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Some Simple Nosocomial Disease Transmission Models

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Abstract The *SARS* epidemic of 2002–2003 drew attention to nosocomial disease transmission as many of the disease cases were transmitted through hospital staff and visitors. Various types of model have been proposed to describe this, including metapopulation models. We formulate and analyze a simple compartmental model with heterogeneous mixing to describe nosocomial transmission and determine the reproduction number and final size relation.

Keywords Nosocomial transmission · Epidemic models · Reproduction number · Final size relation

Mathematics Subject Classification 92D30

1 Introduction

Nosocomial (in-hospital) disease transmission is an important problem. It has been estimated by the Centers for Disease Control that in the USA, there are 1,700,000 cases of nosocomial transmission per year and 99,000 deaths attributable to nosocomial infections. In many cases, these are infections acquired in the hospital, not the disease that caused the hospital stay. Two examples are nosocomial diarrhea caused by the bacteria C. difficile and MRSA (methycillin-resistant stapylococcus aureus). How-

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ever, there are also diseases such as pneumonia, tuberculosis and *Bordetella pertussis* (whooping cough) that are often transmitted from patient to patient. The SARS epidemic of 2002–2003 drew attention to nosocomial transmission because in the Greater Toronto Area and in Taiwan about 75 % of SARS cases were transmitted in-hospital and nosocomial transmission was present in all other locations affected by *SARS* as well, Chen et al. (2004), Hsieh et al. (2004), Lipsitch et al. (2003), Riley et al. (2003).

One of the beneficial contributions of the *SARS* epidemic of 2002–2003 was to draw attention to nosocomial disease transmission, and this led to the first dynamic model, a compartmental model formulated for the 2002–2003 *SARS* epidemic in the Greater Toronto area, Webb et al. (2004). Another more recent model viewing nosocomial transmission as a metapopulation model with travel to and from a hospital location is Hsieh et al. (2014), with particular attention to pertussis.

Nosocomial transmission can be viewed as an instance of heterogeneity in disease transmission in which health care workers may have many contacts with hospital patients. The most important measures to counteract nosocomial transmission are hygienic practices, beginning with frequent and careful handwashing by hospital personnel. As these are often neglected routinely, implementation of stricter routines can often produce a rapid decrease in nosocomial transmission. If a disease is infectious enough to spread without a large number of in-hospital case, then the addition of nosocomial transmission can make a disease outbreak considerably more serious.

The greater Toronto area saw about 350 SARS cases between February and June 2003, with 44 deaths. Almost all diagnosed cases were hospitalized, but it was not realized initially how readily SARS could be transmitted. As a result, there were many cases of in-hospital disease transmission. About 75 % of the cases in the Greater Toronto Area were transmitted in hospital. About 60 % of these were health care workers and 20 % were hospital visitors, while 20 % were hospital patients (with other medical problems). The rate of nosocomial disease cases of SARS was similar in other cities.

The response was to take more care with hospital procedures, and this produced an immediate reduction in nosocomial transmission—until a perception that the epidemic had passed and less care in hygienic measures resulted in a second wave of cases. Nosocomial transmission is very sensitive to care in hygienic procedures but in the Greater Toronto Area, SARS was not sufficiently infectious to spread without nosocomial transmission.

2 A First Model

In the simplest model for nosocomial infections, we include only people hospitalized with an infectious disease (T) and the population of health care workers and visitors in frequent contact with such people, a population of initial total size N, subdivided into susceptible (S), infectious (I), and removed (R). For the moment, we ignore the much larger general population in which this sub-population is embedded.

The model is

$$\begin{aligned} S' &= -S\left[a\frac{I}{N} + \rho\frac{T}{N}\right] \\ I' &= S\left[a\frac{I}{N} + \rho\frac{T}{N}\right] - (\alpha+\gamma)I \\ T' &= \gamma I - \eta T, \end{aligned} \tag{1}$$

with

$$S(0) + I(0) = N, T(0) \geq 0.$$

In this model, a is the rate of contacts between workers, ρ is the rate of contacts between workers and hospitalized patients, α is the recovery rate of infectious workers, γ is the rate of hospitalization of infectious workers, and η is the recovery rate of hospitalized patients.

