

Mathematical models of vaccination

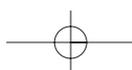
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Mathematical models of epidemics have a long history of contributing to the understanding of the impact of vaccination programmes. Simple, one-line models can predict target vaccination coverage that will eradicate an infectious agent, whilst other questions require complex simulations of stochastic processes in space and time. This review introduces some simple ordinary differential equation models of mass vaccination that can be used to address important questions about the predicted impact of vaccination programmes. We show how to calculate the threshold vaccination coverage rate that will eradicate an infection, explore the impact of vaccine-induced immunity that wanes through time, and study the competitive interactions between vaccine susceptible and vaccine resistant strains of infectious agent.

One of the very earliest mathematical models in epidemiology concerned the impact of vaccination. In 1760, Swiss mathematician Daniel Bernoulli published a study of the predicted impact of immunization with cowpox upon the expectation of life of the immunised population¹. Nearly 150 years later, around the time of the First World War, Ronald Ross produced a series of mathematical models of the spread of malaria that laid the foundations of the modern theory of the control of infectious disease². Ross's great advance was to recognise, through the exploration of mathematical models, that malaria transmission could be prevented through mosquito control – without removing every last mosquito. The recognition that disease transmission could be stopped by control programmes with incomplete coverage had wide-spread impact on the design of intervention strategies throughout the 20th century³⁻⁵. For vaccination strategies, some of the simplest questions that arise are: (i) what fraction of the population must be successfully vaccinated to eradicate the infectious agent; (ii) what happens if the target coverage for eradication is not met; (iii) does it matter if vaccine induced immunity wanes with time; and (iv) what happens if there are vaccine resistant sub-types? The following sections introduce mathematical models that address these questions.

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Simple models

Amplification factors and eradication thresholds

All that is required for the incidence of an infectious disease to go into decline is that each case should generate, on average, less than one other case. The number of secondary infections caused by one infectious individual is often referred to as the effective reproductive number and denoted R . Epidemics often peak and go into decline as R falls below 1 because the pool of susceptible individuals has been temporarily exhausted. For the trajectory of incidence to remain on a downward course until the agent is eradicated requires that the effective reproductive rate should remain below 1, even when the number of susceptible individuals is at its maximum. There are two further amplification factors that pertain (Table 1). R_0 , the basic reproductive number is the number of secondary cases caused by one primary case introduced into a population that is wholly susceptible. R_{0p} , the basic reproductive number under vaccination is the number of secondary cases caused by one primary case introduced into a population in which a proportion p have been vaccinated. For a perfect vaccine that confers life-long protection

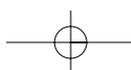
$$R_{0p} = (1 - p)R_0 \quad \text{Eq. 1}$$

The critical vaccination proportion that will achieve eradication, p_c , is that for which the basic reproductive number under vaccination is just equal to 1. This yields:

$$p_c = 1 - \frac{1}{R_0} \quad \text{Eq. 2}$$

Table 1 Different amplification factors in mathematical models of vaccination

Amplification factor	Name	Definition	Properties
R_0	Basic reproductive number	Number of secondary cases caused by one primary case introduced into a population that is wholly susceptible.	A fixed summary parameter a property of the infectious agent the host population and their interactions
R_{0p}	Basic reproductive number under vaccination	Number of secondary cases caused by one primary case introduced into a population in which a proportion p have been vaccinated	A function of R_0 , the proportion vaccinated and the properties of the vaccine
R	Effective reproductive number	The number of secondary cases caused by one primary case in a population with the extant susceptible population	A function of R_0 and of the size of the susceptible population. R changes through time with the depletion and replenishment of the susceptible population



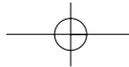


Table 2 Numerical values of the basic reproductive number R_0 and the critical vaccination proportion p_c

Infection	Location	Date	R_0	p_c	Reference
Measles	Senegal	1964	18	94%	Boue ¹³
Smallpox	West Africa	1960s	2.3	57%	Foegen <i>et al</i> ¹⁴
Mumps	UK	1987	8	87%	Farrington ¹⁵
Rubella	USA	1967	6	83%	Hayden <i>et al</i> ¹⁶

To calculate numerical values of p_c requires estimates of R_0 (Table 2), these illustrate how the ease with which an infectious agent can be eradicated varies widely across agents for which cheap safe and effective vaccines are already available. This highlights the issue that the development of such a vaccine, although a necessary prerequisite, is not sufficient to guarantee eradication of an infectious agent.

