# A review of a model for imperfect vaccination, honeymoon periods and methods to characterize transient dynamics

by

Nazila Akhavan Kharazian

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# Abstract

Vaccination is a common method for protecting newborns from some childhood diseases like measles, mumps, and rubella. This control measure has proven to be very successful as evidenced by large decreases in the incidence of these diseases after the start of mass vaccination programs. However, the control of some diseases, such as pertussis, has recently become more difficult in some countries with high vaccination coverage. Mathematical models can be used to help understand the ramifications of different types of imperfect vaccines on post-vaccination disease dynamics and to harness this understanding to develop more efficient vaccination strategies. In this project, we review the VSIR compartmental model analyzed in (Magpantay et al., 2014) where people can be classified into one of four states: vaccinated ($V$), susceptible ($S$), infected ($I$), and recovered ($R$). This model allows for a vaccine that can exhibit different types of vaccine failures: in degree (leakiness), in take (all-or-nothing) and in duration (waning of vaccine-derived immunity). We also review existing methods in ecology for characterizing transient dynamics of disease systems such as the honeymoon period after start of mass vaccination programs.

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# Chapter 1

# EPIDEMIOLOGICAL BACKGROUND

## 1.1 Introduction

Vaccines are biological preparations that induce a host's immunity against a disease by imitating an infection without causing the actual illness. The first vaccine was developed by Edward Jenner for smallpox in 1798. He observed that milkmaids who had previously caught cowpox did not later catch smallpox. He then inoculated an eight-year-old boy with weakened cowpox virus and the boy later demonstrated immunity to smallpox (Stern and Markel, 2005).

Today, vaccination remains an effective weapon in the battle against childhood diseases. It is one of the most important and effective public health measures against disease, disability and death. However there has been a resurgence of some diseases, such as pertussis, in countries with high vaccination coverage. Different factors may be responsible for the difficulty in controlling these diseases using vaccines, and mathematical modeling is a tool that we can use to help test our hypotheses on how individual-level effects of a vaccine can result in different population-level dynamics.

Figure 1.1: Nurse giving a baby a vaccine shot. Image source: Centers for Disease Control and Prevention (CDC). Photo Credit: James Gathany

In this project we review a model of childhood vaccination and consider both the steady-state and transient dynamics that arise from it. This includes a discussion of the so-called "honeymoon periods." McLean and Anderson (1988) observed that after the initiation of a mass vaccination program, the drop in the number of infected people may be followed by a honeymoon period, a long period of low incidence before a resurgence or rebound in the number of cases of the disease. In Figure 1.2 the number of reported infected cases of pertussis (whooping cough) in Massachusetts are shown between years 1950 and 2013. At the beginning of the mass vaccination program in 1967, there is a drop in cases and a yellow band is drawn to show the honeymoon period which lasted for about 10 years until a 1977 resurgence of the disease.

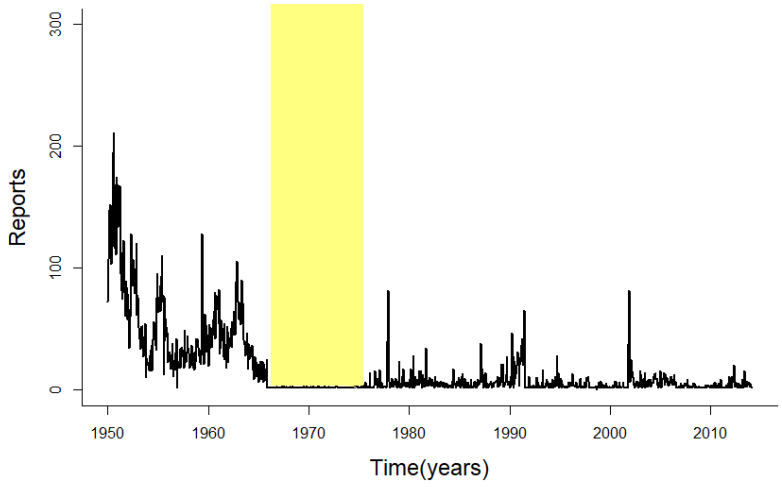



Figure 1.2: Honeymoon period for Pertussis in Massachusetts, USA. Data source: Project TYCHO

## 1.2 Goals of this project

Most research is focused on the equilibrium dynamics of epidemiological systems. However, transient dynamics can also have some very unique and informative characteristics, complementing the steady state analysis of systems. For instance, the honeymoon period is a transient feature that is displayed by some disease models that is an important consideration for public health planning. There are many papers that note the occurrence of honeymoon periods in their model dynamics but do not investigate this further. In this project, we review some existing models of vaccination and literatures on honeymoon periods and methods to measure transient dynamics (Neubert and Caswell (1997), McLean and Anderson (1988)). We also review a simple model of vaccination which allows for three different modes of vaccine failure. We perform steady-state analysis on these models and investigate if honeymoon periods occur in these models. We review existing linearization methods for

measuring transient dynamics in ecology, such as reactivity and amplification envelope (Neubert and Caswell, 1997), and conclude that these are not enough to determine the characteristics of honeymoon periods. Instead we present numerical measurements of honeymoon periods under different modes of vaccine failure, by measuring the dip and recovery of the susceptible class. In the end we present some suggestions for future work on ways to look at honeymoon periods.

## 1.3 Outline of the project

In Chapter 2, we present the mathematical preliminaries required for this study. In Chapter 3 we present a review of the imperfect vaccination model analyzed in Magpantay et al. (2014). The three different modes of vaccine failure and their effects on epidemiological dynamics are discussed. Expressions and calculations of how the endemic steady states vary with changing parameters are also presented. In Chapter 4 we discuss honeymoon periods and review three measures of transient dynamics defined by Neubert and Caswell (1997) and Aldridge et al. (2006). We note that these three measures are not helpful in distinguishing between models that display honeymoon periods and those that do not, highlighting the need for a nonlinear analysis of honeymoon periods. We also present different measurements of the honeymoon periods by numerically computing solutions and focusing on the behaviour of the susceptible class. In the last chapter we present a summary of the project and discuss some future directions for studying transient dynamics in vaccination models.

# Chapter 2

# MATHEMATICAL BACKGROUND

## 2.1 Preliminaries

Here we present some background material for the analysis of disease models with vaccination. The material for this section is based on Allen et al. (2008) and Strogatz (2018). We begin with some mathematical preliminaries on ordinary differential equations. Let $d \in \mathbb{N}$ and let $f : \mathbb{R}^d \to \mathbb{R}^d$. Consider a system of autonomous ordinary differential equations with the initial condition given by,

$$\begin{aligned} z' &= f(z) \\ z(0) &= z_0 \end{aligned} \tag{2.1}$$

**Theorem 2.1.** (Existence and Uniqueness Theorem from Strogatz (2018) p. 27*)* *Suppose that $f(z)$ and $f'(z)$ are continuous on $\mathbb{R}^d$ and suppose that $z(0)$, is a point in $\mathbb{R}^d$. Then the initial value problem* (2.1) *has a solution $z(t)$ on a time interval containing zero and the solution is unique.*

For proofs of the existence and uniqueness theorem, see Borelli and Coleman (1987) and Lin and Segel (1988).

**Definition 2.2** (Equilibrium points and stability)**.** *A point $z^*$ is an equilibrium point of (2.1), if $f(z^*) = 0$.*

*An equilibrium point $z^*$ is said to be Lyapunov stable if for every $\varepsilon > 0$ there exists $\delta > 0$ such that if $\|z(0) - z^*\| < \delta$ then $\|z(t) - z^*\| < \varepsilon$ for all $t \geq 0$.*

*An equilibrium point $z^*$ is said to be asymptotically stable if it is Lyapunov stable and there exists $\delta > 0$ such that if $\|z(0) - z^*\| < \delta$ then $\lim_{t\to\infty} \|z(t) - z^*\| = 0$.*

**Definition 2.3** (Linearization)**.** *Let $J(z)$ be the Jacobian matrix of $f(z)$ where $f$ is differentiable,*

$$J(z) = \begin{bmatrix} \frac{\partial f_1}{\partial z_1} & \cdots & \frac{\partial f_1}{\partial z_d} \\ \vdots & \ddots & \vdots \\ \frac{\partial f_d}{\partial z_1} & \cdots & \frac{\partial f_d}{\partial z_d} \end{bmatrix}.$$

*Let $z^* \in \mathbb{R}^d$ be an equilibrium point of (2.1). The linearized system of (2.1) at $z = z^*$ is given by*

$$(z - z^*)' = J(z^*)(z - z^*). \tag{2.2}$$

**Proposition 2.4.** *Let $z^*$ be an equilibrium point and $J$ be the Jacobian of the linearized system (2.2) at $z^*$. If all eigenvalues have negative real parts then the equilibrium point $z^*$ is asymptotically stable.*

We now move on to compartmental disease-transmission models that are formed using systems of ordinary differential equations.

