

Timely Identification of Control Strategies for Emerging Infectious Diseases: Severe Acute Respiratory Syndrome in Singapore

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ABSTRACT

While new human pathogens may evolve from old ones, recent experience suggests new diseases often arise through adaptation of non-human pathogens to human hosts. Insofar as the effectiveness of existing vaccines at preventing infections or medications at mitigating symptoms depends on the extent to which newly emerged pathogens and the diseases they cause resemble those for which these pharmaceuticals were formulated, authorities cannot rely on them to prevent or control outbreaks of new diseases. Among available means of containment, quarantine of exposed persons is indicated if people are infectious before becoming symptomatic. Otherwise, more efficient strategies may be preferable. We model a generic disease apparently transmitted by close contact, but about which little else is known, via a system of differential equations. We calculate \mathcal{R} , take its partial derivatives with respect to possible interventions, and show that we could have advocated a more efficient strategy before quarantine began in Singapore.

Keywords: modeling, emerging infections, infection-control strategies, social responses

INTRODUCTION

Within weeks of a traveler from Guangdong Province, China, infected with the pathogen causing the disease later named Severe Acute Respiratory Syndrome (SARS), infecting others in their Hong Kong hotel, several case-series were published and the pathogen was identified (Gerberding 2003).

Faced with serious diseases of unknown etiology, health authorities must decide quickly which available intervention(s) to implement. Case-series will be among the earliest information sources (e.g., presenting symptoms, duration of distinguishable clinical stages, and outcomes). Upon isolation of etiologic agents, experience with illnesses caused by related pathogens becomes germane. Here we argue that such information, which probably will be available to policymakers early in the course of future outbreaks, especially of new diseases causing serious morbidity, suffices for modelers to assess the likely impact of available interventions on morbidity, if not mortality.

To be most useful in weighing possible interventions to control outbreaks of new infectious diseases, models must capture all phenomena affecting transmission. Ours allows infected people to become infectious before or after becoming symptomatic. 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 effective health communications could influence these social phenomena, moreover, our model allows the specific (or per capita) rates of medical-care seeking, diagnosis during distinguishable clinical phases, and quarantine to evolve. When and how effectively cases are isolated, and when authorities begin searching for their contacts, if ever, also may vary temporally. We include drugs, as existing medications may be active (e.g., oseltamivir against influenza), but not vaccines. Several pharmaceutical companies are developing “universal” influenza vaccines, but no clinical trial has yet begun.

Policymaking is difficult enough with accurate and complete information, neither of which is available during outbreaks of new diseases. Equipped with our model, one could

use preliminary information to determine which available intervention(s) were most promising, advise policymakers, revise early estimates of parameter values as additional or better information became available, monitor intervention effects, and change recommendations if necessary. This would ensure the best possible use of available public health resources and minimize social disruption.

METHODS

To assist in controlling infectious diseases that emerge in future, we modeled a respiratory illness caused by any pathogen transmitted by close interpersonal contact. To evaluate the impact of interventions, we adjusted parameters to fit the 2003 probable SARS case series in Singapore, and calculated outbreak sizes under alternative scenarios. Motivated by the social cost of quarantine relative to its contribution to SARS control in this setting, we derived analytical expressions that modelers could use with limited information to aid policymakers in determining the most effective strategy for controlling future outbreaks of new diseases.

Mathematical model

Our model of generic newly emerged infectious diseases characterizes persons by disease, control or immune state (figures 1; compartments): People are susceptible, S; exposed (infected, and possibly infectious), E; ill (and infectious), I; or recovered (and immune), R. To investigate public health measures to control infection, we distinguish prodromal and acute respiratory stages, I_P and I_R . People who have been exposed may be quarantined, Q, or seek medical care early or late in their illnesses, M_E and M_L (figure 1b), whereupon they may be diagnosed and hospitalized, H_P and H_R .

Thus, we have modified the classic SEIR (susceptible-exposed-infectious-recovered) model to allow for an incubation (versus latent) period, prodrome and acute illness during which infection rates may differ, as these contain information that essentially determines the utility of quarantine (Fraser et al. 2004). And we have included other states to reflect possible responses by patients, clinicians, hospital infection-control staff, and public health authorities. While we believe this model is generic, our experiences with SARS

and others' with avian influenza guided its development. Should future new diseases expose limitations, we will modify this classic model further.

In compartmental models, people can occupy only one state at any time, but may change state (figures 1; arrows): Susceptible people may be infected at rate $\lambda(t)$, whereupon they progress through asymptomatic and then symptomatic stages, at specific rates α and δ_i , where subscripts refer to successive symptomatic stages. They may be quarantined while incubating at rate $\gamma(t)$, and seek medical care while ill at rates $\varepsilon_i(t)$. Among those seeking care, some will be diagnosed at rates $\phi_i(t)$, and isolated with effectiveness $\rho_i(t)$.

Ill people progress from prodrome to acute stage at rates δ_i ($i=1, 3, 5$), after which most recover ($i=2, 4, 6$) with or without medical care. Progression rates indexed 1 and 2 are biological. Others are calculated via the constraints below to ensure that quarantine and hospitalization per se do not affect pathophysiological processes. For this purpose, we distinguish, among patients hospitalized during the prodrome, those who had been quarantined while asymptomatic, H_{PQ} , from those who had not, $H_{P\bar{Q}}$. Similarly, among patients hospitalized during their respiratory stage, we distinguish those who had been hospitalized during their prodrome, H_{RH_P} , from those who had not, $H_{R\bar{H}_P}$.

We omit mortality from these diagrams for clarity, but our equations incorporate death from disease or other causes at specific rates κ and μ , respectively. Our simulation model is non-autonomous by virtue of time-varying parameters that describe social phenomena affecting disease transmission, but we analyze the underlying autonomous system to investigate the impact of changes in each conditional on fixed, but otherwise reasonable, values of the others. Constant parameters are not only convenient mathematically, but appropriate to the circumstances in which we envision using these analytical results (i.e., to help policymakers decide, at some time, how to intervene in the near future).

Equations

Our first model is a system of ten differential equations, several of whose parameters may vary with time, and other identities that simplify these formulae.

$$\frac{dS}{dt} = \mu N + \kappa(I_R + H_R) + \omega R - [\lambda(t) + \mu]S$$

$$\frac{dE}{dt} = \lambda(t)S - ([1 - \chi_A(t)]\alpha_1 + \chi_A(t)\gamma(t) + \mu)E$$

$$\frac{dQ}{dt} = \chi_A(t)\gamma(t)E - [\alpha_2(t) + \mu]Q$$

$$\frac{dI_P}{dt} = [1 - \chi_A(t)]\alpha_1 E - [\varepsilon_1(t)\phi_1(t) + \delta_1 + \mu]I_P$$

$$\frac{dI_R}{dt} = \delta_1 I_P - [\delta_2 + \varepsilon_2(t)\phi_2(t) + \kappa + \mu]I_R$$

$$\frac{dH_{PQ}}{dt} = \alpha_2(t)Q - (\delta_1 + \mu)H_{PQ}$$

$$\frac{dH_{P\tilde{Q}}}{dt} = \varepsilon_1(t)\phi_1(t)I_P - [\delta_3(t) + \mu]H_{P\tilde{Q}}$$

$$\frac{dH_{RH_P}}{dt} = \delta_1 H_{PQ} + \delta_3(t)H_{P\tilde{Q}} - (\delta_2 + \kappa + \mu)H_{RH_P}$$

$$\frac{dH_{R\tilde{H}_P}}{dt} = \varepsilon_2(t)\phi_2(t)I_R - [\delta_4(t) + \kappa + \mu]H_{R\tilde{H}_P}$$

$$\frac{dR}{dt} = \delta_2(I_R + H_{RH_P}) + \delta_4(t)H_{R\tilde{H}_P} - (\omega + \mu)R$$

$$\lambda(t) = \{\beta_A E + \beta_P(I_P + [1 - \rho_1(t)]H_P) + \beta_R(I_R + [1 - \rho_2(t)]H_R)\} / N$$

$$\alpha_2^{-1} = \alpha_1^{-1} - \gamma^{-1}, 0 \leq \chi_i \leq 1, \delta_{i+2}^{-1} = \delta_i^{-1} - \varepsilon_i^{-1}, 0 \leq \phi_i \leq 1, i = 1, 2$$

$$N = S + E + I + Q + H + R, H = H_P + H_R, H_P = H_{PQ} + H_{P\tilde{Q}}, H_R = H_{RH_P} + H_{R\tilde{H}_P}$$

The positive terms in the first equation exactly balance natural and disease-induced mortality with natality, ensuring that population size remains constant. This simplifying assumption is justified only insofar as outbreaks are controlled quickly (e.g., SARS). It would be inappropriate for AIDS, which emerged decades ago. The penultimate equations ensure that interventions do not affect duration of biological stages.

Motivated by SARS in Taiwan (Hsieh et al. 2005) and avian influenza, we add two features. We allow people to seek care at outpatient clinics and in emergency rooms, during their prodrome and acute illnesses respectively, settings where patients only suspected of having SARS may have been poorly isolated, if at all, compared with the infectious disease wards to which probable SARS patients were transferred. While patients are hospitalized, we also allow treatment that mitigates duration if begun during the prodrome, as well as severity (and, possibly, infectiousness) whenever begun. This requires two additional equations and modification of others.

$$\frac{dI_P}{dt} = \alpha_1 E - \{[1 - \chi_P(t)]\delta_1 + \chi_P(t)\varepsilon_1(t) + \mu\}I_P$$

$$\frac{dM_E}{dt} = \chi_P(t)\varepsilon_1(t)I_P - [\phi_1(t) + \delta_5(t) + \mu]M_E$$

$$\frac{dH_{PQ}}{dt} = \alpha_2(t)Q - (\sigma_1\delta_1 + \mu)H_{PQ}$$

$$\frac{dH_{P\tilde{Q}}}{dt} = \phi_1(t)M_E - [\sigma_1\delta_3(t) + \mu]H_{P\tilde{Q}}$$

$$\frac{dI_R}{dt} = [1 - \chi_R(t)]\delta_1 I_P + \delta_5(t)M_E - \{[1 - \chi_R(t)]\delta_2 + \chi_R(t)\varepsilon_2(t) + \kappa + \mu\}I_R$$

$$\frac{dM_L}{dt} = \chi_R(t)\varepsilon_2(t)I_R - [\phi_2(t) + \delta_6(t) + \mu]M_L$$

$$\frac{dH_{RH_p}}{dt} = \sigma_1[\delta_1 H_{PQ} + \delta_3(t)H_{P\tilde{Q}}] - (\sigma_2\delta_2 + \kappa + \mu)H_{RH_p}$$

$$\frac{dH_{R\tilde{H}_p}}{dt} = \phi_2(t)M_L - [\delta_4(t) + \kappa + \mu]H_{R\tilde{H}_p}$$

$$\frac{dR}{dt} = \delta_2 \{ [1 - \chi_R(t)]I_R + \sigma_2 H_{RH_p} \} + \delta_4(t)H_{R\tilde{H}_p} + \delta_6(t)M_L - (\omega + \mu)R$$

$$\lambda(t) = \{ \beta_A E + \beta_P (I_P + M_E + \psi_1 [1 - \rho_1(t)] H_P) + \beta_R (I_R + M_L + \psi_2 [1 - \rho_2(t)] H_R) \} / N$$

$$\sigma_1 \delta_3^{-1} \leq \delta_1^{-1} - (\varepsilon_1^{-1} + \phi_1^{-1}), \delta_4^{-1} = \delta_2^{-1} - (\varepsilon_2^{-1} + \phi_2^{-1}), \delta_5^{-1} = \delta_1^{-1} - \varepsilon_1^{-1}, \delta_6^{-1} = \delta_2^{-1} - \varepsilon_2^{-1}$$

$$N = S + E + I + Q + M + H + R, I = I_P + I_R, M = M_E + M_L, H = H_{PQ} + H_{P\tilde{Q}} + H_{RH_p} + H_{R\tilde{H}_p}$$

The ϕ_i ($i=1, 2$) are probabilities of diagnosis on presentation in the first model (figure 1a), but rates (i.e., reciprocals of mean pre-diagnosis sojourns in M_E and M_L , respectively) in the second (figure 1b). Isolation may be imperfect even after probable cases are hospitalized (i.e., $\rho_i < 1$) if infection-control facilities (e.g., negative pressure rooms) are defective or saturated. Sigma are factors by which medications shorten illness (i.e., $\sigma_i \geq 1$), but only if begun before the acute phase (as, e.g., in people who receive chemoprophylaxis, contacts who are quarantined, patients who seek care during the prodrome), and ψ_i are diminutions (i.e., $\psi_i \leq 1$) of infectiousness ($i=1, 2$) during treatment regardless of when begun.

