M matrix and has all its eigenvalues with nonpositive real parts.

2) $-(\mathcal{M} - c\mathbb{I})$ is a nonsingular M matrix.

3) $-(\mathcal{M} - c\mathbb{I}) > 0$

4) $\mathcal{M} - c\mathbb{I}$ has all its eigenvalues with real parts less than or equal to $-c$

5) If $m_{wr} > 0$ and $m_{rw} > 0$, then $\mathcal{M}, -\mathcal{M}, \mathcal{M} - c\mathbb{I}$ and $-(\mathcal{M} - c\mathbb{I})$ are irreducible and $-(\mathcal{M} - c\mathbb{I})^{-1} >> 0$

Computing the convergence of the total population yields

$$\mathbf{b} - d\mathbf{N} + \mathcal{M}\mathbf{N} = \mathbf{0} \tag{6.3}$$

and solving for $\mathbf{N}$ in equation (6.3)

$$\mathbf{b} = (d\mathbb{I} - \mathcal{M})\mathbf{N}$$
$$\mathbf{N} = (d\mathbb{I} - \mathcal{M})^{-1}\mathbf{b}.$$

From Lemma 6.4, it is clear that $(d\mathbb{I} - \mathcal{M})$ is invertible because $d > 0$. Thus, the total population converges to $(d\mathbb{I} - \mathcal{M})^{-1}\mathbf{b}$, more specifically,

$$N_w = \frac{m_{wr}(b_w + b_r) + b_w d}{d(d + m_{rw} + m_{wr})} \tag{6.4}$$

$$N_r = \frac{m_{rw}(b_w + b_r) + b_r d}{d(d + m_{rw} + m_{wr})}. \tag{6.5}$$

When the patches are uncoupled by setting $m_{wr} = m_{rw} = 0$ in (6.4) and (6.5), the total populations in the large city and small city converge to $\frac{b_w}{d}$ and $\frac{b_r}{d}$, respectively.

6.3 Reducing a system of equations

In both the uncoupled and coupled cases, it is possible to reduce the systems to 3 and 6 equations, respectively. This is possible since the total population in each patch converges, the total population in the coupled system converges and also because the dynamics of S, V and I do not depend on R. Thus, R_w and R_r can be removed from both the coupled and uncoupled systems.

Thus, System 5.1 can be reduced to 6 equations

$$S_w' = b_w - \alpha_w S_w - \frac{\beta_w S_w I_w}{N_w} + m_{wr} S_r - m_{rw} S_w - d S_w \tag{6.6a}$$

$$V_w' = \alpha_w S_w - \frac{\sigma_w \beta_w V_w I_w}{N_w} + m_{wr} V_r - m_{rw} V_w - d V_w \tag{6.6b}$$

$$I_w' = \frac{\beta_w S_w I_w}{N_w} + \frac{\sigma_w \beta_w V_w I_w}{N_w} - \gamma I_w - m_{rw} I_w + m_{wr} I_r - d I_w \tag{6.6c}$$

$$S_r' = b_r - \alpha_r S_r - \beta_r S_r I_r - m_{wr} S_r + m_{rw} S_w - d S_r \tag{6.6d}$$

$$V_r' = \alpha_r S_r - \sigma_r \beta_r V_r I_r - m_{wr} V_r + m_{rw} V_w - d V_r \tag{6.6e}$$

$$I_r' = \beta_r S_r I_r + \sigma_r \beta_r V_r I_r - \gamma I_r + m_{rw} I_w - m_{wr} I_r - d I_r \tag{6.6f}$$

6.4 Existence of Disease Free Equilibria (DFE)

The general procedure for finding the disease free equilibria consists in assuming that all infected compartments are empty and finding the corresponding equilibria of the system. Generally, it is found that only one such equilibrium point exists.

6.4.1 Uncoupled systems without vaccination

Considering the uncoupled systems without vaccination and without travel, i.e. $m_{wr} = 0$ and $m_{rw} = 0$, the system for the large city takes the form

$$S'_w = b_w - \frac{\beta_w S_w I_w}{N_w} - dS_w \tag{6.7a}$$

$$I'_w = \frac{\beta_w S_w I_w}{N_w} - \gamma I_w - dI_w \tag{6.7b}$$

which is a typical SIR model that has been reduced to 2 equations, has proportional incidence and includes demography. The system of equations for the small city can be reduced in similar manner as above, and will yield a system of 2 equations with demography and mass action incidence.

The DFE for this system is simple to compute and takes the form

$$DFE_{w_0} = \left(\frac{b_w}{d}, 0\right) = (N_w^*, 0).$$

The DFE for the small city when no vaccination is present takes a similar form to that of the large city

$$DFE_{r_0} = \left(\frac{b_r}{d}, 0\right) = (N_r^*, 0).$$

6.4.2 Uncoupled systems with vaccination

Consider the large city first where $m_{wr} = 0$ and $m_{rw} = 0$. The total population in this patch, N_w, converges to $\frac{b_w}{d}$ and the system has already been reduced to 3 equations, i.e. equations (6.6a) to (6.6c). The system for the large city in isolation takes the form

$$S'_w = b_w - \alpha_w S_w - \frac{\beta_w S_w I_w}{N_w} - dS_w \tag{6.8a}$$

$$V'_w = \alpha_w S_w - \frac{\sigma_w \beta_w V_w I_w}{N_w} - dV_w \tag{6.8b}$$

$$I'_w = \frac{\beta_w S_w I_w}{N_w} + \frac{\sigma_w \beta_w V_w I_w}{N_w} - \gamma I_w - dI_w \tag{6.8c}$$

Equilibria are determined by setting the time derivatives of each state variable in System (6.8) equal to 0.

To calculate the DFE, let $I_w = 0$ as there is no disease. This leaves equations (6.8a) and (6.8b), which, when set to 0, take the form

$$0 = b_w - \alpha_w S_w - dS_w$$

$$0 = \alpha_w S_w - dV_w.$$

Thus, the disease free equilibrium is

$$DFE_w = (S^*_w, V^*_w, 0) = \left(\frac{b_w}{\alpha_w + d}, \frac{\alpha_w b_w}{d(\alpha_w + d)}, 0 \right). \tag{6.9}$$

Next, consider the small city where $m_{wr} = 0$ and $m_{rw} = 0$, i.e., equations (6.6d) to (6.6f). The total population in this patch, N_r, converges to $\frac{b_r}{d}$. The system for the small city in isolation takes the form

$$S_r' = b_r - \alpha_r S_r - \beta_r S_r I_r - dS_r \tag{6.10a}$$

$$V_r' = \alpha_r S_r - \sigma_r \beta_r V_r I_r - dV_r \tag{6.10b}$$

$$I_r' = \beta_r S_r I_r + \sigma_r \beta_r V_r I_r - \gamma I_r - dI_r \tag{6.10c}$$

To calculate the DFE, follow the same procedure as for the larger city. Thus, in $\mathbb{R}^3$, the DFE of the small city is

$$DFE_r = (S_r^*, V_r^*, 0) = \left(\frac{b_r}{\alpha_r + d}, \frac{\alpha_r b_r}{d(\alpha_r + d)}, 0 \right). \tag{6.11}$$

6.4.3 Coupled system without vaccination

Setting the time derivatives of each state variable in System 6.6 to 0, as well as setting $I_w = 0$ and $I_r = 0$ in System 6.6, removing the V_w' and V_r' equations and setting $\alpha_w = 0$ and $\alpha_r = 0$ results in the following disease free equilibrium of the coupled system without vaccination

$$DFE_0 = (S_w^*, 0, S_r^*, 0), \tag{6.12}$$

where

$$S_w^* = \frac{b_w(m_{wr} + d) + m_{wr} b_r}{(m_{rw} + d)(m_{wr} + d) - m_{wr} m_{rw}}$$
$$S_r^* = \frac{b_r(m_{rw} + d) + m_{rw} b_w}{(m_{rw} + d)(m_{wr} + d) - m_{wr} m_{rw}}$$

6.4.4 Coupled system with vaccination

Setting the time derivatives of each state variable in System (6.6) to 0 and setting $I_w = 0$ and $I_r = 0$ in system (6.6) results in the following disease free equilibrium

$$DFE = (S_w^*, V_w^*, 0, S_r^*, V_r^*, 0), \tag{6.13}$$

where

$$\begin{aligned}
S_w^* &= \frac{b_w(\alpha_r + m_{wr} + d) + m_{wr}b_r}{(\alpha_w + m_{rw} + d)(\alpha_r + m_{wr} + d) - m_{wr}m_{rw}} \\
S_r^* &= \frac{b_r(\alpha_w + m_{rw} + d) + m_{rw}b_w}{(\alpha_w + m_{rw} + d)(\alpha_r + m_{wr} + d) - m_{wr}m_{rw}} \\
V_w^* &= \frac{\alpha_w S_w^* + m_{wr}\alpha_r S_r^*}{(m_{rw} + d)(m_{wr} + d) - m_{wr}m_{rw}} \\
V_r^* &= \frac{\alpha_r S_r^* + m_{rw}\alpha_w S_w^*}{(m_{rw} + d)(m_{wr} + d) - m_{wr}m_{rw}}
\end{aligned}$$

6.5 Reproduction number

The basic reproduction number, $\mathcal{R}_0$, is defined as the expected number of secondary infections produced by an initial case in a population which is wholly susceptible. The basic reproduction number is a measure of the potential for a disease to spread within a population. If $\mathcal{R}_0 < 1$, then it is clear there are not enough new infections to have the disease persist, and thus the disease will die out. However, if $\mathcal{R}_0 > 1$, then the number of infected individuals will increase with each generation and the disease will spread [44].

6.5.1 Uncoupled systems without vaccination

The reproduction number of the large city without vaccination can be calculated using the next generation matrix method as seen in Theorem 3.4. In the uncoupled case, the calculations produce scalars rather than matrices since there is only one compartment containing infected individuals.

First, taking the infected compartment to be I_w gives

$$\mathcal{F} = \frac{\beta_w S_w I_w}{N_w} \text{ and } \mathcal{V} = \gamma I_w + dI_w.$$

Hence,

$$F = \frac{\beta_w S_w}{N_w} \text{ and } V = \gamma + d.$$

As V is scalar,

$$V^{-1} = \frac{1}{\gamma + d}.$$

Therefore,

$$FV^{-1} = \frac{\beta_w S_w}{N_w(\gamma + d)}$$

and the reproduction number for the large city is given by

$$\mathcal{R}_0^w = \frac{\beta_w}{\gamma + d} \frac{S_w^*}{N_w^*}.$$

The previous equation simplifies to

$$\mathcal{R}_0^w = \frac{\beta_w}{\gamma + d}. \tag{6.14}$$

It should also be noted that $\mathcal{R}_0^w > 0$ since $\mathcal{R}_0^w$ above consists of all positive terms.

A similar method can be followed to calculate the reproduction number for the small city without vaccination, and the result is

$$\mathcal{R}_0^r = \frac{\beta_r}{\gamma + d} \frac{b_r}{d}. \tag{6.15}$$

6.5.2 Uncoupled systems with vaccination

The reproduction number of the large city can be calculated using the next generation matrix method as seen in Theorem 3.4. In the uncoupled case, the calculations will produce scalars rather than matrices since there is only one compartment containing new infections.

