Implications of vaccination and waning immunity

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For infectious diseases where immunization can offer lifelong protection, a variety of simple models can be used to explain the utility of vaccination as a control method. However, for many diseases, immunity wanes over time and is subsequently enhanced (boosted) by asymptomatic encounters with the infection. The study of this type of epidemiological process requires a model formulation that can capture both the within-host dynamics of the pathogen and immune system as well as the associated population-level transmission dynamics. Here, we parametrize such a model for measles and show how vaccination can have a range of unexpected consequences as it reduces the natural boosting of immunity as well as reducing the number of naive susceptibles. In particular, we show that moderate waning times (40–80 years) and high levels of vaccination (greater than 70%) can induce large-scale oscillations with substantial numbers of symptomatic cases being generated at the peak. In addition, we predict that, after a long disease-free period, the introduction of infection will lead to far larger epidemics than that predicted by standard models. These results have clear implications for the long-term success of any vaccination campaign and highlight the need for a sound understanding of the immunological mechanisms of immunity and vaccination.

Keywords: within-host dynamics; measles; waning immunity; vaccination

1. INTRODUCTION

Prophylactic vaccination has long been seen as an important, and in many ways, ideal tool for controlling infectious diseases. From its earliest beginning in controlling (and finally eradicating) smallpox, vaccination has been observed to reduce the incidence of infection by reducing the proportion of the population that is susceptible. A range of mathematical models have shown that when immunity is lifelong, prophylactically vaccinating a proportion $p_c = 1 - 1/R_0$ of the population at (or shortly after) birth can eradicate infection (where R_0 , the basic reproductive ratio, is an infection and population-specific parameter).

Here, we consider the situation in which immunity is not lifelong, but wanes over time. We postulate that the continued lifelong immunity observed for many diseases could be the product of waning immunity and immune boosting through continued exposure to infection (Whittle *et al.* 1999). While models of waning immunity have been considered in the past (Rouder *et al.* 1994; Mossong *et al.* 1999; Glass & Grenfell 2003, 2004; Mossong & Muller 2003), a true understanding of the interaction between waning immunity and subsequent boosting requires a mechanistic model of the immune system. Here, we present such a model, parametrized for measles infection, and consider the long-term implications of vaccination under these assumptions. This framework allows one to explicitly determine parameters of the between-host model from the behaviour of the within-host model—and hence predict the transmission consequences of waning immunity. Previous studies have used nested

models to link within-host and epidemiological characteristics to study the relationship between transmission and virulence (Sasaki & Iwasa 1991; Antia *et al.* 1994; Ganusov *et al.* 2002; Gilchrist & Sasaki 2002; André *et al.* 2003; Krakauer & Komarova 2003; Alizon & Van Baalen 2005; Gilchrist & Coombs 2006; Read & Keeling 2006; Coombs *et al.* 2007), while other studies have developed immuno-epidemiological models, where the classes of hosts are delineated by immune or infection status (Kostova 2005; Vickers & Osgood 2007; Cornell *et al.* 2008; Mitchell *et al.* 2008). However, with the exception of a select few (e.g. Reluga *et al.* 2008), a realistic model of infection within the host has not been used to inform the epidemiological model. Instead, assumptions regarding different compartments of immunity or infectious individuals are used to delineate the host population.

Epidemiological models have had a long and very successful history. From the early investigations of disease models by Kermack & McKendrick (1927), to large-scale simulation models of pandemics (Ferguson *et al.* 2006), compartmental approaches have been used—this type of model groups individuals into one of a finite number of classes depending on their history of infection. The compartmental susceptible, exposed, infectious and recovered (SEIR) model has been intensively developed to understand the observed dynamics of acute infections, such as measles; extensions to the basic formulation include stochasticity (Bartlett 1956; Bolker & Grenfell 1996; Keeling & Grenfell 1997, 2002; Keeling *et al.* 2001; Finkenstädt *et al.* 2002; Grenfell *et al.* 2002), temporal forcing (Keeling & Grenfell 1997; Keeling *et al.* 2001; Finkenstädt *et al.* 2002; Bauch & Earn 2003), age-structure (Bolker 1993; Keeling & Grenfell 1997; Mossong & Muller 2003; Huang & Rohani 2006) and spatial structure (Bolker & Grenfell 1996; Keeling & Grenfell 1997;

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Earn *et al.* 1998, 2000; Grenfell *et al.* 2001). Measles has been the subject of many studies for two fundamental reasons: the first is that measles is still a significant cause of mortality and morbidity (20 million cases and 345 thousand deaths worldwide per year; WHO 2007), despite the existence of an inexpensive vaccine; the second is that extensive and detailed case-report records exist for measles in many countries and these records show interesting temporal dynamics (Finkenstädt & Grenfell 2000; Finkenstädt *et al.* 2002).

In contrast to the research into the population-level behaviour of infection, the mathematical study of the interaction between a pathogen and the host's immune system is a relatively new concept. Work in this area has primarily focused on two chronic infections: HIV (Herz *et al.* 1996; Perelson *et al.* 1997; Nowak & May 2000) and hepatitis B virus (Herz *et al.* 1996; Nowak & May 2000), where the interaction between pathogen and the immune system is known to be key to the disease's progression. Immunological models of acute infections have received far less interest, in part this is due to the difficulty in collecting detailed data about the progression of acute infections, but additionally it is due to the expectation that immunologically based models will provide little extra insight not afforded by simpler compartmental models.

Here, we seek to combine immunological and epidemiological models for measles infection. This will allow us to examine in some detail the interplay between disease incidence, waning immunity and boosting. In particular, we show that when appropriately parametrized, a model with waning immunity produces dynamics comparable to the standard SEIR model in the absence of vaccination; however, when vaccination is introduced, waning immunity can have a profound qualitative impact on the predicted dynamics. However, we first begin by reviewing the dynamics of simple compartmental models that include waning immunity.

