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Published online: 19 Jul 2016.

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ABSTRACT

We consider an epidemic model in which all disease transmission is through shedding of virus by infectives and acquisition by susceptibles, rather than by direct contact. This leads to an susceptible-infectious-virus-removed (SIVR) model for which we can determine the basic reproduction number and the final size relation. We extend the model to an age of infection model with virus shedding a function of the age of infection.

1. Introduction

In epidemic models, the transmission of infection is usually described as taking place by direct contact, often without specification of the meaning of contact. Some diseases may be spread in more than one manner. For example, cholera may be spread both directly by person-to-person contact and indirectly through a pathogen released by infectives through a medium such as contaminated water. A model has been developed by Tien and Earn [8] to describe a disease with both direct and indirect transmission, including staged progression to incorporate differential infectivity. A multi-stage model has been studied by Shuai and van den Driessche [7] to include multiple stages of infectious individuals and multiple infectious pathogen stages. Age of infection has been included in a cholera model in [3]. In recent years, there have been several outbreaks of Ebola, which can be spread directly or by contact during funeral ceremonies with bodies of Ebola victims [6, 9].

In fact, common airborne infections may also be spread indirectly through virus transferred via an intermediate object such as contaminated hands or inanimate objects in the vicinity of the susceptible such as counters and doorknobs [1, 4, 5]. Our purpose in this note is to describe an epidemic model in which it is assumed that all transmission is indirect through shedding of a pathogen by infectives, that is, we consider infections through aerosols to be indirect. We suggest that in some respects this may be a more appropriate way than the simple Kermack–McKendrick model to describe many disease outbreaks.

2. A simple epidemic model with indirect transmission

Consider an epidemic model with direct (person-to-person) and indirect (through a medium such as contaminated water). We describe this by adding a pathogen V shed by

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infectious individuals to a simple *SIR* model, and we assume that the infectivity of the pathogen is proportional to its concentration. A simple model with these aspects is given by the system

$$
\begin{aligned}
S' &= -\beta_d SI - \beta_i SV, \\
I' &= \beta_d SI + \beta_i SV - \alpha I, \\
R' &= \alpha I, \\
V' &= rI - \delta V
\end{aligned}
\tag{1}
$$

with initial conditions

$$
S(0) = S_0, \quad I(0) = I_0, \quad V(0) = V_0, \quad R(0) = 0,
$$

in a population of constant total size $N = S + I + R = S_0 + I_0$. In this model, r represents the rate at which an infectious individual sheds pathogen and δ represents the rate at which the pathogen loses infectivity, both assumed constant for the moment. This model, with the addition of demographic effects, is the starting point of Tien and Earn [8].

The analysis of the model (1) follows the approach to the analysis of the simple Kermack–McKendrick epidemic model [2, Chapter 9]. From the sum of the equations for S and I in Equation (1)

$$
(S + I)' = -\alpha I.
$$

This shows that $(S + I)$ decreases to a limit, and since $(S + I)$ is a smooth function it is possible to show that its derivative approaches zero, from which it can be deduced that

$$
I_\infty = \lim_{t \to \infty} I(t) = 0.
$$

Also, integration of this equation gives

$$
\alpha \int_0^\infty I(t)\, dt = N - \lim_{t \to \infty} S(t) = N - S_\infty,
\tag{2}
$$

implying that $\int_0^\infty I(t)\, dt < \infty$.

The basic reproduction number for Equation (1) is

$$
\mathcal{R}_0 = \frac{\beta_d N}{\alpha} + \frac{r \beta_i N}{\alpha \delta}.
$$

In this expression, the first term represents secondary infections caused directly by a single infective introduced into a wholly susceptible population, infecting $\beta_d N$ susceptible individuals per unit time for a time period $1/\alpha$, while the second term represents secondary infections caused indirectly through the pathogen since a single infective sheds a quantity r of pathogen per unit time for a time period $1/\alpha$ and this pathogen infects $\beta_i N$ susceptible individuals per unit time for a time period $1/\delta$.

We assume that the disease outbreak begins at time $t = 0$, so that $S(u) = N$ for $u < 0$ and there may be a discontinuity in $S(u)$ at $u = 0$ corresponding to an initial infective distribution.

