A Stochastic Model for the spread of Pertussis

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Abstract

This thesis treats a stochastic model describing the spread of the Pertussis disease with waning immunity in a large demography population.
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## Contents

1. Introduction ........................................... 4  
2. Description of the model .............................. 5  
3. Deterministic approximation .......................... 7  
   3.1 The case $\theta = 0$ .............................. 11  
   3.2 Case $\theta \to \infty$ .............................. 12  
   3.3 The case $\varepsilon = 0$ ........................... 13  
   3.4 The case $\nu = 0$ ............................... 13  
4. Diffusion approximation .............................. 15  
5. The quasi-stationary distribution and time to extinction ... 16  
   5.1 The quasi-stationary distribution ................. 17  
   5.2 The distribution of the time to extinction from quasi-stationarity ................. 18  
   5.3 Diffusion approximation .......................... 19  
6. Simulation and Sensitivity analysis .................... 20  
7. Conclusion and a more realistic model for further consideration 23  
Appendix A ............................................. 24  
Bibliography ............................................ 31
List of Figures

1  Schematic picture of the model. ............................ 6
2  SIR model. .................................................... 11
3  Model of $\theta \to \infty$. .................................... 12
4  Model of $\varepsilon = 0$. ..................................... 13
5  Model of $\nu = 0$. ........................................... 14
6  Simulated results of parameter set 1. ....................... 21
7  Simulated results of the parameter set 1 (more detailed). . . . . 27
8  Simulated results with changing in $\theta$. ..................... 28
9  Simulated results without vaccination control. ............... 29
10 Model for further consideration. ............................... 30
1 Introduction

Pertussis, also known as whooping cough, is a highly contagious disease caused by the bacterium Bordetella pertussis. It is spread by contact with airborne discharges from the mucous membranes of infected people, who are most contagious during the catarrhal stage. Because the symptoms during the catarrhal stage are nonspecific, pertussis is usually not diagnosed until the appearance of the characteristic cough of the paroxysmal stage [9]. Empirical evidence shows that the force of infection for pertussis is age dependent. Childhood is the time of greatest exposure and greatest risk.

Before the vaccination program was induced, Pertussis was a common disease of infants and children in Sweden. The overall incidences during the vaccine-free period had reached more than 100 cases/100,000 person years, and up to 1,000 cases/100,000 infant years [6]. Infant vaccination with DTP vaccines was hence introduced. It has greatly reduced the morbidity and mortality, but the protection it offer lasts only a few years. The vaccine-induced immunity to pertussis wanes with time, as well as immunity acquired from infection.

Amongst the younger children who has not been immunized or has not yet completed the primary vaccination series, the symptoms could persist for as long as several months. In adults, older children and partially immunized individuals, symptoms may consist of only an irritating cough that lasts one to two weeks which almost always is treated as a normal cold. However, in the disease spreading process, the asymptomatic infective adults are the main reservoir for pertussis. Combined the influence of disease, waning immunity and demographic forces, the persistence of Pertussis can be explained. This kind of diseases which maintain in the population without the need for external inputs are called endemic.

In our Pertussis model all individuals are classified as being in one of the states $S$, $I$, $R$, $S_a$, $I_a$ corresponding to being susceptible, infectious, recovered and immune, asymptomatic (partially) susceptible, asymptomatic infectious. In section 2, the model is defined fully in terms of the possible transitions between these five states.

To find the exact distribution of the epidemic process is not manageable. A first step, before analyzing the stochastic model described in section 2, is to consider its deterministic counterpart. Even though it may seem unrealistic to consider such a model, many valuable insights may still be gained. In section 3, it is shown what deterministic model the stochastic model converges to, when the community size becomes large. We also discuss the long-term endemic behavior of the model which is related to the stationary solutions of the deterministic model. Moreover, several simpler models derived from our model are analyzed with special parameter values. In section 4, by using diffusion approximation theory, we show that when the population size is large, the centered and scaled epidemic process may
be approximated by an Ornstein-Uhlenbeck process.

The time to extinction is an important measure of the persistence of the infection. In section 5, first we give the definition of a stationary conditional distribution, the so-called quasi-stationary distribution, which serves the role of approximating the state of the process if it is known that the process has been going on for a long time, and that extinction has not occurred. When this is done we show that the time to extinction given that we start the process in the quasi-stationary distribution is exponentially distributed. Even though the expression for this time to extinction can be expressed, the problem still remains that the quasi-stationary distribution itself is unknown and that the aim of section 5.4 is to obtain an approximation of the quasi-stationary distribution. In the last section 6, computer simulations of our model with some choice of parameter sets are used to approximate the spread of pertussis. No effort is made to estimate the parameters but it is our view that the chosen parameters are reasonably realistic.

2 Description of the model

The epidemiologic-demographic model developed here for pertussis is a simplified approximation of pertussis transition and vaccination, the description of the model in this section follows from the same lines as Andersson and Britton 2000 [1], [3].

Since we are interested in exploring the longer-term persistence and endemic dynamics of pertussis in a large population, a clearly demographic process will be important. Assume that individuals are born into the population at constant rate $\mu N$ and live, independently of everything else, for an $\exp(\mu)$-distributed time, i.e. the average lifetime is given by $1/\mu$. The population size $N(t)$ will thus fluctuate around the quantity $N$, a parameter which hence should be interpreted as the (average) population size or the 'equilibrium' of the birth and death process. The reason for choosing size-independent birth rates is to avoid population extinction or explosion.

We let the population be homogeneous and homogeneously mixing. All newborns enter directly into the class $S$ of susceptible individuals. When susceptibles are vaccinated, a fraction of them become immune and enter the class $R$ of recovered. This vaccination coverage rate is $\nu$. The other fraction which do not get immune becomes infectious and enter the class $I$ of infective, when contact with an infective (symptomatic or asymptomatic) is sufficient for transmission to occur. Assume that this contact results in infection accords to a Poisson process of constant rate $\beta/N$. Once an individual gets infected he/she stays infectious for a time period that is exponentially distributed with intensity $\gamma$. The vaccine-induced immunity and infection-acquired immunity in class $R$ fade with time, then the recovered
individuals are moved to, $S_a(t)$ class of partially susceptible. This period of temporary immunity is $\exp(\theta)$-distributed. For these partially susceptible, the contact rate with a given infective (symptomatic or asymptomatic) which results in asymptomatic infection is $\varepsilon \beta / N$, where $0 < \varepsilon < 1$. Assume that the recovery rate for the class $I_a$ of asymptomatic infectious is the same as before. All contact processes, vaccination, infectious periods, immunity reducing periods, births and deaths are defined as mutually independent.

![Schematic picture of the model.](image)

Figure 1: Schematic picture of the model.

Denote the number of susceptible individuals in state $S$ at time $t$ by $S(t)$, and let $I(t), R(t), S_a(t), I_a(t)$ be defined analogously. Hence it holds that $N(t) = S(t) + I(t) + R(t) + S_a(t) + I_a(t)$. Moreover, let $\hat{I}(t) = I(t) + I_a(t)$ be the actual number of infected individuals. Then we can write $X^N(t) = \{(S(t), I(t), R(t), S_a(t), I_a(t)); t > 0\}$ as a five dimensional continuous time Markov process with state space $\mathbb{Z}_5^+$, where $\mathbb{Z}_+$ denotes the set of nonnegative integers. Given the value $\xi = (a, b, c, d, e)$ in space, the process has the transition rates in Table 1.