**Definition 2.5.** *Consider a compartmental model with $n$ disease compartments (such*

*as exposed or infected compartments) and m non-disease compartments (such as susceptible and recovered compartments). Let* $x = (x_1, \ldots, x_n)$ *be the disease compartments and* $y = (y_1, \ldots, y_m)$ *be the non-disease compartments and*

$$\begin{cases} \dfrac{dx_i(t)}{dt} = \mathcal{F}_i(x(t), y(t)) - \mathcal{V}_i(x(t), y(t)), & \text{for } i = 1, \ldots, n, \\ \dfrac{dy_j(t)}{dt} = \mathcal{G}_j(x(t), y(t)), & \text{for } j = 1, \ldots, m. \end{cases}$$

*where* $\mathcal{F}_i$, $\mathcal{V}_i$ *and* $\mathcal{G}_j$ *are functions on* $\mathbb{R}^{n+m}$ *into* $\mathbb{R}$. *Here* $\mathcal{F}_i$ *and* $\mathcal{V}_i$ *represent the rate of appearance of new infections, and the rate of progression of individuals through the disease compartments respectively.*

**Definition 2.6** (Disease-free Equilibrium $z^0 = (0, y^0)$)**.** *An equilibrium point at which a population is free of the disease (*$x_1 = x_2 = ... = x_n = 0$*).*

**Definition 2.7** (Endemic Equilibrium $z^* = (x^*, y^*)$)**.** *An endemic equilibrium point is a steady state where the disease has not been eradicated and remains in the population. At least one of the x values is positive at this point.*

**Definition 2.8** (Well-posedness)**.** *The system defined in (2.1) is called well-posed if there exists a unique solution that changes continuously with the initial conditions.*

**Definition 2.9** (Invariant set)**.** *A set* $\omega \subset \Omega$ *is called invariant with respect to the system (2.1) if any solution with initial condition in* $\omega$ *of the system does not leave* $\omega$.

**Assumption 2.10** (Well-posedness of compartmental disease transmission models)**.** *The following assumptions were presented by Van den Driessche and Watmough (2008) as sufficient conditions for the well-posedness and invariance of the system with non-negative initial values close to the disease-free equilibrium.*

*(A1)* $\mathcal{F}_i(0, y) = \mathcal{V}_i(0, y) = 0$ *for all* $y \geq 0$

*(no new infections arise if initially there are no infections)*

*(A2)* $\mathcal{F}_i(x, y) \geq 0$ *for all* $y \geq 0$

*(the rate of generation of new infections cannot be negative)*

*(A3)* $\mathcal{V}_i(x, y) \leq 0$ *whenever* $x_i = 0, i = 1, \ldots, n$ *for all* $y \geq 0$.

*(if the compartment is empty, you only have inflow)*

*(A4)* $\sum_{i=1}^{n} \mathcal{V}_i(x, y) \geq 0$ *for all* $x \geq 0$ *and* $y \geq 0$

*(the net outflow is always non-negative)*

*(A5) The system* $y' = \mathcal{G}(0, y)$ *has a unique, asymptotically stable equilibrium.*

The stability of the disease-free equilibrium is determined by the basic reproduction number. The basic reproduction number can be calculated as the spectral radius of the so-called "next generation matrix".

**Definition 2.11** (Next generation matrix and basic reproduction number)**.** *Let* $F = D\mathcal{F}(z^0)$ *and* $V = D\mathcal{V}(z^0)$ *where* $D$ *is the differential operator. Then next generation matrix is* $K = FV^{-1}$ *and basic reproduction number is* $R_0 = \rho(K)$ *where* $\rho$ *is the spectral radius. Basic reproduction number is the average number of secondary infections caused by an average infective in a fully susceptible population. If it is less than one a disease will die out, while if it exceeds one the disease becomes endemic in the population.*

Here we review how to prove the stability of the disease-free equilibrium when $R_0 < 1$. In order to do this, we need following definitions and lemmas.

**Definition 2.12** (Z-matrix)**.** *A matrix $A = sI - B$, with $B \geq 0$. These are matrices whose off-diagonal entries are non-positive.*

**Definition 2.13** (M-matrix)**.** *A Z-matrix with $s \geq \rho(B)$ where $\rho(B)$ is the spectral radius of the matrix $B$.*

**Remark 2.14.** *All eigenvalues of an M-matrix have a positive real part.*

**Proposition 2.15.** *$V$ is an M-matrix.*

*Proof.* Using assumptions (A1) and (A3), all off-diagonal values of $V$ are non-positive. Thus $V$ is a Z-matrix. By assumptions (A1) and (A4) we know the sum of any column of V is non-negative. Therefore, diagonal values are zero or positive. Thus $V$ is an M-matrix (Condition M35 of Theorem 6.2.3 from Berman and Plemmons (1994)). □

In what follows, it is assumed that V is non-singular.

**Lemma 2.16.** *(*Lemma 1 from Allen et al. (2008)*) If $A$ is a Z-matrix, then $A^{-1} \geq 0$ if and only if $A$ is a non-singular M-matrix.*

**Lemma 2.17.** *(*Lemma 2 from Allen et al. (2008)*) If $F$ is non-negative and $V$ is a non-singular M-matrix, then $R_0 = \rho(FV^{-1}) < 1$ if and only if all eigenvalues of $(F - V)$ have negative real parts.*

*Proof.* It is assumed that $V$ is a non-singular M-matrix then by Lemma 2.16 we have $V^{-1} \geq 0$. Also, it is supposed that $F$ is non-negative, thus $FV^{-1} \geq 0$ which leads $I - FV^{-1}$ be a Z-matrix that is a non-singular M-matrix if and only if $\rho(FV^{-1}) < 1$. Using Lemma 2.16, $(I - FV^{-1})^{-1} \geq 0 \iff \rho(FV^{-1}) < 1$. On the other hand we can write $(V - F)^{-1} = V^{-1}(I - FV^{-1})^{-1}$. We have already shown that $V^{-1} \geq 0$ therefore, $(V - F)^{-1} \geq 0 \iff (I - FV^{-1})^{-1} \geq 0$ and finally we conclude that

$(V-F)^{-1} \geq 0 \iff \rho(FV^{-1}) < 1.$

Again by Lemma 2.16 $(V-F)^{-1} \geq 0$ if and only if $(V-F)$ is a non-singular M-matrix and by Remark 2.14 has eigenvalues with positive real parts. Therefore we can say $(F-V)$ has eigenvalues with negative real parts if and only if $\rho(FV^{-1}) < 1$. □

**Theorem 2.18.** *(*Theorem 1 from Allen et al. (2008)*) Let $R_0$ be a basic reproduction number, obtained by the next generation method. Then*

- *If $R_0 < 1$, the disease-free equilibrium is locally asymptotically stable.*
- *If $R_0 > 1$, the disease-free equilibrium is unstable.*

*Proof.* Let $J_{21}$ and $J_{22}$ be the matrices of partial derivatives of the function $\mathcal{G}$ in Definition 2.5 with respect to $x$ and $y$ evaluated at the disease-free equilibrium. Then the Jacobian of the system in Definition 2.5 at the disease-free equilibrium is,

$$J = \begin{bmatrix} F-V & 0 \\ J_{21} & J_{22} \end{bmatrix}$$

If all the eigenvalues of $J$ have negative real parts then the disease-free equilibrium $z^0 = (0, y^0)$ is locally asymptotically stable. Considering the block structure of $J$, eigenvalues of $J$ are the union of those for $(F-V)$ and $J_{22}$. Assumption (A5) provides asymptotic stability of $y^0$ for the system $y' = \mathcal{G}(0, y)$ which implies that all eigenvalues of $J_{22}$ have negative real parts. It remains to show all eigenvalues of $(F-V)$ have negative real parts. Using Proposition 2.15, $V$ is a non-singular M-matrix and by the definition, $F$ is non-negative. Hence by Lemma 2.17 all eigenvalues of $(F-V)$ have negative real part if and only if $\rho(FV^{-1}) < 1$. Thus, the disease-free equilibrium is locally asymptotically stable if $R_0 = \rho(FV^{-1}) < 1$.

To prove instability when $R_0 > 1$, it is sufficient to show $R_0 = \rho(FV^{-1}) \leq 1$ if and only if all eigenvalues of $(V - F)$ have non-negative real part. Then by contraposition we conclude $(F - V)$ has at least one eigenvalue with positive real part if and only if $\rho(FV^{-1}) > 1$. Therefore the disease-free equilibrium is unstable whenever $R_0 > 1$.
By the proof of Lemma 2.17 we know $FV^{-1} \geq 0$. If $\rho(FV^{-1}) \leq 1$ then for any $\varepsilon > 0$ we have $(1 + \varepsilon) > 1 \geq \rho(FV^{-1})$ so $((1 + \varepsilon)I - FV^{-1})$ is a non-singular M-matrix and all its eigenvalues have positive real parts (by the Remark 2.14). Thus, $((1+\varepsilon)I - FV^{-1})^{-1} \geq 0$ and by the proof of Lemma 2.17 all eigenvalues of $(1+\varepsilon)V - F$ have positive real parts. Since we considered $\varepsilon > 0$ arbitrary, and eigenvalues are continuous functions of the entries of the matrix, then all eigenvalues of $(V - F)$ have non-negative real parts.
Now suppose all eigenvalues of $(V - F)$ have non-negative real parts. It follows that all eigenvalues of $((V + \varepsilon I) - F)$ have positive real part that leads it to be non-singular M-matrix, and by the proof of Lemma 2.17, $\rho(F(V + \varepsilon I)^{-1}) < 1$, $\forall \varepsilon > 0$. So $\rho(FV^{-1}) \leq 1$. □

One of the base models in epidemiology is the SIR model. Many other models are extensions of it.

