EVALUATION OF COMBINED MEASLES-SMALLPOX VACCINE IN CHILE[1]

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An account is given of five experiments carried out on Chilean children with a view to evaluating the combined effect of measles vaccine and smallpox vaccine by observing the clinical and skin reactions and serologic response to the combination as compared with the same vaccines administered separately.

Introduction

Virological and immunological research on vaccines against measles has produced new and more attenuated live vaccines which cause fewer clinical reactions while maintaining excellent immunogenic power. Simultaneously, significant advances have been made in combining these vaccines with the smallpox vaccine. These achievements are of considerable practical interest for the Chilean health services, which have to conduct vaccination programs against both diseases to cope with the country's epidemiological situation.

A study was made of the clinical reactions produced by the combination Attenuvax-smallpox vaccine; the results were compared with the reactions produced by each vaccine administered separately, and note was taken of the frequency of the different types of skin reaction to the smallpox vaccine component in susceptible children and in children previously vaccinated with smallpox vaccine and showing the scar. The frequency and type of skin reactions was also noted when revaccination was carried out with smallpox vaccine by the multipuncture method in children who had been given the combined vaccine two months before. At the same time the serologic response produced by the combined vaccine and by each of the vaccines administered separately was studied by observing the hemagglutination inhibition reaction.

Material Used

The experiment was based on the combined freeze-dried and preblended Attenuvax-smallpox vaccine (Merck Laboratories, batch 285) and the freeze-dried smallpox "Dryvax" vaccine (Wyeth Laboratories, batch 286-106). The smallpox vaccine administered intradermally by jet injector is less potent than that used in the multipuncture technique; the vaccine virus content of the combined vaccine is $10^{5.6}$ PFU.

The children vaccinated were between 1 and 5 years of age (average 1.6 years) and they were kept under supervision in the maternal and child consultation center of the National Health Service (SNS), Santiago.

Procedure

The combined vaccine was administered by means of a jet injector fitted with a nozzle leaving a space of 4 mm between the skin and the orifice of the injector. It injects 0.5 ml at a time, 0.1 ml being deposited intradermally to form a blister, and 0.4 ml penetrating more deeply. The measles vaccine was administered subcutaneously only. The smallpox vaccine was inoculated exclusively by the multipuncture technique. Both were diluted in distilled water immediately before use.

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All the children vaccinated were observed daily for 15 days in their homes by nurses from the University who checked the course of the smallpox vaccine "take" and the general and local reactions to the measles vaccine. They also took the rectal temperature each day. The study was divided into five experiments in accordance with the different objectives laid down (see Annex I).

For the serologic study, blood samples were taken before and 30 days after vaccination. The principles on which the smallpox vaccine take was classified were as follows:

1) Primary vaccination reaction: growth of the vaccinal lesion for eight to 14 days with extensive erythema 2.5 to 5 cm in diameter forming blisters and pustules for 10 to 12 days and developing a scab.

2) Vaccinoid reaction: this reaches its peak 5-6 days following vaccination and is accompanied by blistering. Erythema is less extensive than in the case of the primary vaccination take, and it subsides rapidly from the sixth day onward.

3) Immunity reaction: occurs between the first and third day following vaccination in the form of a small reddened or indurated area which appears at the site of the vaccination and disappears rapidly.

Findings

Experiment A

The combined vaccine was administered by jet injector to 161 children with negative histories of measles, measles vaccine, and smallpox vaccine. Of these, 44 were revaccinated two months later with smallpox vaccine alone, by the multipuncture method.

The clinical reactions show that the majority of the children vaccinated with Attenuvax-smallpox vaccine had no fever; 47.8 per cent showed a feverish rise in temperature, only 1.2 per cent of the cases exceeding 38°C. When the Attenuvax vaccine was used alone, similar results were obtained (Table 1).

Analysis of the clinical symptoms reveals no appreciable difference between the effects on the children who received the combined vaccine and those inoculated with the Attenuvax vaccine only, though the one case of pneumonia attributable to a vaccine reaction occurred in the group of children vaccinated with the combined vaccine (Table 2).

The serologic results showed a conversion rate for the vaccine virus of 97.1 per cent in the 139 initially susceptible children, and for the measles virus 97.2 per cent in the 141 such children (Table 3).

