Annotation**Mumps and varicella vaccines**

In a previous Annotation on measles and rubella vaccines¹ attention was drawn to the importance of tests for safety and efficacy of modern vaccines. In effect this applies to any drug, be it a therapeutic substance or biological product. Now that the old Therapeutic Substances Act has been withdrawn, responsibility rests with the licensing authority on the advice of the Committee on Safety of Medicines for issuing clinical trial certificates or product licences for newly developed products. A newly established Committee on Review of Medicines also considers details of licensing for well-established products—such as triple vaccine, diphtheria and tetanus vaccine, TAB vaccine—that is, the products which were granted product licences of right without detailed examination when the Medicines Act was implemented. Safety, potency, and antigenicity are essentially the responsibility of government by licensing, and also of the manufacturers, but there is another factor which should in effect always be considered first, namely the need for a prophylactic, particularly in the case of vaccines. This is an area where those responsible for licensing increasingly turn to clinicians for advice on the need for a new product.

30 years ago there were only three vaccines in common use, smallpox vaccine, diphtheria, and tetanus toxoids, with pertussis vaccines showing signs of being useful in paediatric practice. Today, it is theoretically possible to produce an immunological product, either a vaccine or an immunoglobulin, against any infectious disease once the causative agent has been isolated in the laboratory. A review in 1978 by Dudgeon² on advances and prospects of new vaccines, both bacterial and viral, is now to a great extent out of date with several new vaccines already licensed and others awaiting clinical trials. The report by Tyrrell *et al.*³ on the isolation of a cytopathic agent with the hallmark of a virus from patients with schizophrenia or chronic neurological disorders makes the mind boggle at prospects for the future.

How can the need for a prophylactic product be evaluated? Should it be in terms of mortality or morbidity from the natural disease, or both? In a sense this is the crux of the problem if one considers the difference in attitudes between this country and

the USA on the use of measles vaccine. In a review, Sabin⁴ reported that since licensure of measles vaccine in 1963, the percentage of children vaccinated aged between 1 and 4 years has risen from 33.2% in 1965 to 65.9% in 1976. Yet despite this, and the fact that in most states, vaccination laws require compulsory vaccination against measles and the other common communicable diseases—pertussis, diphtheria, tetanus, mumps, and rubella—before school entry, the number of *estimated* cases in 1977 was not far short of a million when compared with the *actual* number reported of about 55 000. In the first 5 months of 1979, the reduction of reported cases in the USA has been even greater.⁵ In this country, the acceptance rate of measles vaccine is very much lower and it is difficult to identify the reasons for this. Certainly measles is a much milder disease than it was 40 years ago, but in terms of morbidity a significant number of cases (500 000–600 000 in an epidemic year) was reported with consistent regularity every other year before the introduction of measles vaccine. And one must recall that some of the earlier measles vaccines were more reactogenic than those in current use. The CNS and respiratory complications are generally considered to be the principal reasons for the introduction of the vaccine. Acute encephalitis of the postinfectious type may occur in 0.1–0.02% of cases of measles, but as this is so often a severe and permanently crippling disease, there is a stronger argument for vaccination against measles than in the case of mumps.

Mumps is an extremely common infectious disease affecting predominantly young children, but it is not a severe disease in terms of mortality. For example, in the USA the fatality rate is about 1.8 deaths per 10 000 reported cases compared with 7, 4, and 3 per 10 000 respectively for measles, chickenpox, and rubella.⁶ What about the complications? The two most important are those affecting the CNS and orchitis. Most cases of CNS involvement in mumps, unlike measles, are of meningoencephalitis with a spectrum of disease ranging from the more commonly encountered aseptic meningitis-like illness presenting with a stiff neck to an encephalitic illness with stupor or drowsiness. The prognosis of aseptic meningitis is extremely good and, as far as is known, there are few reports of long-term sequelae of any

4 Dudgeon

severity. However deafness can occur after mumps; it appears to be rare, but although usually unilateral, it is often profound. Orchitis is another common complication of mumps and although frequently thought to be a cause of sterility in the male, there is no evidence that this is so. The oft-repeated statement that it is, is based on fear rather than on facts. In a retrospective study of complications from mumps initiated by the Research Unit of the Royal College of General Practitioners⁷ only 40 complications were encountered in 1642 cases (851 males) a rate of 24 per 1000 cases, but as there were only 5 cases of encephalitis among CNS defects, no conclusions on the risk of such complications can be drawn from such a small and retrospective survey, and a subsequent prospective survey did not add much further evidence.⁷

