Rubella vaccination: remaining problems

Rubella vaccines were first licensed over 12 years ago both in the United States and in Britain. The two countries have different vaccination policies. In the United States the vaccine programme was at first directed toward prepubertal children of both sexes¹ with the aim of substituting vaccine-induced infection for naturally acquired disease, thereby reducing the risk of transmitting rubella to pregnant women. This strategy was also intended to reduce the need for hazardous vaccination during pregnancy or at an age when reactions are more likely to occur.

The programme has resulted² in a noticeable decline in both congenitally acquired as well as postnatally acquired rubella, at first among those aged under 15.² During 1978 and 1979, however, susceptibility and attack rates rose among adolescents and young adults. Numerous outbreaks of rubella among students, soldiers, and hospital staff showed an immunity gap; this has since been closed with a resulting substantial reduction in rubella notifications among all age groups, but mostly in the 15-24-year-olds. In 1980 only 3904 cases of rubella were notified, 67% less than in the previous year; figures so far available for 1981 are even better.³

Despite these encouraging findings some rather disquieting evidence was produced by Horstmann⁴ and Balfour and Amren,⁵ who showed that 29 out of 342 (8.5%) and 58 out of 159 (36%) children, respectively, lacked haemagglutination inhibition antibody when tested three to nine years after vaccination with the HPV77-DE5 vaccine. Subsequent challenge with rubella vaccine (RA27/3) showed, however, that despite having lost detectable rubella antibody these children were immune, since no viraemia could be detected and typical secondary immune responses occurred with undetectable or only very low concentrations of rubella-specific IgM.⁶ More sensitive tests showed that in fact many of these children had had rubella antibody in their initial sera. Though this episode may appear encouraging, the crucial point is that rubella vaccination must confer immunity throughout the childbearing years—which means at least 40 years if rubella vaccine is given in infancy. Might people vaccinated in infancy and exposed to natural infection many years later develop rubella viraemia with its attendant risks to the fetus? Since January 1979 the HPV77-DE5 vaccine has been replaced by one which has the advantage of inducing immune responses that more closely resemble those induced by naturally acquired disease than other vaccines⁷⁻⁹; the only other vaccine licensed in the United States (Cendehill strain) is no longer distributed there. There are no plans to re-vaccinate children in the United States given HPV77-DE5

vaccine—but financial constraints, together with the resources now committed to other very important vaccination programmes such as hepatitis B, should not be allowed to push into the background the need for long-term studies to determine the immune status of vaccinees previously given HPV77-DE5, so that they may be given booster doses of vaccine if necessary.

In Britain the two licensed vaccine strains are RA27/3 and Cendehill. At first the rubella vaccination programme was directed towards 11-14-year-old schoolgirls¹⁰ and later it was extended to adult women, provided they had been screened before vaccination.^{11 12} As yet, there has been no decline in the incidence of congenitally acquired rubella. Though the increase in its incidence after the extensive epidemic in Britain in 1978-9 was somewhat less than expected this was probably due to so many pregnancies being terminated for maternal rubella.¹³ Provided substantially more schoolgirls are given rubella vaccine and more rubella-susceptible women of childbearing age are also vaccinated the incidence of congenitally acquired rubella may be expected to decline later this decade. Health authorities have been encouraged to attain a vaccination uptake rate among schoolgirls initially of 90% and ultimately 95%, and to ensure that 90% of seronegative women attending antenatal clinics are vaccinated post partum.¹⁴ Some data are encouraging; between 1979 and 1981 the proportion of schoolgirls given rubella vaccine in England and Wales increased from 73% to 84%,¹⁵ and studies among young blood donors and students showed that whereas 12% to 14% of men were susceptible the proportions of women were only 3% to 6%.¹⁶ As several health authorities who mounted vigorous campaigns reported, however, a hard core of 8-10% of children were not vaccinated because of parental refusal, and in present circumstances the national target of 95% may well be unattainable. A recent report from Glasgow¹⁷ found that 12% of teenage girls and 16% of teenage boys were susceptible, suggesting that the vaccine programme there had failed. Perhaps the recent recommendation that rubella vaccination should be now offered to 10-year-old girls will increase the vaccination uptake rate¹⁵ since truancy is less common in primary schools. Another encouraging pointer is that between 1978 and 1980 the numbers of women screened for rubella antibodies at antenatal clinics and non-pregnant women screened before vaccination increased by 15% and 49%, respectively. A greater response might be achieved if antibody screening before vaccination of women of childbearing age could be abandoned; perhaps it might be left to the doctor's discretion whether to screen or not. Against this has to be weighed the increased cost of having to give rubella vaccine to more women, many of whom would be

