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THE ROLE OF VACCINATION IN THE CONTROL OF SARS

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Abstract. We assess pre-outbreak and during-outbreak vaccination as control strategies for SARS epidemics using a mathematical model that includes susceptible, latent (traced and untraced), infectious, isolated and recovered individuals. Scenarios focusing on policies that include contact tracing and levels of self-isolation among untraced infected individuals are explored. Bounds on the proportion of pre-outbreak successfully vaccinated individuals are provided using the the basic reproductive number. Uncertainty and sensitivity analyses on the reproductive number are carried out. The final epidemic size under different vaccination scenarios is computed.

1. **Introduction.** Severe acute respiratory syndrome (SARS) is a viral respiratory illness caused by SARS coronavirus (SARS-CoV). SARS is believed to have emerged in the southern China province of Guangdong in November of 2002 [1]. The 2003 SARS epidemic was initially driven by international travel and lack of knowledge of the disease's etiological agent. The outbreak in Toronto, Canada, was contained by expediting the rates of diagnosis and isolation of infectious cases. The World Health Organization reported a total of 8,422 cases with 916 deaths as of August 2003, with China being the most affected country [1]. A mortality rate of

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1% was recorded 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 [2].

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 [3]. Most SARS patients develop pneumonia [3]. SARS is mainly transmitted by direct close contact [3]. The mean latency period for SARS (the period that a person is infected but not yet infectious) is approximately 6.4 days [4]. Suspected cases were hospitalized at a mean rate of $1/4.85$ days^{-1}. Recovered individuals were discharged from hospitals on average 23.5 days after diagnosis; others died 35.9 days after diagnosis [4].

A search for a SARS vaccine began during the outbreak. The National Institute of Allergy and Infectious Diseases (NIAID) has conducted vaccine studies on mice, which developed SARS antibodies after the first dose and became immune after a second dose [5]. Experiments on African green monkeys (*Cercopithecus Aethiops*) have also been conducted [6]. Researchers from the NIAID modified a vaccine for a known respiratory disease virus similar to SARS, HPIV3, through the insertion of the SARS-S protein (the only protein compound which aids in the process of attaching to cells of the human respiratory tract and infecting the cells as well [7]). This intranasal vaccine was given to four monkeys while the control group (four monkeys) received the modified HPIV3 without the SARS-S protein [6, 7]. The four immunized test monkeys did not develop SARS infection when exposed 28 days after vaccination. The four monkeys in the control developed SARS after exposure [6, 8]. This vaccine would be ineffective for highly susceptible humans, because most adults have immunity to the generalized vector of HPIV3 from childhood illness [8]. That is, their immune systems cannot produce antibodies against the SARS-S protein in the HPIV3 vector [8].

Sinovac Biotech, a Chinese company, is in the process of testing a SARS vaccine made of dead samples of the SARS-CoV on humans. The high-dosage (32 su/ml antigen) SARS vaccine was administered 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" [9].

In this paper, we explore the impact of two vaccination strategies, namely the effect of pre-outbreak vaccination (where the susceptible population is reduced by a fraction of successfully vaccinated individuals before the disease invades) and the impact of during-outbreak vaccination. The role of these intervention strategies is also evaluated when these are implemented along with different levels of isolation of infectious individuals.

This paper is organized as follows: section 2 introduces our epidemic model and vaccination strategies; section 3 explores numerical pre-outbreak and during-outbreak vaccination scenarios under different levels of isolation effectiveness; section 4 focuses on the uncertainty and sensitivity analysis of the effective reproductive number, the key to our control strategies; and section 5 collects our conclusions.

2. **Methods.**

Our model is based on previous work on SARS [10] and smallpox [11]. We considered a single SARS outbreak and the possible implementation of two different vaccination strategies (pre-outbreak and during-outbreak vaccination).

2.1. **Pre-outbreak vaccination framework.**

Starting with a population of N individuals, pre-outbreak vaccination reduces the susceptible population to $(1 -$

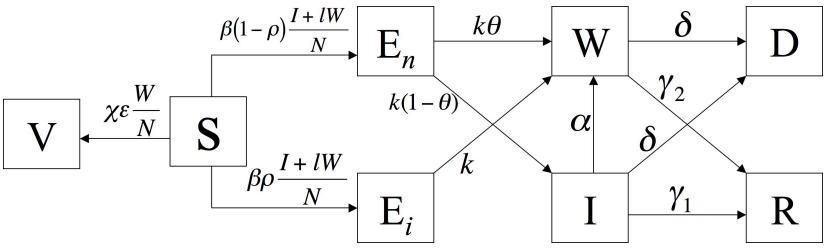

FIGURE 1. Schematic representation of the state progression of individuals: Susceptible individuals move at the rate $\chi\epsilon\frac{W}{N}$ into the vaccination class V where χ is the rate at which susceptibles are vaccinated per day and ϵ is the efficacy of the vaccine. It is assumed that the rate of vaccination depends on the proportion of people in the isolation class (W/N). E_n denotes the untraced latent (infected, not yet infectious) individuals, and E_i are the traced latent individuals. I denotes the infectious, untraced individuals, and W denotes the infectious individuals (from classes E_i and I) placed into isolation. D and R denote the dead and recovered classes, respectively. For parameter descriptions see Table 1.

