Problems in the Use of Vaccines

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Vaccines licensed for sale in the UK (Table 1) pose diverse problems for those concerned with their use, namely, advisers on the formulation and implementation of national vaccination policies, the licensing authorities, the manufacturers, the doctors and nurses who administer vaccines, and members of the public for whom the vaccines are intended.

Table 1. Vaccines licensed for sale in the UK.

| Recommended Usage | Vaccine            |
|-------------------|--------------------|
| 1. Routine vaccination during childhood | Diphtheria        | Measles |
|                   | Tetanus            | BCG     |
|                   | Pertussis          | Rubella |
|                   | Poliomyelitis      | (Mumps) |
| 2. Vaccination of special groups | Smallpox          | BCG     |
|                   | Typhoid            | Influenza |
|                   | Cholera            | Rubella |
|                   | Typhus             | Rabies  |
|                   | Poliomyelitis      | Yellow fever |
|                   | Diphtheria         | Pneumococcal |

Problems in Formulation and Implementation of National Vaccination Policies

Consideration has to be given from time to time to the routine use of vaccines on a national scale for the prevention and control of certain communicable diseases, taking into account the efficiency, effectiveness and possible undesired repercussions of national vaccination programmes.

The selection of vaccines for use in national programmes is based on availability, documented evidence of safety and efficacy, expected benefits on morbidity and mortality and on the cost and difficulties envisaged in launching and maintaining the programme. The institution of a national vaccination programme against mumps, for instance, has been deferred because available evidence indicates that mumps is not a sufficiently serious national problem to warrant a vaccination programme for its control or eradication.

The primary aim of the continuing vaccination programme against diphtheria, poliomyelitis, pertussis and measles is the control and eradication of these diseases. This has been virtually achieved in the case of diphtheria and poliomyelitis, was almost achieved for a period in the case of pertussis, but remains a target in the case of measles. However, it is only by resolving certain problems concerned with the use of these vaccines on a national scale that the control and eradication of these diseases can be achieved or maintained.

Routine immunisation of infants with diphtheria toxoid was widely practised in the UK during the late 1930s and early 1940s without producing a tangible impact on diphtheria notifications in the country. A national immunisation campaign was launched in 1942 (Fig. 1) directed at all diphtheria-susceptible children between the ages of 6 months and 15 years, that is, the section of the population which accounted for 95 per cent of all notified cases of diphtheria. An efficiently conducted campaign with a highly efficacious vaccine rendered a high proportion of the diphtheria-susceptible section of the population immune to infection, leaving only a small number of children capable of participating in a chain of diphtheria infection. Thus opportunities for contact between the diphtheria-susceptible subjects and sources of infection were greatly reduced, with the result that diphtheria notifications rapidly declined.

The poliomyelitis vaccination campaign of the late 1950s/early 1960s also brought about the immunisation of the great majority of the poliomyelitis-susceptible section of the population, namely, children and adults...
between the ages of 6 months and 41 years. Again, the effect on notifications was dramatic (Fig. 2).

The pertussis immunisation programme developed gradually, in an unco-ordinated manner, each local health authority in turn introducing a local vaccination scheme during the 1940s and 1950s (Fig. 3). By 1954, nearly all local authorities in England and Wales had superimposed an efficient infant pertussis vaccination programme on their well-established infant diphtheria immunisation programme. But, in their schemes, vaccination was restricted to infants; older pre-school children and children of school age, who accounted for the vast majority of notified cases of whooping cough, were not vaccinated. Thus only gradually, as increasing cohorts of vaccinated children reached school age, were reductions made in the size of the pertussis-susceptible section of the population. As a result, notifications only gradually decreased and only from 1957 onwards. By the 1970s they were down to very low levels.

Allegations of minimal efficacy and of a high incidence of serious reactions, including encephalopathy, had constantly been levelled at pertussis vaccines, but they were renewed with some vigour in the UK after 1966 and accorded widespread publicity by the mass media from 1975 onwards. The adverse publicity caused a sharp decline in vaccination rates and, as new cohorts of unimmunised children reached school age, when whooping cough is most prevalent, an epidemic occurred in 1978-79. This experience confirmed the view that pertussis immunisation rates for infants need to be maintained at a high level if outbreaks of whooping cough are to be controlled. The current vaccination rate of 33 per cent for infants is clearly too low to provide herd immunity.

