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THE UTILITY OF PREEMPTIVE MASS INFLUENZA VACCINATION IN CONTROLLING A SARS OUTBREAK DURING FLU SEASON

Qingling Zeng

Department of Mathematics and Statistics, York University
4700 Keele Street, Toronto, ON M3J 1P3, Canada

Kamran Khan

The Centre for Research on Inner City Health,
The Keenan Research Centre in the Li Ka Shing Knowledge Institute
of St. Michael's Hospital, University of Toronto
30 Bond Street, Toronto, ON M5B 1W8, Canada

Jianhong Wu

Department of Mathematics and Statistics, York University
4700 Keele Street, Toronto, ON M3J 1P3, Canada

Huaiping Zhu

Department of Mathematics and Statistics, York University
4700 Keele Street, Toronto, ON M3J 1P3, Canada

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Abstract. During flu season, respiratory infections can cause non-specific influenza-like-illnesses (ILIs) in up to one-half of the general population. If a future SARS outbreak were to coincide with flu season, it would become exceptionally difficult to distinguish SARS rapidly and accurately from other ILIs, given the non-specific clinical presentation of SARS and the current lack of a widely available, rapid, diagnostic test. We construct a deterministic compartmental model to examine the potential impact of preemptive mass influenza vaccination on SARS containment during a hypothetical SARS outbreak coinciding with a peak flu season. Our model was developed based upon the events of the 2003 SARS outbreak in Toronto, Canada. The relationship of different vaccination rates for influenza and the corresponding required quarantine rates for individuals who are exposed to SARS was analyzed and simulated under different assumptions. The study revealed that a campaign of mass influenza vaccination prior to the onset of flu season could aid the containment of a future SARS outbreak by decreasing the total number of persons with ILIs presenting to the health-care system, and consequently decreasing nosocomial transmission of SARS in persons under investigation for the disease.

2000 *Mathematics Subject Classification.* 92D30.

Key words and phrases. Severe acute respiratory syndrome (SARS), influenza, respiratory tract infections, mass immunization, disease outbreaks, theoretical models.

1. **Introduction.** When a previously unrecognized infectious disease like SARS emerges, initial control and containment options are often hindered by limited information about the disease's clinical presentation and the absence of a diagnostic test to detect the new pathogen rapidly and accurately. Moreover, the development of a vaccine to prevent disease can take years before becoming available in clinical trials. Thus, early outbreak prevention and control measures typically include developing a case definition for the disease, tracing suspected cases and contacts, isolating persons with compatible symptoms, and quarantining potential contacts. However, if the new disease has a very non-specific clinical presentation, developing an accurate case definition can be problematic [1], thereby significantly compromising downstream public health efforts to identify and control the disease.

As observed during the 2003 SARS outbreak in Toronto, health-care providers were unable to definitively distinguish SARS from other common influenza-like-illnesses (ILIs) by excluding infection with the SARS-associated coronavirus through diagnostic testing. This inability led to the mass isolation and quarantine of thousands of individuals, a process which significantly contributed to public anxiety, had damaging economic consequences, and proved very inefficient in controlling the spread of the disease. An alternate control strategy that was frequently utilized was to confirm the presence of another likely pathogen, such as the influenza virus, as the cause of a particular illness and thus indirectly rule out infection with SARS. Thus, early control efforts can be directed at the new disease itself, or, in some circumstances, towards other diseases with which the new disease might be confused.

This work was inspired by two previous studies: an analysis identifying the most effective and cost-effective strategies to contain a hypothetical outbreak of SARS in New York City during peak respiratory infection season [2]; and a deterministic model focusing on nosocomial transmission of SARS in health-care institutions in Toronto [3]. We should mention here that nosocomial transmission of SARS has been modeled and investigated by others [4, 5, 6, 7, 8, 9, 10, 11].

Herein we examine the potential role of targeting influenza infection as an indirect means to control the transmission of SARS during peak flu season. Specifically, we explore the impact of mass influenza vaccination with the trivalent vaccine prior to the onset of flu season. By significantly reducing the number of ILIs circulating in the general population, fewer persons with ILIs would require medical attention in high risk settings for SARS, thereby minimizing the possibility of ongoing nosocomial transmission. For our analysis, we developed a deterministic compartmental model focusing on the management of persons with non-specific ILIs (a majority of whom would have illnesses other than SARS, such as influenza) who are potentially at risk of developing SARS during their investigation and workup in the health-care setting. Thus, in our model an important parameter is the total number of individuals with ILIs who subsequently seek medical attention in the outpatient or inpatient health-care setting.

2. **Setting up the model.** A deterministic compartmental model, a system of ordinary differential equations, is proposed to describe the dynamics at work that resulted in rapid epidemic growth during the period observed in Toronto. To address the issue of nosocomial transmission, we partitioned the total population into two groups: (1) the general public (GP) and (2) high risk individuals(HR) in health-care settings. We define high risk individuals as patients with clinical symptoms

