Mathematical Modeling Of Smallpox With optimal Intervention Policy

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MATHEMATICAL MODELING OF SMALLPOX
WITH
OPTIMAL INTERVENTION POLICY

by

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B.A. Bennington College, 2003

A thesis submitted in partial fulfillment of the requirements
for the degree of Master of Science
in the Department of Mathematics
in the College of Sciences
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Orlando, Florida

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ABSTRACT

In this work, two differential equation models for smallpox are numerically solved to find the optimal intervention policy. In each model we look for the range of values of the parameters that give rise to the worst case scenarios. Since the scale of an epidemic is determined by the number of people infected, and eventually dead, as a result of infection, we attempt to quantify the scale of the epidemic and recommend the optimum intervention policy. In the first case study, we mimic a densely populated city with comparatively big tourist population, and heavily used mass transportation system. A mathematical model for the transmission of smallpox is formulated, and numerically solved. In the second case study, we incorporate five different stages of infection: (1) susceptible (2) infected but asymptomatic, non infectious, and vaccine-sensitive; (3) infected but asymptomatic, noninfectious, and vaccine-in-sensitive; (4) infected but asymptomatic, and infectious; and (5) symptomatic and isolated. Exponential probability distribution is used for modeling this case. We compare outcomes of mass vaccination and trace vaccination on the final size of the epidemic.
I would like to dedicate this to my mother and father.
ACKNOWLEDGMENTS

I would like to thank Dr. R.N. Mohapatra, Dr. D.K. Rollins, and D. Bryant for all their help and support in this endeavor.
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CHAPTER ONE

1.1 Introduction

What would happen if biological agents such as smallpox were deliberately released in a large population where individuals gather randomly? What would be the worst-case scenarios? Are there measures in place to prevent such scenarios? According to World Health Organization smallpox was eradicated in 1980, but there are still official repositories in both the U.S and Russia. Not only do these repositories exist, but also in special adaptations, they are easily usable in bombs and missiles. Hence, it is quite logical that there is great concern about readiness of a state or nation in the events of a smallpox attack. After 9/11, the U.S. government has responded to such threat by stockpiling an estimated 300 million doses of smallpox vaccines alone compared to just 50 million worldwide before September 11, 2001 [4]. Obviously, the U.S. government wouldn’t have reacted so quickly and in such a magnitude if the threat were insignificant. Besides, what makes smallpox a weapon of terror is it kills 30% of infected (unvaccinated) individuals, and there are no specific treatments [4]. And since smallpox vaccination programs ended about 30 years ago, and effectiveness of a smallpox vaccine is assumed to last for 10 to 30 years [9], we can assume that most of the population has no immunity. Therefore, if such an event were to take place, the result would be devastating.

Potential threat of bioterrorism is a big concern for many policy makers, scientists and public health officials. As a result, it necessitates a rational contingency planning that integrates as many variables as possible. Nevertheless the main focus should be at identifying control measures that minimizes the total number of deaths. Since mass vaccination is often the
recommended strategy, proper planning needs to account for adverse side effects that some
experience due to vaccination. It would be unfortunate if a national mass vaccination campaign
caused more deaths than an isolated epidemic. Even worse, there is tendency to extrapolate
crucial parameter values from past epidemic outbreaks. Unfortunately, this practice is misleading
because in last 35 years, there has been so much change in the population size, mobility patterns,
and social interactions.

Mathematical models of the transmission of infectious disease are essential tools in
making timely assessment of the spread of an infectious disease. Models can integrate
epidemiological and biological data to give quantitative analysis of pattern of spread and the
effect of control strategies. The model can also provide an approximate scale of fatalities and
identify specific control strategies that produce an optimal result.

1.2 Epidemiological Principles

A disease is infectious if at some stage in the life cycle (of the appropriate organism), it is
transmissible from an infected host to an unaffected susceptible with or without intermediate
vector. Once an individual receives the infectious organism via direct contact, breathing in, or
eating etc, the person is said to be exposed to the infection. Not every single exposure results in
the infection. Sometimes the individual is naturally immune to the organism concerned due to
previous exposure to the disease or through immunization. The invading organism, on the other
hand, follows its own life cycle. Usually, we observe the elapse of a latent period during which
there is internal development but the person is not capable to transmitting infectious material.
The actively infectious person is usually called infective and the period during which s/he is
infectious is called the infectious period [5]. At some stage the infected person shows clinical symptoms, which for an acute infection, is the signal for isolating the person from the community until recovery or death. If symptoms appear before the onset of infectious period, isolating the person will prevent the spread of infection significantly. But generally, symptoms appear after the onset of infectiousness, in which case, the relevant period of time for the transmission of disease is from the end of the latent period to the removal from circulation [8]. Although there is slight chance of transmission after the isolation, it is ignored. Sometimes, the symptoms appear after the infectious period has ended, in which case, the length and time of infectious period is not certain. In any case, the latent period and incubation period is used interchangeably, although the latter is the time elapsed between the exposure and the appearance of symptoms [8]. The difference between the two is obvious when we look at a disease where the symptoms occur either during or after the infectious period. In this case, the incubation period is the sum of the latent period and the part of the infectious period during which the person is capable of transmitting disease.

From a mathematical modeling perspective, the lengths of the latent and infectious periods are represented by some probability distribution functions. For example, the continuous model by Mc Kendrick and Bartlett [2] assume the latent period to be zero and infectious period to be negative exponentially distributed. Bailey [2], in the chain-binomial model, uses a normal frequency distribution for length of the latent period and some constant for the length of infectious period. Therefore, depending on the choice of distribution function, the final size of an epidemic varies significantly among different models.

Given that there is a contact between an infective and a susceptible, whether the disease is transmitted or not, is a matter of chance. The magnitude of this chance depends on various
factors like the virulence of the disease, the extent to which virus has been discharged, the immunity level of the susceptible, the proximity of the infective to the susceptible etc. [8]. In the binomial model [2], term adequate contact is used to refer to those contacts that result in the transmission of the disease. In the continuous model [5], the chance of a new infection during a short interval of time is proportional to the product of the length of the interval, the number of susceptibles and the number of infectives. In addition, the continuous model [5] assumes that all the susceptibles and the infectives mix together homogeneously in the community, clearly at variance with the observed facts of the social behavior. For example, children from a particular school/community are more likely to mix with children from the same school/community closely compared to those from neighboring districts.

1.3 Smallpox

Smallpox is a viral disease that can be transmitted from a person to person via inhalation of air droplets or from the aerosols from an infected person or via direct contact with the infected person [4]. Transmission of this disease can take place at a 7-foot-radius of the infected person [4]. The incubation period is approximately 21 days, with an uninfected incubation period of about 12 days, typically followed by a 2-4 days of prodomal period associated with mild symptoms and low infectiousness, then a highly infectious period of about 9 days [9].

Smallpox is believed to have appeared around 6000 B.C [4]. For many centuries, the material from smallpox pustules was used for the process of variolation in Africa, China, India, countries in Europe, and in Americas [8]. In 1796, Edward Jenner started vaccinating people with cowpox to immunize against smallpox [8]. By early 1800s, the smallpox vaccine was
widely available. Although smallpox immunization programs existed in many parts of the globe, smallpox remained endemic. Smallpox was gradually eradicated after the World Health Organization (WHO) started global smallpox eradication program in 1967. The program involved extensive vaccination and rigorous surveillance to detect any signs of a smallpox outbreak. By the end of 1979, smallpox was officially eradicated from the globe [8]. Ever since, the world has been saving many lives and an estimated expenditure of 2 billion dollars every year [8].

1.4 History of Smallpox modeling

The first model for smallpox was formulated and analyzed by Daniel Bernoulli in 1760 [8]. In 1906, Hamer formulated a model that assumed the incidence (number of new cases per unit time) to be proportional to the product of the densities of the susceptibles and infectives [6]. In 1926, Kermack and McKenrick came up with an epidemic threshold result (where density of susceptibles has to exceed a critical value in order for an outbreak occur [8]). Bailey followed the footsteps of Ross and McKendrick. Since then, mathematical models for infectious disease have grown exponentially. The recent models have incorporated many more parameters which were ignored in the previous models. There are deterministic differential equation models [4, 9], integral equation models [1], stochastic models [3, 6] etc., each with its own merits and demerits.

For deterministic models, compartments with labels such as M, S, E, I, and R are often used as epidemiological classes, where M, S, E, I, and R stand for immune, susceptible, exposed, infected and recovered respectively. The class M contains infants or individuals with passive or permanent immunity. Once there is adequate contact between susceptible and infective,
transmission occurs, then S becomes the exposed class E. E incorporates latency or incubation period, individuals who are infected but not infectious. At the end of latent period, individuals enter the class I, infectives. Individuals in class I are infectious, and are capable of transmitting the infection. When the infectious period ends, the individual enters the recovered class R consisting of those who are either dead or have life-long immunity. The choice of different compartments depends on the characteristics of the particular disease that is being modeled. Categorization of models into MSEIR, MSEIRS, SEIR, SEIRS, SIR, SIRS, SEI, SEIS, SI, or SIS solely depends on the flow patterns between compartments.

1.5 Threshold quantities: $R_0$, $\sigma$, and $R_n$

The threshold for many epidemiology models is the basic reproduction number $R_0$, defined as the average number of secondary infections produced by a single infected individual after entering the host population [10]. For most of the deterministic models, $R_0$ determines the onset, the length, and the final size of an epidemic. Sometimes, $R_0$ is also called the basic reproductive ratio or basic reproductive age.

The contact number $\sigma$: is the average number of adequate contacts a typical infected individual makes during the entire infectious period. Note that adequate contact means a contact that is sufficient for transmission of disease.

The replacement number $R_n$: is defined as the average number of secondary infections produced by a typical infective during the entire infectious period. Note that $R_0$, $\sigma$, and $R_n$ are equal (at the beginning) when the entire host population is susceptible. Also note that, $\sigma$ and $R_n$ are defined all throughout the epidemic whereas $R_0$ is defined only at the time of invasion. For
most of the models, the reproduction number and the contact number remains constant, and can be used interchangeably. On the contrary, the replacement number changes, and is less than the reproductive number. This is because the fraction of susceptible population decreases as the infection spreads, and as a result, not all adequate contacts will produce an infection. In summary, $R_o \geq \sigma \geq R_n$ with equality at the time of invasion.
2.1 Formulating Model Equations and variables

At a given time $t$, suppose $S(t)$ is the number of susceptibles, $I(t)$ is the number of infectives, $E(t)$ is the number exposed, $R(t)$ is the number of removals or recoveries (Removed individuals represent those who have suffered the disease and have died or recovered, or have been vaccinated, or have been isolated from the population), and $N$ is the total population. Here, $s(t)$, $e(t)$, $i(t)$, and $r(t)$ represent fractions of respective classes in the total population. Suppose $\beta$ is the average number of contacts per person per unit time, then $\beta I/N = \beta_i$ is the average number of contacts made by one susceptible with infectives per unit time, and hence, $\beta N i_s$ is the number of new cases generated per unit time.

Note that transfer rates like $\delta M$, $\varepsilon E$, and $\gamma I$ in the model, correspond to exponentially distributed waiting times in the compartments. For example, the transfer rate $\gamma I$ corresponds to $P(t) = \exp(-\gamma t)$, the fraction that is still in the infective class $t$ units later, with $1/\gamma$ as the mean waiting time. For smallpox, $1/\gamma$ is about 9 days, while $1/\varepsilon$ is 12 days [9]. But, there is no general agreement on exact value of $1/\gamma$ and $1/\varepsilon$, and on kind of distribution for waiting time. For example, one could construct a model with waiting time distribution as a step function given by $P(t) = 1$ if $0 \leq t \leq \tau$, and $P(t) = 0$ otherwise.

The simplest model:

Assumptions:

1. Disease spreads through contact only.
2. Everyone is identical with respect to their susceptibility and immunity.

3. A contact is an instantaneous event with no duration in time.

4. The population mixes homogeneously and instantaneously.

5. All susceptibles are equally at risk of infection from infected individuals.

6. All infected individuals have a constant and equal infectiousness.

7. Each of the classes is differentiable functions of a continuous variable say, time \( t \).

The population is divided into two classes: susceptibles and infectives. An individual is susceptible if s/he is capable of being infected after coming in a contact with an infected individual. An individual is said to be infective if s/he is carrying the virus and is capable of transmitting the disease. Once a susceptible is infected, s/he becomes infective and remains in that state indefinitely. And the infectives continues to spread the disease until the end of the epidemic. Note: The total population is assumed to be closed for \( t \geq 0 \) in the sense that there is no immigration or emigration.

By assumption, every time an infected person comes in contact with a susceptible, s/he will communicate the disease. Thus, during \([t, t + \Delta t]\) each infected individual will produce certain number of new cases. Using the Law of mass action (which states that the interaction between different kinds of particles is proportional to their masses [5]), the number of new infectives is given by \( \beta_1 \beta_2 \Delta t S(t) \). Here \( \beta_1, \beta_2 \in [0,1] \) and \( \beta_2 \Delta t \) is the fraction of the susceptible population that come in contact with infectives, and \( \beta_1 \) is the fraction of these that become infected during the interval. Combining \( \beta_1 \) and \( \beta_2 \), we get just \( \beta \), the contact rate. Therefore, the
number of new infectives $\Delta I(t)$, during the time interval $[t, t + \Delta t]$ is given by $\beta IS\Delta t$. As limit of $\Delta t$ tends to zero, the number of infectives at time $t$ is given by

$$\frac{dI}{dt} = \beta I(N - I)$$

(2.1)

with $S(0) = S_0 \geq 0$, $I(0) = I_0 \geq 0$, $S(t) + I(t) = N$.

