The Current Status of Immunisation

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'It is generally recognised that immunisation is one of the best and most effective investments which any government can make towards the health of its citizens.'

This statement came from the opening paragraph of the recommendations of a conference on 'Immunisations in Africa' held in Kampala in December 1971 (Seminar, 1971), and although it was referring specifically to the countries of Africa, it holds true for every country in the world. It is an undoubted fact that immunisation is a most effective method of controlling infectious diseases, but it must also be accepted that immunisation alone cannot control the communicable diseases, certainly not all of them, unless backed up by general public health measures, which include sanitation and hygiene, medical, social and educational services, by legislation where necessary and, most important, by adequate financial resources to ensure that all preventive measures are not only implemented, but maintained and, where necessary, expanded. Once a nation has embarked upon a campaign to control a disease by immunisation, be it smallpox, diphtheria, whooping-cough, or poliomyelitis, there is no going back. Immunisation programmes must be maintained until such time as the disease can be eradicated or controlled in some other way.

HISTORICAL ASPECTS
The history of immunisation is one of great fascination about which much has been written, but the interesting fact is that immunisation procedures, or artificial attempts at prevention, were carried out long before the concept of the microbial theory of infectious disease was introduced, and even longer before the principles of immunology, which form the basis for preventive measures, were elucidated. Many of the earlier attempts to prevent diseases such as smallpox, measles and poliomyelitis were motivated by fear. By modern standards quite extraordinary risks were taken in the late seventeenth and early eighteenth centuries in using procedures such as variolation, 'cowpoxing' or vaccination, and the artificial inoculation of measles, and more recently, in the 1930s, by the use of poliovaccines prepared from spinal cord tissue (Kolmer, 1935; Brodie, 1935).

During the past 100 years, developments have taken place in a more logical and scientific fashion. The recognition of the microbial theory of infectious disease, first of bacteria and then of viruses, during the period 1870-1910 was the first
major step forward. Coincident with this was the discovery of the role of toxins in diphtheria and tetanus infections, which led directly to the development of antitoxins and later of toxoids as artificial means of prevention. The principal factors responsible for immunity were then discovered; the role of humoral immunity and later of cellular immunity, culminating in the 1920s with the recognition of the primary and secondary immune response, was an immunological phenomenon of fundamental importance as far as immunisation was concerned.

Historically, rabies vaccine prepared by Pasteur was the first vaccine per se to be produced in the laboratory. Although inoculation with variola virus and cowpox virus preceded it by many years, these materials came from natural sources. The main impetus to the development of specific immunisation procedures came with the recognition that diphtheria and tetanus could be prevented either by passive administration of the appropriate antitoxin or by active immunisation with detoxicated toxoid. Progress by modern standards was slow; this was probably just as well, as during the period 1910-1935 there were several major incidents following the use of faulty diphtheria and other prophylactics (Wilson, 1967). In the early days of vaccine development, it may have taken 25 years or longer before a vaccine passed from the clinical trial stage to that of a licensed product. In recent years the interval has been narrowed to five or ten years. The speed with which some modern vaccines have been developed is largely due to the great increase in technical developments for culturing pathogenic micro-organisms, particularly viruses. The discovery in 1949 that poliovirus could be cultured in tissue culture was probably the most significant development in this field in modern times. The fact that this simple technique of growing viruses in cell cultures in small flasks or tubes could be adapted to production on a large scale brought together the experiences of the microbiologist and the biomedical and chemical engineer. Almost overnight the problem of bulk production of vaccines was resolved, but it had its dangers, because speed is seldom an important factor in vaccine production whereas safety always is. As we were to learn to our cost, the rush to issue poliovaccine in the United States in 1955, within a few months of the issue of the Francis Report (1955) on the result of the clinical trials carried out in the USA in 1954, ended in disaster. Faulty batches of inactivated poliovaccine containing residual live virus were issued from one manufacturer. The explanation for this episode, usually referred to as the Cutter incident, was that the intricacies of virus inactivation with formaldehyde were imperfectly understood. The Cutter incident, disastrous though it was, served as a salutary lesson to governments and manufacturers to pay heed to safety and to good manufacturing procedures. A decade later, there was another disaster, not this time in the biological field, but after the marketing of a tranquilliser, thalidomide, before it was realised that the drug had teratogenic properties. This had an even more profound effect on the
Table 1. Current status of bacterial and viral vaccines

