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A model for influenza with vaccination and antiviral treatment

Julien Arino[a], Fred Brauer[b], P. van den Driessche[c], James Watmough[d,*], Jianhong Wu[e]

[a]Department of Mathematics, University of Manitoba, Winnipeg, Man., Canada R3T 2N2
[b]Department of Mathematics, University of British Columbia, Vancouver, BC, Canada V6T 1Z2
[c]Department of Mathematics and Statistics, University of Victoria, Victoria, BC, Canada V8W 3R4
[d]Department of Mathematics and Statistics, University of New Brunswick, Fredericton, NB, Canada E3B 5A3
[e]Centre for Disease Modeling, Department of Mathematics and Statistics, York University, Toronto, Ont., Canada M3J 1P3

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Abstract

Compartmental models for influenza that include control by vaccination and antiviral treatment are formulated. Analytic expressions for the basic reproduction number, control reproduction number and the final size of the epidemic are derived for this general class of disease transmission models. Sensitivity and uncertainty analyses of the dependence of the control reproduction number on the parameters of the model give a comparison of the various intervention strategies. Numerical computations of the deterministic models are compared with those of recent stochastic simulation influenza models. Predictions of the deterministic compartmental models are in general agreement with those of the stochastic simulation models.

Keywords: Disease transmission model; Sensitivity; Elasticity; Control reproduction number; Final size

1. Introduction

The spread through much of the world of a strain of avian influenza (H5N1) that has been infecting some humans has been causing a great deal of concern about pandemic influenza if it should evolve into a strain with human to human transmission. Several recent studies, including Balicer et al. (2005), Colizza et al. (2007), Ferguson et al. (2005), Gani et al. (2005), Longini et al. (2004, 2005) and Wu et al. (2007) have examined models to attempt to control such a pandemic influenza should one develop. These recent models have all been based on networks and stochastic simulations. Such models have great potential for predictions of outcomes and design of control strategies. However, some of the model parameters have considerable uncertainty, and such models are not very amenable to sensitivity analysis. A further very difficult question to answer is the sensitivity of the model predictions to inaccuracies in the simulation or changes in the network structure during the course of the epidemic.

The model described in Longini et al. (2004) is a discrete-time stochastic simulation based on a detailed network contact structure, and it is used to describe the influenza H2N2 epidemic of 1957–58. Our purpose is to try to formulate a simple deterministic model with similar behaviour. While a detailed simulation model could provide more precise predictions when an epidemic is under way, we suggest that, for planning in advance of a possible approaching epidemic, a simple model, in which the sensitivity to parameters can be analysed, may be more useful. Since compartmental models are easier to analyse qualitatively, especially for the effects of mixed strategies, and their sensitivity analysis is easier, we believe that such models also have a place in the study of control strategies for epidemics. The classical deterministic compartmental models for epidemic spread can be extended to include the important features of influenza, and we suggest that such extensions may be able to give predictions comparable to some of the simulation model predictions, thus adding credence to both kinds of model.

*Corresponding author.
E-mail addresses: arinoj@cc.umanitoba.ca (J. Arino), brauer@math.ubc.ca (F. Brauer), pvdd@math.uvic.ca (P. van den Driessche), watmough@unb.ca (J. Watmough), wujh@mathstat.yorku.ca (J. Wu).

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Here we develop compartmental models for influenza, including control by vaccination and antiviral treatment, and establish their theoretical analyses. Numerical simulations of the deterministic models are compared with those of recent stochastic simulation influenza models: in all cases examined, predictions of the two modelling approaches are in general agreement. Moreover, the deterministic framework in which we operate greatly simplifies model analysis and allows a more thorough comparison of the various intervention strategies. We conclude that deterministic models remain an essential tool for pandemic planning.

2. An influenza treatment model

Our model for influenza is based on the standard *SEIR* model. We assume that individuals who have been infected go first into a latent (exposed) stage during which they may have a low level of infectivity. In addition, our model includes two additional properties suggested by Longini et al. (2004), first that some members of the population who are infected never develop symptoms but go directly from the latent stage to an asymptomatic infective stage and then to the recovered stage, and second that some infective individuals withdraw from contact after developing symptoms. We also include in the model vaccination of susceptible members and antiviral treatment of latent, infective, and asymptomatically infected members of the population. We ignore the possibility of the emergence of drug resistant strains.

Our analysis begins with the case of no treatment. This provides a baseline for parameter estimation. In later sections we analyse the full model with treatment and examine two special cases. The first includes only pre-epidemic vaccination, as for annual influenza epidemics. The second, appropriate for a possible pandemic influenza when no specific vaccine has yet been developed, includes only antiviral treatment of latent, infective, and asymptomatically infected members of the population.

Specifically, we make the following assumptions, where S, S_T, L, L_T, I, I_T, A, A_T and R denote the numbers of individuals in the susceptible, treated susceptible, latent, treated latent, infective, treated infective, asymptomatic, treated asymptomatic and recovered compartments, respectively, and N is the total population size.

(A1) Initially the total population size is N_0, of which a small number $I(0)=I_0$ are infective and the remainder, $S_0=N_0-I_0$, are susceptible. A fraction γ, $0\leqslant\gamma\leqslant 1$, of the susceptible population is vaccinated before a disease outbreak, so that $S(0)=(1-\gamma)S_0$, and $S_T(0)=\gamma S_0$. All other compartments are initially empty.

(A2) Vaccinated members have susceptibility to infection reduced by a factor σ_S with $0\leqslant\sigma_S\leqslant 1$.

(A3) A fraction p of latent members proceed to the (symptomatic) infective compartment at a rate κ, while the remainder goes directly to an asymptomatic infective compartment, also at a rate κ.

(A4) Infective individuals leave the infective compartment at a rate α.

(A5) The rates of departure from L_T, I_T and A_T are κ_T, α_T and η_T, respectively. It is reasonable to assume that $\alpha\leqslant\alpha_T$ and $\eta\leqslant\eta_T$, but there is no obvious relation between κ and κ_T. While these inequalities are plausible for influenza, they are not necessarily valid for other diseases. However, except where explicitly stated, our analysis does not depend on them.

(A6) The fractions of members recovering from disease when they leave I and I_T are f and f_T, respectively, giving case fatalities $(1-f)$ and $(1-f_T)$, respectively. It is reasonable to assume that $f\leqslant f_T$.

(A7) Antiviral treatment reduces the fraction of latent members who will develop symptoms by a factor τ, with $0\leqslant\tau\leqslant 1$.

(A8) There is a treatment rate φ_L in L and a rate θ_L of relapse from L_T to L, a treatment rate φ_I in I and a rate θ_I of relapse from I_T to I, and a treatment rate φ_A in A and a rate θ_A of relapse from A_T to A.

(A9) Latent members have infectivity reduced by a factor ε, with $0\leqslant\varepsilon\leqslant 1$. Technically, the term 'latent' implies $\varepsilon=0$, so if $\varepsilon>0$, then this compartment represents an initial asymptomatic and mildly infectious stage.

(A10) Asymptomatic individuals have infectivity reduced by a factor δ, with $0\leqslant\delta\leqslant 1$, and go to the recovered compartment at a rate η.

(A11) Infectivity in L_T, I_T and A_T is reduced by a factor σ_L, σ_I and σ_A, respectively, with $0\leqslant\sigma_L\leqslant 1$, $0\leqslant\sigma_I\leqslant 1$ and $0\leqslant\sigma_A\leqslant 1$.

(A12) On average infective individuals reduce their contact rate by a factor q. This gives a mixing population size (Brauer, 2006)

$$N_M(N,I,I_T)=N-qI-qI_T.$$

Note that $N_M=N$ if $q=0$. Much of our analysis extends easily to more general formulations of the mixing population.

(A13) The number of contacts sufficient to transmit infection per unit time per individual is a non-decreasing function $N_M\beta(N_M)$ of the mixing population size N_M. We assume that $\beta(N_M)$ is a non-increasing function of N_M with $\beta(0)<\infty$. These assumptions include mass action incidence, $\beta(N_M)=\beta_0/S_0$, for some constant β_0, and standard incidence, $\beta(N_M)=\beta_0/N_M$ (provided $\beta(N_M)$ is redefined near $N_M=0$ to be biologically plausible and keep $\beta(0)$ finite), as well as many forms of saturating incidence.