**Example 2.19** ($SIR$ model)**.** *In this model we divide the population into three compartments: susceptible* $(S)$*, infected* $(I)$*, recovered* $(R)$ *(Kermack and McKendrick, 1927). It is given by the following system of equations,*

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

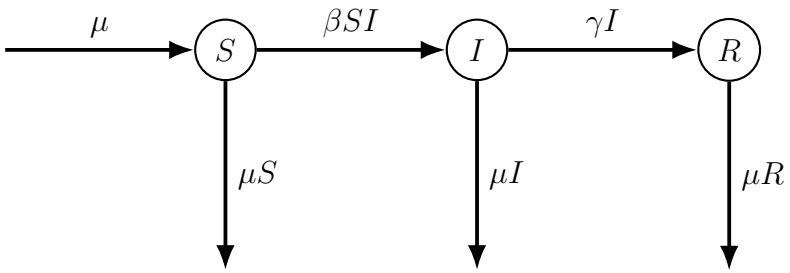



Figure 2.1: Standard $SIR$ model

*Here $\beta$ is the transmission rate, $\gamma$ is the recovery rate and $\mu$ is the birth and death rate. We note that $S(t) + I(t) + R(t) = 1$. The model is illustrated in Figure 2.1.*

By comparing the standard SIR model with Definition 2.5, here we find that there is only one disease class ($n = 1$, $x = I$) and two non-disease classes ($m = 2, y = (S, R)$). Using the next generation method we can define $\mathcal{F} = \beta SI, \mathcal{V} = \gamma I + \mu I$. Their derivatives evaluated at the disease-free equilibrium $(S^0, I^0, R^0) = (1, 0, 0)$ are $F = \beta$ and $V = \gamma + \mu$. Thus, the basic reproduction number is $R_0 = \rho(FV^{-1}) = \frac{\beta}{\gamma+\mu}$.

## 2.2 VSIR model

By adding a vaccinated class to the SIR model, we obtain a simple model of vaccination. The simplest model of vaccination (see figure 2.2) is defined as following,

$$\begin{aligned}
\frac{dV}{dt} &= p\mu - \mu V \\
\frac{dS}{dt} &= (1-p)\mu - \beta SI - \mu S \\
\frac{dI}{dt} &= \beta SI - \gamma I - \mu I \\
\frac{dR}{dt} &= \gamma I - \mu R
\end{aligned} \tag{2.4}$$

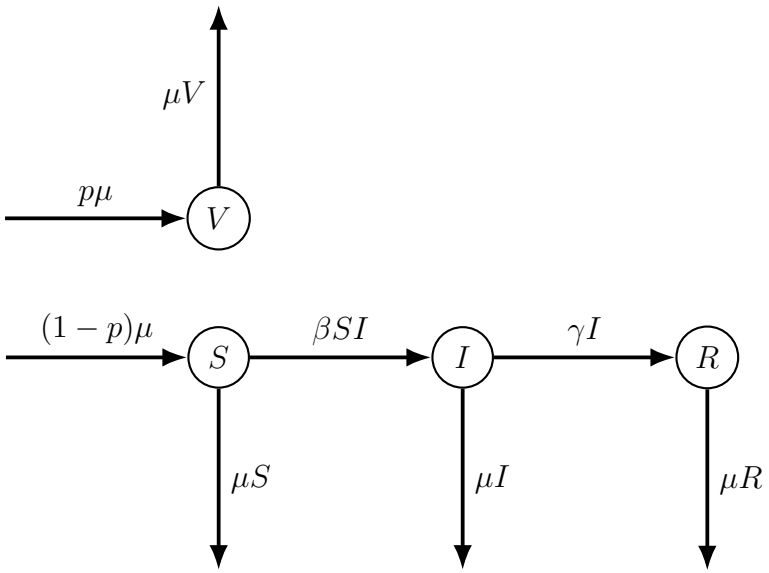



Figure 2.2: Standard VSIR Model

In this case $x = I, y = (V, S, R)$ and disease-free equilibrium is $(V^0, S^0, I^0, R^0) = (p, 1-p, 0, 0)$. Also we remind that $V(t)+S(t)+I(t)+R(t) = 1$. We denote $R_p$ as the basic reproduction number for this model which involves vaccination with coverage $p$ ($p = 0$ when there is no vaccination). We can calculate the basic reproduction number using the next-generation method as before. Here we derive $R_p = \frac{\beta}{\mu+\gamma}(1-p) = R_0(1-p)$.

**Definition 2.20** (Critical vaccination proportion ($p_c$))**.** *The minimum proportion of the population that needs to be vaccinated in order to achieve eradication of the disease.*

By Theorem (2.18) we have local asymptotic stability at the disease-free equilibrium if $R_p < 1$. Also,

$$R_p < 1 \iff R_0(1-p) < 1 \iff p > (1 - \frac{1}{R_0})$$

Thus for this simple model of vaccination we can always derive a critical vaccination proportion $p_c = 1 - \frac{1}{R_0}$. If $p > p_c$, then $R_p < 1$ and the disease-free equilibrium is locally asymptotically stable.

# Chapter 3

# MODEL OF AN IMPERFECT VACCINE

In the previous chapter we reviewed the simple model of vaccination which assumes that vaccination provides perfect protection to vaccinees. In this chapter we review a general model of an imperfect vaccine with three modes of vaccine failure that was analyzed in Magpantay et al. (2014). The model is an extension of the VSIR model with unstructured population described by a system of ordinary differential equations (ODEs) similar to that presented by McLean and Blower (1993).

**Example 3.1.** *Let us consider three types of vaccines:*

- *Vaccine I: Reduces the probability of infection upon exposure to only 0.1 times the probability for an unvaccinated individual.*
- *Vaccine II: Provides no protection to 10% of the vaccinees and perfect lifetime immunity to the remainder.*
- *Vaccine III: Provides perfect protection to each vaccinee for an exponentially distributed "waning time," after which the vaccinee becomes as a susceptible. Average waning time is 9 times the average lifetime of an individual.*

Later we will go back to this example and will see why we choose these values. The previous descriptions describe how the vaccine can directly affect an individual in a population, however in order to explain its population-level dynamics, it is necessary to write down a model that includes all our assumptions on the vaccine, disease transmission and population demographics. We now build this model in the next section and go back to this example.

## 3.1 Different modes of vaccine failure

We consider the three different modes of vaccine failure discussed in (Magpantay et al., 2014):

- **Leakiness** ("failure in degree")

  The probability of getting infected upon exposure is decreased but not eliminated by vaccination.

- **All-or-nothingness or primary vaccine failure** ("failure in take")

  Lifelong perfect protection is only provided to a fraction of the vaccinated population while the remaining fraction remains as susceptible as if they were never vaccinated.

- **Waning** ("failure in duration")

  Perfect protection is provided to all vaccinees for an exponentially distributed period of time after which each vaccinee becomes as a susceptible as if they were never vaccinated.

Looking at the definitions, it is clear that these three modes of vaccine failures are different. They actually have different epidemiological consequences but it is difficult

to determine with using the mathematical model.

## 3.2 ODE Model

Let $S(t)$, $I(t)$ and $R(t)$ respectively be the fraction of susceptible, infected and recovered individuals in a population at time $t$. Let $V(t)$ be the proportion of individuals that gained immunity upon vaccination that has not waned yet. We note that $V(t)+S(t)+I(t)+R(t) = 1$. The model is given by the following system of equations

$$\frac{dV}{dt} = (1-\varepsilon_A)p\mu - \varepsilon_L\beta VI - \alpha V - \mu V \tag{3.1a}$$
$$\frac{dS}{dt} = (1-(1-\varepsilon_A)p)\mu - \beta SI + \alpha V - \mu S \tag{3.1b}$$
$$\frac{dI}{dt} = \beta SI + \varepsilon_L\beta VI - \gamma I - \mu I \tag{3.1c}$$
$$\frac{dR}{dt} = \gamma I - \mu R \tag{3.1d}$$

with the following requirement on the initial conditions at time $t = 0$,

$$V(0) + S(0) + I(0) + R(0) = 1. \tag{3.2}$$

Here $\mu \geq 0$, $\gamma > 0$ , $\beta > 0$, $p \in [0,1]$ , and $(\varepsilon_L, \varepsilon_A, \varepsilon_W) \in [0,1)^3$. The case when $(\varepsilon_L, \varepsilon_A, \varepsilon_W) = (0,0,0)$ then this model becomes the perfect vaccine model (2.4). This full model is illustrated in Figure 3.1 and the parameters are described in Table 3.1.

We note that we can consider this system as (2.1) with $z = (V, S, I, R)$ and

$$f(z) = \begin{bmatrix} (1-\varepsilon_A)p\mu - \varepsilon_L\beta VI - \alpha V - \mu V \\ (1-(1-\varepsilon_A)p)\mu - \beta SI + \alpha V - \mu S \\ \beta SI + \varepsilon_L\beta VI - \gamma I - \mu I \\ \gamma I - \mu R \end{bmatrix}. \tag{3.3}$$

Since $f$ and $f'$ are continuous then by Theorem 2.1 we have local existence and uniqueness of the solutions.