Parameters

Our model's biological parameters derive entirely from clinical observations of early SARS patients in Hong Kong (table 1); we estimated time-varying control parameters from observations during the outbreak in Singapore (table 2). Trial periods correspond to before 14 March, when cumulative cases more than doubled, between 14 and 24 March, when home quarantine began, and between 24 March and 4 April, when cumulative cases abruptly increased by about 10%. We estimated intervals as well as parameter values by minimizing sums of squared differences between cumulative $\alpha_2 Q + \varepsilon_1 \phi_1 I_P + \varepsilon_2 \phi_2 I_R$ (or, in the second model, $\alpha_2 Q + \varepsilon_1 \phi_1 M_E + \varepsilon_2 \phi_2 M_L$) and probable cases hospitalized.

Control amounts to preventing infectious people from infecting more than one susceptible person on average. Quarantine refers to isolation during the incubation period (interval between infection and onset of symptoms). As it is difficult to determine who is infected (i.e., was exposed to an infectious person intimately enough for infection, if susceptible) before they become infectious, authorities typically err on the side of caution, especially if diseases are lethal. Because people are restricted to their homes or designated facilities, where they may not only be unproductive, but also require care, quarantine is costly as well as socially disruptive.

Gamma is the reciprocal of the period contacts (people who have been infected, but whose symptoms have not yet appeared) remain at large before being restricted to their

homes or designated facilities, if ever (i.e., $\chi(t)$ in the first model, and $\chi_A(t)$ in the second, is the proportion identified). The reciprocal of α_2 is the difference between the incubation period (interval between infection and symptom onset), α_1^{-1} , and γ^{-1} .

Because authorities will find contacts of patients diagnosed during the prodrome sooner post-exposure than those of patients not diagnosed until acutely ill, γ^{-1} varies with proportion diagnosed during acute illness, $p(t) = \varepsilon_2\phi_2I_R / [\varepsilon_1\phi_1I_P + \varepsilon_2\phi_2I_R]$ (or, in the second model, $\varepsilon_2\phi_2M_L / [\varepsilon_1\phi_1M_E + \varepsilon_2\phi_2M_L]$). This ensures contacts of people seeking medical care and being diagnosed during the prodrome are quarantined soon after exposure, whereas contacts of those misdiagnosed or presenting with acute respiratory symptoms are quarantined later, if at all. Other contacts become symptomatic at rate α_1^{-1} and quarantined ones are isolated at rate $\alpha_2(t)^{-1} = \alpha_1^{-1} - \gamma(t)^{-1}$.

Unless infected people become infectious before developing symptoms, other interventions may be preferable. The ε_i^{-1} are mean durations of prodromal and acute respiratory symptoms before patients seek medical care ($i=1, 2$), while χ_P and χ_R are proportions seeking medical care during the prodrome and acute illness, respectively. As infectiousness may increase with symptoms, infected people may be encouraged to seek care before becoming acutely ill. Whenever they seek care, clinicians must diagnose and hospital personnel isolate them effectively before they infect more than one susceptible person on average (i.e., the number of secondary infections, $\mathfrak{R} < 1$).

Experiments

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 comparison of model outbreaks with and without interventions, or with intervention at different times, assesses their marginal impacts.

We compared final outbreak sizes with our best estimates of time-varying quarantine rates and times post-exposure at which authorities began searching for possible contacts in Singapore with hypothetical alternatives. Differences with and without quarantine, or with advanced or delayed timing, are cases and deaths averted by this intervention, conditional on others. Such assessments are conservative insofar as we tacitly assume that quarantine of possible contacts did not affect the timeliness with which actual ones who developed compatible symptoms sought medical care.

Analyses

Results of these calculations motivated our derivation of an expression for the number of secondary infections per infectious person, typically denoted \mathfrak{R} , from our generic new disease model's underlying system of autonomous differential equations, and calculation of its partial derivatives with respect to available interventions. The resulting expressions quantify the impact on \mathfrak{R} of quarantine, seeking medical care, diagnosis, and isolation during the prodrome and acute illness. We illustrate informative composite scenarios.

Population biologists compare pathogens in host populations via \mathfrak{R}_0 , the average number of effective contacts while a person is infectious, which is equivalent to people infected on average by a newly infectious person on introduction to a wholly susceptible population. We calculate \mathfrak{R}_0 mostly to facilitate comparison of our modeling of SARS in Singapore with others' (e.g., Lipsitch et al. 2003). \mathfrak{R} is more useful than \mathfrak{R}_0 , as it must be reduced below one for control, and its partial derivatives with respect to available interventions indicate their effectiveness. Thus, these analytical functions could help policymakers decide how to intervene. We also describe relations between \mathfrak{R} and \mathfrak{R}_0 .

RESULTS

We will present analytical results first to illustrate how we could have assisted had our work been completed before SARS emerged, as indeed it has in preparation for the next new human disease. We begin by deriving an expression for \mathfrak{R} from the first model and, assuming people are not infectious until symptomatic (i.e., incubation and latent periods coincide, implying $\beta_A=0$), contributions of potentially infectious stages. Then we derive

expressions with which modelers could predict the impact on \mathfrak{R} of possible interventions given information likely to be available soon after the next new disease emerges.

Next we use observations of the initial case-series and experience with other diseases caused by related etiologic agents (i.e., other coronaviruses) to calculate \mathfrak{R} and its constituents. We also estimate parameters from the first 30 days, after which authorities began quarantining possible contacts in Singapore, and entire outbreak. As parameters include the timing, intensity and efficiency of interventions, we calculate final outbreak sizes under alternative control scenarios.

Because our early estimates indicated that patients were not particularly infectious until acutely ill, and symptomatic people are more easily identified than asymptomatic ones, we compare quarantining possible contacts with encouraging people with compatible symptoms to seek care, especially if they might have been exposed to someone since diagnosed, and isolating ones with SARS. We also use field observations (e.g., apparent difficulty identifying probable cases while incubating) to distinguish the actual from possible impact of quarantine.

Analytical

To assist policymakers, we must know the number of infections per infectious person, and – as the average must be reduced below one to control outbreaks – be able to quantify the impact of available interventions. We fix time-varying parameters and derive an expression for \mathfrak{R} . Then we take its partial derivatives with respect to the rates at which ill people seek medical care, are diagnosed, and efficiencies with which they are isolated during successive clinical stages, and to the rate at which a proportion of their contacts is quarantined. Finally, we illustrate how these analytical results could have assisted policymakers to intervene more effectively when SARS first emerged.

Calculation of \mathfrak{R}

The reproduction number, \mathfrak{R} , is defined as secondary infections per infectious person. Because infectious people might be in any of several states (excluding the incubation

period, six in the first model and eight in the second), this essentially is a weighted average of contributions from those in each. In the first model,

$$\mathfrak{R} = \mathfrak{R}_{I_P} + \mathfrak{R}_{H_{PQ}} + \mathfrak{R}_{H_{P\bar{Q}}} + \mathfrak{R}_{I_R} + \mathfrak{R}_{H_{RH_P}} + \mathfrak{R}_{H_{R\bar{H}_P}}.$$

In analyses of this model, it is convenient to write χ_A without the subscript, which is necessary only in the second model. Denoting by T_{ij} the fraction of individuals entering stage i who survive until stage j and by D_k the duration of stage k , we have

$$\begin{aligned} \mathfrak{R}_{I_P} &= \beta_P T_{EI_P} D_{I_P}, \\ \mathfrak{R}_{H_{PQ}} &= (1 - \rho_1) \beta_P T_{EQ} T_{QH_{PQ}} D_{H_{PQ}}, \\ \mathfrak{R}_{H_{P\bar{Q}}} &= (1 - \rho_1) \beta_P T_{EI_P} T_{I_P H_{P\bar{Q}}} D_{H_{P\bar{Q}}}, \\ \mathfrak{R}_{I_R} &= \beta_R T_{EI_P} T_{I_P I_R} D_{I_R}, \\ \mathfrak{R}_{H_{RH_P}} &= (1 - \rho_2) \beta_R \left(T_{EQ} T_{QH_{PQ}} T_{H_{PQ} H_{RH_P}} + T_{EI_P} T_{I_P H_{P\bar{Q}}} T_{H_{P\bar{Q}} H_{RH_P}} \right) D_{H_{RH_P}}, \\ \mathfrak{R}_{H_{R\bar{H}_P}} &= (1 - \rho_2) \beta_R T_{EI_P} T_{I_P I_R} T_{I_R H_{R\bar{H}_P}} D_{H_{R\bar{H}_P}}. \end{aligned}$$

In terms of the original parameters (see tables A.1 and A.2), we have

$$\begin{aligned} \mathfrak{R}_{I_P} &= \frac{\beta_P (1 - \chi) \alpha_1}{[(1 - \chi) \alpha_1 + \chi \gamma + \mu] (\varepsilon_1 \phi_1 + \delta_1 + \mu)}, \\ \mathfrak{R}_{I_R} &= \frac{\beta_R (1 - \chi) \alpha_1 \delta_1}{[(1 - \chi) \alpha_1 + \chi \gamma + \mu] (\varepsilon_1 \phi_1 + \delta_1 + \mu) (\delta_2 + \varepsilon_2 \phi_2 + \kappa + \mu)}, \\ \mathfrak{R}_{H_{PQ}} &= \frac{\beta_P (1 - \rho_1) \chi \gamma \alpha_2}{[(1 - \chi) \alpha_1 + \chi \gamma + \mu] (\alpha_2 + \mu) (\delta_1 + \mu)}, \\ \mathfrak{R}_{H_{P\bar{Q}}} &= \frac{\beta_P (1 - \rho_1) [(1 - \chi) \alpha_1] \varepsilon_1 \phi_1}{[(1 - \chi) \alpha_1 + \chi \gamma + \mu] (\varepsilon_1 \phi_1 + \delta_1 + \mu) (\delta_3 + \mu)}, \\ \mathfrak{R}_{H_{RH_P}} &= \left(\frac{\beta_R (1 - \rho_2) \chi \gamma \alpha_2 \delta_1}{[(1 - \chi) \alpha_1 + \chi \gamma + \mu] (\alpha_2 + \mu) (\delta_1 + \mu)} + \frac{\beta_R (1 - \rho_2) (1 - \chi) \alpha_1 \varepsilon_1 \phi_1 \delta_3}{[(1 - \chi) \alpha_1 + \chi \gamma + \mu] (\varepsilon_1 \phi_1 + \delta_1 + \mu) (\delta_3 + \mu)} \right) \frac{1}{\delta_2 + \kappa + \mu}, \\ \mathfrak{R}_{H_{R\bar{H}_P}} &= \frac{\beta_R (1 - \rho_2) (1 - \chi) \alpha_1 \delta_1 \varepsilon_2 \phi_2}{[(1 - \chi) \alpha_1 + \chi \gamma + \mu] (\varepsilon_1 \phi_1 + \delta_1 + \mu) (\varepsilon_2 \phi_2 + \delta_2 + \kappa + \mu) (\delta_4 + \kappa + \mu)}. \end{aligned}$$

Our derivation of \mathfrak{R} is given in the appendix. Absent interventions, it reduces to the intrinsic contact or reproductive number, \mathfrak{R}_0 , defined respectively as the average number of effective contacts (i.e., sufficiently intimate for transmission were persons contacted susceptible) or secondary infections caused by a newly infectious person on introduction to a wholly susceptible population:

$$\mathfrak{R}_0 = \frac{\beta_P \alpha_1}{(\alpha_1 + \mu)(\delta_1 + \mu)} + \frac{\beta_R \alpha_1 \delta_1}{(\alpha_1 + \mu)(\delta_1 + \mu)(\delta_2 + \kappa + \mu)}.$$

Relationship between \mathfrak{R} and \mathfrak{R}_0

Because they are often confused, we derive \mathfrak{R} as a function of \mathfrak{R}_0 . We set

$\rho_1 = \rho_2 = \rho < 1$ and suppose that $\mu \ll 1$, $\phi_1 = \phi_2 = 0$, and $\eta = \chi\gamma > 0$. Then

$$\mathfrak{R} \approx \mathfrak{R}_0 \left[\frac{(1-\rho)\eta + \alpha_1}{\eta + \alpha_1} \right].$$

Evidently $\mathfrak{R}=\mathfrak{R}_0$ only when $\rho=0$ (i.e., isolation is wholly ineffective); otherwise, $\mathfrak{R}<\mathfrak{R}_0$.

