Can we prevent the next epidemic? The elimination of childhood diseases by mass vaccination

M.G. ROBERTS   robertsm@agresearch.cri.nz

AgResearch, Wallaceville Animal Research Centre, P.O.Box 40063, Upper Hutt, New Zealand

Abstract. Recently in New Zealand there have been outbreaks of measles and pertussis every six and five years respectively. A model has been used to compare the dynamics of these diseases, and to determine the optimum ages at which children should be vaccinated against them. Whereas measles could be eliminated by giving the second vaccination at five years instead of eleven, it is difficult to devise a practical scheme that would eliminate pertussis. It is then necessary to consider vaccination schemes in the light of the age-structure of future epidemics as well as their timing.

1. Introduction

The childhood diseases that are controlled by vaccination programmes in New Zealand include measles, mumps, rubella and pertussis (commonly known as whooping cough) (Mansoor, 1999). Protection against the first three is via MMR vaccination at 15 months and eleven years, whereas four vaccinations against pertussis are given prior to 15 months. Despite these interventions epidemics of measles and pertussis still occur.

A quantity that is commonly used as an aid to understanding the population dynamics of an infectious disease is the basic reproduction ratio (R_0). This is defined as the expected number of secondary cases that would arise from a single primary case introduced into a fully susceptible population (Diekmann et al., 1990; Anderson & May, 1991; Roberts & Heesterbeek, 1993). If $R_0 < 1$ the disease cannot persist in the population and will, over time, be eliminated. If $R_0 > 1$ the disease persists. Hence the objective of a disease elimination programme is to reduce the basic reproduction ratio below one. If a fraction q of the population is immunised, then the basic reproduction ratio effectively becomes $R_V = (1 - q) R_0$, and to eliminate the disease it is necessary to maintain an immune fraction $q > 1 - 1/R_0$, hence guaranteeing that $R_V < 1$ (Edelstein-Keshet, 1988; Anderson & May, 1991; Roberts & Heesterbeek, 1993; McLean, 1994). Details of the community structure, especially patterns of contact between different age groups and at different times of the year, complicate this argument but do not fundamentally change it.

Until the introduction of measles vaccination in New Zealand in 1970 there was an epidemic of measles every two years. The effect of the vaccination programme was to increase the inter-epidemic period to six years, the last epidemic occurring in 1997. A mathematical model developed in 1996 successfully reproduced the

historical pattern of epidemics and predicted the epidemic of 1997 (Mansoor et al., 1998; Tobias & Roberts, 1998; Roberts & Tobias, 2000). It was then shown that to reduce R_V below one, and hence to prevent further epidemics, it is necessary to change the timing of the second vaccination from eleven years to six years or earlier (Tobias & Roberts, 1998; Roberts & Tobias, 2000). Similar models have been used to study the dynamics and control of measles in other countries, with similar results (e.g. Agur et al., 1993; Babad et al., 1995; Lévy-Bruhl et al., 1997; Gay et al., 1998).

Epidemics of pertussis occurred in New Zealand in 1971, 1974, 1978, 1982, 1986, 1991 and 1996 (Blakely 1999a). In this paper we report on an investigation into vaccination strategies against pertussis, and compare the results with those from the previous study for measles.

2. The pertussis model

We proceed by dividing a theoretical population that resembles New Zealand's into compartments, each of which has a specific disease status. Threshold conditions are then derived for the vaccination coverage that would be required to eliminate the disease. To demonstrate the method a population without age structure is considered. We then apply the method to a population where contact patterns depend on age. The model is similar to that previously used to model measles (Tobias & Roberts, 1998; Roberts & Tobias, 2000). The major difference is that, in contrast to measles, permanent immunity to pertussis is not conferred upon recovery or vaccination.

