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Vaccination against rubella of susceptible schoolgirls in Reading

By D. F. ROWLANDS
Department of Health Services, County Borough of Reading
and D. S. FREESTONE
Department of Clinical Immunology, The Wellcome Research Laboratories, Beckenham, Kent

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SUMMARY

This study of 724 13-year-old schoolgirls in the County Borough of Reading showed that approximately 25% were susceptible to rubella. 96·1% of the 129 seronegative girls and significant numbers of girls with low rubella HAI antibody titres responded to subcutaneous vaccination with Wistar RA. 27/3 rubella vaccine. The incidence of most reactions after vaccination was similar in those who responded to vaccine and those who were initially immune but did not develop rising antibody titres, but rash, lymphadenopathy and headache occurred significantly more frequently in the susceptible group.

INTRODUCTION

It has been estimated that an epidemic of rubella caused the birth of between 10,000 and 20,000 infants with congenital rubella malformations in the United States between 1964 and 1966 (Cooper & Krugman, 1966). In the United Kingdom some 200 infants with rubella malformations are thought to be born annually in non-epidemic years (Dudgeon, 1969). In addition, an unrecorded number of abortions are carried out each year as a result of rubella or exposure to rubella during pregnancy.

Vaccination against rubella is unique in immunizing practices. Vaccination is aimed to give protection, not to the vaccinee, but to any children that may be conceived. Furthermore, it has not been shown that vaccine virus is devoid of embryotoxic and teratogenic properties. The potential teratogenicity of vaccine virus has led to 11- to 13-year-old schoolgirls in whom the risk of pregnancy is slight, being chosen as the prime group for vaccination against rubella in the United Kingdom (Godber, 1970).

This report describes the results of screening and subsequent vaccination of schoolgirls in the County Borough of Reading. The study was designed to:

1. Determine the immunological status of 13-year-old schoolgirls against rubella as evidenced by haemagglutinating inhibiting (HAI) antibody titres.
2. Identify rubella-susceptible schoolgirls.

3. Determine the serological response to subcutaneous administration of Wistar RA. 27/3 rubella vaccine.

4. Determine the incidence of reactions to rubella vaccine.

PLAN OF STUDY

Thirteen-year-old schoolgirls in State schools in the County Borough of Reading were offered serological screening for rubella HAI antibody, and vaccination if necessary. Formal consent was secured from parents or guardians. Subsequently, seronegative girls and girls with low rubella HAI antibody titres were vaccinated. Schoolgirls with low titres were vaccinated in the light of reports which have suggested that subjects with low antibody titres may respond to vaccination with fourfold or greater increases in titre (Dudgeon, Marshall, Peckham & Hawkins, 1969).

During the 21-day post-vaccination period girls completed a calendar record card which listed symptoms of sore throat, rash, pain and shivering attacks (fever). They were bled 6 weeks after vaccination and HAI antibody again titrated.

Serology

Rubella HAI antibody titrations were carried out as described by Draper & Kelly (1969), at The Wellcome Research Laboratories. In this technique, Whatman No. 3 chromatography paper disks are saturated with capillary blood from a finger prick, and later eluted for antibody titration.

Vaccine

Lot No. AR. 5/1 Wistar RA. 27/3 rubella vaccine was administered subcutaneously. This vaccine was prepared at the Wellcome Research Laboratories, Beckenham, at a titre of $10^{2.53}$ TCID 50/dose.

RESULTS

Serological results

Results were obtained from 724 of 787 (92%) 13-year-old schoolgirls offered a determination of rubella antibody. The response of parents to offers of pre-vaccination screening for rubella immunity and vaccination if necessary was high – over 90% consented to both procedures (Table 1).

The distribution of HAI antibody titres of these girls is shown in Fig. 1. HAI antibody titres of 1/40 or less were found for 285 girls (39·4%). A total of 255 girls were vaccinated, 232 with titres of 1/40 or less, 19 with titres of 1/80 and four with titres of $> 1/80$. Some girls were not vaccinated because they were away from school, while vaccine was deliberately withheld from three girls, one with diabetes mellitus, one with petit mal, and one with a past history of thrombocytopenic purpura. No significant differences were found between rubella HAI antibody titres at screening and those obtained during re-titration of pre-vaccination blood with the 6-week post-vaccination sample. Pre-vaccination and 6-week post-

vaccination HAI antibody titres are shown in Table 2. A sero-conversion rate (fourfold or greater increase in antibody titre) of 96·1 % resulted from vaccination of those with pre-vaccination titres of < 1/10. However, the seroconversion rate decreased with increasing pre-vaccination titres (Table 3). Thus 8 of 20 (40 %) and 14 of 52 (26·9 %) girls with pre-vaccination titres of 1/20 and 1/40 respectively developed fourfold or greater increases in antibody. No such effects were seen in 19 girls with pre-vaccination titres of 1/80.

