March 27, 2019

Siri & Glimstad LLP
Aaron Siri, Esq.
200 Park Ave
17th Floor
New York, NY 101066

In reply refer to file: **2018-6847**

Dear Mr. Siri,

This is in reply to your Freedom of Information Act (FOIA) request dated August 20, 2018 in which you requested "a copy of the report for each clinical trial relied upon by the FDA when approving M-M-R II in 1978." Your request was received in the Center for Biologics Evaluation and Research (CBER) on August 21, 2018.

Enclosed are the documents responsive to your request.

We have withheld portions of pages under Exemption (b)(4), 5 U.S.C. § 522(b)(4). That exemption permits the withholding of trade secrets and commercial or financial information that was obtained from a person outside the government and that is privileged or confidential. The withholding of such information is permitted if disclosure is likely to cause substantial competitive harm to the person who submitted the information.

In addition, we have withheld portions of pages under Exemption (b)(6), 5 U.S.C. § 522(b)(6). That exemption protects information from disclosure when its release would cause a clearly unwarranted invasion of personal privacy. FOIA Exemption 6 is available to protect information in personnel or medical files and similar files. This requires a balancing of the public's right to disclosure against the individual's right to privacy.

You have the right to appeal this determination. By filing an appeal, you preserve your rights under FOIA and give the agency a chance to review and reconsider your request and the agency's decision.

Your appeal must be mailed within 90 days from the date of this response to:

Ms. Catherine Teti
Deputy Agency Chief FOIA Officer
U.S. Department of Health and Human Services
Office of the Assistant Secretary for Public Affairs
Room 729H
200 Independence Avenue, S.W.
Washington, DC 20201

Please clearly mark both the envelope and your letter "FDA Freedom of Information Act Appeal."

If you would like to discuss our response before filing an appeal to attempt to resolve your dispute without going through the appeals process, please contact:

Beth Brockner-Ryan, Branch Chief
Center for Biologics Evaluation and Research (CBER)
Access Litigation and Freedom of Information Branch
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Building 71, Room 1114
Silver Spring, MD 20993-0002
Email:beth.brocknerryan@fda.hhs.gov
Main Line 240-402-7800
FOI Line 240-402-8008

You also have the right to contact:

FDA FOIA Public Liaison
Office of the Executive Secretariat
5630 Fishers Lane
Room-1050
Rockville, MD 20857
Email: FDAFOIA@fda.hhs.gov

If you are unable to resolve your FOIA dispute through our FOIA Public Liaison, the Office of Government Information Services (OGIS), the Federal FOIA Ombudsman's office, offers mediation services to help resolve disputes between FOIA requesters and Federal agencies. The contact information for OGIS is:

Office of Government Information Services
National Archives and Records Administration
8601 Adelphi Road–OGIS
College Park, MD 20740-6001
Telephone: 202-741-5770
Toll-Free: 1-877-684-6448
E-mail: ogis@nara.gov
Fax: 202-741-5769

If you have any questions or if we can be of further assistance, please let us know by referencing the above file number. You can contact John Hyder by phone at 240-402-8079 or by e-mail at John.Hyder@fda.hhs.gov.

Sincerely,

Beth A. Brockner Ryan -S

Digitally signed by Beth A. Brockner Ryan -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300052489, cn=Beth A. Brockner Ryan -S
Date: 2019.03.27 10:26:33 -04'00'

Beth Brockner Ryan
Chief, Access Litigation and Freedom of Information Branch

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
BETHESDA, MARYLAND 20014

SEP 15 1978

Our Reference Nos. 76-316, 77-303 and 77-304

Alan Gray, Ph.D.
Merck Sharp & Dohme
Division of Merck and Co., Inc.
West Point, Pennsylvania 19486

Dear Dr. Gray:

This is to inform you that the amendments to your product license applications to include the use of the RA27/3 strain rubella virus grown in human diploid cells have been accepted for manufacture of the following products:

Rubella Virus Vaccine, Live
Measles, Mumps and Rubella Virus Vaccine, Live
Measles and Rubella Virus Vaccine, Live

We agree that the results of stability testing of vaccines prepared with the buffered sorbitol-gelatin diluent support your request for a longer dating period. Accordingly, your license applications for the three products are also amended to include the use of the diluent and a dating period of two years at 2°-8°C from date of issue.

Please continue to submit stability data as they become available.

Sincerely yours,

Paul Parkman

for Harry M. Meyer, Jr., M.D.
Director
Bureau of Biologics

Summary No. 1
of
Clinical Investigative Studies
of

Combined Live Measles Virus Vaccine (Moraten Line-ATTENUVAX)
Jeryl Lynn Mumps Virus Vaccine (MUMPSVAX)
RA 27/3 Rubella Virus Vaccine

for Purpose of Support for
a License to Manufacture and Sell.

M. R. Hilleman, Ph.D.

Prepared: April 27, 1978
Merck Institute for Therapeutic Research
West Point, Pennsylvania

Clinical Investigative Studies of Combined Live Measles-Mumps-Rubella (RA 27/3) Virus Vaccine

1. Background

On January 11, 1978, we submitted "Summary No. 2 of Clinical Investigative Studies of RA 27/3 Strain Live Rubella Virus Vaccine for Support for a License to Manufacture and Sell" to the Bureau. That summary showed the RA 27/3 rubella virus vaccine to be safe and highly effective in inducing rubella hemagglutination-inhibition (HI) antibodies in persons of various ages.

In extension of clinical tests with RA 27/3 strain rubella virus vaccine, studies were conducted to evaluate its immunizing capability when combined with live attenuated Moraten line measles virus vaccine (ATTENUVAX) and Jeryl Lynn mumps virus vaccine (MUMPSVAX). The present submission relates to clinical investigative studies of combined live measles-mumps-rubella (RA 27/3) virus vaccine.

All clinical studies were conducted under BB-IND-1016.

2. Lot Numbers of Vaccine Tested

Experimental lot prepared by Virus and Cell Biology Research, Merck Sharp and Dohme Research Laboratories:

621/C-D763

Consistency lots prepared by Merck Sharp and Dohme Biologics Manufacturing:

60664/C-E810
60665/C-E811
60666/C-E812

3. Serologic Testing

Serologic determinations were made in the laboratories of Virus and Cell Biology Research, Merck Institute, and in the Control Laboratories of the Merck Sharp and Dohme Division of Merck & Co.

The hemagglutination-inhibition (HI) test was used to determine both measles antibody response and rubella antibody response. Starting dilutions in these two tests were 1:5 and 1:8, respectively. The serum neutralization test was used to measure mumps antibody response with a starting dilution of 1:2.

4. Clinical Studies

The clinical studies were conducted under the overall responsibility of Dr. Maurice R. Hilleman, Vice President, Virus and Cell Biology Research, Merck Institute for Therapeutic Research, West Point, Pennsylvania.

The clinical tests were carried out by five groups of workers:

a. Dr. Robert E. Weibel, Director, Division of Preventive Medicine, Joseph Stokes, Jr. Research Institute, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania

b. Dr. Victor M. Villarejos, Director, Louisiana State University - International Center for Medical Research and Training, San Jose, Costa Rica

c. Dr. Stephen J. Lerman, Director, Pediatric Infectious Disease Unit, Department of Pediatrics, The University of Nebraska Medical Center, Omaha, Nebraska

d. Dr. Anne A. Gershon, Associate Professor, Department of Pediatrics, New York University Medical Center, New York, New York

e. Dr. Robert W. McCollum and Dr. Dorothy M. Horstmann, Department of Epidemiology and Public Health, Yale University School of Medicine, New Haven, Connecticut

Clinical studies fall into two main categories:

	Reference
a. Comparison of M-M-R (RA 27/3) and M-M-R (HPV-77) vaccines in children	3, 4, 5, 6
b. Serologic and clinical responses to measles-mumps-rubella (RA 27/3) vaccine	1, 2, 7, 8

The clinical studies were carried out by the physicians at the locations in the individual study summaries to follow. The populations employed were defined with respect to age, location and other pertinent parameters necessary to permit analysis by statistical sampling procedures.

Subjects in the sampled groups were bled initially and again 6 to 8 weeks later. The sera were tested to define the initial serostatus and the subsequent antibody response.

Clinical surveillance was by two procedures. In studies by Drs. Weibel, Lerman, Gershon, and McCollum, the observations were recorded daily by the mother. The parent was asked to contact the physician should any significant or bothersome reaction occur. In the studies by Dr. Villarejos, observations were made on a routine basis by medical or paramedical personnel; physicians were notified of any significant illness which occurred subsequent to vaccination.

The data presented in the following sections are self explanatory. The detailed background records are on file in Virus and Cell Biology Research, Merck Institute for Therapeutic Research, West Point, Pennsylvania. These records are available for review at any time.

5. Clinical Study Summaries

Reference 1 - Study 442 - Dr. Victor Villarejos

Details of the study plan are given in the clinical test protocol. The study was designed to measure antibody and clinical responses to the RA 27/3 rubella component when given alone or combined with mumps and/or measles vaccine. Findings presented in the summary tables indicate excellent antibody response to all components among children receiving live measles-mumps-rubella (RA 27/3) virus vaccine. No untoward clinical reactions were noted following vaccination.

Reference 2 - Study 443 - Dr. Robert Weibel

Details of the study plan are presented in the clinical protocol. The purpose of the study was to measure antibody and clinical responses to the RA 27/3 rubella component when given alone or combined with measles and mumps virus components. Findings are presented in the summary tables. Each of the three viruses produced excellent antibody responses when administered in combined form. Both vaccines were well tolerated.

Reference 3 - Study 459 - Dr. Stephen Lerman

Study 459 is being conducted in children to compare responses to HPV-77 and RA 27/3 rubella vaccines when given alone or combined with measles and mumps vaccines. Details of the study plan are given in the clinical test protocol. Preliminary findings presented in the summary tables show excellent antibody response to measles, mumps, and rubella components and lack of suppression when the three viruses are combined. Reaction rates were as expected.

Reference 4 - Study 467 - Dr. Robert Weibel

Study 467 was conducted among children to compare responses to combined measles-mumps-rubella vaccines containing either the HPV-77 or RA 27/3 rubella component. Details of the study plan are given in the clinical test protocol, and study results are presented in the summary tables. Antibody responses to both vaccines were excellent, indicating no reduced affect on any component in combined form. Reaction rates were as expected for both vaccines.

Reference 5 - Study 473 - Dr. Robert McCollum

Study 473 is being conducted among children to compare responses to combined measles-mumps-rubella virus vaccines containing either the HPV-77 or RA 27/3 rubella component. Details of the study plan are given in the clinical test protocol. No results are available at this time.

Reference 6 - Study 484 - Dr. Anne Gershon

Study 484 is being conducted among children to compare responses to combined measles-mumps-rubella virus vaccines containing either the HPV-77 or RA 27/3 rubella component. Preliminary findings are presented in the report from Dr. Gershon. The study continues in progress.

Reference 7 - Study 511 - Dr. Victor Villarejos

Study 511 was conducted to measure antibody and clinical responses to three consecutive lots of combined measles-mumps-rubella vaccine containing the RA 27/3 rubella component. Details of the study plan are given in the clinical test protocol, and study results are presented in the summary tables. Responses to the rubella component were excellent. Seroconversion rates for measles and mumps were somewhat lower than expected, and the decreased seroconversion rates were attributed to some overheating of the vaccine during transport in the field. Reaction rates were comparable among the lots.

Reference 8 - Study 513 - Dr. Robert Weibel

Study 513 is being conducted to measure antibody and clinical responses to three consecutive lots of combined measles-mumps-rubella vaccine containing the RA 27/3 rubella component. Study details are given in the clinical protocol, and preliminary findings are given in the summary tables. To date, all three lots of vaccine have produced good antibody responses and have been well tolerated.

6. Overall Summary

The total numbers of vaccinations for which supporting data have been given are as follows:

		No. Seroconverting/No. Triple Negatives (%)		
Lot #	No. Vacc.	Measles	Mumps	RA 27/3 Rubella
621	480	143/150 (95)	145/150 (97)	150/150 (100)
60664	144	50/55 (91)	52/55 (95)	55/55 (100)
60665	104	37/39 (95)	37/39 (95)	38/39 (97)
60666	106	34/35 (97)	34/35 (97)	34/35 (97)
Total	834	264/279 (95)	268/279 (96)	277/279 (99)

The data show that combined live measles-mumps-rubella vaccine containing the RA 27/3 rubella virus component is safe and effective.

Summary of Clinical Tests of Combined Live
Measles-Mumps-Rubella (RA 27/3) Virus Vaccine

Study No.	Investigator	Lot No.	Age		No. Vacc.	Antibody Responses among Triple Seronegatives									Re.
						Measles			Mumps			RA 27/3 Rubella			
			Range	Mean (Yrs.)		No. Conv./ No. Seroneg. (%)		GMT	No. Conv./ No. Seroneg. (%)		GMT	No. Conv./ No. Seroneg. (%)		GMT	
442	Villarejos	621	10m- 7y	3.7	199	23/23	(100)	99	22/23	(96)	7	23/23	(100)	149	1
443	Weibel	621	11m- 8y	1.7	105	65/69	(94)	56	66/69	(96)	8	69/69	(100)	133	2
459	Lerman	60664	14m- 4y	1.6	41	13/14	(93)	62	13/14	(93)	17	14/14	(100)	269	3
467	Weibel	621	11m- 7y	1.9	137	55/58	(95)	71	57/58	(98)	7	58/58	(100)	146	4
473	McCollum	621													5
484	Gershon	621	13m-15y		39										6
511	Villarejos	60664	8m-11y	3.3	50	9/11	(82)	20	10/11	(91)	5	11/11	(100)	226	7
		60665	11m- 7y	3.3	50	4/5	(80)	25	4/5	(80)	11	5/5	(100)	169	
		60666	11m-11y	4.2	50	2/2	(100)	28	2/2	(100)	8	2/2	(100)	256	
513	Weibel	60664	12m- 7y	1.7	53	28/30	(93)	70	29/30	(97)	19	30/30	(100)	256	8
		60665	12m- 4y	1.5	54	33/34	(97)	70	33/34	(97)	23	33/34	(97)	200	
		60666	11m- 4y	1.4	56	32/33	(97)	66	32/33	(97)	26	32/33	(97)	251	
		Totals			834	264/279	(95)	63	268/279	(96)	11	277/279	(99)	178	

4/24/78

Program: Study #442

Vaccine: Combined Live Measles-Mumps-Rubella (RA 27/3) Virus Vaccine
Lot No. 621/C-D763

Combined Live Measles-Rubella (RA 27/3) Virus Vaccine
Lot No. 622/C-D764

Live Attenuated Rubella (RA 27/3) Virus Vaccine
Lot No. 579/C-D418

Responsible Clinical Investigator:

Victor M. Villarejos, M.D.
Director
Louisiana State University
International Center for Medical
Research and Training
Apartado 10.155
San Jose, Costa Rica

Study Location: Rivas, Nicaragua

Date Study Initiated: January 19, 1976

Date Study Completed: April 28, 1976

Study Procedure:

A total of 589 children, 10 months to 7 years of age, from the open population were included in the study. Each participant received a 0.5 ml subcutaneous dose of one of the three vaccines. Blood samples were obtained prior to and six weeks after vaccination.

Clinical Protocol - Study #442

Combined Live Measles-Mumps-Rubella (RA 27/3) Virus Vaccine
Combined Live Measles-Rubella (RA 27/3) Virus Vaccine
Live Attenuated Rubella (RA 27/3) Virus Vaccine

Purpose: To determine antibody and clinical responses to combined live measles-mumps-rubella (RA 27/3) virus vaccine, to combined live measles-rubella (RA 27/3) virus vaccine, and to live attenuated rubella (RA 27/3) virus vaccine.

Vaccines:

a) Combined live measles-mumps-rubella (RA 27/3) virus vaccine
Lot No. 621

Vaccine dose is 0.5 ml given subcutaneously.

The vaccine is supplied in two-dose vials. Each vial of vaccine should be rehydrated with 1.2 ml of sterile, pyrogen-free distilled water.

b) Combined live measles-rubella (RA 27/3) virus vaccine
Lot No. 622

Vaccine dose is 0.5 ml given subcutaneously.

The vaccine is supplied in two-dose vials. Each vial of vaccine should be rehydrated with 1.2 ml of sterile, pyrogen-free distilled water.

c) Live attenuated rubella (RA 27/3) virus vaccine
Lot No. 579

Vaccine dose is 0.5 ml given subcutaneously.

The vaccine is supplied in single dose vials. Each vial of vaccine should be reconstituted with 0.7 ml of sterile, pyrogen-free distilled water.

CAUTION: The combined vaccines contain egg protein and should not be given to persons with known sensitivity to egg, chicken, or chicken feathers. All three vaccines contain neomycin and should not be given to persons with sensitivity to neomycin. Persons with leukemia or other immunologic disorders and persons receiving immunosuppressive drugs should not be vaccinated. Also, the vaccines should not be given to persons with any febrile respiratory illness or other active febrile infection.

Keep dried vaccines stored at -20°C until used.

Keep dried vaccines at 4°C in transport.

Keep reconstituted vaccines on ice. Discard unused vaccine 4 hours after rehydration.

Procedure: The study population will consist of children 1 to 6 years of age.

Children receiving a given vaccine will have a negative history for vaccination with and illness caused by viruses represented in that vaccine. Children will be assigned to receive one of the three vaccines as follows:

Vaccine	Vaccine Lot	No. Children
measles-mumps-rubella	621	150-200
measles-rubella	622	150-200
rubella	579	150-200

Informed consent will be obtained from each child's parent or guardian prior to his participation in the study.

Each child will be bled (10-15 ml) immediately prior to vaccination and 6 weeks following vaccination.

Vaccine dose is 0.5 ml given subcutaneously.

Each child will be followed clinically for 42 days following vaccination. All local and systemic complaints will be recorded on the case report form.

Schedule:

Time	Action
Day 0	Bleed 10-15 ml. Vaccinate 0.5 ml, subcutaneously.
Days 0-42	Clinical follow-up for local and systemic reactions.
Week 6	Bleed 10-15 ml.

Laboratory: Remove sera from clot aseptically and store frozen at -20°C until shipped. It is imperative that sera are sterile to avoid interference with the serologic assay.

Serology: Circulating levels of antibody to each vaccine component will be determined for samples drawn before and after vaccination. Measles and rubella antibody levels will be determined by hemagglutination-inhibition test. Mumps antibody levels will be determined by serum neutralization test.

Clinical Forms: Attached.

Adverse Reactions: Any serious or alarming reaction, including death due to any cause during the investigation, whether related or not related to the test material, must be reported immediately to Merck & Co., Inc., through Dr. Maurice R. Hilleman, telephone (215) 699-5311, Ext. 5532, or in his absence, Dr. Allen F. Woodhour, telephone (215) 699-5311, Ext. 5588.

Unused Vaccine: All unused vaccine should be returned immediately to Merck Sharp & Dohme Research Laboratories, West Point, Pa. 19486.

Shipping of Sera & Records:

a) Send sera frozen within insulated containers which are supplied.

b) Send sera and records to Dr. Maurice R. Hilleman, Virus and Cell Biology Research, Merck Sharp & Dohme Research Laboratories, West Point, Pa. 19486.

c) Alert Dr. Hilleman by cable as soon as possible as to flight number, air bill, and date of arrival.

M. R. Hilleman, Ph.D.

VACUNACIÓN CONTRA SARAMPIÓN PAPERAS RUBÉOLA

Estudio No. _____ (1-3) NO. DEL CASO _____ (4-9)

CT 2	Nombre Completo del Niño	Sexo (35) M F	Fecha de nacimiento (36-41) día mes año	(46-47)
CT 6 Dupe CT 2 (141)- (54-59)	Dirección completa de Padres o Guardián:			

CT 2 — INDIQUE SI INDIVIDUO HA: S = Sarampión P = Paperas R = Rubéola

	S (70)	P (71)	R (72)
1. Tenido Enfermedad	1	1	1
2. Sido Vacunado	2	2	2
3. Estado Expuesto (Durante Ultimas Cuatro Semanas)	3	3	3

Fecha de expuesto ___/___/___
Fecha de expuesto ___/___/___
Fecha de expuesto ___/___/___

PERÍODO DE VACUNACIÓN O CONTROL

(48) ☐ Vacunado ☐ Control

No. de Lote _____ (49-51)

Fecha de vacunación ___/___/___ (52-57)
Fecha de primer sangrado (antes de vacunado) ___/___/___ (52-57)
Fecha de segundo sangrado (despues de vacunado) ___/___/___ (58-63)

SEROLOGÍA

SARAMPIÓN				PAPERAS		RUBÉOLA			
HI		Neut		Neut		HI		Neut	
Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post

Indique si el niño contrajo Sarampión clínico: 1 = Sí 2 = No
Indique si el niño contrajo Paperas clínica: 1 = Sí 2 = No
Indique si el niño contrajo Rubéola clínica: 1 = Sí 2 = No

CT 4 — Fecha de comienzo: ___/___/___
Quién hizo diagnóstico? _____

Otras quejas u observaciones clínicas:

Despues de completadas, devuelva formas al: (Retenga copia rosa para sus archivos)	*Firma del Médico:*	*Fecha:*
M. R. HILLEMAN, PhD. DSc MERCK SHARP & DOHME RESEARCH LABS., WEST POINT, PENNSYLVANIA 19486	*Nombre del Médico (en letra de molde):*	

P3957-0875(SPANISH & ENGLISH) (*3957-0875)

NOTA AL INVESTIGADOR:
1. No escriba en areas obscurecidas
2. Asegurese de llenar todos los blancos aplicables.

PRECAUCIÓN: Use mecanografía o letra de molde. No escriba en esta forma si esta encima de otras formas NCR (semejantes a esta).

VACUNACIÓN CONTRA SARAMPIÓN PAPERAS RUBÉOLA

HOJA CLINICA

B

NO. DE CASO _____

FECHA DE VACUNACION ____/____/____
día mes año

NOMBRE:

DIA	FECHA	Temperatura	Malestar	Anorexia	Gastroenteritis	Irritabilidad	Cefalea	I. V. R. S.	Otitis	Conjuntivitis	Linfadenopatia*	Reaccion Local* (Diametro mm)	Exantema*	RASH* Rubelliforme	RASH* Morbilliforme	Artralgia*	Artritis*	*Especifique tipo en esta seccion / OTRAS REACCIONES
		24	16	25	08	15	14	01	03	06		12	50	51	52	11	32	
0																		
1																		
2																		
3																		
4																		
5																		
6																		
7																		
8																		
9																		
10																		
11																		
12																		
13																		
14																		
15																		
16																		
17																		
18																		
19																		
20																		
21																		
22																		
23																		
24																		
25																		
26																		
27																		
28																		
29																		
30																		
31																		
32																		
33																		
34																		
35																		
36																		
37																		
38																		
39																		
40																		
41																		
42																		

PRECAUCION: Papel carbón no es nec. Use maquina de escribir o pluma esferografica con tinta negra. No escriba encima de otras formas "NCH." KFormas semejantes a ustasl
NOTA: No escriba en areas obscuracidas.

Al terminar el estudio, devuelva copia blanca y copia amarilla de esta form a, adjuntas a la forma "A" al: (Retenga copia color de rosa para sus archivos)

M.R. Hilleman, PhD, DSc
MERCK SHARP & DOHME RESEARCH LABORATORIES
WEST POINT, PENNSYLVANIA, 19486, U.S.A.

Firma del medico:

Nombre del medico (en letra de molde):

Fecha:

Table 1

Serological Findings Among Children Who Received Combined Live
Measles-Mumps-Rubella (RA 27/3) Virus Vaccine, Lot No. 621/C-D763 (Study #442)

Age	Total No. Vacc.	No. Serol. Tested	Initially Seronegative to:											Initially Seropositive to:
			Measles-Mumps-Rubella Conversions/Total			Measles-Mumps Conversions/Total		Measles-Rubella Conversions/Total		Mumps-Rubella Conversions/Total		Measles Only Conversions/ Total	Mumps Only Conversions/ Total	Rubella Only Conversions/ Total	Measles Mumps and Rubella
			Measles	Mumps	Rubella	Measles	Mumps	Measles	Rubella	Mumps	Rubella				
10 Months	1	0													
11 Months	2	2	1/1	1/1	1/1			1/1	1/1						
1 Year	29	21	7/7	7/7	7/7			4/5	5/5	3/3	3/3		2/2	3/3	1
2 Years	18	15	3/3	3/3	3/3	1/1	1/1	4/4	4/4	2/3	3/3			3/3	1
3 Years	41	33	6/6	6/6	6/5	1/1	1/1	3/3	3/3	6/6	6/6			14/14	3
4 Years	39	34	2/2	2/2	2/2			5/5	5/5	7/8	8/8	1/1		15/15	3
5 Years	32	25	3/3	2/3	3/3			2/2	2/2	2/3	3/3	2/2		13/13	2
6 Years	36	28	1/1	1/1	1/1			8/8	8/8	2/2	2/2		1/1	15/15	1
7 Years	1	1						1/1	1/1						
Total	199	159	23/23 (100%)	22/23 (95.7%)	23/23 (100%)	2/2	2/2	28/29 (96.6%)	29/29 (100%)	22/25 (88.0%)	25/25 (100%)	3/3	3/3	63/63 (100%)	11
Mean Age: 3.7 Years															

Overall Conversion Rates

Measles	Mumps	Rubella
56/57 (98.2%)	49/53 (92.5%)	140/140 (100%)

10/3/77

Table 2

Serological Findings Among Children Who Received Combined Live Measles-Rubella (RA 27/3) Virus Vaccine, Lot No. 622/C-D764 (Study #442)

Age	Total No. Vacc.	No. Serol. Tested	Initially Seronegative to: Measles-Rubella Conversions/Total Measles	Measles-Rubella Conversions/Total Rubella	Measles Only Conversions/ Total	Rubella Only Conversions/ Total	Initially Seropositive to: Measles and Rubella
1 Year	22	16	11/11	11/11		4/4	1
2 Years	20	16	7/9	9/9	2/2	3/3	2
3 Years	46	36	14/16	15/16	1/1	13/13	6
4 Years	40	31	5/5	5/5	2/2	20/20	4
5 Years	28	19	5/5	5/5	1/1	11/11	2
6 Years	37	24	7/8	8/8	4/4	9/9	3
Total	193	142	49/54	53/54	10/10	60/60	18
Mean Age: 3.7 Years			(90.7%)	(98.1%)	(100%)	(100%)	

Overall Conversion Rates

Measles	Rubella
59/64 (92.2%)	113/114 (99.1%)

4/28/77

Table 3

Distribution of Fold Rises of Hemagglutination-Inhibition Antibody Titers Among Children Who Received Live Attenuated Rubella (RA 27/3) Virus Vaccine, Lot No. 579/C-D418 (Study #442)

Age	Total No. Vacc.	No. Serol. Tested	Initially Seropositive			Initially Seronegative			
			Fold Rise						
			≥4X	Indet.	Total	No. Conv.	Failures	Total	Conv. Rate
1 Year	13	10		1	1	9		9	9/9
2 Years	17	15		1	1	14		14	14/14
3 Years	30	24		2	2	22		22	22/22
4 Years	38	32	1	1	2	30		30	30/30
5 Years	42	29		3	3	26		26	26/26
6 Years	56	48		8	8	40		40	40/40
7 Years	1	0							
Total	197	158	1	16	17	141	0	141	100%
Mean Age: 4.3 Years									

4/28/77

Table 4

Distribution of Post-Vaccination Antibody Titers Among Children Who Were Initially Seronegative to Measles, Mumps and Rubella and Who Received Combined Live Measles-Mumps-Rubella (RA 27/3) Virus Vaccine, Lot No. 621/C-D763 (Study #442)

Measles (HI)		Mumps (Neut.)		Rubella (HI)	
Post-Vaccination Titer	No. of Children	Post-Vaccination Titer	No. of Children	Post-Vaccination Titer	No. of Children
<5		<2	1	<8	
5		2	4	8	
10		4	4	16	
20	2	8	5	32	1
40	5	16	7	64	4
80	5	32	2	128	9
160	6			256	7
320	5			512	2
Total	23		23		23
Geometric Mean Titer	98.8		7.1		148.8

10/3/77

Table 5

Distribution of Post-Vaccination Antibody Titers Among Children
Who Were Initially Seronegative to Measles and Rubella and Who Received
Combined Live Measles-Rubella (RA 27/3) Virus Vaccine, Lot No. 622/C-D764 (Study #442)

Measles (HI)		Rubella (HI)	
Post-Vaccination Titer	No. of Children	Post-Vaccination Titer	No. of Children
<5	5	<8	1
5		8	
10	1	16	
20	9	32	1
40	4	64	3
80	22	128	30
160	9	256	13
320	3	512	6
≥640	1		
Total	54		54
Geometric Mean Titer	≥48.7		151.2

4/28/77

Table 6

Distribution of Post-Vaccination Antibody Titers Among Children Who Were Initially Seronegative to Rubella and Who Received Live Attenuated Rubella (RA 27/3) Virus Vaccine, Lot No. 579/C-D418 (Study #442)

Rubella (HI)	
Post Vaccination Titer	No. of Children
<8	
8	
16	
32	2
64	20
128	70
256	41
≥512	8
Total	141
Geometric Mean Titer	≥150.5

4/28/77

Table 7

Maximum Temperatures Reported Among Children Who Received Combined Live Measles-Mumps-Rubella (RA 27/3) Virus Vaccine, Lot No. 621/C-D763 (Study #442)

Maximum Temperature (°F, Oral)	Total Vaccinees (199 Children)						Initially Seronegative to: Measles, Mumps and Rubella (23 Children)					
	Days Post-Vaccination					No. with Max. Temp.	Days Post-Vaccination					No. with Max. Temp.
	0-4	5-12	13-18	19-28	29-42		0-4	5-12	13-18	19-28	29-42	
<99	147 (73.9%)	138 (69.3)	160 (81.6)	130 (68.4)	137 (72.5)	83	18 (78.3)	20 (87.0)	23 (100.0)	14 (73.7)	16 (84.2)	16
99 - 100.9	51 (25.6)	57 (28.6)	35 (17.9)	59 (31.1)	52 (27.5)	109	5 (21.7)	3 (13.0)		5 (26.3)	3 (15.8)	7
101 - 102.2		2 (1.0)	1 (0.5)			3						
103 - 104.0	1 (0.5)	2 (1.0)		1 (0.5)		4						
Not Taken			3	9	10					4	4	

Patient #	Temperature	Days	Clinical Complaint	Serology: Measles		Mumps		Rubella	
(b) (6)	102.2	8	Upper Respiratory Illness, Malaise	≥20	320	≥8	32	<8	1024
	103.1	20	Irritability, Malaise	≥20	160	≥8	128	<8	64
	103.1	11	Tonsillitis, Anorexia, Headache, Malaise	≥20	≥640	<2	4	<8	128
	104.0	1	Irritability, Malaise	Serologies Not Done					
	104.0	5	Upper Respiratory Illness, Irritability, Anorexia, Malaise	≥20	320	<4	16	<8	256

10/3/77

Table 8

Maximum Temperatures Reported Among Children Who Received Combined Live Measles-Rubella (RA 27/3) Virus Vaccine, Lot No. 622/C-D764 (Study #442)

Maximum Temperature (^{o}F, Oral)	Total Vaccinees (193 Children) Days Post-Vaccination						Initially Seronegative to: Measles and Rubella (54 Children) Days Post-Vaccination					
	0-4	5-12	13-18	19-28	29-42	No. with Max. Temp.	0-4	5-12	13-18	19-28	29-42	No. with Max. Temp.
<99	146 (76.0)	135 (70.3)	138 (72.3)	123 (64.4)	114 (59.7)	67	42 (77.8)	35 (64.8)	39 (72.2)	38 (70.4)	35 (64.8)	23
99 - 100.9	46 (24.0)	56 (29.2)	53 (27.7)	68 (35.6)	77 (40.3)	124	12 (22.2)	19 (35.2)	15 (27.8)	16 (29.6)	19 (35.2)	31
102.0		1 (0.5)				1						
Not Taken	1	1	2	2	2	1						

Patient #	Temperature	Day	Clinical Complaint	Serology: Measles	Serology: Rubella
(b) (6)	102.0	5	Upper Respiratory Illness, Irritability, Malaise	≥20, 160	≥32, 256

4/28/77

Table 9

Maximum Temperatures Reported Among Children Who Received Live Attenuated Rubella (RA 27/3) Virus Vaccine, Lot No. 579/C-D418 (Study #442)

Maximum Temperature (°F, Oral)	Total Vaccinees (197 Children) Days Post-Vaccination 0-4	5-12	13-18	19-28	29-42	No. with Max. Temp.	Initially Seronegative to: Rubella (141 Children) Days Post-Vaccination 0-4	5-12	13-18	19-28	29-42	No. With Max. Temp.
<99	162 (82.2%)	131 (66.5)	148 (75.1)	125 (64.4)	138 (71.5)	67	116 (82.3)	97 (68.8)	110 (78.0)	94 (67.6)	104 (74.8)	51
99-100.9	35 (17.8)	66 (33.5)	48 (24.4)	68 (35.1)	55 (28.5)	128	25 (17.7)	44 (31.2)	30 (21.3)	44 (31.7)	35 (25.2)	88
101 - 102.2			1 (0.5)	1 (0.5)		2			1 (0.7)	1 (0.7)		2
Not Taken				3	4					2	2	

Patient #	Temperature	Day	Clinical Complaint	Serology
(b) (6)	102.2	20	Upper Respiratory Illness, Anorexia, Malaise	<8, 128

4/29/77

Table 10

Clinical Complaints Reported Among Children Who Received Combined Live Measles-Mumps-Rubella (RA 27/3) Virus Vaccine, Lot No. 621/C-D763 (Study #442)

Clinical Complaint	Total Vaccinees (199 Children)						Initially Seronegative to: Measles, Mumps and Rubella (23 Children)					
	Days Post-Vaccination					No. with Complaint	Days Post Vaccination					No. with Complaint
	0-4	5-12	13-18	19-28	29-42		0-4	5-12	13-18	19-28	29-42	
Irritability	32 (16.1%)	9 (4.5)	2 (1.0)	4 (2.1)		39	5 (21.7)			1 (5.0)		5
Malaise	30 (15.1)	14 (7.0)	3 (1.5)	7 (3.6)	1 (0.5)	43	5 (21.7)	1 (4.3)		2 (10.0)		7
Headache		1 (0.5)	2 (1.0)			2						0
Upper Respiratory Illness	9 (4.5)	11 (5.5)	5 (2.5)	8 (4.1)	5 (2.6)	23	1 (4.3)	1 (4.3)	1 (4.3)	2 (10.0)	1 (5.0)	3
Otitis			2 (1.0)	3 (1.5)		3			1 (4.3)	1 (5.0)		1
Ophthalmopathy		1 (0.5)				1						0
Gastrointestinal Illness	13 (6.5)	7 (3.5)	2 (1.0)	5 (2.6)	1 (0.5)	22		1 (4.3)				1
Anorexia	5 (2.5)	3 (1.5)	2 (1.0)	5 (2.6)		13				1 (5.0)		1
Mild Dermatitis		1 (0.5)				1						0
Persons with Complaints:	49 (24.6)	22 (11.1)	11 (5.5)	19 (9.8)	6 (3.1)	73	6 (26.1)	2 (8.7)	1 (4.3)	4 (20.0)	1 (5.0)	10
Persons with No Complaints:	150 (75.4)	177 (88.9)	188 (94.5)	175 (90.2)	187 (96.9)	123	17 (73.9)	21 (91.3)	22 (95.7)	16 (80.0)	19 (95.0)	12
Negative Physician Surveillance				5	6					3	3	

10/3/77

Table 11

Clinical Complaints Reported Among Children Who Received Combined
Live Measles-Rubella (RA 27/3) Virus Vaccine, Lot No. 622/C-D764 (Study #442)

Clinical Complaint	Total Vaccinees (193 Children)						Initially Seronegative to: Measles and Rubella (54 Children)					
	Days Post-Vaccination					No. with Complaint	Days Post-Vaccination					No. with Complaint
	0-4	5-12	13-18	19-28	29-42		0-4	5-12	13-18	19-28	29-42	
Irritability	29 (15.1)	11 (5.7)	6 (3.1)	9 (4.7)	6 (3.1)	52	13 (24.1)	4 (7.4)	2 (3.7)	1 (1.9)	1 (1.9)	18
Malaise	33 (17.2)	21 (10.9)	15 (7.9)	15 (7.9)	7 (3.7)	65	12 (22.2)	8 (14.8)	4 (7.4)	2 (3.7)	1 (1.9)	18
Headache	4 (2.1)	3 (1.6)	2 (1.0)	2 (1.0)		9		1 (1.9)	1 (1.9)			1
Upper Respiratory Illness	1 (0.5)	9 (4.7)	8 (4.2)	8 (4.2)	1 (0.5)	21	1 (1.9)	5 (9.3)	2 (3.7)	1 (1.9)		6
Bronchitis			1 (0.5)	1 (0.5)		1			1 (1.9)	1 (1.9)		1
Otitis	1 (0.5)	2 (1.0)	2 (1.0)	1 (0.5)	1 (0.5)	6		2 (3.7)	1 (1.9)			3
Gastrointestinal Illness	5 (2.6)	7 (3.6)	6 (3.1)	4 (2.1)	3 (1.6)	23	1 (1.9)	2 (3.7)	1 (1.9)	1 (1.9)		5
Anorexia	5 (2.6)	4 (2.1)	6 (3.1)	4 (2.1)		17	2 (3.7)	1 (1.9)	1 (1.9)			4
Hepatitis	1 (0.5)	1 (0.5)				1						0
Asthma		1 (0.5)				1						0
Persons with Complaints:	36 (18.8)	24 (12.5)	17 (8.9)	18 (9.4)	8 (4.2)	70	13 (24.1)	9 (16.7)	4 (7.4)	3 (5.6)	1 (1.9)	19
Persons with No Complaints:	156 (81.3)	168 (87.5)	174 (91.1)	173 (90.6)	183 (95.8)	121	41 (75.9)	45 (83.3)	50 (92.6)	51 (94.4)	53 (98.1)	35
Negative Physician Surveillance: 1		1	2	2	2	1						

4/29/77

Table 12

Clinical Complaints Reported Among Children Who Received Live Attenuated Rubella (RA 27/3) Virus Vaccine, Lot No. 579/C-D418 (Study #442)

Clinical Complaint	Total Vaccinees (197 Children)						Initially Seronegative to: Rubella (141 Children)					
	Days Post-Vaccination					No. with Complaint	Days Post-Vaccination					No. with Complaint
	0-4	5-12	13-18	19-28	29-42		0-4	5-12	13-18	19-28	29-42	
Irritability	22 (11.2)	4 (2.0)	3 (1.5)	5 (2.6)	2 (1.0)	32	15 (10.6)	4 (2.8)	2 (1.4)	2 (1.4)	1 (0.7)	23
Malaise	28 (14.2)	10 (5.1)	5 (2.5)	9 (4.6)	4 (2.1)	46	19 (13.5)	9 (6.4)	2 (1.4)	5 (3.5)	2 (1.4)	32
Headache	2 (1.0)	1 (0.5)		3 (1.5)	1 (0.5)	6	1 (0.7)			1 (0.7)		2
Upper Respiratory Illness	4 (2.0)	8 (4.1)	1 (0.5)	6 (3.1)	2 (1.0)	15	3 (2.1)	6 (4.3)	1 (0.7)	5 (3.5)	2 (1.4)	13
Otitis	2 (1.0)			2 (1.0)	1 (0.5)	4	1 (0.7)			1 (0.7)	1 (0.7)	2
Ophthalmopathy	1 (0.5)	1 (0.5)				1	1 (0.7)	1 (0.7)				1
Gastrointestinal Illness	5 (2.5)	6 (3.0)	1 (0.5)	1 (0.5)	1 (0.5)	11	4 (2.8)	5 (3.5)	1 (0.7)		1 (0.7)	8
Anorexia	7 (3.6)	1 (0.5)		5 (2.6)		13	4 (2.8)			4 (2.8)		8
Persons with Complaints:	35 (17.8)	18 (9.1)	7 (3.6)	16 (8.2)	7 (3.6)	60	23 (16.3)	14 (9.9)	4 (2.8)	10 (7.1)	5 (3.5)	43
Persons with No Complaints:	162 (82.2)	179 (90.9)	190 (96.4)	180 (91.8)	188 (96.4)	137	118 (83.7)	127 (90.1)	137 (97.2)	131 (92.9)	136 (96.5)	98
Negative Physician Surveillance				1	2							

4/29/77

MEMO

To File Location Date 2/2/78

From T. Schofield Location

Subject Statistical Analysis - Study #442

Analysis of variance was conducted on post titers of children who were initially seronegative to rubella who received rubella vaccine, lot #579 (Group 1), combined measles-mumps-rubella vaccine, lot #621 (Group 2), and combined measles-rubella vaccine, lot #622 (Group 3).

