Conference on immunisation

A summary of the conference held at The Royal College of Physicians

The decision to prevent a particular infectious disease by vaccination depends on weighing up the balance between risks, benefits and costs related on the one side to the infection — ie its overall frequency and secular trends, its distribution within the population, its severity, the presence of alternative, more appropriate preventive measures and, on the other side, to the vaccine — its safety, effectiveness, feasibility of production, cost, availability and acceptability to the target population. The ‘weights’ on the infection side of the balance form the fundamentals of epidemiological surveillance which in turn is crucial to the evaluation of existing immunisation programmes as well as to decision taking about the introduction of new vaccines.

Infections on the decline in Britain include most of the major scourges of the late 19th and early 20th centuries; eg diphtheria, scarlet fever, tuberculosis, poliomyelitis, tetanus and cholera. Immunisation has played a partial role in this decline but there is no cause for complacency for three reasons: there is a risk of importation from areas of the world where these diseases are still highly endemic; antigenic mutation may occur, as happened recently with poliovirus in Finland; ‘reservoirs’ of infection in certain sub-groups of the population (eg tuberculosis in the elderly indigenous population) still exist.

Stationary infections, or those with no clear trends include only one, rubella, for which there is a national immunisation campaign although there are others, such as meningococcal and pneumococcal disease, for which vaccines are available but usually only used on a selective basis. Effective vaccines are also available against mumps and chickenpox, but they are more often used overseas than in Britain.

Increasing and new infections far outnumber those on the decline and they represent the major problem still posed by these diseases in the 1980’s. They include Haemophilus influenzae B disease, food poisoning and gastroenteritis, legionellosis, imported malaria, human parvovirus, whooping cough and acquired immune deficiency syndrome. Some are preventable by vaccines already available, others represent a challenge for future vaccine research and development.

It is fortunate therefore, that in recent years there have been major advances in virological techniques which have permitted the study of viruses at molecular level. This work has, for example, opened up the possibility of developing synthetic peptide vaccines through knowledge of the structure of the antigenic sites of the virus. Such vaccines would be stable indefinitely, pose no problems of ‘reversion to virulence’ and be capable of easy, cheap, reliable and large-scale processing. Examples of the use of the new technology will be given below when considering specific vaccines.

Vaccination for travel

The only vaccine for which there is an absolute legal requirement is yellow fever vaccine when the traveller is going to enter the endemic zones in certain parts of Africa and South America. The decision to use other vaccines depends on examining criteria such as the length of the traveller’s stay and his activities once in the foreign country, the mortality and morbidity of the disease, the efficacy, side effects and cost of the vaccines.

On this basis, typhoid vaccine is probably over-prescribed for the average holiday maker as most cases in this country occur in people returning from the Indian Sub-Continent, the vaccine is not very effective and the disease now has a relatively low morbidity and mortality. The same applies to cholera vaccine although it is important to ascertain before travelling whether it is likely to be required if travelling between countries overseas. In contrast, yellow fever is a serious infection, the vaccine is highly effective and only persons with absolute contraindications such as immunosuppression, pregnancy or age under nine months can be exempted if they are entering an endemic zone. If they do so, they should not go into rural areas.

Rabies is a serious disease and the vaccine is effective. However, a subject usually knows when he has possibly become exposed and post-exposure prophylaxis is effective so there is no indication for routine vaccination of travellers unless they are going to visit rabies endemic areas far from medical aid or to work with animals in these areas. Pre-exposure vaccination is available from the British Airways Office in London. Two doses are required.

Travellers aged under 40 should have a booster of oral polio vaccine; those over 40 are recommended to have a course of Salk vaccine because they are unlikely to have been immunised previously and run a small risk of vaccine-induced poliomyelitis if given the oral vaccine.

Human normal immunoglobulin for the prevention of hepatitis A should be advised for travellers to Africa and Asia. It is not indicated for European holidays.

Information on the availability of ‘unusual’ vaccines such as for plague, tickborne encephalitis and Japanese B encephalitis is summarised in the Communicable Disease Report No. 86/07 (obtainable on request from the PHLS Communicable Disease Surveillance Centre). These are
only indicated for special cases and not for the average holiday maker.

