REVIEWS IN MEDICAL MICROBIOLOGY

Application of mathematical models to the design of immunization strategies

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Summary. This article is the second part* of a review of the application of mathematical models of the transmission dynamics of infectious disease in the design of community-wide immunization programmes. We illustrate the use of models in predicting the potential impact of different vaccination strategies for a variety of viral infections with emphasis on the design of optimal policies for mass vaccination. Details of the structure and assumptions of the mathematical models, and the underlying epidemiological concepts upon which they are based, were the subject of the first part of the review.[1] Case studies are used to illustrate the application of mathematical models to three issues of recent concern, namely: (i) the debate over the control of congenital rubella infection, (ii) the merits and possible hazards of mass vaccination against varicella-zoster, and (iii) whether or not it is always in the interests of the community to adopt a vaccine with the lowest complication rate. These illustrate the broad range of issues to which models may be applied and the topicality of the modelling approach to immunization policy design. Finally, we indicate future applications of mathematical models to other important issues facing public health authorities.

Introduction

Why use mathematical models?

Many vaccine-preventable viral and bacterial infections continue to thwart concerted efforts to control their circulation by community-based immunization programmes in populations in both developed and developing countries. For many industrialized countries the persistence of, for example, measles and rubella continues (albeit at greatly reduced levels than pre-vaccination), despite the input of considerable resources, the existence of a well-developed health infrastructure, and, for a growing number of countries, the attainment of high levels of coverage. Much effort has and continues to be directed towards the development of effective, safe and cheap vaccines as a first, and vital, step towards the eventual control of common viral and bacterial infections by mass immunization. Recent advances in this area, such as the production of synthetic hepatitis B (HBV) vaccine, a killed hepatitis A (HAV) vaccine, high potency measles vaccine strains, meningococcal and *Haemophilus influenzae* type B vaccines, and the advent of enteric vaccines against typhoid, cholera and rotavirus, provide great promise for the future.[2–5] However, it is increasingly clear that much thought and effort needs to be targeted at the strategy for delivering these vaccines to human populations if mass immunization is to achieve the desired goal of the long-term interruption of transmission.[6,7]

A good example of this issue is provided by the resurgence of measles, mumps and rubella in the USA despite high coverage and the requirement of a vaccine certificate before school entry. Observations from recent outbreaks indicate a preponderance of cases both in those too young to receive vaccine and in older children and particularly teenagers – at ages above the typical age at infection prior to the introduction of mass immunization.[8–10] A significant proportion of these older individuals have a history of vaccination. These events raise many questions about the epidemiology of these infections under the influence of mass immunization and the adopted strategies of vaccination. For example, what is the optimal age at which to vaccinate, and how important is heterogeneity (socially and spatially) in vaccine uptake? Is there a need to introduce two stage immunization strategies? Is vaccine efficacy lower than suspected or are we seeing the result of waning vaccine-induced immunity? The USA shares these and other problems with many other industrialized countries. In the UK much improvement in vaccine uptake accompanied the introduction of MMR, (measles, mumps, rubella vaccine) and variation in coverage between health authorities has been overcome by operational measures such as the designation of regional coordinators responsible for vaccine uptake.[11] However, the very success of vaccination programmes in reducing the incidence of cases generates conflict between the interest of the community and the interest of the individual. The conflict arises from the need to weigh the risks to the individual arising from vaccination against those to the individuals in the community who do not receive the vaccine and acquire natural infection. Examples of confusion over the risk of vaccination and natural infection in the UK include the pertussis vaccine episode in the mid 1970s and current discussion concerning the relative merits of different mumps vaccines.[12,13] The development of new vaccines generates further questions about the type of implementation strategy most appropriate, as illustrated by potential uses of the HBV vaccine (would a targeted or mass cohort programme be most appropriate?)[14] and the generation of new high potency measles vaccines which allow for reductions in the recommended age at vaccination.[3]

Faced with these sorts of issues there is a need for precise scientific methods with which to assess the community benefits (or drawbacks) of different immunization policies and to predict the potential impact of each vaccination programme. Mathematical models lend themselves to this task. In providing a quantitative framework in which to incorporate factors important in determining patterns of spread of infection and the incidence of associated disease, models are ideally suited both to measuring and comparing the merits of different strategies of immunization, and to improving our understanding of the observed impact of present vaccination programmes. Models can be thought of as tools to assist in health policy design particularly when combined with detailed data on the epidemiology of the infection and vaccination uptake.[15]

