Immunisation practice and policy

DAVID L MILLER

From the Department of Community Medicine, St Mary's Hospital Medical School, London

SUMMARY Immunisation has proved to be a generally safe and effective means of disease control, particularly where environmental approaches are impractical. Recent developments in vaccine production, aimed at selecting or synthesising in pure form the antigens needed to evoke a protective response, give hope of more effective and less toxic vaccines in future. Adequate trials of improved vaccines may, however, be difficult to carry out under modern conditions. Policies for the use of vaccines are sometimes controversial, particularly when there is concern about reactions, as with pertussis vaccine. Acceptance rates for measles and rubella vaccines in the UK have hitherto been disappointingly low and need to be increased if the aims of elimination of measles and congenital rubella are to be achieved. Cost-benefit analyses generally support the use of immunisation in disease control.

Ideally, action to prevent communicable diseases concentrates on safeguarding people from exposure to infection by environmental measures that will eliminate natural reservoirs or interrupt paths of transmission. The main advantage of this approach is that it does not depend on the cooperation of individuals. Where such measures are impractical, it may be possible to persuade people to change their behaviour in ways that avoid unnecessarily exposing themselves to harmful agents, which can be equally effective. The use of vaccines to stimulate or enhance specific host immunity is in many ways the least satisfactory preventive option. This is partly because vaccination affords no guarantee of protection to the individual and, more seriously, because it involves the parenteral injection of foreign proteins in the form of whole (or components of) killed microbes or the administration of living (attenuated) organisms, which inevitably carries risks of evoking adverse reactions in a proportion of vaccinees. Nonetheless, active immunisation is the only practical strategy for the prevention of many infections. It has proved highly successful in disease control, and serious reactions are comparatively rare. Therefore vaccines are likely to remain an essential weapon in the public health armamentarium, and research to improve the efficacy, to reduce their toxicity and to develop policies for their optimum deployment must continue to occupy a high priority.

In this paper my aim is to identify and discuss some topical issues related to the development of vaccines and policies for their use, particularly those currently in routine use for childhood immunisation in the UK.

Vaccines in disease control

Several distinct and sometimes conflicting factors influence decisions on how best to use a vaccine in disease control. The first is the way in which the vaccine operates. In some infections, such as tetanus or rabies, control depends exclusively on the protection the vaccine offers the individual recipient. In other instances, such as poliomyelitis and measles vaccines, their success also owes much to the fact that immunisation of a proportion of the population to some extent protects those who are not immunised. The relative contributions of individual and population immunity to disease control will affect immunisation strategies. Secondly, the efficacy and safety of recommended vaccines must be clearly established and of a high order if their use is to gain acceptance by the professions and the public. Thirdly, administrative and economic factors are important, particularly in poor countries. Much of the controversy that surrounds the use of vaccines derives from a lack of reliable data regarding some of these factors, as well as disagreement over the weights to be attached to them. Examples of each will be considered, but first some recent advances in vaccine development will be described.

VACCINE DEVELOPMENT

Active immunisation depends on stimulating an immune response in the host similar to that which occurs after natural infection, thereby preventing or inhibiting reinfection with and/or invasion by the specific causal organism or neutralising its toxic

effects. Current vaccines are of three main types: whole killed organisms, live attenuated organisms, or components of the organism or its detoxified products. Most of them protect by inducing a serum antibody response (IgG) and priming the specific immunologic memory. Some, for example oral poliomyelitis vaccine, also lead to the development of local immunity which inhibits invasion with natural (wild) virus in the gut, while the protection afforded by BCG vaccine is attributed to a cell mediated immune mechanism. These vaccines, however, are somewhat crude products which contain many unnecessary antigenic and toxic substances. Moreover, the immunity induced by them is only partial in some diseases, and in others repeated reinforcing doses are needed to maintain protection. Vaccines that are immunogenically more sharply focussed, giving better protection with fewer reactions, would be welcome.