2. SIMPLE MODELS OF WANING IMMUNITY

We begin by considering a simple compartmental model for waning immunity based upon the standard susceptible, infectious, recovered (SIR)-type dynamics; we use the SIR model for simplicity, although it can be noted that the results based upon the SEIR are qualitatively similar. To match more closely with the predictions of the full immuno-epidemiological model (described later), we separate those individuals who have acquired immunity through natural infection (class R) from those whose immunity is due to vaccination (class V); we further assume that vaccination and infection can give rise to different levels of immune response and therefore these two groups may experience different rates of waning immunity—reflecting the different expected times from vaccination/infection to susceptibility

$$\begin{aligned}\frac{dS}{dt} &= B(1-p) + \omega_R R + \omega_V V - \beta SI - dS, \\ \frac{dI}{dt} &= \beta SI - gI - dI, \quad \frac{dR}{dt} = gI - \omega_R R - dR, \\ \frac{dV}{dt} &= Bp - \omega_V V - dV.\end{aligned}\quad (2.1)$$

Here, p is the proportion of newborns that are vaccinated; ω is the rate at which immunity wanes; β is the transmission rate; g is the recovery rate; while B and d

are the birth and death rates (generally assumed to be equal); S , I , R and V refer to the proportion of the population in the susceptible, infectious, recovered and vaccinated classes, respectively. Given such epidemiological dynamics, vaccination can be successful only if $\omega_V(R_0 - 1) < d$ (where R_0 is the basic reproductive ratio and is equal to $\beta/(g + d)$); in such cases, the critical level of vaccination is

$$p_c = \left(1 + \frac{\omega_V}{d}\right) \left(1 - \frac{1}{R_0}\right).$$

We note that when $\omega_V = 0$ and immunity is lifelong, the standard critical vaccination threshold is regained ($p_c = 1 - 1/R_0$). Figure 1a shows the behaviour of the critical vaccination level as ω_V changes; for these measles-like parameters we observe that although incredibly small values of ω_V have little effect on the vaccination threshold, for $\omega_V > 3.4375 \times 10^{-6}$ (waning period of around 800 years), it is impossible to control the disease by prophylactic vaccination at birth. Hence, only a small deviation away from the SIR ideal of lifelong immunity is needed to prevent eradication by vaccination. When the vaccination level is below the threshold p_c , the prevalence of infection can be calculated as follows:

$$I^* = \frac{[(\beta - g - d)\omega_V + (\beta(1-p) - g - d)d](\omega_R + d)}{\beta(d + \omega_V)(g + d + \omega_R)}.$$

The behaviour of I^* with respect to the two waning rates (ω_R and ω_V) is shown in figure 1b. Four distinct regions are visible (labelled A–D): when both waning rates are low (region A), the dynamics are essentially the same as the SIR model with lifelong immunity; in region B the protection offered by vaccination is short-lived, hence the dynamics are similar to the standard SIR model without vaccination; in regions C and D the behaviour approaches that of an susceptible, infected, susceptible (SIS)-type model as the immune period decreases; and in region D the effect of vaccination is again negligible.

Although equation (2.1) is useful at illustrating the sensitivity of the SIR model to waning immunity, the simple compartmentalization leads to two naive assumptions. First, waning immunity acts by moving individuals from a class where they are totally immune, to a class where they are totally susceptible, rather than modelling a continuous decay between these two extremes. Second, it is not possible to include boosting within this model which is again due to the existence of a single immune state. Clearly, to capture the effects of waning immunity, a model with a range of immune states (a greater number of compartments) is required; here, we use a relatively detailed model of within-host dynamics to predict the population-level epidemiological parameters associated with each immune state and the boosting effects of re-exposure to the pathogen.

3. WITHIN-HOST MODEL AND ASSOCIATED EPIDEMIOLOGICAL TRANSMISSION

In a previous paper (Heffernan & Keeling 2008), we developed and parametrized a within-host model of measles infection including the development of immune system memory to the pathogen. The model (which is given below for completeness) was shown to capture the observed dynamics of measles infection in an individual, including the T-cell-mediated immune response, which is

Figure 1. Behaviour of the simple SIR model with waning immunity (equation (2.1)). (a) The critical vaccination level is shown as the waning rate of immunity, ω_v , increases. (b) The equilibrium behaviour of I^* with respect to the two waning rates ω_R and ω_v . The values of all other model parameters are: $g=1/7 \text{ day}^{-1}$; $d=1/(74 \times 365) \text{ day}^{-1}$; and $\beta=17(g+d) \text{ day}^{-1}$ such that $R_0=17$: in general, these are comparable to measles parameters and human demography in developed countries. In (b), a vaccination level of $p=0.6$ was assumed.

the component of the immune system that is most responsible for clearing the virus (Griffin *et al.* 1989; Permar *et al.* 2004). For this, the within-host model effects due to humoral and innate immunity have been ignored, as we are only concerned with the components of the immune system that clear infection once it has been established (Griffin *et al.* 1989; Jaye *et al.* 1998; Permar *et al.* 2004).

The within-host model consists of uninfected peripheral blood mononuclear cells (PBMCs, the main target of measles infection; x), infected PBMCs (y) and virus (v), as well as naive (w), activated (z) and memory (m) CD8 T-cells:

$$\begin{aligned} \frac{dx}{dt} &= \lambda_x - d_x x - \beta \phi x v, & \frac{dy}{dt} &= \beta \phi x v - d_y y - \xi y z, \\ \frac{dv}{dt} &= k y - u v - \beta \phi v x, & \frac{dw}{dt} &= \lambda_z - \frac{c \phi w v}{C_1 \phi v + K_1} - d_w w, \\ \frac{dz}{dt} &= \frac{c \phi v w}{C_1 \phi v + K_1} + \frac{p \phi v z}{C_2 \phi v + K_2} - \frac{(\rho + d_z) z}{C_3 \phi v + K_3} \\ &\quad + \frac{f c_m \phi v m}{C_4 \phi v + K_4}, \\ \frac{dm}{dt} &= \frac{\rho z}{C_3 \phi v + K_3} - d_m m - \frac{c_m \phi v m}{C_4 \phi v + K_4}. \end{aligned} \quad (3.1)$$

