An in-host model of acute infection: Measles as a case study

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Abstract

The epidemiology of acute infections is strongly influenced by the immune status of individuals. In-host models can provide quantitative predictions of immune status and can thus offer valuable insights into the factors that influence transmission between individuals and the effectiveness of vaccination protocols with respect to individual immunity. Here we develop an in-host model of measles infection. The model explicitly considers the effects of immune system memory and CD8 T-cells, which are key to measles clearance. The model is used to determine the effects of waning immunity through vaccination and infection, the effects of booster exposures or vaccines on the level of immunity, and the immune system characteristics that result in measles transmission (R0 > 1) even if an individual has no apparent clinical symptoms. We find that the level of immune system CD8 T-cells at the time of exposure to measles determines whether an individual will experience a measles infection or simply a boost in immunity. We also find that the infected cell dynamics are a good indicator of measles transmission and the degree of symptoms that will be experienced. Our results indicate that the degree of immunity in adults is independent of the source of exposure in early childhood, be it vaccine or natural infection.

Keywords: Measles; Waning immunity; Vaccine; Basic reproductive ratio; Epidemiology; Immunology; Immune system memory; Virus dynamics; Acute infection

1. Introduction

The field of mathematical immunology is relatively new, emerging in the 1970s. However, interest in this area has been increasing steadily, in part because experimental advances have made quantitative data readily available, and in part because of some successful collaborations between mathematical and experimental scientists (see Bell et al., 1978; Perelson and Weisbuch, 1997; Perelson, 2002). Indeed, much has been learned regarding the immune system and how it fights infection, however the great majority of the work in this field has focused on long term infections such as HIV (Nowak and Bangham, 1996; Nowak and May, 2000; Perelson, 2002) and hepatitis (Nowak and May, 2000; Perelson, 2002), and the development of in-host models of acute infections has, for the most part, been ignored. The epidemiology of acute infections is strongly influenced by the immune status of individuals. In-host models can provide quantitative predictions of immune status and can thus offer valuable insights into the factors that influence transmission between individuals and the effectiveness of vaccination protocols with respect to individual immunity.

In the last few years a small number of studies have employed general models to describe the pathogenesis of an acute infection in-host (for examples see Wodarz et al., 1998, 2000; Moss and Polack, 2001; Wodarz and Lloyd, 2004). These models have provided some insight into the acquisition of immunity, however, a number of factors that are crucial to accurately describe the pathogenesis of specific acute infections have been ignored (i.e. cellular and humoral immune system components are folded together, immune system memory is ignored, waning and boosting of immunity are overlooked, observed virus/immune system dynamics from laboratory and clinical...
experiments are not explicitly included in the general models, etc.). In this paper we focus on the development of an in-host model parameterized to match the observed dynamics of measles infection including immune system memory.

Measles is a highly contagious respiratory infection. Like most acute viral pathogens, measles cannot be treated directly, but can be suppressed in a population by the administration of vaccine. The measles vaccine is a live attenuated vaccine, meaning that it will activate the immune system to generate immune system memory/immunity (memory CD8 T-cells). Indeed, measles vaccination is one of the major successes of modern medical distribution, with a global coverage of over 80% of individuals. However, measles still remains the fifth leading cause of death worldwide and is the number one cause of vaccine preventable death in children under 5 years of age (Murray et al., 2001).

In developed countries, which have the highest level of vaccine coverage, it was thought that measles could be eliminated. Even with a 99% reduction of measles cases there are many cases reported per year (Frank et al., 1985; Gustafson et al., 1987). Some of these cases are imported from low vaccine coverage areas (van den Hof et al., 2001; Papania et al., 2004; Dayan et al., 2005), but in many instances, the original source of new infections is not evident (Papania et al., 2004; Dayan et al., 2005). Studies of populations in the absence of seronegative (susceptible/naiive) individuals indicate that measles virus can circulate among seropositive persons without signs of clinical measles (Pederson et al., 1989). Some subjects, with specific IgG-positivity, an antibody that helps prevent infection, can also develop a very mild disease after exposure to measles (Aaby et al., 1986; Edmonson et al., 1990) and protected/immune individuals can develop asymptomatic secondary immune responses (Gustafson et al., 1987; Pederson et al., 1989; Ozanne and d’Halewijn, 1992; Huiss et al., 1997). Therefore, even though measles is often thought to follow the classic SEIR paradigm (Anderson and May, 1992; Bolker and Grenfell, 1993; Earn et al., 2000) it is clear that the true pathogen–immune system interaction is more complex. In this work, measles transmission is investigated in the context of subclinical infections and waning immunity.

Waning immunity, whether the immunity is derived from vaccination or natural infection, involves the loss of immune system memory (T-cells and B-cells) that pertain to a particular illness. This occurs most often when a subject is not exposed to the pathogen antigens for an extended period, a situation consistent with a well immunized population. Conversely, reexposure to a pathogen can provide a boost to the subject’s immunity (Pederson et al., 1989; Whittle et al., 1999), reducing the extent of waning. The dual aims of reducing the incidence of the disease (by vaccinating heavily) and minimizing waning immunity to avoid outbreaks (by vaccinating selectively, allowing booster exposures to the wildtype virus) are at the centre of the debate about the most effective vaccination strategy for measles.