Assumptions (A9) through (A12) lead to an infectivity

$$\Lambda=\varepsilon L+\varepsilon\sigma_L L_T+(1-q)I+(1-q)\sigma_I I_T+\delta A+\delta\sigma_A A_T.$$

Together with Assumption (A13) this leads to a force of infection $\beta(N_M)\Lambda$ for untreated susceptibles. It is also

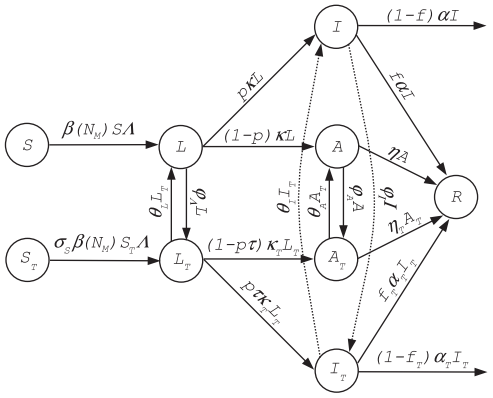

Fig. 1. SLIAR epidemic model with treatment.

possible that infectivity is reduced through preventative measures without reducing the contact rate. This case is modelled by taking $N_M = N$ with q representing a reduction in infectivity due to these measures. Our results are easily extended to more general models combining both effects.

The resulting model is

$$\begin{aligned}
S' &= -\beta(N_M)S\Lambda,\\
S'_T &= -\sigma_S\beta(N_M)S_T\Lambda,\\
L' &= \beta(N_M)S\Lambda - \kappa L - \varphi_L L + \theta_L L_T,\\
L'_T &= \sigma_S\beta(N_M)S_T\Lambda - \kappa_T L_T + \varphi_L L - \theta_L L_T,\\
I' &= p\kappa L - \alpha I - \varphi_I I + \theta_I I_T,\\
I'_T &= p\tau\kappa_T L_T - \alpha_T I_T + \varphi_I I - \theta_I I_T,\\
A' &= (1-p)\kappa L - \eta A - \varphi_A A + \theta_A A_T,\\
A'_T &= (1-p\tau)\kappa_T L_T - \eta_T A_T + \varphi_A A - \theta_A A_T,\\
R' &= f\alpha I + f_T\alpha_T I_T + \eta A + \eta_T A_T,\\
N' &= -(1-f)\alpha I - (1-f_T)\alpha_T I_T.
\end{aligned} \tag{1}$$

Here and elsewhere, a prime denotes differentiation with respect to t. Since N is the total population size, one variable can be removed from the system, and it is convenient to remove the variable R. A flow diagram for the model (1) is shown in Fig. 1.

The model (1) is an extension of the treatment model described in Arino et al. (2006), in which $\varepsilon = q = 0$, the incidence is mass action, and there is no treatment of asymptomatic individuals. It also extends the vaccination model with mass action incidence in Arino et al. (2007, Section 7.3).

Treatment of diagnosed infective individuals means making a choice of treatment rate φ_I. Treatment of latent and asymptomatic members means choosing a treatment rate of members identified by contact tracing. In practise this means treating a mixture of susceptible, latent and asymptomatic members. For simplicity we neglect the susceptible individuals who would be included. Contact tracing to try to identify latent individuals before they develop symptoms leads to a constant multiple of new infectives, which is a constant multiple of L, thus making the rate of treatment of latent individuals proportional to L, the size of the latent compartment. Alternately, the identification of individuals by contact tracing could be modelled as proportional to the incidence of infection (Lipsitch et al., 2003; McCaw and McVernon, 2007). However, even in this case, the simpler assumption of constant treatment rates is a reasonable first approximation. The ratio of latent individuals to asymptomatic individuals included would depend on the speed with which treatment is implemented. For example, if contacts are treated immediately before they reach the end of the latent period, we would take $\varphi_A = 0$, while if treatment is delayed longer than the duration of the latent period, we would take $\varphi_L = 0$.

3. Analysis of the untreated influenza model

If there is no treatment, either before or during an epidemic, then the treatment model (1) reduces to the following model:

$$\begin{aligned}
S' &= -\beta(N_M)S\Lambda,\\
L' &= \beta(N_M)S\Lambda - \kappa L,\\
I' &= p\kappa L - \alpha I,\\
A' &= (1-p)\kappa L - \eta A,\\
R' &= f\alpha I + \eta A,\\
N' &= -(1-f)\alpha I,
\end{aligned} \tag{2}$$

with $\Lambda = \varepsilon L + (1-q)I + \delta A$, $N_M = N - qI$, and initial conditions

$$S(0) = S_0, \quad L(0) = 0, \quad I(0) = I_0,$$

$$A(0) = 0, \quad R(0) = 0, \quad N(0) = N_0 = S_0 + I_0.$$

A flow diagram for the model (2) is shown in Fig. 2.

As with model (1), the variable R may be removed. It is easy to show that the problem (2) is properly posed in the sense that all variables remain non-negative for $0 \leqslant t < \infty$. We take $\varepsilon = 0$ in our numerical simulations because in Longini et al. (2004) it is assumed that there is no infectivity in the latent stage. However, for some diseases, including some strains of influenza, there is a possibility of infectivity in the latent stage. The special case $\varepsilon = 0$, $p = 1$, $q = 0$, which gives $A = 0$, is the standard *SEIR* model (Diekmann and Heesterbeek, 2000, Exercise 2.2).

Model (2) has a set of disease-free equilibria with

$$L = I = A = 0$$

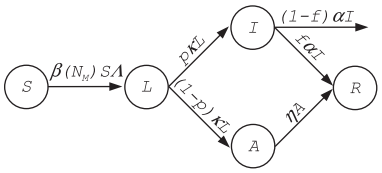

Fig. 2. SLIAR epidemic model.

and $S = N$ arbitrary. We use the approach of Diekmann and Heesterbeek (2000) and van den Driessche and Watmough (2002) to calculate the basic reproduction number

$$\mathscr{R}_0 = \beta_0\left(\frac{\varepsilon}{\kappa} + \frac{(1-q)p}{\alpha} + \frac{\delta(1-p)}{\eta}\right), \tag{3}$$

where $\beta_0 = S_0\beta(N_0)$ as per Assumptions (A12) and (A13). This calculation corresponds to the disease-free equilibrium with $S = N = S_0$. The basic reproduction number given by (3) is the sum over the infected compartments of the product of infectivity and mean duration.

We adopt the notations g_∞ for $\lim_{t\to\infty} g(t)$ and $\hat{g}$ for $\int_0^\infty g(s)\,\mathrm{d}s$ if g is a non-negative integrable function defined for $0 \leqslant t < \infty$. A special case of the model (2) with $\varepsilon = q = 0$ and mass action incidence has been analysed in Arino et al. (2006), where it is shown that

$$L_\infty = I_\infty = A_\infty = R_\infty = 0,$$

and the final size relation is

$$\ln\frac{S_0}{S_\infty} = \mathscr{R}_0\left(1 - \frac{S_\infty}{S_0}\right) + \frac{\beta_0 I_0}{\alpha S_0}. \tag{4}$$

For the more general model (2) with $\varepsilon > 0$ and $q > 0$ and a general incidence term, we still have that $L_\infty = I_\infty = A_\infty = R_\infty = 0$, and the final size relation, which gives S_∞, can be computed as follows. Dividing the first equation of model (2) through by $S(t)$ and integrating yields

$$\begin{aligned}\ln\frac{S_\infty}{S_0} &= -\int_0^\infty \beta(N_M(t))(\varepsilon L + I + \delta A)\,\mathrm{d}t \\ &= -\beta(N_M^*)(\varepsilon\hat{L} + \hat{I} + \delta\hat{A}),\end{aligned} \tag{5}$$

for some N_M^* in the range of $N_M(t)$.