No significant difference exists among the three groups. Geometric mean titers were:

Vaccine	GMT
Rubella	150.5
MMR	143.4
MR	155.5

There is no significant difference in conversion rate among these three groups.

T.S.

Reference No. 2

Program: Study #443

Vaccine: Combined Live Measles-Mumps-Rubella (RA 27/3) Virus Vaccine, Lot No. 621/C-D763

Live Attenuated Rubella (RA 27/3) Virus Vaccine, Lot No. 579/C-D418

Responsible Clinical Investigator:

Robert E. Weibel, M.D.
Director, Division of Preventive Medicine
Joseph Stokes, Jr. Research Institute
Children's Hospital of Philadelphia
34th Street and Civic Center Boulevard
Philadelphia, Pennsylvania 19104

Study Location:

Children's Hospital of Philadelphia
Darby Child Health Clinic, Darby, Pennsylvania
G. Starkweather, M.D., Havertown, Pennsylvania

Date Study Initiated: October 28, 1975

Date Study Completed: January 20, 1977

Study Procedure:

A total of 194 children 10 months to 8 years of age from the open population were included in the study. One hundred ninety-one children received a 0.5 ml subcutaneous dose of one of two vaccines. Three children received a 1.0 ml subcutaneous dose of the combined live measles-mumps-rubella (RA 27/3) virus vaccine. Blood samples were obtained prior to and six weeks after vaccination.

Clinical Protocol - Study #443

Combined Live Measles-Mumps-Rubella (RA 27/3) Virus Vaccine

Live Attenuated Rubella (RA 27/3) Virus Vaccine

Purpose: To determine antibody and clinical responses to combined live measles-mumps-rubella (RA 27/3) virus vaccine and to live attenuated rubella (RA 27/3) virus vaccine.

Vaccines: a) Combined live measles-mumps-rubella (RA 27/3) virus vaccine, lyophilized
Lot No. 621

Vaccine dose is 0.5 ml given subcutaneously.

The vaccine is supplied in two-dose vials. Each vial of vaccine should be rehydrated with 1.2 ml of sterile, pyrogen-free distilled water.

b) Live attenuated rubella (RA 27/3) virus vaccine, lyophilized
Lot No. 579

Vaccine dose is 0.5 ml given subcutaneously.

The vaccine is supplied in single-dose vials. Each vial of vaccine should be rehydrated with 0.7 ml of sterile, pyrogen-free distilled water.

CAUTION: The combined vaccine may contain egg protein and should not be given to persons with known sensitivity to egg, chicken or chicken feathers. Both vaccines contain neomycin and should not be given to persons with known sensitivity to neomycin. Persons with leukemia or other immunologic disorders and persons receiving immunosuppressive drugs should not be vaccinated. Also, the vaccines should not be given to persons with any febrile respiratory illness or other active febrile infection.

Keep dried vaccines stored at -20°C until used.

Keep dried vaccines at 4°C in transport.

Keep reconstituted vaccine on ice. Discard unused vaccine 4 hours after rehydration.

Procedure: Establish two groups of 50 to 100 children 1 to 6 years of age as follows:

Group	Vaccine	No. Children
Group 1	measles-mumps-rubella	50-100
Group 2	rubella	50-100

Children in Group 1 will have a negative history for vaccination and illness for measles, mumps, and rubella. Children in Group 2 will have a negative history for rubella vaccination and illness.

Informed consent will be obtained from each child's parent or guardian prior to his participation in the study.

Each child will be bled (10-15 ml) immediately prior to vaccination and 6 weeks following vaccination.

Vaccine dose is 0.5 ml given subcutaneously.

Each child will be followed clinically for 42 days following vaccination. All local and systemic complaints will be recorded on the case report form.

Schedule:

Time	Action
Day 0	Bleed 10-15 ml. Vaccinate 0.5 ml, subcutaneously.
Days 0-42	Clinical follow-up for local and systemic reactions.
Week 6	Bleed 10-15 ml.

Serology: Circulating levels of antibody before and after vaccination will be determined. Measles and rubella antibody levels will be determined by hemagglutination-inhibition test. Mumps antibody levels will be determined by serum neutralization test.

Clinical Forms: Attached.

Adverse Reactions: Any serious or alarming reaction, including death due to any cause during this investigation, whether related or not related to the test material, must be reported immediately to Merck & Co., Inc., through Dr. Maurice R. Hilleman, telephone (215) 699-5311, Ext. 5532, or in his absence, Dr. Allen F. Woodhour, telephone (215) 699-5311, Ext. 5588.

Unused Vaccine: All unused vaccine should be returned immediately to the Virus and Cell Biology Laboratories of the Merck Sharp & Dohme Research Laboratories, West Point, Pennsylvania 19486.

M. R. Hilleman, Ph.D.

MEASLES-MUMPS-RUBELLA VACCINAT[illegible] -

FAMILY No. _____ CASE No. _____

CHILD'S NAME _____ (LAST / FIRST / MIDDLE)

SEX _____ BIRTHDATE _____ AGE _____ HISTORY: MEASLES _____ MUMPS _____ RUBELLA _____

PARENTS NAME _____ (LAST / FIRST / MIDDLE) TELEPHONE No. _____

ADDRESS _____ (NUMBER / STREET / CITY / STATE)

LOCATION _____

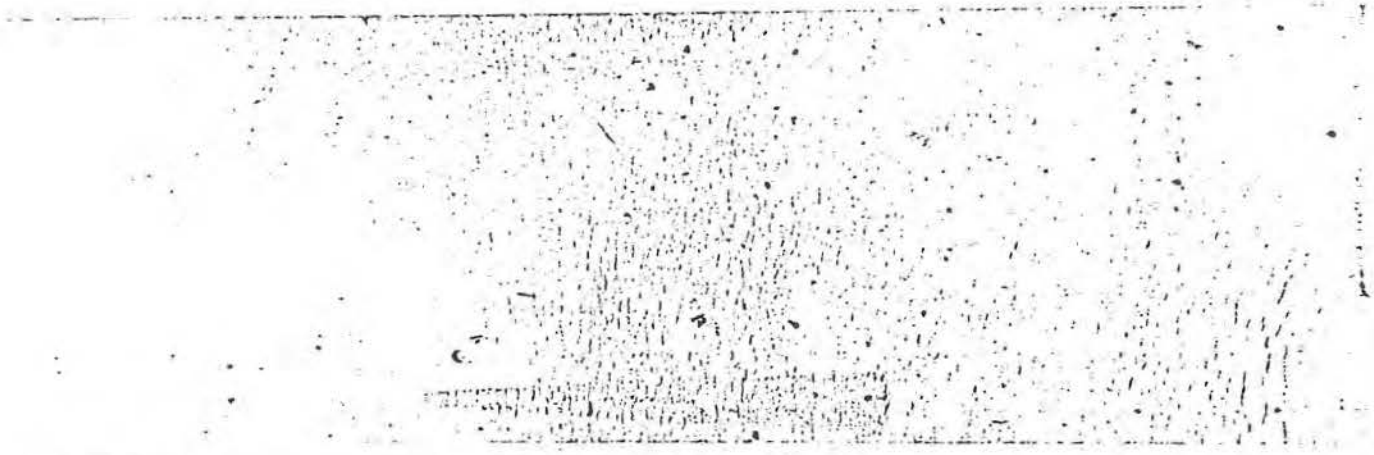
PRE-VACCINATION _____

CLINICAL _____

I consent to have my child, named above, receive live attenuated measles, mumps, rubella virus vaccine.

SIGNATURE _____

DATE _____



VACCINATION: VACCINE _____ LOT _____ (13-15) BLEEDINGS

1. DATE _____ (17-22) VOL. _____ SITE _____ PRE-VACCINATION _____ (17-22) CASE No. _____ (5-8)

POST-VACCINATION _____ (29-34)

BLEEDING DATE	SEROLOGY								
	MEASLES			MUMPS			RUBELLA		
TEST	1	2	3	1	2	3	1	2	3
TECHNIQUE									
1.									
2.									
3.									
4.									
	PRE	POST		PRE	POST		PRE	POST	
SUMMARY									

CLINICAL MEASLES ☐ MUMPS ☐ RUBELLA ☐ DATE ONSET _____

Isolation _____ Dx _____

CLINICAL SUMMARY

POST VAC.	MAX. TEMP.	CODE	COMPLAINTS	CODE	CODE
DAYS					
0-4	27-30	31		32-33	34-35
5-12	36-39	40		41-42	43-44
13-18	45-48	49		50-51	52-53
19-28	54-57	58		59-60	61-62

COMMENTS:

_____ PHYSICIAN

SYMPTOM RECORD

M-M-R Study No. _____

CHILD'S NAME _____ CASE NO. _____
(Last) (First) (Middle)

DAY	DATE	Temperature ☐ Rectal ☐ Oral *(Check One)*	NONE	RUNNY NOSE	SORE THROAT	COUGH	EAR ACHE	SWOLLEN GLANDS	SORE EYES	THROWING UP	DIARRHEA	STOMACH ACHE	RASH (describe)	SORE JOINTS	SORE ARM (at shot)	HEADACHE	HURTS ALL OVER	FEVER	WON'T EAT	COMMENTS
0																				
1																				
2																				
3																				
4																				
5																				
6																				
7																				
8																				
9																				
10																				
11																				
12																				
13																				
14																				
15																				
16																				
17																				
18																				
19																				
20																				
21																				
22																				
23																				
24																				
25																				
26																				
27																				
28																				
29																				
30																				
31																				
32																				
33																				
34																				
35																				
36																				
37																				
38																				
39																				
40																				
41																				
42																				

ver or unusual reaction develops, call:

DR. R. E. WEIBEL
Havertown, Pennsylvania – Phone: Hilltop 6-1110
OR
Children's Hospital of Philadelphia – EV 7-1309

PLEASE RETURN FOR FOLLOW-UP VISIT ON: _____

BE SURE TO BRING THIS RECORD ALONG WITH YOU.

P3954-0775(DOM)

Table 1

Serological Findings Among Children Who Received a 0.5 Ml Dose of Combined Live Measles-Mumps-Rubella (RA 27/3) Virus Vaccine, Lot No. 621/C-D763 (Study #443)

Age	Total No. Vacc.	No. Serol. Tested	Initially Seronegative to: Measles-Mumps-Rubella Conversions/Total Measles	Measles-Mumps-Rubella Conversions/Total Mumps	Measles-Mumps-Rubella Conversions/Total Rubella	Measles-Mumps Conversions/Total Measles	Measles-Mumps Conversions/Total Mumps	Measles-Rubella Conversions/Total Measles	Measles-Rubella Conversions/Total Rubella	Mumps-Rubella Conversions/Total Mumps	Mumps-Rubella Conversions/Total Rubella	Measles Only Conversions/ Total	Mumps Only Conversions/ Total	Rubella Only Conversions/ Total	Initially Seropositive to: Measles Mumps and Rubella
(Months) 11	8	6	6/6	6/6	6/6										
(Years) 1	68	64	48/52	50/52	52/52	0/1	1/1	7/7	7/7	2/2	2/2			2/2	
2	10	10	7/7	6/7	7/7	1/1	1/1			2/2	2/2				
3	5	5	3/3	3/3	3/3			1/1	1/1	1/1	1/1				
4	2	2								1/1	1/1	1/1			
5	3	3						1/1	1/1	2/2	2/2				
6	4	4								1/1	1/1			3/3	
7	1	0													
8	1	1													1
Total	102	95	64/68	65/68	68/68	1/2	2/2	9/9	9/9	9/9	9/9	1/1		5/5	1
Mean Age: 1.7 Years			(94.1%)	(95.6%)	(100%)										

Overall Conversion Rate

Measles	Mumps	Rubella
75/80 (93.8%)	76/79 (96.2%)	91/91 (100%)

5/4/77

Table 2

Serological, Temperature and Clinical Findings for 3 Children Who Received a 1.0 Ml Dose of Combined Live Measles-Mumps-Rubella (RA 27/3) Virus Vaccine, Lot No. 621/C-D763 (Study #443)

Vaccinee No.	Age (Years)	Serology Results			Days Post-Vaccination	Maximum Temperature (°F, Oral)	Clinical Complaints
(b) (6)	3	Measles	Pre	≥20	0-4	100.0	Gastrointestinal Illness
			Post	80	5-12	98.6	Gastrointestinal Illness
		Mumps	Pre	≥8	13-18	98.6	None Reported
			Post	64	19-28	98.6	None Reported
		Rubella	Pre	≥32	29-42	98.6	None Reported
			Post	256			
	4	Measles	Pre	<5	0-4	99.4	None Reported
			Post	20	5-12	100.0	Non-Specific Rash, Day 5
		Mumps	Pre	4	13-18	99.8	None
			Post	8	19-28	99.7	None
		Rubella	Pre	<8	29-42	99.6	None
			Post	256			
	1	Measles	Pre	<5	0-4	Not Taken	Upper Respiratory Illness, Otitis
			Post	10	5-12	Not Taken	Otitis
		Mumps	Pre	<2	13-18	98.6	None Reported
			Post	4	19-28	98.6	None Reported
		Rubella	Pre	<8	29-42	98.6	None Reported
			Post	32			

5/5/77

Table 3

Serological Findings Among Children Who Received a 0.5 Ml Dose of
Live Attenuated Rubella (RA 27/3) Virus Vaccine, Lot No. 579/C-D418 (Study #443)

Age	Total No. Vacc.	No. Serol. Tested	Initially Seropositive				Initially Seronegative			
			Fold Rise							
			2x	≥4x	Indet.	Total	No. Conv.	Failures	Total	Conv. Rate
(Months)										
10	1	1					1		1	1/1
11	8	8		1		1	7		7	7/7
(Years)										
1	42	41		3	3	6	35		35	35/35
2	13	12			4	4	8		8	8/8
3	11	11			4	4	7		7	7/7
4	9	9			3	3	6		6	6/6
5	3	3	1			1	2		2	2/2
6	1	1					1		1	1/1
7	1	0								
Total	89	86	1	4	14	19	67	0	67	100%
Mean Age: 1.9 Years										

5/4/77

Table 4

Distribution of Post-Vaccination Antibody Titers Among Children Who Were Initially Seronegative to Measles, Mumps and Rubella and Who Received a 0.5 Ml Dose of Combined Live Measles-Mumps-Rubella (RA 27/3) Virus Vaccine, Lot No. 621/C-D763 (Study #443)

Measles (HI)		Mumps (Neut.)		Rubella (HI)	
Post-Vaccination Titer	No. of Children	Post-Vaccination Titer	No. of Children	Post-Vaccination Titer	No. of Children
<5	4	<2	3	<8	
5		2	3	8	
10	2	4	16	16	1
20	9	8	26	32	2
40	13	16	8	64	18
80	20	32	11	128	19
160	12	64		256	25
320	7	128	1	512	3
640	1				
Total	68		68		68
Geometric Mean Titer:	57.0		8.2		136.1

5/4/77

Table 5

Distribution of Post-Vaccination Antibody Titers Among Children
Who Were Initially Seronegative to Rubella and Who Received a 0.5 ml Dose
of Live Attenuated Rubella (RA 27/3) Virus Vaccine, Lot No. 579/C-D418 (Study #443)

Rubella (HI)	
Post-Vaccination Titer	No. of Children
<8	
8	
16	1
32	4
64	10
128	21
256	20
≥512	11
Total	67
Geometric Mean Titer:	≥159.1

5/5/77

Table 6

Maximum Temperatures Reported Among Children Who Received a 0.5 Ml Dose of Combined Live Measles-Mumps-Rubella (RA 27/3) Virus Vaccine, Lot No. 621/C-D763 (Study #443)

Maximum Temperature (°F, Oral)	Total Vaccinees (102 Children)						Initially Seronegative to: Measles, Mumps, and Rubella (68 Children)					
	Days Post-Vaccination					No. with Max. Temp.	Days Post-Vaccination					No. with Max. Temp.
	0-4	5-12	13-18	19-28	29-42		0-4	5-12	13-18	19-28	29-42	
<99	53 (60.9%)	52 (59.1)	71 (83.5)	60 (71.4)	55 (65.5)	32	40 (63.5)	39 (61.9)	52 (83.9)	43 (70.5)	41 (68.3)	23
99 - 100.9	26 (30.0)	22 (25.0)	12 (14.1)	15 (17.9)	20 (23.8)	31	18 (28.6)	14 (22.2)	8 (12.9)	10 (16.4)	14 (23.3)	23
101 - 102.9	7 (8.0)	13 (14.8)	1 (1.2)	5 (5.9)	7 (8.3)	21	5 (7.9)	9 (14.3)	1 (1.6)	4 (6.6)	4 (6.7)	14
103 - 104.9	1 (1.1)	1 (1.1)	1 (1.2)	3 (3.6)	2 (2.4)	6		1 (1.6)	1 (1.6)	3 (4.9)	1 (1.7)	4
105.0				1 (1.2)		1				1 (1.6)		1
Not Taken	15	14	17	18	18	11	5	5	6	7	8	3

5/5/77

Table 7

High Temperatures Reported Among Children Who Received a 0.5 Ml Dose of Combined Live Measles-Mumps-Rubella (RA 27/3) Virus Vaccine, Lot No. 621/C-D763 (Study #443)

Vaccinee No.	Temperature (°F, Oral)	Days	Clinical Complaints	Serology					
				Measles		Mumps		Rubella	
				Pre	Post	Pre	Post	Pre	Post
(b) (6)	102.2	5	None Reported (Had Measles-Like Rash Days 7-10)	<5	160	<2	4	<8	64
	102.0	2, 5	URI	<5	20	<2	4	<8	256
	104.0	17	URI, Otitis, Ophthalmopathy, Anorexia, Allergic Rash						
	105.0	23	URI						
	104.0	24	URI						
	102.0	25	URI						
	103.0	27, 32	Teething						
	102.0	33	Teething						
	102.0	32	Anorexia	<5	40	<2	8	16	128
	102.0	10	None Reported	<5	40	<2	4	<8	64
	102.0	9	URI, Irritability, Gastrointestinal Illness	<5	20	<2	16	<8	512
	102.0	35-36	URI	<5	160	≥8	≥128	<8	256
	102.0	2	URI	<5	<5	<2	2	≥32	32
	102.0	7	None Reported (Developed Measles-Like Rash on Day 12)	<5	80	≥8	8	<8	128
	102.0	10	URI, Lymphadenopathy, Anorexia	<5	40	≥8	8	<8	128
	103.0	7	URI, Otitis, Ophthalmopathy, Gastrointestinal Illness	<5	80	<2	4	<8	256
	102.0	8	URI, Otitis, Ophthalmopathy, Gastrointestinal Illness						
	103.0	28	URI, Otitis, Ophthalmopathy, Lymphadenopathy, Non-Specific Rash on Arms, Legs, Face	<5	80	<2	4	<8	128
	103.0	4	URI, Gastrointestinal Illness	QNS	QNS	QNS	QNS	<8	8
	102.0	0	URI, Anorexia	<5	80	≥8	≥128	<8	512
	103.0	20-21	Herpes Stomatitis, Anorexia	<5	40	<2	8	<8	256
	102.7	33	URI	<5	<5	<2	8	<8	256
	102.0	3-4	URI	<5	80	<2	8	<8	128
	103.0	24	Gastrointestinal Illness	<5	80	<2	32	<8	256
	103.5	38-42	Allergic Rash	NS	NS	NS	NS	NS	NS

5/6/77

Table 8

Maximum Temperatures Reported Among Children Who Received a 0.5 Ml Dose of Live Attenuated Rubella (RA 27/3) Virus Vaccine, Lot No. 579/C-D418 (Study #443)

Maximum Temperature (°F, Oral)	Total Vaccinees (89 Children)						Initially Seronegative to: Rubella (67 Children)					
	Days Post-Vaccination					No. with Max. Temp.	Days Post-Vaccination					No. with Max. Temp.
	0-4	5-12	13-18	19-28	29-42		0-4	5-12	13-18	19-28	29-42	
<99	54 (70.0%)	53 (69.7)	57 (80.3)	55 (78.6)	57 (83.8)	40	38 (66.7)	37 (66.1)	40 (78.4)	37 (74.0)	37 (77.1)	26
99 - 100.9	19 (24.7)	17 (22.4)	11 (15.5)	8 (11.4)	10 (14.7)	25	16 (28.1)	14 (25.0)	9 (17.6)	8 (16.0)	10 (20.8)	21
101 - 102.9	4 (5.2)	5 (6.6)	2 (2.8)	5 (7.1)	1 (1.5)	10	3 (5.3)	4 (7.1)	1 (2.0)	3 (6.0)	1 (2.1)	8
103 - 104.9		1 (1.3)	1 (1.4)	1 (1.4)		3		1 (1.8)	1 (2.0)	1 (2.0)		3
105.0				1 (1.4)		1				1 (2.0)		1
Not Taken	12	13	18	19	21	10	10	11	16	17	19	8

5/6/77

Table 9

High Temperatures Reported Among Children Who Received a 0.5 Ml Dose of Live Attenuated Rubella (RA 27/3) Virus Vaccine, Lot No. 579/C-D418 (Study #443)

Vaccinee No.	Temperature (^{o}F, Oral)	Days	Clinical Complaints	Serology	
				Pre	Post
(b) (6)	102.2	7-8	None Reported	<8	128
	102.0	23	Upper Respiratory Illness	<8	64
	102.0	36	Upper Respiratory Illness, Otitis, Lymphadenopathy, Myalgia	<8	128
	102.0	6	Upper Respiratory Illness	<8	128
	105.0	24	Pneumonia	<8	64
	102.1	9	Upper Respiratory Illness	≥32	≥1024
	102.0	18	None Reported		
	102.0	27	None Reported		
	103.0	18	Gastrointestinal Illness, Anorexia	<8	≥1024
	104.0	27	Upper Respiratory Illness	<8	512
	103.0	12	Upper Respiratory Illness	<8	256

5/5/77

Table 10

Clinical Complaints Reported Among Children Who Received a 0.5 Ml Dose of Combined Live Measles-Mumps-Rubella (RA 27/3) Virus Vaccine, Lot No. 621/C-D763 (Study #443)

Clinical Complaint	Total Vaccinees (102 Children)						Initially Seronegative to: Measles, Mumps and Rubella (68 Children)					
	Days Post-Vaccination					No. with Complaint	Days Post-Vaccination					No. with Complaint
	0-4	5-12	13-18	19-28	29-42		0-4	5-12	13-18	19-28	29-42	
Soreness at Injection Site	4 (4.2%)			1 (1.0)		5	2 (3.0)					2
Lymphadenopathy	2 (2.1)	3 (3.1)		2 (2.1)	2 (2.1)	6	1 (1.5)	1 (1.5)		2 (3.0)	2 (3.0)	3
Measles-Like Rash	1 (1.0)	9 (9.4)	6 (6.2)	1 (1.0)		11	1 (1.5)	7 (10.4)	5 (7.5)	1 (1.5)		9
Arthralgia			1 (1.0)	1 (1.0)		1			1 (1.5)	1 (1.5)		1
Myalgia		1 (1.0)				1		1 (1.5)				1
Irritability	3 (3.0)	3 (3.0)	1 (1.0)	1 (1.0)	1 (1.0)	4	2 (2.9)	2 (2.9)	1 (1.5)	1 (1.5)		3
Headache	2 (2.1)	2 (2.1)				2	2 (3.0)	2 (3.0)				2
Upper Respiratory Illness	38 (39.6)	37 (38.5)	24 (25.0)	35 (36.5)	32 (33.3)	64	28 (41.8)	27 (40.3)	20 (29.8)	25 (37.3)	20 (29.8)	46
Otitis	1 (1.0)	7 (7.3)	2 (2.1)	5 (5.2)	4 (4.2)	14	1 (1.5)	4 (6.0)	2 (3.0)	3 (4.5)	2 (3.0)	9
Ophthalmopathy	2 (2.1)	3 (3.1)	2 (2.1)	4 (4.2)	2 (2.1)	6	2 (3.0)	3 (4.5)	2 (3.0)	4 (6.0)	2 (3.0)	6
Gastrointestinal Illness	18 (18.7)	24 (25.0)	9 (9.4)	17 (17.7)	15 (15.6)	43	14 (20.9)	19 (28.4)	9 (13.4)	14 (20.9)	11 (16.4)	35
Anorexia	13 (13.5)	19 (19.8)	8 (8.3)	10 (10.4)	13 (13.5)	28	10 (14.9)	12 (17.9)	6 (9.0)	9 (13.4)	11 (16.4)	20
Fatigue				1 (1.0)		1				1 (1.5)		1
Rash-Chafing, Diaper, Heat, Herpes	4 (4.2)	4 (4.2)	1 (1.0)	4 (4.2)	5 (5.2)	12	3 (4.5)	4 (6.0)	1 (1.5)	3 (4.5)	3 (4.5)	9
Allergy, Asthma	1 (1.0)	2 (2.1)	3 (3.1)	2 (2.1)	3 (3.1)	6		1 (1.5)	2 (3.0)	1 (1.5)		3
Fever	1 (1.0)	1 (1.0)		2 (2.1)	1 (1.0)	4		1 (1.5)		1 (1.5)		2
Sudoresis	1 (1.0)					1	1 (1.5)					1
Teething	3 (3.0)			1 (1.0)	3 (3.0)	6	3 (4.4)			1 (1.5)	3 (4.4)	6
Persons with Complaints:	50 (52.1)	50 (52.1)	23 (34.4)	43 (44.8)	44 (45.8)	78	38 (56.7)	38 (56.7)	29 (43.3)	32 (47.8)	30 (44.8)	58
Persons with No Complaints:	46 (47.9)	46 (47.9)	63 (65.6)	53 (55.2)	52 (54.2)	18	29 (43.3)	29 (43.3)	38 (56.7)	35 (52.2)	37 (55.2)	9
Negative Physician Surveillance	6	6	6	6	6	6	1	1	1	1	1	1

5/6/77

Table 11

Clinical Complaints Reported Among Children Who Received a 0.5 Ml Dose of Live Attenuated Rubella (RA 27/3) Virus Vaccine, Lot No. 579/C-D418 (Study #443)

Clinical Complaint	Total Vaccinees (89 Children)						Initially Seronegative to: Rubella (67 Children)					
	Days Post-Vaccination					No. with Complaint	Days Post-Vaccination					No. with Complaint
	0-4	5-12	13-18	19-28	29-42		0-4	5-12	13-18	19-28	29-42	
Soreness at Injection Site	7 (8.4%)					7	6 (9.5)					6
Lymphadenopathy		1 (1.2)		1 (1.2)	1 (1.2)	3		1 (1.6)		1 (1.6)	1 (1.6)	3
Rubella-Like Rash		2 (2.4)	1 (1.2)			3		2 (3.2)	1 (1.6)			3
Arthralgia	1 (1.2)				1 (1.2)	1	1 (1.6)				1 (1.6)	1
Myalgia	1 (1.2)		1 (1.2)	1 (1.2)	1 (1.2)	3	1 (1.6)		1 (1.6)	1 (1.6)	1 (1.6)	3
Irritability	1 (1.2)	3 (3.6)		1 (1.2)	2 (2.4)	5	1 (1.6)	3 (4.8)		1 (1.6)	2 (3.2)	5
Headache	3 (3.6)	2 (2.4)		2 (2.4)		6	3 (4.8)	1 (1.6)		2 (3.2)		5
Upper Respiratory Illness	30 (36.1)	23 (27.7)	13 (15.7)	14 (16.9)	15 (18.1)	45	24 (38.1)	18 (28.6)	9 (14.3)	12 (19.0)	12 (19.0)	37
Lower Respiratory Illness				1 (1.2)		1				1 (1.6)		1
Otitis	1 (1.2)	5 (6.0)	1 (1.2)	1 (1.2)	5 (6.0)	10	1 (1.6)	4 (6.3)	1 (1.6)	1 (1.6)	5 (7.9)	9
Ophthalmopathy	1 (1.2)	1 (1.2)	3 (3.6)	2 (2.4)	1 (1.2)	4	1 (1.6)	1 (1.6)	2 (3.2)	1 (1.6)	1 (1.6)	3
Gastrointestinal Illness	12 (14.5)	11 (13.3)	4 (4.8)	9 (10.8)	10 (12.0)	30	11 (17.5)	9 (14.3)	4 (6.3)	7 (11.1)	7 (11.1)	25
Anorexia	12 (14.5)	8 (9.6)	7 (8.4)	6 (7.2)	5 (6.0)	16	9 (14.3)	7 (11.1)	6 (9.5)	5 (7.9)	4 (6.3)	13
Fatigue			1 (1.2)			1			1 (1.6)			1
Rash-Chafing, Diaper, Heat	10 (12.0)	6 (7.2)	6 (7.2)	7 (8.4)	4 (4.8)	15	8 (12.7)	5 (7.9)	5 (7.9)	6 (9.5)	4 (6.3)	13
Allergy, Asthma	2 (2.4)	1 (1.2)	2 (2.4)	1 (1.2)	2 (2.4)	3	1 (1.6)	1 (1.6)	2 (3.2)	1 (1.6)	2 (3.2)	2
Fever					1 (1.2)	1					1 (1.6)	1
Depression		1 (1.2)				1		1 (1.6)				1
Teething		1 (1.2)	1 (1.2)	1 (1.2)	1 (1.2)	2		1 (1.6)	1 (1.6)	1 (1.6)	1 (1.6)	2
Impetigo, Mosquito Bites			1 (1.2)	1 (1.2)		2			1 (1.6)	1 (1.6)		2
Persons with Complaints:	50 (60.2)	37 (44.6)	29 (34.9)	31 (37.3)	31 (37.3)	65	39 (61.9)	30 (47.6)	24 (38.1)	27 (42.9)	26 (41.3)	53
Persons with No Complaints:	33 (39.8)	46 (55.4)	54 (65.1)	52 (62.7)	52 (62.7)	18	24 (38.1)	33 (52.4)	39 (61.9)	36 (57.1)	37 (58.7)	10
Negative Physician Surveillance:	6	6	6	6	6	6	4	4	4	4	4	4

5/6/77

CLINICAL SUMMARY

Study Name - Combined Live Measles-Mumps-Rubella (RA 27-3) Virus Vaccine and Live Rubella (RA 27/3) Virus Vaccine

Study Number - Clinical Protocol - 443

Material - M-M-R Lot #621/C-D763
Rubella Lot #579/C-D418

Initiated - October 28, 1975

Completed - January 20, 1977

Medical Opinion

For 15 months 194 children (ages 10 months to 8 years) from the open population were enrolled in this study at Children's Hospital of Philadelphia, Philadelphia, Pennsylvania; Darby Health Clinic, Darby, Pennsylvania; and Dr. G. Starkweather's office, Havertown, Pennsylvania. Informed consent was obtained from the parent for each child and a blood sample was obtained from 184 children initially and approximately 6 weeks later. All vaccine was given subcutaneously in the arm. One hundred and two children (mean 1.7 years) received 0.5 ml. M-M-R; 3 (mean 2.7 years) received 1.0 ml. M-M-R; and 89 children (mean 1.9 years) received 0.5 ml. rubella vaccine. All but 12 parents returned report cards with daily temperatures and clinical observations for 42 days following administration of the vaccine. Parents were instructed to report high fevers and rash by telephone to R. E. W. and on follow-up were queired on recorded observations for greater detail.

Among susceptible and immune vaccinees temperature elevations were scattered randomly throughout the observation period with no greater association with either vaccine. Most temperature elevations probably reflect unrelated infection occurring among the vaccinees at various time periods. Upper respiratory and gastrointestinal infections were reported in about 55% and 40% of vaccinees respectively. Temperatures were not recorded on approximately 10% of the vaccinees. A faint measles-like rash occurred in 9 triple susceptible children receiving M-M-R and 3 ausceptibles receiving rubella vaccine alone. Mild transient arthralgia was reported by the parent but not observed by a medical person in one M-M-R susceptible vaccinee, age 12 months, on day 17-20 (4 days); and one rubella susceptible vaccinee age 5 years on day one and 30 (2 days). No arthritis or adverse clinical reaction was reported.

Of 68 children initially susceptible to measles-mumps-rubella receiving 0.5 ml. M-M-R vaccine 94%, 96%, and 100% respectively, responded serologically with geometric mean titers as follows: measles (HI) 57.0; mumps (neut.) 8.2; and rubella (HI) 136.1. All 67 rubella susceptible vaccinees responded serologically with a geometric mean hemagglutination titer equal to or greater than 159.1. Of the three children receiving 1.0 ml. M-M-R, all susceptibles responded, however, one was initially immune to M-M-R and one to mumps.

Seroconversion of susceptible children to rubella vaccine alone or in combined M-M-R was 100% with comparable hemagglutination inhibiting geometric mean titers. Seroconversion rates and geometric mean titers to measles and mumps vaccine following M-M-R (RA 27/3) are similar to those following M-M-R (HPV-77) reported in earlier studies. Live RA 27/3 rubella virus vaccine alone or combined with live measles and live mumps virus vaccine induced measureable antibodies in all rubella susceptible vaccinees with no significant clinical reaction.

Jan. 7, 1977 Robert E. Weibel

Robert E. Weibel, M.D.

REW:ceb

MEMO

To File Location Date 2/2/78

From T. Schofield Location

Subject Statistical Analysis - Study #443

Analysis of variance was conducted on post titers of children who were initially seronegative to rubella who received rubella vaccine, lot #579 (Group 1), and combined measles-mumps-rubella vaccine, lot #621 (Group 2).