Because outbreaks will subside when $\mathfrak{R}<1$, the goal of control is to reduce \mathfrak{R} below 1 when $\mathfrak{R}_0>1$. Thus, to achieve $\mathfrak{R}<1$, the isolation efficiency, ρ , must be sufficiently high; e.g., $\rho > 1-1/\mathfrak{R}_0$. Otherwise, $\mathfrak{R}_0(1-\rho) \geq 1$ and therefore $\mathfrak{R}>1$ for all $\eta>0$ (i.e., control is impossible by quarantine alone). Moreover, if $\rho > 1-1/\mathfrak{R}_0$,

$$\mathfrak{R}<1 \text{ for all } \eta > \eta_c =: \frac{\alpha_1(\mathfrak{R}_0 - 1)}{1 - (1-\rho)\mathfrak{R}_0}.$$

That is, if the effective rate of quarantine, η , does not exceed the critical value, η_c , control is impossible (under the conditions specified in deriving the relationship between \mathfrak{R} and \mathfrak{R}_0). One could derive similar conditions for other control parameters.

Intervention effects

In calculating the partial derivatives of \mathfrak{R} with respect to rates at which authorities quarantine χ contacts, γ , ill people seek care, are diagnosed and isolated, ε_i , ϕ_i and ρ_i , where $i=1$ again denotes the prodrome and $i=2$ the acute respiratory phase, we further simplify notation by numbering the T_{ij} and D_k (table A.1 and A.2) and set

$$\mathfrak{R}_1 = \mathfrak{R}_{I_p}, \mathfrak{R}_2 = \mathfrak{R}_{H_{PQ}}, \mathfrak{R}_3 = \mathfrak{R}_{H_{P\bar{Q}}}, \mathfrak{R}_4 = \mathfrak{R}_{I_R}, \mathfrak{R}_5 = \mathfrak{R}_{51} + \mathfrak{R}_{52}, \mathfrak{R}_6 = \mathfrak{R}_{H_{R\bar{H}P}}, \text{ where}$$

$$\mathfrak{R}_{51} = (1 - \rho_2) \beta_R T_{EQ} T_{QH_{PQ}} T_{HPQH_{RH_P}} D_{H_{RH_P}} \text{ and } \mathfrak{R}_{52} = (1 - \rho_2) \beta_R T_{EI_p} T_{I_p H_{P\bar{Q}}} T_{H_{P\bar{Q}} H_{RH_P}} D_{H_{RH_P}}.$$

Quarantine:

The partial derivative of \mathfrak{R} with respect to γ , the reciprocal of the period during which infected people are at large before quarantine, is

$$\frac{\partial \mathfrak{R}}{\partial \gamma} = -\frac{1}{\gamma} (T_4 \mathfrak{R} - \mathfrak{R}_2 - \mathfrak{R}_{51}).$$

And its partial with respect to χ , the proportion of contacts quarantined, is

$$\frac{\partial \mathfrak{R}}{\partial \chi} = -\frac{\gamma - \alpha}{\chi \gamma} T_4 \mathfrak{R} - \frac{1}{1 - \chi} (\mathfrak{R}_1 + \mathfrak{R}_3 + \mathfrak{R}_4 + \mathfrak{R}_{52} + \mathfrak{R}_6) + \frac{1}{\chi} (\mathfrak{R}_2 + \mathfrak{R}_{51}).$$

Seeking medical care, ε_1 , and being diagnosed, ϕ_1 , during the prodrome:

The partial derivative of \mathfrak{R} with respect to ε_1 is

$$\frac{\partial \mathfrak{R}}{\partial \varepsilon_1} = -\phi_1 D_1 \mathfrak{R} + \phi_1 D_1 (\mathfrak{R}_2 + \mathfrak{R}_{51}) + \frac{1}{\varepsilon_1} (\mathfrak{R}_3 + \mathfrak{R}_{52}).$$

And its partial with respect to ϕ_1 is

$$\frac{\partial \mathfrak{R}}{\partial \phi_1} = -\varepsilon_1 D_1 \mathfrak{R} + \varepsilon_1 D_1 (\mathfrak{R}_2 + \mathfrak{R}_{51}) + \frac{1}{\phi_1} (\mathfrak{R}_3 + \mathfrak{R}_{52}).$$

Seeking medical care, ε_2 , and being diagnosed, ϕ_2 , while acutely ill:

The partial derivative of \mathfrak{R} with respect to ε_2 is

$$\frac{\partial \mathfrak{R}}{\partial \varepsilon_2} = -\phi_2 D_4 (\mathfrak{R}_4 + \mathfrak{R}_6) + \frac{1}{\varepsilon_2} \mathfrak{R}_6.$$

And its partial with respect to ϕ_2 is

$$\frac{\partial \mathfrak{R}}{\partial \phi_2} = -\varepsilon_2 D_4 (\mathfrak{R}_4 + \mathfrak{R}_6) + \frac{1}{\phi_2} \mathfrak{R}_6.$$

Efficiency of isolation during the prodrome, ρ_1 , and while acutely ill, ρ_2 :

The partial derivative of \mathfrak{R} with respect to ρ_1 is

$$\frac{\partial \mathfrak{R}}{\partial \rho_1} = -\frac{1}{1-\rho_1}(\mathfrak{R}_2 + \mathfrak{R}_3).$$

And its partial with respect to ρ_2 is

$$\frac{\partial \mathfrak{R}}{\partial \rho_2} = -\frac{1}{1-\rho_2}(\mathfrak{R}_5 + \mathfrak{R}_6).$$

Our second model includes states for patient evaluation before diagnosis or reclassification as a probable case, when isolation may be less efficient than afterwards. This elaboration is motivated by the Taiwanese experience, where patients sometimes spent several days inadequately isolated pending diagnosis (Hsieh et al. 2005). This model also permits medications that may shorten clinical stages, if begun soon enough, and reduce infectiousness whenever begun.

The impact of isolation or reduced infectiousness on \mathfrak{R} is straightforward, but effect of medications via stage duration is more complex. We defer publication of our analysis of this model until we have experience with a disease to which its features are applicable.

Effectiveness of Interventions

We wish to know not only which control measures or combinations would reduce $\mathfrak{R} < 1$, but which is most effective. The disease-free equilibrium is attained more quickly with smaller fractions infected when \mathfrak{R} is smaller (figure 2). Evidently the most effective interventions reduce \mathfrak{R} the most. The disease-free and endemic equilibria are derived in the appendix, and figure 3 shows that both are stable.

We illustrate the joint effects of quarantine and hospitalization (rate at which people seek medical care times their probability of diagnosis in the first model) during either stage in various ways: Figure 4 illustrates how different levels of quarantine affect the relationship between \mathfrak{R} and probability of diagnosis, given a fixed rate at which patients seek care during successive stages. Figure 5 illustrates the partial derivative of \mathfrak{R} with respect to some of these combinations. And figure 6 is a 3-D plot of \mathfrak{R} as a function

simultaneously of quarantine and diagnosis during the prodrome and phase diagram showing regions in joint parameter space where \mathfrak{R} is >1 and <1 .

Empirical

Because information about emerging infectious diseases is inaccurate and incomplete early in outbreaks, we calculate \mathfrak{R} via Latin hypercube sampling from appropriate probability distributions with parameters estimated from the initial case series in Hong Kong (Lee et al. 2003, Tsang et al. 2003). Then we ascertain sensitivity of results with and without quarantine to parameters whose values we are least certain. Subsequently, we estimate parameters from the first 30 days and entire outbreak in Singapore. Then we calculate final outbreak sizes under various hypothetical conditions, including earlier, later and no quarantine. In our discussion, we compare these assessments of available means of controlling SARS.

Estimation of \mathfrak{R}

Times from infection to fever (onset of prodrome), fever to dyspnea (onset of acute illness), and dyspnea to defervescence (by which time few patients will have regained full respiratory function, but none will be infectious) should be gamma distributed. We chose means of six (Lee et al. 2003), four (Tsang et al. 2005), and eight days (difference between mean hospitalization in Singapore, less 48 hours without fever, and the prodrome) for our incubation, prodrome and acute stage sojourns, respectively (table 1).

Initial case series permit only crude estimates of the variation about these means.

Assuming further that infection rates have the exponential and control parameters the triangular distributions shown in table 3, the corresponding values of \mathfrak{R} and its six constituents with and without quarantine are shown in table 4. Figures 7 are histograms of the \mathfrak{R}_i ($i=1, \dots, 6$) from which were derived the tabulated means, variances, and probabilities of $\mathfrak{R}>1$, with and without quarantine, respectively.

We describe the sensitivity of \mathfrak{R} to these parameters via partial rank correlation coefficients and associated p-values (table 5). The coefficient of $\varepsilon_1\phi_1$ is not statistically

significant, but its absolute value is greater than that of $\varepsilon_2\phi_2$, indicating that \mathfrak{R} is more sensitive to hospitalization during the prodrome than while acutely ill. Given quarantine, this effect all but disappears, suggesting these interventions are interchangeable. The coefficient of $\rho_2 > \rho_1$ simply because $\beta_2 \gg \beta_1$.

Social Response

During the outbreak in Singapore, cases increased abruptly on 14 March and 4 April (figure 8) as the outbreak spread from one hospital to another and to a busy marketplace. Authorities began quarantining possible contacts on 24 March, one month after symptom onset in the first of several cases infected in Hong Kong, with contacts directed to remain at home or, to minimize inconvenience to family members beginning on 12 May, in government housing. Hospital infection-control measures were strengthened several times between 17 March and 7 April (Goh et al. 2006).

Accordingly, we estimate χ for two epochs, $t < \tau_2$ and $t \geq \tau_2$ and ρ_i and $\varepsilon_i\phi_i$ ($i=1, 2$) for four, $t < \tau_1$, $\tau_1 \leq t < \tau_2$, $\tau_2 \leq t < \tau_3$, and $t > \tau_3$, where $13 \text{ March} \leq \tau_1 \leq 15 \text{ March}$, $\tau_2 \geq 24 \text{ March}$, and $\tau_3 > 7 \text{ April}$.

Fixing the biological parameters at mean values deduced from the initial case series (table 1) and assuming those quarantined spent 3 days at large on average, we estimated control parameters by minimizing sums of squared differences between observed and estimated cumulative cases either during the first 30 days or entire outbreak (table 2). Parameters differ quantitatively (e.g., infection rates during the acute phase are six or eight times those during the prodrome when, respectively, the first 30 days or entire outbreak is used), but not qualitatively (i.e., patients are not particularly infectious during the prodrome regardless of whether the partial or complete time-series is used).

Isolation efficiency among those hospitalized during the prodrome increased from 0.14 during the first epoch to 0.94 during the last. Among those hospitalized while acutely ill, efficiency increased from 0.2 to 0.99. Similarly, the rate of hospitalization (product of the rate of presentation and probability of diagnosis) during the prodrome increased from

0.26 to 0.6, while that during acute illness increased from 0.35 to 0.66. The former corresponds to an increase in the proportion of probable cases seeking care and being diagnosed during the prodrome from 0.1 or less to 0.9 or more (figure 9).

