Multiple dose vaccination against childhood diseases: high coverage with the first dose remains crucial for eradication.

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ABSTRACT

The high vaccination coverage required to eradicate communicable diseases like measles, mumps and rubella, with a single dose of vaccine, has prompted many countries to introduce a second dose. In this paper we investigate the conditions to eradicate childhood diseases with multiple doses of vaccine by obtaining explicit analytical solutions to the classical compartment model that assumes an age-independent force of infection and conceptualises the host population as divided into maternally protected (P), susceptibles (S), latents (E), infectious (I), and removed (R). The solutions allow a quantitative discussion of the long-term impact of vaccination schedules with an arbitrary number of doses of vaccine. It becomes possible to determine the effect of the number of doses, ages at vaccination, and coverage rates of vaccines against childhood diseases. In an example with a two-dose vaccination schedule against measles, we show that, in spite of a second dose, a high (>90%) immunization coverage in the first dose is still crucial to achieve eradication. With a high first-dose coverage, however, eradication is relatively insensitive to the age of the second dose and requires only moderate coverage rates in the latter.

Keywords: multiple doses, vaccination schedules, childhood diseases, disease eradication

1. INTRODUCTION

An important goal of modern epidemiology is to predict the impact of immunization by vaccination upon the incidence of communicable diseases. Vaccination schemes are introduced in mathematical models of host-parasite dynamics in order to assess the reduction in the number of new infectives and other epidemiological changes in the host population following mass vaccination. For some childhood diseases, like measles, rubella and others, the host population is conceptualised as divided into distinct epidemiological classes of individuals connected by a flow. All individuals are assumed to be born protected by maternal antibodies, then become susceptible to the disease, and eventually may become latent, i.e. infected but not infectious. Latents become infectious and the latter, once recovered, become removed from the transmission process. This PSEIR model (P=protected, S=susceptible, E=latent, I=infected, R=removed) has been discussed by Anderson and May (1983, 1991) and Greenhalgh (1987) who present explicit solutions for the number of individuals by age and class.

Several authors have used mathematical models to investigate the impact of single-dose vaccination programmes upon communicable childhood infections (e.g. Dietz 1981; Anderson and May 1983, 1984, 1985; Greenhalgh 1988). The models predict that disease eradication requires very high vaccination coverage rates of the host population and, indeed, childhood diseases like measles, mumps, and rubella have proved very difficult to eliminate through single dose programmes. Accordingly, in the recent past many countries in the European region of the World Health Organisation (WHO) introduced a second dose of the MMR (measles-mumps-rubella) vaccine as part of an international effort to eradicate these diseases.

Mathematical models with two-dose strategies have been considered by Dietz (1981), Katzmann and Dietz (1984), and Anderson and Grenfell (1986). In a line of

approach similar to ours, Dietz (1981) used an equilibrium analysis of an age-structured model, with constant transmission rate, to examine the consequences of single- and two-dose vaccination programmes against rubella. He did not take into account passive immunity and latent (i.e. infected but not infectious) individuals, but considered the possibility of loss of vaccine induced immunity. When loss of immunity is assumed negligible, Dietz's (1981) solutions are coincident with the ones we present in this paper for a programme with no more than two doses of vaccine. Katzmann and Dietz (1984) derived analytical results for eradication in a model with constant transmission rate, passive immunity in children born of immune mothers, and loss of vaccine induced immunity. In the particular case of two-dose vaccination, their formulae are in agreement with ours. Anderson and Grenfell (1986) chose to integrate numerically their model equations, studying different scenarios of rubella vaccination strategies with two and three doses of vaccine, but did not deduce analytical solutions.

To our knowledge, Greenhalgh (1990) was the first to extend the analytical results of the previous authors to vaccination programmes with more than two doses of vaccine. He conducted an equilibrium analysis of an age-structured model with age-dependent transmission rate, in order to establish the immunization programmes that eliminate the disease. When analysing multiple dose programmes, however, Greenhalgh (1990) assumed a constant transmission rate, as we have done here, but did not account for passive immunity. Using a method that differs from ours, he derived an equation for the minimum immunization proportions required for elimination, which is in agreement with our results. Greenhalgh and Dietz (1994) considered a model with age-dependent transmission rate and derived a formula to estimate the basic reproductive ratio for communicable childhood diseases. They have then examined the impact of one and two-dose vaccination programmes upon the reproductive ratio of the disease, in the context of different patterns of transmission rates among age classes.