Research on a malaria vaccine is currently in progress but even when it does become available, it will still have to be ‘backed up’ by chemoprophylaxis because it will only be directed against *P. falciparum* and it will probably be stage-specific.

### Poliomyelitis

The currently used oral and injectable vaccines are effective and relatively safe but require sophisticated technology for their production. In view of the massive problem that poliomyelitis still poses in the poor countries of the world, research continues into new approaches to developing alternative safe and effective vaccines which can be produced cheaply and simply on a large scale.

These new approaches, including synthetic peptide vaccines, controlled gene expression in yeast, attenuation by genetic modification, as well as that of developing better detection of reversion to virulence (which would improve the safety of OPV) will be dependent on the current research into the molecular basis of the antigenicity of polioviruses. The only ‘new’ vaccine in actual usage, in Europe, is a cheaper, two-dose Salk vaccine developed using a new culture method that produces high yields of virus.

### Respiratory virus vaccines

The only vaccine currently available in the UK for protection against viral respiratory infections is that against influenza. The extensive range of respiratory viruses and their types, diseases, ages affected and the importance of local secretory antibody in combating infection as well as that of circulatory antibody, have all compounded the difficulties in producing respiratory virus vaccines. However, prospects for development of new vaccines such as those against respiratory syncytial virus (RSV) and adenovirus have dramatically improved in recent years with the advent of molecular virology. Genome mapping and identification of antigenic sites is currently in progress using RSV and para-influenza viruses.

### Hepatitis

Six different hepatitis viruses are now recognised, but the vaccines, either already available or under research and development, are only directed against hepatitis A and B.

Hepatitis A is hyperendemic all over the world. Passive immunisation using immunoglobulin is effective and well-established for use in travellers and contacts of cases in certain circumstances, but vaccine development has been hampered because the virus is difficult to grow in tissue culture. However, two vaccines containing live virus attenuated by serial passages are currently being evaluated and a killed vaccine is undergoing trials in the USA.

Hepatitis B is also a major global public health problem. Passive post-exposure immunisation using hyper-

### Vaccination against Epstein-Barr Virus (EBV)

This is another vaccine of the near future whose development has depended on new technology, which has enabled delineation of the molecular structure of the viral antigen, and on the use of a suitable animal model, the cotton top tamarin, to test protective efficacy. Although the new vaccine will probably be evaluated initially for its effectiveness in preventing infectious mononucleosis, this is not envisaged as its primary use. The most important public health problems associated with EBV are those of Burkitt’s lymphoma in tropical Africa and New Guinea and nasopharyngeal carcinoma in parts of Asia and Africa.

### Prospects for vaccines for viral gut infections

Approximately five million deaths a year worldwide are caused by diarrhoeal disease, most of them in developing countries in children under five. One of the most important causes is rotavirus, although there may be geographical differences in incidence ranging from 25 per cent of children with diarrhoea in the Vellore area of India to 70 per cent in the population around Calcutta. Rotavirus also causes epidemics every winter in Britain especially in children under two years of age. Several other viruses (eg adenovirus, coronavirus, calcivirus, astrovirus) have been identified as gastrointestinal pathogens, but in many published series at least one-third of the cases have no identifiable microbial aetiology so that, clearly, many more organisms are awaiting discovery.

The recent discovery of a tissue culture method for growing rotavirus has led to the development of a live attenuated oral vaccine (RIT 4237, Smith, Kline and French) derived from a calf strain of the virus. Preliminary trials over two winters in Northern Europe demonstrated a high protective efficacy and this vaccine, which has the advantage of being stable at room temperature for six months, is now being evaluated in Peru and the Gambia, although early results from Peru are less encouraging than those from Europe. The disadvantages of the
vaccine include its expense, the need for it to be given with a formula feed and possible interference with or by polio vaccine which, logically, would be given at the same time.

A new Rhesus rotavirus vaccine is now also on trial in the USA, Scandinavia and South America; other options for the future include synthetic polypeptide and calf-human reassortant vaccines.

