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Modeling the trade-off between transmissibility and contact in infectious disease dynamics

Chiu-Ju Lin*, Kristen A. Deger, Joseph H. Tien

Department of Mathematics, The Ohio State University, Columbus, OH 43210, USA

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ABSTRACT

Symptom severity affects disease transmission both by impacting contact rates, as well as by influencing the probability of transmission given contact. This involves a trade-off between these two factors, as increased symptom severity will tend to decrease contact rates, but increase the probability of transmission given contact (as pathogen shedding rates increase with symptom severity). This paper explores this trade-off between contact and transmission given contact, using a simple compartmental susceptible-infected-recovered type model. Under mild assumptions on how contact and transmission probability vary with symptom severity, we give sufficient, biologically intuitive criteria for when the basic reproduction number varies non-monotonically with symptom severity. Multiple critical points are possible. We give a complete characterization of the region in parameter space where multiple critical points are located in the special case where contact rate decreases exponentially with symptom severity. We consider a multi-strain version of the model with complete cross-immunity and no super-infection. In this model, we prove that the strain with highest basic reproduction number drives the other strains to extinction. This has both evolutionary and epidemiological implications, including the possibility of an intervention paradoxically resulting in increased infection prevalence.

1. Introduction

Many pathogens exhibit a wide range of symptom severity following infection, ranging from asymptomatic to severe. How does this variation affect disease dynamics? Symptom severity is often correlated with pathogen loads and shedding rates [2,13,15,19,22,25,30,31] and thus to the probability of disease transmission given contact with a susceptible individual. On the other hand, disease symptoms will also influence contact rates of infected individuals, for example due to illness affecting an individual's ability to attend school, go to work, travel, or have sexual encounters. There is thus a trade-off between transmissibility and contact, similar to the classic trade-off between transmission and host mortality in the study of pathogen virulence evolution [2,6,7,14,15,20]. Understanding this trade-off has both evolutionary and epidemiological implications, for example regarding strain competition and pathogen virulence, and for evaluating control strategies such as vaccination and chemotherapy.

The purpose of this paper is to examine these questions using a simple mathematical model, with the following basic assumptions: (i) infection can result in a range of symptoms, from mild to severe; (ii) the probability of transmission given contact is a monotone increasing function of symptom severity; (iii) contact rate is a monotone decreasing function with respect to symptom severity. To biologically motivate these assumptions, note that variation in symptoms is observed across taxa and disease transmission routes. Specific examples include El Tor cholera, with 75% asymptomatic, 23% mild or moderate, and 2% severe infection [19]; pertussis, where age and immunization status influence symptom severity [21]; influenza, where neuraminidase inhibitors can reduce symptom severity and duration [23]; herpes simplex virus (HSV), with frequent subclinical viral shedding [31], and many more. For (ii), pathogen shedding rates are often correlated with symptoms, both in magnitude (e.g. 10^3 vibrios per gram of stool for asymptomatic cholera patients [25], versus 10^7–10^8 vibrios per gram of stool for severely symptomatic individuals [19]) and frequency (e.g. symptomatic individuals with HSV experienced more frequent shedding than asymptomatic individuals [31]). Shedding rates relate to transmission probabilities through dose-response curves, which are typically monotone functions of dose [18]. Specifics on how variation in shedding rates vary with symptom severity, and how this translates into corresponding variation in transmission probability, will depend upon the shape of the dose-response curve for the pathogen in question. For example, asymptomatic

* Corresponding author. Tel.: +1 6148861832.
E-mail address: cjlin886@gmail.com, lin.2142@osu.edu (C.-J. Lin).

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transmission of norovirus is believed widespread, due to comparable shedding rates of asymptomatic and symptomatic individuals, together with a very low infectious dose [26]. Regarding (iii), certain types of contact clearly decrease with symptom severity, for example illness-induced absences from school or the workplace. Recent empirical studies examining how illness affects contact patterns include Chen et al. [9] and van Kerckhove et al. [33].

The model we consider is a simple extension of the classical susceptible-infected-recovered (SIR) ordinary differential equation model. The infected compartment is divided into two compartments, corresponding to infected individuals with mild (I_m) or severe (I_s) disease symptoms. This model has been considered by others, for example by Brauer et al. [5] and Vivas-Barber et al. [35] in the context of influenza dynamics. What is new here is our consideration of the trade-off between contact and transmissibility in this setting. Specifically, we use this model to examine under what conditions this trade-off selects for intermediate levels of pathogen virulence, and what are the corresponding evolutionary and epidemiological implications. In particular, we find conditions for which $\mathcal{R}_0$ exhibits local maxima at intermediate symptom severity, and prove a competitive exclusion principle showing that for this model the pathogen strain with highest basic reproduction number will drive the other strains to extinction.

The remainder of this paper is organized as follows. Section 2 presents the basic model together with analysis of the equations, including computation of $\mathcal{R}_0$ and proving global stability for the system. In Section 3, we explore the effects of the trade-off between contact and transmissibility on $\mathcal{R}_0$ in detail. In particular, we give conditions for when $\mathcal{R}_0$ varies non-monotonically with symptom severity, and discuss the number of critical points that can arise. Section 4 extends the model to include multiple pathogen strains. We prove that the highest $\mathcal{R}_0$ strain will drive the other strains to extinction. We also present an adaptive dynamics treatment of virulence evolution, together with simulations of evolutionary dynamics. The paper concludes with a discussion in Section 5.