The whooping cough experience raises the question of whether outbreaks of diphtheria or poliomyelitis may occur unless there is an improvement in the current vaccination rates of approximately 66 per cent. Low vaccination rates provide an opportunity for wild poliovirus strains or, indeed, vaccine virus-derived strains to become established in the community and give rise to endemic poliomyelitis. There is some evidence to indicate that the vaccine live poliovirus, which is constantly used, may, on human passage, regain a little of its original virulence and be responsible for sporadic cases of poliomyelitis. The controversy between the use of killed and live poliovirus vaccines for routine vaccination remains unresolved but increasing concern is being expressed over the incidence of cases of vaccine-associated poliomyelitis. There were, on average, approximately 18 cases of acute poliomyelitis a year in the USA during the last 10 years, about 7 of which were vaccine-associated.

In countries where there have been intensive national vaccination campaigns against measles, morbidity and mortality have rapidly fallen to negligible levels (Fig. 4). These campaigns were directed at vaccination of all measles-susceptible children between the ages of one and 15 years, that is, almost the entire measles-susceptible section of the population. A similar campaign was launched in the UK but the uptake of measles vaccine has been disappointing (Fig. 5). Only 50 per cent of infants are now vaccinated, so the chances of measles-susceptible subjects meeting a source of infection remain high and the vaccination programme has not had the dramatic effect on notifications that was obtained with the diphtheria and poliomyelitis campaigns. Since the vaccination programme has nevertheless reduced the risk of contact with a case of measles, there is a distinct possibility that contact between a measles-susceptible child and measles will be postponed—in some cases until
adulthood, when measles is reputed to run a more severe course than during childhood. The overall long-term effects of the current programme, where only half the child population is vaccinated, are therefore still not clear. In the USA and a number of other countries where high immunisation rates have been achieved, there are good grounds for the belief that measles can be eradicated by an efficiently organised vaccination programme.

With regard to rubella, it was intended that the current UK immunisation programme should not have a discernable impact on the epidemiology of rubella in children. It would not therefore reduce the risk of susceptible adults, including pregnant women, being exposed to infection. Approximately 300,000 girls between the ages of 11 and 14 years have been vaccinated in England and Wales each year since 1970 but, as 75 per cent of these would have had natural rubella, only about 80,000 derived immunity by vaccination, a number insufficient to affect the epidemiology of the disease. Since the primary aim of vaccination is to protect women of child-bearing age against infection or re-infection, there is a time lapse before the programme can prove effective in reducing the incidence of congenital rubella. Only by expansion of the immunisation programme to include rubella-susceptible women of child-bearing age can an earlier impact be made. But such an extension carries problems and difficulties. There is a risk that women may already be pregnant or may become pregnant soon after vaccination (despite warnings and precautions) and that the vaccine virus may have an adverse effect on the embryo. Restriction of vaccination to rubella-susceptible women of child-bearing age entails additional costs and demotivating blood tests and delays, whereas vaccination without preliminary testing for immunity means that about 90 per cent of the women vaccinated will not derive benefit from the procedure. Inadvertent vaccination of women already pregnant, or who become pregnant soon after, causes additional problems especially if it is not known whether they were immune at the time of vaccination.

In the USA the rubella immunisation programme provides for the immunisation of children of both sexes up to school-leaving age, that is, the section of the population which fosters infection. The primary aim of the programme has been largely realised (Fig. 6) since there has been a substantial decline in the number of notified cases of rubella and of infants born with congenital rubella. The continued success of this programme depends on vaccines administered early in childhood providing lifelong immunity. If immunity were to wane significantly over a period of 10 to 20 years, the proportion of women of child-bearing age susceptible to infection or re-infection could be increased rather than decreased by the programme.

The Medical Research Council's controlled trials of BCG showed that the vaccine used conferred substantial protection on tuberculin-negative adolescents for some 15 years after vaccination. The risk of tuberculosis has substantially declined since then and chemotherapy has developed to such a degree as to bring doubt about the
need to continue routine vaccination of tuberculin-negative school-leavers. So is it necessary to vaccinate and thereby scar an increasingly large number of children every year in order to prevent a single treatable case of tuberculosis?