No significant difference exists between these two groups. Geometric mean titers were:

Vaccine	GMT
Rubella	159.1
MMR	130.9

There is no significant difference in conversion rate among these two groups.

T.S.

SYMPTOM RECORD

RUBELLA Study No. _____

LD'S NAME _____ CASE NO. _____
(Last) (First) (Middle)

DAY	DATE	Temperature ☐ Rectal ☐ Oral (Check One)	NONE	RUNNY NOSE	SORE THROAT	COUGH	EAR ACHE	SWOLLEN GLANDS	SORE EYES	THROWING UP	DIARRHEA	STOMACH ACHE	RASH (describe)	SORE JOINTS	SORE ARM (at shot)	HEADACHE	HURTS ALL OVER	FEVER	WON'T EAT	COMMENTS
0																				
1																				
2																				
3																				
4																				
5																				
6																				
7																				
8																				
9																				
10																				
11																				
12																				
13																				
14																				
15																				
17																				
18																				
19																				
20																				
21																				
22																				
23																				
24																				
25																				
26																				
27																				
28																				
29																				
30																				
31																				
32																				
33																				
34																				
35																				
36																				
37																				
38																				
39																				
40																				

with combination vaccines.

INFORMATION AND CONSENT FORM: Attached

REACTION REPORTING FORM: Attached

Stephen J. Lerman, M.D.
Director - Pediatric Infectious Disease Unit
University of Nebraska Medical Center

11/30/76

THE UN. _RSITY OF NEBRASKA MEDICAL C. .TER
42ND AND DEWEY AVENUE
OMAHA, NEBRASKA 68105

ARTMENT OF PEDIATRICS

Glen.. C. Rosenquist, M.D.
402/541-4941
Chairman
William R. Brown
402/541-4942
Administrator

CARDIOLOGY
402/541-4741, 4742 or 4166
Paul K. Mooring, M.D., Director
Glenn C. Rosenquist, M.D.
Philip J. Hofschire, M.D.
Edward B. Clark, M.D.
Roger N. Ruckman, M.D.
Tancy Jahn, R.N., Nurse Associate

CYSTIC FIBROSIS
402/541-415[illegible]
Gordon E. Gibbs, M.D., Ph.D.

DENTISTRY
402/541-7344
John F. Simon, D.D.S., Director
L. Russel Misner, D.D.S.
Curtis G. Kuster, D.D.S.

DEVELOPMENTAL PEDIATRICS
402/541-7766
Paul H. Pearson, M.D., Director
E. Jack Trembath, M.B., B.S.
Donald Wuori, M.D.

ENDOCRINOLOGY
402/541-7335
Carol A. Huseman, M.D.

FAMILY SERVICE SECTION
402/541-4885
Louise F. Eaton, M.D.
Director, Psychiatry
Jeal Kittell, ACSW, Social Worker
[illegible]n Lathrop
[illegible]hild Life Coordinator

GASTROENTEROLOGY
402/541-7348
Jon A. Vanderhoof, M.D.

GENERAL AND AMBULATORY PEDIATRICS
402/541-7346
Mark B. Horton, M.D., Director
402/541-4208
Peter W. Bickers, M.D.
Samuel Perry, M.D.
Bonnie Shearer, P.A.

HEMATOLOGY & ONCOLOGY
402/541-7349
Rashid Al-Rashid, M.D.

HUMAN GENETICS
402/541-4570
James Eisen, Ph.D., Director
Warren G. Sanger, Ph.D.

INFECTIOUS DISEASE
402/541-7336
Stephen J. Lerman, M.D.

METABOLISM
402/541-7350
Hobart E. Wiltse, M.D., Ph.D.

NEONATOLOGY
402/541-7340
Yoshio Miyazaki, M.D., Director
David L. Bolam, M.D.
Charles L. Paxson, M.D.

NEPHROLOGY
402/541-7339
Carol R. Angle, M.D.

NEUROLOGY
402/541-4084
[illegible]rd Pellegrino, M.D.
[illegible]Kader, M.D.

PSYCHOLOGY SECTION
402/541-7608
J. Michael Leibowitz, Ph.D.
Director
402/541-4886
Lee Matthews, Ph.D.
Susan Ogborn, M.S.

April 11, 1978

To: Measles-Mumps-Rubella Vaccine Study Participants

From: Jan Brunken RN
Pediatric Infectious Disease Unit

Subject: March M-M-R Vaccine Study Progress Report

Here is the current breakdown of the numbers of children participating in the study to date (March 31):

	Entered	Completed
Zahller	9	9
Nelson/Rice	2	2
Wax/McAveney	13	13
Ellison/Glow/Oberst	2	2
Maragos	0	0
Pott. Co. Immun. Clinic	19	18
Offutt AFB	147	97
UNMC Pediatric Clinic	53	36
Cogley Clinic	11	7
UNMC-South Omaha Clinic	0	0
UNMC-5 North	1	1
Total	257	185

Our goal for the month of April is to pass the halfway mark of 275 children enrolled in the study!

Program: Study #459 - To evaluate and compare clinical and immunological responses to two combined measles-mumps-rubella virus vaccines and component vaccines of these.

Vaccine: Combined live measles-mumps-rubella (RA 27/3) virus vaccine
Lot #60664/C-E810
Combined live measles-mumps-rubella (HPV-77) virus vaccine
M-M-R
Live attenuated RA 27/3 rubella virus vaccine
Lot #60151/C-E665
Live attenuated HPV-77 + 5 duck embryo cell passages rubella virus vaccine
MERUVAX
Live measles virus vaccine
ATTENUVAX
Live mumps virus vaccine
MUMPSVAX
Rubella placebo

Responsible Clinical Investigator:

Stephen J. Lerman, M.D.
Assistant Professor of Pediatrics
and Medical Microbiology
Director, Pediatric Infectious Disease Unit
42nd Street and Dewey Avenue
Omaha, Nebraska 68105

Study Locations:

F. Marshall Zahller, M.D., Omaha, Nebraska
Larry Rice, M.D., Paul J. Nelson, M.D., Omaha, Nebraska
James I. Wax, M.D., Omaha, Nebraska
Joseph R. Ellison, M.D., Omaha, Nebraska
George D. Maragos, M.D., Omaha, Nebraska
Mark B. Horton, M.D., Outpatient Clinic, University of Nebraska Medical Center, Omaha, Nebraska
Colonel James Hart, M.D., Burt Culpepper, M.D., Offutt Air Force Base, Omaha, Nebraska
William J. McAveney, M.D., Omaha, Nebraska
Donald T. Glow, M.D., Byron B. Oberst, M.D., Omaha Children's Clinic, Omaha, Nebraska
Yuksel Inankur, M.D., Izzat Jabro, M.D., Dennis Jones, M.D., C. Edwards, M.D., Jim Mulry, M.D., Anthony Romano, M.D., Cogley Clinic, Council Bluffs, Iowa
Pottawattamie County Immunization Clinic, Lee Martin Therapy Center, Council Bluffs, Iowa

Date Study Initiated: May 31, 1977

Date Study Completed: In Progress

Study Procedure:

To date, 257 children have entered the study. Each received a 0.5 ml subcutaneous dose of one of the vaccines. Blood samples were obtained on the day of vaccination and 6 weeks after vaccination, at which time each child received vaccine with those components not in the initial injection. Each child was followed 6 weeks for clinical complaints.

STUDY #459

COMPARISON OF MEASLES - MUMPS - RUBELLA (HPV-77:DE-5 and RA 27/3) VACCINES IN YOUNG CHILDREN

PURPOSE

This study will compare antibody and clinical responses in young children to live, attenuated measles, mumps, and rubella vaccines, given singly and together, utilizing either HPV-77:DE-5 or RA 27/3 as the rubella components.

BACKGROUND

HPV-77:DE-5 rubella vaccine was licensed in 1969 and is the most widely-used rubella vaccine in the United States. Although HPV-77:DE-5 vaccinees appear to be protected against viremia and fetal infection, HPV-77:DE-5 vaccine has been criticized because up to 80% of vaccinees may experience asymptomatic re-infection (antibody titer boost and pharyngeal virus excretion) on exposure to wild rubella virus. In comparison with natural rubella infection the serum antibody response to HPV-77:DE-5 is quantatively and qualitatively diminished, and secretory antibody is lacking. RA 27/3 rubella vaccine has been proposed as a better immunizing agent because the serum and secretory antibody responses more closely resemble natural rubella infection, and because the rate of asymptomatic re-infection on exposure to wild rubella virus is almost as low as that seen in naturally immune subjects. In addition, RA 27/3 rubella vaccine, grown in human tissue culture, should obviate any problem of allergy to foreign protein. Both rubella vaccines have shown similar age-dependent rates of arthralgia and arthritis.

VACCINES

Vaccines will be supplied in single-dose, coded vials by Merck Sharp & Dohme. Measles (Attenuvax), mumps (Mumpsvax), rubella (Meruvax), and the combination of the three (M-M-R) are licensed products. RA 27/3 rubella virus was originally isolated in Dr. Stanley Plotkin's laboratory from the third

explant of the 27th fetus aborted because of rubella infection during the 1964 epidemic. It has been attenuated by (b) (4) in WI-38 human diploid fibroblast tissue culture.

The lot of vaccine to be used has been fully tested for potency and safety at the Merck Sharp & Dohme Research Laboratories. Vaccine dose is 0.5 ml. given subcutaneously. Dried vaccine should be stored at -20° C (freezer) until used. Reconstituted vaccine should be kept at 4° C (refrigerator), and unused rehydrated vaccine should be discarded after four hours.

STUDY POPULATION

Children one through four years of age who have a negative history of measles, mumps, and rubella, both disease and vaccination, will be recruited by their private or clinic physician at the time they are due to receive these vaccinations.

CAUTION

Any child in the following categories should not be vaccinated.

1. Known sensitivity to chicken or duck, chicken or duck eggs or feathers, or to neomycin.
2. Leukemia or other malignancies, immunologic disorders, immunosuppressive or steroid therapy.
3. Current febrile illness. (Children with non-febrile upper respiratory infection may be vaccinated).

STUDY PROCEDURE

After informed consent has been obtained, an 8-10 cc blood sample will be drawn and children will be randomly assigned to receive one of the following:

Vaccine	No. of Children
Measles-Mumps-HPV-77:DE-5 Rubella	150
Measles-Mumps-RA 27/3 Rubella	150
Measles	50
Mumps	50

Vaccine	No. of Children
HPV-77:DE-5 Rubella	50
RA 27/3 Rubella	50
Placebo	50
Total	550

The parent will be given a reaction reporting form and a thermometer and will be instructed in taking temperatures. They will be asked to take daily temperatures and record all symptoms which occur during the following six weeks.

Six weeks after vaccination, children will return for a second 8-10 cc. blood sample. At this time, reaction reporting forms will be reviewed with the parent and collected. All children will then receive the standard measles, mumps, and rubella vaccine to assure immunization for all three diseases.

SEROLOGIC STUDIES

Participating physicians will refrigerate blood samples which will be picked up by messenger three times a week. Serum will be separated, with an aliquot sent to Merck Sharp & Dohme for rubella preciptin antibody testing and the remainder retained for rubella and measles hemagglutination inhibition antibody and mumps neutralization antibody testing in the University of Nebraska Medical Center Virus Laboratory of Dr. Roberta White.

DATA ANALYSIS

We will compare symptoms (e.g. rash, fever, arthralgia), seroconversion rates and geometric mean titers in children who received combination vaccines, individual component vaccines, or placebo. We will look specifically for evidence of either enhanced reactogenicity or diminished serologic responsiveness

Table 1

Seroconversions and Geometric Mean Titers for Children
Who Were Initially Seronegative Prior to Vaccination (Study #459)

	Age		Measles	Mumps	Rubella
Vaccine	Range	Mean	No. Conv./Total (GMT)	No. Conv./Total (GMT)	No. Conv./Total (GMT)
ATTENUVAX	14m - 3y	1.5	6/6 (90)		
MUMPSVAX	14m - 4y	1.7		11/12 (12)	
RUBELLA (HPV-77)	14m - 2y	1.4			6/7 (95)
RUBELLA (RA 27/3)	14m - 4y	1.6			11/11 (199)
M-M-R (HPV-77)	14m - 4y	1.5	20/20 (77)	20/20 (14)	20/20 (111)
M-M-R (RA 27/3)	14m - 4y	1.6	13/14 (62)	13/14 (17)	14/14 (269)

Statistical nonparametric comparison shows no suppression of post-vaccination antibody titer of any component when administered in combined form with rubella RA 27/3 or HPV-77.

4/20/78

Table 2

Completed Serology for Children
Receiving ATTENUVAX, Study #459

	Measles HI	
Case #	Pre	Post
(b) (6)	<5	80
	<5	
	<5	
	<5	
	<5	40
	<5	80
	<5	160
	<5	160
	<5	80

4/19/78

Table 3

Completed Serology for Children
Receiving MUMPSVAX, Study #459

Case #	Mumps Neut. Pre	Mumps Neut. Post
(b) (6)	<2	<2
	<2	>64
	<2	4
	<2	64
	<2	
	4	8
	<2	32
	<2	2
	<2	16
	2	8
	<2	8
	<2	16
	<2	32
	<2	8
	<2	16

4/19/78

Table 4

Completed Serology for Children
Receiving Rubella (HPV-77), Study #459

Case #	Rubella HI Pre	Rubella HI Post
(b) (6)		<8
	<8	
	<8	
		≥512
	<8	128
	<8	≥512
	<8	128
	<8	≥512
	<8	32
	<8	≥512
	<8	<8

4/19/78

Table 5

Completed Serology for Children
Receiving Rubella (RA 27/3), Study #459

	Rubella HI	
Case #	Pre	Post
(b) (6)	<8	128
	<8	256
	<8	128
	<8	64
	<8	≥512
	<8	64
	<8	≥512
	<8	
	<8	≥512
	256	≥512
	<8	256
	<8	≥512
	<8	64

4/20/78

Table 6

Completed Serology for Children
Receiving M-M-R (HPV-77), Study #459

	Measles HI		Mumps Neut.		Rubella HI	
Case #	Pre	Post	Pre	Post	Pre	Post
(b) (6)						
	<5	160	<2	16	<8	256
	<5		<2		<8	
		64		160		8
	<5	≥320	<2	8	<8	256
		160	<2			64
	<5	80	<2	4	<8	256
	<5	20	2	≥64	<8	256
	<5	160	<2	≥64	<8	64
	<5		<2		<8	
	<5	40	<2	64	<8	64
	<5	20	<2	16	<8	256
	<5	40	<2	32	<8	64
	<5	160	<2	16	<8	256
	<5	160	<2	16	<8	128
	<5	40	<2	4	<8	16
		80		32		64
	<5	80	<2	8	8	32
	QNS	QNS	QNS	QNS	<8	128
	<5	80	<2	QNS	<8	64
	QNS	120	QNS	32	<8	≥512
	<5	80	<2	32	<8	256
	<5		<4*		<8	
	<5		<2		<8	
	<5	40	<2	16	<8	256
	<5	80	<2	8	<8	64
	<5		<2		<8	
	<5	80	<2	8	<8	≥512
	<5		<2		<8	
	<5	160	2	≥64	<8	128
	<5		QNS		<8	
	<5	40	<2	4	<8	32
	<5	160	<2	4	<8	64
	<5	160	<2	32	<8	128
	<5	40	<2	32	<8	≥512
	<5	40	<2	32	<8	16

* Toxicity at 1:2 level

4/20/78

Table 7

Completed Serology for Children
Receiving M-M-R (RA 27/3), Study #459

	Measles HI		Mumps Neut.		Rubella HI	
Case #	Pre	Post	Pre	Post	Pre	Post
(b) (6)						
	<5	<5	<2	16	<8	256
	<5	160	<2	64	<8	256
	<5	20	8	8	<8	256
	<5	40	<2	<2	<8	256
	<5	80	<2	4	<8	128
	80	20	<2	4	<8	128
	<5	20	<2	16	<8	256
	<5	40	2	32	<8	≥512
	<5	160	4	4	256	≥512
	<5	20	QNS	8	<8	256
	<5	160	<2	16	<8	256
	<5	80	<4*	32	<8	128
	<5	80	QNS	<4*	<8	8
	<5	80	<2	≥64	<8	≥512
	<5	QNS	<2	QNS	<8	256
	<5	160	<2	32	<8	≥512
	<5	160	<2	16	<8	256
	<5	≥320	<2	16	<8	128
	<5	40	<2	8	<8	≥512
		80		8		256
	<5	80	<2	≥64	<8	≥512
	80	80	QNS	16	32	≥512
	<5	40	≥64	≥64	<8	256
	<5	40	<2	16	<8	256
	<5		16		<8	
	<5		<2		<8	
	QNS		QNS		<8	
	<5	QNS	<2	QNS	<8	8

* Toxicity at 1:2 level

4/20/78

Table 8

Maximum Temperatures Reported Among Children Who Received Combined
Live Measles-Mumps-Rubella (RA 27/3) Virus Vaccine, Lot #60664/C-E810 (Study #459)

Maximum Temperature (°F, Oral)	Total Vaccinees (41 Children)						Initially Seronegatives (16 Children)					
	Days Post Vaccination					No. with Max. Temp.	Days Post Vaccination					No. with Max. Temp.
	0-4	5-12	13-18	19-28	29-42		0-4	5-12	13-18	19-28	29-42	
<99	33 (80.5%)	32 (78.0)	34 (82.9)	32 (78.0)	30 (75.0)	17	13 (81.3)	12 (75.0)	14 (87.5)	10 (62.5)	13 (86.7)	7
99 - 100.9	7 (17.1)	3 (7.3)	2 (4.9)	4 (9.8)	3 (7.5)	4	3 (18.8)	2 (12.5)	1 (6.3)	3 (18.8)	1 (6.7)	2
101 - 102.9	1 (2.4)	5 (12.2)	3 (7.3)	3 (7.3)	5 (12.5)	14		2 (12.5)		2 (12.5)	1 (6.7)	5
103 - 104.9		1 (2.4)	2 (4.9)	2 (4.9)	1 (2.5)	6			1 (6.3)	1 (6.3)		2
Fever - No Temperature Taken					1 (2.5)							
Temperature Not Taken					1						1	

Case No.	Max. Temp.	Days	Clinical Complaint	Serology Measles		Mumps		Rubella	
(b) (6)	103.0	20-21	Upper Respiratory Illness, Gastrointestinal Illness	<5	160	<2	64	<8	256
	103.0	36	Gastrointestinal Illness						
	102.0	11-12	Upper Respiratory Illness, Gastrointestinal Illness						
	102.4	24-25	Upper Respiratory Illness, Nonspecific Rash, Anorexia						
	102.2	40-41	Upper Respiratory Illness, Ophthalmopathy, Anorexia, Irritability, Teething	<5	20	8	8	<8	256
	103.0	13-17	Upper Respiratory Illness, Anorexia						
	102.1	10-11	Upper Respiratory Illness, Anorexia	<5	80	<2	4	<8	128
	102.0	11-12	None	<5	20	QNS	8	<8	256
	103.0	5-12	Upper Respiratory Illness, Gastrointestinal Illness, Anorexia, Measles-Like Rash	<5	80	QNS	<4	<8	8
	102.0	39-42	Upper Respiratory Illness, Otitis, Gastrointestinal Illness						
	102.3	24	Upper Respiratory Illness, Anorexia	<5	80	<2	≥64	<8	≥512
	102.2	38-39	Anorexia	<5	QNS	<2	QNS	<8	8
	102.6	17-18	Upper Respiratory Illness, Gastrointestinal Illness, Anorexia	NS	80	NS	8	NS	256
	102.8	0-4	Upper Respiratory Illness, Ophthalmopathy, Anorexia, Herpes-Type Rash, Soreness at Injection Site	<5	40	≥64	≥64	<8	256
	104.5	15	Otitis	<5	40	<2	16	<8	256
	103.8	22	Upper Respiratory Illness, Gastrointestinal Illness, Anorexia						

4/21/78

Table 9

Clinical Complaints Reported Among Children Who Received Combined
Live Measles-Mumps-Rubella (RA 27/3) Virus Vaccine, Lot #60664/C-E810 (Study #459)

Clinical Complaint	Total Vaccinees (41 Children)						Initially Seronegatives (16 Children)					
	Days Post Vaccination					No. with Complaint	Days Post Vaccination					No. with Complaint
	0-4	5-12	13-18	19-28	29-42		0-4	5-12	13-18	19-28	29-42	
Injection Site:												
Soreness	2 (4.9%)					2						0
Systemic:												
Measles-Like Rash		4 (9.8)	2 (4.9)			5			1 (6.3)			1
Irritability	1 (2.4)	3 (7.3)	2 (4.9)		3 (7.5)	6	1 (6.3)				1 (6.7)	2
Anorexia	8 (19.5)	5 (12.2)	8 (19.5)	9 (22.0)	7 (17.5)	20	3 (18.8)	1 (6.3)	2 (12.5)	3 (18.8)	3 (20.0)	6
Disturbed Sleep		1 (2.4)				1		1 (6.3)				1
Upper Respiratory Illness	16 (39.0)	17 (41.5)	10 (24.4)	11 (26.8)	16 (40.0)	28	5 (31.3)	5 (31.3)	2 (12.5)	6 (37.5)	7 (46.7)	10
Otitis		2 (4.9)	1 (2.4)	3 (7.3)	3 (7.5)	8		1 (6.3)	1 (6.3)	2 (12.5)	1 (6.7)	4
Ophthalmopathy	3 (7.3)	1 (2.4)			3 (7.5)	7		1 (6.3)				1
Gastrointestinal Illness	9 (22.0)	9 (22.0)	6 (14.6)	10 (24.4)	9 (22.5)	24	3 (18.8)	1 (6.3)	2 (12.5)	5 (31.3)	3 (20.0)	10
Nonspecific Rash	2 (4.9)	4 (9.8)	2 (4.9)	3 (7.3)	3 (7.5)	5	1 (6.3)	2 (12.5)	2 (12.5)	2 (12.5)	1 (6.7)	3
Varicella				1 (2.4)		1				1 (6.3)		1
Allergy		1 (2.4)				1		1 (6.3)				1
Teething	1 (2.4)	3 (7.3)	1 (2.4)	1 (2.4)	2 (5.0)	4	1 (6.3)	1 (6.3)	1 (6.3)	1 (6.3)	1 (6.7)	1
Herpes-Type Rash	1 (2.4)					1						0
Persons with Complaint:	20 (48.8)	26 (63.4)	18 (43.9)	16 (39.0)	22 (55.0)	34	7 (43.8)	8 (50.0)	6 (37.5)	8 (50.0)	9 (60.0)	14
Persons with No Complaint:	21 (51.2)	15 (36.6)	23 (56.1)	25 (61.0)	18 (45.0)	7	9 (56.3)	8 (50.0)	10 (62.5)	8 (50.0)	6 (40.0)	2
Negative Surveillance					1						1	

4/21/78

Program: Study #467 - To compare antibody and clinical responses to combined live measles-mumps-rubella virus vaccine containing the RA 27/3 rubella virus strain or the HPV-77 duck rubella virus strain.

Vaccine: Combined live measles-mumps-rubella (RA 27/3) virus vaccine Lot #621/C-D763

Combined live measles-mumps-rubella (HPV-77) virus vaccine M-M-R

Responsible Clinical Investigator:

Robert E. Weibel, M.D.
Director, Division of Preventive Medicine
Joseph Stokes, Jr. Research Institute
Children's Hospital of Philadelphia
34th and Civic Center Boulevard
Philadelphia, Pennsylvania 19104

Study Locations:

De La Wair Clinic, Wilmington, Delaware
The Northeast Clinic, Wilmington, Delaware
The Riverside Health Clinic, Riverside, New Jersey
The Deborah Clinic, Browns Mill, New Jersey
The Mt. Holly Clinic, Mt. Holly, New Jersey
G. Starkweather, M.D., Havertown, Pennsylvania
E. M. Craven, M.D., Wilmington Medical Center, Wilmington, Delaware
James W. Williams State Service Center, Dover, Delaware
Lankenau Hospital, Philadelphia, Pennsylvania
Children's Clinic of Chester and Vicinity, Chester, Pennsylvania

Date Study Initiated: June 7, 1976

Date Study Completed: May 12, 1977

Study Procedure:

Two hundred seventy-five children, 10 months to 7 years of age, from the open population, were included in the study. Two hundred fifty-five children received a 0.5 ml subcutaneous dose of 1 of 2 vaccines. Twenty children received a 1.0 ml subcutaneous dose of combined live measles-mumps-rubella (RA 27/3) virus vaccine. Blood samples were obtained prior to and 6 weeks after vaccination from approximately one half of the children. Each child was followed 6 weeks for clinical complaints.

Clinical Protocol - Study #467

Combined Live Measles-Mumps-Rubella (RA 27/3) Virus Vaccine

Purpose: To compare antibody and clinical responses to combined live measles-mumps-rubella virus vaccine containing the RA 27/3 rubella virus strain or the HPV-77 duck rubella virus strain.

Vaccines:

1. Combined live measles-mumps-rubella (RA 27/3) virus vaccine Lot #621

   Vaccine dose is 0.5 ml given subcutaneously.

   The vaccine is supplied in two-dose vials. Each vial of vaccine should be rehydrated with 1.2 ml of sterile, pyrogen-free distilled water.

2. Combined live measles-mumps-rubella (HPV-77 duck) virus vaccine Lot #0131V

   Vaccine dose is 0.5 ml given subcutaneously.

   The vaccine is supplied in single dose vials. Each vial of vaccine should be rehydrated with 0.7 ml of sterile, pyrogen-free distilled water.

CAUTION: Both vaccines contain egg protein and should not be given to persons with known sensitivity to chicken or duck, chicken or duck eggs or feathers. The vaccines also contain neomycin and should not be given to persons with sensitivity to neomycin. Persons with leukemia or other immunologic disorders and persons receiving immunosuppressive drugs should not be vaccinated. The vaccines should not be given to persons with any febrile respiratory illness or other active febrile infection.

Keep dried vaccines stored at -20°C.

Keep dried vaccines at 4°C in transport.

Keep reconstituted vaccine on ice. Discard unused vaccine 4 hours after rehydration.

Procedure: The study population will consist of children 1 to 4 years old having a negative history of vaccination for and illness caused by measles, mumps and rubella. Children will be randomly assigned to receive one of the two vaccines as follows:

Group	Vaccine	No. of Children
Group 1	M-M-R (RA 27/3)	100-200 children
Group 2	M-M-R (HPV-77 duck)	100-200 children

Informed written consent will be obtained from each child's parent or guardian prior to his participation in the study.

Each child will receive a single 0.5 ml subcutaneous injection of one of the two combined live measles-mumps-rubella virus vaccines.

Bleeding samples (10-15 ml) will be obtained from approximately one-third of the study participants. They will be bled immediately prior to vaccination and 6-8 weeks following vaccination.

Each child will be followed clinically for 42 days following vaccination. All local and systemic complaints will be recorded on the case report form.

Schedule:

Time	Vaccination and Follow-up (All Children)	Bleeding (Approx. 1/3 of Children)
Day 0	Vaccinate 0.5 ml, subcutaneously.	Bleed 10-15 ml.
Days 0-42	Clinical follow-up for local and systemic reactions.	--
Week 6-8	--	Bleed 10-15 ml.

Serology: Circulating levels of antibody before and after vaccination will be determined. Measles and rubella antibody levels will be determined by hemagglutination-inhibition test. Mumps antibody levels will be determined by serum neutralization test.

Clinical Forms: Attached.

Adverse Reactions: Any serious or alarming reaction, including death due to any cause during this investigation, whether related or not related to the test material, must be reported immediately to Merck & Co., Inc., through Dr. Maurice R. Hilleman, telephone (215) 699-5311, Ext. 5532, or in his absence, Dr. Allen F. Woodhour, telephone (215) 699-5311, Ext. 5588.

Unused Vaccine: All unused vaccine should be returned immediately to the Virus and Cell Biology Laboratories of the Merck Sharp & Dohme Research Laboratories, West Point, Pennsylvania 19486.

M. R. Hilleman, Ph.D.

SYMPTOM RECORD

M-M-R Study No. _____

CHILD'S NAME _____ CASE NO. _____
(Last) (First) (Middle)

DAY	DATE	Temperature ☐ Rectal ☐ Oral *(Check One)*	NONE	RUNNY NOSE	SORE THROAT	COUGH	EAR ACHE	SWOLLEN GLANDS	SORE EYES	THROWING UP	DIARRHEA	STOMACH ACHE	RASH (describe)	SORE JOINTS	SORE ARM (at shot)	HEADACHE	HURTS ALL OVER	FEVER	WON'T EAT	COMMENTS
0																				
1																				
2																				
3																				
4																				
5																				
6																				
7																				
8																				
9																				
10																				
11																				
12																				
13																				
14																				
15																				
16																				
17																				
18																				
19																				
20																				
21																				
22																				
23																				
24																				
25																				
26																				
27																				
28																				
29																				
30																				
31																				
32																				
33																				
34																				
35																				
36																				
37																				
38																				
39																				
40																				
41																				
42																				

er or unusual reaction develops, call:

DR. R. E. WEIBEL
Havertown, Pennsylvania – Phone: HIlltop 6-1110
OR
Children's Hospital of Philadelphia – EV 7-1309

PLEASE RETURN FOR FOLLOW-UP VISIT ON: _____

BE SURE TO BRING THIS RECORD ALONG WITH YOU.

P3954-0775(DOM)

INSTRUCTIONS TO PARENT:

1. Please fill in the date each day.
2. Please take temperature once daily at the same time and record exact thermometer reading.
3. If no symptoms are present, place a check ($\surd$) under "NONE" beside that day's date.
4. If a symptom is present, place a check ($\surd$) under it beside that day's date.
5. Describe other symptoms and any RASH in the space under "COMMENTS."
6. THIS IS VERY IMPORTANT INFORMATION. ***Please do not misplace this card.***

MEASLES-MUMPS-RUBELLA VACCINATION -

FAMILY No. _____ CASE No. _____

CHILD'S NAME _____
LAST FIRST MIDDLE

SEX _____ BIRTHDATE _____ AGE _____ HISTORY: MEASLES _____
MUMPS _____
RUBELLA _____

PARENTS NAME _____ TELEPHONE No. _____
LAST FIRST MIDDLE

ADDRESS _____
NUMBER STREET CITY STATE

LOCATION _____

PRE-VACCINATION _____

CLINICAL _____

I consent to have my child. named above. receive live attenuated measles, mumps, rubella virus vaccine.

SIGNATURE _____

DATE _____

VACCINATION: VACCINE _____ LOT _____ (13-15) BLEEDINGS

1. DATE _____ (17-22) VOL. _____ SITE _____ PRE-VACCINATION _____ (17-22) CASE No. _____ (5-8)

POST-VACCINATION _____ (29-34)

BLEEDING DATE	SEROLOGY								
	MEASLES			MUMPS			RUBELLA		
TEST	1	2	3	1	2	3	1	2	3
TECHNIQUE									
1.									
2.									
3.									
4.									
SUMMARY	PRE	POST		PRE	POST		PRE	POST	

CLINICAL SUMMARY					
POST VAC.	MAX. TEMP.	CODE	COMPLAINTS	CODE	CODE
DAYS					
0-4	(27-30)	(31)		(32-33)	(34-35)
5-12	(36-39)	(40)		(41-42)	(43-44)
13-18	(45-48)	(49)		(50-51)	(52-53)
19-28	(54-57)	(58)		(59-60)	(61-62)

COMMENTS:

Table 1

Serological Findings Among Children Who Received a 0.5 ml Dose of Combined Live Measles-Mumps-Rubella (RA 27/3) Virus Vaccine, Lot #621/C-D763 (Study #467)

Age	Total No. Vacc.	No. Serol. Tested	Initially Seronegative to: Measles-Mumps-Rubella Conversions/Total			Measles-Rubella Conversions/Total		Mumps-Rubella Conversions/Total		Mumps Only Conversions/ Total	Rubella Only Conversions/ Total	Initially Seropositive to: Measles Mumps and Rubella
			Measles	Mumps	Rubella	Measles	Rubella	Mumps	Rubella			
(Months)												
11	8	7	6/7	7/7	7/7							
(Years)												
1	63	32	29/30	30/30	30/30	0/1	1/1	1/1	1/1			
2	17	10	7/8	7/8	8/8			1/1	1/1	1/1		
3	11	6						1/1	1/1	3/3	2/2	
4	9	6	3/3	3/3	3/3	2/2	2/2					1
5	5	4	1/1	1/1	1/1	1/1	1/1			1/1		1
6	3	1									1/1	
7	1	0										
Total	117	66	46/49	48/49	49/49	3/4	4/4	3/3	3/3	5/5	3/3	2
Mean Age: 1.9 Years			(93.9%)	(98.0%)	(100%)							

Overall Conversion Rates

Measles	Mumps	Rubella
49/53 (92.5%)	56/57 (98.2%)	59/59 (100%)

8/24/77

Table 2

Serological Findings Among Children Who Received a 1.0 ml Dose of Combined Live Measles-Mumps-Rubella (RA 27/3) Virus Vaccine, Lot #621/C-D763 (Study #467)

Age	Total No. Vacc.	No. Serol. Tested	Initially Seronegative to: Measles-Mumps-Rubella Conversions/Total			Measles-Rubella Conversions/Total		Mumps Only Conversions/ Total	Initially Seropositive to: Measles Mumps and Rubella
			Measles	Mumps	Rubella	Measles	Rubella		
(Months) 11	1	1	1/1	1/1	1/1				
(Years) 1	11	8	7/7	7/7	7/7			1/1	
2	5	2				1/1	1/1	1/1	
3	1	0							
5	2	1	1/1	1/1	1/1				
Total	20	12	9/9 (100%)	9/9 (100%)	9/9 (100%)	1/1	1/1	2/2	0
Mean Age: 1.7 Years									

Overall Conversion Rates

Measles	Mumps	Rubella
10/10 (100%)	11/11 (100%)	10/10 (100%)

8/24/77

Table 3

Serological Findings Among Children Who Received a 0.5 ml Dose of Combined Live Measles-Mumps-Rubella (HPV-77) Virus Vaccine, M-M-R (Study #467)

Age	Total No. Vacc.	No. Serol. Tested	Initially Seronegative to: Measles-Mumps-Rubella Conversions/Total			Measles-Rubella Conversions/Total		Mumps-Rubella Conversions/Total		Measles Only Conversions/ Total	Mumps Only Conversions/ Total	Initially Seropositive to: Measles Mumps and Rubella
			Measles	Mumps	Rubella	Measles	Rubella	Mumps	Rubella			
(Months)												
10	1	0										
11	2	2	1/2	1/2	2/2							
(Years)												
1	88	46	36/42	36/42	40/42	3/3	3/3				1/1	
2	19	10	3/3	2/3	3/3	2/2	2/2	1/1	1/1	1/1	2/2	1
3	12	6	4/4	4/4	3/4	1/1	1/1	1/1	1/1			
4	12	3	1/1	1/1	0/1	2/2	2/2					
5	3	2	1/1	1/1	1/1	1/1	1/1					
7	1	1										1
Total	138	70	46/53	45/53	49/53	9/9	9/9	2/2	2/2	1/1	3/3	2
Mean Age: 1.7 Years			(86.8%)	(84.9%)	(92.5%)							

Overall Conversion Rates

Measles	Mumps	Rubella
56/63 (88.9%)	50/58 (86.2%)	60/64 (93.8%)

8/24/77

Table 4

Distribution of Post-Vaccination Antibody Titers Among Children Who Were Initially Seronegative to Measles, Mumps and Rubella, Who Received a 0.5 ml Dose of Combined Live Measles-Mumps-Rubella (RA 27/3) Virus Vaccine, Lot #621/C-D763 (Study #467)

Measles (HAI)		Mumps (Neut.)		Rubella (HAI)	
Post Titer Distribution	Number of Children	Post Titer Distribution	Number of Children	Post Titer Distribution	Number of Children
<5	3	<2	1	16	1
5	2	2	8	32	1
10	2	4	11	64	11
20	4	8	8	128	22
40	9	>8	1	256	10
80	8	16	10	512	4
160	17	32	7		
320	4	64	3		
Total	49		49		49
Geometric Mean Titer	56.2		8.3		131.7

8/24/77

Table 5

Distribution of Post-Vaccination Antibody Titers Among Children Who Were Initially Seronegative to Measles, Mumps and Rubella, Who Received a 1.0 ml Dose of Combined Live Measles-Mumps-Rubella (RA 27/3) Virus Vaccine, Lot #621/C-D763 (Study #467)

Measles (HAI)		Mumps (Neut.)		Rubella (HAI)	
Post Titer Distribution	Number of Children	Post Titer Distribution	Number of Children	Post Titer Distribution	Number of Children
160	4	2	2	64	1
320	4	4	5	128	2
640	1	8	1	256	3
		16	1	512	2
				1024	1
Total	9		9		9
Geometric Mean Titer	254.0		4.3		256.0