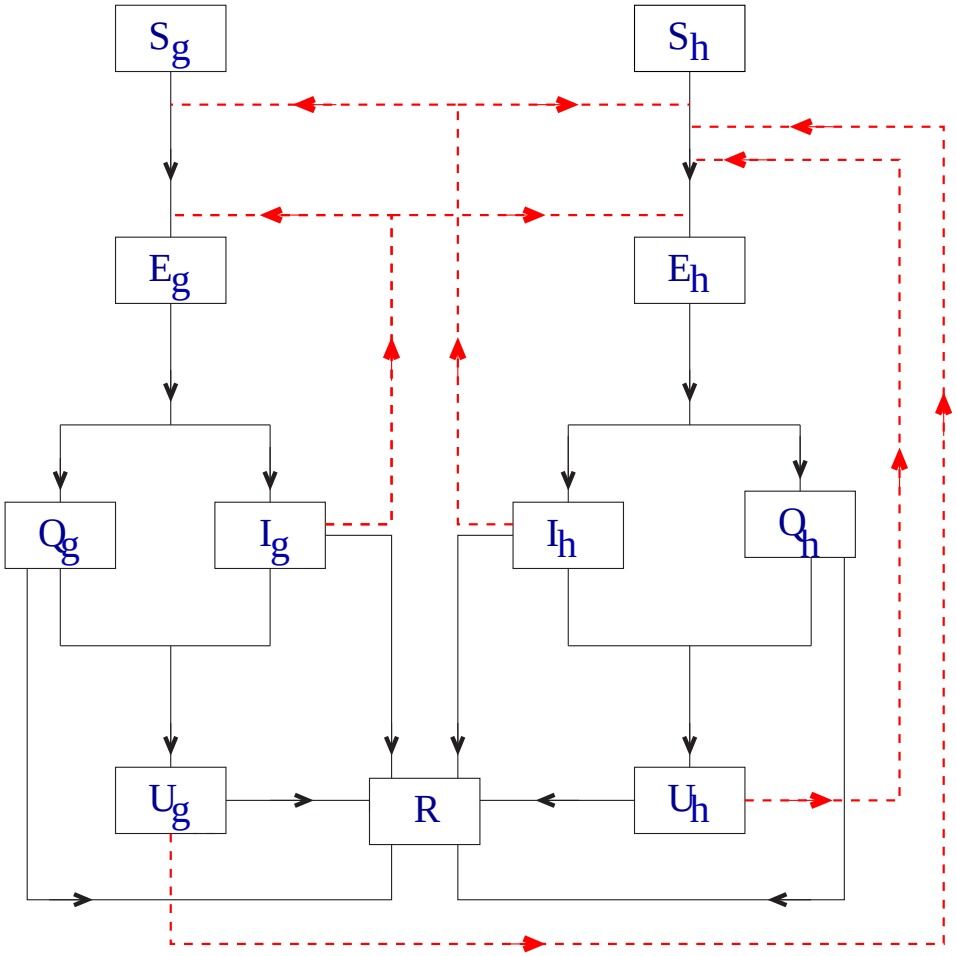


FIGURE 1. Schematic diagram for the transmission of a specific emerging infectious disease in a population divided into the community of the general public and the community of high risk individuals, with each community being further partitioned into compartments.

compatible with SARS and health-care workers working with such patients. In the following, sub-indices g refers to the group of general public and h refers to the (HR) community. Each group consists of susceptible(S), Exposed(E), Infective(I), Quarantined Infective(Q)–infective individuals who are still under the separation and restriction of movement before they are admitted into(or never admitted to) the health-care setting, Cared Infective(U)–infective who are under the care of health-care workers (these individuals are not considered to pose any risk to the general public, but may infect others in HR), and Removed(R)–individuals who have been either exposed or infective, or have died, and who are considered to no longer be susceptible. The model describes the flow, depicted in Figure 1, obtained for the

specific emerging infectious disease:

$$
\begin{cases}
\frac{d}{dt}S_g(t) = -a_g S_g(t)\Big(I_g(t) + I_h(t)\Big); \\
\frac{d}{dt}S_h(t) = -a_h S_h(t)\Big(I_g(t) + I_h(t)\Big) - a_u S_h(t)\Big(U_h(t) + U_g(t)\Big); \\
\frac{d}{dt}E_g(t) = a_g S_g(t)\Big(I_g(t) + I_h(t)\Big) - q_g b_g E_g(t) - (1-q_g) b_g E_g(t); \\
\frac{d}{dt}E_h(t) = a_h S_h(t)\Big(I_g(t) + I_h(t)\Big) \\
\qquad\qquad + a_u S_h(t)\Big(U_h(t) + U_g(t)\Big) - q_h b_h E_h(t) - (1-q_h) b_h E_h(t); \\
\frac{d}{dt}Q_g(t) = q_g b_g E_g(t) - c_g Q_g(t) - r_g Q_g(t); \\
\frac{d}{dt}Q_h(t) = q_h b_h E_h(t) - c_h Q_h(t) - r_h Q_h(t); \\
\frac{d}{dt}I_g(t) = (1-q_g) b_g E_g(t) - c_g I_g(t) - r_g I_g(t); \\
\frac{d}{dt}I_h(t) = (1-q_h) b_h E_h(t) - c_h I_h(t) - r_h I_h(t); \\
\frac{d}{dt}U_g(t) = r_g(I_g(t) + Q_g(t)) - \epsilon_g U_g(t); \\
\frac{d}{dt}U_h(t) = r_h(I_h(t) + Q_h(t)) - \epsilon_h U_h(t).
\end{cases}
\tag{1}
$$

The time scale considered in the above model is assumed to be so short that changes in the values of demographic parameters over time can be ignored, and that the simple mass action law can be used here for the sake of simplicity.

The parameters involved are listed below:

a_g, a_h: the transmission coefficients of infectives for the general public and HR respectively;
a_u: the transmission coefficient of cared infective for HR;
b_g, b_h: the transition coefficients of exposed individuals to the infective class;
c_g, c_h: the transition coefficients of infective individuals to the removed class;
r_g, r_h: the transition coefficients of infectives to the category of cared infectives;
ϵ_g, ϵ_h: the transition coefficients to the removed class. These terms measure the effectiveness of the treatment;
q_g, q_h: the percentages of exposed general public and HR that have been quarantined, respectively.

Table 1 gives values of some parameters, identified mainly from the 2003 Toronto SARS data, to be used for our simulation purpose.

In this model, we tie several control strategies to parameters such as the quarantine rate (q), and the ratio (α) of the number of initial HR susceptible over the number of initial susceptible in the community of GP ($\alpha = \frac{S_h(0)}{S_g(0)}$) can be affected by the different vaccination rates for influenza.