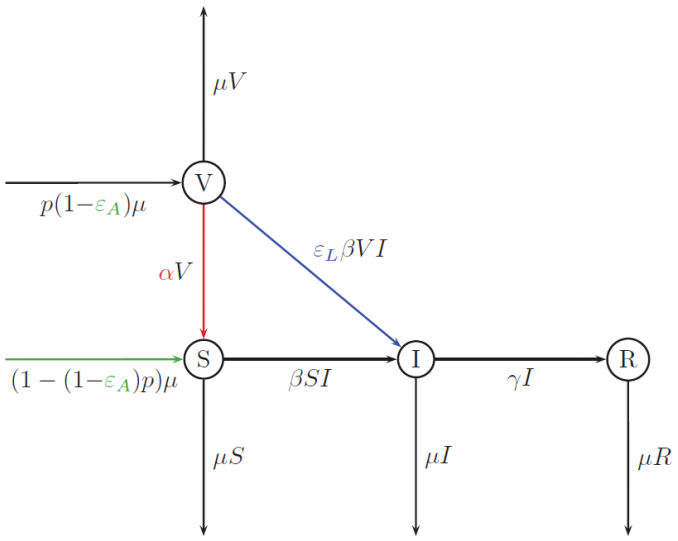



Figure 3.1: Illustration of the VSIR model from (Magpantay et al., 2014)

Table 3.1: Description of parameters of the model in Figure 3.1

| Symbol | Description |
|---|---|
| $\mu$ | Birth and death rate . |
| $\gamma$ | Recovery rate. |
| $\beta$ | Transmission rate. |
| $\varepsilon_L$ | Ratio of the probability a vaccinated individual will get infected after exposure relative to that of a susceptible individual. |
| $\varepsilon_A$ | Probability of not getting protected after vaccination. |
| $\alpha$ | Waning rate of vaccine-derived immunity. |
| $\varepsilon_W$ | Probability that the vaccine protection of individuals in the class $V$ wanes within a lifetime, equal to $\varepsilon_W = \frac{\alpha}{\alpha+\mu}$. |
| $p$ | Constant fraction of the newborns who are vaccinated. |

The model is an extension of the VSIR model from the previous chapter with the addition of the three modes of vaccine failure. We assume a constant fraction $p$ of newborns are vaccinated soon after birth but the vaccination fails in a fraction $\varepsilon_A$ of the vaccinees. Thus $(1-p)+\varepsilon_A p = 1-(1-\varepsilon_A)p$ of newborns go to the susceptible compartment while the remaining $(1-\varepsilon_A)p$ go to the vaccinated compartment. Individuals in the vaccinated compartment can become infected due to failure in degree of the vaccine. This term is given by $\varepsilon_L\,\beta V I$ where $\varepsilon_L$ is the leakiness parameter that reflects the reduction in probability of infection upon exposure of individuals in the $V$ class relative to those in the $S$ class. Additionally, we assume that vaccine protection wanes at a rate of $\alpha$. As shown in Table 3.1, we can re-parametrize from the waning rate $\alpha$ to a waning probability $\varepsilon_W$ by setting $\varepsilon_W = \frac{\alpha}{\alpha+\mu}$ .

The disease-free equilibrium and the steps for solving for the basic reproduction number of the system is presented in the next section. Here we use the result that

$R_p = R_0(1-(1-\varepsilon_L)(1-\varepsilon_A)(1-\varepsilon_W)p)$. From this expression we can define the vaccine impact $\varphi$ and derive the critical vaccination proportion $p_c$ for this model by setting $R_{p_c} = 1$.

**Definition 3.2** (Vaccine failure parameters and vaccine impact)**.** *We define the set* $(\varepsilon_L, \varepsilon_A, \varepsilon_W)$ *to be the* ***vaccine failure parameters*** *and*

$$\varphi = (1-\varepsilon_L)(1-\varepsilon_A)(1-\varepsilon_W)$$

*to be the* ***vaccine impact****. We also define*

$$p_c = \frac{1}{\varphi}\big(1-\frac{1}{R_0}\big),$$

*to be the* ***critical vaccination proportion*** *if this quantity is less than one.*

Now, going back to the Example 3.1, we see from Table 3.2 that all three types of vaccines have the same vaccine impact of $\varphi = 0.9$. This also means that all three vaccines have the same critical vaccination proportion required to eradicate the disease.

Table 3.2: Vaccine impacts for the different vaccines in Example 3.1

| Vaccine type | $\varepsilon_L$ | $\varepsilon_A$ | $\varepsilon_W$ | $\varphi$ |
|---|---|---|---|---|
| I | 0.1 | 0 | 0 | 0.9 |
| II | 0 | 0.1 | 0 | 0.9 |
| III | 0 | 0 | $\frac{\frac{\mu}{9}}{\frac{\mu}{9}+\mu} = 0.1$ | 0.9 |

## 3.3 Disease-free equilibrium

To find the disease-free equilibrium, we set all the equations in (3.1) equal zero with $I = 0$. We derive,

$$\begin{aligned} (1-\varepsilon_A)p\mu - \alpha V - \mu V &= 0 \\ (1-(1-\varepsilon_A)p)\mu + \alpha V - \mu S &= 0 \\ \mu R &= 0 \end{aligned} \tag{3.4}$$

Solving (3.4) yields the disease-free equilibrium given by

$$\begin{aligned} z^0 =& (V^0, S^0, I^0, R^0) \\ =& ((1-\varepsilon_A)(1-\varepsilon_W)p,\ 1-(1-\varepsilon_A)(1-\varepsilon_W)p,\ 0,\ 0) \end{aligned} \tag{3.5}$$

### 3.3.1 Well-posedness near the disease-free equilibrium

To show the system (3.1) is well-posed at $z^0$, let

$$\begin{aligned} \mathcal{F} &= \beta SI + \varepsilon_L \beta VI \\ \mathcal{V} &= (\gamma + \mu)I \\ \mathcal{G}_1 &= (1-\varepsilon_A)p\mu - \varepsilon_L \beta VI - \alpha V - \mu V \\ \mathcal{G}_2 &= (1-(1-\varepsilon_A)p)\mu - \beta SI + \alpha V - \mu S \\ \mathcal{G}_3 &= \gamma I - \mu R \end{aligned} \tag{3.6}$$

which clearly satisfy all assumptions (A1) to (A5). Then the system is well-posed and the domain is invariant close to the disease-free equilibrium.

### 3.3.2 Stability of the disease-free equilibrium

To establish the conditions for the stability of the disease-free equilibrium we derive the basic reproduction number. As before, we need to divide the terms in $\frac{dI}{dt} = \beta SI + \varepsilon_L \beta VI - \gamma I - \mu I$ into two functions. We set $\mathcal{F} = \beta SI + \varepsilon_L \beta VI$ since these terms are involved in the appearance of new infections, and $\mathcal{V} = (\gamma + \mu)I$ is the rate of progression from the infected compartment. The derivatives of these functions evaluated at the disease-free equilibrium are

$$F = \beta S^0 + \varepsilon_L \beta V^0,$$
$$V = \gamma + \mu,$$

and by using next generation formula from Definition 2.11, we can calculate the basic reproduction number as follows,

$$\begin{aligned} R_p &= \rho(FV^{-1}) = \frac{\beta}{\mu+\gamma}[S^0 + \varepsilon_L V^0] \\ &= R_0(1 - (1-\varepsilon_A)(1-\varepsilon_W)(1-\varepsilon_L)p) = R_0(1-\varphi p) \end{aligned} \tag{3.7}$$

where $R_0 = \frac{\beta}{\mu+\gamma}$ is the basic reproduction number in the absence of vaccination. If $R_p < 1$, then by theorem (2.18) the disease-free equilibrium is locally asymptotically stable. For $R_0 < 1$ we can extend this stability to the global asymptotic stability. In order to do this, we need following definition.

**Definition 3.3** (Lyapunov function and global asymptotic stability)**.** *A Lyapunov function for the system (2.1) with an equilibrium point $z^*$, is a function $L : \Omega \to \mathbb{R}$ where $\Omega \subset \mathbb{R}^d$ that is continuous, has continuous first derivatives, and satisfying the following properties:*

1. $L(z) > 0$ *for all* $z \neq z^*$, *and* $L(z^*) = 0$.

2. $\frac{d}{dt}L(t) < 0$ *for all* $z \neq z^*$.

*If the system has a Lyapunov function at an equilibrium* $z^*$, *then* $z^*$ *is globally asymptotically stable i.e. if* $z_0 \in \Omega \Longrightarrow \lim_{t\to\infty} z(t) = z^*$.

□

In 3.1 by defining a Lyapunov function $L(I(t)) = I(t) \geq 0$, we have

$$\frac{d}{dt}L(I(t)) = (\beta(S(t) + \varepsilon_L V(t)) - (\mu + \gamma))I(t) = (\mu + \gamma)(R_0(S(t) + \varepsilon_L V(t)) - 1)I(t)$$

which is negative in the case $R_0 < 1$, since $S(t) + \varepsilon_L V(t) \leq S(t) + V(t) \leq 1$ for all $t \geq 0$. Thus we have shown that the disease-free equilibrium is globally asymptotically stable if the stronger condition $R_0 < 1$ holds.

## 3.4 Endemic equilibrium

To obtain the endemic equilibrium (Definition 2.7) $z^* = (V^*, S^*, I^*, R^*)$ of the system we have to solve (3.1) directly assuming that $I^* > 0$. We set,

$$\begin{aligned}
(1 - \varepsilon_A)p\mu - \varepsilon_L\beta VI - (\alpha + \mu)V &= 0,\\
(1 - (1 - \varepsilon_A)p)\mu - \beta SI + \alpha V - \mu S &= 0,\\
\beta S + \varepsilon_L\beta V - (\gamma + \mu) &= 0,\\
\gamma I - \mu R &= 0.
\end{aligned} \tag{3.8}$$

Thus we derive that $V^*$ is given by,

$$V^* = \begin{cases} \frac{a-\sqrt{a^2-4R_0\varepsilon_L(1-\varepsilon_W)\varphi p}}{2R_0\varepsilon_L(1-\varepsilon_L)(1-\varepsilon_W)}, & \text{if } \varepsilon_L \neq 0, \\ (1-\varepsilon_A)(1-\varepsilon_W)p, & \text{if } \varepsilon_L = 0, \end{cases} \tag{3.9}$$

where $a = \varepsilon_L - (1-\varepsilon_W)(R_0-1)+1$ and $R_0 = \frac{\beta}{\mu+\gamma}$. Using this, the endemic equilibrium expression is found to be,

$$\begin{aligned} z^* =& (V^*, S^*, I^*, R^*) \\ =& (V^*, \frac{1}{R_0} - \varepsilon_L V^*, \frac{\mu}{\beta}(R_0(1-(1-\varepsilon_L)V^*)-1), \frac{\gamma}{\beta}(R_0(1-(1-\varepsilon_L)V^*)-1). \end{aligned} \tag{3.10}$$

### 3.4.1 Stability of the endemic equilibrium

We can show that the endemic equilibrium is locally asymptotically stable when $R_0 > 1$. In order to prove this we require the concept of the second additive compound matrix.