Summing the first two equations of model (2) yields

$$\hat{L} = \frac{1}{\kappa}(S_0 - S_\infty).$$

Similarly, from the third equation,

$$\hat{I} = \frac{p\kappa}{\alpha}\hat{L} + \frac{I_0}{\alpha} = \frac{p}{\alpha}(S_0 - S_\infty) + \frac{I_0}{\alpha}, \tag{6}$$

and from the fourth,

$$\hat{A} = \frac{(1-p)\kappa}{\eta}\hat{L} = \frac{1-p}{\eta}(S_0 - S_\infty).$$

Thus,

$$\begin{aligned}\varepsilon\hat{L} + \hat{I} + \delta\hat{A} &= \left[\frac{\varepsilon}{\kappa} + \frac{p}{\alpha} + \frac{\delta(1-p)}{\eta}\right](S_0 - S_\infty) + \frac{I_0}{\alpha} \\ &= \frac{\mathscr{R}_0}{\beta(N_0)}\left(1 - \frac{S_\infty}{S_0}\right) + \frac{I_0}{\alpha},\end{aligned}$$

and the final size relation (5) for model (2) can be written as

$$\ln\frac{S_0}{S_\infty} = \frac{\beta(N_M^*)}{\beta(N_0)}\left(\mathscr{R}_0\left(1 - \frac{S_\infty}{S_0}\right) + \frac{I_0\beta(N_0)}{\alpha}\right). \tag{7}$$

In the special case of mass action incidence, $\beta(N_M) = \beta_0/S_0$, and (7) reduces to (4). It is common to assume that I_0 is small enough to be neglected in this formula, and (4) with $I_0 = 0$ is a standard result for simple epidemic models (Diekmann and Heesterbeek, 2000, Section 1.3). The assumption that $I_0 = 0$ implies $S_0 = N_0$, and then S_0 would be replaced by N_0 in the formulae for the analysis of the model (2).

The *attack ratio*, often called the attack rate, is defined as the fraction of the susceptible population that develops disease symptoms over the course of the epidemic. In our notation this is, for a general incidence term,

$$p\left(1 - \frac{S_\infty}{S_0}\right).$$

The basic reproduction number $\mathscr{R}_0$ is related to the attack ratio through the final size relation.

We consider an example with parameters used in Longini et al. (2004) with time measured in days:

$$\begin{aligned}&\kappa = \tfrac{1}{1.9} = 0.526, \quad \alpha = \eta = \tfrac{1}{4.1} = 0.244, \\ &p = 0.667, \quad f = 0.98, \quad S_0 = 1988, \quad I_0 = 12, \\ &N_0 = 2000, \quad \varepsilon = 0, \quad \delta = 0.5.\end{aligned}$$

In Longini et al. (2004) an attack ratio is assumed for each of four age groups, and the average attack ratio for the entire population is 0.326. If we use an attack ratio of 0.326 with $p = 0.667$, we obtain $S_\infty = 1016$. If we assume $q = 0$ and mass action incidence so that we may use the final size relation (4), with $I_0 = 0$, we obtain $\mathscr{R}_0 = 1.37$, which gives, from (3), $\beta_0 = 0.402$. The number of cases of influenza (including the original I_0) is

$$C = I_0 + p(S_0 - S_\infty),$$

and this gives 660 cases (including the original 12) of influenza compared to the estimate 668 in Longini et al. (2004).

In order to calculate $\mathscr{R}_0$ if $q > 0$, we must simulate the dynamic model (2) with different choices of β_0 to find the value of β_0 that gives $S_\infty = 1016$. If we now take $q = 0.4$, an average value for the assumptions in Longini et al. (2004), and assume standard incidence, that is $\beta(N_M) = \beta_0/N_M$, we find that, $\beta_0 = 0.581$ and $\mathscr{R}_0 = 1.35$. It is worth noting that the error introduced by using a final size equality (assuming mass action incidence and taking $q = 0$) instead of using a more accurate dynamic simulation is only about 0.6% for this set of parameter values: using $\beta_0 = 0.395$ with $q = 0$, so that $\mathscr{R}_0 = 1.35$, and the remaining parameters as above in (7) (with $N_M^* = N_0$) gives $S_\infty = 1022$.

In the special case of no withdrawal, $q = 0$, we can also derive an upper bound of this error for a general function $\beta(N_M)$. First note that if $q = 0$, then $N_M = N$. If additionally $f = 1$, then $N_M^* = N_0$, but in general for $f < 1$ and $q = 0$, $N_0 - (1-f)\alpha\hat{I} \leqslant N_M^* \leqslant N_0$. Using

expression (6) for $\hat{I}$,

$$\begin{aligned} N_M^* &\geqslant N_0 - (1-f)[p(S_0 - S_\infty) + I_0] \\ &= (1-(1-f)p)S_0 + (1-f)pS_\infty + fI_0 \\ &\geqslant f(S_0 + I_0) \\ &= fN_0. \end{aligned}$$

Now, a simple argument shows that if $\mathscr{R}_0\beta(fN_0) > \beta(N_0)$, then there exists

$$r(f) \in (0, \beta(N_0)/\mathscr{R}_0\beta(fN_0))$$

that solves the algebraic equation

$$g(z;f) = \ln z + \frac{\beta(fN_0)}{\beta(N_0)}\left(\mathscr{R}_0(1-z) + \frac{I_0\beta(N_0)}{\alpha}\right) = 0. \tag{8}$$

Furthermore, if $g(z;f) \geqslant 0$, then $z \geqslant r(f)$.

We now use $S_{f,\infty}$ to denote the final size that depends on the fraction, f, recovering from the infection. The final size equation (7) with $f = 1$ and $q = 0$ gives (4). Therefore, $S_{1,\infty} = r(1)S_0$. Now for general incidence, since $N_M^* \geqslant fN_0$, the monotonicity $\beta(N_M^*) \leqslant \beta(fN_0)$ and final size equation yield that

$$\ln\frac{S_0}{S_{f,\infty}} \leqslant \frac{\beta(fN_0)}{\beta(N_0)}\left(\mathscr{R}_0\left(1 - \frac{S_{f,\infty}}{S_0}\right) + \frac{I_0\beta(N_0)}{\alpha}\right).$$

Thus, the upper bound for the error between $S_{1,\infty}$ using mass action incidence and $S_{f,\infty}$ for a general incidence function $\beta(N_M)$ is given by the following estimates:

$$S_{1,\infty} = r(1)S_0 \geqslant S_{f,\infty} \geqslant r(f)S_0, \tag{9}$$

$$0 \leqslant \frac{S_{1,\infty} - S_{f,\infty}}{S_{f,\infty}} \leqslant \frac{r(1) - r(f)}{r(f)}. \tag{10}$$

The inequality in (10) gives the percentage of error in calculating $S_{f,\infty}$. This yields, in terms of the parameters used above with $q = 0$ and $\beta(N_M) = \beta_0/N$, the error bound of 2.24% if $f = 0.99$, 4.56% if $f = 0.98$ and 6.97% if $f = 0.97$ (recall that $f = 0.97$ corresponds to a 3% mortality of infective individuals).

4. Analysis of the treatment model

To analyse the model (1) we use the formulation of Arino et al. (2007), writing the model in the form

$$\begin{aligned} x' &= \beta(N_M)\Pi D y b x - Vx, \\ y' &= -\beta(N_M) D y b x, \\ N' &= -wx. \end{aligned} \tag{11}$$

Here, $x \in \mathbb{R}^n$ represents the set of infected compartments, $y \in \mathbb{R}^m$ represents the set of susceptible compartments and N is the total population. The $n \times n$ matrix V describes the transitions between infected states as well as removals from infected states through death and recovery. It is pointed out in Arino et al. (2007) that V is a non-singular M-matrix. Thus the eigenvalues of V all have positive real parts, and V^{-1} is a matrix with all entries non-negative. The $m \times m$ diagonal matrix D has diagonal entries $\sigma_i > 0$ that are the relative susceptibilities of the corresponding susceptible compartment, Π is an $n \times m$ matrix with the property that the (i,j) entry represents the fraction of the jth susceptible compartment that goes into the ith infective compartment on becoming infected, and b and w are n-dimensional row vectors of relative horizontal transmission and disease death rates, respectively.

