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Modelling strategies for minimizing the impact of an imported exotic infection

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The global epidemic of severe acute respiratory syndrome (SARS) in 2003 demonstrated the need to determine control strategies for exotic infections. The prior determination of such strategies, and the use of mathematical models to assist this, is hampered by the obvious lack of data. We propose an integral equation model of Kermack–McKendrick type that may be used to compare strategies based on the isolation of infectious individuals. The model structures the incidence of infection according to the location of an infected individual at exposure, and requires knowledge of the infectivity kernel and the initial rate of exponential increase of cases. The model's use in the design of strategies to minimize the risk of SARS in a previously unexposed community is demonstrated.

Keywords: mathematical epidemiology; infectious diseases; exotic infections; SARS

1. INTRODUCTION

The motivations for this paper were the recent epidemic of severe acute respiratory syndrome (SARS) (Pearson *et al.* 2003; WHO 2003; Lingappa *et al.* 2004), and the perceived threat from smallpox as a weapon of bioterrorism (Ferguson *et al.* 2003). For an isolated geographical region both pose the same problem, assuming that the region itself is not the terrorist target. The scenario is that an epidemic is occurring elsewhere in the world and we wish to minimize its impact on the local community. The infectious agent is not one that has recently been present in the region, so the local population may be regarded as having no herd immunity to infection.

In an ideal world, a response strategy for an infectious outbreak would be planned in advance (Anon. 2002). This is not always realistic even when the infection is a known one. However, when an infectious agent poses a threat the authorities rapidly require a response strategy. This is often based on prior experience with similar infections, the experience of other countries, and local expert knowledge. The methodology described here is designed as a means for comparing potential strategies and determining the likely outcome of an importation of infection, in terms of the number of local cases and the time-course of the epidemic. It is simple in concept and requires a minimum amount of data, which is necessary for novel infections where little information is available.

The model is derived from the original formulation of Kermack & McKendrick (1927; also Diekmann & Heesterbeek 2000). At the simplest level an estimate of the shape of the integral kernel (product of contact rate and probability of transmission given contact, as functions of time since infection) and of the basic reproduction number (R_0) is all that is required. Alternatively, the initial growth rate or doubling time of the epidemic may be used to estimate R_0. For the structured model presented here, an estimate of the initial distribution of infections among the locations where transmission took place is also required to determine weight parameters. In either case the model is linear; thus the total number infected in the epidemic can be explicitly determined when $R_0 < 1$.

In § 2, we describe the features of the model and its analysis. We then illustrate the model's use in planning intervention strategies for SARS, extending the model to include the isolation of infectious cases. Some mathematical details are included in Appendix A.

2. THE MODEL

The primary variable modelled is the incidence of infection. The infected population is structured into four types: those who were infected by contact with members of one's immediate household; with others at one's place of work (including school); with others in the wider community; and with others in a healthcare facility. Subscripts 1–4 are used to denote the incidence of these infection types in the population, respectively, and the total incidence is $|i(t)| = \sum_{k=1}^{4} i_k(t)$. It should be stressed that the infected subpopulation is structured on the location of individuals at the time of infection, or the *state at birth* (see Diekmann & Heesterbeek 2000). For the examples presented in this paper, and for the development of the model just four locations have been chosen as most appropriate for our purposes. For other infections or in other geographical regions other choices may be appropriate, although the model would be similar. In this type of model individuals do not necessarily remain in one compartment, as in those discussed by Anderson & May (1991). In fact, almost all members of the population will have contact with others at more than one of the locations. However, the original location of infection is an attribute that an infected individual retains.

