



## Timely identification of optimal control strategies for emerging infectious diseases <sup>☆</sup>

Zhilan Feng <sup>a</sup>, Yiding Yang <sup>a</sup>, Dashun Xu <sup>a,1</sup>, Pei Zhang <sup>a,2</sup>, Mary Mason McCauley <sup>b</sup>, John W. Glasser <sup>b,\*</sup>

<sup>a</sup> Department of Mathematics, Purdue University, 150 North University Street, West Lafayette, IN 47907, USA

<sup>b</sup> National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, 1600 Clifton Road, NE Atlanta, GA 30333, USA

### ARTICLE INFO

#### Article history:

Received 4 December 2008

Received in revised form

24 February 2009

Accepted 3 March 2009

Available online 14 March 2009

#### Keywords:

Mathematical modeling

Emerging infections

Outbreak-control strategies

Social responses

### ABSTRACT

**Background:** Health authorities must rely on quarantine, isolation, and other non-pharmaceutical interventions to contain outbreaks of newly emerging human diseases.

**Methods:** We modeled a generic disease caused by a pathogen apparently transmitted by close interpersonal contact, but about which little else is known. In our model, people may be infectious while incubating or during their prodrome or acute illness. We derived an expression for  $\mathfrak{R}$ , the reproduction number, took its partial derivatives with respect to control parameters, and encoded these analytical results in a user-friendly Mathematica™ notebook. With biological parameters for SARS estimated from the initial case series in Hong Kong and infection rates from hospitalizations in Singapore, we determined  $\mathfrak{R}$ 's sensitivity to control parameters.

**Results:** Stage-specific infection rate estimates from cases hospitalized before quarantine began exceed those from the entire outbreak, but are qualitatively similar: infectiousness was negligible until symptom onset, and increased 10-fold from prodrome to acute illness. Given such information, authorities might instead have emphasized a strategy whose efficiency more than compensates for any possible reduction in efficacy.

**Conclusions:** In future outbreaks of new human diseases transmitted via close interpersonal contact, it should be possible to identify the optimal intervention early enough to facilitate effective decision-making.

Published by Elsevier Ltd.

### 1. Introduction

Early in 2003, a physician infected while treating patients with atypical pneumonia in Guangdong Province, China, infected other travelers in their Hong Kong hotel. On returning home to Singapore, Taiwan, Toronto, and Vietnam, they transmitted the pathogen causing the disease, later named severe acute respiratory syndrome (SARS), to local residents. Global spread of this hitherto unknown pathogen led WHO to issue travel advisories and some national health authorities to quarantine travelers from affected areas. As subsequent infections were largely nosocomial, hospital infection-control procedures were increasingly enforced. Absent knowledge of the onset of infectiousness, local authorities also quarantined community contacts.

Faced with an infectious disease of unknown etiology, policy-makers acted quickly (Gerberding, 2003). Case-series were among the earliest sources of information (e.g., presenting symptoms, duration of distinguishable clinical stages, and outcomes). Upon isolation of the etiologic agent, experience with illnesses caused by related pathogens became germane. While these actions were thoughtful, in retrospect some were unnecessary. We have since developed a model with which policymakers could use similar information—which should be available in future outbreaks, especially of new diseases causing serious morbidity—to assess the likely impact of available interventions.

Because identifying infected people before they become ill is difficult, quarantine is inefficient; e.g., only 11 of 238 probable cases were identified before symptom onset in Singapore (Tan, 2005) and 24 of 480 in Taiwan (Hsieh et al., 2005). Isolating people with symptoms that may herald disease, especially if they might have been exposed to someone since diagnosed, would be more efficient. Impact is proportional to the product of efficiency and efficacy, which must exceed  $1 - 1/\mathfrak{R}_0$  for control, where  $\mathfrak{R}_0$  is the average number of sufficiently intimate contacts for transmission while infectious. Consequently, infected people must be highly infectious or infectious long before becoming ill for quarantine to be a better strategy than simply encouraging those

<sup>☆</sup> The opinions expressed by authors do not necessarily reflect those of the Centers for Disease Control and Prevention or other institutions with which they are affiliated.

\* Corresponding author. Tel.: +1404 639 8780; fax: +1404 639 1307.

E-mail address: [jglasser@cdc.gov](mailto:jglasser@cdc.gov) (J.W. Glasser).

<sup>1</sup> Mathematics Department, Southern Illinois University, Mail Code 4408, 1245 Lincoln Drive, Carbondale, IL 62901, USA.

<sup>2</sup> 1130 South Michigan Avenue, Apartment 3305, Chicago, IL 60605, USA.

with early symptoms to seek care and ensuring their proper disposition.

To weigh possible interventions to control infectious disease outbreaks, modelers must faithfully represent transmission. Our model allows infected people to become infectious before or after becoming ill. It permits quarantine while asymptomatic or isolation on seeking medical care and being diagnosed, at rates and with efficiencies that depend on clinical stage. Because health communications could influence these social phenomena, our model also allows hospitalization rates during distinguishable clinical stages to evolve. How effectively cases are isolated, when authorities begin searching for their contacts, if ever, and the proportion found, also may vary temporally.

Policymaking is difficult enough with accurate and complete information, neither of which is available during outbreaks of new diseases. Using only the Hong Kong case series (Lee et al., 2003; Tsang et al., 2003) and admissions to Tan Tock Seng Hospital (TTSH) through 24 March, when quarantine began, we estimated that infected people were not particularly infectious until acutely ill, a consensus reached months later (WHO, 2003). As the distribution of infectiousness largely determines the intervention of choice (Fraser et al., 2004; Day et al., 2006), this information is critical.

Armed with such results, we might have dissuaded policymakers from quarantine, suggesting they instead encourage people with symptoms that might herald disease to seek care, especially if exposed to someone since diagnosed, and—if indicated—ensure their proper isolation. This would have minimized the number of non-infected individuals detained without substantially compromising efficacy. Besides recommending the most promising interventions in future outbreaks, we could revise early estimates of parameter values as additional or better information became available, monitor intervention impacts, and recommend changing course if necessary. This would ensure the best possible use of available public health resources and minimize social disruption.

The belief that quarantine contributed substantially to the control of SARS persists despite the modest number of secondary infections that could have been prevented (e.g., the product of roughly 0.9 secondary infections per probable case in Singapore<sup>3</sup> and 11 probable cases quarantined—assuming perfect isolation and no competing risks—is roughly 10 cases). But modeling enables one to calculate final outbreak sizes with and without interventions conditional on others (i.e., to relax both assumptions). Moreover, 116 possible contacts per probable case were restricted to their homes in Taiwan, 316 including travelers (Hsieh et al., 2005). In Singapore and Beijing, 38 and 13 contacts per probable case were restricted, respectively (Tan, 2005; Pang et al., 2003). As others cared for these well, but unproductive people, the economic cost was enormous.