In this paper we generalise the equilibrium solutions of the PSEIR model, for an arbitrary number of doses of vaccine, with an age-independent force of infection. We present explicit solutions for the number of individuals by age and epidemiological class in the steady state that ensues a multi-dose vaccination programme. These equations may be used by public health workers concerned with cost-benefit studies of number of doses, age at vaccination, and coverage of vaccines against childhood diseases. Finally, we discuss necessary conditions for long-term disease eradication with two-dose vaccination programmes.

2. THE BASIC MODEL

Consider the host population divided in individuals who are protected by maternal antibodies, susceptibles, latents, infectious, and immunes (= removed). The densities with respect to age of each class of individuals at age x are, respectively, P(x), S(x), E(x), I(x), R(x), and the total density of individuals in the population at age x is N(x)=P(x)+S(x)+E(x)+I(x)+R(x). The proportion of individuals in each class is represented by lower case symbols. For example, p(x)=P(x)/N(x) is the proportion of maternally protected at age x, s(x)=S(x)/N(x) is the proportion of susceptibles, etc.. At equilibrium, the total population density is assumed constant, with death and birth rates exactly balancing each other. The variation with age of N(x) is given by

$$\frac{dN}{dx} = -\mu(x)\ N$$

where μ(x) is the natural mortality rate.

Common assumptions about μ(x), lead to Type I and II survivorship curves. In Type I, μ(x) is a step function whereby hosts do not die before a given average age of longevity, L, when they all die. Thus N(x)=N(0) if x<L and N(x)=0 if x>L, where N(0) is the average number of newborns. In Type II, $\mu(x)=\mu=1/L$, thus $N(x)=N(0)e^{-\mu x}$. In both

types of survivorship, the total number of individuals is N=N(0)L. Throughout this paper we assume Type I survivorship, which is better adapted to developed countries (Anderson and May 1991).

At equilibrium the proportion of individuals in the various classes depends only on age, as given by the system of first order linear ordinary differential equations Anderson and May (1991),

$$\frac{dp}{dx} = -d\,\mathrm{p} \tag{2.1a}$$

$$\frac{ds}{dx} = d\,\mathrm{p} - \lambda\,\mathrm{s} \tag{2.1b}$$

$$\frac{de}{dx} = \lambda s - \sigma e \tag{2.1c}$$

$$\frac{di}{dx} = \sigma\mathrm{e} - \upsilon i \tag{2.1d}$$

$$\frac{dr}{dx} = \upsilon i \tag{2.1e}$$

The coefficients in these equations are the per capita rates discussed in detail by Anderson and May (1983, 1991): *d* is the rate at which hosts move out of the protected into the susceptible class, λ is the force of infection, σ is the rate at which hosts move out of the latent into the infectious class, and υ is the recovery rate. For simplicity, it is assumed that the force of infection is age independent and related to the total number of infectious individuals through the transmission rate β :

$$\lambda = \beta \int_0^\infty I(x)\,dx \tag{2.2}$$

The set of initial conditions that completes the description of system (2.1), is usually provided by assuming that all hosts are born protected by maternal antibodies, *i.e.* p(0)=1, and s(0) = e(0) = i(0) = r(0) = 0.

3. IMMUNIZATION

Let us consider immunization at age, whereby every cohort is immunized *n* times, at ages x_t ($x_t>0$ for t=1, 2, …, n), thus dividing its life into a succession of *n+1* age intervals. We define x_0 =0 and x_{n+1}=L. Solutions for system (2.1) are obtained in the Appendix (equation A3) by piecewise integration from age 0 to the assumed longevity (L) of the population. The solutions, valid for $x_t<x<x_{t+1}$ (t=0, ..., n), are as follows,

$$p(x) = p(x_t)\, e^{-d(x-x_t)} \tag{3.1a}$$

$$s(x) = \frac{d}{\lambda - d}\left[p(x) - e^{-\lambda(x-x_t)}\, p(x_t)\right] + s(x_t)\, e^{-\lambda(x-x_t)} \tag{3.1b}$$

