Economic Evaluation of Vaccination Programs: The Impact of Herd-Immunity

M. Brisson, MSc, BSc, W. J. Edmunds, PhD, MSc, BSc

The unique characteristic of vaccination is that it not only reduces the incidence of disease in those immunized but also indirectly protects nonvaccinated susceptibles against infection (produces herd-immunity). The bulk of economic evaluations of vaccination programs continue to use models that cannot take into account the indirect effects produced by herd-immunity. Here, the authors illustrate the importance of incorporating herd-immunity externalities when assessing the cost-effectiveness of vaccination programs. To do this, they compare 2 methods of estimating the benefits of routine mass vaccination: one that includes herd-immunity (dynamic approach) and one that does not (static approach). Finally, they use the results to clarify a number of misconceptions that are common in the literature concerning herd-immunity and dynamical effects produced by models. Key words: infectious diseases; externality; modeling; vaccination; dynamic models. (Med Decis Making 2003;23:76-82)

The demand for economic evaluation of health interventions has risen dramatically in the past decade and is increasingly being used by agencies and government organizations as an aid to decision making. To ensure the quality of economic evaluation and standardization/comparability of methods/results, numerous guidelines have been published.

It has been suggested that additional specific guidelines may be needed for the economic evaluation of vaccination programs. The reasoning behind this stems from the unique characteristic of vaccination against infectious disease: Mass vaccination not only reduces the incidence of disease in those immunized but also indirectly protects nonvaccinated susceptibles against infection. The concept of indirect protection of susceptibles (e.g., nonvaccinees) is termed herd-immunity. These herd-immunity effects have many of the characteristics of public goods (or even public bads, see later); hence, vaccination programs tend to be funded wholly or partially by governments to help ensure optimal uptake. Therefore, the appropriate perspective of most economic analyses of immunization programs is that of society rather than the individual, requiring herd-immunity effects to be incorporated in the analysis.

Although there are many types of models that are used to predict the impact of vaccination, they can be broken down into 2 main categories: 1) dynamic and 2) static. The major difference between these types of analysis is that in dynamic models, the rate at which susceptibles become infected is dependent on the number of infectious individuals in the population (thus, the system is inherently nonlinear) whereas static models treat this rate as a fixed parameter. Since mass vaccination results in fewer infectious individuals in the population, under the dynamic framework, the rate at which susceptibles become infected will decline, whereas under a static framework, this rate remains unaltered (although there may be fewer

Received from the Immunisation Division, PHLS Communicable Disease Surveillance Centre, London NW9 5EQ, UK, and the Department of Economics, City University, London EC1V 3HD, UK. This study was funded by the UK Medical Research Council (grant number G9818303). Address correspondence and reprint requests to Dr. Edmunds, PHLS Communicable Disease Surveillance Centre, 61 Colindale Avenue, London NW9 5EQ, United Kingdom; telephone: +44 (0) 208 200 6968 x4410; fax: +44 (0) 208 200 7968; e-mail: jedmunds@phls.org.uk.

DOI: 10.1177/0272989X02239651

76 • MEDICAL DECISION MAKING/JAN–FEB 2003
susceptibles to act on due to vaccination). Thus, dynamic models capture herd-immunity effects, whereas static models omit them.

Currently, the bulk of economic evaluations of vaccination programs continue to use static models, such as decision analysis Markov models and cohort models, and therefore do not take into account the indirect effects produced by herd-immunity. Furthermore, authors using static models occasionally claim to be taking account of herd-immunity effects. This comes from a misunderstanding of what herd-immunity is, what its effects are, and how to incorporate it into decision analyses. In this article, we illustrate and describe the effect of herd-immunity on the dynamics of infection using routine varicella vaccination as an example. We compare results from a dynamic model with those of a static model to illustrate and quantify the impact of incorporating herd-immunity externalities. It should be noted that the dynamic model used here is a simplified version of the one recently used for predicting the impact of varicella vaccination (for further results, see refs. 14–16). These simplifications are made for ease of exposition.