$\sigma)N$ before the start of the outbreak. That is, σN individuals are removed by vaccination.

We follow the approach of Gani and Leach [11] and divide the latent subpopulation (individuals that are infected but cannot transmit the disease to others) into two classes, untraced latent (E_n) and traced latent individuals (E_i). Our baseline value for the latent period ($1/k$) is taken to be 6.37 days [12]. The average time before a latent individual was either traced and isolated, or decided self-isolation is $1/k$. Specifically, untraced latent individuals self-isolate at the rate θk or progress into the infectious class I at a rate $(1-\theta)k$, where θ is the proportion of untraced latent individuals that self-isolate, and I denotes the symptomatic, undiagnosed, and infectious individuals [10]. Infectious individuals can also move into the isolation class W at rate α, die at rate δ, or recover at rate γ_1. Once under isolation, individuals either die at the rate δ or recover at rate γ_2. That is, individuals in the isolation class are assumed to recover faster than undiagnosed individuals ($\gamma_2 < \gamma_1$) [12].

It is also assumed that isolated individuals are less likely to interact with susceptibles and therefore contribute less to infection. This is modeled by parameter l, which determines the isolation effectiveness as a reduction factor in the transmission rate of individuals in the isolation class W [10]. Table 1 describes the parameters, as well as the baseline values used. The model that describes the transmission dynamics of SARS, control measures, and pre-outbreak vaccination only is given by the following system of nonlinear differential equations:

$$\begin{cases} \dot{S} &= -\beta(1-\rho)\frac{(I+lW)}{N}S - \beta\rho\frac{(I+lW)}{N}S, \\ \dot{E_n} &= -k\theta E_n - k(1-\theta)E_n + \beta(1-\rho)\frac{(I+lW)}{N}S, \\ \dot{E_i} &= -kE_i + \beta\rho\frac{(I+lW)}{N}S, \\ \dot{W} &= k\theta E_n + kE_i + \alpha I - (\delta+\gamma_2)W, \\ \dot{I} &= k(1-\theta)E_n - (\alpha+\delta+\gamma_1)I, \\ \dot{R} &= \gamma_1 I + \gamma_2 W, \\ \dot{D} &= \delta I + \delta W. \end{cases} \tag{1}$$

TABLE 1. Parameter definition and baseline values

Parameter	Definition	Baseline value
β	Transmission rate per day	0.25
$1/k$	Mean latent period (days)	6.37
$1/\gamma_1$	Mean infectious period (days)	28.4
$1/\gamma_2$	Mean infectious period for diagnosed individuals (days)	23.5
$1/\alpha$	Mean period before diagnosis (days)	4.85
δ	Disease induced death rate per day	0.0279
σ	Proportion of susceptibles successfully vaccinated	$[0, 1]$
ρ	Proportion of latent population traced	$[0, 1]$
θ	Proportion of untraced latent that self-isolate	$[0, 1]$
l	Effectiveness of isolation	$[0, 1]$
χ	Vaccination rate	$[0.2, 0.5]$
ϵ	Vaccine efficacy	$[0.5, 0.9]$

Note: Parameters β, $1/k$, $1/\gamma_1$, $1/\gamma_2$, $1/\alpha$, δ, and l were taken from [12].

where $S(0) = (1-\sigma)N$. The effective reproductive number under pre-outbreak vaccination can be obtained using the next generation method [13, 14] and is given by:

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

Here, β is the transmission rate; $(1-\sigma)$ denotes the proportion of the population still susceptible at the start of the outbreak; $\frac{(1-\rho)l\theta}{\delta+\gamma_2}$ is the contribution (to infection) of untraced individuals who self-isolate; $\frac{(1-\rho)l(1-\theta)\alpha}{(\delta+\gamma_2)(\alpha+\delta+\gamma_1)}$ is the contribution of untraced diagnosed individuals; $\frac{(1-\rho)(1-\theta)}{\alpha+\delta+\gamma_1}$ is the contribution of untraced undiagnosed individuals; and, $\frac{\rho l}{\delta+\gamma_2}$ is the contribution of those traced and isolated individuals. Parameter $\sigma > 0$ means pre-outbreak vaccination has been implemented, which reduces the value of $R_0 \equiv R_0^*(\sigma = 0)$. Control parameters $\sigma, \rho, \theta, \alpha$, and l are amenable to intervention by public health interventions.