Vaccines for preventing meningitis

Each year in the UK 400-500 children develop *H. influenzae* meningitis. Most are under two years of age and a substantial proportion, probably 10-15 per cent, are left with neurological damage, particularly sensorineural hearing loss. It is known that serum antibodies to the capsular polysaccharide antigen of the organism, which is the major virulence determinant, are protective and a vaccine consisting of this purified antigen has been available for some years. Unfortunately, it is of no value in protecting those at greatest risk since it is not immunogenic in children under the age of two years. Recently, however, workers have conjugated the polysaccharide antigen with other proteins such as diphtheria toxin and successfully induced antibody responses in infants. The prospects for a conjugated *H. influenzae* vaccine which can be used to protect those at greatest risk are now good.

In the case of meningococcal meningitis, the majority of which is caused by organisms belonging to serogroups A, B or C, purified polysaccharide antigen vaccines have proved equally disappointing. Protection of children under two years has been achieved with group A vaccines but the immune response to group C — the more important serogroup — is poor in this age group. In the case of group B infections, which are currently causing concern in some parts of the UK, the polysaccharide antigen is not immunogenic in any age group and no effective vaccine is available. Research to develop a conjugate vaccine or to use alternative antigens such as outer membrane proteins, is urgently required and already in progress.

Pneumococcal vaccines

Pneumococcal vaccines were beginning to be developed about 50 years ago but research was dampened by the advent of sulphonamides and penicillin. However, there is still a need for prophylaxis in certain high risk groups. These include the elderly, whose waning immunity places them at risk, and those with chronic diseases particularly asplenism and Hodgkins disease. The major problem in developing an effective vaccine has been to include all the necessary capsular polysaccharide serotypes. The original Pneumovax vaccine was a 14-valent vaccine, but this has now been replaced by a 23-valent preparation which should provide protection against 85-90 per cent of all pneumococcal infections in the UK. Efficacy studies have shown evidence of good protection in healthy adults and some protection in the elderly. Unfortunately, children under two years of age and those with asplenism and Hodgkins disease do not respond well and the vaccine is therefore of limited value in those groups where the need for prophylaxis is greatest. However, the option of using the vaccine for prophylaxis in the elderly remains and perhaps should be given further consideration in the UK.

Whooping cough vaccines

Although the controversy surrounding the safety and efficacy of pertussis vaccine has now been largely resolved it has left a legacy of poor uptake and as a result whooping cough continues to be a substantial health problem in the UK. The arrival of a new generation of purified acellular pertussis vaccines could provide the means whereby control of pertussis is regained. These new vaccines, made by purifying the protective antigens from the *B. pertussis* organism and inactivating those with toxic activity, should be less reactogenic and potentially more effective than whole cell preparations. Efficacy will however depend on including the right antigens and there is as yet insufficient evidence as to which these should be.

The three most likely candidates are lymphocytosis promoting factor (LPF), filamentous haemagglutinin (FHA) and agglutinogens. LPF is also a major toxin and for inclusion in an acellular vaccine has to be specially treated (toxoided) to render it non-toxic while still retaining its immunogenicity. Other toxins of the *B. pertussis* organism which are not thought to be important for protection are excluded. Unlike whole cell vaccines, therefore, which contain biologically active toxins, acellular preparations should be virtually free of toxic activity, allowing larger antigenic doses to be given to infants. It is hoped that this will result in good immunity after only one or two doses so that infants can be protected at a very early age when the consequences of infection are most severe.

Acellular vaccines containing variable amounts of LPF, FHA and agglutinogens have been in routine use in Japan for five years and although there is now good evidence of their protective efficacy this is confined to children over two years old. Clinical protection trials in children aged 6-10 months are underway in Sweden and preliminary immunogenicity and reactogenicity studies with acellular vaccines are to begin shortly in the UK. However, if these vaccines are to be licensed here we must be sure that they are as effective as the current preparation, and it may be some years before such evidence becomes available. An even more difficult task will be to assess the relative safety of these preparations since the risk of neurological damage from the present vaccine, if it exists at all, is so low. The lack of a pertussis vaccine reaction syndrome, and the absence of an established biological mechanism for the brain damage attributed to whole cell vaccine, makes surveillance of the possible neurological effects of immunisation particularly difficult. Despite the difficulties, it will be imperative that such studies are done when the new generation of pertussis vaccines comes into use.