2. Model

We consider a simple extension of the basic susceptible-infected-recovered (SIR) framework by differentiating between mild (I_m) and severe (I_s) infection. A fraction f of infected individuals experience mild symptoms and enter the I_m compartment following infection, with the remaining fraction $1-f$ entering the I_s class. Individuals experiencing mild versus severe symptoms have potentially different infectious periods ($1/\gamma_m$ and $1/\gamma_s$, respectively), and transmission parameters β_m, β_s. A flow diagram of the model is given in Fig. 1. This model has been introduced previously in the literature, for example by Vivas-Barber et al. [35]. What is novel here is consideration of how symptom severity affects the transmission parameters β_m, β_s, through the trade-off between contact and transmission given contact.

The dynamics comply with the following equations:

$$\begin{aligned}
\dot{S} &= d - dS - S(\beta_m I_m + \beta_s I_s),\\
\dot{I}_m &= fS(\beta_m I_m + \beta_s I_s) - (\gamma_m + d)I_m,\\
\dot{I}_s &= (1-f)S(\beta_m I_m + \beta_s I_s) - (\gamma_s + d)I_s,
\end{aligned} \tag{1}$$

where $\dot{} = \frac{d}{dt}$. Here we assume the population has a constant birth rate and natural death rate d. Because the equations of S, I_m, I_s are independent of the variable R, we only focus on them and ignore the dynamics of R. We further assume the total population size N is constant, let $N = S + I_m + I_s + R = 1$ after scaling. Thus all variables are fractions of the population. We consider the initial condition $(S, I_m, I_s)(0) \in \Omega$, where

$$\Omega := \{(S, I_m, I_s) \in [0,1]^3 : \quad S > 0, S + I_m + I_s \le 1\}.$$

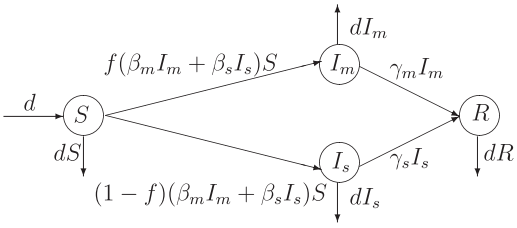

Fig. 1. Flow diagram of the SI_mI_sR model (1).

The solutions of (1) with initial condition in Ω are positive and bounded, i.e., the system is well defined.

To understand how the contact-transmission trade-off affects the parameters β_m, β_s in (1), we will use the probability p of transmission given contact as a surrogate for symptom severity, allowing expression of β as a function of p. Then the force of infection term is $c(p)pI$, where the contact rate $c(p)$ depends upon the probability of transmission. The transmission parameters β can thus be written as the product of two factors, the contact rate c, times the probability p of transmission given contact with a susceptible individual.

To incorporate the trade-off between contact and transmission given contact, we assume that p is a monotone increasing function of symptom severity, and c is monotone decreasing with symptom severity. Let p denote the transmission probability for individuals in I_s, and let σp denote the transmission probability for individuals in I_m, where $0 \le \sigma \le 1$. The resulting transmission parameters for the mild and severe symptom classes are then:

$$\begin{aligned}
\beta_m &= c(\sigma p)\sigma p,\\
\beta_s &= c(p)p.
\end{aligned} \tag{2}$$

The trade-off between transmissibility and contact affects the transmission parameters β_m, β_s (cf. (2)). To understand the corresponding effect on the dynamics of system (1), we will focus on how the trade-off affects the basic reproduction number $\mathcal{R}_0$. In fact we will see that $\mathcal{R}_0$ determines both the long term dynamics of system (1) (Theorem 1), as well as the outcome of multi-strain competition (Theorem 2). We first establish some preliminary facts about system (1). Let $E_0 = (1, 0, 0)$ denote the disease-free equilibrium (DFE). Using the next generation matrix approach to compute $\mathcal{R}_0$ [11,32] gives:

$$\mathcal{R}_0 = f\frac{\beta_m}{\gamma_m + d} + (1-f)\frac{\beta_s}{\gamma_s + d} = f\mathcal{R}_{01} + (1-f)\mathcal{R}_{00}, \tag{3}$$

where $\mathcal{R}_{01}$ and $\mathcal{R}_{00}$ are the basic reproduction numbers corresponding to $f = 1$ and $f = 0$, respectively. Hence $\mathcal{R}_0$ is a linear combination of $\mathcal{R}_{01}$ and $\mathcal{R}_{00}$. When $\mathcal{R}_0 > 1$, there exists an endemic equilibrium (EE) $E^* = (S^*, I_m^*, I_s^*)$ with

$$\begin{aligned}
S^* &= \frac{1}{\mathcal{R}_0}, \quad I_m^* = \frac{f}{\gamma_m + d}d\left(1 - \frac{1}{\mathcal{R}_0}\right),\\
I_s^* &= \frac{1-f}{\gamma_s + d}d\left(1 - \frac{1}{\mathcal{R}_0}\right).
\end{aligned} \tag{4}$$

From the following theorem we know that the global behavior of (1) is determined by the basic reproduction number $\mathcal{R}_0$.

Theorem 1. *Suppose $d > 0, \beta_m, \beta_s \ge 0, \gamma_m, \gamma_s > 0$ and $f \in [0, 1]$. The dynamics of (1) with initial condition in Ω is one of the following scenarios:*

(a) If $\mathcal{R}_0 \le 1$, then the disease free equilibrium E_0 is globally stable.
(b) If $\mathcal{R}_0 > 1$, then the endemic equilibrium E^* is globally stable.