The SI model is a very special case of MSEIR model, in which, the immune class $M$, the exposed class $E$, and the removed or the recovered class $R$ is omitted.

Separating variables and integrating both sides of equation (2.1) we get,

$$\int_{I_0}^{I} \frac{dI}{I(N - I)} = \int_{0}^{\beta dt} \Rightarrow I(t) = \frac{Nl_0}{l_0 + (N - l_0)e^{-\beta Nt}}$$

(2.2)

![Figure 1: Solution of the SI model](image-url)

Fig.1 predicts that the disease will spread until there is no more susceptibles left to infect.

Although oversimplified, the model is suitable when the disease is highly contagious and spreads rapidly in the closed community.
At steady state, \( \frac{dI}{dt} = 0 \). Clearly, there are two equilibrium solutions, \( I(t) = 0 \), and \( I(t) = N \). The first one is not an interesting solution. The second one on the other hand, means that an introduction of one infectious individual will infect the whole population, and the epidemic is independent of the initial size of attack. This is the simplest epidemic model.

Now let us improve the model by allowing the possibility of recovery or removal during the period of the epidemic. Following recovery or removal, an individual either becomes immune or dies.

Table 1: Parameters SI, SIR, and SEIR model.

<table>
<thead>
<tr>
<th>M</th>
<th>Immune</th>
</tr>
</thead>
<tbody>
<tr>
<td>S</td>
<td>Susceptible</td>
</tr>
<tr>
<td>E</td>
<td>Exposed</td>
</tr>
<tr>
<td>I</td>
<td>Infective</td>
</tr>
<tr>
<td>R</td>
<td>Recovered</td>
</tr>
<tr>
<td>m,s,e,i,r</td>
<td>Fractions of the population in the above classes</td>
</tr>
<tr>
<td>( \beta )</td>
<td>Contact rate</td>
</tr>
<tr>
<td>( 1/\omega )</td>
<td>Average period of immunity</td>
</tr>
<tr>
<td>( 1/\epsilon )</td>
<td>Average latent/incubation period</td>
</tr>
<tr>
<td>( 1/\gamma )</td>
<td>Average infectious period</td>
</tr>
<tr>
<td>( R_0 )</td>
<td>Basic reproduction number</td>
</tr>
<tr>
<td>( \sigma )</td>
<td>Contact number</td>
</tr>
<tr>
<td>( R_n )</td>
<td>Replacement number</td>
</tr>
</tbody>
</table>

2.2 **The Classic Epidemic model**

Using the notation in the table 1 and section 2.1, the classic Kermack and McKendrick epidemic model is given below.
\[
\begin{align*}
\frac{dS}{dt} &= \beta IS / N, \\
\frac{dI}{dt} &= \beta IS / N - \gamma I, \\
\frac{dR}{dt} &= \gamma I,
\end{align*}
\]
(2.3)

with  \(S(0) = S_0 \geq 0, I(0) = I_0 \geq 0, R(t) = R_0 \geq 0, S(t) + I(t) + R(t) = N\).

Note that the number of people recovering per unit time is dependent on the number of infectives. This model uses the standard incidence and has recovery rate of  \(\gamma I\), corresponding to an exponential waiting time  \(e^{-\gamma t}\). Dividing (2.3) by \(N\) and denoting \(d/dt\) as \(\dot{\cdot}\), we get

\[
\begin{align*}
\dot{s} &= -\beta is, \quad s(0) = s_0 \geq 0, \\
\dot{i} &= \beta is - \gamma i, \quad i(0) = i_0 \geq 0, \\
\dot{r}(t) &= 1 - s(t) - i(t).
\end{align*}
\]
(2.4)

where  \(r(t), i(t), s(t)\) are the fractions in the given classes. Here,  \(\beta / \gamma = \sigma\), the contact number, the product of contact rate  \(\beta\) per unit time and the average infectious period  \(1/\gamma\). Similarly, the replacement number  \(R_0 = \sigma S_0\), at the beginning of the epidemic.
Fig. 2 shows the solutions of SIR model with contact number 3, and average infectious period of 3 days. According to Fig.2, a typical epidemic outbreak follows a bell-shaped curve, with the fraction of infective population increasing from $I_0$ (near zero) reaching a maximum and gradually coming back towards zero. The susceptible fraction on the other hand, starts near 1 and decreases to a small positive value at steady state. Note that when the fraction of susceptible population goes below $1/\sigma$, the replacement number $\sigma S(t) < 1$, as a result the epidemic dies out.

At time $t = 0$, the fraction of susceptible and infective population are $s_0$ and $i_0$ respectively, with $s_0 + i_0 = 1$ (since initially there is no removal term). Thus equation 2.4 (ii) becomes

$$\left[i'(t)\right]_{t=0} = i_0(\beta s_0 - \gamma).$$

Unless $\beta s_0 - \gamma > 0$, that is, $s_0 > \gamma/\beta$ there will be no epidemics. Let $\gamma/\beta = \lambda$ be the relative removal rate. In order for the epidemic to start, the susceptible population has to be greater than
the relative removal rate. If $i_o$ is small then $s_o \approx 1$, and in this case, $\lambda$ can be regarded as the threshold susceptible population. In general, the susceptible population is a decreasing function of time and hence, $s(t) > s_o$ for all $t > 0$.

By dividing $di/ dt$ by $ds/ dt$ one obtains a quotient differential equation.

$$\frac{di}{ds} = \frac{\beta s i - \gamma i}{-\beta s i} = -1 + \frac{\gamma}{\beta s} = -1 + \frac{1}{\sigma s} \left(= -1 + \frac{\lambda}{s}\right)$$

$$\frac{di}{ds} = -1 + \frac{1}{\sigma s} \Rightarrow di = \left(-1 + \frac{1}{\sigma s}\right) ds$$

The solution paths shown in Fig.3 are obtained from this equation. According to the figure, for $s > 1/\sigma$, the equilibrium points along s-axis are neutrally unstable and vice versa for $s < 1/\sigma$.

![Figure 3: Phase plane portrait for the classic SIR model with contact number $\alpha = 3$.](image-url)

Figure 3 shows the phase plane portrait of SIR model with contact number 3 and average infectious period 3 of days. The explicit solution for $i$ can be found by integrating,

$$di = \left(-1 + \frac{1}{\sigma s}\right) ds$$. Integrating both sides, we get
\[ i = -s + \frac{\ln s}{\sigma} + C, \text{ where } C \text{ is an integrating constant. Applying initial conditions, we get} \]

\[ C = i_0 + s_0 - \frac{1}{\sigma} \ln s_0 \]

\[ i = -s + \frac{\ln s}{\sigma} + i_0 + s_0 - \frac{\ln s_0}{\sigma} \]

Observe that the solution path is given by,

\[ i + s - \frac{\ln s}{\sigma} = i_0 + s_0 - \frac{\ln s_0}{\sigma} \quad (2.5) \]

We can summarize the characteristics of a SIR model by the following theorem.

**Theorem 1.1** [8] Suppose \((s(t), i(t))\) is a solution of SIR model given in (2.3). If \(\sigma s_0 \leq 1\), \(i(t)\) decreases to zero as \(t\) tends to infinity. If \(\sigma s_0 > 1\), then \(i(t)\) first increases up to a maximum value \(i_{\text{max}} = i_0 + s_0 - 1/\sigma - \left[\ln(\sigma s_0)\right]/\sigma\) and then decreases to zero as \(t\) tends to infinity. The susceptible fraction is a decreasing function of \(t\) and at the steady state, value of \(s(\infty)\) is the unique root in \((0, 1/\sigma)\) of the equation \(i_0 + s_0 - s_\infty + \ln\left(s_\infty/s_0\right)/\sigma = 0\).

One interpretation of the Theorem 1.1 is that if there are enough people who are already immune such that a typical infective can only replaces itself with no more than one infective, then \(i(t)\) decreases, and there is no epidemic outbreak. But if a typical infective initially infect more than one person i.e. \(\sigma s_0 > 1\), then \(i(t)\) increases and as a result, an epidemic outbreak occurs.

Since \(r(t)\) is a quantity that is measurable, let us seek the solution for \(r(t)\). If we can obtain data for \(r(t)\) we might be able to validate the conclusion of the model.
Dividing $ds/dt$ by $dr/dt$, we get $ds/dr = -\sigma s = -Rn$ where $Rn$ is the replacement number.

$ds/s = -\sigma dr$. Now integrating both sides, and using the initial condition we get, $s = s_0 e^{-\sigma r}$

So, $r' = \gamma (1 - r - s) = \gamma (1 - r - s_0 e^{-\sigma r})$

Let $\sigma r$ be small quantity. Taking the first three terms of the Taylor series expansion of $e^{-\sigma r}$, we get

$$r' = \gamma \left(1 - r - s_0 \left[1 - \sigma r + \frac{\sigma^2 r^2}{2!}\right]\right)$$

Integrating both sides, we get

$$r(t) = \frac{1}{\sigma^2 s_0} \left[(s_0 \sigma - 1) - \tan \left(\gamma t \left(-2\sigma^2 s_0 + \sigma^2 s_0 + 2\sigma s_0 - 1\right)^{1/2}\right) \left((-2\sigma^2 s_0 + \sigma^2 s_0 + 2\sigma s_0 - 1)^{1/2}\right)\right]$$

$$\Rightarrow r(t) = \frac{1}{\sigma^2 s_0} \left[(s_0 \sigma - 1) - \zeta \tan \left(\frac{\gamma t}{2}\right)\right] \quad \text{or} \quad r(t) = \frac{1}{\sigma^2 s_0} \left[(s_0 \sigma - 1) + \zeta \tanh \left(\frac{\gamma t}{2} - \theta\right)\right]$$

Where $\zeta = \left[(\sigma s_0 - 1)^2 + 2\sigma^2 s_0\right]^{1/2}$ and $\theta = \tan^{-1} \left(\frac{1}{\zeta} (\sigma s_0 - 1)\right)$.

If we differentiate equation for $r(t)$, we get

$$r'(t) = \frac{\zeta^2 \gamma}{2\sigma^2 s_0} \sec h^2 \left(\frac{\gamma t}{2} - \theta\right)$$
Figure 4: Shows the plot of $i(t)$ and $r'(t)$ versus $t$.

From the Figure 4 we can see that the rate of recovery builds up and gradually dies away. The time at which there is maximum number of infected individuals match with peak of $r'(t)$ ($r_{\text{prime}}(t)$). To determine the size of the epidemic, we need to find eventual number of removals, let it be $\tilde{r}(t)$. When $t \to \infty$, we get

$$
\tilde{r}(\infty) = \left[ \left( \frac{\sigma s_0 - 1}{\sigma s_0} \right) + \zeta \right].
$$

Using Taylor expansion for $\zeta$, and using only first term $\zeta = \sigma s_0 - 1$, we get

$$
\tilde{r}(\infty) = \frac{2}{\sigma} \left( 1 - \frac{1}{\sigma s_0} \right) = \frac{2}{3} \quad \text{[taking } \sigma = 3 \text{ and } s_0 = 1].
$$

Note: There is a noticeable difference in value of $\tilde{r}(\infty)$ compared to $r(40)$ in figure 2. The error is due to an approximation used to obtain $r'(t)$ and $\zeta$.

Now, let us consider a model with vital dynamics (births and deaths). This model is relevant when the disease is endemic. Smallpox was endemic for a long period of time, until it was finally eradicated. The classic endemic model is given below.
2.3 The Classic Endemic SIR model

\[
\begin{align*}
\frac{dS}{dt} &= \mu N - \mu S - \frac{\beta IS}{N}, \quad S(0) = S_0 \geq 0, \\
\frac{dI}{dt} &= \frac{\beta IS}{N} - \gamma I - \mu I, \quad I(0) = I_0 \geq 0, \\
\frac{dR}{dt} &= \gamma I - \mu R, \quad R(0) = R_0 \geq 0, \\
S(t) + I(t) + R(t) &= N.
\end{align*}
\] (2.6)

The difference between classic SIR epidemic and endemic model is that in the case of latter, there is constant inflow of new susceptibles $\mu N$ (due to births), and outflows (as natural deaths) at rate $\mu S, \mu I, \text{and } \mu R$ in respective classes. However, the total population $N$ is assumed to be constant, that is, at any given time, total number of births equal to total number of deaths. The mean life time varies from country to country but for our purpose, we will take one for the United States which is about 75 years [8]. Like in the previous model, dividing each of the equations in (2.6) by $N$ we obtain equation (2.7) given below

\[
\begin{align*}
\frac{ds}{dt} &= \mu s - \mu s - \beta is, \quad s(0) = s_0 \geq 0, \\
\frac{di}{dt} &= \beta is - \gamma i - \mu i, \quad i(0) = i_0 \geq 0, \\
\text{with } r(t) &= 1 - s(t) - i(t).
\end{align*}
\] (2.7)

The triangle $T$ in the $si$ phase plane given by $T = \{(s, i) \mid s \geq 0, i \geq 0, s + i \leq 1\}$ is positively invariant and unique solution exists in $T$ for all time [8]. Like in the previous model, the contact
number stays constant throughout and is equal to the reproductive number \( R_0 \). From (2.7),

\[ i'(t) = i[\beta s - (\gamma + \mu)]. \]

Simplifying the right hand side, we get

\[ i'(t) = (\gamma + \mu)(\beta s - 1). \]

So, the threshold quantity \( R_0(\sigma) = \frac{\beta}{\gamma + \mu} \) for this model. It is the product of the contact rate \( \beta \) and death adjusted infectious period \( \frac{1}{\gamma + \mu} \).