We have previously reviewed the major epidemiological concepts and principles that underlie the impact of community-based immunization on the transmission dynamics of infectious diseases.[1] In addition, in the first part of this review,[1] we provided an outline to the formulation of an age-structured mathematical model with which to describe the transmission dynamics of infectious diseases transmitted by direct or close contact (other than sexual contact). The aim of this review is to illustrate the application of mathematical models of this nature to a range of issues concerning the design and implementation of mass immunization programmes. We emphasize two main uses, namely:

1. The way models can draw attention to the potentially harmful outcomes following the introduction of immunization policies.
2. As a means of making objective decisions about which is the best vaccination policy to adopt in a given country with respect to age at vaccination, level of uptake, etc.

On the basis of these models, and various refinements of them we illustrate their use in helping to clarify a number of topical problems in the epidemiology and control of infection, namely:

1. The choice of selective, cohort or dual-stage immunization programmes in the control of rubella infection and congenital rubella syndrome (CRS)
2. The control of varicella and herpes-zoster; could there be potential hazards associated with a mass-childhood vaccination programme?
3. The conflict between community vs individual interests and the concern over the reactogenicity of different strains of the mumps virus vaccine.

Dual stage policies and the control of rubella

The debate which has surrounded rubella immunization in the UK over the past 2 decades provides a good example of the difficulty in distinguishing between alternative strategies. It highlights the importance of quantifying both the effects of vaccination (i.e. increased average age at infection, increased inter-epidemic period) and the age-dependent risk of severe disease arising from infection, when evaluating the merits of different vaccination policies.[16–18]

The goal of rubella immunization is the prevention of maternal infection, in particular during the first 17 weeks of pregnancy where the risk of severe abnormalities associated with CRS is highest. Two major options are available for the control of congenital rubella. A selective programme of immunization in which adolescent girls are vaccinated before entering the childbearing age classes aims to supplement naturally acquired herd immunity developed before the age at vaccination in order to reduce the proportion of women who are susceptible as they move into the at-risk fertility age classes. This approach has the advantage that herd immunity within the population is largely naturally acquired – immunity which is known to typically provide lasting solid protection from reinfection. In addition, individuals immunized

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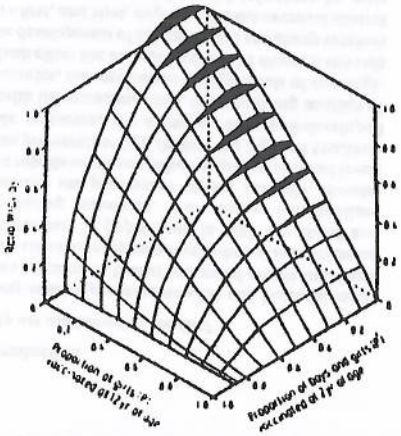


Fig. 1 Benefit of a dual-stage rubella vaccination policy. The long-term (or equilibrium) impact of a particular immunization strategy is measured as the ratio (w/a_1, a_2) denoting the predicted number of cases of maternal infection (primary cases in pregnant women between ages 16 (a_1) and 40 (a_2) years) after the introduction of immunization divided by the predicted number in the same age range before control measures. A ratio of less than 1 indicates a beneficial impact of immunization. The results are plotted as a three-dimensional surface to illustrate the relative benefits of a single stage policy of childhood immunization or of selective schoolgirl immunization or a combination of the two at a variety of levels of vaccine uptake. In the shaded regions, a two-stage policy is predicted to increase the number of CRS cases over that predicted from a programme of selective immunization alone. (Adapted from Anderson and May, 1983[18]).

(from vaccine or natural infection) will continue to experience the boosting effect provided by re-exposure to the virus which circulates in the male segment of the community and younger females. However, the fact that the vaccine is administered to, at most, only half of the population at an age when the majority of infections have taken place will have only a marginal impact on the circulation of virus within the general population. Thus, those women who escape infection in their younger years and who miss vaccination are exposed to almost the same risk of infection during pregnancy that would have been the case before the introduction of this type of immunization programme. For this policy to be successful in preventing all cases of CRS, 100% of women must be vaccinated before entering the childbearing age classes.

