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Modeling inoculum dose dependent patterns of acute virus infections

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AUTHOR-HIGHLIGHTS

- Acute viral infections show consistent patterns of inoculum dose dependence.
- Most existing models fail to reproduce the observed inoculum dependent patterns.
- Models including innate and adaptive immunity can reproduce the observed patterns.

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ABSTRACT

Inoculum dose, i.e. the number of pathogens at the beginning of an infection, often affects key aspects of pathogen and immune response dynamics. These in turn determine clinically relevant outcomes, such as morbidity and mortality. Despite the general recognition that inoculum dose is an important component of infection outcomes, we currently do not understand its impact in much detail. This study is intended to start filling this knowledge gap by analyzing inoculum dependent patterns of viral load dynamics in acute infections. Using experimental data for adenovirus and infectious bronchitis virus infections as examples, we demonstrate inoculum dose dependent patterns of virus dynamics. We analyze the data with the help of mathematical models to investigate what mechanisms can reproduce the patterns observed in experimental data. We find that models including components of both the innate and adaptive immune response are needed to reproduce the patterns found in the data. We further analyze which types of innate or adaptive immune response models agree with observed data. One interesting finding is that only models for the adaptive immune response that contain growth terms partially independent of viral load can properly reproduce observed patterns. This agrees with the idea that an antigen-independent, programmed response is part of the adaptive response. Our analysis provides useful insights into the types of model structures that are required to properly reproduce observed virus dynamics for varying inoculum doses. We suggest that such models should be taken as basis for future models of acute viral infections.

1. Introduction

Inoculum dose, i.e. the number of pathogens at the beginning of an infection, can affect key aspects of pathogen dynamics following infection, such as the initial rate of pathogen growth, peak pathogen levels, time at which pathogen peak is reached, and total pathogen load (Prince et al., 1993; Ottolini et al., 1996; Liu et al., 2009; Ginsberg and Horsfall, 1952; Callison et al., 2006; Powell et al., 2006; Hughes et al., 2002; Legge and Braciale, 2005). Pathogen dynamics in turn affects the ensuing immune response (Powell et al., 2006; Legge and Braciale, 2005; Marois et al., 2012; Hatta et al., 2010). Pathogen dynamics and immune response together determine clinically relevant outcomes, such as morbidity and mortality (Goldberg et al., 1954; La Gruta et al., 2007; Gowthaman et al., 2010; Leggett et al., 2012; Moskophidis et al., 1995). Maybe surprisingly, despite the general recognition that inoculum dose is an important component of infection outcomes, we currently do not understand in any detail how and why changes in inoculum dose impact infection outcomes. While concepts such as the 50% infectious or lethal dose – which acknowledge the importance of inoculum – are commonly used (Blaser and Newman, 1982; Schmid-Hempel and Frank, 2007; Boon et al., 2009), little effort has been made to understand the impact of inoculum dose on infection outcomes in a systematic manner.

Mathematical models are well suited for the detailed analysis of infection dynamics and have contributed much to our understanding (e.g. Nowak and May, 2000; Perelson, 2002; Asquith and

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Bangham, 2003; Antia et al., 2005). Previous models have been able to describe many important features of the dynamics of pathogens and the host response upon infection. At the same time, as we continue to better understand the within-host dynamics of many infectious diseases and obtain better data, model limitations are being realized. An ongoing process of model refinement ensures their ability to properly reproduce the observed data. One pattern often seen in a variety of different infections is a dependence of the pathogen and immune response dynamics on the inoculum dose. While a few recent models considered the role of the inoculum (Howey et al., 2009; Steinmeyer et al., 2010), a systematic understanding of the types of models needed to reproduce the inoculum dose dependent patterns that are observed in pathogen and immune response dynamics is lacking. This study is intended to fill this gap by analyzing existing models with regard to their ability to reproduce inoculum dependent patterns of viral load dynamics. We find that models including components of both the innate and adaptive immune response are needed to describe the patterns found in the data. We further show that only some of the ways in which the innate or adaptive immune response have been modeled in the past agree with observed data. Our analysis provides useful insights into the types of model structures that are required to properly reproduce observed virus dynamics for varying inoculum doses.

