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RUBELLA EPIDEMIC IN AN INSTITUTION: PROTECTIVE VALUE OF LIVE RUBELLA VACCINE AND SEROLOGICAL BEHAVIOR OF VACCINATED, REVACCINATED AND NATURALLY IMMUNE GROUPS

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SUMMARY A rubella epidemic occurred in an institutional population composed of 189 susceptible, 37 naturally immune, 35 previously vaccinated and 38 serologically uncharacterized children and nursing staff. The epidemic lasted 3.5 months and showed more than 5 waves. Detailed clinical and serological examinations of these subjects were made. A rash appeared in 156 (52%) of 299 persons, including 145 (87%) of 166 unvaccinated and serologically uncharacterized subjects, but not in the 72 immune persons.

In the middle of the 3rd wave urgent vaccination of 61 children aged 0 to 2 years of the susceptible group reduced the rate of appearance of a rash to 11 of the children (18%), as compared with 126 (98%) of 128 subjects in the unvaccinated non-immune group. The epidemic only reached a 4th wave in the vaccinated group, but it extended to a 5th wave or more in unvaccinated subjects. None of the 35 subjects in a previously vaccinated group developed rubella, although the rate of subclinical reinfection in this previously vaccinated group was higher (35%) than that in the naturally immune group (17%). Three cases of subclinical reinfection were detected even among 6 previously revaccinated subjects.

INTRODUCTION

The purpose of immunization with live rubella vaccine is mainly to prevent women of child-bearing age from producing malformed babies. But it is also important to increase the popula-

tion of immune children and thus indirectly to decrease the chance of rubella virus infection in pregnant women. Thus immunization has been performed in the USA since 1968. It is also important to prevent children from infection with "the exanthematous disease of childhood" rubella.

Several workers have reported that vaccine-induced immunity persists for many years and that this immunity is effective against clinical rubella (Chang et al., 1970; Horstman et al., 1970; Ogra et al., 1971). However, no precise comparison has been made between vaccine-induced and naturally acquired immunity.

This paper reports a rubella epidemic in a closed population in the Osaka district, Japan, where the serological status of almost all persons was known, the protective effect of live rubella vaccine "Biken" when given by previous vaccination or by urgent vaccination, the retention of vaccine-induced or naturally acquired immunity, and the booster effects observed in different immunological groups during this rubella epidemic.

MATERIALS AND METHODS

1. *Population studied*

A total of 244 healthy children of 0 to 15 years old institutionalized in two separate buildings in the Osaka district, Japan, together with 55 nursing staff were studied clinically and serologically during a rubella epidemic. In building A, 95 babies of 0 to 2 years old and 32 children of 13 to 15 years old lived on the 1st and 2nd floors, respectively, while 117 children of 3 to 12 years old lived in building B. Fifty-five nursing staff were attached to the two buildings, working in both. The physical condition of the children was checked daily by pediatricians and the nursing staff.

2. *Serological assay of rubella*

Blood specimens were taken from children and nursing staff before, within 1 week and several weeks after the appearance of the 1st case of rubella.

Serological assay of the rubella antibody titer was performed by the hemagglutination-inhibition (HI) method as described before (Suzuki et al., 1973).

3. *Vaccine and vaccination*

Live rubella vaccine "Biken", which was passaged and attenuated in Japanese quail embryo fibroblast (QEF) cells as reported elsewhere (Minekawa et al., 1973) was used throughout the study. The vaccine was injected subcutaneously into the upper arm.

RESULTS

1. *A rubella epidemic in an institutionalized population*

On March 8, 1976, rubella developed in a 6-year-old girl in building B at the time of a severe rubella epidemic outside the institution. The route of introduction of rubella virus into the population is unknown. The immunological status of the population within one week after the appearance of this 1st case was as follows: Among 127 subjects in building A, there were 108 susceptible (85%), 9 naturally immune (7%) and 10 previously vaccinated (8%); among 117 subjects in building B there were 51 susceptible (44%), 3 naturally immune (3%), 25 vaccinated (21%) and 38 serologically uncharacterized (32%) subjects; and there were 30 susceptible (55%) and 25 naturally immune (45%) staff members (Table 1). As a 2nd wave of the epidemic, two cases of rubella occurred on the 1st floor of building A on March 21 and 24, 1976, respectively, where the 0- to 2-year-old babies and 13- to 15-year-old children were accomodated together with the 55 nursing staff, who also worked in building B. Within 1 week after this 2nd wave of the epidemic, 95 of the 0- to 2-year-old babies and 55 of the nursing staff were examined for serum HI antibody titer against rubella. All the children and 30 of the nursing staff were found to be seronegative.