2.2. **During-outbreak vaccination.** During outbreak vaccination is modeled by the addition of a vaccinated class V (Figure 1). Susceptible moved at the rate $\chi\epsilon\frac{W}{N}$ into V; that is,

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

where χ is the rate at which susceptibles are vaccinated per day, and ϵ is the efficacy of the vaccine. It is assumed that the rate of vaccination depends on the proportion of people in the isolation class (W/N).

3. Results.

3.1. **Pre-outbreak vaccination.** Pre-outbreak vaccination consists in reducing the susceptible class by a fraction σ through vaccination. To find the critical vaccination rates, we solved $R_0^*(\sigma) = 1$ to get an expression for σ in terms of l by substituting the baseline parameter values (Table 1). In Figure 2, we assume 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 [12]. This means that 40% of the

isolated population can contribute to infection while in isolation. We choose four values for ρ and θ and plotted σ versus l while fixing ρ for each plot and varying θ. We explore four values for ρ and θ in the interval $[0, 1]$. We choose the values for $\rho = [0.25, 0.5, 0.75, 0.975]$ and $\theta = [0.25, 0.5, 0.75, 0.95]$ (Table 2).

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 SARS, without any isolation effectiveness ($l = 1$) an outbreak can be controlled with 73% pre-outbreak successful vaccination of the population. When $l < 0.15$ (a reduction of at least 75% in the transmissibility of those under isolation), vaccination is unnecessary (see Figure 2).

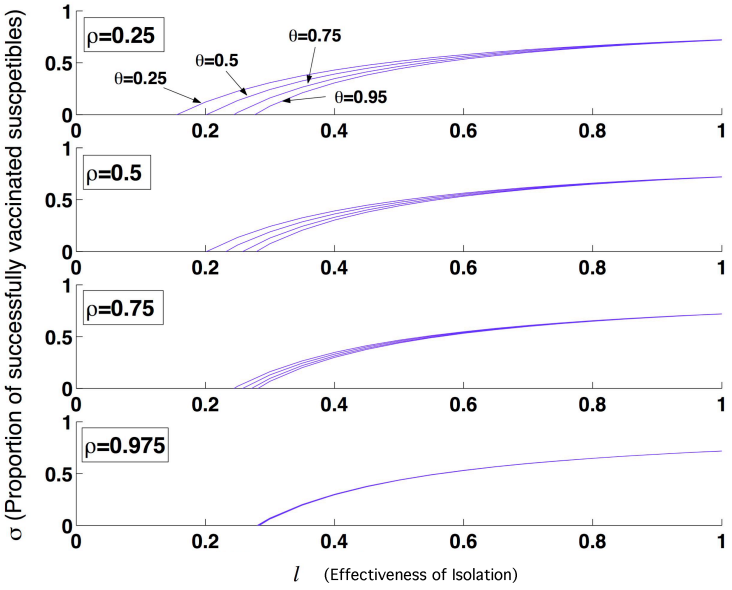

FIGURE 2. $R_0^*(\sigma, l) = 1$ boundary curves to determine the critical vaccination coverage as a function of the isolation effectiveness. When transmission rate $\beta = 0.25$, the minimum pre-outbreak vaccination proportion of the population when isolation is not effective ($l = 1$), is $\sigma = 0.73$.

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 3). When $\beta = 0.15$, it is observed that when isolation is completely ineffective, the minimum proportion of the population needed to be vaccinated does not exceed 54%. When $\beta = 0.4$, this percentage does not exceed 84%.

3.2. **Pre-outbreak vaccination simulations.** We calculated the total number of cumulative cases using numerical simulations while varying σ in two cases: (1) assuming constant isolation effectiveness of $l = 0.4$ (Hong Kong scenario) and (2) assuming improvement of isolation effectiveness over time due to improvement of interventions by using a piecewise function with $l_0 = 0.4$:

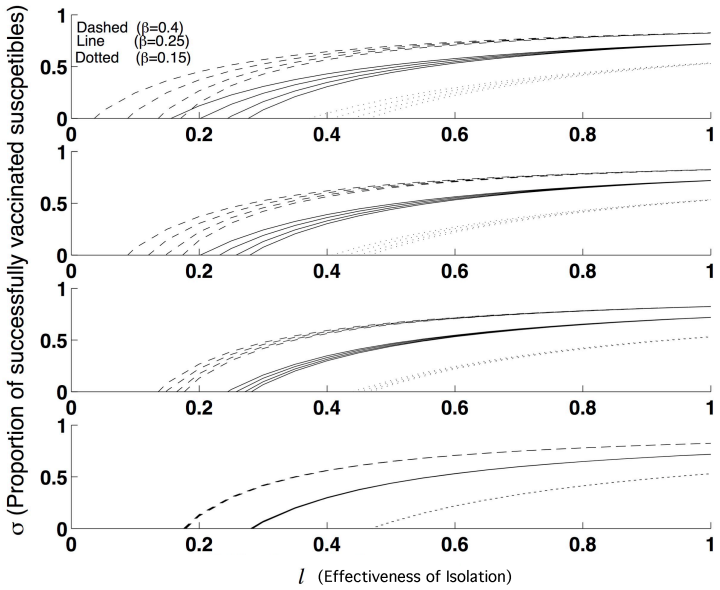

FIGURE 3. $R_0^*(\sigma, l) = 1$ boundary curves for $\beta = [0.15, 0.25, 0.40]$ to determine the critical vaccination coverage as a function of the isolation effectiveness. As β increases, the minimum σ needed to control an outbreak increases.

$$l(t) = \begin{cases} l_0 & \text{if } 0 \le t < 28, \\ 0.5l_0 & \text{if } 28 \le t < 70, \\ 0.3l_0 & \text{if } t \ge 70. \end{cases} \tag{2}$$

Taking an initial value of $l_0 = 0.4$ (from the Hong Kong data) for the first four weeks of the outbreak, parameter l 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 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 [15]. When $\theta = 0.25$ (meaning 25% of the untraced latent individuals self-isolate), the total epidemic size is 53.22% of the total population. When $\theta = 0.95$ (95% of the untraced latent individuals self-isolate) 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.

TABLE 2. R_0^* values for different θ and ρ when $\sigma = 0$ and $l = 0.4$

Parameter	R_0^*	Parameter	R_0^*
$\theta = 0.25$	1.43	$\rho = 0.25$	1.64
$\theta = 0.5$	1.427	$\rho = 0.5$	1.57
$\theta = 0.75$	1.423	$\rho = 0.75$	1.49
$\theta = 0.95$	1.42	$\rho = 0.975$	1.43

However, varying ρ, while fixing all other parameters, has a greater effect on the cumulative cases (see Figure 4 for the changes in the cumulative cases when $\theta = 0.5$ and ρ varies). Again, the values for ρ we test are $\rho = [0.25, 0.5, 0.75, 0.975]$. When $\rho = 0.25$ (25% of the contacts of an average infected person were 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% of the total population size. 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, which is the proportion of untraced latent individuals that self-isolate. We choose $\rho = 0.975$ as in [15]. We assume that 97.5% of the latent people can be traced with modern technology and resources. This estimate is taken from Kaplan et al. [15] on the role of mass vaccination in the case of a smallpox attack in New York City. We assume that the same resources used for tracing smallpox can be used to trace SARS cases.

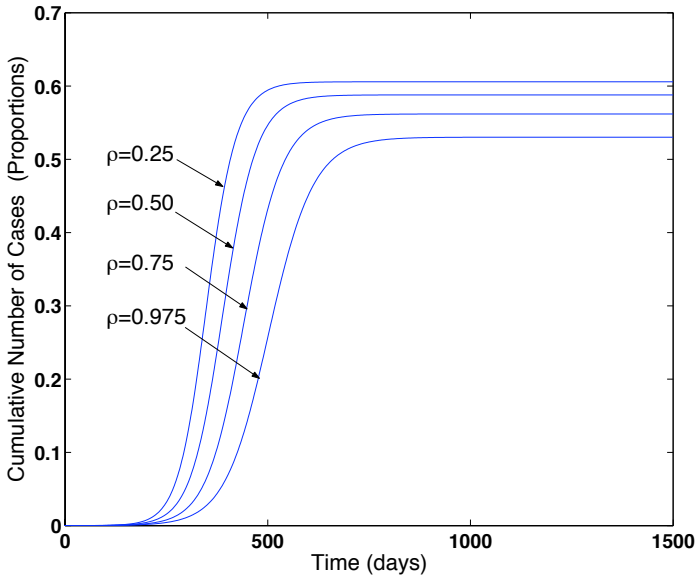

FIGURE 4. Percentage of cumulative number of cases with $\sigma = 0$, $\theta = 0.5$, and $\rho = [0.25, 0.5, 0.75, 0.975]$. There is a more significant change in cumulative cases when varying ρ than when varying θ. The percent change in the total number of cases when $\rho = 0.25$ to $\rho = 0.95$ is a 7.56% decrease.

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

$$\rho(t) = \begin{cases} \rho = 0.5 & \text{if } t < y, \\ \rho = 0.975 & \text{if } t \geq y. \end{cases} \tag{3}$$

That is, we assume that 50% of the latent individuals are traced in 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 time y. We observed that the number of cumulative cases does not change significantly when $\rho = 0.975$ during the entire outbreak.