## 2. Methods

To assist in controlling other newly emerging diseases, we modeled a generic respiratory illness caused by pathogens transmitted by close interpersonal contact. To evaluate actual interventions for SARS, we estimated some biological parameters from the case series in Hong Kong, adjusted others to fit clinically diagnosed probable cases in Singapore, and calculated outbreak sizes under alternative scenarios. Motivated by the social cost of

quarantine relative to its contribution to control in Singapore, we also derived analytical expressions policymakers could use with limited information to determine the most effective strategy for controlling future outbreaks of new human diseases.

### 2.1. Sojourn distributions

Because models are hypotheses, their predictions must be evaluated and the causes of any disparities identified and remedied (Quine and Ullian, 1970), especially before use to inform public policy. Because complex models are difficult to evaluate, Einstein advocated modeling as simply as possible (May, 2004). To simplify, modelers commonly assume individuals move among disease stages at constant specific rates, whereupon sojourns are exponentially distributed. A property of exponential distributions—that time spent in any stage is independent of time elapsed before entry—is inconsistent with the natural history of infectious diseases.

Depending on one's purpose, this discrepancy between biology and mathematics may be inconsequential. But it affects conclusions about the impact of quarantine and isolation (Feng et al., 2007), public health interventions differing only in timing. The gamma distribution does not have the memory-less property, so is more realistic biologically (Wearing et al., 2005). Models with gamma distributed sojourns are equivalent to ones in which stages of duration  $T$  are composed of  $n$  sub-stages each with duration  $T/n$ .

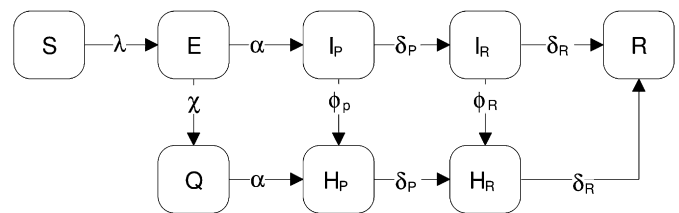
To illustrate the difference, Feng et al. (2007) use the expected remaining sojourn at time-in-stage  $s$ ,  $M_n(s)$ . For the gamma distribution with  $n \geq 2$ ,

$$M_n(s) = \int_0^\infty \frac{p_n(t+s)}{p_n(s)} dt = \frac{1}{p_n(s)} \int_0^\infty p_n(t) dt$$

$$= \frac{1}{n\theta} \frac{\sum_{k=0}^{n-1} \sum_{j=0}^k \frac{(n\theta s)^j}{j!}}{\sum_{k=0}^{n-1} \frac{(n\theta s)^k}{k!}}$$

As  $M'_n(s) < 0$  and  $\lim_{s \rightarrow \infty} M_n(s) \rightarrow T/n$ , here  $T = 1/\theta$ , evidently  $M_n(s)$  strictly decreases with stage time  $s$ . When  $s$  is large, moreover, the expected remaining sojourn can be as small as  $T/n$ . Hence, time remaining depends on time already spent. The gamma distribution [ $p_n(s)$  for  $n \geq 2$ ] thus provides a more realistic description of disease natural history than the exponential [ $p_1(s)$ , for which  $M_1(s) = T$  for all  $s$ ].

Feng et al. (2007) derived a system of ordinary differential equations from a general integral equation model suitable for evaluating quarantine and isolation by replacing the exponential with the gamma distribution. Our model resembles theirs (Fig. 1), but we distinguish the prodrome and acute respiratory phase and allow infected people to become infectious before or after becoming ill, at rates—products of contact rates and probabilities of transmission on contact—that may differ among stages.



**Fig. 1.** Minimum states (susceptible,  $S$ ; incubating,  $E$ ; ill,  $I$ ; immune,  $R$ ) and state-transition processes (infection,  $\lambda$ ; progression to the prodrome,  $\alpha$ ; and through acute illness,  $\delta$ ; quarantine,  $\chi$ ; hospitalization,  $\phi$ ), required to represent control of emerging infectious diseases transmitted via close contact via non-pharmaceutical interventions.

<sup>3</sup> The 206 clinically diagnosed probable cases caused 190 secondary infections. Thirty-two suspect SARS patients were reclassified as probable post-discharge by virtue of laboratory test results, but we do not know how many secondary infections they caused.

2.2. Empirical methods

Our model's biological parameters derive mostly from observations of early SARS patients in Hong Kong (Lee et al., 2003; Tsang et al., 2003). We estimated time-varying control parameters by minimizing sums of squared differences between cumulative model hospitalizations,  $\chi E + \phi_P I_P + \phi_R I_R$ —where  $\chi E$  are those hospitalized from quarantine and  $\phi I$  from successive symptomatic stages, denoted by subscripts—and probable cases admitted to Tan Tock Seng Hospital (TTSH). We estimated these parameters twice, once from the first 30 days of hospital admissions (Table 1), before quarantine began, and once from admissions during the entire outbreak (Table 2).

As we were uncertain of many parameter values, we chose either gamma or triangular distributions for Latin hypercube sampling (Table 3). From the literature just mentioned, we obtained mean values for  $1/\alpha$ ,  $1/\delta_P$  and  $1/\delta_R$  of 6, 4, and 8 days, respectively. Because the gamma's mean is the product of its parameters, here called  $A$  and  $B$ , we know that  $B = \text{mean}/A$ . Note that  $A = 1$  corresponds to the exponential distribution, and that the gamma's variance decreases with increasing  $A$ . We chose  $A = 3$  for all three distributions, and thus,  $B = \frac{6}{3} = 2$ ,  $\frac{4}{3}$ , and  $\frac{8}{3}$ , respectively. ( $A = 3$  also corresponds to three sub-stages in these respective states.) As for their upper and lower values, we chose ones for which the area under the probability density function (pdf) in between was 95–98%. Similarly, for the gamma distributions of  $\beta_E$ ,  $\beta_P$  and  $\beta_R$ , we used our best estimates as means (Table 2). We chose  $A$  values of 2, 2, and 3 (i.e., assumed the

Table 1

Parameter estimates ( $\beta$  represents infection,  $\rho$  isolation efficiency,  $\phi$  hospitalization; subscripts  $E$ ,  $P$  and  $R$  refer to pre-symptomatic, prodrome, and acute respiratory stage) from fitting predicted to observed cumulative admissions to TTSH during the first 30 days of the outbreak (cf. Fig. 2).