The daily cumulative number of reported probable cases $X(t)$, the total cumulative number of infected and cared infected individuals at time t, from February 23 to May 14, 2003, in Toronto, are available through official reports or statistics in hospital settings (see Figure 2) [14, 15]. We developed our model to correspond to the two

TABLE 1. Partial list of the parameters, from the available sources [12, 13], for the 2003 SARS outbreak in Toronto.

b_g b_h	1/6 1/6	the median time from self-reported exposure to onset of symptoms was 6 days (3-10 days)
r_g r_h	1/3 1/3	the median time until these infective individuals were admitted to the hospitals was 3 days (2-5 days)
c_g c_h	0.003 0.003	SARS-induced mortality per day is 0.003
ϵ_g ϵ_h	0.1 0.1	among patients who survived, the median hospital stay was 10 days (6-15 days)

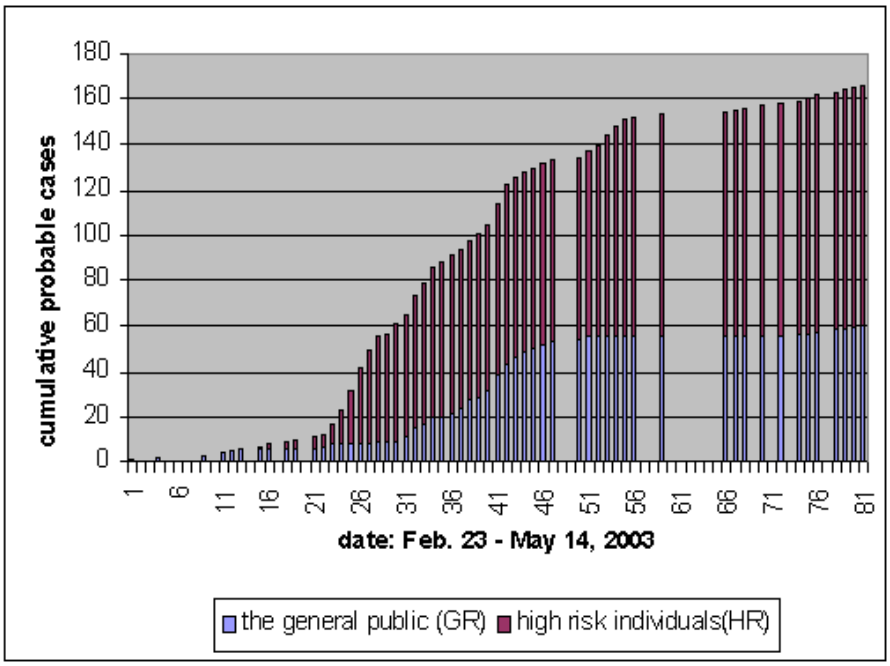


FIGURE 2. The curve of the number of probable cases for the 2003 SARS outbreak in Toronto.

stages of the SARS outbreak in Toronto: stage I (February 23 through March 30, 2003) when no quarantine measures were implemented; stage II (March 31 through May 14, 2003) when implementation of strict infection control precautions in institutional settings, isolation of cases and symptomatic contacts and quarantining asymptomatic close contacts were enforced. We chose the data period February 23 through May 14 for reasons of expediency: it reflects what truly happened clinically and in hospital settings during the first SARS outbreak in Toronto.

To simplify our estimation procedure, we discard the time dependence of each parameter, thus considering the parameters as mean estimates of the variable parameters over the period considered. We use the least squares procedure to estimate

the value of unknown parameters such as contact rates a_g, a_h and a_u in stage I and stage II, respectively.

It should be emphasized that though our model parameters are identified from the 2003 SARS outbreak in Toronto, the methods and techniques developed in this work could be applied to future outbreaks of novel infectious diseases such as pandemic influenza.

3. **Qualitative analysis.** Using the model, we calculated the basic control reproduction number R_0 (the average number of secondary cases of infection generated by a typical infectious individual in a population of susceptible individuals) under the control measures implemented [9, 16, 17] and study how this number changes when the control parameters vary. The total number of the cumulative probable cases $X(\infty)$ during the whole course of the SARS epidemic was calculated and expressed implicitly as a function of the control parameters α and q. The functional relationship between vaccination rate against influenza and quarantine rate for SARS was then analyzed, using the formula.

3.1. **The basic control reproduction number: R_0.** Recall that $\alpha = \frac{S_h(0)}{S_g(0)}$, $S_g(0) + S_h(0) = S(0)$. Let

$$\begin{aligned} A &= a_g\epsilon_g S_g + a_h\epsilon_g S_h + a_u r_g S_h, \\ B &= a_g\epsilon_g S_g q_g + a_h\epsilon_g S_h q_h, \\ C &= (c_g + r_g)\epsilon_g. \end{aligned}$$

Using the standard method developed in [18], we obtain

$$R_0 = \frac{1}{2C}[(A - B) + \sqrt{(A - B)^2 - 4a_g\epsilon_g S_g a_u r_g S_h(q_h - q_g)}] \tag{2}$$

for model (1), where we assume $b_g = b_h$, $c_g = c_h$, $r_g = r_h$, and $\epsilon_g = \epsilon_h$.

If we let $q_g = q_h = q$, then R_0 can be simplified as

$$R_0 = \big[\frac{a_u r_g}{(c_g + r_g)\epsilon_g}\frac{\alpha}{1+\alpha} + \frac{a_h(1-q)}{c_g + r_g}\frac{\alpha}{1+\alpha} + \frac{a_g(1-q)}{c_g + r_g}\frac{1}{1+\alpha}\big]S(0). \tag{3}$$

It is evident from the above formulae that strengthening hospital infection control measures (decreasing a_u) and enforcing quarantine measures (increasing q) can render $R_0 < 1$ if α is fixed. Reducing α can also decrease R_0 significantly.

3.2. **The best scenario.** The model allows us to calculate and predict the number of accumulative probable cases $X(t)$, which includes the accumulative number of cared infective, recovered individuals, and deaths.

We denote $E_g^\infty = \int_0^\infty E_g(s)ds$, and define $Q_g^\infty, I_g^\infty, U_g^\infty, E_h^\infty, Q_h^\infty, I_h^\infty, U_h^\infty$ similarly. We also assume that

$$b = b_g = b_h, \epsilon = \epsilon_g = \epsilon_h, r = r_g = r_h, c = c_g = c_h, q = q_g = q_h, \eta = c_g + r_g = c_h + r_h,$$

$$Q_g(0) = Q_h(0) = 0, I(0) = I_g(0) + I_h(0), U(0) = U_g(0) + U_h(0), E(0) = E_g(0) + E_h(0),$$

$E^\infty = E_g^\infty + E_h^\infty$.