First, taking the infected compartment to be I_w gives

$$\mathcal{F} = \frac{\beta_w S_w I_w + \sigma_w \beta_w V_w I_w}{N_w} \text{ and } \mathcal{V} = \gamma I_w + d I_w.$$

Hence,

$$F = \frac{\beta_w S_w + \sigma_w \beta_w V_w}{N_w} \text{ and } V = \gamma + d.$$

Since V is scalar,

$$V^{-1} = \frac{1}{\gamma + d}.$$

Therefore,

$$FV^{-1} = \frac{\beta_w S_w + \sigma_w \beta_w V_w}{N_w(\gamma + d)}$$

and the reproduction number for the large city is given by

$$\mathcal{R}^w_{vac} = \frac{\beta_w}{\gamma + d} \frac{S^*_w + \sigma_w V^*_w}{N^*_w}.$$

The previous equation simplifies to

$$\mathcal{R}^w_{vac} = \frac{\beta_w}{\gamma + d} \frac{d + \sigma_w \alpha_w}{d + \alpha_w}. \tag{6.16}$$

It should also be noted that $\mathcal{R}^w_{vac} > 0$ since $\mathcal{R}^w_{vac}$ above consists of all positive terms.

In the small city, the reproduction number can be calculated using the same method as above. Taking the infected compartment to be I_r gives

$$\mathcal{F} = \beta_r S_r I_r + \sigma_r \beta_r V_r I_r \text{ and } \mathcal{V} = \gamma I_r + d I_r.$$

Hence,

$$F = \beta_r S_r + \sigma_r \beta_r V_r \text{ and } V = \gamma + d.$$

As V is scalar,

$$V^{-1} = \frac{1}{\gamma + d}.$$

Therefore,

$$FV^{-1} = \frac{\beta_r S_r + \sigma_r \beta_r V_r}{\gamma + d}$$

and the reproduction number for the small city is given by

$$\mathcal{R}^r_{vac} = \frac{\beta_r}{\gamma + d}(S^*_r + \sigma_r V^*_r),$$

which simplifies to

$$\mathcal{R}^r_{vac} = \frac{\beta_r}{\gamma + d} \, \frac{d + \sigma_r \alpha_r}{d + \alpha_r} \, \frac{b_r}{d}. \tag{6.17}$$

It should also be noted that $\mathcal{R}^r_{vac} > 0$ since $\mathcal{R}^r_{vac}$ above consists of all positive terms.

6.5.3 Comparison of $\mathcal{R}_0$ and $\mathcal{R}_{vac}$

In theory, vaccination should reduce the incidence of disease. Thus, the reproduction number involving vaccination should be less than or equal to the true reproduction number without vaccination.

Proposition 6.5. *The reproduction number modified by vaccination is less than or equal to the true reproduction number in both uncoupled patches.*

Proof. Beginning with the reproduction number including vaccination (6.17) and without vaccination of the small city (6.15) respectively,

$$\mathcal{R}^r_{vac} = \frac{\beta_r}{\gamma + d} \frac{(d + \sigma_r \alpha_r)}{(d + \alpha_r)} \frac{b_r}{d}$$

$$\mathcal{R}^r_0 = \frac{\beta_r}{\gamma + d} \frac{b_r}{d}$$

It is clear that $\mathcal{R}^r_{vac}$ consists of $\mathcal{R}^r_0$ and therefore $\mathcal{R}^r_{vac}$ can be rewritten as

$$\mathcal{R}^r_{vac} = \mathcal{R}^r_0 \frac{d + \sigma_r \alpha_r}{d + \alpha_r}.$$

Since $\sigma_r \leq 1$, $\mathcal{R}^r_{vac} \leq \mathcal{R}^r_0$. In addition, equality will only hold if and only if $\sigma_r = 1$. □

The same proof holds for the reproduction numbers of the large city as well.

6.5.4 Global stability of DFE_r and DFE_w with vaccination

Theorem 6.6. *The disease free equilibrium of the small city and large city are globally asymptotically stable for $\mathcal{R}^r_{vac} < 1$ and $\mathcal{R}^w_{vac} < 1$, respectively.*

See Appendix A for proof.

6.5.5 Coupled system with vaccination

The next generation method of van den Driessche and Watmough [44] can also be used to determine the reproduction number for metapopulation models. This was shown by Arino and van den Driessche [4].

Taking the infected compartments to be I_w and I_r gives

$$\mathcal{F} = \begin{pmatrix} \frac{\beta_w S_w I_w + \sigma_w \beta_w V_w I_w}{N_w} \\ \beta_r S_r I_r + \sigma_r \beta_r V_r I_r \end{pmatrix} \text{ and } \mathcal{V} = \begin{pmatrix} (\gamma + m_{rw} + d) I_w - m_{wr} I_r \\ (\gamma + m_{wr} + d) I_r - m_{rw} I_w \end{pmatrix}.$$

Hence,

$$F = \begin{pmatrix} \frac{\beta_w S_w + \sigma_w \beta_w V_w}{N_w} & 0 \\ 0 & \beta_r S_r + \sigma_r \beta_r V_r \end{pmatrix} \text{ and } V = \begin{pmatrix} \gamma + m_{rw} + d & -m_{wr} \\ -m_{rw} & \gamma + m_{wr} + d \end{pmatrix}.$$

If follows that

$$V^{-1} = \frac{1}{(\gamma + d)(\gamma + d + m_{wr} + m_{rw})} \begin{pmatrix} \gamma + m_{wr} + d & m_{wr} \\ m_{rw} & \gamma + m_{rw} + d \end{pmatrix}.$$

Is it possible to re-write F in terms of the uncoupled reproduction numbers.

$$F = \begin{pmatrix} (\gamma + d)\mathcal{R}^w_{vac} & 0 \\ 0 & (\gamma + d)\mathcal{R}^r_{vac} \end{pmatrix}.$$

Therefore,

$$FV^{-1} = \frac{1}{\gamma + d + m_{wr} + m_{rw}} \begin{pmatrix} (\gamma + d + m_{wr})\mathcal{R}^w_{vac} & m_{wr}\mathcal{R}^w_{vac} \\ m_{rw}\mathcal{R}^r_{vac} & (\gamma + d + m_{rw})\mathcal{R}^r_{vac} \end{pmatrix}. \quad (6.18)$$

Eigenvalues of FV^{-1} are

$$\frac{[(\gamma+d+m_{wr})\mathcal{R}^w_{vac}+(\gamma+d+m_{rw})\mathcal{R}^r_{vac}]\pm\sqrt{\Delta}}{2(\gamma+d+m_{wr}+m_{rw})},$$

where

$$\Delta=((\gamma+d+m_{wr})\mathcal{R}^w_{vac}+(\gamma+d+m_{rw})\mathcal{R}^r_{vac})^2-4(\gamma+d)(\gamma+d+m_{wr}+m_{rw})\mathcal{R}^w_{vac}\mathcal{R}^r_{vac}.$$

Theorem 6.7. *The reproduction number of the coupled system is the spectral radius of the matrix FV^{-1}, thus*

$$R_{vac}=\frac{(\gamma+d+m_{wr})\mathcal{R}^w_{vac}+(\gamma+d+m_{rw})\mathcal{R}^r_{vac}+\sqrt{\Delta}}{2(\gamma+d+m_{wr}+m_{rw})}. \tag{6.19}$$

Proof. Since the matrix FV^{-1} (6.18) is a positive, 2×2 matrix, it follows that the eigenvalues of the matrix are either both real or a complex conjugate pair. Considering the case where the eigenvalues are a complex conjugate pair, then the spectral radius is the modulus of the eigenvalues and would be equal in this case. However, by Theorem 2.20, the spectral radius must be greater than all other eigenvalues and therefore, the eigenvalues must both be real and the greater of the two is the eigenvalue which is stated in equation 6.19 [18]. □

6.5.6 Coupled system without vaccination

The reproduction number for the coupled system with no vaccination will take the same form as equation (6.19), but with the uncoupled reproduction numbers taking the form $\mathcal{R}^w_0$ (6.14) and $\mathcal{R}^r_0$ (6.15) where vaccination has been excluded.

6.5.7 Summary of reproduction numbers

	Large City	Small City
Uncoupled: without vaccine	$\mathcal{R}_0^w = \frac{\beta_w}{\gamma + d}$ (6.14)	$\mathcal{R}_0^r = \frac{\beta_r}{\gamma + d} \frac{b_r}{d}$ (6.15)
Uncoupled: with vaccine	$\mathcal{R}_{vac}^w = \frac{\beta_w}{\gamma + d} \frac{d + \sigma_w \alpha_w}{d + \alpha_w}$ (6.16)	$\mathcal{R}_{vac}^r = \frac{\beta_r}{\gamma + d} \frac{d + \sigma_r \alpha_r}{d + \alpha_r} \frac{b_r}{d}$ (6.17)

TABLE 6.1: Summary of reproduction numbers for uncoupled systems

Coupled: without vaccine	$\mathcal{R}_0 = \frac{(\gamma + d + m_{wr})\mathcal{R}_0^w + (\gamma + d + m_{rw})\mathcal{R}_0^r + \sqrt{\Delta_0}}{2(\gamma + d + m_{wr} + m_{rw})}$
Coupled: with vaccine	$\mathcal{R}_{vac} = \frac{(\gamma + d + m_{wr})\mathcal{R}_{vac}^w + (\gamma + d + m_{rw})\mathcal{R}_{vac}^r + \sqrt{\Delta}}{2(\gamma + d + m_{wr} + m_{rw})}$ (6.19)

TABLE 6.2: Summary of reproduction numbers for coupled systems

Where,

$$\Delta_0 = ((\gamma + d + m_{wr})\mathcal{R}_0^w + (\gamma + d + m_{rw})\mathcal{R}_0^r)^2 - 4(\gamma + d)(\gamma + d + m_{wr} + m_{rw})\mathcal{R}_0^w \mathcal{R}_0^r,$$

and

$$\Delta = ((\gamma + d + m_{wr})\mathcal{R}_{vac}^w + (\gamma + d + m_{rw})\mathcal{R}_{vac}^r)^2 - 4(\gamma + d)(\gamma + d + m_{wr} + m_{rw})\mathcal{R}_{vac}^w \mathcal{R}_{vac}^r.$$

6.5.8 Localisation of $\mathcal{R}_{vac}$

In this section, we investigate what effect each of the individual reproduction numbers has on the coupled reproduction number. By Theorem 2.14, the coupled reproduction number is bounded by the minimum and the maximum row sums and the minimum and maximum column sums of FV^{-1} (6.18).