Let us consider 2 cases:

Case 1: \( R_0 = \sigma \leq 1, \quad i_0 > 0 \)

Since \( s(t) \) can never be greater than 1, the replacement number \( R = \sigma s < 1 \), making \( i'(t) \) always less than 1. This means infective fraction quickly goes to zero. Fig. 6 shows that this conclusion is indeed true. In the long run (over 100 or more years), people who were infected but recovered, slowly die off. Since there is constant inflow of new susceptibles, fraction \( s(t) \) gradually increases until \( s(t) = 1, \) and \( i(t) = 0. \) This is a disease-free equilibrium.

Case 2: \( R_0 = \sigma > 1, \quad i_0 > 0 \)

In this case, the replacement number \( R = \sigma s > 1 \), making \( i'(t) \) always greater than 1. This means the infective fraction grows exponentially until it reaches a peak and then decays just like in the SIR epidemic model. However, in the long run (10 to 20 years), once the infective fraction has been reduced to a low level, the process of deaths of recovered people and the births of new susceptibles increases susceptible fraction to the point when \( \sigma s \) is large enough to incite a smaller epidemic. This process of an alternation between rapid epidemics and slow regeneration continues until solution paths approaches the endemic equilibrium. The value of the endemic equilibrium is given in Theorem 2.2 below.
Note: The endemic equilibrium occurs when replacement number $\sigma s = 1$. As soon as $\sigma s > 1$, the infective fraction increases resulting in an epidemic and vice versa.

**Theorem 2.2** [8] Suppose $(s(t), i(t))$ is the solution of equation (2.7). If $\sigma \leq 1$ or $i_0 = 0$, then solution paths starting in $T$ approach the disease-free equilibrium given by $s = 1$ and $i = 0$. If $\sigma > 1$, then all solution paths with $i_0 > 0$ approach the endemic equilibrium given $s_e = 1/\sigma$ and $i_e = \mu(\sigma - 1)/\beta$. Fig. 6 and Fig.7 illustrate the two cases given in theorem.

![Figure 5: Solutions of the classic SIR endemic model with contact number $\sigma = 3$ and $\mu = 1/60$.](image1)

![Figure 5: Solutions of the classic SIR endemic model with contact number $\sigma = 3$ and $\mu = 1/60$.](image2)
Let us use linear stability analysis and investigate the nature of trajectory in a small region near the endemic equilibrium solution. From Theorem 2.2, equilibrium solution is

\[
\begin{pmatrix}
\frac{1}{\sigma}, \\
\frac{\mu(\sigma - 1)}{\beta}
\end{pmatrix}.
\]

Let \( s(t) = \frac{1}{\sigma} + \xi(t) \), \( i(t) = \frac{\mu(\sigma - 1)}{\beta} + \eta(t) \) where \( \xi(t) \) and \( \eta(t) \) are small perturbations in \( s \) and \( i \) respectively. Plugging new \( s(t) \) and \( i(t) \) into equation (2.7) and retaining only linear terms in \( \xi(t) \) and \( \eta(t) \), we get

\[
\xi'(t) = -\frac{\beta \eta(t)}{\sigma} - \mu \sigma \xi(t) \quad \text{and} \quad \eta'(t) = \mu \xi(t)(\sigma - 1).
\]

and after eliminating \( \xi(t) \) we get,

\[
\sigma \eta''(t) + \mu \sigma^2 \eta'(t) + \beta \mu (\sigma - 1) \eta(t) = 0.
\]

This second order differential equation describes the behavior of the solution of (2.7) near the equilibrium state. The exact nature of the solution of (2.7) depends on the parameters \( \beta, \mu, \gamma \) and \( \sigma \). As long as contact number \( \sigma > 1 \) and all the parameters are positive, both \( \xi(t) \) and \( \eta(t) \)
tends to 0 as $t \to \infty$. This indicates that the equilibrium solution is a stable solution corresponding to endemic state of the disease. In particular, when $\mu \sigma^3 < 4 \beta (\sigma - 1)$, the solution of 2nd order differential equation becomes a damped harmonic oscillation. Thus when vital dynamic is included, the model displays periodic epidemic behavior.

Notice that there is exchange of stability at $\sigma = 1$. For $\sigma < 1$, there is a stable disease free equilibrium along line $i = 0$. As soon as $\sigma$ is slightly greater than one then $i > 0$. The equilibrium given by $s_e = \frac{1}{\sigma}, \quad i_e = \frac{\mu(\sigma - 1)}{\beta}$ is unstable for $\sigma < 1$, however for $\sigma > 1$, the same equilibrium solution is locally asymptotically stable. The disease free equilibrium given by $s = 1$ and $i = 0$ is locally stable for $\sigma < 1$, however it is unstable for $\sigma > 1$. Thus these two equilibria exchange stabilities as the endemic equilibrium moves from one to another.

### 2.4 SEIR Model

The equations governing the SEIR model is given by

$$
\begin{align*}
\frac{dS}{dt} &= \mu N - \mu S - \frac{\beta IS}{N}, \quad S(0) = S_0 \geq 0, \\
\frac{dE}{dt} &= \frac{\beta IS}{N} - \varepsilon E - \mu E, \quad E(0) = E_0 \geq 0, \\
\frac{dI}{dt} &= \varepsilon E - \gamma I - \mu I, \quad I(0) = I_0 \geq 0, \\
\frac{dR}{dt} &= \gamma I - \mu R, \quad R(0) = R_0 \geq 0, \\
S(t) + E(t) + I(t) + R(t) &= N.
\end{align*}
$$
The SEIR model is similar to SIR endemic model except that it has an additional compartment E or exposed class. This compartment reflects an inclusion of incubation period. Individuals in this class are infected but not infectious. Dividing equation by N, we get

\[
\begin{align*}
\frac{d}{dt} s(t) &= \mu - \mu s - \beta is, \quad s(0) = s_0, \\
\frac{d}{dt} e(t) &= \beta is - \epsilon e - \mu e, \quad e(0) = e_0, \\
\frac{d}{dt} i(t) &= \epsilon e - \gamma i - \mu i, \quad i(0) = i_0, \\
\frac{d}{dt} r(t) &= \gamma i - \mu r, \quad r(0) = r_0,
\end{align*}
\]

(2.9)

with \( s(t) = 1 - (e(t) + i(t) + r(t)) \).

Letting \( e'(t) = 0 \), the second equation of (2.9) yields \( \epsilon(t) = \frac{\beta is}{\mu + \epsilon} \). Substituting expression for \( e(t) \) in the third equation gives, \( i'(t) = \frac{\beta e}{(\mu + \epsilon)(\gamma + \mu)} s - 1 \). So \( \frac{\beta \epsilon}{(\mu + \epsilon)(\gamma + \mu)} \) is the threshold quantity. The threshold quantity can be interpreted as the product of the contact rate \( \beta \) and average fraction \( \frac{\epsilon}{\mu + \epsilon} \) surviving the incubation period and average infectious period \( \frac{1}{\gamma + \mu} \) [8].

The SEIR model always has at least one solution given by \( s = 1, e = i = r = 0 \). If threshold quantity is greater than one then there is a unique endemic equilibrium solution in \( D \) where \( D = \{(e, i, r) | e \geq 0, i \geq 0, r \geq 0, e + i + r \leq 1\} \) [8]. Note: The replacement number \( R_n = \sigma s_e \) is equal to one at the endemic equilibrium. At steady state, all the time derivatives are equal to zero. That is,
\( \mu - \mu s - \beta is = 0 \) ..(i), \( \beta is - \varepsilon e - \mu e = 0 \) ..(ii), \( \varepsilon e - \gamma i - \mu i = 0 \) ..(iii), and \( \gamma i - \mu r = 0 \) ..(iv).

Note: \( R_o = \sigma = \frac{\beta e}{(\mu + \varepsilon)(\gamma + \mu)} \) and \( s_e, e_e, i_e, \) and \( r_e \) are endemic equilibrium solutions for respective states. Substituting \( e = 1 - s - i - r \) into (iii) yields,

\[ \varepsilon(1 - s - i - r) - (\gamma + \mu)i = 0 \]

\[ \Rightarrow \varepsilon(1 - s) - \varepsilon i - \varepsilon r - (\gamma + \mu)i = 0 \] . Substituting value of \( r \) in terms of \( i \) from (iv), we get

\[ \varepsilon(1 - s) - \varepsilon i - \varepsilon \gamma \frac{i}{\mu} - (\gamma + \mu)i = 0 \]

\[ \Rightarrow \varepsilon(1 - s_e) - \frac{i}{\mu}[(\mu + \gamma)(\varepsilon + \mu)] = 0 \Rightarrow i_e = \frac{\mu e(1 - s_e)}{(\mu + \gamma)(\varepsilon + \mu)} \]

From (i), we get \( s_e = \frac{\mu}{\mu + \beta i_e} \). And substituting value of \( i_e \), we get

\[ s_e = \frac{\mu}{\mu + \frac{\beta \mu e(1 - s_e)}{(\mu + \gamma)(\varepsilon + \mu)}} = \frac{1}{1 + R_o(1 - s_e)} \]

\[ \Rightarrow (1 - s_e)(R_o s_e - 1) = 0 \]

\[ \Rightarrow \text{Either } s_e = 1, \text{or } s_e = \frac{1}{R_o}. \]

The first solution \( s_e = 1 \) is trivial. Substituting the second solution \( (s_e = 1 / R_o) \) for \( s_e \), we get

\[ i_e = \frac{\mu e}{(\mu + \gamma)(\varepsilon + \mu)}(1 - \frac{1}{R_o}). \] Substituting \( i_e \) from above in (iii), we get

\[ e_e = \frac{(\gamma + \mu)}{\varepsilon} - \frac{(\gamma + \mu)}{\varepsilon} i_e = \frac{(\gamma + \mu)}{\varepsilon} \frac{\mu e}{(\mu + \gamma)(\varepsilon + \mu)}(1 - \frac{1}{R_o}) = \frac{\mu}{\varepsilon + \mu}(1 - \frac{1}{R_o}) \]

And finally, \( r_e = \frac{\gamma e}{(\gamma + \mu)(\varepsilon + \mu)}(1 - \frac{1}{R_o}). \)
Figure 8: Solutions of the SEIR model with contact number $\sigma = 3$, contact rate $\beta = 6/5$, average fraction surviving latent period $\frac{\varepsilon}{\varepsilon + \mu} = 5/6$ and average infectious period $\frac{1}{\gamma + \mu} = 3$.

Figure 9: Shows the phase plane portrait for SEIR model with contact number $\sigma = 3$, contact rate $\beta = 6/5$, average fraction surviving latent period $\frac{\varepsilon}{\varepsilon + \mu} = 5/6$ and average infectious period $\frac{1}{\gamma + \mu} = 3$. 

mu = 1/60
beta = 6/5
gamma = 19/60
Figure 10: Shows the phase plane portrait for SEIR model with contact number $\sigma = 0.5$, contact rate $\beta = 1/5$, average fraction surviving latent period $\frac{\epsilon}{\epsilon + \mu} = 5/6$ and average infectious period $\frac{1}{\gamma + \mu} = 3$.