Further, define our Markov process $X^N_t$ governed by the jump intensities $N_q l(N^{-1} \xi)$ given in Table 1. This means that:

$$P(X^N(t + \Delta t) = \xi + l | X^N(t) = \xi) = \Delta t N_q l(N^{-1} \xi) + o(\Delta t), \quad (1)$$

where $\xi, l \in \mathbb{Z}_5^+$. Here, we simplify the index $l$ of $q_l$ by showing the changes in the affected states. As an example, we write $q_{0,-1,1,0,0}$ as $q_{b-1,c+1}$.

Then all the possible $q_l$ are classified as:

- $q_{a+1}(\xi) = \mu$; $q_{a-1,b+1}(\xi) = \beta a(b + e)$; $q_{a-1,c+1}(\xi) = \nu a$; $q_{a-1}(\xi) = \mu a$;
- $q_{b-1,c+1}(\xi) = \gamma b$; $q_{b-1}(\xi) = \mu b$; $q_{c+1,e-1}(\xi) = \gamma e$; $q_{c-1,d+1}(\xi) = \theta c$;
- $q_{c-1}(\xi) = \mu c$; $q_{d-1,e+1}(\xi) = \varepsilon \beta d(b + e)$; $q_{d-1}(\xi) = \mu d$; $q_{e-1}(\xi) = \mu e$.

It’s worth noting that the set of disease-free states $(a, 0, c, d, 0)$ is an absorbing class. Hence all other states are transient.

A Schematic picture of the model is shown in Figure 1.
### Table 1: Transition rates of the model

<table>
<thead>
<tr>
<th>Event</th>
<th>Transition</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth of susceptible individual</td>
<td>((a, b, c, d, e) \to (a + 1, b, c, d, e))</td>
<td>(\mu N)</td>
</tr>
<tr>
<td>Death of susceptible individual</td>
<td>((a, b, c, d, e) \to (a - 1, b, c, d, e))</td>
<td>(\mu a)</td>
</tr>
<tr>
<td>Infection of susceptible individual</td>
<td>((a, b, c, d, e) \to (a - 1, b + 1, c, d, e))</td>
<td>(\frac{b \beta (b + e) N}{N})</td>
</tr>
<tr>
<td>Vaccination of susceptible individual</td>
<td>((a, b, c, d, e) \to (a - 1, b, c + 1, d, e))</td>
<td>(\nu a)</td>
</tr>
<tr>
<td>Recovery of infected individual</td>
<td>((a, b, c, d, e) \to (a, b - 1, c + 1, d, e))</td>
<td>(\gamma b)</td>
</tr>
<tr>
<td>Death of infected individual</td>
<td>((a, b, c, d, e) \to (a, b - 1, c, d, e))</td>
<td>(\mu b)</td>
</tr>
<tr>
<td>Immunity fade of recovered individual</td>
<td>((a, b, c, d, e) \to (a, b - 1, c - 1, d, e))</td>
<td>(\theta c)</td>
</tr>
<tr>
<td>Death of recovered individual</td>
<td>((a, b, c, d, e) \to (a, b - 1, c - 1, d, e))</td>
<td>(\mu c)</td>
</tr>
<tr>
<td>Infection of partially susceptible individual</td>
<td>((a, b, c, d, e) \to (a, b, c - 1, d - 1, e))</td>
<td>(\frac{\epsilon \beta d (b + e) N}{N})</td>
</tr>
<tr>
<td>Death of partially susceptible individual</td>
<td>((a, b, c, d, e) \to (a, b, c - 1, d - 1, e))</td>
<td>(\mu d)</td>
</tr>
<tr>
<td>Recovery of asymptomatic infected individual</td>
<td>((a, b, c, d, e) \to (a, b, c + 1, d - 1, e))</td>
<td>(\gamma e)</td>
</tr>
<tr>
<td>Death of asymptomatic infected individual</td>
<td>((a, b, c, d, e) \to (a, b, c, d - 1, e))</td>
<td>(\mu e)</td>
</tr>
</tbody>
</table>

### 3 Deterministic approximation

The general ideas in the section are from Andersson and Britton 2000 [3], and Andersson [5].

Assume that \(N\) is large. Define the scaled Markov process

\[ x_N^t = x^N(t)/N = \left( \frac{S(t)}{N}, \frac{I(t)}{N}, \frac{R(t)}{N}, \frac{S_a(t)}{N}, \frac{I_a(t)}{N} \right), t \geq 0. \]

The analogous deterministic model is then given by the following ODE system with solution

\[ x(t) = (s(t), i(t), r(t), s_a(t), i_a(t)), t \geq 0: \]

\[
\frac{\partial s}{\partial t} = \mu - \beta s (i + i_a) - \nu s - \mu s, \\
\frac{\partial i}{\partial t} = \beta s (i + i_a) - \gamma i - \mu i, \\
\frac{\partial r}{\partial t} = \gamma (i + i_a) + \nu s - \theta r - \mu r, \\
\frac{\partial s_a}{\partial t} = \theta r - \epsilon \beta s_a (i + i_a) - \mu s_a, \\
\frac{\partial i_a}{\partial t} = \epsilon \beta s_a (i + i_a) - \gamma i_a - \mu i_a, \\
1 = s + i + r + s_a + i_a,
\]

where \(s, i, r, s_a, i_a\) are the asymptotic proportions of susceptible, infectious and recovered individuals, respectively. The differential equations correspond to the jump intensities of the model (see Table 1) with everything divided by \(N\) since we now consider population proportions.

Start both processes at time 0, and chose \(x_0^N\) sufficiently close to the initial condition \(x(0)\) for \(x(t)\). We now show that the normalized sequence
$x^N_t$ converges weakly to the deterministic motion $x(t)$.

Towards this end let us define the drift vector $F$ by:

$$F(\xi) = \sum_l lq_l(\xi) = (\mu - \beta a(b + e) - \nu a - \mu a, \beta a(b + e) - \gamma b - \mu b, \nu a + \gamma(b + e) - \theta c - \mu c, \theta c - \varepsilon \beta d(b + e) - \mu d, \varepsilon \beta d(b + e) - \gamma e - \mu e).$$

(2)

The following theorem can be found in Chapter 11 of Ethier and Kurtz [7]:

**Theorem 1 (Law of Large numbers).** Suppose that for each compact $K \subset \mathbb{R}^5$ it holds that $\sum_l llq_l(\xi) < \infty$, and there exists $M_K > 0$ such that $|F(\xi) - F(\eta)| \leq M_K|\xi - \eta|, \xi, \eta \in K$. Suppose that $\lim_{N \to \infty} x^N_0 = x(0)$, and that $x(t)$ is the unique solution of $x'(t) = F(x(t))$. Then for every $t > 0$, $\lim_{N \to \infty} \sup_{s \leq t} |x^N_s - x(s)| = 0$ a.s.

In our model, the two conditions in the first assumption of the Theorem are fullfilled. Since $q_l$ are continuous for every $l$, which implies that $\sup_{\xi \in K} q_l(\xi) < \infty$ with compact $K$, the first condition satisfied. Further we know that the drift vector $F$ is locally Lipschitz and that $F(\xi)$ is continuously differentiable, and a locally Lipschitz function restricted to a compact set is Lipschitz which implies the second condition. Take our deterministic solution $x(t)$ of the ODE system into equation (2), the second assumption can be easily satisfied if we can fulfill that $x(t)$ is the unique solution.