METHODS

Mathematical Models

The dynamic model used here is the realistic age-structured deterministic model of varicella presented in Brisson and others (see the appendix for a description of the model). The single difference between the static model and the dynamic model used here is that the force of infection (per-susceptible rate of infection, sometimes termed the attack rate) in the static model remains constant through time, whereas in the dynamic model, the rate at which susceptibles become infected is assumed to be a function of the number of infectious individuals in the population at a given point in time, multiplied by the effective contact rate between susceptibles and infectious individuals. That is, \( \lambda = \text{fixed (static)} \) and \( \lambda(t) = \beta I(t) \) (dynamic),

where \( \lambda \) is a \((1 \times k)\) vector representing the force of infection in each of the \( k \) age groups, \( \beta \) is a \( k \times k \) matrix representing the effective contact rate between individuals by age group, and \( I(t) \) gives the number of infectious individuals in each age group at time \( t \). Static models are usually applied to a single aging cohort, whereas dynamic models are run for many years to allow the full effects of the intervention to become apparent. For comparability, the static model presented here is applied to multiple cohorts. It should be noted that in a cohort model, since the force of infection is constant with respect to time, the cost-effectiveness results are identical for single or multiple cohort models provided that all cohorts are followed for the same length of time (usually until death).

Parameter Estimates

Simulations were performed for a population with characteristics similar to England and Wales. The population size and average life expectancy were assumed to be 50 m and 75 years, respectively. The age-specific force of varicella infection (the per-susceptible rate of infection) in England and Wales was taken from pre-vaccination data. The different health outcomes were taken from Brisson and others. The predicted number of cases of varicella was estimated directly from the models. The estimated varicella case fatality was applied to the predicted number of cases. For simplicity, we assume that vaccine is perfect; that is, all vaccine recipients will derive lifelong immunity after a single dose.

Vaccination Programs

All simulations are with 80% coverage unless otherwise stated. The different vaccination strategies investigated were

- routine vaccination at 1 year of age (infant vaccination) and
- routine vaccination at 11 years of age (adolescent vaccination).

RESULTS

Dynamics and Incidence of Infection

The introduction of routine infant mass vaccination typically produces dynamic effects that are composed of 3 phases (Figure 1a).

- Honeymoon period: Shortly after the start of vaccination (at high levels of coverage), the number of susceptibles falls to such low levels that continued endemic transmission is no longer possible. This results in a period of very low incidence, which is commonly called the “honeymoon period.”
- Posthoneymoon epidemic: Over time, the low incidence of infection allows susceptibles (here, individu-
als who have not been vaccinated) to accumulate via births. Once a threshold of susceptibles is surpassed, an epidemic occurs, which is called the “posthoneymoon epidemic.”

- Postvaccination endemic equilibrium: After the posthoneymoon epidemic, infection settles into a new equilibrium with much lower incidence than before vaccination.

Such dynamics have been observed following measles and mumps vaccination. Static models cannot capture these dynamics; instead, the incidence of infection steadily declines as the number of cohorts vaccinated increases in the population (Figure 1b). Figure 1c shows the predicted incidence of varicella following vaccination using both the static and dynamic model. The impact of herd-immunity on the incidence of infection can be visualized as the difference between the dynamic (full line) and the static model (dotted line). Quantitatively, with the infant strategy (80% coverage), herd-immunity (difference between the 2 models) is estimated to prevent 10 m cases of varicella over the first 80 years of vaccination in a country similar to England and Wales (50 m).

The extent of protection conferred by herd-immunity depends on the amount of continuing infection in the community. If only a small proportion of the population is immunized (low coverage and/or targeted vaccination and/or poor vaccine efficacy), then vaccination confers little or no herd-immunity since the force of infection acting on those who remain susceptible remains relatively unchanged. Here, we illustrate this point using adolescent vaccination against varicella as an example. The predicted number of cases of varicella over time is similar using the dynamic and static approaches (Figure 1c). This is expected since the
bulk of cases (85%) are in children younger than 11 years; thus, vaccinating 11-year-olds has little effect on the overall force of infection of varicella (i.e., the risk of children getting chicken pox).

**Shift in the Age at Infection and Morbidity of Disease**

Routine infant vaccination will cause the average age at infection to rise. The shift in the age at infection is due to 2 factors:

- **Cohort effect**: For routine infant immunization, as vaccinated cohorts age, infection becomes concentrated in the older unvaccinated cohorts. This cohort effect can be clearly seen with the static model (Figure 1b) since herd-immunity effects do not confound it. In Figure 1b, incidence first declines in children while it is constant in the older age groups. Hence, the proportion of adult cases increases. Only when all cohorts are vaccinated does this effect disappear.