The biweekly incidence of the epidemic is summarized in Fig. 1. The epidemic reached peaks in the 8th and 12th weeks in the A and B buildings, respectively.

A total of 156 (52%) of the 299 total, and 145 (87%) of 166 susceptible subjects, includ-

TABLE 1. *Numbers of individuals with clinical rubella in various immunological groups in the institution*

Building	Age in years (Total number)	Non-immune		Immune		Unknown
		Urgently vaccinated	Unvaccinated	Previously vaccinated	Naturally immune	
A	0-2 (95)	11/61	32/34	0	0	0
	13-15 (32)	0	13/13	0/10	0/9	0
B	3-12 (117)	0	51/51	0/25	0/3	19/38
A, B	Nursing staff (55)	0	30/30	0	0/25	0
Total number (Attack rate)	156/299 (52%)	11/61 (18%)	126/128 (98%)	0/35 (0%)	0/37 (0%)	19/38 (50%)

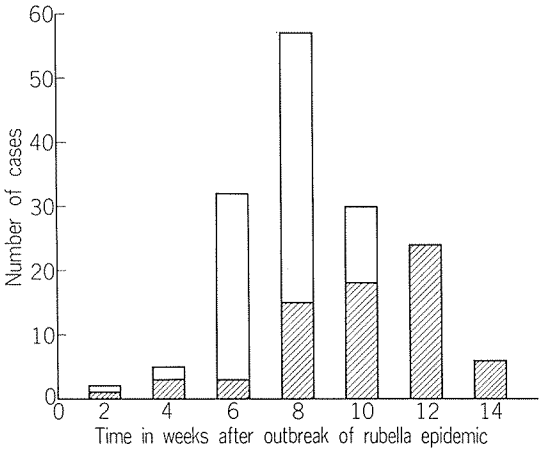

FIGURE 1. Biweekly incidence of cases of clinical rubella among 299 subjects. In all 156 subjects showed a rash. ▭, building A; ▨, building B.

ing immunologically uncharacterized subjects suffered clinical rubella.

2. *The protective value of urgent vaccination during the rubella epidemic*

As shown in Fig. 2, during the 3rd wave of the epidemic, live rubella vaccine was urgently inoculated into 61 seronegative 0- to 2-year-old babies in building A. The epidemic in the vaccinated group stopped in the 4th wave and a rash appeared in 18% (11/61), whereas in the unvaccinated control group, including 30 nursing staff, the epidemic extended to a 5th wave and a rash appeared in 95% (62/64) persons. Blood specimens were taken from persons in both groups and tested for rubella HI antibody before the rubella outbreak in building B and 4 weeks after the 5th wave of the epidemic. As seen in Table 2, subclinical infection was seen in only one of 32 subjects tested in the control group, excluding one person who was not infected, as revealed by the HI test. The geometric mean titer of antibody (GMT) in the vaccinated subjects who showed no clinical manifestations was higher than that observed previously in subjects vaccinated at a time when there was no epidemic (Minekawa et al., 1973, 1974, 1975). This higher titer is possibly due to the sum of the titers resulting from subclinical infection and vaccination.

3. *Retention of HI antibody and the protective value of vaccination several years before the outbreak of an epidemic*

Some children of 3 to 15 years old in both buildings had been vaccinated against rubella several years before this rubella epidemic.