A spectacular attempt was made in the USA in the last quarter of 1976 to forestall the spread of a new endemic strain of influenza virus by mass vaccination of the adult population. Over 40 million adults received swine influenza virus vaccine but, as the campaign progressed, it became evident that the wild strain did not have the capacity for epidemic spread. However, during the campaign, more than 500 cases of Guillain-Barré syndrome were reported, with a peak incidence between 7 and 21 days after vaccination. This experience highlights a problem in the use of vaccines in that the public response to a call for vaccination was highly gratifying but the campaign proved to be unnecessary and revealed a hitherto unsuspected one per 100,000 risk of triggering Guillain-Barré syndrome by vaccination.

Problems Encountered by the Licensing Authority

The licensing authority is concerned with the safety, efficacy and quality of vaccines.

Safety

Therapeutic products are normally administered to patients, so drug reactions have to be identified as clinical events occurring additionally to the signs and symptoms associated with the illness. Occasionally, fortuitous additional clinical events may complicate the situation. Vaccines, on the other hand, are normally administered to subjects at a time when they are well, so it would appear reasonable to assume that adverse events occurring within a given period are attributable to vaccination. The situation is complicated by the fact that diphtheria, tetanus, pertussis, poliovirus and measles vaccines are routinely given to children at an age when sudden unpredictable and often severe clinical events of unknown aetiology may occur.

Epidemiological surveys have shown that each day 7 in every million children between the ages of 3 and 6 months are subject to sudden, unexpected death (cot death). The incidence of a first convulsion in hitherto healthy children between the ages of 6 and 18 months is between 10 and 50 per million children per day and approximately 2 per cent of these children suffer residual brain damage. Between one and two million doses of DTP are administered to children in this age group each year and therefore between 20 and 40 children can be expected by chance to have a convulsion unrelated to vaccination on each subsequent day and one may have residual brain damage. Since the aetiology of these convulsions is unclear, it is understandable that those occurring within a few days of vaccination have been attributed to vaccination. Retrospective enquiries, especially when carried out years later, are liable to show clustering of these episodes during the first few days after vaccination because a cause and effect association is more readily brought to mind when the interval between the two events is short.

Infantile spasms also occur in children of vaccination age, that is, between 9 and 18 months. The aetiology of this condition is unknown but if, by chance, children have been vaccinated during preceding days there has been a tendency to ascribe the condition to the vaccination. Epidemiological evidence has now refuted allegations of a cause and effect association between infantile spasms and the administration of vaccines.

The licensing authority has the difficult problem of assessing whether some or any of these relatively common, sudden and sometimes crippling clinical events occurring after vaccination are in some way associated with, or precipitated by, the procedure. This proves particularly difficult to unravel in the absence of evidence that will distinguish what might be a vaccine reaction from a background type of clinical event of unknown aetiology. With polio vaccine, on the other hand, epidemiological studies have revealed clustering of paralytic poliomyelitis during the period 7 to 21 days after vaccination in recipients and between 20 and 29 days in household contacts of vaccine recipients. Since poliomyelitis is not endemic in the UK, it can be assumed that all cases of poliomyelitis occurring during these periods are attributable to the vaccine virus.
With measles vaccine, which is also given at an age when children are particularly susceptible to febrile convulsions, there is a clustering of convulsions and, to a much lesser extent, of encephalopathy 5 and 9 days after vaccination, that is, at the time when the fever attributable to vaccine is at its highest. The incidence of encephalopathy during this period after vaccination is probably in the region of 1 per 100,000 children vaccinated, that is, at least ten times less than the incidence associated with natural measles.

Efficacy

The licensing authority is primarily concerned with the efficacy of each vaccine in the individual. With most vaccines efficacy can be assessed according to the titre and persistence of specific antibodies produced in response to vaccination. It is generally acknowledged that serum antibodies correlate with protection against measles, poliomyelitis, tetanus, diphtheria, rubella and yellow fever and that the induction of tuberculin sensitivity is an indication of successful BCG vaccination, but there are no tests available to establish whether pertussis, typhoid, paratyphoid or cholera vaccines have protected the individual. The licensing authorities are obliged to rely on epidemiological data collected from field trials in order to assess the efficacy of these bacterial vaccines.

Quality

The licensing authorities are concerned with the approval of specified methods of manufacture and standardised procedures for testing each batch for potency and toxicity. In the case of influenza, it is necessary for the licensing authority and the manufacturer to agree each year in advance on the strain of virus to be used for vaccine manufacture in preparation for the following influenza ‘season’.

Problems Encountered by the Manufacturers

Manufacturers are also concerned with the safety, efficacy and quality of the products they issue. Nevertheless, their problems are to some extent different from those encountered by licensing authorities.