Constant parameters	Estimates	
$\beta_E$	0.032	
$\beta_P$	0.259	
$\beta_R$	0.694	
Two epochs	$t \leq 3/14$	$t > 3/14$
$\rho_E$	0.049	0.12
$\rho_P$	0.133	0.65
$\rho_R$	0.15	0.745
$\phi_P$	0.123	0.72
$\phi_R$	0.25	0.759

The  $\rho$  are factors by which isolation reduces contributions to the force of infection; the other parameters are per-capita rates.

Table 2

Parameter estimates from fitting predicted to observed cumulative admissions to TTSH during epochs bounded by  $\tau_1$ ,  $\tau_2$ , and  $\tau_3$ .

Constant parameters	Estimates			
$\beta_E$	0.024			
$\beta_P$	0.152			
$\beta_R$	0.582			
Two epochs	$t \leq \tau_2$	$t > \tau_2$		
$\chi$	0	0.0487		
Four epochs	$t < \tau_1$	$\tau_1 < t < \tau_2$	$\tau_2 < t < \tau_3$	$t > \tau_3$
$\rho_E$	0.049	0.195	0.432	0.575
$\rho_P$	0.157	0.361	0.627	0.757
$\rho_R$	0.162	0.5	0.957	1.0
$\phi_P$	0.165	0.381	0.45	0.695
$\phi_R$	0.245	0.465	0.579	0.877

Times correspond to 14 and 24 March, and 8 April, when control efforts changed (e.g., began or intensified).  $\chi$  represents the per capita rate at which exposed individuals are quarantined.

Table 3

Input parameters for uncertainty analysis.

Parameter	Before 3/24		After 3/24	
	Distribution	Range	Distribution	Range
$1/\alpha$	G (3,2)	(1, 15)	Same	
$1/\delta_P$	G (3,4/3)	(0, 10)		
$1/\delta_R$	G (3,8/3)	(0, 20)		
$\beta_E$	G (2,0.024/2)	(0, 0.06)		
$\beta_P$	G (2,0.152/2)	(0, 0.55)		
$\beta_R$	G (3,0.582/3)	(0, 2)		
$\chi$	None		T (0.063)	(0.057,0.07)
$\phi_P$	T (0.381)	(0.343,0.419)	T (0.47)	(0.423,0.517)
$\phi_R$	T (0.465)	(0.419,0.512)	T (0.579)	(0.521,0.636)
$\rho_E$	T (0.195)	(0.176,0.215)	T (0.432)	(0.388,0.475)
$\rho_P$	T (0.361)	(0.325,0.398)	T (0.627)	(0.564,0.69)
$\rho_R$	T (0.5)	(0.45,0.55)	T (0.957)	(0.928,0.986)

Assumed distributions before and after introduction of control measures on 3/24—including not only quarantine and isolation, but exemplary health communications—are either gamma (G) or triangular (T).

variance of  $\beta_E$  and  $\beta_P$  exceed that of  $\beta_R$ ), so the  $B$  values are  $\frac{0.024}{2}$ ,  $\frac{0.152}{2}$ , and  $\frac{0.582}{3}$ . Each range was again chosen so that the area under the pdf in between was 95–98%. Results are similar if the  $A$  values are neither too large nor close to 1.

Next we stratified the area under the corresponding density function (pdf) into  $M$  equally probable intervals (i.e., each having area  $1/M$ , where  $M$  is at least  $\frac{3}{4}$  the number of uncertain variables,  $K$ ). Letting  $x_0, x_1, \dots, x_N$  be sub-interval end points, the parameter's pdf to be  $f(x)$ , and its cumulative distribution function (cdf) to be  $F(x)$ :

$$\frac{1}{M} = \int_{x_{i-1}}^{x_i} f(x) dx = F(x_i) - F(x_{i-1}) \quad \text{for } i = 1, 2, \dots, M$$

Because  $x_0$  is the lower limit of  $f(x)$ , the remaining  $x_i$ 's can be obtained from  $x_i = F^{-1}[F(x_{i-1}) + 1/M]$ ,  $i = 1, \dots, M$ . Finally, we selected points at random from each interval. The  $M$  samples drawn for one input parameter were paired randomly with the  $M$  for another, those  $M$  pairs were paired randomly again with the  $M$  for a third, and so on. Random paring continued until samples of all  $K$  input parameters had been paired to form an  $M$  by  $K$  table. We estimated the infectious stage-specific contributions to the realized reproduction number,  $\Re_i$ , using these  $M$  sets of input parameters.

We compared final outbreak sizes with our best estimates of time-varying control parameters (i.e., quarantine and hospitalization rates and isolation efficiencies) in Singapore with hypothetical alternatives. Differences with and without interventions, or with advanced or delayed timing, are estimates of cases (and hence deaths) averted, conditional on others. Such assessments tacitly assume independence (e.g., quarantine of possible contacts did not affect the timeliness with which actual ones who developed compatible symptoms sought medical care). Social distancing may have increased with quarantine in Hong Kong (Lo et al., 2005), but synergistic population responses in Singapore were more likely due to very effective health communications.

3. Results

Our analytical results include an expression for the realized reproduction number  $\Re$ , its partial derivatives with respect to control parameters and relationship to  $\Re_0$ , the intrinsic reproduction number (Appendix A). A Mathematica™ notebook that evaluates these expressions for user-supplied parameter values, comparing the impact of non-pharmaceutical interventions on any disease transmitted by close contact, is available from the

corresponding author. Version 6 or higher of this software or its player, available from <http://www.wolfram.com/products/player/>, also is required.

Empirical results for SARS include parameter estimates from hospital admissions during the first 30 days and entire outbreak in Singapore by epoch; assessment of the reproduction number  $\mathfrak{R}$ , and impact of control measures via sensitivity analyses and final outbreak sizes under hypothetical scenarios.

Trial periods in Table 1 correspond to before 14 March, when the second generation of cases began being reported, and between 14 and 24 March, when home quarantine began. In addition to these, Table 2's trial periods correspond to between 24 March and 8 April, when cumulative cases abruptly increased by about 10%, and after 8 April. Fig. 2 illustrates model fits to hospital admissions with these two parameter sets.

### 3.1. Parameter estimates

The infection rates,  $\beta$ , differ quantitatively (e.g., those during the acute phase are two to three times those during the prodrome and 21–25 times those during the incubation period, respectively subscripted R, P, and E) when estimated from admissions during the first 30 days or entire outbreak (Tables 2 and 3, respectively), but not qualitatively (i.e., infectiousness is negligible until patients are acutely ill). Isolation efficiency  $\rho$  among those hospitalized during the prodrome increased from 0.16 during the first epoch to 0.76 during the last. Among those hospitalized while acutely ill, efficiency increased from 0.16 to almost 1. Similarly, the hospitalization rate  $\phi$  increased from 0.16 to 0.7 during the prodrome, while that during acute illness increased from 0.25 to 0.88. Both isolation efficiencies and hospitalization rates are respectively subscripted P and R. Estimates for intervening periods are intermediate (Table 2).