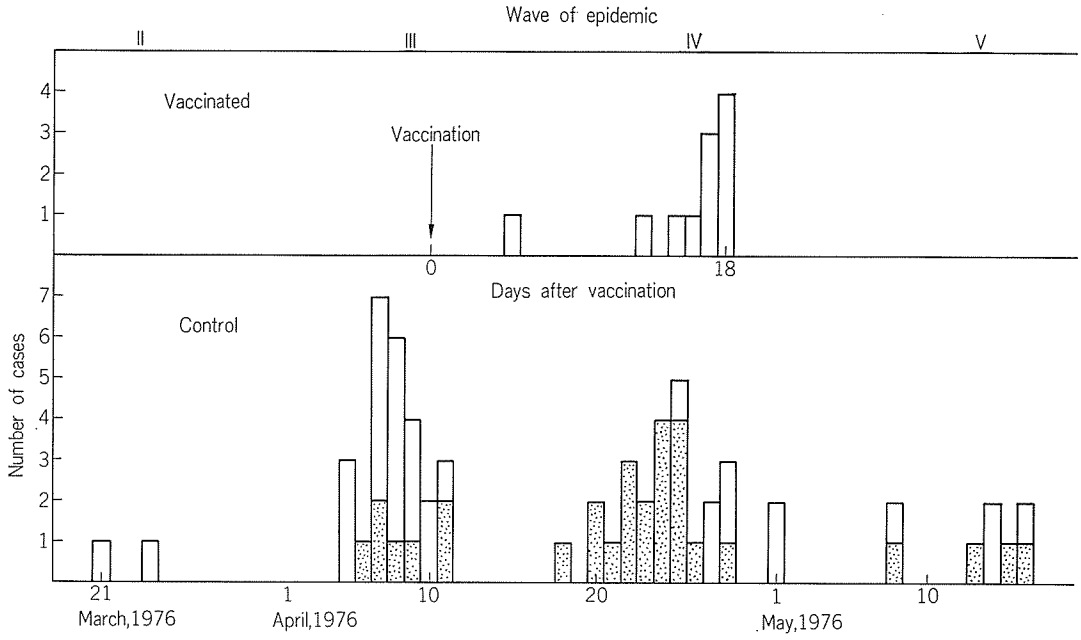

FIGURE 2. Daily incidences of clinical rubella in building A in 61 vaccinated and 64 unvaccinated control subjects. In the vaccinated group the epidemic stopped at the 4th wave and only 11 cases (18%) developed a rash, while among unvaccinated subjects it lasted to the 5th wave and 62 cases (95%) of clinical rubella were seen. ☐, 0- to 2-year-old children; ▨, nursing staff.

TABLE 2. *Seroconversion of seronegative subjects by natural infection or by urgent vaccination during rubella outbreak*

Rubella HI titers after epidemic	Unvaccinated		Vaccinated	
	Clinical rubella	No apparent symptoms	Clinical rubella	No apparent symptoms
512	5	0	6	3
256	15	0	3	17
128	7	0	1	8
64	3	0	1	7
32	1	0	0	3
16	0	0	0	0
8	0	1	0	3
<8	0	1	0	0
Seroconversion rate	31/31	1/2	11/11	41/41
GMT (2^n)	7.6	3.0	8.3	7.0

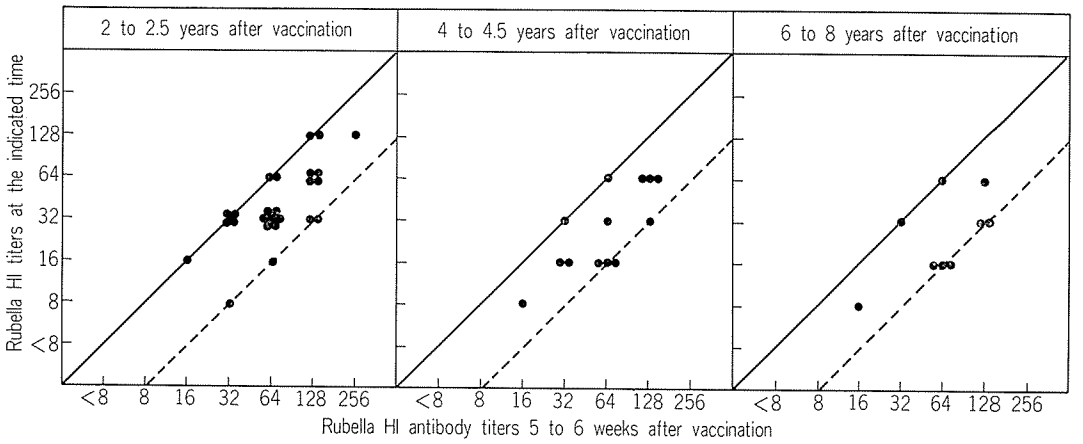

FIGURE 3. Retention of rubella HI antibody after administration with live rubella QEF vaccine was tested at the indicated times, before the present rubella epidemic. Sixteen, 30.8 and 55.6% of the vaccinees showed 4-fold decrease in HI titer 2 to 2.5, 4 to 4.5 and 6 to 8 years after vaccination, respectively.