Subclinical infection refers to an asymptomatic infection, or an infection that has such a mild course that it does not sufficiently alert the patient to consult with a physician. A subclinically infected host will acquire some immunity, though lower in magnitude than that expected from more severe infections. Nonetheless, subclinical hosts may exhibit sufficient levels of measles to be infectious (Aaby et al., 1986; Pederson et al., 1989; Damien et al., 1998; Whittle et al., 1999). The subclinical population is not often considered in models of infectious diseases, though it can drastically affect the level of individual immunity and the dynamics of disease transmission in a population.

Mathematical models have greatly contributed to our understanding the incidence of measles infection in human populations. Epidemiological studies, describing the spread of measles at the population level are widespread in the literature. Some of these models have predicted the effects of the introduction of vaccination on measles prevalence or persistence in a population (McLean and Anderson, 1988; Keeling, 1998; Earn et al., 2000; Grenfell et al., 2002). A handful of other studies have looked at the impact of loss of vaccine-induced immunity on the overall levels of infection (Mossong et al., 1999; Glass and Grenfell, 2003, 2004), or the effect of the waning and boosting of immunity in a population (Glass and Grenfell, 2003, 2004). However, these models either ignore the effects of immune system dynamics on the spread of infection or assume that the pathogenesis of measles in-host can be folded into a few simple model parameters.

The pathogenesis of measles virus is intimately linked to the immune status of the infected individual (Jaye et al., 1998; Permar et al., 2004, 2006). The degree of immunity acquired post-infection, for example, is directly related to the levels of immune system cells present at the beginning of infection (WHO, 1993; Whittle et al., 1999). The degree of immunity in hosts, in turn, affects the herd immunity of a population and the level of infection that is observed. Thus, the underlying immunology of individuals has a profound impact on the prevalence of measles in a population through the correlation between immunity and transmissibility. An explicit consideration of the underlying immunology also permits the effects of waning and boosting of immunity to be addressed directly.

In this paper we present an in-host model that is targeted specifically at measles infection. The model explicitly considers the effects of the CD8 T-cell component of the immune system and immune system memory. Using this model we study the relationship between immune system status and immunity gained after infection or vaccination. We also demonstrate how the model can be used to supply information regarding the spread of measles in a population through determination of the basic reproductive ratio for individuals with different initial immunological characteristics.
2. Measles pathogenesis and the immune response

2.1. Measles pathogenesis

Measles virus is an enveloped, negative, nonsegmented strand RNA virus. It is transmitted from person to person by the respiratory airborne route as large aerosolized droplet nuclei (quanta). It enters a host through the respiratory tract where it first starts to replicate in the cells of the respiratory epithelium. From there, the virus gains entry to some cells of the immune system, particularly monocytes which account for 70–80% of infected cells (Salonen et al., 1988), but also B and T lymphocytes. All three of these cells types are peripheral blood mononuclear cells (PBMCs). Since PBMCs circulate around the body, they provide a means by which measles can spread away from the respiratory tract. The virus then replicates further in the lymphoid tissues before spreading to the skin and other organs. Measles virus replicates in endothelial cells before spreading to the overlying epidermis. The measles rash, which is a smooth discolouration of the skin, coincides with the onset of an antibody response. It reflects the immune complex formation in the skin, and fades as virus is cleared. In the same way, Koplik’s spots, a diagnostic feature of measles infection, form on mucosal surfaces of the mouth.

The dynamics/timeline of measles in-host is shown in Fig. 1. Primary viremia occurs 2 to 3 days after exposure to measles, and an intense secondary viremia occurs 3 to 4 days later. The appearance of Koplik’s spots 10–12 days after exposure marks the start of the prodromal period (appearance of early symptoms) and the measles rash usually appears 14 days after exposure, eventually spreading from the head to the extremities over 3 to 4 days. Over the next 3 to 4 days, the rash fades. Measles is most infectious during the prodromal stage, however, infectiousness lasts until 3–4 days after the appearance of the rash, totalling approximately 7 days of infectiousness. The peak level of virus in the blood and infected tissues usually coincides with the appearance of the rash, however, it can occur between 11 and 14 days after exposure. After peak levels, the virus falls off rapidly over the next 2 to 3 days (Forthal et al., 1992; WHO, 1993).

2.2. Immune response

The immune response is made up of two components: the innate and adaptive immune systems. The innate
immune system provides the first line of defense against many common microorganisms and is essential for the control of common infections. However, it cannot always eliminate infectious microorganisms. The adaptive immune system has evolved to provide a more versatile defense and increased protection against subsequent infections by the same pathogen. The adaptive immune system is composed of the humoral and cell mediated immune responses. The humoral immune response is the aspect of immunity that is mediated by secreted antibodies, produced in cells of the B lymphocyte lineage (B cell). Secreted antibodies bind to antigens on the surfaces of invading microbes (such as viruses or bacteria), which marks them for elimination. Cell-mediated immunity involves the activation of macrophages, natural killer cells (NK), antigen-specific cytotoxic T-lymphocytes, and the release of various cytokines in response to an antigen. It recognizes and destroys cells infected by the invading pathogen.

