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The potential of targeted antibody prophylaxis in SARS outbreak control: A mathematic analysis

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KEYWORDS
- SARS
- Antibody prophylaxis
- Outbreak control
- Mathematical model
- Reproduction number

Summary
Background: Severe acute respiratory syndrome (SARS) coronavirus-like viruses continue to circulate in animal reservoirs. If new mutants of SARS coronavirus do initiate another epidemic, administration of prophylactic antibodies to risk groups may supplement the stringent isolation procedures that contained the first SARS outbreak.

Method: We developed a mathematical model to investigate the effects of hospital admission and targeted antibody prophylaxis on the reproduction number $R$, defined as the number of secondary cases generated by an index case, during different SARS outbreak scenarios.

Results: Assuming a basic reproduction number $R_0 = 3$, admission of patients to hospital within 4.3 days of symptom onset is necessary to achieve outbreak control without the need to further reduce community-based transmission. Control may be enhanced by providing pre-exposure prophylaxis to contacts of hospitalized patients, and through contact tracing and provision of post-exposure prophylaxis. Antibody prophylaxis may also be employed to reduce $R$ below one and thereby restrict outbreak size and duration.

Conclusions: Patient isolation alone can be sufficient to control SARS outbreaks provided that the time from onset to admission is short. Antibody prophylaxis as supplemental measure generally allows for containment of higher $R_0$ values and restricts both the size and duration of an outbreak.

Introduction
Severe acute respiratory syndrome (SARS) was the first major outbreak of a newly emergent communicable disease in the 21st century, affecting over 8000 persons on multiple
of control. Its appearance stirred an unprecedented coordinated effort to control transmission and morbidity, motivated by fears that local outbreaks might give rise to a major pandemic within months. From the onset, mathematical modeling has proven to be a very useful tool for evaluating the impact of the control measures instigated.2–4

The SARS outbreak originated in the Guangdong province of China, from where it spread to Hong Kong and next to Vietnam, Singapore and Canada. On 15 March 2003, the World Health Organization (WHO) issued a second global alert together with a name for the new disease and a case definition.1 The outbreak was fully contained by July 2003, the last case occurring in Canada. SARS coronavirus, the causative agent of the new disease,5,6 most likely was transmitted to humans by the masked palm civet (Paguma larvata).7 Adaptation to human transmission is possible through a single mutation in the spike glycoprotein of a civet SARS-like virus.8,9 As SARS-like viruses continue to circulate in animal reservoirs,10,11 the risk of another major outbreak remains.

The identification of measures that make SARS controllable is key in planning a public health response to future outbreaks.12 Measures that successfully controlled the 2003 SARS epidemic could probably be supplemented by specific antiviral strategies, such as protective ring vaccination or targeted antibody prophylaxis. Although a protective vaccine against SARS is still elusive, antibodies with neutralizing capacity have been characterized, specifically human monoclonal antibodies directed against the spike glycoprotein of SARS coronavirus.13 Prophylactic administration of such an antibody in ferrets before intratracheal challenge with a high dose of human SARS coronavirus completely prevented the development of lung pathology and abolished viral shedding in pharyngeal secretions.14 These data suggest that antibody prophylaxis might offer clinical protection against SARS and block air-borne transmission of SARS coronavirus.

To evaluate the potential of antibody administration as prophylaxis in SARS outbreak control, we designed a mathematical model. In this model a distinction was made between SARS transmission before and after an infected individual was hospitalized. We considered two qualitatively different strategies of antibody administration: first, pre-exposure prophylaxis targeted at susceptible persons coming into contact with hospitalized SARS cases (e.g. health care workers or close friends and relatives); and second, post-exposure prophylaxis targeted at exposed persons having been identified through contact tracing of hospitalized SARS cases. Based on our model, we derived an expression for the effective reproduction number of SARS to study conditions for containment and we explored how the size and duration of an outbreak depend on the efficacy of control.

**Methods**

**Mathematical model**

The model is a modification of the discrete-time SEIR model,15 the modification being that we distinguish between infectious individuals in the community and those that are hospitalized and possibly put in quarantine (Fig. 1). We suppose that death or recovery only occur after a person has been admitted to hospital. In addition, we suppose that those infected or removed constitute only a small fraction of the total population, i.e. $S$ is taken to be approximately constant. This simplifies the transmission dynamics to an essentially linear system. Consequently, the model does not apply to the stage of an epidemic where saturation of incidence will occur due to high prevalence of infection and/or natural immunity.

