J. Hyg., Camb. (1977), **78**, 419
Printed in Great Britain

Rubella in Orkney: seroepidemiology and vaccination

By MARGARET A. J. MOFFAT
Department of Bacteriology, Foresterhill, Aberdeen
S. N. HEYWOOD* and EILEEN LAUGHTON
Health Centre, Kirkwall, Orkney
and JANINE J. GOULD and D. S. FREESTONE
The Wellcome Research Laboratories, Beckenham, Kent

(*Received* 15 *November* 1976)

SUMMARY

Rubella haemagglutination inhibiting (HAI) antibody titres were determined in 54 seronegative women and 31 naturally immune women after vaccination and revaccination with Wistar RA27/3 strain rubella vaccine administered by the intranasal or subcutaneous routes or revaccination with the Cendehill strain administered subcutaneously. In addition, HAI antibody titres were determined in 46 seronegative schoolgirls after vaccination with the Cendehill strain and revaccination with the RA27/3 strain.

All seronegative women vaccinated with the RA27/3 strain developed antibody, peak titres being reached 6 weeks after vaccination. Six months after vaccination with the Cendehill strain, 45 (98%) of the 46 seronegative girls had developed antibody, but 11 (24%) had not reached their peak titre by 6 weeks, suggesting a slower response than that elicited by the RA27/3 strain. Revaccination did not induce significant antibody responses in the seronegative women vaccinated 6 months previously with RA27/3 but 4 naturally immune women developed an eightfold increase in antibody. In 10 (22%) of 46 schoolgirls previously vaccinated with the Cendehill strain a significant rise in antibody followed revaccination with RA27/3. These results provide further evidence of the more rapid antibody responses elicited by the RA27/3 vaccine in comparison with the Cendehill vaccine.

An outbreak of natural rubella occurred in 1972 and 97 cases were confirmed serologically. The clinical disease was more common in older school-children and in adults. More males than females were affected in the 11–15 age group, the sex ratio being 18:12; this may be explained by the routine vaccination of girls of this age group as part of the national programme which began in 1970. The significance of the persistence of high HAI antibody titres after natural infection and the effect of the epidemic on the serological status of the population are discussed.

* Present address: Neepawa Medical Clinic, Neepawa, Manitoba, Canada.

INTRODUCTION

The percentage of subjects with rubella antibody has been shown to vary in different communities and to be influenced by age, sex, population density, geographical location and the occurrence of recent epidemic rubella. In England, neutralizing antibody was found in 80–96 % of women of child-bearing age (Report of P.H.L.S. Working Party, 1968), whereas island populations may have a lower degree of immunity (Brody *et al.* 1965; Hattis, Halstead, Herrmann & Witte, 1973; Ross, 1974; Tómasson and Ögmundsdóttir, 1975).

The present investigation was undertaken to determine the rubella antibody status of pregnant women in Orkney and to vaccinate groups of seronegative and seropositive women *post partum* with Wistar RA27/3 strain live attenuated rubella vaccine. Routine immunization of schoolgirls with Cendehill strain rubella vaccine was also in progress at that time. Rubella HAI antibody titres after vaccination and revaccination with RA27/3 and Cendehill strains were measured in all groups. An epidemic of natural rubella occurred during these studies and allowed a comparison of the rubella antibody status of pregnant women and 11–15-year-old girls before and after the outbreak.

MATERIALS AND METHODS

Study population

Orkney consists of a group of islands located 25 miles (40 km) north-east of the Scottish mainland: the total population is approximately 18000. Three groups of subjects were studied: (1) 97 patients who in 1972 had clinical rubella which was confirmed serologically; (2) 759 women attending antenatal clinics during the period 1970–74; (3) two groups of schoolgirls (95 in December 1970 before the rubella epidemic and 25 after it in December 1972).