**Definition 3.4** (Second Additive Compound Matrix)**.** *Let $A = [a_{ij}]_{3\times 3}$ be a matrix with real-valued elements. The second additive compound matrix of $A$ is*

$$A^{[2]} = \begin{bmatrix} a_{11}+a_{22} & a_{23} & -a_{13} \\ a_{32} & a_{11}+a_{33} & a_{12} \\ -a_{31} & a_{21} & a_{22}+a_{33} \end{bmatrix}$$

**Proposition 3.5** (Proposition 4.2 from Li and Muldowney (1996))**.** *Let $\lambda_1, \lambda_2, \lambda_3$ be*

*eigenvalues of A, then eigenvalues of* $A^{[2]}$ *have the form* $\{\lambda_i + \lambda_j\,, 1 \leq i < j \leq 3\}$.

Since $V(t) + S(t) + I(t) + R(t) = 1$ for all $t$, we can just consider a system of the first three equations in (3.1).

$$\begin{aligned} \frac{dV}{dt} &= (1-\varepsilon_A)p\mu - \varepsilon_L\beta VI - \alpha V - \mu V \\ \frac{dS}{dt} &= (1-(1-\varepsilon_A)p)\mu - \beta SI + \alpha V - \mu S \\ \frac{dI}{dt} &= \beta SI + \varepsilon_L\beta VI - \gamma I - \mu I \end{aligned} \tag{3.11}$$

The Jacobian matrix of this system at the endemic equilibrium is

$$J = \begin{bmatrix} -\varepsilon_L\beta I^* - \mu - \alpha & 0 & -\varepsilon_L\beta V^* \\ \alpha & -\beta I^* - \mu & -\beta S^* \\ \varepsilon_L\beta I^* & \beta I^* & 0 \end{bmatrix}.$$

Assume $\lambda_1, \lambda_2, \lambda_3$ are eigenvalues of $J$ with $Re(\lambda_1) \leq Re(\lambda_2) \leq Re(\lambda_3)$. It is easy to show that if $R_p > 1$ then,

$$\lambda_1 + \lambda_2 + \lambda_3 = \mathrm{Tr}(J) < 0 \tag{3.12}$$

$$\lambda_1\lambda_2\lambda_3 = \mathrm{Det}(J) < 0 \tag{3.13}$$

Negative determinant in (3.13) allows for two possibilities; either $\mathrm{Re}(\lambda_1) \leq \mathrm{Re}(\lambda_2) \leq \mathrm{Re}(\lambda_3) < 0$ or $\mathrm{Re}(\lambda_1) < 0 \leq \mathrm{Re}(\lambda_2) \leq \mathrm{Re}(\lambda_3)$. In the first case all eigenvalues have a negative real part and this establishes the local asymptotic stability. So we consider the latter case. We note that the negative trace in (3.12) leads to

$$\mathrm{Re}(\lambda_1 + \lambda_2) < 0 \quad \textit{and} \quad \mathrm{Re}(\lambda_1 + \lambda_3) < 0 \tag{3.14}$$

Now consider the second additive compound matrix of $J$ that is

$$J^{[2]} = \begin{bmatrix} -\varepsilon_L\beta I^* - 2\mu - \alpha - \beta I^* & -\beta S^* & \varepsilon_L\beta V^* \\ \beta I^* & \varepsilon_L\beta I^* - \mu - \alpha & 0 \\ -\varepsilon_L\beta I^* & \alpha & -\beta I^* - \mu \end{bmatrix}$$

The determinant of $J^{[2]}$ has a negative sign. By the previous proposition, the eigenvalues of $J^{[2]}$ are $(\lambda_1 + \lambda_2)$, $(\lambda_1 + \lambda_3)$, and $(\lambda_2 + \lambda_3)$. Assuming the inequalities in (3.14) we derive,

$$\mathrm{Det}(J^{[2]}) = (\lambda_1 + \lambda_2)(\lambda_1 + \lambda_3)(\lambda_2 + \lambda_3) < 0 \quad \Rightarrow \quad \mathrm{Re}(\lambda_2 + \lambda_3) < 0 \tag{3.15}$$

However this last result contradicts the assumption that $\mathrm{Re}(\lambda_1) < 0 \leq \mathrm{Re}(\lambda_2) \leq \mathrm{Re}(\lambda_3)$. Thus we conclude that the only possibility is $\mathrm{Re}(\lambda_i) < 0$ for $i = 1, 2, 3$ and this proves that the endemic equilibrium is locally asymptotically stable when $R_p > 1$.

**Proposition 3.6.** *(*Proposition 3.3 from Magpantay et al. (2014)*)*
*"For a fixed vaccine impact parameter $\varphi$ such that $R_p > 1$, the vaccine failure parameter set $(\varepsilon_L, \varepsilon_A, \varepsilon_W)$ that leads to the highest value of the endemic steady state value of the infected class is $(1 - \varphi, 0, 0)$; that is the purely leaky model."*

*Proof.* Let $x = \varepsilon_L(1 - \varepsilon_W)$. We derive the following equality for $I^*$ from (3.4),

$$I^* = \frac{\mu}{2\beta}[R_0 - 1 - \frac{1}{x} + \sqrt{(R_0 - 1 - \frac{1}{x})^2 + \frac{4}{x}(R_p - 1)}] \tag{3.16}$$

To find the maximum value of $I^*$ for fixed values of $\varphi$, we find the derivative of (3.16)

with respect to $x$, that is

$$\frac{dI^*}{dx} = \frac{\mu}{2\beta x^2}(1 + \frac{a-b}{\sqrt{a^2+c}}),$$

where $a = R_0 - 1 - \frac{1}{x}, b = 2(R_p - 1), c = \frac{4}{x}(R_p - 1)$. It is clear that if $a \geq b$ ,then $\frac{dI^*}{dx} \geq 0$. Now consider $a < b$, we claim that again $\frac{dI^*}{dx} \geq 0$. That is,

$$\frac{\mu}{2\beta x^2}(1 + \frac{a-b}{\sqrt{a^2+c}}) \geq 0 \iff 1 + \frac{a-b}{\sqrt{a^2+c}} \geq 0 \iff \frac{a^2 - 2ab + b^2}{a^2+c} \leq 1$$
$$\iff b^2 - 2ab - c \leq 0. \qquad (3.17)$$

Substituting in the values of $a, b, c$ we find that the last term is equivalent to $-4R_0\varphi p(R_p - 1) \leq 0$ which is true from the proposition assumption ($R_p > 1$). It follows that the value of $I^*$ increases with $x$. since $x = \varepsilon_L(1 - \varepsilon_W)$, then the maximum occurs when $\varepsilon_L = 1, \varepsilon_A = \varepsilon_W = 0$ or equivalently $\varepsilon_L = 1 - \varphi$ and $\varepsilon_A = \varepsilon_W = 0$. □

In Figure 3.2 we plot the equilibria for the purely leaky, all-or-nothing, and waning vaccine models as parameter values are changed. Here, we do observe that the purely leaky model provides an upper bound for the infected class at the equilibrium point. In the Figure 3.2(a) we see that increasing the relevant vaccine failure parameter from 0 to 1 leads to an increase in $I^*$, the number of infected at the endemic steady state, for all models but this growth is considerably sharper for the leaky model. Increasing the transmission rate in Figure 3.2(b) leads to a rise in $I^*$ and once again the leaky model has the biggest increase. In Figure 3.2(c), as the vaccination fraction has increased and there is a decrease in $I^*$ in all cases.

The stability of the system can change as parameters are varied. The qualitative changes in the dynamics are called bifurcations. In particular, when the stability of

| Parameter | $\mu$ | $\gamma$ | $\beta$ | p | $\varepsilon_L/\varepsilon_A/\varepsilon_W$ |
|---|---|---|---|---|---|
| Default value for plots | $\frac{1}{70}\,\mathrm{yr}^{-1}$ | $20\,\mathrm{yr}^{-1}$ | $120\,\mathrm{yr}^{-1}$ | 0.8 | 0.2 or 0 |