2.5 Model with two interacting groups of individuals

Let us consider a deterministic model involving two groups of individuals interacting with each other. Interaction could be in terms of daily visits or emigration. For simplicity, we exclude incubation period. To incorporate interaction, let us introduce emigration rates, $\theta$ and $\phi$: the first one for the susceptibles and the latter for the infectives. So the equations for this model are given by
\[ s'_i(t) = \Pi - (\beta_i i_i + \beta_i z) s_i + \theta(s_i - s_i), \]
\[ i'_i(t) = (\beta_i i_i + \beta_i z) s_i - \gamma_i i_i + \phi(i_i - i_i), \]
\[ s'_2(t) = \Pi - (\beta_i i_i + \beta_i z) s_2 - \theta(s_2 - s_2), \]
\[ i'_2(t) = (\beta_i i_i + \beta_i z) s_2 - \gamma_2 i_2 - \phi(i_2 - i_2), \]
with \( r_i(t) = 1 - s_i(t) - i_i(t) \) and \( r_2(t) = 1 - s_2(t) - i_2(t) \). \hspace{1cm} (2.10)

\( \Pi \) is the adjusted net inflow (birth rate – death rate) into the susceptible populations. Letting the state derivatives equal to zero, we find the equilibrium solutions. They are

\[ s_i = s_2 = \frac{\gamma}{\beta_i + \beta_2} \text{ and } i_i = i_2 = \frac{\Pi}{\gamma}. \]

Let us see what happens when we slightly deviate from the equilibrium solutions. Let

\[ s_i = \frac{\gamma}{\beta_i + \beta_2} (1 + \xi), \quad i_i = \frac{\Pi}{\gamma} (1 + \xi), \quad i = 1, 2. \hspace{1cm} (2.11) \]

Substituting (2.11) in (2.10), we get

\[
\begin{aligned}
(D + \frac{1}{J'} + \theta) \xi_1 + \eta \frac{\eta}{J'} \xi_1 - \theta \xi_2 + \frac{1-\eta}{J'} \xi_2 &= 0, \\
-\gamma \xi_1 + [D + \gamma(1-\eta) + \phi] \xi_1 - [\gamma (1-\eta_1) + \phi] \xi_2 &= 0,
\end{aligned}
\]

\[ D \equiv \frac{d}{dt}, \hspace{1cm} (2.12) \]

where \( \eta = \frac{\beta_i}{\beta_i + \beta_2} \), and \( J' = \frac{\gamma}{\Pi(\beta_i + \beta_2)} \). \hspace{1cm} (2.13)
Note that there are two other equations similar to (2.12), with suffixes 1 and 2 are interchanged.

Now lets add equation (2.12) with corresponding equation (where suffixes are interchanged), and we get

\[
\begin{align*}
(D + \frac{1}{J'})\zeta_1 + \zeta_2 + \frac{\bar{J}_1 + \bar{J}_2}{J'} &= 0, \\
D(\xi_1 + \xi_2) - \gamma(\zeta_1 + \zeta_2) &= 0.
\end{align*}
\]

(2.14)

On the contrary, if we subtract corresponding pair of equations, we get

\[
\begin{align*}
(D + \frac{1}{J'} + 2\theta)(\zeta_1 - \zeta_2) + \frac{1-2\eta}{J'}(\xi_1 - \xi_2) &= 0, \\
-\gamma(\zeta_1 - \zeta_2) + [D + 2\gamma(1 - J') + 2\phi](\xi_1 - \xi_2) &= 0.
\end{align*}
\]

(2.15)

Eliminating \((\zeta_1 - \zeta_2)\) and \((\xi_1 - \xi_2)\) from (2.15), we get an equation which is a quadratic in D.

The roots of this equation determine the nature of solutions for equation (2.10). Next, we consider the simulink diagram for such an interacting model.
Figure 11: Simulink diagram for a model with two interacting groups of individuals
For the simulation, the values of the parameters used are listed below:
\[ \beta_i = \beta_i = 10^{-7}, \quad \Pi = 10^{-5}, \quad \theta = 10^{-3}, \quad \phi = 3 \times 10^{-1}, \quad S_i (0) = 1.5 \times 10^4, \quad S_i (0) = 5 \times 10^4 \]
\[ I_i (0) = 20, \quad I_i (0) = 0, \quad \text{and} \quad \gamma = 10^{-5} \]

Figure 12: Solutions of the model with two interacting groups of individuals
In the absence of any interventions, Fig. 12 shows that the solution curves for two interacting groups look similar to those of a pair of SIR models.
CHAPTER THREE

3.1 Interventions

The goal of any interventions is to prevent an outbreak from sustaining itself. This can be done if the intervention carried out is able to reduce the reproductive number to less than one. There is general agreement that the control measure like isolation of infected individuals is relatively effective if the length of time between onset of infectiousness and the isolation is quite short. Therefore, a process of rapid case isolation and surveillance alone, as recommended by Eichner [6] is effective, if we can isolate most of the infectious individuals within one or two days after they have been infected. Eichner [6] argues that 1 to 2 days is reasonable time frame because an individual infected with smallpox, is infectious for at most 2 days before general rash appears. When rash appears, it is expected that infected individuals restrict their free movement and thus reduce the contact rate to a minimum value. However, Kaplan [9] argues that this measure is effective only for a small epidemic, but for larger epidemic driven by larger initial size of infectious individuals, he claims that Mass Vaccination is the best option.

According to WHO, there is no proven cure for smallpox, but can be prevented through vaccination. Vaccination is one of the major weapons against the spread of smallpox. Vaccination creates an artificial immunity amongst those individuals who otherwise would be susceptible. Vaccination given before exposure or within 3 to 4 days after the exposure to the infection protects up to 97% of the (vaccinated) individuals [4]. In any case, the goal is to acquire herd immunity i.e. have enough people immune to the infection so that an introduction of an infective does not lead to an epidemic. In the SIR model, this means keeping the susceptible
population fraction less than $1/\sigma$ ($\sigma$ is contact number), i.e. keeping the immune fraction more than $1 - 1/\sigma = 1 - 1/R_0$. For example, if $R_0 = 3$, then the immune fraction has to be greater than $2/3$, if $R_0 = 5$, then the immune fraction has to be greater than $4/5$, and so on. Let us use the estimates of the basic reproductive numbers for measles 16, mumps 12, rubella 7, and smallpox 5 (upper end approximation) [8] to calculate immune fractions. Using the given values, immune fractions for measles, mumps, rubella and smallpox are 0.94, 0.89, 0.86 and 0.8 respectively. Measles, Mumps, and Rubella still persists, but smallpox has been eradicated. The reason is quite obvious. It is easier to achieve 80% immune fraction than 86, 89 or 94%.

### 3.2 Vaccination model

Suppose that in any given day, the probability that one or more infectious individuals arrive to a neighborhood of population $N$ is $a$, some constant. Let $G$ be a random variable that represents the number of days since an outbreak occurred and has geometric probability distribution given by

$$Pr \{ G = g \} = a(1-a)^{g-1}, g = 0,1,2,..., \text{with mean value } \bar{G} = a^{-1}.$$

One of the goals of the vaccination (implemented before an outbreak) is to keep the number of the susceptibles down to a fixed level, say $s_0$. Let $f$ be the vaccine fatality rate. It is known that the chance of death from the vaccination vary according to age, the state of health, the vaccination status etc. [2]. With smallpox, there is much higher risk of complication following a vaccination among children, pregnant women, and those who have fatal diseases like
cancer, AIDS etc. Here, \( f \) represents the average fatality rate. Let \( q(s) \) be the average number of vaccinations carried out per day. So \( q(s) \) depends on the number of vaccinators that are available 24/7 and the average number of people each can vaccinate per day. However, for a given number of vaccinations, we assume that the number of deaths follow a Poisson Distribution, with parameters \( G, f, \) and \( q(s) \). Hence, the average number of deaths due to vaccination is given by

\[
U(s) = fq(s)/a \quad [2]
\]  

(3.1)

Using the same notation as in the previous models, i.e. \( \beta \) for contact rate, \( i(t) \) for number of individuals infected at given time \( t \), etc, the number of new infectives during \( \Delta t \) is given by \( \beta s_i(t)\Delta t \). The probability that one infective at a given time, give rise to \( k \) infectives (including the initial one) is given by

\[
P_k(t) = e^{-\beta t}(1 - e^{-\beta t})^{k-1}, \quad k \geq 1 \quad [2]
\]  

(3.2)

Let us assume that the time taken to identify an infective is another random variable, independent of already existing infectives \( i(t) \) and has some distribution \( X(t) \). Therefore, using (3.2), the probability that there are \( k \) infectives (at the time this new infective is identified) is given by

\[
P_k(t) = \int_0^\infty e^{-\beta t}(1 - e^{-\beta t})^{k-1}dX(t) \quad [2]
\]  

(3.3)
With smallpox, an infective is identified when s/he shows clinical symptoms. Let us assume that the time taken to identify an infective is uniformly distributed over the interval \((0, \tau)\) where \(\tau\) is the incubation period. Suppose

\[
X(t) = \begin{cases} 
0 & t < 0 \\
\frac{t}{\tau} & 0 \leq t < \tau \\
1 & \tau \leq t
\end{cases} \tag{3.4}
\]

Substituting (3.4) into (3.3), and integrating, we get

\[
P_k = \frac{(1-e^{-\beta S_0 \tau})^k}{\beta S_0 \tau k}, \quad k \geq 1 \tag{3.5}
\]

Therefore, at the time of new discovery, the expression for the expected number of infectives is given by

\[
E(k) = \frac{e^{\beta S_0 \tau} - 1}{\beta S_0 \tau}. \quad [2] \tag{3.6}
\]

Note: In order to control the epidemics, the removal rate \(\gamma\) has to be greater than the birth rate \(\beta S_0\) (infection rate). By [3], the average number of infectives including previous \(k-1\), is given by \(\frac{\gamma(k - 1)}{\gamma - \beta S_0}\), and the average number of deaths due to the infection is given by
\[ D(s_0) = \delta \left[ 1 + \frac{\gamma}{\gamma - \beta s_0} \left( \frac{e^{\beta s_0} - 1}{\beta s_0^2} - 1 \right) \right] \]  

(3.7)

where \( \delta \) is the death rate due to smallpox.

Adding (3.7) and (3.1), we get the total number of deaths due to the disease. Therefore, the best strategy, according to this model would be to implement a vaccination program that minimizes the sum of (3.7) and (3.1).

### 3.3 Case Study 1: An epidemic model with Mass Transportation

We extend SEIR and vaccination model to develop a frame-work for the spread of the smallpox on a mass transportation. In the model, the city is divided into two neighborhoods: first is composed of long term residents (neighborhood 1) and the second consist of tourist (neighborhood 2). Each neighborhood is sub-divided into two groups: those who use Mass Transportation (Mass Transportation Users) and those who don’t (Non-Mass Transportation Users). The model assumes that individuals mix proportionally. In order to explain proportionate mixing, let us introduce the mixing matrix \( P_{ij}(t) \), where \( P_{ij}(t) \) represents proportion of contacts of individuals in neighborhood \( i \) with individuals in neighborhood \( j \) given that individual in neighborhood \( i \) had a contact with a member of total population at time \( t \). The proportionate mixing here corresponds to case where \( P_{ij}(t) \) is independent of \( i \), that is, \( P_{ij} = P_j = \frac{C_j Q_j}{\sum_{k=1}^{2} C_k Q_k} \)

where \( C_k \) denotes the average activity level (the contact rate) of individuals in group \( k = 1, 2 \) [11].

35
Within a neighborhood, those who are MTU have contacts with other MTU and NMTU. MTU can also have a contact with MTU from the other neighborhood while sharing the same ride, otherwise, a contact between MTU from the two different neighborhoods is negligible. In addition, it is assumed that NMTU make most of the contacts (that leads to infection) only within their own neighborhood.

Suppose, at some point in time, a fixed number of infected individuals are introduced in the MTS (Mass Transportation System). These infected individuals take the infection back to their respective neighborhoods and start transmitting infection to individuals with whom they have close contacts. When a symptomatic individual comes to a hospital for treatment, at $t = 0$, the smallpox is officially detected, and a wide-spread vaccination policy is implemented. Depending on the epidemiological status of the disease, the individuals fall into one of the five classes: susceptible, exposed, infected, recovered, and dead, $S_i, E_i, I_i, R_i$ and $D_i$ for MTU and $W_i, X_i, Y_i, Z_i$ and $U_i$ for NMTU. The total population of MTU is denoted by $Q_i(t) = S_i(t) + E_i(t) + I_i(t) + R_i(t)$ and of NMTU is given by $T_i(t) = W_i(t) + X_i(t) + Y_i(t) + Z_i(t)$.