Thus the approximation of our Markov process $x^N_t$ with the deterministic process $x(t)$ can be obtain if the solution of the deterministic system is unique. This deterministic system cannot be solved explicitly, but we can understand its behavior for large $t$ by finding the stationary points.

In order to analyze the long-term equilibrium behavior of the model, we now explore when the deterministic system reaches the unique stationary point, with unique solution satisfying $\frac{\partial s}{\partial t} = \frac{\partial i}{\partial t} = \frac{\partial r}{\partial t} = \frac{\partial s^a}{\partial t} = \frac{\partial i^a}{\partial t} = 0$. By applying the law of large numbers, the equilibrium phase of our stochastic model can converge to the stationary point of the deterministic system. When $i + i_a = 0$, the stationary state corresponds to a disease-free scenario where the disease has suffered extinction and, in the long run, everyone in the population is susceptible. This extinction problem will be discussed in the later stochastic section, here we therefore concentrate on $i + i_a > 0$ and call the corresponding equilibrium phase as endemic equilibrium.

Set all the differential equations equal to zero. Denote the stationary state by index $^*$, to obtain,

$$s^* = \frac{\mu}{\beta + \nu + \mu}, \ i^* = \frac{\beta s^* i^*}{\gamma + \mu}, \ r^* = \frac{\gamma i^* + \nu s^*}{\theta + \mu}, \ s^a = \frac{\theta r^*}{\varepsilon \beta + \mu}, \ i^a = \frac{\varepsilon \beta s^* i^*}{\gamma + \mu}. $$
where $\bar{i}^* = i^* + i_0^*$ is the solution of $A\bar{i}^2 + B\bar{i} + C = 0$, with

\[ A = \varepsilon\beta(\frac{\gamma}{\theta+\mu} + 1), \]

\[ B = \frac{\varepsilon(\nu+\mu)}{\theta+\mu} + \gamma - \varepsilon\beta + \mu + \varepsilon\nu + \varepsilon\mu, \]

\[ C = -\mu - \frac{\varepsilon\theta}{\theta+\mu} + \frac{(\gamma+\mu)(\nu+\mu)}{\beta}. \]

If we assume that all parameters are non-negative, the conditions for getting a unique positive stationary solution are:

**When $C = 0$** i.e. \(\frac{(\gamma+\mu)(\nu+\mu)}{\beta} = \mu + \frac{\varepsilon\theta}{\theta+\mu}\), we get a unique positive solution at $\bar{i}^* = -\frac{B}{2A}$ only if $B < 0$ which means that $\varepsilon(\nu+\mu)(\frac{\gamma}{\theta+\mu} + 1) < \varepsilon\beta - \gamma - \mu$. But this inequality requirement could not be fulfilled under the equality assumption. Thus there is no unique positive stationary solution in this case.

**When $C < 0$** i.e. \(\frac{(\gamma+\mu)(\nu+\mu)}{\beta} < \mu + \frac{\varepsilon\theta}{\theta+\mu}\), we get a unique positive stationary solution at $\bar{i}^* = -\frac{B}{2A} + \sqrt{(\frac{B}{2A})^2 - C}$. 

**When $C > 0$** i.e. \(\frac{(\gamma+\mu)(\nu+\mu)}{\beta} > \mu + \frac{\varepsilon\theta}{\theta+\mu}\), no unique positive stationary solution exist. If $B < 0$, the positive solution is not unique for both $\bar{i}^* = -\frac{B}{2A} \pm \sqrt{(\frac{B}{2A})^2 - C} > 0$ and if $B > 0$, there are no positive solutions.

Thus we can conclude that only if the positive parameters satisfy the condition \(\frac{(\gamma+\mu)(\nu+\mu)}{\beta} < \mu + \frac{\varepsilon\theta}{\theta+\mu}\), the unique positive stationary solution of the deterministic system can be obtain with value :

\[ \bar{i}^* = -\frac{B}{2A} + \sqrt{(\frac{B}{2A})^2 - C}. \]

From the definition of equilibrium, we know that if the system reaches the equilibrium state, then it will remain in it. But when the system is perturbed from the equilibrium state, we need to determine the consequence. The stability of stationary point is ensured if the real part of all eigenvalues of its Jacobian are negative.

The Jacobian of the stationary deterministic ODE system at the station-
The eigenvalues $\Lambda_i$ are the solutions of $\det(J^* - \Lambda I) = 0$, which gives:

\[
(\beta_\bar{i}^* + \nu + \mu + \Lambda)(\beta s^* - \gamma - \mu - \Lambda)(\theta + \mu + \Lambda)(\varepsilon\beta_\bar{i}^* + \mu + \Lambda)(\varepsilon\beta s_a^* - \gamma - \mu - \Lambda)
+ \beta_\bar{s}^2 \varepsilon^2 s^* \gamma \theta \varepsilon = 0.
\] (3)

From the stationary condition \( \frac{\partial s}{\partial t} = \frac{\partial i}{\partial t} = \frac{\partial r}{\partial t} = \frac{\partial s}{\partial a} \frac{\partial t}{\partial t} = \frac{\partial i}{\partial a} \frac{\partial t}{\partial t} = 0 \), we get the following equations:

\[
\begin{align*}
\beta_\bar{i}^* + \nu + \mu &= \frac{\mu}{s^*}, \\
\beta s^* - \gamma - \mu &= -\beta s_a^*, \\
\theta + \mu &= \frac{\gamma i^* + \nu s^*}{r}, \\
\varepsilon\beta_\bar{i}^* + \mu &= \frac{\theta \gamma}{s_a^*}, \\
\varepsilon\beta s_a^* - \gamma - \mu &= -\beta s^*.
\end{align*}
\]

Then equation (3) turns into:

\[
(\frac{\mu}{s^*} + \Lambda)(\beta s_a^* + \Lambda)(\frac{\gamma i^* + \nu s^*}{r} + \Lambda)(\frac{\theta \gamma}{s_a^*} + \Lambda)(\beta s^* + \Lambda) + \beta_\bar{s}^2 \varepsilon^2 s^* \gamma \theta \varepsilon = 0.
\]

Under our conditions on the parameters, the stationary solution and all parameters are positive, then we can easily get that all of the eigenvalues are negative. In other words, the stationary solution is unique and stable.

In all, when the parameters of our model satisfy the condition \( (\gamma + \mu) (\mu + \theta) < \mu + \frac{\varepsilon \theta \gamma}{s_a^*} \), the equilibrium of our stochastic model converges to an endemic equilibrium state with proportion of infected individuals:

\[
\bar{i}^* = -\frac{B}{2A} + \sqrt{\frac{(B \gamma / 2A)^2 - C}{A}}
\]

In the following, we derive some special cases with certain fixed parameters:
3.1 The case $\theta = 0$

When $\theta \to 0$, all infected individuals have life long immunity, and only the states S, I and R remain. Then we obtain a simple SIR model with demography and vaccination control. See figure 2.

![Figure 2: SIR model.](image)

Define $R_0$ the basic reproduction number as the average number of secondary cases arising from a single infected individual in an entirely susceptible population. Consequently, $R_0$ has threshold value 1, in the sense that an epidemic will result from the introduction of the infective agent when $R_0 > 1$, while the number of infected is expected to decline right after the introduction when $R_0 < 1$. In this case,

$$ R_0 = \frac{\beta \mu}{(\mu + \gamma)(\nu + \mu)}. $$

The parameter $\beta$ represents the transmission rate per infective, $\frac{1}{\mu+\nu}$ represents the average time units each infectious individual spends. The factor $\frac{\mu}{\mu+\nu}$ accounts for the susceptible individuals that do not get vaccination and can be infected. Then the average number of new infections per infectious individual is determined by the susceptible proportion multiplied by the transmission rate and the infectious period.