Using the parameter values from Table 1 and the values for $\theta = 0.5$, $\rho = 0.95$, initial population $N_0 = 10^7$, the initial number of infectious cases $I_0 = 100$ individuals, assuming constant isolation effectiveness during the outbreak, and increasing σ (the proportion of susceptible vaccinated prior to the outbreak), the duration of the outbreak decreases over time. Since a large percentage of latent individuals are traced (97.5%), they are sent directly to the isolation class, W. The increase in the W class causes susceptible individuals to move faster into the infected classes, because a higher number of isolated individuals can infect susceptible individuals. Thus, cases accumulate faster and the outbreak is over sooner (see Figure 5).

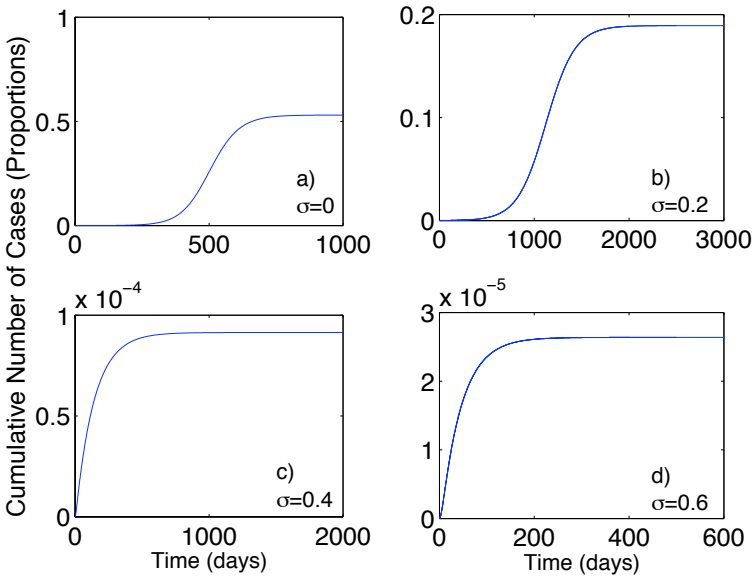

FIGURE 5. The cumulative number of cases over time as a function of σ. For this simulation $l = 0.4$ (Hong Kong data). For $\sigma = 0$ ($R_0^* = 1.43$) the cumulative number of cases is 53.02% of the population size, $\sigma = 0.2$ ($R_0^* = 1.14$) the cumulative number of cases is 18.93%, $\sigma = 0.4$ ($R_0^* = 0.86$) the cumulative number of cases is 0.00914%, $\sigma = 0.6$ ($R_0^* = 0.57$) the cumulative number of cases is 0.0026374%. Initial conditions: $N_0 = 10^7$ and $I_0 = 100$.

To further explore the effect of pre-vaccination on the total number of cases, we construct a plot of the proportion of total cumulative cases from the total population versus σ (see Figure 6). There is a significant reduction in the total number of cumulative cases when $0 \leq \sigma \leq 0.27$. 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 a coverage of 27% will be needed to observe a significant decrease in the total cumulative cases.

Improving isolation during the outbreak, as in equation (2), and increasing σ decreases the duration of the outbreak as well (Figure 7).

If isolation improves earlier than four weeks into the outbreak, there will be a

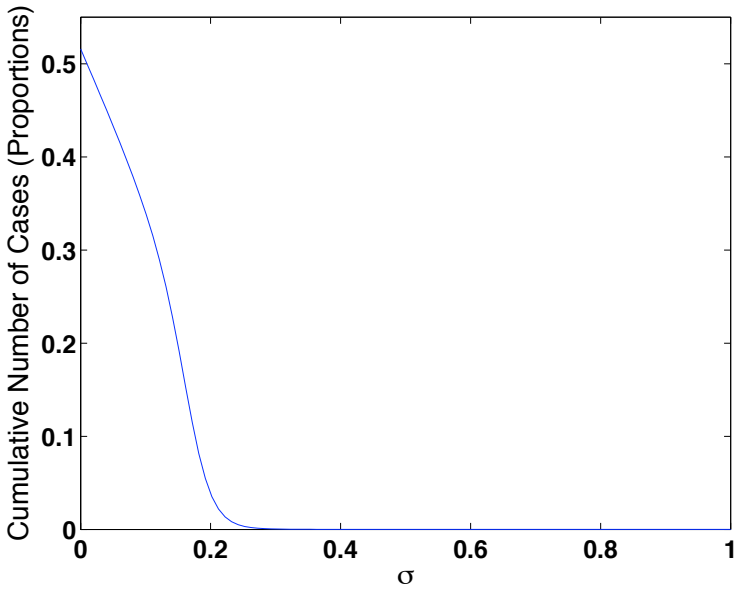

FIGURE 6. The cumulative number of cases as the proportion of successful vaccinated susceptibles σ varies between 0 and 1. For this simulation, $l = 0.4$ (Hong Kong data) and remains constant throughout the outbreak. Initial conditions: $N_0 = 10^7$ and $I_0 = 100$.