For the simulation, we assume that the size of the resident population is 8 million and the tourist population is around 200000. Other, parameters have been estimated roughly using historical knowledge about smallpox. For example, the average case-fatality is adjusted to be 0.15 instead of 0.3 used by Kaplan [9]. The choice reflects an assumption that a person vaccinated 30 years ago still has some immunity. The model also assumes that death due to smallpox is exponentially distributed, so death rate is given by $d = -\ln(0.85)/14 = 0.0116$. The next table outlines the rest of the parameters.
Table 2: Parameters and their corresponding values. i refers to the index of a neighborhood [4]:

<table>
<thead>
<tr>
<th>Definitions</th>
<th>Parameters</th>
<th>Baseline Values</th>
<th>Suitable range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Natural Death rate</td>
<td>$\mu$</td>
<td>0.033</td>
<td></td>
</tr>
<tr>
<td>Net inflow rate of MTU and NMTU</td>
<td>$\Pi, \Gamma_i$, i = 1, 2.</td>
<td>0.166, 0.166</td>
<td></td>
</tr>
<tr>
<td>Death rate due to smallpox</td>
<td>$\delta$</td>
<td>0.0116</td>
<td>[0.0116, 0.0255]</td>
</tr>
<tr>
<td>Vaccination rate</td>
<td>$q_i$ and $q_2$</td>
<td>Control parameter</td>
<td>[0.2, 1.0], [0.2, 1.0]</td>
</tr>
<tr>
<td>Progression rate from latency to infectious</td>
<td>$\Omega$</td>
<td>0.086</td>
<td></td>
</tr>
<tr>
<td>Recovery rate</td>
<td>$\alpha$</td>
<td>0.086</td>
<td></td>
</tr>
<tr>
<td>Per capita Contact rate of NMTU</td>
<td>$a_i$, i = 1, 2.</td>
<td>5 and 15</td>
<td></td>
</tr>
<tr>
<td>Per capita Contact rate of MTU</td>
<td>$b_i$, i = 1, 2.</td>
<td>10 and 30</td>
<td></td>
</tr>
<tr>
<td>Transmission rate per contact</td>
<td>$\beta_i$, i = 1, 2.</td>
<td>0.5, 0.5</td>
<td></td>
</tr>
<tr>
<td>Proportion of time spent on MTS</td>
<td>$r_i$, i = 1, 2.</td>
<td>0.6 and 0.1</td>
<td></td>
</tr>
<tr>
<td>Proportion of time spent off MTS</td>
<td>$w_i$, i = 1, 2.</td>
<td>0.4 and 0.9</td>
<td></td>
</tr>
<tr>
<td>Vaccination efficacy in susceptible and exposed</td>
<td>$v_i$ and $v_2$</td>
<td>0.97 and 0.3</td>
<td>[0.95,1.0],[0.3, 0.95]</td>
</tr>
<tr>
<td>Vaccine fatality rate</td>
<td>$f$</td>
<td>0.000001</td>
<td></td>
</tr>
</tbody>
</table>

The choice of $r_1 = 0.6$ and $r_2 = 0.1$ tells us that, on average, the proportion of time that tourists spend on MTS is much higher than local residents. Baseline values for per capita contact rates reflect residents spending more time in their own neighborhood (in less crowded place) compared to tourists. The mixing probabilities (MP) of different neighborhoods are given below:
Table 3: Expressions for Mixing Probabilities of individuals from different neighborhoods (i refers to the index of a neighborhood) [4]

<table>
<thead>
<tr>
<th>Mixing Probabilities between/of</th>
<th>Notation</th>
<th>Expression</th>
</tr>
</thead>
<tbody>
<tr>
<td>NMTU and NMTU in the same neighborhood</td>
<td>$P_{a_ia_i}$</td>
<td>$\frac{a_iT}{a_iT + b_ir_iQ_i}$</td>
</tr>
<tr>
<td>NMTU and MTU from same neighborhood</td>
<td>$P_{a_ib_i}$</td>
<td>$\frac{b_ir_iQ_i}{a_iT + b_ir_iQ_i}$</td>
</tr>
<tr>
<td>MTU and NMTU from same neighborhood</td>
<td>$P_{b_ia_i}$</td>
<td>$\frac{a_iT}{a_iT + b_ir_iQ_i}$</td>
</tr>
<tr>
<td>MTU and MTU from same neighborhood</td>
<td>$P_{b_ib_i}$</td>
<td>$\frac{b_ir_iQ_i}{a_iT + b_ir_iQ_i}$</td>
</tr>
<tr>
<td>MTU from neighborhood i and j</td>
<td>$P_{b_ib_j}$</td>
<td>$\frac{b_sw_iQ_j}{b_sw_iQ_j + b_sw_2Q_2}$</td>
</tr>
<tr>
<td>NMTU from neighborhood i and j (Assume $i \neq j$)</td>
<td>$P_{a_ia_j}$</td>
<td>0</td>
</tr>
<tr>
<td>NMTU from neighborhood i and MTU from neighborhood j (Assume $i \neq j$)</td>
<td>$P_{a_ib_j}$</td>
<td>0</td>
</tr>
</tbody>
</table>

The 6th entry of Table 3 tells us that NMTU from neighborhood i and NMTU from neighborhood j does not have any contacts, and 7th entry tells us that the same is true between NMTU from one neighborhood and MTU from the other. In addition, $w_i$ and $r_i$ that appear on the table are fractions of contact times that MTU spend on or off the MTS, respectively. We assume that for each neighborhood, $w_i + r_i = 1$, $i = 1, 2$. The model is described by following equations [4].
Equations for MTU in neighborhood $i$ are given below:

\[
\begin{align*}
\frac{dS_i}{dt} &= \Pi_i - \Lambda_i(t) - (\mu + q_{i1}v_1)S_i, \\
\frac{dE_i}{dt} &= \Lambda_i(t) - (\mu + \Omega + q_{i2}v_2)E_i, \\
\frac{dI_i}{dt} &= \Omega E_i - (\mu + \alpha + d)I_i, \\
\frac{dR_i}{dt} &= \alpha I_i - \mu R_i + (1 - f)q_{i1}v_1S_i + (1 - f)q_{i2}v_2E_i, \\
\frac{dU_i}{dt} &= f(q_{i1}v_1S_i + q_{i2}v_2E_i) + (\mu + d)I_i,
\end{align*}
\]  

(3.8)

Corresponding equations for NMTU are given below:

\[
\begin{align*}
\frac{dW_i}{dt} &= \Gamma_i - B_i(t) - (\mu + q_{i1}v_1)W_i, \\
\frac{dX_i}{dt} &= B_i(t) - (\mu + \Omega + q_{i2}v_2)X_i, \\
\frac{dY_i}{dt} &= \Omega X_i - (\mu + \alpha + d)Y_i, \\
\frac{dZ_i}{dt} &= \alpha I_i - \mu Z_i + (1 - f)q_{i1}v_1W_i + (1 - f)q_{i2}v_2X_i, \\
\frac{dD_i}{dt} &= f(q_{i1}v_1W_i + q_{i2}v_2X_i) + (\mu + d)Y_i,
\end{align*}
\]  

(3.9)

$\Lambda_i(t)$ and $B_i(t)$ corresponds to the infection rates of MTU, and NMTU respectively. The expressions for each of the term is given by,
\[ \Lambda_i(t) = \beta_i b_i S_i \left( P_{h_i} \frac{Y_i}{Q_i + T_i r_i} + P_{l_i} \frac{r_i I_i}{Q_i + T_i r_i} + \sum_{j=1}^{\infty} P_{h_i} b_j \frac{Y_j}{T_j \sigma_j} \right) \]  \hspace{1cm} (3.10)

\[ B_i(t) = \beta_i a_i W_i \left( P_{a_i} \frac{Y_i}{Q_i + T_i r_i} + P_{a_i} \frac{r_i I_i}{Q_i + T_i r_i} \right) \]  \hspace{1cm} (3.11)

“According to the author [4], the probability that an individual at neighborhood 1 has contact with individuals in neighborhood 2, given that s/he has had a contact, is given by weighted proportion of neighborhood 2 individuals’ activity in the total population. The probability is independent of neighborhood 1 individuals.” It is obvious that MTU do not spend all their time in their own neighborhoods, therefore to accommodate this fact, MTU contacts are distributed appropriately. For example, \[ P_{a_i} = \frac{b_i r_i Q_i}{a_i T_i + b_i r_i Q_i} \], is the mixing probability of NMTU and MTU from same neighborhood i. Here, the numerator represents the average activity of MTU and denominator represents the average total activities in the neighborhood i.

**Simulation Results:**

Other initial values are: \( S_1(0) = W_1(0) = 4000000 \), \( S_2(0) = W_2(0) = 100000 \), \( I_1(0) = 70 \), \( I_2(0) = 30 \), and rest of the states are initially zero. In the simulation, we vary two key parameters, \( q_1 \) and \( q_2 \) and look at impact on total number of cases and deaths respectively. The following graphs show the result of simulation for different values of \( q_1 \) and \( q_2 \).
(a) 

(b) 

(c) 

damped oscillations
q1=0.9
q2=0.9

(d) 

(e) 

damped oscillations
q1=0.5
q2=0.5

(f) 

Cumulative Deaths
q1=0.9
q2=0.9

Cumulative Deaths
q1=0.5
q2=0.5
Figure 13: (a), (c), (e), (g) and (i) show the infective cases in the entire population, and (b), (d), (f), (h), and (j) show cumulative deaths.

Fig. 13(a) and (b) show that if 90% of each of the neighborhoods is vaccinated, the epidemic is rapidly controlled. Fig. 13(a) shows that by 50 days, there are barely any new infectives coming into the population. Fig. 13(b) show that total number of deaths is around 43. The next set of graphs, Figure 13(c) and 13(d) with 50% vaccination of each of the neighborhoods show that epidemic could still be controlled but at the cost of more lives. The graph on the right hand side, Fig. 13(d) shows that cumulative deaths at the end of 50 days exceed 125. The lower two graphs, Figure 13(e) and 13(f) show that with only 30% of population vaccinated, the epidemic lasts longer and results in much higher deaths that when 50% of population is vaccinated. At end of 50 days, there are almost 900 deaths. Fig. 13(g) and 13(h) represent 90% vaccination of neighborhood 1 and 10% vaccination of neighborhood 2. These graphs clearly indicate a growing epidemic. Fig. 13(h) shows that the cumulative deaths exceed 2200 at the end of 50 days. With \( q_1 = 0.9 \) and \( q_2 = 0.1 \), even though 90.25% of the total population is vaccinated, it is not sufficient to prevent an epidemic. The result clearly suggests that even though tourist population is much smaller in size, it should not be ignored while planning a vaccination policy.

The last two graphs, 13(i) and 13(j), with \( q_1 = 0.1 \) and \( q_2 = 0.9 \) show much greater outbreak as expected, with cumulative deaths exceeding 13000 at the end of 30 days. The following table gives cumulative deaths at the end of 100 days for 49 different combinations of \( q_1 \) and \( q_2 \).
Table 4: Cumulative deaths at the end of 100 days corresponding to 49 combinations of vaccination levels. Rows correspond to $q_1$ and columns to $q_2$.

<table>
<thead>
<tr>
<th>$q_1$</th>
<th>1.0</th>
<th>0.9</th>
<th>0.8</th>
<th>0.7</th>
<th>0.6</th>
<th>0.5</th>
<th>0.4</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0</td>
<td>41</td>
<td>45</td>
<td>52</td>
<td>62</td>
<td>79</td>
<td>112</td>
<td>200</td>
</tr>
<tr>
<td>0.9</td>
<td>42</td>
<td>48</td>
<td>53</td>
<td>63</td>
<td>80</td>
<td>115</td>
<td>208</td>
</tr>
<tr>
<td>0.8</td>
<td>43</td>
<td>48</td>
<td>54</td>
<td>64</td>
<td>83</td>
<td>120</td>
<td>219</td>
</tr>
<tr>
<td>0.7</td>
<td>44</td>
<td>49</td>
<td>56</td>
<td>67</td>
<td>86</td>
<td>128</td>
<td>239</td>
</tr>
<tr>
<td>0.6</td>
<td>46</td>
<td>51</td>
<td>59</td>
<td>71</td>
<td>93</td>
<td>140</td>
<td>276</td>
</tr>
<tr>
<td>0.5</td>
<td>51</td>
<td>57</td>
<td>66</td>
<td>82</td>
<td>110</td>
<td>172</td>
<td>365</td>
</tr>
<tr>
<td>0.4</td>
<td>66</td>
<td>75</td>
<td>91</td>
<td>116</td>
<td>164</td>
<td>280</td>
<td>668</td>
</tr>
</tbody>
</table>

Table 5: Cumulative deaths at the end of 100 days corresponding to 49 combinations of vaccination levels, if vaccination is delayed by 1 day. Rows correspond to $q_1$ and columns to $q_2$.

<table>
<thead>
<tr>
<th>$q_1$</th>
<th>1.0</th>
<th>0.9</th>
<th>0.8</th>
<th>0.7</th>
<th>0.6</th>
<th>0.5</th>
<th>0.4</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0</td>
<td>68</td>
<td>77</td>
<td>89</td>
<td>108</td>
<td>141</td>
<td>206</td>
<td>374</td>
</tr>
<tr>
<td>0.9</td>
<td>69</td>
<td>78</td>
<td>91</td>
<td>110</td>
<td>144</td>
<td>212</td>
<td>389</td>
</tr>
<tr>
<td>0.8</td>
<td>71</td>
<td>80</td>
<td>93</td>
<td>113</td>
<td>149</td>
<td>220</td>
<td>411</td>
</tr>
<tr>
<td>0.7</td>
<td>73</td>
<td>83</td>
<td>97</td>
<td>119</td>
<td>157</td>
<td>234</td>
<td>450</td>
</tr>
<tr>
<td>0.6</td>
<td>78</td>
<td>88</td>
<td>104</td>
<td>128</td>
<td>170</td>
<td>261</td>
<td>523</td>
</tr>
<tr>
<td>0.5</td>
<td>87</td>
<td>100</td>
<td>118</td>
<td>148</td>
<td>202</td>
<td>323</td>
<td>698</td>
</tr>
<tr>
<td>0.4</td>
<td>118</td>
<td>137</td>
<td>167</td>
<td>216</td>
<td>311</td>
<td>537</td>
<td>1290</td>
</tr>
</tbody>
</table>

Table 6: Cumulative deaths at the end of 100 days corresponding to 49 combinations of vaccination levels, when vaccination is delayed by 3 day. Rows correspond to $q_1$ and columns with $q_2$.