The stationary point in the deterministic model is

$$ x^* = (s^*, i^*, r^*) = \left( \frac{\mu}{\mu + \nu R_0}, \frac{\mu + \nu}{\beta R_0 - 1}, 1 - \frac{\gamma - \nu}{\beta} - \frac{\mu}{\gamma + \mu} \right), $$

therefore the endemic equilibrium is feasible only if $R_0 > 1$.

The Jacobian matrix and its eigenvalues equation are,

$$ J^* = \begin{pmatrix} -\beta i^* - \nu - \mu & -\beta s^* & 0 \\ \beta i^* & \beta s^* - \gamma - \mu & 0 \\ \nu & \gamma & -\mu \end{pmatrix}, $$

$$ \det(J^* - \Lambda I) = (-\beta i^* - \nu - \mu - \Lambda)(\beta s^* - \gamma - \mu - \Lambda)(\mu - \Lambda) - \beta s^* \beta i^* (\mu + \Lambda) = 0, $$
with solution $A_1 = -\mu$, $A_{2,3} = -\frac{(\mu + \nu)R_0}{2} \pm \frac{\sqrt{[(\mu + \nu)R_0]^2 - \frac{4}{\mu + \nu}}}{2}$, where $G = \frac{1}{\mu + \gamma}$ determines the typical infectious period and $A = \frac{1}{(R_0 - 1)(\mu + \nu)}$ denotes the mean age at infection. For this equilibrium to be stable, $R_0 > 1$ ensures that all eigenvalues are negative.

Hence, if $R_0 > 1$, the endemic equilibrium under condition $\theta = 0$ is feasible and stable.

### 3.2 Case $\theta \to \infty$

When $\theta \to \infty$, the waiting time of moving from state $R$ to state $S_a$ tends to 0. Here, we union the $R$ and $S_a$ to a new $S_a$ state, which means no fully immunity exist. See Figure 3.

The corresponding deterministic systems is:

\[
\begin{align*}
\frac{\partial s}{\partial t} &= \mu - \beta s(i + i_a) - \nu s - \mu s \\
\frac{\partial i}{\partial t} &= \beta s(i + i_a) - \gamma i - \mu i \\
\frac{\partial r}{\partial t} &= \gamma(i + i_a) + \nu s - \mu s_a - \epsilon\beta s_a(i + i_a) \\
\frac{\partial i_a}{\partial t} &= \epsilon\beta s_a(i + i_a) - \gamma i_a - \mu i_a \\
1 &= s + i + s_a + i_a
\end{align*}
\]

If we assume $\epsilon \neq 0$, can obtain the stationary solution at

\[i^* = i^* + i_a^* = \frac{-B}{2A} \pm \sqrt{\left(\frac{B}{2A}\right)^2 - \frac{C}{A}} \text{ , where ,}
\]

\[A = \epsilon \beta > 0 \]

\[B = -\epsilon \beta + \mu + \epsilon \nu + \epsilon \mu + \gamma \]

\[C = -\mu - \epsilon \nu + \frac{(\gamma + \mu)(\nu + \mu)}{\beta} \]

Then only if $C < 0$, i.e. $\frac{(\gamma + \mu)(\nu + \mu)}{\beta} < \mu + \epsilon \nu$ can get unique positive
stationary solution:

\[ \tilde{i}^* = \frac{-B}{2A} + \sqrt{\left(\frac{B}{2A}\right)^2 - \frac{C}{A}} \geq 0 \]

The Jacobian matrix and its eigenvalues equation are:

\[
\begin{pmatrix}
-\beta \tilde{i}^* - \nu - \mu & -\beta s^* & 0 & 0 \\
\beta \tilde{s}^* & \beta s^* - \gamma - \mu & 0 & 0 \\
\nu & \gamma - \varepsilon \beta s_a^* & -\mu - \varepsilon \beta \tilde{i}^* & \gamma - \varepsilon \beta s_a^* \\
0 & \varepsilon \beta s_a^* & \varepsilon \beta \tilde{i}^* & \varepsilon \beta s_a^* - \gamma - \mu
\end{pmatrix}
\]

\[
\det(\mathbf{J}^* - \Lambda \mathbf{I}) = (\beta \tilde{i}^* + \nu + \mu + \Lambda)(\beta s^* - \gamma - \mu - \Lambda)(\mu + \varepsilon \beta \tilde{i}^* + \Lambda)
\]

\[
(\varepsilon \beta s_a^* - \gamma - \mu - \Lambda) + \beta^3 \tau \gamma^2 s^*(\gamma - \varepsilon \beta s_a^*)\varepsilon
\]

\[
= (\frac{\mu}{s^*} + \Lambda)(\frac{\beta s^* i_a^*}{\iota^*} + \Lambda)(\gamma \tilde{i}^* + \nu s^*) + \Lambda) + (\frac{\varepsilon \beta i^* s_a^*}{i_a^*} + \Lambda)
\]

\[
+ \beta^3 \tau \gamma^2 s^*(\gamma - \varepsilon \beta s_a^*)\varepsilon
\]

\[
= 0
\]

If we can fulfill \(\gamma - \varepsilon \beta s_a^* > 0\), then all the eigenvalues are negative. The feasibility and stability of endemic epidemic level could be obtained consequently.

3.3 The case \(\varepsilon = 0\)

When \(\varepsilon = 0\), the partially susceptible moved from the immune state cannot become reinfected, i.e. \(I_a = 0\). This is the case if the waning of immunity is too slow compared to the life span. It is similar to the first case we introduced with vaccination and lifelong immunity, and the endemic equilibrium is \(i^* = \frac{\beta \mu}{\beta (\gamma + \mu)}\). See Figure 4.

![Figure 4: Model of \(\varepsilon = 0\).](image)

3.4 The case \(\nu = 0\)

In the pre-vaccine era, nearly all children were infected with pertussis by about age 15 with an average age of attack of about 5 years. Without
vaccination control, see Figure 5.