Therefore,

$$\min\{\tfrac{(\gamma+d+2m_{wr})\mathcal{R}^w_{vac}}{\gamma+d+m_{wr}+m_{rw}}, \tfrac{(\gamma+d+2m_{rw})\mathcal{R}^r_{vac}}{\gamma+d+m_{wr}+m_{rw}}\} \leq \mathcal{R}_{vac} \leq \max\{\tfrac{(\gamma+d+2m_{wr})\mathcal{R}^w_{vac}}{\gamma+d+m_{wr}+m_{rw}}, \tfrac{(\gamma+d+2m_{rw})\mathcal{R}^r_{vac}}{\gamma+d+m_{wr}+m_{rw}}\}$$

and

$$\min\{\frac{(\gamma+d+m_{wr})\mathcal{R}^w_{vac}+m_{rw}\mathcal{R}^r_{vac}}{\gamma+d+m_{wr}+m_{rw}}, \frac{(\gamma+d+m_{rw})\mathcal{R}^r_{vac}+m_{wr}\mathcal{R}^w_{vac}}{\gamma+d+m_{wr}+m_{rw}}\} \leq \mathcal{R}_{vac} \leq \max\{\frac{(\gamma+d+m_{wr})\mathcal{R}^w_{vac}+m_{rw}\mathcal{R}^r_{vac}}{\gamma+d+m_{wr}+m_{rw}}, \frac{(\gamma+d+m_{rw})\mathcal{R}^r_{vac}+m_{wr}\mathcal{R}^w_{vac}}{\gamma+d+m_{wr}+m_{rw}}\}.$$

In addition, since both diagonal entries of FV^{-1} are positive, then $\mathcal{R}_{vac}$ must also be strictly positive.

Proposition 6.8. *If $\mathcal{R}^w_{vac} = \mathcal{R}^r_{vac} = \mathcal{R}$, then $\mathcal{R}_{vac} = \mathcal{R}$.*

Proof. Let $\mathcal{R}^w_{vac} = \mathcal{R}^r_{vac} = \mathcal{R}$ in equation (6.19). Factoring and cancelling, the expression for $\mathcal{R}_{vac}$ reduces to

$$\frac{\mathcal{R}((\gamma+d+m_{wr})+(\gamma+d+m_{rw}))+\mathcal{R}\sqrt{m^2_{wr}+m_{wr}m_{rw}+m^2_{rw}}}{2(\gamma+d+m_{rw}+m_{wr})}$$

which further reduces to

$$\frac{\mathcal{R}(2\gamma + 2d + 2m_{rw} + 2m_{wr})}{2(\gamma + d + m_{rw} + m_{wr})} = \mathcal{R}.$$

□

Proposition 6.9. *The coupled reproduction number is bounded by the individual, uncoupled reproduction numbers, hence* $\min\{\mathcal{R}^w_{vac}, \mathcal{R}^r_{vac}\} < \mathcal{R}_{vac} < \max\{\mathcal{R}^w_{vac}, \mathcal{R}^r_{vac}\}$.

Proof. By Theorem 2.14, the spectral radius of the matrix FV^{-1} (6.18) must be bounded by the minimum and maximum column sums (or row sums).
Taking the column sums of the matrix FV^{-1}, we can see that the sum of column one is:

$$\frac{(\gamma + d + m_{wr})\mathcal{R}^w_{vac} + m_{rw}\mathcal{R}^r_0}{(\gamma + d + m_{wr} + m_{rw})}$$

and the sum of column two is

$$\frac{(\gamma + d + m_{rw})\mathcal{R}^r_{vac} + m_{wr}\mathcal{R}^w_{vac}}{(\gamma + d + m_{wr} + m_{rw})}.$$

Now assume

$$\frac{(\gamma + d + m_{wr})\mathcal{R}^w_{vac} + m_{rw}\mathcal{R}^r_{vac}}{(\gamma + d + m_{wr} + m_{rw})} > \frac{(\gamma + d + m_{rw})\mathcal{R}^r_{vac} + m_{wr}\mathcal{R}^w_{vac}}{(\gamma + d + m_{wr} + m_{rw})}$$

After cancelling terms, we get

$$\frac{(\gamma + d)\mathcal{R}^w_{vac}}{(\gamma + d + m_{wr} + m_{rw})} > \frac{(\gamma + d)\mathcal{R}^r_{vac}}{(\gamma + d + m_{wr} + m_{rw})}$$

Which further simplifies to

$$\mathcal{R}^w_{vac} > \mathcal{R}^r_{vac}$$

.

Since the initial claim was $\mathcal{R}^w_{vac} > \mathcal{R}^r_{vac}$ it follows that the sum of column one is greater than the sum of column two.

Therefore, $\mathcal{R}^r_{vac} < \mathcal{R}_{vac} < \mathcal{R}^w_{vac}$.

The converse will be true following the same process as above. □

6.6 Endemic equilibrium

The general procedure for finding endemic equilibria consists in assuming that infected compartments are not empty and finding the corresponding equilibria of the system. Determining the existence of endemic equilibria can prove to be more difficult then showing the existence of a disease free equilibrium since there can be a unique endemic equilibrium or multiple endemic equilibria.

6.6.1 Uncoupled systems with vaccination

Consider the uncoupled patches first. In the rural town, the endemic equilibrium is found by setting $I_r = I_r^{**} > 0$.

$$S_r' = b_r - \alpha_r S_r - \beta_r S_r I_r - dS_r \tag{6.20a}$$

$$V_r' = \alpha_r S_r - \sigma_r \beta_r V_r I_r - dV_r \tag{6.20b}$$

$$I_r' = \beta_r S_r I_r + \sigma_r \beta_r V_r I_r - \gamma I_r - dI_r \tag{6.20c}$$

$$R_r' = \gamma I_r - dR_r \tag{6.20d}$$

To solve for the endemic equilibrium, set the left hand side of the equations in System 6.20 to 0.

First, solve (6.20d) for R_r^{**} in terms of I_r^{**}

$$R_r^{**} = \frac{\gamma}{d} I_r^{**}$$

Next, solve (6.20a) for S^{**} in terms of I^{**}

$$S_r^{**} = \frac{b_r}{d + \alpha_r + \beta_r I_r^{**}} \tag{6.21}$$

Third, solve (6.20b) for V_r^* in terms of I^*

$$V_r^{**} = \frac{\alpha_r S_r^{**}}{\sigma_r \beta_r I_r^{**} + d} = \frac{\alpha_r b_r}{(d + \alpha_r + \beta_r I_r^{**})(\sigma_r \beta_r I_r^{**} + d)} \tag{6.22}$$

Lastly, solve (6.20c) for S_r^* in terms of V_r^*

$$S_r^{**} = \frac{d + \gamma - \sigma_r \beta_r V_r^{**}}{\beta_r} \tag{6.23}$$

Substituting (6.21) and (6.22) into (6.24) yields

$$\frac{b_r}{d + \alpha_r + \beta_r I_r^{**}} = \frac{\gamma + d}{\beta_r} - \frac{\sigma_r \alpha_r b_r}{(d + \alpha_r + \beta_r I_r^{**})(\sigma_r \beta_r I_r^{**} + d)} \tag{6.24}$$

Rearranging equation (6.24) yields a polynomial of the form

$$P(I_r^{**}) = A{I_r^{**}}^2 + BI_r^{**} + C \tag{6.25}$$

Where

$$A = \beta_r \sigma_r (\gamma + d) \geq 0, \tag{6.26a}$$

$$B = \gamma d \sigma_r + \gamma \sigma_r \alpha_r + d \alpha_r \sigma_r + d^2 + \gamma d + d^2 \sigma_r - \beta_r b_r \sigma_r, \tag{6.26b}$$

$$C = \gamma d^2 + \gamma \alpha_r d + d^3 + d^2 \alpha_r - \beta_r b_r (d + \sigma_r \alpha_r) = \frac{d(d + \gamma)(d + \alpha_r)(1 - \mathcal{R}_{vac}^r)}{\beta_r}. \tag{6.26c}$$

The following is based on the method presented in [6]. All of the coefficients A, B and C are functions of β_r and the condition $C = 0$ or $\mathcal{R}^r_{vac} = 1$ corresponds to a critical value β_c of β_r given by

$$\beta_c = \frac{d(d+\gamma)(d+\alpha_r)}{b_r(d+\alpha_r\sigma_r)}. \tag{6.27}$$

Theorem 6.10. *System (6.20) has a unique endemic equilibrium for $\mathcal{R}^r_{vac}$(6.17) > 1.*

Proof. It is clear that A(6.26a) > 0 and when $\mathcal{R}^r_{vac} > 1$, C(6.26c) < 0. Descartes' Rule of Sign states that for every sign change in the coefficients of a polynomial, there is a positive real root and for every even multiple, there are that many positive real roots or two less. Therefore the sign of B is irrelevant as it will yield one sign change whether it is positive or negative and thus, one positive, real root. □

It is also important to eliminate the possibility of an endemic equilibrium existing when $\mathcal{R}^r_{vac} < 1$ because this would indicate backward bifurcation. This phenomenon has critical public health implications since reducing $\mathcal{R}_{vac}$ below 1 may not be sufficient in eliminating a disease [8]. Brauer [6] states that $B(\beta_c)$(6.26b) < 0 is a necessary and sufficient condition for the existence of a positive endemic equilibrium and backward bifurcation at $\mathcal{R}^r_{vac} = 1$. With some algebraic manipulation, it can be shown that

$$\gamma d\sigma_r + \gamma\sigma_r\alpha_r + d\alpha_r\sigma_r + d^2 + \gamma d + d^2\sigma_r < \frac{\sigma_r d(d+\gamma)(d+\alpha_r)}{(d+\alpha_r\sigma_r)}.$$

This factors further to

$$(\gamma+d)[(d\sigma_r + \sigma_r\alpha_r) + d] < \frac{\sigma_r d(d+\gamma)(d+\alpha_r)}{(d+\alpha_r\sigma_r)}$$

$$(\gamma+d)(d+\alpha_r\sigma_r)[(d\sigma_r + \sigma_r\alpha_r) + d] < \sigma_r d(\gamma+d)(d+\alpha_r).$$

Cancelling common factors results in

$$(d+\alpha_r\sigma_r)[(d\sigma_r+\sigma_r\alpha_r)+d]<\sigma_r d(d+\alpha_r)$$

and expanding the left hand side of the inequality yields

$$\sigma_r d(d+\alpha_r)+d\sigma_r^2\alpha_r+\alpha_r^2\sigma_r^2+d^2+d\alpha_r\sigma_r<\sigma_r d(d+\alpha_r).$$

Thus, it is clear that the inequality does not hold, therefore, there is no possibility of backward bifurcation in this patch.

The unique endemic equilibrium point (EEP_r) of System 6.20 is

$$(S_r^{**},V_r^{**},I_r^{**},R_r^{**})=\left(\frac{b_r}{d+\alpha_r+\beta_r I_r^{**}},\frac{\alpha_r b_r}{(d+\alpha_r+\beta_r I_r^{**})(\sigma_r\beta_r I_r^{**}+d)},I_r^{**},\frac{\gamma}{d}I_r^{**}\right). \tag{6.28}$$

For the larger city, use the limiting factor $N_w(t)=\frac{b_w}{d}$ to simplify the system (6.8).

$$S_w'=b_w-\alpha_w S_w-\frac{d\beta_w S_w I_w}{b_w}-dS_w \tag{6.29a}$$

$$V_w'=\alpha_w S_w-\frac{d\sigma_w\beta_w V_w I_w}{b_w}-dV_w \tag{6.29b}$$

$$I_w'=\frac{d\beta_w S_w I_w}{b_w}+\frac{d\sigma_w\beta_w V_w I_w}{b_w}-\gamma I_w-dI_w \tag{6.29c}$$

$$R_w'=\gamma I_w-dR_w \tag{6.29d}$$

Using the substitution $\tilde{\beta}=\frac{d\beta_w}{b_w}$, system 6.29 can be further simplified and using the same process as for System 6.20 above, the endemic equilibrium point (EEP_w) of System 6.29 is

$$(S_w^{**}, V_w^{**}, I_w^{**}, R_w^{**}) = \left(\frac{b_w}{d + \alpha_w + \tilde{\beta} I_w^{**}}, \frac{\alpha_w b_w}{(d + \alpha_w + \tilde{\beta} I_w^{**})(\sigma_w \tilde{\beta} I_w^{**} + d)}, I_w^{**}, \frac{\gamma}{d} I_w^{**} \right). \tag{6.30}$$

Determining the characteristics of the roots in the polynomial in $P(I_w^{**}) = A{I_w^{**}}^2 + BI_w^{**} + C$ will follow the same process as for I_r^{**} by using the limiting factor $N_w(t) = \frac{b_w}{d}$ and the substitution $\tilde{\beta} = \frac{d\beta_w}{b_w}$ since the total population converges.