### 3.2. Reproduction numbers

Our estimates of  $\mathfrak{R}$  and contributions of each infectious state before and after control measures were introduced, given the assumed distributions and ranges described in Table 3, are shown with their associated uncertainties in Table 4 and Fig. 3. Our estimates of  $\mathfrak{R}$ , 3.16 and 0.86 before and after 24 March are comparable to Wallinga's and Teunis' (2004) 3.1 and 0.7 before and after 12 March, respectively.

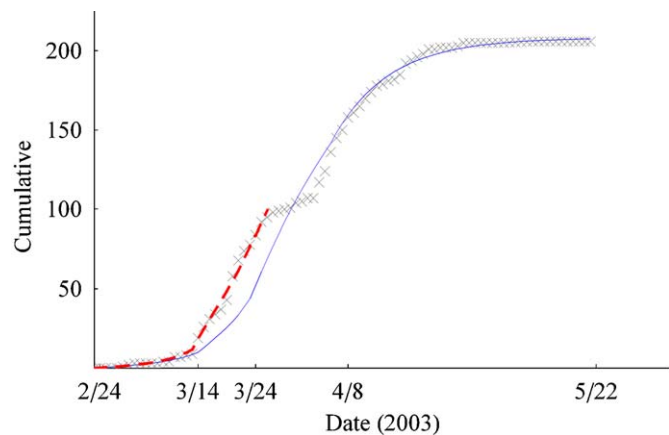


Fig. 2. Cumulative probable cases by date of symptom onset in Singapore (symbols) and fits to the first 30 days (dashed line) and entire outbreak (solid line). Parameter estimates differ quantitatively (i.e., they are higher initially), but are similarly qualitatively (Tables 1 and 3), particularly the ratio of infection rates during successive clinical phases.

Table 4 Results of uncertainty analysis.

$\mathfrak{R}_i$	Before 3/24			After 3/24		
	Mean	Std. Dev.	$P(\mathfrak{R}_i > 1)$	Mean	Std. Dev.	$P(\mathfrak{R}_i > 1)$
$\mathfrak{R}_E$	0.147	0.147	0.002	0.114	0.103	0.0002
$\mathfrak{R}_Q$	0	0	0	0.017	0.024	0
$\mathfrak{R}_{I_P}$	0.259	0.2	0.007	0.175	0.137	0.0007
$\mathfrak{R}_{I_R}$	0.382	0.318	0.05	0.203	0.187	0.007
$\mathfrak{R}_{QH_P}$	0	0	0	0.052	0.061	0
$\mathfrak{R}_{I_P H_P}$	0.217	0.265	0.02	0.109	0.131	0.002
$\mathfrak{R}_{I_R H_R}$	0.644	0.806	0.19	0.036	0.049	0
$\mathfrak{R}_{H_P H_R}$	1.511	1.475	0.528	0.155	0.155	0.003
$\mathfrak{R}$	3.159	2.25	0.922	0.861	0.413	0.295

These  $\mathfrak{R}_i$  are contributions to  $\mathfrak{R}$ , their sum, by infectious individuals in transit (see Appendix A for definitions).

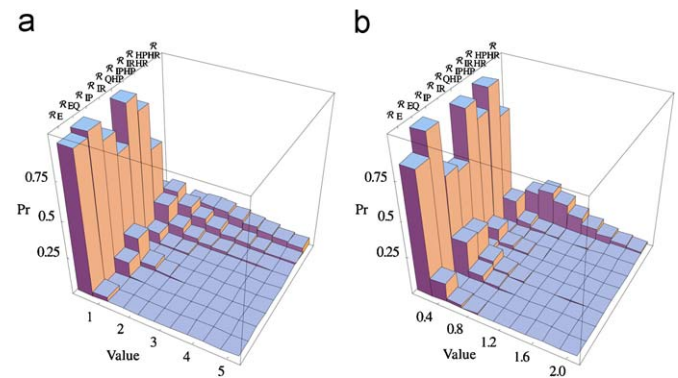


Fig. 3. a and b. Histograms of  $\mathfrak{R}_i$  ( $i = 1, \dots, 8$ ) and  $\mathfrak{R}$  before and after 24 March, when quarantine began and hospital infection control measures were more stringently enforced, from which the statistics in Table 4 were calculated.

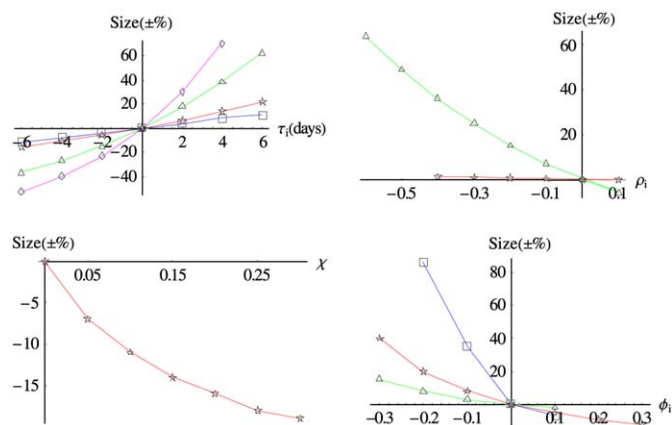
Table 5 Sensitivity of  $\mathfrak{R}$  to uncertain parameters.

Parameter	Before 3/24		After 3/24	
	PRCC	p-Value	PRCC	p-Value
$1/\alpha$	0.164	<0.0001	0.162	<0.0001
$1/\delta_P$	0.309	<0.0001	0.192	<0.0001
$1/\delta_R$	0.906	<0.0001	0.581	<0.0001
$\beta_E$	0.19	<0.0001	0.459	<0.0001
$\beta_P$	0.552	<0.0001	0.786	<0.0001
$\beta_R$	0.919	<0.0001	0.783	<0.0001
$\chi$			-0.029	0.004
$\phi_P$	-0.032	0.002	-0.061	<0.0001
$\phi_R$	-0.013	0.185	-0.032	0.001
$\rho_E$	-0.004	0.726	-0.0004	0.97
$\rho_P$	-0.005	0.62	-0.051	<0.0001
$\rho_R$	-0.124	<0.0001	-0.255	<0.0001

Sensitivity to control parameters is shown in Table 5. Isolation efficiency during the incubation period hardly affects  $\mathfrak{R}$ , as infectiousness is negligible then. Because people did not seek care until acutely ill prior to 24 March,  $\mathfrak{R}$  also is relatively insensitive to isolation efficiency during the prodrome or, by virtue of nosocomial transmission during that epoch (Leo et al., 2003), hospitalization while acutely ill.