immune (this being partly offset by a reduction in the number of screening tests), and also an increased risk of vaccination in pregnancy. Indeed, the number of terminations carried out because of inadvertent vaccination in pregnancy is unacceptably high. In both 1979 and 1980, 25-30% of all pregnancies terminated because of rubella in pregnancy were as a result of rubella vaccination.

What are the risks of vaccinating rubella-susceptible women in early pregnancy? In the United States the Centre for Disease Control has kept a register of women given rubella vaccine within a period ranging from three months before to three months after conception and has recorded no major malformation among 364 infants whose mothers were vaccinated and who elected to go to term, 112 infants being delivered of mothers known to be susceptible to rubella.¹⁸ Many of these infants have been followed up, and though about 10% have serological evidence of intrauterine infection all have remained healthy. The risk of rubella-induced major malformations among infants delivered of susceptible mothers was calculated (based on a 95% confidence limit) as 3.3%—a figure similar to the risk in normal pregnancies. The United States Immunisation Practices Advisory Committee still recommends that pregnant women should not be given rubella vaccine but it now states that inadvertent vaccination should no longer be a reason routinely to recommend termination of pregnancy.¹⁸ Why, then, should we not vaccinate women of childbearing years without screening and without worrying unduly about whether they are or are likely to become pregnant?

Most of the data collected in the United States relate to HPV77-DE5 and Cendehill vaccines and as yet we know relatively little about the teratogenic potential of RA27/3. Unlike other vaccine strains it was first isolated from a rubella-infected conceptus, and during attenuation had a less extensive passage history in cell culture than other attenuated vaccine strains (perhaps this is why it is a particularly good immunogen). The recent report from the Centre for Disease Control records only 17 live births to rubella-susceptible women given RA27/3. Though all the infants were healthy, only nine mothers had been vaccinated at the critical period between the date of conception and the end of the first month of pregnancy. These preliminary findings are encouraging, but rather more data are required before the teratogenic potential of this vaccine strain can also be established as negligible. Until then it would still be prudent to adhere to the recommendation that rubella vaccine should be given only to women who have been screened and found to be seronegative, after which they should be advised not to become pregnant for three months.¹⁹

Since rubella screening programmes will continue for the foreseeable future, reliable tests must be used. Until recently the haemagglutination inhibition test was used, but this is inherently unreliable for screening since low concentrations of antibody cannot easily be distinguished from non-specific inhibitors that may be present at a concentration equivalent to 15 000 IU of rubella haemagglutination inhibition antibody per l.²⁰ Most laboratories in Britain, however, are now screening by single radial haemolysis, which provides a much more reliable and sensitive test.²¹ Indeed, a case may be made for all women screened by haemagglutination inhibition in previous pregnancies being retested by single radial haemolysis in subsequent pregnancies. Any such patients exposed to rubella-like illnesses in pregnancy should be retested and followed up serologically with no reliance on a previous and perhaps inaccurate immune response.²²

Recently, Mortimer and his colleagues²³ suggested that the

practice of accepting people as susceptible to rubella because single radial haemolysis showed a rubella antibody concentration below 15 000 IU/l resulted in many women being vaccinated unnecessarily; indeed, they found that any level of antibody detected by single radial haemolysis or by other reliable methods indicated rubella immunity, since such people, in contrast with those with no detectable antibody, failed to develop a virus-specific IgM response when vaccinated. They suggested that lowering the threshold from below 15 000 IU/l might not only save rubella vaccine but also result in fewer women being inadvertently vaccinated in pregnancy. There have, however, been two recent reports of adult women with rubella antibody below 15 000 IU/l who, when challenged with rubella vaccine, developed low levels of rubella viraemia; one woman developed rubella-specific IgM.^{6, 24} Though such a low level of viraemia may well not result in fetal damage, it may be premature to reduce the minimum immune titre much below 15 000 IU until further studies have determined the concentration of antibody that is protective.