Theorem 6.11. *System 6.8 has a unique endemic equilibrium for $\mathcal{R}_{vac}^w > 1$.*

Proof. The proof follows the above proof for System 6.20 and there will be no occurrence of backward bifurcation in this patch. □

6.6.2 Uncoupled systems without vaccination

In the above endemic equilibria above, set α_r and σ_r to 0 to determine the endemic equilibrium when there is no vaccination.

Beginning first with the small city, the coefficients of the polynomial in I_r^{**} is

$$\begin{aligned} A &= 0 \\ B &= d(\gamma + d) \\ C &= \frac{d^2(d+\gamma)(1 - R_0^r)}{\beta_r}. \end{aligned}$$

Solving for I_r^{**} yields

$$\begin{aligned} d(\gamma + d) I_r^{**} + \frac{d^2(d+\gamma)(1 - R_0^r)}{\beta_r} &= 0 \\ I_r^{**} &= \frac{d(R_0^r - 1)}{\beta_r}. \end{aligned}$$

Thus, the endemic equilibrium point when vaccination is not present is

$$(S_r^{**}, I_r^{**}, R_r^{**}) = \left(\frac{\gamma + d}{\beta_r}, \frac{d(R_0^r - 1)}{\beta_r}, \frac{\gamma(R_0^r - 1)}{\beta_r} \right) \tag{6.31}$$

Using the same process as above,

$$(S_w^{**}, I_w^{**}, R_w^{**}) = \left(\frac{\gamma + d}{\tilde{\beta_w}}, \frac{d(R_0^w - 1)}{\tilde{\beta_w}}, \frac{\gamma(R_0^w - 1)}{\tilde{\beta_w}} \right) \tag{6.32}$$

where $\tilde{\beta_w} = \frac{d\beta_w}{b_w}$.

6.6.3 Global Stability of EEP_r and EEP_w

Theorem 6.12. *The endemic equilibrium of each uncoupled patch with vaccination is globally stable.*

See Appendix A for proof.

6.6.4 Coupled system with vaccination

To simplify the system, substitute $\lambda_w = \frac{\beta_w I_w}{N_w}$ and $\lambda_r = \beta_r I_r$.

Since the total population remains constant, we have that $N_w = \frac{m_{wr}(b_w+b_r)+b_w d}{d(d+m_{rw}+m_{wr})}$ and $N_r = \frac{m_{rw}(b_w+b_r)+b_r d}{d(d+m_{rw}+m_{wr})}$. Thus, the endemic equilibrium of system (5.1) is

$$S_w^* = \frac{N_w + b_w(\alpha_r + \lambda_r)}{(d + \alpha_w + m_{rw} + \lambda_w)(d + \alpha_r + m_{wr} + \lambda_r) - m_{rw}m_{wr}} \tag{6.33}$$

$$S_r^* = \frac{S_w^* m_{rw} + b_r}{\lambda_r + \alpha_r + d + m_{wr}} \tag{6.34}$$

$$V_w^* = \frac{S_w^* \alpha_w(\sigma_r + m_{wr} + d) + m_{wr}\alpha_w S_r^*}{(\sigma_w\lambda_w + m_{rw} + d)(\sigma_r\lambda_r + m_{wr} + d) - m_{rw}m_{wr}} \tag{6.35}$$

$$V_r^* = \frac{S_r^* \alpha_r(\sigma_w + m_{rw} + d) + m_{rw}\alpha_r S_w^*}{(\sigma_w\lambda_w + m_{rw} + d)(\sigma_r\lambda_r + m_{wr} + d) - m_{rw}m_{wr}} \tag{6.36}$$

$$I_w^* = \frac{m_{wr} I_r^* N_w}{N_w(\gamma + m_{rw} + d) - \beta_w(S_w^* + \sigma_w V_w^*)} \tag{6.37}$$

$$I_r^* = \frac{m_{rw} I_w^*}{\gamma + d + m_{wr} - \beta_r(S_r^* + \sigma_r V_r^*)} \tag{6.38}$$

$$R_w^* = \frac{\gamma I_w^*(d + m_{wr}) + m_{wr}\gamma I_r^*}{(d + m_{rw})(d + m_{wr}) - m_{wr}m_{rw}} \tag{6.39}$$

$$R_r^* = \frac{\gamma I_r^*(d + m_{rw}) + m_{rw}\gamma I_w^*}{(d + m_{rw})(d + m_{wr}) - m_{wr}m_{rw}} \tag{6.40}$$

where all variables are in terms of I_w^* and I_r^*.

Chapter 7

Numerical Considerations

In this chapter, numerical simulations are performed on System 5.1 in order to investigate the dynamics of disease spread as well as compliment the mathematical analysis in the previous chapter.

7.1 Parameter Values

The parameters used in the numerical analysis are estimated based on related literature as well as based on the dynamics of measles and its related vaccine schedules and average life expectancy. Birth rates in each patch are estimated using the convergence of the total populations in each patch. Vaccine efficacy is approximated using the fact that a single dose the MMR vaccine is 85% to 95% effective [33]. The most difficult parameters to estimate are the transmission rates. However, using the relationship between the disease transmission rates and the reproduction numbers, one can approximate an appropriate rate of disease transmission for the cases where the reproduction numbers are less than or greater that one.

In the simulations, the values for the parameters will be taken as in Table 7.1 below unless otherwise stated.

Parameter	Definition	Value
β_w	disease transmission rate in large city (per capita)	0.1
β_r	disease transmission rate in small city (per capita/ per contact)	0.00001
b_w	birth rate in large city (per day)	27.39
b_r	birth rate in small city (per day)	0.18
α_w	rate of vaccination in large city	1/400
α_r	rate of vaccination in small city	1/400
$1-\sigma_w$	vaccine efficacy in large city	90 %
$1-\sigma_r$	vaccine efficacy in small city	90 %
m_{rw}	movement of individuals from large city to small city (per day)	1 %
m_{wr}	movement of individuals from small city to large city (per day)	11 %
d	death rate (per day)	1/(75*365)
γ	recovery rate (days)	1/24

TABLE 7.1: Definition of parameters with values based on disease dynamics for measles [3, 32, 33]

7.1.1 Estimation of movement and birth rates

In this section, the method presented in [2] is followed.

Estimates for total populations as well as travel rates are determined using values from Table 7.2, considering the large city to be Winnipeg, the capital city of Manitoba, and the small cities to be Portage la Prairie, Morden and Peguis First Nations. The last column in the table indicates average daily travellers to Winnipeg.

City	Population	Distance (km)	Average daily travellers
Winnipeg	663,617	-	-
Portage la Prairie	12,996	85	4,115
Morden	7,812	130	1,630
Peguis First Nations	2,609	184	650

TABLE 7.2: 2011 Canadian census and Traffic on Manitoba Highways [36]

To estimate movement rates, consider the large city and its population, N_w. Assuming that m_{rw} is the movement of individuals from the large city to the small city, thus $N'_w =$

$-m_{rw}N_w$. Solving this differential equation yields $N_w(t) = -N_w(0)e^{-m_{rw}t}$. Therefore, after one day, $N(1) = N_w(0)e^{-m_{rw}}$. Solving for the movement rate yields

$$m_{rw} = -ln\left(\frac{N_w(1)}{N_w(0)}\right).$$

To compute the total population in the large city with several days of travel considered, let T_{rw} be the number of individuals travelling from the large city to the small city each day. Therefore, $N(1) = N_w(0) - T_{rw}$ and

$$m_{rw} = -ln\left(1 - \frac{T_{rw}}{N_w(0)}\right).$$

Given the movement rates and the population numbers, $\mathbf{b}$ is then set so that the travel rates are conserved. It follows that

$$\mathbf{b} = (d\mathbb{I} - \mathcal{M})\mathbf{N}^*.$$

Substituting this value of $\mathbf{b}$ into

$$\mathbf{N}' = \mathbf{b} - (d\mathbb{I} - \mathcal{M})\mathbf{N}$$

gives

$$\mathbf{N}' = (d\mathbb{I} - \mathcal{M})\mathbf{N}^* - (d\mathbb{I} - \mathcal{M})\mathbf{N} = (d\mathbb{I} - \mathcal{M})(\mathbf{N}^* - \mathbf{N}).$$

Therefore, starting with $\mathbf{N}(\mathbf{0}) = \mathbf{N}^*$ allows numerical simulations at the population equilibrium to be computed so that the only effects visible are those due to disease.

7.2 Uncoupled patches with vaccination

When the patches are uncoupled, it seems as though the transmission coefficients, β_w and β_r, have the largest impact on $\mathcal{R}^w_{vac}$ and $\mathcal{R}^r_{vac}$ respectively. This can be seen in Figures 7.1 and 7.2 below. The reproduction number of each patch increases rapidly with small perturbations in the infection rates. It is difficult to determine what is a realistic infection rate for a particular disease; however, it possible to use a approximated reproduction number for a given disease to work backwards and determine an approximate transmission coefficient.