No remarkable clinical reactions, such as fever, rash or other side effects, were detected after the vaccination. As shown in Fig. 3, during the periods 6 to 8, 4 to 4.5 and 2 to 2.5 years before the present epidemic, their HI antibody titers decreased 4-fold in 5 of 9 subjects (55.6%), 5 of 13 subjects (30.8%) and 4 of 25 subjects (16.0%), respectively. However, antirubella immunity was retained through the 8th observation year without substantial decline in the titer, and none of these subjects showed any clinical manifestations of rubella during the epidemic.

4. *Booster effect of exposure to rubella on vaccine-induced or naturally acquired immunity*

In Fig. 4, the antibody levels of vaccinated and naturally infected persons before and after the epidemic are compared. A booster effect (4-fold or greater increase) was detected in 34.8% of the vaccinated subjects and in 16.7% of the naturally immune children. All subjects with rubella HI antibody levels on the borderline (1: 8 antibody titer), showed a booster effect, irrespective of whether their primary immunity was induced by vaccination or by natural infection. But even comparatively low levels of pre-existing antibodies effectively protected children against clinical manifestations of the disease.

Six initially rubella seronegative persons vaccinated more than 5 to 8 years before this rubella outbreak were revaccinated 1 to 4 years later. As shown in Fig. 5, booster effects of revaccination were seen in 2 (33.3%) of these 6 persons. Their HI antibodies were also retained without marked decrease for more than 4 years after revaccination and they showed no clinical manifestations of rubella during the present epidemic, although subclinical reinfection, evidenced by antibody increase, was seen in 3 (50%) of the 6 revaccinees. Thus it seems unlikely that revaccination was very effective in decreasing the occurrence of reinfection on exposure to natural rubella virus.

DISCUSSION

The aim of rubella immunization is to provide girls directly with immunity to rubella and to prevent congenital rubella by providing indirect protection of mothers with rubella-susceptible children, because direct vaccination of susceptible women of child-bearing age seems to be accompanied by a considerable risk.