2.1. The simple model

Let the population of N individuals be divided into S susceptible to pertussis; I infected and infectious; R naturally immune; P susceptible to infection but not disease (hence partially protected); Q infected and infectious but not diseased; and V vaccinated and immune. The flow rates between the compartments are shown in Figure 1. We assume a constant net birth rate B, and approximate early childhood vaccination by allocating a proportion q of new-borns to the vaccinated compartment. Those vaccinated remain immune for an average period of $1/\rho$ years, after which a proportion r become susceptible to infection but not disease, and the remainder become susceptible to infection and disease. If a susceptible becomes infected, they remain infectious for an average period of $1/\gamma$ years, then immune for $1/\sigma$ years. At the end of the period of immunity a proportion s become partially protected, the remainder becoming susceptible. If a member of the P compartment is infected, he becomes infectious but not diseased for a mean time of $1/\delta$ years, after which she joins the immune (R) compartment. The force of infection from the S compartment to the I compartment is $\lambda = \beta I + \zeta Q$, and from the P compartment to the Q compartment $\kappa = \alpha I + \xi Q$.
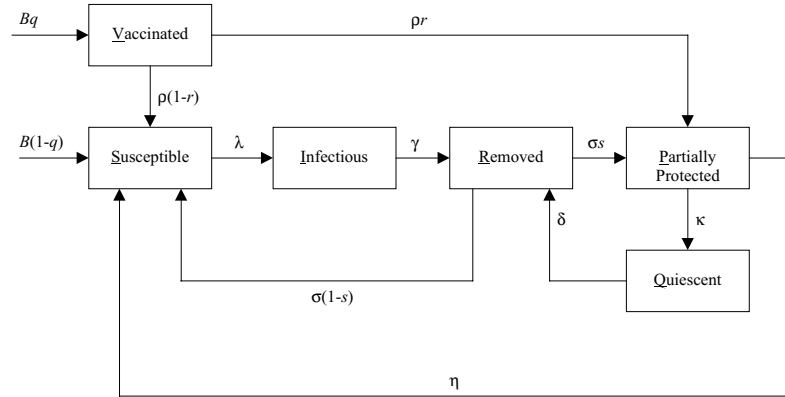
Figure 1. The structure of the model for the dynamics of pertussis. The model without age structure is shown, and for simplicity deaths (which affect all compartments equally) are not included on the diagram.

The equations describing the dynamics of the system are

$$\frac{dS}{dt} = B\,(1-q) - (\beta I + \zeta Q + d)\,S + \sigma\,(1-s)\,R + \eta P + \rho\,(1-r)\,V$$

$$\frac{dI}{dt} = (\beta I + \zeta Q)\,S - (\gamma + d)\,I$$

$$\frac{dR}{dt} = \gamma I + \delta Q - (\sigma + d)\,R$$

$$\frac{dP}{dt} = \sigma s R + \rho r V - (\alpha I + \xi Q)\,P - (\eta + d)\,P$$

$$\frac{dQ}{dt} = (\alpha I + \xi Q)\,P - (\delta + d)\,Q$$

$$\frac{dV}{dt} = Bq - (\rho + d)\,V$$

Choosing $N = B/d$, births and deaths balance and the population size is constant. The equations add to $dN/dt = 0$, hence we can dispense with the need to model one variable explicitly. When no disease is present the steady state solutions are $I^* = Q^* = R^* = 0$ and

$$S^* = N - P^* - V^* \qquad P^* = \frac{\rho r}{\eta + d}V^* \qquad V^* = \frac{Bq}{\rho + d}$$

In the absence of vaccination $S^* = N$, $P^* = V^* = 0$, and it is a trivial matter to show that the disease cannot maintain itself in the population when the basic reproduction number $R_0 = \beta N/(\gamma + d)$ is less than one. Typical values of R_0 for pertussis in developed countries are in the range $16 - 18$ (Anderson & May, 1991). For more complex models R_0 can be obtained from the next generation matrix,

which specifies the expected number of secondary infections in each compartment due to a single introduction of infection in one compartment in a susceptible population (Diekmann et al., 1990). For example, the next generation matrix derived from the above model in the presence of vaccination is

$$M = \begin{pmatrix} \frac{\beta S^*}{\gamma+d} & \frac{\varsigma S^*}{\delta+d} \\ \frac{\alpha P^*}{\gamma+d} & \frac{\xi P^*}{\delta+d} \end{pmatrix}.$$

The entry M_{11} represents the mean number of secondary infections in the I compartment due to a primary infection in the I compartment and an otherwise infection-free population. It is calculated by multiplying the transmission rate β, the number of susceptibles S^*, and the mean period of infectiousness $1/(\gamma+d)$. Similarly M_{12}, M_{21} and M_{22} represent the numbers of secondary infections in the I, Q and Q compartments respectively due to primary infections in the Q, I and Q compartments respectively, in an otherwise infection-free population. A vaccination strategy will achieve elimination of the disease if $R_V = \mathcal{R}(M) < 1$, where $\mathcal{R}$ signifies spectral radius. For the values of R_0 quoted above, vaccination coverage would have to maintain immunity in more than 93% of the population.