8/24/77

Table 6

Distribution of Post-Vaccination Antibody Titers Among Children Who Were Initially Seronegative to Measles, Mumps and Rubella, Who Received a 0.5 ml Dose of Combined Live Measles-Mumps-Rubella (HPV-77) Virus Vaccine, M-M-R (Study #467)

Measles (HAI)		Mumps (Neut.)		Rubella (HAI)	
Post Titer Distribution	Number of Children	Post Titer Distribution	Number of Children	Post Titer Distribution	Number of Children
<5	7	<2	8	<8	4
5	2	2	9	8	9
20	2	4	14	16	7
40	6	8	9	32	11
80	14	>8	1	64	7
160	17	16	6	128	9
320	4	32	4	256	4
640	1	64	2	512	1
				1024	1
Total	53		53		53
Geometric Mean Titer	51.1		5.0		32.4

8/24/77

Table 7

Maximum Temperatures Reported Among Children Who Received a 0.5 ml Dose of Combined Live Measles-Mumps-Rubella (RA 27/3) Virus Vaccine, Lot #621/C-D763 (Study #467)

Maximum Temperature (°F, Oral)	Total Vaccinees (117 Children)						Initially Seronegatives (61 Children)					
	Days Post Vaccination					No. with Max. Temp.	Days Post Vaccination					No. with Max. Temp.
	0-4	5-12	13-18	19-28	29-42		0-4	5-12	13-18	19-28	29-42	
<99	61 (73.5%)	53 (64.6)	61 (75.3)	59 (73.8)	57 (72.2)	39	34 (77.3)	29 (69.0)	34 (79.1)	34 (81.0)	32 (78.0)	25
99 - 100.9	20 (24.1)	23 (28.0)	17 (21.0)	16 (20.0)	16 (20.3)	26	10 (22.7)	8 (19.0)	7 (16.3)	7 (16.7)	8 (19.5)	12
101 - 102.9	1 (1.2)	5 (6.1)	2 (2.5)	3 (3.8)	4 (5.1)	13		4 (9.5)	1 (2.3)	1 (2.4)		5
103 - 104.0	1 (1.2)	1 (1.2)	1 (1.2)	2 (2.5)	2 (2.5)	7		1 (2.4)	1 (2.3)		1 (2.4)	3
Not Taken	34	35	36	37	38	32	17	19	18	19	20	16

8/24/77

Table 8

High Temperatures Reported Among Children Who Received a 0.5 ml Dose of Combined Live Measles-Mumps-Rubella (RA 27/3) Virus Vaccine, Lot #621/C-D763 (Study #467)

Patient No.	Max. Temp.	Time Period (Days)	Clinical Complaints	Serology					
				Measles		Mumps		Rubella	
				Pre	Post	Pre	Post	Pre	Post
(b) (6)	102.0	29-31	Upper Respiratory Illness	NS	NS	NS	NS	NS	NS
	102.0	3	Anorexia	NS	NS	NS	NS	NS	NS
	102.0	24-28	Upper Respiratory Illness, Gastro-intestinal Illness, Irritability						
	102.0	27	No Clinical Complaints	NS	NS	NS	NS	NS	NS
	103.0	26-29	Anorexia, Teething	NS	NS	NS	NS	NS	NS
	103.0	0-3	Upper Respiratory Illness	NS	NS	NS	NS	NS	NS
	103.2	9-11	Upper Respiratory Illness, Otitis, Lymphadenopathy, Ophthalmopathy, Gastrointestinal Illness, Anorexia, Soreness at Injection Site	<5	160	<2	32	<8	512
	104.0	22-23	Upper Respiratory Illness, Gastro-intestinal Illness, Headache	≥20	40	2	4	≥32	128
	103.6	40-41	Upper Respiratory Illness, Headache Anorexia	≥20	80	<2	16	≥32	128
	102.0	7-8	No Clinical Complaints	<5	80	<2	4	<8	128
	102.0	12	Upper Respiratory Illness, Ophthalmo-pathy	<5	<5	<2	8	<8	128
	103.0	30-33	Upper Respiratory Illness, Gastro-intestinal Illness	<5	10	<2	2	<8	128
	103.0	18	Upper Respiratory Illness, Teething	<5	5	<2	32	<8	256
	102.0	10-12	No Clinical Complaints	<5	40	<2	32	<8	256

8/24/77

Table 9

Maximum Temperatures Reported Among Children Who Received a 1.0 ml Dose of Combined Live Measles-Mumps-Rubella (RA 27/3) Virus Vaccine, Lot #621/C-D763 (Study #467)

Maximum Temperature (°F, Oral)	Total Vaccinees (20 Children)						Initially Seronegatives (11 Children)					
	Days Post Vaccination					No. with Max. Temp.	Days Post Vaccination					No. with Max. Temp.
	0-4	5-12	13-18	19-28	29-42		0-4	5-12	13-18	19-28	29-42	
<99	13 (76.5%)	11 (64.7)	13 (81.3)	12 (70.6)	13 (76.5)	9	7 (70.0)	7 (70.0)	8 (80.0)	6 (60.0)	7 (70.0)	6
99 - 100.9	3 (17.6)	4 (23.5)	2 (12.5)	4 (23.5)	3 (17.6)	5	3 (30.0)	2 (20.0)	1 (10.0)	3 (30.0)	2 (20.0)	3
101.0		2 (11.8)			1 (5.9)	1		1 (10.0)			1 (10.0)	0
103.0	1 (5.9)		1 (6.3)	1 (5.9)		2			1 (10.0)	1 (10.0)		1
Not Taken	3	3	4	3	3	3	1	1	1	1	1	1

Patient No.	Max. Temp.	Time Period (Days)	Clinical Complaint	Measles		Mumps		Rubella	
(b) (6)	103.0	0	No Clinical Complaint	NS	NS	NS	NS	NS	NS
	103.0	13-15	No Clinical Complaint	<5	160	<2	4	<8	256
	103.0	22	No Clinical Complaint						

8/24/77

Table 10

Maximum Temperatures Reported Among Children Who Received a 0.5 ml Dose of Combined Live Measles-Mumps-Rubella (HPV-77) Virus Vaccine, M-M-R (Study #467)

Maximum Temperature (°F, Oral)	Total Vaccinees (138 Children) Days Post Vaccination 0-4	5-12	13-18	19-28	29-42	No. with Max. Temp.	Initially Seronegatives (70 Children) Days Post Vaccination 0-4	5-12	13-18	19-28	29-42	No. with Max. Temp.
<99	73 (74.5%)	66 (68.0)	78 (81.3)	75 (78.1)	73 (78.5)	53	38 (76.0)	35 (70.0)	43 (86.0)	40 (80.0)	39 (81.3)	29
99 - 100.9	22 (22.4)	24 (24.7)	15 (15.6)	16 (16.7)	14 (15.1)	27	10 (20.0)	9 (18.0)	5 (10.0)	8 (16.0)	4 (8.3)	10
101 - 102.9	3 (3.1)	4 (4.1)	2 (2.1)	2 (2.1)	5 (5.4)	14	2 (4.0)	3 (6.0)	1 (2.0)		4 (8.3)	8
103 - 104.9		3 (3.1)	1 (1.0)	3 (3.1)	1 (1.1)	6		3 (6.0)	1 (2.0)	2 (4.0)	1 (2.1)	5
Not Taken	40	41	42	42	45	38	20	20	20	20	22	18

Patient No.	Max. Temp.	Time Period (Days)	Clinical Complaint	Measles		Mumps		Rubella	
(b) (6)	102.0	5-6	Otitis	<5	320	<2	4	<8	16
	104.0	19-23	Upper Respiratory Illness, Nonspecific Viral Rash, Anorexia	<5	320	2	8	8	64
	103.0	34-39	Teething	<5	<5	<2	32	<8	1024
	103.0	8-10	No Clinical Complaints	<5	320	<2	8	<8	<8
	104.0	28	No Clinical Complaints						
	103.2	13-14	No Clinical Complaints	<5	640	<2	8	<8	256
	103.2	25	No Clinical Complaints						
	102.0	4-5	No Clinical Complaints	QNS	80	QNS	4	QNS	64
	102.0	27-36	Gastrointestinal Illness, Nonspecific Rash, Anorexia	<5	40	<2	≥8	<8	32
	102.0	5-10	Upper Respiratory Illness, Anorexia	<5	160	<2	<2	<8	128
	102.0	15	Upper Respiratory Illness, Otitis	NS	NS	NS	NS	NS	NS
	102.0	30-34	Upper Respiratory Illness	<5	40	<2	<2	<8	8
	102.4	1	No Clinical Complaints	<5	160	<2	32	<8	128
	103.0	7-12	Gastrointestinal Illness, Irritability, Anorexia, Teething	<5	160	<2	32	<8	32
	103.0	8-10	Ophthalmopathy	<5	160	<2	2	<8	32

Table 11

Clinical Complaints Reported Among Children Who Received a 0.5 ml Dose of Combined Live Measles-Mumps-Rubella (RA 27/3) Virus Vaccine, Lot #621/C-D763 (Study #467)

Clinical Complaint	Total Vaccinees (117 Children)						Initially Seronegatives (61 Children)					
	Days Post Vaccination					No. with Complaint	Days Post Vaccination					No. with Complaint
	0-4	5-12	13-18	19-28	29-42		0-4	5-12	13-18	19-28	29-42	
Soreness at Injection Site	2 (2.2%)	1 (1.1)	1 (1.1)			3	1 (2.1)	1 (2.1)	1 (2.1)			2
Lymphadenopathy		2 (2.2)		1 (1.1)		3		2 (4.3)		1 (2.1)		3
Measles-Like Rash	1 (1.1)	5 (5.6)	3 (3.4)			7	1 (2.1)	4 (8.5)	1 (2.1)			5
Headache		1 (1.1)		1 (1.1)	1 (1.1)	3		1 (2.1)				1
Irritability	4 (4.4)	4 (4.5)		1 (1.1)		8	3 (6.3)	1 (2.1)				4
Fever-Temperature Not Reported	1 (1.1)	1 (1.1)				2		1 (2.1)				1
Anorexia	10 (11.1)	12 (13.5)	6 (6.7)	7 (8.0)	6 (6.8)	23	5 (10.4)	7 (14.9)	4 (8.3)	2 (4.3)	1 (2.1)	11
Flush					1 (1.1)	1						0
Disturbed Sleep	2 (2.2)					2						0
Myalgia	1 (1.1)					1	1 (2.1)					1
Upper Respiratory Illness	15 (16.7)	29 (32.6)	17 (19.1)	20 (22.7)	31 (35.2)	53	6 (12.5)	13 (27.7)	9 (18.8)	9 (19.1)	10 (21.3)	22
Otitis	1 (1.1)	2 (2.2)	2 (2.2)	1 (1.1)	1 (1.1)	2		1 (2.1)	1 (2.1)			1
Ophthalmopathy		5 (5.6)	4 (4.5)	3 (3.4)	4 (4.5)	9		3 (6.4)	3 (6.3)	2 (4.3)	1 (2.1)	4
Gastrointestinal Illness	9 (10.0)	15 (16.9)	10 (11.2)	12 (13.6)	13 (14.8)	31	4 (8.3)	12 (25.5)	6 (12.5)	7 (14.9)	4 (8.5)	16
Nonspecific Rash	1 (1.1)	1 (1.1)	1 (1.1)	1 (1.1)	4 (4.5)	6		1 (2.1)				1
Poison Ivy		1 (1.1)	1 (1.1)			1						0
Allergy		1 (1.1)		1 (1.1)		2		1 (2.1)		1 (2.1)		2
Teething	1 (1.1)	4 (4.5)	4 (4.5)	2 (2.3)	2 (2.3)	10	1 (2.1)	2 (4.3)	2 (4.2)			5
Negative Surveillance	27	28	28	29	29	27	13	14	13	14	14	13
Persons with Complaint:	30 (33.3)	44 (49.4)	28 (31.5)	30 (34.1)	37 (42.0)	56	12 (25.0)	21 (44.7)	14 (29.2)	14 (29.8)	13 (27.7)	25
Persons with No Complaint:	60 (66.7)	45 (50.6)	61 (68.5)	58 (65.9)	51 (58.0)	33	36 (75.0)	26 (55.3)	34 (70.8)	33 (70.2)	34 (72.3)	23

8/24/77

Table 12

Clinical Complaints Reported Among Children Who Received a 1.0 ml Dose of Combined Live Measles-Mumps-Rubella (RA 27/3) Virus Vaccine, Lot #621/C-D763 (Study #467)

Clinical Complaint	Total Vaccinees (20 Children)						Initially Seronegatives (11 Children)					
	Days Post Vaccination					No. with Complaint	Days Post Vaccination					No. with Complaint
	0-4	5-12	13-18	19-28	29-42		0-4	5-12	13-18	19-28	29-42	
Soreness at Injection Site	1 (5.9%)					1	1 (10.0)					1
Lymphadenopathy	1 (5.9)					1	1 (10.0)					1
Arthralgia			1 (5.9)			1						0
Measles-Like Rash			1 (5.9)			1			1 (10.0)			1
Irritability	1 (5.9)	1 (5.9)				1	1 (10.0)	1 (10.0)				1
Fever - Temperature Not Reported				1 (5.9)		1				1 (10.0)		1
Anorexia			1 (5.9)	1 (5.9)		2			1 (10.0)			1
Upper Respiratory Illness	4 (23.5)	5 (29.4)	2 (11.8)	4 (23.5)	1 (5.9)	8	1 (10.0)	1 (10.0)		2 (20.0)		4
Otitis			1 (5.9)	1 (5.9)	1 (5.9)	1			1 (10.0)	1 (10.0)	1 (10.0)	1
Gastrointestinal Illness	3 (17.6)		1 (5.9)	1 (5.9)		4	2 (20.0)		1 (10.0)			2
Impetigo				1 (5.9)		1				1 (10.0)		1
Negative Surveillance	3	3	3	3	3	3	1	1	1	1	1	1
Persons with Complaint:	7 (41.2)	6 (35.3)	5 (29.4)	5 (29.4)	2 (11.8)	9	3 (30.0)	2 (20.0)	2 (20.0)	3 (30.0)	1 (10.0)	5
Persons with No Complaint:	10 (58.8)	11 (64.7)	12 (70.6)	12 (70.6)	15 (88.2)	8	7 (70.0)	8 (80.0)	8 (80.0)	7 (70.0)	9 (90.0)	5

8/24/77

Table 13

Clinical Complaints Reported Among Children Who Received a 0.5 ml Dose of Combined Live Measles-Mumps-Rubella (HPV-77) Virus Vaccine, M-M-R (Study #467)

Clinical Complaint	Total Vaccinees (138 Children)						Initially Seronegatives (70 Children)					
	Days Post Vaccination					No. with Complaint	Days Post Vaccination					No. with Complaint
	0-4	5-12	13-18	19-28	29-42		0-4	5-12	13-18	19-28	29-42	
Injection Site:	7 (6.9%)					7	3 (5.7)					3
Soreness	6					6	2					2
Soreness and Induration	1					1	1					1
Systemic:												
Measles-Like Rash		5 (5.0)	2 (2.0)			5		1 (1.9)				1
Headache	1 (1.0)		1 (1.0)		2 (2.0)	2					1 (1.9)	1
Irritability	3 (3.0)	4 (4.0)	2 (2.0)	3 (3.0)		9	2 (3.8)	1 (1.9)		1 (1.9)		4
Anorexia	11 (10.9)	17 (16.8)	5 (5.0)	6 (5.9)	4 (4.0)	24	6 (11.3)	9 (17.0)	1 (1.9)	3 (5.7)	3 (5.7)	14
Flush	1 (1.0)					1						0
Disturbed Sleep		1 (1.0)				1						0
Myalgia	2 (2.0)					2	1 (1.9)					1
Upper Respiratory Illness	18 (17.8)	19 (18.8)	15 (14.9)	18 (17.8)	24 (23.8)	45	10 (18.9)	9 (17.0)	6 (11.3)	7 (13.2)	8 (15.1)	20
Otitis	1 (1.0)	4 (4.0)	2 (2.0)	1 (1.0)	1 (1.0)	7	1 (1.9)	2 (3.8)				3
Ophthalmopathy	2 (2.0)	3 (3.0)		1 (1.0)	2 (2.0)	6	2 (3.8)	2 (3.8)				4
Gastrointestinal Illness	15 (14.9)	12 (11.9)	5 (5.0)	5 (5.0)	6 (5.9)	27	7 (13.2)	3 (5.7)	3 (5.7)	2 (3.8)	4 (7.5)	11
Rash-Nonspecific	1 (1.0)	3 (3.0)	5 (5.0)	3 (3.0)	4 (4.0)	12	1 (1.9)	1 (1.9)	4 (7.5)	1 (1.9)	1 (1.9)	6
Varicella				1 (1.0)	1 (1.0)	1						0
Other*	1 (1.0)	1 (1.0)				2	1 (1.9)					1
Genitourinary Infection				1 (1.0)	1 (1.0)	1						0
Allergy	2 (2.0)	2 (2.0)		1 (1.0)		3	2 (3.8)	2 (3.8)				2
Teething		2 (2.0)	4 (4.0)	5 (5.0)	2 (2.0)	8		1 (1.9)		1 (1.9)	2 (3.8)	3
Negative Surveillance	37	37	37	37	37	37	17	17	17	17	17	17
Persons with Complaint:	36 (35.6)	41 (40.6)	24 (23.8)	26 (25.7)	30 (29.7)	57	20 (37.7)	18 (34.0)	9 (17.0)	10 (18.9)	12 (22.6)	27
Persons with No Complaints	65 (64.4)	60 (59.4)	77 (76.2)	75 (74.3)	71 (70.3)	44	33 (62.3)	35 (66.0)	44 (83.0)	43 (81.1)	41 (77.4)	26

* Includes ingested lighter fluid and bloody nose.

MEMO

To File Location Date 9/27/77

From T. Schofield Location W26-285

Subject Statistical Analysis - Study #467

Significant differences in seroconversion rates for measles, mumps, and rubella and clinical reaction rates among three groups of vaccinees were investigated. The groups were those who received a 0.5 ml dose of combined live measles-mumps-rubella (RA 27/3) virus vaccine (Group 1), those who received a 1.0 ml dose of the same (Group 2), and those who received a 0.5 ml dose of combined live measles-mumps-rubella (HPV-77) virus vaccine (Group 3).

Significant difference exists in the mumps seroconversion rate among these groups. 56 out of 57 (98.2%) converted in Group 1, 11 out of 11 (100.0%) in Group 2, and 50 out of 58 (86.2%) in Group 3. No significant differences exist for other rates.

Analysis of variance was performed on post-titer values of triple-negative vaccinees. The log transformation was used. Significant differences among the groups existed for all three components. Multiple comparisons showed the following:

a) For measles, children in Group 2 (GMT = 254.0) had significantly greater post titer (in the log scale) than did those in Group 1 (GMT = 56.2) and those in Group 3 (GMT = 51.1);

b) For mumps, children in Group 1 (GMT = 8.3) had significantly greater post titer than did those in Group 2 (GMT = 4.3) and those in Group 3 (GMT = 5.0);

c) For rubella, children in Group 1 (GMT = 131.7) and Group 2 (GMT = 256.0) had significantly greater post titer than did those in Group 3 (GMT = 32.4).

T.S.
6801

CLINICAL SUMMARY

Study Name - Combined Live Measles-Mumps-Rubella (RA 27/3) Virus Vaccine

Study Number - Clinical Protocol - 467

Material - Combined live measles-mumps-rubella (RA 27/3) virus vaccine
Lot #621/C-D763

Combined live measles-mumps-rubella (HPV-77) virus vaccine
Lot #0131V

Purpose - To compare clinical and antibody responses to combined live measles-mumps-rubella virus vaccine containing the RA 27/3 rubella virus strain or the HPV-77 duck rubella virus strain.

Time Period of Observation - Initiated: June 7, 1976; completed: May 12, 1977

Medical Opinion

At the following locations: Burlington County Health Care Clinics-Riverside Clinic, Zurbrugg Memorial Hospital, Riverside, New Jersey, Browns Mills Clinic, Deborah Hospital, Browns Mills, N.J., Mount Holly Clinic, Mt. Holly, N.J.; Delaware State Health Clinics, Dover Delaware and the DeLaWar Clinic and Northeast Clinic, Wilmington, Delaware; Elizabeth M. Craven, M.D., Pediatric Clinics, Wilmington Medical Center, Wilmington, Delaware; The Lankenau Hospital Pediatric Clinic, Philadelphia, Pa.; and George A. Starkweather, M.D.'s office, Havertown, Pa.; 275 children, 10 months to seven years of age were enrolled in this study with parental consent. Two-hundred fifty-five children received a 0.5 ml. subcutaneous dose of either vaccine. Inadvertently, twenty children received a 1.0 ml. subcutaneous dose of combined measles-mumps-rubella (RA 27/3) virus vaccine. Each child received a report card and the parents were encouraged to record local and systemic reactions for 42 days. Paired blood samples were obtained prior to and 6 weeks follwing vaccination from 148 of 275 (54%) children to perform measles hemagglutination inhibition, mumps neutralization and rubella hemagglutination inhibition tests.

Measles-mumps-rubella (RA 27/3) virus vaccine was given to 137 children, ages 11 months to 7 years (mean age 1.9 years) with 78 paired sera, seropositive to m-m-r in two and seronegative as follows: m-m-r 58, measles-rubella 5, mumps-rubella 3, mumps 7, rubella 3 - 13 m-m-r seronegatives had only a pre-injection serology test. Measles-mumps-rubella (HPV-77) virus vaccine was given to 138 children, ages 10 months to seven years (mean age 1.7 years) with 70 paired sera seropositive to m-m-r in 2 and seronegative as follows: m-m-r 53, measles-rubella 9, mumps-rubella 2, measles 1, mumps 3 - 17 m-m-r seronegatives had only a pre-injection serology tested. Seroconversion rates for triple seronegatives were similar to the overall seroconversion rates which are as follows with the geometric mean titers: m-m-r (RA 27/3) vaccine 0.5 ml. dose; measles 49/53 (92.5%, 56.2); mumps 56/57 (98%, 8.3); rubella 59/59 (100%, 131.7); m-m-r RA 27/3 vaccine 1.0 dose; measles 10/10 (254); mumps 11/11 (4.37); rubella 10/10 all 100% (256); m-m-r HPV-77 vaccine 0.5 ml. dose; measles 56/63 (88.9%, 51.1); mumps 50/58 (86.2%, 50) rubella 60/64 (98.8%, 32.4).

Medical Opinion (cont.)

The seroconversion rates and geometric mean titers are greater following 0.5 ml. m-m-r RA 27/3 than 0.5 ml. m-m-r HPV as follows: measles - 92.5% vs. 88.8%, 56.2 vs. 51.1; mumps - 98.2% vs 86.2%, 8.3 vs. 5.0; rubella - 100% vs. 93.8%, 131.7 vs. 32.4. The difference in the mumps seroconversion rates, mumps geometric mean titers and rubella geometric mean titers are statistically significant. Interestingly, all (11) measles vaccine failures were less than 15 months of age (2-11, 6-12, 2-13, 1-14 months) and may be related to the persistence of maternal antibody. This pattern was not observed in previous studies. Two of 4 rubella failures (13 months) and 4 of 8 mumps failures were less than 15 months old (1-11, 2-12, 1-13 months.

Clinical report cards were returned on 202 of 275 (73%) of vaccinees with nosignificant vaccine related clinical reaction reported. Temperature elevations were similar among both vaccine groups with no definite pattern during the observation period. Most temperature elevations are related to intercurrent infection with minimal vaccine related fever occurring between days 5 and 12. Injection site soreness was rarely reported in each group. Measles-like rash was reported in m-m-r RA 27/3 vaccinees as follows: 0.5 ml. - 7, 1.0 ml. -1, and in 5 m-m-r HPV vaccinees. No arthralgia or arthritis were reported. Lymphadenopathy was reported by 4 m-m-r RA 27/3 vaccinees only. Non-specific complaints were similar in both groups.

Comparing combined m-m-r RA 27/3 vaccine with m-m-r HPV-77 vaccine reveals no difference in the mild clinical complaints and temperature elevations reported but a greater seroconversion rate and geometric mean titer to all three viruses following m-m-r RA 27/3 vaccine. Although both vaccines are excellent for immunization, m-m-r RA 27/3 combined vaccine is superior and recommended.

Robert E. Weibel, M.D.
October 5, 1977

REW:ceb

Reference No. 5

Clinical Protocol - Study #473

Combined Live Measles-Mumps-Rubella (RA 27/3) Virus Vaccine

Program: Testing of combined live measles-mumps-rubella vaccines in children.

Purpose: To evaluate and compare clinical and immunological responses to two measles-mumps-rubella virus vaccines.

Vaccines:

1. Combined live measles-mumps-rubella (RA 27/3) virus vaccine Lot #621/C-D763

   Vaccine dose is 0.5 ml given subcutaneously.

   The vaccine is supplied in two-dose vials. Each vial of vaccine should be rehydrated with 1.2 ml of sterile, pyrogen-free distilled water.

2. Combined live measles-mumps-rubella (HPV-77 duck) virus vaccine Lot #2127V or 2209V

   Vaccine dose is 0.5 ml given subcutaneously.

   The vaccine is supplied in single dose vials. Each vial of vaccine should be rehydrated with 0.7 ml of sterile, pyrogen-free distilled water.

CAUTION: Both vaccines may contain egg protein and should not be given to persons with known sensitivity to chicken or duck, chicken or duck eggs or feathers. The vaccines also contain neomycin and should not be given to persons with sensitivity to neomycin. Persons with leukemia or other immunologic disorders and persons receiving immunosuppressive drugs should not be vaccinated. The vaccines should not be given to persons with any febrile respiratory illness or other active febrile infection.

Keep dried vaccine stored at -20° C.

Keep dried vaccines at 4° C in transport.

Keep reconstituted vaccine on ice. Discard unused vaccine 4 hours after rehydration.

Procedure: The study population will consist of children 1 to 10 years of age who have a negative history of vaccination for and illness caused by measles, mumps and rubella. The children will be assigned to receive one of the two vaccine as follows:

Clinical Protocol - Study #473
Combined Live Measles-Mumps-Rubella (RA 27/3) Virus Vaccine

Procedure: (continued)

Group	Vaccine	No. of Persons
1	M-M-R (HPV-77 + 5 duck)	up to 200 children
2	M-M-R (RA 27/3)	up to 200 children

Informed written consent will be obtained from a parent or guardian of each child prior to his participation in the study.

Each child will be bled (10-15 ml) immediately prior to vaccination and 6-8 weeks following vaccination. Each child will receive 0.5 ml of vaccine given subcutaneously.

Each child will be followed clinically for occurrence of local and systemic reactions within 6 weeks following vaccination. Observations should include special notation for rash, nodes, arthralgia, arthritis, fever, malaise, and anorexia. The person(s) observing reactions should not know which preparation the child received.

Schedule:

Time	Action
Day 0	Bleed 10-15 ml. Vaccinate 0.5 ml, subcutaneously.
Days 0-42	Clinical follow-up for local and systemic reactions.
Weeks 6-8	Bleed 10-15 ml.

Laboratory: Remove serum from clot aseptically and store frozen at -20° C.

Serology: Levels of circulating antibody before and after vaccination will be determined. Measles and rubella antibody levels will be determined by hemagglutination-inhibition test. Mumps antibody levels will be determined by serum neutralization test.

Clinical Forms: Attached.

Adverse Reactions: Any serious or alarming reaction, including death due to any cause during this investigation, whether related or not related to the test material, must be reported immediately to Merck & Co., Inc., through Dr. Maurice R. Hilleman, telephone (215) 699-5311, Ext. 5532, or in his absence, Dr. Arlene McLean, telephone (215) 699-5311, Ext. 6383.

Clinical Protocol - Study #473
Combined Measles-Mumps-Rubella (RA 27/3) Virus Vaccine

Unused
Vaccine: All unused vaccine should be returned immediately to the Virus and Cell Biology Laboratories of the Merck Sharp & Dohme Research Laboratories, West Point, Pennsylvania 19486.

M. R. Hilleman, Ph.D.

Yale University *New Haven, Connecticut 06510*

SCHOOL OF MEDICINE

Department of Epidemiology and Public Health

60 College Street

October 12, 1977

Dr. Arlene McClaine
Merck Institute For Therapeutic
Research
West Point, Pennsylvania

Dear Doctor McClaine:

As a follow-up to our recent telephone conversation, I submit the following information about our current participation in studies concerned with comparisons of HPV-77 DE$_6$ and RA27/3 live attenuated rubella virus vaccines (b) (4), (b) (6) Our studies in children have now been approved at all levels in each of the various pediatric clinic settings, but have not yet been started. After several prolonged difficulties in filling the position of central coordinator, we now have a good person whose interest, capabilities and prior record give both Dr. Horstmann and me a feeling of re-assurance about essential features of recruitment and follow-up of eligible participants. We anticipate a vast improvement in the studies, both qualitative and quantitative.

To date (b) (4), (b) (6)
(b) (4), (b) (6)

I will send you a progress report on the (b) (4), (b) (6) after our new organizational effort has begun to bear fruit.

Sincerely,

Robert W. McCollum, M.D.
Chairman

RWM/fn

SYMPTOM RECORD

M-M-R STUDY NO. _____

AME _____ CASE NO. _____
(Last) (First) (Middle)

DAY	DATE	Temperature ☐ Rectal ☐ Oral *(Check One)*	NONE	RUNNY NOSE	SORE THROAT	COUGH	EAR ACHE	SWOLLEN GLANDS	SORE EYES	VOMITING	DIARRHEA	NAUSEA	RASH *	SORE JOINTS	SORE ARM (at shot) *	HEADACHE	ACHINESS	FEVER	LOSS OF APPETITE	*Describe COMMENTS
0																				
1																				
2																				
3																				
4																				
5																				
6																				
7																				
8																				
9																				
10																				
11																				
12																				
13																				
14																				
15																				
16																				
17																				
18																				
19																				
20																				
21																				
22																				
23																				
24																				
25																				
26																				
27																				
28																				
29																				
30																				
31																				
32																				
33																				
34																				
35																				
36																				
37																				
38																				
39																				
40																				
41																				
42																				

ever or unusual reaction develops, call:

PLEASE RETURN FOR FOLLOW-UP VISIT ON: _____

BE SURE TO BRING THIS RECORD ALONG WITH YOU.

INSTRUCTIONS:

1. Please fill in the date each day.
2. Please take temperature once daily at the same time and record exact thermometer reading.
3. If no symptoms are present, place a check (✓) under "NONE" beside that day's date.
4. If a symptom is present, place a check (✓) under it beside that day's date.
5. Describe other symptoms and any RASH in the space under "COMMENTS."
6. THIS IS VERY IMPORTANT INFORMATION. ***Please do not misplace this card.***

MEASLES – MUMPS – RUBELLA

Study No. _____ (1-3) Case No. _____ (5-9)

CT 2 | Name | Sex (35) M F | Birthdate (36-41) mo day yr | (46-47)

Address

Indicate if this child:

☐ had disease
☐ been vaccinated
☐ been exposed

Date of exposure _____

Did child develop clinical disease: 1 = YES 2 = NO

Date of onset: _____

Comments: _____

Diagnosed by: _____

(48)
☐ Vaccinee ☐ Control

Lot No. _____ (49-51)

Date of Vaccination _____ (52-57)

Bleeding Dates: _____ (58-63) _____ (70-75)

CT 3 DAY	DATE	Temperature Oral	Temperature Rectal	Malaise 16	Anorexia 25	Gastrointestinal 08	Irritability 15	Headache 14	Upper Respiratory Illness 01	Otitis 03	Conjunctivitis 06	Lymphadenopathy 05	Local Reaction* 12	Exanthema* 50	Rash* Rubella-like 51	Rash* Measles-like 52	Arthralgia 11	Arthritis 32	*Specify (Type, Location) OTHER REACTIONS
		24																	
0																			
1																			
2																			
3																			
4																			
5																			
6																			
7																			
8																			
9																			
10																			
11																			
12																			
13																			
14																			
15																			
16																			
17																			
18																			
19																			
20																			
21																			
22																			
23																			
24																			
25																			
26																			
27																			
28																			
29																			
30																			
31																			
32																			
33																			
34																			
35																			
36																			
37																			
38																			
39																			
40																			
41																			
42																			

Please return completed forms to: (Retain PINK copy for your files)

M. R. HILLEMAN, PhD, DSc
MERCK SHARP & DOHME RESEARCH LABORATORIES
WEST POINT, PENNSYLVANIA, 19486, U.S.A.

Physician's Signature

Physician's Name (Type or Print)

Date

P4662-0177(DOM)

(*4662-0177) (*4230-0376)R

Program: Study #484 - To evaluate and compare clinical and immunological responses to two combined live measles-mumps-rubella virus vaccines.

Vaccine: Comblined live measles-mumps-rubella (RA 27/3) virus vaccine

Lot #621/C-D763

Combined live measles-mumps-rubella (HPV-77) virus vaccine

M-M-R

Responsible Clinical Investigator:

Anne Gershon, M.D.
8th Floor North 16
Bellevue Hospital
1st Avenue and East 27th Street
New York, New York 10016

Study Location: New York, New York

Date Study Initiated: December 23, 1976

Date Study Completed: In Progress

Study Procedure:

Sixty-three children, 13 months to 15 years of age, and one adult, have been included in the study thus far. Thirty received a 0.5 ml subcutaneous dose of one of the two vaccines. Thirty-four children received a 1.0 ml subcutaneous dose of combined live measles-mumps-rubella (RA 27/3) virus vaccine. Blood samples were obtained on day of vaccination and 8-12 weeks after vaccination. Each child was followed 6 weeks for clinical complaints. The study continues in progress.

NEW YORK UNIVERSITY MEDICAL CENTER
School of Medicine
550 FIRST AVENUE, NEW YORK, N.Y. 10016
AREA 212 679-3200
CABLE ADDRESS: NYUMEDIC

Department of Pediatrics

December 19, 1977

Arlene McLean, Ph.D.
Merck Sharp & Dohme
Research Laboratories
West Point, PA
19486

Dear Arlene,

Enclosed is a follow-up on the progress report I sent you in August. I have simply updated the tables because they really tell the whole story. If you want anything more detailed than this, please let me know.

With best regards.

Sincerely yours,

Anne

Anne A. Gershon, M.D.
Associate Professor
Dept. of Pediatrics

AAG/mac
Enclosure

MMR Study: Children 1-15 years old 12/19/77

	RA 27/3	HPV 77
Number vaccinated	39	25
Number vaccinated with follow-up serum specimens	13	7
Number susceptible	13/13	7/7
Number with seroconversion	13/13	7/7
Number with reaction	0/13	0/7

Reactions (none)

NEW YORK UNIVERSITY MEDICAL CENTER
School of Medicine
550 FIRST AVENUE, NEW YORK, N.Y. 10016
AREA 212 679-1200
CABLE ADDRESS NYUMEDIC

Department of Pediatrics

August 17, 1977

Maurice R. Hilleman, Ph.D.
Director
Virus & Cell Biology Research
Merck Sharp & Dohme
West Point, Pennsylvania 19486

Dear Dr. Hilleman,

I am enclosing a progress report on our study of rubella vaccines RA 27/3 vs HPV 77, in adults and children. We are continuing to immunize and more data should be forthcoming.

With best regards.

Sincerely yours,

Anne

Anne A. Gershon, M.D.
Associate Professor
Dept. of Pediatrics

AAG/mac
Enclosure

cc: Dr. Arlene McLean ✓

2. Infants and children were given rubella RA 27/3 or HPV 77 in combination with their regular measles and mumps vaccine (MMR). The ages of the subjects ranged from 13 months to 15 years. Informed parental consent was obtained. At the time of MMR immunization a blood sample was obtained to determine the child's immune status with regard to rubella. A second blood sample was obtained approximately 8-12 weeks after MMR immunization for rubella HI titer.

The subjects who received HPV 77 rubella vaccine in MMR received the standard dose of vaccine. Those who received RA 27/3 rubella vaccine in MMR received double the usual dose of vaccine. All vaccines were given by subcutaneous injection.

Thirty four children received RA 27/3 rubella vaccine as MMR. There has been follow-up on 5 of these subjects so far. All have developed rubella HI antibody with a titer of 1:128 or 1:256. No reactions to the vaccine have been reported. Follow-up on more of these vaccine recipients will be obtained with time.

Seventeen children and 1 adult received HPV 77 rubella vaccine as MMR. To date follow-up has been obtained on 3 of these children; additional follow-ups are expected to be forthcoming. Of the 3 who have been followed, one had an initial rubella HI titer of $\geq$ 32 at immunization and an HA

titer of 1:128 after vaccination. Two children had titers which were <1:8 at vaccination and increased to 1:16 and 1:32 after vaccination.