Integration of the equation for S in Equation (1) gives

$$\log \frac{S_0}{S_\infty} = \beta_d \int_0^\infty I(t)\, dt + \beta_i \int_0^\infty V(t)\, dt, \tag{3}$$

and integration of the linear equation for V in Equation (1) gives

$$V(t) = V_0 e^{-\delta t} + r \int_0^t e^{-\delta(t-s)} I(s)\, ds. \tag{4}$$

Next, we must show that

$$\lim_{t\to\infty} \int_0^t e^{-\delta(t-s)} I(s)\, ds = \lim_{t\to\infty} \frac{\int_0^t e^{\delta s} I(s)\, ds}{e^{\delta t}} = 0.$$

If the integral in the numerator of this expression is bounded, this is clear; and if the integral is unbounded, l'Hôpital's rule shows that the limit is $\lim_{t\to\infty} I(t)/\delta = 0$. Then Equation (4) implies that

$$V_\infty = \lim_{t\to\infty} V(t) = 0.$$

But integration of Equation (4), interchange of the order of integration, and use of Equation (2) gives

$$\int_0^\infty V(t)\, dt = \frac{r}{\delta} \int_0^\infty I(t)\, dt, \tag{5}$$

implying that $\int_0^\infty V(t)\, dt < \infty$.

Substitution of Equation (5) into Equation (3) gives

$$\log \frac{S_0}{S_\infty} = \left[\beta_d + \beta_i \frac{r}{\delta}\right] \int_0^\infty I(t)\, dt + \beta_i \frac{V_0}{\delta} + \frac{V_0}{\delta},$$

and now substitution of Equation (3) gives the final size relation

$$\log \frac{S_0}{S_\infty} = N \frac{\beta_d \delta + \beta_i r}{\alpha \delta} \left[1 - \frac{S_\infty}{N}\right] + \beta_i \frac{V_0}{\delta}$$
$$= \mathcal{R}_0 \left[1 - \frac{S_\infty}{N}\right] + \beta_i \frac{V_0}{\delta}.$$

This implies $S_\infty > 0$. If the outbreak begins through direct contact with an infective, $V_0 = 0$, and then the final size relation takes the form

$$\log \frac{S_0}{S_\infty} = \mathcal{R}_0 \left[1 - \frac{S_\infty}{N}\right].$$

3. A virus shedding epidemic model

We now consider an epidemic model in which we assume that all transmission is indirect through a pathogen shed by infectives, and use an indirect transmission model of the form

Equation (1) with $\beta_d = 0$. Thus we begin with a simple model

$$
\begin{aligned}
S' &= -\beta SV, \\
I' &= \beta SV - \alpha I, \\
R' &= \alpha I, \\
V' &= rI - \delta V
\end{aligned}
\tag{6}
$$

with initial conditions

$$
S(0) = S_0, \quad I(0) = I_0, \quad V(0) = V_0, \quad R(0) = 0
$$

in a population of constant total size $N = S + I + R = S_0 + I_0$. Since the model (6) is just the model (1) with $\beta_d = 0, \beta_i = \beta$, we see that for the model (6)

$$
\mathcal{R}_0 = \frac{r\beta N}{\alpha \delta}.
\tag{7}
$$

The linearization of Equation (6) at the equilibrium $S = N, I = 0, V = 0$ is

$$
\begin{aligned}
u' &= -\beta Nw, \\
v' &= -\alpha v + \beta Nw, \\
w' &= rv - \delta w.
\end{aligned}
$$

The corresponding characteristic equation is

$$
(\lambda + \alpha)(\lambda + \delta) - r\beta N = 0.
\tag{8}
$$

Combination of Equation (7) and (8) gives

$$
\mathcal{R}_0 = \frac{(\lambda + \alpha)(\lambda + \delta)}{\alpha \delta}.
$$

It is clear that $\lambda > 0$ corresponds to $\mathcal{R}_0 > 1$. The value of λ is also the initial exponential growth rate of solutions of Equation (6) if $\mathcal{R}_0 > 1$. As the quantity λ may be measured experimentally, this gives a way to estimate the basic reproduction number if the disease recovery rate α and the virus decay rate δ are known.