Although the formulation of the model is explained more completely in Heffernan & Keeling (2008), it may be briefly described as follows: uninfected PBMCs are produced by the bone marrow at rate λ_x and naive CD8 T-cells are produced by the thymus with rate λ_z . Infected PBMCs (y) are produced upon the infection of uninfected PBMCs by infectious virus (ϕv) at a rate β , where $0 < \phi < 1$ is the probability that a virion is infectious. Measles virions are produced by infected PBMCs at rate k . Activated CD8 T-cells are produced by the activation of naive (c) or memory (c_m) CD8 T-cells or by proliferation (p). Activation and proliferation depend on the level of antigen in the system, proportional to the infectious viral load (ϕv). It is assumed that $c_m > c$, reflecting the fact that the activation of memory CD8 T-cells occurs at a rate faster than that of naive CD8 T-cells (Veiga-Fernandes *et al.* 2000). After a period of activation, the activated cells become memory CD8 T-cells with rate ρ . Uninfected and infected PBMCs die at rates d_x and d_y , CD8 T-cells die at rates d_w , d_z and d_m , and virions are cleared from the system at rate u . Infected PBMCs are killed by activated CD8 T-cells (ξ). Parameter values for equation (3.1) are given in table 1 of the electronic supplementary material. The methods and references used to determine parameter values of equation (3.1), and the description of the biological and immune system processes observed during measles infection are detailed in Heffernan & Keeling (2008). It is found that the within-host model agrees well with the observed pathogenesis of measles infection and vaccination (Heffernan & Keeling 2008).

It has been observed that the pathogenicity of measles virus is intimately linked to the immune status of the infected individual (Permar *et al.* 2006). Equation (3.1) replicates this result; in particular, the level of immune memory, m , determines whether the ensuing infection is symptomatic or asymptomatic, as well as controlling the subsequent level of transmission, the duration of infection and the degree of immune boosting (see Heffernan & Keeling (2008) and the electronic supplementary material for details). Figure 2 shows the predicted within-host behaviour from equation (3.1); graphs (a) and (b) show the level of infected cells (y) and the memory cells (m) following infection for 14 different initial levels of memory, $m(0)$. Graphs (c) and (d) show the predicted amount of onward transmission (as captured by R_0) and the level of boosting (peak level of memory after the infection has been cleared) against initial memory levels. As expected, R_0 drops from its observed value of approximately 17 for fully naive individuals to 0 as the memory levels increase. However, the degree of boosting shows a non-monotonic behaviour: when $m(0)$ is small, the infection within the host is large, which leads to a large immune response and hence a large final memory level; when $m(0)$ becomes large then the final memory is increased slightly in controlling the infection; however, for intermediate values of $m(0)$, the infection is not sufficient to greatly boost the memory and hence we observe a minimum.

These observations allow us to formulate an alternative compartmental model of the population, which captures the essence of the within-host dynamics. This change from looking at the within-host dynamics of an individual to a population perspective necessitates a major conceptual shift. It is not practical to model the dynamics of all six within-host components for every individual in the population. Instead, we add an extra level of heterogeneity

Figure 2. The in-host model. (a, b) The infected cells (y) and memory cells (m) following infection for 14 different levels of memory: $m(0)=0, 3, 6, 9, 12, 20, 30, 40, 50, 60, 70, 80, 90, 100 \mu\text{l}^{-1}$ of plasma. (c, d) The calculated value of R_0 (see the electronic supplementary material) and the boosted level of memory cells ($m(\text{end})$) for a range of different initial memory levels, $m(0)$. Parameter values for the in-host model are listed in table 1 of the electronic supplementary material. Parametrization of the in-host model is discussed in Heffernan & Keeling (2008) and in the electronic supplementary material.

to the SEIR equations to include the level of CD8 T-cell memory, which is boosted by infection and waning during disease-free periods. As an extra simplification, we discretize the level of immune memory (m from equation (3.1)), which we now label as $i \in \mathbb{N}$

$$\begin{aligned} \frac{dS_0}{dt} &= B + qR_0 + w_1S_1 - \lambda S_0 - dS_0, \\ \frac{dS_i}{dt} &= qR_i + w_{i+1}S_{i+1} - \lambda S_i - dS_i - w_iS_i, \\ \frac{dE_i}{dt} &= \lambda S_i - a_iE_i - dE_i, \\ \frac{dI_i}{dt} &= a_iE_i - g_iI_i - dI_i, \\ \frac{dR_i}{dt} &= w_{i+1}R_{i+1} + \sum_j b_{i,j}g_jI_j - w_iR_i - qR_i, \\ \lambda &= \sum_i \beta_i I_i. \end{aligned} \quad (3.2)$$

In contrast to the simple model of waning immunity (equation (2.1)), we stress that the compartments S and R have slightly modified meanings. Class R refers to individuals protected by short-term immune memory (or humoral responses), who clear the virus before T-cell activation preventing boosting. Class S refers to those individuals who have lost this short-term protection and therefore may experience boosts in cellular immunity, even though they may be prevented from developing symptomatic infections. It is assumed that short-term immune memory wanes such that the recovered

individuals do not become susceptible again during the same epidemic, but can experience boosts in their cellular immunity in consecutive epidemics. Here, q was chosen to have the value 0.5 years^{-1} , which reflects the biennial measles pattern in unvaccinated populations. This assumption ensures that maximal boosting of an individual's immunity can occur from biennial epidemics, but is unlikely from the same epidemic during which they experienced infection.

The epidemiological parameters (in particular, the exposed period ($1/a_i$), the infectious period ($1/g_i$) and the transmission rate (β_i)) are determined by the full within-host model (see equation (3.1), Heffernan & Keeling (2008) and the electronic supplementary material for details) and hence depend upon the level of immune memory, i , prior to exposure. We note that for a sufficiently large i ($i \geq 15$), the infection does not lead to subsequent transmission and hence $\beta_i = 1/g_i = 0$, for all $i \geq 15$. We also note that we assume individuals with $6 > i > 15$ at the time of exposure to the virus will incur asymptomatic infections and transmit the virus unknowingly (see the electronic supplementary material for details). Finally, the parameter $b_{i,j}$ captures the boosting of the immune memory (from j to i) due to infection, again parametrized from the within-host model (see the electronic supplementary material).

