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A two-phase within-host model for immune response and its application to serological profiles of pertussis

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ABSTRACT

We present a simple phenomenological within-host model describing both the interaction between a pathogen and the immune system and the waning of immunity after clearing of the pathogen. We implement the model into a Bayesian hierarchical framework to estimate its parameters for pertussis using Markov chain Monte Carlo methods. We show that the model captures some essential features of the kinetics of titers of IgG against pertussis toxin. We identify a threshold antibody level that separates a large increase in antibody level upon infection from a small increase and accordingly might be interpreted as a threshold separating clinical from subclinical infections. We contrast predictions of the model with observations reported in the literature and based on independent data and find a remarkable correspondence.

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Introduction

Increasingly it has been realized that for many infectious diseases immunity (whether deriving from vaccination or from infection) is not lifelong as the traditional picture suggests. Pertussis serves as a prime example, but there are many other infectious diseases for which waning of immunity has been observed and accordingly the success of large scale vaccination programs may be threatened.

In order to incorporate the effects of temporary immunity in population level (*p*-level) transmission models that can be used in a public health context, we need individual level (*i*-level) models of the waning of immunity. With the immune system being as complex as it is, it is not an easy task to formulate such *i*-level models. Moreover, a detailed understanding of the processes underlying the loss of immunity at the long timescale is as yet missing. Finally, to be useful as an ingredient in a *p*-level transmission model, the *i*-level submodel needs to be tractable, preferably by pencil and paper analysis (to allow for an analytical formulation of the *p*-model). While a number of modeling studies have investigated the impact of waning immunity on the epidemiology of infectious diseases (Glass and Grenfell, 2003, 2004; Gomes et al., 2004; Reluga et al., 2008; Alexander et al., 2006; Rouderfer et al., 1994), there are fewer studies that model the within-host dynamics of the rise and decay of immunity (Heffernan and Keeling, 2009).

In work in progress (de Graaf et al., in preparation) we develop a model that aims to describe the *p*-level heterogeneity in immune status resulting from the interplay of (re)infection and waning immunity. Motivated by the tractability issue mentioned above, we developed a highly stylized submodel for the within-host dynamics of pathogen concentration and immune response. In order to test the performance of this submodel in the context of actual *i*-level data, we estimated the parameters from time course data of titers of IgG against pertussis toxin (IgG PT) in serum of 121 patients with acute respiratory symptoms. Pertussis is a respiratory infection caused by the pathogen *Bordetella pertussis*. It is mostly an asymptomatic to mild infection, but can also lead to serious complications and even death in young children. Therefore, it is included in the national immunization program of most industrialized countries. In recent years, a resurge of pertussis incidence among children has occurred in many countries with high vaccination coverage, the suspected reasons being a shift of pertussis strains toward ones for which the current vaccine is less efficacious, and the relatively short duration of immune protection after vaccination (Mooi et al., 2014; Jackson and Rohani, 2014). Estimates of seroincidence suggest that pertussis is circulating in adult populations as well, despite a high

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vaccination coverage (Kretzschmar et al., 2010). Such estimates are based among others on longitudinal data on rise and decay of IgG PT after a diagnosed infection (Teunis et al., 2002; Versteegh et al., 2005).

Here we present a highly simplified within-host model describing both the interaction between pathogen and the immune system and the waning of immunity after clearing of the pathogen. Our aim is not to describe the complexities of an immune response mechanistically, but to describe phenomenologically the rise and decline of antibody levels after infection. We do this in order to interpret available longitudinal serological data and to design a tool that helps us relate an observed level of antibodies in an individual host to the probability of observing a symptomatic infection of that host in a next infection event. We present the mathematical analysis of the model. Then we estimate the model parameters from time course data of titers of IgG against pertussis toxin using a Bayesian hierarchical framework and Markov chain Monte Carlo methods. The model with the estimated parameters generates predictions about observable quantities. In Section 'Model performance' we contrast these predictions with observations reported in the literature and based on independent data.

The rise and fall of immunity

The immune status of individuals is often measured in terms of serum antibody levels, which can then be classified as positive or negative relative to a specified cut-off value. However, one would preferably want to judge immune status on the basis of the full information available in an antibody titer instead of just using a dichotomous classification. To do this, some understanding of the time course of antibody levels after infection or vaccination is necessary. Sometimes we are in the advantageous situation that longitudinal information on the rise and decay of antibody levels after infection is available. To interpret such data in terms of infection events, we need to design a model that describes how antibody levels rise as a consequence of boosting events and how they decline after the pathogen has been cleared from the host individual.

