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Trials with a live attenuated rubella virus vaccine, Cendehill strain

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SUMMARY

This report summarizes closed, family, and open studies conducted sequentially over a 10 month period with the Cendehill rubella virus vaccine in more than 16,000 children and adolescents. This strain of rubella was attenuated by serial propagation on primary rabbit kidney cell cultures. Inoculation of the Cendehill vaccine produced seroconversion in 97% of the 3589 susceptible (seronegative) vaccinated persons. There was no spread of the virus to susceptible controls living in close contact with those vaccinated. The vaccine was well tolerated. No arthritis or arthralgia occurred in 860 female subjects 13–18 years of age who were included in the study. The Cendehill vaccine would appear to meet the requirements of an acceptable vaccine.

INTRODUCTION

The Cendehill strain of rubella virus was isolated in May 1963, at the University of Louvain, Belgium, from a patient with clinical signs of rubella. It was attenuated by serial propagation in primary rabbit kidney cell cultures derived from a select colony of animals bred and reared in isolation under pathogen-free conditions. Details on the Cendehill strain and its biological characteristics, the resultant vaccine, and safety test methods have been dealt with by others at two international symposia on rubella vaccines (Huygelen *et al.* 1969; Prinzie, Huygelen, Gold & Farquhar, 1969).

The studies in Jamaica began in March 1968. Before this, vaccine trials had been conducted in Switzerland (Martin duPan, Peetermans, Huygelen & Prinzie, 1967, 1968; Majer, 1967). Our initial studies were conducted in a closed setting in order to ascertain that the virus did not spread to susceptible contacts in the local environment. Upon fulfilling this prerequisite and confirming the findings of the Swiss studies that the virus was not being disseminated, the investigation was extended first to a family setting, and then to large scale studies in children in the community. This paper reports pertinent findings from these studies.

METHOD

Closed study

This study was conducted with 54 rubella susceptible (seronegative) children residing in two institutions, the Maxfield Home and the Alpha School. The children were from 3 to 17 years old. They ate, played, attended classes, and slept together in the respective dormitories for boys or girls.

Twenty-eight were vaccinated with the Cendehill rubella vaccine, receiving a subcutaneous dose of 0·5 ml. (5000 TCID 50); the rest served as unvaccinated controls. At the Maxfield Home quarters were very crowded and the beds were very close to each other, a condition which should have allowed for efficient transmission of virus, if transmission were to occur. Specimens were taken with swabs from the nose and throat of the vaccinated children daily from days 9 to 15, and from the controls on days 2, 20, 29 and 32, for virus isolation studies; the method of Plotkin *et al.* (1968) was used. Blood specimens were taken before vaccination and, subsequently, on day 45 from the vaccinated children and on day 65 from the controls, to determine rubella antibody titres. A modification of the haemagglutination inhibition (HI) test, described by Stewart *et al.* (1967), was used. All of the children, vaccinated and controls, were interviewed and examined daily throughout the study for clinical symptoms and signs by a physician and nurse.

Family study

We selected only families which had at least two seronegative children, and had no rubella seronegative women of child-bearing age in the immediate families or in other families with whom they had frequent contact. We screened 103 families and found 67 which qualified under these restrictions. These families had 115 seronegative children, and we vaccinated 52 of them, and reserved the other 63 as controls. Virus isolation tests were carried out on all those vaccinated, from throat and nose specimens collected 11–12 days after the vaccination day. Physicians and nurses from our research team visited the homes frequently during the study, and examined the vaccinated children, controls, and other members of the family. Repeat blood samples for the determination of HI titres were taken from all of the vaccinated and control children 2 months after vaccination.

Open study

In this study, we drew blood samples for determination of HI titres and then vaccinated the subjects on the same day. Our medical teams visited a total of 19 primary and secondary schools in and around Kingston and vaccinated 14,610 children with the Cendehill vaccine. One thousand five hundred and sixty-one children constituted a control group and received an injection of sterile saline solution to provide a baseline for the monitoring of lymphadenopathy, fever, or other reactions which may have been provoked by agents other than rubella virus.

Registered nurses visited all the schools twice a week for 3 weeks to check on absenteeism due to illness. These cases were more closely followed up at home and school. All seronegative vaccinated children or controls who were absent because

of illness were visited in their homes by one of our physicians. Test results subsequently showed that 5207 of those vaccinated were seronegative; 3847 (almost 74%) were available for retesting and follow-up 2 months after vaccination. Serological data by age groups for more than 11,000 of these children are shown in Table 1.

RESULTS

Serological tests

Seroconversion occurred in 100% (closed), 98% (family) and 97% (open) of the seronegative vaccinated children; there was no spread of the virus to the seronegative controls. Details of the postvaccination serological results are shown in Tables 2–4.