| Advances       | Problems                              | Recently developed vaccines                                      | Future development                  |
|----------------|---------------------------------------|------------------------------------------------------------------|-------------------------------------|
| Diphtheria     | Influenza                             | Meningococcal polysaccharide types A, C and B                    | Pseudomonas vaccines                |
| Tetanus        | Acute respiratory disease complex     | Haemophilus type B capsular                                      | E. coli enterotoxoids               |
| Pertussis      | Respiratory syncytial virus           | Polyvalent pneumococcal                                          | Cytomegalovirus                     |
| Tuberculosis   |                                       | Cholera toxoid                                                   | Hepatitis A and B                   |
| Smallpox       |                                       |                                                                  | Varicella Zoster                    |
| Yellow fever   | Pertussis                             |                                                                  |                                     |
| Poliomyelitis  | Rabies                                |                                                                  |                                     |
| Measles        |                                       |                                                                  |                                     |
| Rubella        |                                       |                                                                  |                                     |
| Mumps*         |                                       |                                                                  |                                     |
| Rabies         |                                       |                                                                  |                                     |
| Influenza      |                                       |                                                                  |                                     |

* Limited information as yet available on protection
development and control of pharmaceutical products in general. In Great Britain, the Committee on Safety of Drugs was set up as a direct consequence. This committee, now superseded by the Committee on Safety of Medicines, has a statutory authority to monitor adverse reactions to drugs. By definition, vaccines and antisera are included within the term 'drug', but it would seem, in view of recent events concerning pertussis vaccines, that the reporting of adverse reactions to vaccines and drugs should be kept separate.

The present status of development in the biological field is such that it is now theoretically possible to develop a vaccine, or some other prophylactic, against any infectious disease once the causative agents has been identified and, where necessary, a means for culturing or purifying it in the laboratory has been developed. A list of vaccines that have been or are being developed is set out in Table 1 and certain areas where problems exist are indicated (col. 2), either in relation to the efficacy or safety of the product or to some other factor.

PRINCIPLES OF IMMUNISATION
It is essential to recognise the basic principles upon which immunological products work and the general strategy governing their use. Four basic principles, set out in Table 2, should be taken into consideration. It is particularly important that they be heeded when the development of a new immunological product is under consideration and equally important when product licences of existing vaccines, antisera and immunoglobulin preparations are being reviewed (Dudgeon, 1976).

IMMUNISATION STRATEGY
Without a clearly defined immunisation strategy there can be no tactical solution. The first requirement is a national administrative organisation that has responsibility for making recommendations on the need for immunisation and for keeping such recommendations under review. The ultimate responsibility for immunisation strategy in this country is vested in the Secretaries of State, but responsibility is delegated to the Chief Medical Officers of England, Scotland, Wales and

| Table 2. Principles of immunisation |
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| 1. The need: is there a need for prevention based on morbidity and mortality data? |
| 2. The method: active or passive immunisation, or both? |
| 3. Safety: safety is a relative term since absolute safety cannot be guaranteed. Measures depend on regulation and good manufacturing process. |
| 4. Potency: effective immunisation depends upon potent vaccines of the correct antigenic composition. |
| 5. Economic production: immunological products are costly to produce and safety and potency tests add to the cost. This is of special importance in the developing areas of the world. |
Northern Ireland, who receive advice from a Joint Standing Committee on Vaccination and Immunisation (JCVI). The JCVI is an advisory body responsible for making recommendations through the Central Health Services Council (and in Scotland through the Scottish Home and Health Department) to the Secretaries of State on all and every aspect of immunisation procedures. The JCVI may make recommendations on the advice of its own members, or with information received from international organisations such as the World Health Organisation. For example, the decision taken in 1971 to recommend that routine vaccination of children in this country against smallpox be discontinued was taken in that light. It may also receive advice or request advice from scientific bodies such as the Medical Research Council (MRC), the Public Health Laboratory Service (PHLS) and the National Institute for Biological Standards and Control (NIBSC). These bodies have, over the years, carried out clinical field trials on the effect of immunisation against whooping-cough, tuberculosis, poliomyelitis, measles and rubella, which have greatly assisted the JCVI in making recommendations. Similarly, the MRC's Committee on Development of Vaccines and Immunisation Procedures (CDVIP) considers the need for the development of new products or the improvement of existing ones. Agreed recommendations are then passed down the line of responsibility to General Practitioners, Area Medical Officers and Area Nursing Officers of Health for implementation under the signature of the Chief Medical Officer and the Chief Nursing Officer of Health, with copies to Regional Officers, Secretaries of Boards of Governors of the Specialist Postgraduate Teaching Hospitals and other responsible bodies. Responsibility for implementation of policy is placed firmly at Area Health level (Dudgeon, 1976).

The JCVI has another important role in ensuring that surveillance is undertaken to determine whether vaccination programmes and policies are effective. Vaccine surveillance is an essential aspect of any programme, and in this country may be carried out by one or more of the scientific bodies such as the PHLS, which has consistently monitored the effect of poliovaccine and measles vaccine, or by hospital and university departments funded by research grants. The National Congenital Rubella Surveillance Programme (Dudgeon et al., 1973) and the National Childhood Encephalopathy Study (DHSS, 1977) are examples; the first surveying vaccine effectiveness (rubella), the second monitoring adverse reactions to a vaccine (triple vaccine).