The corresponding deterministic systems is:

\[ \begin{aligned}
\frac{\partial s}{\partial t} &= \mu - \beta s(i + i_a) - \mu s, \\
\frac{\partial i}{\partial t} &= \beta s(i + i_a) - \gamma i - \mu i, \\
\frac{\partial r}{\partial t} &= \gamma(i + i_a) - \theta r - \mu r, \\
\frac{\partial s_a}{\partial t} &= \theta r - \varepsilon \beta s_a(i + i_a) - \mu s_a, \\
\frac{\partial i_a}{\partial t} &= \varepsilon \beta s_a(i + i_a) - \gamma i_a - \mu i_a, \\
1 &= s + i + r + s_a + i_a.
\end{aligned} \]

The stationary state, \( \bar{i}^* = i^* + i_a^* \) is the solution of \( A\bar{i}^2 + B\bar{i} + C = 0 \), with

\[ \begin{aligned}
A &= \varepsilon \beta \left( \frac{-\gamma}{\sigma + \mu} + 1 \right), \\
B &= \frac{\varepsilon \gamma \mu}{\sigma + \mu} + \gamma - \varepsilon \beta + \mu + \varepsilon \mu, \\
C &= -\mu + \frac{(\gamma + \mu)\mu}{\beta}.
\end{aligned} \]

Then, only if \( C < 0 \), i.e. \( \gamma + \mu < \beta \), we can obtain a unique positive stationary solution at:

\[ \bar{i}^* = \frac{-B}{2A} + \sqrt{\frac{B}{2A}^2 - \frac{C}{A}} > 0. \]

The Jacobian matrix and its eigenvalues equation are:

\[ \mathbf{J}^* = \begin{pmatrix}
-\beta i^* - \mu & -\beta s^* & 0 & 0 & -\beta s^* \\
\beta i^* & \beta s^* - \gamma - \mu & 0 & 0 & \beta s^* \\
0 & \gamma & -\theta - \mu & 0 & \gamma \\
0 & -\varepsilon \beta s_a^* & \theta & -\varepsilon \beta i^* - \mu & -\varepsilon \beta s_a^* \\
0 & \varepsilon \beta s_a^* & 0 & \varepsilon \beta i^* & \varepsilon \beta s_a^* - \gamma - \mu
\end{pmatrix}, \]
\[
\text{det}(J^* - \Lambda I) = (\beta \bar{t}^* + \mu + \Lambda)(\beta s^* - \gamma - \mu - \Lambda)(\theta + \mu + \Lambda)(\varepsilon \beta \bar{t}^* + \mu + \Lambda)
\]
\[
(\varepsilon \beta s^* - \gamma - \mu - \Lambda) + \beta^3 v^2 s^* \gamma \theta \varepsilon
\]
\[
= \left(\frac{\mu}{s^*} + \Lambda\right)(\beta s^* + \Lambda)(\frac{\gamma t^*}{r} + \Lambda)(\frac{\theta s}{s^*} + \Lambda)(\beta s^* + \Lambda) + \beta^3 v^2 s^* \gamma \theta \varepsilon
\]
\[
= 0.
\]

Under our conditions on the parameters, the stationary solution and all parameters are positive, then we can easily get all of the eigenvalues are negative. In other words, the stationary solution is unique and stable.

In all, when the parameters of our model satisfy the condition \(\gamma + \mu < \beta\), the equilibrium of the model without vaccination control converges to an endemic equilibrium.

4 Diffusion approximation

In the previous section, it was shown that the scaled jump Markov vector process \(x_N\) for a large population, was approximately equal to the deterministic vector \(x(t)\) when \(t \to \infty\), under the condition of \(\frac{(\gamma + \mu)(\nu + \mu)}{3} < \mu + \frac{\theta \mu}{s + \mu}\).

Now we proceed by studying the deviations between the two, that is to derive a central limit theorem. The analysis in this section are based on Andersson and Britton 2000 [3] and Andersson [5].

Define the centered and scaled process by

\[
X^N_t = \sqrt{N}(x^N_t - x(t)),
\]

with initial condition \(X^N_0 = \sqrt{N}(x^N_0 - x(0))\), which sufficiently close to 0.

Let a process \(V(t)\) defined by the integral equation

\[
V(t) = V(0) + \sum_l W_l \left( \int_0^t q_l(x(s)) \, ds \right) + \int_0^t \partial F(x(s)) V(s) \, ds, V(0) = 0, \quad (4)
\]

where the \(W_l\)'s are 5-dimensional Wiener processes. Then we have a central limit theorem by Kurtz [7]:

**Theorem 2** (Central Limit Theorem). If \(\sum_l |l|^2 \sup_{\xi \in K} q_l(\xi) < \infty\) and \(\partial F(\xi)\) is a bounded, continuous function of \(\xi\), then \(X^N_t \Rightarrow V(t)\) (converges in distribution).

Because of the proved stability of the stationary point \(x^*(t)\), there is some compact set \(K \subset \mathbb{R}^5\) such that the trajectory of \(x(t)\) is contained in \(K\). But the restriction of \(\partial F\) and \(q_l\) to \(K\) is bounded, which is what we need in order to be able to apply Theorem 2 to our model.
Rewriting the equation (4) as a stochastic differential equation we have
\[ dV(t) = \partial F(x(t)) V(t) \, dt + G(x(t)) \frac{dW}{2} \, dt, \]
where \( W \) is the 5-dimensional Wiener process and \( G(\xi) = \sum l^T q_l(\xi) \). Due to that \( x(t) \) will tend to its stable positive stationary point \( x^* \) as \( t \to \infty \) it follows that \( \partial F(x(t)) \to \partial F(x^*) \equiv J^* \) and \( G(x(t)) \to G(x^*) \equiv G^* \). Therefore \( V(t) \) approaches a stationary Ornstein-Uhlenbeck process described by the stochastic differential equation:
\[ dV(t) = J^* V(t) \, dt + G^* \frac{dW}{2}, \]
where
\[ G^* = \sum_l l^T q_l(x^*) = \begin{bmatrix} \mu x^* + \nu x^* + \mu s^* & -\nu x^* & 0 & 0 \\ -\nu x^* & \nu s^* + \gamma + \gamma^* + \mu r^* & 0 & 0 \\ 0 & 0 & -\nu \gamma^* + \mu s^* \\ 0 & 0 & -\nu \gamma^* \\ \end{bmatrix}. \]

This Ornstein-Uhlenbeck process is an example of a Gaussian process with zero-mean and covariance matrix \( \Sigma \), where the matrix \( \Sigma \) is determined from the matrices \( G^* \) and \( J^* \) through the relationship
\[ J^* \Sigma + \Sigma J^{* T} = -G^* \]

It is hard to obtain an analytic solution but it is enough for us to know that our stochastic process converges to an Ornstein-Uhlenbeck process which has a Gaussian stationary distribution with mean 0 and covariance matrix \( \Sigma \) defined above. This result will be used in the numerical study. In the following section we will use the limiting Gaussian distribution given above to study the distribution of the time to extinction of the Pertussis.

In summary, we have showed that when the population size is fairly large then the epidemic process may be approximated by an Ornstein-Uhlenbeck process with a specified multivariate normal distribution as its stationary distribution. This approximation can only be valid before the epidemic goes extinct. But the extinction is always caused by random fluctuations from the deterministic curve. Once it happens, the spread of pertussis in the population completely stops. We are interested in the behavior of the disease after a long time until disease extinction.

5 The quasi-stationary distribution and time to extinction

The ideas presented in this section come from Näsell 1999 [4] and Andersson and Britton [3].
Define $T = \inf\{ t \geq 0 : I(t) = 0, I_a(t) = 0 \}$ as the time to extinction which is of great interest because of its epidemiological interpretation. Its distribution depends on the initial state $(S(0), I(0), R(0), S_a(0), I_a(0))$.

Let $p_{(a,b,c,d,e)}(t) = P(S(t) = a, I(t) = b, R(t) = c, S_a(t) = d, I_a(t) = e)$ denote the joint distribution at time $t$, $t \geq 0$. Further, let $p_{\bullet,b,e} = \sum_{a,c,d} p_{(a,b,c,d,e)}(t)$ denote the marginal distribution of the number of infected individuals at time $t$. As before, we also simplify the index of $p_{(a,b,c,d,e)}$ by only showing the changed states.

