Simple models for containment of a pandemic Supplementary Information

Julien Arino Fred Brauer P. van den Driessche
James Watmough Jianhong Wu

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1 The basic epidemic model

Our basic epidemic model is a slight extension of the standard $SLIR$ model allowing a fraction of infected members to go from the latent stage to an asymptomatic infective stage in which they have some infectivity.

Specifically, we make the following assumptions.

1. Initially the total population size is K, of which a small number I_0 are infective and the remainder S_0 are susceptible, with $S_0 + I_0 = K$.
2. We assume mass action incidence, that is, the number of effective contacts in unit time per individual is a constant fraction β of total population size.
3. Latent members (L) are not infective.
4. A fraction p of latent members proceeds to the (symptomatic) infective class (I) at rate κ, while the remainder goes directly to an asymptomatic infective stage (A), also at rate κ.
5. Infectives leave the infective class at rate α, with a fraction f recovering and going to the removed class (R) and the remainder dying of infection.
6. Asymptomatics have infectivity reduced by a factor δ, and go to the removed stage at rate η.

These assumptions lead to the model

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

with initial conditions

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

Here, $N = S+L+I+A+R$ is the total population size. It is convenient to use N as one of the model variables rather than R, especially if a more general incidence function depending on total population size is assumed. A flow diagram for the model (1) is shown in Figure 1 of the main paper. The special case $p = 1$, which gives $A = 0$, is the standard $SLIR$ model [2], [3, Exercise 2.2]. The variable N does not appear in the model except in the equation for N. Thus N is determined when the other variables are known, and the equation for N may be discarded from the model. In particular, this means that we do not need to specify the recovery fraction f in the model (although, of course, f must be specified in order to determine the number of disease deaths).

It is easy to see that the model (1) has disease-free equilibria with

$$L = I = A = R = 0$$

and S arbitrary, $0 \le S \le S_0$. We make the restriction $0 \le S \le S_0$ because $S(0) = S_0$ and S is a monotone decreasing function. We may use the approach of [9] to calculate the basic reproduction number

$$\mathcal{R}_0 = S_0\beta[\frac{p}{\alpha} + \frac{\delta(1-p)}{\eta}] = \frac{S_0\beta\rho}{\alpha}, \tag{2}$$

where

$$\rho = \alpha\big[\frac{p}{\alpha} + \frac{\delta(1-p)}{\eta}\big].$$

This calculation corresponds to the disease-free equilibrium $S = S_0, L = I = A = R = 0$.

There is also a *final size relation*

$$S_0[\ln S_0 - \ln S_\infty] = \mathcal{R}_0(S_0 - S_\infty) + \frac{\mathcal{R}_0 I_0}{\rho}. \tag{3}$$

It is common to assume that I_0 is small enough to be neglected in this formula. Then (3) with $I_0 = 0$ is a standard result for simple epidemic models [3, Sec. 1.3]. The assumption that $I_0 = 0$ implies $S_0 = K$, and then S_0 would be replaced by K in the formulae for the analysis of the model (1).

To establish the final size relation, we proceed as follows. First, we adopt the notations g_∞ for $\lim_{t\to\infty} g(t)$ and $\hat{g}$ for $\int_0^\infty g(t)ds$ if g is any non-negative integrable function defined for $0 \le t < \infty$. We add the first two equations of (1) and integrate with respect to t from 0 to ∞, obtaining

$$S_0 - S_\infty = \kappa\hat{L}. \tag{4}$$

Integration of the third and fourth equations of (1) gives

$$\alpha\hat{I} = p\kappa\hat{L} + I_0 \tag{5}$$

and

$$\eta \hat{A} = (1-p)\kappa \hat{L}. \tag{6}$$

We now divide the first equation of (1) by S and integrate, obtaining

$$\ln S_0 - \ln S_\infty = \beta[\hat{I} + \delta \hat{A}].$$

Then substitution of (2), (4), (5), and (6) gives the final size relation (3).