Table 1. *Distribution of rubella antibodies in* 11,609 *Jamaican children and adults*

Age years	Seropositive		Seronegative	
	Number	%	Number	%
< 5	3	60	2	40
5–9	3414	62	2101	38
10–14	4263	72	1694	28
15–20	96	73	36	27
Totals	7776		3833	

Table 2. *Serological results of the closed study using the Cendehill vaccine. Seronegative persons only*

Group	Seroconversion	GMT*	Haemagglutination inhibition after vaccination	
			No. of children	Titres
28 Vaccinated	100%	1/77	2	16
			7	32
			7	64
			8	128
			4	256
26 Controls	0	0	26	< 8

* Geometric mean titre.

Virus isolation

As Table 5 shows, no rubella virus was isolated at any time from the specimens taken from the nose and throat of the 26 seronegative controls in the closed study. Rubella virus was isolated once from five of the seronegative vaccinated children in the closed study, 11–13 days after vaccination, and from one in the family study, 12 days after vaccination.

Clinical symptoms

Vaccine-related side effects and other clinical symptoms have not been problems in our studies with the Cendehill vaccine. In the closed study, an almost equal number of vaccinated persons and controls had lymphadenopathy before and during the study. Lymphadenopathy, however, is common in Jamaican children and, therefore, was not considered to be related to vaccination. During this study, sporadic outbreaks of measles, mumps and chicken pox occurred in

Table 3. *Serological results of the family study using the Cendehill vaccine. Seronegative persons only*

Group	Seroconversion	GMT	Haemagglutination inhibition after vaccination	
			No. of children	Titres
52 Vaccinated	98%	1/56	1	< 8
			1	8
			6	16
			14	32
			19	64
			9	128
			1	256
			1	1024
63 Controls	0		63	<8

Table 4. *Serological results of the open study using the Cendehill vaccine*

Group	No. of subjects	No. of seronegatives	Number tested after vaccination	Seroconversion		GMT
				No.	%	
Vaccine	14,610	4711	3509	3410	97·1	1/51
Placebo	1,561	496	338	0	—	—

Table 5. *Results of virus isolation tests*

	Specimens examined	Positive specimens*	
		Vaccinees	Controls
Closed study	274	5	0
Family study	76	1	Not taken

* Taken 11–13 days after vaccination.

both vaccinated children and controls, but did not interfere with the stimulation of rubella antibodies in those vaccinated. Nor did the intercurrent infections aggravate the benign clinical response to the vaccine. In the family study, one vaccinated child developed a rubella-like reaction characterized by rash and temperature elevation.

Dengue fever was endemic during the open study, and approximately 175 subjects reported symptoms such as: rash, which occurred primarily on the face and trunk, but in a few subjects, on the limbs; temperature elevations, which ranged from 101·8–103·2° F. in eight of the subjects; and regional lymphadenopathy, which was postcervical in only one of the subjects. The incidence of these effects was *ca.* 1% in the seronegative and seropositive vaccinated children, and was *ca.* 0·4% in the seronegative and seropositive placebo controls. This difference is not statistically significant. In the entire group of almost 5000 seronegative persons vaccinated in this study, only one was considered to have had a rubella-like reaction; namely, a rash on the head and trunk which developed on the 17th post-vaccination day, persisted for 6 days, and was accompanied by a temperature elevation. There was no evidence of arthralgia or arthritis in the 860 vaccinated females, aged 13–18 years (275 seronegatives, 585 seropositives) who were included in these studies.

DISCUSSION

Our findings in large scale clinical trials bear out the earlier reported preliminary findings that the Cendehill rubella virus vaccine evokes a good immunogenic response and does not spread virus to susceptible persons in close contact with those vaccinated. Preliminary studies carried out 24 months after vaccination suggest that the Cendehill vaccine provides long-lasting immunity (Prinzie *et al.* 1969). Recently, we retested 14 of the vaccinated children from our first, closed study and found that relatively high antibody titres had persisted for 12 months. With two possible exceptions, there were no side effects or reactions attributable to the vaccine. Rash, lymphadenopathy, and fever have occurred with about equal frequencies in rubella susceptible and rubella immune vaccinated children and in children who were not vaccinated. Although our series disclosed no problems from arthralgia or arthritis, joint pains have been reported by others in adult women receiving rubella vaccines, but these manifestations have occurred less frequently and have been milder with the Cendehill than with the HPV-77 strain (Dudgeon, Marshall, Peckham & Hawkins, 1969; Cooper *et al.* 1969; Horstmann *et al.* 1969). The degree of attenuation of the Cendehill vaccine may account for its causing fewer joint manifestations (Gold, Prinzie & McKee, 1969; Farquhar & Corretjer, 1969).

On the basis of our experience, along with that of others, the Cendehill rubella virus vaccine appears to be a highly effective and safe vaccine. Based on our findings there is no contraindication to administering the vaccine during times when mumps, chicken pox, and measles are prevalent.

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