Nonspecific innate immune mechanisms may be important in the control of the measles virus over the first days following infection, however, it is the adaptive, ‘measles specific’, response that mediates viral clearance and provides protection against subsequent infections. Humoral immunity is certainly important in preventing infection (Chen et al., 1990). It is, however, unclear if antibodies aid in the clearance of the virus (Permar et al., 2004). Indeed, the second part of adaptive immune response, cell mediated immunity, appears to be the predominant mechanism through which the virus is cleared from the host (Griffin et al., 1989; Jaye et al., 1998; Permar et al., 2004). This has been mainly attributed to the CD8 T-lymphocyte cytolytic response. This is what we model.

3. In-host model

We have developed a model of in-host measles infection including the T-cell mediated immune response. The model consists of uninfected PBMC cells (x), infected PBMC cells (y), virus (v) and naive (w), activated (z) and memory (m) CD8 T-cells:

\[
\frac{dx}{dt} = \lambda_x - d_x x - \beta qv x,
\]

\[
\frac{dy}{dt} = \beta qv x - d_y y - \xi y z,
\]

\[
\frac{dw}{dt} = k y - w - \beta qv x,
\]

\[
\frac{dz}{dt} = \lambda_z - \frac{c qw}{C_1 qv + K_1} - d_z w,
\]

\[
\frac{dm}{dt} = \rho z - d_m m - \frac{c_m q m v}{C_3 qv + K_3}.
\]

The model is explained graphically in Fig. 2 and can be described as follows. Uninfected PBMCs (x) are produced by the bone marrow with rate \( \lambda_x \). Infected PBMCs (y) are produced by the infection of uninfected PBMCs by infectious virus \( (qv) \) via mass action dynamics where \( \beta \) describes the efficacy of this process. In addition, it is assumed that fraction \( q \) of the virus population is infectious, and thus, are capable of infecting cells. Virus is produced by infected PBMCs at rate \( k \). Naive CD8 T-cells are produced by the thymus with rate \( \lambda_z \). Activated CD8 T-cells (z) are produced by the activation of naive (c) or memory (\( c_m \)) CD8 T-cells by antigen which are proportional to the infectious viral load \( (qv) \). Memory CD8 T-cells (m) are activated at a faster rate than their naive counterparts, thus it is assumed that \( c_m > c \). Activated CD8 T-cells \( (z) \) are also produced by antigen-induced proliferation (p), which is proportional to the infectious viral load \( (qv) \). Activated CD8 T-cells kill infected PBMCs \( (\xi) \). After a period of activation, activated cells become memory CD8 T-cells with rate \( \rho \). Uninfected and infected PBMCs die at rates \( d_x \) and \( d_y \), CD8 T-cells die at rates \( d_w \) and \( d_z \), and virions are cleared from the system at rate \( u \).

Note that the memory cell activation term is augmented by a factor \( f \) in the equation for \( z \). This represents the potential of activated memory cells to proliferate before they acquire effector functions.

Activation and proliferation terms are modified by saturating functions. These are used to implement biological factors associated with the immune system. For example, at the beginning of infection, immune activation will be slow and will increase as the virus population increases. It will then reach a maximum threshold for
large viral populations since there is only a limited amount of activation that can take place in the system. Likewise, the proliferation rate is slow soon after activation of a cell, but increases and reaches a maximum threshold related to the antigen (proportional to the virus) in the system.

4. Parameter estimation

The parameter values used for the in-host model are provided in Table 1. Estimates for 12 of the 25 parameter values can be obtained directly from the literature, leaving 13 unknowns. In addition, we have approximate estimates of the cell counts before infection, viral load and cell counts during infection and a further condition that the basic reproductive ratio, $R_0$, be greater than one. Discrepancies in parameter estimates from different sources, however, can provide a range of possible values.

Some parameter constraints needed for our model are not available from human studies. For example, it is extremely rare to find information of viral load and cells counts before symptoms are apparent. Information regarding the beginning of infection, however, can be gained from studies of measles infection in rhesus macaques. Rhesus monkeys provide a reasonable human analogue for studies of measles pathogenesis (Auwaerter et al., 1999; Permar et al., 2003a,b, 2004); Cell and virus population estimates are taken from rhesus macaques studies to constrain the parameter values in the model.