An alternative strategy is that of mass childhood immunization of boys and girls. The aim of this policy is to interrupt the spread of wild virus in the community and it is best achieved by vaccinating as soon after birth as possible and reducing susceptible numbers in the childhood ages where virus circulation is most intense. Mass cohort vaccination, as outlined in our previous review,[1] acts to increase the average age at which infection is typically acquired. For an infection in which the risk of serious disease increases with age (i.e. directly related to fertility) these indirect effects are therefore of great concern.

Simulations of the long-term (i.e. equilibrium) impact of combinations of the two types of vaccination strategies are shown in Figure 1 for various levels of coverage using an age- and time-structured mathematical model.[1,17,19] The model incorporates forces of infection derived from UK serological data and the risk of congenital infection is determined from the probability that an infected individual is pregnant (using age-specific England and Wales fertility data). The effectiveness of each vaccination strategy is measured as a ratio, w, denoting the predicted number of cases of maternal rubella infection (i.e. summation of cases between ages 16 and 40 years and weighted by age-specific fertility data) after the introduction of the immunization programme, divided by the predicted number of maternal infections before immunization. Figure 1 predicts that the relationship between the proportion of schoolgirls vaccinated and the ratio, w, in the absence of any childhood immunization (proportion of girls and boys vaccinated at 2 years of age is 0), is linear; as vaccination coverage increase, the benefit increases as proportionally fewer susceptible women enter the childbearing years.

In contrast, the impact of vaccinating boys and girls at age 2 only (no selective schoolgirl vaccination) on the efficacy ratio is non-linearly related to the proportion vaccinated. This is a clear example of the herd immunity effect of mass immunization which acts both to reduce the rate of circulation of infection, whilst decreasing the total number of cases of infection in the population, and to increase the proportion of cases in the older age classes where the risk of serious complications is greater. Paradoxically, at low level coverage (up to 40%) mass childhood immunization is predicted to result not just in a higher proportion, but an increase in the number, of cases of maternal infection after the introduction of vaccination when compared to that pertaining before the introduction of mass immunization (ratio w exceeds unity). Comparison of the merits of the two alternative policies (each administered without the other) suggests that not until vaccination uptake is in excess of 80% is childhood immunization more beneficial than selective immunization. However, mass immunization has the advantage that its effects are likely to be more rapidly manifest than selective immunization because of the reduction in the rate of virus circulation. As such it can eliminate maternal infection at coverage well below 100% by the complete interruption of transmission in the community.

After 18 years of a selective schoolgirl policy for rubella immunization in the UK it was decided, in late 1988, to initiate a dual-stage policy with the introduction of MMR immunization of boys and girls in their second year of life in the hope of blocking rubella virus circulation in the community. The predicted impact on the ratio w of a combination of the two vaccine strategies in a two-stage programme at various levels of coverage of each, shown in the two-dimensional surface of Figure 1, indicates the circumstances in which a two-stage policy could actually be less effective than a selective programme alone (see shaded areas in the diagram). The main conclusion is that as long as high levels of selective immunization are maintained (80% or above) the addition of mass-immunization of children would do no harm, and, more importantly, that little good would result unless high levels of coverage could be achieved at around 2 years of age.

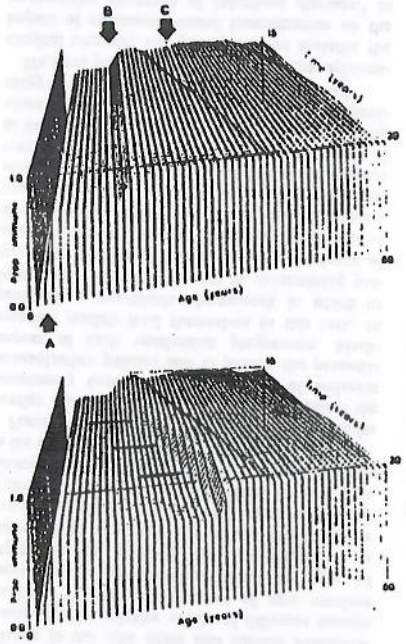
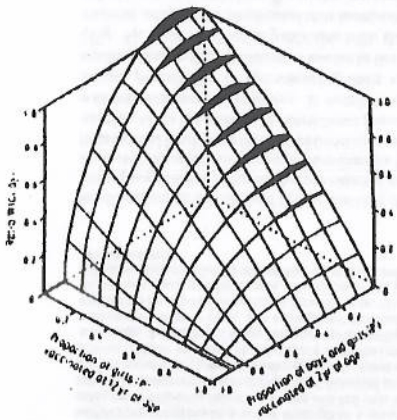