<table>
<thead>
<tr>
<th>$q_1$</th>
<th>1.0</th>
<th>0.9</th>
<th>0.8</th>
<th>0.7</th>
<th>0.6</th>
<th>0.5</th>
<th>0.4</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0</td>
<td>159</td>
<td>182</td>
<td>215</td>
<td>265</td>
<td>351</td>
<td>521</td>
<td>967</td>
</tr>
<tr>
<td>0.9</td>
<td>162</td>
<td>185</td>
<td>219</td>
<td>270</td>
<td>359</td>
<td>537</td>
<td>1006</td>
</tr>
<tr>
<td>0.8</td>
<td>167</td>
<td>190</td>
<td>224</td>
<td>278</td>
<td>370</td>
<td>558</td>
<td>1066</td>
</tr>
<tr>
<td>0.7</td>
<td>172</td>
<td>197</td>
<td>233</td>
<td>290</td>
<td>389</td>
<td>593</td>
<td>1165</td>
</tr>
<tr>
<td>0.6</td>
<td>182</td>
<td>209</td>
<td>249</td>
<td>312</td>
<td>423</td>
<td>660</td>
<td>1353</td>
</tr>
<tr>
<td>0.5</td>
<td>204</td>
<td>235</td>
<td>283</td>
<td>360</td>
<td>500</td>
<td>812</td>
<td>1789</td>
</tr>
<tr>
<td>0.4</td>
<td>274</td>
<td>322</td>
<td>394</td>
<td>517</td>
<td>754</td>
<td>1318</td>
<td>3173</td>
</tr>
</tbody>
</table>

Now, let us assume the average case fatality rate to be 0.3 not 0.15 as used by Kaplan [9], and the vaccine efficacy on susceptibles to be 0.95, and on exposed to be 0.8, as used by G.K. Aldis, and M.G.Roberts in the integral equation paper [1]. With average case fatality rate of 0.3, mortality rate due to smallpox $d = -\ln(0.7)/14 = 0.0255$. The rest of the parameter values
remain the same. The following table shows the simulation results for 64 combinations of vaccination levels.

Table 7: Total number of deaths due to smallpox infection at the end of 100 days for \( d = 0.0255, v_1 = 0.95, \) and \( v_2 = 0.8, \) and 64 combinations of vaccination levels. Rows corresponds to \( q_1 \) and column to \( q_2 \)

<table>
<thead>
<tr>
<th></th>
<th>1.0</th>
<th>0.9</th>
<th>0.8</th>
<th>0.7</th>
<th>0.6</th>
<th>0.5</th>
<th>0.4</th>
<th>0.3</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0</td>
<td>46</td>
<td>49</td>
<td>54</td>
<td>62</td>
<td>74</td>
<td>97</td>
<td>148</td>
<td>315</td>
</tr>
<tr>
<td>0.9</td>
<td>46</td>
<td>50</td>
<td>55</td>
<td>62</td>
<td>74</td>
<td>97</td>
<td>150</td>
<td>319</td>
</tr>
<tr>
<td>0.8</td>
<td>46</td>
<td>50</td>
<td>55</td>
<td>63</td>
<td>75</td>
<td>97</td>
<td>151</td>
<td>325</td>
</tr>
<tr>
<td>0.7</td>
<td>47</td>
<td>51</td>
<td>56</td>
<td>63</td>
<td>76</td>
<td>100</td>
<td>154</td>
<td>333</td>
</tr>
<tr>
<td>0.6</td>
<td>48</td>
<td>52</td>
<td>57</td>
<td>64</td>
<td>78</td>
<td>102</td>
<td>158</td>
<td>346</td>
</tr>
<tr>
<td>0.5</td>
<td>49</td>
<td>53</td>
<td>58</td>
<td>66</td>
<td>80</td>
<td>106</td>
<td>165</td>
<td>371</td>
</tr>
<tr>
<td>0.4</td>
<td>52</td>
<td>56</td>
<td>62</td>
<td>71</td>
<td>86</td>
<td>114</td>
<td>182</td>
<td>430</td>
</tr>
<tr>
<td>0.3</td>
<td>62</td>
<td>67</td>
<td>74</td>
<td>86</td>
<td>106</td>
<td>145</td>
<td>245</td>
<td>681</td>
</tr>
</tbody>
</table>

According to Table 5, one day delay corresponds to 27 more deaths, and 3 days delay (Table 6) corresponds to 118 more deaths compared to no delay both with 100% vaccination level. From Table 5 and 6, we can conclude that delay in vaccination imply higher deaths. Table 7 tells us that even though we used higher value of \( d, \) with higher value for \( v_2, \) we observe a slightly lower deaths overall.
Figure 14: Cumulative incidence and deaths for $d = 0.0255$, $v_1 = 0.95$, $v_2 = 0.8$, and (a) $q_1 = 0.3$ and $q_2 = 0.8$, (b) $q_1 = 0.8$ and $q_2 = 0.3$.

Fig. 14(a) shows that for $q_1=0.3$ and $q_2=0.8$ the total number of deaths is about 320. Fig. 14(b) shows that for $q_1=0.8$ and $q_2=0.3$ the total number of deaths is about 74.

3.4 Case study 2: An epidemic model with five different stages of infection

For this case study, we are going to look at a recent study done by Edward H. Kaplan, David L. Craft, and Lawrence M. Wein [9]. With the help of a simulink model, the smallpox attack in a large city is simulated, and analyzed. The scale of the epidemic is measured by the total number of deaths and cases during the epidemic. Using the simulation results, different proposed responses like Trace Vaccination (TV), Mass Vaccination (MV), and Quarantine are evaluated for their effectiveness. We also perform approximate analysis for MV, which leads to a closed-form expression for the total number of deaths.
It is important to understand that TV and MV operate on very different time scales. TV requires contact tracing i.e. trace the contacts of infected cases and then perform vaccination, and thus proceeds at the pace of the epidemic. TV is not effective if there is no efficient mechanism to identify new infected cases before they are infectious. In contrast, MV only depends on the number of available vaccinators and the rate at which they can vaccinate, independently of the state of the epidemic. Because of these differences, effectiveness of different interventions to control the infection is expected to vary.

The model incorporates five stages of infections: (1) susceptible (2) infected but asymptomatic (showing no clinical symptoms), noninfectious, and vaccine-sensitive; (3) infected but asymptomatic, noninfectious, and vaccine-in-sensitive; (4) infected but asymptomatic and infectious; and (5) infected, symptomatic, and isolated, each exponentially distributed in the duration with mean $r_j^{-1}$ days spent in the each stage $j = 1, 2, 3$ or 4. We assume that population is mixing homogeneously. And at the start of the epidemic, reproductive number $R_0 = \beta S_0^0 / r_3$, where $S_0^0$ is the number of susceptibles immediately after the attack, and $\beta$ is the transmission rate per unit time. The model is designed so that it can identify the worst-case scenario, that is, identify conditions that lead to maximum deaths. Note that number of deaths depends directly on the total number of infected persons, so when emergency response is activated, a delay in detection of infectives is expected to lead to higher deaths.

An infective with smallpox cannot be detected until s/he is symptomatic (show clinical symptoms like rashes). Once the person with clinical symptoms is detected, preferred response policy is implemented. The newly symptomatic infective become so called index case [9]. The index case then is isolated and interviewed to find out all the recent contacts. Let $c$ be the list of individuals who are now potentially exposed to the disease. In this list there are those who are
actually infected by the index case and those who are not. The distinction is important because in order to know the disease status of an infected individual, one needs to know the length of time the individual has been infected since the detection of the index case. Even more important is the probability that this contact is still in the vaccine sensitive stage i.e. in stage 1 of infection at the time the index is detected. This is because vaccine is effective only till stage 1 of the infection. Out of all the true contacts made by an index, only fraction $p$ is named and traced. Hence, instead of grouping all infected individuals into one big group, the model places them correctly into their appropriate stages of disease. All the susceptibles and the asymptomatic individuals located via contact tracing enter a verifying/vaccination queue. People are entering the tracing/vaccination queue via two ways: (i) via local tracing – tracing of contacts actually infected by index i.e. $pR_0(t)$, and (ii) via random tracing – tracing of those who are on the list but not infected by index i.e. $c - pR_0(t)$.

Assume that there are $n$ vaccinators/nurses available 24/7, and on average, each can vaccinate $\mu$ individuals per day. Note: Those who can be protected by vaccines are susceptibles and those in stage 1 of infection, with effective probability of $v_0$ and $v_1$. Those who are vaccinated unsuccessfully enter the freely mixing population. A fraction $h$ of individuals in stage 3 are found febrile, and on average, quarantined for $\alpha^{-1}$ days. A fraction $f$ of those who are vaccinated will die of complications. A fraction $\delta$ of symptomatic cases die of disease. The overall model is described by Ordinary differential equations given in the Appendix A [9].

**Contact Tracing:**

Contact tracing is vital because unlike many infectious diseases, a person who is infected with smallpox can avoid serious disease complications and infectiousness if vaccinated shortly
after infection. CDC’s interim response plan, therefore, does not call for mass vaccination in the event of a smallpox attack, instead, calls for a surveillance-containment strategy which combines the isolation of symptomatic cases accompanied by vaccination of those traced as contacts of index cases. The following table provides the list of parameters, baseline values, and suitable range for sensitivity analysis.

Table 8: Parameters for the model with five stages of infection [4, 9].

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
<th>Baseline values</th>
<th>Suitable range</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\beta$</td>
<td>Contact rate</td>
<td>$10^{-7}$</td>
<td>$[10^{-7}, 2 \times 10^{-7}]$</td>
</tr>
<tr>
<td>$\delta$</td>
<td>Smallpox death rate</td>
<td>0.3</td>
<td>$[0.15, 0.3]$</td>
</tr>
<tr>
<td>$N$</td>
<td>Population size</td>
<td>$10^7$</td>
<td>$10^7$</td>
</tr>
<tr>
<td>$n$</td>
<td>Number of vaccinators</td>
<td>$5 \times 10^3$</td>
<td>$[10^3, 10^4]$</td>
</tr>
<tr>
<td>$v_0$</td>
<td>Vaccine efficacy for susceptible</td>
<td>1.0</td>
<td>$[0.95, 1.0]$</td>
</tr>
<tr>
<td>$v_1$</td>
<td>Vaccine efficacy for exposed</td>
<td>1.0</td>
<td>$[0.3, 1]$</td>
</tr>
<tr>
<td>$c$</td>
<td>Names generated per index</td>
<td>50</td>
<td>$[10, 50]$</td>
</tr>
<tr>
<td>$p$</td>
<td>Fraction of infectees named by index</td>
<td>0.5</td>
<td>$[0.1, 1.0]$</td>
</tr>
<tr>
<td>$f$</td>
<td>Vaccination fatality rate</td>
<td>$10^{-6}$</td>
<td>$10^{-6}$</td>
</tr>
<tr>
<td>$r_1$</td>
<td>Disease stage 1 rate</td>
<td>$(3 \text{ days})^{-1}$</td>
<td>$(3 \text{ days})^{-1}$</td>
</tr>
<tr>
<td>$r_2$</td>
<td>Disease stage 2 rate</td>
<td>$(8 \text{ days})^{-1}$</td>
<td>$(8 \text{ days})^{-1}$</td>
</tr>
<tr>
<td>$r_3$</td>
<td>Disease stage 3 rate</td>
<td>$(3 \text{ days})^{-1}$</td>
<td>$(3 \text{ days})^{-1}$</td>
</tr>
<tr>
<td>$r_4$</td>
<td>Disease stage 4 rate</td>
<td>$(12 \text{ days})^{-1}$</td>
<td>$(12 \text{ days})^{-1}$</td>
</tr>
<tr>
<td>$\mu$</td>
<td>Service rate</td>
<td>$50/\text{day (TV)}, 200/\text{day (MV)}$</td>
<td>$50/\text{day (TV)}, 200/\text{day (MV)}$</td>
</tr>
<tr>
<td>$I_0(-\tau)$</td>
<td>Initial number infected</td>
<td>$10^3$</td>
<td>$10^3$</td>
</tr>
<tr>
<td>$\tau$</td>
<td>Detection Delay</td>
<td>5 days</td>
<td>$[0, 5]$</td>
</tr>
</tbody>
</table>

I have left the derivation for future work, but will use the equations in the Appendix A to simulate and find the approximate solutions. First, let us look at a model without intervention. In absence of any interventions, the model reduces to five equations given below. We assume that initial attack occurs at $t = -\tau$. 