### 3.3. Experiments

Final outbreak sizes (when birth and death are ignored, i.e.,  $\mu = 0$ ) would have been larger had interventions been delayed



**Fig. 4.** (a–d) Impact (percentage change) on final outbreak size of intervention timing (top left; stars are  $\tau_1$ , triangles  $\tau_2$ , squares  $\tau_3$  and diamonds  $\tau$ ), efficiency of isolation during the prodrome and acute phases (top right; stars and triangles, respectively), proportion of contacts quarantined (bottom left; stars) and hospitalization rates during the prodrome and acute phases (bottom right; stars and triangles, squares or both).

(Fig. 4a), or had isolation efficiency declined, especially of acutely ill patients (Fig. 4b). Final size would have been smaller had greater proportions been quarantined (Fig. 4c) or hospitalized, particularly during the prodrome (Fig. 4d).

#### 4. Discussion

Motivated by the desire to contribute more to the control of newly emerging diseases in future than mathematical epidemiologists contributed to past control efforts, we modeled a generic disease caused by a pathogen transmitted by close interpersonal contact, (1) derived some general analytical results and (2) analyzed one SARS outbreak to determine how we might have helped had (a) this model been available and (b) authorities used it to inform their decision-making.

Our model is suitable for any directly transmitted pathogen (Fig. 1), though inevitably less so than pathogen-specific models. Its biological states are clinical, so sojourns are estimable from early case series. To model SARS, we set the incubation period at 6 days (Lee et al., 2003) and prodrome and acute respiratory stages at 4 and 8 days (Tsang et al., 2003); these references were available at <http://www.nejm.org> on  $\frac{4}{7}$  and  $\frac{3}{31}$ , respectively.

We assumed quarantined people spent half of their incubation periods at large, and varied only the proportion quarantined, but when infected people are quarantined must be a function of the stage at which those who infected them are diagnosed. Similarly, we combined the rate at which people sought medical care and their probability of diagnosis, but as these phenomena involve different social systems, they may evolve independently. Social responses are exceedingly important, but this model must be useful with insufficient information to fully characterize them.

Infection is a more familiar composite parameter than quarantine or hospitalization, being decomposed into constituent contact rates and probabilities of transmission on contact only as needed (e.g., in sexually transmitted diseases, asymmetric transmission between genders or other partners may affect the impact of available interventions). Transmission of pathogens causing respiratory diseases also may be asymmetric (e.g., between children and adults), but the impact on interventions is less clear, so the composite is used.

Parameter estimates based on the first 30 days of hospital admissions indicate that—consistent with numbers of secondary infections among patients isolated on successive days after

symptom onset (Lipsitch et al., 2003) and observed viral loads (Peiris et al., 2003)—infectiousness of patients with SARS was negligible until symptom onset and only one third during their prodrome as while acutely ill (Tables 2 and 3). Estimates based on the entire outbreak indicate temporal variation in the rates at which ill people sought care, probabilities of diagnosis and efficacy of isolation (Table 2).

Identifying infected people before they become ill is so difficult that quarantine is exceedingly inefficient. Consequently, unless infected people could infect many susceptible ones before becoming symptomatic—by virtue of being very infectious or infectious long before symptomatic—public health authorities should focus on identifying people with symptoms that may herald disease, encouraging them to seek care, especially if they might have been exposed to someone since diagnosed. Similarly, they should assist clinicians in diagnosing, and hospital infection control personnel in isolating effectively, those people before they become acutely ill.

To evaluate actual or hypothetical control measures, one must compare otherwise identical scenarios. Community intervention trials approach this ideal, but only modeling attains it. Not using all available measures that could be effective as expeditiously as possible during actual outbreaks of potentially lethal diseases would be unthinkable, but model outbreaks can be compared with and without interventions, alone or in various combinations, or with interventions at different times, to assess their impacts.

Our final size calculations with and without quarantine, but all else equal (i.e., experiments), indicate its impact would have been comparable to hospitalization during the prodrome (cf. Figs. 4c and d). But this assumes authorities could identify infected people during their incubation period. Reassuringly, our independent estimate of the rate at which exposed people were quarantined,  $\chi$  (Table 2) resembles the proportion of probable SARS patients actually quarantined,  $\frac{11}{238}$  (Tan, 2005). In Taiwan, where this proportion was strikingly similar,  $\frac{24}{480}$  (Hsieh et al., 2005), quarantined individuals were suspected of having SARS earlier than others (within 1.2 versus 2.89 days, respectively), but not reclassified any sooner (Hsieh et al., 2005). Our final size calculations illustrate the importance of timely interventions, but as only probable cases had priority for limited isolation facilities, evidently these shorter onset-diagnosis intervals contributed little.

In contrast, the rate at which probable cases were hospitalized during the prodrome,  $\phi_h$  increased from about 0.16 to 0.7 during the outbreak in Singapore (Table 2), contributing much more to control. The potential impact of quarantine has been so regularly confused with its actual contribution to SARS' control that one wonders if this longtime staple of public health (McNeill, 1977; Rosner, 1995) has been rigorously evaluated before. Day et al. (2006) refine Fraser et al.'s (2004) conditions for quarantine to be effective: the number of asymptomatic infections and fraction preventable—essentially the number of pre-symptomatic infections—must be large and the probability of infected individuals being quarantined high. Short of everyone staying home after a household member becomes ill, the last condition will be difficult to meet for respiratory diseases.

#### 5. Conclusions

As the temporal distribution of infectiousness largely determines the optimal public health response (Fraser et al., 2004; Day et al., 2006), this is among the most important epidemiological unknowns early in outbreaks of new human diseases. If patients could be infectious before developing symptoms, quarantine must be considered. But identifying people whose contacts were

sufficiently intimate for infection is extremely difficult, especially given uncertainty about the mode of transmission. The gain in efficiency—by ensuring instead that people with early signs and symptoms seek medical care, clinicians diagnose, and infection-control personnel isolate them effectively—may more than compensate for any loss of efficacy due to infections during the prodrome. Modeling can help to determine this distribution and, conditional on that essential information, to evaluate the relative impact of various possible public health interventions.