To allow for time-dependent transition and transmission probabilities, we divided every state into categories that denote either the time since infection or the time since onset of clinical symptoms. Within each model state and category, independent identically distributed Bernoulli trials are performed for every person to determine whether an asymptomatically infected person becomes symptomatic and thus infective (probability $\phi$); whether a symptomatic and infectious person is admitted to hospital (probability $\eta$); or whether a hospitalized patient recovers or dies from complications due to SARS (probability $\gamma$). The parameter $\phi$ depends on the time since infection, whereas the parameters $\eta$ and $\gamma$ depend on the time since onset of clinical symptoms. The infectivity of an individual also depends on the time since onset of clinical symptoms.

The time from infection to onset of clinical symptoms and the duration of the symptomatic period reflect specific biological features of the virus–host interaction. We assume that their distributions are not affected by intervention measures. The assumption of invariant distributions seems reasonable because therapeutic treatment is currently not available for SARS coronavirus infection. It follows that hospitalization does not alter the overall duration of the symptomatic period, although it may affect infectivity. Conversely, the conditional probability that a hospitalized patient recovers or dies from complications due to SARS depends on the cumulative probability that a person has

![Figure 1](https://example.com/figure1.png)
been admitted to hospital, as follows:

\[ \phi_t = \frac{(F_t - F_{t-1})}{(1 - F_{t-1})}, \]
\[ \eta_t = \frac{(H_t - H_{t-1})}{(1 - H_{t-1})}, \]
\[ \gamma_t = \frac{(G_t - G_{t-1})}{(H_t - G_{t-1})}. \]

Here, \( F_t \) denotes the cumulative probability that an infected person becomes symptomatic at or before day \( t \) of infection; \( G_t \) denotes the cumulative probability that a symptomatic person recovers or dies at or before day \( t \) of disease; and \( H_t \) denotes the probability that a symptomatic person is admitted to hospital at or before day \( t \) of disease.

With \( \beta_t \), we denote the expected number of secondary infections at day \( t \) since onset of clinical symptoms. It is the product of the infectivity of an infected individual and the daily number of close contacts with susceptible persons. For simulation purposes, we assume that the number of secondary infections follows a Poisson distribution with expectation \( c/\beta_t \), with \( c < 1 \).

**Reproduction number**

Let \( h_t \) denote the unconditional probability that a person is admitted to hospital at day \( t \) of disease. Let \( u_{t,k} \) be the probability that a person admitted to hospital at day \( t \) of disease is not discharged at or before day \( t + k \). We assume that discharge only occurs after a person has been admitted to hospital, hence \( G_t < H_t \). The probability that a person is not discharged at or before day \( t + k \), conditional on being admitted to hospital at day \( t \), is

\[ u_{t,k} = \prod_{j < k} \frac{(H_{t+j} - G_{t+j})}{(H_{t+j} - G_{t+j-1})}. \]

The reproduction number of an infectious disease is defined as the expected number of secondary cases generated by an index case. Assuming that transmission before onset of clinical symptoms does not occur, the reproduction number can be formulated as

\[ R = \sum_t (1 - H_t) \beta_t + \sum_t h_t \sum_k u_{t,k} c/\beta_{t+k}. \]

We assume that \( F_t \) and \( G_t \) are both determined by the biological features of the virus and the human host. In contrast, \( H_t \) and \( \beta_t \) will change through adaptive behavior, although the extent to which these can be manipulated is limited by infrastructural and behavioral constraints. Given functions for the distribution of onset-to-admission time and transmission rate before the implementation of public health measures, we define the basic reproduction number \( R_0 \) as the average number of secondary cases before intervention is in place.

**Intervention strategies**

General control measures are those not specifically aimed at SARS coronavirus infection per se. In this paper, we focus on transmission rate reduction following hospitalization (lowering \( c \)) and shortening the time from onset of disease to hospital admission (altering \( H_t \)). Contact rate reduction in the general population, also known as social distancing, will affect the expected number of secondary infections for any day prior to hospitalization (altering \( \beta_t \)).