Therefore, if we consider $X(\infty)$ as a function of the two control parameters α and q, we get

$$X_{\alpha,q}(\infty) = X(0) + I(0) + bE^\infty, \tag{4}$$

where E^∞ is solved implicitly, using the following relation:

$$\begin{aligned} bE^\infty \quad &= E(0) + S_g(0)(1 - e^{-\frac{a_g}{\eta} I(0)} e^{-\frac{a_g}{\eta}(1-q)bE^\infty}) \\ &+ S_h(0)(1 - e^{-\frac{a_h}{\eta} I(0)} e^{-\frac{a_u}{\epsilon\eta} rI(0) - \frac{a_u}{\epsilon} U(0)} e^{-\frac{a_h}{\eta}(1-q)bE^\infty} e^{-\frac{a_u}{\epsilon\eta} rbE^\infty}). \end{aligned} \tag{5}$$

Obviously, $X_{\alpha,q}(\infty)$ is a very useful index for policy-makers to decide whether massive quarantine is worthwhile. For example, from the above equation, we can calculate the best scenario when perfect quarantine and hospital procedures can be achieved (i.e., $a_u = 0$ and $q = 1$). This gives

$$\begin{aligned} X_{\alpha,1}^{best} : \quad &= X_{\alpha,1}(\infty) \\ &= X(0) + I(0) + E(0) + \tfrac{1}{1+\alpha} S(0)(1 - e^{-\frac{a_g}{\eta} I(0)}) \\ &+ \tfrac{\alpha}{1+\alpha} S(0)(1 - e^{-\frac{a_h}{\eta} I(0)}). \end{aligned}$$

3.3. **Functional relationship between vaccination rate against influenza and quarantine rate (for SARS).** During a hypothetical SARS outbreak in flu season, α can be quite large, while this ratio can be reduced by preemptive mass vaccination against influenza. A critical issue is the comparison of costs of mass influenza vaccination with quarantine (for those exposed to SARS). For this purpose, we need to answer the following question: When α is increased to $\gamma\alpha$ with $\gamma > 1$, how much should we increase q (to δq with $\delta > 1$) to achieve the same $X_{\alpha,q}(\infty)$? In other words, given $\gamma > 1$, what is δ ($\delta > 1$) such that

$$X_{\gamma\alpha,\delta q}(\infty) = X_{\alpha,q}(\infty)?$$

Using (4) and (5), we obtain

$$\begin{aligned} &\tfrac{1}{1+\gamma\alpha} S(0)(1 - e^{-\frac{a_g}{\eta} I(0)} e^{-\frac{a_g}{\eta}(1-\delta q)bE^\infty}) \\ &\quad + \tfrac{\gamma\alpha}{1+\gamma\alpha} S(0)(1 - e^{-\frac{a_h}{\eta} I(0)} e^{-\frac{a_u}{\epsilon\eta} rI(0) - \frac{a_u}{\epsilon} U(0)} e^{-\frac{a_h}{\eta}(1-\delta q)bE^\infty} e^{-\frac{a_u}{\epsilon\eta} rbE^\infty}) \\ &\quad - \tfrac{1}{1+\alpha} S(0)(1 - e^{-\frac{a_g}{\eta} I(0)} e^{-\frac{a_g}{\eta}(1-q)bE^\infty}) \\ &\quad - \tfrac{\alpha}{1+\alpha} S(0)(1 - e^{-\frac{a_h}{\eta} I(0)} e^{-\frac{a_u}{\epsilon\eta} rI(0) - \frac{a_u}{\epsilon} U(0)} e^{-\frac{a_h}{\eta}(1-q)bE^\infty} e^{-\frac{a_u}{\epsilon\eta} rbE^\infty}) \\ &\quad = 0. \end{aligned} \tag{6}$$

This relationship between γ and δ is important because γ and δ are closely related to the societal costs of strategies for managing a SARS outbreak during a flu season.

4. **Results.** The parameters estimated are a_g, a_h (the contact rates of infectives for the general public and HR respectively) and a_u(the contact rate of cared infective for HR, the latter of which reflects the level of nosocomial transmission) for stage I and stage II respectively.

We start with stage I. In this case, $a_g = a_h$ is a good approximation. Among the 144 early patients, 111 (77 %) were exposed to SARS in the health-care setting during the first stage [12, 19, 20]. The exposures occurred in association with the care of patients who were not diagnosed with SARS but were not practising isolation precautions, and also in association with family members accompanying or visiting the patients in the hospitals. Besides that, clinicians who were initially unaware of the modes of transmission of the SARS coronavirus, had used positive pressure ventilation methods to alleviate respiratory symptoms, inadvertently augmenting dispersion of contagious droplets, which is believed to be one source of transmission of SARS within the hospital settings. Because the changes in the number of susceptible S_g and S_h are very small in the first stage, we can ignore the small changes and treat S_g and S_h as constants. Then we can combine a_g and S_g as one parameter $A_g = a_g S_g$, which means an average infective makes contact sufficient to

transmit infection with A_g persons in GP per unit time. Similarly, we can define another parameter $A_u = a_u S_h$. Also, a_h and S_h are very small, we can ignore the effect of $a_h S_h$ in the model. The total population in GTA is 5081826 [Peel: 988948, Toronto: 2481494, York: 729,254, Halton: 375229, Durham: 506901][21]. This, coupled with reported data from Public Health Agency of Canada [14, 19], gives the initial population data in Table 4.

TABLE 2. Initial conditions for the simulations of stage I (February 23 through March 30), based on 2003 SARS outbreak in Toronto.

$E_g(0)$	$E_h(0)$	$I_g(0)$	$I_h(0)$	$U_g(0)$	$U_h(0)$	$X_g(0)$	$X_h(0)$
6	3	0	0	1	0	1	0

The least square method was used to estimate the parameters $A_g = 0.0723$ and $A_u = 0.2843$. Using the parameter values, we carried out some numerical simulations, reported in Figure 3(a), that provide a very good agreement with the actual data of $X(t)$ in Toronto for the first five weeks of the outbreak. We calculate that $R_0 \approx 3.048 > 1$, which would result in further transmission of SARS and a subsequent outbreak of the disease. The percentage of those getting an infection from HR is $A_u/(A_u + A_g) = 0.2843/(0.2843 + 0.0723) = 0.797$. This calculation is in excellent agreement with the report [12] for the first stage of the 2003 SARS outbreak in Toronto.