Infection is transmitted during a contact between an infectious individual and a susceptible recipient. The contact rate function $C(\tau)$ is a four by four matrix, and a function of the time since the infectious individual was infected. In other respects, it is similar in concept to the familiar *WAIFW* matrix (Anderson & May 1991; Roberts & Tobias 2000). Its elements are $C_{kl}(\tau)$, being the contact rates of

those that were infected within their own household, at work, in the wider community or in a healthcare facility ($\ell = 1, 2, 3, 4$, respectively) with others within their own household, at work, in the wider community or in a healthcare facility ($k = 1, 2, 3, 4$, respectively). In the examples given, it is assumed that (in the absence of control interventions) each of these contactee categories experience equal contact rates with contactors, except that after two generations of infection have arisen within the same household it is unlikely that there will be further intra-household contact within that particular household. In other words, after one household member has been infected outside the household, and this person has transmitted the infection to one or more members of that household, then the remaining uninfected members take precautions to avoid becoming infected. The general presentation is also made using this assumption, as further progress in model analysis may then be made. Hence,

$$C_{k\ell}(\tau) = \begin{cases} 0 & : \quad k = l = 1 \\ c_k(\tau) & : \quad \text{otherwise} \end{cases}. \tag{2.1}$$

Although this contact structure would be appropriate at the beginning of an epidemic, it may change as public behaviour changes in response to the epidemic or as a consequence of control interventions. The analysis presented in this section relates to the initial stages of the epidemic before these changes take place.

The time-course of infection within an individual is assumed to be independent of the infection category into which they fall, and the probability of transmitting infection given contact with a susceptible is denoted by $p(\tau)$. The number of susceptibles in the population at time t is

$$S(t) = S(0) - \left| \int_0^t i(\tau)\, \mathrm{d}\tau \right| \tag{2.2}$$

and we define $S_0 = S(0)$. If the entire population is susceptible initially, then $S_0 = N$ (the population size). However, the effective number of susceptibles that are available to be infected will depend on their location at the time of exposure to infection: either at home, at work, in the wider community or in a healthcare facility. To account for this, weights w_k relating these to the overall community size, or to the numbers of susceptibles in the community, are introduced.

The equation for the incidence of infection is (see Diekmann & Heesterbeek 2000)

$$i_k(t) = \alpha_k(t) + w_k S(t) \sum_{l=1}^{4} \int_0^\infty p(\tau) C_{kl}(\tau) i_l(t-\tau)\, \mathrm{d}\tau \tag{2.3}$$

for $k = 1, 2, 3, 4$. The index cases are represented by the term $\alpha_k(t)$. The basic reproduction number for the model defined by equation (2.3) is $R_0 = \rho(K_0)$ (the largest eigenvalue of K_0), where the next generation matrix is defined by

$$(K_0)_{kl} = \begin{cases} 0 & : \quad k = l = 1 \\ K_k = w_k \int_0^\infty p(\tau) c_k(\tau)\, \mathrm{d}\tau & : \quad \text{otherwise} \end{cases}. \tag{2.4}$$

Hence

$$R_0 = \frac{K_2 + K_3 + K_4}{2} \left(1 + \sqrt{1 + \frac{4K_1}{K_2 + K_3 + K_4}} \right). \tag{2.5}$$

Following the introduction of an index case there will be a small epidemic if $R_0 < 1$, or a large epidemic if $R_0 > 1$.

(a) *Small epidemics*

Assume now that a single case is introduced into the community at time $t = 0$. If $R_0 < 1$, then the course of the epidemic may be approximated by assuming that there is an effectively inexhaustible supply of susceptibles, and hence approximating $S(t) \equiv S_0$ in equation (2.3) to obtain a linear equation. Although an analytic solution may still not be easy (see Appendix A), the total number infected at each location throughout the epidemic may be readily calculated as the components of the vector

$$\frac{1}{1-(1+K_1)(K_2+K_3+K_4)} \begin{pmatrix} K_1 \\ (1+K_1)K_2 \\ 1-(1+K_1)(K_2+K_4) \\ (1+K_1)K_4 \end{pmatrix} \tag{2.6}$$

and the total number infected is

$$\left| \int_0^\infty i(t)\, \mathrm{d}t \right| = \frac{1+K_1}{1-(1+K_1)(K_2+K_3+K_4)}. \tag{2.7}$$

Finally, it should be noted that the small epidemic solution is the result of a linear process. Hence, the solution of the deterministic model is also the mean of the solution of the corresponding stochastic model, and confidence limits about the curve are readily derived from the Poisson distribution.