In a slight modification to the within-host model (equation (3.1)), the waning of immunity, governed by

parameter w_i , is modelled as follows:

$$w_i = \begin{cases} (i-L)d_m & \text{if } i > L, \\ 0 & \text{otherwise,} \end{cases} \quad (3.3)$$

allowing the presence of a non-zero asymptotic level of immunity (L) following infection. Two values of L are considered in this work. $L=0$ corresponds most closely to the behaviour of equation (2.1) where individuals can regain complete naivety to infection. The alternative assumption $L=L_A (=6)$ ensures that sufficient immunity is retained such that any subsequent infection is asymptomatic. While these two assumptions are medically very different, we note that the choice of assumption has a limited qualitative impact on the observed dynamics of infection; results within the paper are given for the case when $L=0$, the alternative model results are shown in the electronic supplementary material.

In equation (3.3), d_m is determined using a specified wane time at which the immunity acquired after natural infection decays in naive individuals. This can be calculated by assuming a continuous decay (which is implied in the in-host model), i.e. $1/d_m = -365\tau/\log(m_i/m_u)$ days where τ is the wane time in years; $m_u (=178)$, acquired from the in-host model) is the level of immunity acquired after natural infection in a naive host; and $m_i (=1.3)$, chosen such to restrict $1 < 1/d_m < 3 \text{ years}^{-1}$ when immunity wanes over 8–16 years; WHO 1993) is the lower bound of immunity. Note that d_m can also be determined using a discrete format such that $\tau = \sum_{n=m_i}^{m_u} d_m/n$. In this study, we choose to use the formula from continuous decay of immunity, which coincides with the in-host model.

Finally, although the transmission terms, β_i , are parametrized from the viral load predicted by equation (3.1), there is still a single arbitrary scaling parameter that informs about the strength of interaction between individuals within the population. In line with the observed data on measles cases in developed countries before vaccination, β_i is scaled such that the average age of the first infection is approximately 4.5 years. Constraining the immuno-epidemiological model to match the data in this way means that the scaling parameter for β_i is dependent on the rate of waning immunity; this effect is slight but is necessary to counteract the extra force of infection from older individuals who have contracted measles for a second time. This change in the transmission rate also affects the basic reproductive ratio R_0 (see the electronic supplementary material).

The extended series of equation (3.2) provides a comprehensive means of including within-host immune dynamics in a population-level epidemiological model. As such, we have a robust framework that can predict the implications of host-level behaviour such as vaccination, waning immunity and boosting as specified by the underlying immunological dynamics and translate these host-level implications into population-level dynamics.

4. EPIDEMIOLOGICAL DYNAMICS

Numerical integration of the immuno-epidemiological equation (3.2) shows that the epidemiological dynamics are qualitatively and quantitatively similar to those of the standard SEIR model. For both $L=0$ and L_A , the prevalence of symptomatic cases and the proportion of

the population that is seropositive ($1-S_0$) correspond closely to the observed values (Anderson & May 1992). Figure 3 compares the aggregate population-level dynamics of equation (3.2) with standard SEIR model dynamics parametrized for measles. (It should be noted that the SEIR model can be recovered from equation (3.2) by setting either $q=0$ or $w_i=0$.) We observe similar damped oscillations for the number of symptomatic primary cases and the number of totally susceptible (seronegative) individuals from the two models—showing that (not surprisingly) our more complex model retains the epidemiological characteristics of the simpler SEIR equations. Also shown as insets in figure 3 are the long-term equilibrium distributions for the level of immune memory (i) for equation (3.2).

Equation (3.2) can be used to determine the life cycle of measles exposure of an individual in a population before vaccination. To do so, we omit the birth rate from equation (3.2). Using the infection rate β_i at the infected equilibrium of equation (3.2) (which is a constant force of infection), starting the model with $S_0=1$ (i.e. the individual starts totally susceptible to the virus) and omitting the birth rate in all classes, we find that, at equilibrium, the life cycle of an individual follows an average pattern. Individuals are born totally susceptible, and are first infected on average at approximately 4–5 years of age, in direct agreement with age of first infection calculations from simple models (Anderson & May 1992). Immunity is then raised to high levels but begins to decay subsequently over the host's lifetime. Equation (3.2) also shows that, given that the rate of encountering infection (λ) is independent of immune status, an individual is expected to be infected (and their immunity boosted) on average every 4–5 years, although the distribution is exponential. Those individuals in the tail of the distribution (such that it is a long time between first and second infections) may transmit the secondary infection at a low level and may even show some clinical symptoms. However, for the vast majority of individuals the time between infection events is relatively short; in this case infection is at a low level and effectively benign, its main impact is to simply boost the immune memory. Thus, in a large population, infection would be seen at a young age and it would seem that, to an observer of this population, that immunity to measles is lifelong, even though it is consecutive exposures that boosts immunity and thus, give lifelong immunity. This is illustrated in figure 3e which shows the proportion of the population that is symptomatically infected as a function of age; for long-lasting immunity, the variation from the standard SEIR prediction is slight and primarily occurs as a mild infection in older individuals.

In essence, all the results shown in equation (3.2) demonstrate that if immunity wanes slowly (over periods of several decades), then the impact of waning immunity is unlikely to be detected in real populations in the absence of control. However, introducing vaccination has the potential to reduce the immunological boosting that is experienced, and therefore invokes qualitative changes in the dynamics.