### Table 1

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Units</th>
<th>Description</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\lambda_v$</td>
<td>100</td>
<td>cells $\mu$L$^{-1}$ day$^{-1}$</td>
<td>Incoming rate from the bone marrow</td>
<td>Janeway et al. (2005)</td>
</tr>
<tr>
<td>$\lambda_c$</td>
<td>600/24</td>
<td>cells $\mu$L$^{-1}$ day$^{-1}$</td>
<td>Incoming rate of naive CD8 T-cells</td>
<td>Janeway et al. (2005)</td>
</tr>
<tr>
<td>$d_v$</td>
<td>0.1</td>
<td>day$^{-1}$</td>
<td>Death rate of uninfected PBMCs</td>
<td>Janeway et al. (2005)</td>
</tr>
<tr>
<td>$d_f$</td>
<td>0.5</td>
<td>day$^{-1}$</td>
<td>Death rate of infected PBMCs</td>
<td>Mohri et al. (2001), Ribeiro et al. (2002), Perelson et al. (1996)</td>
</tr>
<tr>
<td>$d_u$</td>
<td>1/24</td>
<td>day$^{-1}$</td>
<td>Death rate of naive CD8 T-cells</td>
<td>Mohri et al. (2001), Janeway et al. (2005)</td>
</tr>
<tr>
<td>$d_a$</td>
<td>1/40</td>
<td>day$^{-1}$</td>
<td>Death rate of activated CD8 T-cells</td>
<td>Ribeiro et al. (2002)</td>
</tr>
<tr>
<td>$d_m$</td>
<td>1/1500</td>
<td>day$^{-1}$</td>
<td>Death rate of memory CD8 T-cells</td>
<td>WHO (1993)</td>
</tr>
<tr>
<td>$u$</td>
<td>3.0</td>
<td>day$^{-1}$</td>
<td>Virus clearance rate</td>
<td>Constrained</td>
</tr>
<tr>
<td>$\beta$</td>
<td>0.00061</td>
<td>(day-virion)$^{-1}$</td>
<td>Infection rate</td>
<td>Estimated</td>
</tr>
<tr>
<td>$g$</td>
<td>0.01</td>
<td>(day-cell)$^{-1}$</td>
<td>Killing rate of infected PBMCs</td>
<td>Jaye et al. (1998)</td>
</tr>
<tr>
<td>$k$</td>
<td>100</td>
<td>virions (day-cell)$^{-1}$</td>
<td>Bud rate</td>
<td>Constrained</td>
</tr>
<tr>
<td>$q$</td>
<td>1/20</td>
<td>scalar</td>
<td>Percent of virus that is infectious</td>
<td>Joseph et al. (1975), Salonen et al. (1988)</td>
</tr>
<tr>
<td>$c$</td>
<td>0.006</td>
<td>(day-virion)$^{-1}$</td>
<td>Activation rate of naive CD8 T-cells</td>
<td>Ribeiro et al. (2002)</td>
</tr>
<tr>
<td>$c_m$</td>
<td>0.16</td>
<td>(day-virion)$^{-1}$</td>
<td>Activation rate of memory CD8 T-cells</td>
<td>Zimmermann et al. (1999)</td>
</tr>
<tr>
<td>$f$</td>
<td>4</td>
<td>constant</td>
<td>Proliferation of newly activated memory CD8 T-cells</td>
<td>Constrained</td>
</tr>
<tr>
<td>$\rho$</td>
<td>0.6</td>
<td>(day-virion)$^{-1}$</td>
<td>Proliferation rate of activated CD8 T-cells</td>
<td>Kacsa et al. (2002)</td>
</tr>
<tr>
<td>$\rho$</td>
<td>0.06</td>
<td>day$^{-1}$</td>
<td>Transition rate to the memory CD8 T-cell class</td>
<td>Estimated</td>
</tr>
<tr>
<td>$K_f$</td>
<td>10</td>
<td>scalar</td>
<td>Saturation term</td>
<td>Estimated</td>
</tr>
<tr>
<td>$C_f$</td>
<td>0.1</td>
<td>virion$^{-1}$</td>
<td>Saturation term</td>
<td>Estimated</td>
</tr>
</tbody>
</table>

4.1. Population sizes

At the uninfected equilibrium (no virus or infected cells) there are approximately 1000 PBMCs (Janeway et al., 2005) and 600 naive CD8 T-cells per $\mu$L of plasma (Mohri et al., 2001; Janeway et al., 2005).

At peak viral load, approximately 14 days after infection (see Section 2), we assume that there are approximately 0.1 to 10 infected cells per $\mu$L of plasma (van Binnendijk et al., 1994; Zhu et al., 1997; Permar et al., 2003a, 2004). After peak viremia, the infected PBMC cell count and viral load decrease. We limit our model parameters so that the infected PBMC cell counts after the rash appearance (2–10 days) are similar to that found by Forthals et al. (1992) (between 12 and 1 infected PBMCs (TCID$_{50}$/10$^5$ PBMC)). We also restrict parameters so that the virus population is cleared (not detectable) a week after rash appearance (Whittle et al., 1978).

We assume that the activated CD8 T-cell population is apparent after at least 4 days of infection (Griffin et al., 1989; Jaye et al., 1998; Permar et al., 2004). Peak activated CD8 cell count, ranging between 24 and 567 cells per $\mu$L of plasma (Permar et al., 2003b), occurs slightly after peak viremia and remains elevated for at least four weeks (Griffin et al., 1989).

The time at which the memory CD8 T-cell population appears is unknown, however, the count is small soon after the rash; there are between 18 and 101 cells per microlitre approximately 4 days after the appearance of the rash (Permar et al., 2003b). Thus, we assume that the memory
cell population appears within 4 days of the rash and at least one day after the appearance of activated CD8 T-cells. Based on Permar et al. (2003b) we assume that the memory CD8 T-cell population should reach peak levels by 8 to 40 days after the rash appearance with cell counts 68 to 205 cells per μL. It is also assumed that memory cells slowly decay post viral clearance (Permar et al., 2003b).