Corresponding values of \mathfrak{R} are 3.79 for $t < \tau_1$, 3.33 for $t < \tau_2$, 0.66 for $t < \tau_3$, and 0.32 for $t > \tau_3$, which resemble Wallinga's and Teunis' (2004) estimates of 3.1 and 0.7 before and after the global alert on March 12, respectively.

Observations

None of these estimates accounts for the 32 suspect cases discharged from Tan Tock Seng Hospital (TTSH) before positive antibody or coronavirus culture results were available. We have been unable to learn anything about them, but the reclassification of suspect cases post-discharge suggests variable clinical presentation, whereupon still milder cases likely remained at large. The observation that six of 45 TTSH staff with antibodies did not become ill (Wilder-Smith et al. 2005) affirms this suggestion. As one might expect virulence to decrease with transmission person-to-person (Ewald 1994), antibodies to SARS coronavirus in ~40% of healthy wild-animal traders serving a Guangdong market (Guan et al. 2003) and ~2% of healthy adults residing in Hong Kong two years before the outbreak (Zheng et al. 2004) also could be interpreted this way.

Few cases were infected at home. Two-thirds were hospital staff (0.41), patients or visitors (0.21), among whom several infected more than 10 others (Leo et al. 2003). Super spreading occurred by virtue of timing (an index case), opportunity (three patients with co-morbid conditions that obscured their diagnoses) or both (a nurse infected early in the outbreak). The probability of being infected in hospital peaked on March 28 (figure 10), roughly one latent period after SARS patients began being admitted solely to TTSH, and decreased as infection-control procedures were strengthened and better enforced.

Transmission was heterogeneous. Three-quarters of clinically diagnosed cases (i.e., 159/206) infected no one (Leo et al. 2003), and of their 7,863 possible contacts quarantined, only 11 (~0.1%) became cases themselves (Tan in press). Goh et al. (2006)

count 58 of the 206 probable plus 32 suspect cases with positive laboratory results among 12,194 persons whose movements were restricted (contacts above) or were telephoned daily (4,331), but only 28 cases were hospitalized on their dates of onset, nine of whom were classified as probable and immediately isolated. These discrepant claims make calculating lives disrupted per probable case quarantined difficult, but authorities also facilitated a social response that prevented the others from infecting anyone.

Experiments

Because the average number of secondary infections is 0.92, quarantining 11 probable cases could have averted at most 10 cases. Final epidemic size was seven fewer with quarantine than without, affirming the modest impact of this intervention conditional on others. Size is sensitive to the start of effective interventions (figure 11a). Advancing τ_2 reduces and retarding it increases size as much as 40 and 70%, respectively, but varying the beginning of home quarantine per se affects size only by $\sim 2\%$ (results not shown).

As no infectious disease with $\mathcal{R}_0 > 1$ can be controlled unless cases are isolated (Lloyd-Smith et al. 2004), it is not surprising that final size is sensitive to ρ_i (figure 11b). The greater sensitivity to ρ_2 than ρ_1 is due simply to $\beta_R > \beta_P$. Final size is more sensitive to χ (figure 11c) than either $\varepsilon_i \phi_i$ ($i=1, 2$) alone, but not both together (figure 11d). In practice, the proportion of contacts quarantined, χ , was limited to about 5% (e.g., 11/238 in Singapore and – from Hsieh et al. (2005) – 24/480 in Taiwan) by inability to identify people who had been infected until they became symptomatic.

Sensitivity to control parameters depends on when assessed (results not shown), whereupon re-evaluation of decisions made earlier could result in mid-course adjustments even if accurate observations were used. When accuracy also changes, sensitivity is even more likely to change, emphasizing the need to monitor outbreaks in progress.

These experimental results are consistent with the observation that 77% of probable cases infected no one (Leo et al. 2003): because patients were minimally infectious during their prodrome (table 2), hospitalization during that stage was virtually equivalent to

quarantine, and its probability increased from 0.1 or less to 0.9 or more during this outbreak (figure 9). The rate of hospitalization during acute illness also increased, as did isolation efficiency (table 2). This social response controlled SARS in Singapore.

DISCUSSION

Motivated by the observation that mathematical epidemiologists contributed little to SARS control efforts, we modeled a generic emerging infectious disease and analyzed one recent experience to determine how we might have helped. We derived an expression for the reproductive number, which must be less than one for control, and took its partial derivatives with respect to possible interventions. We based biological parameter values on the initial case series in Hong Kong, and estimated control parameter values from observations during the first 30 days and entire outbreak in Singapore. Finally, we calculated hypothetical outbreak sizes under alternative response scenarios.

Our model is suitable for any directly transmitted disease (figures 1), though inevitably less so than disease-specific models. Its biological states are clinical, so their durations are estimable from early case series. Its control parameters are time varying (table 2), because sojourns in non-biological states change as relevant social systems (e.g., clinicians, health authorities, infection control staff, and populace) respond to public-health emergencies. The probability of diagnosis during the prodrome changes similarly in social systems supposedly valuing freedom over democracy (i.e., abiding by rules established by elected officials) and vice-versa (figure 9), suggesting that seeking medical care and being diagnosed earlier as outbreaks progress may be ubiquitous (see also Liang et al. 2004). Finally, when infected people are quarantined or encouraged to seek medical care is a function of the stage at which those who infected them are diagnosed.

While quarantine could be very effective (figures 4-6), its contribution to SARS control was modest, at least in Singapore. Interventions reaching only 5% of the target population cannot control any disease whose $\mathfrak{R}_0 > 1.05$ (i.e., set $p=0.05$ in $\mathfrak{R}_0(1-p) < 1$ and solve for \mathfrak{R}_0). Neither our estimate of χ (table 2b) nor observation that only nine cases were diagnosed as probable and isolated on their onset dates is consistent with Goh et

al.'s (2006) claim that 24% were quarantined or telephoned. Perfect isolation of this larger proportion would only raise the threshold \mathcal{R}_0 to 1.5, and estimates for SARS range from 2 to 4 (WHO 2003). Any intervention misclassifying more than 99% (e.g., 1-11/7,863 or 1-58/12,194) of those affected will be costly, but quarantined people are unproductive and require care (i.e., cannot work, attend school, or even shop for groceries). Was our experience with SARS unusual or has this ancient public health intervention (McNeill 1977, Rosner 1995) never been evaluated?

Modelers may have inadvertently reinforced a belief – quarantine is (versus could be) effective – that not only cost the global economy billions during 2003, but also could have even more negative impact in the very near future. The lowest estimate of the 1918 influenza strain's \mathcal{R}_0 is 1.8 (Ferguson et al. 2005), influenza's incubation period is shorter than SARS', and peak viral excretion occurs earlier (Peiris 2003). These observations suggest quarantine should be no more effective against pandemic influenza. Yet some of us have modeled movement restrictions, together with drugs that may shorten clinical course and reduce infectiousness, to inform pandemic planning.

CONCLUSIONS

When infected people become infectious is among the most important epidemiological unknowns early in outbreaks of new human diseases because it largely determines the optimal public health response (Fraser et al. 2004). If infectiousness precedes symptoms, possible contacts must be quarantined. But identifying people whose contacts were sufficiently intimate for infection is extremely difficult, especially given uncertainty about the mode of transmission. Quarantine is a very expensive and disruptive public health intervention. Consequently, the gain in efficiency by ensuring instead that people with early signs and symptoms seek medical care, clinicians diagnose and hospital infection-control staff isolate them effectively may more than compensate for any infections caused during their prodrome. Modeling can help to determine the onset of infectiousness and, conditional on that essential information, to evaluate the relative impact of various possible public health interventions.

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Joe Bresee recognized that modeling could assist in controlling the newly emerged disease later named SARS; Mark Chen, Annelies Wilder-Smith, Heng Bee Hoon, and Leo Yee-Sin shared their observations from Tan Tock Seng Hospital; and Larry Anderson, Louisa Chapman, Susan Chu, Joanne Cono, and Gina Mootrey 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. Finally, Ying-Hen Hsieh shared his observations from the SARS outbreak in Taiwan.

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Table 1. Information from initial case series and other sources.

Phenomenon	Parameter	Value	Source
Incubation	α	6^{-1}	Lee et al. 2003
Prodrome	δ_1	4^{-1}	Tsang et al. 2003
Respiratory	δ_2	8^{-1}	Tsang et al. 2003
Hospitalization	Σ	14^{-1}	TTSH data
Pr(Dying Disease)	κ	$-\ln(1-0.18) / 12$	Ping Yan, PHAC (personal communication)
Death rate due to other causes	μ	$365.25 * 70^{-1}$	Reciprocal of average age at death

Notes: Public Health Agency of Canada (PHAC), Tan Tock Seng Hospital (TTSH)

Tables 2. Parameter estimates from fitting the predicted and observed cumulative admissions to TTSH during a) the first 30 days or b) entire outbreak in Singapore. The parameters τ_1 , τ_2 , and τ_3 , which correspond to 14 and 24 March, and 8 April, estimate times at which control efforts changed (e.g., began or intensified).

2a.

Constant Parameters	Estimates	
β_P	0.134	
β_R	0.8239	
τ_1	18.4	
Two Epochs	$t \leq \tau_1$	$t > \tau_1$
ρ_1	0.11	0.34
ρ_2	0.2	0.557
$\varepsilon_1\phi_1$	0.27	0.525
$\varepsilon_2\phi_2$	0.3	0.616

2b.

Constant Parameters	Estimates			
β_P	0.083			
β_R	0.6962			
τ_1	17.94			
τ_2	28.45			
τ_3	42.8			
Two Epochs	$t \leq \tau_2$	$t > \tau_2$		
χ	0	0.0634		
Four Epochs	$t < \tau_1$	$\tau_1 < t < \tau_2$	$\tau_2 < t < \tau_3$	$t > \tau_3$
ρ_1	0.144	0.3	0.875	0.9388
ρ_2	0.2	0.344	0.934	0.99
$\varepsilon_1\phi_1$	0.263	0.393	0.537	0.595
$\varepsilon_2\phi_2$	0.35	0.5	0.625	0.66

Table 3. Input parameters for uncertainty analysis.

Parameter	Before Control		After Control	
	Distribution	Range	Distribution	Range
$1/\alpha_1$	Gamma (2.4, 2.6)	(0, 15)	Same	
$1/\delta_1$	Gamma (1.6, 2.5)	(0, 10)		
$1/\delta_2$	Gamma (3.2, 2.5)	(2, 23)		
β_P	Exponential (0.083)	(0, 0.5)		
β_R	Exponential (0.696)	(0, 2)		
$1/\gamma$	None		Gamma (2, 2)	(0, 12)
$\varepsilon_1\phi_1$	Triangular (0.39)	(0.351, 0.429)	Triangular (0.54)	(0.486, 0.594)
$\varepsilon_2\phi_2$	Triangular (0.54)	(0.486, 0.594)	Triangular (0.63)	(0.567, 0.693)
ρ_1	Triangular (0.3)	(0.144, 0.176)	Triangular (0.875)	(0.765, 0.935)
ρ_2	Triangular (0.344)	(0.31, 0.378)	Triangular (0.934)	(0.83, 0.995)
χ	None		Triangular (0.063)	(0.04, 0.07)

Table 4. Results of uncertainty analysis (cf. figures 7).