- **Herd-immunity effect**: Vaccination at high levels of coverage leads to reduced circulation of infection. As a result, susceptibles are less likely to come into contact with infectious individuals and therefore tend to be older when they eventually become infected. The shift in the age at infection can clearly be seen in Figure 1a. The number of cases of varicella in adults older than 45 years of age is expected to increase by more than 3-fold after vaccination. Note that here the number of adult cases increases, not just the proportion. Also remember that there is no waning immunity: Waning vaccine-induced immunity is not necessary to induce an increase in the number of adult cases.

An increase in the number of adult cases can lead to a rise in mortality and morbidity if disease severity increases with age at infection. Many viral infections are more severe if contracted as adults; examples include polio, hepatitis A virus, and mumps, and such perverse outcomes arising from mass infant vaccination have been observed for rubella in Greece (rubella is a benign childhood infection, which can have devastating effects on the fetus if a mother contracts the virus during pregnancy). These shifts in the age at infection can also have beneficial effects if disease is most severe in young children (e.g., pertussis and measles in developing countries).

Since static models cannot predict an absolute increase in adult cases, the choice of model can have an important impact on the overall assessment of the benefit of vaccination. We illustrate this by comparing the predicted number of varicella deaths in England and Wales following vaccination using the dynamic and static models (Figure 2). Varicella deaths are used as an example since varicella-associated case fatality increases dramatically with age. The dynamic model initially produces a rapid decrease in deaths following vaccination (Figure 2a). However, after 50 years, the number of deaths due to varicella rises and surpasses the prevaccination level due to the increase in the number of cases in adults. In contrast, using the static model, the number of deaths falls as the number of cohorts that are vaccinated increases (Figure 2b). Over the first 80 years of vaccination, the dynamic model predicts that vaccination will produce 315 deaths over the prevaccination level whereas the static model predicts...
that 765 deaths will be prevented. Thus, herd-immunity (difference between the 2 models) is estimated to cause 1080 deaths over the first 80 years of vaccination in England and Wales.

The extent to which the average age at infection will rise following routine infant vaccination depends on the amount of continuing infection in the community. As the proportion of immunized individuals increases in the population, so does the average age at infection due to increased herd-immunity. To illustrate this, in Figure 3, we present the estimated number of varicella deaths in England and Wales at postvaccination equilibrium by vaccine coverage (Figure 3). Here, coverage is equal to the proportion immunized since the vaccine is assumed to be perfect. For the dynamic model, the proportion of deaths in adults increases between 0% and 60% coverage (Figure 3a). Furthermore, only when coverage exceeds 80% does vaccination seem to diminish varicella transmission sufficiently to reduce adult mortality to levels below the prevaccination state. In contrast, without herd-immunity (Figure 3b), the number of deaths decreases linearly with increased coverage and there is no shift in the age distribution of deaths; for example, 50% coverage will reduce the number of deaths by 50% in all age groups. This leads to our final point: For the static model, the number of cases or deaths prevented per immunized individual is independent of the overall number of individuals vaccinated (coverage). This means that the cost-effectiveness ratio is independent of coverage (overall size of the vaccine program), assuming there are no fixed costs associated with setting up the program.

However, Figure 3a clearly shows that if herd-immunity is taken into account, the size of the program has a major impact on effectiveness and thus cost-effectiveness.

CONCLUSION

The aim of this article was to illustrate the importance of incorporating herd-immunity externalities when assessing the health benefits of vaccination programs. To do this, we compared 2 methods of estimating the benefits of routine mass vaccination: one that includes herd-immunity (dynamical approach) and one that does not (static approach). We showed that because they take into account herd-immunity effects, dynamic models

- produce nonlinear dynamics following vaccination (Figure 1a),
- predict a higher number of cases prevented by vaccination (Figure 1c),
- produce proportional and absolute shifts in the age at infection (Figure 2a), and
- can predict increases (or decreases) in morbidity and mortality due to shifts in the age at infection following vaccination (Figures 2 and 3).