We may give an age of infection version, defining $\varphi(t)$ as the total infectivity at time t,

$$
\begin{aligned}
S'(t) &= -\beta S(t)V(t)], \\
\varphi(t) &= \int_0^\infty [-S'(t - \tau)]A(\tau)\, d\tau, \\
V(t) &= \int_0^\infty r\varphi(t - \tau)\Gamma(\tau)\, d\tau.
\end{aligned}
\tag{9}
$$

In this model, $A(\tau)$ represents the mean infectivity of individuals at the age of infection τ, normally the product of the fraction of infectious individuals still infective at the age of infection τ and the relative infectivity at that infection age, and $\Gamma(\tau)$ represents the fraction of pathogen remaining τ time units after having been shed by an infectious individual.

The function Γ is monotone non-increasing with $\Gamma(0) = 1$, $\int_0^\infty \Gamma(\tau)\,d\tau < \infty$. The function A is not necessarily non-increasing, but we assume $\int_0^\infty A(\tau)\,d\tau < \infty$.

For the model (9), the basic reproduction number is

$$\mathcal{R}_0 = r\beta N \int_0^\infty A(\tau)\,d\tau \int_0^\infty \Gamma(\tau)\,d\tau, \tag{10}$$

representing secondary infections caused by an infectious individual indirectly through shedding of pathogen.

Integration of the equation for S in Equation (9) gives

$$\log\frac{S_0}{S_\infty} = \beta \int_0^\infty V(t)\,dt. \tag{11}$$

Routine calculations involving interchange of the order of integration and using $S(u) = N$ for $u < 0$ give

$$\int_0^\infty \varphi(t)\,dt = [N - S_\infty]\int_0^\infty A(\tau)\,d\tau,$$

$$\int_0^\infty V(t)\,dt = r\int_0^\infty \varphi(\tau)\,d\tau \int_0^\infty \Gamma(\tau)\,d\tau$$

$$= r[N - S_\infty]\int_0^\infty A(\tau)\,d\tau \int_0^\infty \Gamma(\tau)\,d\tau.$$

Then substitution into Equation (11) gives

$$\log\frac{S_0}{S_\infty} = \mathcal{R}_0\left[1 - \frac{S_\infty}{N}\right]. \tag{12}$$

It is also possible to obtain an invasion criterion. The linearization of the model (9) at the equilibrium $S = N, \varphi = 0, V = 0$ is

$$S'(t) = -N\beta V(t),$$

$$\varphi(t) = \int_0^\infty [-S'(t - \tau)]A(\tau)\,d\tau,$$

$$V(t) = \int_0^\infty r\varphi(t - \tau)\Gamma(\tau)\,d\tau.$$

The characteristic equation, the condition that the linearization has a solution

$$S(t) = S_0 e^{\lambda t}, \quad \varphi(t) = \varphi_0 e^{\lambda t}, \quad V(t) = V_0 e^{\lambda t}$$

is

$$r\beta N \int_0^\infty e^{-\lambda\tau}A(\tau)\,d\tau \int_0^\infty e^{-\lambda\tau}\Gamma(\tau)\,d\tau = 1.$$

It is easy to see from Equation (10) that $\lambda > 0$ is equivalent to $\mathcal{R}_0 > 1$.

However, to describe a more realistic epidemic model, it would be necessary to allow the pathogen shedding rate r to depend on the infection age of the shedding individual. In particular, the shedding rate should decrease to zero eventually. This requires a more complicated model.

4. Variable pathogen shedding rates

We let $Q(s)$ be the virus shedding rate for an infective with infection age s and $\Gamma(u)$ be the fraction of infectivity remaining for virus that has been shed u time units earlier. It is reasonable to assume that the infectivity as a function of age of infection is the effective virus at time t shed by an infective with infection age τ at time t, which is $Q(\tau)$. This suggests $A(\tau) = Q(\tau)$, and we make this change in the equation for φ in Equation (9). We retain the equation for S from Equation (9), but we need to develop a more general equation for V.