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- ¹ Public Health Service Advisory Committee on Immunisation Practices. Collected recommendations. *Morbidity and Mortality* 1972;125, suppl: 23.
- ² Anonymous. Rubella and congenital rubella, United States, 1977-1978. *Morbidity and Mortality Weekly Report* 1978;27:495-7.
- ³ Anonymous. Rubella—United States, 1978-1981. *Morbidity and Mortality Weekly Report* 1981;30:513-5.
- ⁴ Horstmann DM. Controlling rubella: problems and perspectives. *Ann Intern Med* 1975;83:412-7.
- ⁵ Balfour HH Jr, Amren DP. Rubella, measles and mumps antibodies following vaccination of children. A potential rubella problem. *Am J Dis Child* 1978;132:573-7.
- ⁶ Balfour HH, Groth KE, Edelman CK, Amren DP, Best JM, Banatvala JE. Rubella viraemia and antibody responses after rubella vaccination and reimmunisation. *Lancet* 1981;ii:1078-80.
- ⁷ Plotkin SA, Farquhar JD, Ogra PL. Immunological properties of RA27/3 rubella virus vaccine. A comparison with strains presently licensed in the US. *JAMA* 1973;225:585-90.
- ⁸ Banatvala JE. Rubella vaccines. In: Waterson AP, ed. *Recent advances in clinical virology*. Edinburgh: Churchill Livingstone, 1977:171-90.
- ⁹ Best JM, Harcourt GC, O'Shea S, Banatvala JE. Rubella vaccines. *Lancet* 1979;ii:690-1.
- ¹⁰ Department of Health and Social Security. Rubella prophylaxis. *DHSS Circular* 1970;9/70.
- ¹¹ Department of Health and Social Security. Vaccination against rubella for women of child-bearing age. *DHSS Circular* 1972;17/72.
- ¹² Department of Health and Social Security. Rubella vaccination. *DHSS Circular* 1976;4/76.
- ¹³ Goldwater PN, Quiney JR, Banatvala JE. Maternal rubella at St Thomas' Hospital: is there a need to change British vaccination policy? *Lancet* 1978;iii:1298-300.
- ¹⁴ Department of Health and Social Security. Rubella vaccination. *DHSS Circular* 1979;14/79.
- ¹⁵ Chief Medical Officer. Vaccination against rubella. *CMO Letters* 1981;81/7.
- ¹⁶ Clarke M, Stitt J, Seagroatt V, et al. Rubella antibody status of young adults in UK. *Lancet* 1980;ii:537-8.
- ¹⁷ Preblud SR, Stetler HC, Frank JA Jr, Greaves WL, Hinman AR, Herrmann KL. Fetal risk associated with rubella vaccine. *JAMA* 1981;246:1413-7.
- ¹⁸ Immunization Practices Advisory Committee. Recommendations. Rubella prevention. *Morbidity and Mortality Weekly Report* 1981;30:37-42,47.
- ¹⁹ Chief Medical Officer. Rubella vaccination. *CMO Letters* 1979;79/6.
- ²⁰ Bradstreet CM, Kirkwood B, Pattison JR, Tobin JO. The derivation of a minimum immune titre for rubella haemagglutination-inhibition (HI) antibody. A Public Health Laboratory Service collaborative study. *J Hyg* 1978;81:383-8.
- ²¹ Best JM, Harcourt GC, Druce A, Palmer SJ, O'Shea S, Banatvala JE. Rubella immunity by four different techniques: results of challenge studies. *J Med Virol* 1980;5:239-47.
- ²² Vaile MSB. Factors influencing rubella immunity in women. *Br Med J* 1981;282:738.
- ²³ Mortimer PP, Edwards JMB, Porter AD, Tedder RS, Mace JE, Hutchinson A. Are many women immunized against rubella unnecessarily? *J Hyg* 1981;87:131-8.
- ²⁴ O'Shea S, Parsons G, Best JM, Banatvala JE, Balfour HH Jr. How well do low levels of rubella antibody protect? *Lancet* 1981;iii:1284.