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Combined live measles-mumps virus vaccine

ROBERT E. WEIBEL, VICTOR M. VILLAREJOS, GUILLERMO HERNÁNDEZ C., JOSEPH STOKES, JR.,* EUGENE B. BUYNAK, and MAURICE R. HILLEMAN

From the Department of Pediatrics, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania; Louisiana State University International Center for Medical Research and Training, San Jose, Costa Rica; and the Division of Virus and Cell Biology Research, Merck Institute for Therapeutic Research, West Point, Pennsylvania, U.S.A.

Weibel, R. E., Villarejos, V. M., Hernández C., G., Stokes, J., Jr., Buynak, E. B., and Hilleman, M. R. (1973). *Archives of Disease in Childhood*, **48**, 532. **Combined live measles-mumps virus vaccine.** Four lots of combined bivalent live Moraten measles-Jeryl Lynn mumps virus vaccine were administered to a total of 334 children 10 months to 6 years of age, who were initially without antibody against either virus. Overall, 99% of the children responded serologically to the measles virus and 96% to mumps. The geometric mean titres were of the same general height as those obtained when the individual vaccines were given alone, and there was no indication of immunological suppression. There was no increase in clinical reaction beyond the mild fever and other reactions that follow the administration of Moraten measles vaccine given alone. The combined measles-mumps vaccine provides a simple means for immunization against both these viruses with no apparent alteration in the immunological or clinical responses.

The need to simplify administration, reduce costs, and minimize the number of contacts of patient with physician has prompted the development of combined single dose formulations of vaccines. Reports from our laboratories have described the development and clinical evaluation of combined measles-mumps-rubella (M-M-R) (Stokes *et al.*, 1971), measles-rubella (M-R-Vax) (Villarejos *et al.*, 1971), and mumps-rubella (Biavax) (Weibel *et al.*, 1971) vaccines. All gave antibody responses equivalent to those obtained when the vaccines were given individually and there was no increase in clinical reaction. All are being used extensively in the U.S.A. and elsewhere. This report presents the findings in tests to evaluate clinically a new combined live measles-mumps vaccine called M-M-Vax.

Methods

Design of the clinical studies. Three clinical studies were carried out. The first was a *pilot study* of a laboratory-prepared lot of measles-mumps vaccine (lot 284) tested in 53 children who had no antibody initially either to measles or to mumps virus. Similar groups of children were given either monovalent measles (27 children) (Attenuvax) or mumps virus vaccine (42 children) (Mumpsvax) for control purpose. The children in the studies were 10 months to 7 years of age with a mean age of 2·8 years. Immunizations were carried out in the paediatric outpatient clinic of Lankenau Hospital, Philadelphia, and in public and church schools in the area. The children were selected for no previous history of vaccination or illness with respect to measles or mumps. Informed written parental consent was obtained. The vaccines were given during the period from 14 September 1967 to 28 March 1968. All the vaccines were administered subcutaneously. The dose for the monovalent vaccines was 0·5 ml, and 1·0 ml for the combined vaccine. All subjects were bled immediately before vaccination and again, 5 to 7 weeks later. The serum samples were stored frozen at −20 °C until tested for measles and mumps antibodies. Clinical observations were made by the mothers, nurses, and physicians. The parents of the children were given a report card for each child for recording temperatures once daily for 28 days, plus any other illness, and they were asked to notify one of us (R.E.W.) immediately when any illness occurred. Finally, the parents were queried by the physician (R.E.W.) and/or the clinic nurse at the time of the second bleeding and asked whether any problems had developed. *The second study* was a larger-scale field trial carried out in a similar way in 105 seronegative children in suburban Philadelphia from 19 January 1972 to 26 April 1972. Three lots of measles-mumps vaccine were used, i.e. numbers C–A514, C–A515, and C–A516. The children were 10 months to 5 years of age with a mean age of 1·4 years.

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*Deceased. Formerly Professor Emeritus of Pediatrics, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania.

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The *third study* was a large-scale field trial of the 3 lots of measles-mumps vaccine carried out among children whose families resided in the environs of Managua, Nicaragua. The studies were carried out from 14 to 24 February 1972, and the children were 10 months to 6 years of age with a mean age of 2·2 years. In these studies, clinical observations for follow-up purposes were made by physicians who saw the children on alternate days for 45 days after vaccination. Further, parents and guardians of the children were instructed to notify the medical staff of any significant illness that occurred during the 28-day period subsequent to vaccination, and they were queried at the time of the second bleeding. Parental co-operation was excellent.