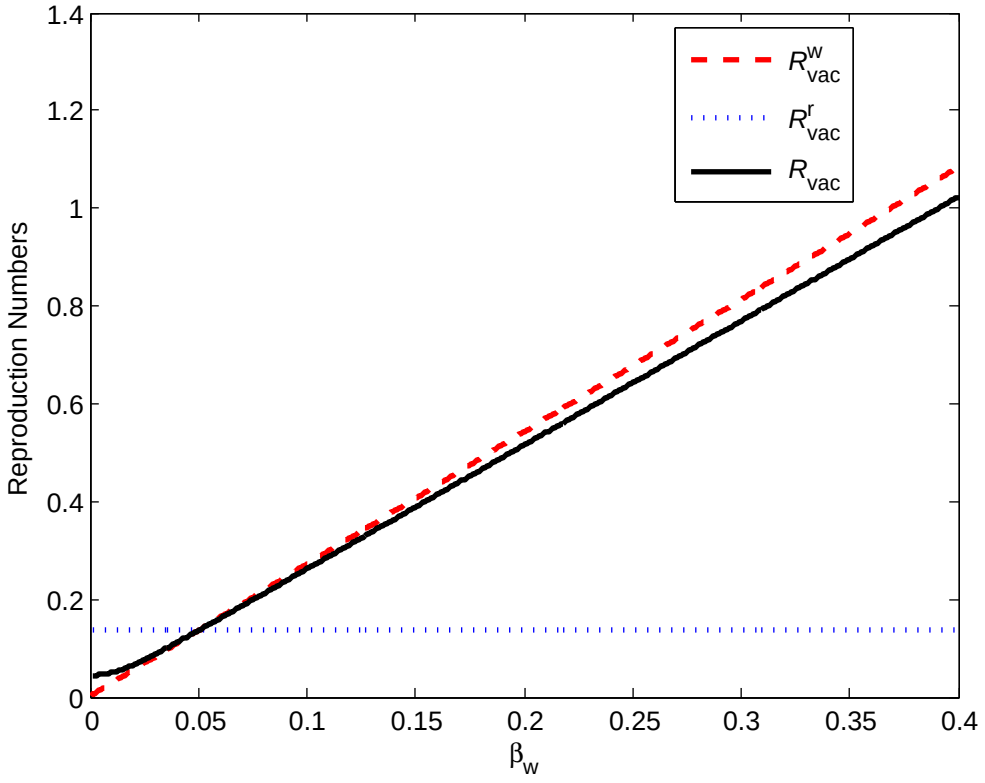

FIGURE 7.1: Varying the disease transmission coefficient in the large city. It can be seen in the figure that the reproduction number in the large city drives the global reproduction number. It should also be noted that the global reproduction number remains bounded by each individual reproduction number which was shown in Proposition 6.9.

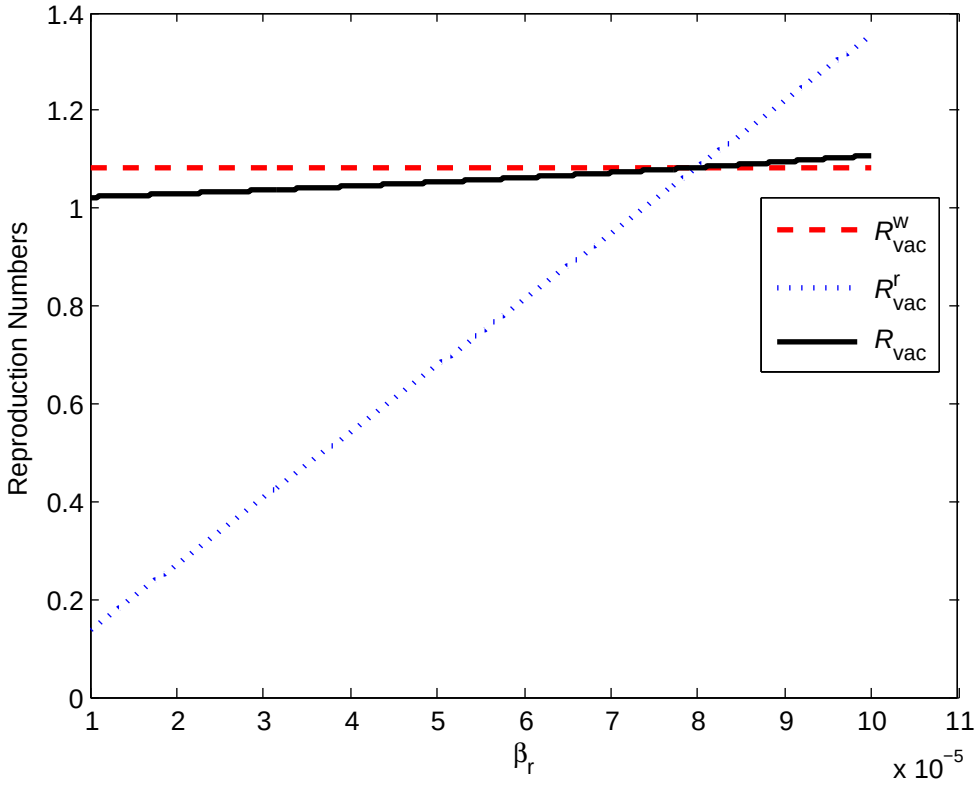

FIGURE 7.2: Varying transmission coefficient in small city. Although the reproduction number in the small city is increasing rapidly with respect to the increasing disease transmission coefficient, the global reproduction number tends to stay within the range of the reproduction number of the larger city.

7.2.1 Vaccine coverage

In public health, vaccine coverage refers to the proportion of individuals in a population which have been vaccinated. In order to maintain herd immunity, a critical threshold of individuals must be vaccinated or have conferred immunity through other means.

Considering the large city first, the vaccine coverage, c_w, is computed by taking the total vaccinated individuals at the disease free equilibrium, V_w^*, and dividing by N_w^*. Thus,

$$c_w = \frac{\alpha_w b_w}{d(d+\alpha_w)} \frac{d}{b_w} = \frac{\alpha_w}{d+\alpha_w}.$$

However, this relationship only holds when $\mathcal{R}^w_{vac} < 1$, since that is when the DFE_w is globally asymptotically stable. Using the coverage, it is possible to rewrite α_w in terms of c_w such that

$$\alpha_w = \frac{dc_w}{1-c_w} \qquad \text{for} \quad c_w \in [0,1).$$

Using this relationship, $\mathcal{R}^w_{vac} < 1$ can be re-written to take the form

$$\mathcal{R}^w_{vac} = \frac{\beta_w b_w (1 - c_w + \sigma_w c_w)}{\gamma + d}.$$

Similarly, coverage is computed for the small city such that

$$c_r = \frac{\alpha_r b_r}{d(d+\alpha_r)} \frac{d}{b_r} = \frac{\alpha_r}{d+\alpha_r}$$

and $\mathcal{R}^r_{vac} < 1$ can be re-written to take the form

$$\mathcal{R}^r_{vac} = \frac{\beta_r b_r (1 - c_r + \sigma_r c_r)}{d(\gamma + d)}.$$

When $\mathcal{R}^w_{vac}$ and $\mathcal{R}^r_{vac}$ are greater than one, the endemic equilibrium values for V^{**} must be considered since the disease free equilibria for either patch is no longer stable. This is the case which is most interesting as the above case implies that the reproduction number remains less than one, regardless of the number of immune individuals. This quantity is difficult to determine mathematically as the endemic equilibrium point is not explicit, thus it will be explored numerically.

Considering the small city first, it can be seen that introducing vaccination into a population has a positive effect in reducing the number of infections (if only slightly).

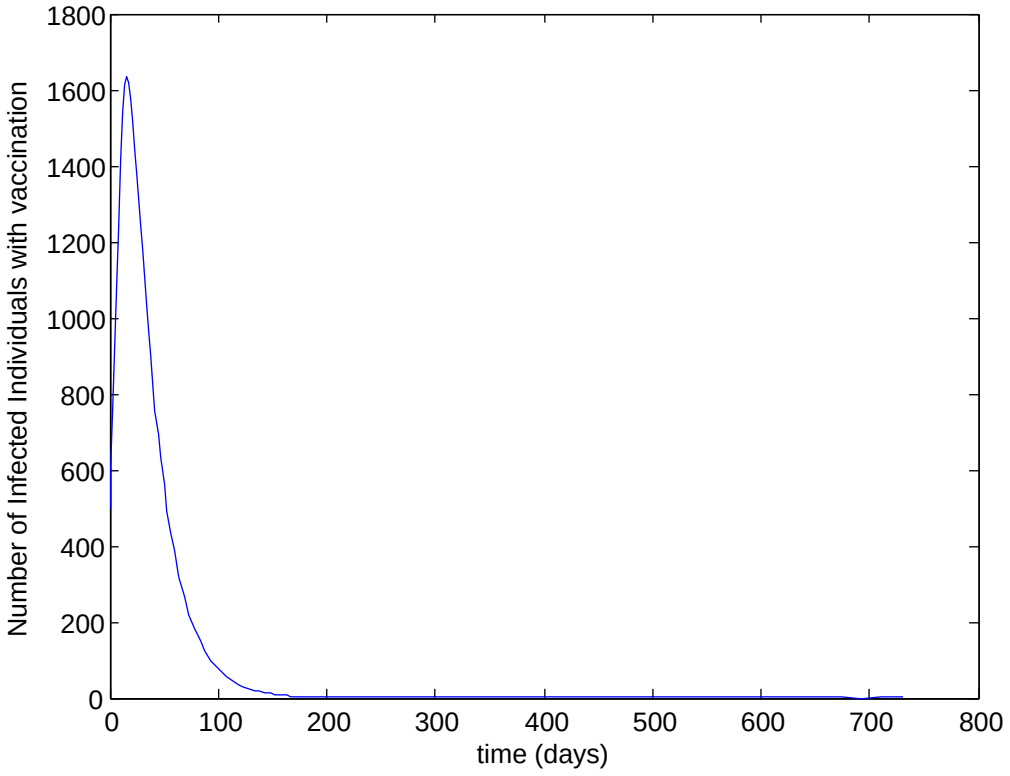

FIGURE 7.3: The number of infected individuals in the small city **with** vaccination over a time span of 2 years. It can be seen in the figure that during the initial 100 days the number of individuals infected becomes large, indicating an epidemic. Here, the initial conditions are taken to be $S_r(0) = 2450$, $V_r(0) = 50$, $I_r(0) = 500$ and $R_r(0) = 2000$ and $\mathcal{R}^r_{vac} = 10$.

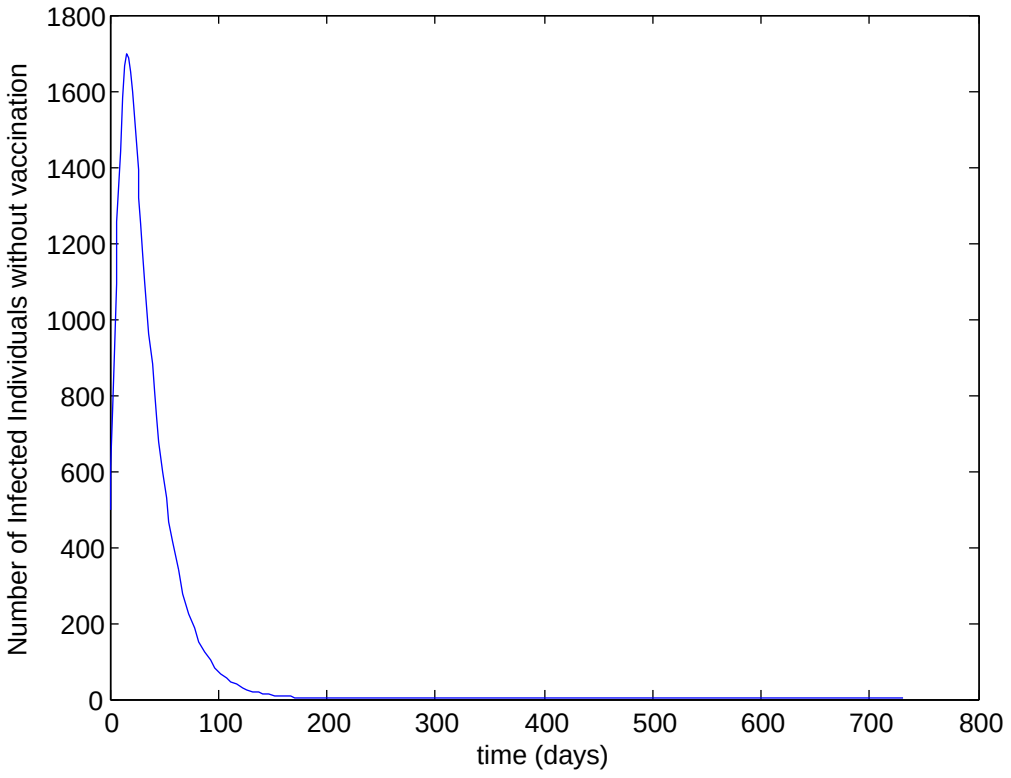

FIGURE 7.4: The number of infected individuals in the small city **without** vaccination over a time span of 2 years. It can be seen in the figure that during the initial 100 days the number of individuals infected becomes large, indicating an epidemic. Here, the initial conditions are taken to be $S_r(0) = 2450$, $V_r(0) = 50$, $I_r(0) = 500$ and $R_r(0) = 2000$ and $\mathcal{R}^r_{vac} = 10$.