2.2. The age-structured model

A subdivision of the population into age groups allows for different inter-group contact rates, and provides a means by which strategies based on vaccinating children at defined ages may be modelled. We choose groups 0-9 to represent ages 0–3 months, 3–4 months, 4–5 months, 5–15 months, 1.25–3 years, 3–5 years, 5–11 years, 11–17 years, 17–40 years and ¿40 years respectively. We assume that group 9 plays no part in the epidemic. Indexing compartments by age group number, our equations become:

$$\frac{dI_0}{dt} = \lambda_0 S_0 - (\gamma + \mu_0) I_0$$

$$\frac{dR_0}{dt} = \gamma I_0 + \delta Q_0 - (\sigma + \mu_0) R_0$$

$$\frac{dP_0}{dt} = \sigma s R_0 - \kappa_0 P_0 - (\eta + \mu_0) P_0$$

$$\frac{dQ_0}{dt} = \kappa_0 P_0 - (\delta + \mu_0) Q_0$$

and $V_0 = 0$; and for $i = 1 \ldots 8$

$$
\begin{aligned}
\frac{dI_i}{dt} &= \mu_{i-1}I_{i-1} + \lambda_i S_i - (\gamma + \mu_i)\,I_i \\
\frac{dR_i}{dt} &= \mu_{i-1}R_{i-1} + \gamma I_i + \delta Q_i - (\sigma + \mu_i)\,R_i \\
\frac{dP_i}{dt} &= \mu_{i-1}P_{i-1} + \sigma s R_i + \rho r V_i - \kappa_i P_i - (\eta + \mu_i)\,P_i \\
\frac{dQ_i}{dt} &= \mu_{i-1}Q_{i-1} + \kappa_i P_i - (\delta + \mu_i)\,Q_i \\
\frac{dV_i}{dt} &= \mu_{i-1}V_{i-1} + q_i \mu_{i-1}S_{i-1} - (\rho + \mu_i)\,V_i
\end{aligned}
$$

where

$$
\lambda_i = \beta \sum_{j=0}^{8} C_{ij}I_j + \zeta \sum_{j=0}^{8} C_{ij}Q_j
$$

and

$$
\kappa_i = \alpha \sum_{j=0}^{8} C_{ij}I_j + \xi \sum_{j=0}^{8} C_{ij}Q_j
$$

are the forces of infection on the susceptible and partially protected compartments respectively, and the terms C_{ij} specify relative rates of contact between different age groups (see below).

The transition rates between age groups μ_i are the reciprocals of the age group width, assuming the death rate is negligible below 40 years of age. Hence the size of each age group is constant and equal to the group width multiplied by the birth rate, which was set at $B = 57435$ person yr.$^{-1}$ to equal that of New Zealand in 1994 (Statistics New Zealand, 1996). The proportion of the population that is successfully vaccinated on entering group i is q_i. Due to the uncertainty of the timing of interventions in the first few weeks of life, the first two vaccinations were approximated by one at 3 months (Blakely et al., 1999b), with subsequent vaccinations at 5 months and 15 months.

Grenfell & Anderson (1989) used a latent period of 7 days and an infectious period of 22 days in their model of pertussis, whereas Anderson & May (1991) quote an incubation period of 6–10 days, latent period of 21–23 days and an infectious period of 7–10 days. Hence we set $\gamma = \delta = 12.6$ yr.$^{-1}$ Other flow rates estimated from the literature were $\rho = \sigma = 0.1$ yr.$^{-1}$ and $\eta = 0$ (see e.g. Grenfell & Anderson, 1989; Hethcote, 1997). The proportions remaining partially protected following loss of immunity were assumed to be $r = s = 0.9$, and in the absence of better information we set α, β, ξ and ζ all equal to 4.06×10^{-5} person^{-1} yr.$^{-1}$, to achieve a suitable value of R_0 (see below).

The contact rates C_{ij} are based on those used for measles (Roberts & Tobias, 2000). We define activity levels $a_1 = 1$ for infants (age groups 0-3), $a_2 = 3$ for

pre-schoolers (groups 4-5), $a_3 = 6$ for primary school children (group 6), and $a_4 = a_5 = 3$ for secondary school children and adults (groups 7&8) respectively. Within group contact rates are then $C_{ii} = a_{k(i)}$, and inter-group contact rates are $C_{ij} = \varepsilon \sqrt{a_{k(i)} a_{k(j)}}$ if $k(i) \neq k(j)$, where $k(i) = 1$ if $i \in [0, 3]$, $k(i) = 2$ if $i \in [4, 5]$, and $k(i) = i - 3$ if $i \in [6, 8]$. This process is equivalent to specifying a WAIFW ("who acquires infection from whom") matrix (Anderson & May, 1991; Hethcote, 1996). By comparison with the measles model we set $\varepsilon = 0.4$ (Roberts & Tobias, 2000).