Vaccine. The measles virus used in the combined vaccine was the Moraten line measles virus (Attenuvax) (Hilleman *et al.*, 1968b), and the mumps virus was the Jeryl Lynn strain (Mumpsvax) (Hilleman *et al.*, 1968a) attenuated by passage in embryonated hen's eggs and chick embryo cell culture. Lot 284 vaccine used in the pilot study was prepared in the Research Laboratories at the Merck Institute for Therapeutic Research. Lots C–A514, C–A515, and C–A516 were prepared in the Biological Production Laboratories of Merck Sharp & Dohme. The individual components of the combined vaccines contained a minimum of one thousand 50% tissue culture infectivity doses ($TCID_{50}$) of measles virus and 5000 $TCID_{50}$ of mumps virus. Experimental monovalent measles virus vaccine (Attenuvax) lot 283A and mumps vaccine (Mumpsvax) lot 253 were given to the controls.

Serological testing. The serum samples were assayed for titres of measles haemagglutination-inhibiting (HI) and mumps neutralizing (Neut) antibodies in our laboratories at the Merck Institute and in the Biologics Control Laboratories of Merck Sharp & Dohme according to procedures described earlier (Hilleman *et al.*, 1968b; Weibel *et al.*, 1967).

Results

Pilot study. Table I presents a summary of the seroconversion rates and the mean antibody responses in the children given combined or monovalent vaccine in the pilot study. It is seen that the seroconversion rates and the geometric mean titres to measles virus were essentially the same after combined or monovalent vaccine (98 *vs* 100% and 64 *vs* 54, respectively for measles; and 91 *vs* 93% and 6 *vs* 7 for mumps).

There were no remarkable clinical findings among the children. Table II shows the maximum temperature, according to time, after vaccination. Mumps virus vaccine caused no apparent reactions (Hilleman *et al.*, 1968a); reactions observed after the bivalent vaccine were due to the measles vaccine component. There was no more fever in the combined vaccine group than in the measles control group. The miscellaneous clinical complaints that were recorded are shown in Table III. Nothing of clinical importance was found. There was no evidence for potentiation of clinical reaction by use of combined vaccine.

Second and third trials with commercial lots of combined vaccine. Table IV shows the seroconversion rates and the geometric mean titres in children who received the various commercial lots of combined vaccine in Philadelphia or Nicaragua. There were no marked differences with regard to vaccine lot or location. The overall seroconversion rate for measles virus was 99·3% and the mean antibody titre was 80. The overall seroconversion rate for mumps virus was 96·8 and the mean titre was 1:10. The individual serum titre values are given in Table V for information purpose.

Clinical observations were made of the children in the same way as for the pilot study. Space limitations prevent inclusion of the detailed information. There was nothing remarkable clinically.

TABLE I

Summary of serological responses in double seronegative children given lot 284 combined measles-mumps vaccine and in single seronegative children given lot 283A measles vaccine or lot 253 mumps vaccine (pilot study)

Vaccine preparation	Antibody responses							
	Measles (HI)*				Mumps (Neut)*			
	Conversion		Titre		Conversion		Titre	
	Rate	%	Range	GM†	Rate	%	Range	GM†
Combined measles-mumps	52/53	98·1	<5–640	64	48/53	90·6	<1–64	6
Monovalent measles	27/27	100	20–160	54				
Monovalent mumps					39/42	92·9	<1–128	7

*HI, haemagglutination-inhibition; Neut, serum neutralization.
†GM, geometric mean.

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TABLE II

Occurrence of fever according to time after vaccination (pilot study)

Days after vaccination	Maximum temperature, oral (°C)								
	<37·2		37·2–38·3		38·3–39·4		39·4–40·5		Not taken
	No.	%	No.	%	No.	%	No.	%	No.
Combined measles-mumps vaccine									
1–4	30	56·6	20	37·7	3	5·7			
5–12	24	45·3	23	43·4	6	11·3			
13–18	37	69·8	14	26·4	1	1·9	1	1·9	
19–28	33	62·3	19	35·8	1	1·9			
Monovalent measles vaccine									
1–4	14	51·9	13	48·1					
5–12	13	48·1	10	37·0	4	14·8			
13–18	18	66·7	9	33·3					
19–28	18	66·7	7	25·9	2	7·4			
Monovalent mumps vaccine									
1–4	29	69·0	11	26·2	2	4·8			
5–12	24	57·1	17	40·5			1	2·4	
13–18	32	78·0	9	22·0					
19–28	34	81·0	8	19·0					

Discussion

The antibody responses to the combined measles-mumps vaccine in this study showed that there was satisfactory immunization against both measles and mumps viruses. There was no evident suppression in the seroconversion rate or in the height of antibody response compared with that when the vaccines were given alone. Such excellent antibody responses have already been obtained with combined measles-mumps-rubella (Stokes *et al.*, 1971), measles-rubella (Villarejos *et al.*, 1971), and mumps-rubella vaccines (Weibel *et al.*, 1971).