49
\[
\begin{align*}
\frac{dS^0(t)}{dt} &= -\beta I^0_3(t)S^0(t), \\
\frac{dI^0_1(t)}{dt} &= \beta I^0_3(t)S^0(t) - r_1I^0_1(t), \\
\frac{dI^0_2(t)}{dt} &= r_{j-1}I^{0}_{j-1}(t) - r_jI^0_j(t), \text{ for } j = 2, 3 \\
\frac{dI^0_j(t)}{dt} &= r_jI^0_1(t) - r_jI^0_j(t).
\end{align*}
\]

(3.12)

We can use Laplace Transformation to find the solution of (3.12). Assuming that there are no infected individuals in other compartments except at \( I^0_1(t) = I^0_1(-\tau) \), and taking the Laplace Transformations of equations given in (3.12), we get

\[
\begin{aligned}
(s + r_1)I_1^0(s) - r_3R_3I_3^0(s) &= I^0_1(-\tau), \\
(s + r_2)I_2^0(s) - r_2I_2^0(s) &= 0, \\
(s + r_2)I_3^0(s) - r_2I_2^0(s) &= 0, \\
(s + r_3)I_3^0(s) - r_3I_3^0(s) &= 0.
\end{aligned}
\]

(3.13)

Note: Majority of infected individuals at stage 3 are those exposed in the initial attack, and at \( t = 0 \), the size is almost negligible. Thus, taking first part of (3.13) and letting \( r_2R_2I_3^0(s) = 0 \), and substituting \( A \) for \( I^0_1(-\tau) \), we get

\[
I^0_1(s) = \frac{-r_2A}{(s + r_1)(s + r_2)(s + r_3)} = \frac{c_1}{s + r_1} + \frac{c_2}{s + r_2} + \frac{c_3}{s + r_3}
\]

where \( c_1, c_2, \) and \( c_3 \) are arbitrary constants to be found. Using partial fraction expansion, we get
\[ c_1 = \left( s + r_1 \right) \frac{-r_2 A}{(s + r_1)(s + r_2)(s + r_3)} \bigg|_{s = -r_1} = \frac{-r_2 A}{(r_1 - r_2)(r_1 - r_3)} \]

\[ c_2 = \left( s + r_2 \right) \frac{-r_2 A}{(s + r_1)(s + r_2)(s + r_3)} \bigg|_{s = -r_2} = \frac{r_2 A}{(r_1 - r_2)(r_2 - r_3)} \]

\[ c_3 = \left( s + r_3 \right) \frac{-r_2 A}{(s + r_1)(s + r_2)(s + r_3)} \bigg|_{s = -r_3} = \frac{-r_2 A}{(r_1 - r_3)(r_2 - r_3)} \]

Therefore,

\[ I_3^0(s) = \frac{-r_2 A}{(s + r_1)(r_1 - r_3)(r_1 - r_2)} + \frac{r_2 A}{(s + r_2)(r_2 - r_3)(r_2 - r_1)} - \frac{r_2 A}{(s + r_3)(r_3 - r_2)(r_3 - r_1)} \]

Taking inverse Laplace transform, we get

\[ (r_1 - r_3)(r_2 - r_1)(r_1 - r_2)I_3^0(t) = -r_2 A\left[ (r_2 - r_1)e^{-rt} - (r_1 - r_3)e^{-\tau r} + (r_1 - r_2)e^{-\tau r} \right], \]

so

\[ I_3^0(t) = \frac{-r_2 A\left[ (r_2 - r_1)e^{-\tau r} + (r_1 - r_3)e^{-\tau r} + (r_1 - r_2)e^{-\tau r} \right]}{(r_1 - r_2)(r_2 - r_1)(r_1 - r_3)} \]

For \( t = [-\tau, 0] \), using \( I_3^0(t) \approx g(t + \tau) \), we get

\[ I_3^0(0) = \frac{-r_2 A e^{(\eta_1 + \eta_2)\tau}}{(r_1 - r_2)(r_2 - r_3)(r_1 - r_3)} \left[ (r_2 - r_1)e^{(\eta_1 + \eta_3)\tau} + (r_1 - r_3)e^{(\eta_1 + \eta_3)\tau} + (r_1 - r_2)e^{(\eta_1 + \eta_3)\tau} \right] \]

\[ I_3^0(-\tau) \]

which gives us growth rate of \( g = \frac{I_3^0(0)}{\tau} \).

Substituting \( g(t + \tau) \) for \( I_3^0(t) \) in second, third, fourth equation of (3.12), and solving them, we get
\[ I_1^0(t) = \frac{e^{-\eta(t+\tau)} \left[ r_1^2 I_1^0(-\tau) + R_0 r_3 g \right] + \left[ r_1(t + \tau) - 1 \right] R_0 r_3 g}{r_1^2}, \]  
(3.15)

\[ I_2^0(t) = \frac{1}{r_1(r_1 - r_2) r_3^2} \left\{ e^{-(\eta + 2\eta X(t)) r_2} \left[ r_1^2 I_1^0(-\tau) + R_0 r_3 g \right] + e^{(\eta + \eta X(t)) r_1} \left[ r_2^2 I_2^0(-\tau) + R_0 r_3 g \right] \\
+ e^{(\eta + 2\eta X(t)) r_2} R_0 (r_1 - r_2) r_3 g \left[ -r_2 + r(t, r_2(t + \tau) - 1) \right] \right\}, \]
(3.16)

\[ I_4^0(t) = \frac{r_4 g (t + \tau)^2}{2}. \]  
(3.17)

Equation (3.14), (3.15), (3.16), and (3.17) are the solutions of the model without any interventions. According to these solutions, the number of people in each of the stages of infection gradually rises to a maximum and then decreases to zero at \( t \) tend to infinity.

The following simulink diagram was used to simulate and find the solution curves shown in Fig. 16, using parameter values listed on Table 8.
Figure 15: The simulink diagram for the model without intervention.

Figure 16: Solutions of the model without intervention using parameter values listed in Table 8.

Fig.16 shows that without intervention, the whole population becomes infected with peak at around 100 days.
**Interventions:**

The question is not whether a disease is going to be endemic or not but under what circumstances can we eradicate the infection with minimum loss of lives and economic activities. For smallpox there is no cure, so the only way to prevent an individual from acquiring the infection is by putting the person into isolation until the disease die out or by vaccinating the individual when s/he is still susceptible.

**Mass Vaccination:**

a) **Perfect vaccination** \( v_0 = v_i = 1 \)

Once the first infection is confirmed, under this measure, nearly everyone threatened by the outbreak will be vaccinated. Except for the last few hours, let us assume that the total number of people waiting in a line to be vaccinated is more than the number of vaccinators. Since there are \( n \) vaccinators and can vaccinate \( \mu \) people per day, vaccination will be completed in \( T = N/n\mu \) days. This implies that in any given day, total number of people waiting in queue is given by \( Q_t = Q(0) - n\mu t \) for \( t \in [0,T] \). So, for \( t \in [0,T] \), the infection term \( \beta I_j(t)S^0(t) \) can be approximated by \( r_3R_0(1 - t/T)I_j(t) \). Note: All the people in \( I_j(t) \) compartments automatically move to \( Q_j(t) \), and we assume that vaccinations per given time follow a uniform distribution between 0 and \( T \).

To approximate the number of people who are going to die under this measure, we have to carefully track the number of people that enter stage 2 of infection. Since it takes some number of days to realize, and decide on the use of a particular intervention, by then, there will be \( \sum_{j=2}^{4} I_j(t) \) number of people in or beyond stage 2 of the infection. Besides, people who are in
stage 1 of infection move to stage 2 if not vaccinated during first three days. According to the model, people in stage 1 progress to stage 2 of infection at a time, that is exponentially distributed with $r_i$ [9]. Although everyone will be vaccinated between 0 to $T$, not everyone will survive. Since the smallpox death rate is $\delta$, of those $I_i^0(0)$ people,

$$\Delta I_i^0(0) \int_0^T \left(1 - e^{-\gamma t}\right) \frac{1}{T} dt$$

will die. Integrating the equation, we get

$$\frac{\Delta I_i^0(0)}{T} \left( T + e^{-\gamma T} - 1 \right).$$

To calculate the number of deaths of susceptibles, the model uses two approximations:

(1) $\beta I_i(t) S_i(t)$ by $r_i R_i(1 - t/T) I_i(t)$, and (2) $I_i(t)$ by linear growth term $g = \frac{I_i(0)}{\tau}$.

Note: Most of the people who die are infected before MV is started. On the other hand, the susceptibles who die during the epidemic, are infected during $t \in [0,T]$, and evolve to stage 2 of infection after spending exponential distributed length of time in stage 1. Although most of the people are vaccinated at a time uniformly distributed between $t$ and $T$, it cannot prevent all the deaths. Hence, the total number of susceptibles at time 0 who die during epidemics is given by

$$\Delta \int_0^T \int_r^T r_i R_i \left[ I_i^0(0) + gt \right] \left(1 - e^{-\gamma[T-t]}\right) \frac{1}{T} \, du \, dt.$$  

Integrating the equation, we get

$$\Delta \int_0^T \int_r^T r_i R_i \left[ I_i^0(0) + gt \right] \left(1 - e^{-\gamma[T-t]}\right) + r_i(-t + T) \frac{1}{r_i T} \, dt$$

$$= \frac{\Delta r_i R_i e^{-\gamma t}}{2T^2} \left[ 2 - e^{-\gamma} (2 + r_i T (-2 + r_i T)) \right]$$

$$= \frac{\Delta r_i R_i e^{-\gamma t}}{6T r_i} e^{-\gamma T} \left[ 6 + e^{\gamma T} (r_i T^3 - 3r_i^2 T^2 + 6r_i T - 6) \right] + 3r_i I_i(0) \left[ e^{\gamma T} (2 - 2r_i T + r_i^2 T^2) - 2 \right]$$  

(3.18)
Note: $fN$ is total number of deaths due to vaccination where $f$ is the fatality rate for the smallpox vaccine.

Finally, the total number of deaths under MV is given by

$$D(\text{final}) = fN + \delta \sum_{j=2}^{4} I_j^0(0) + \frac{\delta I_3^0(0)}{T} \left( T + \frac{e^{-\alpha T} - 1}{r} \right) +$$

$$\delta \frac{r_i R_0}{6 T r_i^3} e^{-\alpha T} \left[ g \left( 6 + e^{\alpha T} (r_i^3 T^3 - 3r_i^2 T^2 + 6r_i T - 6) \right) + 3r_i J_3(0) \left[ e^{\alpha T} \left( 2 - 2r T + r_i^2 T^2 \right) - 2 \right] \right]$$

(3.19)

$$= 585 \text{ (for parameter values given in Table 8)}$$

According to equation (3.19), the total number deaths under MV depend mostly on $I_3^0(0)$ the initial size of attack, and very little on the size of the population. The total deaths also scale with basic reproduction number $R_0$, and the vaccination capacity $n\mu = N/T$. The following graphs show the simulation result for Mass Vaccination using parameters given in Table 8.

(a) 

(b)
Figure 17: The number of deaths under MV versus (a) time, and for Ro = 3, (b) time, and for Ro = 6, (c) the reproductive number, (d) the number of vaccinators, (e) the vaccine efficacy at stage 1, (f) the number initially infected, and (g) time delays for Ro = 3, and Ro = 6.
Fig. 17(a) and (b) show that for $Ro = 3$ and 6, the total number of deaths are 580 and 810 respectively. Fig.17(c)-(f) show the number of deaths, as a function of, the reproductive number, the number of vaccinators, the vaccine efficacy at stage 1, and the initial size of attack respectively. Fig. 17(g) shows the number of deaths as a function of time delay. Clearly, the total number of deaths scale with the reproductive number, the number of people initially infected, and time delays. According to simulation result, higher reproductive number corresponds to higher deaths. Bigger initial size of attack also translates to higher casualties. As for time delays, it is quite clear from Fig. 17(g) that sooner the response less the number of casualties and vice versa. Fig. 17(d) shows that increasing the number of vaccinators decreases the number of deaths, but only up to certain point. From the figure, it is clear that increasing the number of vaccinators beyond 5500 have very little effect on the size of epidemic. Role of vaccine efficacy in stage 1 of infection is quite clear as well. Fig. 17(e) confirms that low vaccine efficacy in stage 1 of infection corresponds to more deaths. There is a difference of 40 deaths for vaccine efficacy of 0.8 and 1.

b) Imperfect Vaccination

For the simulation, we used $v_u = 0.95$ and $v_i = 0.9$.
Fig. 18(a) shows that at the end of 100 days, total number of deaths under imperfect vaccination, (with $\nu_0 = 0.95$ and $\nu_1 = 0.9$) exceeds 900, almost 320 more than under perfect vaccination. The number of people in the queue sharply drops down to zero within 10 days.

Table 9: Lists of cumulative deaths for 49 combinations of vaccine efficacies. Columns correspond to $\nu_1$ and the rows correspond to $\nu_0$.

<table>
<thead>
<tr>
<th>$\nu_0$</th>
<th>1.0</th>
<th>0.95</th>
<th>0.9</th>
<th>0.85</th>
<th>0.8</th>
<th>0.75</th>
<th>0.7</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0</td>
<td>580</td>
<td>590</td>
<td>599</td>
<td>609</td>
<td>619</td>
<td>628</td>
<td>638</td>
</tr>
<tr>
<td>0.95</td>
<td>654</td>
<td>665</td>
<td>677</td>
<td>688</td>
<td>699</td>
<td>711</td>
<td>722</td>
</tr>
<tr>
<td>0.9</td>
<td>759</td>
<td>773</td>
<td>786</td>
<td>800</td>
<td>814</td>
<td>828</td>
<td>842</td>
</tr>
<tr>
<td>0.85</td>
<td>922</td>
<td>939</td>
<td>957</td>
<td>974</td>
<td>992</td>
<td>1009</td>
<td>1027</td>
</tr>
<tr>
<td>0.8</td>
<td>1205</td>
<td>1229</td>
<td>1253</td>
<td>1277</td>
<td>1301</td>
<td>1326</td>
<td>1350</td>
</tr>
<tr>
<td>0.75</td>
<td>1809</td>
<td>1845</td>
<td>1884</td>
<td>1922</td>
<td>1960</td>
<td>1999</td>
<td>2038</td>
</tr>
<tr>
<td>0.7</td>
<td>3551</td>
<td>3627</td>
<td>3704</td>
<td>3782</td>
<td>3859</td>
<td>3938</td>
<td>4016</td>
</tr>
</tbody>
</table>

According to Table 9, higher vaccine efficacy corresponds to lower deaths and vice versa.
Trace Vaccination:

We used a simulink model to find the numerical solutions to the set of equations given in the Appendix A. The results are given below.