Clinical rubella

Blood samples were collected from patients in the acute stage of the illness and 10 days later. Further samples were collected where possible 6 weeks, 6 months, 12 months and 2 years after infection. All samples were titrated for rubella haemagglutination inhibiting (HAI) antibody.

Vaccination programmes

Women attending antenatal clinics. Blood samples were collected from pregnant women and titrated for rubella HAI antibody. Further samples were collected after delivery from women found in the first test to be seronegative ($< 1/8$) and also from those with low antibody titres (1/8–1/64). Fifty-four seronegative women were vaccinated *post partum* with RA27/3 rubella vaccine by the intranasal or subcutaneous routes and 6 months later were revaccinated with either RA27/3 intranasally or RA27/3 or Cendehill subcutaneously. Thirty-one women with low antibody titres were vaccinated and revaccinated as above but using only the RA27/3 strain. Blood samples were collected 6 weeks and 6 months after each

dose of vaccine and 2 years after primary vaccination and were titrated for rubella HAI antibody. Nasal washings and throat swabs were collected 12 days after primary vaccination for virus isolation studies. A card was issued to each vaccinee to record details of any reactions occurring during the 3 weeks after vaccination. Vaccines were administered only to women who agreed to take oral contraceptives for a minimum of 9 months after primary vaccination.

Schoolgirls. In 1970 blood samples were collected from 95 schoolgirls on the day they received Cendehill vaccine; 46 (48·4 %) were found to be seronegative. Six months later these 46 girls were revaccinated subcutaneously or intranasally with RA27/3 rubella vaccine. Blood samples were collected 6 weeks and 6 months after each dose of vaccine and were titrated for rubella HAI antibody. In 1972, after the outbreak, only 2 (8 %) of the 25 schoolgirls tested were seronegative and further studies were not carried out.

Vaccines

Wistar RA27/3 strain rubella vaccine (lot RU5/1) was supplied by the Wellcome Research Laboratories. The titre per dose was $10^{3.60}$ TCD 50 and the vaccine was administered intranasally as nose drops, or subcutaneously. Cendehill vaccine was supplied through the Local Health Authority as part of the programme for immunization of schoolgirls and was administered subcutaneously.

Serological tests

HAI tests for rubella antibody were carried out in the Virus Laboratory, Department of Bacteriology, Foresterhill, Aberdeen, by the method described by Moffat *et al.* (1972).

Virus isolation

Nasal washings and throat swabs were collected into transport medium containing virus stabilizer and antibiotics and were sent refrigerated to London by air. Virus isolation studies were carried out at the Wellcome Research Laboratories by methods described by Moffat *et al.* (1972).

RESULTS

Outbreak of natural rubella in Orkney

An outbreak of clinical rubella occurred during the first 7 months of 1972, one-third of the total confirmed cases being reported in April. The age and sex distribution of 97 cases which were serologically confirmed is shown in Table 1. Clinical rubella was first seen in older school-age children and thereafter in adults. There was a slight total preponderance of female cases but in the 11–15 year age group the male:female ratio was 18:12. The results of HAI tests on sera collected at intervals after infection show that the HAI antibody titre was at its maximum 10 days after the development of symptoms and gradually declined thereafter (Table 2).

Table 1. *Age and sex distribution of 97 serologically confirmed cases of natural rubella – Orkney, 1972*

	January	February	March	April	May	June	July	Total
Total	1	20	25	34	10	5	2	97
Male	0	12	16	14	3	0	0	45
Female	1	8	9	20	7	5	2	52
Age: Range	13	10–33	5–33	9–46	4–47	19–27	31	
Average	13	15·5	17·8	22·9	24·6	22.4	31	

Table 2. *HAI antibody titres after natural rubella infection in two age groups*

Number in group	Age		HAI titres after infection*				
	Range	Average	10 days	6 weeks	6 months	12 months	2 years
13	10–17	12·9	256–2048 (704·7)	256–2048 (633·4)	128–2048 (371·7)	32–512 (158·4)	64–512 (185·9)
13	20–34	26.6	128–2048 (826·9)	128–1024 (460·3)	64–1024 (270·1)	16–512 (150·2)	8–512 (98·0)

* Geometric mean titre in parentheses.