For the model (1), $n = 6$, $m = 2$,

$$x = \begin{bmatrix} L \\ L_T \\ I \\ I_T \\ A \\ A_T \end{bmatrix}, \quad x_0 = \begin{bmatrix} 0 \\ 0 \\ I_0 \\ 0 \\ 0 \\ 0 \end{bmatrix}, \quad y = \begin{bmatrix} S \\ S_T \end{bmatrix},$$

$$y(0) = y_0 = \begin{bmatrix} (1-\gamma)S_0 \\ \gamma S_0 \end{bmatrix},$$

$$\Pi = \begin{bmatrix} 1 & 0 \\ 0 & 1 \\ 0 & 0 \\ 0 & 0 \\ 0 & 0 \\ 0 & 0 \end{bmatrix}, \quad D = \begin{bmatrix} 1 & 0 \\ 0 & \sigma_S \end{bmatrix},$$

$$w = [0,\ 0,\ (1-f)\alpha,\ (1-f_T)\alpha_T,\ 0,\ 0]$$

and

$$b = [\varepsilon,\ \varepsilon\sigma_L,\ (1-q),\ (1-q)\sigma_I,\ \delta,\ \delta\sigma_A].$$

We write the matrix V in the block form

$$V = \begin{bmatrix} V_L & 0 & 0 \\ -V_{LI} & V_I & 0 \\ -V_{LA} & 0 & V_A \end{bmatrix},$$

where

$$V_L = \begin{bmatrix} \kappa + \varphi_L & -\theta_L \\ -\varphi_L & \kappa_T + \theta_L \end{bmatrix},$$

$$V_{LI} = \begin{bmatrix} p\kappa & 0 \\ 0 & p\tau\kappa_T \end{bmatrix},$$

$$V_I = \begin{bmatrix} \alpha + \varphi_I & -\theta_I \\ -\varphi_I & \alpha_T + \theta_I \end{bmatrix},$$

$$V_{LA} = \begin{bmatrix} (1-p)\kappa & 0 \\ 0 & (1-p\tau)\kappa_T \end{bmatrix},$$

$$V_A = \begin{bmatrix} \eta + \varphi_A & -\theta_A \\ -\varphi_A & \eta_T + \theta_A \end{bmatrix}.$$

Then

$$V^{-1} = \begin{bmatrix} V_L^{-1} & 0 & 0 \\ V_I^{-1}V_{LI}V_L^{-1} & V_I^{-1} & 0 \\ V_A^{-1}V_{LA}V_L^{-1} & 0 & V_A^{-1} \end{bmatrix}.$$

Because the model (1) may include pre-epidemic treatment and describe the introduction of infective individuals into a population that is not wholly susceptible, we speak of a control reproduction number $\mathscr{R}_c$ as in Gumel et al. (2004), rather than a basic reproduction number $\mathscr{R}_0$. Since the matrix $\beta(N_0)\Pi D y_0 b$ of new infections has rank 1, one of the results in Arino et al. (2007) is that the control reproduction number $\mathscr{R}_c$ for the model (11) at a disease-free equilibrium $(0, y_0, N_0)$ is given by

$$\mathscr{R}_c = (1-\gamma)\mathscr{R}_u + \gamma\mathscr{R}_v, \tag{12}$$

where $\mathscr{R}_u$ and $\mathscr{R}_v$ are the components of the row vector $S_0\beta(N_0)bV^{-1}\Pi D$. For model (1), exploiting the lower block of zeros in Π, these can be expressed as

$$[\mathscr{R}_u, \mathscr{R}_v] = \beta_0(\varepsilon[1,\ \sigma_L]V_L^{-1}D + (1-q)[1,\ \sigma_I] \times V_I^{-1}V_{LI}V_L^{-1}D + \delta[1,\ \sigma_A]V_A^{-1}V_{LA}V_L^{-1}D), \tag{13}$$

where, as stated in Assumption (A13), $\beta_0 = S_0\beta(N_0)$. Note that these results all hold for a general incidence term. Since the entries of V^{-1} can be interpreted as durations, each term in $\mathscr{R}_c$ is again a weighted product of infectivity and mean duration in an infected compartment. This is clear in the special cases below. It is important to note here that this decomposition of $\mathscr{R}_c$ into a sum of infectivity times duration may also be derived for more general models that do not assume an exponential distribution for sojourn times in each compartment. Further details can be found in the text of Diekmann and Heesterbeek (2000).

Two special cases are of particular interest. The first is the case of pre-epidemic treatment only, as would be the practise in preparation for annual influenza epidemics that are not expected to reach pandemic status and for which a vaccine is available. For this case, susceptible individuals are vaccinated, but no other compartment is treated, thus

$$\varphi_L = \theta_L = \varphi_I = \theta_I = \varphi_A = \theta_A = 0$$

in the model (1). We obtain

$$\mathscr{R}_u = \beta_0\left[\frac{\varepsilon}{\kappa} + \frac{(1-q)p}{\alpha} + \frac{\delta(1-p)}{\eta}\right], \tag{14}$$

$$\mathscr{R}_v = \sigma_S\beta_0\left[\frac{\varepsilon\sigma_L}{\kappa_T} + \frac{(1-q)\sigma_I p\tau}{\alpha_T} + \frac{\delta\sigma_A(1-p\tau)}{\eta_T}\right], \tag{15}$$

with $\mathscr{R}_c$ given by (12). To control the epidemic means to choose γ large enough to make $\mathscr{R}_c < 1$, and this is possible if $\mathscr{R}_v < 1$, in particular if σ_S is small.

A second special case of interest is that of treatment without pre-epidemic vaccination, as would be the case for a new strain of influenza with no vaccine available. In this case, $\gamma = 0$, and $\mathscr{R}_c = \mathscr{R}_u$, with $\mathscr{R}_u$ given by (13).

5. The final size relation

Calculation of the basic and control reproduction numbers is only part of the process of analysing the epidemic model (1). There is an extension of the final size relation (7) to the treatment model (1), and this gives information about the number of cases of disease during the epidemic. Integrating the first two equations of (1), using the notation of (11), gives

$$\ln\frac{S(0)}{S_\infty} = \frac{1}{\sigma_S}\ln\frac{S_T(0)}{S_{T\infty}} = \beta(N_M^*)b\hat{x}, \tag{16}$$

for some N_M^* in the range of $N_M(t)$, x^* in the range of $x(t)$ and $\hat{x}$ given by (17) below.

Since $x_\infty = 0$, integration of the sum of the first and second equations of (11) gives $V\hat{x} = x_0 + \Pi(y_0 - y_\infty)$. Solution of this equation for $\hat{x}$ gives

$$\hat{x} = V^{-1}x_0 + V^{-1}\Pi(y_0 - y_\infty). \tag{17}$$

From the block form of V^{-1}, the components of $\hat{x}$ for model (1) can be expressed as

$$\begin{bmatrix} \hat{L} \\ \hat{L}_T \end{bmatrix} = V_L^{-1}(y_0 - y_\infty),$$
$$\begin{bmatrix} \hat{I} \\ \hat{I}_T \end{bmatrix} = V_I^{-1}\begin{bmatrix} I_0 \\ 0 \end{bmatrix} + V_I^{-1}V_{LI}V_L^{-1}(y_0 - y_\infty),$$
$$\begin{bmatrix} \hat{A} \\ \hat{A}_T \end{bmatrix} = V_A^{-1}V_{LA}V_L^{-1}(y_0 - y_\infty). \tag{18}$$

If the incidence is mass action then $\beta(N_M^*)$ is replaced by the constant β_0/S_0. When treatment is included, (16) and (17) give

$$\ln\frac{S(0)}{S_\infty} = (1-\gamma)\mathscr{R}_u\left(1 - \frac{S_\infty}{S(0)}\right) + \gamma\mathscr{R}_v\left(1 - \frac{S_{T\infty}}{S_T(0)}\right) + \frac{\beta_0 I_0(\alpha_T + \theta_I + \sigma_I\varphi_I)}{S_0(\alpha\alpha_T + \theta_I\alpha + \varphi_I\alpha_T)} \tag{19}$$

together with the first equality from (16), where $\mathscr{R}_u$ and $\mathscr{R}_v$ are given by (13). We have a pair of equations determining S_∞ and $S_{T\infty}$ in terms of the parameters of the model. Then $S(0) - S_\infty$ is the number of untreated members not infected during the epidemic, and $S_T(0) - S_{T\infty}$ is the number of treated members not infected during the epidemic. The number of cases of disease over the course of the epidemic is

$$I_0 + p[S(0) - S_\infty] + p\tau[S_T(0) - S_{T\infty}],$$

and this may be calculated from (19) if the incidence is mass action.