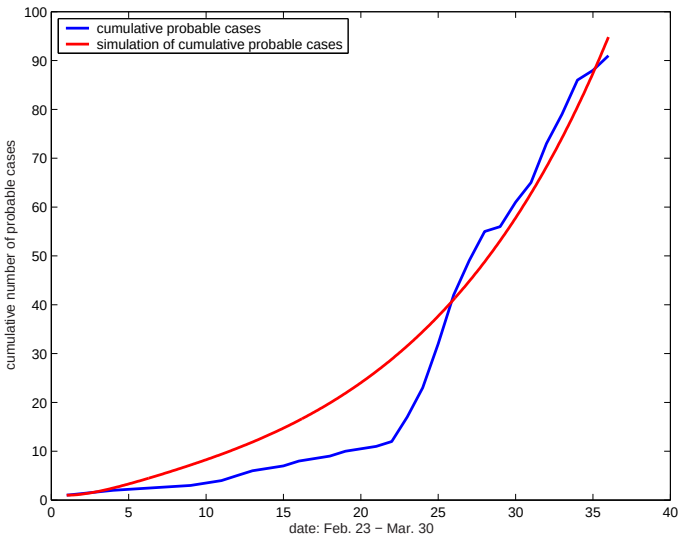
The role of nosocomial transmission was then recognized, and hospitals and other health settings became an obvious focus for SARS control efforts, with particular concern for preventing dispersion of the disease from hospitals back into the surrounding communities. This new focus marked the beginning of the second stage of 2003 SARS outbreak in Toronto (March 31 through May 14, 2003): implementation of strict infection control precautions in institutional settings, isolation of cases and symptomatic contacts, and the quarantining of asymptomatic close contacts.

It is then necessary to estimate the impact of these control measures on a_u, and on $q = q_g = q_h$. From 2132 potential cases of SARS investigated by Toronto Public Health, 23,103 contacts are identified of SARS patients as requiring quarantine, among them 13,291 were confirmed to be in compliance with the quarantine [15], which indicates quarantine rate $q = q_g = q_h = 57.5\%$. The estimation based on the least square method yields $A_g = 0.0701$ and $A_u = 0.0009$, based on the initial conditions for stage II given in Table 4, a table from the combined sources of the reported data from Public Health Agency of Canada [14, 19] and the simulated values in stage I.

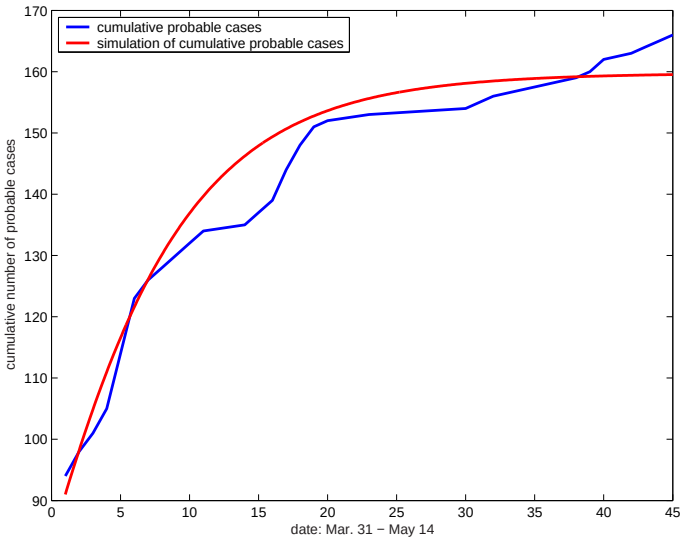
TABLE 3. Initial conditions for the simulations of stage II (March 31- May 14) based on 2003 SARS outbreak in Toronto.

$E_g(0)$	$E_h(0)$	$Q_g(0)$	$Q_h(0)$	$I_g(0)$	$I_h(0)$	$U_g(0)$	$U_h(0)$	$X_g(0)$	$X_h(0)$
21	16	0	0	7	15	10	44	22	69

Figure 3(b) compares the numerical calculation based on the estimated parameters with the actual reported data for the second stage. Using the formulae in section 3, we obtain that the best outcome (after the initial outbreak) would be $X_\alpha^{best} = 154$ when a perfect quarantine ($q = 1$) and isolation measure ($a_u = 0$) can



(a) Stage I (February 23 through March 30, 2003).



(b) Stage II (March 31 through May 14, 2003).

FIGURE 3. Comparison of the simulation of probable cases with real data.

be realized. Note that the total reported number is $X = 166$. The excellent agreement of the simulation with the actual data also provides additional validation of the model and the good estimation of the parameters. The sharp reduction of A_u reflects the effectiveness of the strict control measures within the health-care settings, and the value of $q = 57.5\%$ indicates a very effective, albeit inefficient, quarantine. This reduction of A_u coupled with a moderate value of q yields a small control reproduction number ($R_0 = 0.1$). The combination of the moderate quarantine

and strict hospital infection control procedures were the keys to the containment of SARS in Toronto.

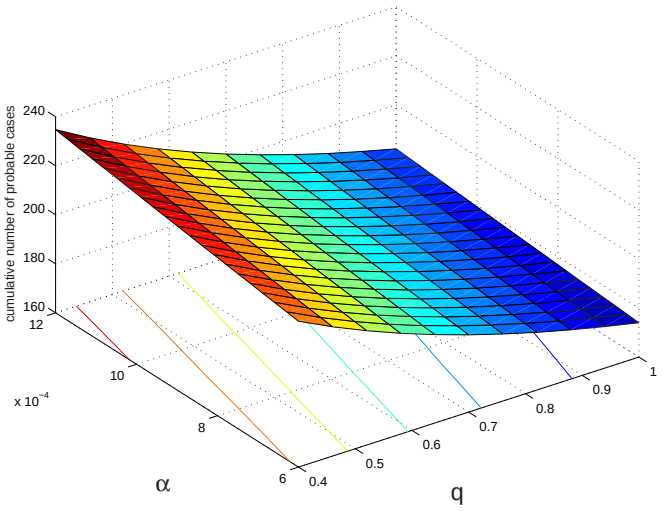
To investigate the potential impact of preemptive mass influenza vaccination on SARS containment during a hypothetical outbreak that coincides with peak flu season, we make the following assumptions:

(1). epidemiologic linkages between SARS cases are not well defined;
(2). SARS cannot reliably be distinguished from other ILIs on clinical grounds alone;
(3). no proven effective treatment for SARS currently exists;
(4). the vaccination is 67 percent effective for preventing influenza;
(5). 10 percent of heath-care workers in the health-care setting are at high risk of contact with SARS.