Considerable progress has been made in recent years in understanding the regulation of immune responses. The production of effective vaccines against some diseases, however, remains difficult. In many cases this is because the microbes responsible are antigenically complex, for example, the pneumococcus. Some are adept at evading host immune responses, for example herpes simplex and varicella viruses, which may persist despite the generation of antibodies to primary infection, and artificial immunisation may similarly not prevent their reactivation. Others are antigenic chameleons either with a multitude of variants, such as the rhinovirus, or with unstable surface antigens, such as the influenza virus. In these instances, there seems to be little hope of producing vaccines with a sufficiently broad antigenic composition to induce protective antibodies against all possible variants. A different type of problem is that presented by infections where the agent is only weakly immunogenic, such as malaria parasites and the gonococcus, or where the immune response to conventional vaccine is paradoxical, such as with inactivated respiratory syncytial virus vaccine, which not only fails to protect but, on subsequent infection, is associated with a high incidence of severe bronchitis.

New approaches which hold promise in overcoming some of these problems lie in the development of vaccines containing selected antigens obtained by disrupting whole organisms, by recombinant DNA technology or peptide synthesis, and by enhanced immunogenicity through the use of adjuvants.¹⁻³ The use of disrupted virus particles in vaccine production, for example purified surface antigen influenza vaccine, is well established but could have wider applications. The DNA techniques can be used to modify microbial genomes so as to

produce stable attenuated live agent vaccines, or to insert genes in suitable vector organisms which may allow large-scale production of selected microbial proteins or oligopeptides for use as vaccines. One problem has been to identify those antigenic components of the microbe that are relevant to the generation of an immune response. Considerable progress has been made in this respect using monoclonal antibody techniques. Encouraging results have also been obtained from the synthesis of small peptides which can mimic the antigenic structure of some agents, such as hepatitis B and rabies viruses.

Adjuvants have long been used to enhance the immunogenicity of vaccine components, although their mode of action is not entirely clear.⁴ The purification of vaccine constituent antigens tends to be associated with loss of immunogenic potency which will increase the importance of adjuvant development. Unfortunately, some known adjuvants, whether inert substances such as mineral oils or whole organisms such as *Bordetella pertussis*, are themselves not free from harmful effects. Further research is needed to develop safe and potent adjuvants.

ADVERSE REACTIONS TO VACCINE

Adverse reactions arise because of either the toxicity of vaccine components or the reversion of live attenuated agents towards natural virulence. Toxicity attributable to impurities incorporated during manufacture is largely avoidable, and modern vaccines are comparatively free from extraneous material. Much of the reactogenicity of vaccines, however, particularly bacterial vaccines such as pertussis, derives from the many toxic substances among the components of the whole organism, some of which are significantly immunogenic, but many of which are immunogenically superfluous. Segregation of the immunogenic components of microbes in purified form, therefore, is likely to be particularly valuable in reducing vaccine toxicity. The new techniques for vaccine production described above are crucially important advances towards this ideal. The consequences of possible vaccine reactions and the public anxiety that they arouse have been highlighted by the controversy over pertussis vaccine in Britain in recent years which led to a dramatic decline in rates of immunisation.⁵ The development of a pertussis component vaccine gives new hope that a safer and more acceptable vaccine may soon become available.^{6,7} Similar developments may now be expected for other agents.

The advantage of live attenuated agent vaccines is that the immunity produced is more 'natural' and long lasting. The balance between adequate

attenuation of the microbe to avoid causing symptoms and loss of immunogenic activity is, however, often a fine one. There is always a risk that some individuals will prove to be exceptionally susceptible to the attenuated agent, or that multiplication in or passage between human hosts will lead to regeneration of virulence, for example the rare cases of paralytic disease in recipients and contacts of recipients of live poliomyelitis vaccine. Moreover some viruses are associated with cellular transformation and are regarded as potentially oncogenic. These concerns, despite the many advantages of live vaccines, have engendered some support for a return to the use of killed poliomyelitis vaccine⁸ and hesitancy, for example, about the use of adenovirus vaccines.

