RUBELLA IN MALE SINGAPORE ADOLESCENTS: INCIDENCE AND EFFECTS OF VACCINATION

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SYNOPSIS

Rubella is a significant cause of morbidity in military camps, particularly among Recruits during their basic training. A serological survey of 560 newly enlisted Recruits aged between 18 and 19 years showed that 360 (64.3%) had immunity against Rubella as demonstrated by serum Haemagglutination Inhibition titres of 16 or more. Vaccination of the sero-negative personnel with the RA 27/3 live attenuated virus vaccine resulted in a 99% sero-conversion rate with a Geometric Mean Titre of 46.1. Antibody titres remained constant or were raised at the end of the one year follow up period. Side effects of vaccination were mild and transient. No cases of clinical Rubella occurred among those vaccinated although several had serological evidence of subclinical reinfection. Routine vaccination proved effective in markedly lowering the incidence of Rubella.

BACKGROUND

Rubella is an infectious disease with exceedingly subtle but severe effects which can cause congenital defects in infants born to mothers who had contracted the infection in early pregnancy. On the other hand, in male adults and in women who are not pregnant, it is usually hardly more than a nuisance although the disease can be associated with severe manifestations or complications like arthritis, encephalitis and thrombocytopenia. Rubella epidemics are commonplace occurrences at military training establishments around the world and the disease is a significant cause of acute febrile illnesses especially amongst soldiers undergoing recruit training (1, 2, 3). Because of the physically taxing nature of their training, Recruits have to be laid off from training for several days if they contract the disease and, since military training is systematically progressive and highly structured, the disease causes much time to be lost from training and leads to disruption of training programmes. Furthermore the recruit training centres also serve as foci from which the infection can be disseminated not only to other military personnel but also to their families and the general population since recruits are permitted to go home on weekends whenever training permits. The control of rubella was therefore a highly desirable objective, and as a first step towards this, a survey was conducted among male National Service Recruits to determine their immunity status. The opportunity was also taken to assess the usefulness of "histories" as indicators of immune status and to evaluate the efficacy and effects of vaccination of susceptibles. This paper reports on the results of that survey and evaluation.

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MATERIALS AND METHODS

560 Recruits, all males and aged between 18 and 19 years who were enlisted together in December 1979 were randomly selected. Since enlistment is determined by the date of birth and conscription is universal, it was considered that there would be no significant systematic bias and the sample would therefore be representative of all male Singaporeans within this age group.

5 ml of venous blood was drawn from each of the selected Recruits and the Rubella Haemagglutination Inhibition (HAI) antibody titre was determined for each specimen by the method described by Cooper et al (4). The Rubella haemagglutination antigen was obtained commercially from Burroughs-Wellcome. Manganese chloride and heparin were employed for the removal of non-specific inhibitors from sera. Red blood cells were obtained from day old chicks. HAI antibody titres of 8 or less were regarded as seronegative.

These Recruits were regarded as non-immunes and were all immunised using the attenuated live virus strain RA 27/3 marketed under the name "Rubeaten Berna" by the Swiss Serum and Vaccine Institute. Each unit dose of the lyohilised vaccine contained 1,000 infectious doses 50% (1,000 TCID50) of live attenuated virus. The vaccine was supplied in vials of 10 doses. 0.5 ml doses of the reconstituted lyophilised vaccine were administered by subcutaneous injection in the upper arm.

After vaccination, all vaccinees were reviewed two weeks and one month from the date of vaccination. In addition, they were encouraged to report to their doctor should they have any ill-effects. At these reviews, the Recruits were specifically questioned as to the occurrence of side effects or adverse reactions such as arthralgia, headache, vomiting and respiratory complaints and were clinically examined specifically for swollen or painful joints, rashes adenopathy, local reactions at the vaccination site, paraesthesias and fever. After the second review, all those without any apparent morbidity were not followed up further.

All vaccinees were however recalled for blood samples to be taken at three months and one year from the date of their vaccination for further Rubella HAI antibody titre measurements. On these occasions, their medical records were also scrutinised for rubella or rubella-like illnesses during the intervening periods.

RESULTS AND DISCUSSION

Past History of Rubella

The purpose of obtaining past histories of rubella infection, contact or immunisation was to determine the value of the medical history as an indicator of rubella susceptibility. The distribution of Recruits by past "history" is shown at Table 1. 124 (22.1%) claimed to have had Rubella and 38 (6.8%) gave a history of past Rubella contact without contracting the disease. None gave a history of having been vaccinated against Rubella.

Of the 398 Recruits who had no past history, 63% were found to have HAI titres of 16 or more, whereas 32% of those who claimed to have had Rubella were found to be sero-negative, and 55% of those with only a history of contact were serologically immune.

The value of historical recall of Rubella as an indicator of immunity to Rubella is therefore doubtful. The main reason for this is probably the difficulty of distinguishing childhood Rubella from other viral exanthems. Similar unreliability was found even among a population of health profession students in the United States who might have been expected to have a greater awareness of health and disease than the general population. Thus Chappel and Taylor (5) found that amongst medical and physician assistant students, the probability of the history being correct was at best 60% in either immune or susceptible categories.