The number of cases and the number of members of the population receiving antiviral treatment depend on $\hat{L}$, $\hat{L}_T$, $\hat{I}$, $\hat{I}_T$, $\hat{A}$ and $\hat{A}_T$, as given by (18). We use these expressions to calculate the number of treatments,

$$T = \varphi_L\hat{L} + \varphi_I\hat{I} + \varphi_A\hat{A},$$

as the (1,1) entry of the 2×1 matrix

$$\varphi_I V_I^{-1} \begin{bmatrix} I_0 \\ 0 \end{bmatrix} + (\varphi_L + \varphi_I V_I^{-1} V_{LI} + \varphi_A V_A^{-1} V_{LA}) V_L^{-1} (y_0 - y_\infty), \tag{20}$$

and the number of disease cases

$$C = I_0 + p\kappa \hat{L} + p\tau\kappa_T \hat{L}_T,$$

as

$$C = I_0 + p[\kappa, \ \tau\kappa_T] V_L^{-1} (y_0 - y_\infty). \tag{21}$$

It is important to note that, except for the initial terms involving I_0 in T and C, presumably small, the number of cases and the number of treatments are linear combinations of the number of untreated and treated members of the population who are infected. These may be found by solving the final size relation (16) or (19). If the control reproduction number $\mathscr{R}_c$ is close to 1 or smaller than 1, the number of infected members is small and depends critically on the initial number of infective individuals. Although different strategies for control can be compared using the model, absolute predictions of the number of disease cases and treatments are unreliable, and this is inherent in the model. This critical dependence on the initial number of infective individuals does indicate the importance of rapid response to an emerging epidemic; beginning action when the number of infective individuals is small means significantly fewer cases of disease and number of treatment doses required to control the epidemic.

Since θ_L is small relative to κ and κ_T, setting $\theta_L = 0$ gives a useful approximation for the number of cases:

$$C \approx I_0 + p(S(0) - S_\infty)\left(\frac{\kappa + \tau\varphi_L}{\kappa + \varphi_L}\right) + p\tau(S_T(0) - S_{T\infty}).$$

This formula can be obtained intuitively from Fig. 1 by noting that a fraction $p\kappa/(\kappa + \varphi_L)$ of people entering compartment L progress to I, and a fraction $p\tau\varphi_L/(\kappa + \varphi_L)$, progress through L_T to I_T. The last term arises since a fraction $p\tau$ of individuals entering L_T from S_T progress to I_T. In the case of no treatment or vaccination, that is $\varphi_L = 0$ and $S_T(0) = 0$, we obtain $C = I_0 + p(S_{(0)} - S_\infty)$; in the case of vaccination, but no treatment of latently infected individuals, we obtain $C = I_0 + p(S(0) - S_\infty) + p\tau(S_T(0) - S_{T\infty})$.

If the incidence is not mass action, the simple final size relation of (19) is not valid. An estimate for the final size of the epidemic for the general model can be obtained by replacing $\beta(N_M^*)$ by $\beta(N_0)$ in (16). In the remainder of this section, we show how bounds on $\beta(N_M^*)$, can be used to place bounds on this estimate.

To simplify the presentation, we replace $\hat{x}$ in (16) using (17), and write the result as follows:

$$\ln \frac{y_{i0}}{y_{i\infty}} = \sigma_i \beta(N_M^*) b V^{-1}(x_0 + \Pi(y_0 - y_\infty)), \quad i = 1, \ldots, m, \tag{22}$$

for some N_M^* in the range of $N_M(t)$. In model (1), y_1 and y_2 correspond to S and S_T respectively, $\sigma_1 = 1$ and $\sigma_2 = \sigma_S$. In general, assume $\sigma_1 = 1$. Hence,

$$\frac{y_{i\infty}}{y_{i0}} = \left(\frac{y_{1\infty}}{y_{10}}\right)^{\sigma_i}, \quad i = 2, \ldots, m.$$

Define γ_i as the initial fraction of individuals in the ith susceptible compartment, so that $y_{i0} = \gamma_i S_0$, and set $\mathscr{R}_i$ to be the ith component of $\beta_0 b V^{-1} \Pi$, so that $\mathscr{R}_c = \sum_{i=1}^m \sigma_i \mathscr{R}_i \gamma_i$ (see (12)). Note that for model (1), $\gamma_1 = 1 - \gamma$, $\gamma_2 = \gamma$, $\mathscr{R}_1 = \mathscr{R}_u$ and $\sigma_S \mathscr{R}_2 = \mathscr{R}_v$. Then

$$y_{i0} - y_{i\infty} = \gamma_i S_0 \left(1 - \left(\frac{y_{1\infty}}{y_{10}}\right)^{\sigma_i}\right), \tag{23}$$

and the final size equation can be written as

$$\ln \frac{y_{10}}{y_{1\infty}} = \frac{\beta(N_M^*)}{\beta(N_0)} \left(\beta(N_0) b V^{-1} x_0 + \sum_{i=1}^m \mathscr{R}_i \gamma_i \left(1 - \left(\frac{y_{1\infty}}{y_{10}}\right)^{\sigma_i}\right)\right). \tag{24}$$

This equation is the extension of (19) to the case of an arbitrary number of susceptible groups and a general incidence. A rough estimate for the final size is obtained by replacing $\beta(N_M^*)$ with $\beta(N_0)$ in (24), giving

$$\ln \frac{y_{10}}{y_{1\infty}} = \beta(N_0) b V^{-1} x_0 + \sum_{i=1}^m \mathscr{R}_i \gamma_i \left(1 - \left(\frac{y_{1\infty}}{y_{10}}\right)^{\sigma_i}\right). \tag{25}$$

Define ω as the ratio $\beta(N_M^*)/\beta(N_0)$, and redefine $g(z;f)$ as

$$g(z;\omega) = \ln z + \omega \left(\beta(N_0) b V^{-1} x_0 + \sum_{i=1}^m \mathscr{R}_i \gamma_i (1 - z^{\sigma_i})\right). \tag{26}$$

It is straightforward to show that $g(z;\omega)$ has a unique root, $z = r(\omega)$ in the interval $0 < z < 1$. This follows immediately from the signs of $\lim_{z \to 0} g(z;\omega)$ and $g(1;\omega)$ and the fact that the derivative of g with respect to z has at most one zero in the interval $0 < z < 1$. Further, if

$$\omega_m \leqslant \frac{\beta(N_M^*)}{\beta(N_0)} \leqslant \omega_M,$$

then the final size satisfies

$$r(\omega_M) \leqslant \frac{y_{1\infty}}{y_{10}} \leqslant r(\omega_m).$$

Hence, we can bound our estimate of the final size of the epidemic if we can place upper and lower bounds on $\beta(N_M)$.

6. Sensitivities of $\mathscr{R}_c$ to parameters

The presence of 27 parameters (including the initial conditions S_0 and I_0), none of which are known with confidence, makes a comparison of the various intervention strategies difficult. However, by focusing on the simple model and several special cases, many general statements can be made.

In the absence of treatment during the epidemic, the basic reproduction number for the system (11) was found to be (12) with (14) and (15), which are repeated here for convenience.

$$\mathscr{R}_c = (1-\gamma)\mathscr{R}_u + \gamma\mathscr{R}_v,$$

with

$$\mathscr{R}_u = \frac{\beta_0}{\alpha}\left[\varepsilon\frac{\alpha}{\kappa} + (1-q)p + \delta(1-p)\frac{\alpha}{\eta}\right],$$

$$\mathscr{R}_v = \frac{\sigma_S\beta_0}{\alpha_T}\left[\varepsilon\sigma_L\frac{\alpha_T}{\kappa_T} + (1-q)\sigma_I p\tau + \delta\sigma_A(1-p\tau)\frac{\alpha_T}{\eta_T}\right].$$

First, since both ε and α/κ, the reduction factor for latent transmission and the ratio of the lengths of the infectious and latent periods, are small, their product is small and in a first examination can be neglected. Similarly, δ and α/η are each less than 1 and so $(1-q)p + \delta(1-p)\alpha/\eta$ is most certainly less than 2, and quite likely near to or slightly less than 1. Thus, the ratio β_0/α, best referred to as the "back of the napkin" $\mathscr{R}_0$, which is the expected number of secondary infections produced by a single (untreated) symptomatic case, is a good rough estimate of $\mathscr{R}_u$.

