

Trials of intranasally administered rubella vaccine

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SUMMARY

No evidence of vaccine virus transmission was found in two studies where Wistar RA 27/3 rubella vaccine was administered intranasally. Vaccine was immunogenic in all of 23 vaccinated children in one study, while in the other only 5 of the 11 vaccinees developed antibody. The reduced seroconversion rate in the latter study appears to have been caused by one or a combination of factors, including the vaccination technique, the presence of infective nasal conditions in vaccinees and the titre of vaccine used.

INTRODUCTION

The intranasal method of administering a vaccine is as convenient and at least as acceptable to recipients as the subcutaneous injection method. Furthermore, intranasal vaccination may produce local immunity at the portal of entry of natural infection, as well as stimulating circulating antibodies, as suggested by Smith (1969). However, in theory, the propensity of a vaccine effective intranasally to spread to susceptible contacts might be greater, and it is conceivable that an intranasally administered vaccine could be less effective if there was a pre-existing local bacterial infection or an allergic condition. The Wistar RA 27/3 attenuated rubella vaccine has now been licensed for subcutaneous administration in the United Kingdom and Republic of Ireland, although not as of now in the United States. It is, however, the only vaccine which is immunogenic when administered intranasally. Because of the theoretical risk of administering extraneous agents with vaccines the intranasal route may be a safer method of using the vaccine. Although preliminary studies by Ingalls, Plotkin, Philbrook & Thompson (1970) suggest that transmission of virus to susceptible contacts following intranasal vaccination is unlikely to constitute a problem, there is probably insufficient published data to justify recommending intranasal inoculation in the general community.

This paper reports on clinical experiences with Wistar RA 27/3 strain rubella vaccine in the first extended trials of intranasally administered vaccine in Ireland and Britain. Two studies were carried out. The first was in a group of children residing for social reasons in an orphanage in the suburbs of Dublin. The second was conducted in a manner similar to that of an earlier investigation of subcutaneously administered Wistar RA 27/3 rubella vaccine (Hillary *et al.* 1969). This second intranasal study took place in a semi-rural area covering 200 square

miles (510 km.²) in the Irish midlands during the 1970 school summer holidays. The area was selected because a previous survey for rubella antibody showed a relatively high proportion of seronegatives in school-children (Hillary, 1971). In all studies, stringent precautions were taken to avoid any possible infection of a pregnant woman from a vaccinated child. Contacts were observed for both clinical and serological evidence of vaccine virus spread.

MATERIALS AND METHODS

Study populations

Study 1

Sixty-nine children aged 2–18 years resident in the orphanage were bled and rubella haemagglutination inhibiting (HAI) antibody titrations were carried out. Seventeen children were found to be rubella seronegative with HAI antibody titres of $< 1/10$. Eleven of these and one seropositive child were vaccinated. The remaining 6 seronegative children in frequent contact with the vaccinated children were retained as indicators of vaccine virus transmission. All children involved in this study showed clinical evidence of upper respiratory infection at the time of vaccination. Nose and throat swabs were taken from vaccinees and contacts on the 8th, 10th and 12th days after vaccination. Vaccinated children were examined clinically on alternate days up to the 28th day after vaccination. Contacts were seen twice during the 14th- to 21st-day period. Blood samples were collected from both vaccinees and contacts 9 weeks after vaccination.

Study 2

Sixteen mothers of large families in a semi-rural area in the Irish midlands gave permission for their children to take part in this study after an explanation of its purposes and procedure. Of 72 children aged between 2 and 15 years, 53 were seronegative (HAI titre $< 1/10$). Of these, 23 females were vaccinated. The remaining 30 (11 females and 19 males) were retained to determine whether virus transmission occurred. Each vaccinated child had at least one non-immune sibling living in the same house (Table 1). There was no clinical evidence of upper respiratory tract infection in any of the participants in this study. Vaccinees only were clinically examined on the 8th, 10th and 12th days after vaccination, while contacts and vaccinees were examined on the 24th and 26th days. Blood samples were collected from both vaccinees and contacts 8 weeks after vaccination.

Serology

In the first study, rubella HAI antibody titrations were carried out using the technique described by Stewart *et al.* (1967), pigeon red cells being substituted for chicken cells as the indicator material on grounds of convenience (Peetermans & Huygelen, 1967). In the second study manganous chloride and heparin were substituted for kaolin for the removal of non-specific inhibitors (Mann, Rossen, Lehrich & Kasel, 1967; Plotkin, Bechtel & Sedwick, 1968), but otherwise the technique was unchanged.

Table 1. *Age and immune status of vaccinees and siblings*

Family	Age in Years														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
A	.	.	0	.	.	0	-	+	.	+	+
B	0	.	.	-	0	.	.	-	-	.	.
C	0	.	-	.	+	.	+	.	+	.	+
D	0	-
E	-	-	.	.	0
F	-	.	.	.	0	.	-
G	0	0	-	.	-
H	.	.	-	0
I	.	.	.	0	.	.	.	-	.	+	.	+	.	+	.
J	0	.	-	.	.	.	0	+	+	-	.
K	.	.	.	-	-	.	.	.	-	+	.	.	0	.	.
L	-	.	0	+
M	.	-	0	.	-	.	.	-	0	-
N	0	-	.	.	.
O	.	-	-	.	.	0	0	.	.	.	+	+	.	+	.
P	.	.	-	.	-	.	-	.	+	0	+

0, Non-immune vaccinees (total 23); -, negative contacts (total 30); +, positive contacts (total 19).