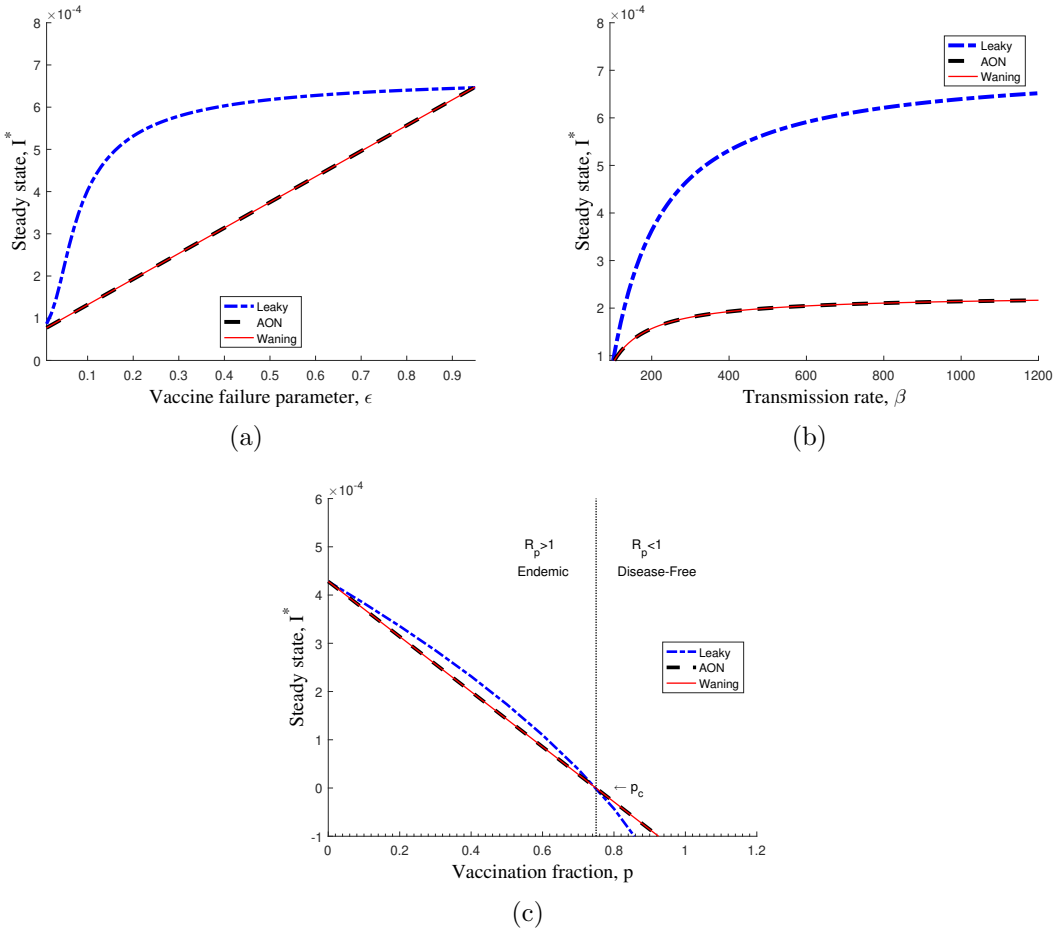



Figure 3.2: The endemic steady state under different modes of vaccine failure

two equilibriums is switched we say transcritical bifurcation has happened. Here the transcritical bifurcation occurs at the same point for all three models at the critical vaccination proportion $p_c = \frac{1}{\varphi}\big(1 - \frac{1}{R_0}\big)$. Before this point $R_p > 1$ and the endemic steady state is asymptotically stable. After the critical vaccination proportion point,

the stability switches and the disease-free equilibrium becomes the one that is asymptotically stable.

We also observe from Figure 3.2 and the expression for the endemic equilibrium that the values of $I^*$ for the all-or-nothing model overlaps with those for the waning model with the same vaccine impact $\varphi$. Thus, we cannot distinguish between these two immunity models by just looking at the equilibrium values of the components. In the next chapter we consider the transient behaviour of these models before they reach steady states. We will see that their dynamics immediately after the start of mass vaccination can be very different.

# Chapter 4

# HONEYMOON PERIODS AND MEASURES OF TRANSIENT DYNAMICS

In the previous chapter we saw that given the same vaccine impact, the all-or-nothing and waning models have the same endemic equilibrium values while that for the leaky model has higher incidence. Thus we cannot distinguish between the all-or-nothing and waning models at equilibrium. However, the non-equilibrium dynamics of the two models can be very different. In Figure 4.1, we present the dynamics of the infected class for the leaky, all-or-nothing and waning models with the same vaccine impact value after the start of mass vaccination. We see clearly different transient dynamics between the three. All three initially start off at the pre-vaccination endemic steady state and then vaccination coverage is gradually increased from $p = 0$ at $t = 30$ to reach its maximum proportion $p = 0.9$ at $t = 50$. The waning model displays a dip below the new equilibrium that lasts for about 30 years and then the solution displays large oscillations as it approaches its new equilibrium. In contrast, the all-or-nothing model displays an initial drop that leaves it close to its new equilibrium and then undergoes smaller oscillations about the new equilibrium that quickly

decay. As expected from the previous chapter, both models approach the same new endemic equilibrium value despite very different transient dynamics before reaching it. The leaky model approaches a different new endemic equilibrium value which has a higher infected population at its new endemic equilibrium. It also approaches this equilibrium in a different manner, after dropping below it at first and then rebounding, taking about 100 years of small oscillations before reaching values close to the new equilibrium value.

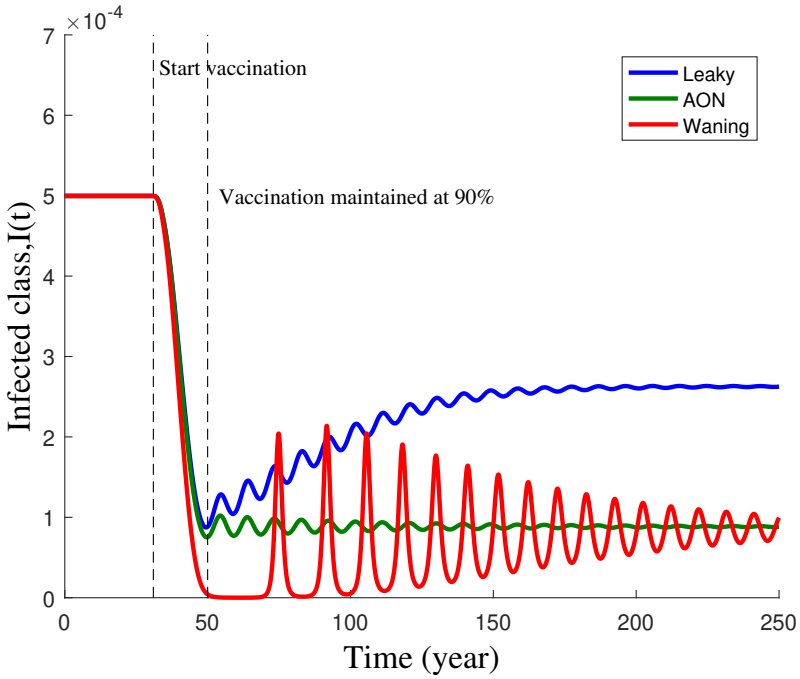



Figure 4.1: Numerical solutions for the infected population

As we can see from Figure 4.1, the initial reduction in incidence after the start of mass vaccination does not necessarily reflect the long-term impact of the control program. McLean and Anderson (1988) introduced the term *honeymoon period* to denote the "long period of low incidence that immediately follows the initiation of a mass vaccination programme." Although we do not see much happening with the

incidence data during this period, there may be some important changes occurring in the components of the system. In Figure 4.1 we see that both the waning and leaky models displayed significant and substantial honeymoon periods. We are interested in how we can determine the occurrence of honeymoon periods in some models using measures of transient dynamics.

Neubert and Caswell (1997) and Aldridge et al. (2006) presented some methods for calculating the sensitivity of various aspects of transient dynamics to model parameters. Their research was focused on stable systems. Here we review some factors that they defined as measurements to calculate sensitivity.

In the next sections we suppose that we have an ODE model given by $x' = f(x)$ with an asymptotically stable equilibrium point at $x = x^*$. Using linearization about the equilibrium as in Definition 2.3, the model can be written as

$$\frac{d}{dt}z(t) = Jz(t), \qquad z(0) = z_0. \tag{4.1}$$

Here $J$ is again the Jacobian of this system evaluated at an asymptotically stable equilibrium value of $x$ (all eigenvalues have a negative real part) and we think of $z = x - x^*$ as the deviations from the equilibrium. The perturbation $z(t)$ will grow or shrink at a rate that depends on the initial condition.

## 4.1 Reactivity

**Definition 4.1** (Definition from Neubert and Caswell (1997))**.**

$$\textit{reactivity} = \max_{\|z_0\|\neq 0} \frac{1}{\|z\|}\frac{d\|z\|}{dt}\bigg|_{t=0} \tag{4.2}$$

*Based on the formula above, the reactivity of an asymptotically stable equilibrium is the maximum, over all perturbations, of the rate per time at which the trajectory departs from the equilibrium in the linearized system. It measures the maximum instantaneous amplification of perturbations of that equilibrium .*

Using the definition $\|z\| := \sqrt{z^T z}$ in (4.2), we derive that

$$\frac{d\|z\|}{dt} = \frac{d\sqrt{z^T z}}{dt} = \frac{z^T(dz/dt) + (dz/dt)^T z}{2\|z\|} = \frac{z^T(J + J^T)z}{2\|z\|} \tag{4.3}$$

Let $H(J) = (J + J^T)/2$. This is called Hermitian part of $J$ and since it is symmetric then has all eigenvalues real. We see that the eigenvalues of $H(J)$ which do not necessarily have the same sign as the eigenvalues of $J$, determine the instantaneous behaviour. Let $\lambda_H$ be the largest eigenvalue of $H(J)$. We find that the reactivity is equal to $\lambda_H$.

$$\text{reactivity} = \max_{\|z_0\|\neq 0} \left.\frac{z^T H(J) z}{\|z\|^2}\right|_{t=0} = \max_{\|z_0\|\neq 0} \frac{{z_0}^T H(J) z_0}{{z_0}^T z_0} = \lambda_H. \tag{4.4}$$

We derived the reactivity about the endemic equilibrium point of the three different vaccine models with the same vaccine impact. In Figure 4.2 we plot the results of reactivity against the vaccine failure parameters. We see that there is only a small difference between the values of reactivity for the all-or-nothing and waning models despite Figure 4.1 showing a large difference in their transient dynamics. This indicates that reactivity is not a good measure to use to determine whether or not a model will display a honeymoon period. Interestingly, it also illustrates that the maximum possible instantaneous rate of amplification in the leaky model is less than the two other models.