5. VACCINATION

Vaccination is included in the basic equations by moving a fraction p of the newborn individuals into class S_v ,

Figure 3. A comparison of the standard SEIR model (dashed lines) and the aggregate population dynamics of equation (3.2), which most closely corresponds to the four standard classes (S_0, E_0, I_0 and $\sum_{i>0}(S_i + R_i)$ correspond to the S, E, I and R compartments from the standard SEIR model, respectively). The solid black lines in (a) susceptible and (d) recovered graphs show $\sum_i S_i$ and $\sum_i R_i$, respectively ((b) exposed and (c) infectious). The insets show the long-term distributions of the immune memory (i) at the infected equilibrium. Here, we have assumed immunity wanes over 80 years ($d_m \approx 1/16 \text{ years}^{-1}$). (e) The predicted number of symptomatic infected individuals ($\sum_i I_i$, $i < 6 \mu\text{l}^{-1}$ of plasma) against age for three wane times, ∞ (dashed line, corresponding to the standard SEIR model, $d_m = 0 \text{ years}^{-1}$), 30 years (dotted line, $d_m \approx 6 \text{ years}^{-1}$) and 80 years (grey line, $d_m \approx 16 \text{ years}^{-1}$).

where v is the level of immunity induced by vaccination. For the susceptible classes, we now have

$$\begin{aligned} \frac{dS_0}{dt} &= B(1-p) + qR_0 + w_1S_1 - \lambda S_0 - dS_0, \\ \frac{dS_v}{dt} &= Bp + qR_v + w_{v+1}S_{v+1} - \lambda S_v - dS_v - w_vS_v, \\ \frac{dS_i}{dt} &= qR_i + w_{i+1}S_{i+1} - \lambda S_i - dS_i - w_iS_i \quad \forall i \neq 0, v, \end{aligned} \quad (5.1)$$

while all other equations are unaffected. We note that, in general, it is assumed that vaccination leads to lower levels of immune memory when compared with natural infection (i.e. immunity is lost in a shorter period of time after vaccination; WHO 1993), and in the specific case considered here $v \approx 90$ compared with a boosting to approximately $i = 178$ following infection. The value $v = 90$ is determined by the within-host model (see fig. 5 of Heffernan & Keeling 2008) and corresponds to the

measured level of CD8 memory T-cells, following initial vaccination followed by a booster vaccine later. (We note that in standard SIR or SEIR models, vaccination moves a fraction p into the recovered class where they remain for life.)

Intuitively, we can foresee that vaccination will have two conflicting effects. First, as in all other models, it will reduce the number of newborn susceptibles and hence should have some of the usual associated public-health benefits reducing the number of cases in young children. However, this reduction in cases will lead to a reduction in boosting and therefore a greater susceptibility to infection in older age classes. Ascertaining the full impact of these conflicting elements requires a well-parametrized mathematical model that can capture all the nonlinear feedbacks.

(a) *Dynamic effects of vaccination*

We first examine the impact of both waning immunity (taking time τ) and the uptake of paediatric vaccination

Figure 4. Behaviour of equations (3.2) and (5.1) showing the impact of vaccination and waning immunity. Vaccination refers to the percentage of newborns that are vaccinated, whereas the period of waning immunity (τ) is related to the death rate of memory cells using the equation $1/d_m = \tau/\log(m_1/m_u)$ years, where m_u is the level of immunity acquired after natural infection in a naive host; and m_1 is the lower bound of immunity. (a) The average prevalence of infection showing how waning immunity can severely limit the effects of vaccination. The wane time of ∞ refers to the standard SEIR assumptions when recovered individuals never re-enter the susceptible class. (b) Examples of the dynamics from equations (3.2) and (5.1); 92% of newborns are vaccinated and immunity gained from natural infection in a totally naive host wanes over 30 (dotted line), 40 (solid line), 50 (dash dotted line) and 60 (dashed line) years. (c) The maximum proportion of infectious cases around the epidemic cycle (upper surface) compared with the average (lower surface), illustrating the large relative amplitude of the infectious cycles that can be induced from high levels of vaccination and slow waning immunity. (d–e) The prevalence of symptomatic cases predicted by equations (3.2) and (5.1) when vaccinating close to the critical threshold ($p=0.94$) for three levels of waning immunity (dashed line, no waning immunity (SEIR); dotted line, 30-year waning immunity; grey line, 80-year waning immunity); the vaccination programme begins on year 80. Prevalence is displayed on both a log and linear scale to better illustrate the dynamics.

(at level p) on the average prevalence of infection. As expected from standard SEIR-type models, when immunity is lifelong ($\tau = \infty$), the prevalence of infection decreases linearly with the vaccination coverage and is

eradicated above a threshold vaccination level (approx. $p=0.94$). When immunity wanes, vaccination has a far more limited impact on the average number of cases (figure 4a). While this observation has clear public-health

implications, the dynamic consequences of the interaction between vaccination, waning immunity and boosting are far more striking. For high levels of vaccination (greater than 80%) and moderate levels of waning immunity (greater than 30 years), large-scale epidemic cycles can be induced (figure 4b). For each stable epidemic cycle (or stable endemic equilibrium), figure 4c shows the maximum proportion of the population that is infectious, highlighting both the scale of the fluctuations away from the mean and the regions in which such oscillations occur.

The cause of these cycles is the synchronization of epidemics due to the time it takes for immunity to wane. In the periodic region, following a large epidemic, most of the population have boosted levels of immunity; it then takes a relatively fixed amount of time (actually gamma-distributed) for the population to become sufficiently susceptible to support a subsequent epidemic. This pattern only occurs for high levels of vaccination; for lower levels, there are sufficiently many new susceptible births entering the population to break the synchrony of the epidemics and to give rise to an endemic equilibrium. We note that simpler models, where immunity is unstructured (such as equation (2.1)), level to individuals moving at a constant rate between recovered and susceptible classes and hence an exponential distribution of waning times; this is unable to maintain synchronized outbreaks, instead leading to endemic stability.