POPULATION IMMUNITY

The control of many infections, particularly those which are spread in the main directly from person to person, is greatly assisted by the so-called "herd" or population immunity effect. Where a high proportion of the population is immune, chains of transmission between infected and susceptible individuals are less readily maintained. This phenomenon played a large part in the strategy for global smallpox eradication,⁹ and has been important in the elimination of endemic poliomyelitis in Britain and most other developed countries. Its relevance in the control of other infections is debated. For example, influenza epidemics can show surprisingly different patterns even in apparently similarly susceptible populations.¹⁰ The effective level of herd immunity probably varies from one infection to another, depending on factors such as opportunities for contact between cases and susceptible individuals, the routes of transmission, and the degree to which immunity from disease prevents carriage of the organism. The elimination of diphtheria in developed countries may have been related to a population effect whereby carriage and transmission of *Corynebacterium diphtheriae* is inhibited in immune populations, although the mechanism for this is not clear. On the other hand, in the case of pertussis it has been suggested that immunisation does not impede circulation of the agent.¹¹ Many attempts have been made to predict minimum effective levels of herd immunity through the use of mathematical models. These have the advantage of being highly flexible and free from the practical and ethical constraints of field trials. They have the major disadvantage that they tend to over-simplify the dynamics of spread of infection and may bear only distant relation to reality. The use of models for constructing infection control policies, including the role of vaccines, was extensively explored in a recent symposium on

influenza models which highlighted the strengths and weaknesses of the technique.¹²

Vaccines also have a role in the management of outbreaks of some infections in which they can be used to interrupt spread. When live attenuated poliovirus vaccine was first introduced, monovalent vaccines were used to interrupt epidemics due to a different poliovirus type, on the principle of competitive colonisation of the bowel.¹³ This use of live vaccine remains recommended practice, although now trivalent vaccine would be used. In some other infections vaccines are used in the face of an outbreak, but in these circumstances the main purpose is to offer individual protection, and the population benefit is seen as a useful bonus rather than as the prime strategy.

TRIALS OF THE EFFICACY AND SAFETY OF NEW VACCINES

The production of new or improved vaccines will require the conduct of large field trials designed to measure not only efficacy but also safety to ever more stringent standards. The design of appropriate trials, never an easy proposition, under modern conditions will be even more difficult for a number of reasons.

First, the evaluation of marginal improvements in the immunogenicity and protective efficacy of vaccines will require very large numbers of participants which creates problems of logistics and cost. The second difficulty arises from the increasing public concern about adverse reactions and the effect this is likely to have on the availability of volunteers and ethical acceptability of trials, particularly where infants and children are involved, as they must be since they are the prime target group for many vaccines. Thirdly, trials are likely to be critically concerned with measuring reductions in the frequency of rare but serious reactions, compared with current vaccines. A particular example is the new component pertussis vaccine. The incidence of encephalopathy after current pertussis vaccines is so rare that no ordinary field trial could measure a significant change in the risk.¹⁴ In such cases we shall probably have to depend on indirect indices of toxicity derived from animal experiments and extrapolation from the incidence of less severe reactions, coupled with prolonged and careful monitoring of reactions to vaccines once they have been accepted into routine use. Finally, careful and sustained surveillance will also be required to monitor the implementation of vaccine policy, the incidence of disease and the duration of immunity.

The public and the profession need to accept and debate the dilemmas presented by carrying out adequate trials of new or improved vaccines in present circumstances, and also to decide what risks,

if any, can be accepted in any recommendations for their routine use after initial trials.

Current immunisation policies

Health authorities and paediatricians are sometimes criticised for lack of consistency in their recommendations on vaccine schedules. In view of the many variables that enter the equation of risks and benefits, some of which are hard to quantify, as well as the logistic problems and economic factors that effect the design of schedules, it is not surprising that they feel compelled to modify their advice from time to time nor that they do not always agree. However, too frequent changes should be avoided since they tend to undermine the credibility of the advice and cause confusion among parents and those responsible for administering the vaccines, which may result in low vaccine acceptance rates.