Fig. 2 Implications of withdrawing selective rubella immunization. The surface traces the predicted impact of immunization on rubella immunity in females in the UK 16–30 years after the introduction of mass immunization of 2-year-old children (arrow A) with about 70% coverage. Simulations are based upon national vaccination figures for teenage girls (arrow B) and 60% immunization of adult (aged 25 years) seronegative women (C). In the upper graph a dual-stage programme of selective and mass cohort immunization is in operation whereas in the lower graph the selective stages (B&C) have been discontinued over the time interval shown. In the lower graph it is clear to see the migrating wave of immunity, representing the last cohort of schoolgirls to be selectively immunized, and in its wake a deficit of immunity encroaching, with time, into the childbearing age classes (arrows). (Adapted from Nokes and Anderson, 1987[29]).

This issue might be viewed in a different way now that mass childhood immunization has been introduced and the question asked (particularly bearing in mind cost factors), under what circumstances would it be possible to discontinue the selective stage of the rubella immunization policy? The immunity surface generated from the model and shown in Figure 2 sheds some light on this issue.[21] The indication is that it will be necessary to achieve very high levels of coverage in infants of both sexes (in excess of 80%) and maintain these levels indefinitely if we wish to remove selective immunization. The reason for this is that the reduced transmission rates resulting from mass immunization, cause an upward shift in the age-distribution of susceptibles, which, if not countered by selective immunization, can create an immunity deficit in the at-risk childbearing age classes. Unless vaccine coverage of infants is in excess of 80% this immunity deficit will leave susceptible mothers vulnerable to periodic outbreaks of rubella. In the UK today levels of MMR are approaching 90% in all regions;[21] results from the model simulations stress the need to maintain such high uptake rates if the selective arm of the immunization programme is to be discontinued.

Disease or infection control: immunization against varicella-zoster virus

The relationship between the two diseases varicella and herpes zoster which have the same aetiological agent, the varicella-zoster virus, illustrates the need for great care in the adoption of a particular vaccination policy without a full understanding of the epidemiological complexities of transmission, the disease association with infection and vaccine characteristics. A live attenuated vaccine against varicella has been developed[22] and is being considered for general use in the USA.[23] While protecting children from varicella,[24] the vaccine itself can cause the re-emergence of the disease herpes zoster.[22] In assessing the primarily economic arguments for and against the general use of this vaccine[25,26] it is important to consider what influence the incidence of varicella has on the incidence of herpes zoster. A mathematical model describing the relationship between the two diseases is presented schematically in Figure 3.[27,28] The implications of a vaccination programme directed against varicella for zoster incidence hinges upon two factors, namely, (i) the probability of vaccine virus recrudescing in comparison with the probability of wild virus recrudescing, and, (ii) the importance (if any) of contact with exogenous varicella in maintaining specific immunity against dormant endogenous virus.[29–30] Both issues are poorly understood at present.[28] The



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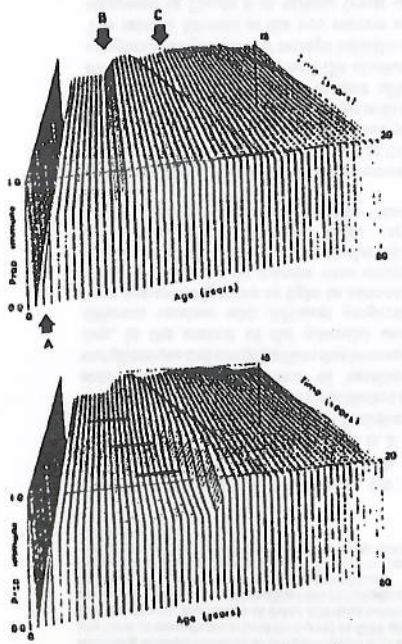

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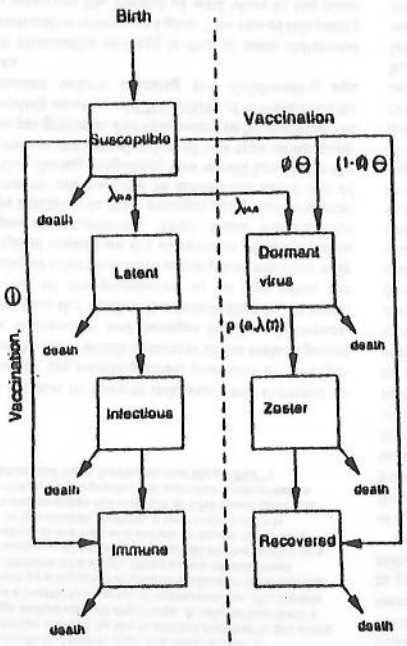

