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The immunoglobulin M response to rubella vaccine in young adult women

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SUMMARY

Rubella vaccination histories were taken from 333 young women working in the head office of a retail organization: 29% said they had had vaccine and 47% said they had not. The remainder did not know. Forty-six per cent of those ⩽ 25 years old (who should have been offered vaccine at school), and 6% of those > 25 years old, said they had been vaccinated. When screened for immunity to rubella by radial haemolysis (RH) 3% had a low level of antibody (< 15 i.u./ml) and 11% had no antibody. After immunization with Cendevax the specific rubella IgM response was measured by an IgM antibody capture radioimmunassay (MACRIA). It was only detectable in the group without RH antibody, and was present in 26/31 of them. The IgM response to Cendevax was strongest in specimens taken 20–39 days after immunization, but in 10 out of 11 cases tested was still present at around 71 days. The specific IgM responses to Cendevax were very similar to those in women given Almevax in an earlier study, when measured in parallel tests.

Taking both vaccines together, specific IgM was present in 35 out of 36 vaccinees without pre-existing antibody tested between 40 and 77 days post-immunization. Detection of specific IgM by MACRIA would therefore be an effective means of determining susceptibility retrospectively in rubella vaccinees found to be pregnant.

INTRODUCTION

Much effort has been devoted to the development of anti-rubella IgM tests for the diagnosis of natural rubella, but they have been little used to investigate serological responses to rubella vaccines. It has been assumed that primary infections with attenuated vaccines mirror natural infection and evoke specific IgM antibody, but until recently tests have been too insensitive to register these responses reliably. The development of a sensitive and convenient M antibody capture radioimmunoassay (MACRIA) that readily detects anti-rubella IgM in

susceptible patients given RA27/3 vaccine (Almevax) had remedied this (Mortimer *et al.* 1981*a*, *b*). The assay will discriminate between vaccinees undergoing primary infection and vaccinees, previously infected naturally or by vaccination, whose antibody concentration has fallen below the arbitrary level taken to indicate immunity (15 i.u. per ml) but who do not make a primary, IgM response.

Because it distinguishes between a primary and a secondary immune response, MACRIA should allow a retrospective determination of susceptibility at the time of vaccination, and this might be useful in the management of vaccinees found to be pregnant. Fear of intercurrent pregnancy has been an obstacle to the use of rubella vaccine in women. If it could be established that MACRIA reliably determined for the two rubella vaccine strains in common use the immune state at the time of vaccination, many vaccinees found to be pregnant could be reassured on the grounds that the vaccine had not led to a primary infection. This has so far only been done for Almevax.

Cendevax has been used in the United Kingdom since 1970, when immunization of adolescent schoolgirls against rubella began. It has been suggested that it evokes a weaker, more sluggish humoral response than Almevax (MacDonald *et al.* 1978), and it is not known whether specific IgM can regularly be detected after it has been given to susceptible vaccinees. In this investigation a group of 346 women were screened for rubella antibody. Vaccination histories were taken. Those with < 15 i.u. of antibody per ml were given Cendevax, and blood was collected post-immunization to measure serological responses. The rubella IgM responses were compared with those of women who had been given Almevax in the previous study.

MATERIALS AND METHODS

Subjects and sera

In the summer of 1981 young women employed in the London office of a large retail organization were asked whether they had been given rubella vaccine before, and offered a test for rubella antibody. Three hundred and thirty-three out of 1687 female staff under 40 years old responded and had their serum tested. A further 13 were tested without a history being elicited. Those with a low concentration of antibody (< 15 i.u. per ml, group I) and those without antibody (group II) were offered Cendevax and asked to give blood specimens 4, and 7 or 10 weeks after immunization. Sera collected during a previous Almevax study were re-tested. They had been drawn from women of about the same age attending a general practice in the north of England.