Jeryl Lynn mumps vaccine causes remarkably little, if any, clinical reaction in man. Moraten line measles vaccine may cause mild febrile reactions, rash, and generalized malaise in a portion of recipients of the preparation. There was no apparent alteration of the clinical reactivity by the

TABLE

Clinical complaints within 28 days

Complaint					Days after
	Measles-mumps vaccine (53 children)				
	1–4	5–12	13–18	19–28	1–4
Upper respiratory illness	7 (13·2)	6 (11·3)	3 (5·7)	6 (11·3)	1 (3·7)
Lower respiratory illness					
Measles rash		2 (3·8)			
Nonmorbilliform rash	1 (1·9)				
Irritability		2 (3·8)	1 (1·9)		2 (7·4)
Fever-temperature not recorded					
Anorexia					
Gastrointestinal illness	2 (3·8)	4 (7·5)		1 (1·9)	
Unrelated illness	1 (1·9)	1 (1·9)		3 (5·7)	
No complaints	42 (79·2)	38 (71·7)	49 (92·5)	43 (81·1)	24 (88·9)

Percentages in parentheses.

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TABLE IV

Summary of serological responses in double seronegative children given 3 lots of combined measles-mumps vaccine (Philadelphia and Nicaragua)

Vaccine lot no.	Antibody responses							
	Measles (HI)*				Mumps (Neut)*			
	Conversion		Titre		Conversion		Titre	
	Rate	%	Range	GM†	Rate	%	Range	GM†
Philadelphia								
C-A514	42/42	100	20–320	86	41/42	97·6	<2–128	10
C-A515	32/33	97·0	<5–320	56	29/33	87·9	<2–128	6
C-A516	29/30	96·7	<5–320	58	29/30	96·7	<2–32	7
Nicaragua								
C-A514	60/60	100	20–320	106	58/60	97·6	<1–64	11
C-A515	62/62	100	20–320	75	61/62	98·4	<1–64	11
C-A516	54/54	100	20–320	91	54/54	100	1–64	11
All groups								
All lots	279/281	99·3	<5–320	80	272/281	96·8	<1–128	10

*HI, haemagglutination-inhibition; Neut, serum neutralization.
†GM, geometric mean.

combined administration of the 2 vaccines in a single dose. The reactions noted were not unlike those expected from Moraten measles vaccine given alone as shown in the present and previous studies (Hilleman *et al.*, 1968b).

Measles, mumps, and rubella virus vaccines have seen widespread routine use in the U.S.A. for a number of years. The combined virus vaccines are now being widely applied in the U.S.A. after concurrence in their use by the Committee on Infectious Diseases of the American Academy of Pediatrics (1971) and by the Public Health Service Advisory Committee on Immunization Practices (1971). To date, approximately 1,308,000 doses of combined measles-mumps-rubella, 3,557,000 doses of measles-rubella, and 695,000 doses of mumps-rubella have been distributed. The combined measles-mumps-rubella vaccine was designed for

II

fter vaccination (pilot study)

accination

Measles vaccine (27 children)			Mumps vaccine (42 children)			
5–12	13–18	19–28	1–4	5–12	13–18	19–28
5 (18·5)	2 (7·4)	4 (14·8)	3 (7·1)	5 (11·9)	1 (2·4)	3 (7·1)
				1 (2·4)		
1 (3·7)						
				1 (2·4)		
			1 (2·4)			
					1 (2·4)	
1 (3·7)						
2 (7·4)					1 (2·4)	
1 (3·7)	1 (3·7)	1 (3·7)	1 (2·4)	1 (2·4)	1 (2·4)	
18 (66·7)	24 (88·9)	22 (81·5)	37 (88·1)	34 (81·0)	39 (92·9)	39 (92·9)

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TABLE V

Distribution of serum antibody titres after vaccination (Philadelphia and Nicaragua)

Measles (HI)*		Mumps (Neut)*	
Titre	No. children	Titre	No. children
		<1	2
<5	2	<2	7
5	1	1	4
10	4	2	27
20	18	4	59
40	62	8	68
80	97	16	48
160	67	32	28
≥320	30	64	33
		≥128	5
Geometric mean			
80		10	

*HI, haemagglutination-inhibition; Neut, serum neutralization.

routine immunization of unvaccinated children. Measles-rubella vaccine is prepared for those who would prefer to give mumps vaccine separately, and mumps-rubella vaccine is for those children who have already received measles vaccine. The new measles-mumps combination is intended for use by those who would prefer to defer immunization against rubella to a later age or for those who would want to give rubella vaccine separately from measles and mumps vaccines.

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Correspondence to Dr. M. R. Hilleman, Virus and Cell Biology Research, Merck Institute for Therapeutic Research, West Point, Pennsylvania 19486, U.S.A.

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