Post-vaccination dynamics

To study the predicted dynamics of infection after the introduction of a vaccination programme requires the use of mathematical models of

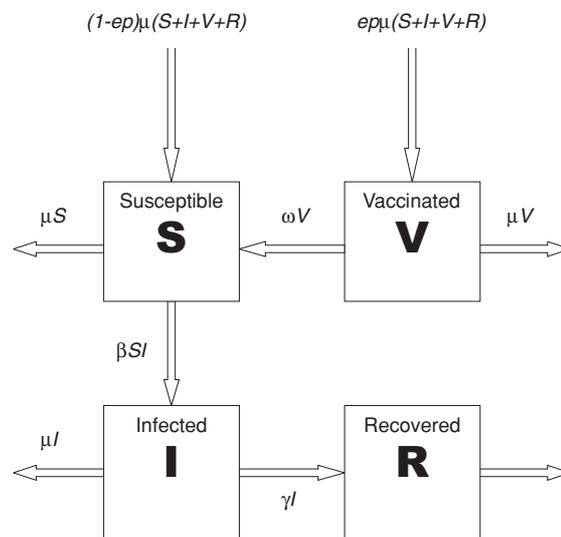
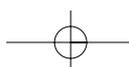
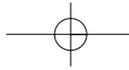


Fig. 1 Modelling childhood vaccination. We consider the dynamics of the following populations: susceptible, S; vaccinated, V; infected, I; and recovered R. The loss from the total population by death (at a rate μ) equals the influx by birth such that the total population is fixed in size. A fraction p of the newly born individuals are vaccinated at birth. This vaccination takes in a fraction e of the vaccinated individuals and protects them for an average period of $1/\omega$ years. Susceptibles become infected at per capita rate $\lambda(t) = \beta I(t)$. Infectious individuals recover at rate γ to become immune, and natural immunity is assumed to be life-long.





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transmission dynamics. The simplest model that can be used to study the impact of vaccination keeps track of three groups of individuals: susceptible, S; infected, I; and recovered R. The model we study here includes a fourth group; those who have been vaccinated, V. This refinement allows the investigation of the impact of waning immunity in the next section (Fig. 1). If vaccine induced immunity is life-long, then the equations of this SVIR model are:

$$\frac{dS}{dt} = \begin{matrix} (1-ep)\mu N & - & \beta IS & - & \mu S \\ \text{unvaccinated births} & & \text{infections} & & \text{deaths} \end{matrix} \quad \text{Eq. 3}$$

$$\frac{dV}{dt} = \begin{matrix} ep\mu N & - & \mu V \\ \text{vaccinated births} & & \text{deaths} \end{matrix} \quad \text{Eq. 4}$$

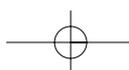
$$\frac{dI}{dt} = \begin{matrix} \beta IS & - & \gamma I & - & \mu I \\ \text{infections} & & \text{recoveries} & & \text{deaths} \end{matrix} \quad \text{Eq. 5}$$

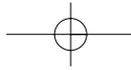
$$\frac{dR}{dt} = \begin{matrix} \gamma I & - & \mu R \\ \text{recoveries} & & \text{deaths} \end{matrix} \quad \text{Eq. 6}$$

Here, N is the total population size. The transitions described by each term of the equations of this model are as labelled and the model's parameters are described in Table 3. Figure 2 uses this model to illustrate the predicted impact of vaccination. The parameters' values are chosen to represent measles in an industrialised country with $R_0 = 11$, and epidemics occurring in biennial cycles. In the pre-vaccine era, the

