PROCEEDINGS OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE 165, 323–326 (1980)

Clinical and Laboratory Studies of Combined Live Measles, Mumps, and Rubella Vaccines Using the RA 27/3 Rubella Virus (40979)

ROBERT E. WEIBEL,* ALFRED J. CARLSON, JR.,† VICTOR M. VILLAREJOS,‡ EUGENE B. BUYNAK,§ ARLENE A. MCLEAN,§ AND MAURICE R. HILLEMAN§

Department of Pediatrics, University of Pennsylvania School of Medicine, and †Children's Hospital of Philadelphia, Philadelphia, Pennsylvania 19104, ‡Louisiana State University International Center for Medical Research and Training, San Jose, Costa Rica, and §Division of Virus and Cell Biology Research, Merck Institute for Therapeutic Research, West Point, Pennsylvania 19486

Abstract. Eleven lots of combined bivalent and trivalent vaccines containing the measles (Moraten), mumps (Jeryl Lynn), and rubella (RA 27/3) viruses gave satisfactory results in tests in initially seronegative children (measles, 493 children; mumps, 377; rubella, 586). There was no apparent suppression of antibody response against any of the viruses in the vaccines. The clinical reactions observed were mild and inconsequential. Substitution of the HPV 77-DE strain employed heretofore with the RA 27/3 is technically acceptable and offers the advantage of higher titer, slightly greater seroconversion rate, and more solid immunity against reinfection in nature.

Combinations of live measles (Moraten line), mumps (Jeryl Lynn strain), and rubella (HPV 77-DE, duck embryo modified) virus vaccines were licensed for general use between 1970 and 1973 and have been employed extensively to immunize against more than one virus when given in a single injection. The combinations included measles–mumps–rubella vaccine (M–M–R), measles–rubella (M–R-VAX), measles–mumps (M–M-VAX), and mumps–rubella (BIAVAX) (1–4). These vaccines have performed well and more than 165 million doses of the combined vaccines have been distributed in the United States.

The RA 27/3 strain of rubella vaccine virus propagated in cell cultures of human embryo fibroblasts (WI-38) was developed by Dr. Stanley A. Plotkin (5). This vaccine has been reported (6–8) to induce higher titers of rubella antibody, higher seroconversion rates, and higher levels of protection against reinfection by wild rubella virus in nature than do other vaccine strains of rubella virus. Additionally, the vaccine induces antibodies against the theta and iota antigens (9) of rubella virus, much as wild rubella virus does.

The potential advantages of RA 27/3 virus were considered to be sufficiently great to substitute the RA 27/3 strain for the HPV 77-DE strain used to prepare rubella vaccine in these laboratories (10). The RA 27/3 strain has also been substituted for the HPV 77-DE strain in all the combined vaccines in which rubella virus is represented. The RA 27/3 rubella vaccine and all the combined vaccines containing the RA 27/3 strain were licensed for general use in 1978. The present report describes the clinical and laboratory findings of studies in which combined vaccines containing the RA 27/3 rubella virus vaccine were tested in man.

Materials and methods. Vaccines. Rubella, measles–mumps–rubella, measles–rubella, and mumps–rubella virus vaccines were prepared in these research laboratories or in commerical production using the RA 27/3 strain of rubella virus obtained from Dr. Stanley A. Plotkin. All vaccines met the quality standards specified by the Bureau of Biologics, U.S. Food and Drug Administration.

Serology. Hemagglutination-inhibiting (HI) tests for measles and rubella antibodies and serum neutralization tests for mumps antibody were carried out by procedures that were described earlier (11–13). The initial dilution in the test for measles antibody was 1:5, for rubella 1:8, and for mumps 1:1 or 1:2.

0037-9727/80/100323-04$01.00/0

Copyright © 1980 by the Society for Experimental Biology and Medicine.
All rights reserved.

Clinical studies. Clinical studies were carried out to measure clinical and serologic responses to the vaccines. The vaccination trials were conducted by physicians in the Philadelphia area and in Costa Rica. Each vaccine was given subcutaneously in a single 0.5-ml dose. Temperatures and complaints were recorded daily by the subjects or by their parents or guardians and all important findings were confirmed by qualified medical personnel. Blood samples for serologic testing were taken routinely immediately prior to vaccination and 6 to 8 weeks later. All studies were carried out with informed written consent and in compliance with the Investigative New Drug Laws.