The *attack rate* is defined as the fraction of the susceptible population which develops disease symptoms over the course of the epidemic. In our notation this is

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

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

We consider an example with mass action incidence and parameters used for influenza in [7]

$$\kappa = 0.526, \quad \alpha = \eta = 0.244, \quad p = 0.667,$$
$$S_0 = 1988, \quad I_0 = 12, \quad K = 2000, \quad \delta = 0.5.$$

In [7] an attack rate is assumed for each of four age groups, and the average attack rate for the entire population is 0.326. If we use an attack rate of 0.326, the final size relation gives $S_\infty = 1016$, which corresponds to 677 cases of influenza compared to the estimate 668 in [7, Table 2]. From the final size relation (3) we obtain $\mathcal{R}_0 = 1.37$, and then (2) gives $S_0\beta = 0.40$. This value will be used for calculations with the treatment model.

2 The treatment model

We consider treatment before a disease outbreak, which we will describe as vaccination and treatment once a disease outbreak has begun, which we will describe as antiviral treatment. This terminology is chosen with influenza treatment in mind, but for modeling purposes the nature of the treatments are irrelevant. Our assumptions require us to introduce additional compartments into the model to follow treated members of the population through the stages of infection. We use the classes S, L, I, A, R as before and introduce S_T, the class of treated susceptibles, L_T, the class of treated latent members, I_T, the class of treated infectives, and A_T, the class of treated asymptomatics.

We assume that a fraction γ of the population is vaccinated before the disease outbreak. Thus, we assume an initial state

$$S(0) = (1-\gamma)S_0, \quad S_T(0) = \gamma S_0, \quad I(0) = I_0,$$
$$L(0) = L_T(0) = I_T(0) = A(0) = A_T(0) = 0,$$
$$N(0) = K = S_0 + I_0,$$

with $0 \le \gamma \le 1$.

We assume that treatment produces a reduction σ_S in susceptibility and that σ_I and σ_A are the respective decreases in infectivity in I_T and A_T. 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. The rates of departure from L_T, I_T and A_T are assumed to be κ_T, α_T and η_T respectively, and τ is the reduction in the fraction of latent members who will develop symptoms.

The resulting model is

$$\begin{aligned}
S' &= -S\beta Q \\
S'_T &= -\sigma_S S_T \beta Q \\
L' &= S\beta Q - \kappa L - \varphi_L L + \theta_L L_T \\
L'_T &= \sigma_S S_T \beta Q - \kappa_T L_T + \varphi_L L - \theta_L L_T \\
I' &= p\kappa L - \alpha I - \varphi_I I + \theta_I I_T \\
I'_T &= p\tau\kappa_T L_T - \alpha_T I_T + \varphi_I I - \theta_I I_T \\
A' &= (1-p)\kappa L - \eta A \\
A'_T &= (1-p\tau)\kappa_T L_T - \eta_T A_T \\
N' &= -(1-f)\alpha I - (1-f_T)\alpha_T I_T,
\end{aligned} \tag{7}$$

with

$$Q = I + \delta A + \sigma_I I_T + \delta\sigma_A A_T.$$

A flow diagram for the model (7) is shown in Figure 2 of the main paper.

The standard method of [9] may be used to calculate the control reproduction number corresponding to any initial state, giving

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

where

$$\begin{aligned}
\mathcal{R}_u &= \frac{S_0\beta\Big[(\alpha_T+\theta_I+\sigma_I\varphi_I)p\kappa(\kappa_T+\theta_L)+(\theta_I+\sigma_I(\alpha+\varphi_I))p\tau\kappa_T\varphi_L\Big]}{\Delta_I\Delta_L} \\
&\quad + \frac{\delta S_0\beta}{\Delta_L}\left(\frac{(1-p)\kappa(\kappa_T+\theta_L)}{\eta}+\frac{\sigma_A(1-p\tau)\kappa_T\varphi_L}{\eta_T}\right)
\end{aligned}$$