Table 3 Parameters of the models, their interpretations and numerical values

Parameter	Interpretation	Value	Interpretation
N	Population size	10 ⁵	
β	Force of infection	0.0029 (year ⁻¹)	Yields R ₀ of 11.15 in combination with N, μ and γ as given below
μ	Death rate	0.02 (year ⁻¹)	Average life expectancy is 50 years
γ	Rate of recovery	26 (year ⁻¹)	The average period of infectiousness is 2 weeks
e	Vaccine take, the fraction of vaccinated population protected by the vaccine	0-1	
p	Fraction of population vaccinated at birth	0-1	
ω	Rate of loss of vaccine-induced immunity	e.g. 0.05 (year ⁻¹)	Vaccine-induced immunity lasts on average for 20 years





effective reproductive ratio rises and falls around the value of 1 as the pool of susceptible individuals is depleted by epidemics of infection and then replenished by births. At time 6 years, vaccination of a fixed proportion of new births is introduced. Scenarios modelling the impact of three different levels of vaccination are presented. The first achieves coverage of 95%, which is above the critical proportion for eradication (91% when $R_0 = 11$). The number of infections immediately plummets, and no further infections are seen. The effective reproductive ratio is depressed below 1 after the introduction of vaccination and never rises above it again. Eradication is achieved. The second scenario represents the impact of a vaccination programme that reaches high levels of coverage (85% of all new-borns) which are, nevertheless, not high enough to lead to eradication of the agent. However, for the first 15 years after the introduction of vaccination, it appears as if eradication has been achieved, there are no infections. Then, suddenly, a new epidemic appears as if from nowhere. This is an illustration of a phenomenon known as the 'honeymoon period'. This is the period of very low incidence that immediately follows the introduction of a non-eradicating mass vaccination policy. This happens because susceptible individuals accumulate much more slowly in

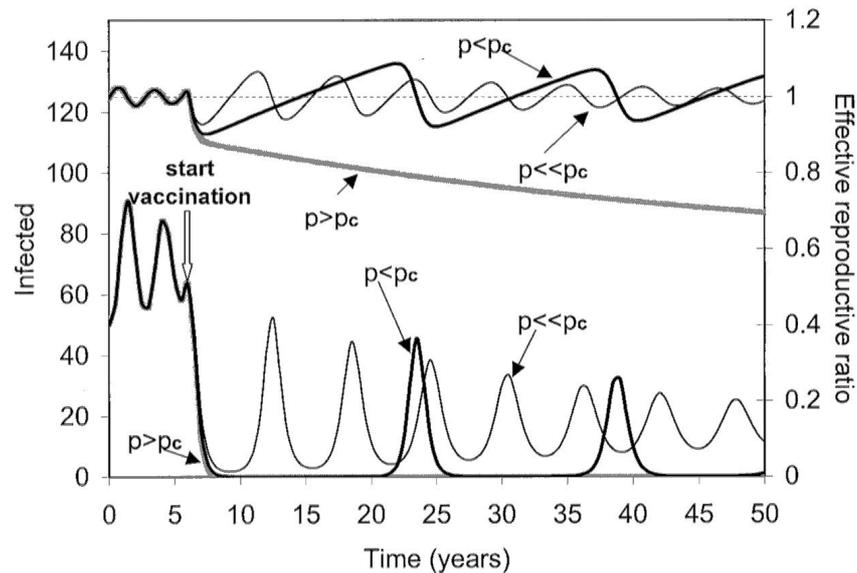


Fig. 2 The dynamics of childhood disease. Vaccination occurs at time 6 years. Depending on the fraction of the population that is vaccinated at birth (p) the disease is either eradicated or relapses after a so-called honeymoon period. Parameter values used in these simulation were the following: $\mu = 0.02$, $\beta = 0.0029$, $\gamma = 26$, $\omega = 0$, $N = 10^5$. This results in an R_0 of 11.15 and a p_c of 0.91. For $p > p_c$, p was equal to 0.95, for $p < p_c$ it was equal to 0.85 and for $p \ll p_c$ it was equal to 0.7. Upper lines depict the dynamics of the effective reproductive number R (right axis) which equals $\beta S / (\gamma + \mu)$. The lower lines depict the dynamics of the infected population (left axis).





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a vaccinated community. Such patterns were predicted using mathematical models in the 1980s⁶ and have since been observed in communities in Asia, Africa and South America⁷. Honeymoon periods are only predicted to occur when the newly introduced vaccination programme has coverage close to the eradication threshold. The third scenario depicted in Figure 2 is of vaccination coverage at 70%. Although epidemics in the era of vaccination are less frequent, there is no obvious honeymoon period.