$$\begin{aligned} e(x) = {} & \frac{\lambda}{(\sigma-\lambda)}\left[s(x) - e^{-\sigma(x-x_t)}\ s(x_t)\right] - \\ & - \frac{\lambda d}{(\sigma-\lambda)(\sigma-d)}\left[p(x) - e^{-\sigma(x-x_t)}\, p(x_t)\right] + e(x_t)\, e^{-\sigma(x-x_t)} \end{aligned} \tag{3.1c}$$

$$\begin{aligned} i(x) = {} & \sigma\, \frac{e(x) - e^{-\upsilon(x-x_t)}\, e(x_t)}{(\upsilon-\sigma)} - \sigma\,\lambda\, \frac{s(x) - e^{-\upsilon(x-x_t)}\, s(x_t)}{(\upsilon-\sigma)(\upsilon-\lambda)} + \\ & + \sigma\,\lambda\, d\ \frac{p(x) - e^{-\upsilon(x-x_t)}\, p(x_t)}{(\upsilon-\sigma)(\upsilon-\lambda)(\upsilon-d)} + i(x_t)\, e^{-\upsilon(x-x_t)} \end{aligned} \tag{3.1d}$$

where $p(x_t)$, $s(x_t)$, $e(x_t)$, and $i(x_t)$ are, respectively, the proportions of protected, susceptible, latent, and infected hosts immediately after vaccination at age x_t. The proportion of removed individuals is r(x)=1-[p(x)+s(x)+e(x)+i(x)].

Immunization transfers proportions q_t (t= 1, 2, …, n) of susceptible individuals directly into the immune class at the *n* ages x_t, affecting the initial condition $s(x_t)$ in equation (3.1b). Let $s_t(x)$ be the proportion of susceptibles at age x ($x_t<x<x_{t+1}$). The proportion of susceptibles at age x_t, immediately following immunization, is

$$s_t(x_t) = (1-q_t)\, s_{t-1}(x_t)$$

Thus, for $x_t<x<x_{t+1}$, from (3.1b),

$$s_t(x) = \frac{d}{\lambda - d}\left(e^{-dx} - e^{(\lambda-d)x_t - \lambda x}\right) + (1-q_t)s_{t-1}(x_t)e^{-\lambda(x-x_t)} \qquad (3.2)$$

If there is a single dose of the vaccine, at age x_1, the proportion of susceptibles is, from (3.2),

$$s_0(x) = \frac{d}{\lambda - d}\left(e^{-dx} - e^{-\lambda x}\right) \qquad for \quad 0 < x < x_1$$

$$s_1(x) = \frac{d}{\lambda - d}\left(e^{-dx} - e^{(\lambda-d)x_1 - \lambda x}\right) + (1-q_1)\, s_0(x_1)\, e^{-\lambda(x-x_1)} \qquad for \quad x_1 < x < L$$

If there are two ages at vaccination, x_1 and x_2, the equation for $s_1(x)$ above is valid for $x_1 < x < x_2$, and a third equation has to be added,

$$s_2(x) = \frac{d}{\lambda - d}\left(e^{-dx} - e^{(\lambda-d)x_2 - \lambda x}\right) + (1-q_2)s_1(x_2)e^{-\lambda(x-x_2)} \qquad for \quad x_2 < x < L$$

If we ignore the maternally protected class ($d \to \infty$) and assume that loss of vaccine immunity is negligible, these equations reduce to the solutions in Dietz (1981, section 3.4). Katzmann and Dietz (1984, eqs (8)) also provide solutions for the proportion of susceptibles when n=2. If in their equation (8) we assume that all newborns are maternally protected and neglect loss of immunity, again we have our solutions for a two-dose programme.