Then define
\[
q_{(a,b,c,d,e)}(t) = P(S(t) = a, I(t) = b, R(t) = c, S_a(t) = d, I_a(t) = e|I(t) \neq 0)
\]
\[
= p_{(a,b,c,d,e)}(t)/(1 - p_{\bullet,b=0,e=0}(t))
\]
to be the probability that the process is in state $(a, b, d, e)$ at time $t$ given that it has not yet become absorbed into the disease-free class of states.

Introduce the definition of quasi-stationary distribution $q_{(a,b,c,d,e)}$ by the distribution after a long time, conditioned on not having gone extinct, i.e.
\[
q_{(a,b,c,d,e)} = \lim_{t \to \infty} q_{(a,b,c,d,e)}(t).
\]

What we discuss in this section is the time until extinction given that the process is started in the quasi-stationary distribution, which is denoted as $\tau_Q$.

5.1 The quasi-stationary distribution

The Kolmogorov forward equations for our stochastic model can be written as:
\[
p'_{(a,b,c,d,e)}(t) = \mu N p_{a-1}(t) + \frac{\beta}{N} (a + 1)(b - 1 + e)p_{a+1,b-1}(t)
\]
\[
\quad + \nu(a + 1)p_{a+1,c-1}(t) + \mu(a + 1)p_{a+1}(t)
\]
\[
\quad + \gamma(b + 1)p_{b+1,c-1}(t) + \mu(b + 1)p_{b+1}(t) + \gamma(e + 1)p_{c-1,e+1}(t)
\]
\[
\quad + \theta(c + 1)p_{c+1,d-1}(t) + \frac{\beta}{N}(d + 1)(b + e - 1)p_{d+1,e-1}(t)
\]
\[
\quad + \mu(d + 1)p_{d+1}(t) + \mu(c + 1)p_{c+1}(t) + \mu(e + 1)p_{e+1}(t)
\]
\[
\quad - \kappa(a, b, c, d, e)p_{(a,b,c,d,e)}(t),
\]
where $\kappa(a, b, c, d, e) = \mu N + \frac{\beta}{N} a(b + e) + \nu a + \mu a + \gamma(b + \mu b + \gamma e + \theta c + \mu c + \frac{\beta}{N} d(b + e) + \mu d + \mu e$.

Then, by summing the forward equations for $b = 0, e = 0$ over all values of $a, c, d$, we obtain
\[
p'_{\bullet,b=0,e=0}(t) = (\mu + \gamma)(p_{\bullet,b=1,e=0}(t) + p_{\bullet,b=0,e=1}(t)).
\]
By differentiating the expression in (6) for quasi-stationary and applying equation (8), we obtain

\[ q'(a,b,c,d,e)(t) = \frac{p'(a,b,c,d,e)(t)}{1 - p(\bullet, b=0, e=0)(t)} \]

\[ + (\mu + \gamma)(q(\bullet, b=1, e=0)(t) + q(\bullet, b=0, e=1)(t)) \frac{p(a,b,c,d,e)(t)}{1 - p(\bullet, b=0, e=0)(t)}. \]

(9)

Applying the Kolmogorov forward equations for \( p(a,b,c,d,e)(t) \) in equation (7) yields:

\[ q'(a,b,c,d,e)(t) = \mu N q_{a-1}(t) + \frac{\beta}{N} (a + 1)(b - 1 + e)q_{a+1,b-1}(t) \]

\[ + \nu(a + 1)q_{a+1,b,c-1}(t) + \mu(a + 1)q_{a+1}(t) \]

\[ + \gamma(b + 1)q_{b+1,c-1}(t) + \mu(b + 1)q_{b+1}(t) \]

\[ + \gamma(c + 1)q_{c-1,d,e+1}(t) + \mu(c + 1)q_{c+1,d-1}(t) \]

\[ + \gamma(e + 1)q_{e-1,d-1}(t) + \mu(e + 1)q_{e+1}(t) \]

\[ + \theta(\nu + 1)q_{\bullet, b=1, e=0}(t) + q(\bullet, b=0, e=1)(t)q_{a,b,c,d,e}(t). \]

(10)

The quasi-stationary distribution \( \{q(a,b,c,d,e)\} \) is the stationary solution of this system of equations.

5.2 The distribution of the time to extinction from quasi-stationarity

The cumulative distribution function of the time to extinction at time \( t \) equals the marginal probability that the number of infected individuals at time \( t \) equal 0, namely

\[ P\{\tau_Q \leq t\} = P\{I(t) = I_a(t) = 0\} = p(\bullet, b=0, e=0)(t) \]

From equation (10), the quasi-stationary distribution can be got in stationary state is obtained by putting \( q'(a,b,c,d,e)(t) = 0 \). Thus we are led to the initial value problem from setting (9) equals 0

\[ p'(a,b,c,d,e) + (\mu + \gamma)(q(\bullet, b=1, e=0) + q(\bullet, b=0, e=1))p(a,b,c,d,e) = 0, \]

\[ p(a,b,c,d,e)(0) = q(a,b,c,d,e), \]

with solution

\[ p(a,b,c,d,e)(t) = q(a,b,c,d,e)exp(-(-\mu + \gamma)(q(\bullet, b=1, e=0) + q(\bullet, b=0, e=1))t). \]
Writing \( q_{*,1} := q_{*,b=1,e=0} + q_{*,b=0,e=1} \) as the marginal quasi-stationary probability that there is exactly 1 individual who is either symptomatic infected or asymptomatic infected.

By adding these expressions for \( p(a,b=1,c,d,e=0)(t) \) and \( p(a,b=0,c,d,e=1)(t) \) over all \( a, c, d \), we get:

\[
p(a,b=1,c,d,e=0)(t) + p(a,b=0,c,d,e=1)(t) = q_{*,1}(e) \exp(-(\mu + \gamma)(q_{*,1})t).
\]

Take this into equation (8), with initial condition \( p_{(*,b=0,e=0)}(0) = P(I(0) + I_a(0)) = 0 \), we obtain:

\[
p_{(*,b=0,e=0)}(t) = 1 - \exp(-(\mu + \gamma)q_{*,1}t)
\]

Thus \( \tau_Q \in \exp((\mu + \gamma)q_{*,1}) \). Accordingly, \( E(\tau_Q) = \frac{1}{(\mu + \gamma)q_{*,1}} \).

The above expression tells us that for fixed parameters, \( \tau_Q \) is completely determined from the parameters \( \mu, \gamma \) and quasi-stationary probability \( q_{*,1} \), which is the marginal distribution for 1 infected individual at time \( t \) conditioned on not having reached any state in the absorbing set.

### 5.3 Diffusion approximation

It is not possible to find explicit expressions for the quasi-stationary distribution or for the time to extinction, and hence we need to try approximate these quantities.

The process \( X_t^N = \sqrt{N}(x_t^N - x(t)) \) for large \( N \) is approximated by a 5-dimensional Ornstein-Uhlenbeck process. This approximation can only be valid before the epidemic goes extinct. Then its stationary distribution is approximated by the quasi-stationary distribution. It is approximately 5-dimensional normal with zero-mean and covariance matrix \( \Sigma = (\Sigma_{ij}) \).