Duration of protection

Modelling waning immunity

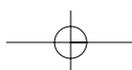
The mathematical model represented in Equations 3–6 and Figure 2 makes the assumption that vaccine-induced protection is life-long. There is no waning of vaccine-induced immunity. Until the 1990s, this was a universal assumption of mathematical models of vaccination. This assumption was routinely made because, for most of the major vaccines against childhood infectious disease, it is approximately correct. It is, however, important to ask about the sensitivity of model predictions to this assumption⁸. The transitions presented in Figure 1 include the possibility that vaccinated individuals will eventually pass into the susceptible class as their vaccine-induced immunity fails. This transition is trivially included in the equations of the model as a term ωV added to Equation 3 and subtracted from Equation 4.

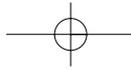
The vaccinated basic reproductive number with waning immunity

With this term in place, equilibrium analysis of Equations 3–6 yields a new expression relating the vaccinated reproductive number to the basic reproductive number:

$$R_{0p} = (1 - e \frac{\mu}{\mu + \omega}) p R_0 \quad \text{Eq. 7}$$

This is for coverage p with a vaccine that takes in a fraction e of recipients and gives protection that wanes with average duration of protection ω in a population with average expectation of life μ . This apparently simple equation introduces a second counter-intuitive insight into the impact of vaccination gleaned from mathematical models. The impact of the level of coverage and the ‘take’ of the vaccine upon the vaccinated reproductive number are as one would expect. However, the impact of the duration of immunity is much greater than intuition might lead one to expect. The term $\mu/(\mu + \omega)$ in Equation 7 is best interpreted





as the fraction of a lifetime for which an individual is protected by a vaccine that gives immunity that wanes at rate ω in a population with fixed death rate μ . If the expectation of life is 50 years ($\mu = 0.02$), then a vaccine with immunity that wanes at the same rate is only as good as a vaccine that gives protection that does not wane, but only takes in 50% of recipients (Fig. 3).

Post-vaccination dynamics with waning immunity

Re-arrangement of Equation 7 yields a new threshold parameter ω_c , the critical duration of immunity for a given coverage p , take e and basic reproductive number R_0 . If vaccine-induced immunity wanes faster than this critical rate, then eradication will not be achieved.

$$\omega_c = \frac{\mu}{(1-R_0)} [R_0(1-ep) - 1] \quad \text{Eq. 8}$$

Such a scenario is illustrated in Figure 4. A vaccine that is otherwise perfect (takes in all recipients) and which achieves total coverage yields eradication when the waning rate is below the critical threshold level (line marked $\omega < \omega_c$ in Fig. 4). But if the duration of protection is shorter than the critical level, the control programme fails after a time of apparent success. This failure is via a process distinct from that which causes the honeymoon period discussed above, as it is through the

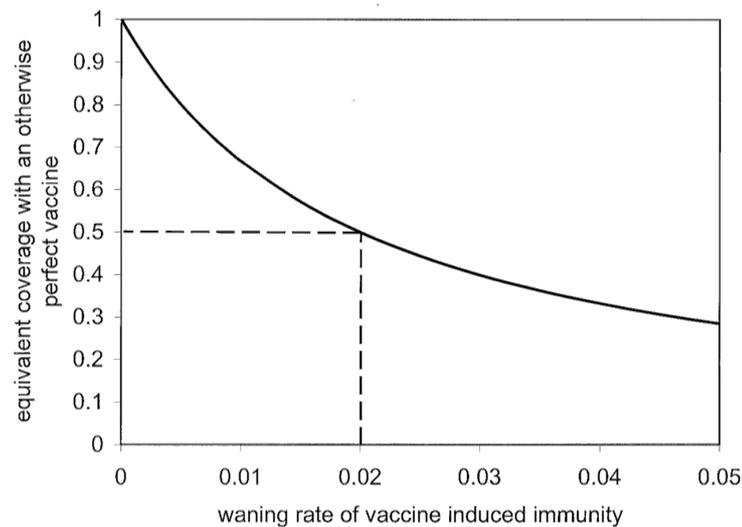


Fig. 3 An otherwise perfect vaccine that protects for 50 years on average is only as good as a vaccine that takes in 50% of vaccinated individuals but gives life-long protection.