Table 1. *Results of offer of serological screening for immunity to rubella and vaccination if required*

Total number of consent forms issued	...		787	—
Consent given to blood test	730	92·7 %	—	—
Consent refused to blood test	39	5·0 %	—	—
Consent given to vaccination	717	91·1 %	—	—
Consent refused to vaccination	52	6·6 %	—	—
Total number of consent forms returned	769	—	769	97·7 %
Consent forms NOT returned	—	—	18	2·3 %

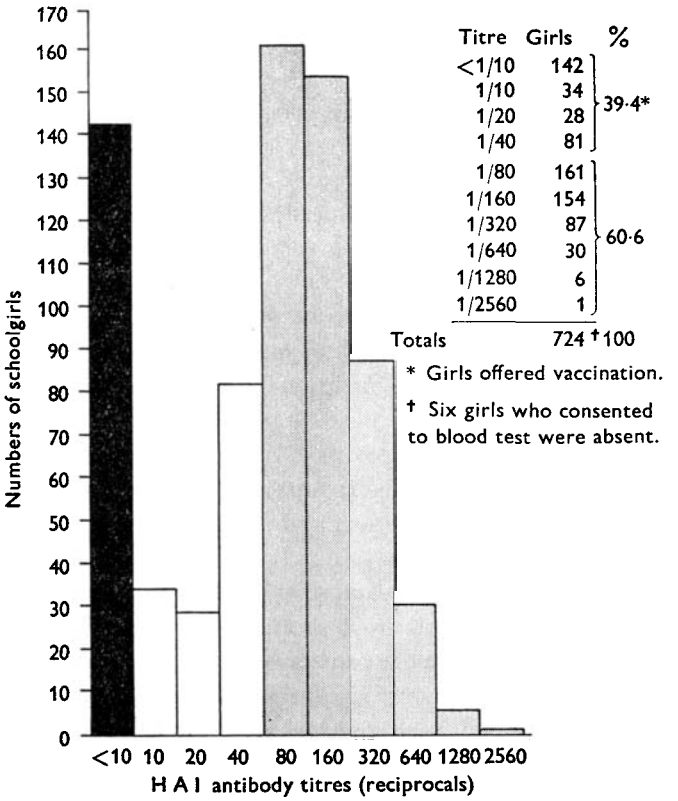

Fig. 1. Pre-vaccination rubella antibody distribution (13-year-old girls).

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Table 2. *Serological responses to Wistar RA. 27/3 rubella vaccine administered subcutaneously to schoolgirls in Reading*

No. of schoolgirls	Pre-vaccination HAI titre	Six-week post-vaccination HAI antibody titres							
		< 1/10	1/10	1/20	1/40	1/80	1/160	1/320	1/640
129	< 1/10	—	1	4	25	51	34	14	—
31	1/10	—	0	1	6	10	10	4	—
20	1/20	—	—	4	8	4	2	2	—
52	1/40	—	—	—	19	19	10	2	2
19	1/80	—	—	—	2	13	4	—	—
4	> 1/80	—	—	—	—	—	3	—	1

Table 3. *Pre-vaccination titres and seroconversion rates*

Pre-vaccination HAI antibody titres	No. of children	Number showing fourfold increase in antibody titre
< 1/10	129	124 (96·1 %)
1/10	31	30 (96·8 %)
1/20	20	8 (40 %)
1/40	52	14 (26·9 %)
1/80	19	0
> 1/80	4	0
Totals	255	176

Reactions

Of the 255 children who were vaccinated, 252 completed their record cards. According to their serological response to vaccine, children were divided into two groups:

Group R (vaccine responders), included children with a fourfold or greater increase in antibody titre between pre- and post-vaccination titres; and

Group N (vaccine non-responders), the remainder who failed to show a fourfold increase.

The distribution of children into groups R and N is shown in Table 4, and the incidence of reactions between the two groups compared in Table 5. The incidence of sore throat, reported to be a common symptom following vaccination against rubella, was not found to be different in our R and N groups. While the incidence of the joint symptoms between the groups is little different, the two cases of obvious swelling of the knee joint in R group children are likely to be vaccine induced. Analysis of daily reports of symptoms shows that lymphadenopathy was most commonly reported at about the 11th day after vaccination, and was still present when the record card finished on the 21st day. Rash occurred most commonly on the 13th to 16th days after vaccination (Table 6). Children suffering from psoriasis, eczema, asthma and hay fever were vaccinated without complication.

Table 4. *Pre-vaccination antibody titres of 'R' and 'N' Group Girls, and serological response to vaccination*

Pre-vaccination HAI antibody titres	Group R*	Group N†
< 1/10	121	5
1/10	30	1
1/20	8	12
1/40	14	38
1/80	—	19
> 1/80	—	4
Total no. of children	173	79

* Group 'R' – (Vaccine responders). Girls showing a fourfold or greater increase in HAI antibody titre after vaccination.

† Group 'N' – (Vaccine non-responders). Girls not showing a fourfold increase in HAI antibody titre after vaccination.