Memory CD8 T-cells acquired after vaccination are indistinguishable from those induced from natural measles infection in terms of lysis, restimulation capacity and recognition of measles virus proteins (Jaye et al., 1998). Thus, the same memory CD8 T-cell population can be used to describe memory both after vaccination and natural infection (Kobune et al., 1996; van Binnendijk et al., 1994). In monkey models it has been shown that natural infection will induce stronger and longer-lasting immunity than vaccine strains. Thus, we assume that the level of immunity gained after vaccination should be less than that acquired from natural infection. This is ensured using a constraint that immunity gained from vaccination lasts approximately 8–16 years (WHO, 1993) using the same decay rate of memory CD8 T-cells that are produced after natural infection.

Note that the model is initiated with 10 virions per microlitre of plasma. This corresponds to 0.5 infectious virions in one microlitre of plasma and reflects the fact that the infected cell that migrates into the plasma may only spend a small part of its life in this environment, reducing the probability that the cell may bud an infectious virion. We assume that a very small fraction of this initial infected cell’s lifetime is spent in the plasma, resulting in a 50% probability that an infectious virion is budded.

In the case of vaccination the model is initiated with 300 virions per microlitre of plasma, corresponding to 15 infectious virions. The fitness of the vaccine virus, which is a live attenuated vaccine, was chosen arbitrarily to be 0.6 of the wildtype virus. The actual fitness of the vaccine virus is unknown. The lower fitness reflects the ability of the vaccine virus to enter cells and replicate. The size of the initial inoculum is a result of the chosen fitness and the model assumptions regarding the wane time and CD8 memory T-cell boost after vaccination or exposure to the natural virus. The fact that the initial inoculum is larger than that of the wildtype virus is not surprising, since more vaccine virions are needed to elicit an immune response that will build a sufficient level of immunity.

4.2. Known parameter values

It is assumed that PBMCs live, on average, 10 days if they are uninfected and an average of 2 days if they are infected. The numbers were taken to be similar to the lifetimes of uninfected and infected CD4 T-cells, a type of PBMC, from the HIV literature (Mohri et al., 2001; Ribeiro et al., 2002; Perelson et al., 1996). Infected cells can also be killed by activated CD8 T-cells; this occurs with a rate of \( \approx 0.01 \) cells day\(^{-1}\) μL\(^{-1}\) (Jaye et al., 1998).

The naive CD8 T-cell lifespan of 24 days was acquired from Mohri et al. (2001). Lifespans of activated cells are constrained to be shorter than those of naive cells and within the range of lifetimes reported by Ribeiro et al. (2002). Lifetimes of memory cells are constrained so as to provide immunity for at least 20 years (WHO, 1993) after natural infection (this corresponds to a waning time of 8–16 years for a vaccinated individual). However, the decay rate of the memory CD8 T-cells can easily be changed to account for shorter or longer waning times. We note that decay of memory CD8 T-cells appear through the displacement of memory through the creation of new memory CD8 T-cells from subsequent infections. Thus, an exponential decay assumption that we use here is reasonable, but not certain.

Naive CD8 T-cells are activated at a rate of \( \approx 0.001 \) cells day\(^{-1}\) in the absence of infection (Ribeiro et al., 2002). We assume that this rate increases with increase in viral load and is approximately 0.04 cells day\(^{-1}\) at peak viral load, similar to the maximum activation rate of CD8 T-cells in HIV studies (Ribeiro et al., 2002). We used 0.001 as a lower bound for parameter \( c/K_1 \) and an upper bound of 0.04 for \( cP/(P + K) \) where \( P \) represents the peak infectious virus in the system.

Memory CD8 T-cells are activated at a faster rate than naive CD8 T-cells (\( c_m > c \)) (Veiga-Fernandes et al., 2000). Memory CD8 T-cells also may divide before effector functions are acquired. Using \( f \) we increase the number of newly activated cells from the memory cell population to account for this greater rate of proliferation.

Activated CD8 T-cells proliferate at least 7 times with stimulation of antigen (Kaech and Ahmed, 2001; Kaech et al., 2002). However, for some infections, activated CD8 T-cells may proliferate at least 20 times (Kaech et al., 2002). Thus, we assume that an activated CD8 T-cells can proliferate between 7 and \( \approx 20 \) times during their lifetime.

An infected PBMC buds infectious and non-infectious virus. We assume 1–6% of the virions are infectious (Joseph et al., 1975; Salonen et al., 1988).

5. Results

Solving the system (1) we obtain two equilibria. The first equilibrium corresponds to the uninfected equilibrium and the second equilibrium relates to an infected equilibrium. While perhaps interesting from a theoretical point of view, the probability of reaching the infected equilibrium is minute. The uninfected equilibrium, therefore, is the only equilibrium that we consider.

The uninfected equilibrium is given by

\[
\begin{align*}
x_0 &= \frac{\lambda_s}{d_s}, & y_0 &= 0, & v_0 &= 0, & w_0 &= \frac{\lambda_e}{d_w}, & z_0 &= 0, & m_0 &= 0
\end{align*}
\]

and the stability of this equilibrium depends on the basic reproductive ratio, \( R_0 \), the number of secondary infections produced by one infected cell/virus in a totally
susceptible population:
\[
R_0 = \frac{k \beta q x_0}{d y (\beta q x_0 + u)}.
\] (3)

When \( R_0 < 1 \) the uninfected equilibrium is stable and no infection will occur, but if \( R_0 > 1 \) the equilibrium is unstable and the infection will progress.