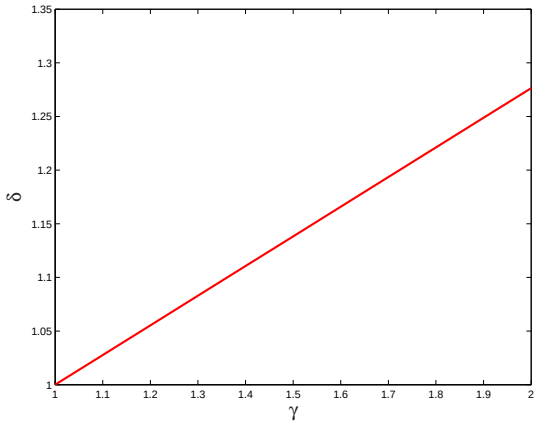
Our goal is to describe the final outcome $X_{\alpha,q,a_u}(45)$ on May 14, 2003, as a function of q, α and a_u. Because the total population in GTA is 5081826 [21], we estimate that a_g is about 10^{-8} in terms of $a_g = A_g/S_g$. We assume $a_g = 5 \times 10^{-8}$, based on the reality that the people in the community still keep their normal social activities and life style. If a SARS outbreak coincides with flu season, patients with SARS or influenza may seek treatment in the same health-care settings. However, it is difficult to know the exact population size in HR. Here we set a baseline of α, then let α vary in a sensitivity analysis. We denote the baseline of $\alpha = 6 \times 10^{-4}$. Because there are about 10 percent of 69,866 health-care workers, including LPN (licensed practical nurses), MD (medical doctors), RN (registered nurses), RT (respiratory therapists), working with patients at high risk for SARS in health-care settings throughout Ontario, and the population of Ontario was approximately 11,410,046 in the year 2001 [22]. Thus the feasible range of α could be in $[6 \times 10^{-4}, 1.2 \times 10^{-3}]$, here the upper boundary is chosen according to Table 2 in [2], which shows that the ratio of persons in the general population presenting with influenza to the health-care system coupled with health-care workers working with patients at high risk for SARS during flu season is around 1.2×10^{-3} (see Appendix 6.1).

We first consider the case where a_u is fixed ($a_u = 2 \times 10^{-6}$, the moderate reduction of a_u based on the simulation on first stage). Figure 4(a) gives a three-dimensional figure for the dependence of $X(45)$ on q and α. Figure 4(b) shows the relation of $X(45)$ with γ and δ. Note that (γ, δ) are correlated in such a way that increasing the ratio α to $\gamma\alpha(\gamma > 1)$ must be compensated by increasing the quarantine rate q to δq ($\delta > 1$) to ensure that the total number of infectives remains unchanged (see section 3). The nearly linear relation between γ and δ shown in Figure 4(b) seems to indicate the insignificant role of preemptive mass vaccination against influenza in the battle against SARS. This is, unfortunately, true only when $a_u = 2 \times 10^{-6}$ is held unchanged whether or not SARS occurs during a respiratory season.

The fact is that when a hypothetical SARS outbreak occurs concurrently with an influenza season, S_h becomes very large as it includes not only health-care workers but also patients with clinical presentations that mimic the symptoms of SARS. If a large number of individuals seek medical attention, difficulties arise in implementing hospital infection control protocols, as such a_u will increase proportionally. Precise relation of a_u on $S_h(0)$ is hard to obtain, we shall assume that if α increases to $n \times \alpha$, then a_u increases to $n^2 \times a_u$. This assumption can be justified following the ideas developed in [17](see Appendix 6.2). So the range for a_u can be taken as $[2 \times 10^{-6}, 8 \times 10^{-6}]$, based on the feasible range of α.



(a) The simulation of (α, q, $X(45)$) at time $t = 45$ (May 14) with a fixed a_u.

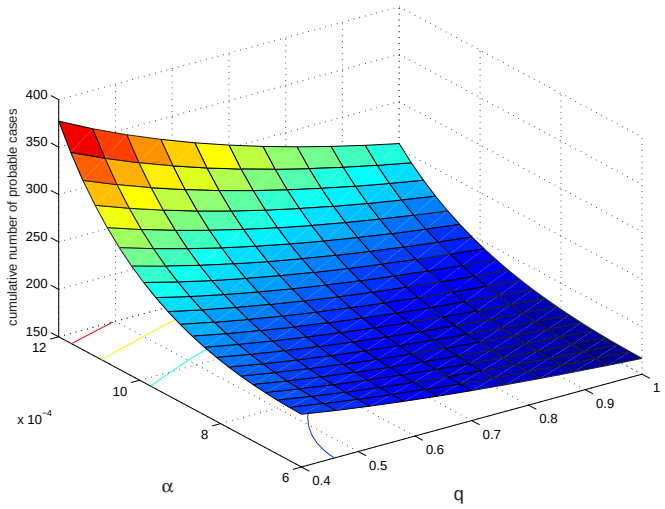


(b) the relationship between γ and δ in order to achieve the same level of infection.

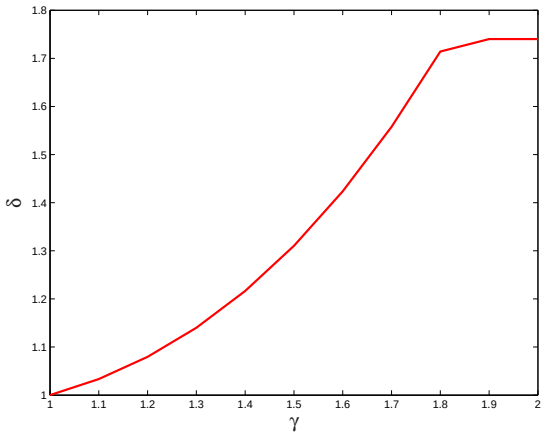
FIGURE 4. The simulations when the transmission rate is fixed ($a_u = 2 \times 10^{-6}$) within the HR community. This rate indicates the insignificant role of preemptive mass vaccination against influenza in the battle against SARS.