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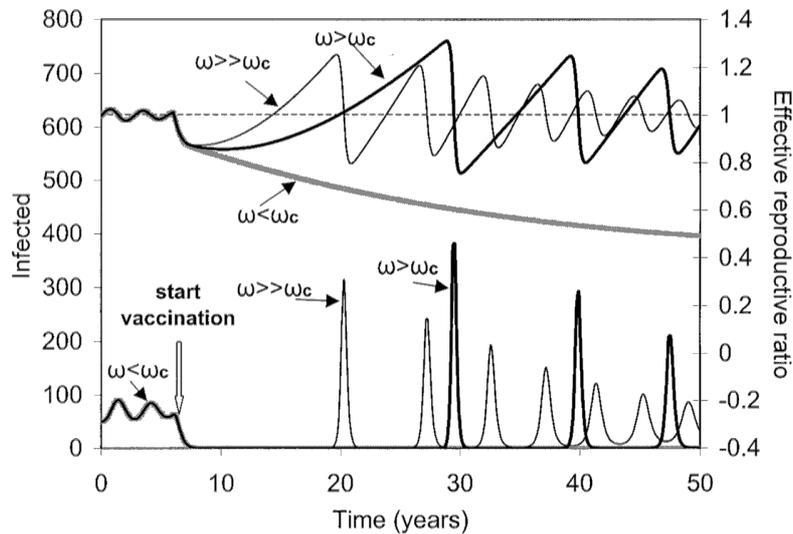


Fig. 4 When the waning rate of a childhood vaccine lies above the critical waning rate, the disease cannot be eradicated. Parameters as in Figure 2, $p = 1$, $e = 1$. For a vaccine that takes and protects in all vaccinated individuals, the critical waning rate is described by: $w_c = \mu/(R_0 - 1)$, which yields $w_c = 0.00197$. For $w < w_c$, w was equal to 0.001, for $w > w_c$ it was equal to 0.02 and for $w \gg w_c$ it was equal to 0.04.

accumulation of susceptible individuals who were vaccinated at birth but whose immunity has since waned. It is worth noting that, as emphasised in Figure 3, the two vaccines that give protection that wanes 'too quickly' in Figure 4 have very long average duration of protection, at mean duration 25 years and 50 years for the two scenarios labelled $\omega \gg \omega_c$ and $\omega > \omega_c$, respectively.

In short, the standard assumption that vaccine-induced immunity will give life-long protection is a very strong assumption indeed. If it is not true, then many of the calculations about coverage levels for eradication will turn out to have been over-optimistic.

The evolution of vaccine resistance

The evolution of vaccine-resistant strains of infectious agents is, potentially, a huge problem for their control by vaccination. Yet, for many infectious diseases, it has been possible to push them to the verge of extinction without vaccine-escape mutants arising. A theoretical framework has recently been developed that allows investigation of why this should be so, what properties of vaccines allow this situation, and what might happen in situations where vaccine-resistant mutants do



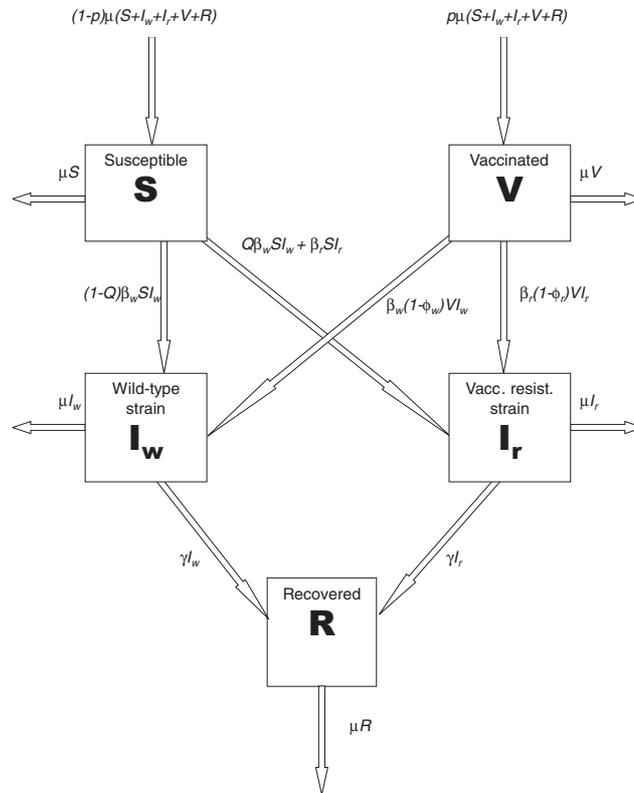
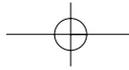
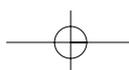