Results. Clinical and serologic findings in children who received measles–mumps–rubella (RA 27/3) vaccine or rubella vaccine (RA 27/3) alone. Children in the numbers shown in Table I received combined measles–mumps–rubella vaccine or rubella vaccine alone. The children resided in the open community of suburban Philadelphia and the mean ages were 1.7 and 1.9 years, respectively, for the recipients of the two vaccines. The RA 27/3 vaccine functioned well in the triple combination without reduction in seroconversion rate or significant reduction in mean antibody titer compared with that for RA 27/3 vaccine given singly. The serologic responses to the measles and mumps components of the vaccine were similar to those found earlier in studies (1–4) in which the HPV 77-DE vaccine was the rubella component.

A small number of children who received the combined vaccine showed the same measles-like or rubella-like rash commonly observed when vaccine containing these viruses is given (1). As shown in Table II, there was no important difference in occurrence of fever, lymphadenopathy, arthralgia, myalgia, or anorexia in recipients of the combined vaccine compared with rubella vaccine given alone. The arthralgia, when noted, was mild and transient and no arthritis was reported in either group.

Large-scale trials of 11 lots of combined vaccines. Groups of children in the numbers shown in Table III were given 0.5-ml doses of the several lots of combined vaccines. The mean ages for the measles–mumps–rubella, measles–rubella, and mumps–rubella vaccine recipients were 2.5, 3.2, and 2.4 years, respectively. The seroconversion rate for each virus in each vaccine lot was in excess of 90% and at least 95% of the total group of children developed antibody against each virus included in the vaccine. The seroconversion rates and the mean antibody titers against measles and mumps viruses were consistent with those reported earlier with combined vaccines in which the HPV 77-DE rubella virus was included (1–4). However, the seroconversion rates and antibody titers against the rubella virus were greater.

Antibody persistence. Fifteen initially seronegative children residing in the Philadelphia area who received combined measles–mumps–rubella vaccine containing the RA 27/3 rubella strain were bled 6 weeks and 2 years after vaccination. Their sera were tested for homologous antibody with the findings shown in Fig. 1. There was excellent persistence of antibody against all three viruses and these findings

TABLE I. ANTIBODY RESPONSES IN INITIALLY SERONEGATIVE CHILDREN WHO RECEIVED COMBINED MEASLES (MORATEN)–MUMPS (JERYL LYNN)–RUBELLA (RA 27/3) OR RA 27/3 RUBELLA VACCINE ALONE (STUDY 443)

Vaccine		Antibody responses vs								
		Measles (HI)			Mumps (Neut.)			Rubella (HI)		
		Conversion		Geom.	Conversion		Geom.	Conversion		Geom.
Kind	Lot	No./total	%	mean	No./total	%	mean	No./total	%	mean
M–M–R	621/C-D763	64/68	94	57	65/68	96	8	68/68	100	136
Rubella	579/C-D418	—	—	—	—	—	—	67/67	100	159

TABLE II. CLINICAL REACTIONS RECORDED AMONG INITIALLY SERONEGATIVE CHILDREN WHO RECEIVED COMBINED MEASLES (MORATEN)–MUMPS (JERYL LYNN)–RUBELLA (RA 27/3) VACCINE OR RA 27/3 RUBELLA VACCINE ALONE (STUDY 443)

	No. persons with complaint, according to time (days) after receiving vaccine							
	Measles–mumps–rubella (68 children)				RA 27/3 rubella (67 children)			
Complaint	5–12	13–18	19–28	29–42	5–12	13–18	19–28	29–42
Fever (°F):								
<99–(0)	39	52	43	41	37	40	37	37
99–100.9	14	8	10	14	14	9	8	10
101–102.9	9	1	4	4	4	1	3	1
103–104.9	1	1	3	1	1	1	1	—
105	—	—	1	—	—	—	1	—
Vaccine-related rash	7	5	1	—	2	1	—	—
Lymphadenopathy	1	—	2	2	1	—	1	1
Arthralgia alone	—	1	1	—	—	—	—	1
Myalgia	1	—	—	—	—	1	1	1
Anorexia	12	6	9	11	7	6	5	4

were substantially the same as those found previously using the measles–mumps–rubella vaccine containing the HPV 77-DE strain of rubella virus (14, 15).