Safety is another vital factor where co-ordination of responsibility is of paramount importance. The DHSS is the licensing authority for all immunological products and it receives advice from the NIBSC and the CDVIP of the MRC, on the one hand, and from the Committee on Safety of Medicines (CSM), on the other. This latter Committee, as far as immunological products are concerned, has a dual statutory role. The Biological Sub-committee considers applications for clinical trial certificates or product licence certificates for all biological products including vaccines, antisera and immunoglobulins. The newly established Com
The Sub-committee on Adverse Reactions is responsible for monitoring adverse reactions to any licensed drug, including vaccines, through a reporting system on yellow cards.

IMMUNISATION SCHEDULES

It is important to have a clearly defined schedule of immunisation if control of infectious disease by immunisation is to be effective. The object of an immunisation schedule is to ensure that a comprehensive basic course of immunisation is introduced at the earliest possible age. In designing or making alterations in schedules, account should be taken of the need for early immunisation wherever possible, correct spacing of injections, flexibility to allow alterations to meet local situations, and comparative simplicity so that both professional groups and the public can understand the necessity for them.

Basically, there are two schedules for primary immunisation of infants and young children. In the USA, Canada and many European countries, immunisation is carried out with a four dose schedule (three plus one) of triple vaccine containing diphtheria-tetanus-pertussis antigens (DTP) and oral poliovaccine (OPV). A series of three doses is given of DTP and OPV at 1 to 2 monthly intervals starting at the age of 2 to 3 months, and a fourth booster dose at 18 months of age. Further booster doses are given at primary school entry (DTP and OPV) and at school leaving (adult type diphtheria and tetanus only), and other vaccines such as measles, rubella and mumps are introduced into the programme. Many European countries adopt the same basic schedule and time intervals, but there are exceptions. For example, Sweden and Finland use inactivated poliovaccine (IPV), as do some of the provinces of Canada. In France, both IPV and OPV are used whereas in The Netherlands a quadruple vaccine (DTP + IPV) is used.

The immunisation programme in the UK differs from all the others. Although a three dose schedule is used, the interval between the first and second doses is six weeks and between the second and third six months, thus obviating the need for the fourth booster dose at 18 months. Thereafter, booster doses are administered as the child grows older, giving diphtheria-tetanus vaccine (DT) and not DTP on school entry, and reinforcing doses of diphtheria, tetanus and oral poliovaccine on leaving school. Measles vaccine is given from the second year of life onwards. Rubella vaccine is given to 11 to 14-year-old schoolgirls and seronegative females on the clear understanding that pregnancy is a major contra-indication to its use.

Whatever method of immunisation is adopted, it is essential to realise that a basic immunity and subsequent reinforcement of immunity can be achieved only by the use of potent and safe vaccines administered at the correct age and with the appropriate intervals between injections.
THE PRESENT STATUS

A glance at Table 1 will rapidly identify the field where major advances have been made. Yellow fever, one of the major scourges of Africa and central America, has been brought under complete control by immunisation of residents in endemic areas and of travellers to those zones. The 17D yellow fever tissue culture vaccine is one of the most effective immunising agents ever developed. This, together with control of the mosquito (the insect vector of yellow fever), has been one of the great advances in preventive medicine. The control of smallpox is another success story following the eradication campaign initiated by the World Health Organisation in 1965. Twelve years later a few isolated reports of variola minor or alastrim have been confirmed in Somalia and Ethiopia. The rest of the world has been freed of this formidable human plague. Tetanus is another success story; the use of tetanus toxoid was a major factor in the control of tetanus in war injuries in the Second World War. Indeed, so successful is tetanus toxoid as an antigen that there are risks of over-immunisation (Edsall et al., 1967; Peebles et al., 1969). As far as the communicable diseases of children are concerned, the most spectacular advances lie in the control of diphtheria and poliomyelitis. In the UK, notifications and deaths from diphtheria prior to immunisation averaged 50,000 and 2500 p.a. The effect of the national immunisation campaign with diphtheria APT toxoid in 1941 was dramatic. The number of notifications was reduced by half in five years and in 1974 there were only three notifications with no deaths for the previous six years. As for paralytic poliomyelitis, in epidemic years between 5000 and 7000 notifications would have been made, with 700 to 800 deaths. In 1974 there were only four notifications with no deaths for the preceding six years, but recently there has been a resurgence of endemic poliomyelitis in unvaccinated children in this country. Fourteen cases notified in 1977 is 14 cases too many. This increase has been attributed to the marked decline in the number of children being immunised against whooping-cough, which has affected acceptance rates for other vaccines such as those for diphtheria and tetanus, polio and measles. The acceptance-rate for whooping cough has fallen nationally from about 75 per cent to as low as 38 per cent in some areas. Figures for diphtheria, tetanus and poliomyelitis are still fairly static at about 74 per cent, but in some areas, polio vaccine acceptance rates, unlike those for diphtheria and tetanus, are as low as 58 per cent. This clearly calls for a nation-wide improvement.

