

Annotation

Measles and rubella vaccines

The development and production of modern viral vaccines is a highly complex and intricate matter requiring great skill and expertise, both on the part of manufacturers and control and licensing authorities. Initial clinical trials with a vaccine are designed to test for safety, antigenicity, and for protective efficacy, but once a product licence is issued and the vaccine is released for general use, it becomes essential to introduce some form of surveillance to check on these points to determine whether the vaccine is performing correctly in the field and that the theoretical considerations upon which vaccination policies are based are in fact correct.

In a recent review in the *Journal of Pediatrics* on the present state of measles and rubella immunization in the United States,¹ Dr. Saul Krugman, a paediatrician who has contributed more than many others to promote immunization of children, has produced an informative progress report on the present status of measles and rubella vaccines.

Both vaccines are live attenuated products prepared by serial propagation of the respective virus strains in a cell culture system acceptable for use in human subjects. Both vaccines are presented as freeze-dried products and are administered as a single dose of 0.5 ml by the deep subcutaneous or intramuscular routes. Both vaccines are extremely labile to heat and to light, and once reconstituted should be used within a short time and in strict accordance with the instructions set out in the manufacturer's leaflet. In the US immunization against measles is increasingly being carried out by administration of combined vaccines such as measles-rubella (MR) or measles-mumps-rubella (MMR). It has been clearly shown that the antibody response to the individual components of the combined products is as good as to the monovalent products.² In the UK measles and rubella vaccines are licensed as monovalent products as they are administered at different ages.

Since 1963, when measles vaccine was first licensed in the US, there has been a progressive decline in the number of reported cases of measles. The natural history of the disease with the typical biennial epidemic pattern, which existed before vaccination, has been completely interrupted and notifications have fallen by approximately 90%. Moreover, reported

cases of postinfectious measles encephalitis, which is probably the main reason for the use of measles vaccine, have also declined proportionally and to a very low level. Information about the duration of immunity after the use of the further attenuated measles vaccine (FAV) is also encouraging.¹ On the whole, measles HI (haemagglutination-inhibition) antibody levels have persisted well for at least 15 years in the majority of children receiving vaccine, but in a small group of 46 children, who were carefully studied serologically, it was found that 38% had no detectable HI antibody at a dilution of 1 : 8 when tested 12 years later. However, when the sera were tested at a dilution of 1 : 2 only 9% were found to be seronegative; moreover, it is probable that this small number of 7 children were immune anyway, because when they were revaccinated they all responded with a typical booster-type response. All 7 remained afebrile and were asymptomatic in the postvaccination period.

The routine use of measles vaccine in an institution for the mentally-handicapped has effectively eradicated the disease where it was once an epidemic scourge.¹ Moreover, immunity has been maintained in this institution for over 10 years where there has been little or no opportunity for re-exposure or reinfection, as all new patients are immunized on admission. In contrast, Krugman has shown that in children living at home and going to school, where there is a constant risk of repeated exposure, immunity has also been well maintained with a somewhat higher level of antibody than in the institutionalized children. In this country a high protection rate has been observed over a 12-year period in children participating in the MRC measles vaccine trials which started in 1964,³ the results of which are shortly to be published.^{3a} Nevertheless, although the international experience of measles vaccine covers a period of 15 years, it would be generally advisable to consider that vaccine-induced immunity against measles will be of long-term duration rather than life-long as with the natural disease, and if for any reason as a result of surveillance there is evidence of a decline in immunity to measles and reappearance of the disease in vaccinated populations, then there is no reason why reimmunization cannot be introduced. On present evidence this seems to be an unlikely requirement.

Despite the general effectiveness of measles vaccines, measles may continue to occur in children who have received measles vaccine or the trivalent measles-mumps-rubella product. Even under the best conditions, it is difficult to achieve an immune response in 100% of those receiving vaccine. This applies to small-scale clinical trials and even more so to large-scale community programmes. In the MRC 1964³ clinical trials, 92% of 105 vaccinated children developed an HI antibody response, thus leaving a small number of children unprotected. In practice, approximately 2–5% of children will for one reason or another fail to develop an immune response and consequently there will always be a small group of 'vaccinated' children who will subsequently develop measles.

'Inoculation' with vaccine is not necessarily synonymous with 'immunization'. There are a number of reasons why this should be so and these have important practical implications. In the first place, as already stated, measles vaccine is a very labile product and sensitive to heat and light and unless special precautions are taken to maintain the vaccine at the correct temperature, both before and after reconstitution, the vaccine may lose potency. Some inoculated children will therefore not be immunized. A second factor is the age at which the vaccine is administered. It is well known that the 'take-rate' of children given vaccine before the first year of life is considerably less (75% at 9 months of age) compared with a much higher figure at one year of age. A recent study by Yeager and associates⁴ from California has shown that a very much better 'take-rate', as measured by detectable HI antibody, is obtained in children at 13 months of age or older compared with those at 12 months. As a result, the US authorities now recommend that if children are immunized in the first year of life, as would be indicated in the developing parts of the world, then a second inoculation should be given at approximately 15 months of age.

