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Persistence of antibody induced by rubella vaccine (Wistar RA 27/3 strain) after six years

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SUMMARY

A total of 21 rubella seronegative children vaccinated subcutaneously with Wistar RA 27/3 strain live attenuated rubella vaccine in a family study of vaccine virus transmissibility were reviewed after 6 years. Haemagglutinating inhibiting (HAI) antibody titres of sera collected 46 days, 2 years and 6 years after vaccination were compared. Antibody titres in the vaccinated subjects were not significantly influenced by time, infection in susceptible siblings or revaccination.

INTRODUCTION

National authorities in most European countries recommend the administration of rubella vaccine to girls immediately before puberty. Ideally therefore the immune responses elicited by vaccination should provide protection throughout the childbearing years and persist for about 30 years after vaccination. Shorter periods of protection might be acceptable since the majority of births occur within about 12 years of puberty (Freestone, 1974).

Mass primary vaccination of adult females against rubella is not recommended since the teratogenicity and embryotoxicity of the available strains of rubella vaccine are not clear and inadvertent vaccination of pregnant women would be unavoidable. Furthermore, there are already a number of reports of recovery of virus from products of conception and from foetal tissue (Phillips, Maeck, Rogers & Savel, 1970; Vaheri *et al.* 1972; Wyll & Herrmann, 1973). Should the duration of protection afforded by primary vaccination be insufficient to span the childbearing years of women, a programme of revaccination would have to be considered. The hazards associated with mass revaccination of women may be less than those of primary vaccination but since not every subject responds to primary vaccination and since fetal infection has been described in the presence of antibody (Eilard & Strannegard, 1974), revaccination is unlikely to be devoid of risks. In general the presence of antibody correlates with protection against rubella, and thus the persistence of antibody after primary immunization is of critical importance.

This paper reports the results of a review of 65 children who took part in a study

of transmissibility of the Wistar RA 27/3 strain of live attenuated rubella vaccine carried out 6 years previously in 1968 (Hillary *et al.* 1969). The results of a 2-year review of these children were reported in 1971 (Hillary, 1971).

METHOD

All 18 families with rubella seronegative children who were included in the original trial agreed to take part in the present review of antibody titres. Venous blood samples were collected during the summer of 1974 from all 21 children who were initially seronegative and vaccinated in the summer of 1968 and from 44 of the 53 unvaccinated children who served as contacts.

Serology

The rubella haemagglutinating inhibiting (HAI) antibody titrations for the original study of transmissibility were carried out by the technique described by Stewart *et al.* (1967) which utilizes kaolin for the removal of non-specific inhibitors. Subsequently, in 1970, sera collected 2 years after vaccination were treated with manganous chloride and heparin to remove non-specific inhibitors (Mann, Rossen, Lehrich & Kasel, 1967; Feldman, 1968; Plotkin, Bechtel & Sedwick, 1968). These sera were titrated in parallel with the 1968 sera which were retreated with manganous chloride and heparin. In the present review, sera collected in 1968, 46 days after vaccination, in 1970, 2 years after vaccination, and in 1974, 6 years after vaccination, were titrated in parallel using the techniques employed in 1970. Sera were stored at $-20°$ C.

RESULTS

None of the vaccinated children suffered any rubella-like illness during the 6 years after vaccination and no child was found to be devoid of rubella HAI antibody. Samples of sera collected 46 days, 2 years and 6 years after vaccination were available for titration from 16 of the 21 vaccinated children (see Table 1). For 15 children antibody titres were unchanged or within one dilution of their 1968 titre. One child from family no. 2 exhibited a fourfold fall in antibody titre over the 6 years. In the remaining 5 children sufficient serum collected 46 days after vaccination was not available in 1974 for retitration. However, in 4 children titration results in 1970 and 1974 of sera collected 2 years after vaccination in 1970 were unchanged indicating that these titrations were of equivalent sensitivity. Thus, the 1970 titration result of the sera collected 46 days after vaccination is included in the present analysis and these results are shown in Table 2 in parentheses.

Serum collected from the remaining child 46 days after vaccination gave a titre of 160 with the use of kaolin to remove non-specific inhibitors. Six years later with the use of manganous chloride and heparin to remove non-specific inhibitors the titre was 40.