Safety

Manufacturers will have collected data on the incidence, nature and severity of reactions in a substantial number of subjects during clinical trials of vaccines developed during the last 10 to 15 years and similar experience of older vaccines. Once a vaccine has become generally available on the market, practitioners are exhorted to report all adverse reactions encountered after vaccination to the Committee on Safety of Medicines. As a result, there is an increasing tendency to leave manufacturers uninformed of these events and, since the Committee on Safety of Medicines has very limited discretionary powers to provide the manufacturer with bare data on product and reported reaction, the manufacturer may feel deprived of opportunities for receiving and investigating reports of adverse events occurring after vaccination. He is dependent on the Committee on Safety of Medicines having the interest, resources and expertise to investigate fully and assess the significance of these events. Finally, he has to assume that the Committee will advise him promptly and appropriately of any action that should be taken with regard to any problem that may have been discerned, giving a full account of its investigations and how it arrived at its decision to issue that advice.

Efficacy

The manufacturer endeavours to maintain a highly reproducible system of vaccine manufacture and of quality assurance in order to ensure that potency or efficacy of batches do not vary. The manufacturer has a problem trying to ensure that vaccines are accorded proper storage conditions during and after distribution. Live viral vaccines, in particular, lose potency and thereby efficacy as a result of exposure to ambient temperatures or sunlight. Failure to adhere to the manufacturer’s instructions on storage may mean loss of potency of a vaccine by the time it is used. It should also be noted that although aluminium adsorbed vaccines should be stored in a refrigerator they are irreversibly damaged by freezing.

Problems Encountered by Doctors and Nurses who Administer Vaccines

Periodic advice on vaccination procedures is issued by the DHSS to all doctors and nurses who administer vaccines. This advice usually relates to who should be vaccinated, at what age, the number of doses, the intervals between administrations, route of administration, warnings and contra-indications, and adverse effects and complications of vaccination. Those responsible for vaccination have to be conversant with this advice and that given by the manufacturers and be prepared to advise parents on the relative risks of vaccination against the risks of withholding vaccination. It may be necessary to explain to a parent that a child will not run the risk of contracting the natural disease or a remote vaccine-associated complication (such as paralytic poliomyelitis after oral poliomyelitis vaccine) provided the vast majority of other children in the country are vaccinated and thereby participate in the maintenance of herd immunity.

Problems in the use of Vaccines Encountered by the Public

The efficiency and consequently the effectiveness of national vaccination campaigns ultimately depend on the attitude of the public towards vaccination. A generation or two ago, certain communicable diseases were so prevalent and so often resulted in severe crippling and fatal disease that they were a constant cause of concern to all parents since all were witnesses of these tragedies. Understandably, fear made them eager to take advantage of any prophylactic inoculation that might give
protection. As control of some of these diseases was achieved by vaccination, the new generation of parents were less aware of the risks associated with these diseases and tended to have more confidence or faith in therapeutic measures that had been developed in the interim period and could be applied if required. This resulted in increasing apathy towards vaccination, an apathy that gradually tended to evolve into antagonism as increasing publicity was given to cases of alleged adverse reactions after vaccination. At the time of the national mass vaccination campaign with oral poliovirus vaccine, it seemed out of place to refer to the one in a million risk of vaccine-associated paralysis in recipients or household contacts since the risk of natural disease was considerably greater. As a result of that campaign and subsequent routine immunisation of children, the risk of poliomyelitis due to wild virus has been negligible in this country over the last 15 years, so increasing regard has been paid to the risk of vaccine-associated paralytic poliomyelitis.

The public is generally lulled into an apathetic state towards vaccination over the years when natural infection does not appear to constitute a hazard to their children. Indeed, they react sharply to news items and mass media commentaries on alleged vaccine reactions only to react, again sharply, in favour of vaccination when similar prominence is given to news of outbreaks of preventable disease. Members of the public are primarily motivated by anxiety to protect themselves and their children. Vaccination rates increase in response to outbreaks of disease but then tend to dwindle during the intervening years. The influence of health visitors and health care physicians, who endeavour to educate the public regarding the risk/benefit ratio of vaccination, is gradually being eroded by the growing influence of the mass media. As a result, public attitudes towards vaccination vacillate between fears provoked by news of outbreaks of infection or of allegedly alarming effects caused by vaccination. The problem of educating the public in the use of vaccines is becoming increasingly difficult to resolve.

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