A new set of recommendations for the United Kingdom has recently been published.¹⁵ This describes the scientific basis of the structuring of immunisation schedules, gives general advice on immunisation techniques, and sets out recommended practice on the use of vaccines and other immunological products for each major infection for which these are routinely available. Similar sets of recommendations exist for many other countries, for example those of the Committee on Infectious Diseases of the American Academy of Pediatrics.¹⁶

The only routinely recommended vaccines in Britain are those given to infants and children, namely, diphtheria, tetanus, pertussis, poliomyelitis, measles, rubella, and BCG. Current policies for the use of diphtheria, tetanus, and polio vaccines have stood the test of time and are not contentious. Acceptance rates, at around 80% on average, are high enough to have eliminated these diseases as important public health problems. Rates for pertussis vaccine, once equally high, have plummeted in the wake of publicity given to cases of alleged brain damage due to the vaccine but are slowly recovering. The effectiveness of the vaccine has been challenged, but the return of epidemics that followed the fall in immunisation rates leaves little doubt that it did control the disease. It is also clear now that the dangers of the vaccine have been grossly exaggerated.⁵ On the balance of risks and benefits, therefore, its use has been consistently recommended in the UK. It is to be hoped that confidence in the vaccine will soon be restored and that the disease will once more be brought under control.

Measles vaccine is highly effective and generally safe, and the eradication of the disease is regarded as a feasible target nationally¹⁷ and even globally.¹⁸ Yet acceptance rates remain very low in many countries,

including the UK. By contrast, the USA, Canada, and some Eastern European countries have achieved very high rates, albeit by making vaccination virtually compulsory. Such compulsion is likely to remain unacceptable in the UK, but it is worth considering why our rates are so low.¹⁹ Undoubtedly this is partly because the disease is perceived to be common and *usually* mild and that the early vaccines carried unacceptably high reaction rates. It is also due to a curious apathy among parents and doctors towards disease prevention, even when this can be achieved simply and safely. The immunisation rate required to eliminate the disease is uncertain but may be quite high.²⁰

Rubella immunisation policies differ between countries, depending on the priority given to personal protection as opposed to reducing the risk of exposure of pregnant women based on disease control through sustained high population immunity.²¹ The elimination of congenital rubella syndrome—the ultimate objective—may well require a combined approach.²² At present the UK policy, based on offering vaccine to prepubertal girls and to seronegative women, is inadequately implemented, and concerted efforts are now being made to remedy this situation. Having opted for a policy that depends on maternal immunity rather than non-exposure to rubella, it is essential that all girls are immune before entering the child-bearing years. In the USA, combined measles, mumps, and rubella vaccine is advocated,¹⁶ which is logical where all three are to be given in early childhood. However, unless acceptance rates very much higher than the present average of around 50% for measles vaccine in the UK were achieved, the incidence of congenital rubella²³ and of mumps²⁴ might even *increase*.

Until comparatively recently little attention was paid to the cost-benefit of disease control programmes, but this situation is changing.²⁵ Such analyses may be made in terms of morbidity and mortality indices or in economic terms. Both are relevant. Where the fatality rate from a disease is high, for example in smallpox, and there is a substantial risk of infection, the health benefits of prevention may seem obvious, and it hardly seems necessary to calculate the costs. As a disease is controlled and becomes rare, however, so the costs loom larger, which may lead some to question the wisdom of continuing current policies, as happened with whooping cough.²⁶ The economic costs and benefits are likely to be particularly relevant in countries with limited health care resources, but even in economically more prosperous countries costs now loom larger in arguments for and against preventive as well as treatment health services. Attempts have been made to assess the net value of both measles²⁷

and whooping cough²⁸ vaccines. These give overwhelming support for elimination policies. By contrast, the economic cost-benefit balance favouring the continued routine use of BCG vaccine in Britain seems likely to be reversed within a few years.²⁹

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