A positive skin reaction was noted in 96.9 per cent (156 children); there were 154 primary vaccination takes; and two children showed immunity reaction (Table 4).

The hemagglutination inhibition titers ranged between 1/32 and 1/64 in most of the children for the vaccine virus and between 1/64 and 1/128 for measles, the geometric mean for those vaccinated being 33.0 and 53.6, respectively. Two months later, 44 of the children were revaccinated with smallpox vaccine by

TABLE 1—Maximum rectal temperatures observed in 161 children vaccinated with Attenuvax-smallpox vaccine and 61 vaccinated with Attenuvax alone, Santiago, Chile, 1969.

Vaccine	No. of children	Maximum temperature (C°)	5-15 days after vaccination	
			No. of children	%
Attenuvax-smallpox	161	Under 37°	84	52.2
		37-37.9°	75	46.6
		38-38.9°	2	1.2
Attenuvax	61	Under 37°	22	36.1
		37-37.9°	35	57.4
		38-38.9°	4	6.5

TABLE 2–Clinical reactions observed in 161 children given the combined vaccine and 61 given Attenuvax, Santiago, Chile, 1969.

Vaccine	Respiratory symptoms		Pneumonia		Conjunctivitis		Gastrointestinal symptoms		Eruption		Total
	No.	%	No.	%	No.	%	No.	%	No.	%	
Attenuvax-smallpox	33	20.5	1	0.62	1	0.6	4	2.5	10	6.2	161
Attenuvax	11	18.0	–	–	1	1.6	–	–	1	1.6	61

multipuncture. The skin reactions were positive in 88.6 per cent (Table 5). The two primary vaccination reactions involved children in whom the combined vaccine had failed to take two months previously.

Experiment B

Subcutaneous inoculation with Attenuvax, by syringe, was performed on 62 children with negative histories of measles and measles vaccination. The clinical and febrile reactions are summarized in Tables 1 and 2, where they are compared with the reactions caused by the combined vaccine. The serologic response of the 51 initially seronegative children was 100 per cent (Table 3). The titer most frequently observed–in 68 per cent of the cases–was 1/64, and the geometric mean of the antibody titer was 69.4.

Experiment C

Sixty children with no history of smallpox vaccination were inoculated by multipuncture with dried smallpox vaccine. The serologic response of the 54 initially susceptible children was positive in 92.6 per cent of the cases (Table 3). All those vaccinated showed skin reactions; 58 per cent had primary vaccination reactions, and two showed vaccinoid reactions. In other words the takes were 100 per cent (Table 4). The smallpox vaccination was repeated on 41 of the children two months later, again by multipuncture, the following skin reactions being observed: in 39 there was immunity reaction, and in two there was a primary vaccination reaction. These two had a primary vaccination reaction and serum conversion when originally vaccinated (Table 5).

Experiment D

Fifty-nine children with smallpox vaccination scars were inoculated with the combined vaccine, and the fever and skin reactions were observed. Two out of the 59 had primary vaccination reactions, 36 had vaccinoid reactions, and 21 immunity reactions. In other words, 100 per cent showed positive reactions. Only 6.8 per cent had a temperature exceeding 37.1°C and the fever never rose as high as 38.1°C.

In 20 of these children with initial positive

TABLE 3–Serum conversion rates in susceptible children 30 days after administration of combined vaccine, Attenuvax and smallpox vaccine, Santiago, Chile, 1969.

Type of vaccine		No. of children	Conversion	
			No.	%
Combined vaccine	a) Measles	141	137	97.2
	b) Vaccine virus	139	135	97.1
Attenuvax		51	51	100.0
Smallpox		54	50	92.6

TABLE 4–Skin reaction produced by the combined vaccine and by smallpox vaccine alone, Santiago, Chile, 1969.

Vaccine	No. of children	Primary vaccination reaction	Vaccinoid reaction	Immunity reaction	No reaction	Positive reactions %
Attenuvax-smallpox	161	154	0	2	5	96.9
Smallpox	60	58	2	0	0	100.0

serologic reactions to both the smallpox and the measles vaccine, the geometric mean of the hemagglutination inhibition reaction titers was calculated before and after administration of the combined vaccine with a view to determining the serologic booster response. The results were as follows:

	Geometric mean	
	Before vaccination	*After vaccination*
Vaccine virus	11.7	21.1
Measles virus	50.2	55.7

Clearly, all have the booster dose effect it was hoped they would have.