A live attenuated mumps virus vaccine was licensed in the USA in 1968.⁸ It was developed from a strain of mumps virus isolated in fertile hens' eggs and after several passages, was adapted to chick embryo cell cultures. It was originally used as a monovalent vaccine in a single dose of 0.5 ml, but in recent years has been used increasingly as a combined vaccine with measles and rubella vaccines (MMR). Numerous studies have been reported by Hilleman *et al.*⁸ and Weibel *et al.*⁹ on the properties, antigenicity, and effectiveness of mumps vaccine. Recently Hayden *et al.*⁶ reported on the current status of mumps vaccine in the USA. One of the most striking features of the epidemiology of mumps in the USA since 1968 has been the progressive decline in the number of reported cases. In 1976 the number reported represented a 42% decrease on the average annual total for the years 1971–75. The incidence of mumps has now reached an all-time 'low' and in a study embracing California, Massachusetts, and New York, the decrease in the 5- to 9-year age group was 68.6% for the years 1972–78 compared with 1967–71. Several other important pieces of information emerged from this report. Mumps vaccine can be expected to produce a seroconversion rate of at least 95% without clinical symptoms in recipients. Postvaccination neutralising antibody titres appear to decline at a slower rate than after natural infection, presumably as a result of subclinical reinfection. Therefore, the duration of vaccine-induced immunity can be expected to be good and there is already evidence of protection for at least 9 years after vaccination.⁶ Adverse reactions are rare, except for the occasional case of parotitis. A few cases of CNS dysfunction have been observed⁶ but they represent a rather heterogeneous group and do not show the temporal clustering observed with live measles vaccine.

There is no question that mumps vaccine as used

in the USA has proved to be an effective and useful prophylactic, particularly as it fits in with the regimen used there of combining it with measles and rubella vaccine for children from age 15 months. Should it be used in this country? In my opinion there is no need for it as a routine procedure. The pain or discomfort from mumps parotitis and orchitis are hardly sufficient grounds for routinely immunising our children, nor is the evidence of long-term ill effects from aseptic meningitis a sufficient reason for doing so, but it could be a useful vaccine for special use—for example, for adults who have not previously had mumps (based on serological evidence) and possibly for special at-risk groups, nursing staff, and the armed Forces. For example, some years ago there was a severe outbreak of mumps in the Gurkhas with many cases of orchitis and aseptic meningitis leading to much discomfort and organisational problems; however these are not of direct concern to paediatricians.

Another possible situation where live mumps vaccine might be useful would be to control the spread of infection in a ward outbreak of mumps. Although in theory this should be effective, present evidence does not suggest that mumps vaccine can be relied on, whereas live attenuated measles vaccine is highly effective in controlling outbreaks of measles in hospital wards and other institutions. Krugman *et al.*¹⁰ state that 'mumps vaccine will not provide protection when administered during the incubation period. There is no contraindication to its use because even if it did not actually prevent infection during the outbreak, the vaccine should produce protection against subsequent infection'.

Another vaccine that has recently aroused considerable interest is the live attenuated varicella vaccine, developed by Takahashi *et al.*¹¹ in Japan. The strain of virus (Oka strain) was adapted by serial passage in various forms of cell culture and finally prepared as an experimental vaccine in human diploid cells (Wistar W1–38 strain). This vaccine was first tested by Takahashi *et al.*¹¹ in 23 children in a hospital ward suffering from a variety of diseases including purpura, hepatitis, and renal disease. All 23 children were known to be susceptible to varicella and all 23 developed complement fixing (CF) antibodies after vaccination, with little difference in the antibody titre between those being treated with corticosteroids and those not. Six children developed mild fever and 2 a mild vesicular eruption. No severe reactions were encountered and there was no spread of varicella. 16 additional children with renal disease, nephritis, or the nephrotic syndrome were also vaccinated without ill effect. They all developed a serological response.