These dynamical effects are dependent on the extent to which vaccination prevents transmission of infection in the population. If only a small proportion of the population is immunized (low coverage or targeted
where the number of individuals in age cohort are varicella susceptible, naturally infected but not infected with the pathogen (as occurs with some vaccines), then herd-immunity effects are negligible (Figures 1 and 3). Under such conditions, static and dynamic models produce similar results. Static models may also be used as a tool to estimate the worst-case scenario when herd-immunity externalities cannot produce negative effects (disease severity does not increase with age). In other circumstances, dynamic models should be used.

These results can be used to clarify a number of misconceptions, which are common in the literature concerning herd-immunity and dynamic effects produced by models:

- Herd-immunity is always a good thing: We show that herd-immunity can cause the age at infection to increase, which can cause serious deleterious consequences (Figures 2 and 3). It is not always a conservative assumption to ignore herd-immunity effects. Indeed, a static model may grossly overestimate the effectiveness of mass vaccination at preventing serious disease if the risk of developing complications increases with age at infection, as is shown here for chicken pox.
- Waning vaccine-induced immunity is necessary to cause an increase in adult cases: Although waning vaccine-induced immunity can exacerbate increases in the average age at infection, it is not necessary, as we have demonstrated here.
- Static models can give rise to shifts in the age at infection: If a static model is applied to successive cohorts, then the models can produce a temporary shift in the age at infection. These shifts are due to a cohort effect (the vaccinated cohorts make up the younger age groups) and not herd-immunity. Once all the cohorts have been vaccinated, the age distribution of infection will be identical to the prevaccination state. Furthermore, this will produce only a temporary proportional increase in adult infections (as opposed to absolute increases) as the rate of infection in the older (unvaccinated) cohorts remains the same as it was before vaccination. Hence, static models cannot investigate whether shifts in the age at infection following vaccination will produce increases (or indeed decreases) in morbidity.

There is a large literature on models of infectious disease transmission dating back to Bernouilli in the 18th century (for a comprehensive textbook on the subject, see Anderson and May9 or Bailey24). Analysts who ignore this literature (because of complexity) and assume that the disease in question is not infectious (as static models implicitly assume) do so at the risk of biasing their results.

**APPENDIX**

**Dynamic Model: Mathematical Structure**

The model possesses 66 age cohorts (0, 1, . . . , 65+). Following Schenzle,25 children enter continuously throughout the year into the 1st age cohort at 6 months of age. Thereafter, individuals change age cohorts at the beginning of each school year (boundary conditions). Vaccination is performed at the end of the year as individuals move up an age class. Within each age cohort i, the differential equations for this deterministic model are as follows:

\[
\frac{dS_i(t)}{dt} = B_i - \left[ \lambda_i(t) + \nu_i \right] S_i(t) \tag{1}
\]

\[
\frac{dE_i(t)}{dt} = \lambda_i(t) S_i(t) - \left( \sigma_i + \mu_i \right) E_i(t) \tag{2}
\]

\[
\frac{dI_i(t)}{dt} = \sigma_i E_i(t) - \left( \alpha_i + \mu_i \right) I_i(t) \tag{3}
\]

\[
\frac{dR_i(t)}{dt} = \alpha_i I_i(t) - \mu_i R_i(t) + \nu S_i(t), \tag{4}
\]

where the number of individuals in age cohort i at time t who are varicella susceptible, naturally infected but not infectious, and immune are given by the state variables \(S_i(t), E_i(t), I_i(t),\) and \(R_i(t)\), respectively; \(B_i\) is the birth rate; \(\mu_i\) is the mortality rate; \(\nu_i\) is the vaccine coverage (by age); \(\sigma_i\) and \(\alpha_i\) are rates of flow from latent to infectious and infectious to immune groups; and \(\lambda_i(t)\) is the force of infection by age group (see the Methods section and Brisson and others14 for details). The initial conditions for the set of equations are taken to be the prevaccination equilibrium number of individuals in each epidemiological class by age, which are determined by treating \(\lambda_i(0)\) as a fixed parameter (i.e., by using the static cohort model). The equations are solved numerically using a fourth-order Runge-Kutta algorithm.26

Note that the model (above) differs from that used by Brisson and others14 only in that vaccination is assumed to result in lifelong immunity; hence, it is no longer necessary to include vaccinated classes (with varying degrees of immunity and infectiousness), as all those who are vaccinated pass directly into the immune class \(R_i(t)\).
REFERENCES