Table 3. *The rubella antibody status of different age groups before and after the epidemic*

Age (years)	11–15		16–25		26–35	
	Before	After	Before	After	Before	After
Subjects tested	113	26	294	92	199	39
Number seropositive	51	24	201	75	155	32
Percentage seropositive	45·1	92·3	68·4	81·5	77·9	82·1
HAI (GMT)	107·3	295·8	87·9	118·9	56·5	79·5

Effect of the epidemic on the rubella antibody status of the population

The rubella HAI antibody titres of sera collected before the epidemic (July 1970–December 1971) were compared with those of sera collected after it (July 1972–May 1974). The percentage of seropositive subjects was considerably higher after the outbreak especially in the 11–15 age group and the GMT increased in all age groups. There was no history of clinical rubella or vaccination in any of these subjects (Table 3). These results show that subclinical infection was widespread during the epidemic.

Vaccine studies

Vaccination and revaccination ('challenge') of seronegative women

Table 4 shows the geometric mean HAI antibody titres of sera from seronegative women after primary vaccination with RA27/3 rubella vaccine (intranasal or subcutaneous) and 'challenge' with RA27/3 (intranasal or subcutaneous) or with Cendehill vaccine (subcutaneously). All 54 women showed fourfold or greater antibody rises 6 weeks after primary vaccination followed by a gradual decrease in titre during the following 2 years of the study. Antibody rises of fourfold or greater

Table 4. *Rubella HAI titres (geometric mean) in 54 seronegative women after vaccination with* RA27/3 *and 'challenge' with* RA27/3 *or Cendehill strains*

No. in group	Average age	Vaccine	Challenge	HAI titres (geometric mean) After vaccine 6 weeks	After vaccine 6 months	After challenge 6 weeks	After challenge 6 months	2 years
11	22·5	RA27/3	RA IN	77·3	53·0	49·7	46·7	29·6 (9)
10	19·3	intranasal	RA SC	97·0	64·0	78·8	52·0	43·5 (9)
6	19·5		CEND SC	80·6	57·0	50·8	45·3	—
10	20·3	RA27/3	RA IN	73·5	43·5 (9)	52·0	48·5	29·3 (8)
11	23·5	subcutaneous	RA SC	72·6	68·2	64·0	64·0	47·0 (9)
6	24·0		CEND SC	114·0	57·0	64·0	50·8	—

Number in parentheses = sera available; RA IN = RA27/3 strain administered intranasally. RA SC = RA27/3 strain administered subcutaneously; CEND SC = Cendehill strain administered subcutaneously.

Table 5. *Rubella HAI titres (geometric mean) in 31 seropositive women after vaccination and 'challenge' with* RA27/3 *strain*

No. in group	Average age	Vaccine	Challenge	HAI titres (geometric mean) Before vaccine	After vaccine 6 weeks	After vaccine 6 months	After challenge 6 weeks	After challenge 6 months	2 years
9	23.9	RA27/3	RA IN	37·3	47·0	40·2	40·2	34·9 (8)	45·3 (4)
6	23·5	intra-nasal	RA SC	25·4	X35·9	35·9	X57·0	40·2	32·0 (4)
7	24·6	RA27/3	RA IN	52·5	X78·0	95·1	78·0	70·7	84·5 (5)
9	28·7	subcu-taneous	RA SC	32·0	X43·5	43·5	53·8 (8)	43·5	35·3 (7)

Number in parentheses = sera available; X = significant antibody rise in one individual. RA IN = RA27/3 strain administered intranasally; RA SC = RA27/3 strain administered subcutaneously.

were not seen after 'challenge' but several women showed twofold increases in antibody which explains the slight increase in GMT 6 weeks after challenge in some groups. Clinical reactions were not reported. Table 4 also shows that the geometric mean titres 18 months after revaccination were higher in the groups challenged subcutaneously with RA27/3 than in those challenged intranasally.