smaller number of SARS cumulative cases. If this improvement takes place later in the outbreak, then the number of SARS cumulative cases will increase. However, if $\sigma > 0.3$ (pre-outbreak vaccination), then the outbreak will be controlled, since $R_0^* < 1$ would be achieved. In other words, effectively vaccinating a small proportion of the population before an outbreak occurs will be the best strategy in controlling the outbreak, and no other measure will be needed.

3.3. **During-outbreak vaccination (with or without pre-outbreak vaccination).** 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 $\sigma \in [0, 1]$).

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

Since previous SARS models and recent data did 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.

Health organizations, drug companies, and universities are still searching for a SARS vaccine. The most promising result in the vaccine research has been a recent vaccine tested on four African green monkeys [6]. Even though all four monkeys that received the vaccine became immune to SARS, no conclusions can be drawn

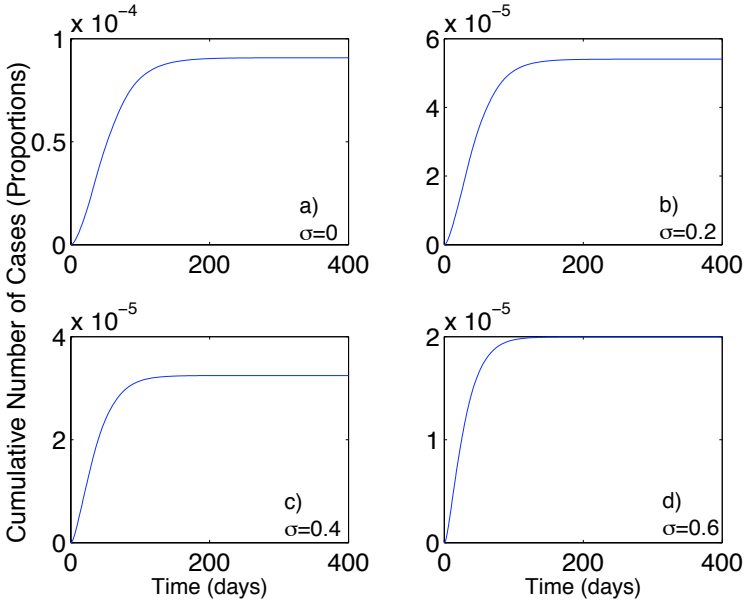

FIGURE 7. The cumulative number of cases over time is changing as the proportion of successful vaccinated susceptibles, σ, changes. For this simulation, the l step-function (eq. (2)) is implemented throughout the outbreak. For $\sigma = 0$ (${R_0}^*_{start} = 1.43$ and ${R_0}^*_{end} = 0.436$) the cumulative number of cases is 0.00908%; for $\sigma = 0.2$ (${R_0}^*_{start} = 1.14$ and ${R_0}^*_{end} = 0.349$) the cumulative number of cases is 0.0054054%; for $\sigma = 0.4$ (${R_0}^*_{start} = 0.856$ and ${R_0}^*_{end} = 0.262$) the cumulative number of cases is 0.003245%; for $\sigma = 0.6$ (${R_0}^*_{start} = 0.571$ and ${R_0}^*_{end} = 0.174$) the cumulative number of cases is 0.0019971%. Initial conditions: $N_0 = 10^7$ and $I_0 = 100$.

yet about its efficacy. Moreover, the SARS vaccine was produced by modifying a vaccine for HPIV3, and in its current form the vaccine would be efficient only for children and infants who are immune to HPIV3 [6, 8]. We assumed the range for the vaccine efficacy to be $0.5 \leq \epsilon \leq 0.9$. To obtain a value for χ, we used data from Kaplan et al. [15]. Using Kaplan et al. [15] estimates, starting with an initial population of 10^7 people, the entire population can be vaccinated in ten days after the start of the epidemic. In our model, we assume that the SARS vaccine will work only for the susceptible population. We assume a range for $\chi \in [0.2, 0.5]$. That is, if susceptible individuals decide to be vaccinated, they can do so within two to five days.

We determine the cumulative number of cases depending on the time at which during-outbreak vaccination is implemented (i.e., after the 30th or 200th day), with constant isolation effectiveness ($l = 0.4$). Table 3 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 3 show that if only during-outbreak vaccination is implemented after 30 days from the start of an outbreak, the total number of cumulative cases will be reduced at least by half, from 53.02% of the population size (no vaccination at all, see Figure 5) to at most 10% ($\chi = 0.5$ and $\epsilon = 0.9$, see Table 3).