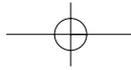
Fig. 5 Modelling competition between strains in childhood disease. Unlike in Figure 1, some of the infection events of strain 1 lead to infection with a mutant variant of the wild-type strain. This strain is assumed to be inferior in terms of force of infection, but partly resistant to the vaccination against the wild-type strain. Before vaccination, the wild-type strain will thus out-compete the vaccine-resistant strain. The vaccine protects against a fraction ϕ_w of infections with the wild-type strain, but only a much lower fraction ϕ_r of infections with the vaccine-resistant strain. Immunity induced by infection with either strain is assumed to confer total cross-immunity against all strains.

arise. A model of the simplest situation for multiple strains is presented here. The simplest situation arises when infection with one strain confers life-long immunity against all other strains⁹. More complex situations are presented elsewhere in the published literature⁹⁻¹².

Modelling infections with total cross immunity

Figure 5 represents the transitions amongst five groups of individuals that must be considered in a model of the vaccine-driven evolution of mutant strains. As before, there are susceptible, vaccinated and recovered individuals. There are two important new features of this model compared





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with the model in Figure 1. First, two strains of agent exist. Occasionally, infection with the wild-type agent will give rise to a mutant strain. In the absence of vaccination, this mutant is at a selective disadvantage (here modelled as being slightly less infectious to susceptible individuals than the wild-type, $\beta_r < \beta_s$). This means that, in the absence of vaccination, this mutant is at a competitive disadvantage and will rarely, if ever, be seen. However, we assume that this mutant is vaccine resistant, *i.e.* the vaccine confers stronger protection against the wild-type than it does against the mutant ($\phi_r > \phi_s$). Under these circumstances, it is possible (although not inevitable) that vaccination can shift the competitive balance between the two strains so that, after vaccination, the new vaccine-resistant strain will emerge. The equations of this new model, with the meaning of each transition labelled as before, are as follows:

$$\frac{dV}{dt} = \begin{array}{cccc} p\mu N & - & \beta_w(1-\phi_w)VI_w & - \beta_r(1-\phi_r)VI_r & - \mu V \\ \text{vaccinated births} & & \text{vfs with wt} & \text{vfs with mutant} & \text{deaths} \end{array} \quad \text{Eq. 9}$$

$$\frac{dS}{dt} = \begin{array}{cccccc} (1-p)\mu N & - & (1-Q)\beta_w SI_w & - & Q\beta_w SI_w & - \beta_r SI_r & - \mu S \\ \text{unvaccinated births} & & \text{true wt infections} & & \text{mutated wt infections} & \text{mutant infections} & \text{deaths} \end{array} \quad \text{Eq. 10}$$

$$\frac{dI_w}{dt} = \begin{array}{cccc} (1-Q)\beta_w SI_w & + & \beta_w(1-\phi_w)VI_w & - \gamma I_w & - \mu I_w \\ \text{true wt infections} & & \text{vfs with wt} & \text{recovery} & \text{deaths} \end{array} \quad \text{Eq. 11}$$

$$\frac{dI_r}{dt} = \begin{array}{cccc} Q\beta_w SI_w & + & \beta_r SI_r & + \beta_r(1-\phi_r)VI_r & - \gamma I_r & - \mu I_r \\ \text{mutated wt infections} & & \text{mutant infections} & \text{vfs with mutant} & \text{recovery} & \text{deaths} \end{array} \quad \text{Eq. 12}$$

$$\frac{dR}{dt} = \begin{array}{cc} \gamma I_w + \gamma I_r & - \mu R \\ \text{recovery} & \text{deaths} \end{array} \quad \text{Eq. 13}$$

The dynamics of the emergence of vaccine resistance

Figure 6 uses the model defined above to illustrate the sequence of events that could lead to the vaccination-driven emergence of a vaccine-resistant strain. Before vaccination is introduced, only one strain is observed. Although the vaccine-resistant strain is continuously generated as a mutant form of the circulating strain, it is less infectious for unvaccinated hosts and is, therefore, at a competitive disadvantage. It is competitively excluded by the wild-type strain. At time 6 years, vaccination is introduced. The vaccination campaign achieves 85% coverage of all new-born individuals with a vaccine that gives 95% protection against the only known strain. The immediate impact is