The general expression for $s_t(x)$ is

$$s_t(x) = \frac{d}{\lambda - d}\left\{e^{-dx} - (1-q_1)(1-q_2)\ldots(1-q_t)e^{-\lambda x} - q_1(1-q_2)\ldots(1-q_t)e^{-\lambda x + \lambda x_1 - dx_1} - \right.$$

$$\left. - q_2(1-q_3)\ldots(1-q_t)e^{-\lambda x + \lambda x_2 - dx_2} - \ldots - q_t e^{-\lambda x + \lambda x_t - dx_t}\right\} \qquad \text{for } x_t < x < x_{t+1},\ t = 0,\ldots, n$$

or,

$$s_t(x) = \frac{d}{\lambda - d}\left\{e^{-dx} - e^{-\lambda x}\left[\prod_{i=1}^{t}(1-q_i) - \sum_{i=1}^{t} e^{(\lambda-d)x_i} q_i \prod_{k>i}^{t}(1-q_k)\right]\right\},$$

$$\text{for } x_t < x < x_{t+1},\ t = 0,\ldots, n \qquad (3.3)$$

where $\prod_{i=m}^{t}(.)=1$ and $\sum_{i=m}^{t}(.)=0$ for m>t.

The proportion of susceptibles at age x thus depends on a factor with the inflow of individuals into the susceptible compartment, the term e^{-dx}, minus the proportion of susceptibles that were not vaccinated up to age x, the term in $\Pi(1-q_i)$, and those susceptibles who were successfully vaccinated at dose *i*, the term in $q_i\Pi(1-q_k)$. The proportion of latent and infectious individuals at age x under immunization may now be computed by substituting equation (3.3) in, respectively, (3.1c) and (3.1d).

4. THE FORCE OF INFECTION AT EQUILIBRIUM WITH MULTIPLE DOSES OF VACCINE

Immunization programmes often fail to eradicate infectious diseases but, by diminishing overall incidence, they diminish the probability that a given susceptible host acquires the infection. In other words, the disease continues to persist but, once settled to its new equilibrium state, it is characterized by a smaller force of infection whose estimation is crucial for practical applications. We thus proceed to derive a general equation for λ under multiple doses of vaccine.

The basic reproductive rate of a disease, R_0, is defined as the average number of secondary infections caused by an infected individual entering a population at the disease-free equilibrium with no vaccination, during his or her infectious lifetime. Assuming a homogeneously mixed population, the number of secondary infections caused by this infected individual is proportional to the probability that any one random contact is made with a susceptible individual, that is S_0/N, where S_0 is the number of susceptibles in the disease-free population. As R_0 is the number of contacts with S_0 susceptibles, the total number of contacts with susceptibles plus maternally protected individuals is $R_0(S_0+P)/S_0 = R_0N/S_0$, where P is the number of protected individuals.

This argument neglects infected individuals who might die before the end of their infectious period. However, in childhood diseases the latent and the infectious periods are usually very small compared with L, so R_0N/S_0 remains a good approximation.

Let us now consider an endemic equilibrium under vaccination, where each infection produces on average exactly one new case, and assume that vaccination does not change the social and environmental factors that determine the total number of potentially infectious contacts. The number of secondary infections is proportional to S/N, the fraction of susceptibles in the population, where

$$S = \frac{N}{L}\sum_{t=0}^{n}\int_{x_t}^{x_{t+1}} s_t(x)dx$$

Hence we write,

$$\frac{R_0 N}{S_0}\frac{S}{N} = R_0\frac{S}{S_0} = 1 \qquad (4.1)$$

The total number of susceptible individuals, at the disease-free equilibrium (λ=0) with no vaccination, is easily calculated from (3.3),

$$S_0 = \frac{N}{L}\int_0^L \left(1 - e^{-dx}\right)dx = N\left(1 - \frac{1}{dL}\right) \qquad (4.2)$$

where we take $e^{-dL} \ll 1$. R_0 may be approximately estimated from the average age at infection before vaccination, A, and from L, neglecting terms of order e^{-dL}, $e^{-\sigma L}$, $e^{-\mu L}$, and $e^{-\lambda L}$ (Anderson and May 1991) by:

$$R_0 \approx \frac{L - 1/d}{A - 1/d} \qquad (4.3)$$

Integrating equation (3.3), we obtain,

$$\sum_{t=0}^{n}\int_{x_t}^{x_{t+1}} s_t(x)dx = \frac{1}{\lambda(\lambda - d)}W \qquad (4.4)$$

where W is,

$$W = \lambda - \lambda e^{-dL} + d\sum_{t=0}^{n}\left[\left(e^{-\lambda x_{t+1}} - e^{-\lambda x_t}\right)\left(\prod_{i=1}^{t}(1-q_i) + \sum_{i=1}^{t} e^{\lambda x_i - dx_i} q_i \prod_{k>i}^{t}(1-q_k)\right)\right]$$