It is reasonable to assume $\eta \geq \alpha$. In nosocomial infections, it is common to have $\rho \gg a$. The basic reproduction number, calculated by the next generation matrix method, van den Driessche and Watmough (2002) is

$$\mathscr{R}_0 = \frac{a}{\alpha+\gamma} + \frac{\rho\gamma}{\eta(\alpha+\gamma)}.$$

The analysis of the model (1) is similar to the analysis of the simple SIR epidemic model. From $(S+I)' = -(\alpha+\gamma)I < 0$, we deduce that $I \to 0$ as $t \to \infty$ and

$$N - S(\infty) = (\alpha+\gamma)\int_0^\infty I(t)\mathrm{d}t.$$

From $(S+I+T)' = -\alpha I - \eta T < 0$, we deduce that $T \to 0$ as $t \to \infty$ and

$$N - S(\infty) + T(0) = \alpha\int_0^\infty I(t)\mathrm{d}t + \eta\int_0^\infty T(t)\mathrm{d}t.$$

These two integral equalities yield

$$\eta\int_0^\infty T(t)\mathrm{d}t = \frac{\gamma}{\alpha+\gamma}[N - S(\infty)] + T(0).$$

Now, integration of the equation for S' in (1) gives

$$\begin{aligned} N\log\frac{S(0)}{S(\infty)} &= a\int_0^\infty I(t)\mathrm{d}t + \rho\int_0^\infty T(t)\mathrm{d}t \\ &= \frac{a\eta+\rho\gamma}{\eta(\alpha+\gamma)}[N - S(\infty)] + \frac{\rho}{\eta}T(0), \end{aligned}$$

and this gives the *final size relation*

$$\log \frac{S(0)}{S(\infty)} = \mathscr{R}_0 \left[1 - \frac{S(\infty}{N}\right] + \frac{\rho}{\eta N} T(0). \tag{2}$$

In order to separate disease cases caused by contact with hospital patients from other cases, we modify the model (1) by letting $I = I_1 + I_2$, where I_1 is the number of patients infected by hospitalized patients and I_2 is the number of patients infected by contact with hospital workers and visitors, so that

$$\begin{aligned} S' &= -S\left[a\frac{I_1 + I_2}{N} + \rho\frac{T}{N}\right] \\ I_1' &= S\rho\frac{T}{N} - (\alpha + \gamma)I_1 \\ I_2' &= S\left[a\frac{I_1 + I_2}{N}\right] - (\alpha + \gamma)I_2 \\ T' &= \gamma I - \eta T. \end{aligned} \tag{3}$$

The models (1) and (3) have the same reproduction numbers and final size relations, but simulations of the model (3) allow separation of disease cases caused by contact with hospital patients from other cases.

It is possible to have a small enough and ρ large enough that the disease spreads because of nosocomial infections caused by contacts with hospitalized cases but would not spread if ρ were decreased enough.

If we think of $\mathscr{R}_0$ as a function of the treatment rate γ,

$$\frac{\partial \mathscr{R}_0}{\partial \gamma} = \frac{\rho\alpha - \eta a}{\eta(\alpha + \gamma)^2},$$

and this is negative if and only if

$$\rho < \frac{a\eta}{\alpha}.$$

Thus, it is important to make $\rho < a\eta/\alpha$ because otherwise increasing the treatment rate would increase the basic reproduction number and the number of disease cases. However, this condition is likely not to be satisfied unless measures are taken to control ρ.

3 A Second Model

In order to control a nosocomial disease outbreak, it may be possible to isolate some infected members and treat them at home rather than hospitalizing all diagnosed infectives. A model corresponding to (1) that includes such isolation in a basic SIR model is

$$\begin{aligned} S' &= -S\left[a\frac{I}{N} + \rho\frac{T}{N}\right] \\ I' &= S\left[a\frac{I}{N} + \rho\frac{T}{N}\right] - (\alpha+\gamma)I \\ Q' &= (\gamma-u)I - \alpha Q \\ T' &= uI - \eta T, \end{aligned} \tag{4}$$

with

$$S(0) + I(0) = N, T(0) \geq 0.$$

Here, Q is the class of isolated members of the health care worker and visitor population, γ is the rate of identifying infectives to be either hospitalized or isolated, and u is the rate of treatment. It is assumed that isolated members have no contacts and do not transmit infection.

The basic reproduction number, calculated by the next generation matrix method, van den Driessche and Watmough (2002) is

$$\mathscr{R}_0 = \frac{a}{\alpha+\gamma} + \frac{\rho u}{\eta(\alpha+\gamma)}.$$

If we think of $\mathscr{R}_0$ as a function of the treatment rate u,

$$\frac{\partial \mathscr{R}_0}{\partial u} = \frac{\rho}{\eta(\alpha+\gamma)} > 0,$$

and, viewing $\mathscr{R}_0$ as a function of of ρ,

$$\frac{\partial \mathscr{R}_0}{\partial \rho} = \frac{u}{\eta(\alpha+\gamma)} > 0.$$

Thus, control of nosocomial infections requires a decrease in the contact rate with treated patients ρ or an increase in the quarantine rate and a corresponding decrease in the hospitalization rate u, or a combination of both measures.