\mathfrak{R}_i	Before Control			After Control		
	Mean	Std Dev	$P(\mathfrak{R}_i > 1)$	Mean	Std Dev	$P(\mathfrak{R}_i > 1)$
\mathfrak{R}_{I_P}	0.150346	0.148007	0	0.086441	0.086694	0
\mathfrak{R}_{I_R}	0.33263	0.257862	0.021997	0.203433	0.169474	0
$\mathfrak{R}_{H_{PQ}}$	0	0	0	0.01121	0.020695	0
$\mathfrak{R}_{H_{P\bar{O}}}$	0.140343	0.151861	0.020305	0.020571	0.037417	0
$\mathfrak{R}_{H_{RH_P}}$	1.848306	1.578784	0.615905	0.242243	0.238854	0.021909
$\mathfrak{R}_{H_{R\bar{H}_P}}$	0.542189	0.513712	0.159052	0.050121	0.059922	0
\mathfrak{R}	3.013815	2.3321628	0.857868	0.6140221	0.428422	0.178404

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

Parameter	Before Control		After Control	
	PRCC	p-value	PRCC	p-value
$1/\alpha_1$	0.56807	<0.001	0.71128	<0.001
$1/\delta_1$	0.96809	<0.001	0.9464	<0.001
$1/\delta_2$	0.02217	<0.001	0.1269	0.0014
β_P	0.09199	0.0121	0.09028	0.0158
β_R	-0.84408	<0.001	-0.73133	<0.001
$1/\gamma$	-0.09055	0.0643	-0.0098	0.8064
$\varepsilon_1\phi_1$	-0.00947	0.8634	-0.02326	0.5608
$\varepsilon_2\phi_2$			-0.27717	<0.001
ρ_1	-0.0005	0.9904	-0.11885	0.0029
ρ_2	-0.01621	0.6961	-0.61335	<0.001
χ			-0.29311	<0.001

Figure legends

- 1a. Minimum states and state-transition processes, boxes and arrows respectively, required to represent control of emerging infectious diseases transmitted via close contact. 1b. Evaluation prior to diagnosis, or reclassification from suspect to probable, and treatment, additional states and a process that increase potential applications.
2. Plots of equilibria for various $\mathfrak{R} < 1$. Time plots of proportion exposed, E/N , on the left and phase plots of E/N and complement of proportion susceptible, $1-S/N$, on the right for various $\mathfrak{R} < 1$. The time plots show that solutions converge to the disease-free equilibrium faster for smaller \mathfrak{R} . The phase plots show that proportions infected increase with \mathfrak{R} .
3. Plots showing that ξ^* is stable when $\mathfrak{R} > 1$ and ξ_0 is stable when $\mathfrak{R} < 1$.
4. The reproduction number, \mathfrak{R} , versus hospitalization, ϕ_i ($i=1$, figure 4a; $i=2$, figure 4b), for several levels of quarantine, $\chi\gamma$. These ϕ_i are probabilities of diagnosis, but rates of care seeking are fixed (i.e., $\varepsilon_1 = \varepsilon_2 = 0.5$), so hospitalization, $\varepsilon_i\phi_i$, varies with ϕ_i .
5. Derivatives of \mathfrak{R} with respect to hospitalization, $\partial\mathfrak{R}/\partial\phi_i$, as functions of ϕ_i for several levels of quarantine, $\chi\gamma$; care-seeking, ε_i ($i=1, 2$), rates are 0.5 and diagnosis in the other stage, $\phi_j = 0.3$ ($j \neq i$). Hospitalization during acute illness, $\varepsilon_2\phi_2$, reduces \mathfrak{R} more than that during the prodrome, $\varepsilon_1\phi_1$, for any level of quarantine, with effects greatest at smallest ϕ_i .
6. Three-dimensional and contour plots illustrating the combined effects of proportions quarantined, χ , and diagnosed on seeking medical care during the prodrome, ϕ_1 ($\gamma = \varepsilon_i = \phi_2 = 0.5$, $i=1, 2$) on the reproductive number, \mathfrak{R} , which must be < 1 to control outbreaks.
- 7a. and b. Histograms of \mathfrak{R}_i ($i=1, \dots, 6$) and \mathfrak{R} absent and present control from which the statistics in table 4 were calculated.

8a and b. Incident (unknown, imported, and generations 1-7) and cumulative probable cases by date of onset in Singapore (symbols) and fits to the first 30 days (dashed line) and entire outbreak (solid line). Parameter estimates are similar (table 2), particularly the ratio of infection rates during the acute phase and prodrome. Quarantine began on 24 March, 30 days after symptom onset in the index case.

9a. Intervals between symptom onset and hospitalization during the outbreaks in Singapore and Taiwan, stars and triangles respectively. 9b. Probabilities of hospitalization during the prodrome (i.e., within four days of symptom onset) in Singapore and Taiwan, long and short dashes respectively. More timely care seeking and diagnosis (shown here), and more effective isolation (table 2), controlled these outbreaks.

10a. Nosocomial infections of hospital staff (stars) and patients or visitors (triangles) by date of symptom onset. 10b. The quadratic model fits the probability of infection in hospital best, but linear model indicates this risk decreased over the entire outbreak.

11. Hypothetical impact (percentage change) on total number of cases, termed final outbreak size, of intervention timing (a; stars are τ , triangles τ_2 , squares τ_3 , and diamonds all three), efficiency of isolation during the prodrome and acute phases (b; stars and triangles, respectively), proportion of contacts quarantined (c; stars), and hospitalization rates during the prodrome and acute phases (d; stars are the prodrome, triangles the acute phase, and squares both). Outbreak size is most sensitive to isolation efficiency during the acute phase simply because the infection rate is greatest then.

Figure 1a.

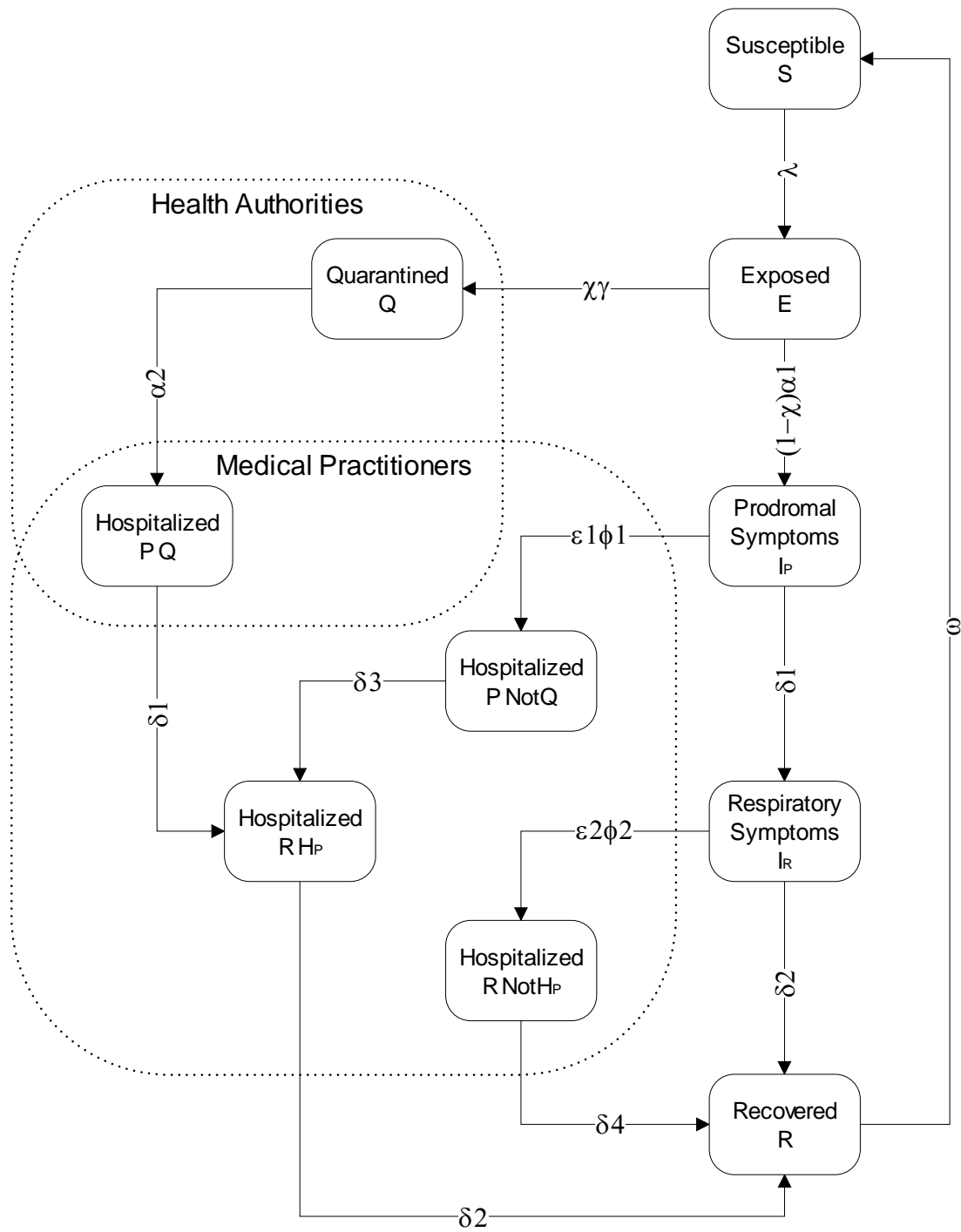


Figure 1b.

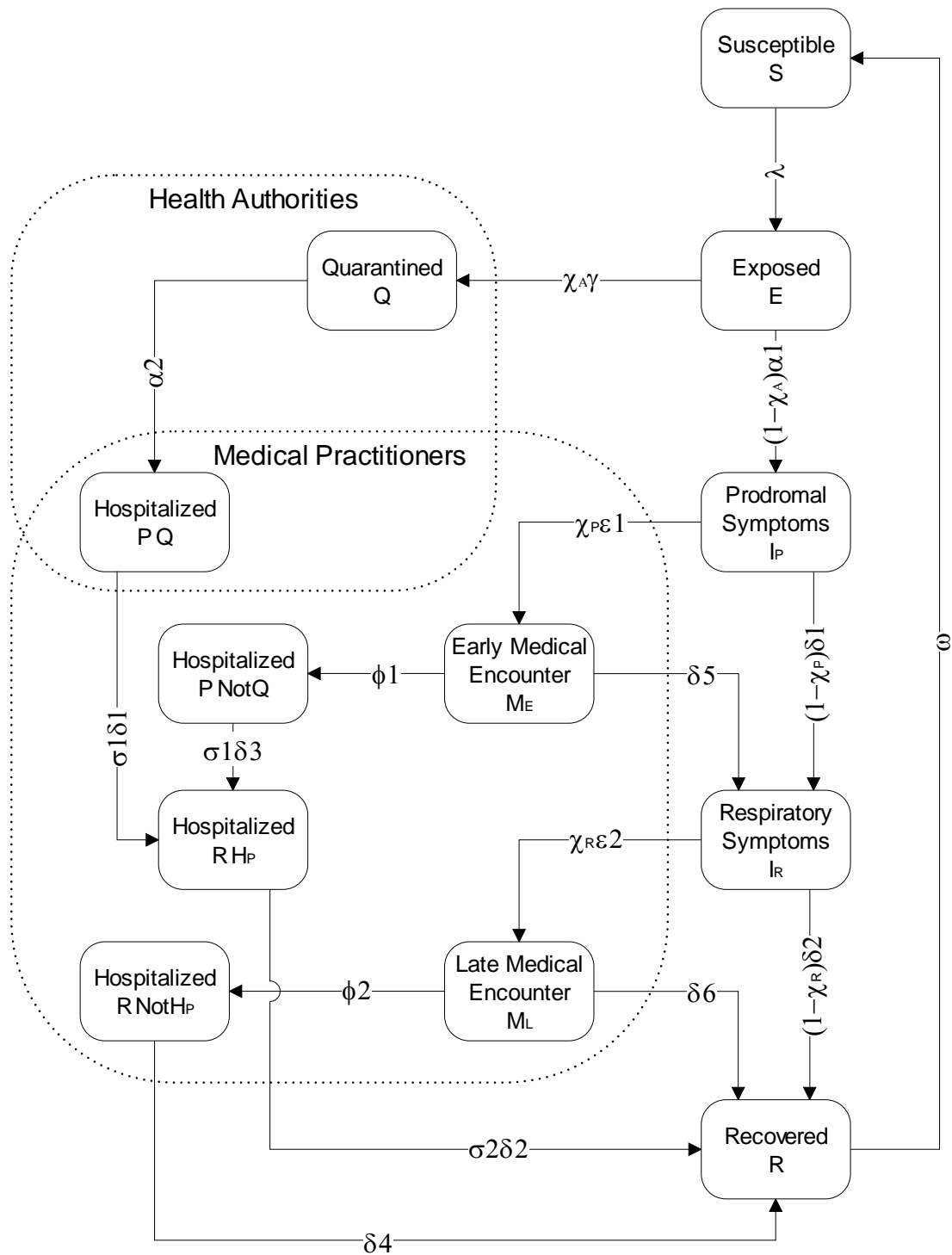


Figure 2.