Discussion. The findings presented here showed satisfactory immunization of children with various combinations of live measles, mumps, and rubella virus vaccines in which the RA 27/3 strain of rubella vaccine virus was substituted for the HPV 77-DE strain employed heretofore. In tests of the 11 lots of combined trivalent (measles–mumps–rubella, 4 lots) and bivalent (measles–rubella, 4 lots; mumps–rubella, 3 lots) vaccines, the overall seroconversion rate was 95% for measles virus, 96% for mumps virus, and 99% for rubella virus. There was no evident suppression of antibody response to the RA 27/3 rubella virus by incorporation into the combined vaccines. The antibody responses to RA 27/3 virus were roughly two times greater than

TABLE III. ANTIBODY RESPONSES IN INITIALLY SERONEGATIVE CHILDREN WHO RECEIVED DIFFERENT LOTS OF COMBINED MEASLES (MORATEN), MUMPS (JERYL LYNN), AND RUBELLA (RA 27/3) VIRUS VACCINES (12 STUDIES)

Vaccine		Antibody responses								
		Measles (HI)			Mumps (neut.)			Rubella (HI)		
Kind	Lot	No. pos./ total	%	Geom. mean	No. pos./ total	%	Geom. mean	No. pos./ total	%	Geom. mean
Measles–mumps–rubella	621/C-D763	143/150	95	67	145/150	97	7	150/150	100	140
	60664/C-E810	52/57	91	55	53/57	93	13	57/57	100	250
	60665/C-E811	39/41	95	63	39/41	95	21	40/41	98	285
	60666/C-E812	35/36	97	63	35/36	97	25	35/36	97	256
	Total	269/284	95	63	272/284	96	11	282/284	99	188
Measles–rubella	622/C-D764	59/64	92	50	—	—	—	63/64	98	166
	62343/C-F021	46/50	92	50	—	—	—	50/50	100	311
	62344/C-F022	45/45	100	60	—	—	—	45/45	100	371
	62345/C-F023	49/50	98	97	—	—	—	50/50	100	367
	Total	199/209	95	61	—	—	—	208/209	99	277
Mumps–rubella	64756/C-F167	—	—	—	32/34	94	12	34/34	100	444
	64757/C-F168	—	—	—	34/34	100	15	34/34	100	393
	64758/C-F169	—	—	—	25/25	100	17	25/25	100	410
	Total				91/93	98	14	93/93	100	416
	Grand Total	468/493	95	62	363/377	96	12	583/586	99	245

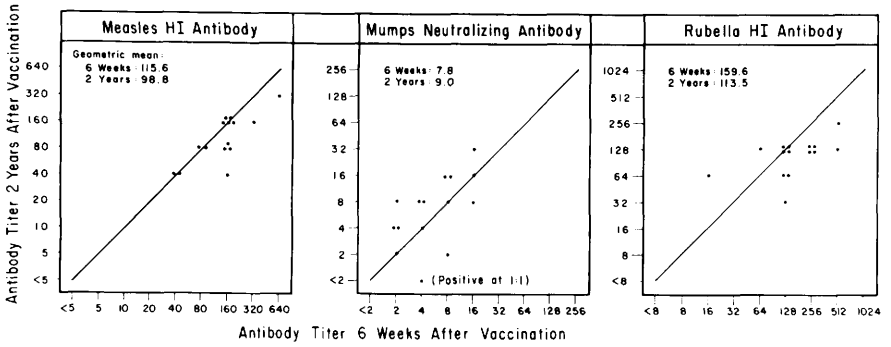

FIG. 1. Persistence of homologous antibodies in children for 2 years after vaccination with combined measles-mumps-rubella (RA 27/3) virus vaccine (Study 443).

those obtained with the HPV 77-DE vaccine (10). Antibody against all three viruses was shown to persist for at least 2 years at essentially the same mean titer as shown at 6 weeks after the vaccine was given.