Rubella antibody tests

Pre- and post-immunization specimens were tested for rubella antibody by radial haemolysis (RH, Kurtz *et al.* 1980) and haemagglutination inhibition, HI (Pattison & Mace, 1973). The 15 i.u. per ml control used gave zone diameters ranging from 7·5 to 8·5 mm in the RH test and an HI titre of 20. Post-immunization specimens were tested for anti-rubella IgM using a modified MACRIA incorporating rubella-specific monoclonal antibody (Tedder, Yao & Anderson, 1982). Specimens from the

Table 1. *Rubella vaccination history and result of antibody screening by radial haemolysis in women affected (⩽ 25 years old) and unaffected (> 25 years old) by the school immunization programme*

Age group	Rubella antibody (i.u. per ml)	Number	Previously vaccinated?		
			Yes	No	Not sure
All ages		333	101	163	69
25 years	> 15	179	85	57	36
	< 15	7	4	—	3
	Negative	16	4	7	5
> 25 years	> 15	110	7	81	22
	< 15	2	—	2	—
	Negative	20	1	16	3

Almevax study were re-examined by the modified MACRIA in parallel with the specimens from the Cendevax study. All MACRIA results are given in arbitrary units per ml (a.u./ml).

RESULTS

Vaccination histories

Twenty-nine per cent of those questioned (101 women aged 18–30 years, mean 22·5) said they had had rubella vaccine previously and 47 % (163 women aged 17–44 years, mean 26·6) said they had not (Table 1). Forty per cent of the women < 25 years and 6 % of those > 25 years old said they had been vaccinated. Ninety-five per cent of the 101 women with a history of vaccination were either immune on screening (92 women), or failed to make an IgM response to Cendevax, i.e. probably had pre-existing immunity (four women). Eighty-six per cent of the 163 who said they had not been vaccinated were either immune on screening (138 women), or failed to make an IgM response to Cendevax (two women). Nine women who said they had been given rubella vaccine in the past either had < 15 i.u. antibody per ml or were seronegative in their screening test: seven, of whom six had been immunized 9–12 years previously, provided follow-up specimens. Six of these seven made no MACRIA response to Cendevax.

Serological responses to Cendevax

Forty-nine (14 %) of the 346 women screened by RH had < 15 i.u. rubella antibody per ml. Nine had a low level of RH antibody (Group I) and 40 were seronegative (Group II). All were given Cendevax and 39 (8 group I, 31 group II) provided follow-up specimens.

Mean RH and HI results on post-immunization specimens were similar in the two groups, but these responses were more scattered in group II than in group I (Table 2). Radial haemolysis antibody was absent in 12 group II vaccinees sampled in the interval 20–39 days after Cendevax had been given, including seven who made a MACRIA response at that time. Five of these seven had RH antibody when tested at 71–76 days.

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Table 2. *Rubella antibody response to Cendevax*

Group	Number	RH zone diam. (mm) Range	RH zone diam. (mm) Mean	HI titre Range	HI titre Mean
			Pre-immunization		
I	8	6·5–8·0*	7·5	20–40	20
II	31	All negative		< 10–20†	—
			3–6 weeks post-immunization		
I	8	7·5–10·0	8·4	20·40	40
II	31	Neg.–12·0	8·9‡	10–320	40
			7–10 weeks post-immunization		
I	8	7·5–9·5	8·4	20–80	40
II	31	Neg.–12·0	9·4§	20–< 640	80

* i.e. < 15 i.u. per ml.
† All < 10, except three 1 in 10 and three 1 in 20.
‡ Twelve negative, mean of 19 positives shown.
§ Four negative, nine not tested, mean of 18 positives shown.

Table 3. *Range and mean of MACRIA results (a.u./ml) in vaccinees who made an anti-rubella IgM response to Cendevax or Almevax*

Vaccine	Observations	MACRIA results (a.u./ml) on stated days post-immunization 20–39	40–59	67–77
Cendevax	Number	18	10*	11*
	Positive	18	10	10
	Range	4·0–23	2·5–17·5	1·2–11·0
	Mean of positives	12·4	9·8	7·1
Almevax	Number	11	17	nil
	Positive	10	17	—
	Range	0·8–40·6	1·7–14·5	—
	Mean of positives	14·8	8·5	—

* One vaccinee only was sampled in both these time intervals.