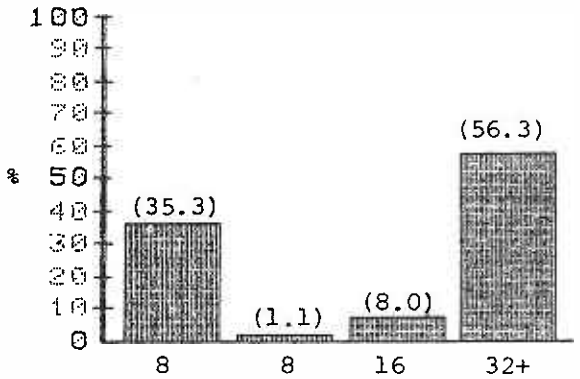
TABLE 1
DISTRIBUTION OF RECRUITS BY HISTORY OF RUBELLA INFECTION OR CONTACT

History	No. of Recruits	%
Past Rubella Infection	124	22.1
Past Rubella contact but no past infection	38	6.8
No past infection, contact or vaccination	398	71.1
Total	560	100.0

Immune Status

The distribution of HAI antibody titres is shown at Figure 1. In view of the relatively large size of the sample population, only dilutions up to 1:32 were done. Therefore all persons with HAI antibody titres of 32 or greater are grouped in the 32 category.

Figure 1 Distribution of HAI titres



360 (64.3%) of the Recruits had titres of 16 or more indicating some degree of immunity to Rubella.

While numerous studies have been carried out elsewhere to determine the Rubella immunity status of their populations, there have been hardly any studies conducted among males, and even among females, the last study done in Singapore was in 1967 when Rawls et at (6) found that 16 of 21 (76%) Singapore women in the 17 to 22 year age range tested were sero-positive. Studies done on women of childbearing age by Lam (7) in 1971/72 in Kuala Lumpur and Tan et al (8) in 1976 found some 60% and 62% respectively to be sero-positive. Studies like those of Pollard et al (9) in America have however found no significant differences in the proportion of susceptible persons in male and female Recruits, and it is likely that this is so in Singapore. (Unpublished data from a survey of 497 Singapore females aged 18 to 20 years carried out by the authors at the same time as the present study showed that 47% were sero-positive).

Side Effects of Vaccination

All the 200 Recruits found to have HAI titres of 8 or less were vaccinated as described earlier using the RA 27/3 attenuated live virus vaccine. The frequency and proportion of side-effects are shown in Table 2. The commonest side effect appears to be a rash which appeared in 12% of those Recruits vaccinated. In most cases, the rash appeared on the exposed parts of the body and persisted for up to 2 days. Since the Recruits were actively undergoing field training at the time, it is possible that in some instances the rash was due to grass allergy or mild dermatographism rather than to the vaccine. The fact that it was commonly found on the exposed parts of the body tends to reinforce this. Similar rashes were also found in a few Recruits who were not vaccinated. None of the side effects were severe or persistent and none occurred after the one-month review. Nonetheless the low incidence of arthralgia is significant especially when seen in the light of studies done elsewhere. For example, in a study of male Recruits undergoing basic military training in the United States, Park and Chouloupek (10) found that out of 873 Recruits who received Rubella vaccination, 12.5% had joint reactions. The high percentage was found despite the fact that the authors had taken care to distinguish the characteristic transient arthritis from the ordinary muscular aches and pains associated with vigorous training.

TABLE 2
SIDE EFFECTS OF RUBELLA VACCINATION

Side Effect	Proportion of Subjects (%)
Rash	12.0
Fever	6.0
Coryza/Sorethroat	1.0
Lymphadenopathy	3.5
Headaches	1.0
Arthralgia	0.5
Any Reaction	15.0

Note: Total percentages add up to more than 15% as some subjects had more than one side effect.

Efficacy of Vaccination

The HAI antibody titres of the vaccinees three months and one year after vaccination are shown at Table 3.

At three months, of the 200 Recruits who were vaccinated, one showed no serological response (<8) and another had a weakly positive titre of 8 at three months. The remainder showed sero-conversion with titres of 16 or more. The Geometric Mean Titre (GMT) was 46.1. As far as sero-conversion is concerned, the practically 100% sero-conversion is similar to those found in other studies. The GMT however appears to be much lower than those reported in other studies using the RA 27/3 vaccine. Moffat et al (11) reported a GMT of 72.6 six weeks post-vaccination in a study amongst sero-negative young women in Orkney, UK, Menser et al (12), in Australia, found a GMT of 76 among 70 subjects vaccinated and, in the United States, Grillner (13) found a GMT of 52. Zealley et al (14) in a study of 1063 sero-negative British schoolgirls aged 16 to 18 years reported a GMT of 225 two months after vaccination.