Vaccine

In study 1, 27th passage level Wistar RA 27/3 titre of $10^{2.94}$ TCID₅₀/dose was used.

In study 2, 28th passage level Wistar RA 27/3 titre of $10^{4.1}$ TCID₅₀/dose was used.

In both studies freeze-dried vaccine was reconstituted in 0.5 ml. of diluent. For vaccination in the first study children were seated in low chairs with their heads hyperextended and 0.25 ml. reconstituted vaccine was administered as nose drops in each nostril. In the second study children lay flat on couches with their unsupported heads hyperextended. This position was maintained for at least 1 min. after the administration of vaccine.

RESULTS

Study 1

Only 5 of the 11 susceptible vaccinees developed antibody following administration of vaccine and only in 4 of these was a clear fourfold or greater increase in titre seen. Nine-week post-vaccination titres of these subjects were 1/20, 1/80 (2), 1/60 (2). None of the 6 contacts developed HAI antibody.

Nasal and throat swabs cultured bacteriologically showed *Staphylococcus aureus*, *Staphylococcus albus*, *Streptococcus viridans*, pneumococci, diptheroids and commensal neisserias. Little difference was evident in the organisms cultured from those responding and those not responding to vaccine administration. Reactions seen following the administration of vaccine are recorded in Table 2.

Study 2

All vaccinated children showed a four-fold or greater rise in antibody titre (Table 3). None of the sibling contacts developed antibody.

Reactions seen in vaccinated subjects were few and included enlarged cervical lymph nodes, rash, tonsillitis and upper respiratory infection with cough. These reactions are summarized in Table 4. Enlarged occipital lymph nodes were also seen in control subjects, but were attributed to *Pediculus capitis* infestation, since no change in serological status was evident in any contact child.

Table 2. *Reactions seen following administration of vaccine - study 1*

Nature of reaction	No. of children	Mean day of onset	Duration (days)
Palpable post-auricular glands	2	9	3½
Cough	1	9	2

Table 3. *Titres 9 weeks after vaccination - study 2*

No. of children	Rubella HAI antibody titrations (reciprocals)							
	Before vaccination	After vaccination						
	< 10	< 10	= 10	20	40	80	160	320
23	23	0	0	0	2	6	11	4

Post-vaccination modal titre: 160; median titre: 160; G.M.T.: 133.6.

Table 4. *Reactions seen following administration of vaccine - study 2*

Nature of reaction	No. of children		Mean day of onset		Duration (days)	
	Vaccinees	Controls	Vaccinees	Controls	Vaccinees	Controls
Lymphadenopathy	16	4	10	0	7	14
Rash	2	0	10	0	1	0
Tonsillitis	2	0	12	0	2	0
Pyrexia > 100° F.	1	0	10	0	2	0
Cough with upper respiratory infection	2	0	12	0	2	0

DISCUSSION

In neither of these studies was there evidence of spread of vaccine virus from vaccinees to susceptible contacts. The conditions in favour of transmission of infection are maximal between children in large-family groups with close and frequent personal contact, particularly where there is a high incidence of rubella susceptibility. Children living in orphanages are less sensitive indicators of vaccine virus spread, since there is less direct contact between the vaccinee and susceptible unvaccinated children. Vaccine at a titre per dose of 10,000 TCID₅₀ was immunogenic in all vaccinated children. The low seroconversion rate seen in the children in the orphanage study, where only 5 of 11 developed antibody, may have been caused by one or a combination of several factors - the vaccination

technique, the presence of infective nasal conditions at the time of vaccination and the lower titre of vaccine used.

Maximum contact between nasal and nasopharyngeal mucosa and vaccine is more likely to be obtained when subjects lie flat with their heads fully hyperextended and where this position is maintained for a brief period following intranasal administration of vaccine. When children are seated, although their heads are hyperextended, vaccine tends to flow over the nasal surfaces of hard and soft palates and be swallowed, allowing a relatively shorter time in contact with the nasal mucosa.

Vaccine at a titre of 500 TCID₅₀ has been shown to be fully immunogenic when given intranasally (Plotkin, Farquhar, Katz & Buser, 1969). Thus the titre of vaccine used in the orphanage study may be significant only in the context of the vaccination technique used and the condition of the noses. The presence of nasal virus or bacterial infection may directly interfere with the ability of the vaccine to infect susceptible cases and in addition nasal discharge or nasal obstruction may physically limit contact between vaccine and nasal mucosa. Further work is needed to clarify the relative importance of these factors and also to determine whether vaccination by the intranasal route has advantages in addition to those of acceptability and convenience. The presence of local immunity is acknowledged to be of considerable importance in protection against other virus infections (Tyrrell, 1969).

If intranasal administration of Wistar RA 27/3 produces local nasal IgA antibody this may limit the re-infection of vaccinated subjects exposed to natural infection (Horstmann *et al.* 1970; Chang, Desrosiers & Weinstein, 1970). Thus investigations are required to determine the extent to which local immunity is produced by rubella vaccines and the degree to which the presence of nasal antibody protects against natural or artificial challenge.

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