(b) *Large epidemics*

The small epidemic solution is also valid for the initial stages of a large epidemic, i.e. when $R_0 > 1$ and the number of susceptibles may be approximated by S_0. At this time the growth of the epidemic is approximately exponential with $|i(t)| \sim \mathrm{e}^{rt}$ with a constant proportion $(\theta_1, \ldots, \theta_4)$ in each infection category (see Appendix A). If the observed data are r and θ_k then these provide estimates of $(w_1, \ldots, w_4)$ and in turn R_0, which is therefore (indirectly) a function of r. If an exotic infection were introduced to a community where the majority of the population were susceptible, and the authorities did not have containment procedures in place, then it is likely that an epidemic would start and follow the large epidemic pattern. Should the authorities then put suitable procedures in place, reducing the basic reproduction number of the infection below one, then the pattern would change to one similar to the small epidemic solution. The most common interventions would be the isolation of those infected and/or their contacts and, where a vaccine is available, the vaccination of targeted sub-populations. The effects of isolation policies are now explored in more detail with reference to SARS as an example. The effects of incorporating vaccination and isolation policies in a similar model for smallpox epidemics are discussed by Aldis & Roberts (2004).

3. EXAMPLE: THE ISOLATION OF CONTACTS TO MINIMIZE THE SPREAD OF SARS

The first known case of SARS appeared in Guangdong Province, China, in November 2002, and in the next nine months a total of 8439 cases and 812 deaths[1] were reported from 28 areas (Pearson *et al.* 2003; WHO 2003; Lingappa *et al.* 2004). Detailed models have been used to describe its epidemiology and to explain the observed patterns of outbreaks (Lipsitch *et al.* 2003; Lloyd-Smith *et al.* 2003; Riley *et al.* 2003). One concern was to deter-

mine the public health measures required to minimize the impact of the infection should it be introduced to a new geographical area. The only intervention available is to isolate members of the community from each other, to reduce contacts and hence transmission. The model described above was used to examine the potential effectiveness of these policies (M. G. Roberts, unpublished report prepared for the Ministry of Health, Wellington).

Suppose that when a time t_q has elapsed after the infection of the index case, a policy is introduced that effectively prevents a fraction q_{kl} of infected individuals of type l from contacting susceptibles at location k at time τ after they were exposed. Then, for times $t > t_q$ equation (2.3) would become

$$i_k(t) = w_k S(t) \sum_{l=1}^{4} \int_0^\infty p(\tau) C_{kl}(\tau) \{1 - u(t - \tau - t_q) q_{kl}(\tau)\} \times i_l(t - \tau)\, \mathrm{d}\tau, \tag{3.1}$$

where $u(\tau) = 1$ when $\tau > 0$ and zero otherwise. The basic reproduction number in the presence of the isolation policy is $R_q = \rho(K_q)$, where

$$(K_q)_{kl} = w_k S_0 \int_0^\infty p(\tau) C_{kl}(\tau) \{1 - q_{kl}(\tau)\}\, \mathrm{d}\tau. \tag{3.2}$$

For the special case where $q_{kl} = q_k$ (the isolation regime is independent of the location where infection occurred) and with contacts isolated before they become infectious, the expression for R_q is similar to that for R_0 in equation (2.5) but with K_k replaced by $(1 - q_k)K_k$. It must be considered that one or more of the q_k values could be negative, for example if withdrawing from contacts at work or in the community results in increased contact within the household or with healthcare workers.

To model the progress of an outbreak of SARS, equation (2.3) was solved numerically (see Appendix A), with $p(\tau)$ increasing linearly from 4 days post-exposure to a maximum at 7 days, then decreasing from 11 days to zero at 14 days (see Appendix A), contact rates constant and other parameters fixed so that $R_0 = 3.2$ (Chowell *et al.* 2003; Wallinga & Teunis 2004). Following introduction of the virus to the population an intervention policy based on the isolation of infected cases is initiated. The effects of varying two parameters, the time after the initiation of the epidemic that the control procedures are in place, and the delay from an individual showing symptoms to being effectively isolated, were explored. As an example, the result for the hypothetical situation where a policy is introduced on day 20 under which all infected individuals are isolated from contact 3 days after the onset of symptoms ($t_q = 20$, $q_k(\tau) = 1$ for $\tau > 7$, 0 otherwise) is shown in figure 1. This was just one of a range of scenarios examined, and has been chosen for presentation because it represents the clearest indication of the system's dynamics. This particular control intervention results in $R_q = 0.78$ and elimination of the infection over time.