NEW YORK UNIVERSITY MEDICAL CENTER
School of Medicine
550 FIRST AVENUE, NEW YORK, N.Y. 10016
AREA 212 679-3200
CABLE ADDRESS: NYUMEDIC

Department of Pediatrics

October 3, 1977

Dr. Arlene McClean
Merck Sharp and Dohme
Research Laboratories
West Point, Pennsylvania 19486

Dear Dr. McClean,

Please find enclosed an information sheet given to the mothers of children receiving the M-M-R vaccine. They are asked to record any reactions to the vaccine and return the slip to the doctor in the Pediatric Clinic. This information is given to Dr. Judy Wallin, who is supervising the study in the Pediatric Clinic at Bellevue Hospital. She keeps this information and we are informed via "word of mouth" with regard to these reactions.

I apologize for the confusion.

Thank you.

Sincerely yours,

Maura Caruth
Secretary to Dr. Anne Gershon
Dept. of Pediatrics

INFORMATION FOR MOTHERS

Baby's Name_____ Date of Vaccination_____

Your baby has just received a measles-mumps-rubella vaccination. He/she will probably have no symptoms afterward. If you think the baby is having a reaction, please take the baby's temperature. Write down any problems the baby is having:

	YES	NO
Fever		
Rash		
Joint pain		
Swelling Where?		

If the baby seems sick please telephone Dr. Gershon or Dr. Reese at 561-3612 between 9 AM-5 PM. If the baby is sick on a weekend or at night take him/her to the PES. They will contact a doctor for you.

These vaccines are safe and an important part of your baby's health care to prevent disease.

We will contact you in 2 months by telephone or letter about drawing a second blood sample from your baby. There will be no charge for the second blood drawing. It will tell you whether your baby is immune to measles and German measles (rubella) because of the vaccination.

PLEASE SAVE THIS LETTER AND BRING IT BACK TO CLINIC WITH YOU

NEW YORK UNIVERSITY MEDICAL CENTER
School of Medicine
550 FIRST AVENUE, NEW YORK, N.Y. 10016
AREA 212 679-3200
CABLE ADDRESS: NYUMEDIC

Department of Pediatrics

September 21, 1976

Arlene A. McLean, Ph.D.
Merck Sharp & Dohme
Research Laboratories
Division of Merck & Co., Inc.
West Point, Pennsylvania 19486

Dear Dr. McLean:

Enclosed is a copy of the revised consent form for measles-mumps-rubella RA 27/3 vaccine, and a letter from the Chairman of the Human Use Committee granting approval of the consent.

I hope we can have the new vaccine soon.

Many thanks.

Sincerely yours,

Anne A. Gershon

Anne A. Gershon, M.D.
Associate Professor
Department of Pediatrics

AAG:rr
Enclosure

NEW YORK UNIVERSITY MEDICAL CENTER
School of Medicine
[illegible] NEW YORK, N.Y. [illegible]
[illegible]
[illegible]

Department of Pediatrics

STUDY OF MEASLES - MUMPS - RUBELLA VACCINE

In the United States, measles, mumps and rubella (German measles) vaccine should be given to babies between the ages of 12 months - 15 months. These vaccines are important because they provide babies and children with long-lasting immunity to measles, mumps and rubella (German measles).

Many clinics are now giving babies a combined measles-mumps-rubella vaccine in one injection. Our clinic has recently received a new vaccine which contains regular measles-mumps vaccine combined with a new, unlicensed rubella vaccine called RA-27. This RA-27 vaccine has been used experimentally in many children (in Europe) and it seems to produce better antibodies than the one which is now licensed for use in the United States.

Our study is designed to see how good this experimental rubella RA-27 vaccine really is. It is combined with the measles-mumps vaccine so that your child will only have to have one injection. We will also have to obtain a small sample of blood (5 ml or about a teaspoonful) before and eight weeks after the vaccine is given.

The known side effects of this type of vaccine are very few and occur only rarely in children. The side effects are fever, rash, and joint pain. Should any of these occur they will disappear after a few days without any treatment.

If you would like your child to receive the measles-mumps-RA-27-rubell vaccine you should sign this sheet in the space provided for your signature. Your child does not have to participate in this study if you do not want him (her) to. In that case your child should receive regular measles-mumps-rubella vaccine in our clinic. Should you decide to have your child participate in this study, his (her) participation will be kept strictly confidential.

_____
SIGNATURE

_____
WITNESS

_____
DATE

NEW YORK UNIVERSITY MEDICAL CENTER

SYNOPSIS OF SPONSORED PROGRAM ACTIVITIES

NAME OF P.I. OR PROJECT DIRECTOR	SOCIAL SECURITY NO.	DEPARTMENT	CODE
Anne A. Gershon, M.D.	(b) (6)	Pediatrics	

TITLE OF PROGRAM
Measles - Rubella Vaccine Trial

NAME OF SPONSOR	GRANT OR CONTRACT NO.

TYPE OF PROGRAM:	N.Y.U.M.C. A/C #
X RESEARCH, ☐ EDUCATION & TRAINING, ☐ FELLOWSHIP, ☐ OTHER (EXPLAIN)	

PART IVA HUMAN SUBJECTS (CONTINUED)

A. List specific procedures to be used which involve human subjects or human materials; detail potential hazards and indicate the probability that they may occur. If procedure is heretofore untried, and hazards are not known, so indicate.

B. Describe the benefit to the subject or advancement of knowledge that will balance the risk involved.

C. Indicate measures proposed to minimize risk and, if applicable, methods for preserving confidentiality and rights of the subjects.

PROTOCOL

A. 1. Venipuncture before and 8 weeks after vaccine is given. No appreciable hazard. 5 ml or less blood will be obtained.

2. Measles-rubella vaccine. No appreciable hazard. Measles component a licensed product routinely given to infants of this age. Rubella vaccine is unlicensed in the United States, but has been widely given to children in Europe. Side effects from this vaccine are very few in children and similar in rate of occurrence to the rubella vaccine which is licensed in the United States. Possible side effects are rash, fever and joint pains all of which are transient. In a recent study conducted by Merck, the following side effects were observed. Those receiving licensed rubella vaccine: 24. rash - 0, arthralgia adenopathy - 0. Those receiving RA-27 rubella vaccine: 26. rash - 3, arthralgia - 1, adenopathy - 0.

B. Benefit to patient - Infant will be immunized against rubella and measles with only one injection and one clinic visit. RA-27 rubella vaccine may provide better immunity than the presently licensed rubella vaccine.

C. Sterile technique will be used at all times and the identity of the patie will not be revealed in any publications concerning this study.

MEASLES – RUbELLA VACCINATION

Study No. _____ (1-3) Case No. _____ (5-9)

CT 3	Name	Sex (35) M F	Birthdate (36-41) mo. day yr	(42-47)
Address				

Indicate if this child:

- ☐ had disease
- ☐ been vaccinated
- ☐ been exposed

Date of exposure _____

Did child develop clinical disease: 1 = YES 2 = NO

Date of onset: _____

Comments: _____

Diagnosed by: _____

(48)

☐ Vaccine ☐ Control

Lot No. _____ (49-51)

Date of Vaccination _____ (52-57)

Bleeding Dates: _____ (58-63) _____ (70-75)

CT 3 DAY	DATE	Temperature Oral	Temperature Rectal	Malaise	Anorexia	Gastrointestinal	Irritability	Headache	Upper Respiratory Illness	Otitis	Conjunctivitis	Lymphadenopathy	Local Reaction*	Exanthema	Rash Rubella-like rash	Arthralgia	Arthritis	*Specify (Type, Location) OTHER REACTIONS
		24		16	25	08	15	14	01	03	06	05	12	50	51	11	32	
0																		
1																		
2																		
3																		
4																		
5																		
6																		
7																		
8																		
9																		
10																		
11																		
12																		
13																		
14																		
15																		
16																		
17																		
18																		
19																		
20																		
21																		
22																		
23																		
24																		
25																		
26																		
27																		
28																		
29																		
30																		
31																		
32																		
33																		
34																		
35																		
36																		
37																		
38																		
39																		
40																		
41																		
42																		

Please return completed forms to: (Retain PINK copy for your files)

M. R. HILLEMAN, PhD, DSc
MERCK SHARP & DOHME RESEARCH LABORATORIES
WEST POINT, PENNSYLVANIA, 19486, U.S.A.

Physician's Signature

Physician's Name (Type or Print)

Date

TR6230-0376(DOM) (06230-0376) (01230-0476)R

Program: Study #511 - To measure antibody and clinical responses to three consecutive lots of combined measles-mumps-rubella virus vaccine.

Vaccine: Combined live measles-mumps-rubella (RA 27/3) virus vaccine, lyophilized

Lot #60664/C-E810
Lot #60665/C-E811
Lot #60666/C-E812

Responsible Clinical Investigator:

Victor M. Villarejos, M.D.
Director
Louisiana State University
International Center for Medical
Research and Training
Apartado 10.155
San Jose, Costa Rica

Study Location: Nicaragua

Date Study Initiated: July 4, 1977

Date Study Completed: September 14, 1977

Study Procedure:

One hundred fifty children, 8 months to 11 years of age, were included in the study. Each received a 0.5 ml subcutaneous dose of combined live measles-mumps-rubella virus vaccine. Blood samples were obtained on day of vaccination and 6 weeks after vaccination. Each child was followed 6 weeks for clinical complaints.

(Dr. Villarejos)

Clinical Protocol - Study #511

Combined Live Measles-Mumps-Rubella (RA 27/3)

Virus Vaccine

Program: Combined live measles-mumps-rubella virus vaccine

Purpose: To measure antibody and clinical responses to three consecutive lots of vaccine.

Vaccine: Combined live measles-mumps-rubella virus vaccine, lyophilized,
Lot. No. 60664/C-E810
Lot. No. 60665/C-E811
Lot. No. 60666/C-E812

Vaccine dose is 0.5 ml given subcutaneously.

The vaccine is supplied in single dose vials. Each vial should be reconstituted with 0.7 ml of sterile, pyrogen-free distilled water which is supplied in prefilled syringes.

CAUTION: The vaccine contains egg protein and should not be given to persons with known sensitivity to chicken or duck, chicken or duck eggs or feathers. The vaccine contains neomycin and should not be given to persons sensitive to neomycin. Persons with leukemia or other immunologic disorder and persons receiving immunosuppressive drugs should not be vaccinated. Also, the vaccine should not be given to persons with a febrile respiratory illness or other active febrile infection.

Keep dried vaccine stored at -20° C until used.

Keep dried vaccine at 4° C in transport.

Keep reconstituted vaccine on ice. Discard unused vaccine 4 hours after rehydration.

Procedure: The study population will consist of up to 150 children with a negative history for vaccination and illness caused by measles, mumps and rubella viruses. The children should range from 1 to 6 years of age.

Approximately 25 to 50 children will receive each of the three vaccine lots.

Informed written consent will be obtained from a parent or guardian of each child who participates in the study.

Revised 4/22/77

Clinical Protocol - Study #511
Combined Live Measles-Mumps-Rubella (RA 27/3) Virus Vaccine

Procedure:
(Continued)

Each child will receive a 0.5 ml subcutaneous injection of vaccine.

Bleeding samples (10-15 ml) will be obtained from each child immediately before and 6 weeks after vaccination.

Each child will be followed clinically for local and systemic complaints occurring within 6 weeks after vaccination. Observations should include special notation for rash, nodes, arthralgia, arthritis, fever, malaise and anorexia. All complaints should be recorded on the case report form.

Schedule:

Time	Action - All Persons
Day 0	Bleed 10-15 ml Vaccinate 0.5 ml, subcutaneously
Days 0-42	Clinical follow-up for local and systemic complaints
Week 6	Bleed 10-15 ml

Laboratory: Remove serum from clot aseptically and store frozen at -20° C until shipped. It is imperative that sera are sterile to avoid interference with the serologic assay.

Serology: Levels of circulating measles and rubella antibodies will be determined by hemagglutination-inhibition test. Levels of mumps antibody before and after vaccination will be determined by serum neutralization test.

Clinical Forms: Attached.

Adverse Reactions: Any serious or alarming reaction, including death due to any cause during the investigation, whether related or not related to the test material, must be reported immediately to Merck & Co., Inc., through Dr. Maurice R. Hilleman, telephone (215) 699-5311, Ext. 5532, or in his absence, Dr. Arlene A. McLean, telephone (215) 699-5311, Ext. 6383.

Clinical Protocol - Study #511
Combined Live Measles-Mumps-Rubella (RA 27/3) Virus Vaccine

Unused Vaccine: All unused vaccine should be returned immediately to Merck Sharp & Dohme Research Laboratories, West Point, Pennsylvania 19486.

Shipping of Sera & Records:

1. Send sera frozen within insulated containers which are supplied.

2. Send sera and records to Dr. Maurice R. Hilleman, Virus & Cell Biology Research, Merck Sharp & Dohme Research Laboratories, West Point, Pennsylvania 19486.

3. Alert Dr. Hilleman by cable as soon as possible regarding flight number, air bill and date of arrival.

M. R. Hilleman, Ph.D.

Estudio No. _____ (1-3)

OBSERVACIONES CLINICAS

No. Del Caso _____ (5-9)

CT 2	Nombre completo del niño:	(35) M F	Fecha de nacimieto (36-41) día mes año	(46-47)
	Dirección completa de Padres o Guardián:			

☐ VACUNADO NO. de LOTE _____ (49-51) FECHAS de SANGRIA _____ SEROLOGIA _____

☐ CONTROL (48) FECHA de VACUNACION _____ (52-57) _____ (56-63) _____

_____ (70-75) _____

Dia	Fecha	Temperatura Oral	Temperatura Retal	Malestar	Anorexia	Gastroenteritis	Irritabilidad	Cafelea	I.V.R.S.	Otitis	Conjuntivitis	Linfadenopatía	Reaccion Local*	RASH* Rubelliforme	RASH* Morbilliforme	Artraigia	Artritis	* Especifique tipo en esta seccion / OTRAS REACCIONES
		24		16	25	08	15	14	01	03	06	05	12	51	52	11	32	
0																		
1																		
2																		
3																		
4																		
5																		
6																		
7																		
8																		
9																		
10																		
11																		
12																		
13																		
14																		
15																		
16																		
17																		
18																		
19																		
20																		
21																		
22																		
23																		
24																		
25																		
26																		
27																		
28																		
29																		
30																		
31																		
32																		
33																		
34																		
35																		
36																		
37																		
38																		
39																		
40																		
41																		
42																		

Al terminar el estudio, devuelva copia blanca y copia amarilla de esta form a (Retenga copia color de rosa para sus archivos)

M. R. HILLEMAN, PhD, DSc
MERCK SHARP & DOHME RESEARCH LABORATORIES
WEST POINT, PENNSYLVANIA, 19486, U.S.A.

Firma del medico:

Nombre del medico (en letra de molde):

Fecha:

Table 1

Serological Findings Among Children Who Received Combined Live
Measles-Mumps-Rubella (RA 27/3) Virus Vaccine, Lot #60664/C-E810 (Study #511)

Age	No. Vacc.	No. Serol. Tested	Initially Seronegative to: Measles-Mumps-Rubella Conversions/Total Measles	Mumps	Rubella	Measles-Mumps Conversions/Total Measles	Mumps	Measles-Rubella Conversions/Total Measles	Rubella	Mumps-Rubella Conversions/Total Mumps	Rubella	Measles Only Conversions/ Total	Mumps Only Conversions/ Total	Rubella Only Conversions/ Total	Initially Seropositive to: Measles, Mumps and Rubella
(Months)															
8	1	1						1/1	1/1						
9	1	1								1/1	1/1				
10	2	2						1/1	1/1					1/1	
11	3	1	1/1	1/1	1/1										
12	2	2	0/1	1/1	1/1			0/1	1/1						
13	3	3	1/1	1/1	1/1			1/1	1/1			0/1			
14	2	2	2/2	2/2	2/2										
17	2	1						0/1	1/1						
18	2	2								1/1	1/1			1/1	
21	1	1												1/1	
(Years)															
2	10	8	2/2	2/2	2/2			1/2	2/2					3/3	1
3	6	6	1/1	1/1	1/1	1/1	1/1			1/1	1/1			3/3	
4	2	2											1/1	1/1	
5	4	4	1/2	1/2	2/2					1/1	1/1		1/1		
6	1	1												1/1	
7	2	2	1/1	1/1	1/1			1/1	1/1						
8	2	2												1/1	1
9	2	2												2/2	
11	2	1						1/1	1/1						
Total	50	44	9/11	10/11	11/11	1/1	1/1	6/9	9/9	4/4	4/4	0/1	2/2	14/14	2
Mean Age:	3.3 Years		(81.8%)	(90.9%)	(100%)	(100%)	(100%)	(66.7%)	(100%)	(100%)	(100%)		(100%)	(100%)	

Overall Conversion Rates

Measles	Mumps	Rubella
16/22	17/18	38/38
(72.7%)	(94.4%)	(100%)

Table 2

Serological Findings Among Children Who Received Combined Live
Measles-Mumps-Rubella (RA 27/3) Virus Vaccine, Lot #60665/C-E811 (Study #511)

Age	No. Vacc.	No. Seroi. Tested	Initially Seronegative to: Measles-Mumps-Rubella Conversions/Total Measles	Measles-Mumps-Rubella Conversions/Total Mumps	Measles-Mumps-Rubella Conversions/Total Rubella	Measles-Mumps Conversions/Total Measles	Measles-Mumps Conversions/Total Mumps	Measles-Rubella Conversions/Total Measles	Measles-Rubella Conversions/Total Rubella	Mumps-Rubella Conversions/Total Mumps	Mumps-Rubella Conversions/Total Rubella	Measles Only Conversions/ Total	Mumps Only Conversions/ Total	Rubella Only Conversions/ Total	Initially Seropositive to: Measles, Mumps and Rubella
(Months)															
11	1	1								1/1	1/1				
12	2	1	1/1	1/1	1/1										
13	1	1						1/1	1/1						
14	2	2								1/1	1/1			1/1	
16	1	1						0/1	1/1						
17	1	1								0/1	1/1				
18	3	3	1/1	1/1	1/1			1/1	1/1	1/1	1/1				
21	1	1								1/1	1/1				
(Years)															
2	9	9	1/2	1/2	2/2			1/1	1/1	1/1	1/1			5/5	
3	7	7								4/4	4/4	1/1		2/2	
4	7	6	1/1	1/1	1/1	1/1	1/1			2/2	2/2			2/2	
5	8	8						1/1	1/1	1/1	1/1			6/6	
6	6	5											1/1	3/3	1
7	1	1												1/1	
Total	50	47	4/5	4/5	5/5	1/1	1/1	4/5	5/5	12/13	13/13	1/1	1/1	20/20	1
Mean Age:	3.3 Years		(80.0%)	(80.0%)	(100%)	(100%)	(100%)	(80.0%)	(100%)	(92.3%)	(100%)	(100%)	(100%)	(100%)	

Overall Conversion Rates

Measles	Mumps	Rubella
10/12	18/20	43/43
(83.3%)	(90.0%)	(100%)

1/27/78

Table 3

Serological Findings Among Children Who Received Combined Live
Measles-Mumps-Rubella (RA 27/3) Virus Vaccine, Lot #60666/C-E812 (Study #511)

Age	No. Vacc.	No. Serol. Tested	Initially Seronegative to: Measles-Mumps-Rubella Conversions/Total Measles	Measles-Mumps-Rubella Conversions/Total Mumps	Measles-Mumps-Rubella Conversions/Total Rubella	Measles-Rubella Conversions/Total Measles	Measles-Rubella Conversions/Total Rubella	Mumps-Rubella Conversions/Total Mumps	Mumps-Rubella Conversions/Total Rubella	Measles Only Conversions/ Total	Mumps Only Conversions/ Total	Rubella Only Conversions/ Total	Initially Seropositive to: Measles, Mumps and Rubella
(Months)													
11	1	1										1/1	
13	1	1										1/1	
17	1	1				1/1	1/1						
19	1	1						1/1	1/1				
(Years)													
2	8	8	1/1	1/1	1/1			0/1	1/1	1/1	1/1	1/1	3
3	8	8						2/2	2/2			4/4	2
4	11	11				2/2	2/2	3/3	3/3			4/4	2
5	8	8	1/1	1/1	1/1			2/4	4/4		1/1	1/1	1
6	4	4									1/1	2/2	1
7	5	4						1/1	1/1		1/1	1/1	1
9	1	1										1/1	
11	1	1										1/1	
Total	50	49	2/2	2/2	2/2	3/3	3/3	9/12	12/12	1/1	4/4	17/17	10
Mean Age:	4.2 Years		(100%)	(100%)	(100%)	(100%)	(100%)	(75.0%)	(100%)	(100%)	(100%)	(100%)	

Overall Conversion Rates

Measles	Mumps	Rubella
6/6	15/18	34/34
(100%)	(83.3%)	(100%)

1/27/78

Table 4

Distribution of Post-Vaccination Antibody Titers Among Children Who Were Initially Seronegative to Measles, Mumps, and Rubella, Who Received Combined Live Measles-Mumps-Rubella (RA 27/3) Virus Vaccine, Lot #60664/C-E810 (Study #511)

Measles (HI)	
Post-Titer Distribution	Number of Children
<5	2
5	
10	1
20	3
40	1
80	3
160	1
Total	11
Geometric Mean Titer:	20.5

Mumps (Neut)	
Post-Titer Distribution	Number of Children
<2	1
2	3
4	2
8	3
16	1
32	1
Total	11
Geometric Mean Titer:	4.8

Rubella (HI)	
Post-Titer Distribution	Number of Children
128	4
256	5
≥512	2
Total	11
Geometric Mean Titer:	≥225.7

1/27/78

Table 5

Distribution of Post-Vaccination Antibody Titers Among Children Who Were Initially Seronegative to Measles, Mumps, and Rubella, Who Received Combined Live Measles-Mumps-Rubella (RA 27/3) Virus Vaccine, Lot #60665/C-E811 (Study #511)

Measles (HI)	
Post-Titer Distribution	Number of Children
<5	1
5	
10	
20	
40	3
80	
160	1
Total	5
Geometric Mean Titer:	25.2

Mumps (Neut)	
Post-Titer Distribution	Number of Children
<2	1
2	
4	1
8	1
16	
32	
64	2
Total	5
Geometric Mean Titer:	10.6

Rubella (HI)	
Post-Titer Distribution	Number of Children
128	3
256	2
Total	5
Geometric Mean Titer:	168.9

1/27/78

Table 6

Distribution of Post-Vaccination Antibody Titers Among Children Who Were Initially Seronegative to Measles, Mumps, and Rubella, Who Received Combined Live Measles-Mumps-Rubella (RA 27/3) Virus Vaccine, Lot #60666/C-E812 (Study #511)

Measles (HI)	
Post-Titer Distribution	Number of Children
20	1
40	1
Total	2
Geometric Mean Titer:	28.3

Mumps (Neut)	
Post-Titer Distribution	Number of Children
8	2
Total	2
Geometric Mean Titer:	8.0

Rubella (HI)	
Post-Titer Distribution	Number of Children
256	2
Total	2
Geometric Mean Titer:	256.0

1/27/78

Table 7

Maximum Temperatures Reported Among Children Who Received Combined
Live Measles-Mumps-Rubella (RA 27/3) Virus Vaccine, Lot #60664/C-E810 (Study #511)

Maximum Temperature (°F, Oral)	Total Vaccinees (50 Children)						Initially Seronegatives (13 Children)					
	Days Post Vaccination					No. with Max. Temp.	Days Post Vaccination					No. with Max. Temp.
	0-4	5-12	13-18	19-28	29-42		0-4	5-12	13-18	19-28	29-42	
<99	48 (96.0%)	44 (88.0)	45 (90.0)	47 (94.0)	50 (100)	35	12 (92.3)	13 (100)	10 (76.9)	13 (100)	13 (100)	9
99 - 100.9	2 (4.0)	6 (12.0)	5 (10.0)	3 (6.0)		15	1 (7.7)		3 (23.1)			4

1/31/78

Table 8

Maximum Temperatures Reported Among Children Who Received Combined Live Measles-Mumps-Rubella (RA 27/3) Virus Vaccine, Lot #60665/C-E811 (Study #511)

Maximum Temperature (°F, Oral)	Total Vaccinees (50 Children)						Initially Seronegatives (6 Children)					
	Days Post Vaccination					No. with Max. Temp.	Days Post Vaccination					No. with Max. Temp.
	0-4	5-12	13-18	19-28	29-42		0-4	5-12	13-18	19-28	29-42	
<99	47 (94.0%)	42 (84.0)	47 (94.0)	45 (90.0)	48 (96.0)	31	6 (100)	5 (83.3)	6 (100)	5 (83.3)	6 (100)	4
99 - 100.9	3 (6.0)	8 (16.0)	3 (6.0)	5 (10.0)	2 (4.0)	19		1 (16.7)		1 (16.7)		2

1/31/78

Table 9

Maximum Temperatures Reported Among Children Who Received Combined
Live Measles-Mumps-Rubella (RA 27/3) Virus Vaccine, Lot #60666/C-E812 (Study #511)

Maximum Temperature (°F, Oral)	Total Vaccinees (50 Children)						Initially Seronegatives (2 Children)					
	Days Post Vaccination					No. with	Days Post Vaccination					No. with
	0-4	5-12	13-18	19-28	29-42	Max. Temp.	0-4	5-12	13-18	19-28	29-42	Max. Temp.
<99	50 (100%)	40 (80.0)	47 (94.0)	50 (100)	47 (94.0)	36	2 (100)	2 (100)	2 (100)	2 (100)	2 (100)	2
99 - 100.9		10 (20.0)	3 (6.0)		3 (6.0)	14						0

1/31/78

Table 10

Clinical Complaints Reported Among Children Who Received Combined
Live Measles-Mumps-Rubella (RA 27/3) Virus Vaccine, Lot #60664/C-E810 (Study #511)

Clinical Complaint	Total Vaccinees (50 Children)						Initially Seronegatives (13 Children)					
	Days Post Vaccination					No. with	Days Post Vaccination					No. with
	0-4	5-12	13-18	19-28	29-42	Complaint	0-4	5-12	13-18	19-28	29-42	Complaint
Headache	1 (2.0%)	1 (2.0)	1 (2.0)	1 (2.0)		4						0
Irritability	5 (10.0)	8 (16.0)	6 (12.0)	5 (10.0)		18	2 (15.4)	3 (23.1)	3 (23.1)	1 (7.7)		7
Malaise	7 (14.0)	9 (18.0)	4 (8.0)	4 (8.0)		17	3 (23.1)	3 (23.1)	3 (23.1)	2 (15.4)		7
Anorexia		1 (2.0)		1 (2.0)		2				1 (7.7)		1
Upper Respiratory Illness	2 (4.0)	6 (12.0)	3 (6.0)	1 (2.0)		9			2 (15.4)			2
Lower Respiratory Illness	1 (2.0)	1 (2.0)				1	1 (7.7)	1 (7.7)				1
Gastrointestinal Illness	1 (2.0)	3 (6.0)	1 (2.0)	4 (8.0)	2 (4.0)	7			1 (7.7)	2 (15.4)	1 (7.7)	3
Persons with Complaint:	7 (14.0)	9 (18.0)	7 (14.0)	8 (16.0)	2 (4.0)	21	3 (23.1)	3 (23.1)	4 (30.8)	2 (15.4)	1 (7.7)	8
Persons with No Complaint:	43 (86.0)	41 (82.0)	43 (86.0)	42 (84.0)	48 (96.0)	29	10 (76.9)	10 (76.9)	9 (69.2)	11 (84.6)	12 (92.3)	5

1/31/78

Table 11

Clinical Complaints Reported Among Children Who Received Combined
Live Measles-Mumps-Rubella (RA 27/3) Virus Vaccine, Lot #60665/C-E811 (Study #511)

Clinical Complaint	Total Vaccinees (50 Children)						Initially Seronegatives (6 Children)					
	Days Post Vaccination					No. with Complaint	Days Post Vaccination					No. with Complaint
	0-4	5-12	13-18	19-28	29-42		0-4	5-12	13-18	19-28	29-42	
Headache	2 (4.0%)	1 (2.0)	4 (8.0)	2 (4.0)		8			1 (16.7)			1
Irritability	2 (4.0)	9 (18.0)	4 (8.0)	5 (10.0)	3 (6.1)	18		1 (16.7)		1 (16.7)		2
Malaise	2 (4.0)	7 (14.0)	2 (4.0)	3 (6.0)		12		1 (16.7)		1 (16.7)		2
Anorexia		1 (2.0)				1						0
Upper Respiratory Illness	2 (4.0)	4 (8.0)				4						0
Lower Respiratory Illness		1 (2.0)	1 (2.0)			1						0
Gastrointestinal Illness	1 (2.0)	3 (6.0)	2 (4.0)	1 (2.0)		5						0
Persons with Complaint:	2 (4.0)	11 (22.0)	7 (14.0)	6 (12.0)	3 (6.1)	20	0	1 (16.7)	1 (16.7)	1 (16.7)	0	3
Persons with No Complaint:	48 (96.0)	39 (78.0)	43 (86.0)	44 (88.0)	46 (93.9)	30	6 (100)	5 (83.3)	5 (83.3)	5 (83.3)	5 (100)	3
Negative Surveillance	0	0	0	0	1	0	0	0	0	0	1	0

1/31/78

Table 12

Clinical Complaints Reported Among Children Who Received Combined
Live Measles-Mumps-Rubella (RA 27/3) Virus Vaccine, Lot #60666/C-E812 (Study #511)

Clinical Complaint	Total Vaccinees (50 Children)						Initially Seronegatives (2 Children)					
	Days Post Vaccination					No. with Complaint	Days Post Vaccination					No. with Complaint
	0-4	5-12	13-18	19-28	29-42		0-4	5-12	13-18	19-28	29-42	
Headache		2 (4.0%)	4 (8.0)			6			1 (50.0)			1
Irritability	1 (2.0)	9 (18.0)	3 (6.0)	1 (2.0)	2 (4.0)	12						0
Malaise	2 (4.0)	6 (12.0)	4 (8.0)		3 (6.0)	13			1 (50.0)			1
Anorexia	1 (2.0)	3 (6.0)	1 (2.0)			5						0
Upper Respiratory Illness	1 (2.0)	2 (4.0)				2						0
Lower Respiratory Illness		1 (2.0)				1						0
Otitis	1 (2.0)					1						0
Gastrointestinal Illness	1 (2.0)	1 (2.0)	1 (2.0)			2						0
Persons with Complaint:	2 (4.0)	11 (22.0)	6 (12.0)	1 (2.0)	3 (6.0)	17	0	0	1 (50.0)	0	0	1
Persons with No Complaint:	48 (96.0)	39 (78.0)	44 (88.0)	49 (98.0)	47 (94.0)	33	2 (100)	2 (100)	1 (50.0)	2 (100)	2 (100)	1

1/31/78

MEMO

To File Location Date 2/6/78

From T. Schofield Location

Subject Statistical Analysis - Study #511, Combined Live Measles-Mumps-Rubella Virus Vaccine

Significant differences in seroconversion rates for measles, mumps, and rubella and clinical reaction rates among vaccinees receiving three lots of combined live measles-mumps-rubella vaccine were investigated. Lots of vaccine were:

Lot #60664/C-E810
Lot #60665/C-E811
Lot #60666/C-E812

No significant differences exist among the three lots with respect to these rates.

Analyses of variance were performed on post-titer values of children who were initially seronegative to the individual components. The log transformation was used in each analysis. No significant differences exist among the groups (lots) for any of the three components.

A multivariate analysis was performed on post-titer values of triple-negative vaccinees. Again, the lot transformation was applied. There was no significant difference among the groups.

T.S.
6801

Program: Study #513 - To measure antibody and clinical responses to three consecutive lots of combined measles-mumps-rubella virus vaccine.

Vaccine: Combined live measles-mumps-rubella (RA 27/3) virus vaccine, lyophilized

Lot #60664/C-E810
Lot #60665/C-E811
Lot #60666/C-E812

Responsible Clinical Investigator:

Robert E. Weibel, M.D.
Director, Division of Preventive Medicine
Joseph Stokes, Jr. Research Institute
Children's Hospital of Philadelphia
34th Street and Civic Center Boulevard
Philadelphia, Pennsylvania 19104

Study Locations:

Lankenau Pediatric Clinic, Philadelphia, Pennsylvania
G. A. Starkweather, M.D., Havertown, Pennsylvania
Elizabeth M. Craven, M.D., Wilmington, Delaware
Pediatric Medical Associates, Havertown, Pennsylvania
Children's Hospital of Philadelphia, Philadelphia, Pennsylvania

Date Study Initiated: June 15, 1977

Date Study Completed: In Progress

Study Procedure:

One hundred sixty-three children, 11 months to 7 years of age, have been included in the study thus far. Each received a 0.5 ml subcutaneous dose of combined live measles-mumps-rubella virus vaccine. Blood samples were obtained on day of vaccination and 6 weeks after vaccination. Each child was followed 6 weeks for clinical complaints. The study continues in progress.

(Dr. Weibel)

Clinical Protocol - Study #513

Combined Live Measles-Mumps-Rubella (RA 27/3)

Virus Vaccine

Program: Combined live measles-mumps-rubella virus vaccine

Purpose: To measure antibody and clinical responses to three consecutive lots of vaccine.

Vaccine: Combined live measles-mumps-rubella virus vaccine, lyophilized,
Lot. No. 60664/C-E810
Lot. No. 60665/C-E811
Lot. No. 60666/C-E812

Vaccine dose is 0.5 ml given subcutaneously.

The vaccine is supplied in single dose vials. Each vial should be reconstituted with 0.7 ml of sterile, pyrogen-free distilled water which is supplied in prefilled syringes.

CAUTION: The vaccine contains egg protein and should not be given to persons with known sensitivity to chicken or duck, chicken or duck eggs or feathers. The vaccine contains neomycin and should not be given to persons sensitive to neomycin. Persons with leukemia or other immunologic disorder and persons receiving immunosuppressive drugs should not be vaccinated. Also, the vaccine should not be given to persons with a febrile respiratory illness or other active febrile infection.

Keep dried vaccine stored at -20° C until used.

Keep dried vaccine at 4° C in transport.

Keep reconstituted vaccine on ice. Discard unused vaccine 4 hours after rehydration.

Procedure: The study population will consist of up to 150 children with a negative history for vaccination and illness caused by measles, mumps and rubella viruses. The children should range from 1 to 6 years of age.

Approximately 25 to 50 children will receive each of the three vaccine lots.

Informed written consent will be obtained from a parent or guardian of each child who participates in the study.

Clinical Protocol - Study #513
Combined Live Measles-Mumps-Rubella (RA 27/3) Virus Vaccine

Procedure:
(Continued)

Each child will receive a 0.5 ml subcutaneous injection of vaccine.

Bleeding samples (10-15 ml) will be obtained from each child immediately before and 6 weeks after vaccination.

Each child will be followed clinically for local and systemic complaints occurring within 6 weeks after vaccination. Observations should include special notation for rash, nodes, arthralgia, arthritis, fever, malaise and anorexia. All complaints should be recorded on the case report form.

Schedule:

Time	Action - All Persons
Day 0	Bleed 10-15 ml Vaccinate 0.5 ml, subcutaneously
Days 0-42	Clinical follow-up for local and systemic complaints
Week 6	Bleed 10-15 ml

Serology: Levels of circulating measles and rubella antibodies will be determined by hemagglutination-inhibition test. Levels of mumps antibody before and after vaccination will be determined by serum neutralization test.

Clinical Forms: Attached.

Adverse Reactions: Any serious or alarming reaction, including death due to any cause during the investigation, whether related or not related to the test material, must be reported immediately to Merck & Co., Inc., through Dr. Maurice R. Hilleman, telephone (215) 699-5311, Ext. 5532, or in his absence, Dr. Arlene A. McLean, telephone (215) 699-5311, Ext. 6383.

Unused Vaccine: All unused vaccine should be returned immediately to Merck Sharp & Dohme Research Laboratories, West Point, Pennsylvania 19486.

M. R. Hilleman, Ph.D.

SYMPTOM RECORD

RUBELLA STUDY NO. _____

NAME _____ CASE NO. _____
(Last) (First) (Middle)

DAY	DATE	Temperature ☐ Rectal ☐ Oral (Check One)	NONE	RUNNY NOSE	SORE THROAT	COUGH	EAR ACHE	SWOLLEN GLANDS	SORE EYES	VOMITING	DIARRHEA	NAUSEA	RASH *	SORE JOINTS	SORE ARM (at shot)*	HEADACHE	ACHINESS	FEVER	LOSS OF APPETITE	* Describe COMMENTS
INSTRUCTIONS ON REVERSE SIDE			99	01	01	01	03	05	06	08	08	08		11	12	14	61	24	25	
0																				
1																				
2																				
3																				
4																				
5																				
6																				
7																				
8																				
9																				
10																				
11																				
12																				
13																				
14																				
15																				
16																				
17																				
18																				
19																				
20																				
21																				
22																				
23																				
24																				
25																				
26																				
27																				
28																				
29																				
30																				
31																				
32																				
33																				
34																				
35																				
36																				
37																				
38																				
39																				
40																				
41																				
42																				

If fever or unusual reaction develops, call:

PLEASE RETURN FOR FOLLOW-UP VISIT ON: _____

BE SURE TO BRING THIS RECORD ALONG WITH YOU.