The combined measles, mumps, and rubella vaccine containing RA 27/3 virus caused little clinical reaction in the children. The expected measles- and rubella-like rashes occurred in a small proportion of the subjects, and lymphadenopathy was an infrequent occurrence. The clinical findings in children were consistent with those reported earlier with single and combined vaccines employing HPV 77-DE or RA 27/3 rubella vaccines (10).

The best present evidence indicates an advantage in employing the RA 27/3 strain in place of the HPV 77-DE strain of rubella virus for vaccinating against rubella. The higher antibody level, slightly greater seroconversion rate, and more solid immunity against reinfection with rubella virus in nature make the vaccine more desirable on a theoretical if not on a practical basis (5–8).

The authors are indebted to the many administrators, nurses, and physicians who provided medical assistance, especially to K. Campbell, B.S., R.N., P. Gerland, B.S., R.N., and C. Rothenberger, R.N. R. Roehm, B.S., S. Brown, B.S., and H. Darmofal, B. S., provided valuable technical assistance. T. Schofield, M.A., performed the data tabulations and analyses.

1. Stokes, J., Jr., Weibel, R. E., Villarejos, V. M., Arguedas G., J. A., Buynak, E. B., and Hilleman, M. R., J. Amer. Med. Assoc. 218, 57 (1971).
2. Villarejos, V. M., Arguedas G., J. A., Buynak, E. B., Weibel, R. E., Stokes, J., Jr., and Hilleman, M. R., J. Pediatr. 79, 599 (1971).
3. Weibel, R. E., Villarejos, V. M., Hernández C., G., Stokes, J., Jr., Buynak, E. B., and Hilleman, M. R., Arch. Dis. Childhood 48, 532 (1973).
4. Weibel, R. E., Stokes, J., Jr., Villarejos, V. M., Arguedas G., J. A., Buynak, E. B., and Hilleman, M. R., J. Amer. Med. Assoc. 216, 983 (1971).
5. Plotkin, S. A., Farquhar, J. D., Katz, M., and Buser, F., Amer. J. Dis. Children 118, 178 (1969).
6. Plotkin, S. A., Farquhar, J. D., and Ogra, P. L., J. Amer. Med. Assoc. 225, 585 (1973).
7. Dudgeon, J. A., Marshall, W. C., and Peckham, C. S., Amer. J. Dis. Children 118, 237 (1969).
8. Ogra, P. L., Kerr-Grant, D., Umana, G., Dzierba, J., and Weintraub, D., N. Engl. J. Med. 285, 1333 (1971).
9. Horstmann, D. M., Liebhaber, H., Le Bouvier, G. L., Rosenberg, D. A., and Halstead, S. B., N. Engl. J. Med. 283, 771 (1970).
10. Weibel, R. E., Villarejos, V. M., Klein, E. B., Buynak, E. B., McLean, A. A., and Hilleman, M. R., Proc. Soc. Exp. Biol. Med. 165, 44 (1980).
11. Hilleman, M. R., Buynak, E. B., Weibel, R. E., Stokes, J., Jr., Whitman, J. E., Jr., and Leagus, M. B., J. Amer. Med. Assoc. 206, 587 (1968).
12. Weibel, R. E., Stokes, J., Jr., Buynak, E. B., Whitman, J. E., Jr., and Hilleman, M. R., N. Engl. J. Med. 276, 245 (1967).
13. Weibel, R. E., Stokes, J., Jr., Buynak, E. B., Whitman, J. E., Jr., Leagus, M. B., and Hilleman, M. R., J. Amer. Med. Assoc. 205, 554 (1968).
14. Weibel, R. E., Buynak, E. B., Stokes, J., Jr., and Hilleman, M. R., Pediatrics 51, 467 (1973).
15. Weibel, R. E., Buynak, E. B., McLean, A. A., and Hilleman, M. R., Pediatrics 61, 5 (1978).

Received May 27, 1980. P.S.E.B.M. 1980, Vol. 165.