In subsequent studies Asano *et al.*¹² demonstrated

the protective efficacy of the vaccine in 18 children with renal disease and other conditions exposed to varicella and zoster in a hospital ward. Some of these children were probably the same as in the previous study reported by Takahashi *et al.*¹¹ but again there was evidence of protection and, more important, of a booster response without symptoms in 3 children. Asano *et al.*¹³ were also able to demonstrate protection against varicella in family contacts by administration of the vaccine within 3 days of contact. In a follow-up study of 181 vaccinated children, originally seronegative, it was found that 85% had seroconverted when tested by the CF test and 97.8% by the neutralisation test.¹⁴ Only one out of 80 children subsequently exposed to varicella contracted a mild infection 16 months after vaccination. After these preliminary findings the vaccine was given to 11 children¹⁵ in remission from acute leukaemia and to 6 children with malignancies such as neuroblastoma and retinoblastoma. Two children with leukaemia developed a minute rash 3 weeks later. All vaccinated children developed a serological response but the neutralisation antibody titre was higher and more persistent than the CF response, although both were generally lower than in children previously studied.¹¹⁻¹⁴ Three of the children were subsequently exposed to varicella in the home but remained free of symptoms.

These clinical trials are encouraging, but it would be premature to think that this vaccine can be given as a routine prophylactic to leukaemic children without more knowledge. More needs to be known about the vaccine, its properties and behaviour in normal healthy individuals in respect of its antigenicity, and about its protective efficacy and lack of communicability. There is no doubt that some means of protection for these highly susceptible children against viral diseases, such as varicella and measles, would be of immense benefit in view of the success of modern treatment for leukaemia. Passive immunisation with zoster-immune globulin¹⁶ has been found successful in preventing varicella in some cases, but its effect is unpredictable and of short duration, and it must be administered in sufficient dosage within 3 days of exposure. It is also in short supply. The only alternative is active immunisation with either a killed or live attenuated vaccine. As far as one can tell, the Japanese workers have only developed a live vaccine and the current dilemma which can be judged from correspondence in the American journals¹⁷⁻²⁰ revolves mainly around the problem of safety. There is also the problem of persistence of the attenuated virus and whether it may lead to zoster in vaccinees later in life as occurs in the natural disease after varicella. It is conceivable that the risk of a latent infection with long-term

sequelae is less with an attenuated vaccine because the degree of dissemination is much less than in natural varicella. Much the same problem concerning latency or persistence arose when attenuated measles vaccines were first introduced. Would this increase the risk of subacute sclerosing panencephalitis (SSPE)? Fortunately these fears seem to have been unfounded as the incidence of SSPE in the USA appears to have declined as the measles vaccination programme has progressed.²¹⁻²² On theoretical grounds therefore, latency dose not seem to be a major obstacle to further studies.

At present the number of children with leukaemia and other disorders for which they are receiving immunosuppressive therapy is small, but at the same time, administration of any live vaccine in patients with these disorders would be considered as a major contraindication. Some years ago, Mitus *et al.*²³ administered live Edmonston B measles vaccine to leukaemic children. Not only were the immune responses poor, but one child died of giant cell pneumonia. The Oka varicella vaccine seems to be a safer product, and it would seem unfortunate if this research did not progress despite the potential hazards. When to start clinical trials is often a difficult decision to make—particularly with biological products—a subject which was recently discussed in detail at an international conference in Geneva.²⁴⁻²⁵ What is required now is a carefully worked out series of clinical trials starting first with healthy susceptible adults and moving progressively into younger age groups with careful evaluation at each step. Many hospitals now screen members of staff, particularly nurses, for rubella antibodies; tests for V-Z antibodies could be included. Those found to be susceptible could be offered varicella vaccine and then studied in detail for evidence of virus transmission and antibody response. It would be important to use a sensitive serological test for V-Z antibody as the CF test is not as sensitive as the neutralisation or fluorescent antibody technique. The use of varicella vaccine might also be considered in the event of a ward outbreak of varicella, using vaccine for those children in whom there is no contraindication for the administration of a live vaccine.

The final step would be to test the vaccine in leukaemic children in remission. Although such a condition would normally be regarded as a contraindication to the use of a live vaccine, the risk from natural varicella is probably a greater hazard. This is a difficult ethical problem, but one that should be faced. It is one in which the risk versus benefit principle in therapeutic research has to be carefully weighed. In my opinion, the risk would be more than minimal, but the potential benefit great.

If these issues are carefully understood by the investigators, they can then be explained to the parents. Many would probably welcome the chance to participate.