REGISTRATION

Study No. _____ (1-3) Case No. _____ (5-9)

CT 2	Name	Sex (35) M F	Birthdate (36-41) mo day yr	(46-47)
Address			Telephone	

BLEEDING DATES:

Date of Vaccination _____ (54-59)

Lot No. _____ (49-51)

Dose & Route _____ (45)

Pre _____

Post _____

SEROLOGY:

INDICATE IF THIS CHILD:

Had disease	☐ measles	☐ mumps	☐ rubella
Been vaccinated	☐ measles	☐ mumps	☐ rubella
Been exposed	☐ measles	☐ mumps	☐ rubella
Date of exposure	_____	_____	_____

INSTRUCTIONS FOR COMPLETING SYMPTOM RECORD (Reverse side):

1. Please fill in the date each day.
2. Please take temperature once daily at the same time and record exact thermometer reading.
3. If no symptoms are present, place a check (✓) under "NONE" beside that day's date.
4. If a symptom is present place a check (✓) under it beside that day's date.
5. Describe other symptoms and any RASH in the space under "COMMENTS."
6. THIS IS VERY IMPORTANT INFORMATION. *Please do not misplace this card.*

Please return completed forms to:	*Physician's Signature*	*Date*
M. R. HILLEMAN, PhD, DSc MERCK SHARP & DOHME RESEARCH LABORATORIES WEST POINT, PENNSYLVANIA, 19486, U.S.A.	*Physician's Name (Type or Print)*	

Table 1

Serological Findings Among Children Who Received Combined Live
Measles-Mumps-Rubella (RA 27/3) Virus Vaccine, Lot #60664/C-E810 (Study #513)

Age	No. Vacc.	No. Serol. Tested	Initially Seronegative to:							Initially Seropositive to:
			Measles-Mumps-Rubella Conversions/Total			Measles-Rubella Conversions/Total		Measles Only Conversions/ Total	Rubella Only Conversions/ Total	Measles Mumps and Rubella
			Measles	Mumps	Rubella	Measles	Rubella			
(Months)										
12	2	2	2/2	2/2	2/2					
14	8	8	5/5	5/5	5/5	3/3	3/3			
15	21	20	11/12	11/12	12/12	6/6	6/6	2/2		
16	4	4	2/2	2/2	2/2	2/2	2/2			
17	7	7	6/6	6/6	6/6	1/1	1/1			
18	2	2				2/2	2/2			
19	1	1	1/1	1/1	1/1					
20	2	2	1/2	2/2	2/2					
21	1	0								
(Years)										
3	1	1				1/1	1/1			
4	1	1							1/1	
5	1	1				1/1	1/1			
6	1	1							1/1	
7	1	0								
Total	53	50	28/30	29/30	30/30	16/16	16/16	2/2	2/2	0
Mean Age:	1.7 Years		(93.3%)	(96.7%)	(100%)	(100%)	(100%)	(100%)	(100%)	

Overall Conversion Rates

Measles	Mumps	Rubella
46/48	29/30	48/48
(95.8%)	(96.7%)	(100%)

1/27/78

Table 2

Serological Findings Among Children Who Received Combined Live
Measles-Mumps-Rubella (RA 27/3) Virus Vaccine, Lot #60665/C-E811 (Study #513)

Age	No. Vacc.	No. Serol. Tested	Initially Seronegative to:								Initially Seropositive to:
			Measles-Mumps-Rubella Conversions/Total			Measles-Mumps Conversions/Total		Measles-Rubella Conversions/Total		Measles Only Conversions/ Total	Measles Mumps and Rubella
			Measles	Mumps	Rubella	Measles	Mumps	Measles	Rubella		
(Months)											
12	2	2	2/2	2/2	2/2						
13	1	1								1/1	
14	5	5	4/4	4/4	4/4			1/1	1/1		
15	21	21	15/15	14/15	15/15	2/2	2/2	4/4	4/4		
16	7	7	3/3	3/3	3/3	1/1	1/1	3/3	3/3		
17	4	4	3/3	3/3	3/3			1/1	1/1		
19	2	1	0/1	1/1	0/1						
20	1	0									
21	3	3	1/1	1/1	1/1	1/1	1/1	1/1	1/1		
22	3	3	3/3	3/3	3/3						
(Years)											
2	2	2	1/1	1/1	1/1						1
4	3	1	1/1	1/1	1/1						
Total	54	50	33/34	33/34	33/34	4/4	4/4	10/10	10/10	1/1	1
Mean Age:	1.5 Years		(97.1%)	(97.1%)	(97.1%)	(100%)	(100%)	(100%)	(100%)	(100%)	

Overall Conversion Rates

Measles	Mumps	Rubella
48/49	37/38	43/44
(98.0%)	(97.4%)	(97.7%)

1/27/78

Table 3

Serological Findings Among Children Who Received Combined Live
Measles-Mumps-Rubella (RA 27/3) Virus Vaccine, Lot #60666/C-E812 (Study #513)

Age	No. Vacc.	No. Serol. Tested	Initially Seronegative to: Measles-Mumps-Rubella Conversions/Total			Measles-Mumps Conversions/Total		Measles-Rubella Conversions/Total		Measles Only Conversions/ Total	Mumps Only Conversions/ Total	Rubella Only Conversions/ Total	Initially Seropositive to: Measles Mumps and Rubella
			Measles	Mumps	Rubella	Measles	Mumps	Measles	Rubella				
(Months)													
11	1	1	1/1	1/1	1/1								
12	1	1	1/1	1/1	1/1								
13	1	0											
14	6	6	5/5	5/5	5/5	1/1	1/1						
15	26	25	18/19	18/19	18/19	1/1	1/1	4/4	4/4			1/1	
16	9	7	4/4	4/4	4/4			2/2	2/2	1/1			
17	4	3	1/1	1/1	1/1	1/1	1/1			1/1			
19	2	2	1/1	1/1	1/1					1/1			
20	1	1						1/1	1/1				
23	2	2						2/2	2/2				
(Years)													
2	1	1									1/1		
4	2	2	1/1	1/1	1/1			1/1	1/1				
Total	56	51	32/33	32/33	32/33	3/3	3/3	10/10	10/10	3/3	1/1	1/1	0
Mean Age: 1.4 Years			(97.0%)	(97.0%)	(97.0%)	(100%)	(100%)	(100%)	(100%)	(100%)	(100%)	(100%)	

Overall Conversion Rates

Measles	Mumps	Rubella
48/49	36/37	43/44
(98.0%)	(97.3%)	(97.7%)

1/27/78

Table 4

Distribution of Post-Vaccination Antibody Titers Among Children Who Were Initially Seronegative to Measles, Mumps, and Rubella, Who Received Combined Live Measles-Mumps-Rubella (RA 27/3) Virus Vaccine, Lot #60664/C-E810 (Study #513)

Measles (HI)	
Post-Titer Distribution	Number of Children
<5	2
5	
10	
20	1
40	7
80	8
160	8
≥320	4
Total	30
Geometric Mean Titer:	≥70.2

Mumps (Neut)	
Post-Titer Distribution	Number of Children
<2	1
2	
4	2
8	6
16	7
32	6
64	4
≥64	4
Total	30
Geometric Mean Titer:	≥19.2

Rubella (HI)	
Post-Titer Distribution	Number of Children
16	1
32	1
64	
128	6
256	9
≥512	13
Total	30
Geometric Mean Titer:	≥256.0

1/27/78

Table 5

Distribution of Post-Vaccination Antibody Titers Among Children Who Were Initially Seronegative to Measles, Mumps, and Rubella, Who Received Combined Live Measles-Mumps-Rubella (RA 27/3) Virus Vaccine, Lot #60665/C-E811 (Study #513)

Measles (HI)	
Post-Titer Distribution	Number of Children
<5	1
5	
10	
20	6
40	2
80	16
160	4
≥320	5
Total	34
Geometric Mean Titer:	≥70.3

Mumps (Neut)	
Post-Titer Distribution	Number of Children
<2	1
2	2
4	1
8	3
16	7
32	8
64	5
≥64	7
Total	34
Geometric Mean Titer:	≥22.6

Rubella (HI)	
Post-Titer Distribution	Number of Children
<8	1
8	
16	
32	1
64	3
128	6
256	12
≥512	11
Total	34
Geometric Mean Titer:	≥200.4

1/27/78

Table 6

Distribution of Post-Vaccination Antibody Titers Among Children Who Were Initially Seronegative to Measles, Mumps, and Rubella, Who Received Combined Live Measles-Mumps-Rubella (RA 27/3) Virus Vaccine, Lot #60666/C-E812 (Study #513)

Measles (HI)	
Post-Titer Distribution	Number of Children
<5	1
5	
10	2
20	5
40	5
80	8
160	6
≥320	6
Total	33
Geometric Mean Titer:	≥65.8

Mumps (Neut)	
Post-Titer Distribution	Number of Children
<2	1
2	1
4	1
8	2
16	7
32	8
64	3
≥64	10
Total	33
Geometric Mean Titer:	≥25.9

Rubella (HI)	
Post-Titer Distribution	Number of Children
<8	1
8	
16	
32	
64	3
128	1
256	14
≥512	14
Total	33
Geometric Mean Titer:	≥250.7

1/27/78

Table 7

Maximum Temperatures Reported Among Children Who Received Combined
Live Measles-Mumps-Rubella (RA 27/3) Virus Vaccine, Lot #60664/C-E810 (Study #513)

Maximum Temperature (°F, Oral)	Total Vaccinees (53 Children)						Initially Seronegatives (30 Children)					
	Days Post Vaccination					No. with Max. Temp.	Days Post Vaccination					No. with Max. Temp.
	0-4	5-12	13-18	19-28	29-42		0-4	5-12	13-18	19-28	29-42	
<99	30 (60.0%)	22 (44.0)	36 (72.0)	27 (54.0)	31 (62.0)	17	18 (60.0)	11 (36.7)	20 (66.7)	14 (46.7)	18 (60.0)	9
99 - 100.9	17 (34.0)	22 (44.0)	13 (26.0)	19 (38.0)	17 (34.0)	21	10 (33.3)	15 (50.0)	9 (30.0)	13 (43.3)	11 (36.7)	12
101 - 102.9	2 (4.0)	5 (10.0)		3 (6.0)	2 (4.0)	10	1 (3.3)	3 (10.0)		3 (10.0)	1 (3.3)	8
103 - 104.0	1 (2.0)			1 (2.0)		2	1 (3.3)					1
Fever - Temp. Not Taken		1 (2.0)	1 (2.0)			0		1 (3.3)	1 (3.3)			0
Not Taken	3	3	3	3	3	3	0	0	0	0	0	0

Case #	Max. Temp.	Days	Clinical Complaint	Serology Measles		Mumps		Rubella	
(b) (6)	102.0	42	Anorexia, Teething	<5	80	2	32	<8	≥512
	102.2	33-35	Gastrointestinal Illness, Irritability, Anorexia, Fatigue	<5	≥320	<2	32	<8	256
	102.6	7-10	Gastrointestinal Illness, Anorexia, Teething	<5	160	<2	16	<8	256
	102.4	6-8	Sores on Face	<5	160	<2	32	<8	256
	102.0	5	No Clinical Complaints	<5	80	2	64	<8	256
	102.0	8-9	Gastrointestinal Illness	<5	40	<2	8	<8	256
	103.0	20-25	Upper Respiratory Illness	<5	40	2	≥64	<8	256
	102.0	18-20	Upper Respiratory Illness	<5	80	<2	16	<8	256
	104.0	0-4	Upper Respiratory Illness, Irritability, Anorexia	<5	80	<2	64	<8	128

1/27/78

Table 8

Maximum Temperatures Reported Among Children Who Received Combined
Live Measles-Mumps-Rubella (RA 27/3) Virus Vaccine, Lot #60665/C-E811 (Study #513)

Maximum Temperature (°F, Oral)	Total Vaccinees (54 Children)						Initially Seronegatives (34 Children)					
	Days Post Vaccination					No. with	Days Post Vaccination					No. with
	0-4	5-12	13-18	19-28	29-42	Max. Temp.	0-4	5-12	13-18	19-28	29-42	Max. Temp.
<99	34 (66.7%)	28 (54.9)	37 (72.5)	35 (68.6)	37 (72.5)	18	22 (64.7)	18 (52.9)	22 (64.7)	22 (64.7)	22 (64.7)	11
99 - 100.9	14 (27.5)	15 (29.4)	14 (27.5)	14 (27.5)	12 (23.5)	21	9 (26.5)	11 (32.4)	12 (35.3)	12 (35.3)	10 (29.4)	16
101 - 102.9	2 (3.9)	7 (13.7)		2 (3.9)	1 (2.0)	10	2 (5.9)	4 (11.8)			1 (2.9)	5
103 - 104.0		1 (2.0)			1 (2.0)	2		1 (2.9)			1 (2.9)	2
Fever - Temp. Not Taken	1 (2.0)					0	1 (2.9)					0
Not Taken	3	3	3	3	3	3	0	0	0	0	0	0

Case #	Max. Temp.	Days	Clinical Complaint	Serology Measles		Mumps		Rubella	
(b) (6)	102.0	8-9	Irritable	NS	NS	NS	NS	NS	NS
	102.0	7-9	Gastrointestinal Illness	<5	80	<2	16	<8	32
	102.6	2-8	Gastrointestinal Illness, Nonspecific Rash	<5	80	<2	64	<8	256
	104.0	3-8	Upper Respiratory Illness, Ophthalmopathy, Gastrointestinal Illness, Anorexia	<5	20	<2	32	<8	256
	103.0	28-34	Teething	<5	80	<2	>64	<8	>512
	102.2	4-11	Upper Respiratory Illness	<5	40	<2	2	<8	256

1/27/78

Table 9

Maximum Temperatures Reported Among Children Who Received Combined
Live Measles-Mumps-Rubella (RA 27/3) Virus Vaccine, Lot #60666/C-E812 (Study #513)

Maximum Temperature (°F, Oral)	Total Vaccinees (56 Children)						Initially Seronegatives (33 Children)					
	Days Post Vaccination					No. with Max. Temp.	Days Post Vaccination					No. with Max. Temp.
	0-4	5-12	13-18	19-28	29-42		0-4	5-12	13-18	19-28	29-42	
<99	31 (57.4%)	22 (40.7)	37 (68.5)	32 (59.3)	26 (48.1)	15	15 (45.5)	9 (27.3)	19 (57.6)	14 (42.4)	11 (33.3)	5
99 - 100.9	20 (37.0)	22 (40.7)	16 (29.6)	22 (40.7)	21 (38.9)	24	16 (48.5)	16 (48.5)	14 (42.4)	19 (57.6)	19 (57.6)	19
101 - 102.9	3 (5.6)	7 (13.0)			6 (11.1)	14	2 (6.1)	6 (18.2)			2 (6.1)	8
103 - 104.0		1 (1.9)			1 (1.9)	1		1 (3.0)			1 (3.0)	1
Fever - Temp. Not Taken		2 (3.7)	1 (1.9)			0		1 (3.0)				0
Not Taken	2	2	2	2	2	2	0	0	0	0	0	0

Case #	Max. Temp.	Days	Clinical Complaint	Serology Measles		Mumps		Rubella	
(b) (6)	102.0	12-13	Herpes-Type Rash	<5	40	<2	32	<8	256
	104.0	8-9	Measles-Like Rash, Anorexia	<5	80	<2	>64	<8	64
	103.0	42	Upper Respiratory Illness, Non-Specific Rash, Anorexia						
	102.0	30-35	Gastrointestinal Illness	NS	NS	NS	NS	NS	NS
	102.0	0-7	No Clinical Complaints	<5	80	<2	16	<8	128
	102.2	1-4	Upper Respiratory Illness, Ophthalmopathy, Anorexia	<5	40	<2	16	<8	256
	102.2	10	Upper Respiratory Illness, Otitis	<5	80	<2	64	<8	256
	102.0	1-3	Upper Respiratory Illness, Headache, Anorexia, Soreness at Injection Site	NT	NT	NT	NT	NT	NT

1/27/78

Table 10

Clinical Complaints Reported Among Children Who Received Combined Live Measles-Mumps-Rubella (RA 27/3) Virus Vaccine, Lot #60664/C-E810 (Study #513)

Clinical Complaint	Total Vaccinees (53 Children)						Initially Seronegatives (30 Children)					
	Days Post Vaccination					No. with Complaint	Days Post Vaccination					No. with Complaint
	0-4	5-12	13-18	19-28	29-42		0-4	5-12	13-18	19-28	29-42	
Injection Site:	2 (3.9%)					2	1 (3.3)					1
Soreness	2					2	1					1
Systemic:												
Arthralgia	1 (2.0)	1 (2.0)				1						0
Measles-Like Rash		6 (11.8)	1 (2.0)	1 (2.0)		6		4 (13.3)	1 (3.3)	1 (3.3)		4
Headache		1 (2.0)				1						0
Irritability	4 (7.8)	2 (3.9)	1 (2.0)	2 (3.9)	2 (3.9)	8	4 (13.3)	2 (6.7)	1 (3.3)	2 (6.7)	1 (3.3)	7
Anorexia	4 (7.8)	3 (5.9)	1 (2.0)	2 (3.9)	5 (9.8)	10	2 (6.7)	2 (6.7)		2 (6.7)	3 (10.0)	7
Disturbed Sleep			1 (2.0)		1 (2.0)	1						0
Fatigue		1 (2.0)			1 (2.0)	1		1 (3.3)			1 (3.3)	1
Myalgia	1 (2.0)	1 (2.0)				1						0
Upper Respiratory Illness	9 (17.6)	12 (23.5)	7 (13.7)	12 (23.5)	11 (21.6)	25	4 (13.3)	7 (23.3)	6 (20.0)	7 (23.3)	8 (26.7)	14
Otitis				1 (2.0)		1				1 (3.3)		1
Ophthalmopathy	1 (2.0)	1 (2.0)		1 (2.0)	1 (2.0)	2		1 (3.3)		1 (3.3)	1 (3.3)	1
Gastrointestinal Illness	12 (23.5)	11 (21.6)	2 (3.9)	4 (7.8)	5 (9.8)	18	9 (30.0)	9 (30.0)	1 (3.3)	3 (10.0)	4 (13.3)	15
Nonspecific Rash	5 (9.8)	4 (7.8)	4 (7.8)	6 (11.8)	8 (15.7)	15	2 (6.7)	4 (13.3)	4 (13.3)	5 (16.7)	5 (16.7)	10
Sores on Face		1 (2.0)				1		1 (3.3)				1
Allergy	1 (2.0)		1 (2.0)			2	1 (3.3)		1 (3.3)			2
Teething	2 (3.9)	4 (7.8)	1 (2.0)	2 (3.9)	3 (5.9)	9	1 (3.3)	4 (13.3)	1 (3.3)	2 (6.7)	1 (3.3)	7
Herpes-Type Rash		1 (2.0)		1 (2.0)		2		1 (3.3)		1 (3.3)		2
Persons with Complaint:	24 (47.1)	27 (52.9)	12 (23.5)	18 (35.3)	19 (37.3)	39	14 (46.7)	19 (63.3)	9 (30.0)	12 (40.0)	13 (43.3)	25
Persons with No Complaint:	27 (52.9)	24 (47.1)	39 (76.5)	33 (64.7)	32 (62.7)	12	16 (53.3)	11 (36.7)	21 (70.0)	18 (60.0)	17 (56.7)	5
Negative Surveillance	2	2	2	2	2	2	0	0	0	0	0	0

1/27/78

Table 11

Clinical Complaints Reported Among Children Who Received Combined
Live Measles-Mumps-Rubella (RA 27/3) Virus Vaccine, Lot #60665/C-E811 (Study #513)

Clinical Complaint	Total Vaccinees (54 Children)						Initially Seronegatives (34 Children)					
	Days Post Vaccination					No. with	Days Post Vaccination					No. with
	0-4	5-12	13-18	19-28	29-42	Complaint	0-4	5-12	13-18	19-28	29-42	Complaint
Injection Site:	2 (3.8%)					2	2 (5.9)					2
Soreness	1					1	1					1
Erythema and Soreness	1					1	1					1
Systemic:												
Lymphadenopathy	2 (3.8)	1 (1.9)				3	1 (2.9)	1 (2.9)				2
Measles-Like Rash		5 (9.6)	4 (7.7)	1 (1.9)		7		3 (8.8)	2 (5.9)			4
Irritability	4 (7.7)	6 (11.5)	1 (1.9)	1 (1.9)	2 (3.8)	9	4 (11.8)	4 (11.8)		1 (2.9)	2 (5.9)	7
Malaise	1 (1.9)	1 (1.9)				1	1 (2.9)	1 (2.9)				1
Anorexia	5 (9.6)	5 (9.6)	3 (5.8)	2 (3.8)	4 (7.7)	13	3 (8.8)	4 (11.8)	2 (5.9)	1 (2.9)	3 (8.8)	9
Disturbed Sleep	1 (1.9)	1 (1.9)	1 (1.9)			2	1 (2.9)	1 (2.9)				1
Fatigue	2 (3.8)					2	2 (5.9)					2
Upper Respiratory Illness	10 (19.2)	9 (17.3)	5 (9.6)	10 (19.2)	11 (21.2)	25	4 (11.8)	6 (17.6)	4 (11.8)	6 (17.6)	7 (20.6)	15
Otitis	2 (3.8)	2 (3.8)	2 (3.8)	1 (1.9)	1 (1.9)	4	2 (5.9)	1 (2.9)	1 (2.9)	1 (2.9)	1 (2.9)	2
Ophthalmopathy	1 (1.9)	3 (5.8)		1 (1.9)	1 (1.9)	5	1 (2.9)	2 (5.9)		1 (2.9)	1 (2.9)	4
Gastrointestinal Illness	9 (17.3)	10 (19.2)	5 (9.6)	4 (7.7)	6 (11.5)	18	6 (17.6)	7 (20.6)	3 (8.8)	3 (8.8)	5 (14.7)	11
Nonspecific Rash	4 (7.7)	3 (5.8)		2 (3.8)	2 (3.8)	7	3 (8.8)	3 (8.8)		2 (5.9)	2 (5.9)	6
Allergy	1 (1.9)					1	1 (2.9)					1
Teething	1 (1.9)	1 (1.9)	1 (1.9)	3 (5.8)	3 (5.8)	4	1 (2.9)	1 (2.9)		1 (2.9)	1 (2.9)	2
Persons with Complaint:	24 (46.2)	26 (50.0)	18 (34.6)	21 (40.4)	18 (34.6)	36	16 (47.1)	18 (52.9)	11 (32.4)	13 (38.2)	12 (35.3)	23
Persons with No Complaint:	28 (53.8)	26 (50.0)	34 (65.4)	31 (59.6)	34 (65.4)	16	18 (52.9)	16 (47.1)	23 (67.6)	21 (61.8)	22 (64.7)	11
Negative Surveillance:	2	2	2	2	2	2	0	0	0	0	0	0

1/27/78

Table 12

Clinical Complaints Reported Among Children Who Received Combined
Live Measles-Mumps-Rubella (RA 27/3) Virus Vaccine, Lot #60666/C-E812 (Study #513)

Clinical Complaint	Total Vaccinees (56 Children)						Initially Seronegatives (33 Children)					
	Days Post Vaccination					No. with Complaint	Days Post Vaccination					No. with Complaint
	0-4	5-12	13-18	19-28	29-42		0-4	5-12	13-18	19-28	29-42	
Injection Site:	4 (7.4%)					4	3 (9.1)					3
Soreness	4					4	3					3
Systemic:												
Lymphadenopathy				1 (1.9)		1				1 (3.0)		1
Measles-Like Rash		6 (11.1)	2 (3.7)	1 (1.9)		8		4 (12.1)	2 (6.1)	1 (3.0)		6
Headache	1 (1.9)					1						0
Irritability	4 (7.4)	4 (7.4)	3 (5.6)	3 (5.6)	2 (3.7)	8	2 (6.1)	3 (9.1)	2 (6.1)	3 (9.1)	2 (6.1)	5
Anorexia	6 (11.1)	9 (16.7)	1 (1.9)	2 (3.7)	11 (20.4)	20	4 (12.1)	5 (15.2)			9 (27.3)	13
Disturbed Sleep	1 (1.9)	2 (3.7)				2	1 (3.0)	2 (6.1)				2
Fatigue		1 (1.9)		1 (1.9)		1		1 (3.0)		1 (3.0)		1
Myalgia				1 (1.9)	2 (3.7)	2				1 (3.0)	1 (3.0)	1
Upper Respiratory Illness	13 (24.1)	19 (35.2)	13 (24.1)	14 (25.9)	15 (27.8)	30	10 (30.3)	12 (36.4)	9 (27.3)	11 (33.3)	12 (36.4)	20
Otitis	1 (1.9)	2 (3.7)		2 (3.7)	2 (3.7)	5		1 (3.0)		2 (6.1)	2 (6.1)	3
Ophthalmopathy	2 (3.7)	1 (1.9)		1 (1.9)	1 (1.9)	4	1 (3.0)			1 (3.0)	1 (3.0)	2
Gastrointestinal Illness	6 (11.1)	4 (7.4)	4 (7.4)	5 (9.3)	7 (13.0)	18	4 (12.1)		3 (9.1)	4 (12.1)	3 (9.1)	12
Nonspecific Rash	4 (7.4)	8 (14.8)	6 (11.1)	7 (13.0)	6 (11.1)	19	3 (9.1)	5 (15.2)	4 (12.1)	4 (12.1)	4 (12.1)	13
Sore from Venipuncture	1 (1.9)					1	1 (3.0)					1
Teething		3 (5.6)	2 (3.7)	3 (5.6)	3 (5.6)	5		3 (9.1)	2 (6.1)	3 (9.1)	2 (6.1)	4
Herpes-Type Rash		1 (1.9)				1		1 (3.0)				1
Persons with Complaint:	27 (50.0)	33 (61.1)	22 (40.7)	24 (44.4)	25 (46.3)	41	20 (60.6)	22 (66.7)	16 (48.5)	19 (57.6)	17 (51.5)	27
Persons with No Complaint:	27 (50.0)	21 (38.9)	32 (59.3)	30 (55.6)	29 (53.7)	13	13 (39.4)	11 (33.3)	17 (51.5)	14 (42.4)	16 (48.5)	6
Negative Surveillance	2	2	2	2	2	2	0	0	0	0	0	0

1/27/78

MEMO

To File Location Date 2/6/78

From T. Schofield Location

Subject Preliminary Statistical Analysis - Study #513, Combined Live Measles-Mumps-Rubella Virus Vaccine

Significant differences in seroconversion rates for measles, mumps, and rubella and clinical reaction rates among vaccinees receiving three lots of combined live measles-mumps-rubella vaccine were investigated. Lots of vaccine were:

Lot #60664/C-E810
Lot #60665/C-E811
Lot #60666/C-E812

A significant difference exists among the three lots in the incidence of non-specific rash. 15 out of 53 exhibited diaper, heat , or contact rash (28.3%) who received Lot #60664/C-E810; 7 out of 54 (12.9%) who received Lot #60665/C-E811; and 19 out of 56 (33.9%) who received Lot #60666/C-E812. No other rates were significant.

Analyses of variance were performed on post-titer values of children who were initially seronegative to the individual components. The log transformation was used in each analysis. No significant differences exist among the groups (lots) for any of the three components.

A multivariate analysis was performed on the post-titer values of triple-negative vaccinees. Again, the log transformation was applied. There was no significant difference among the groups.

T.S.
6801

Summary No. 1
of
Clinical Investigative Studies
of

Combined Live Measles Virus Vaccine (Moraten Line-ATTENUVAX)
RA 27/3 Rubella Virus Vaccine

for Purpose of Support for
a License to Manufacture and Sell.

M. R. Hilleman, Ph.D.

Prepared: August 11, 1978
Merck Institute for Therapeutic Research
West Point, Pennsylvania

Clinical Investigative Studies of Combined Live Measles-Rubella (RA 27/3) Virus Vaccine

1. Background

In a separate submission, "Summary No. 2 of Clinical Investigative Studies of RA 27/3 Strain Live Rubella Virus Vaccine for Support of a License to Manufacture and Sell," dated January 11, 1978, and in Addendum No. 1 to that submission dated June 26, 1978, the RA 27/3 strain rubella virus vaccine was shown to be safe and highly effective in eliciting an antibody response in persons of various ages.

In extension of clinical tests with RA 27/3 rubella virus vaccine, studies were conducted to evaluate its immunizing capability when combined with live attenuated Moraten measles virus vaccine (ATTENUVAX). The present submission relates to clinical investigative studies of combined live measles-rubella (RA 27/3) virus vaccine.

All clinical studies were conducted under BB-IND-1015, Combined Live Measles-Rubella (RA 27/3) Virus Vaccine.

2. Lot Numbers of Vaccine Tested

Experimental lot prepared by Virus and Cell Biology Research, Merck Sharp and Dohme Research Laboratories:

622/C-D764

Consistency lots prepared by Merck Sharp and Dohme Biologics Manufacturing:

62343/C-F021
62344/C-F022
62345/C-F023

3. Serologic Testing

Serologic determinations were made in the laboratories of Virus and Cell Biology Research, Merck Institute, and in the Control Laboratories of the Merck Sharp and Dohme Division of Merck and Co.

The hemagglutination-inhibition (HI) test was used to determine rubella antibody response. The starting dilution was 1:8.

In most cases, measles antibody determinations were by HI assay with a starting dilution of 1:5. Where noted, sera were retested by serum neutralization test at a starting dilution of 1:2.

4. Clinical Studies

The clinical studies were conducted under the overall responsibility of Dr. Maurice R. Hilleman, Vice President, Virus and Cell Biology Research, Merck Institute for Therapeutic Research, West Point, Pennsylvania.

The clinical tests were carried out by three groups of workers:

a. Dr. Robert E. Weibel, Director, Division of Preventive Medicine, Joseph Stokes, Jr. Research Institute, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania

b. Dr. Victor M. Villarejos, Director, Louisiana State University - International Center for Medical Research and Training, San Jose, Costa Rica

c. Dr. Louis Z. Cooper, Director, Pediatric Service, The Roosevelt Hospital, New York, New York

Clinical studies fall into two main categories:

	Reference
a. Comparison of measles-rubella (RA 27/3) and measles-rubella (HPV-77) vaccines	2
b. Serologic and clinical responses to measles-rubella (RA 27/3) vaccine	1, 3, 4

The clinical studies were carried out by the physicians at the locations in the individual study summaries to follow. The populations employed were defined with respect to age, location and other pertinent parameters.

Subjects were bled initially and again 6 to 8 weeks later. The sera were tested to define the initial serostatus and the subsequent antibody response.

Clinical surveillance was by two procedures. In studies by Drs. Weibel and Cooper, the observations were recorded daily by the mother. The parent was asked to contact the physician should any significant or bothersome reaction occur. In the studies by Dr. Villarejos, observations were made on a routine basis by medical or paramedical personnel; physicians were notified of any significant illness which occurred subsequent to vaccination.

The data presented in the following sections are self-explanatory. The detailed background records are on file in Virus and Cell Biology Research, Merck Institute for Therapeutic Research, West Point, Pennsylvania. These records are available for review at any time.

5. Clinical Study Summaries

Reference 1 - Study 442 - Dr. Victor Villarejos
Details of the study plan are given in the clinical test protocol. The study was designed to measure antibody and clinical responses to the RA 27/3 rubella component when given alone or combined with mumps and/or measles vaccine. Findings presented in the summary tables indicate excellent antibody response to both virus components among children receiving combined live measles-rubella (RA 27/3) virus vaccine. No significant clinical reactions were noted following vaccination.

Reference 2 - Study 470 - Dr. Louis Cooper
This study is being conducted among children to compare responses to HPV-77 and RA 27/3 rubella vaccines when given alone or combined with live measles virus vaccine. Details of the study plan are given in the clinical test protocol, and results, to date, are presented in the summary tables. The study continues in progress.

Reference 3 - Study 512 - Dr. Victor Villarejos
Study 512 was conducted to measure antibody and clinical responses to three consecutive lots of combined measles-rubella vaccine containing the RA 27/3 rubella component. Study details are given in the clinical protocol. Findings presented in the summary tables indicate excellent antibody response to both components of all three lots of vaccine. No significant clinical reactions were noted.

Reference 4 - Study 514 - Dr. Robert Weibel
Study 514 is being conducted to measure antibody and clinical responses to three consecutive lots of combined measles-rubella vaccine containing the RA 27/3 rubella component. Details of the study plan are given in the clinical test protocol and results are presented in the summary tables. All three lots showed excellent antibody response while no significant clinical reactions were noted.

6. Overall Summary

The total numbers of vaccinations for which supporting data have been given are as follows:

		No. Seroconverting/No. Double Negatives (%)	
Lot #	No. Vacc.	Measles	RA 27/3 Rubella
622	216	59/64 (92)	63/64 (93)
62343	107	46/50 (92)	50/50 (100)
62344	105	45/45 (100)	45/45 (100)
62345	100	49/50 (98)	50/50 (100)
Unknown	30	26/28 (93)	28/28 (100)
Totals	558	225/237 (95)	236/237 (99)

The data show that combined live measles-rubella vaccine containing the RA 27/3 rubella virus component is safe and effective.

Summary of Clinical Tests of Combined Live Measles-Rubella (RA 27/3) Virus Vaccine

Study No.	Investigator	Lot No.	Age		No. Vacc.	Antibody Responses among Double Negatives				Reference No.
						Measles		Rubella		
			Range	Mean (Yrs.)		No. Conv./ No. Seroneg. (%)	GMT	No. Conv./ No. Seroneg. (%)	GMT	
442	Villarejos	622	1 - 6y	3.7	193	49/54 (91)	49	53/54 (98)	151	1
470	Cooper	622	14m- 6y	2.0	23	10/10 (100)	57	10/10 (100)	274	2
512	Villarejos	62343	10m- 9y	4.4	60	12/15 (80)	17	15/15 (100)	308	3
		62344	11m- 8y	4.3	60	18/18 (100)	40	18/18 (100)	376	
		62345	13m- 6y	4.1	55	16/17 (94)	70	17/17 (100)	289	
514	Weibel	62343	13m- 3y	1.4	47	34/35 (97)	80*	35/35 (100)	312	4
		62344	14m- 4y	1.8	45	27/27 (100)	78	27/27 (100)	367	
		62345	13m- 4y	1.4	45	33/33 (100)	114	33/33 (100)	415	
		Unknown	13m-10y	1.7	30	26/28 (93)	51*	28/28 (100)	371	
		Totals			558	225/237 (95)	60	236/237 (99)	287	

* GMT based on Measles HI results only.

Reference No. 1

Program: Study #442

Vaccine: Combined Live Measles-Mumps-Rubella (RA 27/3) Virus Vaccine
Lot No. 621/C-D763

Combined Live Measles-Rubella (RA 27/3) Virus Vaccine
Lot No. 622/C-D764

Live Attenuated Rubella (RA 27/3) Virus Vaccine
Lot No. 579/C-D418

Responsible Clinical Investigator:

Victor M. Villarejos, M.D.
Director
Louisiana State University
International Center for Medical
Research and Training
Apartado 10.155
San Jose, Costa Rica

Study Location: Rivas, Nicaragua

Date Study Initiated: January 19, 1976

Date Study Completed: April 28, 1976

Study Procedure:

A total of 589 children, 10 months to 7 years of age, from the open population were included in the study. Each participant received a 0.5 ml subcutaneous dose of one of the three vaccines. Blood samples were obtained prior to and six weeks after vaccination.

Clinical Protocol - Study #442

Combined Live Measles-Mumps-Rubella (RA 27/3) Virus Vaccine
Combined Live Measles-Rubella (RA 27/3) Virus Vaccine
Live Attenuated Rubella (RA 27/3) Virus Vaccine

Purpose: To determine antibody and clinical responses to combined live measles-mumps-rubella (RA 27/3) virus vaccine, to combined live measles-rubella (RA 27/3) virus vaccine, and to live attenuated rubella (RA 27/3) virus vaccine.

Vaccines:

a) Combined live measles-mumps-rubella (RA 27/3) virus vaccine
Lot No. 621

Vaccine dose is 0.5 ml given subcutaneously.

The vaccine is supplied in two-dose vials. Each vial of vaccine should be rehydrated with 1.2 ml of sterile, pyrogen-free distilled water.

b) Combined live measles-rubella (RA 27/3) virus vaccine
Lot No. 622

Vaccine dose is 0.5 ml given subcutaneously.

The vaccine is supplied in two-dose vials. Each vial of vaccine should be rehydrated with 1.2 ml of sterile, pyrogen-free distilled water.

c) Live attenuated rubella (RA 27/3) virus vaccine
Lot No. 579

Vaccine dose is 0.5 ml given subcutaneously.

The vaccine is supplied in single dose vials. Each vial of vaccine should be reconstituted with 0.7 ml of sterile, pyrogen-free distilled water.

CAUTION: The combined vaccines contain egg protein and should not be given to persons with known sensitivity to egg, chicken, or chicken feathers. All three vaccines contain neomycin and should not be given to persons with sensitivity to neomycin. Persons with leukemia or other immunologic disorders and persons receiving immunosuppressive drugs should not be vaccinated. Also, the vaccines should not be given to persons with any febrile respiratory illness or other active febrile infection.