The effectiveness of a reduction in contacts to control the outbreak depends on the magnitude of $\delta(1-p)\alpha/(1-q)p\eta$, which is the ratio of secondary infections caused by asymptomatic cases to those caused by symptomatic cases. More accurately, the elasticity of $\mathscr{R}_u$ to q, which is one useful measure of sensitivity, is given by

$$\frac{q}{\mathscr{R}_u}\frac{\partial\mathscr{R}_u}{\partial q} = -qp\left(\varepsilon\frac{\alpha}{\kappa} + (1-q)p + \delta(1-p)\frac{\alpha}{\eta}\right)^{-1},$$

which is approximately

$$-q\left(1-q+\frac{\delta(1-p)\alpha}{p\eta}\right)^{-1} \quad \text{since} \quad \frac{\varepsilon\alpha}{\kappa} \ll 1.$$

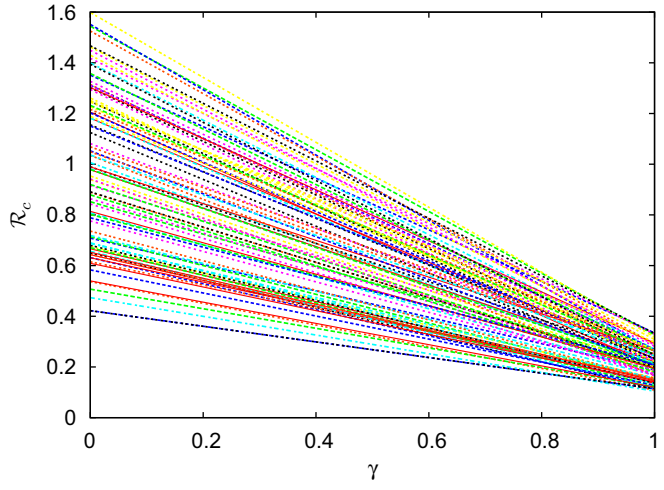

Fig. 3. Dependence of $\mathscr{R}_c$ on γ for 100 sets of parameter values randomly sampled as detailed in the text.

Second, we observe that since treatment will probably have little effect on the ratios of the latent and infectious periods, that is, α_T/κ_T and α_T/η_T are likely very close to their untreated counterparts, a reasonable estimate of $\mathscr{R}_v$ is $\sigma_S\sigma_I\beta_0/\alpha$. Since the effect of pre-epidemic treatment or vaccination is to reduce $\mathscr{R}_c$ from $\mathscr{R}_u$ to $\mathscr{R}_v$, it is required that $\sigma_S\sigma_I < \alpha/\beta_0$ for vaccination to control an outbreak. The dependence of $\mathscr{R}_c$ on γ is shown in Fig. 3. This figure was generated by drawing the line $\mathscr{R}_c(\gamma)$ for 100 sets of parameter values as explained below. Each of the 100 lines intercepts the left boundary of the figure ($\gamma = 0$) at $\mathscr{R}_u$ and the right boundary ($\gamma = 1$) at $\mathscr{R}_v$.

To unfold the dependence of $\mathscr{R}_c$ on the treatment parameters φ_A, φ_L and φ_I, it is reasonable to assume that $\theta_L \ll \kappa_T$, $\theta_I \ll \alpha_T$ and $\theta_A \ll \eta_T$. This is similar to assuming that most people recover or advance to the next disease stage before completing treatment. Setting $\theta_L = \theta_I = \theta_A = 0$, leads to

$$\begin{aligned}\mathscr{R}_c = {} & \frac{\varepsilon\beta_0}{\kappa}[v_1 + \bar{\sigma}_L v_2] \\ & + \frac{p(1-q)\beta_0}{\alpha}[v_1(1-a_I+\bar{\sigma}_I a_I) + v_2\tau\bar{\sigma}_I] \\ & + \frac{\delta\beta_0}{\eta}[v_1(1-p)(1-a_A+\bar{\sigma}_A a_A) + v_2(1-p\tau)\bar{\sigma}_A],\end{aligned}$$

where $a_I = \varphi_I/(\alpha+\varphi_I)$, $a_A = \varphi_A/(\eta+\varphi_A)$ and $a_L = \varphi_L/(\kappa+\varphi_L)$ are the fractions treated in each of the stages of infection, and $v_1 = (1-\gamma)(1-a_L)$, $v_2 = a_L(1-\gamma) + \sigma_S\gamma$, $\bar{\sigma}_L = \sigma_L\kappa/\kappa_T$, $\bar{\sigma}_I = \sigma_I\alpha/\alpha_T$, $\bar{\sigma}_A = \sigma_A\eta/\eta_T$.

The dependence of $\mathscr{R}_c$ on the treatment rate φ_I is through the fraction a_I, which appears in the second component of $\mathscr{R}_c$. Assuming that treatment reduces, or at least does not increase, the infectious period, then $\bar{\sigma}_I < 1$, and it follows that the effect of increasing φ_I depends on the ratio of $v_1 + v_2\tau\bar{\sigma}_I$ to $(v_1 + \tau v_2)\bar{\sigma}_I$. These quantities are obtained by setting a_I to 0 and 1, respectively in the second term of $\mathscr{R}_c$ above. The smaller $\bar{\sigma}_I$ is, the more effective treatment of infective individuals will be. Similarly, the effectiveness of increasing φ_A depends on the magnitude of $\bar{\sigma}_A$.

The dependence of $\mathscr{R}_c$ on φ_L is through v_1 and v_2. Assuming no pre-epidemic vaccination or treatment, so that $\gamma = 0$, increasing φ_L decreases the second component of $\mathscr{R}_c$ from $(1-(1-\bar{\sigma}_I)a_I)$ to $\tau\bar{\sigma}_I$, and decreases the third component of $\mathscr{R}_c$ from $(1-p)(1-a_A+\bar{\sigma}_A a_A)$ to $(1-p\tau)\bar{\sigma}_A$. Thus, the impact of increased φ_L depends largely on the value of τ and on the magnitudes of $\bar{\sigma}_I$ and $\bar{\sigma}_A$. Additionally, the effectiveness of increasing φ_A and φ_I diminishes with increased φ_L.

A more general picture of the elasticity of $\mathscr{R}_c$ with respect to the parameters is given in Fig. 4. To generate Figs. 3 and 4, 100 sets of parameter values were randomly sampled from uniform distributions with the ranges indicated in Table 1, with γ ranging from 0 to 1 for Fig. 3 and $\gamma = 0$ for Fig. 4.

Fig. 4 shows boxplots of the elasticities of $\mathscr{R}_c$ to each parameter. For example, the elasticity of $\mathscr{R}_c$ with respect

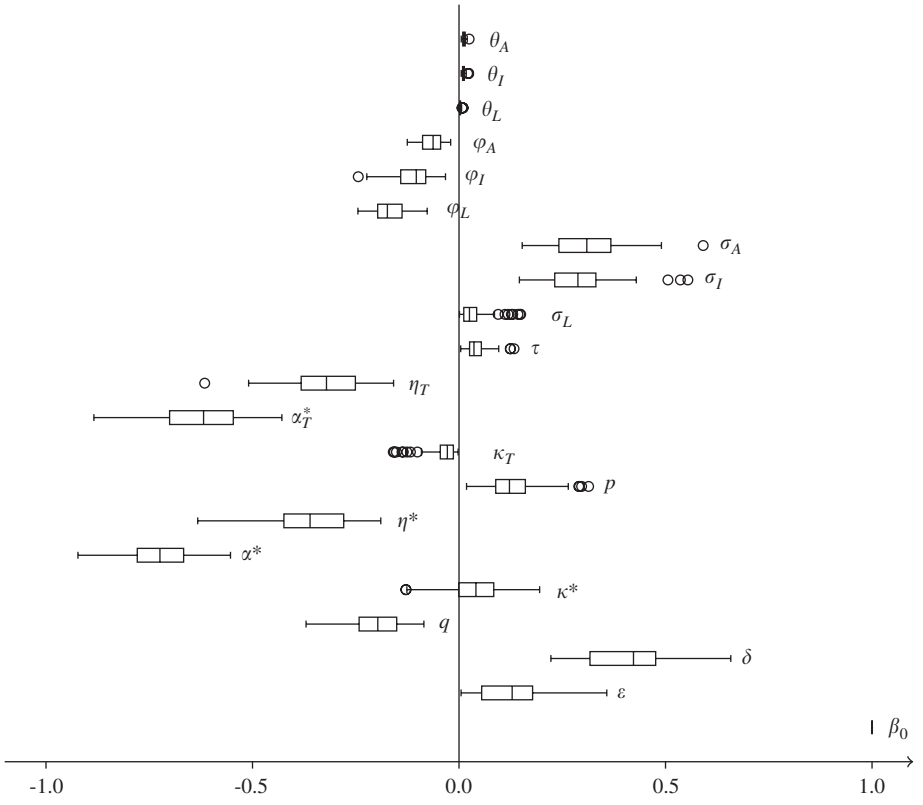

Fig. 4. Elasticities of $\mathscr{R}_c$ with respect to each parameter for 100 sets of parameter values randomly sampled as detailed in the text.