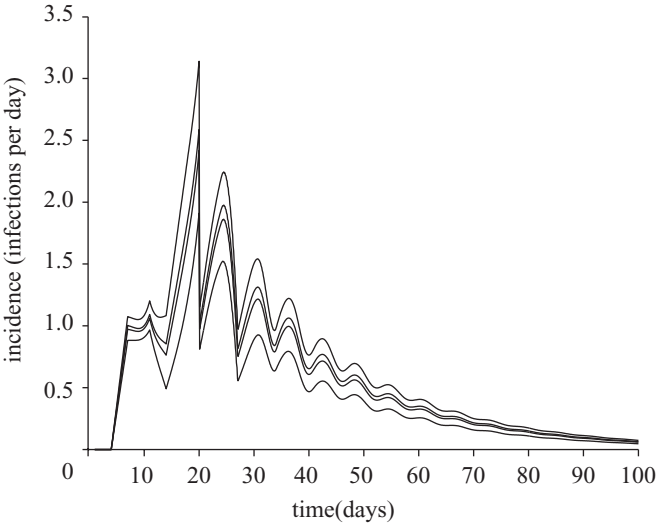

Figure 1. The hypothetical incidence of SARS following the introduction of a single case infected at day zero into an otherwise susceptible population. An isolation programme as described in § 3 is initiated at day 20. The curves are from bottom to top: i_1, $i_1 + i_2$, $i_1 + i_2 + i_3$ and $|i(t)|$.

4. DISCUSSION

We have presented a method by which the incidence of an exotic infection introduced to a susceptible population may be predicted. In common with all predictions, the results taken in isolation are unreliable. In fact, the methodology being based on a linear model is a Poisson process, and the outcome being the mean of that process has a variance of equal magnitude. Hence, large confidence limits about the mean will be observed and are easily estimated. The purpose of the model is, however, to assist in the design of control interventions rather than to provide accurate predictions. Given the limited availability of data it would be unwise to rely on predictions from any model of an exotic infection.

Our proposal enables an estimate of the potential time-course of an epidemic to be made based only on knowledge of the infection kernel, an estimate of R_0 or of the initial exponential growth rate, and an estimate of the initial distribution of incidence among different locations at infection. At the beginning of an epidemic these pieces of information may be readily obtained, even for previously unknown infections. The model has considerable advantages over the more traditional compartmental models, despite being less familiar. Models of this type were presented in the original publications of Kermack & McKendrick (1927). The infection kernel can be derived directly from the lengths of the pre-infectious and infectious periods, without the assumption that the durations of these periods are exponentially distributed. This also removes the feature of differential equation models that a small proportion of the population may progress through these periods in an unrealistically small amount of time, thus distorting the effect of timely intervention strategies. Specification of the kernel proceeds directly from the epidemiological data, and the basic reproduction number may be estimated from the initial growth rate of the epidemic. Fraser *et al.* (2004) have also shown that the initial time-course of an epidemic is determined by R_0 and the mean generation time, which is derived from the infection kernel.

As the model (equation (2.3)) is linear, it is only necessary to simulate the consequences of a single primary case; the result of multiple introductions is then the summation over the individual outcomes. A single primary case generates an incidence of secondary cases that has the same

profile as the infection kernel $p(\tau)C(\tau)$. This can be seen in the beginning of the hypothetical SARS epidemic shown in figure 1, but the second generation of infection rapidly obscures the trapezoidal shape of the first generation. Figure 1 shows the expected incidence of infection, the corresponding cumulative number of cases is a smooth function of time.