In Figure 7.3, the maximum number of individuals that become infected in the small city during the given time span is 1635; however, it can be seen in Figure 7.4 that the maximum number of individuals which become infected is 1696. Thus, vaccination has a positive effect on reducing the incidence of disease. The same can be observed in the large city.

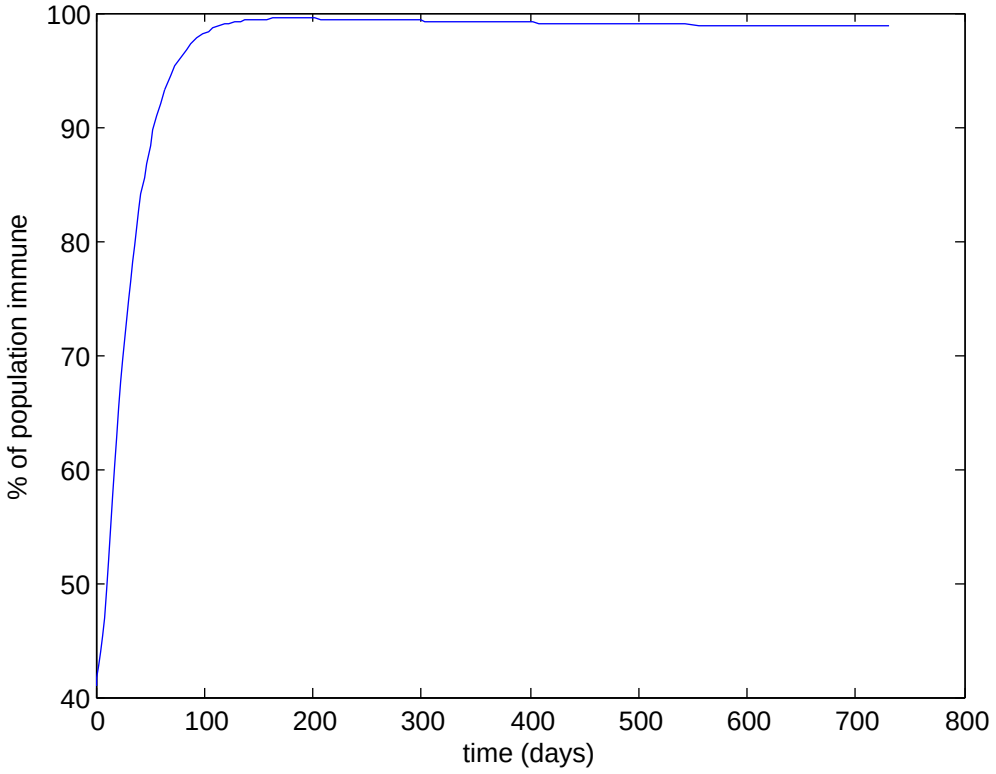

FIGURE 7.5: The percentage of the population immune to the disease. During the time span, nearly 100 % of individuals in the small patch must be immune by either vaccination or natural immunity in order for the disease to remain at a low endemic equilibrium.

7.2.2 Cases averted

In this section, the number of cases averted in each uncoupled patch is studied by examining the effect of a vaccine on disease transmission when reproduction number is larger than one.

Beginning with the small city, the endemic equilibrium points of both cases; where vaccination is present (6.28) and where vaccination is not present (6.31), are considered.

In addition, the reproduction number varied in these simulations is the reproduction number where no vaccination is present (6.15). This is due to the fact that $\mathcal{R}_0^r > \mathcal{R}_{vac}^r$. Since the transmission coefficient is tied into the varying reproduction number, β_r is written as a function of $\mathcal{R}_0^r$.

$$\beta_r = \frac{\mathcal{R}_0^r d(d+\gamma)}{b_r}$$

$$\mathcal{R}_{vac}^r = \frac{\mathcal{R}_0^r (d+\sigma_r \alpha_r)}{d+\alpha_r}$$

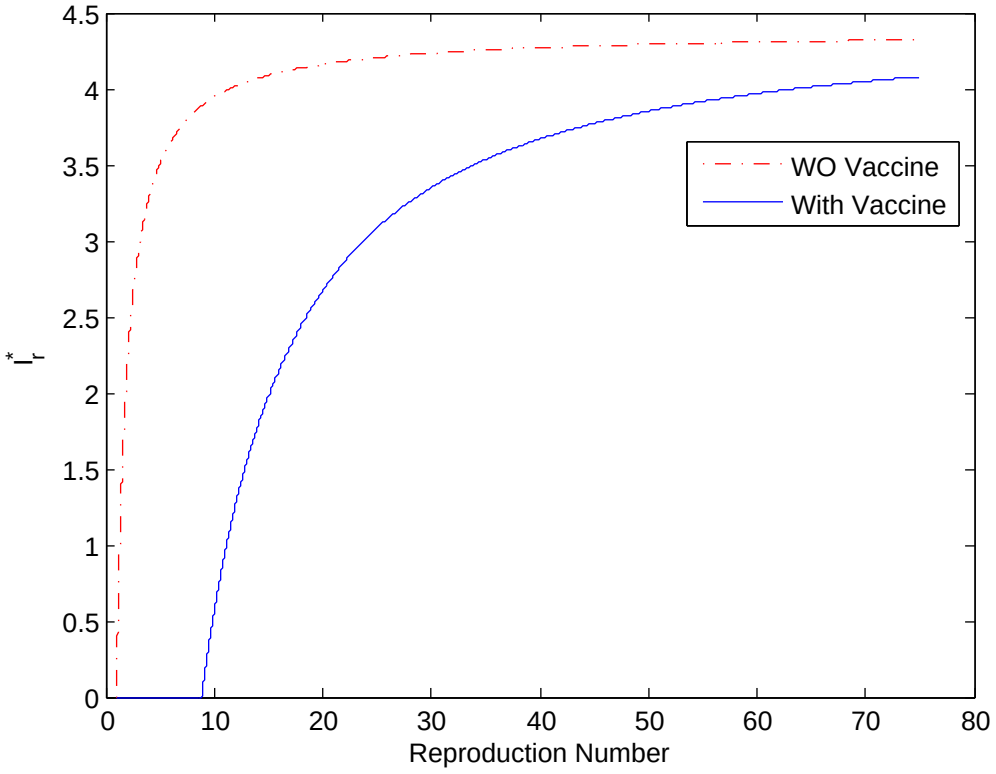

FIGURE 7.6: A depiction of the cases averted in the small city. As the reproduction number increases, the proportion of cases also becomes smaller. This figure shows that the number of infective individuals at the endemic equilibrium is slightly above 4 for both the cases with and without vaccine.

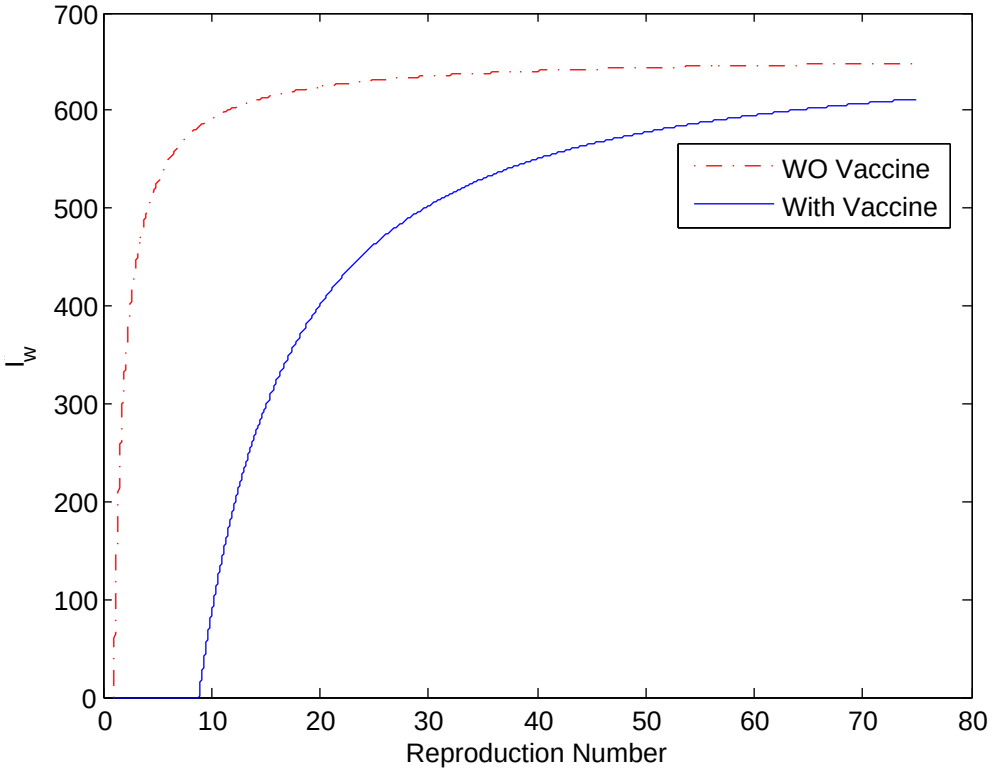

FIGURE 7.7: A depiction of the cases averted in the large city. As the reproduction number increases, the proportion of cases also becomes smaller. This figure shows that the number of infective individuals at the endemic equilibrium is slightly above 600 for both the cases with and without vaccine.