Rubella virus was isolated from 5 of 32 vaccinees studied after primary vaccination; from 3 of 15 women after intranasal RA27/3 and from 2 of 17 women after subcutaneous RA27/3.

Vaccination and revaccination ('challenge') of seropositive women

Table 5 shows the geometric mean HAI antibody titres of sera from seropositive women after primary vaccination and 'challenge' with RA27/3 rubella vaccine

Table 6. *Rubella HAI titres (geometric mean) in 46 seronegative schoolgirls after vaccination with Cendehill and revaccination with* RA27/3 *strains*

No. in group	Average age	Vaccine	Challenge	HAI titres (geometric mean) After vaccine 6 weeks	After vaccine 6 months	After challenge 6 weeks	After challenge 6 months
23	13	Cendehill subcutaneous	RA IN	37·2	76·7	248·4	89·2
23	13		RA SC	36·1	58·5	103·6	70·0

RA IN = RA27/3 strain administered intranasally; RA SC = RA27/3 strain administered subcutaneously.

Table 7. *Effect on HAI titres of revaccination with* RA27/3 *(intranasal or subcutaneous) in 10 schoolgirls vaccinated 6 months previously with the Cendehill strain*

Intranasal challenge: 6 months after vaccine	Intranasal challenge: 6 weeks after challenge	Intranasal challenge: Total	Subcutaneous challenge: 6 months after vaccine	Subcutaneous challenge: 6 weeks after challenge	Subcutaneous challenge: Total
32	128	1	< 8	128	1*
32	256	1	32	128	1†
32	⩾512	1	64	⩾512	1
64	256	3			
128	⩾512	1			
		7			3

* = no seroconversion after primary vaccination.
† = < 8 weeks after primary vaccination.

administered intranasally or subcutaneously. Three women showed an eightfold rise in antibody titre 6 weeks after the first dose of vaccine; one after intranasal vaccination and two after subcutaneous vaccination. A fourth individual showed an eightfold rise after subcutaneous 'challenge'. The women with antibody rises had low antibody titres of 1/8 or 1/16 initially.

Rubella virus was not isolated from 13 vaccinees studied after primary vaccination; 8 after intranasal RA27/3 and 5 after subcutaneous RA27/3.

Vaccination and revaccination ('challenge') of seronegative schoolgirls

In December 1970, 95 schoolgirls were vaccinated with Cendehill rubella vaccine and 46 (48 %) were found to be seronegative at the time of vaccination. Table 6 shows the geometric mean HAI antibody titres of the sera from these 46 girls after primary vaccination with Cendehill vaccine and 'challenge' with RA27/3 rubella vaccine. Six weeks after primary vaccination 44 (96 %) of the 46 girls had antibody titres of 1/16 or greater; however, 10 girls showed a further fourfold or greater increase in titre between the 6-week and 6-month samples and one girl who was seronegative 6 weeks after vaccination had a titre of 1/64 at 6 months. After 'challenge', 10 (22 %) of the 46 girls showed fourfold or greater increases in titre; 7 after intranasal and 3 after subcutaneous RA27/3 (Table 7).

DISCUSSION

The population of Orkney was found to have a high rate of susceptibility to rubella and the outbreak in 1972 was short and well-defined which is typical of an island epidemic. Hattis, Halstead, Herrmann & Witte (1973) studying rubella in Hawaii, emphasized the important factors in the transmissibility of the disease; it is relatively non-infectious, depending on close contact for transmission, and is most likely to be spread in residential institutions especially if respiratory infections are present. Such conditions are limited in an island population. Nevertheless the effect of the Orkney epidemic on the rubella antibody status of the population was dramatic particularly in the 11–15 year schoolgirls where the percentage of seronegatives fell from 55% to 8%. It is possible that the susceptibility rate in Orkney may remain permanently lower now that communications have improved and it has become a less typical island population. A large-scale serological survey was carried out in Israel after an extensive rubella epidemic and the percentage of seronegative women in the population was much the same as it was 4 years before the epidemic (Swartz *et al.* 1975).

