The Role of Vaccination in the Control of SARS

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Abstract

In this paper we explore pre-outbreak and during-outbreak vaccination as control strategies for SARS epidemics. We construct a mathematical model that includes susceptible, latent (traced and untraced), infectious, quarantined/isolated, recovered, and dead classes. Using data from the 2002-2003 SARS outbreak in Hong Kong (China), we assume different scenarios where the percentage of traced infectious contacts and untraced individuals that self-quarantine varies. We predict the minimal necessary proportion of the population that needs to be successfully vaccinated prior to an outbreak to control an epidemic.

We calculate the basic reproductive number, R_0, and carry out an uncertainty and sensitivity analysis. The final epidemic size under different vaccination scenarios is estimated. Vaccination is shown to be a good control strategy to reduce the total epidemic size with an increased impact when combined with effective isolation of the quarantined/isolated individuals.

1 Introduction

Severe acute respiratory syndrome (SARS) is a viral respiratory illness caused by SARS coronavirus (SARS-CoV). In November 2002, the first cases emerged in the Southern China Province of Guangdong [13]. The 2003 epidemic was ultimately driven by international travel and the lack of preparatory actions for a disease outbreak. This was especially true for the outbreak in China. However, the outbreak in Toronto, Canada, was contained due to the early implementation of control measures, such as early diagnosis and isolation effectiveness. According to the World Health Organization, as of August 2003, there were total $8,422$ cases with 916 deaths, with China being the most affected country [13]. The

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disease induced mortality is age-dependent, with less than 1% death rate for people 24 years or younger, 6% for people between 25 and 44, 15% for people between 45 and 64, and greater than 50% for people older than 65 years [3].

SARS symptoms include high fever, headaches, body aches, mild respiratory symptoms at the outset, diarrhea, and usually a development of a dry cough within seven days [10]. In most cases SARS patients develop pneumonia [10]. SARS is transmitted by close person-to-person contact [10]. According to data from the Hong Kong epidemic, the mean latency period for SARS (the period that a person is infected but not infectious) is approximately 6.4 days [5]. Suspected cases are hospitalized at rate $1/4.85$ days^{-1} and recovered individuals leave hospitals in an average of 23.5 days after diagnosis, while infected individuals die after a mean of 35.9 days after diagnosis [5].

Since the SARS virus was isolated in March 2003, hospital workers were able to effectively diagnose SARS [12], and many health organizations, medical companies and universities began the search for a SARS vaccine. Most preliminary vaccine research has been done on animals. The National Institute of Allergy and Infectious Diseases (NIAID) has conducted testing on mice. In this study, the mice developed antibodies after the first dosage of SARS and then became immune to the second dosage [1], [18]. Experiments on African green monkeys (*Cercopithecus Aethiops*) have also been conducted [4]. A protein called SARS spike (SARS-S) has been identified as the only protein compound which aids in the process of attaching to cells of the human respiratory tract and infecting the cells as well [9]. Researchers from the NIAID modified a vaccine for a known respiratory disease virus similar to SARS, HPIV3, by inserting the SARS-S protein. This intranasal vaccine was given to four test monkeys, while another four monkeys received the modified HPIV3 without the SARS-S protein [4], [9]. The four immunized test monkeys did not shed the virus when they were exposed to it 28 days after receiving the vaccine. However, the other four monkeys developed SARS after exposure [11], [4]. The drawback of this vaccine is that it would not be effective for adults, that is, most adults would have immunity to the generalized vector of HPIV3 from childhood illness [11]. Due to this existing immunity, adult immune systems would not produce antibodies against the SARS-S protein in the HPIV3 vector [11] and hence not be immune to the SARS *coronavirus*.

Besides research on animals, Sinovac Biotech, a Chinese company, is in the process of testing a SARS vaccine made of dead samples of the SARS-CoV on humans. They gave the high-dosage (32 su/ml antigen) SARS vaccine to the "first 6 people of the second group of 18 volunteers, and after a 72-hour observation period, no adverse side-effects were observed" [14]. The first group of 18 people who received the low-dosage (16 su/ml antigen) SARS vaccine were in good health condition [14]. Other companies and universities in the world are not planning human testing of a SARS vaccine until the end of 2004 or late 2005 [15].

In the advancement of the development of a SARS vaccine, no research has been done to address how the vaccine should be used to control an outbreak. In this paper we explore the impact of several vaccination strategies in different situations in which a SARS outbreak may occur. The effect of pre-outbreak vaccination, where the susceptible population is reduced by a fraction of successfully vaccinated individuals before they enter into the system

is implemented. We also investigate the impact of during-outbreak vaccination, as well as pre-outbreak vaccination combined with during-outbreak vaccination. The impact of quarantine and isolation effectiveness with respect to these vaccination policies is analyzed. We envisage the proportion of the population that needs to be successfully vaccinated before an outbreak to control a SARS epidemic. When considering during-outbreak vaccination, we explore the total epidemic size when vaccination is introduced at different times after the start of the outbreak. Comparing different scenarios, we build a body of evidence that may help determine what strategy of vaccination would be best to implement before or during an outbreak. Effectiveness is naturally correlated with the capabilities of the area to trace infected people and to implement a solid quarantine/isolation policy.

In section 2 we describe the pre-outbreak vaccination model, compute the basic reproductive number, R_0, and and introduce the during-outbreak model. In section 3 we explore several different numerical scenarios with pre-outbreak and during-outbreak vaccination, under different quarantine/isolation effectiveness. In section 4 we perform uncertainty and sensitivity analysis on R_0. Finally, in section 5 we present our conclusions and in section 6 we suggest possible directions of future work.

2 Methods

We present a model for a single SARS outbreak that considers the impact on survival of the population, disregarding all demographic processes such as natural births and deaths. Our approach is based on previous work on SARS [8], and a model for the spread of smallpox that includes a vaccination framework by Gani and Leach [16]. By implementing two different vaccination strategies (pre-outbreak and during-outbreak vaccination), we estimate R_0 and predict the total epidemic size for various outbreak scenarios.

2.1 Pre-Outbreak vaccination

We consider pre-outbreak vaccination as a control strategy in which a proportion of the total population is vaccinated prior to an outbreak. Therefore, a key question is: "What is the critical effective vaccination coverage to prevent an epidemic?"

Figure 1: Pre-vaccination model: Susceptibles in the population are reduced by successfully vaccinating a proportion σ of the initial population before the outbreak. E_n are the untraced latent (infected, not infectious) individuals and E_i are the traced latent individuals. The class I denotes the infectious, untraced individuals, while the class W denotes the diagnosed, infectious individuals placed into quarantine/ioslation who were given supportive treatment. D and R denote the dead and recovered classes, respectively. For parameter descriptions see Table 1.

Figure 1 describes the pre-outbreak vaccination model. Starting with a population of N_0 individuals, we implement pre-outbreak vaccination, reducing the susceptible population to $(1-\sigma)N_0$ when the outbreak starts, since σN_0 is removed by vaccinating before the outbreak. The starting susceptible population consists of susceptible individuals that were

either not vaccinated, or susceptible individuals vaccinated before the outbreak, for which vaccine did not work. Hence, we can assume vaccine efficacy is not 100% effective.

We use the approach from Gani's model [16] to divide the latent [1] class into two classes and model the contacts of an infected person, as untraced latent (E_n) and traced latent individuals (E_i). The latency period for SARS is approximately 6.37 days [7]. It is assumed that once a contact of an infected individual has been traced, he/she is immediately quarantined/isolated once they become infectious. However, the untraced latent individuals can either self-quarantine with rate θk or can progress into the infectious class, I, at a rate $(1-\theta)k$, where I denotes the symptomatic, infectious, and undiagnosed individuals [8]. Infectious individuals move into the class W, quarantine and isolation, at rate α, die at rate δ, or recover at rate γ_1. Once in quarantine, individuals either die at the same rate δ or recover at rate γ_2. Individuals in quarantine/isolation are assumed to be treated with care, and thus, they recover faster than undiagnosed individuals ($\gamma_2 < \gamma_1$) from [7].