Fig. 3 A schematic representation of a model describing infection with varicella-zoster virus.[27,28] On infection, susceptibles enter an incubating category from which they progress to an infectious through to an immune category. At the same time they enter a virus carrier category from which they progress to a zoster through to a recovered category. Following infection a host will fall into 1 of the 3 left-hand categories (describing initial disease) and 1 of the 3 right-hand categories (describing recrudescent disease phases). Upon vaccination (Θ) people become immune, but also enter the dormant virus category (probability ϕ) or the recovered category (1-ϕ). The emergence of zoster is controlled by the recrudescence function p (a, λ(t)), which is dependent upon age (a), and is a function of the forces of infection experienced by the carrier host since initial infection (λ(t)).

implications of the second factor are that if a vaccination programme reduces the prevalence of varicella then the decrease in immune stimulation for carrier hosts could lead to an increased incidence of zoster. If vaccine virus is unlikely to recrudesce then this effect will be transitory. However, if vaccine virus has a strong probability of recrudescing then vaccination could increase the incidence of zoster in the long-term (Fig. 4). Other potential problems with the varicella vaccine include the likelihood that immunity to initial infection wanes over time[26] and the increased severity of varicella in older people by comparison with younger persons.[31]

The relationship between varicella and zoster argues for caution over the widespread use of varicella vaccine. However, it should be pointed out that if varicella vaccine, through a reduction in the number of people with dormant virus, decreases the incidence of zoster, then the arguements for its use are greatly enhanced.

Mumps vaccine efficacy and reactogenicity: a conflict between community and individual interests

Most vaccines carry some risk of inducing disease in the recipient. However, these risks are, in general, small comparison with the risk of severe disease resulting from infection with wild virus against which they provide protection. Unfortunately, the high levels of coverage attained in many communities today, responsible for very marked reductions in the incidence of natural infection, have paradoxically created a conflict of interest between, on the one hand, the community, and, on the other, the individual. For the susceptible individual afforded the protective effect of high vaccine-induced herd immunity the risk (whether real or perceived) associated with natural infection is exceeded by that associated with the vaccine. In contrast, at the community level, continued success of the vaccination programme is dependent upon the maintenance of high vaccine coverage. This conflict of interest is likely to be exacerbated in the light of increasing evidence to suggest that improved vaccine immunogenicity may well be associated with increased reactogenicity in recipients.[13,31]

Although the assessment of community benefit from mass immunization in its broadest sense must

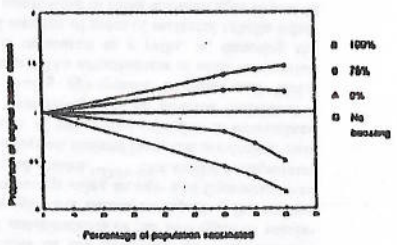

Fig. 4 The impact of vaccination on equilibrium zoster incidence in the VZV model.[27,28] The proportion of the endemic equilibrium number of zoster cases before vaccination, which still occur after the inclusion of vaccination is shown. A value of this risk function below unit y indicates a reduction in the number of cases and a value above unit y an increase in the number of cases. The values shown as open squares are those calculated when vaccine virus does not recrudesce and when varicella does not boost specific immunity (the best case). The other values are the results of calculations where varicella does act to boost specific immunity, and where in 0%, 75%, 100% (the worst case) of those vaccinated the vaccine virus has the potential to recrudesce.

Table Mumps vaccine efficacy and complication rates*

Vaccine type	Efficacy (95% confidence limits)	Complication rates (higher (pessimistic)	Lower (optimistic)
Urabe Am9	97.9 (97.1-98.7)	1:62[illegible]	1:[illegible]
Jeryl Lynn	94.8 (92.2-95.4)	1:[illegible]	1:[illegible]

*Data from reference[13]

