

Vaccination of schoolgirls against rubella

Assessment of serological status and a comparative trial of Wistar RA 27/3 and Cendehill strain live attenuated rubella vaccines in 13-year-old schoolgirls in Dudley

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Freestone, D. S., Reynolds, G. M., McKinnon, J. A., and Prydie, J. (1975). *British Journal of Preventive and Social Medicine*, **29**, 258-261. **Vaccination of schoolgirls against rubella.** A total of 1525 schoolgirls aged 13 years from 21 schools in the County Borough of Dudley, were bled for titration of rubella haemagglutinating inhibiting antibody and then were immediately vaccinated with either Wistar RA 27/3 or Cendehill strain live attenuated vaccines. Both vaccines were administered subcutaneously by syringe and needle but the Wistar RA 27/3 vaccine was also given by multiple injection apparatus. Significantly higher conversion rates and geometric mean haemagglutinating inhibiting antibody titres were obtained in girls initially seronegative given the Wistar RA 27/3 than in those given the Cendehill vaccine, regardless of the method of vaccination. The RA 27/3 strain was associated with a small but significantly greater incidence of local pain immediately on injection. With this exception, differences in the occurrence of reactions were not found between vaccines, between those initially susceptible and immune or with the level of antibody response.

In the United Kingdom, the Department of Health and Social Security recommend the administration of rubella vaccine to all girls between their 11th and 14th birthdays and to seronegative adult women who are at special risk of infection or of transmitting infection to others (Department of Health and Social Security and Central Office of Information, 1972). By the age of 11-13 years, it is likely that the majority of girls will have been infected naturally and vaccination provides immunity for the susceptible minority on an individual basis. This policy allows the epidemiology of rubella in boys and girls under 11 years in whom it occurs most commonly to remain unaltered by the use of vaccine. The relative merits of this policy, compared with that adopted in the USA of vaccinating all boys and girls at a younger age have been discussed in a previous paper (Freestone, 1974).

The present study was carried out:

1. To determine the incidence of rubella haemagglutinating inhibiting antibody in 13-year-old girls attending various schools in the county borough of Dudley so as to provide an indication of the proportion of girls protected as a result of childhood infection.
2. To determine acceptance rates to an offer of rubella vaccine in an industrial conurbation in Britain.
3. To assess any practical advantages for the administration of live attenuated rubella vaccine by multiple injection apparatus.
4. To compare Wistar RA 27/3 and Cendehill strain live attenuated rubella vaccines in terms of seroconversion rates, antibody responses, and reactivity.

The Wistar RA 27/3 strain vaccine was developed by Plotkin in the USA. It was attenuated and prepared in WI-38 human diploid cells (Plotkin, 1969; Plotkin, Cornfeld, and Ingalls, 1965). The Cendehill strain vaccine was developed by Peetermans and Huygelen at Recherche et Industrie Thérapeutiques in Belgium (Peetermans and Huygelen, 1967; Huygelen and Peetermans, 1967). It was passaged initially in monkey kidney and thereafter in primary rabbit kidney and is prepared in this substrate.

PLAN OF STUDY

A total of 2500 13-year-old schoolgirls attending 21 schools in the county borough of Dudley were offered rubella vaccine and asked if they would agree to the collection of blood samples before and after vaccination. Consent was obtained from 1721 (69%) parents or guardians but some girls were absent on the day the study was carried out while vaccination proved to be contraindicated in others. Capillary blood was collected on to Whatman No. 3 chromatography paper discs from 1525 girls who were then randomly allocated to vaccination with a single subcutaneous dose of vaccine containing not less than 1000 TCID₅₀ of one of the following:

Wistar RA 27/3 strain vaccine given by needle and syringe.

Wistar RA 27/3 strain vaccine given by multiple injection apparatus (Port-o-jet, Schuco International London Ltd), or

Cendehill strain vaccine given by needle and syringe.

A further sample of capillary blood was collected six weeks after vaccination from 1432 (94%) of vaccinated girls.

For three weeks after vaccination, reactions were assessed and recorded daily by the vaccinated girls, under the guidance of non-medical personnel. Symptoms were self-rated as nil, mild, moderate, or severe against a general checklist headed 'sore throat, fever, rash, pain, and other'.