Administration of antibodies can be considered in two ways. Pre-exposure prophylaxis is aimed at preventing infection, whereas post-exposure prophylaxis to persons already infected may prevent clinical symptoms and block further transmission. To this end, we define \( v_t \) as the probability that a contact of a person who transmitted infection at day \( t \) of disease will be supplied with antibodies before development of symptomatic disease. Let \( w_{t,k} \) denote the conditional probability that a person who transmitted infection at day \( t \) of disease is hospitalized at day \( t + k \), then we can write

\[ v_t = \sum_k w_{t,k}(1 - F_{t+k})p. \]

Here, \( p \) denotes the traceable fraction of an index case’s contacts, where we adopted a fixed duration of \( r \) days for a contact to be traced. If transmission occurs within the hospital, \( w_{t,0} = 1 \) and the expression reduces to

\[ v_t = (1 - F_t)p. \]

Else, \( w_{t,k} \) should be evaluated conditional on the probability of not being admitted to hospital before day \( t \). Hence,

\[ w_{t,k} = \frac{(H_{t+k} - H_{t+k-1})}{(1 - H_t)}. \]

If we assume that contact tracing with post-exposure prophylaxis will be performed once pre-exposure prophylaxis has brought hospital-based transmission to an end, then the expected number of secondary cases generated by an index case reduces to

\[ R = \sum_t (1 - H_t)(1 - v_t)\beta_t. \]

We define the critical immunization coverage as the minimal fraction \( p \) of contacts traced within \( r \) days to be immunized in order to reduce \( R \) below one given a particular \( R_0 \).

**Parameter values**

Model parameters and their baseline values are listed in Table 1. \( F_t \) has been fitted to a gamma distribution with mean 4.6 days and variance 15.9 days$^2$. \( G_t \) was obtained by fitting a Weibull distribution to the times from symptom onset to either death or recovery. Using percentage survival minus discharge from hospital as reported for three age categories,$^{16}$ we obtained a mean duration of 24.3 days. Taken together, the total time spent in compartments \( E \) and \( I \) thus averages 1 month.

The expected number of secondary infections at day \( t \) since onset of clinical symptoms was assumed to obey the functional form:

\[ \beta_t = a_1 \exp[-a_2 t]. \]

This form is suggested by the observation that viral load in pharyngeal secretions peaks in the second week after onset of clinical symptoms and declines thereafter.$^{17}$ Additional follow-up studies of viral shedding showed that one in four SARS patients still tested positive 1 month after symptom onset.$^{18}$ By fitting \( \beta_t \) to the percentage testing positive over time we obtained an estimate of the parameter \( a_2 \). The
Table 1 Overview of model parameters and their baseline values.

| Model parameter                  | Notation | Baseline value |
|----------------------------------|----------|----------------|
| Basic model                      |          |                |
| Basic reproduction number*       | $R_0$    | 3              |
| CDF of transition to infectious stage³ | $F$      | Gamma ($\mu = 4.6$, $\sigma^2 = 16$)³ |
| CDF of recovery or death³        | $G$      | Weibull ($\alpha = 2.1$, $\beta = 28$)³ |
| CDF of hospital admission³       | $H$      | Gamma ($\mu = 7.4$, $\sigma^2 = 27$)³ |
| Relative transmission rate in hospital** | $c$      | 0.20           |
| Secondary infections per person per day | $N$     | Poisson ($\lambda = \beta_i$)⁷⁷ |
| Infectivity per person per day   | $\beta_i$| 0.129: $\exp(-0.114t)$⁷⁷ |
| Antibody prophylaxis¹⁰            |          |                |
| Fraction susceptible after immunization | $e$  | —              |
| Traceable fraction of contacts   | $p$      | —              |
| Duration of contact tracing      | $r$      | —              |

*Before implementation of control measures.¹⁹

¹³The mean and variance of the distribution are denoted by $\mu$ and $\sigma^2$, respectively.

³Cumulative distribution function in days since onset of clinical symptoms.¹⁶

⁴The shape and scale of the distribution are denoted by $\alpha$ and $\beta$, respectively.

**Before implementation of control measures.³

⁷Fitted to the percentage SARS patients with viral shedding in nasopharyngeal aspirate.¹⁷,¹⁸ and subsequently scaled to $R_c$.¹⁹

¹⁰Applies to model with pre- and/or post-exposure antibody prophylaxis.