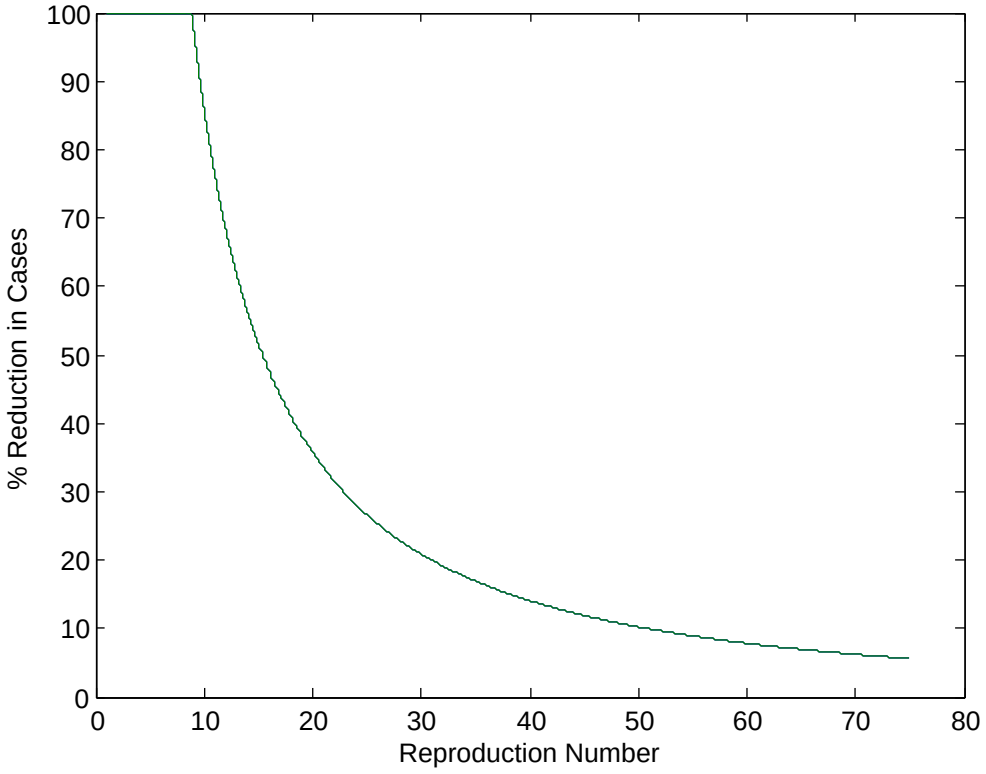

FIGURE 7.8: The figure shows the percentage reduction in cases in both the small city and large city. The greatest number of cases averted occur when $\mathcal{R}_0 < 10$.

7.3 Coupled patches with vaccination

Movement between patches has an effect on the global reproduction number, $\mathcal{R}_{vac}$. It can be seen in Figures 7.9 and 7.10 below that varying travel between the patches when one of the patches has a reproduction number larger than one can drive the global reproduction number, $\mathcal{R}_{vac}$, below one.

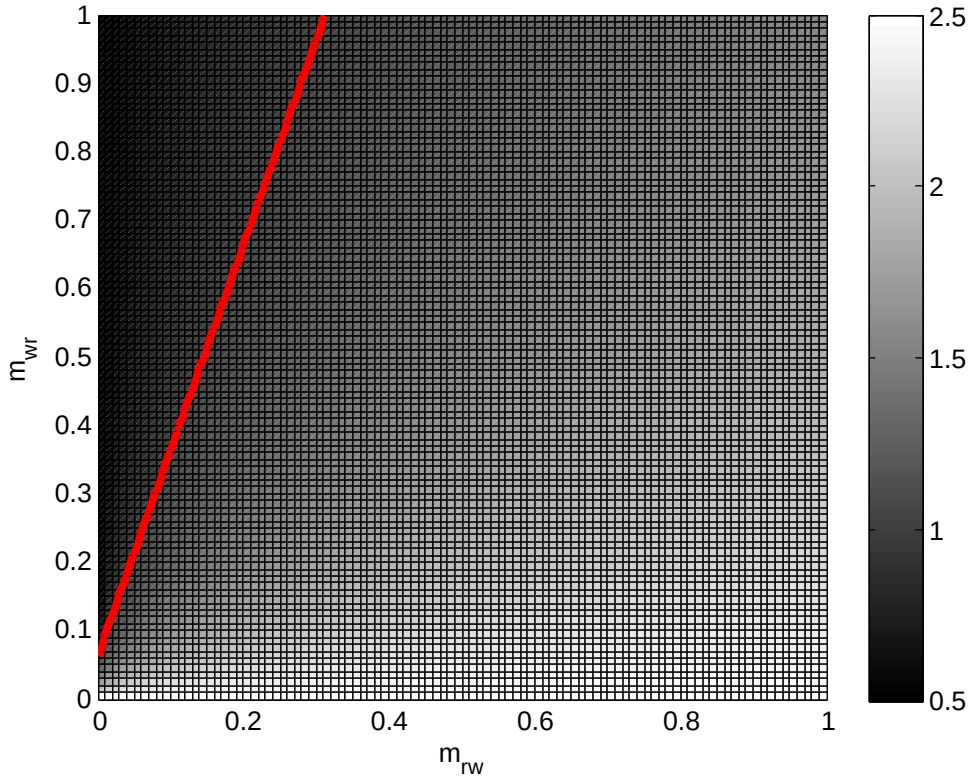

FIGURE 7.9: Varying movement to and from the large and small city with $\mathcal{R}^r_{vac} = 2.5$ and $\mathcal{R}^w_{vac} = 0.5$. The line on the plot indicates where $\mathcal{R}_{vac} = 1$ and the gradient scale indicates the changing value of $\mathcal{R}_{vac}$ for the different movement rates. In this case, increased movement from the small city to the large city in conjunction with decreased travel from the large city to the small city can push the global reproduction number below one (as seen to the left of the line $\mathcal{R}_{vac} = 1$).

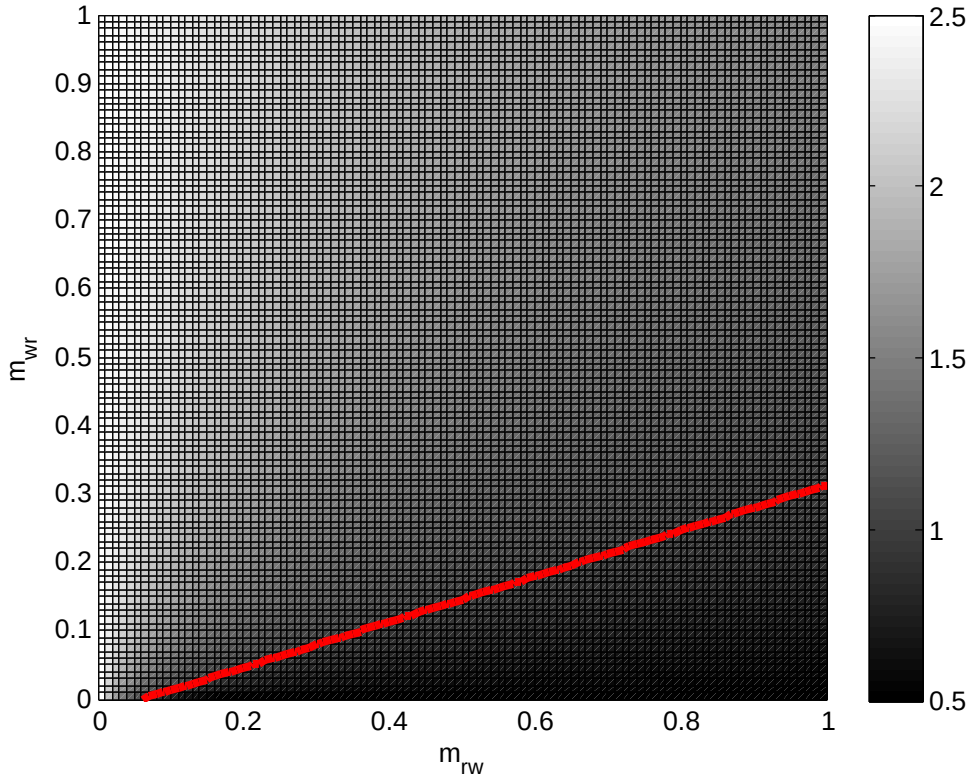

FIGURE 7.10: Varying movement to and from the large and small city with $\mathcal{R}^w_{vac} = 2.5$ and $\mathcal{R}^r_{vac} = 0.5$. The line on the plot indicates where $\mathcal{R}_{vac} = 1$ and the gradient scale indicates the changing value of $\mathcal{R}_{vac}$ for the different movement rates. In this case, increased movement from the large city to the small city in conjunction with decreased travel from the small city to the large city can drive the global reproduction number below one (as seen to the right of the line $\mathcal{R}_{vac} = 1$).

As stated earlier, vaccine efficacy is fairly standard and it is estimated that a single dose the MMR vaccine is 85% to 95% effective [33]. However, it is interesting to consider cases where vaccines may be less effective or ineffective in order to predict what might happen under these circumstances. Thus, varying vaccine efficacy in each patch has a great effect on $\mathcal{R}_{vac}$. It can be seen in the figure below that if there is a vaccine administered with very low efficacy in the large city, this would drive the global $\mathcal{R}_{vac}$ above one, even if the vaccine is perfect in the small city.

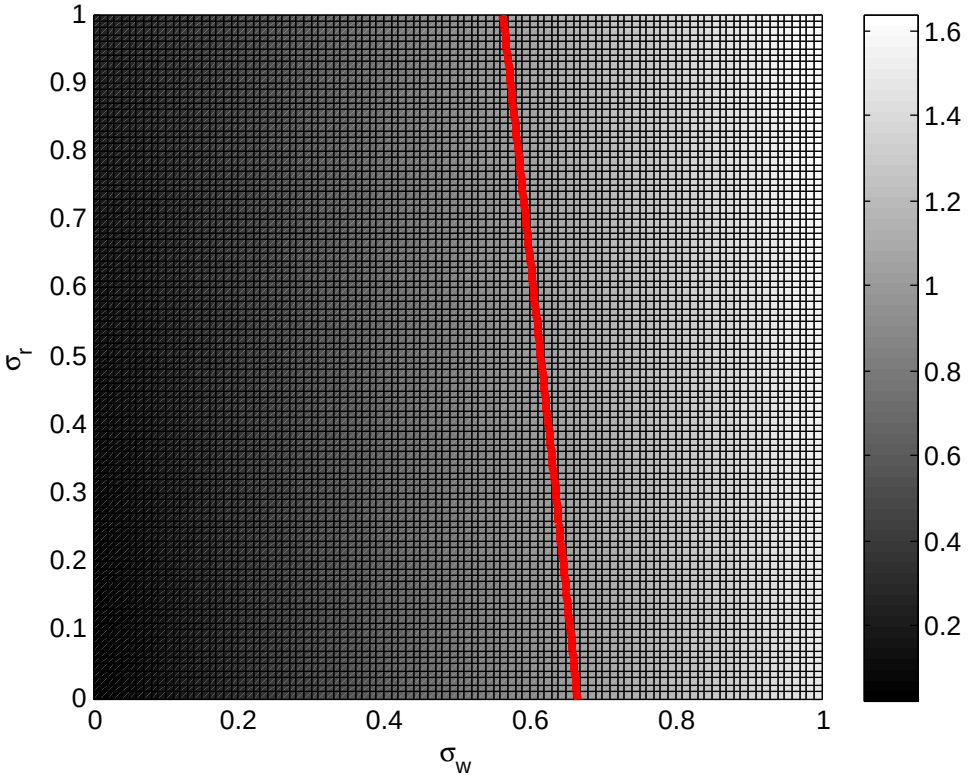

FIGURE 7.11: Varying vaccine efficacy and the effect on $\mathcal{R}_{vac}$. The global reproduction number is driven by the effectiveness of vaccination in the large city. Hence, if vaccine efficacy of the vaccines administered in the large city is approximately 30% or less and the vaccines administered in the small city are perfect or near perfect vaccine, the global reproduction number falls above one.