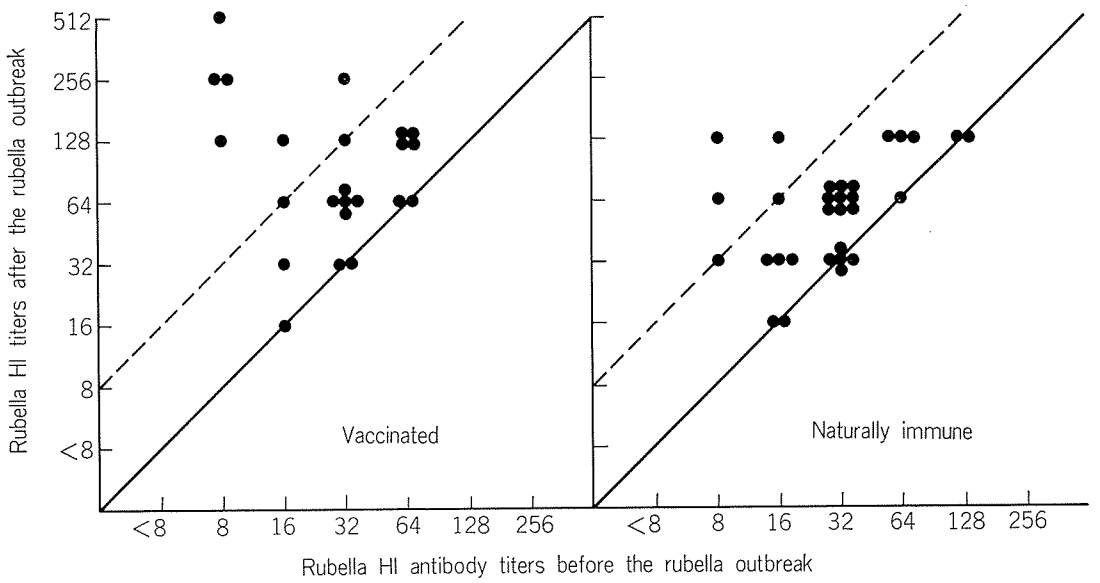

FIGURE 4. Subclinical reinfection at the time of outbreak of rubella in the institution was compared in subjects vaccinated 2 to 8 years before the outbreak and in those naturally immune for more than 8 years. In all, 35% and 17% of the vaccinated and naturally immune groups, respectively, were reinfected. Subjects who had HI titers of less than 1: 32 in the two groups tended to show a booster response.

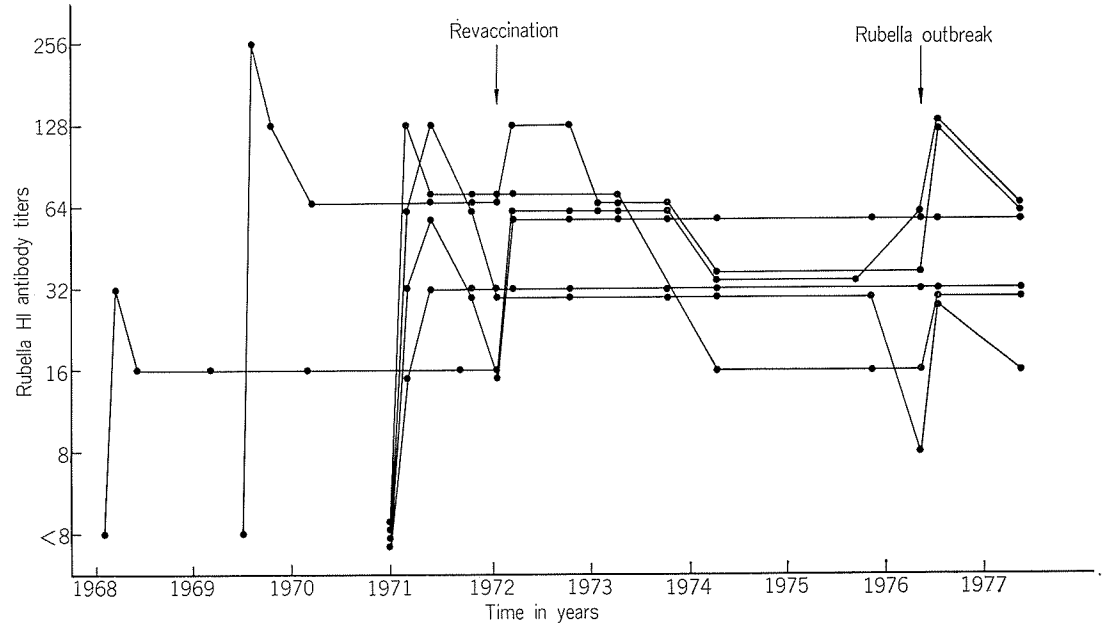

FIGURE 5. Follow-up studies on 6 revaccinated subjects were made for more than 6 to 9 years. Subclinical infection was detected in 3 subjects at the outbreak of the rubella epidemic in the institution.

It is also of value in preventing children from "the eruptive disease of childhood" rubella.

Live rubella vaccine should be safe and potent, and the immunity induced should be high, long-lasting and effective against natural rubella infection. From the results of this field-study we conclude that urgent vaccination is safe and effective since it reduced the number of rubella cases among vaccinees, judging by comparison with the number of cases among unvaccinated controls in the closed population. These findings support the data of Furukawa et al. (1970). In an open population where contact of susceptible subjects with cases of rubella is much less, urgent vaccination must be even more effective than in this closed population. Moreover it could be used for children in institutions, hospitals, kindergartens or schools.

With regard to persistence of immunity, none of the children vaccinated previously or immunized by natural infection developed clinical rubella, although some with rather low antibody titers showed a booster response, the rate of which was higher in vaccinees than in naturally immune children. Routine administration of a second dose of rubella vaccine is not recommended, because it was ineffective in enhancing resistance to reinfection, as shown in Fig. 5, as reported by Wyll et al. (1971) and Brandling-Bennett et al. (1976).

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