The simulation results are summarized in Figures 5(a) and 5(b) and show a significant change. Increasing α to the realistic value 9×10^{-4} yields close to 200 total infections even when the quarantine rate is 100%. When the quarantine rate is 40% (a very high rate of quarantine, considering the large number of individuals with symptoms that are compatible with SARS during flu season), over 250 infections will result.

With $\alpha = 6 \times 10^{-4}$, the relationship between γ and δ becomes highly nonlinear, and δ must be over 1.4 when γ is close to 1.6, which corresponds to a required



(a) The simulation of (α, q, $X(45)$) at time $t = 45$ (May 14) but with an increased a_u.



(b) The relationship between γ and δ in order to achieve the same level of infection.

FIGURE 5. The simulations for an increased transmission rate a_u, where a_u increases to $n^2 \times a_u$ when α increases to $n \times \alpha$ and baseline of a_u is 2×10^{-6}. These two graphs show that by increasing influenza vaccination coverage to a particular threshold among the general population prior the onset of flu season, the need for quarantine to control SARS could be reduced significantly.

quarantine rate $0.575 \times 1.4 = 80.5\%$. From Appendix 6.1, we know $\gamma = 1.70$, 1.56, 1.47, 1.23 corresponding to zero, 30%, 50%, 100% vaccination for influenza respectively, and having 0.67 influenza vaccine effectiveness. It shows that without effective vaccination coverage and in the absence of a reliable and rapid test to distinguish SARS from other common ILIs, mass quarantine becomes the only feasible control strategy, despite its enormous socioeconomic burden for the increase of δ.

5. **Conclusions and discussions.** We examine a hypothetical situation where a SARS outbreak coincides with flu season. Because of the lack of widely available and reliable, rapid diagnostic tests, it is exceptionally difficult to distinguish SARS rapidly and accurately from other ILIs, given the non-specific clinical presentation of SARS.

In a hypothetical SARS outbreak coinciding with the flu season, the combined total number of both flu and SARS patients seeking treatment in the same health-care settings would increase. This would then increase the nosocomial transmission of SARS substantially. We formulate a deterministic mathematical model to address such a scenario and explore the functional relationship between vaccination rate against influenza and quarantine rate for SARS. Doing so allows us to discuss the qualitative impact of mass influenza vaccination on the containment of SARS. Our simulations and analysis show that the combination of effective vaccination coverage for influenza and moderate quarantine would be important strategies in containing an outbreak of SARS that coincides with flu season. By increasing influenza vaccination coverage to a particular threshold among the general population prior the onset of flu season, the need for quarantine to control SARS could be reduced significantly, thereby saving lives and valuable public health resources. Conversely, without effective influenza vaccination coverage, massive quarantine may be the only feasible control strategy for SARS, despite its enormous costs and practical limitations.

6. Appendix.

6.1. Influenza vaccination rate.

Here, we calculate the corresponding γ for different influenza vaccination rates, with a baseline rate of 30%. Effectiveness of the vaccine is estimated to be 0.67 [2], while approximately 0.33 of the general population would become infected with some ILIs during flu season. Among all ILIs, 0.33 are estimated to be resulting from the influenza virus (meaning an estimated 0.1089 of the total population would become infected with influenza).

According to Table 2 in [2], if we assume 0% vaccination coverage for influenza, the proportion of the total population that would likely develop influenza is

$$\frac{0.1089}{1 - 0.30 \times 0.67} = 0.1363.$$

Similarly, for 50% vaccination, $0.1363 \times (1 - 0.5 \times 0.67) = 0.09064$ of population would become infected with influenza; and for 100% vaccination, $0.1363 \times (1 - 1 \times 0.67) = 0.045$ of population would become infected with influenza.

We estimated that 33.4%(33% outpatient, 0.4% inpatient) of the individuals with influenza would seek medical attention. We assume that outpatients would be managed on the same day, while the median stay for inpatients would be ten days [2], and the period for flu season is about 120 days (from the beginning of November to the end of February). Thus the total number of individuals with influenza in the health-care setting per day during flu season would be, in the case of 0% vaccination, calculated as follows:

$$[0.1363 \times 0.33 \times 1 + 0.1363 \times 0.004 \times 10]/120 = 4.21 \times 10^{-4}.$$

Similarly, the total number of individuals with influenza in the health-care setting would be, for 30%, 50% and 100% vaccination percentage, 3.35×10^{-4}, 2.80×10^{-4} and 1.39×10^{-4}, respectively.

Thus, basing on the baseline $\alpha = 6 \times 10^{-4}$, we have the corresponding γ as $(6+4.21)/6 = 1.70$, $(6+3.35)/6 = 1.56$, $(6+2.80)/6 = 1.47$ and $(6+1.39)/6 = 1.23$, to the vaccination rate 0%, 30%, 50% and 100%, respectively.

6.2. **The relation between a_u and α.** We now justify the statement that if α increases to $n \times \alpha$, then a_u increases to $n^2 \times a_u$.

To justify the statement, we need to introduce a few notations following [17].

T_h: expected "handling time" of a susceptible that has been "caught" (the period between being "caught" and being "infected", or called contact duration);
T: total time available to an infective for searching and "infecting";
N_s: the susceptible density within health-care setting;
N: the total population;
a: effective search rate (also called search efficiency) within health-care setting;
T_s: the actual search time (or called search duration);
Z: the number of susceptible "caught" by an infective in time T within a health-care setting.