Despite scrupulous attention to these two points, a small proportion of children in whom there is no reason to believe there is any immunological abnormality, who are immunized at the correct age with a potent vaccine (which retains its potency during the vaccination session), will fail to develop an immune response. It is a very small number. The reasons for the failure are not understood and moreover, it is occasionally encountered with other vaccines. The important practical point is that vaccination failures can be reduced to an absolute minimum if the manufacturer's recommendations are strictly adhered to. This is particularly important in clinics where multidose vials are often used and where at the end of a vaccination session the vaccine

may have reached the ambient temperature of the clinic room.

Advice is frequently sought by family doctors and paediatricians concerning the use of measles vaccine in children with a history of convulsions or epilepsy, or where there is a family history of either of these two conditions. Neither is an absolute contraindication to measles vaccine provided the convulsions are under control, and indeed the risk of convulsions after measles vaccine is substantially less than after the natural disease. For this reason, measles vaccine is recommended for children who have previously suffered from convulsions provided that human normal immunoglobulin with a specific content of measles antibody is administered at the same time, into the contralateral arm to the vaccine, and with a separate syringe.^{4a} This preparation, normal human immunoglobulin for use only with measles vaccine, is presented as a single dose preparation of 0.5 ml and contains 4–8 international units of measles antibody. In addition, doctors may be inclined to prescribe phenobarbitone for 10–14 days after administration of measles vaccine in case postvaccination fever might precipitate a fit, but experience has shown that combined use of vaccine and immunoglobulin is a most satisfactory procedure in reducing the incidence of postvaccination reactions. The same special considerations can be given to children suffering from chronic diseases of the heart or lungs in whom it may be desirable to modify reactions to the vaccine by itself.

When consideration was first given to the licensure of measles vaccine, a major problem for licensing authorities was the possibility that large-scale use of live measles vaccine might lead to an increase in the incidence of subacute sclerosing panencephalitis (SSPE), a progressive neurological condition which is almost certainly due to a reactivation of a latent infection with measles or measles-like virus. However, the surveillance data in the US⁵ indicate that in recent years there has been a downward trend in the number of reported cases of SSPE which has been associated with the declining incidence of natural measles, during which period 80 million children had received measles vaccine in the US. It is reassuring to know that measles can be controlled by the judicious use of vaccine, and that this is leading to a decline in the disease with a concomitant decline in postinfectious measles encephalitis and, equally important, a decline in SSPE. Nevertheless, continuous surveillance will be necessary for some years.

As far as this country is concerned the record of measles immunization, except for a few areas, is disturbing. At the most a 50% acceptance rate has been achieved, but with a wide variation from 33% in some areas to 60% in others. Unless this improves

the disease will continue. Admittedly some of the earlier measles vaccines prepared from the Edmonston strain were too reactogenic and one vaccine in this country was withdrawn. However, currently licensed vaccines are considerably less reactive and are acceptable for general use. The argument, or excuse, that this low figure is due to the reorganization of the health service is no longer tenable, if it ever was. Health authorities responsible for immunization must make a greater effort to improve the present uptake of measles vaccine in this country.

Basically there is little difference in the immunization practices in respect of measles vaccines in this country and the US. The vaccine is recommended at any age after infancy for children who have not had measles. In the UK the precise recommendation is 'in the second year and up to 15 years'; in the US the recommended age for starting is 15 months. Measles vaccine can also be used effectively for postexposure treatment of contacts as the incubation period of vaccine-induced measles is several days shorter than the natural disease. Measles vaccine, as opposed to immunoglobulin, is useful in preventing spread of measles in hospital and home-contacts provided there is no known contraindication. The main difference between the immunization policies of the two countries is that in the US more use is made of combined viral vaccines so that both boys and girls are immunized against measles and rubella at the same age.

SSPE continues to be seen in this country, but Bellman and Dick⁶ consider that the number of cases is falling along with the decline in measles notifications. It is too early to be certain about this, and therefore essential that the surveillance of SSPE in the UK should continue.

Immunization against rubella presents a different and, in many senses, a unique problem in preventive medicine. Immunization is directed not so much towards protection of the recipient of the vaccine but indirectly to protect the fetus should the recipient become pregnant. It is also unique in that there has never been a test to determine whether rubella vaccines will prevent rubella embryopathy as opposed to preventing rubella. Current vaccination schemes are based on the assumption that they will; although this is a reasonable assumption, it has not been proven. The only analogy to this is the use of tetanus vaccine before or during pregnancy to prevent neonatal tetanus.