The model structure, where those that have been infected are categorized according to the location where infection occurred, allows more detail to be gained from the model. Whereas individuals in a population may spend time in more than one, or even in all, of the categories of household, workplace, wider community and healthcare facility, the infection is transmitted to them at only one location. Hence, the structure is of the type referred to as 'infection type at birth' (Diekmann & Heesterbeek 2000) or 'contact group' (Longini *et al.* 2004). Rather than tracking individuals moving between compartments and specifying transition rates, it is only necessary to include weights in the model to account for the different effective availability of susceptibles at each location. The categories may vary according to the infection under study: we included the healthcare facility to include workers and other patients because this type of transmission is important for both SARS (Lloyd-Smith *et al.* 2003) and smallpox (Gani & Leach 2001).

Concern that terrorist organizations may use an infectious agent as a weapon has led several authors to evaluate the potential for smallpox to spread in contemporary societies, and the most efficient strategy for vaccinating at-risk sections of the population (for a review see Ferguson *et al.* 2003). We have used a similar model to examine the scenario where a country or region may not be under threat of attack, but may wish to protect itself against importation of the infection. For smallpox, a vaccine is available, but stocks are limited and it is unlikely that mass vaccination of the population would be warranted. However, as the smallpox vaccine provides protection if administered within a few days after exposure to infection, a trace and vaccinate policy for contacts is feasible (Ferguson *et al.* 2003). Hence, the model was extended to examine the effectiveness of vaccinating some sections of the community in response to an outbreak, as well as combining vaccination with an isolation or quarantine policy. For details of the modifications required for this model see G. K. Aldis and M. G. Roberts (unpublished data).

The utility of the method described is in providing an assessment of the relative merits of alternative control strategies. For all interventions the policy specified by the authorities is only approximated in reality. For exotic infections, especially new ones such as SARS, even the biological parameters are poorly known. A framework has been provided within which a broad view of the merits of different interventions may be rapidly reached.

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APPENDIX A

(a) *The small epidemic solution*

If $R_0 < 1$, $S(t) \equiv S_0$ in equation (2.3) is approximated to obtain a linear equation, which may be solved in the Laplace transform domain. A single infected individual introduced to the population at time $t = 0$ results in the incidence of index cases taking the form $\alpha_k = \delta(t)$ for $k = 3$ and $\alpha_k = 0$ otherwise, where $\delta(t)$ is the Dirac delta function. Defining a matrix function of the transform variable s by

$$\left(\overline{K}(s)\right)_{kl} = \begin{cases} 0 & : \quad k = l = 1 \\ \kappa_k(s) = w_k S_0 \int_0^\infty p(t) c_k(t) e^{-st}\, \mathrm{d}t & : \quad \text{otherwise} \end{cases}$$

and I to be the identity matrix, we obtain

$$\begin{aligned} \bar{i}(s) &= \left(I - \overline{K}(s)\right)^{-1} \alpha \\ &= \frac{1}{1 - (1 + \kappa_1(s))(\kappa_2(s) + \kappa_3(s) + \kappa_4(s))} \\ &\quad \times \begin{pmatrix} \kappa_1(s) \\ (1 + \kappa_1(s))\kappa_2(s) \\ 1 - (1 + \kappa_1(s))(\kappa_2(s) + \kappa_4(s)) \\ (1 + \kappa_1(s))\kappa_4(s) \end{pmatrix} \end{aligned}$$

The number infected in each category over the course of the epidemic may be found by taking the limit of the equation as $s \to 0$. By definition $R_0 = \rho\left(\overline{K}(0)\right)$, hence the limit exists for $R_0 < 1$, and the total number infected in each category is given by equation (2.6).