**Acknowledgments**

Mark Chen, Annelies Wilder-Smith, Heng Bee Hoon, and Leo Yee-Sin shared their observations from Tan Tock Seng Hospital, and many colleagues reviewed earlier drafts of this manuscript. We are grateful to Klaus Dietz for the opportunity to participate in the workshop, Design and Analysis of Infectious Disease Studies, at the Mathematisches Forschungsinstitut Oberwolfach, and for subsequent correspondence about sojourns. The reviewers' helpful comments and suggestions further improved the manuscript. Z. Feng's research was partially supported by the CDC via contract 200-2007-M-23524 and the National Science Foundation via grant DMS-0719697.

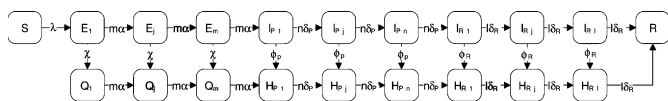
**Appendix A**

Here we present the system of equations corresponding to Fig. A1; an expression for  $\mathfrak{R}$ , the realized reproduction number, derived via the approach of Feng et al. (2007); take its partial derivatives with respect to control parameters, and describe the intrinsic number,  $\mathfrak{R}_0$ , as a special case. A Mathematica™ notebook available from the corresponding author evaluates these expressions for user-supplied parameter values.

**A.1. Mathematical model**

Let  $S = S(t)$ ,  $E = E(t)$ ,  $Q = Q(t)$ ,  $I_{PR} = I_{PR}(t)$ ,  $H_{PR} = H_{PR}(t)$  and  $R = R(t)$  denote numbers susceptible, exposed (infected, but not yet symptomatic), quarantined, symptomatic, hospitalized (isolated), and recovered (or immune) individuals at time  $t$ , respectively. Primes denote derivatives, lettered subscripts the prodrome and acute respiratory stages and numbered ones sub-stages, of which there are  $m$ ,  $n$  and  $l$ , respectively (Fig. A1):

$$\begin{aligned}
 S' &= \mu N - \lambda(t)S - \mu S, \\
 E'_1 &= \lambda(t)S - (\chi + m\alpha + \mu)E_1, \\
 E'_j &= m\alpha E_{j-1} - (\chi + m\alpha + \mu)E_j, \quad j = 2, \dots, m, \\
 Q'_1 &= \chi E_1 - (m\alpha + \mu)Q_1, \\
 Q'_j &= \chi E_j + m\alpha Q_{j-1} - (m\alpha + \mu)Q_j, \quad j = 2, \dots, m, \\
 I'_{p1} &= m\alpha E_m - (\phi_p + n\delta_p + \mu)I_{p1}, \\
 I'_{pj} &= n\delta_p I_{p(j-1)} - (\phi_p + n\delta_p + \mu)I_{pj}, \quad j = 2, \dots, n, \\
 H'_{p1} &= m\alpha Q_n + \phi_p I_{p1} - (n\delta_p + \mu)H_{p1}, \\
 H'_{pj} &= \phi_p I_{pj} + n\delta_p H_{p(j-1)} - (n\delta_p + \mu)H_{pj}, \quad j = 2, \dots, n,
 \end{aligned}$$



**Fig. A1.** Model diagram with sub-stages denoted by lettered and numbered subscripts, e.g., the incubation period is partitioned into  $E_1, E_1 < E_j < E_m$ , and  $E_m$ ; the prodrome into  $I_{p1}, I_{p1} < I_{pj} < I_{pn}$ , and  $I_{pn}$ , and the acute respiratory phase into  $I_{R1}, I_{R1} < I_{Rj} < I_{Rl}$ , and  $I_{Rl}$ .

$$\begin{aligned}
 I'_{R1} &= n\delta_p I_{pn} - (\phi_R + l\delta_R + \mu)I_{R1}, \\
 I'_{Rj} &= l\delta_R I_{R(j-1)} - (\phi_R + l\delta_R + \mu)I_{Rj}, \quad j = 2, \dots, l, \\
 H'_{R1} &= n\delta_p H_{pn} + \phi_R I_{R1} - (l\delta_R + \mu)H_{R1}, \\
 H'_{Rj} &= \phi_R I_{Rj} + l\delta_R H_{R(j-1)} - (l\delta_R + \mu)H_{Rj}, \quad j = 2, \dots, l, \\
 R' &= l\delta_R I_{Rl} + l\delta_R H_{Rl} - \mu R,
 \end{aligned}$$

and  $N = S + E + Q + I_p + I_R + H_p + H_R + R$  is the total population, whose size is constant by virtue of equal per capita rates of birth and death,  $\mu$ . Other rates, reciprocals of mean sojourns, are:  $\chi$ , quarantine;  $\phi$ , hospitalization; and progression during the incubation,  $\alpha$  and successive stages of acute illness denoted by subscripts,  $\delta$ :

$$\begin{aligned}
 \lambda(t) &= \frac{1}{N} \{ \beta_E [E + (1 - \rho_E)Q] + \beta_P [I_p + (1 - \rho_P)H_p] \\
 &\quad + \beta_R [I_R + (1 - \rho_R)H_R] \}, \quad E = \sum_{j=1}^m E_j, \quad Q = \sum_{j=1}^m Q_j, \\
 I_p &= \sum_{j=1}^n I_{pj}, \quad H_p = \sum_{j=1}^n H_{pj}, \quad I_R = \sum_{j=1}^l I_{Rj}, \quad H_R = \sum_{j=1}^l H_{Rj}.
 \end{aligned}$$

In  $\lambda(t)$ , the force of infection, the  $\beta_{E,P,R}$  are transmission coefficients and  $\rho_{E,P,R}$  fractional reductions due to quarantine at home or other suitable facilities and isolation in hospitals.

**A.2. Realized reproduction number**

Given the transition probabilities,  $T_i$  and  $\mathcal{T}_i$  and sojourns,  $D_i$  and  $\mathcal{D}_i$  defined in Table A1,  $\mathfrak{R}$  is given by  $\mathfrak{R} = \mathfrak{R}_E + \mathfrak{R}_Q + \mathfrak{R}_{I_p} + \mathfrak{R}_{I_R} + \mathfrak{R}_{QH_p} + \mathfrak{R}_{I_p H_p} + \mathfrak{R}_{I_R H_R} + \mathfrak{R}_{H_p H_R}$ , where

$$\begin{aligned}
 \mathfrak{R}_E &= \beta_E \mathcal{D}_E, \\
 \mathfrak{R}_Q &= (1 - \rho_E) \beta_E (D_E - \mathcal{D}_E), \\
 \mathfrak{R}_{I_p} &= \beta_P \mathcal{T}_E \mathcal{D}_{I_p}, \\
 \mathfrak{R}_{I_p H_p} &= (1 - \rho_P) \beta_P \mathcal{T}_E (D_{I_p} - \mathcal{D}_{I_p}), \\
 \mathfrak{R}_{QH_p} &= (1 - \rho_P) \beta_P (\mathcal{T}_E - \mathcal{T}_E) D_{I_p}, \\
 \mathfrak{R}_{I_R} &= \beta_R \mathcal{T}_E \mathcal{T}_{I_p} \mathcal{D}_{I_R}, \\
 \mathfrak{R}_{I_R H_R} &= (1 - \rho_R) \beta_R \mathcal{T}_E \mathcal{T}_{I_p} (D_{I_R} - \mathcal{D}_{I_R}), \\
 \mathfrak{R}_{H_p H_R} &= (1 - \rho_R) \beta_R (\mathcal{T}_E \mathcal{T}_{I_p} - \mathcal{T}_E \mathcal{T}_{I_p}) D_{I_R}.
 \end{aligned}$$

**Table A1**  
Definitions of transition probabilities,  $T_i$  and  $\mathcal{T}_i$ , and sojourns,  $D_i$ , and  $\mathcal{D}_i$ .