Table 1: Parameter definition and baseline values for the model parameters.

Parameter	Definition	Baseline Value	Ref
β	Transmission rate per day	0.25	[7]
$1/k$	Mean incubation period (days)	6.37	[7]
$1/\gamma_1$	Mean infectious period (days)	28.4	[7]
$1/\gamma_2$	Mean infectious period for diagnosed individuals (days)	23.5	[7]
$1/\alpha$	Mean period before diagnosis (days)	4.85	[7]
δ	Disease induced death rate per day	0.0279	[7]
σ	Proportion of susceptibles successfully vaccinated	$[0,1]$	
ρ	Proportion of latent population traced	$[0,1]$	
θ	Proportion of untraced latent that self-quarantine	$[0,1]$	
l	Effectiveness of quarantine/isolation	$[0,1]$	[7]

We assume that quarantined/isolated individuals are less likely to interact with susceptibles and therefore contribute less to the infection. This is modeled by introducing l, which determines the effectiveness of the quarantine/isolation. If l is small, fewer quarantined people will transmit SARS to susceptibles [8]. Table 1 describes the parameter values of the model. Our model is given by the system of Nonlinear Differential Equations (1)-(7):

[1] Latent implies that an individual is infected but cannot transmit the disease to others

$$
\begin{aligned}
\dot{S} &= -\beta(1-\rho)\frac{(I+lW)}{N}S - \beta\rho\frac{(I+lW)}{N}S, && (1)\\
\dot{E}_n &= -k\theta E_n - k(1-\theta)E_n + \beta(1-\rho)\frac{(I+lW)}{N}S, && (2)\\
\dot{E}_i &= -kE_i + \beta\rho\frac{(I+lW)}{N}S, && (3)\\
\dot{W} &= k\theta E_n + kE_i + \alpha I - (\delta+\gamma_2)W, && (4)\\
\dot{I} &= k(1-\theta)E_n - (\alpha+\delta+\gamma_1)I, && (5)\\
\dot{R} &= \gamma_1 I + \gamma_2 W, && (6)\\
\dot{D} &= \delta I + \delta W. && (7)
\end{aligned}
$$

2.2 The Basic Reproductive Number

The basic reproductive number, R_0, represents the expected number of secondary cases produced by a "typical" infectious individual at the beginning of the epidemic in a completely susceptible population at a demographic steady state. To compute the basic reproductive number for this model, we used the next generation operator method from [17], where $\mathcal{F}$ is the vector of rates of the appearance of new infections in each compartment; $\mathcal{V} = \mathcal{V}^+ + \mathcal{V}^-$, where $\mathcal{V}^-$ is a vector of rates of transfer of individuals out of the particular compartment; and, $\mathcal{V}^+$ is the vector of rates of transfer of individuals into the particular compartment by all other means. Then,

$$
\mathcal{F} = \begin{pmatrix} \beta(1-\rho)\frac{(I+lW)}{N}S \\ \beta\rho\frac{(I+lW)}{N}S \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix}, \mathcal{V} = \begin{pmatrix} kE_n \\ kE_i \\ -k\theta E_n - kE_i - \alpha I + (\delta+\gamma_1)W \\ -k(1-\theta)E_n + (\alpha+\delta+\gamma_1)I \\ 0 \\ 0 \\ 0 \end{pmatrix}.
$$

The infected classes are E_i, E_n, I, and W; thus the dimension of the matrices F and V (the partial derivatives of $\mathcal{F}$ and $\mathcal{V}$ with respect to the infected classes) are 4 x 4 square matrices. The infection-free state implies that, $E_n = E_i = I = W = 0$. Then,

$$
F = \begin{pmatrix} 0 & 0 & \beta(1-\rho)l(1-\sigma) & \beta(1-\rho)(1-\sigma) \\ 0 & 0 & \beta\rho l(1-\sigma) & \beta\rho(1-\sigma) \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix}
$$

and

$$V = \begin{pmatrix} k & 0 & 0 & 0 \\ 0 & k & 0 & 0 \\ -k\theta & -k & (\delta+\gamma_2) & -\alpha \\ -k(1-\theta) & 0 & 0 & (\alpha+\delta+\gamma_1) \end{pmatrix}.$$

Once we compute FV^{-1}, then the basic reproductive number is the spectral radius of FV^{-1}, i.e. $\rho(FV^{-1})$. We obtain

$$R_0 = \beta(1-\sigma)\left(\frac{(1-\rho)l\theta}{\delta+\gamma_2} + \frac{(1-\rho)l(1-\theta)\alpha}{(\delta+\gamma_2)(\alpha+\delta+\gamma_1)} + \frac{(1-\rho)(1-\theta)}{\alpha+\delta+\gamma_1} + \frac{\rho l}{\delta+\gamma_2}\right).$$

This dimensionless quantity may be interpreted as follows: $\beta(1-\sigma)$ is the reduced transmission rate due to vaccination before an outbreak; $\frac{(1-\rho)l\theta}{\delta+\gamma_2}$ is the rate at which untraced individuals who self-quarantine can infect susceptibles. $\frac{(1-\rho)l(1-\theta)\alpha}{(\delta+\gamma_2)(\alpha+\delta+\gamma_1)}$; is the rate at which untraced infected individuals who get diagnosed can infect susceptibles; $\frac{(1-\rho)(1-\theta)}{\alpha+\delta+\gamma_1}$ is the rate at which untraced and undiagnosed infected individuals contribute to infections; and, $\frac{\rho l}{\delta+\gamma_2}$ is the rate at which traced, quarantined individuals infect susceptibles.

$\sigma > 0$ means pre-outbreak vaccination has been implemented, which reduces the value of R_0. $\sigma, \rho, \theta, \alpha$ and l are control parameters amenable to intervention by public health officials, which indicates what type of control methods should be implemented. In our model having $R_0 < 1$ is a sufficient condition for the disease to die out.

2.3 During-Outbreak Vaccination

Figure 2: During-outbreak vaccination model: all classes have the same meaning as in Figure 1, except for the V class, which denotes susceptible individuals vaccinated during the outbreak. Susceptibles move into the vaccinated class during the outbreak at rate $\chi\epsilon\frac{W}{N}$ where χ is the rate at which susceptibles are vaccinated per day and ϵ is the vaccine efficiency. This rate also depends on the proportion of diagnosed individuals.

This model differs from the previous because of the introduction of a new class: vaccinated individuals during an outbreak (V). In this approach we introduce the parameters χ and ϵ, and

$$\dot{V} = \chi\epsilon\frac{W}{N}.$$

Susceptibles move into the V class at rate $\chi\epsilon\frac{W}{N}$. χ is the rate at which susceptible are vaccinated per day, and ϵ is the efficacy of the vaccine. The progression into the V class depends on the proportion of people in the quarantine/isolation class (W/N). The rate at which susceptibles are vaccinated is not dependent on the I class, due to the fact that undiagnosed infected individuals are unknown to the public.

3 Results

3.1 Pre-outbreak vaccination

Pre-outbreak vaccination implies the susceptible class is reduced by a fraction (σ) that is initially vaccinated. To find the critical vaccination rates, we solved $R_0 = 1$ to get an expression for σ in terms of l and substituted the parameter values from Table 1. For the results of Figure 3, we assumed a "worst" case scenario, in which $l = 0.4$ is constant throughout the time of the epidemic from the Hong Kong outbreak in 2002-2003 [7]. This means that 40% of the quarantined/isolated population can contribute to the infection while in quarantine/isolation throughout the outbreak. We chose four values for ρ and θ and plotted σ versus l while fixing ρ for each plot and varying θ. The plots can be interpreted the same way when θ is fixed and ρ is varied. We explored four values for ρ and θ, approximately uniformly distributed in the interval $[0, 1]$. We chose the values for $\rho = [0.25, 0.5, 0.75, 0.975]$ and $\theta = [0.25, 0.5, 0.75, 0.95]$.