There are two problems concerned with pertussis vaccine, which is normally administered in the form of triple vaccine. Doubts have been expressed about both the protective efficacy and the safety of pertussis-containing vaccines. Miller et al. (1974) and Miller and Fletcher (1976) from the PHLS have argued that the attack rates in immunised children are lower than in unimmunised children, whereas Bassili and Stewart (1976) consider that the declining incidence of pertussis is related to improved socio-economic conditions rather than to
vaccination. It has also been argued that the decline in the incidence of pertussis following the introduction of a national campaign in 1957 has been less dramatic than the rapid decline in notifications of diphtheria following the national immunisation campaign with diphtheria toxoid in 1941. Any comparison between the immunising effect of a bacterial toxoid such as diphtheria and tetanus, which should give virtually 100 per cent protection, with that of a whole cell bacterial vaccine such as pertussis, typhoid or cholera, is meaningless. At the most, a protection rate of 80 to 85 per cent can be achieved, given a potent pertussis vaccine containing the correct serotypes. This was the opinion expressed in a recent report on whooping cough vaccination from the Department of Health (DHSS, 1977).

The problem of safety is a vastly more difficult question to answer, mainly because the associated events of convulsions and encephalopathy can occur as natural events as well as after immunisation, and there is no way (even by a time-relationship) of distinguishing one from the other. Figures which have been quoted of severe brain damage following triple vaccine of 1 in 30,000 or 1 in 300,000 are meaningless unless there is a very effective reporting system and some method of identifying a vaccine-related event from a naturally occurring one. For this reason, a National Childhood Encephalopathy Study (DHSS, 1977) has been initiated to try to answer the difficult question: ‘How many children develop illnesses after immunisation in excess of those that would have occurred spontaneously?’

The whole pattern of tuberculosis has changed dramatically in the past 30 years. It is likely that BCG vaccine has played a part in the control of the disease, but not the main part. The reduction in the incidence of tuberculous meningitis in the developing countries of the world is very likely to have been the result of BCG vaccination, but in this country it has been estimated by Springett (1975) that one notification of tuberculosis will be prevented by the BCG vaccination of 5,000 to 80,000 individuals in the 1980s. A review of current BCG vaccination policy is required in the not too distant future.

Effective vaccines are now available against measles and rubella, but neither of these two vaccines is being properly utilised in this country (Dudgeon, 1977). Until they are, measles will continue to occur in the unvaccinated. It has been argued that nowadays measles is not a serious disease and that immunity from the vaccine may not be as long-lasting as after natural infection, but there is good evidence from carefully controlled studies (Krugman, 1977) and the Medical Research Council’s study (1977) in this country of long-term immunity following vaccination. Even if it was found that immunity was waning 20 to 25 years after measles vaccination, there is no reason why re-vaccination could not be introduced. Until rubella vaccines are widely utilised in school-girls aged 11 to 14 years and seronegative women with due regard to the contra-indications for rubella vaccines, we shall continue to see congenital rubella defects occurring
unabated. It has been suggested that we should change our policy of selective immunisation against rubella in the UK and adopt the method used in the USA, where rubella vaccine (either monovalent or trivalent measles – mumps – rubella MMR vaccine) is offered to all children aged 15 months to puberty. In the author's opinion, it could come to this, but before taking this step, it would be advisable to have further information on the long-term protective effect of rubella vaccines given in early childhood. Krugman (1977) has produced some convincing evidence of well maintained antibody levels to rubella over a seven-year period, but Horstmann (1975) has shown that vaccine-induced immunity to one type of rubella vaccine appears to be less durable than natural immunity, particularly in children whose initial antibody response was low. As with all other immunisation procedures, careful surveillance is required and, depending on the outcome, vaccination policy may have to be reviewed.

Over the past 50 years, some powerful, effective vaccines which have materially affected the natural history of many of the communicable diseases have been developed. Further progress lies in the development of new vaccines (shown in Table 1), such as the meningococcal polysaccharide, haemophilus type B capsular vaccine and the polyvalent pneumococcal vaccine, to combat the increasingly important antibiotic-resistant organisms, and in the improvement and purification of existing vaccines.

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