Let $i(t, s)$ be the number of individuals with infection age s at time t, possibly including individuals with zero infectivity who are no longer infective. Then

$$i(t, s) = i(t - s, 0) = -S'(t - s).$$

We consider infectives infected at time $t-u$, $0 \leq u \leq \infty$ with infection age v, $0 \leq v \leq u$ and their virus contribution at time t. At time $t - u + v$ there are

$$i(t - u + v, v) = i(t - u, 0) = -S'(t - u).$$

Their rate of shedding is $Q(v)$ and the remaining virus at time t is $Q(v)\Gamma(u - v)$. Thus

$$V(t) = \int_0^\infty \int_0^u [-S'(t - u)]Q(v)\Gamma(u - v) \, dv \, du$$

$$= \int_0^\infty \int_v^\infty [-S'(t - u)]\Gamma(u - v) \, du Q(v) \, dv$$

$$= \int_0^\infty \int_0^\infty [-S'(t - z - v)]\Gamma(z) \, dz Q(v) \, dv.$$

Our general model is now

$$S'(t) = -\beta S(t)V(t)],$$

$$\varphi(t) = \int_0^\infty [-S'(t - \tau)]Q(\tau) \, d\tau, \tag{13}$$

$$V(t) = \int_0^\infty \left[\int_0^\infty [-S'(t - z - v)]\Gamma(z) \, dz \right] Q(v) \, dv.$$

We may write the model (13) as a single equation for S, substituting the equation for V into the equation for S to give

$$S'(t) = -\beta S(t) \int_0^\infty \left[\int_0^\infty [-S'(t - z - v)]\Gamma(z) \, dz \right] Q(v) \, dv.$$

In order to determine the basic reproduction number for Equation (13), we begin with a new infective and calculate the virus shed over the duration of the infection. The effective

virus at time t is

$$\int_0^t Q(s)\Gamma(t-s)\,\mathrm{d}s = \int_0^t Q(t-u)\Gamma(u)\,\mathrm{d}u,$$

and the total infectivity over the duration of the infection is

$$\int_0^\infty \int_0^t Q(t-u)\Gamma(u)\,\mathrm{d}u\,\mathrm{d}t = \int_0^\infty \left[\int_u^\infty Q(t-u)\,\mathrm{d}t\right]\Gamma(u)\,\mathrm{d}u$$

$$= \int_0^\infty \left[\int_0^\infty Q(v)\,\mathrm{d}v\right]\Gamma(u)\,\mathrm{d}u$$

$$= \int_0^\infty Q(v)\,\mathrm{d}v \int_0^\infty \Gamma(u)\,\mathrm{d}u.$$

Therefore, the basic reproduction number is

$$\mathcal{R}_0 = \beta N \int_0^\infty Q(v)\,\mathrm{d}v \int_0^\infty \Gamma(u)\,\mathrm{d}u. \tag{14}$$

The final size relation is obtained by integrating the equation for S in Equation (13),

$$\log \frac{S_0}{S_\infty} = \beta \int_0^\infty V(t)\,\mathrm{d}t.$$

But

$$\int_0^\infty V(t)\,\mathrm{d}t = \int_0^\infty \int_0^\infty \left[\int_0^\infty [-S'(t-z-v)]\Gamma(z)\,\mathrm{d}z\right] Q(v)\,\mathrm{d}v\,\mathrm{d}t.$$

We interchange the order of integration, integrating first with respect to t, obtaining

$$\int_0^\infty V(t)\,\mathrm{d}t = \int_0^\infty \int_0^\infty \left[\int_0^\infty [-S'(t-z-v)]\,\mathrm{d}t\right]\Gamma(z)\,\mathrm{d}z Q(v)\,\mathrm{d}v$$

$$= \int_0^\infty \int_0^\infty [S(-z-v) - S_\infty]\Gamma(z)\,\mathrm{d}z]Q(v)\,\mathrm{d}v$$

$$= \int_0^\infty \int_0^\infty [N - S_\infty]\Gamma(z)\,\mathrm{d}z Q(v)\,\mathrm{d}v \tag{15}$$

$$= [N - S_\infty]\int_0^\infty \Gamma(z)\,\mathrm{d}z \int_0^\infty Q(v)\,\mathrm{d}v.$$