For any values of ρ and θ, the minimum percentage of the total population that needs to be vaccinated to control an outbreak ($R_0 < 1$) does not exceed 73%. Thus, even though isolation effectiveness plays an important role in the control of a SARS epidemic, without any isolation effectiveness ($l = 1$) an outbreak can be controlled with 73% pre-outbreak successful vaccination of the population. In all cases, when $l < 0.15$ the disease dies out, therefore, vaccination is unnecessary (see Figure 3).

Figure 3: $R_0(\sigma, l) = 1$ boundary curves to determine the critical vaccination coverage as a function of the quarantine/isolation effectiveness. When transmission rate $\beta = 0.25$, the minimum pre-outbreak vaccination proportion of the population when isolation is not effective ($l = 1$), is $\sigma = 0.73$.

As we vary the transmission rate β, we obtain different critical vaccination rates required to prevent an outbreak. We determine the critical values for σ when $\beta = 0.15$, $\beta = 0.25$ (Hong Kong scenario) and $\beta = 0.4$ (see Figure 4). When $\beta = 0.15$ it can be observed that when quarantine/isolation is completely ineffective, the minimum proportion of the population that needs to be vaccinated does not exceed 54%. When $\beta = 0.4$, this percentage does not exceed 84%. Thus, as β increases, the proportion of the population that needs to be vaccinated before the outbreak increases (see Figure 4 for comparisons of the minimum σ as dependent on the change of β).

Figure 4: $R_0(\sigma, l) = 1$ boundary curves for $\beta = [0.15, 0.25, 0.40]$ to determine the critical vaccination coverage as a function of the quarantine/isolation effectiveness. As β increases, the minimum σ needed to control an outbreak increases.

3.2 Pre-outbreak vaccination simulations

We calculated the total number of cumulative cases using numerical simulations [2], while varying σ in two cases: (1) assuming constant isolation effectiveness of $l_0 = 0.4$ (Hong Kong scenario) and (2) assuming improvement of isolation effectiveness as time varies due to improvement of interventions by using a piece-wise function for $l_0 = 0.4$:

$$l(t) = \begin{cases} l_0 & \text{if } 0 \leq t < 28 \\ 0.5l_0 & \text{if } 28 \leq t < 70 \\ 0.3l_0 & \text{if } t \geq 70. \end{cases} \tag{8}$$

Taking an initial value of $l_0 = 0.4$ (from the Hong Kong data) for the first four weeks of the outbreak $l = 0.4$, then reduces to 0.2 for the next six weeks, and finally reduces to $l = 0.12$ for the rest of the outbreak. This decrease means that fewer people in the quarantine/isolated class can infect susceptibles as the outbreak progresses.

We explore θ and ρ to find reasonable baseline values. We test the values, $\theta = [0.25, 0.5, 0.75, 0.95]$ while fixing $\rho = 0.975$ from [6]. When $\theta = 0.25$ (meaning 25% of the untraced latent individuals self-quarantine), the total epidemic size is 53.22% of the total population. When $\theta = 0.95$ (95% of the untraced latent individuals self-quarantine) the percentage of cumulative cases is 52.65%. The small difference of 0.57% in cumulative cases shows that θ is not crucial for the final epidemic size. Figure 5 shows the minimal changes in the cumulative cases when $\rho = 0.975$ and θ varies. Since the impact on the cumulative cases does not depend significantly on θ, we choose the medium value for $\theta \in [0, 1]$, $\theta = 0.5$.

Figure 5: Percentage of cumulative number of cases with $\sigma = 0$, $\rho = 0.975$, and $\theta = [0.25, 0.5, 0.75, 0.95]$. When varying θ, there is a small decrease in the total cumulative cases. The total difference in cases from when $\theta = 0.25$ to $\theta = 0.95$ is only 0.57%. We chose the mean value $\theta = 0.5$ for the numerical simulations.

However, varying ρ, while fixing all other parameters, has a greater effect on the cumulative cases (see Figure 6 for the changes in the cumulative cases when $\theta = 0.5$ and ρ varies). Again, the values for ρ we tested are $\rho = [0.25, 0.5, 0.75, 0.975]$. When $\rho = 0.25$ (25% of the contacts of an average infected person are traced), the total epidemic size is 60.58% of the total population, and when $\rho = 0.975$ (97.5% of the contacts are traced) the total epidemic size is 53.02%. The difference from the lowest to the highest values of ρ is 7.56%. This implies that varying ρ, the proportion of latent contacts that are traced, has a greater impact on the final epidemic size than θ, the proportion of untraced latent individuals that self-quarantine. We chose $\rho = 0.975$ from [6]. We assume that 97.5% of the latent people can be traced with modern technology and resources. This estimate comes from Kaplan's paper on mass vaccination in the case of a smallpox outbreak in New York City [6]. We assume that the same resources used for tracing smallpox can be used to trace SARS cases in the case of an outbreak.

[2] We used the Matlab ® software to perform numerical simulations

Figure 6: Percentage of cumulative number of cases with $\sigma = 0$, $\theta = 0.5$, and $\rho = [0.25, 0.5, 0.75, 0.975]$. There is a more significant change in cumulative cases when varying ρ than when varying θ. The percent change in the total number of cases when $\rho = 0.25$ to $\rho = 0.95$ is a 7.56% decrease.

Since the impact of ρ on the total epidemic size is more significant than the impact of θ, we explored different scenarios where ρ varies during the outbreak. Using a step function for ρ, we assumed that a smaller proportion of the latent individuals is traced at the beginning of the outbreak.

$$\rho(t) = \begin{cases} \rho = 0.5 & \text{if } t < y \\ \rho = 0.975 & \text{if } t \geq y \end{cases} \tag{9}$$

We assume that 50% of the latent individuals are traced in either the first $28, 100, 200,$ or 300 days of the outbreak ($y \in [28, 100, 200, 300]$), and then tracing improves to 97.5% at the end of the outbreak. We observe that the number of cumulative cases does not change significantly from the case when $\rho = 0.975$ during the entire outbreak.

Using the parameters from Table 1 and the values for $\theta = 0.5$ and $\rho = 0.975$ from the previous discussion, we analyze results from the numerical simulations where the initial population is $N_0 = 10^7$ people and the initial number of infected is $I_0 = 100$ individuals. We observe a decrease in the total epidemic size as σ increases. This is expected because you are increasing the number of susceptibles vaccinated prior to the outbreak. Assuming constant quarantine/isolation effectiveness during the outbreak and increasing σ (the proportion of susceptibles vaccinated prior to the outbreak), the duration of the outbreak decreases. Since a large percentage of latent individuals are traced (97.5%), they are sent directly to the quarantine/isolation class, W. The increase in the W class causes susceptibles to move faster into the infected classes due to the fact that a higher number of quaratine/isolated individuals can infect susceptibles. Thus, cases accumulate faster and the outbreak is over sooner (see Table 2 and Figure 7).

Figure 7: The cumulative number of cases versus time is changing as the proportion of successful vaccinated susceptibles, σ changes. For this simulation $l = 0.4$ (Hong Kong data) and remains constant throughout the outbreak. Initial conditions: $N_0 = 10^7$ and $I_0 = 100$.

Table 2: Description of simulation: Quarantine/Isolation Effectiveness $l = 0.40$ (Hong Kong scenario) is kept constant. Initial conditions: $N_0 = 10^7$ and $I_0 = 100$.