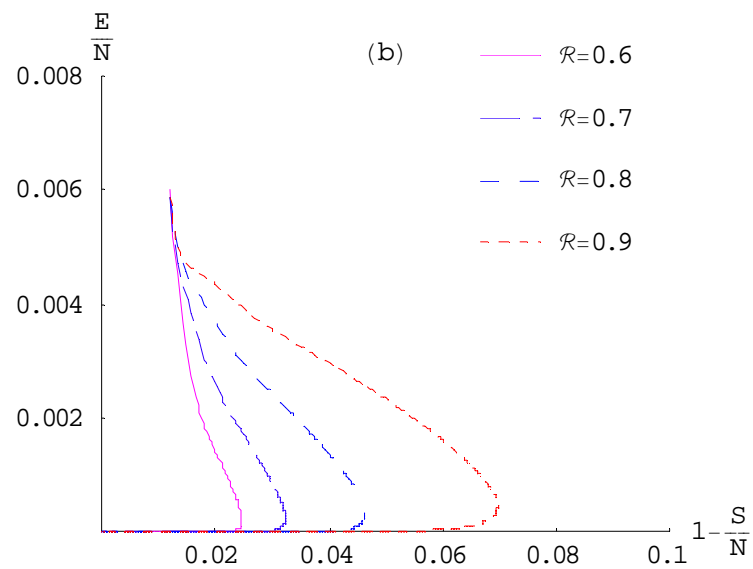
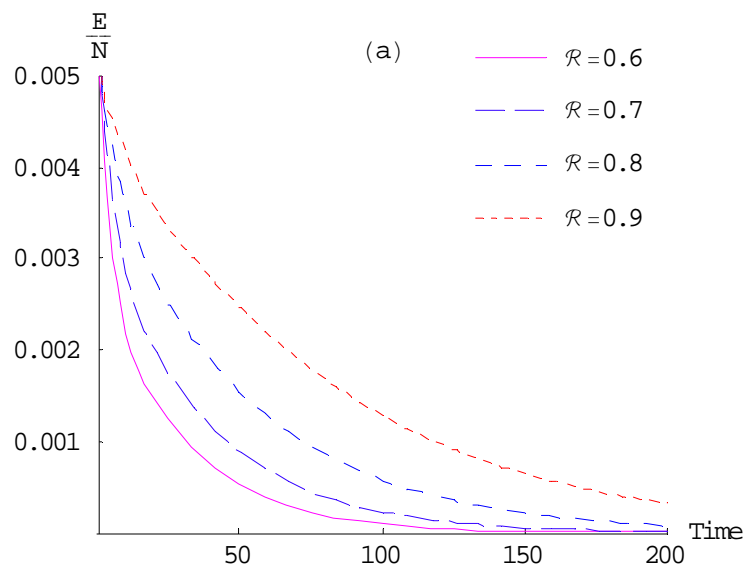


Figure 3.

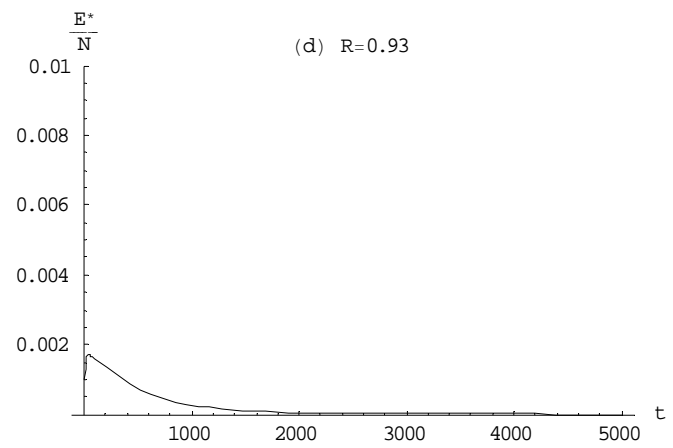
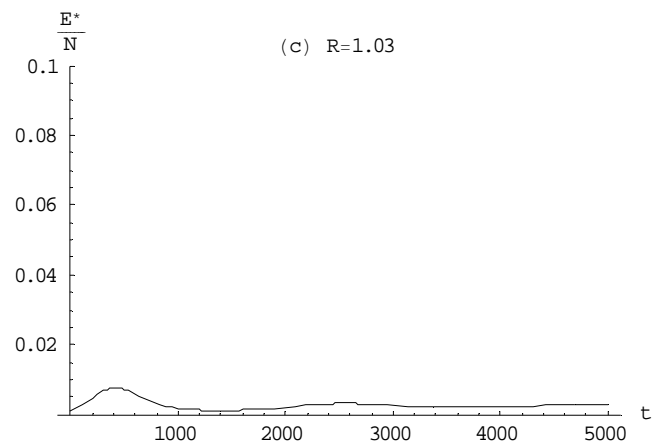
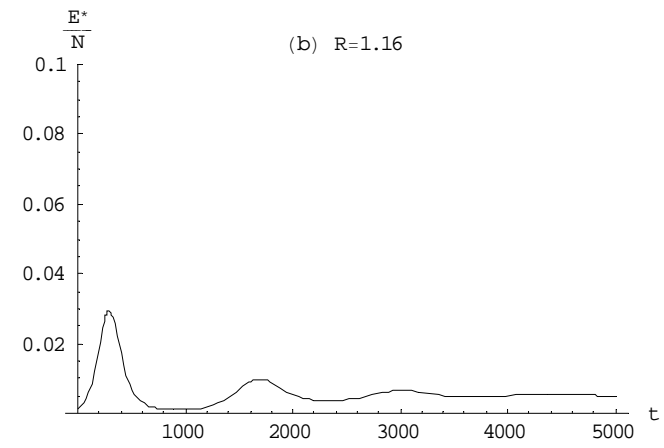
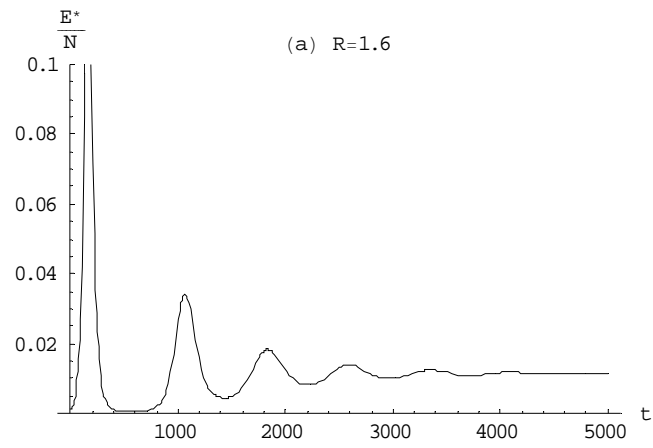


Figure 4.

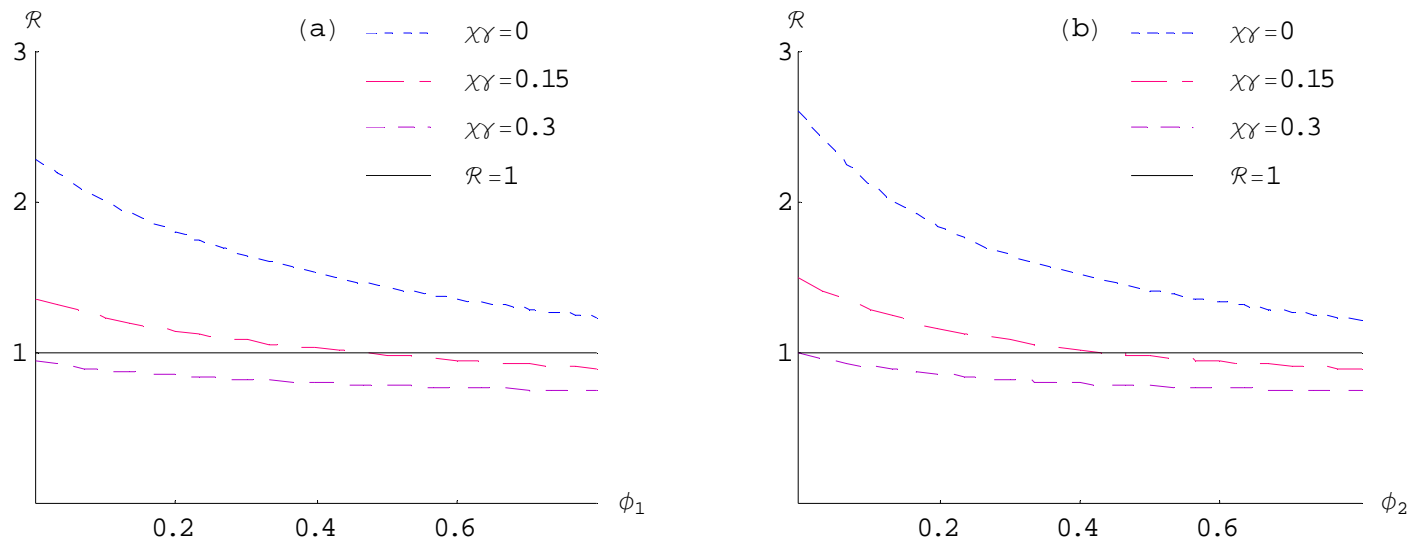


Figure 5.

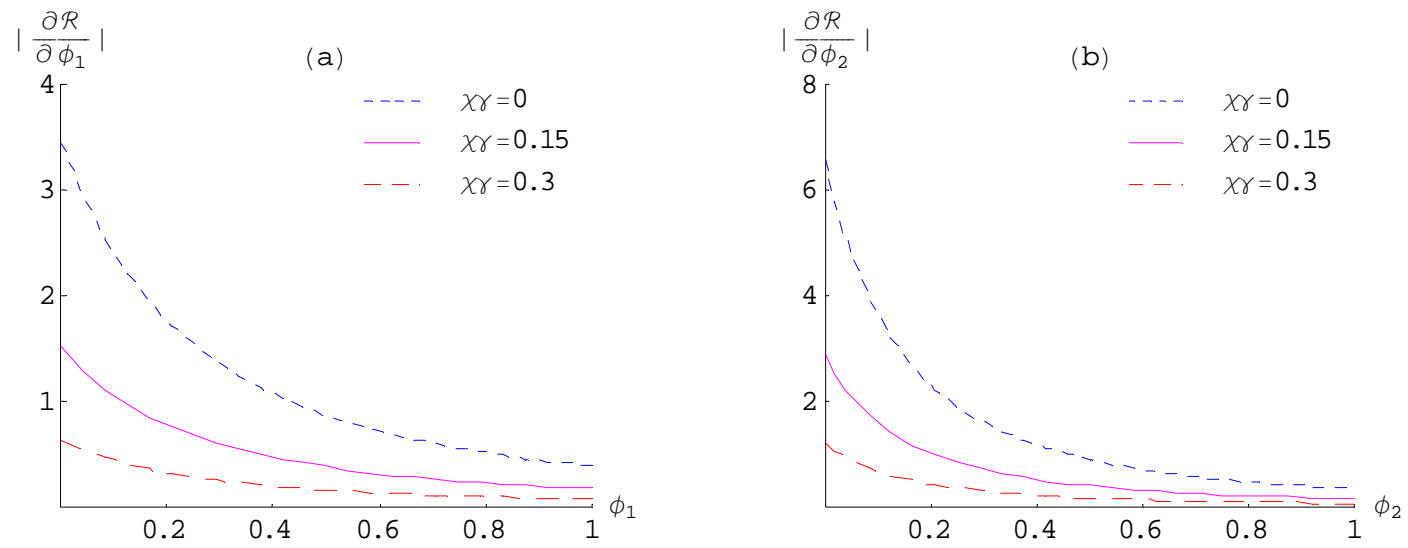


Figure 6.