(b) *The large epidemic solution*

The linear approximation is also valid for the initial stages of a large epidemic. At this time the growth of the epidemic will be approximately exponential, with the dominant exponent the solution of

$$(1 + \kappa_1(r))(\kappa_2(r) + \kappa_3(r) + \kappa_4(r)) = 1$$

and the proportions in each infection category equal to

$$(\theta_1, \theta_2, \theta_3, \theta_4) = \left(\frac{\kappa_1(r)}{1 + \kappa_1(r)}, \kappa_2(r), \kappa_3(r), \kappa_4(r)\right).$$

(c) *The numerical solution*

To obtain a numerical solution of equation (2.3) with $S(t) \equiv S_0$, and hence the epidemic curve, it is easiest to solve for successive infection generations. The incidence in the zeroth generation is $i_3^0(t) = \delta(t)$ and $i_k^0(t) = 0$ for $k \neq 3$. Substituting this in the integral in equation (2.3) we obtain the incidence in the first infection generation $i_k^1(t) = w_k S_0 p(t) C_{k3}(t)$, and the incidence in subsequent infection generations

$$i_k^{j+1}(t) = w_k S_0 \sum_{l=1}^{4} \int_0^\infty p(\tau) C_{kl}(\tau) i_l{}^j(t - \tau)\, \mathrm{d}\tau.$$

The epidemic curve is found by summing the result over all infection generations. If the equation is to be solved over the interval $[0, T]$, and $p(\tau) = 0$ for $\tau < \tau_a$, then the number of infection generations calculated should be greater than T/τ_a.

(d) *The SARS example*

Details of the functions and parameters for the example presented in the text now follow. We set

$$p(\tau) = \begin{cases} p_0 \frac{\tau - \tau_a}{\tau_b - \tau_a} & : \quad \tau \in (\tau_a, \tau_b) \\ p_0 & : \quad \tau \in (\tau_b, \tau_c) \\ p_0 \frac{\tau - \tau_c}{\tau_d - \tau_c} & : \quad \tau \in (\tau_c, \tau_d) \\ 0 & : \quad \text{otherwise} \end{cases}$$

with $(\tau_a, \tau_b, \tau_c, \tau_d) = (4, 7, 11, 14)$ days, and contact rates $c(\tau)$ constant. Defining the functions

$$\phi(\tau_a, \tau_b, s) = \int_{\tau_a}^{\tau_b} \mathrm{e}^{-s\tau}\, \mathrm{d}\tau = \frac{\mathrm{e}^{-s\tau_a} - \mathrm{e}^{-s\tau_b}}{s}$$

and

$$\psi(\tau_a, \tau_b, s) = \int_{\tau_a}^{\tau_b} \tau \mathrm{e}^{-s\tau}\, \mathrm{d}\tau = \frac{\mathrm{e}^{-s\tau_a} - \mathrm{e}^{-s\tau_b}}{s^2} + \frac{\tau_a \mathrm{e}^{-s\tau_a} - \tau_b \mathrm{e}^{-s\tau_b}}{s}$$

we have

$$\begin{aligned} \kappa_k(s) &= w_k S_0 \int_0^{\infty} p(t) c_k(t) \mathrm{e}^{-st}\, \mathrm{d}t \\ &= w_k S_0 p_0 \left(\frac{\psi(\tau_a, \tau_b, s) - \tau_a \phi(\tau_a, \tau_b, s)}{\tau_b - \tau_a} + \phi(\tau_b, \tau_c, s) \right. \\ &\quad \left. + \frac{\tau_d \phi(\tau_c, \tau_d, s) - \psi(\tau_c, \tau_d, s)}{\tau_d - \tau_c} \right) \end{aligned} \tag{3.2}$$

for $k = 1, \ldots 4$. Then using

$$\phi(\tau_a, \tau_b, 0) = \tau_b - \tau_a, \psi(\tau_a, \tau_b, 0) = \frac{\tau_b^2 - \tau_a^2}{2}$$

we have

$$\kappa_k(0) = w_k S_0 p_0 \frac{\tau_d + \tau_c - \tau_b - \tau_a}{2}.$$

For the initial part of the epidemic, it was assumed that incidence would be distributed in the proportions $(\theta_1, \theta_2, \theta_3, \theta_4) = (0.65, 0.15, 0.05, 0.15)$.

[1]*Note added in proof*. These figures were subsequently revised downwards to 8096 cases and 774 deaths. See http://www.who.int/csr/sars/country/table2004_04_21/en/en/.

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