σ	Cumulative	Recovered	Dead	Duration
0	53.02%	32.11%	21.06%	$\approx 1,000$ days
0.5	0.00427%	0.00272%	0.00180%	≈ 450 days
0.6	0.00264%	0.00173%	0.00115%	≈ 280 days
0.7	0.00182%	0.00123%	0.00083%	≈ 210 days
0.8	0.00133%	0.00093%	0.00063%	≈ 120 days

To further explore the impact of pre-vaccination on the total number of cases, we constructed a plot of proportion of total cumulative cases from the total population versus σ (see Figure 8). There is a significant reduction in the total number of cumulative cases when for $0 \leq \sigma \leq 0.27$. If more than 27% of the total population is vaccinated before the outbreak, then the number of cumulative cases still decreases, but at a slower rate. Therefore, if pre-outbreak vaccination is implemented, then at least 27% of the total population needs to be vaccinated before an outbreak to observe the significant decrease in the total cumulative cases.

Figure 8: The cumulative number of cases as the proportion of successful vaccinated susceptibles, σ varies between 0 and 1. For this simulation $l = 0.4$ (Hong Kong data) and remains constant throughout the outbreak. Initial conditions: $N_0 = 10^7$ and $I_0 = 100$.

Improving quarantine/isolation during the outbreak as in Equation 8 and increasing σ, decreases the duration of the outbreak as well. This decrease is not as significant as in the case of l constant since quarantine/isolation effectiveness is the second most sensitive parameter after σ in the expression for R_0 (see Figure 9 and Table 3). Thus, when quarantine/isolation effectiveness is good, vaccination before the outbreak does not play a big role in the outcome of the epidemic. If no pre-outbreak vaccination is implemented, then the percentage of cumulative cases is 0.00908% and if 50% of the population is vaccinated before the outbreak, then the percentage of cumulative cases is 0.00256% (reducing the cumulative cases from 908 to 256 with $N_0 = 10^7$, see Table 3).

If quarantine/isolation improves earlier (than four weeks) in the outbreak, there would be a smaller number of SARS cumulative cases. If this improvement takes place later in the outbreak, then the number of SARS cumulative cases increases.

Figure 9: The cumulative number of cases versus time is changing as the proportion of successful vaccinated susceptibles, σ changes. For this simulation, the l step-function 8 is implemented throughout the outbreak. Initial conditions: $N_0 = 10^7$ and $I_0 = 100$.

Table 3: Description of simulation: Quarantine/Isolation Effectiveness l improves during the outbreak: $l_0 = 0.4$ when $0 \leq t < 28$, $l = 0.5l_0$ when $28 \leq t < 70$, and $l = 0.3l_0$ when $t \geq 70$. Initial conditions: $N_0 = 10^7$ and $I_0 = 100$.

σ	Cumulative	Recovered	Dead	Duration
0	0.00908%	0.00563%	0.00371%	$\approx$ 250 days
0.5	0.00254%	0.00167%	0.00111%	$\approx$ 150 days
0.6	0.00200%	0.00134%	0.00090%	$\approx$ 150 days
0.7	0.00158%	0.00109%	0.00073%	$\approx$ 150 days
0.8	0.00125%	0.00088%	0.00060%	$\approx$ 150 days

When quarantine/isolation improves during the outbreak as in Equation 8, the difference in the total cumulative cases for $\sigma = 0.5$ and $\sigma = 0.8$ is not significant (see Table

3). To explore the sensitivity of the cumulative cases on σ, we plot the total cumulative cases versus σ (see Figure 10). The difference in the total number of cumulative cases when $\sigma = 0$ (no pre-outbreak vaccination) and when $\sigma = 1$ (all susceptibles are vaccinated before the outbreak) is less than 0.008%. This implies that the proportion of susceptibles vaccinated prior to the outbreak is irrelevant, the outcome of vaccination would save at most 800 people (when $N_0 = 10^7$). Hence, good quarantine/isolation effectiveness is sufficient to control a SARS outbreak, *i.e.* no vaccination is needed.

Figure 10: The cumulative number of cases as the proportion of successful vaccinated susceptibles, σ varies between 0 and 1. For this simulation, the l step-function, as in Equation 8 is implemented throughout the outbreak. Initial conditions: $N_0 = 10^7$ and $I_0 = 100$.

The reported cumulative, recovered and dead cases are all given as percentages of the population. These percentages do not change significantly if the population size varies. The proportion of cumulative cases is sensitive to I_0 (number of infected individuals at the beginning of the epidemic) and N_0 (the initial population size).

3.3 During-outbreak vaccination (with or without pre-outbreak vaccination) numerical simulations

We now consider different scenarios for our single outbreak model: during-outbreak vaccination (where the proportion of pre-outbreak successfully vaccinated individuals $\sigma = 0$) and pre-outbreak vaccination combined with during-outbreak vaccination (where $\sigma \in [0, 1]$). The total epidemic size changes based on the vaccination strategy, in this case, how long before you start vaccinating after the beginning of the epidemic.

As in the case with pre-outbreak vaccination, we run two types of simulations where we explore the total epidemic size when: (1) quarantine/isolation effectiveness $l = 0.4$ (Hong Kong data) is kept constant during the outbreak (worst case scenario), and (2) a more realistic scenario where l is a step function as in Equation 8.

Since previous SARS models and recent data do not discuss the efficacy of a SARS vaccine, ϵ, and the rate at which susceptibles are vaccinated during the outbreak, χ, we examine ranges for these parameters and their effect on the total epidemic size. The public health officials, and other health organizations and universities are still in search for a SARS vaccine. The most promising result in the vaccine research has been a recent vaccine tested on four African green monkeys [4]. Even though all four monkeys who received the vaccine became immune to SARS, no conclusions can be drawn about its efficiency because of the nature of the vaccine. The SARS vaccine was produced by modifying a vaccine for HPIV3, and in its current form the vaccine would only be efficient for children and infants who are immune to HPIV3 [4], [11]. Even though the vaccine worked 100% for the four tested monkeys, a vaccine efficacy of $\epsilon = 1$ is not realistic. We assume a range for the vaccine efficacy of $0.5 \leq \epsilon \leq 0.9$. To obtain a value for χ, we used data from a smallpox outbreak in New York City [6]. In this paper, Kaplan estimates the number of nurses in the public health system and the number of people they can vaccinate per day [6]. Using Kaplan's estimates, starting with an initial population of 10^7 people, the entire population could be vaccinated in ten days after the start of the epidemic. It is unreasonable to use these estimates for SARS, since in the case of smallpox a vaccine already exists and it works for susceptibles as well as for latent individuals. In our model, we assume that the SARS vaccine would only work for susceptibles (worst case scenario). Hence, we assume a range for $\chi \in [0.2, 0.5]$. If a susceptible individual decides to receive a vaccine, they could obtain it within two to five days.

We determined the cumulative number of cases depending on when during-outbreak vaccination is implemented (i.e. after the 30^{th} or 200^{th} day), with constant quarantine/isolation effectiveness $l_0 = 0.4$. Table 4 shows the percentages of cumulative cases as dependent on the time of the start of the vaccination, with or without pre-outbreak vaccination.

The results in Table 4 show that if only during-outbreak vaccination is implemented after 30 days from the start of an outbreak, the total number of cumulative cases is reduced at least by half, from 53.02% (no vaccination at all, see Table 2) to at most 10% ($\chi = 0.5$ and $\epsilon = 0.9$, see Table 4). When pre-outbreak vaccination is implemented along with during-outbreak vaccination, then the percentage of cumulative cases is reduced from 10% to about 0.00427% (see Table 4). However, the number of days after which during-

Table 4: Percentage of cumulative number of cases based on the number of days after which vaccination begins from the start of an outbreak. Quarantine/isolation effectiveness $l_0 = 0.4$ (Hong Kong scenario) is kept constant. When pre-outbreak vaccination is implemented, the total number of cumulative cases does not change when χ varies in $[0.2, 0.5]$ and ϵ varies in $[0.5, 0.9]$. Initial conditions: $N_0 = 10^7$, $I_0 = 100$.