A product of infectivity and contact rate was subsequently rescaled through $\alpha_i$ to obtain a given basic reproduction number $R_0$. The average number of secondary cases generated by an index case before the issuance of the first global SARS alert was approximately 3, but varied substantially over time and between geographic locations.¹⁹

Scaling of $\beta_i$ preserves knowledge of $H$, and $c$. $H$, was assumed to follow a gamma distribution, with variance set equal to $\frac{1}{2}$ mean.²,¹² As we obtained most parameters from the literature pertaining to the 2003 SARS outbreak in Hong Kong, we scaled infectiousness conditionally on a mean time from onset of disease to diagnosis of 7.4 days, which was the average interval for hospital admission during the weeks prior to the first global SARS alert.¹⁹ In line with initial estimates that hospitalized patients transmitted infection at about 20% of the rate of symptomatic patients in the community,³ we took a baseline value $c = 0.20$.

### Results

#### Conditions for outbreak control

An outbreak cannot be contained whenever the expected number of secondary infections generated by an index case exceeds one. The condition for outbreak control can be formulated as

$$\theta R + (1 - \theta) R < 1.$$  

Here, $\theta$ is the proportion of secondary infections occurring prior to hospital admission. Clearly, an outbreak can only be contained when the average index case has not transmitted infection prior to hospital admission. Thus, $\theta R < 1$ is a necessary condition for outbreak control. If this condition is not met, community-based transmission is enough to sustain epidemic growth.

The condition $\theta R < 1$ can be met through social distancing or through admission interval reduction. Using baseline parameter values, we estimate $\theta R_0 = 2.09$, i.e. with a mean admission interval of 7.4 days approximately two out of every three infections occur prior to hospital admission. If social distancing alone was to account for outbreak control, contact rate would have to decline by $(R_0 - 1)/R_0 = 96\%$. Shortening the time from onset of disease to hospital admission and thereby decreasing the opportunity for community-based transmission, is more efficient to control the spread of SARS. An average admission interval of 4.3 days would bring $\theta R$ just below one. However, at $c = 0.20$ the number of secondary infections occurring within hospitals is in itself enough to sustain epidemic growth with an admission interval of 4.3 days (Fig. 2a). Hospital transmission rate needs to be less than 15% of community-based transmission in order to achieve $R < 1$ without having to rely on contact rate reduction in the general population (Fig. 2b).

The SARS outbreaks in 2003 were characterized by a considerable degree of heterogeneity in the number of secondary cases generated by an index case.¹⁹ Epidemic curves were particularly shaped by the occurrence of clusters of exceptionally high transmission, termed “super-spreading events” (SSEs).³,¹⁸ The extent to which SSEs affect the reproduction number of infection depends on their relative frequency and magnitude,³ and these in turn determine the opportunity for outbreak control. We therefore investigated the robustness of control through admission interval reduction and patient isolation procedures in the containment of SARS transmission over a range of basic reproduction numbers.

Reduction of the admission interval is insufficient to contain SARS outbreaks with $R_0 = 3$ at $c = 0.20$. If patients were already admitted to hospital before onset of clinical symptoms, corresponding to a zero admission interval, an hospital outbreak could be contained if $R_0 < 2.2$ at $c = 0.20$; if $R_0 < 4.5$ at $c = 0.10$; or if $R_0 < 9.0$ at $c = 0.05$ (Fig. 2c). Reducing the relative rate of hospital transmission thus...
facilitates control over an extended range of \( R_0 \) values, especially for short admission intervals.

### Pre-exposure antibody prophylaxis

Pre-exposure prophylaxis targeted at susceptible persons coming into contact with hospitalized SARS patients could be very effective in reducing hospital transmission. Even if prophylaxis would have limited efficacy, the range of reproduction numbers over which outbreak control can be achieved may increase significantly. If patients are already admitted to hospital before onset of clinical symptoms, the range of reproduction numbers that can be contained increases by a factor \( e^{-1} \), where \( e \) denotes the fraction of the target population that remains susceptible in spite of immunization. As an example, if antibody prophylaxis would render three out of four persons non-susceptible to infection, i.e. \( e = \frac{1}{4} \), the range of reproduction numbers that can be contained would increase by a factor four (Fig. 2c).