In the Orkney epidemic clinical rubella with rash was first observed in older children (average age 15 years). It is known that the ratio of clinical to subclinical infection is higher amongst those aged 15–19 years than among younger children (Brody *et al.* 1965) although the incidence of rubella infection is greatest in young children (Sever *et al.* 1965; Brown, Hambling & Ansari, 1969). These young children with subclinical infections could provide a hazard to women during pregnancy but no cases of congenital rubella were reported in Orkney as a direct result of the epidemic. The ratio of males to females in the 11–15 year age group was 18:12; the numbers are small but the findings suggest that vaccination of schoolgirls, begun in 1970, may have limited the spread of clinical rubella in the girls. None of the serologically confirmed clinical cases gave a history of vaccination. One year after infection HAI titres ranged from 32 to 512 which emphasizes that a single high HAI antibody titre in the absence of specific IgM does not necessarily indicate recent infection. Antibody persisted at a high titre in most patients for at least 2 years.

Vaccination of seronegative women in Orkney with RA27/3 rubella vaccine resulted in 100% seroconversion, and peak HAI antibody titres were reached 6 weeks after vaccination. After vaccination with Cendehill vaccine seroconversion occurred in 45 of the 46 girls by 6 months; however, 11 of the 45 girls had not reached the peak antibody titre by 6 weeks and showed further significant antibody increases between 6 weeks and 6 months. Many workers have already reported lower antibody titres with Cendehill than with RA27/3 vaccine 6–8 weeks after vaccination (Tobin, 1971; Plotkin, Farquhar & Ogra, 1973; Thomssen, 1973; Grillner, 1975; Freestone, Reynolds, McKinnon & Prydie, 1975). Other reports have suggested that these lower titres may be due to a slower initial response and that by 6–7 months the differences are less (Fogel, Moshkowitz, Rannon & Gerichter, 1971; Plotkin & Farquhar, 1972). It has been suggested that the faster replication of RA27/3 strain provides a prolonged antigenic stimulus, thus in-

ducing better immunity than the more attenuated Cendehill strain (Paul, Rhodes, Campbell & Labzoffsky, 1974). The higher rate of reinfection after Cendehill than after RA27/3 is well documented although neither vaccine provides the protection given by natural infection (Plotkin *et al.* 1973). Infection of the fetus may rarely follow reinfection during pregnancy (Chang, 1974; Eilard & Strannegård, 1974) and this must be considered when planning vaccination programmes.

Challenge studies have shown that the RA27/3 strain may be useful for revaccination. In our series there were no significant antibody responses when women were 'challenged' with RA27/3 6 months after primary vaccination with the same vaccine. However, when the schoolgirls were 'challenged' with RA27/3 6 months after primary vaccination with Cendehill, 10 girls (22%) showed significant increases in antibody titre. These results provide further evidence for the efficacy of the RA27/3 strain compared with the Cendehill strain.

The vaccine trial was approved by the MRC Sub-Committee on Rubella Vaccines. We would like to acknowledge the help of many people who assisted us during the study. Especially we would mention Dr J. S. Walker and the secretarial staff in the Health Centre, Kirkwall, Orkney, Dr I. F. G. Haddow, Chief Administrative Officer, Orkney Health Board (until March 1976), and Professor A. Macdonald, Dr T. Brown and Mr A. Massie in the Department of Bacteriology, University of Aberdeen.

The work was partly supported by the Wellcome Foundation.

REFERENCES

BRODY, J. A., SEVER, J. L., MCALISTER, R., SCHIFF, G. M. & CUTTING, R. (1965). Rubella epidemic on St Paul Island in the Pribilofs, 1963. *Journal of the American Medical Association* **191**, 83.