BCG vaccination: pros and cons

The Medical Research Council trial of BCG vaccine in 1954 showed 80 per cent protection in 13-year-old chil-
dren over the first 10 years, and following this the vaccination of school children was introduced. It is now considered that with the continuing fall in the incidence of tuberculosis the programme is no longer justified, and by 1990 should be replaced by the vaccination of groups most at risk.

BCG has probably not had a great effect on the incidence of tuberculosis. The fall in annual deaths from tuberculosis from 1900 to 1965 is more likely to have been due to other anti-tuberculosis measures. In two countries, one of which (Norway) had a BCG programme while the other (Netherlands) had none, the decline in the incidence of tuberculosis in the 15–24 age group showed little difference. Thus tuberculosis can be expected to continue to decline in the absence of a BCG programme. Unlike other vaccines, the secondary effect of protection from BCG on unimmunised people is not detectable. One argument for continuing the schools’ programme is that unvaccinated young people from areas of low incidence would be at risk when moving to high incidence areas. However, cross infection between Asians and non-Asians appears to be slight, and the rate of decline in tuberculosis in the 15–24 and under-13 age groups is similar in both races.

Side effects of the vaccine include abscesses which at school age should not be significant provided the intradermal technique is good and the children are tuberculin negative. Disseminated BCG is almost unknown except in immunosuppressed children. Hypertrophic or keloid scars occur but are uncommon, from personal experience perhaps one in two years.

The cost of the programme is considerable. In 1953 it was estimated that 94 vaccinations were needed to prevent one case, whereas in 1986 12,000 vaccinations would be necessary. In 1975 Stillwell estimated that the BCG programme cost twice the sum saved from preventing tuberculosis, while in 1985 the programme would cost 10 times as much. It has been predicted that if the programme was stopped there would be an increase in the number of cases, but only by 75 per annum. The epidemiological data from the annual tuberculin survey would be lost, and probably more chemoprophylaxis would be used. On the benefit side would be the saving of the financial cost of the BCG programme, no side effects, and the return of tuberculin testing as a diagnostic tool. However, it should be taken into consideration that the cost of one child significantly handicapped through tuberculous meningitis would more than exceed the cost of the programme for 5 years.

Rubella vaccine — at what age?

The selective rubella vaccination programme in the UK has achieved considerable success and relatively few women now enter pregnancy still at risk of the disease. However, when rubella is prevalent in the community, the infection rate in the 2–3 per cent of pregnant women who are susceptible results in an unacceptably high number of congenital rubella cases and therapeutic abortions. In view of this it has been suggested that our present strategy should be supplemented by mass rubella immunisation of infants of both sexes, possibly using a combined measles/mumps/rubella vaccine. Intuitively this seems a sensible suggestion since by reducing the pool of infection in young children transmission to susceptible pregnant women will be interrupted. However, recent work involving mathematical modelling of infectious disease transmission and of the impact of vaccination has shown that mass immunisation may not produce a beneficial effect unless high uptake rates are achieved. The partial suppression of disease transmission that can result from a poorly implemented mass immunisation programme carries with it the risk of deferring infection until later in life which, in the case of rubella, could have disastrous consequences. This risk would be much less if mass immunisation is combined with selective immunisation of schoolgirls and adult women. However, there is still the prospect of occasional large epidemics if uptake in infancy remains only 60–65 per cent. To avoid this, uptake rates of at least 80 per cent are necessary and, in view of the poor record with measles vaccine in the UK, many of the participants at the Conference felt that serious consideration should now be given to adopting a system whereby evidence of immunisation is required for school entry. This need not be regarded as compulsory vaccination but could consist of a system of checks and balances designed to make districts answerable for any child remaining unvaccinated at the time of school entry. With the prospect of a new generation of viral and bacterial vaccines on the horizon, the present challenge is to ensure that the vaccines we already have available in the UK are used to maximum effect.

This summary is based on papers given at the Conference on Immunisation of Children and Adults held at the Royal College of Physicians of London in June 1986. It has been prepared by Dr Susan Hall, MB, MSc, MFCM, Consultant Epidemiologist and Dr Elizabeth Miller, MB, BS, Senior Microbiologist, Public Health Laboratory, London.