TABLE 3. Percentage of cumulative number of cases based on the number of days from the start of an outbreak after which vaccination begins

# of days after which vaccination begins	During-outbreak vaccination $\sigma = 0$	Pre-outbreak $\sigma = 0.2$	and $\sigma = 0.4$	During-outbreak $\sigma = 0.6$
30	$10 - 26\%$	6.35%	0.00913%	0.0026376%
250	$11 - 26\%$	6.41%	0.00913%	0.0026376%
300	$12 - 28\%$	6.44%	0.00913%	0.0026376%
350	$14 - 29\%$	6.48%	0.00913%	0.0026376%
400	$20 - 33\%$	6.54%	0.00913%	0.0026376%
450	$29 - 39\%$	6.62%	0.00913%	0.0026376%

Note: 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: $N_0 = 10^7$, $I_0 = 100$.

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 3). However, the number of days after which during-outbreak vaccination begins has little influence 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 (see Table 3).

4. **Uncertainty and sensitivity analysis.**

4.1. **Uncertainty analysis for R_0^*.** We performed an uncertainty analysis on the effective reproductive number R_0^* using the variability in parameter values. We assume baseline values for α, β, γ_2, and l from [12] 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 [12], based on Hong Kong data. The proportion of successfully vaccinated individuals, denoted by σ, the proportion of individuals traced, ρ, and the proportion of latent individuals that self-isolate, θ, are assumed uniformly distributed in $[0, 1]$. We explore four different distributions for l: $l \sim$ Unif(0,1), that is, l is uniformly distributed in the interval [0,1]; $l \sim$ Beta(a=2, b=2) where the likelihood of l is a bell-shaped curve with mean= 0.5 and variance= 0.05; $l \sim$ Beta(a=1, b=2), which means l decreases linearly in the interval [0,1]; $l \sim$ Beta(a=2, b=1), which means l increases linearly in the interval [0,1] [12]. We sample 10^5 times using these probability distributions for the model parameters. We compute R_0^* using different distributions for l from each sampling set (see Figure 8 when $l \sim$ Beta(a=1,b=2)).

TABLE 4. Results of uncertainty for R_0^* for different distributions of l (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)	1.070	1.63	0.450	69%

Using the cumulative probability density of R_0^*, we determine the probability that $R_0^* < 1$ for different l distributions (see Table 4). The distribution of l that has the most impact on R_0^* is given by $l \sim$ Beta(a=1, b=2), since it yielded the

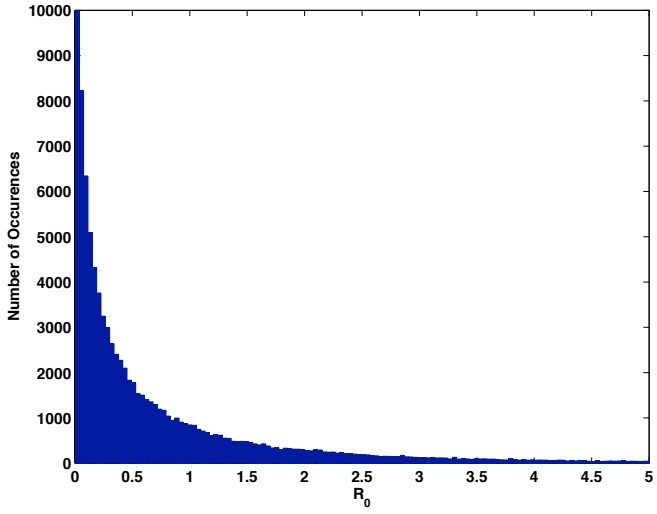

FIGURE 8. Histogram for R_0^* for $l \sim$ Beta(a=1, b=2). The mean of R_0^* is 0.586, with a standard deviation of 1.02. The median is 0.224 and 83% of $R_0^* < 1$.

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 most cases of $R_0^* < 1$ occurred when the distribution for l (isolation effectiveness) was assumed linearly decreasing 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 [16]. We defined the sensitivity index for parameter λ as

$$S_\lambda = \frac{\Delta R_0^*}{R_0^*} \Big/ \frac{\Delta\lambda}{\lambda} = \frac{\lambda}{R_0^*} \cdot \frac{\partial R_0^*}{\partial \lambda},$$

where λ is a parameter in the quantity R_0^*.