The range of reproduction numbers that can be contained with an admission interval greater than zero may also improve significantly through targeted pre-exposure antibody prophylaxis. If hospital transmission could be blocked completely, the range of \( R_0 \) values that can be contained increases steeply with admission interval reduction (Fig. 2c). When general measures (such as patient isolation procedures) are able to reduce hospital transmission rate to \( c = 0.05 \), outbreaks can be contained if \( R_0 < 5.0 \) with a 2-day admission interval. Pre-exposure antibody prophylaxis targeted at those coming into contact with hospitalized SARS patients could improve the condition for outbreak control to \( R_0 < 6.8 \) for \( e = \frac{1}{4} \) and to \( R_0 < 8.4 \) for \( e = \frac{1}{2} \).

### Post-exposure antibody prophylaxis

The critical coverage of an index case’s contacts that must be supplied with post-exposure prophylaxis to achieve \( R < 1 \) increases with \( R_0 \) and with the time from onset of disease to hospital admission. For large admission intervals, outbreak control via contact tracing and post-exposure prophylaxis is only possible with relatively low transmissibility. For instance, full coverage with a 5-day admission interval would just suffice to keep an outbreak at bay if \( R_0 < 4.2 \), assuming no transmission occurs after hospitalization and 1

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**Figure 2** The reproduction number \( R \), the number of secondary cases produced by an index case, in relation to the time from onset of disease to hospital admission and the rate of hospital transmission relative to community-based transmission. (a) and (b) are based on a basic reproduction number \( R_0 = 3 \) which corresponds to a mean admission interval of 7.4 days and a relative rate of hospital transmission \( c = 0.20 \) (see Table 1). The dotted line in (a) refers to the condition for containment \( R < 1 \). In (b), the dotted line refers to the baseline value of \( c = 0.20 \). (c) shows how the condition for containment depends on the basic reproduction number, with the dotted line referring to the baseline value \( R_0 = 3 \).
day is needed for a contact to be traced, i.e. \( c = 0 \) and \( r = 1 \) (Fig. 3a). With a 2-day admission interval, full coverage could be sufficient to contain an outbreak characterized by \( R_0 < 27 \). Post-exposure prophylaxis generally extends the range of \( R_0 \) values that can be contained, but the extent to which control is facilitated depends on the admission interval.

The extent to which post-exposure prophylaxis in the community can enhance control is also limited by the time that is required for contact tracing. The range of reproduction numbers that can be contained declines when more days are needed for a contact to be traced. For instance, with \( p = 0.50 \) the range of reproduction numbers that can be contained with a 2-day admission interval reduces from \( R_0 < 15.3 \) to \( R_0 < 13.2 \) if contact tracing takes 3 days instead of one (Fig. 3b). Ongoing hospital transmission effectively reduces the range over which control can be achieved, especially for less effective contact tracing (Fig. 3c).

**Outbreak size and duration**

Antibody prophylaxis may be employed to achieve \( R < 1 \) if this has not been achieved already through admission interval reduction and patient isolation procedures. Antibody prophylaxis might also be employed to reduce \( R \) below one. The size and duration of an outbreak become increasingly restricted as \( R \) approaches zero. As the number of secondary infections follows a Poisson distribution, the probability of an index case not transmitting infection is \( \exp(-R) \). The distribution of the size of an outbreak \( X \) generated from \( n \) initial cases is of the form:

\[
P(X = x; n) = nx^{x-n-1}R^{n-x} \exp(-xR)/(x! - n!)
\]

This distribution is appropriately defined for \( x \geq n \) and \( R < 1 \). When \( R \) is reduced by a factor \( \varphi \) then the probability that no transmission occurs from \( n \) initial cases increases by a factor \( \exp((1-\varphi)pR) \). On the other hand, the probability that an outbreak generated from \( n \) initial cases attains a final size \( x > n \) decreases by a factor \( \varphi^{x-n} \exp((1-\varphi)pR) \). From this it can be inferred that the expectation of the size of an outbreak diminishes as \( R \) approaches zero. The benefit of antibody prophylaxis in reducing \( R \) below one was verified by stochastic simulation.

Estimates of outbreak size and duration are based on a thousand model runs, each seeded with \( n = 10 \) initial cases and \( R_0 = 3 \). In simulations, the average time from onset of disease to hospitalization is assumed to decline from the baseline value of 7.4 to 3 days once the first couple of SARS patients have been identified. Hospital transmission rate is set at 5% of community-based transmission. These measures

![Figure 3](image-url)
yield $R = 0.87$, hence they are in principle enough to contain an outbreak. To investigate the additional benefit of antibody prophylaxis, we compare this baseline model to a model with pre-exposure prophylaxis, given to all persons who come into contact with hospitalized SARS patients, and to a model with both pre- and post-exposure prophylaxis, given to a fraction of persons contacted prior to hospital admission. In the latter model, it is assumed that 50% of contacts can be traced within 2 days of an index case’s hospital admission.