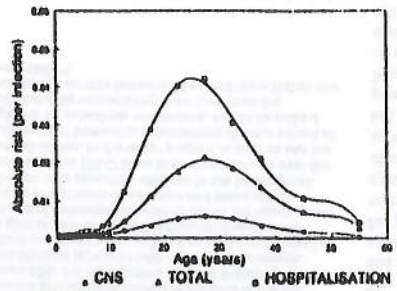

Fig. 5 Age-specific risk of complications associated with mumps infection in England and Wales. Absolute risk following mumps infection of hospitalization (top curve), any form of complication (middle curve) or CNS disorder (bottom curve). Estimation of these absolute values is based on age-stratified information about the per capita risks of infection (clinical or sub-clinical) per unit of time (determined from serological data[28,29]), and mumps-related complications per unit of time (Modified from Nokes and Anderson, 1991).[13]

take into consideration motivational (to do with perceived risk) and ethical (to do with vaccine-induced complications) issues, there is a need to provide an objective framework for decision making. Mathematical models facilitate quantitative comparisons between the numbers of vaccine-induced complications and complications due to natural infection, in the context of the potential use of two different vaccines with different properties. This issue has recently come to light in connection with different strains of the mumps virus component of MMR vaccines in which one, the Urabe Am 9 strain, has superior efficacy over the other, Jeryl Lynn, whilst eliciting a significantly higher complication rate.[13]

A quantitative assessment of the community benefit of these two mumps vaccine strains for the UK was carried out[13] using the model framework previously outlined.[1] Necessary requirements for such an assessment are good estimates of vaccine efficacy and complication rates (Table) and the absolute risk of complications per case of mumps infection (Fig. 5). The relative benefits of the two vaccine strains are compared in Figure 6 at various levels of vaccine coverage and assuming a pessimistic (higher) level of vaccine-induced complications. In this example complications associated with natural infection are those resulting in hospital attendance. When comparing the benefits to the community of mass immunization, all cases severe enough to warrant hospitalization deserve consideration. The results are not altered in substance, only in degree, if the risk of natural induced complications is limited to those involving the central nervous system.

Analyses indicate that at the lower levels of vaccine coverage (where the infection persists in the community) most benefit is derived from the vaccine with the higher efficacy (Urabe Am 9), in spite of a higher complication rate. At higher levels of coverage (around 80% or over) the infection is predicted to be effectively eliminated from the population using either vaccine strain. In these circumstances the Jeryl Lynn strain which offers the lower risk of complications is marginally better than the Urabe vaccine. Clearly, if the infection can be eliminated then the vaccine offering the lower complication rate will always be the better option.

In this example the decision about which vaccine is best at the community level is not clear cut. The results are dependent upon the precision of the parameter estimates (e.g. efficacy and complication rates and the level of vaccination coverage). Evidence is accumulating that the protective effect of mumps vaccines during outbreaks may be lower than suggested from efficacy levels recorded in clinical

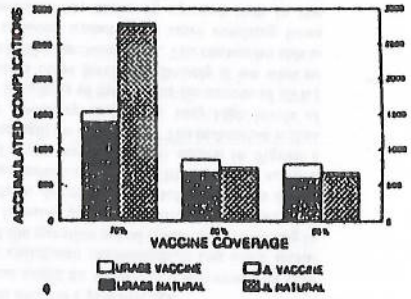

Fig. 6 Urabe vs Jeryl Lynn vaccines: benefit related to level of coverage.[13] The predicted number of complications due to mumps infection (lower portion of each bar) and to vaccine side effects (upper portion) predicted to arise over a 20-year period under three levels of mass childhood immunization, is recorded for each of the two mumps vaccine strains.

trials. Vaccine efficacies significantly lower than the estimates given in the Table, will increase the relative benefit of the vaccine with the higher efficacy even at high levels of vaccination coverage.[11,34]

Conclusion

The multitude of processes (many of which are age-dependent) that are affected by the introduction of mass immunization, make it unlikely that intuition alone can confidently predict the outcome of a particular policy, or indeed allow comparison between alternative strategies. Mathematical models, if soundly based upon observation and empirical data, do provide a framework for the quantitative assessment of different vaccination strategies. We hope that the examples given in this review give an indication of their use as aids in the design of public health policy. Future applications might include assessment of the optimal use for vaccines against HBV, meningococcal infection, HAV, and *Haemophilus influenza* tybe b.

Whether dealing with the issue of optimal vaccination policy for the prevention of measles-associated mortality in developing countries, or debating the implications of wide-spread introduction of modern vaccines such as recombinant hepatitis B or varicella-zoster vaccines, a quantitative methodology now exists to assist in the decision-making process. It is to be hoped that policy makers will make use of these scientific methods when considering both the introduction of new vaccines and changes in the usage of current vaccines.

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