The PBMC, CD8 T-cell and virus dynamics are shown in Fig. 3 for system (1). It is evident that the model captures the characteristics of natural measles infection as described in the previous section. The inset in the top right panel is given for comparison to Fig. 1.

5.1. Vaccination

The model can also be used to investigate the effects of the measles vaccine. Fig. 4 plots the cell and virus dynamics for an initial dose of vaccination. Comparing Figs. 3 and 4 we find that the cell and virus dynamics are similar, but the magnitude of change during vaccination is approximately half of what is seen in natural infection. It is important to note here that the level of infected PBMC cells \( y \), Fig. 6) is much lower than what is seen during natural infection, and thus, it is unlikely that an individual will experience any adverse affects from the vaccine (see Section 5.2.1). We also note that, with the large initial inoculum of virus, the memory CD8 T-cell population after vaccination reaches a level that is approximately half of what is incurred after natural infection. However, our model indicates that the level of immunity gained after one dose of vaccine is the same as the level seen after four years have passed since natural infection. Thus, the level of immunity achieved after one dose of vaccine should be sufficient to preclude reexposure to the pathogen for many years (see Section 5.2.1).

In Fig. 5 we explore the effects of a primary dose of vaccine at age 1 year and a secondary dose, or booster shot, at age 5 years. Here, the model predicts that the immunity gained from the initial dose of vaccine will wane, but the second dose boosts the memory CD8 T-cell population to a level slightly higher than the previous peak of immunity. The model also demonstrates that individuals that have successful primary and secondary vaccinations will only be slightly better off than someone that experienced primary vaccine failure (5% of individuals vaccinated, Meissner et al., 2004) and a successful second dose of the vaccine at 5 years of age.

![Fig. 3. The cell and virus dynamics of measles infection in-host are shown: uninfected PBMCs (x), infected PBMCs (y), virus (v), naive CD8 T-cells (w), activated CD8 T-cells (z) and memory CD8 T-cells (m). In the top right panel the virus (v) population is shown on a shorter time scale for comparison to the description of measles pathogenesis (Section 2). Initial inoculum is assumed to be 10 virions per microlitre of plasma. The parameter values used are given in Table 1.](image-url)
5.2. Immunity and transmission

As mentioned previously, it has been observed that measles virus can circulate among seropositive persons without signs of clinical measles. Thus, subjects with immunity can develop asymptomatic immune responses and obtain a boost in their immunity to the pathogen. To understand how these subclinical ‘booster’ infections affect epidemiological characteristics of measles, we need to address the ability of seropositive individuals, either symptomatically or asymptotically, to transmit measles together with the magnitude of immunity boosts provided by reexposure to the virus.

Transmission, the degree of symptoms, and boosts in immunity, are intimately linked to the initial immunity of an individual at the time of infection. By focusing on the infected cell, virus and memory CD8 T-cell populations, we can examine the relationship between initial immunity and measles transmission, symptomatic or asymptomatic infection, as well as the boosting of immunity. Note that we use the infected PBMC population dynamics as opposed to the virus dynamics so that we do not need to distinguish between vaccinated and wildtype measles strains.

5.2.1. Transmission

The transmission rate of a pathogen, \( B \), is proportional to the basic reproductive ratio of the disease, \( R_0 \) and the infectious period \( L \), i.e. \( B \approx \frac{R_0}{L} \). Considering a population of individuals with varying levels of immunity, \( i \), we must determine the various transmission rates, \( B_i = \frac{R_0}{L_i} \) that will be observed within such a population.

Consider the infected PBMC cell dynamics for a measles naive individual. Since we know approximately when the infectious period starts (3 days before symptoms appear) and how long it is (\( L_i \approx 7 \) days), we can determine the threshold level of infection needed to transmit the virus, and the level of infection needed to achieve the known basic reproductive ratio of measles, \( R_{0,0} \approx 17 \) in England and Wales. Fig. 6 (top left panel) plots the infected PBMC cell dynamics experienced by individuals that have no immunity at the time of infection. The dashed line spans the infectious period. We find that approximately 3.78 infected PBMCs per microlitre of plasma are needed to initiate the infectious period of measles (dot). This represents the threshold of quanta that is needed to overcome the immune system, for any initial level of memory CD8 T-cells.
The area (A), bounded by the dashed line and infected cell curve determines the ‘amount’ of infection during the infectious period, and can be related to the basic reproductive ratio $R_{0,0} = 17$. Here, the slope of the dashed line can represent the clearance rate of infectious quanta, either through breathing or clearance by the immune system, and thus, should be the same for any initial level of memory CD8 T-cells.

Using the characteristics of the dashed line described above, the initial threshold and the slope of the line, we can determine the infectious periods $L_i$ and $R_{0,i}$ for all $i > 0$. The three remaining panels in Fig. 6 plot the infected PBMC dynamics for natural measles infection for individuals with 5 (top right), 10 (bottom left) and 15 (bottom right) memory CD8 T-cells per microlitre of plasma at the time of infection. In these cases, the initial level of 3.78 infected PBMCs needed to enter the infectious period starts later in the course of infection i.e. the infectious period starts on day 10 and day 12 of infection if 5 and 10 memory CD8 T-cells per microlitre of plasma are present at the beginning of infection, and individuals with 15 memory CD8 T-cells per microlitre of plasma present at exposure will never transmit the disease.