References

- ¹ Dudgeon J A. Measles and rubella vaccines. *Arch Dis Child* 1977; **52**: 907-11.
- ² Dudgeon J A. The current status of immunisation. *J R Coll Physicians Lond* 1978; **12**: 350-8.
- ³ Tyrrell D A J, Parry R P, Crow T J, Johnstone E, Ferrier I N. Possible virus in schizophrenia and some neurological disorders. *Lancet* 1979; **1**: 839-41.
- ⁴ Sabin A B. Overview and horizons in prevention of some human infectious diseases by vaccination. *Am J Clin Pathol* 1978; **70**: 114-27.
- ⁵ Center for Disease Control. Report. *Morbidity and Mortality Weekly Report* 1979; **28**: No. 18, 205.
- ⁶ Hayden G F, Preblud S R, Orenstein W A, Conrad J L. Current status of mumps and mumps vaccine in the United States. *Pediatrics* 1978; **62**: 965-9.
- ⁷ Research Unit of the Royal College of General Practitioners. The incidence and complications of mumps. *J R Coll Gen Pract* 1974; **24**: 545-51.
- ⁸ Hilleman M R, Buynak E B, Weibel R E, Stokes D, Jr. Live attenuated mumps-virus vaccine. *N Engl J Med* 1968; **278**: 227-32.
- ⁹ Weibel R E, Buynak E B, McLean A A, Hilleman M R. Persistence of antibody after administration of monovalent and combined live attenuated measles, mumps, and rubella virus vaccines. *Pediatrics* 1978; **61**: 5-11.
- ¹⁰ Krugman S, Ward R, Katz S L. Mumps (epidemic parotitis). In: *Infectious diseases of children*. 6th ed. St Louis: CV Mosby, 1977; 181-93.
- ¹¹ Takahashi M, Otsuka T, Okuno Y, Asano Y, Yazaki T, Isomura S. Live vaccine used to prevent the spread of varicella in children in hospital. *Lancet* 1974; **2**: 1288-90.
- ¹² Asano Y, Nakayama H, Yazaki T, Ito S, Isomura S, Takahashi M. Protective efficacy of vaccination in children in four episodes of natural varicella and zoster in the ward. *Pediatrics* 1977; **59**: 8-12.
- ¹³ Asano Y, Nakayama H, Yazaki T, *et al.* Protection against varicella in family contacts by immediate inoculation with live varicella vaccine. *Pediatrics* 1977; **59**: 3-7.
- ¹⁴ Asano Y, Takahashi M. Clinical and serologic testing of a live varicella vaccine and two-year follow-up for immunity of the vaccinated children. *Pediatrics* 1977; **60**: 810-4.
- ¹⁵ Izawa T, Ihara T, Hattori A, *et al.* Application of a live varicella vaccine in children with acute leukemia or other malignant diseases. *Pediatrics* 1977; **60**: 805-9.
- ¹⁶ Brunell P A, Gershon A A, Hughes W T, Riley H D, Jr, Smith J. Prevention of varicella in high risk children: a collaborative study. *Pediatrics* 1972; **50**: 718-22.
- ¹⁷ Brunell P A. Protection against varicella. *Pediatrics* 1977; **59**: 1-2.
- ¹⁸ Kempe C H, Gershon A A. Varicella vaccine at the crossroads. *Pediatrics* 1977; **60**: 930-1.
- ¹⁹ Plotkin S A. Letter: Varicella vendetta: Plotkin's plug. *Pediatrics* 1977; **59**: 953-4.
- ²⁰ Brunell P A. Letter: Brunell's brush off. *Pediatrics* 1977; **59**: 954.
- ²¹ Modlin J F, Jabbour J T, Witte J T, Halsey N A. Epidemiologic studies of measles, measles vaccine, and subacute sclerosing panencephalitis. *Pediatrics*, 1977; **59**: 505-12.
- ²² Krugman S. Present status of measles and rubella immunization in the United States. A medical progress report. *J Pediatr* 1977; **90**: 1-12.
- ²³ Mitus A, Holloway A, Evans A E, Enders J F. Attenuated measles vaccine in children with acute leukemia. *Am J Dis Child* 1962; **103**: 413-18.
- ²⁴ Robbins F C. The demand for human trials in biologicals research. In proceedings of the International Conference on the Role of the Individual and the Community in the Research, Development, and Use of Biologicals, Geneva, March 1976. *Bull WHO* 1977; **55**: Supplement 2, 73-80.
- ²⁵ Dudgeon J A. When to begin human trials? In proceedings of the International Conference on the Role of the Individual and the Community in the Research, Development, and Use of Biologicals, Geneva, March 1976. *Bull WHO* 1977; **55**: Supplement 2, 85-7.

J A DUDGEON

Department of Microbiology,
The Hospital for Sick Children,
Great Ormond Street,
London WC1N 3JH