Several factors have been postulated to account for such observed differences, among them: ethnic differences, socio-economic status and cultural beliefs and practices, but these have not been confirmed by studies. In practice, the two main reasons are probably:

TABLE 3
PERCENTAGE DISTRIBUTION OF RUBELLA HAI TITRES AT 3 MONTHS AND 1 YEAR AFTER VACCINATION OF SERO-NEGATIVE PERSONNEL (N = 200)

HAI Titre	3 months	1 year
8	0.5	0.5
8	0.5	0.5
16	4.5	3.5
32	31.0	24.0
64	51.0	42.5
128	11.0	23.0
256	1.5	6.0
Geometric Mean Titre	46.1	61.1

a. loss of potency of vaccine — Rubella vaccines are labile products and very sensitive to the effects of heat and light and unless meticulous attention is paid to details of storage, particularly after reconstitution, potency can be rapidly lost (15). This is especially likely in the tropics.
b. differences in standardisation techniques use for HAI estimation — this is particularly so because of different materials used for the removal of non-specifii inhibitors in serum and the inherent variability of the HAI technique which is such that in any given situation, at least a two-fold variation can be expected if tests are conducted in different laboratories.

At one year, all the Recruits had either maintained or increased their antibody titres. None showed a drop in titre. The GMTs at three months and one year after vaccination are compared at Table 3. A substantial rise of GMT from 46.1 to 61.1 was seen. Nine of the Recruits had four-fold or greater increases in HAI titre, probably due to re-infections.

These findings are comparable to those found in other studies. Grillner (13) found that in the majority of RA 27/3 vaccinees titres after two years were within one titration step of the titres at 8 weeks after vaccination. In the study by Zealley (14), 93% of vaccinees had, after one year, antibody titres the same as or within a two-fold variation of the titres obtained at two months after vaccination.

Both the Recruits who failed to sero-convert, i.e. had HAI titres of 8 or less at 3 months did not show any increase in HAI titres at one year. This represents a 1% primary vaccine failure. There were no secondary vaccine failures. This is consistent with the findings of other studies where it has also been observed that persons who mount a feeble initial antibody response to immunisation are also most likely maintain low or

undetectable antibody titres (15). The implications of such feeble antibody responses after vaccination are not clear but there is evidence of some protection despite serological failure. Though re-infection occurs in individuals with both natural and vaccine induced immunity, viraemia has not been documented. Some individuals with low or absent post-immunisation antibody titres seem to have a degree of residual rubella immunity that prevents viraemia but their serological responses do not exactly fit a primary or anamnestic pattern (16).

RE-INFECTION AFTER VACCINATION

Two of the vaccinees gave a history of having "rubella" in the year following vaccination. Four months after vaccination one of them developed a fever with rash and cervical lymphadenopathy. The fever persisted for three days whilst the rash was present only on the first day of illness. The HAI titre was 64 at three months and also at one year after vaccination. The other subject had a fever and rash lasting two days at five months after vaccination. His HAI titre was 64 at three months and 32 at one year after vaccination. Thus it was unlikely that these two recruits were re-infected with Rubella.

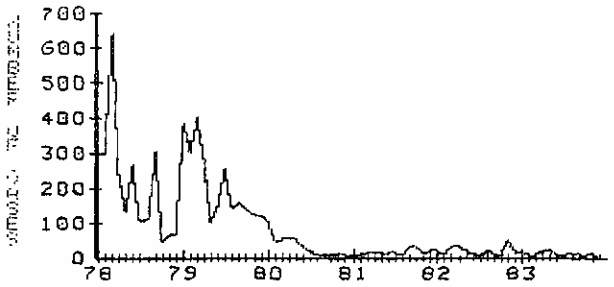
Nine of the vaccinees had four-fold or greater rises in titre between three months and one year after vaccination, indicative of re-infection with Rubella. None of them admitted to having been aware of being re-infected, but four recalled having been in close contact with clinical cases of Rubella. These findings are again consistent with those of other studies. Krugman (17), in summarising the status of Rubella vaccination in the United States, stated that Rubella re-infection is typically an asymptomatic inapparent infection characterised by (a) no viraemia, (b) either no or minimal transient virus shedding at the pharynx and (c) a prompt four-fold or greater rise in Rubella HAI titre. However he concedes that full blown clinical cases of Rubella re-infection have been known to occur.

CONCLUSION

The survey shows that among male Singapore adolescents, some 35% are susceptible to Rubella infection. It has been shown that vaccination of such susceptibles with RA 27/3 Rubella vaccine is a safe and effective procedure for the prevention of clinical Rubella. Side effects occur in only a small percentage of vaccinees and even then are minimal and transitory. Effectiveness is shown by the 99% sero-conversion when susceptible sero-negative subjects were vaccinated. No cases of clinical Rubella occurred amongst the vaccinees during the one year follow up period.

Routine vaccination of Recruits against Rubella immediately on enlistment was accordingly progressively instituted from mid 1980. This was followed by a prompt and significant fall in the incidence of Rubella cases, as reflected in statistics of monthly health returns. The low incidence has persisted up to the end of 1983 (Figure 2).

Figure 2 Monthly Rubella Incidence.



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