SEROLOGY

Rubella haemagglutinating inhibiting (HAI) antibody titrations were carried out in parallel on pre- and post-vaccination blood samples at the Wellcome Research Laboratories, according to the method described by Draper and Kelly, 1969. Titrations were carried out blind, without knowledge of the allocation of girls to vaccine groups.

RESULTS

SEROLOGICAL SURVEY

From a total of 1525 girls screened for rubella antibody 446 (29.3%) were found to be susceptible to rubella with HAI antibody titres of <1:10. Between schools, susceptibility rates ranged from 12.8% to 41.9% and geometric mean titres for seropositive girls from 45.4 to 115. No parallels between susceptibility rates and mean antibody titres per school were found.

A total of 16 498 inspections for head lice infestation were made in 8699 boys and girls aged between 11 and 15 years attending these schools. These inspections included the cohort of 13-year-old girls taking part in the serological survey for rubella antibody and the vaccination study described above. An unexpected correlation was found between infestation rates and the rate at which rubella antibody was detected in the 13-year-old girls in the various schools in the study ($r = +0.483$, $P < 0.01$). Thus, in schools where the rubella susceptibility rates in 13-year-old girls were less than 30%, infestation rates were 293 of 9136 (3.21%) inspections; while in schools in which the rubella susceptibility rates in 13-year-old girls were greater than 30%, infestation rates were 39 of 7362 (0.53%) inspections, $P < 0.01$.

RESPONSE TO VACCINE

The distribution of the 1525 girls vaccinated is shown in Table I. The percentage susceptibility rates per vaccine group are similar. In those initially seronegative, seroconversion rates (antibody titres after vaccination of ≥ 20) of 97.2% and 98.5%

TABLE I
ALLOCATION OF SCHOOLGIRLS TO
VACCINATION GROUPS

	Wistar RA 27/3		Cendehill Syringe	Total
	Syringe	Multiple Injection Apparatus		
Vaccinated total	477	532	516	1525
Serological control before and after vaccination: total ..	441	504	487	1432
Seronegative no. ..	144	133	142	419
% ..	32.7	26.4	29.2	29.3

TABLE II
COMPARISON OF HAI ANTIBODY RESPONSES SIX WEEKS AFTER VACCINATION BY VACCINE AND PREVACCINATION TITRE

Prevaccination Titre	RA 27/3—Syringe			RA 27/3 Multiple Injection Apparatus			Cendehill—Syringe		
	Post-vaccination GMT†	Seroconversion* Rate %		Post-vaccination GMT†	Seroconversion* Rate %		Post-vaccination GMT†	Seroconversion* Rate %	
<10	64.7**	97.2 (144)		68.3**	98.5 (133)		47.8**	90.1 (142)	
10	50.4	66.7 (6)		40.0	53.8 (13)		40.0	38.5 (13)	
20	58.8	44.4 (36)		48.2	32.4 (37)		50.1	46.5 (43)	
40	49.7	4.2 (48)		62.3	0.0 (47)		55.2	4.3 (69)	
80	89.0	0.9 (111)		85.3	0.7 (140)		86.7	0.0 (121)	
≥160	NC	0.0 (96)		NC	0.0 (134)		NC	0.0 (99)	

†Geometric mean titre

All titres expressed as reciprocals

*Fourfold or greater increases in antibody titre in girls with titres before vaccination of ≥10. Increase to a titre of ≥20 for girls with antibody titres before vaccination of <10. Number of girls studied shown in brackets

**RA 27/3 syringe, RA 27/3 multiple injection apparatus significantly greater than Cendehill syringe P<0.01

NC Not calculated

were obtained in the Wistar RA 27/3 strain vaccine, but the seroconversion rate (90.1%) for the Cendehill strain was marginally but significantly lower (P<0.01)—see Table II.

The geometric mean titres of antibodies six weeks after vaccination were significantly greater with the RA 27/3 strain regardless of the method of administration than with the Cendehill strain vaccine (P<0.01). Consistent differences were not found in the ability of the two vaccine strains to elicit fourfold or greater antibody responses in girls with low levels of pre-existing naturally induced antibody (Table II). In none of the 329 girls with antibody titres before vaccination of ≥160 was a fourfold or greater serological response elicited.