The existence of such sustained large-amplitude epidemic cycles induced by vaccination has important ramifications for long-term disease control. Although the average number of cases decreases with increasing vaccination (figure 4a), the peaks of infection associated with large-scale cycles could place an extra burden on public-health resources. In addition, the model predicts long-period cycles with 4–8 years between epidemic peaks; such dynamics could readily be interpreted as symptomatic of a change in underlying behaviour rather than a simple dynamical consequence of vaccination. Figure 4d,e illustrates the dynamics leading these pronounced cycles to arise following the onset of vaccination. The standard SEIR model ($\tau = \infty$, dashed line) shows a monotonic decrease in the prevalence of infection following the start of a vaccination programme at the critical threshold $p = p_c \approx 0.94$; by contrast, when immunity wanes over a period of 30 years (dots), levels of symptomatic infection rapidly recover close to pre-vaccination levels. For longer periods of waning immunity the dynamics are more pronounced: for at least 20 years, the levels of infection drop mimicking the standard SEIR results; however, at much longer times, large-scale epidemics can arise with the first substantial epidemic not arising until 52 years after the vaccination programme was begun (figure 4e).

6. DISCUSSION

This is one of the first times that a realistic immunological model has been incorporated within an epidemiological framework. Such a mixed immuno-epidemiological approach allows us to extrapolate from known within-host behaviour and predict the long-term population-level impacts of changes. Here we have considered the complex feedbacks between vaccination, waning immunity and

boosting. In the absence of vaccination, lifelong immunity is maintained through frequent encounters with infection, which act to boost the waning immune memory (this agrees with the findings of Whittle *et al.* 1999). However, when vaccination is introduced the prevalence of infection declines, which in turn reduces the amount of boosting and hence the level of immunity (in agreement with Muller 2001). What is more surprising is that the interaction between vaccination and waning immunity can lead to pronounced epidemic cycles in which the peak levels of infection can be of the orders of magnitude greater than the mean.

The inclusion of realistic immunological processes in a population-level epidemiological framework is achieved by a two-step process. First, the immunological model (equation (3.1)) is formulated and parametrized with the observed behaviour of the within-host infection; this process is detailed in Heffernan & Keeling (2008). Given that measles has a relatively short incubation and infectious period, we find that when encountering infection, it is the level of immune memory (at the moment of encounter) that determines the disease outcome and the subsequent amount of onward transmission. This observation allows us to incorporate an immunological response into the standard SEIR equations by simply adding an extra dimension, the level of immune memory prior to infection.

While this model provides a first step in combining immunological insights with epidemiological transmission processes, there are many additional attributes that could be considered. The within-host model can be extended to include the components of the humoral immune system (B-cell and antibodies). The humoral immune system is responsible for preventing infection and thus would affect the degree of boosting an individual would receive from consecutive epidemics. Inclusion of this facet would also enable us to determine the probability of infection upon exposure to the virus. In addition, a more observation-driven formulation of the interaction between various elements within the infected host would increase the accuracy of our extrapolation from the case of simple infection in a naive individual. Stochasticity and individual-level heterogeneity could also be incorporated in the within-host model. This would enable us to determine distributions for (and correlations between) the epidemiological parameters a_i , g_i , β_i and $b_{i,j}$ instead of just the mean values. In terms of epidemiological transmission, the model is deterministic and homogeneous; a wealth of previous modelling studies has demonstrated the importance of age structure, seasonal forcing and stochasticity for the dynamics of measles. Age structure could be included by adding an extra level of heterogeneity to the model, while seasonality could be included by modifying the transmission rate (between school children) throughout the year and stochasticity introduced by making all epidemiological processes event driven. Finally, given the long time scales involved with waning immunity, it may be prudent to consider more realistic models of life expectancy. However, in this work these extra complications have been ignored, as we wished to retain the simplicity of the standard SEIR model to observe the impact of immunology on the basic infection dynamics. We can, however, comment on the likely impact of these additional heterogeneities. The effect of seasonal

forcing is likely to amplify any short-duration epidemic cycles exhibited by the unforced model, particularly when the unforced period is annual or multi-annual. Second, in an age-structured model, boosting would rely to a significant extent on the transmission between children and adults, and unfortunately this part of the mixing matrix is often very difficult to parametrize due to the rarity of reported symptomatic cases in adults. Finally, although stochasticity is likely to be very important—as chance extinctions of infection allow for waning of immunity (see the electronic supplementary material)—it would generally necessitate a far more computationally intensive approach, modelling the immune status of every individual in the population. These three modifications are important considerations for the future, especially if we wish to make detailed predictions about the consequences of waning immunity. However, by far the greatest uncertainty comes from the immunological behaviour, in particular strong observational data are needed on the precise way in which immunity wanes over time.

Despite the simplifications and uncertainties involved in developing and parametrizing an immuno-epidemiological model, we feel that this work highlights two important points that may have far-reaching public-health consequences. First, even very slow rates of waning immunity can have a profound effect on the reduction in disease prevalence expected due to a vaccination programme, as seen in [figure 4a](#). Second, the interaction between immunological and epidemiological processes can have unexpected dynamic consequences (as seen in [figure 4a–c](#)). While the results here have been specifically parametrized to match the immunological and epidemiological observations of measles (in developed countries), we expect similar conclusions to hold for a range of acute infections. We therefore believe that the integration of immunology and epidemiology will be a significant growth area in the near future. We are only recently developing the tools and methodologies to elucidate the mechanisms and parameters needed for robust immunological models. Much of the work to date has been motivated by the within-host dynamics of HIV infection ([Nowak & May 2000](#); [Perelson 2002](#)), but the interest in influenza and other acute infections is allowing mathematical models to be developed for a range of other diseases ([Baccam *et al.* 2006](#); [Heffernan & Keeling 2008](#)). It is to be hoped that incorporating such mechanisms into epidemiological models will allow for greater insights into issues such as repeat infections, partial immunity, cross-reaction between strains, heterogeneous response to infection and transmission-virulence trade-offs ([Gilchrist & Coombs 2006](#); [Read & Keeling 2006](#); [Coombs *et al.* 2007](#)) for general models. This merging of scales is also clearly necessary if epidemiology and public-health modelling are to exploit the wealth of new genetic and molecular information available on many pathogens.