Denote by $b(t)$ the pathogen concentration (or any measure for the severity of the (a)symptomatic infection) and by $y(t)$ the immune or antibody level at time t. In order to reflect time scale differences, we distinguish between two episodes: the **infection episode** and the **waning immunity episode**.

Infection episode. The infection episode is characterized by $b(t) > 0$. During this episode the dynamics of b and y are governed by

$$\frac{db}{dt} = \mu_0 b - cy \tag{1}$$

$$\frac{dy}{dt} = \mu_1 y \tag{2}$$

with parameters μ_0, μ_1 and c. The parameter μ_0 describes the rate at which the pathogen concentration would grow during the infection episode if there were no immune response, while the parameter μ_1 describes the growth rate of the antibody level during the infection episode. The parameter c describes the rate at which antibodies eliminate pathogen. Arguably the term $-cy$ should be replaced by an expression that incorporates a factor b. Closest to our approach is André and Gandon (2006). Pugliese and Gandolfi (2008) give a short overview (see also references in there, e.g., Gilchrist-Sasaki and Nowak-May) of within-host models in which the rate of change of the pathogen concentration incorporates a Lotka–Volterra predator-prey term $-cby$. However, we choose to sacrifice the mechanistic underpinning in order to gain a feature that is borne out by observations, viz., that b reaches the level zero in finite time. This may also be achieved by a term $-cb^\alpha y$ with

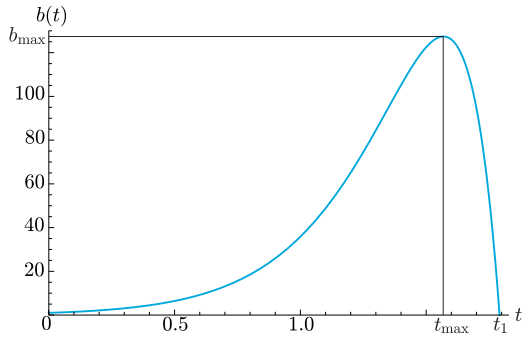

Fig. 1. The pathogen concentration $b(t)$ as a function of time t. The graph is drawn for the parameter values $\mu_0 = 4$, $\mu_1 = 5$, $c = 5$, $b_0 = 1$ and $y_0 = 1/25$.

$0 < \alpha < 1$, but an additional advantage of working with a term $-cy$ is that we can solve the system (1)–(2) explicitly, which is helpful for an efficient statistical data analysis.

Waning immunity episode. The waning immunity episode is characterized by $b(t) = 0$. The antibody level decreases exponentially with parameter w:

$$\frac{dy}{dt} = -wy \tag{3}$$

In the present paper we focus on one infection episode and the subsequent waning immunity episode. In work in progress (de Graaf et al., in preparation) we shall incorporate the possibility of reinfection.

Explicit solution for the infection episode

Let infection take place at time $t = 0$ with pathogen concentration $b(0) = b_0$ (we will refer to this initial pathogen concentration at the start of the infection episode as 'dose') and let the initial antibody level at time $t = 0$ be $y(0) = y_0$. Assume that the antibody level is increasing as fast as, or faster than, the pathogen concentration, i.e., assume that $\mu_1 \geq \mu_0$, to guarantee that the infection is cleared. We now discuss the generic case $\mu_1 > \mu_0$. The special case $\mu_1 = \mu_0$ is treated in Appendix A.

The generic case $\mu_1 > \mu_0$.

The solution of the system of differential equations (1)–(2) describing the dynamics in the infection episode is given by

$$\begin{aligned} b(t) &= b_0 e^{\mu_0 t} - \frac{cy_0}{\mu_1 - \mu_0}(e^{\mu_1 t} - e^{\mu_0 t}) \\ y(t) &= y_0 e^{\mu_1 t} \end{aligned}$$

In order to show the qualitative behavior of b, its graph is drawn for the parameter values $\mu_0 = 4$, $\mu_1 = 5$, $c = 1/5$, $b_0 = 1$ and $y_0 = 1$ in Fig. 1.

At a certain time t_1 the infection is cleared (so t_1 is the duration of the infection episode). Solving $b(t_1) = 0$ for t_1 we find that

$$t_1 = \frac{1}{\mu_1 - \mu_0} \log\left(1 + \frac{(\mu_1 - \mu_0) b_0}{cy_0}\right) \tag{4}$$

So the pathogen concentration indeed reaches the zero concentration in a finite time.

The peak antibody level y_1 at time t_1 can then be calculated to be

$$y_1 := y(t_1) = f(y_0)$$

where the function f is defined by

$$f(y_0) := y_0\left(1 + \frac{(\mu_1 - \mu_0) b_0}{cy_0}\right)^{\mu_1/(\mu_1 - \mu_0)} \tag{5}$$

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