The next generation matrix in the absence of vaccination is defined by

$$(M_0)_{i+1,j+1} = \frac{\beta C_{ij} N_i + \epsilon_{i-1,j} \mu_j}{\mu_i + \gamma}$$

where $\epsilon_{i-1,j} = 1$ if $i - 1 = j$ and zero otherwise. We then have $R_0 = \mathcal{R}(M_0)$. Using the parameter values above we obtain $R_0 = 15.8$.

The steady state under vaccination with no disease solves

$$V_i^* = \frac{q_i \mu_{i-1} S_{i-1}^* + \mu_{i-1} V_{i-1}^*}{\rho + \mu_i} \qquad P_i^* = \frac{\mu_{i-1} P_{i-1}^* + \rho r V_i^*}{\eta + \mu_i}$$

and $S_i^* = N_i - P_i^* - V_i^*$ for $i = 0 \ldots 8$, with $S_0^* = N_0$ and $P_0^* = V_0^* = 0$. The next-generation matrix is then

$$M_V = \begin{pmatrix} M_1 & M_2 \\ M_3 & M_4 \end{pmatrix}$$

where M_1 is equal to M_0 with N_i replaced by S_i^*; M_2 is equal to M_0 with N_i replaced by S_i^* and β replaced by ζ; M_3 is equal to M_0 with N_i replaced by P_i^*, β replaced by α and γ replaced by δ; and M_4 is equal to M_0 with N_i replaced by P_i^*, β replaced by ξ and γ replaced by δ. The basic reproduction ratio under vaccination is then $R_V = \mathcal{R}(M_V)$. Estimates of current vaccine coverage in New Zealand are 80-90% by 3 months and at 5 months, and 80% at 15 months. Efficacy is estimated at 50-80% by 3 months and 80-95% at 5 and 15 months. Hence $q_1 = 0.5525$, $q_3 = 0.74375$, $q_4 = 0.7$, $q_i = 0$ otherwise; leading to $R_V = 13.33$. Further epidemics of pertussis are therefore inevitable with the present strategy.

3. Optimising vaccination strategies

The model described above is more complex than that used by Roberts & Tobias (2000) to describe the epidemiology of measles in New Zealand. In fact, the measles model may be derived from it by deleting the P and Q compartments, and changing parameter values. In particular, immunity to measles may be regarded as life-long whether it is acquired through vaccination or infection, hence $\rho = \sigma = 0$. For measles we have $R_0 = 12.8$, which is reduced by the current vaccination programme to $R_V = 2.85$. The current programme based on vaccinations at 15 months and eleven years, leaves an interval between treatments sufficient for the number not effectively vaccinated to accumulate to a critical level. Hence to eradicate measles

it is necessary to bring forward the timing of the second vaccination, school entry at five years would provide a suitable opportunity.

The results obtained for pertussis vaccination showed that eradication is a long way from being achieved. The fundamental difference between the two diseases is the lack of permanent immunity conferred by infection or vaccination against pertussis. It was determined that if a pertussis vaccine were to confer life-long immunity, the current vaccination schedule would achieve $R_V = 0.64$. These results are similar to those obtained from a similar study in the USA (Hethcote, 1997). However, childhood vaccination against pertussis does reduce the number of cases in early years when the effects of the disease are more severe, and is therefore beneficial in itself.

The pattern of repeated epidemics is due to seasonal forcing of transmission arising from closer contact between children during the school year (Grenfell & Bolker, 1994). Numerical solution of the measles model confirmed this, and established a relationship between R_V for the non-forced model and the inter-epidemic period of the forced model. Although the values of R_V are not equal for the two models, a lower value of R_V calculated from the non-forced model would lead to less frequent epidemics in the seasonally forced model, and $R_V \ll 1$ implies elimination of the disease. It has been found in the UK that regular epidemics of measles, correlated between major cities, have given way to irregular uncorrelated outbreaks post-vaccination; whereas pertussis vaccination strategies have synchonised a previously uncorrelated epidemic pattern (Rohani et al., 1999). It is argued that the longer infectious period of pertussis makes the dynamics less sensitive to seasonal forcing, and concluded that pertussis outbreaks can be explained by simple deterministic arguments. The success of our previous investigation into measles provides hope that this may be the case in New Zealand, and that analytical tools may prove valuable in optimising vaccination strategies against the common childhood diseases.

Acknowledgments

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