An outbreak may take considerable time to subside if public health measures result in $R = 0.87$ (Fig. 4a). The total size of an outbreak expected from $n = 10$ initial cases is 109 (SD 97), while it takes on average 176 (SD 90) days until the last patient is discharged from hospital. Pre-exposure prophylaxis, given to all persons who come into contact with hospitalized SARS patients, results in $R = 0.56$ (Fig. 4b). The impact of this reduction in the reproduction number is readily apparent, with outbreak size and duration decreasing to 33 (SD 16) cases and 75 (SD 19) days, respectively. Adding post-exposure prophylaxis with $p = 0.50$ and $r = 2$ days to the spectrum of control measures further reduces the reproduction number to $R = 0.44$ (Fig. 4c). Accordingly, the expected size of the outbreak is decreased to 26 (SD 11) cases and the time until the last patients is discharged from hospital is decreased to 68 (SD 15) days.

The normal variation on a double logarithmic scale implies highly skewed distributions for both outbreak size and duration. Indeed, large-scale outbreaks represent a significant proportion of outcomes with $R = 0.87$. The 95th percentiles for outbreak size and duration are 295 cases and 346 days, respectively (Fig 4a). Large outbreaks are still possible, yet they become less likely, at lower reproduction numbers. The 95th percentile of outbreak size is 66 cases with $R = 0.56$ (Fig. 4b) and 47 cases with $R = 0.44$ (Fig. 4c).

Further reductions may be achieved through faster and more effective contact tracing or through admission interval reduction. With a 2-day interval for hospital admission and 1 day for contact tracing, $R = 0.20$ and the 95th percentiles of outbreak size and duration are 31 cases and 77 days, respectively (Fig. 4d).

**Discussion**

In this paper we present a generic model for the initial stage of a SARS epidemic and evaluate the effect of different infection control measures on the reproduction number $R$, defined as the number of secondary cases generated by an index case. Specifically, we studied how targeted administration of prophylactic antibodies might supplement stringent patient isolation procedures in a future SARS outbreak. Mathematical analysis and numeric simulation demonstrate that the addition of antibody prophylaxis to control measures generally allows for containment of higher $R_0$ values and restricts both the size and duration of an outbreak.

![Figure 4](image-url) Scatter plots of outbreak size versus duration in 1000 stochastic model runs for simulated outbreaks with $n = 10$ initial cases. In (a), general control measures are chosen such that $R = 0.87$. Supplemental measures may yield $R = 0.56$ (b), $R = 0.44$ (c) or $R = 0.20$ (d), thus restricting both outbreak size and duration. Outbreak size is the cumulative number of persons infected, including the $n = 10$ initial cases. Outbreak duration is the time until the last patient is discharged from hospital. The shaded area demarcates the 95th percentiles of outbreak size and duration.
Our model differs from most published mathematical SARS models,\textsuperscript{3,4,21–23} in that we allow for non-constant infectivity over the course of infection. There is strong evidence that viral shedding slowly increases over the course of infection and reaches a peak in the second week after onset of clinical symptoms,\textsuperscript{7,16} suggesting that the assumption of a constant infectivity does not hold. Analysis of a model using non-constant infectivity revealed that control of SARS through patient isolation was mainly established due to the relatively late infectivity peak during infection.\textsuperscript{16} Hence, failure to capture this aspect in the transmission dynamics of SARS could have led to misleading conclusions.

Our approach differs from other mathematical SARS models where non-constant infectivity was used,\textsuperscript{12,24} in that we explicitly allow for an asymptomatic period of infection during which transmission does not occur. Hence, our model cannot be classified an "age of infection" model because infectivity depends on the time since onset of clinical symptoms rather than the time since infection. An "age of infection" model would allow transmission to occur before onset of clinical symptoms, a supposition that is—in the case of SARS—not supported by data. However, our conclusions would not alter if we allowed for the possibility of pre-symptomatic transmission given that infectivity in the early stages of infection would be typically low.\textsuperscript{17,18}

Finally, our model is parameterized through empirically defined waiting times. It has recently been demonstrated that ignoring the latent period of infection or making the common approximation of exponentially distributed waiting times gives rise to overly optimistic predictions for the outcome of control strategies.\textsuperscript{25} Although we have made simplifications in other aspects, notably the assumption of a constant pool of susceptible individuals, we feel that the model accurately describes the initial stage of an epidemic.