Keep dried vaccines stored at -20°C until used.

Keep dried vaccines at 4°C in transport.

Keep reconstituted vaccines on ice. Discard unused vaccine 4 hours after rehydration.

Procedure: The study population will consist of children 1 to 6 years of age.

Children receiving a given vaccine will have a negative history for vaccination with and illness caused by viruses represented in that vaccine. Children will be assigned to receive one of the three vaccines as follows:

Vaccine	Vaccine Lot	No. Children
measles-mumps-rubella	621	150-200
measles-rubella	622	150-200
rubella	579	150-200

Informed consent will be obtained from each child's parent or guardian prior to his participation in the study.

Each child will be bled (10-15 ml) immediately prior to vaccination and 6 weeks following vaccination.

Vaccine dose is 0.5 ml given subcutaneously.

Each child will be followed clinically for 42 days following vaccination. All local and systemic complaints will be recorded on the case report form.

Schedule:

Time	Action
Day 0	Bleed 10-15 ml. Vaccinate 0.5 ml, subcutaneously.
Days 0-42	Clinical follow-up for local and systemic reactions.
Week 6	Bleed 10-15 ml.

Laboratory: Remove sera from clot aseptically and store frozen at -20°C until shipped. It is imperative that sera are sterile to avoid interference with the serologic assay.

Serology: Circulating levels of antibody to each vaccine component will be determined for samples drawn before and after vaccination. Measles and rubella antibody levels will be determined by hemagglutination-inhibition test. Mumps antibody levels will be determined by serum neutralization test.

Clinical Forms: Attached.

Adverse Reactions: Any serious or alarming reaction, including death due to any cause during the investigation, whether related or not related to the test material, must be reported immediately to Merck & Co., Inc., through Dr. Maurice R. Hilleman, telephone (215) 699-5311, Ext. 5532, or in his absence, Dr. Allen F. Woodhour, telephone (215) 699-5311, Ext. 5588.

Unused Vaccine: All unused vaccine should be returned immediately to Merck Sharp & Dohme Research Laboratories, West Point, Pa. 19486.

Shipping of Sera & Records:

a) Send sera frozen within insulated containers which are supplied.

b) Send sera and records to Dr. Maurice R. Hilleman, Virus and Cell Biology Research, Merck Sharp & Dohme Research Laboratories, West Point, Pa. 19486.

c) Alert Dr. Hilleman by cable as soon as possible as to flight number, air bill, and date of arrival.

M. R. Hilleman, Ph.D.

VACUNACIÓN CONTRA SARAMPIÓN PAPERAS RUBÉOLA

Estudio No. _____ (1-3)

NO. DEL CASO _____ (4-5)

NOTA AL INVESTIGADOR: 1. No escriba en areas obscurecidas 2. Asegurese de llenar todos los blancos aplicables.

PRECAUCIÓN: Use mecanografía o letra de molde. No escriba en esta forma si esta encima de otras formas NCR (semejantes a esta).

CT 2	Nombre Completo del Niño	Sexo (35) M F	Fecha de nacimiento (36-41) día mes año	(46-47)
CT 6 Dupe CT 2 (141)- (54-59)	Dirección completa de Padres o Guardián:			

CT 2 — **INDIQUE SI INDIVIDUO HA:** S = Sarampión P = Paperas R = Rubéola

	S (70)	P (71)	R (72)
1. Tenido Enfermedad	1	1	1
2. Sido Vacunado	2	2	2
3. Estado Expuesto (Durante Últimas Cuatro Semanas)	3	3	3

Fecha de expuesto ___/___/___

Fecha de expuesto ___/___/___

Fecha de expuesto ___/___/___

PERÍODO DE VACUNACIÓN O CONTROL

(48) ☐ Vacunado ☐ Control

No. de Lote _____ (49-51)

Fecha de vacunación ___/___/___ (52-57)

Fecha de primer sangrado (antes de vacunado) ___/___/___ (52-57)

Fecha de segundo sangrado (despues de vacunado) ___/___/___ (58-63)

SEROLOGÍA

SARAMPIÓN				PAPERAS		RUBÉOLA			
HI		Neut		Neut		HI		Neut	
Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post

Indique si el niño contrajo Sarampión clínico: 1 = Sí 2 = No

Indique si el niño contrajo Paperas clínica: 1 = Sí 2 = No

Indique si el niño contrajo Rubéola clínica: 1 = Sí 2 = No

CT 4

Fecha de comienzo: ___/___/___

Quién hizo diagnóstico? _____

Otras quejas u observaciones clínicas:

Despues de completadas, devuelva formas al: (Retenga copia rosa para sus archivos)

M. R. HILLEMAN, PhD, DSc

MERCK SHARP & DOHME RESEARCH LABS., WEST POINT, PENNSYLVANIA 19486

Firma del Médico:

Nombre del Médico (en letra de molde):

Fecha:

VACUNACIÓN CONTRA SARAMPIÓN PAPERAS RUBÉOLA

HOJA CLINICA

NO. DE CASO _____

B

FECHA DE VACUNACION ____/____/____
día mes año

NOMBRE:

DIA	FECHA	Temperatura	Malestar	Anorexia	Gastroenteritis	Irritabilidad	Cefalea	I. V. R. S.	Otitis	Conjuntivitis	Linfadenopatia*	Reaccion Local* (Diametro mm)	Exantema*	RASH* Rubelliforme	RASH* Morbiliforme	Artralgia*	Artritis*	*Especifique tipo en esta seccion / OTRAS REACCIONES
		24	16	25	08	15	14	01	03	06		12	50	51	52	11	32	
0																		
1																		
2																		
3																		
4																		
5																		
6																		
7																		
8																		
9																		
10																		
11																		
12																		
13																		
14																		
15																		
16																		
17																		
18																		
19																		
20																		
21																		
22																		
23																		
24																		
25																		
26																		
27																		
28																		
29																		
30																		
31																		
32																		
33																		
34																		
35																		
36																		
37																		
38																		
39																		
40																		
41																		
42																		

PRECAUCION: Papel carbón no es nec... con tinta negra. No escriba encima de otras... NOTA: No escriba en areas obscurecidas.

'se maquina de escribir o pluma esferografica ...nas "NCR." KFormas semejantes a estas!

Al terminar el estudio, devuelva copia blanca y copia amarilla de esta form a, adjuntas a la forma "A" al: (Retenga copia color de rosa para sus archivos)

M.R. Hilleman, PhD, DSc
MERCK SHARP & DOHME RESEARCH LABORATORIES
WEST POINT, PENNSYLVANIA, 19486, U.S.A.

Firma del medico:

Nombre del medico (en letra de molde):

Fecha:

(+3957-0875)

Table 1

Serological Findings Among Children Who Received Combined Live Measles-Rubella (RA 27/3) Virus Vaccine, Lot No. 622/C-D764 (Study #442)

Age	Total No. Vacc.	No. Serol. Tested	Initially Seronegative to: Measles-Rubella Conversions/Total Measles	Measles-Rubella Conversions/Total Rubella	Measles Only Conversions/ Total	Rubella Only Conversions/ Total	Initially Seropositive to: Measles and Rubella
1 Year	22	16	11/11	11/11		4/4	1
2 Years	20	16	7/9	9/9	2/2	3/3	2
3 Years	46	36	14/16	15/16	1/1	13/13	6
4 Years	40	31	5/5	5/5	2/2	20/20	4
5 Years	28	19	5/5	5/5	1/1	11/11	2
6 Years	37	24	7/8	8/8	4/4	9/9	3
Total	193	142	49/54	53/54	10/10	60/60	18
Mean Age: 3.7 Years			(90.7%)	(98.1%)	(100%)	(100%)	

Overall Conversion Rates

Measles	Rubella
59/64 (92.2%)	113/114 (99.1%)

4/28/77

Table 2

Serological Findings Among Children Who Received Combined Live
Measles-Mumps-Rubella (RA 27/3) Virus Vaccine, Lot No. 621/C-D763 (Study #442)

Age	Total No. Vacc.	No. Serol. Tested	Initially Seronegative to:											Initially Seropositive to:
			Measles-Mumps-Rubella Conversions/Total			Measles-Mumps Conversions/Total		Measles-Rubella Conversions/Total		Mumps-Rubella Conversions/Total		Measles Only Conversions/ Total	Mumps Only Conversions/ Total	Rubella Only Conversions/ Total	Measles Mumps and Rubella
			Measles	Mumps	Rubella	Measles	Mumps	Measles	Rubella	Mumps	Rubella				
10 Months	1	0													
11 Months	2	2	1/1	1/1	1/1			1/1	1/1						
1 Year	29	21	7/7	7/7	7/7			4/5	5/5	3/3	3/3		2/2	3/3	1
2 Years	18	15	3/3	3/3	3/3	1/1	1/1	4/4	4/4	2/3	3/3			3/3	1
3 Years	41	33	6/6	6/6	6/6	1/1	1/1	3/3	3/3	6/6	6/6			14/14	3
4 Years	39	34	2/2	2/2	2/2			5/5	5/5	7/8	8/8	1/1		15/15	3
5 Years	32	25	3/3	2/3	3/3			2/2	2/2	2/3	3/3	2/2		13/13	2
6 Years	36	28	1/1	1/1	1/1			8/8	8/8	2/2	2/2		1/1	15/15	1
7 Years	1	1						1/1	1/1						
Total	199	159	23/23 (100%)	22/23 (95.7%)	23/23 (100%)	2/2	2/2	28/29 (96.6%)	29/29 (100%)	22/25 (88.0%)	25/25 (100%)	3/3	3/3	63/63 (100%)	11
Mean Age: 3.7 Years															

Overall Conversion Rates

Measles	Mumps	Rubella
56/57 (98.2%)	49/53 (92.5%)	140/140 (100%)

10/3/77

Table 3

Distribution of Fold Rises of Hemagglutination-Inhibition Antibody Titers Among Children Who Received Live Attenuated Rubella (RA 27/3) Virus Vaccine, Lot No. 579/C-D418 (Study #442)

Age	Total No. Vacc.	No. Serol. Tested	Initially Seropositive			Initially Seronegative			
			Fold Rise						
			≥4X	Indet.	Total	No. Conv.	Failures	Total	Conv. Rate
1 Year	13	10		1	1	9		9	9/9
2 Years	17	15		1	1	14		14	14/14
3 Years	30	24		2	2	22		22	22/22
4 Years	38	32	1	1	2	30		30	30/30
5 Years	42	29		3	3	26		26	26/26
6 Years	56	48		8	8	40		40	40/40
7 Years	1	0							
Total	197	158	1	16	17	141	0	141	100%
Mean Age: 4.3 Years									

4/28/77

Table 4

Distribution of Post-Vaccination Antibody Titers Among Children
Who Were Initially Seronegative to Measles and Rubella and Who Received
Combined Live Measles-Rubella (RA 27/3) Virus Vaccine, Lot No. 622/C-D764 (Study #442)

Measles (HI)		Rubella (HI)	
Post-Vaccination Titer	No. of Children	Post-Vaccination Titer	No. of Children
<5	5	<8	1
5		8	
10	1	16	
20	9	32	1
40	4	64	3
80	22	128	30
160	9	256	13
320	3	512	6
≥640	1		
Total	54		54
Geometric Mean Titer	≥48.7		151.2

4/28/77

Table 5

Distribution of Post-Vaccination Antibody Titers Among Children Who Were Initially Seronegative to Measles, Mumps and Rubella and Who Received Combined Live Measles-Mumps-Rubella (RA 27/3) Virus Vaccine, Lot No. 621/C-D763 (Study #442)

Measles (HI)		Mumps (Neut.)		Rubella (HI)	
Post-Vaccination Titer	No. of Children	Post-Vaccination Titer	No. of Children	Post-Vaccination Titer	No. of Children
<5		<2	1	<8	
5		2	4	8	
10		4	4	16	
20	2	8	5	32	1
40	5	16	7	64	4
80	5	32	2	128	9
160	6			256	7
320	5			512	2
Total	23		23		23
Geometric Mean Titer	98.8		7.1		148.8

10/3/77

Table 6

Distribution of Post-Vaccination Antibody Titers Among Children Who Were Initially Seronegative to Rubella and Who Received Live Attenuated Rubella (RA 27/3) Virus Vaccine, Lot No. 579/C-D418 (Study #442)

Rubella (HI)	
Post Vaccination Titer	No. of Children
<8	
8	
16	
32	2
64	20
128	70
256	41
≥512	8
Total	141
Geometric Mean Titer	≥150.5

4/28/77

Table 7

Maximum Temperatures Reported Among Children Who Received Combined
Live Measles-Rubella (RA 27/3) Virus Vaccine, Lot No. 622/C-D764 (Study #442)

Maximum Temperature (°F, Oral)	Total Vaccinees (193 Children)						Initially Seronegative to: Measles and Rubella (54 Children)					
	Days Post-Vaccination					No. with	Days Post-Vaccination					No. with
	0-4	5-12	13-18	19-28	29-42	Max. Temp.	0-4	5-12	13-18	19-28	29-42	Max. Temp.
<99	146 (76.0)	135 (70.3)	138 (72.3)	123 (64.4)	114 (59.7)	67	42 (77.8)	35 (64.8)	39 (72.2)	38 (70.4)	35 (64.8)	23
99 - 100.9	46 (24.0)	56 (29.2)	53 (27.7)	68 (35.6)	77 (40.3)	124	12 (22.2)	19 (35.2)	15 (27.8)	16 (29.6)	19 (35.2)	31
102.0		1 (0.5)				1						
Not Taken	1	1	2	2	2	1						

Patient #	Temperature	Day	Clinical Complaint	Serology: Measles		Rubella	
(b) (6)	102.0	5	Upper Respiratory Illness, Irritability, Malaise	≥20	160	≥32	256

4/28/77

Table 8

Maximum Temperatures Reported Among Children Who Received Combined Live Measles-Mumps-Rubella (RA 27/3) Virus Vaccine, Lot No. 621/C-D763 (Study #442)

Maximum Temperature (°F, Oral)	Total Vaccinees (199 Children)						Initially Seronegative to: Measles, Mumps and Rubella (23 Children)					
	Days Post-Vaccination					No. with Max. Temp.	Days Post-Vaccination					No. with Max. Temp.
	0-4	5-12	13-18	19-28	29-42		0-4	5-12	13-18	19-28	29-42	
<99	147 (73.9%)	138 (69.3)	160 (81.6)	130 (68.4)	137 (72.5)	83	18 (78.3)	20 (87.0)	23 (100.0)	14 (73.7)	16 (84.2)	16
99 - 100.9	51 (25.6)	57 (28.6)	35 (17.9)	59 (31.1)	52 (27.5)	109	5 (21.7)	3 (13.0)		5 (26.3)	3 (15.8)	7
101 - 102.2		2 (1.0)	1 (0.5)			3						
103 - 104.0	1 (0.5)	2 (1.0)		1 (0.5)		4						
Not Taken			3	9	10					4	4	

Patient #	Temperature	Days	Clinical Complaint	Serology: Measles		Mumps		Rubella	
(b) (6)	102.2	8	Upper Respiratory Illness, Malaise	≥20	320	≥8	32	<8	1024
	103.1	20	Irritability, Malaise	≥20	160	≥8	128	<8	64
	103.1	11	Tonsillitis, Anorexia, Headache, Malaise	≥20	≥640	<2	4	<8	128
	104.0	1	Irritability, Malaise	Serologies Not Done					
	104.0	5	Upper Respiratory Illness, Irritability, Anorexia, Malaise	≥20	320	<4	16	<8	256

10/3/77

Table 9

Maximum Temperatures Reported Among Children Who Received Live Attenuated Rubella (RA 27/3) Virus Vaccine, Lot No. 579/C-D418 (Study #442)

Maximum Temperature (°F, Oral)	Total Vaccinees (197 Children) Days Post-Vaccination 0-4	5-12	13-18	19-28	29-42	No. with Max. Temp.	Initially Seronegative to: Rubella (141 Children) Days Post-Vaccination 0-4	5-12	13-18	19-28	29-42	No. With Max. Temp.
<99	162 (82.2%)	131 (66.5)	148 (75.1)	125 (64.4)	138 (71.5)	67	116 (82.3)	97 (68.8)	110 (78.0)	94 (67.6)	104 (74.8)	51
99-100.9	35 (17.8)	66 (33.5)	48 (24.4)	68 (35.1)	55 (28.5)	128	25 (17.7)	44 (31.2)	30 (21.3)	44 (31.7)	35 (25.2)	88
101 - 102.2			1 (0.5)	1 (0.5)		2			1 (0.7)	1 (0.7)		2
Not Taken				3	4					2	2	

Patient #	Temperature	Day	Clinical Complaint	Serology
(b) (6)	102.2	20	Upper Respiratory Illness, Anorexia, Malaise	<8 128

4/29/77

Table 10

Clinical Complaints Reported Among Children Who Received Combined
Live Measles-Rubella (RA 27/3) Virus Vaccine, Lot No. 622/C-D764 (Study #442)

Clinical Complaint	Total Vaccinees (193 Children)						Initially Seronegative to: Measles and Rubella (54 Children)					
	Days Post-Vaccination					No. with Complaint	Days Post-Vaccination					No. with Complaint
	0-4	5-12	13-18	19-28	29-42		0-4	5-12	13-18	19-28	29-42	
Irritability	29 (15.1)	11 (5.7)	6 (3.1)	9 (4.7)	6 (3.1)	52	13 (24.1)	4 (7.4)	2 (3.7)	1 (1.9)	1 (1.9)	18
Malaise	33 (17.2)	21 (10.9)	15 (7.9)	15 (7.9)	7 (3.7)	65	12 (22.2)	8 (14.8)	4 (7.4)	2 (3.7)	1 (1.9)	18
Headache	4 (2.1)	3 (1.6)	2 (1.0)	2 (1.0)		9		1 (1.9)	1 (1.9)			1
Upper Respiratory Illness	1 (0.5)	9 (4.7)	8 (4.2)	8 (4.2)	1 (0.5)	21	1 (1.9)	5 (9.3)	2 (3.7)	1 (1.9)		6
Bronchitis			1 (0.5)	1 (0.5)		1			1 (1.9)	1 (1.9)		1
Otitis	1 (0.5)	2 (1.0)	2 (1.0)	1 (0.5)	1 (0.5)	6		2 (3.7)	1 (1.9)			3
Gastrointestinal Illness	5 (2.6)	7 (3.6)	6 (3.1)	4 (2.1)	3 (1.6)	23	1 (1.9)	2 (3.7)	1 (1.9)	1 (1.9)		5
Anorexia	5 (2.6)	4 (2.1)	6 (3.1)	4 (2.1)		17	2 (3.7)	1 (1.9)	1 (1.9)			4
Hepatitis	1 (0.5)	1 (0.5)				1						0
Asthma		1 (0.5)				1						0
Persons with Complaints:	36 (18.8)	24 (12.5)	17 (8.9)	18 (9.4)	8 (4.2)	70	13 (24.1)	9 (16.7)	4 (7.4)	3 (5.6)	1 (1.9)	19
Persons with No Complaints:	156 (81.3)	168 (87.5)	174 (91.1)	173 (90.6)	183 (95.8)	121	41 (75.9)	45 (83.3)	50 (92.6)	51 (94.4)	53 (98.1)	35
Negative Physician Surveillance:	1	1	2	2	2	1						

4/29/77

Table 11

Clinical Complaints Reported Among Children Who Received Combined Live Measles-Mumps-Rubella (RA 27/3) Virus Vaccine, Lot No. 621/C-D763 (Study #442)

Clinical Complaint	Total Vaccinees (199 Children)						Initially Seronegative to: Measles, Mumps and Rubella (23 Children)					
	Days Post-Vaccination					No. with Complaint	Days Post Vaccination					No. with Complaint
	0-4	5-12	13-18	19-28	29-42		0-4	5-12	13-18	19-28	29-42	
Irritability	32 (16.1%)	9 (4.5)	2 (1.0)	4 (2.1)		39	5 (21.7)			1 (5.0)		5
Malaise	30 (15.1)	14 (7.0)	3 (1.5)	7 (3.6)	1 (0.5)	43	5 (21.7)	1 (4.3)		2 (10.0)		7
Headache		1 (0.5)	2 (1.0)			2						0
Upper Respiratory Illness	9 (4.5)	11 (5.5)	5 (2.5)	8 (4.1)	5 (2.6)	23	1 (4.3)	1 (4.3)	1 (4.3)	2 (10.0)	1 (5.0)	3
Otitis			2 (1.0)	3 (1.5)		3			1 (4.3)	1 (5.0)		1
Ophthalmopathy		1 (0.5)				1						0
Gastrointestinal Illness	13 (6.5)	7 (3.5)	2 (1.0)	5 (2.6)	1 (0.5)	22		1 (4.3)				1
Anorexia	5 (2.5)	3 (1.5)	2 (1.0)	5 (2.6)		13				1 (5.0)		1
Mild Dermatitis		1 (0.5)				1						0
Persons with Complaints:	49 (24.6)	22 (11.1)	11 (5.5)	19 (9.8)	6 (3.1)	73	6 (26.1)	2 (8.7)	1 (4.3)	4 (20.0)	1 (5.0)	10
Persons with No Complaints:	150 (75.4)	177 (88.9)	188 (94.5)	175 (90.2)	187 (96.9)	123	17 (73.9)	21 (91.3)	22 (95.7)	16 (80.0)	19 (95.0)	12
Negative Physician Surveillance				5	6					3	3	

10/3/77

Table 12

Clinical Complaints Reported Among Children Who Received Live
Attenuated Rubella (RA 27/3) Virus Vaccine, Lot No. 579/C-D418 (Study #442)

Clinical Complaint	Total Vaccinees (197 Children)						Initially Seronegative to: Rubella (141 Children)					
	Days Post-Vaccineation					No. with Complaint	Days Post-Vaccination					No. with Complaint
	0-4	5-12	13-18	19-28	29-42		0-4	5-12	13-18	19-28	29-42	
Irritability	22 (11.2)	4 (2.0)	3 (1.5)	5 (2.6)	2 (1.0)	32	15 (10.6)	4 (2.8)	2 (1.4)	2 (1.4)	1 (0.7)	23
Malaise	28 (14.2)	10 (5.1)	5 (2.5)	9 (4.6)	4 (2.1)	46	19 (13.5)	9 (6.4)	2 (1.4)	5 (3.5)	2 (1.4)	32
Headache	2 (1.0)	1 (0.5)		3 (1.5)	1 (0.5)	6	1 (0.7)			1 (0.7)		2
Upper Respiratory Illness	4 (2.0)	8 (4.1)	1 (0.5)	6 (3.1)	2 (1.0)	15	3 (2.1)	6 (4.3)	1 (0.7)	5 (3.5)	2 (1.4)	13
Otitis	2 (1.0)			2 (1.0)	1 (0.5)	4	1 (0.7)			1 (0.7)	1 (0.7)	2
Ophthalmopathy	1 (0.5)	1 (0.5)				1	1 (0.7)	1 (0.7)				1
Gastrointestinal Illness	5 (2.5)	6 (3.0)	1 (0.5)	1 (0.5)	1 (0.5)	11	4 (2.8)	5 (3.5)	1 (0.7)		1 (0.7)	8
Anorexia	7 (3.6)	1 (0.5)		5 (2.6)		13	4 (2.8)			4 (2.8)		8
Persons with Complaints:	35 (17.8)	18 (9.1)	7 (3.6)	16 (8.2)	7 (3.6)	60	23 (16.3)	14 (9.9)	4 (2.8)	10 (7.1)	5 (3.5)	43
Persons with No Complaints:	162 (82.2)	179 (90.9)	190 (96.4)	180 (91.8)	188 (96.4)	137	118 (83.7)	127 (90.1)	137 (97.2)	131 (92.9)	136 (96.5)	98
Negative Physician Surveillance				1	2							

4/29/77

MEMO

To File Location Date 2/2/78

From T. Schofield Location

Subject Statistical Analysis - Study #442

Analysis of variance was conducted on post titers of children who were initially seronegative to rubella who received rubella vaccine, lot #579 (Group 1), combined measles-mumps-rubella vaccine, lot #621 (Group 2), and combined measles-rubella vaccine, lot #622 (Group 3).

No significant difference exists among the three groups. Geometric mean titers were:

Vaccine	GMT
Rubella	150.5
MMR	143.4
MR	155.5

There is no significant difference in conversion rate among these three groups.

T.S.

Program: Study #470 - To evaluate and compare clinical and immunological responses to two rubella vaccines, administered alone and in combination with measles virus vaccine.

Vaccine: Combined live measles-rubella (RA 27/3) virus vaccine
Lot #662/C-D764

Combined live measles-rubella (HPV-77) virus vaccine
M-R-VAX

Live attenuated RA 27/3 rubella virus vaccine
Lot #579/C-D418
Lot #60664/C-E668

Responsible Clinical Investigator:

Louis Z. Cooper, M.D.
Director, Pediatric Service
The Roosevelt Hospital
428 West 59th Street
New York, New York 10019

Study Location: New York, New York

Date Study Initiated: June 25, 1976

Date Study Completed: In Progress

Study Procedure:

Fifty-four children, 11 months to 18 years of age, have been included in the study thus far. Thirty-six received a 0.5 ml subcutaneous dose of combined live measles-rubella virus vaccine; eighteen received a 0.5 ml subcutaneous dose of live attenuated RA 27/3 rubella virus vaccine. Blood samples were obtained immediately prior to vaccination and six weeks after vaccination from a sample of the population. Each child was followed 6 weeks for clinical complaints. The study continues in progress.

Addendum #1

Clinical Protocol - Study #470

Combined Live Measles-Rubella (RA 27/3) Virus Vaccine

Purpose of Addendum: To permit vaccination with monovalent RA 27/3 or HPV-77 duck rubella virus vaccines.

Vaccines:

1. Combined live measles-rubella (RA 27/3) virus vaccine
   Lot #622/C-D764

   Vaccine dose is 0.5 ml given subcutaneously.

   The vaccine is supplied in two-dose vials. Each vial should be rehydrated with 1.2 ml of sterile, pyrogen-free distilled water without preservative.

2. Combined live measles-rubella (HPV-77 duck embryo) virus vaccine
   Lot #0619W

   Vaccine dose is 0.5 ml given subcutaneously.

   The vaccine is supplied in single dose vials. Each vial should be rehydrated with 0.7 ml of sterile, pyrogen-free distilled water without preservative.

3. Live HPV-77 duck embyro rubella virus vaccine
   Lot #0406W

   Vaccine dose is 0.5 ml given subcutaneously.

   The vaccine is supplied in single dose vials. Each vial should be rehydrated with 0.7 ml of sterile, pyrogen-free distilled water without preservative.

4. Live RA 27/3 rubella virus vaccine
   Lot #60640/C-E668

   Vaccine dose is 0.5 ml given subcutaneously.

   The vaccine is supplied in single dose vials. Each vial should be rehydrated with 0.7 ml of sterile, pyrogen-free distilled water without preservative.

Addendum #1
Clinical Protocol - Study #470
Combined Live Measles-Rubella (RA 27/3) Virus Vaccine

Vaccines: (continued)

CAUTION: Both combined vaccines and the HPV-77 duck rubella virus vaccine contain egg protein and should not be given to persons with known sensitivity to chicken or duck, chicken or duck eggs or feathers. All of the vaccines contain neomycin and should not be given to persons sensitive to neomycin. Persons with leukemia or other immunologic disorder and persons receiving immunosuppressive drugs should not be vaccinated. The vaccines should not be given to persons with any febrile respiratory illness or other active febrile infection.

Keep dried vaccines stored at -20°C.

Keep dried vaccines at 4°C in transport.

Keep reconstituted vaccine on ice. Discard unused vaccine 4 hours after rehydration.

Procedure:

The study population will consist of children 1 to 6 years old having negative histories for vaccination and illness caused by measles and/or rubella. Children will receive one of the four vaccines as follows:

Group	Vaccine	No. of Children
1	Measles-rubella (RA 27/3)	Up to 500
2	Measles-rubella (HPV-77 duck)	Up to 500
3	HPV-77 duck rubella	Up to 200
4	RA 27/3 rubella	Up to 200

Informed written consent will be obtained from a parent or guardian of each child participating in the study.

Each child will receive a single 0.5 ml subcutaneous injection of one of the four vaccines.

Bleeding samples (10-15 ml) will be obtained from approximately one-third of the study participants. Samples will be drawn immediately before and 6-8 weeks following vaccination.

Each child will be followed clinically for 42 days after vaccination. All local and systemic complaints will be recorded on the case report form.

Addendum #1
Clinical Protocol - Study #470
Combined Live Measles-Rubella (RA 27/3) Virus Vaccine

Schedule:

Time	Vaccination and Follow-Up (All Children)	Bleeding (Approx. 1/3 of Children)
Day 0	Vaccinate 0.5 ml, subcutaneously.	10-15 ml
Days 0-42	Clinical follow-up for local and systemic reactions.	--
Week 6-8	--	10-15 ml

Laboratory: Remove serum from clot aspectically and store frozen at -20°C.

Serology: Circulating levels of measles and rubella antibodies before and after vaccination will be determined by hemagglutination-inhibition test.

Clinical Form: Attached.

Adverse Reactions: Any serious or alarming reaction, including death due to any cause during the investigation, whether related or not related to the test material, must be reported immediately to Merck & Co., Inc., through Dr. Maurice R. Hilleman, telephone (215) 699-5311, Ext. 5532, or in his absence, Dr. Allen F. Woodhour, telephone (215) 699-5311, Ext. 5588.

Unused Vaccine: All unused vaccine should be returned immediately to Merck Sharp & Dohme Research Laboratories, West Point, Pennsylvania 19486.

M. R. Hilleman, Ph.D.

Clinical Protocol - Study #470

Combined Live Measles-Rubella (RA 27/3) Virus Vaccine

Purpose: To compare antibody and clinical responses to combined live measles-rubella virus vaccine containing the RA 27/3 rubella virus strain or the HPV-77 duck rubella virus strain.

Vaccine:

1. Combined live measles-rubella (RA 27/3) virus vaccine
   Lot #622 or Lot #623

   Vaccine dose is 0.5 ml given subcutaneously.

   The vaccine is supplied in two-dose vials. Each vial of vaccine should be rehydrated with 1.2 ml of sterile, pyrogen-free distilled water.

2. Combined live measles-rubella (HPV-77 duck) virus vaccine
   Lot #2412T

   Vaccine dose is 0.5 ml given subcutaneously.

   The vaccine is supplied in single dose vials. Each vial of vaccine should be rehydrated with 0.7 ml of sterile, pyrogen-free distilled water.

CAUTION: Both vaccines contain egg protein and should not be given to persons with known sensitivity to chicken or duck, chicken or duck eggs or feathers. The vaccines also contain neomycin and should not be given to persons with sensitivity to neomycin. Persons with leukemia or other immunologic disorders or persons receiving immunosuppressive drugs should not be vaccinated. The vaccines should not be given to persons with any febrile respiratory illness or other active febrile infection.

Keep dried vaccines stored at -20°C.

Keep dried vaccines at 4°C in transport.

Keep reconstituted vaccine on ice. Discard unused vaccine 4 hours after rehydration.

Procedure: The study population will consist of children 1 to 6 years old having negative histories for vaccination and illness caused by measles and rubella. Children will be randomly assigned to receive one of the two vaccines as follows:

Group	Vaccine	No. of Children
1	measles-rubella (RA 27/3)	up to 500 children
2	measles-rubella (HPV-77 duck)	up to 500 children

Informed written consent will be obtained from each child's parent or guardian prior to participating in the study.

Each child will receive a single 0.5 ml subcutaneous injection of one of the two combined live measles-rubella virus vaccines.

Bleeding samples (10-15 ml) will be obtained from approximately one-third of the study participants. They will be bled immediately prior to vaccination and 6-8 weeks following vaccination.

Each child will be followed clinically for 42 days after vaccination. All local and systemic complaints will be recorded on the case report form.

Schedule:

Time	Vaccination and Follow-up (All Children)	Bleeding (Approx. 1/3 of Children)
Day 0	Vaccinate 0.5 ml, subcutaneously.	10-15 ml
Days 0-42	Clinical follow-up for local and systemic reactions.	--
Week 6-8	--	10-15 ml

Laboratory: Remove serum from clot aseptically and store frozen at -20°C.

Serology: Circulating levels of measles and rubella antibodies before and after vaccination will be determined by hemagglutination-inhibition test.

Clinical Form: Attached.

Adverse Reactions: Any serious or alarming reaction, including death due to any cause during the investigation, whether related or not related to the test material, must be reported immediately to Merck & Co., Inc., through Dr. Maurice R. Hilleman, telephone (215) 699-5311, Ext. 5532, or in his absence, Dr. Allen F. Woodhour, telephone (215) 699-5311, Ext. 5588.

Unused Vaccine: All unused vaccine should be returned immediately to Merck Sharp & Dohme Research Laboratories, West Point, Pa. 19486.

M. R. Hilleman, Ph.D.

MEASLES – RUBELLA VACCINATION

Study No. _____ (1-3) Case No. _____ (5-9)

CT 2	Name	Sex (35) M F	Birthdate (36-41) mo day yr	(46-47)
	Address			

Indicate if this child:

☐ had disease Did child develop clinical disease: 1 = YES 2 = NO

☐ been vaccinated Date of onset: _____

☐ been exposed Comments: _____

Date of exposure _____ Diagnosed by: _____

(48)

☐ Vaccinee ☐ Control Date of Vaccination _____ (52-57) Bleeding Dates: _____ (58-63) _____ (70-75)

Lot No. _____ (49-51)

CT 3 DAY	DATE	Temperature Oral	Temperature Rectal	Malaise	Anorexia	Gastrointestinal	Irritability	Headache	Upper Respiratory Illness	Otitis	Conjunctivitis	Lymphadenopathy	Local Reaction*	Exanthema	Rash Rubella-like rash	Arthralgia	Arthritis	*Specify (Type, Location) OTHER REACTIONS
		24		16	25	03	15	14	01	03	06	05	12	50	51	11	32	
0																		
1																		
2																		
3																		
4																		
5																		
6																		
7																		
8																		
9																		
10																		
11																		
12																		
13																		
14																		
15																		
16																		
17																		
18																		
19																		
20																		
21																		
22																		
23																		
24																		
25																		
26																		
27																		
28																		
29																		
30																		
31																		
32																		
33																		
34																		
35																		
36																		
37																		
38																		
39																		
40																		
41																		
42																		

Please return completed forms to: (Retain PINK copy for your files)

M. R. HILLEMAN, PhD, DSc
MERCK SHARP & DOHME RESEARCH LABORATORIES
WEST POINT, PENNSYLVANIA, 19486, U.S.A.

Physician's Signature

Physician's Name (Type or Print)

Date

TR4230-0376(DOM)

(*4230-0376) (*3735-0475)R

Table 1

Serological Findings Among Children Who Received Combined Live Measles-Rubella (RA 27/3) Virus Vaccine, Lot #622/C-D764 (Study #470)

Age	No. Vacc.	No. Serol. Tested	Initially Seronegative to: Measles-Rubella Conversions/Total		Initially Seropositive to:
			Measles	Rubella	Measles and Rubella
Not Given	1	1			1
(Months)					
14	4	1	1/1	1/1	
15	3	1	1/1	1/1	
16	3	0			
17	1	1	1/1	1/1	
18	1	1	1/1	1/1	
(Years)					
2	6	3	3/3	3/3	
4	2	2	1/1	1/1	1
5	1	1	1/1	1/1	
6	1	1	1/1	1/1	
Total	23	12	10/10 (100%)	10/10 (100%)	2
Mean Age: 2.0 Years					

Overall Conversion Rates

Measles	Rubella
10/10 (100%)	10/10 (100%)

5/18/78

Table 2

Serological Findings Among Children Who Received
Combined Live Measles-Rubella (HPV-77) Virus Vaccine, M-R-VAX (Study #470)

Age	Total No. Vacc.	No. Serol. Tested	Initially Seronegative to:				Initially Seropositive to:
			Measles-Rubella Conversions/Total		Measles Only Conversions/ Total	Rubella Only Conversions/ Total	
			Measles	Rubella			Measles and Rubella
(Months)							
11	1	0					
14	2	0					
15	2	2	2/2	2/2			
16	2	2	1/1	1/1	1/1		
21	1	1				1/1	
(Years)							
4	1	1			1/1		
5	1	1	1/1	1/1			
7	1	1	1/1	1/1			
9	1	1					1
18	1	1	1/1	1/1			
Total	13	10	6/6	6/6	2/2	1/1	1
Mean Age: 4.1 Years							

Overall Conversion Rates

Measles	Rubella
8/8	7/7
(100%)	(100%)

10/6/77

Table 3

Distribution of Fold Rises of Hemagglutination Inhibition Antibody Titers Among Children Who Received Live Attenuated RA 27/3 Rubella Virus Vaccine, Lot #579/C-D418 (Study #470)

Age (Years)	No. Vacc.	No. Serol. Tested	Initially Seropositive	Initially Seronegative					
				Paired Sera					
			Total	No. Conv.	No. Fail.	Total	Conv. Rate	Pre-Vacc. Sera Only	Total
1	6	0							
2	2	2		2		2	2/2		2
4	1	1		1		1	1/1		1
5	1	1						1	1
Total	10	4	0	3	0	3	100%	1	4
Mean Age = 2.1 Years									

4/3/78

Table 4

Distribution of Fold Rises of Hemagglutination Inhibition Antibody Titers Among Children Who Received Live Attenuated RA 27/3 Rubella Virus Vaccine, Lot #60664/C-E668 (Study #470)

Age (Years)	No. Vacc.	No. Serol. Tested	Initially Seropositive		Initially Seronegative
			Paired Sera		
			≥4x Rise	Total	Total
1	7	0			
5	1	1	1	1	
Total	8	1	1	1	0
Mean Age: 1.8 Years					

4/3/78

Table 5

Distribution of Post-Vaccination Antibody Titers Among Children Who Were Initially Seronegative to Measles and Rubella, Who Received Combined Live Measles-Rubella (RA 27/3) Virus Vaccine, Lot #622/C-D764 (Study #470)

Measles (HI)	
Post-Titer Distribution	Number of Children
10	1
20	1
40	2
80	5
160	-
≥320	1
Total	10
Geometric Mean Titer:	≥56.6

Rubella (HI)	
Post-Titer Distribution	Number of Children
128	3
256	3
≥512	4
Total	10
Geometric Mean Titer:	≥274.4

5/18/78

Table 6

Distribution of Post-Vaccination Antibody Titers Among Children Who Were Initially Seronegative to Measles and Rubella, Who Received Combined Live Measles-Rubella (HPV-77) Virus Vaccine, M-R-VAX (Study #470)

Measles (HI)	
Post Titer Distribution	Number of Children
20	1
40	2
80	1
160	1
≥320	1
Total	6
Geometric Mean Titer:	≥71.3

Rubella (HI)	
Post Titer Distribution	Number of Children
128	2
256	1
≥512	3
Total	6
Geometric Mean Titer:	≥287.3

10/6/77

Table 7

Distribution of Post-Vaccination Antibody Titers Among Initially Seronegative Children Who Received Live Attenuated RA 27/3 Rubella Virus Vaccine, Lot #579/C-D418 (Study #470)

Rubella (HI)	
Post-Titer Distribution	Number of Children
256	1
≥512	2
Total	3
Geometric Mean Titer: ≥406.4	

1/5/78

STUDY #470

Thus far, two children in the study have exhibited clinical complaints:

CASE NO. - (b) (6)

AGE - 4 Years

VACCINE - Measles-Rubella (RA 27/3)

CLINICAL COMPLAINT - Rubella-Like Rash, Days 2-3

SEROLOGY -

Rubella HI	32	≥512
Measles HI	≥320	160

CASE NO. - (b) (6)

AGE - 15 Months

VACCINE - Measles-Rubella (RA 27/3)

CLINICAL COMPLAINT - Upper Respiratory Illness, Day 3

SEROLOGY -

Rubella HI	NS	128
Measles HI	NS	20

1/5/78

Program: Study #512 - To measure antibody and clinical responses to three consecutive lots of combined measles-rubella virus vaccine.