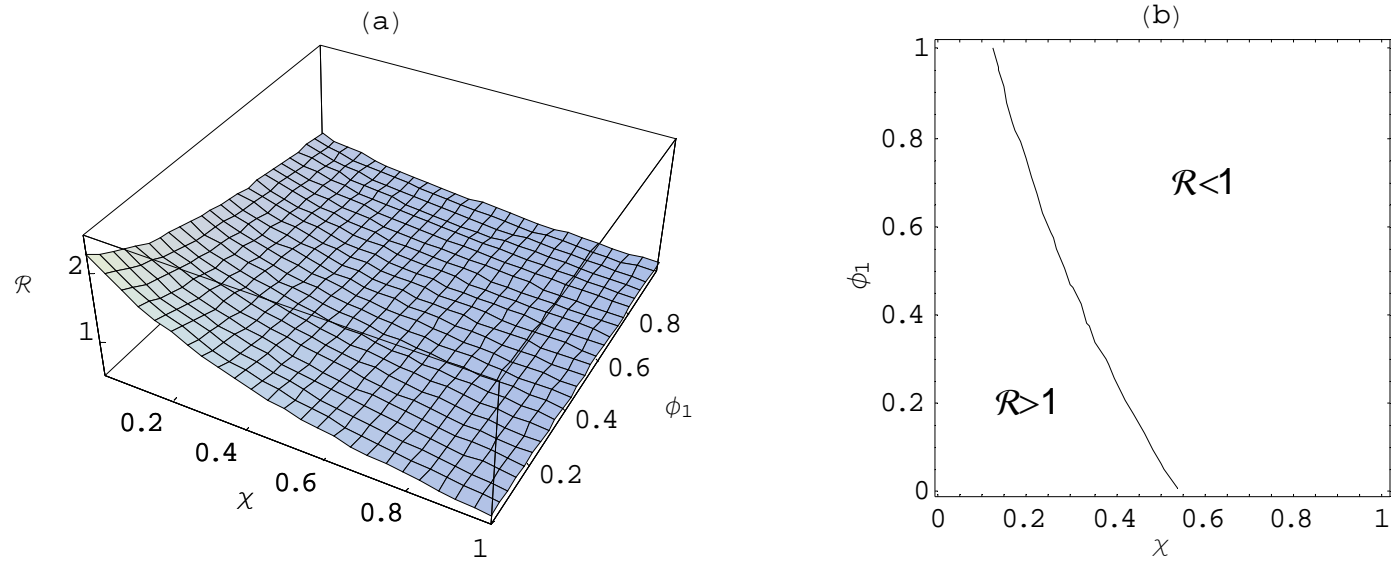


Figure 7.

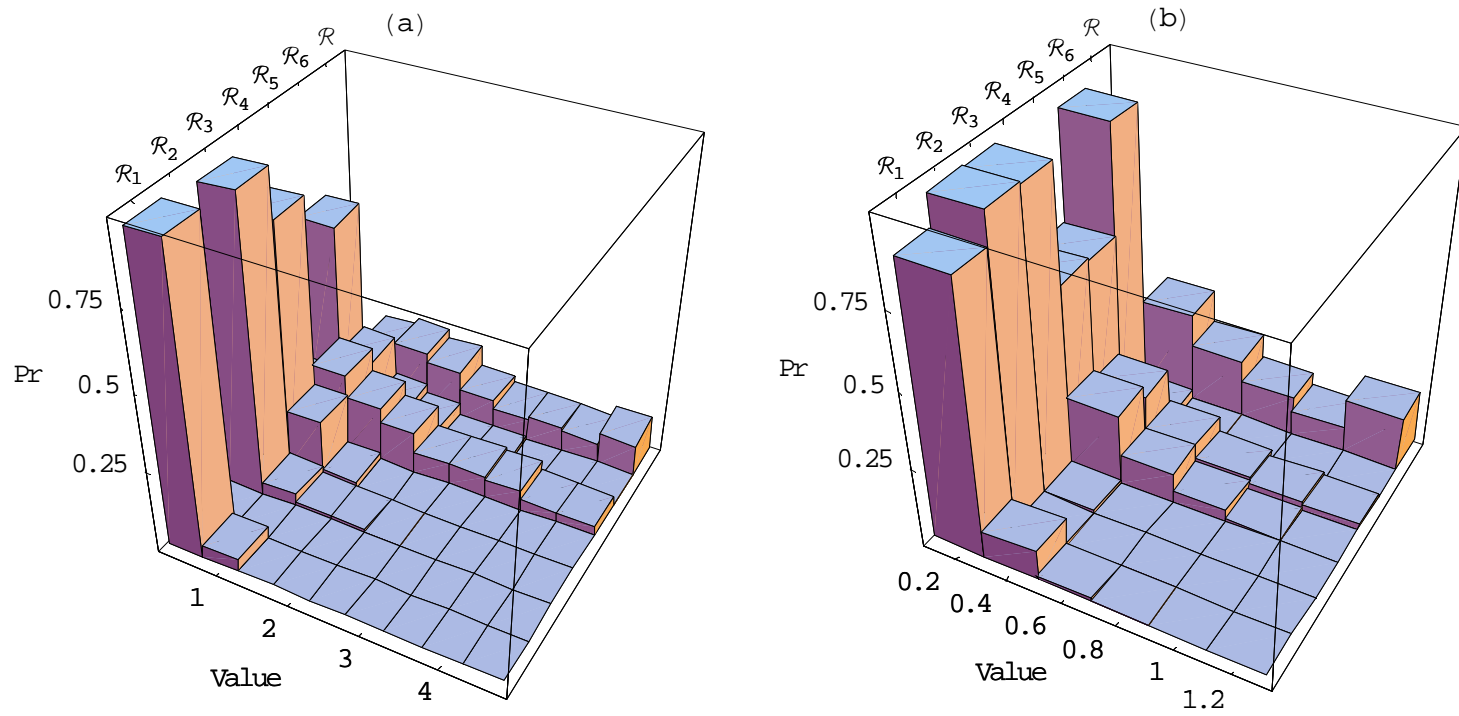


Figure 8.

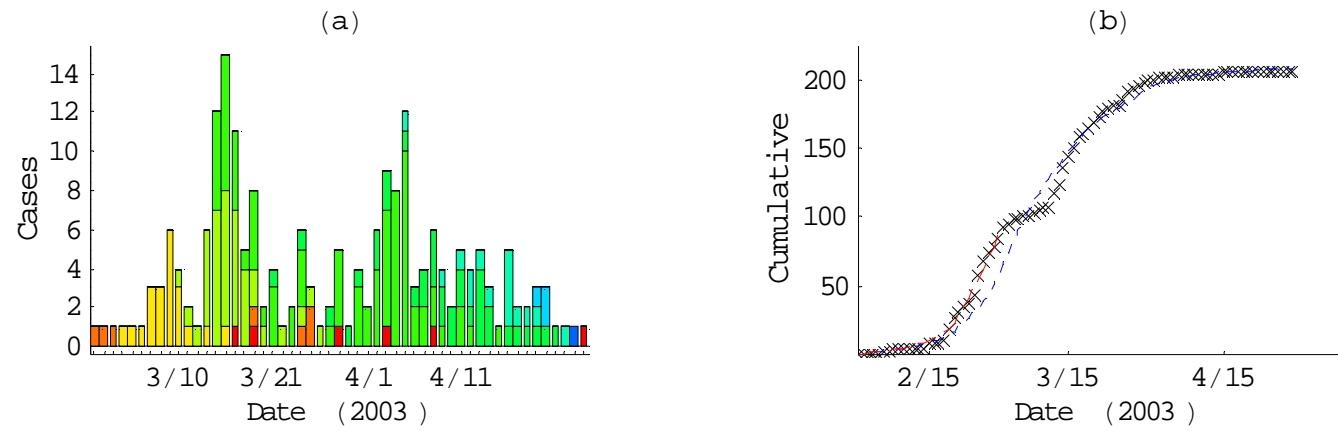


Figure 9.

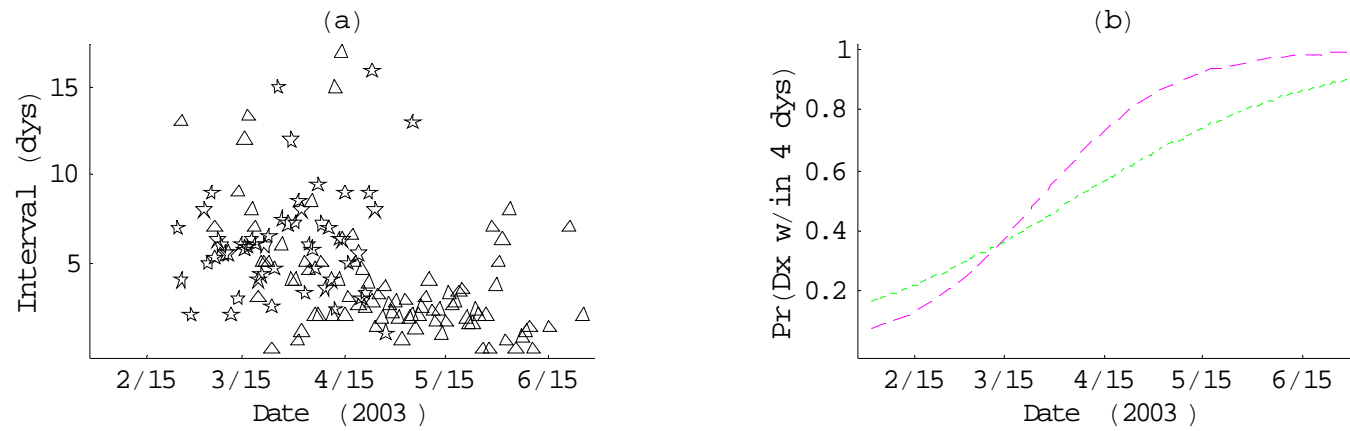


Figure 10.