A total of 31 of 44 (70 %) siblings who initially served as contacts were found to have developed antibody in the intervening period although clinical rubella was recognized only in 2 (5 %) – see Table 3. Five of these (11 %) had been vaccinated immediately before puberty in a school immunization programme. Natural rubella

Table 1. *Rubella HAI antibody titres for sera collected*

Family no. of vaccinee	46 days after vaccination (1968)	2 years after vaccination (1970)	6 years after vaccination (1974)
1	160	40	160
2	160	80	40
2	40*	160	160
3	40	80	80†
4	80	80	80
5	160	160	160
6	160*	160	80
7	80	160	160†
8	160	160	160
9	160*	160	160
10	80	80	80
10	160	80	80†
11	80	160	160
11	80	80	80
12	80	160	80
13	160	160	80
14	160*	80	80
15	40	80	80
16	80	80	80
17	160	160	160
18	160*	Not done	40
GMT in parallel titrations	99·4	103·8 109·3	99·1 (16) 102·0 (20) 97·5 (21)

* Not titrated in parallel.
† Revaccinated at school.

Table 2. *Rubella HAI antibody titres in sera collected from vaccinated children* 46 *days and* 6 *years after vaccination*

Titres at 46 days	Titres at 6 years: 20	40	80	160	320
20	—	—	—	—	—
40	—	—	2	(1)	—
80	—	—	5 (2)	2	—
160	—	1 (1*)	2 (1)	4	—
320	—	—	—	—	—

* 1968 sera, kaolin treated; 1974 sera, manganous chloride-heparin treated. Not titrated in parallel.

had occurred in the district between 1970 and 1974. However, despite this and the revaccination of three children in school immunization programmes, there was no evidence that any significant increases in antibody titre resulted in vaccinated children.

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Table 3. *Rubella HAI antibody titres in sera of contact children, collected 46 days and 6 years after vaccination of their siblings and tested in parallel*

Reasons for seroconversion	No. of children	Titre 6 years after vaccination							
		<10	10	20	40	80	160	320	640
Clinical rubella	2	.	.	.	.	.	1	1	.
Unrecognized rubella	24	.	.	.	.	5	8	6	5
Vaccination	5	.	.	.	2	.	2	1	.
No seroconversion	13	13	.	.	.	.	.	.	.

All 46-day samples showed titres of <10.
All sera titrated in parallel.

DISCUSSION

Studies of the persistence of antibody induced by rubella vaccines incur difficulties which relate directly to the time which has elapsed since initial vaccination. Firstly, increasing practical problems are encountered in securing blood samples as the time from initial vaccination increases. In this study samples were collected from all seronegative children who were vaccinated and most of their siblings who served as contacts. Secondly, with a longer period of follow-up there is more opportunity for intercurrent natural infections which might boost antibody titres. Thus, antibody estimations measure persisting vaccine-induced antibody and antibody boosted by natural infection. In the present study there is evidence of natural infection in unvaccinated children in all except 3 of the 18 families, although the disease was clinically recognized in only one family. There is, however, no evidence that this resulted in an increase in antibody titre in the vaccinated children. Thirdly, there is the possibility that antibody in sera might deteriorate in storage at $-20°$ C. over long periods. The stability of rubella HAI antibody has been described (Phillips & O'Brien, 1969) and these results do not suggest that the sera collected in 1968 and 1970 have lost titre during storage.

In a $4\frac{1}{2}$-year follow-up of antibody persistence after administration of the Cendehill strain, Schiff *et al.* (1974) found that 3·9 % of vaccinees lacked detectable HAI antibody. In contrast, antibody titres in the children in this study appear remarkably stable. This stability of antibody, anti-iota precipitin responses, the higher HAI, complement fixing and neutralizing antibody titres elicited by the RA 27/3 in comparison with other strains of vaccine correlate with an apparently sturdier protection against reinfection (Plotkin, Farquhar & Ogra, 1973). However, directly comparative studies of the long term persistence of antibody induced by the RA 27/3 and other strains are clearly required.

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