# of days after which vaccination begins	Range of percentage of cumulative cases for $\sigma = 0$	$\sigma = 0.5$	$\sigma = 0.6$	$\sigma = 0.7$
30	$10 - 26\%$	0.0042702%	0.0026376%	0.0018194%
250	$11 - 26\%$	0.0042703%	0.0026376%	0.0018194%
300	$12 - 28\%$	0.0042703%	0.0026376%	0.0018194%
350	$14 - 29\%$	0.0042703%	0.0026376%	0.0018194%
400	$20 - 33\%$	0.0042703%	0.0026376%	0.0018194%
450	$29 - 39\%$	0.0042703%	0.0026376%	0.0018194%

outbreak vaccination begins has little impact on the final epidemic size. If 50% of the initial population is vaccinated before an epidemic, then the percentage of cumulative cases is the same whether during-outbreak vaccination starts after 30 days or after 450 days into the outbreak (see Table 4).

We conclude that there is little difference in the cumulative number of cases when pre-outbreak vaccination is implemented alone, in comparison to the case when both vaccination policies are implemented simultaneously (assuming constant quarantine/isolation effectiveness during the outbreak), (see Table 2 and Table 4). If $\sigma = 0.5$ in both scenarios the percentage of cumulative cases is 0.00427% (for different number of days after which during-outbreak vaccination starts). As σ increases, the percentage of cumulative cases remains the same for both pre-outbreak vaccination, compared to pre-outbreak combined with during-outbreak vaccination. Hence, if vaccination is implemented before the outbreak, then there would be no need to vaccinate during the outbreak. A sample 3-D plot of the percentage of cumulative cases when χ and ϵ vary is shown in Figure 11.

Figure 11: Percentage of the cumulative number of cases if vaccination begins 30 days after the start of the outbreak. χ is the rate at which people are vaccinated ($0.2 \leq \chi \leq 0.5$) and ϵ is the vaccination efficiency ($0.5 \leq \epsilon \leq 0.9$). For this simulation $l_0 = 0.4$ (Hong Kong data) and remains constant throughout the outbreak.

If we assume improvement of quarantine/isolation effectiveness during the outbreak as in Equation 8, implementing during-outbreak vaccination produces the same percentage of cumulative cases as when vaccination is not implemented. Thus, for $\sigma = 0$, the percentage of cumulative cases is 0.00908 and as σ increases, the percentage of cumulative cases remains the same for during-outbreak vaccination as for pre-outbreak vaccination in Table 3. The number of days after which during-outbreak vaccination begins, has no impact on the cumulative cases. Therefore, effective quarantine/isolation is more important to control an outbreak rather than implementing during-outbreak vaccination (same conclusion when implementing pre-outbreak vaccination).

4 Uncertainty and Sensitivity Analysis

4.1 Uncertainty Analysis for R_0

We perform uncertainty analysis in the quantity R_0 to estimate the variability of R_0 as a result of the uncertainty in estimating the parameter values. We assume baseline values for α, β, γ_2, and l from [7] and use Monte Carlo simulations (simple random sampling) to determine the uncertainty of R_0. We assume that $\frac{1}{\alpha} \sim Gamma(a = 1.9, b = 2.5)$, $\frac{1}{\delta} \sim Gamma(a = 2.25, b = 16)$, $\frac{1}{\gamma_2} \sim Gamma(a = 8.9, b = 2.6)$ and $\beta \sim \exp(\mu = 0.25)$ from [7] based on Hong Kong data. For the proportion of successfully vaccinated individuals, denoted by σ, the proportion of individuals traced, ρ, and the proportion of latent individuals that self-quarantine, θ, we assume a uniform distribution in $[0, 1]$. We explored four different distributions for l: $l \sim Unif(0, 1)$ which means l is uniformly distributed in the interval [0,1], $l \sim Beta(a = 2, b = 2)$ where the likelihood of l is bell-shaped curve with mean= 0.5 and variance= 0.05, $l \sim Beta(a = 1, b = 2)$ which means l decreasing linearly in the interval [0,1], $l \sim Beta(a = 2, b = 1)$ which means l increasing linearly in [0,1] from [7]. We sampled 10^5 times using these probability distributions for the model parameters. We computed R_0 using different distributions for l from each sampling set and provide a histogram for R_0 for each distribution of l (see Figure 12 when $l \sim Beta(a = 1, b = 2)$).

Figure 12: Histogram for R_0 for $l \sim Beta(a = 1, b = 2)$. The mean of R_0 is 0.586, with a standard deviation of 1.02. The median is 0.224 and 83% of $R_0 < 1$.

Table 5: Results of uncertainty for R_0 for different distributions of l (quarantine/isolation effectiveness)

Distribution of l	Mean of R_0	Standard Deviation of R_0	Median of R_0	% of $R_0 < 1$
$Unif(0, 1)$	0.833	1.41	0.328	76%
$Beta(a = 2, b = 2)$	0.833	1.32	0.365	75%
$Beta(a = 1, b = 2)$	0.586	1.02	0.224	83%
$Beta(a = 2, b = 1)$	1.07	1.63	0.45	69%

Using the cumulative probability density of R_0 we determined the probability that $R_0 < 1$ for different l distributions (see Table 5). The distribution of l that has the most impact on R_0 is given by $l \sim Beta(a = 1, b = 2)$ since it yields the largest percentage of $R_0 < 1$ and gives the smallest mean of 0.586 for R_0, with a standard deviation of 1.02. This implies that the most cases of $R_0 < 1$ occur when the quarantine/isolation effectiveness is small, which is when l is decreasing linearly in $[0, 1]$.

4.2 Sensitivity Analysis for R_0

To explore the sensitivity of R_0 to the variability of the parameters for the pre-outbreak vaccination model, we let λ represent any of the eight parameter values (σ, l, γ_2, δ, ρ, θ, α, γ_1). Considering a small perturbation of λ by $\Delta\lambda$, a perturbation will appear in R_0 (ΔR_0)

as well. The normalized sensitivity index S_λ is the ratio of the corresponding normalized changes [2]. We define the sensitivity index for parameter λ as

$$S_\lambda = \frac{\Delta R_0}{R_0} / \frac{\Delta \lambda}{\lambda} = \frac{\lambda}{R_0} \cdot \frac{\partial R_0}{\partial \lambda}$$

where λ is a parameter in the quantity R_0.

When determining the sensitivity of each parameter (see Appendix), we used $\theta = 0.5$ and $\rho = 0.975$ from [6], $l = 0.4$ using estimates from the Hong Kong outbreak [7]. We notice that successful vaccination coverage, σ, is the most sensitive parameter when $\sigma > 0.495$, followed by the effectiveness of quarantine/isolation, l. The sensitivity of σ is independent of all other parameters. Therefore, the sensitivity index of σ decreases as the value of σ decreases. We observed that l surpasses the sensitivity of σ when $\sigma \leq 0.495$.

Table 6: Sensitivity Analysis of R_0. In this table, we use $\sigma = 0.7$ and other parameters from Table 1. When $\sigma < 0.495$, l has a higher sensitivity index.