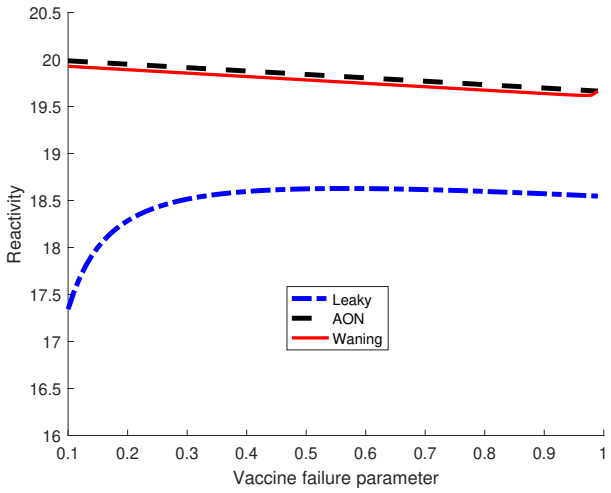



Figure 4.2: Reactivity versus vaccine failure parameter ($\varepsilon_L$ for the leaky model, $\varepsilon_A$ for the all-or-nothing model and $\varepsilon_W$ for the waning model)

## 4.2 Amplification envelope

**Definition 4.2** (Definition from Neubert and Caswell (1997))**.**

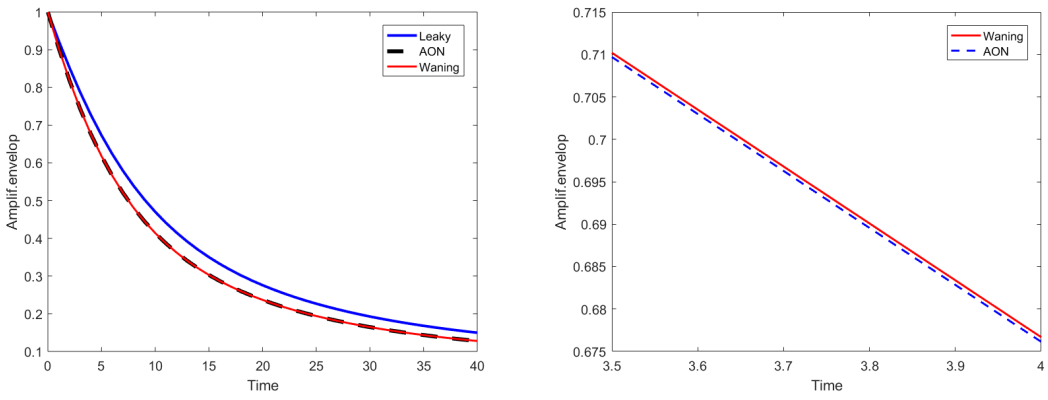
$$\textit{amplification envelope} = \max_{\|z_0\|\neq 0} \frac{\|z(t)\|}{\|z_0\|}. \tag{4.5}$$

*Based on the formula above, amplification envelope is the maximum possible deviation from the equilibrium at any time following a perturbation.*

Consider solutions of the linearized system (4.1) as $z(t) = e^{Jt}z_0$, where $e^{Jt} = \sum_{n=0}^{\infty} \frac{(Jt)^n}{n!}$. By the above definition we have,

$$\text{amplification envelope} = \max_{\|z_0\|\neq 0} \frac{\|z(t)\|}{\|z_0\|} = \max_{\|z_0\|\neq 0} \frac{\|e^{Jt}z_0\|}{\|z_0\|} = \|e^{Jt}\| = \sigma(e^{Jt}) \tag{4.6}$$

and $\sigma(e^{Jt})$ is the square root of the largest eigenvalue of $(e^{Jt})^T(e^{Jt})$. We note that the amplification envelope changes with time.




(a) (b)

Figure 4.3: Amplification envelope versus time

We derived the amplification envelope of the three different vaccine models and plotted the results in Figure 4.3. We see once again that we cannot see much of a difference between the results for the all-or-nothing and waning models, the leaky model is also only slightly different from the other two. Since the starting value is far from the equilibrium, amplification envelope is not a good approximation. This indicates that we also cannot use the amplification envelope to determine whether a system will display a substantial honeymoon period or not.

## 4.3 Direct Lyapunov exponent

Direct finite-time Lyapunov exponent (DLE) were developed to determine phase-space domains of high sensitivity to initial conditions. The definition is given below.

**Definition 4.3** (Definition from Aldridge et al. (2006))**.** *The Direct Lyapunov Exponent is a scalar value which characterizes the amount of stretching about the trajectory of point* $z \in D$ *over the time interval* $[t, t+T]$.

Direct Lyapunov Exponent is defined by $DLE = \log(\|J\|) = \frac{1}{2}\log(\lambda_{\max}(J^T J))$ and

we will show later how to derive it.

Following (Aldridge et al., 2006) we define trajectory separation as below,

$$\xi(t) := z(t, t_0, z_0 + \xi_0) - z(t, t_0, z_0) = \frac{\partial z(t)}{\partial z_0}\xi_0 + O(|\xi|^2).$$

Using linearization, $\xi(t) \simeq \frac{\partial z(t)}{\partial z_0}\xi_0$. Then, stretching is defined as the matrix norm of the deformation gradient $\frac{\partial z(t)}{\partial z_0}$ which is denoted by $J$. Recall that $\|J\|^2 = \lambda_{\max}(J^T J)$, where $\lambda_{\max}$ is the eigenvalue of $J^T J$ with the largest real part. The finite-time maximal stretching rate experienced along the trajectory $z(t, t_0, z_0)$ is defined as:

$$\text{DLE} = \log(\|J\|) = \frac{1}{2}\log(\lambda_{\max}(J^T J))$$

We derived the DLE of the three different vaccine models and plotted the results in Figure 4.4. We see once more that there is not much of a difference between the results for the all-or-nothing and waning models. The leaky model is the most different from the other two. This indicates that we also cannot use the Direct Lyapunov Exponent to determine whether a system will display a substantial honeymoon period or not.

## 4.4 Numerical solutions

The plots of reactivity, amplification envelope and Direct Lyapunov Exponent in the previous section show that we are unable to determine which models will display significant honeymoon periods using these linearization-based methods for measuring transient dynamics in ecology. So far, we have only been able to determine if honeymoon periods will occur if we numerically solve the model and look at the solutions, as in Figure 4.1. In this section we return to using numerical methods to determine

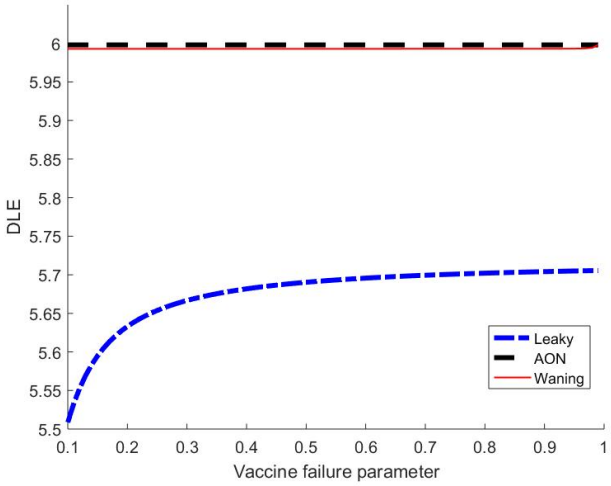



Figure 4.4: Direct Lyapunov Exponent versus vaccine failure parameter ($\varepsilon_L$ for the leaky model, $\varepsilon_A$ for the all-or-nothing model and $\varepsilon_W$ for the waning model)

the size and degree of the honeymoon periods we obtain for the models evaluated at a range of different parameter values.

It is interesting to also look at what is happening to the "effective" susceptible class instead of the infected class during the honeymoon period. By "effective susceptible class" we mean $S(t)$ for the all-or-nothing and waning models, but $S(t) + \varepsilon_L V(t)$ for the leaky model. The drop in incidence during a honeymoon period is actually due to a significant drop in the effective number of susceptibles before reaching the steady state. Large outbreaks at the end of the honeymoon period are due to a buildup in susceptible individuals during the low incidence period. In Figure 4.5 we present numerical solutions of what is happening to the effective susceptible class as vaccination is changed as in Figure 4.1. The leaky and all-or-nothing models show very similar behavior whereas the waning model displays very different dynamics.

In Figure 4.6 we present the relative size of the maximum drop in the effective susceptible class after the start of mass vaccination. By this we mean that we took the

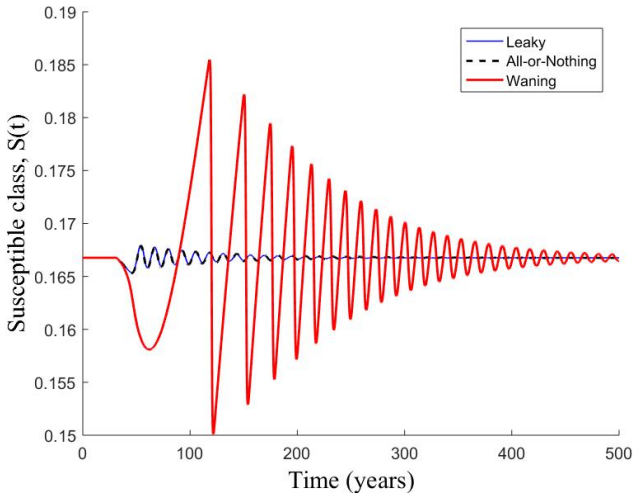



Figure 4.5: Numerical solutions of the effective susceptible compartment under the conditions shown in Figure 4.1

relative change of lowest value attained by the effective susceptible class versus its equilibrium value (which is the same in both the pre-vaccine and vaccine era). The relative drop is indicated in Figure 4.6 using colours at different parameter regions. The value of the relative drop is shown for the different models at different values of the transmission rate $\beta$ and the vaccine failure parameter $\varepsilon$. We see that the waning model has the biggest relative drop in effective susceptibles, at about 0.16, whereas the leaky and all-or-nothing models both show drops to only about 0.035. The border between the colored and white area is the place that stability is switched and transcritical bifurcation happens ($R_p = 1$).