When determining the sensitivity of each parameter (see appendix B), we use $\theta = 0.5$ and $\rho = 0.975$ from [15], $l = 0.4$ using estimates from the Hong Kong outbreak [12]. We noticed that parameter l is the most sensitive parameter whenever σ is less than about 0.5. That is, the isolation effectiveness parameter is the most sensitive whenever the pre-vaccination coverage does not exceed about 50% (Table 5 and

appendix B).

TABLE 5. Sensitivity analysis of R_0^*

Sensitivity index	Value
S_σ	-2.3333
S_l	0.9918
S_{γ_2}	-0.5990
S_δ	-0.3946
S_ρ	-0.2035
S_θ	-0.0052
S_α	-0.0040
S_{γ_1}	-0.0023

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

5. **Discussion.** A number of approaches to modeling the transmission and control of SARS have been recently used (e.g., [10, 17, 18, 19, 20, 21, 22, 23]). Here, 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 the possibility of pre-outbreak vaccination. By using parameters estimated from the SARS outbreak in Hong Kong (China) [12], we predict the minimal proportion of susceptibles that need to be successfully vaccinated before an outbreak strikes to achieve control.

The parameters explored most extensively are ρ (the proportion of contacts traced), θ (the proportion of untraced latent individuals that self-isolate), l (the effectiveness of isolation), and σ (the percentage of initial population successfully vaccinated before the outbreak unfolds). We observe that increasing θ does not reduce the total cumulative cases as much 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 go toward improving tracing policies rather than urging people to self-isolate. We explored the scenario when a small percentage of latent individuals are traced at the beginning of the outbreak, and there is 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 computed the reproductive number $R_0^*(\sigma)$ to obtain results for possible outbreak scenarios. By varying ρ, θ, and l in R_0^* we determine a minimum percentage of susceptibles that need to be vaccinated 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 carried out simulations for different SARS outbreak scenarios: 1) using constant isolation effectiveness throughout the outbreak and 2) improving effectiveness during the outbreak. Constant isolation effectiveness ($l_0 = 0.4$ from Hong Kong data), which is our worst-case scenario, leads to a large number of cumulative cases even when vaccination is implemented. If effective isolation is constant, a significant reduction in total cumulative cases is observed after at least 27% of the initial susceptible population is vaccinated.

We also explore during-outbreak vaccination. When the relative isolation effectiveness reduces the transmissibility of the isolation class by 60% (Hong Kong), pre-outbreak vaccination along with during-outbreak vaccination are needed to reduce the total number of cumulative cases in a significant way. Efforts should also be spent on tracing people after the start of the outbreak.

Parameter σ was the most sensitive parameter in the reproductive number R_0^*, whenever pre-vaccination coverage exceeded about 50% ($\sigma = 0.5$) otherwise, isolation effectiveness (via parameter l) was the most sensitive parameter (appendix B). This means that efforts should be spent on strategies that focus on effective isolation of infectious cases followed by a pre-outbreak vaccination strategy (if a vaccine becomes available) and then on improving l, ρ, and θ, respectively.

If a SARS vaccine were to become available, we recommend that vaccination be implemented as soon as a SARS outbreak is identified in some region of world, and if necessary, as soon as SARS cases are identified in the population of interest. Whether vaccination can be administered or not, most efforts should be directed towards improving effectiveness of isolation and tracing policies. The identification and isolation of latent (asymptomatic and not yet infectious) individuals through contact tracing strategies is crucial to achieving global control [24].

Vaccination programs must not only achieve a certain global percentage of coverage but also ensure that such a level is evenly achieved, since pockets of unvaccinated individuals within vaccinated cities may allow the virus to re-invade. Given that SARS is a relatively new infectious disease, a vaccine is lacking, and consequently, so are appropriate data on the vaccine efficacy, conferred immunity, and possible sequelae. Antibody titer decay is also influenced by the age of the host. Therefore, intervention outcomes may be influenced by spatial factors that could be distributed in a complex fashion.

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Appendix A. **The basic reproductive number.** The basic reproductive number (R_0) is defined as the number of secondary cases produced by a "typical" infectious individual at the beginning of an epidemic in a completely susceptible population at a demographic steady state. The reproductive number was computed using the next-generation operator method [13], 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. For our model, it follows that

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

Since the infected classes are E_i, E_n, I, and W, then the dimension of the matrices F and V (the partial derivatives of $\mathcal{F}$ and $\mathcal{V}$ with respect to the infected classes) are 4×4 at the infection-free state ($E_n = E_i = I = W = 0$). Hence,

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

and

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

R_0^* is the spectral radius of FV^{-1}. Hence, $R_0^*(\sigma)$ is given by

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

Appendix B. **Sensitivity indices.** We performed a 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 sensitivity indices in terms of R_0^* and the other parameters (see Table 5):

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

$$S_\sigma = \tfrac{\sigma}{\sigma-1},$$

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

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

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

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

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

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

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