If a is large enough that the disease would spread even without nosocomial infections, then a model needs to include the general population as well as the subpopulation of health care workers and hospital visitors.

4 A Full Population Model

We now consider a population consisting of hospitalized people and the subpopulation of health care workers and hospital visitors who may have contact with hospitalized people, and in addition a general population. This general population, initially of size N_G, is subdivided into S_G susceptible, I_G infectious, and R_G removed members. We assume that the general population members make a contacts in unit time with the

general population and the health care population, but do not have contact with the hospitalized population.

It is necessary to make some assumptions about the mixing between the general population and the health care worker and hospital visitor subpopulation. We assume the mixing between general and health care population members is given by the mixing matrix

$$\begin{bmatrix} p_{11} & p_{12} \\ p_{21} & p_{22} \end{bmatrix}.$$

Perhaps proportionate mixing for the general population and preferred mixing in the health care worker population is a reasonable assumption.

Our assumptions lead to the model

$$\begin{aligned} S_G' &= -aS_G\left[p_{11}\frac{I_G}{N_G} + p_{12}\frac{I}{N}\right] \\ I_G' &= aS_G\left[p_{11}\frac{I_G}{N_G} + p_{12}\frac{I}{N}\right] - (\alpha+\gamma)I_G \\ S' &= -aS\left[p_{21}\frac{I_G}{N_G} + p_{22}\frac{I}{N}\right] - S\rho\frac{T}{N} \\ I' &= aS\left[p_{21}\frac{I_G}{N_G} + p_{22}\frac{I}{N}\right] + S\rho\frac{T}{N} - (\alpha+\gamma)I \\ T' &= \gamma(I_G + I) - \eta T. \end{aligned} \tag{5}$$

We can show, in much the same way as for the simpler model (1), that as $t \to \infty$,

$$I \to 0, \quad I_G \to 0, \quad T \to 0.$$

In addition,

$$\begin{aligned} N_G - S_G(\infty) &= (\alpha+\gamma)\int_0^\infty I_G(t)\mathrm{d}t \\ N - S(\infty) &= (\alpha+\gamma)\int_0^\infty I(t)\mathrm{d}t \\ \eta\int_0^\infty T(t)\mathrm{d}t &= \gamma\left(\int_0^\infty I_G(t)\mathrm{d}t + \int_0^\infty I(t)\mathrm{d}t\right) + T(0) \end{aligned}$$

Integration of the equations for S_G' and S' in (5) gives

$$\begin{aligned} \log\frac{S_G(0)}{S_G(\infty)} &= \frac{ap_{11}}{N_G}\int_0^\infty I_G(t)\mathrm{d}t + \frac{ap_{12}}{N}\int_0^\infty I(t)\mathrm{d}t \\ \log\frac{S(0)}{S(\infty)} &= \frac{ap_{21}}{N_G}\int_0^\infty I_G(t)\mathrm{d}t + \frac{ap_{22}}{N}\int_0^\infty I(t)\mathrm{d}t + \frac{\rho}{N}\int_0^\infty T(t)\mathrm{d}t. \end{aligned}$$

Table 1 $\gamma = 0.3$

ρ	$\mathscr{R}_0$	Disease cases
0	0.36	8
0.1	0.58	13
0.2	0.80	27
0.3	1.02	125
0.4	1.24	376
0.5	1.45	561

Substitution of the expressions for $\int_0^\infty I_G(t)\mathrm{d}t$, $\int_0^\infty I(t)\mathrm{d}t$, $\int_0^\infty T(t)\mathrm{d}t$ gives the final size relations

$$\log\frac{S_G(0)}{S_G(\infty)} = \frac{ap_{11}}{\alpha+\gamma}\left[1-\frac{S_G(\infty)}{N_G}\right]+\frac{ap_{12}}{\alpha+\gamma}\left[1-\frac{S(\infty)}{N}\right]$$

$$\log\frac{S(0)}{S(\infty)} = \left[\frac{ap_{21}}{\alpha+\gamma}+\frac{\rho\gamma N_G}{\eta(\alpha+\gamma)N}\right]\left[1-\frac{S_G(\infty)}{N_G}\right] + \left[\frac{ap_{22}}{\alpha+\gamma}+\frac{\rho\gamma}{\eta(\alpha+\gamma)}\right]\left[1-\frac{S(\infty)}{N}\right]+\frac{\rho}{\eta N}T(0). \quad (6)$$

5 Dependence on Parameters

To illustrate how much the rate of nosocomial transmission can affect the severity of a disease outbreak, here are some simulations for the simple model (1), not based on any particular disease, using the parameter values

$$a = 0.2, \quad \alpha = \eta = 0.25$$

in a population of 1,000 members with an initial state

$$S(0) = 995, \quad I(0) = 4, \quad T(0) = 1,$$

for a range of values of ρ, first with $\gamma = 0.3$ and then with $\gamma = 0.4$. The values suggest that decreasing ρ is essential to control the spread of disease. Decreasing ρ enough to make $\mathscr{R}_0 < 1$ is particularly beneficial. Increasing the rate γ at which infectious members of the population are identified for hospitalization may also be useful, but only if nosocomial transmission can be controlled (Tables 1, 2).