BROWN, T., HAMBLING, M. H. & ANSARI, B. M. (1969). Rubella-neutralizing and haemagglutinin-inhibiting antibodies in children of different ages. *British Medical Journal* iv, 263.

CHANG, T-W. (1974). Rubella reinfection and intrauterine involvement. *Journal of Pediatrics* **84**, 617.

EILARD, T. & STRANNEGÅRD, Ö. (1974). Rubella reinfection in pregnancy followed by transmission to the foetus. *Journal of Infectious Diseases* **129**, 594.

FOGEL, A., MOSHKOWITZ, A., RANNON, L. & GERICHTER, C. B. (1971). Comparative trials of RA27/3 and Cendehill rubella vaccines in adult and adolescent females. *American Journal of Epidemiology* **93**, 392.

FREESTONE, D. S., REYNOLDS, G. M., MCKINNON, J. A. & PRYDIE, J. (1975). Vaccination of schoolgirls against rubella. *British Journal of Preventive and Social Medicine* **29**, 258.

GRILLNER, LENA (1975). Neutralizing antibodies after rubella vaccination of newly delivered women: a comparison between three vaccines. *Scandinavian Journal of Infectious Diseases* **7**, 169.

HATTIS, R. P., HALSTEAD, S. B., HERRMANN, K. L. & WITTE, J. J. (1973). Rubella in an immunized island population. *Journal of the American Medical Association* **223**, 1019.

MOFFAT, MARGARET A. J., GOULD, JANINE J., FORBES, F. A., FREESTONE, D. S. & MACDONALD, A. (1972). Studies with rubella vaccine (RA27/3) using the subcutaneous and intranasal routes. *Scottish Medical Journal* **17**, 140.

PAUL, N. R., RHODES, A. J., CAMPBELL, J. B. & LABZOFFSKY, N. A. (1974). Rubella precipitin response in natural infection and in vaccination. *Archiv für die gesamte Virusforschung* **45**, 335.

PLOTKIN, S. A. & FARQUHAR, J. D. (1972). Immunity to rubella: comparison between naturally and artificially induced resistance. *Postgraduate Medical Journal* **48**, Suppl. (3) 47.

PLOTKIN, S. A., FARQUHAR, J. D. & OGRA, P. L. (1973). Immunologic properties of RA27/3 rubella virus vaccine. *Journal of the American Medical Association* **225**, 585.

PUBLIC HEALTH LABORATORY SERVICE (1968). Studies on rubella in pregnancy. *British Medical Journal* iii, 203.

ROSS, M. G. R. (1974). A serological survey for rubella antibody. *Fiji Medical Journal* **2**, 133.

SEVER, J. L., SCHIFF, G. M., BELL, J. A., KAPIKIAN, A. Z., HUEBNER, R. J. & TRAUB, R. G. (1965). Rubella antibody in children and adults. *Pediatrics* **35**, 996.

SWARTZ, T. A., PRAISS, I., ISACSON, M., NISHMI, M., BEN-PORATH, EDNA & HORNSTEIN, LEAH (1975). Early results of an extensive rubella epidemic. *International Journal of Epidemiology* **4**, 331.

THOMSSEN, R. (1973). Vergleich der Antikörperbildung nach parenteraler Schutzimpfung mit den Rubella-Impfstoffen 'Cendehill' und RA27/3. *Deutsche medizinische Wochenschrift* **98**, 1555.

TOBIN, J. O'H. (1971). Rubella vaccination of postpartum women and of adolescents in the North West of England. *Canadian Journal of Public Health* **62**, Suppl. 64.

TÓMASSON, H. Ó. and ÖGMUNDSDÓTTIR, HELGA M. (1975). Rubella in Iceland. *Acta pathologica et microbiologica scandinavica* B **83**, 275.