Sensitivity index	Value
S_σ	-2.3333
S_l	0.99187
S_{γ_2}	-0.59908
S_δ	-0.39462
S_ρ	-0.20353
S_θ	-0.00522
S_α	-0.00400
S_{γ_1}	-0.00231

5 Discussion and Conclusions

We have presented a model that incorporates vaccination as a possible strategy to control an outbreak of SARS. In contrast to other models for SARS, our model distinguishes between traced and untraced latent individuals, and includes a susceptible class with a reduced number of individuals due to vaccination prior to the outbreak. By using parameters estimated from the SARS outbreak in Hong Kong (China) [7], we predict the minimal proportion of susceptibles that needs to be successfully vaccinated before an outbreak to control an epidemic.

The parameters explored most extensively are ρ (the proportion of contacts traced), θ (the proportion of untraced latent individuals that self-quarantine), l (the effectiveness of quarantine/isolation), and σ (the percentage of initial population successfully vaccinated before the outbreak). We observe that increasing θ does not reduce the total cumulative cases as significantly as increasing ρ, hence we used $\theta = 0.5$ for our numerical simulations. This implies that in the case of a SARS outbreak, efforts should be towards improving tracing policies rather than urging people to self-quarantine. We explored the scenario when a small percentage of latent individuals are traced at the beginning of the outbreak, and an increase of this percentage at a later time (*i.e.* considered a step function for ρ), but observed a very small change in the total cumulative cases compared to using constant $\rho = 0.975$ for the whole outbreak.

We compute the basic reproductive number, R_0, to obtain results for possible outbreak scenarios. By varying ρ, θ, and l in R_0 we determine a minimum percentage of susceptibles that needs to be vaccinated in order to control an outbreak ($R_0 < 1$). This strategy depends on the transmission rate, β. Higher vaccination requirements to control an outbreak are due to higher transmission rates.

We ran simulations for different SARS outbreak scenarios: (1) using constant quarantine/isolation effectiveness throughout the outbreak and (2) improving effectiveness during the outbreak. Constant quarantine/isolation effectiveness ($l_0 = 0.4$ from Hong Kong data), which is the worst-case scenario, leads to a large number of cumulative cases even when vaccination is implemented. If quarantine/isolation effectiveness is constant, a significant reduction in total cumulative cases is observed after at least 27% of the initial population is vaccinated. Higher vaccination rates do not affect the percentage of cumulative cases as significantly, but may have an impact in the reduction of the total epidemic size. Thus, when quarantine/isolation is constant, pre-outbreak vaccination plays an important role in the reduction of the total cumulative cases.

However, with improvements in quarantine/isolation effectiveness, pre-outbreak vaccination does not play such a major role in reducing the total cumulative cases. Table 3 shows that with no vaccination the percentage of total cumulative cases is reduced to 0.00908% by improving quarantine/isolation effectiveness (compared to 53.02% of cases when the effectiveness is constant). Hence, when improving quarantine/isolation effectiveness during the outbreak, pre-outbreak vaccination is not needed to control an outbreak.

We also explored during-outbreak vaccination as well. Assuming constant quarantine/isolation effectiveness, in the case of a sudden outbreak of SARS when no pre-outbreak

vaccination can be implemented. Vaccination during the outbreak does reduce the total epidemic size. We assume that the efficacy of the vaccine, ϵ, is at least 50%, but not more than 90%, and the rate at which people are vaccinated is $0.2 \leq \chi \leq 0.5$. If the efficacy of the vaccine and the rate at which susceptibles are vaccinated increases, the number of cumulative cases decreases. If during-outbreak vaccination is implemented sooner into the outbreak, then the number of cumulative cases decreases compared to when vaccination starts later into the outbreak. The total number of cumulative cases also reduces when both vaccination policies are implemented compared to only implementing pre-outbreak vaccination. However, the number of days from the start of the outbreak when during-outbreak vaccination begins, does not affect the cumulative cases significantly. Therefore, if quarantine/isolation effectiveness is 0.4 (Hong Kong), pre-outbreak vaccination as well as during-outbreak vaccination are needed to reduce the total number of cumulative cases. Efforts should also be spent on tracing people after the start of the outbreak.

If quarantine/isolation effectiveness improves during the outbreak, then no vaccination is necessary to control an epidemic.

σ is the most sensitive parameter in the basic reproductive number R_0, when $\sigma > 0.495$. This means that efforts should be spend on pre-outbreak vaccination first, and then on improving l, ρ, and θ, respectively. However, if $\sigma \leq 0.495$ the l is the most sensitive parameter, and thus, resources should be spent on improving quarantine/isolation effectiveness.

We estimated a distribution for R_0 through an uncertainty analysis using different probability distributions of the parameters. We conclude that the distribution for l which gives the smallest of mean= 0.586, standard deviation= 1.02, and median=0.224 for R_0, is $l \sim Beta(a = 1, b = 2)$. Using this distribution, in 83% of the cases $R_0 < 1$.

We recommend that vaccination is implemented before an outbreak, and if possible during the outbreak as soon as it starts. Whether vaccination can be administered or not, most efforts should be towards improving effectiveness of quarantine/isolation. If pre-outbreak vaccination cannot be implemented, during-outbreak vaccination should be administered as quickly as possible from start of the outbreak. Tracing policies should also be improved to reduce the total cumulative cases.

6 Future Work

Based on the conclusions from the two vaccination models, future research may entail exploring the economic impact of the different strategies to control an outbreak. These strategies include improving quarantine/isolation effectiveness, vaccination prior to an outbreak and during an outbreak, and tracing contacts of infected individuals. Since the SARS virus affected the elderly more significantly, future work could be done on an age structured model where the elderly would be vaccinated with a higher priority. Another possible model could include vaccinating people based on their activities in society, where health care workers would be vaccinated first in the case of an outbreak.

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7 Appendix

7.1 Sensitivity indices

We preformed sensitivity analysis on R_0, using the formula

$$S_\lambda = \frac{\partial R_0}{\partial \lambda}\frac{\lambda}{R_0}$$

where λ is any parameter in the expression for R_0. The following are the expressions of the sensitivity indices in terms or R_0 and the other parameters (see Table 6 for the values of the indices).

$S_l = \frac{l\beta(1-\sigma)[(1-\rho)\theta+\rho]}{(\delta+\gamma_2)R_0}$

$$S_\sigma = \frac{\sigma}{\sigma-1}$$

$$S_\delta = \frac{\delta\beta(1-\sigma)[(1-\rho)(1-\theta)-(1-\rho)l\theta-\rho l]}{R_0(\delta+\gamma_2)(\alpha+\delta+\gamma_1)} - \frac{\delta[(\delta+\gamma_2)+(\alpha+\delta+\gamma_1)]}{(\delta+\gamma_2)(\alpha+\delta+\gamma_1)}$$

$$S_\rho = \frac{\beta(1-\sigma)}{R_0}\left[\frac{l\rho(1-\theta)}{\delta+\gamma_2} - \frac{\rho(1-\theta)\alpha}{(\delta+\gamma_2)(\alpha+\delta+\gamma_1)} - \frac{\rho(1-\theta)}{\alpha+\delta+\gamma_1}\right]$$

$$S_\theta = \frac{-\beta(1-\sigma)}{R_0}\left[\frac{(1-\rho)l\theta}{\delta+\gamma_2} - \frac{(1-\rho)\alpha\theta}{(\delta+\gamma_2)(\alpha+\delta+\gamma_1)} - \frac{(1-\rho)\theta}{\alpha+\delta+\gamma_1}\right]$$

$$S_{\gamma_1} = \frac{-\beta(1-\sigma)\gamma_1}{R_0(\alpha+\delta+\gamma_1)}\left[\frac{(1-\rho)(1-\theta)\alpha}{(\delta+\gamma_2)(\alpha+\delta+\gamma_1)} + \frac{(1-\rho)(1-\theta)}{\alpha+\delta+\gamma_1}\right]$$

$$S_{\gamma_2} = \frac{-\gamma_2}{\delta+\gamma_2} + \frac{\beta(1-\sigma)\gamma_2(1-\rho)(1-\theta)}{(\delta+\gamma_2)(\alpha+\delta+\gamma_1)}$$

$$S_\alpha = \frac{\alpha\beta(1-\sigma)(1-\rho)(1-\theta)-(1-\rho)l\theta-\rho l}{R_0(\delta+\gamma_2)(\alpha+\delta+\gamma_1)} - \frac{\alpha}{\alpha+\delta+\gamma_1}$$