In Figure 4.7 we present the length of the honeymoon period (measured to be the length of time from the start of mass vaccination to the first time the effective susceptible class crosses its equilibrium value). It is similarly illustrated in the logarithmic scale by the color bar, with the vaccine failure parameter in the $x$-axis and the transmission rate in the $y$-axis. We observe that the longest period in the waning model

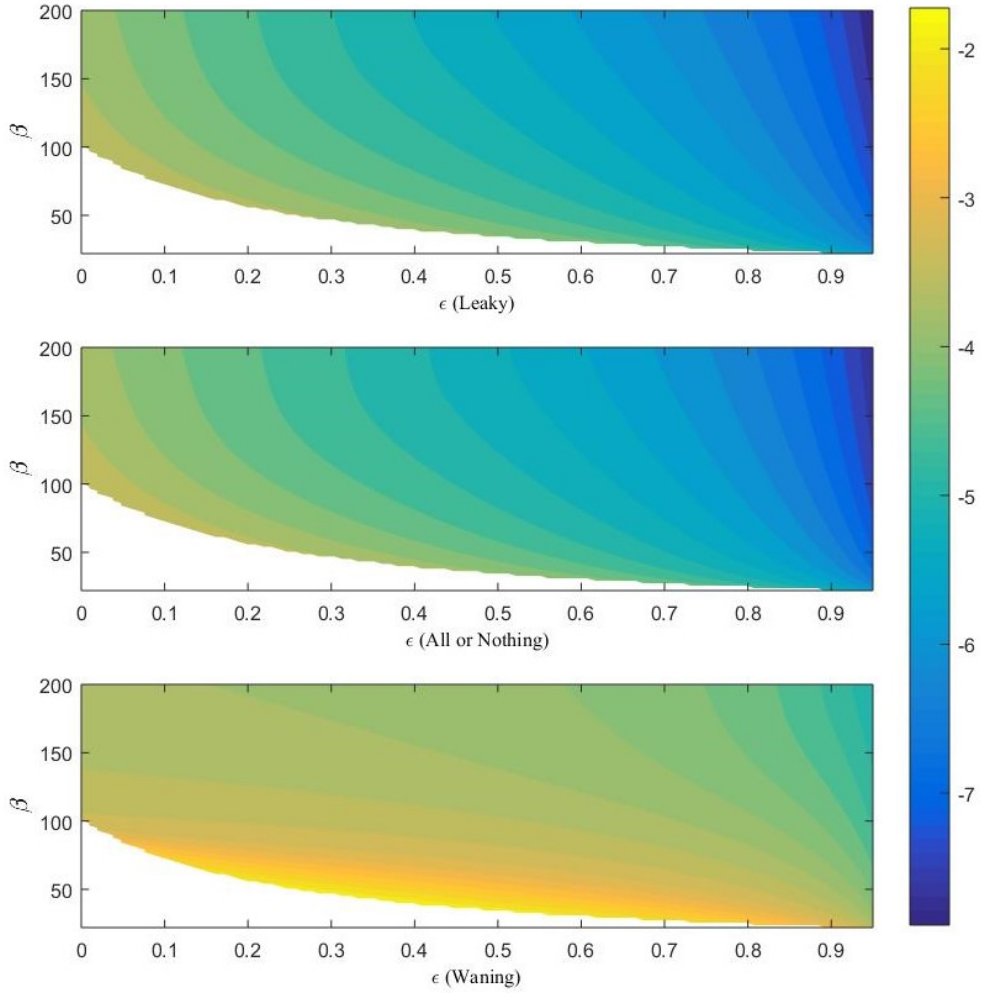



Figure 4.6: Relative drop in the effective susceptible class after start of mass vaccination (log scale). White indicates the region where $R_p < 1$.

which is 350 years. In two other models the largest duration of the honeymoon period is about 80 years.

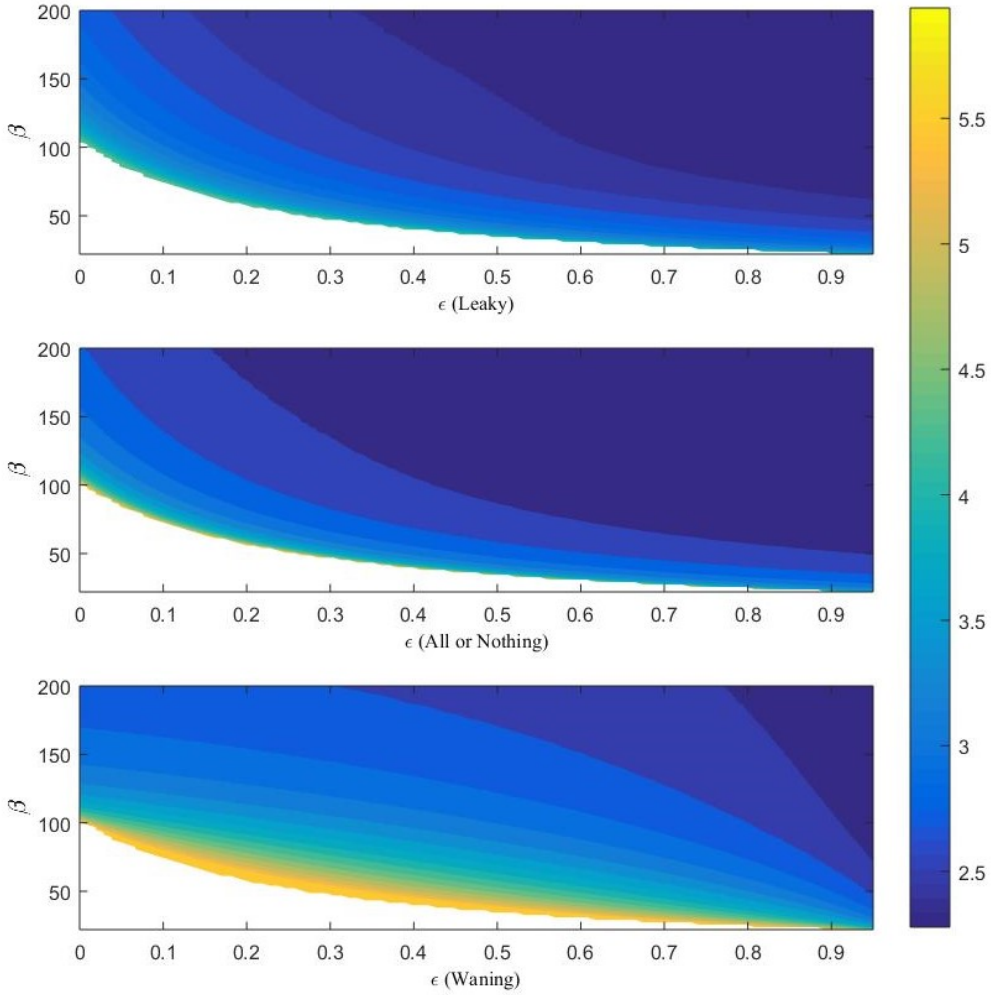



Figure 4.7: Honeymoon period in the susceptible class

# Chapter 5

# SUMMARY AND CONCLUSIONS

Mathematical modeling is one way to encode our ideas on the mechanisms behind certain phenomena into systems of equations that have verifiable and testable dynamics. The study of childhood diseases and vaccination is one for which we do not yet have good mathematical models (Allotey, 2017). It is interesting to try to model these correctly because vaccination is one of the most powerful and cost-effective interventions for diseases. While most studies focus on the equilibrium behavior of these systems, measuring and understanding the transient behavior is also important as they can last for very long periods of time. Transient behaviors, such as honeymoon periods can also provide clues into the type of imperfect vaccine that is being used, and that can be very important for the design and cost-benefit evaluation of the rollout of vaccination for some diseases.

In this project we reviewed the VSIR model analyzed by Magpantay et al. (2014) which allows for three modes of vaccine failure: leaky, all-or-nothing, and waning. It was observed that, given the same value of vaccine impact, the purely leaky model at the asymptotically stable endemic steady state attains a higher proportion of infected individuals compared to the models that involve a mix of the other types of vaccine

failure. Additionally, if they have the same level of vaccine impact the all-or-nothing and waning models have the same values at the endemic equilibrium and it is not possible to distinguish between them. However, by studying their transient dynamics numerically, especially the dynamics after the start of mass vaccination, we can observe significant differences in their behaviors. For some parameter values, the waning model may display a very pronounced honeymoon period while the all-or-nothing model with the same vaccine impact displays a less eventful drop in incidence to its new equilibrium value.

We attempted to use linearization methods in ecology to characterize when and which models can display honeymoon periods. We reviewed the reactivity, amplification envelope (Neubert and Caswell, 1997) and, Direct Lyapunov Exponent (Aldridge et al., 2006), however results show that these cannot distinguish between the transient dynamics of the all-or-nothing and waning models.

The only way we have been able to determine if a model displays a significant period is by actually numerically solving for the trajectory of the models. We did this for the three different models at a range of values for transmission rate and vaccine failure parameter. We measured the relative drop in the susceptible class and the length of the honeymoon period and plotted them in Figures 4.6–4.7. From this we saw that the waning model can have the largest relative drop in susceptibles after the start of mass vaccination, and the longest honeymoon period. Interestingly, the trajectory of the effective number of susceptibles for the leaky model is similar to that of the all-or-nothing model.

The results of this study indicate that honeymoon periods need to be studied using non-linear techniques. For future work, we can focus on some energy-like functions

(such as the pseudo-potential functions) to gain information on where the solutions spend a long time before converging to its asymptotically stable equilibrium values.

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