In particular, with one and two doses of vaccine, W reduces to, respectively,

$$W_1 = \lambda - \lambda e^{-dL} - d + de^{-\lambda x_1} + d\left(e^{-\lambda L} - e^{-\lambda x_1}\right)\left(1 - q_1 + e^{\lambda x_1 - dx_1} q_1\right)$$

and

$$W_2 = \lambda - \lambda e^{-dL} - d + de^{-\lambda x_1} + d\left(e^{-\lambda x_2} - e^{-\lambda x_1}\right)\left(1 - q_1 + e^{\lambda x_1 - dx_1} q_1\right) +$$
$$+ d\left(e^{-\lambda L} - e^{-\lambda x_2}\right)\left[(1-q_1)(1-q_2) + e^{\lambda x_1 - dx_1} q_1 (1-q_2) + e^{\lambda x_2 - dx_2} q_2\right]$$

Combining with equations (4.1) to (4.4), we arrive at an equation for λ,

$$1 = \frac{W}{\left(A - \frac{1}{d}\right)(\lambda - d)\lambda} \qquad (4.5)$$

5. DISEASE ERADICATION WITH TWO-DOSE IMMUNIZATION SCHEDULES

In recent years, several national reports have claimed that the eradication of childhood diseases like measles, mumps, and rubella, requires the routine administration of two doses of vaccine to within approximately 12 years following birth (Bottiger *et al.* 1987, Gay *et al.* 1997a, b; Levy-Bruhl *et al.* 1997, AAP 1998). Controversy on the best age to vaccinate cohorts for the first time usually centers on the likelihood of young children to make and maintain antibodies after taking the vaccine (Wilkins and Wehrle 1979, Preblud and Katz 1988, Anderson and May 1991, Gonçalves 1996). In developed countries, the age recommended for routine administration of the first dose of the MMR vaccine, for example, is usually between 12 and 15 months of age (Helwig *et al.* 1998). However, the optimum age at which to

deliver the second dose is less transparent. In the European Union, for example, the second dose of the MMR vaccine is given at ages that vary between 3 and 13 years old (Helwig *et al.* 1998). In 1989, in the United States, the American Academy of Pediatrics recommended that the second dose of the MMR vaccine be given at 11-12 years of age, but recently revised this to be at 4 to 6 years of age (AAP 1998).

The perspectives of disease eradication with two, or indeed any number of doses of vaccine, and the long-term consequences of different age schedules, may be investigated within the mathematical framework presented above. A general procedure to find the critical level of immunization coverage $(q_1, q_2, \ldots, q_n)$ with n doses of vaccine at ages $x_1, x_2, \ldots, x_n$, leading to long-term eradication, can be found from equation (4.4), by taking the limit $\lambda \to 0$ and solving for $(q_1, q_2, \ldots, q_n)$. Consider, for example, a vaccination strategy with n =2 doses of vaccine. Taking $\lambda \to 0$ in (4.5), and solving for q_2,

$$q_2 = \frac{L - A + q_1\left(1 - e^{-dx_1}\right)\left(x_1 - L\right)}{\left(L - x_2\right)\left[1 - e^{-dx_2} - q_1\left(1 - e^{-dx_1}\right)\right]} \qquad (5.1)$$

Equation (5.1) gives the critical value of q_2 that eradicates the disease when the proportion immunized in the first dose is q_1. It is assumed that there are no secondary vaccine failures, *i.e.* no individuals that respond to the vaccine but lose immunity thereafter. Primary vaccine failures (no response to the vaccine) may be taken into account by substituting q_i by $q_i' = q_i \mathrm{VE}$, VE being an estimate of vaccine efficacy (equal to the ratio of the number of immunized individuals to the number of vaccinated individuals).