Variable	Definition
$T_E = \left(\frac{m\alpha}{m\alpha + \mu}\right)^m$	Probability of surviving exposure to enter the prodrome
$\mathcal{T}_E = \left(\frac{m\alpha}{m\alpha + \chi + \mu}\right)^m$	Quarantine adjusted probability of surviving exposure
$T_{I_p} = \left(\frac{n\delta_p}{n\delta_p + \mu}\right)^n$	Probability of surviving the prodrome to become acutely ill
$\mathcal{T}_{I_p} = \left(\frac{n\delta_p}{n\delta_p + \phi_p + \mu}\right)^n$	Quarantine adjusted probability of surviving the prodrome
$D_E = \frac{1}{m\alpha + \mu} \sum_{i=0}^{m-1} \left(\frac{m\alpha}{m\alpha + \mu}\right)^i$	Mean death—adjusted sojourn in the exposed stage
$\mathcal{D}_E = \frac{1}{m\alpha + \chi + \mu} \sum_{i=0}^{m-1} \left(\frac{m\alpha}{m\alpha + \chi + \mu}\right)^i$	Mean quarantine—and death—adjusted sojourn in the exposed stage
$D_{I_p} = \frac{1}{n\delta_p + \mu} \sum_{i=0}^{n-1} \left(\frac{n\delta_p}{n\delta_p + \mu}\right)^i$	Mean death—adjusted sojourn in the prodrome
$\mathcal{D}_{I_p} = \frac{1}{n\delta_p + \phi_p + \mu} \sum_{i=0}^{n-1} \left(\frac{n\delta_p}{n\delta_p + \phi_p + \mu}\right)^i$	Mean quarantine—and death—adjusted sojourn in the prodrome
$D_{I_R} = \frac{1}{l\delta_R + \mu} \sum_{i=0}^{l-1} \left(\frac{l\delta_R}{l\delta_R + \mu}\right)^i$	Mean death—adjusted sojourn with acute respiratory symptoms
$\mathcal{D}_{I_R} = \frac{1}{l\delta_R + \phi_R + \mu} \sum_{i=0}^{l-1} \left(\frac{l\delta_R}{l\delta_R + \phi_R + \mu}\right)^i$	Mean isolation—and death—adjusted sojourn while acutely ill

A.3. Impact of control measures

The derivatives of  $\mathfrak{R}$  with respect to quarantine, hospitalization during the prodrome and acute illness and the efficacy of isolation during these stages are

$$\begin{aligned} \frac{\partial \mathfrak{R}}{\partial \chi} &= \beta_E \rho_E D'_E + (\beta_P \rho_P D_{I_P} + \beta_R \rho_R D_{I_R} T_{I_P}) T'_E \\ &= -\beta_E \rho_E \frac{1}{(m\alpha + \chi + \mu)^2} \sum_{i=0}^{m-1} (i+1) \left( \frac{m\alpha}{m\alpha + \chi + \mu} \right)^i \\ &\quad - \left\{ \begin{aligned} &\beta_P \rho_P \frac{1}{n\delta_P + \phi_P + \mu} \sum_{i=0}^{n-1} \left( \frac{n\delta_P}{n\delta_P + \phi_P + \mu} \right)^i + \\ &\beta_R \rho_R \frac{1}{l\delta_R + \phi_R + \mu} \sum_{i=0}^{l-1} \left( \frac{l\delta_R}{l\delta_R + \phi_R + \mu} \right)^i \left( \frac{n\delta_P}{n\delta_P + \phi_P + \mu} \right)^n \end{aligned} \right\} \\ &\quad \times \left( \frac{m(m\alpha)^m}{(m\alpha + \chi + \mu)^{m+1}} \right) \leq 0, \end{aligned}$$

$$\begin{aligned} \frac{\partial \mathfrak{R}}{\partial \phi_P} &= (\beta_P \rho_P D'_{I_P} + \beta_R \rho_R T'_{I_P} D_{I_R}) T_E \\ &= - \left\{ \begin{aligned} &\beta_P \rho_P \sum_{i=0}^{n-1} \frac{i(n\delta_P)^i}{(n\delta_P + \phi_P + \mu)^{i+2}} \\ &+ \beta_R \rho_R \frac{n(n\delta_P)^n}{(n\delta_P + \phi_P + \mu)^{n+1}} \sum_{i=0}^{l-1} \frac{(l\delta_R)^i}{(l\delta_R + \phi_R + \mu)^{i+1}} \end{aligned} \right\} \\ &\quad \times \left( \frac{m\alpha}{m\alpha + \chi + \mu} \right)^m \leq 0, \end{aligned}$$

$$\begin{aligned} \frac{\partial \mathfrak{R}}{\partial \rho_R} &= \beta_R \rho_R \mathcal{T}_E \mathcal{T}_{I_P} \mathcal{D}'_{I_R} \\ &= -\beta_R \rho_R \left( \frac{m\alpha}{m\alpha + \chi + \mu} \right)^m \left( \frac{n\delta_P}{n\delta_P + \phi_P + \mu} \right)^n \\ &\quad \times \sum_{i=0}^{l-1} \frac{(i+1)(l\delta_R)^i}{(l\delta_R + \phi_R + \mu)^{i+2}} \leq 0, \end{aligned}$$

$$\begin{aligned} \frac{\partial \mathfrak{R}}{\partial \rho_E} &= -\beta_E (D_E - D'_E) \\ &= -\beta_E \left\{ \frac{1}{m\alpha + \mu} \sum_{i=0}^{m-1} \left( \frac{m\alpha}{m\alpha + \mu} \right)^i \right. \\ &\quad \left. - \frac{1}{m\alpha + \chi + \mu} \sum_{i=0}^{m-1} \left( \frac{m\alpha}{m\alpha + \chi + \mu} \right)^i \right\} \leq 0, \end{aligned}$$