According to the above definition, we have

$$T_s = T - T_h Z. \tag{7}$$

By Holling's assumption [17], we have

$$Z = aN_s T_s. \tag{8}$$

Using equations (7) and (8), we obtain

$$Z = \frac{aN_s T}{1 + aN_s T_h}.$$

Therefore,

$$\frac{Z}{T} = \frac{aN_s}{1 + aN_s T_h},$$

where Z/T is the number of susceptible persons caught per unit of time by an infective within the health-care setting. Let $C(N_s) = Z/T$, an average infective makes contact sufficient to transmit infection with $aN_s/(1 + aN_s T_h)$ susceptible within health-care setting per unit of time. Since

$$C(N_s)(S_h/N)I = a_u S_h I,$$

where S_h/N is the probability that a random contact by an infective with a susceptible, we have

$$a_u = \frac{C(N_s)}{N} = \frac{1}{N}\frac{aN_s}{(1 + aN_s T_h)}.$$

Because the contact duration is very short for respiratory illness, we can assume $T_h \to 0$, and hence we obtain

$$a_u = \frac{aN_s}{N} \tag{9}$$

In [17], the effective search rate a is the product of the area covered per unit of time while searching and the probability that a susceptible existing in this area is actually "caught". Since the area is fixed, but the probability that a susceptible individual in this area is actually "caught" is proportional to the patient's time in the health care setting which is proportional to the density N_s, we argue that a is proportional to N_s. Therefore, from equation (9), a_u is proportional to N_s^2, a fact which implies that if α increases to $n \times \alpha$, then a_u increases to $n^2 \times a_u$.

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REFERENCES

[1] T. H. Rainer, P. A. Cameron, D. Smit, K. L. Ong, A. N. W. Hung, D. C. P. Nin, et al., Evaluation of WHO criteria for identifying patients with severe acute respiratory syndrome out of hospital: prospective observational study. BMJ 326 (2003), 1354-1358.

[2] K. Khan, P. Muennig, M. Gardam, J. G. Zivin, et al., Managing Febrile Respiratory Illnesses during a Hypothetical SARS Outbreak. Emerging Infectious Diseases 11(2): 191-200, 2005. Available online at: http://www.cdc.gov/ncidod/EID/vol11no02/04-0524.htm.

[3] G. F. Webb, M. J. Blaser, H. Zhu, S. Ardal, J. Wu, Critical Role of Nosocomial Transmission in the Toronto SARS Outbreak. Math. Biosc & Eng. 1 (2004), 1-13.

[4] M. Lipsitch, T. Cohen, B. Cooper, J. M. Robbins, S. Ma, J. Lyn, et al., Transmission dynamics and control of severe acute respiratory syndrome. Science 300 (2003) 1966-70.

[5] S. Riley, C. Fraser, C. A. Donnelly, A. C. Ghani, L. J. Abu-Raddad, A. J. Hedley, et al., Transmission Dynamics of the Etiological Agent of SARS in Hong Kong: Impact of Public Health Interventions. Science 300 (2003) 1961-66.

[6] G. Chowell, P. W. Fenimore, M. A. Castillo-Garsow, and C. Castillo-Chavez, SARS outbreaks in Ontario, Hong Kong and Singapore: the role of diagnosis and isolation as a control mechanism. J Theoret Biol 224 (2003), 1-8.

[7] G. Chowell, C. Castillo-Chavez, P. W. Fenimore, C. M. Kribs-Zaleta, L. Arriola, J .M. Hyman, Model Parameters and Outbreak Control for SARS. Emerging Infectious Diseases 10(7): 1258-1263, 2004. Available online at: http://www.cdc.gov/ncidod/EID/vol10no7/03-0647.htm.

[8] W. Wang, S. Ruan, Simulating the SARS outbreak in Beijing with limited data. J. Theoret. Biol. 227 (2004), 369-379.

[9] A. B. Gumel, S. Ruan, T. Day, J. Watmough, F. Brauer, P. van den Driessche, J. Wu, et al.,Modelling strategies for controlling SARS outbreaks. Proc.R.Soc.Lond.B, 2004 (doi:10.1098/rspb.2004.2800).

[10] Y. H. Hsieh, C. W. S. Chen, S. B. Hsu, SARS outbreak, Taiwan, 2003. Emerging Infectious Diseases. 10(2): 201-206, 2004. Available online at: http://www.cdc.gov/ncidod/eid/vol10no2/03-0515.htm.

[11] Y. H. Hsieh, C. C. King, C. W. S. Chen, M. S. Ho, J. Y. Lee, et al., Quarantine for SARS, Taiwan. Emerging Infectious Diseases 11 (2): 278-282, 2005. Available online at: http://www.cdc.gov/ncidod/EID/vol11no02/04-0190.htm.

[12] C. M. Booth, L. M. Matukas, G. A. Tomlinson, A. R. Rachlis, D. B. Rose, H. A. Dwosh, et al., Clinical features and short-term outcomes of 144 patients with SARS in the Greater Toronto area. JAMA 289(2003) 2801-10.

[13] BBC news, Ministers may review SARS status. 2003. http://news.bbc.co.uk/1/hi/health/2979623.stm.

[14] Public Health Agency of Canada, 2003a. Archive Reports: Severe Acute Respiratory Syndrome(SARS) Cases, Canada and International. http://www.phac-aspc.gc.ca/sars-sras/sars.html#numbers.

[15] T. Svoboda, B. Henry, L. Shulman, E. Kennedy, E. Rea, T. Wallington, et al., Public Health Measures to Control the Spread of the Severe Acute Respiratory Syndrome during the Outbreak in Toronto. N. Engl. J. Med., 350 (2004), 2352-2361.

[16] R. M. Anderson, & R. M. May, Infectious Diseases of Humans. Oxford University Press, London, 1991.

[17] O. Diekmann and J. A. P. Heesterbeek, Mathematical Epidemiology of Infectious Diseases: Model Building, Analysis and Interpretation. Wiley, New York, 2000.

[18] P. van den Driessche, J. Watmough, Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission. Math. Biosci. 180 (2002), 29-48.
[19] Public Health Agency of Canada, 2003b. SARS Epidemiologic Summaries: April 26, 2003. http://www.phac-aspc.gc.ca/sars-sras/pef-dep/sars-es20030426_e.html.
[20] CDC (Centers for Disease Control), Severe Acute Respiratory Syndrome (SARS). 2003. http://www.cdc.gov/ncidod/sars/index.htm.
[21] Census (2001 Census information), 2001 Census GTA Population Comparison. 2001. http://www.region.peel.on.ca/planning/stats/2001/2001_pop_gta.htm.
[22] CIHI(Canadian Institute for Health Information), Health Personnel Trend in Canada, 1993-2002. 2004.

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E-mail address: qlzeng@mathstat.yorku.ca
E-mail address: km.khan@utoronto.ca
E-mail address: wujh@mathstat.yorku.ca
E-mail address: huaiping@mathstat.yorku.ca