6 *SARS* in the Greater Toronto Area

It is difficult to estimate parameter values for a model from data because the amount of nosocomial transmission is very sensitive to changes in procedures. One would have to break a nosocomial outbreak into stages, re-estimating parameter values to correspond

Table 2 $\gamma = 0.4$

ρ	$\mathscr{R}_0$	Disease cases
0	0.31	7
0.1	0.55	12
0.2	0.80	27
0.3	1.02	125
0.4	1.29	430
0.5	1.54	613

to each change in procedures. The simple model covering only the hospital worker and visitor population may be easier to use than the full population model, because of the lack of knowledge of the mixing pattern and the difficulty in estimating contact rates. An extension which may be more useful would be to separate the hospital population into workers and visitors, as workers are likely to have more contact with more patients and a correspondingly higher value of the associated ρ than visitors.

In Webb et al. (2004) nosocomial data for SARS in Toronto in 2003 was used to parametrize a model to fit the data for the period March 18–31 until an emergency was declared and protective measures were taken and to fit data for the next phase of the outbreak by including quarantine and decreasing the nosocomial contact rate.

We use an $SEIR$ analog of the model (3) with a rate κ of transfer from exposed to infective classes

$$\begin{aligned} S' &= -S\left[a\frac{I_1 + I_2}{N} + \rho\frac{T}{N}\right] \\ E_1' &= S\rho\frac{T}{N} - \kappa E_1 \\ E_2' &= Sa\frac{I_1 + I_2}{N} - \kappa E_2 \\ I_1' &= \kappa E_1 - (\alpha + \gamma) I_1 \\ I_2' &= \kappa E_2 - (\alpha + \gamma) I_2 \\ T' &= \gamma I - \eta T, \end{aligned} \tag{7}$$

with

$$N = 3000,\ a = 0.18,\ \alpha = \eta = 0.05,\ \gamma = 1/3,\ \kappa = 1/6,\ \rho = 0.32$$

and initial conditions

$$S(0) = 2985,\ E_1(0) = 0,\ E_2(0) = 12,\ I_1(0) = 0,\ I_2(0) = 1,\ T(0) = 1$$

for the first two weeks of the outbreak, we obtain

$$S(13) = 2931,\ E_1(13) = 5,\ E_2(13) = 18,\ I_1(13) = 2,\ I_2(13) = 6,\ T(13) = 6.$$

At this point, much stricter hygienic measures were imposed, and if we use these as initial values for the next 40 days with $\rho = 0.024$, we obtain

$$S(40) = 2886,\ E_1(40) = 4,\ E_2(40) = 3,\ I_1(40) = 2,\ I_2(40) = 2,\ T(40) = 24.$$

This choice of ρ gives 114 cases by day 53, similar to observations. Continuation with these parameter values leads to a final epidemic size of 352, close to observations. The choice of parameter values is dictated by the ultimate final size of the epidemic, which is very sensitive to the values of the contact rates a and ρ. The model is more useful for explaining observations than for predicting outcomes because of this sensitivity.

7 Conclusions

We have formulated a simple model for nosocomial transmission and suggested various ways in which it could be generalized, for example, by distinguishing between hospital workers and hospital visitors. If there is a danger that the infection will extend to the general public, it is necessary to include the general public in the model, but otherwise we suggest confining the model to that portion of the general population that has contact with the hospital. Because the size of an epidemic depends strongly on the rate of nosocomial transmission and because this rate may vary in time as control measures are changed, it is very difficult to make useful quantitative predictions. We should view the model more as a qualitative conceptual model than as a useful predictive model. The formulation of a predictive model depending on parameters that can be measured or estimated is an important challenge for the future.

The model (3) can be made more realistic by introducing separate compartments for hospital workers and visitors. The size of the hospital visitor compartment should depend on the number of hospitalized patients. Moreover, flows between compartments can be considered more realistically, although making the model more complex. The model (3) is especially meaningful for a disease in which many infected persons have mild symptoms but are contagious; treatment at home rather than in a hospital may decrease the number of nosocomial infections and thus soften the impact of the disease outbreak.

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