The area above the dashed line in panels (b) and (c) can be used to determine $R_{0,5}$ and $R_{0,10}$ by comparison to the area (A) in panel (a) which represents $R_{0,0} = 17$ for measles in a naive host. We find that $R_{0,5} \approx 9.9$ and $R_{0,10} \approx 4.7$. Fig. 7 plots $R_{0,i}$ for $0 \leq i \leq 14$. This figure demonstrates that $R_{0,i}$ decreases to zero in approximately a linear fashion as the initial immunity $i$ increases.

5.2.2. Symptoms

Using similar methods to that above we can determine if an individual will demonstrate symptoms during the infectious period. It is assumed that the infected cell population is a good indicator of an individual’s symptoms, since the infected cell population dictates the strength of the immune response. Area (B) in panel (a) of Fig. 6, bounded by the dashed line, dotted line and infected cell curve, represents the level of infection needed to observe a clinical infection, which occurs on day $\approx 14$ of infection in a naive host. Comparing this area to the corresponding regions in panels (c) and (d) we can predict the threshold at which individuals with initial memory CD8 T-cell population $i$ demonstrate symptoms. Individuals with $i < \approx 6$ memory CD8 T-cells at the beginning of infection will
show clinical signs of the disease, however, individuals with $6 < i < 14.3$ are asymptomatic and will unknowingly transmit the virus.

### 5.2.3. Boosting

Fig. 8 plots the memory CD8 T-cell population after infection versus the initial level of memory CD8 T-cells before infection. Interestingly, we find that boosted memory first decreases for $0 < i < 110$ and then increases for larger levels of memory CD8 T-cells at the time of infection. This effect depends largely on the level of activated CD8 T-cells produced during infection. When $0 < i < 110$ the memory CD8 T-cells will not produce enough activated CD8 T-cells to fight the infection and must wait for newly activated CD8 T-cells produced by the naive CD8 T-cell population to enter the system. The combination of quickly activated memory CD8 T-cells and slowly activated naive CD8 T-cells results in a level of activated CD8 T-cells that are sufficient to clear the infection, but is not high enough to produce the level of immunity observed if only naive CD8 T-cells were activated. This indicates that a relationship exists between the level of boosted immunity and the severity of symptoms/infection.
5.3. Waning and boosting of immunity

It is obvious that there is a tradeoff between the severity of symptoms and the degree of immunity boosting that a host will experience. It has long been believed that an individual’s experiencing natural infection will be ‘better off’ immune status-wise than an individual that has been vaccinated. In this section we compare two individuals that experience the same time course of exposure to the virus after either a natural infection and a booster exposure, or vaccination and a booster vaccine. In this example it is assumed that measles cycles biennially, which can occur in populations with low vaccination coverage.

Fig. 9 (left column) shows the infected cell (i), virus (v) and memory CD8 T-cell (m) dynamics for an individual that is exposed to measles at various stages in their lifetime. In this case the individual is first exposed to measles at age 1 year. This may occur if older siblings bring the virus home from school. Here, a full blown measles infection is experienced and a high level of immunity is gained. The immunity wanes over time and eventually, at age 5, the individual is again exposed to the virus, when s/he enters school. This results in a low level of virus and infected cells and a boost in the current immune status of the individual, but the level of immunity is well below that resulting from a full blown measles infection. At ages 7, 9 and 11 years the individual also experiences boosts in immunity after reexposure to the virus (biennial cycles) and reaches levels of immunity similar to that experienced after natural infection at age 1 year. However, after leaving primary school it is assumed that contact with the most common carrier of measles infection (young school children) no longer exists and immunity wanes until exposure to the virus at age 24 years, when the individual has new contacts with school children. At age 24 the level of immunity has waned to very low levels and the level of infection is large. The infection that occurs at this stage has the potential to transmit the virus, but still be asymptomatic. Thus, this individual may unknowingly contribute to the spread of the disease. At ages 30 and 32 years the individual experiences boosts in immunity from reexposure to the

![Memory CD8 T-cell levels after infection/exposure graph](image)

Fig. 8. Memory CD8 T-cell levels after infection/exposure are plotted versus the initial level of memory CD8 T-cells at the time of exposure.

![Infected cell, virus and immune system memory CD8 T-cells dynamics graph](image)

Fig. 9. Infected cell (i), virus (v) and immune system memory CD8 T-cells (m) are shown for an individual that experiences natural infection (left) and vaccination with a booster shot (right). Initial inoculum of wildtype virus (left) is assumed to be 10 virions per microlitre of plasma, but it is 300 virions per microlitre of plasma for the vaccine case (right). It is assumed that the vaccine virus has fitness 0.6 of the wildtype. All other parameter values are given in Table 1.
pathogen, most likely from their children. Note that, if the individual is first exposed to measles at age 7, which may occur if the individual is an only child, the results at ages 9, 11, 24, 30 and 32 will be very similar.