Conclude from the above that the marginal distribution of the number of infected individuals \( I(t) = I_a(t) + I_t(t) \) in quasi-stationarity is approximately normal with mean \( \mu_I \) and variance \( \sigma_I^2 \), where

\[
\mu_I = \mu_t + \mu_I = N_i^* + N_i^* = N_i^*
\]

\[
\sigma_I^2 = \sigma_I^2 + \sigma_{I_a}^2 + 2\text{Cov}(I, I_a) = N\Sigma_{22} + N\Sigma_{55} + 2N\Sigma_{25}
\]

Modify the approximating normal distribution by truncation at 0.5 to achieve consistency with the fact that \( I \) is positive. Thus we find that this quasi-stationary marginal distribution can be approximated by the expression:

\[
q_{*,n} \approx \frac{1}{\sigma_I \Phi((n - \mu_I)/\sigma_I)} \phi\left\{(n - \mu_I)/(\sigma_I)\right\},
\]

where \( \Phi \) and \( \phi \) denote the standard normal cumulative distribution function and density function respectively.
Then the diffusion approximation to $E(\tau_Q)$ can be expressed by inserting the approximation to $q_{*,1}$:

$$E(\tau_Q) \approx \frac{\sigma_I}{\mu + \gamma} \Phi\{(\mu_I - 0.5)/\sigma_I\}$$

$$\varphi\{(\mu_I - 1)/\sigma_I\}.$$  \hspace{1cm} (12)

6 Simulation and Sensitivity analysis

Now, we build a computer simulation with specific choices of parameter sets to exemplify the pertussis transmission. No effort is made to estimate the parameters but it is our view that the chosen parameters are reasonably realistic.

<table>
<thead>
<tr>
<th>Table 2: parameter set 1.</th>
</tr>
</thead>
<tbody>
<tr>
<td>$N$</td>
</tr>
<tr>
<td>100000</td>
</tr>
</tbody>
</table>

In the set of parameters in Table 2, the choice $N = 100000$ is only a matter of scale. Set the average lifespan in this population to 60 years. $\beta=2/5$ represents the probability of disease transition happening between a given infected individual and a symptomatic susceptible is $4/5$. The vaccination coverage is $1/10$ which is not high. Choosing $\theta = 1/(5 \cdot 365)$ represents a 5-year’s duration of immune loss on average. The choice of $\gamma=50 \text{days}$ can be seen as a choice of 50 recovery days for an infected case. Having set $\varepsilon$ to $1/2$ represents the disease transition between a infected individual and a partially susceptible reducing to half the possibility compared to a fully susceptible individual. Again this is hard to give any precise motivation other than that is seems to be a reasonable order of scale. Plugging these values into the deterministic ODE equation system, we obtain a unique positive stationary solution at

$$x^* = \{0.00041657, 0.00019887, 0.8763, 0.0994, 0.0237\}$$

and multiplying by $N$ gives integer-values around

$$Nx^* \approx (41, 19, 87630, 9940, 2370).$$

Taking these values into the expressions for $G^*$ and $J^*$, solving the equation $J^*\Sigma + \Sigma J^*^T = -G^*$ gives us,
The matlab code for solving this equation is listed in Appendix A.

Obtain \( \mu_\bar{I} = 2389, \sigma_\bar{I} = 106.58. \)

We now ready to calculate

\[
E(\tau_Q) \approx \frac{106.58 \Phi(22.4)}{0.02 \cdot \varphi(22.4)} \approx 5.26 \times 10^{109} \text{ years}
\]

Assume that our simulation starts from the deterministic equilibrium of the model. The evaluation of how good the approximation of time to distinction is for a range of different values of large \( N \) and large running end time which is not feasible at the moment since it takes too long time on a home PC. The simulation code is listed in Appendix A. The sample trajectory is plotted in Figure 6 and more detailed in Figure 7.

![Figure 6: Simulated results of parameter set 1.](image)

We can see from Figure 6 that the pertussis model with parameter set 1 stays in equilibrium (endemic phase) during these 800 days. Figure 7 shows how the numbers in these five states fluctuate around their equilibrium values.

If we change the years needed for immune loss from 5 years to 15 years when all other parameters are kept fixed, we can get new stationary solution.
of the deterministic model at

\[ x^* = \{4.423e - 04, 7.0378e - 05, 0.892, 0.0993, 0.0079\}. \]

Then same calculation as we did in the previous case gives,

\[ \Sigma = 10^{-5} \begin{pmatrix} 44.259 & -0.143 & -5.426 & -19.897 & -15.967 \\ -0.143 & 7.754 & 86.047 & -154.582 & 75.989 \\ -5.426 & 86.047 & 206658.152 & -108922.611 & 1281.656 \\ 19.897 & -154.582 & -108922.611 & 118812.19 & -9836.030 \\ -15.967 & 75.989 & 1281.656 & -9836.03 & 9419.985 \end{pmatrix}, \]

\[ \mu_I = 800, \sigma_I = 97.876, \text{ and } \]

\[ E(\tau_Q) \approx \frac{97.876 \Phi(8.17)}{0.02 \varphi(8.16)} \approx 9.7 \times 10^5 \text{years}. \]

A simulation starting from the equilibrium level is shown in Figure 8. We can see all the five states fluctuate around the endemic equilibrium level \((44, 7.99223, 9933, 793)\). Comparing the two equilibrium states, the number of recovered individuals grows with the increase of immune lost duration. As a sequence, the number of individuals in the immunity state increases, followed by the drop of both infectious individuals. The total number of infected individuals is reduced from 2540 to 800. From our calculation result, the extinction duration sharply decreases. Thus we can say that the parameter of \(\theta\) plays a big role in the infected incidence which means strong sensitivity.

If we remove the vaccination control without changing other parameters, the endemic equilibrium level changes to \((436, 227, 87807, 9151, 2379)\). A simulation starting from this equilibrium state is shown in Figure 9. We get,


\[ \mu_I = 2606, \sigma_I = 104.8 \text{ and } \]

\[ E(\tau_Q) \approx \frac{104.8 \Phi(26.24)}{0.02 \varphi(26.23)} \approx 1.03 \times 10^{151} \text{years}. \]

Without vaccination, the number of newborn susceptible infants obviously increases which leads to the increase of asymptomatic infectious individuals. The total infected incidences increase from 2570 to 2606. The time to extinction increases but not so much.
Finally, a simulation with 100% vaccination coverage, which means \( \nu = 1 \), gives endemic equilibrium phase at \((4,2,87608,10014,2372)\). Then the total infected incidence drops from 2570 to 2374. Thus we can conclude that the vaccination could help to control the disease but could not extinct the pertussis due to the waning of vaccination-acquired immune. The sensitivity of the parameter \( \nu \) is not so strong as that of the parameter \( \theta \).

7 Conclusion and a more realistic model for further consideration

In our thesis, the deterministic model is built to describe the spread under the assumption of mass action. It is simple to analysis but not realistic due to unpredictable factors especially in the phenomenon of persistence and its complement extinction. These problems can only be analyzed in a stochastic model. Only in a stochastic model can we derive the expression for the time to extinction, variation around the equilibrium and so on.

If we do a more proper calibration of the model, we could give suggestions for the number of asymptomatic cases and partially susceptible based on observed cases. In our simulations it has been shown that with parameter values in parameter set 1, if we would observe 19 cases there would still be 2370 unseen asymptomatic cases spreading disease and a similar parallel exists between the number of susceptible and partially susceptible.

In our simulation part, we omitted to evaluate how good the approximations are for different values of \( N \) because of long simulation times. It should be investigated in future work.

The construction of our model in this thesis is simple under analytical consideration. For further study, the death rates should not be the same in different states and ages, disease induced mortality should not be ignored. Mortality from pertussis should be higher, especially for infants under 6 months of age. Proportion recovered must increase with age, and the vaccination program for pertussis consists of giving multiple doses of pertussis vaccine to young children.