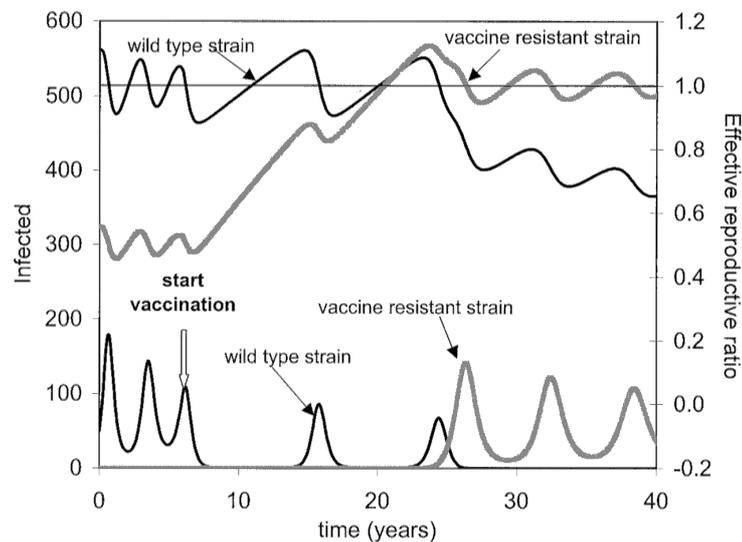
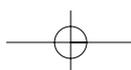


Fig. 6 Vaccination can change the competitive balance between two strains. Parameters as in Figure 2, $p = 0.85$, $\beta_w = 0.0029$, $\beta_r = 0.00145$, $e_w = 0.95$, $e_r = 0.5$, $Q = 0.0001$.

dramatic and there follows a honeymoon period of apparent eradication. This is ended with an epidemic of the wild-type strain for the reasons discussed above. Thus, although under this vaccination regimen the vaccine-resistant strain will eventually have the competitive advantage, that advantage is not immediately manifest and indeed is only established after a very large proportion of the population have been vaccinated. Thus, it is only after the effective reproductive number for the vaccine-resistant strain has exceeded that of the wild-type strain that an epidemic of the vaccine-resistant strain emerges. It is important to note that the strain emerges not because of a *de novo* mutation, but because the substrate required by the strain (large numbers of vaccinated hosts) passes a threshold number that gives the vaccine-resistant strain the competitive advantage.

Is the emergence of vaccine resistance inevitable?

Although Figure 6 illustrates an example in which the vaccine-resistant strain eventually dominates, such emergence is not an inevitable consequence of vaccination. If the cost of resistance is high ($\beta_r \ll \beta_s$), the vaccine-resistant strain will never become competitively superior. This is equally true if the vaccine is sufficiently broad in specificity, so that vaccine efficacy against any new strain is only barely less than efficacy





against the existing strain ($\phi_r = \phi_s$). Alternatively, low levels of vaccination simply fail to ever generate enough vaccinated individuals to give competitive dominance to the vaccine resistant strain.

Concluding remarks

We conclude by summarising the responses to the questions posed in our introduction. The fraction of the population that must be successfully vaccinated to eradicate an infectious agent can be expressed in terms of that agent's basic reproductive number, the amplification factor from one generation to the next in a wholly susceptible population. Agents with a low basic reproductive number (*e.g.* for smallpox $R_0 = 3$) have low threshold coverage levels for eradication. If the target coverage for eradication is not met, there are some counter-intuitive effects of vaccination, in particular the honeymoon-period, an interval of particularly low incidence immediately following the introduction of a mass vaccination programme. The assumption, inherent in many models of vaccination, that vaccine induced immunity will be life-long, has large consequences for the predictions of such models. If vaccine-induced immunity wanes, the predicted target coverage for eradication is higher than if immunity is life-long. Finally, the emergence of vaccine-resistant strains is not an inevitable consequence of vaccination. If vaccines have high enough efficacy and cross-reactivity or are targeted at a small enough section of the population, vaccine-resistant strains will not be expected ever to gain competitive dominance.

The non-linear nature of host-parasite interactions can lead to non-intuitive responses to apparently straightforward interventions. Mathematical models can act as an aid to our intuition in such circumstances, and, when sufficient data are available, can be used to advise on strategic objectives for vaccination programmes.

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Author Queries

- 6 McLean AR, Anderson RM. Year of publication?
- 12 Reference missing?