Table 5. *RA. 27/3 rubella vaccine – comparison of reactions reported in schoolgirls between groups R and N*

Reactions	Group 'R' (total 173)*		Group 'N' (total 79)†	
No reactions	64	37·0 %	35	44·3 %
Sore throat	63	36·4 %	32	40·5 %
Fever	20	11·6 %	13	16·5 %
Rash	25	14·5 %	3	3·8 %‡
Joint or muscle pain	16	9·2 %	9	11·4 %
Coryza	17	9·8 %	9	11·4 %
Stomach pain	23	13·3 %	7	8·7 %
Post-injection pain or inflammation	7	4·0 %	2	2·5 %
Headache	34	19·6 %	5	6·3 %‡
Pain in neck	5	2·9 %	1	1·3 %
Other	4 (Earache; Earache and conjunctivitis; Vomiting; Nausea)		3 (Earache; Malaise; Nausea)	
Lymphadenopathy	13	7·5 %	0	—‡
Break-down of subjects showing joint involvement	Pains in arm	4		4
	Pains in arm and hands	2		—
	Pain in legs	3		1
	Pain in knees	1		—
	Swelling in knees	2		—
	Pain in hips	2		—
	Generalized	0		3
	Other	2		1

* Group 'R' – (Vaccine responders). Girls showing a fourfold or greater increase in HAI antibody titre after vaccination.

† Group 'N' – (Vaccine non-responders). Girls not showing a fourfold increase in HAI antibody titre after vaccination. ‡ – $P < 0{\cdot}05$.

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Table 6. *Comparison on a daily basis of reactions reported by group 'R' children and group 'N' children*

Symptom	Group	1+2	3+4	5+6	7+8	9+10	11+12	13+14	15+16	17+18	19+20
Rash	R	2	2	7	3	1	6	26	23	7	8
	N	0	0	2	2	2	0	0	0	0	0
Lymphad-enopathy	R	0	1	2	2	6	20	19	18	18	18
	N	0	0	0	0	0	0	0	0	0	0
Sore throat	R	22	23	28	21	19	23	32	23	10	10
	N	8	10	10	16	14	9	9	9	4	9
Headache	R	13	12	12	9	8	16	12	9	8	2
	N	2	2	1	1	1	0	0	0	2	0
Pain in neck	R	1	3	2	0	2	4	2	2	2	2
	N	2	0	0	0	0	0	0	0	0	0
Abdominal pain	R	2	3	3	10	4	7	6	2	1	4
	N	6	3	1	1	2	3	1	1	1	0
Joint in-volvement	R	2	4	1	3	3	1	3	4	4	5
	N	6	3	1	1	2	3	1	1	1	0

Group R (vaccine responders). Total number of children, 173.
Group N (vaccine non-responders). Total number of children, 79.

DISCUSSION

In this study the use of Whatman No. 3 chromatography paper disks proved highly satisfactory in contrast to experiences in an earlier study (Rowlands & Gatherer, 1970) where difficulties were encountered in obtaining full saturation of disks in a proportion of 15-year-old girls.

HAI antibody determinations are widely carried out as an index of immunity to rubella. It is clear, however, that subjects with low antibody titres may respond to subcutaneous vaccination. Similarly, there are an increasing number of reports which show that subjects with low titres of antibody induced by vaccination are open to re-infection with rubella virus (Horstmann *et al.* 1970; Wilkins, Leedom, Portnoy & Salvatore, 1969; Meyer *et al.* 1969). The critical point is whether or not subjects re-infected after natural infection or vaccination develop viraemia with consequent fetal risk. Viraemia has not been demonstrated in such instances but the evidence available is limited. At present therefore it seems unreasonable not to vaccinate girls with low antibody titres. Thus, if those who respond to vaccine are susceptible to rubella, 25% of this population are not immune to the natural infection. Therefore, if schoolgirls with low HAI antibody titres cannot be presumed to be immune, this forms a point in favour of vaccination of all 11- to 13-year-old girls, since there may be difficulties in determining the degree to which low-titre seropositive girls should be vaccinated, in view of the differences in the sensitivity of HAI antibody titrations between laboratories. Although approximately 25% of girls were susceptible to rubella in this study, it was necessary for approximately 40% to be vaccinated to ensure that no susceptible girl with a low titre was left unprotected.

Initial cost analysis suggests that serological screening and vaccination of susceptibles alone would be less expensive than vaccination of all 11- to 13-year-old girls. This study has shown that screening and vaccination of rubella susceptibles is a practical procedure, of the type normally carried out by the School Health Service. It may be that at the present time laboratory facilities are not sufficient to deal with screening on a national scale, but it is clearly inadvisable for 60% of schoolgirls to be vaccinated against rubella unnecessarily.

The incidence of reactions in this study is high. Clearly any sensitive subjective daily reporting system inevitably collects many intercurrent symptoms, while related clinical signs may be under-reported. Nevertheless, this method of recording reactions is convenient, clearly effective, and appears to be reliable in recording critical factors of patient disease.

Although unrelated to the method of recording reactions, difficulties were experienced in the assessment of joint symptoms. It seems clear that non-specific muscular pain has been included as joint involvement in both R and N groups.

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