7.2 Matlab Code

To determine the minimal percentage of proportion that needs to be vaccinated before an outbreak, σ we use plot_sigma.m.

```
 function plot_sigma

% MTBI 2004
% Authors: Julijana Gjorgjieva, Jessica Snyder, Kelly Smith
% Date: July 21, 2004
%
% To call the function just use:
% plot_sigma
% This program is used to produce the R_0<1 curves to determine the minimum
% percentage of total population, sigma, that needs to be vaccinated before the
% outbreak to control it.

beta=0.25;          % This value can be changed to produce different minimal sigma's
k=1/6.37; gamma1=1/28.4; gamma2=1/23.5; alpha=1/4.85; delta=0.0279;

% Ranges for theta and rho to be tested.
theta=[ 0.25 0.5 0.75 0.95]; rho1=[0.25 0.5 0.75 0.975];

t=length(theta); r=length(rho1); l=linspace(0,1,21);

% 4 plots are obtained here, since we are testing for values for rho.
```

```
for z=1:r
    rho=rho1(z);
    subplot(r,1,z);
    for i=1:t
      hold on
      R=[];
      for j=1:21
          % We solve R_0 for sigma in terms of l
          sigma=1-1/(beta*((((1-rho)*l(j)*theta(i))/(delta+gamma2))+(((1-rho)*l(j)*
          (1-theta(i))*alpha)/((delta+gamma2)*(alpha+delta+gamma1)))+((1-rho)*
          (1-theta(i))/(alpha+delta+gamma1))+(rho*l(j))/(delta+gamma2)));
          R=[R sigma];
     end
     % Different plot styles for the different values of theta on each plot
     % for fixed rho.
     if i==1
         plot(l,R,'k-');
     elseif i==2
         plot(l,R,'k-');
     elseif i==3
         plot(l,R,'k-');
     elseif i>=4
         plot(l,R,'k-');
     end
     AXIS([0 1 0 1])
     end
end

hold off xlabel('l (Effectivness of Quarantine/Isolation)');
ylabel('sigma (Proportion of successfully vaccinated
susceptibles'));
```

Code to run the simulations to obtain the final epidemic size of an outbreak. For only pre-outbreak vaccination: MODEL.m and PLOTSARS.m.

```
function dx=MODEL(t,x)

% MTBI 2004
% Authors: Julijana Gjorgjieva, Jessica Snyder, Kelly Smith
% Date: July 22, 2004
%
% This m file is used in PLOTSARS to obtain simulations for different
% outbreak scenarios. We only implement pre-outbreak vaccination in these
% simulations.
```

```
global beta rho l theta k N alpha delta gamma1 gamma2 sigma INF
% defines global variables that are defined/used in PLOTSARS.m

% a step function for isolation effectiveness l
if t<28               % l is 0.4 for the first 4 weeks of the outbreak
    l2=l;
elseif t>=28 & t<70   % l improves to 0.2 up to the 10th week of the outbreak
    l2=0.5*l;
else                  % l improves further after the 10th week of the outbreak
    l2=0.3*l;
end

%l2=l;                % l is kept constant during the outbreak

% Note: When we run simulations for constant isolation effectiveness l=0.4
% the code for step function l is commented out.
% When we run simulations when isolation effectiveness improving during the
% outbreak, then the code for l constant is commented out.

dx=zeros(8,1);


% The system of equations:

% Susceptibles S
dx(1)=-beta*(1-rho)*((x(5)+l2*x(4))/N).*x(1)-beta*rho*((x(5)+l2*x(4))/N).*x(1);

% Latent untraced individuals E_n
dx(2)=beta*(1-rho)*((x(5)+l2*x(4))/N).*x(1)-x(2)*(k*theta+k*(1-theta));

% Latent traced individuals E_i
dx(3)=beta*rho*((x(5)+l2*x(4))/N).*x(1)-x(3)*k;

% Infected diagnosed individuals W
dx(4)=k*theta*x(2)+k*x(3)+alpha*x(5)-x(4)*(delta+gamma2);

% Infected undiagnosed individuals I
dx(5)=x(2)*k*(1-theta)-x(5)*(alpha+delta+gamma1);

% Dead individuals from SARS
dx(6)=delta*x(4)+delta*x(5);

% Recovered diagnosed and recovered undiagnosed individuals
dx(7)=gamma2*x(4)+gamma1*x(5);
```

```
% Total number of cumulative cases; total epidemic size
dx(8) = delta*x(4) + gamma2*x(4);
```

PLOTSARS.m

```
function
y=PLOTSARS(ti,tf,b,g1,g2,alpha1,delta1,k1,rho1,theta1,l1,sigma1,
totN,totI)

% MTBI 2004
% Authors: Julijana Gjorgjieva, Jessica Snyder, Kelly Smith
% Date: July 22, 2004
%
% To call the function use:
% PLOTSARS(0,1500,0.25,1/28.4,1/23.5,1/4.85,.0279,1/6.37,.975,.5, .4, 0, 10000000,100)
% This program is used to plot the total number of cumulative cases versus
% time with only pre-outbreak vaccinated where the proportion of people
% vaccinated before the outbreak is given by the parameter sigma.


global  beta rho l theta k N alpha delta gamma1 gamma2 INF sigma
% defines global variables that are used in MODEL.m

% sets the global variables
beta=b; gamma1=g1; gamma2=g2; alpha=alpha1; delta=delta1; k=k1;
N=totN; INF=totI; sigma=sigma1; rho=rho1; theta=theta1; l=l1;
tspan=[ti,tf];

% uses ode45 to solve the system of equations in MODEL.m
[t,x]=ode45('MODEL',tspan,[(N*(1-sigma)-INF);0;0;0;INF;0;0;0]);


% plots the total number of cumulative cases
plot(t,x(:,8)/N,'-');

xlabel('t'); ylabel('C(t)');

hold on

% finally, prints out the total number of individuals in each class
'total S=',x(length(x),1)/N 'total En=',x(length(x),2)/N

'total Ei=',x(length(x),3)/N 'total W=',x(length(x),4)/N
```

```
'total I=',x(length(x),5)/N 'total D=',x(length(x),6)/N

'total R=',x(length(x),7)/N 'total C=',x(length(x),8)/N
```