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REFERENCES

- Alizon, S. & Van Baalen, M. 2005 Emergence of a convex trade-off between transmission and virulence. *Am. Nat.* **165**, E155–E167. (doi:10.1086/430053)
- Anderson, R. M. & May, R. M. 1992 *Infectious diseases of humans*. Oxford, UK: Oxford University Press.
- André, J. B., Ferdy, J. B. & Godelle, B. 2003 Within-host parasite dynamics, emerging trade-off, and evolution of virulence with immune system. *Evolution* **57**, 1489–1497. (doi:10.1554/02-667)
- Antia, R., Levin, B. R. & May, R. M. 1994 Within-host population dynamics and the evolution and maintenance of microparasite virulence. *Am. Nat.* **144**, 457–472. (doi:10.1086/285686)
- Baccam, P., Beauchemin, C., Macken, C. A., Hayden, F. G. & Perelson, A. S. 2006 Kinetics of influenza A virus infection in humans. *J. Virol.* **80**, 7590–7599. (doi:10.1128/JVI.01623-05)
- Bartlett, M. S. 1956 Measles periodicity and community size. *J. R. Stat. Soc. A* **120**, 48–70. (doi:10.2307/2342553)
- Bauch, C. T. & Earn, D. J. D. 2003 Transients and attractors in epidemics. *Proc. R. Soc. Lond. B* **270**, 1573–1578. (doi:10.1098/rspb.2003.2410)
- Bolker, B. M. 1993 Chaos and complexity in measles models: a comparative numerical study. *IMA J. Math. Appl. Med. Biol.* **10**, 83–95. (doi:10.1093/imammb/10.2.83)
- Bolker, B. M. & Grenfell, B. T. 1996 Impact of vaccination on the spatial correlation and persistence of measles dynamics. *Proc. Natl Acad. Sci. USA* **93**, 12 648–12 653. (doi:10.1073/pnas.93.22.12648)
- Coombs, D., Gilchrist, M. A. & Ball, C. L. 2007 Evaluating the importance of within- and between-host selection pressures on the evolution of chronic pathogens. *Theor. Popul. Biol.* **72**, 576–591. (doi:10.1016/j.tpb.2007.08.005)
- Cornell, S. J., Bjørnstad, O. N., Cattadori, I. M., Boag, B. & Hudson, P. J. 2008 Seasonality, cohort-dependence and the development of immunity in a natural host–nematode system. *Proc. R. Soc. B* **275**, 511–518. (doi:10.1098/rspb.2007.1415)
- Earn, D. J. D., Rohani, P. & Grenfell, B. T. 1998 Persistence chaos and synchrony in ecology and epidemiology. *Proc. R. Soc. Lond. B* **265**, 7–10. (doi:10.1098/rspb.1998.0256)
- Earn, D. J. D., Rohani, P., Bolker, B. M. & Grenfell, B. T. 2000 A simple model for complex dynamical transitions in epidemics. *Science* **287**, 667–670. (doi:10.1126/science.287.5453.667)
- Ferguson, N. M., Cummings, D. A. T., Fraser, C., Cajka, J. C., Cooley, P. C. & Burke, D. S. 2006 Strategies for mitigating an influenza pandemic. *Nature* **442**, 448–452. (doi:10.1038/nature04795)
- Finkenstädt, B. F. & Grenfell, B. T. 2000 Time series modelling of childhood diseases: a dynamical systems approach. *Appl. Stat.* **49**, 187–205. (doi:10.1111/1467-9876.00187)
- Finkenstädt, B. F., Bjørnstad, O. N. & Grenfell, B. T. 2002 A stochastic model for extinction and recurrence of epidemics: estimation and inference for measles outbreaks. *Biostatistics* **3**, 493–510. (doi:10.1093/biostatistics/3.4.493)
- Ganusov, V. V., Bergstrom, C. T. & Antia, R. 2002 Within-host population dynamics and the evolution of microparasites in a heterogeneous host population. *Evolution* **56**, 213–223. (doi:10.1111/j.0014-3820.2002.tb01332.x)
- Gilchrist, M. A. & Coombs, D. 2006 Evolution of virulence: interdependence, constraints, and selection using nested models. *Theor. Popul. Biol.* **69**, 145–153. (doi:10.1016/j.tpb.2005.07.002)