An identical result for multidose vaccination programmes has been deduced by Greenhalgh (1990). Working with an age-structured SEIR model, Type I survivorship, and age-independent force of infection, Greenhalgh shows that the critical level of

immunization coverage *(q_1, q_2, …,q_n)* for eradication, to be given at ages A_1, A_2, …, A_n , satisfies,

$$1 = R_0(L) - q_1 \frac{L - A_1}{L} R_0(L - A_1) - q_2(1 - q_1) \frac{L - A_2}{L} R_0(L - A_2) - \ldots$$
$$\ldots - q_n(1 - q_1)(1 - q_2)\ldots(1 - q_{n-1}) \frac{L - A_n}{L} R_0(L - A_n) \qquad (5.2)$$

Assuming that the infectious and latent periods are both very small, compared with L, it can be shown that R_0 becomes independent of L and, for n=2, (5.2) becomes,

$$1 = R_0 \left[(1 - q_1)(1 - q_2) + q_1 \frac{A_1}{L} + q_2(1 - q_1) \frac{A_2}{L} \right] \qquad (5.3)$$

which is our equation (5.1), when we take $d \to \infty$.

Figure 1 illustrates the relation between q_1 and q_2 (equation 5.1), assuming a population longevity of L = 75 years and an age at first infection of A = 6 years (Anderson and May 1983, 1991; McLean and Anderson 1988). The age of vaccination in the first dose was fixed at 15 months, whereas the age in the second dose varied between 3 and 11 years old. Although the values in Figure 1 depend on the assumption of homogeneous mixing and constant force of infection of the PSEIR model, they point to some interesting trends.

It is very difficult to eliminate measles with low to moderate vaccination coverages in the first dose. An immunization coverage below approximately 60% in the first dose would require coverage rates above 90% in the second dose for eradication. In particular, with a second dose at 11 years old, eradication would be impossible (Figure 1). Estimates of vaccination coverage in the second dose are difficult to obtain, as individuals are usually not asked about previous vaccination status or disease history. However, it seems reasonable to expect that, in general, $q_2 < q_1$. Can moderate immunization coverages in the second dose eradicate the disease? With high levels of

coverage in the first dose, Figure 1 suggests that moderate levels in the second dose might indeed be enough to eliminate the disease. For example, for q_1 = 90%, eradication is achieved with q_2 = 55%, 58%, and 62%, depending on whether x_2= 3, 6, or 11 years.

Finally, does age of vaccination at the second dose matter ? The answer, once again, depends critically on percent coverage in the first dose. Under our assumption of an age-independent force of infection (equation 2.2), with high (>90%) immunization coverage in the first dose, options for the second dose within the age range currently practised (3-13 years old) probably make little difference, insofar as eradication is concerned. For a moderate (50-70%) coverage in the first dose, however, age at the second dose might decide whether there is any chance of eradicating the disease. In the case of measles, for example, for q_1= 50%, eradication appears impossible with x_2=11, but possible if x_1=3 or 6 and q_2 is high enough (Figure 1). We thus conclude that while it seems crucial to maintain high levels of vaccination coverage in the first dose, once this is achieved, logistic considerations might become a crucial factor in determining the age of the second dose.

APPENDIX

In this appendix we obtain analytical solutions for system (2.1) that allow for the introduction of an immunization programme with an arbitrary number of doses of vaccine. System (2.1) can be written in the general form of a linear equation,

$$\frac{df_i(x)}{dx} + a_i f_i(x) = a_{i-1} f_{i-1}(x) \quad ; \quad i = 1, \ldots, 5 \qquad \text{(A1)}$$

Where *i* identifies the class of hosts and the transfer rate out of that class. The functions $f_1, \ldots, f_5$ are, respectively, the solutions *p(x), s(x)*, *e(x)*, *i(x),* and *r(x).* The coefficients $a_1, a_2, a_3,$ and a_4 represent d , λ , σ and υ respectively, whereas a_5=0.