Experiment E

Thirty children with no history of smallpox vaccination were inoculated with smallpox vaccine by the multipuncture technique, and the skin reaction was compared with the reactions of those revaccinated against smallpox during the same period. All the 30 children vaccinated (100 per cent) reacted positively: 28 showed primary vaccination reactions, and two showed vaccinoid reactions.

As already stated, of the 44 children in group A and the 41 in group C vaccinated by multipuncture two months after inoculation with the combined vaccine, a large proportion showed immunity skin reactions (88.6 per cent of the children in group A and 100 per cent of those in group C).

Summary

The article describes the results of a series of five experiments carried out, under the auspices of the National Health Service in Chile, on a group of children 1 to 5 years of age. The purpose was to compare the clinical reactions to a combination of an attenuated measles vaccine and a smallpox vaccine, both freeze-dried, with the reactions to each of the vaccines administered separately. The combined vaccine was jet injected, the measles vaccine was administered subcutaneously, and the smallpox vaccine by multipuncture.

The new preblended and combined Attenuvax-smallpox vaccine administered by jet injection produces general clinical reactions similar to or milder than those caused by each vaccine administered separately. Takes were recorded in 96.9 per cent of the children inoculated with the combined vaccine, which is excellent.

To judge from the rise in the serologic

TABLE 5–Skin reactions in 44 children revaccinated with smallpox vaccine two months after receiving the combined vaccine and in 41 children two months after receiving smallpox vaccine, Santiago, Chile, 1969.

	Effects of smallpox revaccination					
Initial vaccination	Primary vaccination reaction	Vaccinoid reaction	Immunity reaction	No take	Positive reactions %	No. of children
Attenuvax-smallpox	2	5	32	5	88.6	44
Smallpox	2	0	39	0	100.0	41

reaction titers for both viruses in the vaccines, there was no evidence of interference between the antigens. The conversion rate for each component closely resembled that obtained when the vaccines were administered separately, and the geometric mean of the hemagglutination inhibition titers was also very similar in either case.

Revaccination against smallpox of children inoculated two months earlier with the combined vaccine produced immunity or vaccinoid skin reactions consistent with the previous presence of antibodies; similar skin reactions were noted in children revaccinated with smallpox vaccine two months after primary vaccination with the same vaccine. The experiments indicated that the combined Attenuvax-smallpox vaccine can be administered by jet injection without risk, producing minimum clinical reactions and an excellent serologic response, while the administrative advantages are considerable. □

ANNEX I

Summary of the experiments carried out to evaluate the combination Attenuvax-smallpox vaccine, Santiago, Chile, 1969.

Experiment	No. of children	0 days	0-15 days	28 days	56 days	
A						
No history of measles or vaccination against measles or smallpox	161	Take blood sample 12 cc. Jet-inject 0.5 cc Attenuvax-smallpox vaccine (batch 285)	Observe local lesion and general reaction	Take blood sample 12 cc	Revaccinate 44 children with smallpox vaccine by multipuncture	Observe local reaction
B						
No history of measles or vaccination against measles	62	Take blood sample 12 cc. Administer 0.5 cc of Attenuvax (batch 283 A) by syringe	Observe general reaction	Take blood sample 12 cc		
C						
No history of vaccination against smallpox	60	Take blood sample 12 cc. Administer smallpox vaccine (Dryvax) by multipuncture	Observe local lesion	Take blood sample 12 cc	Revaccinate 41 children with smallpox vaccine by multipuncture	Observe local lesion
D						
Previously vaccinated against smallpox (showing scar)	59	Take blood sample 12 cc. Jet-inject 0.5 cc of Attenuvax-smallpox vaccine (batch 285)	Observe local lesion and general reaction	Take blood sample 12 cc		
E						
No history of smallpox vaccination	30				Inoculate 10 children with smallpox vaccine by multipuncture, to coincide with the revaccination in experiments A and C	Observe local lesion

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