REACTIVITY

The assessment of reactivity of rubella vaccine in any large-scale study presents some difficulties. In this study, frequent observation of vaccinees by trained personnel was impractical and as an alternative self-rating of reactions by the vaccinees under the guidance of their teachers was employed.

An overall assessment of reactions within each vaccinated group, regardless of previous antibody status, is shown in Table III. The incidence of reactions was not significantly different between the vaccine groups, with the exception of local pain immediately on injection. A low incidence of local pain at the injection site was encountered with both vaccines but this was reported more frequently after administration of the Wistar RA 27/3 than of the Cendehill strain (P<0.05). Wistar RA 27/3 strain vaccine was tolerated equally well whether administered by needle or syringe by multiple injection apparatus.

TABLE III
REACTIONS RECORDED DURING THE THREE WEEKS AFTER VACCINATION

	Vaccine Strain and Mode of Administration		
	RA 27/3—Syringe	RA 27/3—MIA*	Cendehill—Syringe
Vaccinated	477	532	516
Completed reaction recordings	444	477	471
Reported reactions	%	%	%
Any reaction	53.2	58.5	56.9
Lymphadenopathy	1.6	1.0	0.8
Sore throat	28.6	32.1	35.9
Rash	7.0	6.5	6.2
Joint pains and myalgia	8.3	5.7	8.5
Coryza	8.8	9.9	9.1
Headache	17.1	19.1	17.2
Pain at injection site	7.4†	7.1†	3.6†
Fever	10.6	13.4	11.5

*MIA = Multiple Injection Apparatus

†Significantly greater after RA 27/3 than Cendehill vaccine P<0.05

Comparisons of the incidence of reactions by symptoms between those initially seronegative who responded to vaccine with a post-vaccination HAI antibody titre of 1:20 or above, and those initially immune with an antibody titre of 1:80 or above, revealed no significant differences with the single exception that a sore throat was recorded more frequently in susceptible (33.8% — 45 of 133) than in immune girls (22.1% — 45 of 203) who

received the Wistar strain by needle and syringe ($P < 0.05$). No significant differences are apparent when reactions of three days or longer duration are considered.

The occurrence of symptoms was also compared in initially seronegative girls according to serological response. However, in none of the vaccinated groups were significant differences found in the occurrence of reactions in initially seronegative girls who after vaccination developed antibody to a titre of 20 or 40 and those who developed antibody to a titre of ≥ 80 .

DISCUSSION

The differences observed in rubella susceptibility rates between schools in Dudley are of interest. An unexpected indirect correlation was found between rubella susceptibility and head lice infestation. It seems possible that similar factors facilitate the spread of rubella and infestation, notably social conditions and family size.

The acceptability of rubella vaccine administered by multiple injection apparatus was satisfactory. The seroconversion rates, antibody responses, and reactions obtained after administration of Wistar RA 27/3 strain vaccine by multiple injection apparatus were equivalent to those after administration of the vaccines by needle and syringe. The procedure is advantageous in that it avoids the reconstitution of individual doses of vaccine, their administration by separate syringes, and it is less time-consuming.

The present findings indicate that the Wistar RA 27/3 strain provides substantially higher immediate post-vaccination antibody titres than the Cendehill strain vaccine. The Wistar RA 27/3 strain of rubella vaccine appears to induce an immunity most closely mimicking that of natural infection in inducing quantitatively greater antibody levels and qualitatively a wider range of antibody types than the Cendehill and HPV-77 derived vaccines (Le Bouvier and Plotkin, 1971; Wallace and Isacson, 1972). In addition, in contrast with other strains, the RA 27/3 strain vaccine stimulates the production of local nasal antibody (Ogra *et al.*, 1971). These characteristics of the RA 27/3 strain vaccine appear to be related to a sturdier resistance to challenge (Horstmann, 1971).

It might be expected that the degree of attenuation and reactogenicity of rubella vaccines would bear a linear relationship to one another and thus the more attenuated vaccine would produce the least satisfactory protection and lowest incidence of reactions. The findings of this study suggest that while the

RA 27/3 strain produces substantially greater titres than the Cendehill strain, its reactogenicity is similar.

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