- Gilchrist, M. A. & Sasaki, A. 2002 Modeling host–parasite coevolution: a nested approach based on mechanistic models. *J. Theor. Biol.* **218**, 289–308. (doi:10.1006/jtbi.2002.3076)
- Glass, K. & Grenfell, B. T. 2003 Antibody dynamics in childhood diseases: waning and boosting of immunity and the impact of vaccination. *J. Theor. Biol.* **221**, 121–131. (doi:10.1006/jtbi.2003.3181)
- Glass, K. & Grenfell, B. T. 2004 Waning immunity and subclinical measles infections in England. *Vaccine* **22**, 4110–4116. (doi:10.1016/j.vaccine.2004.02.047)
- Grenfell, B. T., Bjørnstad, O. N. & Kappey, J. 2001 Travelling waves and spatial hierarchies in measles epidemics. *Nature* **414**, 716–723. (doi:10.1038/414716a)
- Grenfell, B. T., Bjørnstad, O. N. & Finkenstädt, B. F. 2002 Dynamics of measles epidemics: scaling noise, determinism, and predictability with the TSIR model. *Ecol. Monogr.* **72**, 185–202. (doi:10.2307/3100024)
- Griffin, D. E., Ward, B. J., Jauregui, E., Johnson, R. T. & Vaisberg, A. 1989 Immune activation in measles. *N. Engl. J. Med.* **320**, 1667–1989.
- Heffernan, J. M. & Keeling, M. J. 2008 An in-host model of acute infection: measles as a case study. *Theor. Popul. Biol.* **73**, 134–147. (doi:10.1016/j.tpb.2007.10.003)
- Herz, A. V. M., Bonhoeffer, S., Anderson, R. M., May, R. M. & Nowak, M. A. 1996 Viral dynamics *in vivo*: limitations on estimates of intracellular delay and virus decay. *Proc. Natl Acad. Sci. USA* **93**, 7247–7251. (doi:10.1073/pnas.93.14.7247)
- Huang, Y. & Rohani, P. 2006 Age-structured effects and disease interference in childhood infections. *Proc. R. Soc. B* **273**, 1229–1237. (doi:10.1098/rspb.2005.3454)
- Jaye, A., Magnusen, A. F., Sadiq, A. D., Corrah, T. & Whittle, H. C. 1998 *Ex vivo* analysis of cytotoxic T lymphocytes to measles antigens during infection and after vaccination in Gambian children. *J. Clin. Invest.* **102**, 1969–1977. (doi:10.1172/JCI3290)
- Keeling, M. J. & Grenfell, B. T. 1997 Disease extinction and community size: modeling the persistence of measles. *Science* **275**, 65–67. (doi:10.1126/science.275.5296.65)
- Keeling, M. J. & Grenfell, B. T. 2002 Understanding the persistence of measles: reconciling theory, simulation and observation. *Proc. R. Soc. Lond. B* **269**, 335–343. (doi:10.1098/rspb.2001.1898)
- Keeling, M. J., Rohani, P. & Grenfell, B. T. 2001 Seasonally forced disease dynamics explored as switching between attractors. *Physica D* **148**, 317–335. (doi:10.1016/S0167-2789(00)00187-1)
- Kermack, W. O. & McKendrick, A. G. 1927 A contribution to the mathematical theory of epidemics. *Proc. R. Soc. Lond. A* **115**, 700–721. (doi:10.1098/rspa.1927.0118)
- Kostova, T. 2005 Persistence of viral infections on the population level explained by an immunoepidemiological model. *Math. Biosci.* **206**, 309–319. (doi:10.1016/j.mbs.2005.08.003)
- Krakauer, D. C. & Komarova, N. L. 2003 Levels of selection in positive-strand virus dynamics. *J. Evol. Biol.* **16**, 64–73. (doi:10.1046/j.1420-9101.2003.00481.x)
- Mitchell, K. M., Mutapi, F. & Woolhouse, M. E. J. 2008 The predicted impact of immunosuppression upon population age-intensity profiles for schistosomiasis. *Parasite Immunol.* **30**, 462–470. (doi:10.1111/j.1365-3024.2008.01043.x)
- Mossong, J. & Muller, C. P. 2003 Modelling measles re-emergence as a result of waning of immunity in vaccinated populations. *Vaccine* **21**, 4597–4603. (doi:10.1016/S0264-410X(03)00449-3)
- Mossong, J., Nokes, D. J., Edmunds, W. J., Cox, M. J., Ratnam, S. & Muller, C. P. 1999 Modeling the impact of subclinical measles transmission in vaccinated populations with waning immunity. *Am. J. Epidemiol.* **150**, 1238–1249.
- Muller, C. P. 2001 Measles elimination: old and new challenges? *Vaccine* **19**, 2258–2261. (doi:10.1016/S0264-410X(00)00455-2)
- Nowak, M. A. & May, R. W. 2000 *Virus dynamics: mathematical principles of immunology and virology*. Oxford, UK: Oxford University Press.
- Perelson, A. S., Essunger, P., Cao, Y., Vesanen, M., Hurley, A., Saksela, K., Markowitz, M. & Ho, D. D. 1997 Decay characteristics of HIV-1-infected compartment during combination therapy. *Nature* **387**, 188–191. (doi:10.1038/387188a0)
- Permar, S. R. *et al.* 2004 Limited contribution of humoral immunity to the clearance of measles viremia in Rhesus monkeys. *J. Infect. Dis.* **190**, 998–1005. (doi:10.1086/422846)
- Permar, S. R., Griffin, D. E. & Letvin, N. L. 2006 Immune containment and consequences of measles virus infections in healthy and immunocompromised individuals. *Clin. Vac. Immunol.* **13**, 437–443. (doi:10.1128/CVI.13.4.437-443.2006)
- Read, J. M. & Keeling, M. J. 2006 Disease evolution across a range of spatio temporal scales. *Theor. Popul. Biol.* **70**, 201–213. (doi:10.1016/j.tpb.2006.04.006)
- Reluga, T. C., Medlock, J. & Perelson, A. S. 2008 Backward bifurcations and multiple equilibria in epidemic models with structured immunity. *J. Theor. Biol.* **252**, 155–165. (doi:10.1016/j.jtbi.2008.01.014)
- Rouder, V., Becker, N. G. & Hethcote, H. W. 1994 Waning immunity and its effects on vaccination schedules. *Math. Biosci.* **124**, 59–82. (doi:10.1016/0025-5564(94)90024-8)
- Sasaki, A. & Iwasa, Y. 1991 Optimal growth schedule of pathogens within a host: switching between lytic and latent cycles. *Theor. Popul. Biol.* **39**, 201–239. (doi:10.1016/0040-5809(91)90036-F)
- Veiga-Fernandes, H., Walter, U., Bourgeois, C., McLean, A. & Rocha, B. 2000 Response of naive and memory CD8⁺ T cells to antigen stimulation *in vivo*. *Nat. Immunol.* **1**, 47–53. (doi:10.1038/76907)
- Vickers, D. M. & Osgood, N. D. 2007 A unified framework of immunological and epidemiological dynamics for the spread of viral infections in a simple network-based population. *Theor. Biol. Med. Model.* **4**, 49–62. (doi:10.1186/1742-4682-4-49)
- Whittle, H. C., Aaby, P., Samb, B., Jensen, H., Bennett, J. & Simondon, F. 1999 Effect of subclinical infection on maintaining immunity against measles in vaccinated children in West Africa. *Lancet* **353**, 98–102. (doi:10.1016/S0140-6736(98)02364-2)
- World Health Organization (WHO) 1993 Measles. Immunological Basis for Immunization/Module 7.
- World Health Organization (WHO) 2007 Measles fact sheet no. 286. See <http://www.who.int/mediacentre/factsheets/fs286>.