2. Methods

2.1. Basic infection dynamics model

We consider a range of different models to describe the dynamics of an acute viral infection. We describe the different model variants in Section 3. All of these model variations are extensions of the basic model for an acute virus infection (Beauchemin and Handel, 2011; Smith and Perelson, 2011), which is given by the following three differential equations:

$$\dot{U} = -bUV$$
$$\dot{I} = bUV - dI$$
$$\dot{V} = pI - cV \qquad \text{(B1)}$$

The model tracks the number of susceptible target cells, U, infected cells, I, and the number of infectious, free virions, V. The infection process is modeled through a mass-action term, bUV. Infected cells produce virus at rate p and die at rate d. Free virus can go on to infect new cells or is cleared from the system at rate c. For more details on this model and similar ones, see e.g. Beauchemin and Handel (2011) and Smith and Perelson (2011).

2.2. Estimating characteristic features of viral load dynamics

While the basic acute virus infection model given by (B1) can capture the observed viral load patterns described below, the model contains too many parameters and unknown initial conditions to allow estimation of all of them (Smith et al., 2010; Beauchemin and Handel, 2011). To prevent overfitting and to obtain more robust results, we therefore make use of a simpler, four parameter phenomenological equation, which was previously shown to fit viral load data from acute infections well (Holder and Beauchemin, 2011). The equation is given by

$$V(t) = \frac{2p_1}{\exp(-p_2(t-p_3)) + \exp(-p_4(t-p_3))} \qquad \text{(P1)}$$

where the p_i are the parameters that are being fit. We fit by minimizing the least squares difference between the logarithm of model and data. We then use the expression $V(t)$ for the viral load to determine the characteristic features as described in Section 3.

2.3. Model implementation

All models were implemented in R (R Development Core Team, 2012). The computer code is available from the authors on request.

3. Results

3.1. Characterization of inoculum dose dependent viral load patterns

Inoculum dose is known to impact the dynamics and outcome of many infectious diseases. For the present study, we focus on pathogen load during acute viral infections. As illustrative examples, we consider two previously published datasets; for adenovirus type 5 (ADV) infection of cotton rats (Prince et al., 1993) and infectious bronchitis virus (IBV) infection in chicken (Callison et al., 2006). Figs. 1 and 2 show viral load data for 3 different inoculum doses for the two infections. Similar inoculum dose dependent pathogen dynamics can be found throughout the literature for other host–pathogen systems (see e.g. Liu et al., 2009; Ottolini

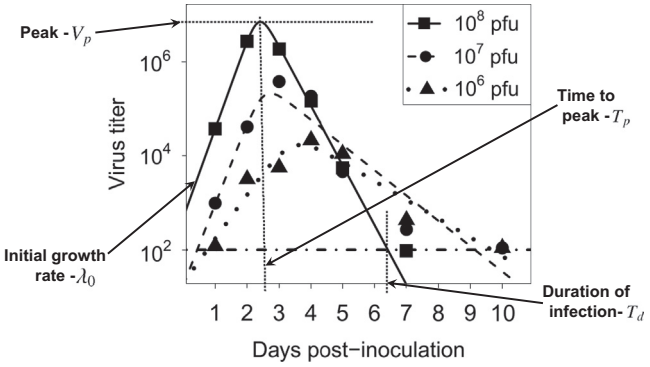

Fig. 1. Adenovirus titer for different inoculum doses. Symbols show experimentally determined viral load data for different inoculum doses for Adenovirus type 5 (ADV) infections of cotton rats. For details see Prince et al. (1993). The lines are obtained by fitting Eq. (P1) to the data. The dash-dotted horizontal line shows the limit of detection.

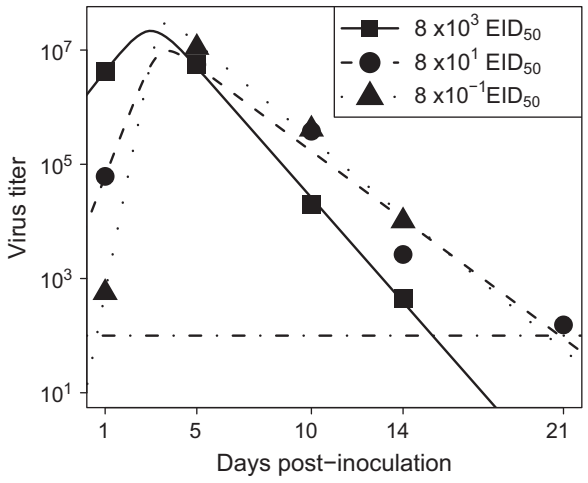

Fig. 2. Infectious bronchitis virus titer for different inoculum doses. Symbols show experimentally determined viral load data for different inoculum doses for infectious bronchitis virus (IBV) infections of chickens. For details see Callison et al. (2006). The lines are obtained by fitting Eq. (P1) to the data. The dash-dotted horizontal line shows the limit of detection.