(a) $R_0 = 3$

(b) $R_0 = 3$

(c) $R_0 = 4.5$

(d) $R_0 = 4.5$

Figure 19: (a) and (c) correspond to the number of people recovered versus time, and (b) and (d) correspond to the number of deaths versus time for $R_0 = 3$ and $R_0 = 4.5$ respectively.
Fig. 19(b) shows that the total number of deaths under TV for $R_0 = 3$ is approximately 140000.

Fig. 19 (d) shows that the total number of deaths under TV for $R_0 = 4.5$ is approximately 260000. The total number of deaths under TV is much higher than compared to MV.

**Quarantine:**

Quarantine is one of the intervention policies considered for simulation. Quarantine of symptomatic cases helps to control the initial phase of an epidemic. Quarantine can lessen the amount of time during which an infectious person can mix in the population, and thus inhibit transmission of the disease. But quarantine alone is not guaranteed to prevent an epidemic, since some infected people will enter and leave quarantine before becoming infectious, and keep transmitting the infection freely. Overall, quarantine reduces the mean time spent on stage 1, stage 2, and stage 3 of infections. For the simulation, we use

\[
\begin{align*}
  r_{new1} &= \prod_{k=1}^{3} \frac{r_k}{r_k + \alpha}, \\
  r_{new2} &= \prod_{k=2}^{3} \frac{r_k}{r_k + \alpha}, \\
  r_{new3} &= \frac{r_3}{r_3 + \alpha},
\end{align*}
\]

where $\alpha^{-1}$ is the average number of days an infected individual is quarantined.
Table 10: Number of days quarantined vs. total deaths.

<table>
<thead>
<tr>
<th>Value of $\alpha$</th>
<th>1</th>
<th>1/2</th>
<th>1/3</th>
<th>1/4</th>
<th>1/5</th>
<th>1/6</th>
<th>1/7</th>
<th>1/8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of deaths</td>
<td>131600</td>
<td>102430</td>
<td>79922</td>
<td>65640</td>
<td>55794</td>
<td>48585</td>
<td>43087</td>
<td>38766</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Value of $\alpha$</th>
<th>1/9</th>
<th>1/10</th>
<th>1/11</th>
<th>1/12</th>
<th>1/13</th>
<th>1/14</th>
<th>1/15</th>
<th>1/16</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of deaths</td>
<td>35285</td>
<td>32426</td>
<td>30040</td>
<td>28021</td>
<td>26294</td>
<td>24800</td>
<td>23498</td>
<td>22353</td>
</tr>
</tbody>
</table>

Sensitivity analysis:

Table 11: Total number of deaths under 49 combinations of vaccinators count, and the service rate. Rows denote number of vaccinators $n$, and columns represent service rate $\mu$.

<table>
<thead>
<tr>
<th></th>
<th>1000</th>
<th>3000</th>
<th>5000</th>
<th>8000</th>
<th>10000</th>
<th>15000</th>
<th>20000</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>2477700</td>
<td>1825600</td>
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Under TV, Table 11 shows that increasing $n$ and $\mu$ beyond 3000 and 70 respectively, does not reduce the total number of deaths. This is because the maximum length of queue is less than the product of $n$ and $\mu$. Fig. 20 confirms this. The difference between product $n \mu$, and the peak values are 85900, 5200, 900, and 1140 for of (a), (b), (c), and (d) respectively. From the trend, we can see that the difference is minimum for the value of $\mu$ equal to 70, and $n$ in the range of 2908 and 2912.
Figure 20: The queue length as a function of time for (a) $n = 3000$ and $\mu = 70$, (b) $n = 3000$ and $\mu = 68$, (c) $n = 2910$ and $\mu = 70$, (d) $n = 2905$ and $\mu = 70$. 
Figure 21: Sensitivity analysis for uncertain model parameters under TV using baseline parameters. The total number of deaths versus (a) Number of contacts per index c, (b) the smallpox death rate $\delta$, (c) Reproductive number $R_0$, (d) Vaccine efficacy, stage 1, (e) the total number of vaccinators $n$, (f) the tracing/ vaccination rate $\mu$, (g) the initial attack size $I_1(\tau)$.

Fig. 21 shows simulated results for number of deaths versus seven key parameters. Fig. 21(a) shows that the number of deaths is roughly inversely proportional to the number of contacts generated per index. Fig. 21(b) shows that the number of deaths is roughly proportional to smallpox death rate. Fig. 21(c) shows two kinks: first one seems to be at around $R_0 = 1$, and the second one seems to be around $R_0 = 4$. Fig. 21(d) shows that the total number of deaths decreases linearly as vaccine efficacy for stage 1 increases. Fig. 21(e) and (f) show that the total number of deaths, are proportional to the inverses of the number of vaccinators and the tracing/vaccination rate. Fig. 21(g) shows that total number of deaths is proportional to initial size of attack.
CHAPTER FOUR

4.1 Discussion

The first case study incorporates 2 neighborhoods each with 2 sub-groups, and the second case study includes 5 stages of infection, however, the fundamental assumption that population mixes more or less homogeneously is unrealistic. Individuals tend to make contact with family members, workplace colleagues and friends at much higher rate than random strangers, and such regular contacts also tends to be in the same neighborhood areas. Hence to get better result, one needs to include socio-spatial structure. More realistic model would have to capture age/social structure, network structure, patch structure and some stochastic effects [7]. The only problem with any such inclusion is that there will be many more parameters, hence is much difficult to formulate equations, and the computation is more much intensive and time consuming. Therefore, stochastic models might capture the random nature of disease transmission, but deterministic models are rapid to simulate, relatively easy to parameterize and captures average behavior.

4.2 Strategies available prevent worst-case scenarios:

In case of a smallpox outbreak, major control strategies that are available to Center for Disease Control (CDC) to implement, are- quarantine/isolation, movement restrictions, trace vaccination, targeted Vaccination, mass vaccination and pre-attack/prophylactic vaccination.
Quarantine/isolation of confirmed index cases can be highly effective in reducing secondary transmission as shown in Table 10, as long as most of index cases and their contacts are rapidly detected. Movement restriction (not explored in our models), can be effective if the host patch is recognized on time. Host patch can be airport, subway stations, schools or some specific neighborhood. On the other hand, TV (trace the contacts and vaccinate when found), coupled with isolation could be highly effective for a small scale attack but not so effective, for big scale outbreak as shown in case study two. For TV to effective, contacts need to be detected in the vaccine sensitive stages of incubation period. On the contrary, targeted vaccination (not explored in our models) does not depend on contact tracing. It requires vaccinating whole population in affected neighborhood or city, and thus increasing herd immunity quickly. A draw back with this intervention policy is that the disease might spread beyond targeted area. Mass vaccination, which we have simulated, is highly effective in stopping the epidemic, if CDC can carry out large scale vaccination program rapidly without creating any chaos. The risk involved is that in case of small isolated outbreak, it might cause more deaths than other methods. The last option, pre-attack vaccination is essential in protecting the health officials who are going to be involved in emergency response.
CHAPTER FIVE: CONCLUSION

An ideal model should have to explicitly incorporate the underlying mechanisms of the control strategies. In addition, the model should have to incorporate realistic logistical constraints [7], and economic costs. For example, the trace vaccination is constrained to the speed of the epidemic, whereas mass vaccination can proceed as quickly as logistics allows. The net result of this would be that it would produce realistic $R_0$. But one has to keep in mind that estimating effect on $R_0$ with all other details is practically impossible for complex models that include population heterogeneity and realistic other parameters. The need to increase accuracy and sophistication makes it difficult to validate models. I think the key is to balance between model complexity and validation. And validation, ideally, should be independent of any epidemiological data used to estimate parameters. Historical data doesn’t capture the status of human populations with respect to immunity, mobility and patterns of social interaction; therefore, extrapolating from historical data to present day population is quite often very inaccurate. While recognizing the limitation of modeling for precise prediction, models still represent the potentially powerful resource in the face of an actual epidemic. The 2001 foot-and-mouth disease epidemic in Britain clearly demonstrates the effectiveness of real time statistical analysis and modeling in predicting the future course of the outbreak and identifying the measures needed for control. For small pox such a role is even more critical in containing the outbreak and thus minimizing the fatalities.
APPENDIX: EQUATIONS FOR THE CASE STUDY 2
Here we consider the equations that govern the model presented by Kaplan, Craft, and Wein. [9]

**Contact tracing**

\[
\frac{dS^0(t)}{dt} = -\beta I_3(t)S^0(t) - \frac{\left\{c - pR_0(t)\right\} S^0(t)}{N} r_3 I_3(t) \quad (A.1)
\]

\[
\frac{dI_0^0(t)}{dt} = \beta I_3(t)S^0(t) - \frac{\left\{c - pR_0(t)\right\} I_0^0(t)}{N} + \frac{p\lambda_1(t)}{N} r_3 I_3(t) - r_3 I_3^0(t) \quad (A.2)
\]

\[
\frac{dI_j^0(t)}{dt} = r_{j-1} I_{j-1}(t) - \frac{\left\{c - pR_0(t)\right\} I_j^0(t)}{N} + \frac{p\lambda_j(t)}{N} r_3 I_3(t) - r_j I_j^0(t) \quad \text{for } j = 2, 3 \quad (A.3)
\]

\[
\frac{dI_j^0(t)}{dt} = r_j I_j^0(t) - r_j I_j^0(t) \quad (A.4)
\]

where

\[
R_0(t) \approx \beta \left[\frac{S^0(t) + Q_0(t) + S^1(t)}{r_3}\right] \quad (A.5)
\]

\[
I_3(t) = I_3^0(t) + Q_3(t) + I_3^1(t) \quad (A.6)
\]

\[
k_0(t) = \frac{\left\{c - pR_0(t)\right\} r_3 I_3(t)}{N} \quad (A.8)
\]

\[
\lambda_j(t) \approx \prod_{i=1}^{j} \frac{r_i}{r_i + r_3 + k(t)} \frac{\beta S^0(t)}{r_j + r_3 + k(t)} \quad (A.9)
\]

**Queuing**

\[
Q(t) = \sum_{j=0}^{3} Q_j(t) \quad (A.10)
\]

\[
\frac{dQ_0(t)}{dt} = \left\{c - pR_0(t)\right\} \frac{S^0(t)}{N} r_3 I_3(t) - \beta I_3(t)Q_0(t) - \mu Q_0(t) \min\left(1, \frac{n}{Q(t)}\right) \quad (A.11)
\]
\[
\frac{dQ_i(t)}{dt} = \beta I_i(t)Q_i(t) + \left\{c - pR_i(t)\right\}\frac{I_i^0(t)}{N} + p\lambda_i(t) r_i I_i(t) - \mu Q_i(t) \min\left(1, \frac{n}{Q(t)}\right) - r_i Q_i(t) \tag{A.12}
\]

\[
\frac{dQ_j^0(t)}{dt} = r_j Q_j(t) - \left\{c - pR_j(t)\right\}\frac{I_j^0(t)}{N} + p\lambda_j(t) r_j I_j(t) - \mu Q_j(t) \min\left(1, \frac{n}{Q(t)}\right) - r_j Q_j^0(t) \text{ for } j = 2, 3 \tag{A.13}
\]

**Vaccination and death**

\[
\frac{dS^i(t)}{dt} = (1 - f)(1 - v_i)\mu Q_i(t) \min\left(1, \frac{n}{Q(t)}\right) - \beta S^i(t)I_i(t) \tag{A.14}
\]

\[
\frac{dI^i_j(t)}{dt} = \beta S^i(t)I_i(t) + (1 - f)(1 - v_i)\mu Q_i(t) \min\left(1, \frac{n}{Q(t)}\right) - r_j I^i_j(t) \tag{A.15}
\]

\[
\frac{dI^i_j(t)}{dt} = r_{j-1} I^i_{j-1}(1 - f)\mu Q_j(t) \min\left(1, \frac{n}{Q(t)}\right) - r_j I^i_j(t) \text{ for } j = 2, 3 \tag{A.16}
\]

\[
\frac{dI^i_j(t)}{dt} = r_j(I^i_j(t) + Q_i(t)) - r_i I^i_j(t) \tag{A.17}
\]

\[
\frac{dZ(t)}{dt} = (1 - f)(v_i Q_i(t) + v_j Q_j(t))\mu \min\left(1, \frac{n}{Q(t)}\right) + (1 - \delta)r_i(I^i_i(t) + I^i_i(t)) \tag{A.18}
\]

\[
\frac{dD(t)}{dt} = f\mu Q(t) \min\left(1, \frac{n}{Q(t)}\right) + \delta r_i(I^i_i(t) + I^i_i(t)) \tag{A.19}
\]
LIST OF REFERENCES