None of the eight group I vaccinees made an anti-rubella IgM response to Cendevax, but 26 out of 31 group II vaccines did. Specific IgM was detected in 18 out of 18 sera taken at 20–39 days, in 10 out of 10 taken at 40–59 days and in 10 out of 11 taken around 71 days from the 26 reactive vaccinees. The IgM responses in the Cendevax recipients were similar in timing and magnitude to those in Almevax recipients, whose samples were assayed in parallel (Table 3). Four of the five group II vaccinees who did not make an IgM response had a weak positive HI result before Cendevax was given (titres 10, 20, 20, 20) and so may already have been immune.

Reactions to Cendevax

One woman complained of an arthralgia lasting five days, but no other reaction was reported by the 49 vaccinees. Though not invited to notify reactions, the women had available a full-time occupational health service, and it is likely that if there had been untoward effects they would have been reported. None was mentioned on the occasions that post-immunization specimens were collected.

DISCUSSION

Susceptibility in vaccinees

The main purpose of this and the earlier Almevax study was to discover whether MACRIA could be used to determine retrospectively the immune status of women inadvertently given rubella vaccine when pregnant. Anti-rubella IgM could be detected within the interval 40–77 days after immunization in 19 out of 20 women given Cendevax and 17 out of 17 given Almevax at a time when they lacked rubella antibody, whereas no woman with RH or definite HI antibody before immunization made a MACRIA response. Responses to vaccine were detectable for longer with the monoclonal antibody-based MACRIA than with the MACRIA previously used to test recipients of Almevax. The new assay is very sensitive and appears to detect all primary vaccine infections. Though the number of observations reported here are too few to be absolutely sure, it is most unlikely that a vaccinee who was susceptible at the time of immunization would fail to make a MACRIA response detectable in a serum sample collected between 20 and 59 days afterwards. It would therefore be hard to justify terminating the pregnancy of a woman inadvertently vaccinated if no IgM response could be detected by the new assay within this interval. In fact a study of the outcome of pregnancies in vaccinees has failed to show that either the Cendehill or the RA 27/3 vaccine strain has any teratogenic effect (Report, 1982); but it is too early to conclude that rubella vaccines are always safe when given in pregnancy to susceptible women. The report takes account of relatively few (33) women vaccinated in the period of greatest risk; so it is worth using MACRIA to determine susceptibility in pregnant vaccinees, at least until more evidence is available.

Serological responses to Cendevax

It has recently been suggested that serological responses to Cendevax are unacceptably weak (Black *et al.* 1983). Our studies have not shown any difference between the IgM responses to Cendevax and Almevax and another study, using immunofluorescence, has also found similar IgM responses in recipients of both vaccines, maximal 21–28 days after immunization and hardly detectable thereafter (Cradock Watson *et al.* 1974). Banatvala and colleagues (1977) on the other hand, have reported that Cendevax evokes a weaker IgM response than Almevax.

Although we found comparable IgM responses we saw more false negative and indistinct RH reactions after Cendevax than after Almevax. This was mostly in women making a primary response to Cendevax, five of whom made an RH response that was delayed for at least a month after the vaccine was given and at least four of whom had made no RH antibody up to the time of their second

post-immunization sample 67–71 days later. Three previously vaccinated women also remained negative in the RH test after Cendevax was given. All three had some HI antibody before and after re-vaccination. Clearly RH is an unsatisfactory method for assessing responses to Cendevax unless follow-up specimens are collected at least 10 weeks after immunization. In earlier samples the RH test is frequently negative when MACRIA and the HI test are positive, a phenonemon not noted after Almevax immunization. It does not follow from this, however, that Cendevax gives poorer protection against intra-uterine infection with rubella.