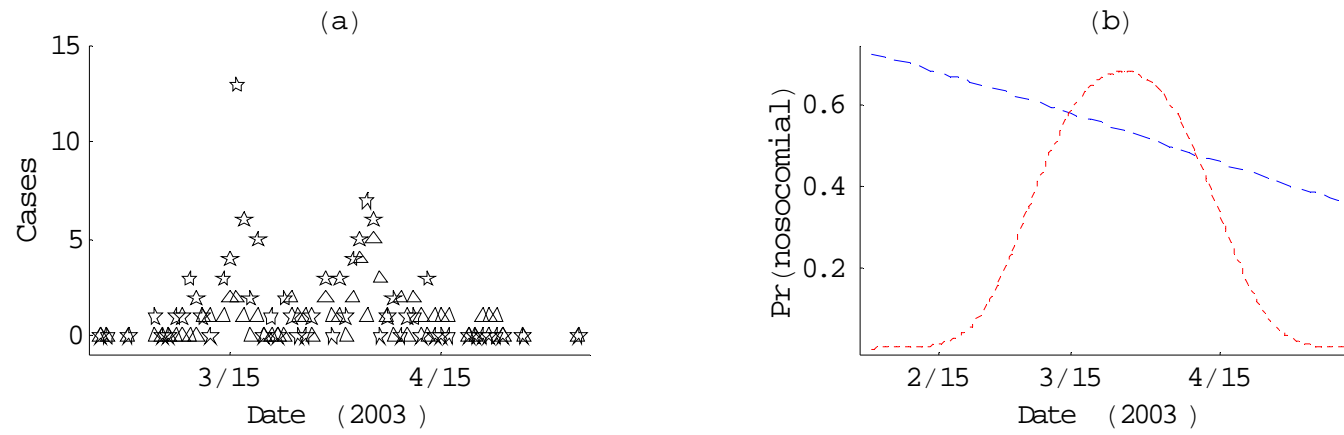
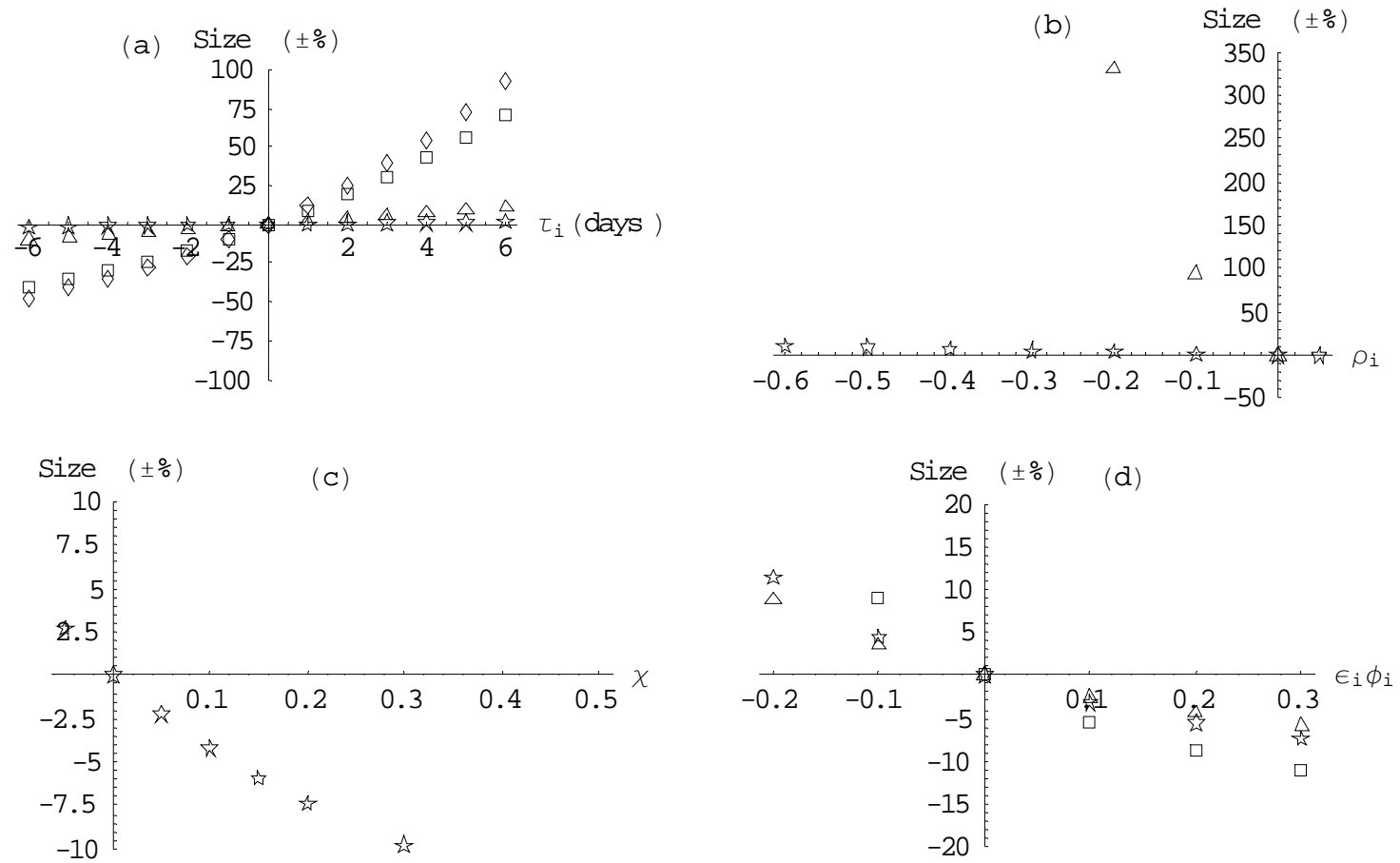


Figure 11.



APPENDIX

Here we define equilibria in the absence and presence of disease. Then we define the reproductive number in the context of the endemic equilibrium. We also define quantities that simplify formulae in the text.

Disease-free equilibrium

Letting $\mathfrak{R} < 1$, the disease-free equilibrium, $\xi_0 = (N, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0)$, always exists. We can show that all solutions converge to ξ_0 globally when $\mathfrak{R} < 1$. Let

$$X^\infty = B_1 I_P^\infty + B_2 I_R^\infty + B_3 (H_{PQ}^\infty + H_{P\tilde{Q}}^\infty) + B_4 (H_{RH_p}^\infty + H_{R\tilde{H}_p}^\infty),$$

with $B_1 = \beta_P$, $B_2 = \beta_R$, $B_3 = (1 - \rho_1)\beta_P$, and $B_4 = (1 - \rho_2)\beta_R$.

The notation \cdot^∞ means the supremum limit [e.g., $I_P^\infty = \lim_{t_1 \rightarrow \infty} \sup_{t \geq t_1} I_P(t)$]. Notice that all variables remain nonnegative with $S/N \leq 1$. Using Proposition A.22 (Thieme 2003) and choosing appropriate sequences for the E, Q, I_P, I_R, H_{PQ}, H_{P \tilde{Q}} , H_{RH_p}, H_{R \tilde{H}_p} equations, we obtain the following inequalities:

$$E^\infty \leq A_1 X^\infty, \quad Q^\infty \leq A_2 X^\infty, \quad I_P^\infty \leq A_3 X^\infty, \quad I_R^\infty \leq A_4 X^\infty,$$

$$H_{PQ}^\infty \leq A_5 X^\infty, \quad H_{P\tilde{Q}}^\infty \leq A_6 X^\infty, \quad H_{RH_p}^\infty \leq A_7 X^\infty, \quad \text{and} \quad H_{R\tilde{H}_p}^\infty \leq A_8 X^\infty,$$

where

$$A_1 = \frac{1}{(1 - \chi)\alpha_1 + \chi\gamma + \mu}, \quad A_2 = \frac{A_1 \chi \gamma}{\alpha_2 + \mu}, \quad A_3 = \frac{A_1 (1 - \chi) \alpha_1}{\delta_1 + \varepsilon_1 \phi_1 + \mu}, \quad A_4 = \frac{A_3 \delta_1}{\delta_2 + \varepsilon_2 \phi_2 + \kappa + \mu},$$

$$A_5 = \frac{A_2 \alpha_2}{\alpha_1 + \mu}, \quad A_6 = \frac{A_3 \varepsilon_1 \phi_1}{\delta_3 + \mu}, \quad A_7 = \frac{A_6 \delta_3 + A_5 \delta_1}{\delta_2 + \kappa + \mu}, \quad \text{and} \quad A_8 = \frac{A_4 \varepsilon_2 \phi_2}{\delta_4 + \kappa + \mu}.$$

It is easy to check that $B_1 A_3 + B_2 A_4 + B_3 (A_5 + A_6) + B_4 (A_7 + A_8) = \mathfrak{R}$.

From the equation for X^∞ and following inequalities, we can obtain $X^\infty \leq \mathfrak{R} X^\infty$, whereupon $X^\infty = 0$ if $\mathfrak{R} < 1$. It follows that all limits in the above-mentioned inequalities equal zero, whereupon all solutions converge to ξ_0 as $t \rightarrow \infty$ if $\mathfrak{R} < 1$. Numerical computations suggest the rate at which solutions converge to ξ_0 increases as \mathfrak{R} decreases (figure 3).

Endemic equilibrium

Let $\xi^* = (S^*, E^*, Q^*, I_P^*, I_R^*, H_{PQ}^*, H_{P\tilde{Q}}^*, H_{RH_P}^*, H_{R\tilde{H}_P}^*, R^*)$ be an endemic equilibrium at which all components are positive. From the existence of ξ^* , we can obtain a formula for \mathfrak{R} as follows. Let

$$\lambda^* = \frac{1}{N} \{ \beta_P [I_P^* + (1 - \rho_1)H_P^*] + \beta_R [I_R^* + (1 - \rho_2)H_R^*] \}.$$

Then for the first model, we have

$$S^* = \frac{N}{\mathfrak{R}}, \quad E^* = A_1 \lambda^* S^*, \quad Q^* = A_2 \lambda^* S^*, \quad I_P^* = A_3 \lambda^* S^*, \quad I_R^* = A_4 \lambda^* S^*, \\ H_{P\tilde{Q}}^* = A_5 \lambda^* S^*, \quad H_{PQ}^* = A_6 \lambda^* S^*, \quad H_{RH_P}^* = A_7 \lambda^* S^*, \quad \text{and} \quad H_{R\tilde{H}_P}^* = A_8 \lambda^* S^*,$$

where the A_i ($i=1, \dots, 8$) are given above. Substituting, we have

$$\lambda^* = \frac{\lambda^* S^*}{N} \{ \beta_P [A_3 + (1 - \rho_1)(A_5 + A_6)] + \beta_R [A_4 + (1 - \rho_2)(A_7 + A_8)] \}.$$

Dividing both sides of the first equation for λ^* by $\lambda^* \neq 0$, we obtain the formula for \mathfrak{R} :

$$\mathfrak{R} = \beta_P [A_3 + (1 - \rho_1)(A_5 + A_6)] + \beta_R [A_4 + (1 - \rho_2)(A_7 + A_8)].$$

On replacing the A_i ($i=1, \dots, 8$), this becomes identical to the earlier expression. Clearly, ξ^* exists if and only if $\mathfrak{R} > 1$. Using the relations

$$S^* + E^* + Q^* + I_P^* + I_R^* + H_{PQ}^* + H_{P\tilde{Q}}^* + H_{RH_P}^* + H_{R\tilde{H}_P}^* + R^* = N,$$

$N/S^* = \mathfrak{R}$ and $\mathfrak{R} = A_9 \lambda^* S^*$, where $A_9 = [\delta_2(A_4 + A_7) + \delta_4 A_8] / (\omega + \mu)$, we can obtain

$$\lambda^* = \frac{\mathfrak{R} - 1}{A_1 + A_2 + \dots + A_9}.$$

We explore the stability of ξ^* only numerically (figure 3). Computations suggest that ξ^* is asymptotically stable when it exists ($\mathfrak{R} > 1$).

Quantities that simplify formulae

We denote the proportion surviving state i and entering state j by T_{ij} (table A1) and mean duration of state k by D_k (table A2).

Table A1. Transitions en route to potentially infectious states.

Number	Symbol	Formula
T ₁	T_{EI_P}	$\frac{(1-\chi)\alpha_1}{(1-\chi)\alpha_1 + \chi\gamma + \mu}$
T ₂	$T_{I_P I_R}$	$\frac{\delta_1}{\delta_1 + \varepsilon_1\phi_1 + \mu}$
T ₃	$T_{I_P H_{P\bar{Q}}}$	$\frac{\varepsilon_1\phi_1}{\delta_1 + \varepsilon_1\phi_1 + \mu}$
T ₄	T_{EQ}	$\frac{\chi\gamma}{(1-\chi)\alpha_1 + \chi\gamma + \mu}$
T ₅	$T_{QH_{PQ}}$	$\frac{\alpha_2}{\alpha_2 + \mu}$
T ₆	$T_{H_{PQ}H_{RH_P}}$	$\frac{\delta_1}{\delta_1 + \mu}$
T ₇	$T_{H_{P\bar{Q}}H_{RH_P}}$	$\frac{\delta_3}{\delta_3 + \mu}$
T ₈	$T_{I_R H_{R\bar{H}_P}}$	$\frac{\varepsilon_2\phi_2}{\delta_2 + \varepsilon_2\phi_2 + \kappa + \mu}$

Table A2. Durations in potentially infectious states.

Number	Symbol	Formula
D ₁	D_{I_p}	$\frac{1}{\delta_1 + \varepsilon_1 \phi_1 + \mu}$
D ₂	$D_{H_{pQ}}$	$\frac{1}{\delta_1 + \mu}$
D ₃	$D_{H_{p\bar{Q}}}$	$\frac{1}{\delta_3 + \mu}$
D ₄	D_{I_R}	$\frac{1}{\delta_2 + \varepsilon_2 \phi_2 + \kappa + \mu}$
D ₅	$D_{H_{RH_P}}$	$\frac{1}{\delta_2 + \kappa + \mu}$
D ₆	$D_{H_{R\bar{H}_P}}$	$\frac{1}{\delta_4 + \kappa + \mu}$