A schematic figure of this more realistic model is given in Figure 10.
Appendix A: Matlab code

1. Code for simulation program in case with parameter set 1

\[
mu = \frac{1}{60 \cdot 365};
\]
\[
beta = \frac{4}{5};
\]
\[
v = \frac{1}{5};
\]
\[
gamma = \frac{1}{50};
\]
\[
theta = \frac{1}{5 \cdot 365};
\]
\[
e = \frac{1}{2};
\]
\[
N = 100000;
\]
\[
timesteps = 300;
\]
\[
T = \text{zeros}(\text{timesteps}, 1);
\]
\[
states = \text{zeros}(\text{timesteps}, 5);
\]
\[
\text{states}(1,:) = [20 20 92470 4970 2520];
\]
\[
\text{endtime} = 800;
\]
\[
i = 1;
\]
\[
\text{change}(1,:) = [+1 0 0 0 0];
\]
\[
\text{change}(2,:) = [-1 0 0 0 0];
\]
\[
\text{change}(3,:) = [-1 +1 0 0 0];
\]
\[
\text{change}(4,:) = [-1 0 +1 0 0];
\]
\[
\text{change}(5,:) = [0 -1 +1 0 0];
\]
\[
\text{change}(6,:) = [0 -1 0 0 0];
\]
\[
\text{change}(7,:) = [0 0 -1 +1 0];
\]
\[
\text{change}(8,:) = [0 0 -1 0 0];
\]
\[
\text{change}(9,:) = [0 0 0 -1 +1];
\]
\[
\text{change}(10,:) = [0 0 0 -1 0];
\]
\[
\text{change}(11,:) = [0 0 +1 0 -1];
\]
\[
\text{change}(12,:) = [0 0 0 0 -1];
\]
\[
\text{while } T(i) < \text{endtime}
\]
\[
\text{Rate}(1) = \mu \times N;
\]
\[
\text{Rate}(2) = \mu \times \text{states}(i,1);
\]
\[
\text{Rate}(3) = \beta \times \text{states}(i,1) \times (\text{states}(i,2) + \text{states}(i,5))/N;
\]
\[
\text{Rate}(4) = v \times \text{states}(i,1);
\]
\[
\text{Rate}(5) = \gamma \times \text{states}(i,2);
\]
\[
\text{Rate}(6) = \mu \times \text{states}(i,2);
\]
\[
\text{Rate}(7) = \theta \times \text{states}(i,3);
\]
\[
\text{Rate}(8) = \mu \times \text{states}(i,3);
\]
\[
\text{Rate}(9) = e \times \beta \times \text{states}(i,4) \times (\text{states}(i,2) + \text{states}(i,5))/N;
\]
\[
\text{Rate}(10) = \mu \times \text{states}(i,4);
\]
\[
\text{Rate}(11) = \gamma \times \text{states}(i,5);
\]
\[
\text{Rate}(12) = \mu \times \text{states}(i,5);
\]
\[
R1 = \text{rand}(1,1);
\]
\[
R2 = \text{rand}(1,1);
\]
\[ \text{step} = -\log(R2)/(\text{sum(Rate)}); \]
\[ T(i+1) = T(i) + \text{step}; \]
\[ \text{ProbRate} = \text{Rate}/\text{sum(Rate)}; \]
\[ \text{sumP} = 0; \]
\[ j = 0; \]
\[ \text{while sumP < R1} \]
\[ \quad j = j + 1; \]
\[ \quad \text{sumP} = \text{sumP} + \text{ProbRate}(j); \]
\[ \text{end} \]
\[ \text{states}(i+1,:) = \text{states}(i,:) + \text{change}(j,:); \]
\[ i = i + 1; \]
\[ \text{end} \]

```
figure(1)
plot(T,states(:,1),'b')
hold on
plot(T,states(:,2),'r')
hold off

figure(2)
plot(T,states(:,3),'g')
hold off

figure(3)
plot(T,states(:,4),'k')
hold on
plot(T,states(:,5),'b')
hold off

figure(4)
plot(T,states(:,1),'b')
hold on
plot(T,states(:,2),'r')
hold on
plot(T,states(:,3),'g')
hold on
plot(T,states(:,4),'k')
hold on
plot(T,states(:,5),'b')
hold off
```
2. Code for computing the stationary solution of the ODE system and the covariance matrix of the diffusion process with parameter set 1

\[ e=1/2; \beta=2/5; \mu=1/(60\times365); \nu=1/10; \theta=1/(5\times365); \gamma=1/50; \]

\[ A=e \beta (\gamma/(\theta+\mu)+1); \]
\[ B=e \gamma (\nu+\mu)/(\theta+\mu)+\gamma-e \beta+\mu+e \nu+e \mu; \]
\[ C=-\mu-e \theta \nu/(\theta+\mu)+(\gamma \nu+\mu \nu+\gamma \mu+\mu^2)/\beta; \]

\[ \bar{ibar}=-B/(2A)+\sqrt{B^2/(4A^2)-C/A}; \]
\[ s=\mu/(\beta \bar{ibar}+\nu+\mu); \]
\[ i=\beta s \bar{ibar}/(\gamma+\mu); \]
\[ r=(\gamma \bar{ibar}+\nu s)/(\theta+\mu); \]
\[ sa=\theta r/(e \beta \bar{ibar}+\mu); \]
\[ ia=e \beta s a \bar{ibar}/(\gamma+\mu); \]

\[ G=[\mu+\beta s \bar{ibar}+\nu s+\mu s -\beta s \bar{ibar} -\nu s 0 0; \]
\[ -\beta s \bar{ibar} \beta s \bar{ibar}+\gamma i+\mu i -\gamma i 0 0; \]
\[ -\nu s -\gamma i \nu s+\gamma \bar{ibar}+\theta r+\mu r -\theta r -\gamma i a; \]
\[ 0 0 -\theta r \theta r+e \beta s a \bar{ibar}+\mu s a-e \beta s s a \bar{ibar}; \]
\[ 0 0 -\gamma i a-e \beta s a \bar{ibar} e \beta s s a \bar{ibar}+\gamma a \mu i a]; \]

\[ J=[-\beta s \bar{ibar} -\nu s -\beta s 0 0 -\beta s; \]
\[ \beta s \bar{ibar} \beta s \bar{ibar}-\gamma \mu 0 \beta s; \]
\[ \nu \gamma \theta r-\gamma i s a \theta -\beta s \bar{ibar} -\beta s a 0 \beta s; \]
\[ 0 e \beta s s a \theta -e \beta s \bar{ibar} -\mu -e \beta s a 0 e \beta s \bar{ibar} e \beta s s a \gamma \mu]; \]

\[ D=-G \text{inv}(J'); \]
\[ X=\text{repmat}(J,5,5); \]
\[ Y=\text{reshape}(\text{repmat}(\text{reshape}(\text{repmat}(\text{inv}(J')',5,1),1,125),5,1),25,25); \]
\[ Z=X \cdot Y+\text{eye}(25); \]
\[ P=\text{reshape}(Z \text{D}(\cdot),5,5); \]
Figure 7: Simulated results of the parameter set 1 (more detailed).
Figure 8: Simulated results with changing in $\theta$. 
Figure 9: Simulated results without vaccination control.
Figure 10: Model for further consideration.
Bibliography