Attitudes to serotesting and vaccination

The subjects of this study were clerical workers and management staff. Most were married or intended to marry, but were nulliparous. We estimate that 10% of the female staff of the office aged 30–40 years and 26% of those under 30 years came forward for rubella screening. Those intending to become pregnant soon were the most co-operative; others would not come, many because they feared a venepuncture. The collection of follow-up specimens was also hampered by this dislike of venepuncture.

It is disappointing that 64 of the 163 women screened for rubella antibody who said that they had not been immunized were < 25 years old and therefore of an age to have had vaccine at school. However, this is consistent with the poor uptake of vaccine by schoolgirls during the 1970s (Peckham, Marshall & Dudgeon, 1977). Either because they had missed vaccination at school through individual refusal or administrative failure, or because they were too old, 14% of the women sampled were possibly at risk from rubella at the time of the study. This proportion is closely similar to that found in other studies of adult British women (Kurtz *et al.* 1980), and it indicates a need to increase the degree of protection of would-be mothers against rubella. The study also shows that, given a free choice, very many adult women will refuse rubella screening. We need a better understanding of this negative attitude in order to succeed with our vaccination policy. Wider use of vaccine and laboratory tests could eliminate congenital rubella, but it is uncertain how this can be achieved without fuller co-operation than at present from those at risk.

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REFERENCES

BANATVALA, J. E., DRUCE, A., BEST, J. M. & AL NAKIB, W. (1977). Specific IgM responses after rubella vaccination: potential application following inadvertent vaccination during pregnancy. *British Medical Journal* ii, 1263–1264.

BLACK, N. A., PARSONS, A., KURTZ, J. B., MCWHINNEY, N., LACEY, A. & MAYON WHITE, R. T. (1983). Post-partum immunisation: a controlled trial of two vaccines. *Lancet* ii, 990–992.

CRADOCK-WATSON, J. E., MACDONALD, H., RIDEHALGH, M. K. S., BOURNE, M. S. & VANDERVELDE, E. M. (1974). Specific immunoglobulin responses in serum and nasal secretions after the administration of attenuated rubella vaccine. *Journal of Hygiene* 73, 127–141.

KURTZ, J. B., MORTIMER, P. P., MORTIMER, P. R., MORGAN-CAPNER, P., SHAFI, M. S. & WHITE, G. B. B. (1980). Rubella antibody measured by radial haemolysis. Characteristics and performance of a simple screening method for use in diagnostic laboratories. *Journal of Hygiene* **84**, 213–222.

MACDONALD, H., TOBIN, J. O'H., CRADOCK-WATSON, J. E., LOMAX, J. & BOURNE, M. S. (1978). Antibody titres in women six to eight years after the administration of RA27/3 and Cendehill rubella vaccines. *Journal of Hygiene* **80**, 337–346.

MORTIMER, P. P., TEDDER, R. S., HAMBLING, M. H., SHAFI, M. S., BURKHARDT, F. & SCHILT, U. (1981*a*). Antibody capture radio-immunoassay for anti-rubella IgM. *Journal of Hygiene* **86**, 139–153.

MORTIMER, P. P., EDWARDS, J. M. B., PORTER, A. D., TEDDER, R. S., MACE, J. E. & HUTCHINSON, A. (1981*b*). Are many women immunized against rubella unnecessarily? *Journal of Hygiene* **87**, 131–138.

PATTISON, J. R. & MACE, J. E. (1973). Rubella screening tests. *Journal of Clinical Pathology* **26**, 161–162.

PECKHAM, C. S., MARSHALL, W. C. & DUDGEON, J. A. (1977). Rubella vaccine uptake of schoolgirls: factors affecting vaccine uptake. *British Medical Journal* i, 760–761.

REPORT (1982). Rubella vaccination during pregnancy – United States, 1971–1981. *Morbidity and Mortality Weekly Report* **31**, 477–481.

TEDDER, R. S., YAO, J. L. & ANDERSON, M. J. (1982). The production of monoclonal antibodies to rubella haemagglutinin and their use in antibody-capture assays for rubella-specific IgM. *Journal of Hygiene* **88**, 335–350.