It has been pointed out before that patient isolation can in principle contain an outbreak of SARS, provided that the time from onset to admission is short.\textsuperscript{12} The contribution of other measures in the control of the 2003 SARS epidemic, e.g. quarantine of exposed individuals and widespread use of facemasks, is debatable. A modeling study aiming at simulating the potential response to SARS in Japan concluded that quarantine of the exposed population would be one of the most effective policy procedures.\textsuperscript{21} It has even been suggested that, despite the considerable costs involved, quarantine measures in Canada have not only saved lives but also costs.\textsuperscript{22} This impact of quarantine is remarkable given the lack of pre-symptomatic transmission of SARS. Within our modeling framework, the benefit of quarantining exposed individuals can only be interpreted in terms of admission interval reduction and contact rate reduction for any day prior to hospitalization. Our results are in line with the finding that personal protection measures in the general population (such as the use of facemasks) offer little protection to the community.\textsuperscript{26} We also demonstrate that patient isolation procedures alone will not prevent a SARS epidemic if the transmission rates are only slightly increased compared to the outbreaks in 2003, unless additional measures—such as contact tracing—are put in place. These findings are reminiscent of modeling results obtained for smallpox control.\textsuperscript{12,26,27}

If new variants of SARS coronavirus do initiate another epidemic, the question is to what extent they will resemble the etiologic agent of the first outbreak. The 2003 SARS epidemic was characterized by a high degree of heterogeneity in the number of secondary cases generated by an index case.\textsuperscript{3,18} Whether this heterogeneity represents variability in viral biology or host behavior is unclear, but the available data suggests that SARS can be highly contagious. As the etiologic agent of SARS continues to circulate in natural host species it may evolve into a more transmissible strain.\textsuperscript{10,11} To maximize the opportunity of containment of potentially more transmissible SARS coronavirus variants, and to minimize the size and duration of an outbreak, existing control strategies should be supplemented with specific antiviral strategies. Passive immunization would seem appropriate in a contingency situation, as it can provide a person with instant albeit short-lived protection against infection and could also be used as a post-exposure prophylaxis to prevent disease progression. In rabies, passive immunization is commonly used in combination with vaccination to prevent rabiexposed individuals from becoming symptomatic.\textsuperscript{28}

Community-wide containment of infectious disease outbreaks by means of antibody prophylaxis has only been described in a number of cases. In the late 1980s, an outbreak of hepatitis A in a religious community provided an opportunity to assess the impact of immune globulin on the course of the outbreak.\textsuperscript{29} Here, the incidence of hepatitis among immune globulin recipients stopped 2 weeks after a 5-day campaign of mass administration.\textsuperscript{29} Passive immunization using polyclonal sera has also been reported to prevent infection with respiratory viruses.\textsuperscript{30} We have previously characterized monoclonal antibodies directed against the spike glycoprotein of SARS coronavirus,\textsuperscript{13} which were highly effective when tested in ferrets.\textsuperscript{14} Results from pre-clinical development demonstrate that a combination of two monoclonal antibodies against SARS acts synergistically,\textsuperscript{31} hinting at the prospect of an antibody cocktail as a feasible and efficient prophylaxis. The monoclonal antibody cocktail is targeted at two distinct epitopes on the receptor-binding domain of the spike glycoprotein, one of which recognizes the residue that was critical for adaptation to human transmission.\textsuperscript{8,13,31} Evolution towards human transmission of novel SARS-like coronaviruses would likely require the same adaptation, thus preserving the neutralization potential of the antibody cocktail in case a new SARS outbreak occurs.

The extent to which antibody prophylaxis may enhance SARS outbreak control measures hinges on the transmissibility of the disease and on the effectiveness with which general infection control measures are introduced. A comprehensive contingency plan for controlling future SARS outbreaks should aim to maximize the range of $R_0$ values that can be contained, and to minimize the size and duration of an outbreak. Our analysis demonstrates that antibody prophylaxis would be an effective addendum to the array of existing public health measures to control SARS.

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