Table 1
Parameter values used in Sections 6 and 7

Parameter	Section 7.1	Table 2	Table 3	Table 4 Fig. 5	Figs. 3 and 4
κ	0.526	0.526	0.526	0.526	0.33–2
κ_T	0.526	0.526	0.526	0.526	$\kappa_T = \kappa$
α	0.244	0.244	0.244	0.244	0.1–0.5
η	0.244	0.244	0.244	0.244	$\eta = \alpha$
α_T	0.323	0.323	0.323	0.323	$0.8\alpha - \alpha$
η_T	0.323	0.323	0.323	0.323	$\eta_T = \alpha_T$
p	0.667	0.667	0.667	0.667	0.33–0.80
τ	0.4	0.4	0.4	0.4	0.4–0.7
S_0	1988	999	999	999	999
I_0	12	1	1	1	1
ε	0	0	0	0	0–0.3
δ	0.5	0.5	0.5	0.5	0.4–0.6
$\varphi_L = \varphi_I = \varphi_A$	1.61	0	0	0	1.61
$\theta_L = \theta_I = \theta_A$	0.0179	0	0	0	0.0179
σ_S	0.7	0.7	0.3	0.3	0.3
$\sigma_L = \sigma_I = \sigma_A$	0.2	0.2	0.2	0.2	0.2
q	0	0	0	0–1	0.2–0.4
f	0.98	0.98	0.98	0.98	Note 1
f_T	1.00	1.00	1.00	1.00	Note 1
γ	0	0–0.7	0–0.7	0	Note 2
β_0	0.581	0.581	0.581	Note 3	Note 4

Parameter values and ranges assume a time unit of 1 day. The values are those assumed in Section 7, and the ranges are used for the sensitivity analyses in Section 6.
Note 1: Figs. 3 and 4 do not depend on f and f_T.
Note 2: γ is zero for Fig. 4 and ranges from 0 to 1 for Fig. 3.
Note 3: β_0 was computed from (3) and the value for $\mathscr{R}_0$ given in the figure.
Note 4: β_0 was computed from (3) for $\mathscr{R}_0$ in the range 2–6.

to ϕ_I is defined as

$$\frac{\phi_I}{\mathscr{R}_c}\frac{\partial \mathscr{R}_c}{\partial \phi_I}.$$

For the numerical computations, these derivatives were approximated by percent changes in $\mathscr{R}_c$ with percent change in the parameter value. Since treatment is expected to reduce the latent and infectious periods, sensitivities to these parameters were computed in a way that preserved this ordering: the elasticity with respect to κ^*, as indicated in the figure, is computed as a percent change in $\mathscr{R}_c$ with a percent change in κ and κ_T while keeping the ratio κ_T/κ fixed. The reason being that we are interested in the effect on $\mathscr{R}_c$ of a change in the latent period, due, for example, to mutation of the virus. Such a change would also affect the latent period of treated individuals. Similarly, the sensitivity to α^* was computed as a percent change in $\mathscr{R}_c$ with a simultaneous percent change in all four parameters α, α_T, η and η_T; the sensitivity to η^* is a percent change in $\mathscr{R}_c$ with a percent change in η and η_T; and the sensitivity to α_T^* is a percent change with respect to α_T and η_T. Thus in the last case we are examining the effect on $\mathscr{R}_c$ of a change to the treatment that affects both symptomatic and asymptomatic cases equally. Computations were repeated for each of the 100 parameter sets, giving the results displayed in Fig. 4 as boxplots for each parameter group. A boxplot, or a box and whisker plot, is a graphical representation of the quartiles of a data set. The box contains the middle 50% of the data, and so extends from the first to the third quartile.

The dividing line in the box is placed at the median. The whiskers show the range of the data, with outliers indicated by circles. In the usual convention for boxplots, the interquartile range (IQR) is the width of the box, or the difference between the first and third quartiles, and all data further than 1.5 IQR below or above the first and third quartiles are denoted as outliers.

As expected, Fig. 4 shows that $\mathscr{R}_c$ is most sensitive to changes in α and β_0, and is very insensitive to the values of θ_L, θ_I and θ_A. Of more importance to the evaluation of treatment strategies are the sensitivities of $\mathscr{R}_c$ to changes in φ_L and φ_I. The elasticities for φ_L and φ_I show a similar range. A closer examination reveals that $\mathscr{R}_c$ was more sensitive to changes in φ_L than φ_I for 85 of the 100 parameter sets sampled, and that $\mathscr{R}_c$ was more sensitive to changes in q than φ_L for 70 of the 100 parameter sets. The large uncertainty in the results, represented by the width of the boxplots, indicates the importance of obtaining better estimates of the effect of treatment on the progression of an infection (as represented by the parameter ratios α_T/α and η_T/η and the parameters τ and p). However, this preliminary analysis suggests that treatment of latently infected individuals is more effective at reducing $\mathscr{R}_c$ than treatment of symptomatic individuals.

7. Numerical computations and sensitivities

7.1. The 1957–58 influenza epidemic

In Section 3 we used the parameter values of Longini et al. (2004) in the model (2) to obtain predictions of our model that are consistent with those of Longini et al. (2004) for an untreated influenza epidemic. The next challenge is to obtain predictions of our model with antiviral treatment consistent with those of Longini et al. (2004). Thus we consider the special case $\varepsilon = \gamma = 0$ of (1). In Longini et al. (2004) it is assumed that 80% of index symptomatic infective individuals and latent members are treated within 1 day. Since the assumption of treatment at a constant rate φ implies treatment of a fraction $1 - \exp(-\varphi t)$ after a time t, we take $\varphi_L = \varphi_I = \varphi_A = -\ln(1 - 0.80) = 1.61$ per day. This overlooks the fact that some of the members treated are not infected, and thus would tend to overestimate the number of cases of influenza. It also overestimates the number of symptomatic infective individuals treated, since in Longini et al. (2004) it is assumed that only index cases are treated, not secondary infections. A course of treatment of 8 weeks for prophylaxis implies $\theta_L = 1/56$ per day, since $1/\theta_L$ is the expected duration of treatment. Actually, Longini et al. indicate in Longini et al. (2004) that there will be some attrition over the course of treatment and suggest an average treatment duration of 4.9 weeks. However, the numerical calculations appear not to depend much on the value of θ_L. When antivirals are used as treatment of exposed (but not necessarily infected) individuals, the course of treatment can be much shorter. However, since the course of treatment will still be much longer than the duration of the latent stage (given by κ), the calculations remain insensitive to θ_L. In addition, we use the parameter values stated in Section 3 and for simplicity of calculation we take $q = 0$. Thus, the full set of parameter values is as given in column 2 of Table 1.

We use these parameters in (19) assuming mass action incidence with $\mathscr{R}_c = 0.312$ given by (12) to estimate $S_\infty \approx 1976.9$. Then the number of cases of influenza over the course of the epidemic is, by (21), on average, 4.08, not including the original 12 cases, which we compare with the mean value of 46 obtained in Longini et al. (2004) (with a stated confidence interval of (4,324)). The number of cases depends very sensitively on β_0: increasing β_0 by 10% increases the number of cases to 4.69, or by a factor of 15%. It would be reasonable to use our model to estimate, for example, the effect of some pre-epidemic antiviral treatment ($\gamma > 0$).

It should be remembered that here we are only comparing simulations obtained for a compartmental model to those obtained by using a stochastic simulation model, not comparing simulations to experimental observations. The point is that predictions from these different models are quite similar.

7.2. Pre-epidemic treatment

It has been suggested recently (Balicer et al., 2005) that pre-epidemic antiviral treatment may be a cost-effective method of coping with an influenza epidemic. This conclusion was reached using the model of Longini et al. (2004), but our model can easily be used to judge the effect of such treatment. We use (19) to determine the number of untreated susceptible individuals, S_∞, and the number of treated susceptible individuals, $S_{T\infty}$, at the end of the epidemic, with the parameters of Longini et al. (2004), including $\sigma_S = 0.7$, in a population of 1000 with 1 infective initially. For simplicity of calculation we assume mass action incidence, so that $\beta(N_M^*) = \beta_0/S_0$ in the final size relations, ignoring the relatively small error inherent in this assumption.

For example, with the parameter values listed in Table 1 we obtain the results shown in Table 2, giving the treatment fraction γ, the number of untreated susceptible individuals S_∞ at the end of the epidemic, the number of treated susceptible individuals $S_{T\infty}$ at the end of the epidemic, and the number of cases of influenza computed from (21). This suggests that pre-epidemic antiviral treatment may indeed be an effective way of preventing an epidemic, at least if supplies of antiviral drugs are sufficient.