and

$$\begin{aligned}
\mathcal{R}_v &= \frac{\sigma_S S_0\beta\Big[(\alpha_T+\theta_I+\sigma_I\varphi_I)p\kappa\theta_L+(\theta_I+\sigma_I(\alpha+\varphi_I))p\tau\kappa_T(\kappa+\varphi_L)\Big]}{\Delta_I\Delta_L} \\
&\quad + \frac{\delta\sigma_S S_0\beta}{\Delta_L}\left(\frac{(1-p)\kappa\theta_L}{\eta}+\frac{\sigma_A(1-p\tau)\kappa_T(\kappa+\varphi_L)}{\eta_T}\right)
\end{aligned}$$

are the reproduction numbers in the case of no individuals and all individuals vaccinated, respectively, where

$$\begin{aligned}
\Delta_L &= (\kappa+\varphi_L)(\kappa_T+\theta_L)-\varphi_L\theta_L \\
\Delta_I &= (\alpha+\varphi_I)(\alpha_T+\theta_I)-\varphi_I\theta_I.
\end{aligned}$$

By integrating some of the individual equations in (7), specifically the first plus third equation, the second plus fourth equation, the fifth equation, and the sixth equation respectively, we obtain the relations

$$\begin{aligned}(\kappa+\varphi_L)\hat{L}-\theta_L\hat{L_T} &= S(0)-S_\infty\\ (\kappa_T+\theta_L)\hat{L_T}-\varphi_L\hat{L} &= S_T(0)-S_{T\,\infty}\\ p\kappa\hat{L}+\theta_I\hat{I_T} &= (\alpha+\varphi_I)\hat{I}-I_0\\ p\tau\kappa_T\hat{L_T}+\varphi_I\hat{I} &= (\alpha_T+\theta_I)\hat{I_T}.\end{aligned} \tag{8}$$

We may derive final size relations for the treatment model (7) much as for the untreated model (1), by integrating the equations for S and S_T in (7), integrating the other equations in (7) to express $\hat{Q}$ in terms of the reproduction number, and combining the results, obtaining

$$\begin{aligned}S_0[\ln(1-\gamma)S_0-\ln S_\infty] &= \mathcal{R}_u\left[(1-\gamma)S_0-S_\infty\right]\\ &+ \mathcal{R}_v\left[\gamma S_0-S_{T\infty}\right]+\frac{\mathcal{R}_0 I_0}{\rho_T}\\ \ln\gamma S_0-\ln S_{T\infty} &= \sigma_S[\ln(1-\gamma)S_0-\ln S_\infty].\end{aligned} \tag{9}$$

In (9) the quantity ρ_T is given by

$$\rho_T=\frac{\rho}{\alpha}\left(\frac{\alpha_T\varphi_I+\alpha(\alpha_T+\theta_I)}{\alpha_T+\theta_I+\sigma_I\varphi_I}\right).$$

If $\varphi_I=\theta_I=0$, then $\rho_T=\rho$.

To apply the model (7) to treatment at rate φ_L of latent members and rate φ_I of infectives, we observe that the number of people treated altogether is

$$\varphi_L\hat{L}+\varphi_I\hat{I}. \tag{10}$$

A similar calculation gives the number of cases of disease

$$\alpha\hat{I}+\alpha_T\hat{I_T}=I_0+p\kappa\hat{L}+p\tau\kappa_T\hat{L_T}. \tag{11}$$

In the special case of no treatment during the latent stage $\varphi_L=\theta_L=0$, the number of cases reduces to $I_0+p[S(0)-S_\infty]$.

In Section 1 we have used the parameter values of [7] in the model to obtain predictions consistent with those of [7] for an untreated influenza epidemic. The next challenge is to obtain predictions consistent with those of [7] with antiviral treatment. Thus we consider the special case $\gamma=0$ of the antiviral treatment model. In this special case, $\mathcal{R}_c=\mathcal{R}_u, \mathcal{R}_u=0$, $S_T(t)\equiv 0$ and only the first equation in (9) is meaningful. In [7] it is assumed that 80% of index symptomatic infectives and latent members are treated within 1 day, and accordingly we take $\varphi_L=\varphi_I=0.8$. 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 infectives treated since in [7] it is assumed that only index cases are treated, not

secondary infections. A course of treatment of 8 weeks implies $\theta_I = \theta_L = 1/56$. In addition we use the parameter values suggested in Section 1, and

$$\kappa_T = 0.526, \quad \alpha_T = \eta_T = 0.323, \quad \tau = 0.4$$
$$\sigma_S = 0.7, \quad \sigma_I = \sigma_A = 0.2.$$