**Fig. 9** (right column) plots the infected cell, virus and memory CD8 T-cell dynamics for a vaccinated individual. The time course of exposure to the virus is the same as in the previous example except that vaccination is experienced at ages 1 and 5 years rather than exposure to the natural virus. This figure demonstrates that although the level of immunity gained after vaccination and booster is considerably lower in magnitude than after natural measles infection (cf. memory CD8 T-cell level at age 5 years), a similar level of immunity is gained after exposure to the natural virus at ages 7, 9 and 11 years. Thus, the level of infection experienced at age 24 is similar to that in the previous example, and may potentially transmit the virus.

6. Discussion

We have developed a model of acute infection describing the pathogenesis of measles in-host. The model explicitly considers the CD8 T-cell component of the immune system and immunity, which are critical for measles clearance within the body. By employing this model to study the pathogenesis of measles in-host we have been able to elucidate key immune system factors that determine the outcome of measles exposure (clinical infection, subclinical infection, immune boosting). We have also investigated the correlation between the severity of measles infection and the immunity of an individual: we can predict the relationship between the immune system status, the degree of symptoms demonstrated by a host and the degree of immunity gained after exposure to the virus. It was also shown that the ability of an infected individual to transmit measles in a population is intimately linked to the immune status of the individual at the time of exposure to the pathogen. The findings of this model are obviously determined to some extent by the assumptions underlying the model formulation; however, we believe that our qualitative findings are generic, although we would welcome extra experimental or observational results to support our findings.

We find that the infected cell curve can be used to determine the degree of symptoms experienced by a host, the onset of the prodromal (infectious) period and the length of this period. In Section 5.2 clinical knowledge of measles pathogenesis was used to mark key points on the infected cell population curve (demonstration of symptoms, the infectious period, the potential to transmit the virus). Using these points we quantified the degree of symptoms that an individual will demonstrate, the length of the exposed and infectious periods of the disease, and the basic reproductive ratio \((R_0)\) or potential to transmit measles as a function of the host's immune status at the time of initial inoculum of virus. We find that individual's with initial immunity \(i < 6\) CD8 memory T-cells per microlitre of plasma will transmit the virus symptomatically, individuals with an initial immunity \(6 < i < 15\) CD8 memory T-cells per microlitre of plasma, however, will unknowingly (asymptomatic) transmit the disease. This has important implications in epidemiological studies of measles transmission, since reported cases will not accurately reflect the true level of transmission. Using the results obtained here, subclinical infections can be incorporated into epidemiological models with realistic detail.

The model also predicts that the degree of CD8 T-cell memory boosting after infection/exposure to the virus is intimately linked to the level of CD8 memory T-cells at the time of exposure. However, Fig. 8 shows an unexpected result: although the level of immunity after exposure/infection is greater than the level at the time of infection, the boosted level starts high, dips down and then increases again. This non-monotonicity suggests that vaccination/booster programs should be aimed at those individuals that have immunity levels to the left of the dip in this graph. A booster shot will augment the memory CD8 T-cell population by at least 70 memory CD8 T-cells per microlitre (data not shown), which brings the individual to the point where they will not become clinically or subclinically infected.

The in-host model also enables us to investigate the effects of waning immunity on an individual. Fig. 9 compares the infection and immunity levels of two individuals that have either experienced natural infection or a vaccination and booster shot protocol. This figure demonstrates that, although the immunity and infection dynamics are very different in childhood, the immunity gained from these experiences is very similar. Thus, individuals that have acquired immunity solely through natural infection may not acquire an immunity superior to vaccinated individuals. Our model, however, assumes that immunity gained from natural infection and vaccination decay at the same rate, an assumption supported by the observation that memory CD8 T-cells acquired after vaccination are indistinguishable from those induced from natural measles infection (Jaye et al., 1998). Nonetheless, it may prove fruitful in future studies to incorporate the possibility of differing rates of decay for natural and vaccine acquired immunity in order to understand the sensitivity of the predicted epidemiology to this parameter.

We have shown using this model that key epidemiological parameters, such as the basic reproductive ratio of the infection between individuals, are strongly influenced by the in-host dynamics of measles infection. It appears that, particularly in the case of acute infections, in-host models are a critical tool in understanding the spread of disease in a population. We are currently using the in-host model to parameterize an epidemiological SEIR model of measles transmission (Heffernan and Keeling, in prep.).

A future consideration of the in-host model will be to explicitly include the effects of the humoral immune system (B-cells and antibodies) and how it aids in the prevention of infection. To maintain the simplicity of the in-host
model this can be done by simply adding a stochastic term that enables the clearance of the virus before infection progresses. Other extensions of the model may be to consider the spatial effects of the lymph nodes and tissues. Recently, Kim et al. (2007) have developed a very detailed model describing the mechanisms that regulate the immune system. The model describes dynamics of key components of the immune network within the lymph nodes and tissue.

Our epidemiological understanding of a number of other acute systems will likely benefit from in-host modelling. For example, the transmission and severity of influenza is highly related to the immune system but complicated by immunity between strains. In-host modelling may also be critical in understanding the potential of emerging infectious diseases to be transmitted between human hosts i.e. SARS, avian influenza.

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References