The global reproduction number, $\mathcal{R}_{vac}$, can also be plotted as a function of the individual reproduction numbers.

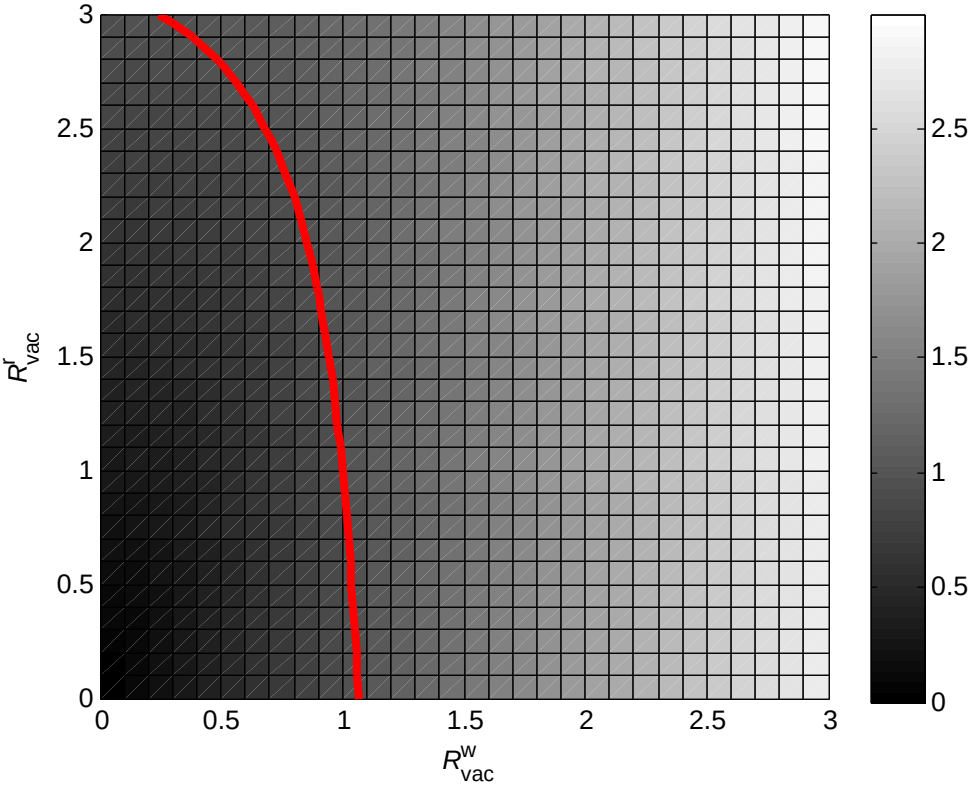

FIGURE 7.12: Varying individual reproduction numbers and the effect on the global reproduction number. It is clear from the figure that the reproduction number in the large city drives the global reproduction number.

7.4 Summary

This chapter explored the dynamics of measles transmission between two patches connected with mobility as well as in the isolation using numerical analysis. While the figures are in no means a proof to any of the conjectures, they do aid in understanding the dynamics of disease transmission under varying circumstances by depicting trends.

Chapter 8

Perspectives and Conclusions

The focus of this thesis was to analyse a two patch model in which the patches were connected with mobility as well as isolated when mobility was ignored. The model also included a single vaccination class and the effect vaccination has on the dynamics of measles in each patch was studied. Summarised below are some of the key findings as well as potential future work.

8.1 Findings

1. The reproduction number of the large city drives the coupled reproduction number. It can be seen in Figure 7.12 that the reproduction number of the coupled system is greatly effected by the value of the reproduction number in the large city. Not only do the numerical simulations in Chapter 7 reinforce the fact that the coupled reproduction number must remain bounded by the maximum and minimum individual reproduction numbers, this was shown mathematically in Proposition 6.9.

2. Travel away from the patch with a reproduction number greater than one to a patch in which the reproduction number is less than one reduces the global reproduction number. It is seen in Figures 7.9 and 7.10 that mobility plays

a key role in the dynamics of disease spread. Moving individuals could be a method adopted by public health officials in order to reduce an epidemic.

3. High vaccine efficacy in the large city drives the coupled reproduction number. In an unlikely and unethical scenario, if a vaccination with very low efficacy were to be introduced into the large patch, it could potentially drive the global reproduction number above one even if individuals in the small patch are receiving a perfect or near perfect vaccine.

4. A significant number of cases are averted when the true reproduction number, $\mathcal{R}_0$, is less than 10. Figure 7.8 demonstrates that as the reproduction number becomes very large (unrealistically large), the number of cases averted due to vaccine administration falls off. However, for a reproduction number below 18 (an estimated reproduction number for measles), greater than 65% of cases are averted in both patches.

5. Herd immunity is increased globally as herd immunity is increased in the large patch. The large patch as the most impact on herd immunity. It can be seen in Chapter 7 that almost 90% of individuals in the total population residing in the large patch are immune over the time span of two years.

8.2 Future work

In Section 6.6.4, the stability of the endemic equilibrium point was undetermined as the expression was not explicit. Given more time, it may be possible to execute many simulations, analyse the Jacobian of the system at the various endemic points found and determine if all eigenvalues have negative real parts. Although this is not a proof, it would show an indication that the endemic equilibrium is at least locally asymptotically stable.

Sensitivity analysis is an area in which attention could be focused in the future in order to determine what effect small perturbations in various parameters has on various quantities

including the individual reproduction numbers as well as the global reproduction number with vaccination and mobility.

Another area to investigate could be the economic impact of travel to and from the large city in order to receive health care as well as the cost to supply remote rural communities with effective vaccines and the proper medical personnel to administer them.

Appendix A

The following is a proof for Theorem 6.6.

Proof. Beginning with the small city and assuming $\mathcal{R}^r_{vac} < 1$, consider the following Lyapunov function taken from [29].

$$L_1 = S_r - S_r^* - S_r^* \ln \frac{S_r}{S_r^*} + V_r - V_r^* - V_r^* \ln \frac{V_r}{V_r^*} + I_r \tag{A.1}$$

where $DFE_r = (S_r^*, V_r^*, 0)$.

Its time derivatives along the solutions of system (6.10) satisfies

$$\begin{aligned}
L_1' &= S_r' + V_r' + I_r' - S_r^* \frac{S_r'}{S_r} - V_r^* \frac{V_r'}{V_r} \\
&= b_r - dS_r - dV_r - dI_r - \gamma I_r - S_r^* \frac{d}{S_r} + dS_r^* + \beta_r S_r^* I_r + \alpha_r S_r^* - \alpha_r \frac{V_r^* S_r}{V_r} + \sigma_r \beta_r V_r^* I_r + dV_r^* \\
&= -dS_r - \frac{\alpha_r S_r^* V_r}{V_r^*} + 2dS_r^* + 3\alpha_r S_r^* - \frac{S_r^*}{S_r}(dS_r^* + \alpha_r S_r^*) - \alpha_r \frac{V_r^* S_r}{V_r} - (d + \gamma - \beta_r S_r^* - \sigma_r \beta_r V_r^*) I_r \\
&= -dS_r^* (\frac{S_r}{S_r^*} + \frac{S_r^*}{S_r} - 2) - \alpha_r S_r^* (\frac{V_r}{V_r^*} + \frac{S_r^*}{S_r} + \frac{V_r^* S_r}{V_r S_r^*} - 3) - (d + \gamma)(1 - \mathcal{R}_0^r) I_r.
\end{aligned}$$

Here, because the arithmetic mean is larger than, or equal to the geometric mean, we have

$$\frac{S_r}{S_r^*} + \frac{S_r^*}{S_r} - 2 \geq 0, \qquad \frac{V_r}{V_r^*} + \frac{S_r^*}{S_r} + \frac{V_r^* S_r}{V_r S_r^*} - 3 \geq 0$$

and the equalities hold if and only if $S_r = S_r^*$ and $V_r = V_r^*$. Since $\mathcal{R}_0^r < 1$, it is clear that $L_1' < 0$. Thus, DFE_r is globally asymptotically stable since (A.1) is a strict Lyapunov function. □

The proof for the global asymptotic stability of DFE_w is found using the same Lyapunov function in (A.1) and follows the same process as above.

The following is a proof for Theorem 6.12.

Proof. Beginning with the rural system, suppose $\mathcal{R}_{vac}^r > 1$. Consider the Lyapunov function

$$L_2 = S_r - S_r^{**} - S_r^{**} \ln \frac{S_r}{S_r^{**}} + V_r - V_r^{**} - V_r^{**} \ln \frac{V_r}{V_r^{**}} + I_r - I_r^{**} - I_r^{**} \ln \frac{I_r}{I_r^{**}}$$

where $EEP_r = (S_r^{**}, V_r^{**}, I_r^{**})$ is the endemic equilibrium system (6.10).

Its time derivative along the solutions of system (6.10) satisfies

$$
\begin{aligned}
L_2' &= S_r' + V_r' + I_r' - S_r + \frac{S_r'}{S_r} - V_r + \frac{V_r'}{V_r} - I_r + \frac{I_r'}{I_r} \\
&= d - dS_r - dV_r - dI_r - d\frac{S_r^{**}}{S_r} + dS_r^{**} + \beta_r S_r^{**} I_r + \alpha_r S_r^{**} \\
&- \alpha_r S_r \frac{V_r^{**}}{V_r} + \sigma_r \beta_r V_r^{**} I_r + dV_r^{**} - \beta_r S_r I_r^{**} - \sigma_r \beta_r V_r I_r^{**} + dI_r^{**} \\
&= 2d - dS_r - \frac{\alpha_r S_r^{**} - \sigma_r \beta_r V_r^{**} I_r^{**}}{V_r^{**}} V_r - (dS_r^{**} + \beta_r S_r^{**} I_r^{**} + \alpha_r S_r^{**}) \frac{S_r^{**}}{S_r} + \alpha_r S_r^{**} \\
&- \alpha_r S_r \frac{V_r^{**}}{V_r} - \beta_r S_r I_r^{**} \\
&= 2(dS_r^{**} + \beta_r S_r^{**} I_r^{**} + \alpha_r S_r^{**}) - dS_r - \frac{\alpha_r S_r^{**} V_r}{V_r^{**}} + \alpha_r S_r^{**} \\
&- \frac{d{S_r^{**}}^2}{S_r} - \frac{\beta_r {S_r^{**}}^2 I_r^{**}}{S_r} - -\frac{\alpha_r {S_r^{**}}^2}{S_r} - \frac{\alpha_r S_r V_r^{**}}{V_r} - \beta_r S_r I_r^{**} \\
&= -(dS_r^{**} + \beta_r S_r^{**} I_r^{**}) \left(\frac{S_r}{S_r^{**}} + \frac{S_r^{**}}{S_r} - 2 \right) - \alpha_r S_r^{**} \left(\frac{V_r}{V_r^{**}} + \frac{S_r^{**}}{S_r} + \frac{S_r V_r^{**}}{S_r^{**} V_r} - 3 \right) \\
&\leq 0.
\end{aligned}
$$

Thus, the endemic equilibrium, EEP_r, is globally stable.

□

The above proof applies to system (6.8) using the fact that $N_w = \frac{b_w}{d}$.

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