We use these parameters to calculate $\mathcal{R}_c = 0.31, \rho_T = 2.33$ and then use the final size relation to estimate $S_\infty \approx 1978$. Then the number of cases of influenza over the course of the epidemic given by (11) is 14, which we compare with the value 46 obtained in [7, Table 2]. Since the number of cases is very sensitive to changes in $\mathcal{R}_c$ these results are not very reliable. There is some correlation with the results of [7] whose confidence interval is large enough to include our value. It would be reasonable to use our model to estimate, for example, the effect of some pre-epidemic antiviral treatment ($\gamma > 0$).

We apply the treatment model to estimate the effect of antiviral treatment once an epidemic has begun as a complement to the approach of [4] and [8]. Our goal is to choose the treatment rates φ_L and φ_I to make $\mathcal{R}_c < 1$, thus achieving disease control. If there is no pre-epidemic treatment ($\gamma = 0$), the final size relation takes the form

$$S_0[\ln S_0 - \ln S_\infty] = \mathcal{R}_c(S_0 - S_\infty) + \frac{\mathcal{R}_0 I_0}{\rho_T}. \tag{12}$$

The main paper shows graphically the results of these calculations for $\mathcal{R}_0 = 1.5$. In planning for a pandemic, one would repeat these calculations for a range of values of $\mathcal{R}_0$. Unfortunately, if $\mathcal{R}_c$ is close to 1, the value of $(S_0 - S_\infty)$ given by the final size relation (12) is very sensitive to changes in the value of I_0. If 2 infectives are introduced into a population of 998 susceptibles and $\mathcal{R}_0 = 1.5$, the value of $(S_0 - S_\infty)$ is approximately 1.4 times its value if 1 infective is introduced into a population of 999 susceptibles. This means that the number of treatments required and the number of disease cases over the course of the epidemic is very sensitive to the initial number of infectives. Since this number can not be predicted in advance of an epidemic, estimates are very unreliable. However, comparison of different control strategies is still feasible.

Another application of the treatment model is to the common annual vaccination program to protect against the strain of influenza thought to be the most likely to invade. The model we have described can be applied to this situation as well, with the final size relation in the form (9). With disease parameters as in [7] and vaccination which reduces susceptibility by 70 % of a fraction γ of the population before an epidemic and introduction of 1 infective into a total population of 1000 individuals, we obtain the results shown in Table 1 of the paper. In this table, setting $\theta_L = \theta_I = \varphi_L = \varphi_I = 0$ in (11) gives the number of disease cases as

$$I_0 + p[(1-\gamma)S_0 - S_\infty] + p\tau(\gamma S_0 - S_{T\,\infty}).$$

It has also been suggested [1] that a possible response to an outbreak of a strain for which no specific vaccine has been developed as yet would be a program

of treatment with a general antiviral as a stopgap until a specific vaccine can be produced. The same calculations applied to the annual vaccination model may be used to analyze this situation. Presumably an antiviral would have a smaller value of σ_S than a vaccine, but the reduction in the number of disease cases might well be large enough for this to be an effective way of preventing an epidemic, at least if supplies of antiviral drugs are sufficient.

Another scenario considered in [6] is antiviral treatment of essentially all symptomatic infectives. Thus the approaches to coping with pandemic influenza that have been proposed very recently include pre-epidemic treatment of susceptibles, treatment during an epidemic of latent infectives identified by contact tracing, and treatment during an epidemic of symptomatic infectives. We calculate from our model with $\mathcal{R}_0 = 1.5$ that if antiviral treatment is applied only to symptomatic infectives, a rate $\varphi_I = 0.4$ would be required to bring the control reproduction number $\mathcal{R}_c$ down below 1 and avert an epidemic.

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