There are two main immunization schemes for prevention of rubella currently being practised in different parts of the world, often referred to as the American and British schemes. These were devised as the result of an international meeting on rubella at Washington, DC, in 1969.⁷ The original US recom-

mendations were that 'live rubella vaccine is recommended for boys and girls between one year and puberty . . . vaccination of adolescents and adult males is of lower priority'.⁸ In the UK selective immunization was recommended⁹ by offering rubella vaccine to *all* girls between their 11th and 14th birthdays. Vaccination was not offered routinely to adult women of child-bearing age. Subsequently both in the US¹⁰ and the UK¹¹ it was recognized that there was a need to extend rubella vaccination to adolescent and adult females known to be susceptible as a result of serological tests for rubella HI antibody.

The US scheme is clearly based on establishing herd immunity and, although Krugman¹ has produced some interesting data to indicate that, after the large-scale use of rubella vaccine since 1969, there has been a marked effect on the epidemiology both of rubella and of congenital rubella, it is still premature to assume that this programme will achieve the long-term objective of the control of congenital rubella.

The mass use of rubella vaccine in the US has coincided with a change in the epidemiology of the disease, certainly in some areas of the country such as New York. Epidemics previously occurred at approximately 6- to 9-year intervals, as in this country, but the epidemics of rubella has never been as consistent as the biennial periodicity of measles. Although the information reported by Krugman is encouraging, evidence that herd immunity has been established by vaccination is not convincing. Several outbreaks of rubella have occurred in communities where 75–85% of the population have been vaccinated.¹² Nevertheless, in New York City and New York State, the number of reported cases of rubella has declined progressively since rubella vaccine was licensed in 1969. In spite of the limitations of surveillance procedures there appears to be a favourable downward trend in the incidence of congenital rubella in New York City¹³ and elsewhere.¹⁴

Krugman¹ has some critical comments to make on the UK vaccination policy against rubella, and he may be right, but other investigators in the US have expressed doubt about the wisdom of the current US vaccination policy.^{15,16} Much will depend on the duration of vaccine-induced immunity. If the widespread use of rubella vaccine in young children replaces the permanent immunizing capacity of natural rubella with a less durable immunity, then there will be a potential hazard to these children when they reach adolescence. It has also been argued by Schoenbaum and colleagues¹⁷ of Boston that there is a greater advantage from the point of view of cost-benefit analysis of the vaccination policy as practised in the UK and many European countries over that

of the US. It is too early to draw any conclusions on policy but it would be a mistake to believe that the answer lies in achieving herd immunity by mass use of rubella vaccines.

Prospective seroepidemiological surveys by investigators in the US, UK, and elsewhere have shown that rubella HI antibody levels are well maintained for 5 to 7 years depending on the length of the observations. However, Horstmann¹⁶ has shown that vaccine-induced antibodies appear to be less stable than those acquired as a result of natural infection. In a study with the HPV duck embryo rubella vaccine, 26% of the vaccinated children with initial low levels of antibody after vaccination had little or no detectable antibody 5 years later.

The problem therefore is to determine whether immunity induced by vaccination in childhood will persist throughout the child-bearing period and whether reinfection, if it follows vaccination, will be a hazard to the fetus. Although reinfection is known to occur in natural rubella it is invariably asymptomatic and, although a few cases of congenital rubella have been reported after natural reinfection,¹⁸ convincing proof that these were cases of true reinfection is lacking. This must be a very rare event, however. The strongest evidence that reinfection does not constitute a hazard to the fetus is that there are no reported cases in the world's literature of more than one case of a congenital rubella infant in a family other than in twins.

In the UK there has been as yet no evidence from the National Congenital Rubella Surveillance Programme of a decline in the incidence of congenital rubella and for reasons of vaccination policy, no clear-cut evidence would be expected by 1977.¹⁹ Nevertheless, there are no grounds for complacency about the matter with a low acceptance rate of vaccine for schoolgirls and an unknown but predictably lower level of vaccination of adult women. It has been suggested that the answer lies in changing over to the US policy.²⁰ It could come to that, but before such a step were taken it would be preferable to attempt to improve our use of rubella vaccines.

First of all it should be remembered that the extent to which rubella vaccines have been used in the US has been largely dependent on the use of combined vaccines. Bearing in mind the lack of use of measles vaccine in children in this country, it is a matter for conjecture whether any improvement would be made by adding rubella vaccine to measles vaccine as a combined product. We have highly effective vaccines available which are not being used. Those responsible for vaccination policy have a clear duty to review the situation continually and to stress the need for vaccination. Those responsible for the implementation of vaccination policy have an equally

clear duty. They are confronted with a challenge which is quite simple—use rubella vaccines, identify difficulties, and overcome them.

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