Equation (A1) is solved by multiplying both sides by an integrating factor, $\mu(x)$, which is defined to account for immunization. If every cohort is immunized *n* times at ages x_t (x_t>0 for t=1, 2, …, n) and for notational convenience we define x_0 = 0, the integrating factor is computed from x_t, the age of vaccination immediately before age *x,* to *x,*

$$\mu(x) = \exp\left[\int_{x_t}^{x} a_i dx'\right] = \exp\left[a_i\left(x - x_t\right)\right]$$

The solution is,

$$f_i(x) = a_{i-1} \int_{x_t}^{x} e^{a_i(x'-x_t)} f_{i-1}(x')\, dx' \; e^{-a_i(x-x_t)} + f_i(x_t)\; e^{-a_i(x-x_t)} \qquad \text{(A2)}$$

We use integration by parts to evaluate the integral,

$$\int_{x_t}^{x} e^{a_i(x'-x_t)} f_{i-1}(x')\, dx' = \left[\frac{e^{a_i(x-x_t)}}{a_i} f_{i-1}(x) - \frac{f_{i-1}(x_t)}{a_i}\right] - \int_{x_t}^{x} \frac{e^{a_i(x'-x_t)}}{a_i} \frac{d f_{i-1}(x')}{dx'} dx'$$

using (A1) to substitute the derivative on the right-hand side,

$$\int_{x_t}^{x} e^{a_i(x'-x_t)} f_{i-1}(x')\,dx' = \left[\frac{e^{a_i(x-x_t)}}{a_i} f_{i-1}(x) - \frac{f_{i-1}(x_t)}{a_i}\right] -$$

$$- \frac{1}{a_i}\int_{x_t}^{x} e^{a_i(x'-x_t)} \left[a_{i-2} f_{i-2}(x') - a_{i-1} f_{i-1}(x')\right] dx'$$

leading to a recurrence relation for the integral

$$\int_{x_t}^{x} e^{a_i(x'-x_t)} f_{i-1}(x')\,dx' = \frac{1}{a_i - a_{i-1}}\left[e^{a_i(x-x_t)} f_{i-1}(x) - f_{i-1}(x_t) - a_{i-2}\int_{x_t}^{x} e^{a_i(x'-x_t)} f_{i-2}(x')\,dx'\right]$$

Substituting into (A2),

$$f_i(x) = \frac{a_{i-1}}{a_i - a_{i-1}}\left[f_{i-1}(x) - e^{-a_i(x-x_t)} f_{i-1}(x_t)\right] - \frac{a_{i-1}}{a_i - a_{i-1}}\frac{a_{i-2}}{a_i - a_{i-2}}\left[f_{i-2}(x) - e^{-a_i(x-x_t)} f_{i-2}(x_t)\right] + \ldots$$

$$\ldots + (-1)^i \prod_{j=1}^{i-1} \frac{a_{i-j}}{a_i - a_{i-j}}\left[f_1(x) - e^{-a_i(x-x_t)} f_1(x_t)\right] + f_i(x_t)\, e^{-a_i(x-x_t)}$$

or, in a more compact form,

$$f_i(x) = \sum_{c=1}^{i-1}\left\{\prod_{j=1}^{c}(-1)^{c+1} \frac{a_{i-j}}{a_i - a_{i-j}}\left[f_{i-c}(x) - e^{-a_i(x-x_t)} f_{i-c}(x_t)\right]\right\} + f_i(x_t)\, e^{-a_i(x-x_t)} \qquad \text{(A3)}$$

The proportion of individuals at age *x* in class i is thus given by the term $f_i(x_t)\, e^{-a_i(x-x_t)}$, representing the decay of the proportion since the age of vaccination before *x*, $f_i(x_t)$, plus a dynamical term representing the contribution of class *i-c* to class i (the factor in square brackets), weighted by a quotient of outflow rates.

For example, $f_2(x)$ is the proportion of susceptibles in equilibrium at age *x*. A direct application of (A3) is,

$$f_2(x) = \frac{a_1}{a_2 - a_1}\left[f_1(x) - e^{-a_2(x-x_t)} f_1(x_t)\right] + f_2(x_t)\, e^{-a_2(x-x_t)}$$

and by substitution of the corresponding transfer rates and classes of hosts, this leads to equation (3.1b) of the main text. Equations (3.1) are solutions for all epidemiological classes obtained in the same way from (A3).

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FIGURE CAPTION

Figure 1. The dependence (see equation 5.1) of the critical proportion immunized in the second dose, q_2, required to eradicate the disease, on the proportion immunized in the first dose, q_1. The lines are for different ages at which the second dose is given (3, 6, 11 years); the age of the first dose of the vaccine was fixed at 15 months. Other parameters used were L= 75 years and A = 6 years.

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