Code to run the simulations to obtain the final epidemic size of an outbreak. For only pre-outbreak vaccination and during-vaccination: MODEL_during.m and PLOTSARS_during.m.

```
function dx=MODEL_during(t,x)

% MTBI 2004, Los Alamos, NM
% Authors: Julijana Gjorgjieva, Jessica Snyder, Kelly Smith
% Date: July 30, 2004
%
% This function is used in PLOTSARS_duing.m to obtain total size
% epidemic for different outbreak scenarios. In this case, during-outbreak
% vaccination is implemented.

global beta rho l theta k N alpha delta gamma1 gamma2 sigma epsilon
chi
% Defines global variables used in model2.m


% a step function for isolation effectiveness l
if t<28               % l is 0.4 for the first 4 weeks of the outbreak
    l2=l;
elseif t>=28 & t<70   % l improves to 0.2 up to the 10th week of the outbreak
    l2=0.5*l;
else                  % l improves further after the 10th week of the outbreak
    l2=0.3*l;
end

%l2=l;                % l is kept constant during the outbreak


% We observe the effect of vaccination different number of days from the
% beginning of the outbreak. Thus, for different scenarios, we change t<30
% to different number of days.

if t<30      % During-outbreak vaccination begins 30 days after the outbreak starts.
    chi1=0;
else
    chi1=chi;
end


dx=zeros(9,1);
```

```
% The system of equations in this case is modified. Notice the term for
% during-outbreak vaccination in the class for susceptibles and the
% introduction of a new class of vaccinated.

% Susceptibles S
dx(1)=-beta*(1-rho)*((x(5)+l2*x(4))/N).*x(1)-beta*rho*((x(5)+l2*x(4))/N).*x(1)-
chi1*epsilon*(x(4)/N).*x(1);

% Latent untraced individuals E_n
dx(2)=beta*(1-rho)*((x(5)+l2*x(4))/N).*x(1)-x(2)*(k*theta+k*(1-theta));

% Latent traced individuals E_i
dx(3)=beta*rho*((x(5)+l2*x(4))/N).*x(1)-x(3)*k;

% Infected diagnosed individuals W
dx(4)=k*theta*x(2)+k*x(3)+alpha*x(5)-x(4)*(delta+gamma2);

% Infected undiagnosed individuals I
dx(5)=x(2)*k*(1-theta)-x(5)*(alpha+delta+gamma1);

% Dead individuals from SARS
dx(6)=delta*x(4)+delta*x(5);

% Recovered diagnosed and recovered undiagnosed individuals
dx(7)=gamma2*x(4)+gamma1*x(5);

% Vaccinated individuals during the outbreak
dx(8)=chi1*epsilon*(x(4)/N).*x(1);

% Total number of cumulative cases; total epidemic size
dx(9)=delta*x(4) + gamma2*x(4);
```

PLOTSARS_during.m

```
function
y=PLOTSARS_during(ti,tf,b,g1,g2,alpha1,delta1,k1,rho1,theta1,l1,sigma1,
totN,totI)

% MTBI 2004, Los Alamos, NM
% Authors: Julijana Gjorgjieva, Jessica Snyder, Kelly Smith
% Date: July 27, 2004
%
% To call the function use:
% PLOTSARS_during(0,1500,0.25,1/28.4,1/23.5,1/4.85,.0279,1/6.37,.975,.5, .4, 0, 10000000,100)
```

```
% This program is used to plot a 3-D surface of the total number of cumulative
% cases versus time with only pre-outbreak vaccination where the proportion of people
% vaccinated before the outbreak is given by the parameter sigma. The x and
% the y axis on the surface plot are chi and epsilon.


global  beta rho l theta k N alpha delta gamma1 gamma2 INF sigma chi
epsilon
% define global variables.

% initialize the global variables
beta=b;

gamma1=g1;

gamma2=g2;

alpha=alpha1;

delta=delta1;

k=k1;

N=totN;

INF=totI;

sigma=sigma1;

rho=rho1;

theta=theta1;

l=l1;

% define ranges for epsilon and chi

epsilon1=linspace(0.5, 0.9,10); chi1=linspace(0.2, 0.5, 10);
tspan=[ti,tf]; c=[];

for i=1:10
    chi=chi1(i);
    c1=[];
    for j=1:10
        epsilon=epsilon1(j);
```

```
        % solve equation each time for each epsilon and chi
        [t,x]=ode45('MODEL_during',tspan,[(N*(1-sigma)-INF);0;0;0;INF;0;0;0;0]);
        % obtain a vector of cum. cases for fixed chi, varied epsilon
        c1=[c1, x(length(x),9)/N];
    end
    % obtain a matrix of cum. cases for varied chi and epsilon
    c=[c; c1];
end

% plot surface
surf(c);
```

To obtain the plot for total number of cumulative cases versus σ we used varysigma.m.

```
function y=varysigma(ti,tf,b,g1,g2,alpha1,delta1,k1,rho1,theta1,l1,
totN,totI)

% MTBI 2004, Los Alamos, NM
% Authors: Julijana Gjorgjieva, Jessica Snyder, Kelly Smith
% Date: August 2, 2004
%
% To call this function, use:
% varysigma(0,1000,0.25,1/28.4,1/23.5,1/4.85,.0279,1/6.37,.975,.5, .4, 0, 10000000,100)
% This program is used to plot the total number of cumulative cases versus
% sigma with only pre-outbreak vaccinated.

global  beta rho l theta k N alpha delta gamma1 gamma2 INF sigma
% defines the global variables.

% initializes the global variables.
beta=b;

gamma1=g1;

gamma2=g2;

alpha=alpha1;

delta=delta1;

k=k1;

rho=rho1;

N=totN;
```

```
INF=totI;

rho=rho1;

theta=theta1;

l=l1;

% uses 100 values for sigma in the interval [0,1]
sigma1=linspace(0, 1,100); tspan=[ti,tf]; c=[];

for i=1:100
        sigma=sigma1(i);
        % solve MODEL.m for each new sigma
        [t,x]=ode45('MODEL',tspan,[(N*(1-sigma)-INF);0;0;0;INF;0;0;0]);
        c=[c, x(length(x),8)/N];   % vector of cumulative cases for each sigma
end
% plots the total cumulative cases versus sigma
plot(sigma1,c);
```

Code to produce the histogram for R_0 after uncertainty analysis for R_0.

```
function uncertaintyR0

% MTBI 2004, Los Alamos, NM
% Authors: Julijana Gjorgjieva, Jessica Snyder, Kelly Smith
% Date: July 29, 2004
%
% To call the fucntion use:
% uncertaintyR0
% This program is used to produce a histogram for Ro based on the
% probability distributions of the parameters in the expression for Ro.


% probability distributions for the different parameters
% in the expression for Ro

beta=wexprnd(.25,[100000,1]);

l=wbetarnd(1,2,[100000,1]);

gamma2=1./(wgamrnd(8.9,2.6,[100000,1]));
alpha=1./(wgamrnd(1.9,2.5,[100000,1]));
k=1./(wgamrnd(2.4,2.6,[100000,1]));
gamma2=1./(wgamrnd(8.9,2.6,[100000,1]));
```

```
delta=1./(wgamrnd(2.25,16,[100000,1]));
gamma1=1./((1./gamma2)+(1./alpha)); sigma=rand([100000,1]);
rho=rand(100000,1); theta=rand(100000,1);

a=zeros(100000,1);

sum1=zeros(100000,1);

sum2=zeros(100000,1);

sum3=zeros(100000,1);

sum4=zeros(100000,1);

R0=zeros(100000,1);

c=0;

% computes Ro for each sample in the set of 10^5 samples
for i=1:100000
    a(i,1)=(1-rho(i,1))*l(i,1)*theta(i,1);
    sum1(i,1)=a(i,1)/(delta(i,1)+gamma2(i,1));
    sum2(i,1)=((1-rho(i,1))*l(i,1)*(1-theta(i,1))*alpha(i,1))/((delta(i,1)
    +gamma2(i,1))*(alpha(i,1)+delta(i,1)+gamma1(i,1)));
    sum3(i,1)=((1-rho(i,1))*(1-theta(i,1)))/(alpha(i,1)
    +delta(i,1)+gamma1(i,1));
    sum4(i,1)=((rho(i,1)*l(i,1))/(delta(i,1)+gamma2(i,1)));
    R0(i,1)=beta(i,1)*(1-sigma(i,1))*(sum1(i,1)+sum2(i,1)
    +sum3(i,1)+sum4 (i,1) );

    if R0(i,1)<1
        c=c+1;
    end
end

hist(R0,100);           % plots a histogram for Ro
axis([0 10 0 40000]);

% prints out mean, standard deviation and median for Ro
'mean' mean(R0) 'std' std(R0) 'median' median(R0)
```