With treatment by a vaccine developed for the specific strain of influenza anticipated ($\sigma_S = 0.3$), the same calculation gives the results shown in Table 3. For both antiviral treatment and vaccination, the fraction γ of susceptible individuals treated to bring the control reproduction number down to 1 is 0.28. The results indicate the benefits in reducing influenza cases of pre-epidemic

Table 2
Number of untreated susceptible individuals S_∞, treated susceptible individuals $S_{T\infty}$ and influenza cases after the epidemic, as a function of the fraction treated prior to the epidemic, when $\sigma_S = 0.7$

Fraction treated	S_∞	$S_{T\infty}$	Influenza cases
0.00	206	0	530
0.05	222	18	494
0.10	240	40	457
0.15	259	65	418
0.20	279	96	376
0.25	301	132	331
0.30	325	175	284
0.35	352	228	232
0.40	380	291	176
0.45	410	366	116
0.50	437	455	55
0.55	433	535	16
0.60	393	593	7
0.65	346	645	5
0.70	298	696	3

Table 3
Number of untreated susceptible individuals S_∞, treated susceptible individuals $S_{T\infty}$ and influenza cases after the epidemic, as a function of the fraction treated prior to the epidemic, when $\sigma_S = 0.3$

Fraction treated	S_∞	$S_{T\infty}$	Influenza cases
0.00	206	0	530
0.05	224	32	489
0.10	243	67	447
0.15	264	106	403
0.20	287	147	356
0.25	313	192	307
0.30	341	242	255
0.35	372	296	200
0.40	406	355	142
0.45	441	421	81
0.50	464	489	27
0.55	440	546	9
0.60	395	597	5
0.65	347	648	3
0.70	298	698	3

vaccination of even a fraction of the population too small to reduce the reproduction number below 1.

7.3. Pandemic influenza preparation

One approach that may be part of a control strategy for pandemic influenza is "social distancing" as described in Ferguson et al. (2005). The isolation of some symptomatic infective individuals is one aspect of social distancing. In (1) the parameter q represents the withdrawal of some infective individuals from contact because of their illness. However, isolation of some diagnosed infective individuals could also be encouraged as a control strategy. Thus if the "natural" value of q is 0.4, a choice $q = 0.46$ represents complete withdrawal of 10% of infective individuals together with 40% withdrawal of the remainder. Similarly, $q = 0.52$ represents complete withdrawal of 20% of diagnosed infective individuals. Complete withdrawal of 10% of infective individuals decreases the reproduction number by about 7% with the parameter values of Longini et al. (2004).

To estimate the effect of such isolation on the course of the epidemic, Table 4 shows the results of simulating the model without treatment (2) with parameters as given in Table 1 for different values of $\mathscr{R}_0$ and q; see also Fig. 5. In preparing for a possible pandemic influenza, one must consider a range of possible basic reproduction numbers or attack ratios because there is no advance indication of the severity of the epidemic.

Table 4
Effect of isolation on final size and cases

q	$\mathscr{R}_0 = 1.5$		$\mathscr{R}_0 = 2.0$		$\mathscr{R}_0 = 2.5$		$\mathscr{R}_0 = 3.0$	
	Final size	Cases	Final size	Cases	Final size	Cases	Final size	Cases
0	584	391	797	532	892	596	940	628
0.1	497	332	747	499	862	576	921	615
0.2	386	258	683	456	822	549	895	598
0.3	242	162	597	399	767	513	859	574
0.4	68	46	480	321	692	462	807	539
0.5	9	7	318	213	584	390	732	490
0.6	3	3	94	63	425	284	620	415
0.7	2	2	6	5	183	123	443	297
0.8	1	2	2	2	6	5	151	102
0.9	0	1	1	1	1	2	2	2
1	0	1	0	1	0	1	0	1

Final size and total cases assuming mass action incidence and parameter values listed in Section 3, but with $S_0 = 999$, $I_0 = 1$, and β_0 set to obtain the listed $\mathscr{R}_0$ value for $q = 0$. Cases are computed using (21) with the final size estimated from (19).

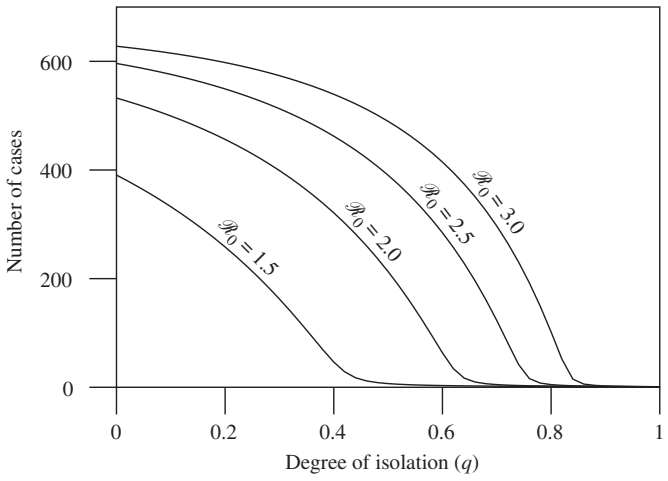

Fig. 5. The effect of isolation on the number of cases. Total cases, as computed from (21) with the final size estimated from (19) assuming mass action incidence, are given as a function of q for the parameter values of Section 3, but with $S_0 = 999$, $I_0 = 1$, and β_0 chosen to achieve the value of $\mathscr{R}_0$ with $q = 0$.

The above results indicate that while isolation of infective individuals can reduce the impact, the level of isolation required to control a pandemic in absence of other interventions is not practical. Thus, it is necessary to use antiviral treatment as well. The process should be to compare different management strategies, that is, different choices of φ_L, φ_I and φ_A, by estimating the resulting number of disease cases. It is important to also estimate the number of treatments required, to assure that the supply of antiviral drugs available is sufficient to implement a chosen strategy. The results will, of course, depend on the severity of the epidemic. Again, it is necessary to consider a range of possible basic reproduction numbers or attack ratios because there is no advance indication of the severity of the disease attack.

8. Discussion

Approaches to coping with pandemic influenza that have been proposed recently include pre-epidemic treatment of susceptible individuals, treatment during an epidemic of latent infective individuals identified by contact tracing, and treatment during an epidemic of symptomatic infective individuals (Public Health Agency of Canada, 2006). Using (12), it is straightforward to calculate treatment rates required to reduce the control reproduction number $\mathscr{R}_c$ below 1 and avert an epidemic. An obvious extension would be to simulate a combination treatment of latent and symptomatic infective individuals at the start of a pandemic, followed by vaccination of susceptible individuals once a targeted vaccine has been produced.

The model formulated here is designed to make such simulations easy. Except for accurate simulations of (2), which require solution of the dynamical system, computations require only algebraic calculations or the numerical solution of one or two transcendental equations, which are easily performed with any computer algebra system. This may be more suitable than the stochastic simulation models that have been the main approach to epidemic studies. Both compartmental models of the type formulated here and stochastic simulation models have obvious shortcomings in the description of an actual epidemic, but the extent to which the predictions of the two types of models are in general agreement adds some confidence in the results of both.

In addition, compartmental models let us do an analytical sensitivity analysis to determine which parameters are important to estimate accurately for prediction and control. The parameters δ, p and η associated with the asymptomatic compartment are largely unknown, and the effectiveness of treatment is very dependent on the values of these parameters, thus stressing the importance of reducing the uncertainty of these quantities. Analysis of the compartmental model is able to deal with a larger range of parameters, effectively allowing a complete analysis of parameter space. The values of the treatment parameters used for simulations in this paper were all taken from a single study. Again, analyses over a large range of parameter values are important.

Calculations indicated that the number of cases is sensitive to the number of index cases when $\mathscr{R}_c$ is near 1, but not for larger values. In effect, if the number of secondary cases is small, the treatment is limited to the index cases.

We have used a simple assumption for the reduction in contacts (through q), but have not properly modelled social distancing. The parameter q models the response of infective individuals, but not that of susceptible individuals. In practise, susceptible individuals would change their behaviour in response to perceived prevalence and morbidity. Several other important extensions to the model remain to be considered: heterogeneity of transmission rates; accounting for different contact rates and immunological responses; and the evolution of strains resistant to the antiviral treatments available. See Alexander et al. (2007) and McCaw and McVernon (2007) for very recent investigations that consider drug resistance and contact tracing, respectively, in influenza control.

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