$$\begin{aligned} \frac{\partial \mathfrak{R}}{\partial \rho_P} &= \beta_P (\mathcal{T}_E \mathcal{D}_{I_P} - T_E D_{I_P}) \\ &= \beta_P \left( \frac{m\alpha}{m\alpha + \chi + \mu} \right)^m \sum_{i=0}^{n-1} \frac{(n\delta_P)^i}{(n\delta_P + \phi_P + \mu)^{i+1}} \\ &\quad - \beta_P \left( \frac{m\alpha}{m\alpha + \mu} \right)^m \sum_{i=0}^{n-1} \frac{(n\delta_P)^i}{(n\delta_P + \mu)^{i+1}} \leq 0, \end{aligned}$$

$$\begin{aligned} \frac{\partial \mathfrak{R}}{\partial \rho_R} &= \beta_R (\mathcal{T}_E \mathcal{T}_{I_P} \mathcal{D}_{I_R} - T_E T_{I_P} D_{I_R}) \\ &= \beta_R \left( \frac{m\alpha}{m\alpha + \chi + \mu} \right)^m \left( \frac{n\delta_P}{n\delta_P + \phi_P + \mu} \right)^n \\ &\quad \times \sum_{i=0}^{l-1} \frac{(l\delta_R)^i}{(l\delta_R + \phi_R + \mu)^{i+1}} \\ &\quad - \beta_R \left( \frac{m\alpha}{m\alpha + \mu} \right)^m \left( \frac{n\delta_P}{n\delta_P + \mu} \right)^n \sum_{i=0}^{l-1} \frac{(l\delta_R)^i}{(l\delta_R + \mu)^{i+1}} \leq 0. \end{aligned}$$

A.4. Intrinsic reproduction number

Absent control, the realized reproduction number reduces to the basic reproduction number,  $\mathfrak{R}_0 = \beta_E D_E + \beta_P T_E D_P + \beta_R T_E T_{I_P} D_{I_R}$ . Their relationship is given by

$$\begin{aligned} \mathfrak{R} &= \mathfrak{R}_0 - [\rho_E \beta_E (D_E - \mathcal{D}_E) + \rho_P \beta_P (T_E D_{I_P} - \Gamma_E \mathcal{D}_{I_P}) \\ &\quad + \rho_R \beta_R (T_E T_{I_P} D_{I_R} - \mathcal{T}_E \mathcal{T}_{I_P} \mathcal{D}_{I_R})]. \end{aligned}$$

Clearly,  $\mathfrak{R} = \mathfrak{R}_0$  when all control parameter values are zero, as  $D_i = \mathcal{D}_i$  and  $T_i = \mathcal{T}_i$ , making the three terms in brackets all equal to zero. Also,  $\mathfrak{R} < \mathfrak{R}_0$  since  $D_i \geq \mathcal{D}_i$  and  $T_i \geq \mathcal{T}_i$ , which implies that the quantity inside the brackets is positive if some control parameters are not zero.

References

Day, T., Park, A., Madras, N., Gumel, A., Wu, J., 2006. When is quarantine a useful control strategy for emerging infectious diseases. *Am. J. Epidemiol.* 163, 479–485.

Feng, Z., Xu, D., Zhao, H., 2007. Epidemiological models with non-exponentially distributed disease stages and applications to disease control. *Bull. Math. Biol.* 69, 1511–1536.

Fraser, C., Riley, S., Anderson, R.M., Ferguson, N.M., 2004. Factors that make infectious disease outbreaks controllable. *PNAS* 101, 6146–6151.

Gerberding, J.L., 2003. Faster ... but fast enough? Responding to the epidemic of severe acute respiratory syndrome. *N. Engl. J. Med.* 348, 2030–2031.

Hsieh, Y.H., King, C.C., Chen, C.W., et al., 2005. Quarantine for SARS, Taiwan. *Emerg. Infect. Dis.* 11, 278–282.

Lee, N., Hui, D., Wu, A., et al., 2003. A major outbreak of severe acute respiratory syndrome in Hong Kong. *N. Engl. J. Med.* 348, 1986–1994.

Leo, Y.-S., Chen, M., Heng, B.H., et al., 2003. Severe acute respiratory syndrome—Singapore. *MMWR* 52, 405–411.

Lipsitch, M., Cohen, T., Cooper, B., et al., 2003. Transmission dynamics and control of severe acute respiratory syndrome. *Science* 300, 1966–1970.

Lo, J.Y., Tsang, T.H., Leung, Y.H., et al., 2005. Respiratory infections during SARS outbreak, Hong Kong. *Emerg Infect. Dis.* 11, 1738–1741.

May, R.M., 2004. Uses and abuses of mathematics in biology. *Science* 303, 790–793.

McNeill, W.H., 1977. *Plagues and Peoples*. Doubleday, New York, 340pp.

Pang, X., Zhu, Z., Xu, F., et al., 2003. Evaluation of control measures implemented in the severe acute respiratory syndrome outbreak in Beijing. *JAMA* 290, 3215–3221.

Peiris, J.S., Chu, C.M., Cheng, V.C., et al., 2003. Clinical progression and viral load in a community outbreak of coronavirus-associated SARS pneumonia: a prospective study. *Lancet* 361, 1761–1766.

Quine, W.V., Ullian, J.S., 1970. *The Web of Belief*. Random House, New York, 95pp.

Rosner, F., 1995. *Medicine in the Bible and the Talmud: Selections from Classical Jewish Sources*. Ktav Publishing, Jersey City, NJ, 328pp.

Tan, C.C., 2005. Public health response: a view from Singapore. In: Peiris, M., Anderson, L., Osterhaus, A., Stohr, K., Yuen, K.-Y. (Eds.), *Severe Acute Respiratory Syndrome: a Clinical Guide*. Blackwell, Oxford, pp. 139–164.

Tsang, K.W., Ho, P.L., Ooi, G.C., et al., 2003. A cluster of cases of severe acute respiratory syndrome in Hong Kong. *N. Engl. J. Med.* 348, 1977–1985.

Wallinga, J., Teunis, P., 2004. Different epidemic curves for severe acute respiratory syndrome reveal similar impacts of control measures. *Am. J. Epidemiol.* 160, 509–516.

Wearing, H.J., Rohani, P., Keeling, M.J., 2005. Appropriate models for the management of infectious diseases. *PLoS Med.* 2, 621–627.

World Health Organization, Consensus document on the epidemiology of severe acute respiratory syndrome. Available at: <http://www.who.int/csr/sars/en/WHOconsensus.pdf>, 2003.