Thus, using Equation (15),

$$\log \frac{S_0}{S_\infty} = \mathcal{R}_0 \left[1 - \frac{S_\infty}{N}\right]. \tag{16}$$

The linearization of Equation (13) at the equilibrium $S = N, \varphi = 0, V = 0$ is

$$S'(t) = -\beta N \int_0^\infty \left[\int_0^\infty [-S'(t-z-v)]\Gamma(z)\,\mathrm{d}z\right] Q(v)\,\mathrm{d}v.$$

The characteristic equation is the condition that the linearization has a solution $S(t) = S_0 e^{\lambda t}$, which is

$$\beta N \int_0^\infty e^{-\lambda v} Q(v) \, dv \int_0^\infty e^{-\lambda u} \Gamma(u) \, du = 1. \tag{17}$$

If $\lambda > 0$, the disease-free equilibrium is unstable, corresponding to an epidemic, while if $\lambda < 0$ the disease-free equilibrium is asymptotically stable and there is no epidemic. Combining Equations (14) and (17), we have

$$\mathcal{R}_0 = \frac{\int_0^\infty Q(v) \, dv \int_0^\infty \Gamma(u) \, du}{\int_0^\infty e^{-\lambda v} Q(v) \, dv \int_0^\infty e^{-\lambda u} \Gamma(u) \, du}.$$

The special case

$$A(s) = e^{-\alpha s}, Q(s) = r, \Gamma(u) = e^{-\delta u}$$

of Equation (13) with $I = \varphi$, but without the replacement of $A(s)$ by $Q(s)$, is the simple model (6). To see this, we first note that

$$I(t) = \int_0^\infty [-S'(t - \tau)] e^{-\alpha \tau} \, d\tau = e^{-\alpha t} \int_- \infty^t [-s'(u)] e^{\alpha u} \, du,$$

and thus

$$I'(t) = -\alpha I + [-S'(t)] = -\alpha I + \beta SI.$$

Next, we observe that

$$\begin{aligned} V(t) &= r \int_0^\infty \int_v^\infty [-S'(t - u)] e^{-\delta(u-v)} \, du \, dv \\ &= r \int_0^\infty \int_{-\infty}^{t-v} [-S'(z)] e^{-\delta(t-z-v)} \, dz \, dv \\ &= re^{-\delta t} \int_0^\infty \int_{-\infty}^{t-v} [-S'(z)] e^{\delta(z+v)} \, dz \, dv \\ &= re^{-\delta t} \int_0^\infty \int_{-\infty}^{t-v} [-S'(z)] e^{\delta z} \, dz e^{\delta v} \, dv. \end{aligned}$$

Then,

$$V'(t) = -\delta V + re^{-\delta t} \int_0^\infty [-S'(t - v)] e^{\delta(t-v)} e^{\delta v} \, dv = -\delta V + rI.$$

Thus Equation (13) reduces to Equation (6) in this special case.

5. Conclusions

We have described an epidemic model in which transmission of infection takes place through shedding and acquisition of a virus rather than by an unspecified kind of contact. The model is slightly more complicated than the simple contact model but has the same qualitative properties. It requires knowledge of the infectivity as a function of infection age

or the effective infectivity of shed virus as a function of the age of infection and the rate at which shed virus loses strength. It may be possible to estimate both of these quantities. We believe that this approach is more realistic than the classical approach, and while the mathematical analysis is more complicated the results are similar.

We have equated the effective virus and the infectivity of infectives. For diseases with two different modes of transmission, this is not valid as there are two independent modes of transmission. It should be possible to extend the derivation here of the age of infection model to this situation. In order to estimate the basic reproduction number using the initial exponential growth rate, it would be necessary to have two pieces of information about the initial exponential growth rate to estimate the two contact rates. If it is possible to estimate the initial growth rate of direct and indirect transmissions separately, this information may lead to an estimate of the two contact rates.

We have considered only the case of homogeneous mixing in the population, but it should be straightforward to extend to the case of heterogeneous mixing.

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

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