Vaccine: Combined live measles-rubella (RA 27/3) virus vaccine, lyophilized,

Lot #62343/C-F021
Lot #62344/C-F022
Lot #62345/C-F023

Responsible Clinical Investigator:

Victor M. Villarejos, M.D.
Director
Louisiana State University
International Center for Medical
Research and Training
Apartado 10.155
San Jose, Costa Rica

Study Location: Nicaragua

Date Study Initiated: October 11, 1977

Date Study Completed: November 26, 1977

Study Procedure:

One hundred seventy-five children, 10 months to 9 years of age were included in the study. Each received a 0.5 ml dose of combined live measles-rubella virus vaccine. Blood samples were obtained on day of vaccination and 6 weeks after vaccination. Each child was followed 6 weeks for clinical complaints.

Clinical Protocol - Study #512

Combined Live Measles-Rubella (RA 27/3) Virus Vaccine

Program: Combined live measles-rubella virus vaccine

Purpose: To measure antibody and clinical responses to three consecutive lots of vaccine.

Vaccine: Combined live measles-rubella virus vaccine, lyophilized,

Lot no. 62343/C-F021
Lot no. 62344/C-F022
Lot no. 62345/C-F023

Vaccine dose is 0.5 ml given subcutaneously.

The vaccine is supplied in single dose vials. Each vial should be reconstituted with 0.7 ml of sterile, pyrogen-free distilled water which is supplied in prefilled syringes.

CAUTION: The vaccine should not be given to persons with known sensitivity to neomycin, chicken, eggs or feathers. Persons with leukemia or other immunologic disorder and persons receiving immunosuppressive drugs should not be vaccinated. Also, the vaccine should not be given to persons with a febrile respiratory illness or other active febrile infection.

Keep dried vaccine stored at -20°C until used.

Keep dried vaccine at 4°C in transport.

Keep reconstituted vaccine on ice. Discard unused vaccine 4 hours after rehydration.

Procedure: The study population will consist of up to 150 children with a negative history for vaccination and illness caused by measles and rubella viruses. The children should range from 1 to 6 years of age.

Informed written consent will be obtained from a parent or guardian of each child who participates in the study.

Each child will receive a 0.5 ml subcutaneous injection of one of the three vaccine lots.

Bleeding samples (10-15 ml) will be obtained from each child immediately before and 6 weeks after vaccination.

Clinical Protocol - Study #512
Combined Live Measles-Rubella (RA 27/3) Virus Vaccine

Procedure: (continued) Each child will be followed clinically for local and systemic complaints occurring within 6 weeks after vaccination. Observations should include special notation for rash, nodes, arthralgia, arthritis, fever, malaise and anorexia. All complaints should be recorded on the case report form.

Schedule:

Time	Action - All Persons
Day 0	Bleed 10-15 ml Vaccinate 0.5 ml, subcutaneously
Days 0-42	Clinical follow-up for local and systemic complaints
Week 6	Bleed 10-15 ml

Laboratory: Remove serum from clot aseptically and store frozen at -20°C until shipped. It is imperative that sera are sterile to avoid interference with the serologic assay.

Serology: Levels of circulating measles and rubella antibodies will be determined by hemagglutination-inhibition test.

Clinical Forms: Attached.

Adverse Reactions: Any serious or alarming reaction, including death due to any cause during the investigation, whether related or not related to the test material, must be reported immediately to Merck & Co., Inc., through Dr. Maurice R. Hilleman, telephone (215) 699-5311, Ext. 5532, or in his absence, Dr. Arlene A. McLean, telephone (215) 699-5311, Ext. 6383.

Unused Vaccine: All unused vaccine should be returned immediately to Merck Sharp & Dohme Research Laboratories, West Point, Pennsylvania 19486.

Shipping of Sera & Records:

1. Send sera frozen within insulated containers which are supplied.
2. Send sera and records to Dr. Maurice R. Hilleman, Virus & Cell Biology Research, Merck Sharp & Dohme Research Laboratories, West Point, Pennsylvania 19486.
3. Alert Dr. Hilleman by cable as soon as possible regarding flight number, air bill and date of arrival.

M. R. Hilleman, Ph.D.

Estudio No. _____ (1-3)

OBSERVACÍONES CLINÍCAS

No. Del Caso _____ (5-9)

CT 2	Nombre completo del niño:	Sexo(35) M F	Fecha de nacimieto (36-41) día mes año	(46-47)
	Dirección completa de Padre o Guardián:			

☐ VACUNADO NO. de LOTE _____ (49-51) FECHAS de SANGRIA _____ SEROLOGIA _____

☐ CONTROL (48) FECHA de VACUNACION _____ (52-57) _____ (56-63) _____

_____ (70-75) _____

Dia	Fecha	Temperatura Oral	Temperatura Retal	Malestar	Anorexia	Gastroenteritis	Irritabilidad	Cefalea	I.V.R.S.	Otitis	Conjuntivitis	Linfadenopatia	Reaccion Local*	RASH* Rubelliforme	RASH* Morbilliforme	Artralgia	Artritis	* Especifique tipo en esta seccion / OTRAS REACCIONES
		24		16	25	08	15	14	01	03	06	05	12	51	52	11	32	
0																		
1																		
2																		
3																		
4																		
5																		
6																		
7																		
8																		
9																		
10																		
11																		
12																		
13																		
14																		
15																		
16																		
17																		
18																		
19																		
20																		
21																		
22																		
23																		
24																		
25																		
26																		
27																		
28																		
29																		
30																		
31																		
32																		
33																		
34																		
35																		
36																		
37																		
38																		
39																		
40																		
41																		
42																		

Al terminar el estudio, devuelva copia blanca y copia amarilla de esta form a (Retenga copia color de rosa para sus archivos)

M. R. HILLEMAN, PhD, DSc
MERCK SHARP & DOHME RESEARCH LABORATORIES
WEST POINT, PENNSYLVANIA, 19486, U.S.A.

Firma del medico:

Nombre del medico (en letra de molde): | *Fecha:*

Table 1

Serological Findings Among Children Who Received
Combined Live Measles-Rubella (RA 27/3) Virus Vaccine, Lot #62343/C-F021 (Study #512)

Age	No. Vacc.	No. Serol. Tested	Initially Seronegative to: Measles-Rubella Conversions/Total Measles	Rubella	Measles Only Conversions/ Total	Rubella Only Conversions/ Total	Initially Seropositive to: Measles Mumps and Rubella
(Months)							
10	1	1	0/1	1/1			
12	1	1	1/1	1/1			
13	2	2	1/2*	2/2			
16	1	1				1/1	
21	1	1	1/1	1/1			
23	1	1			1/1		
(Years)							
2	7	6	1/2**	2/2		4/4	
3	9	7	3/3	3/3		4/4	
4	6	6	1/1	1/1		5/5	
5	12	11	1/1	1/1	1/1	6/6	3
6	9	9	1/1	1/1		7/7	1
7	7	7	2/2	2/2	1/1	2/2	2
8	2	2				2/2	
9	1	1				1/1	
Total	60	56	12/15	15/15	3/3	32/32	6
Mean Age: 4.4 Years			(80.0%)	(100%)	(100%)	(100%)	

Overall Conversion Rates

Measles	Rubella
15/18	47/47
(83.3%)	(100%)

* Antibody titer QNS,2 by serum neutralization.
** Antibody titer QNS,4 by serum neutralization.

3/23/78

Table 2

Serological Findings Among Children Who Received
Combined Live Measles-Rubella (RA 27/3) Virus Vaccine, Lot #62344/C-F022 (Study #512)

Age	No. Vacc.	No. Serol. Tested	Initially Seronegative to:				Initially Seropositive to:
			Measles-Rubella Conversions/Total		Measles Only Conversions/ Total	Rubella Only Conversions/ Total	Measles Mumps and Rubella
			Measles	Rubella			
(Months)							
11	1	1	1/1	1/1			
13	3	3	2/2	2/2			1
17	1	1				1/1	
22	1	1				1/1	
(Years)							
2	4	2	1/1	1/1			1
3	9	9	3/3	3/3		4/4	2
4	9	8	3/3	3/3	0/1	3/3	1
5	14	14	1/1	1/1		8/8	5
6	16	14	6/6	6/6	1/1	3/3	4
7	1	1	1/1	1/1			
8	1	1				1/1	
Total	60	55	18/18	18/18	1/2	21/21	14
Mean Age:	4.3 Years		(100%)	(100%)	(50.0%)	(100%)	

Overall Conversion Rates

Measles	Rubella
19/20	39/39
(95.0%)	(100%)

3/23/78

Table 3

Serological Findings Among Children Who Received
Combined Live Measles-Rubella (RA 27/3) Virus Vaccine, Lot #62345/C-F023 (Study #512)

Age	No. Vacc.	No. Serol. Tested	Initially Seronegative to:				Initially Seropositive to:
			Measles-Rubella Conversions/Total		Measles Only Conversions/ Total	Rubella Only Conversions/ Total	Measles Mumps and Rubella
			Measles	Rubella			
(Months)							
13	1	1				1/1	
14	1	1	1/1	1/1			
17	2	2				2/2	
20	1	1	1/1	1/1			
22	1	0					
(Years)							
2	3	3	2/2	2/2		1/1	
3	9	8	3/3	3/3	1/1	4/4	
4	14	12	4/4	4/4	0/1	7/7	
5	12	11	3/3	3/3		6/6	2
6	11	8	2/3	3/3		5/5	
Total	55	47	16/17	17/17	1/2	26/26	2
Mean Age: 4.1 Years			(94.1%)	(100%)	(50.0%)	(100%)	

Overall Conversion Rates

Measles	Rubella
17/19	43/43
(85.5%)	(100%)

8/11/78

Table 4

Distribution of Post-Vaccination Antibody Titers Among Children
Who Were Initially Seronegative to Measles and Rubella, Who Received
Combined Live Measles-Rubella (RA 27/3) Virus Vaccine, Lot #62343/C-F021 (Study #512)

Measles (HI)	
Post-Titer Distribution	Number of Children
<5	3*
5	
10	
20	4
40	6
80	2
Total	15
Geometric Mean Titer:	17.4

Rubella (HI)	
Post-Titer Distribution	Number of Children
32	1
64	
128	1
256	5
≥512	8
Total	15
Geometric Mean Titer:	≥308.0

3/23/78

* Two cases post-positive by serum neutralization.

Table 5

Distribution of Post-Vaccination Antibody Titers Among Children
Who Were Initially Seronegative to Measles and Rubella, Who Received
Combined Live Measles-Rubella (RA 27/3) Virus Vaccine, Lot #62344/C-F022 (Study #512)

Measles (HI)	
Post-Titer Distribution	Number of Children
5	1
10	1
20	3
40	8
80	3
160	1
≥320	1
Total	18
Geometric Mean Titer:	≥40.0

Rubella (HI)	
Post-Titer Distribution	Number of Children
128	1
256	6
≥512	11
Total	18
Geometric Mean Titer:	≥376.3

3/23/78

Table 6

Distribution of Post-Vaccination Antibody Titers Among Children
Who Were Initially Seronegative to Measles and Rubella, Who Received
Combined Live Measles-Rubella (RA 27/3) Virus Vaccine, Lot #62345/C-F023 (Study #512)

Measles (HI)	
Post-Titer Distribution	Number of Children
<5	1
5	
10	
20	2
40	2
80	5
160	5
≥320	2
Total	17
Geometric Mean Titer:	≥69.9

Rubella (HI)	
Post-Titer Distribution	Number of Children
128	4
256	6
≥512	7
Total	17
Geometric Mean Titer:	≥289.3

8/11/78

Table 7

Maximum Temperatures Reported Among Children Who Received
Combined Live Measles-Rubella (RA 27/3) Virus Vaccine, Lot #62343/C-F021 (Study #512)

Maximum Temperature (°F, Oral)	Total Vaccinees (60 Children)						Initially Seronegatives (15 Children)					
	Days Post Vaccination					No. with Max. Temp.	Days Post Vaccination					No. with Max. Temp.
	0-4	5-12	13-18	19-28	29-42		0-4	5-12	13-18	19-28	29-42	
<99	50 (83.3%)	43 (71.7)	45 (75.0)	42 (70.0)	41 (68.3)	20	14 (93.3)	14 (93.3)	11 (73.3)	11 (73.3)	11 (73.3)	8
99 - 100.9	10 (16.7)	17 (28.3)	14 (23.3)	18 (30.0)	19 (31.7)	39	1 (6.7)	1 (6.7)	4 (26.7)	4 (26.7)	4 (26.7)	7
101 - 101.9			1 (1.7)			1						0

3/23/78

Table 8

Maximum Temperatures Reported Among Children Who Received
Combined Live Measles-Rubella (RA 27/3) Virus Vaccine, Lot #62344/C-F022 (Study #512)

Maximum Temperature (°F, Oral)	Total Vaccinees (60 Children)						Initially Seronegatives (19 Children)					
	Days Post Vaccination					No. with Max. Temp.	Days Post Vaccination					No. with Max. Temp.
	0-4	5-12	13-18	19-28	29-42		0-4	5-12	13-18	19-28	29-42	
<99	47 (78.3%)	29 (48.3)	41 (68.3)	35 (58.3)	33 (55.0)	14	15 (78.9)	5 (26.3)	13 (68.4)	11 (57.9)	12 (63.2)	4
99 - 100.9	13 (21.7)	31 (51.7)	19 (31.7)	25 (41.7)	27 (45.0)	46	4 (21.1)	14 (73.7)	6 (31.6)	8 (42.1)	7 (36.8)	15

3/23/78

Table 9

Maximum Temperatures Reported Among Children Who Received
Combined Live Measles-Rubella (RA 27/3) Virus Vaccine, Lot #62345/C-F023 (Study #512)

Maximum Temperature (°F, Oral)	Total Vaccinees (55 Children)						Initially Seronegatives (17 Children)					
	Days Post Vaccination					No. with Max. Temp.	Days Post Vaccination					No. with Max. Temp.
	0-4	5-12	13-18	19-28	29-42		0-4	5-12	13-18	19-28	29-42	
<99	44 (80.0%)	27 (49.1)	33 (60.0)	33 (60.0)	38 (69.1)	8	12 (70.6)	8 (47.1)	8 (47.1)	11 (64.7)	10 (58.8)	3
99 -100.9	10 (18.2)	27 (49.1)	22 (40.0)	21 (38.2)	17 (30.9)	44	5 (29.4)	9 (52.9)	9 (52.9)	5 (29.4)	7 (41.2)	13
101 - 101.9	1 (1.8)	1 (1.8)		1 (1.8)		3				1 (5.9)		1

8/11/78

Table 10

Clinical Complaints Reported Among Children Who Received
Combined Live Measles-Rubella (RA 27/3) Virus Vaccine, Lot #62343/C-F021 (Study #512)

Clinical Complaint	Total Vaccinees (60 Children)						Initially Seronegatives (15 Children)					
	Days Post Vaccination					No. with Complaint	Days Post Vaccination					No. with Complaint
	0-4	5-12	13-18	19-28	29-42		0-4	5-12	13-18	19-28	29-42	
Headache			1 (1.7%)			1						0
Irritability				1 (1.7)	1 (1.7)	1						0
Malaise			1 (1.7)			1						0
Upper Respiratory Illness	2 (3.3)	1 (1.7)	2 (3.3)	3 (5.0)	2 (3.3)	7				1 (6.7)		1
Gastrointestinal Illness		2 (3.3)	2 (3.3)	2 (3.3)	2 (3.3)	5		1 (6.7)		1 (6.7)	1 (6.7)	2
Persons with Complaint:	2 (3.3)	3 (5.0)	4 (6.7)	5 (8.3)	4 (6.7)	12	0	1 (6.7)	0	2 (13.3)	1 (6.7)	3
Persons with No Complaint:	58 (96.7)	57 (95.0)	56 (93.3)	55 (91.7)	56 (93.3)	48	15 (100)	14 (93.3)	15 (100)	13 (86.7)	14 (93.3)	12

3/23/78

Table 11

Clinical Complaints Reported Among Children Who Received
Combined Live Measles-Rubella (RA 27/3) Virus Vaccine, Lot #62344/C-F022 (Study #512)

Clinical Complaint	Total Vaccinees (60 Children)						Initially Seronegatives (19 Children)					
	Days Post Vaccination					No. with Complaint	Days Post Vaccination					No. with Complaint
	0-4	5-12	13-18	19-28	29-42		0-4	5-12	13-18	19-28	29-42	
Headache				1 (1.7%)		1						0
Malaise		1 (1.7)		3 (5.0)	2 (3.3)	4						0
Upper Respiratory Illness	1 (1.7)	3 (5.0)	2 (3.3)	3 (5.0)	3 (5.0)	6	1 (5.3)	1 (5.3)				1
Gastrointestinal Illness	1 (1.7)	3 (5.0)	1 (1.7)		1 (1.7)	4	1 (5.3)	1 (5.3)				1
Persons with Complaint:	2 (3.3)	6 (10.0)	3 (5.0)	3 (5.0)	4 (6.7)	10	2 (10.5)	2 (10.5)	0	0	0	2
Persons with No Complaint:	58 (96.7)	54 (90.0)	57 (95.0)	57 (95.0)	56 (93.3)	50	17 (89.5)	17 (89.5)	19 (100)	19 (100)	19 (100)	17

3/23/78

Table 12

Clinical Complaints Reported Among Children Who Received
Combined Live Measles-Rubella (RA 27/3) Virus Vaccine, Lot #62345/C-F023 (Study #512)

Clinical Complaint	Total Vaccinees (55 Children)						Initially Seronegatives (17 Children)					
	Days Post Vaccination					No. with Complaint	Days Post Vaccination					No. with Complaint
	0-4	5-12	13-18	19-28	29-42		0-4	5-12	13-18	19-28	29-42	
Malaise		1 (1.8%)	2 (3.6)	1 (1.8)		2						0
Anorexia		1 (1.8)	1 (1.8)			1						0
Upper Respiratory Illness	2 (3.6)	3 (5.5)	3 (5.5)	4 (7.3)	2 (3.6)	8				2 (11.8)	1 (5.9)	2
Gastrointestinal Illness	2 (3.6)	3 (5.5)	3 (5.5)		1 (1.8)	6	1 (5.9)	1 (5.9)	1 (5.9)		1 (5.9)	3
Persons with Complaint:	3 (5.5)	6 (10.9)	6 (10.9)	3 (5.5)	2 (3.6)	14	1 (5.9)	1 (5.9)	1 (5.9)	2 (11.8)	2 (11.8)	5
Persons with No Complaint:	52 (94.5)	49 (89.1)	49 (89.1)	52 (94.5)	53 (96.4)	41	16 (94.1)	16 (94.1)	16 (94.1)	15 (88.2)	15 (88.2)	12

8/11/78

MEMO

To File Location Date 8/14/78

From T. Schofield Location

Subject Statistical Analysis - Study #512

No significant differences exist in seroconversion rates for measles and rubella or clinical reaction rates among three lots of combined measles-rubella (RA 27/3) virus vaccine.

Multivariate analysis of variance was performed on post-titer values for children who were initially seronegative to both measles and rubella by the HI test. The log transformation was used. While sample sizes were small, a significant difference exists between the measles HI titers for children who received Lot #62343/C-F021 and children who received Lot #62345/C-F023. No other differences could be determined. Geometric mean titers were:

	Measles	Rubella
Lot #62343/C-F021 (n=15)	17.4	308.0
Lot #62344/C-F022 (n=18)	40.0	376.3
Lot #62345/C-F023 (n=17)	69.9	289.3

T.S.

Program: Study #514 - To measure antibody and clinical responses to three consecutive lots of combined measles-rubella virus vaccine.

Vaccine: Combined live measles-rubella virus vaccine, lyophilized

Lot #62343/C-F021
Lot #62344/C-F022
Lot #62345/C-F023

Responsible Clinical Investigator:

Robert E. Weibel, M.D.
Director, Division of Preventive Medicine
Joseph Stokes, Jr. Research Institute
Children's Hospital of Philadelphia
34th Street and Civic Center Boulevard
Philadelphia, Pennsylvania 19104

Study Locations:

Pediatric Medical Associates, Havertown, Pennsylvania
Lansdale Medical Group, Lansdale, Pennsylvania
Geisinger Medical Center, Danville, Pennsylvania
G. F. Schultheis, Jr., M.D. and W. W. Holm, M.D., King of Prussia, Pennsylvania
G. A. Starkweather, M.D., Havertown, Pennsylvania
Children's Clinic of Chester and Vicinity, Chester, Pennsylvania

Date Study Initiated: September 9, 1977

Date Study Completed: May 13, 1978

Study Procedure:

One hundred sixty-seven children, 13 months to 12 years of age, were included in the study. Each received a 0.5 ml subcutaneous dose of combined live measles-rubella virus vaccine. Blood samples were obtained on day of vaccination and 6 weeks after vaccination. Each child was followed 6 weeks for clinical complaints.

Clinical Protocol - Study #514

Combined Live Measles-Rubella (RA 27/3) Virus Vaccine

Program: Combined live measles-rubella virus vaccine

Purpose: To measure antibody and clinical responses to three consecutive lots of vaccine.

Vaccine: Combined live measles-rubella virus vaccine, lyophilized,

Lot no. 62343/C-F021
Lot no. 62344/C-F022
Lot no. 62345/C-F023

Vaccine dose is 0.5 ml given subcutaneously.

The vaccine is supplied in single dose vials. Each vial should be reconstituted with 0.7 ml of sterile, pyrogen-free distilled water which is supplied in prefilled syringes.

CAUTION: The vaccine should not be given to persons with known sensitivity to neomycin, chicken, eggs or feathers. Persons with leukemia or other immunologic disorder and persons receiving immunosuppressive drugs should not be vaccinated. Also, the vaccine should not be given to persons with a febrile respiratory illness or other active febrile infection.

Keep dried vaccine stored at -20°C until used.

Keep dried vaccine at 4°C in transport.

Keep reconstituted vaccine on ice. Discard unused vaccine 4 hours after rehydration.

Procedure: The study population will consist of up to 150 children with a negative history for vaccination and illness caused by measles and rubella viruses. The children should range from 1 to 6 years of age.

Informed written consent will be obtained from a parent or guardian of each child who participates in the study.

Each child will receive a 0.5 ml subcutaneous injection of one of the three vaccine lots.

Bleeding samples (10-15 ml) will be obtained from each child immediately before and 6 weeks after vaccination.

Clinical Protocol - Study #514
Combined Live Measles-Rubella (RA 27/3) Virus Vaccine

Procedure: (continued) Each child will be followed clinically for local and systemic complaints occurring within 6 weeks after vaccination. Observations should include special notation for rash, nodes, arthralgia, arthritis, fever, malaise and anorexia. All complaints should be recorded on the case report form.

Schedule:

Time	Action - All Persons
Day 0	Bleed 10-15 ml Vaccinate 0.5 ml, subcutaneously
Days 0-42	Clinical follow-up for local and systemic complaints
Week 6	Bleed 10-15 ml

Serology: Levels of circulating measles and rubella antibodies will be determined by hemagglutination-inhibition test.

Clinical Forms: Attached.

Adverse Reactions: Any serious or alarming reaction, including death due to any cause during the investigation, whether related or not related to the test material, must be reported immediately to Merck & Co., Inc., through Dr. Maurice R. Hilleman, telephone (215) 699-5311, Ext. 5532, or in his absence, Dr. Arlene A. McLean, telephone (215) 699-5311, Ext. 6383.

Unused Vaccine: All unused vaccine should be returned immediately to Merck Sharp & Dohme Research Laboratories, West Point, Pennsylvania 19486.

M. R. Hilleman, Ph.D.

SYMPTOM RECORD

RUBELLA STUDY NO. _____

N. _____ CASE NO. _____
(Last) (First) (Middle)

DAY	DATE	Temperature ☐ Rectal ☐ Oral *(Check One)*	NONE	RUNNY NOSE	SORE THROAT	COUGH	EAR ACHE	SWOLLEN GLANDS	SORE EYES	VOMITING	DIARRHEA	NAUSEA	RASH *	SORE JOINTS	SORE ARM (at shot) *	HEADACHE	ACHINESS	FEVER	LOSS OF APPETITE	* Describe COMMENTS
INSTRUCTIONS ON REVERSE SIDE			99	01	01	01	03	05	06	08	08	08		11	12	14	61	24	25	
0																				
1																				
2																				
3																				
4																				
5																				
6																				
7																				
8																				
9																				
10																				
11																				
12																				
13																				
14																				
15																				
16																				
17																				
18																				
19																				
20																				
21																				
22																				
23																				
24																				
25																				
26																				
27																				
28																				
29																				
30																				
31																				
32																				
33																				
34																				
35																				
36																				
37																				
38																				
39																				
40																				
41																				
42																				

If fever or unusual reaction develops, call:

PLEASE RETURN FOR FOLLOW-UP VISIT ON: _____

BE SURE TO BRING THIS RECORD ALONG WITH YOU.

THE JOSEPH STOKES, JR. RESEARCH INSTITUTE
THE CHILDREN'S HOSPITAL OF PHILADELPHIA
UNIVERSITY OF PENNSYLVANIA
34TH & CIVIC CENTER BLVD.
PHILADELPHIA, PA. 19104

ROBERT E. WEIBEL, M.D., DIRECTOR
DIVISION OF PREVENTIVE MEDICINE

(215) EV 7-6000
(215) EV 7-1309

November 10, 1977

Arlene A. McLean, Ph.D.
Director, Biologics Evaluation & Analysis
Merck Sharp & Dohme Research Laboratories
West Point, Pennsylvania 19486

RE: Clinical Protocol - Study #514
Combined Live Measles-Rubella Vaccine

Dear Arlene:

At the conclusion of the first thirty vaccinees (b) (6) at Pediatric Associates it was noted by Dr. Al Carlson that the lot number on the last vial C-F022 did not correspond with the lot required on the work sheet. After a thorough review of the situation it can not be determined when the lot of vaccine not corresponding to the record was given. This information must be considered in the evaluation of all clinical and serologic records from these vaccinees.

The following steps have been taken to prevent the recurrence of this situation:

1. In addition to the color code for each lot, as now used, the required vaccine lot will be placed on the study registration sheet in the required color of the lot.

2. Each lot will be placed in a separate color coded box rather than in a single box with color coded areas as now used.

These changes have been instituted to insure the accuracy of the records.

Sincerely,

Robert E. Weibel, M.D.

REW:ceb

cc: Alfred Carlson, M.D.
Karen Campbell, R.N.

Table 1

Serological Findings Among Children Who Received
Combined Live Measles-Rubella (RA 27/3) Virus Vaccine, Lot #62343/C-F021 (Study #514)

Age	No. Vacc.	No. Serol. Tested	Initially Seronegative to: Measles-Rubella Conversions/Total Measles	Measles-Rubella Conversions/Total Rubella	Measles Only Conversions/ Total	Rubella Only Conversions/ Total	Initially Seropositive to: Measles and Rubella
(Months)							
13	1	0					
14	8	8	7/8	8/8			
15	17	16	13/13*	13/13	3/3		
16	8	8	8/8	8/8			
17	2	2	2/2	2/2			
18	3	3	2/2	2/2	1/1		
19	1	0					
20	1	1			1/1		
21	1	1				1/1	
23	1	1	1/1	1/1			
(Years)							
2	3	3	1/1	1/1	2/2		
3	1	1				1/1	
Total	47	44	34/35	35/35	7/7	2/2	0
Mean Age: 1.4 Years			(97.1%)	(100%)	(100%)	(100%)	

Overall Conversion Rates

Measles	Rubella
41/42	37/37
(97.6%)	(100%)

* One sample pair tested by serum neutralization.

8/11/78

Table 2

Serological Findings Among Children Who Received
Combined Live Measles-Rubella (RA 27/3) Virus Vaccine, Lot #62344/C-F022 (Study #514)

Age	No. Vacc.	No. Serol. Tested	Initially Seronegative to: Measles-Rubella Conversions/Total Measles	Measles-Rubella Conversions/Total Rubella	Measles Only Conversions/ Total	Rubella Only Conversions/ Total	Initially Seropositive to: Measles and Rubella
(Months)							
14	5	5	5/5	5/5			
15	16	16	12/12	12/12	3/4		
16	6	4	2/2	2/2	2/2		
17	5	4	2/2	2/2	1/2		
18	5	5	4/4	4/4	1/1		
19	1	1	1/1	1/1			
21	2	1	1/1	1/1			
(Years)							
2	2	1			1/1		
4	1	0					
8	1	1				1/1	
12	1	1				1/1	
Total	45	39	27/27	27/27	8/10	2/2	0
Mean Age:	1.8 Years		(100%)	(100%)	(80.0%)	(100%)	

Overall Conversion Rates

Measles	Rubella
35/37	29/29
(94.6%)	(100%)

6/27/78

Table 3

Serological Findings Among Children Who Received
Combined Live Measles-Rubella (RA 27/3) Virus Vaccine, Lot #62345/C-F023 (Study #514)

Age	No. Vacc.	No. Serol. Tested	Initially Seronegative to: Measles-Rubella Conversions/Total Measles	Measles-Rubella Conversions/Total Rubella	Measles Only Conversions/ Total	Rubella Only Conversions/ Total	Initially Seropositive to: Measles and Rubella
(Months)							
13	1	1	1/1	1/1			
14	7	6	5/5	5/5	1/1		
15	13	13	11/11	11/11	2/2		
16	14	14	9/9	9/9	4/4	1/1	
17	4	4	3/3	3/3	1/1		
18	2	2	1/1	1/1	1/1		
21	1	1	1/1	1/1			
(Years)							
2	2	1	1/1	1/1			
4	1	1	1/1	1/1			
Total	45	43	33/33	33/33	9/9	1/1	0
Mean Age: 1.4 Years			(100%)	(100%)	(100%)	(100%)	

Overall Conversion Rates

Measles	Rubella
42/42	34/34
(100%)	(100%)

6/27/78

Table 4

Serological Findings Among Children Who Received
Combined Live Measles-Rubella (RA 27/3) Virus Vaccine, Lot # Unknown (Study #514)

Age	No. Vacc.	No. Serol. Tested	Initially Seronegative to:				Initially Seropositive to:
			Measles-Rubella Conversions/Total		Measles Only Conversions/ Total	Rubella Only Conversions/ Total	Measles and Rubella
			Measles	Rubella			
(Months)							
13	2	2	1/2	2/2			
14	5	5	5/5	5/5			
15	18	18	16/17*	17/17	1/1		
17	1	1	1/1	1/1			
18	1	1	1/1	1/1			
(Years)							
2	1	1				1/1	
7	1	1	1/1	1/1			
10	1	1	1/1	1/1			
Total	30	30	26/28	28/28	1/1	1/1	0
Mean Age: 1.7 Years			(92.9%)	(100%)	(100%)	(100%)	

Overall Conversion Rates

Measles	Rubella
27/29	29/29
(93.1%)	(100%)

* One sample pair tested by serum neutralization.

8/11/78

Table 5

Distribution of Post-Vaccination Antibody Titers Among Children Who Were Initially Seronegative to Measles and Rubella, Who Received Combined Live Measles-Rubella (RA 27/3) Virus Vaccine (Study #514)

	Post-Titer Distribution	Number of Children			
		Lot #62343/C-F021	Lot #62344/C-F022	Lot #62345/C-F023	Lot # Unknown
Measles (HI)	<5	1			2
	5				1
	10				1
	20		2	1	2
	40	12	10	4	5
	80	9	6	12	8
	160	6	5	9	5
	≥320	6	4	7	3
	Total	34	27	33	27
	Geometric Mean Titer:	≥79.5*	≥78.0	≥114.3	≥50.9*
Rubella (HI)	64	1		1	1
	128	5	2		4
	256	12	9	7	2
	≥512	17	16	25	21
	Total	35	27	33	28
	Geometric Mean Titer:	≥312.1	≥366.7	≥415.0	≥371.1

* One titer determined by serum neutralization not included in calculation of G.M.T.

8/11/78

Table 6

Maximum Temperatures Reported Among Children Who Received
Combined Live Measles-Rubella (RA 27/3) Virus Vaccine, Lot #62343/C-F021 (Study #514)

Maximum Temperature (°F, Oral)	Total Vaccinees (47 Children)						Initially Seronegatives (38 Children)					
	Days Post Vaccination					No. with Max. Temp.	Days Post Vaccination					No. with Max. Temp.
	0-4	5-12	13-18	19-28	29-42		0-4	5-12	13-18	19-28	29-42	
<99	30 (66.7%)	15 (33.3)	30 (66.7)	28 (63.6)	22 (50.0)	12	27 (75.0)	13 (36.1)	25 (69.4)	27 (75.0)	20 (55.6)	11
99 - 100.9	13 (28.9)	22 (48.9)	13 (28.9)	14 (31.8)	15 (34.1)	14	8 (22.2)	17 (47.2)	9 (25.0)	7 (19.4)	9 (25.0)	9
101 - 102.9		7 (15.6)	2 (4.4)	1 (2.3)	5 (11.4)	15		5 (13.9)	2 (5.6)	1 (2.8)	5 (13.9)	13
103 - 104.0	2 (4.4)	1 (2.2)		1 (2.3)	2 (4.5)	4	1 (2.8)	1 (2.8)		1 (2.8)	2 (5.6)	3
Not Taken	2	2	2	3	3	2	2	2	2	2	2	2

Case #	Max. Temp.	Days	Clinical Complaint	Serology Measles		Rubella	
(b) (6)	102.2	35-38	Upper Respiratory Illness, Gastrointestinal Illness, Nonspecific Rash, Teething	<5	80	<8	≥512
	102.0	9-11	Upper Respiratory Illness, Otitis, Anorexia	<5	160	<8	≥512
	103.0	10	None	<5	80	<8	≥512
	103.4	29-31	Upper Respiratory Illness, Nonspecific Rash				
	102.0	13-14	Teething	<5	80	<8	256
	103.0	3-6	Upper Respiratory Illness	<5	<5	<8	256
	102.0	41-42	Upper Respiratory Illness, Irritability, Anorexia, Myalgia	<5	40	<8	≥512
	104.0	7-10	Measles-Like Rash	<5	40	<8	≥512
	103.0	32-36	Lower Respiratory Illness, Gastrointestinal Illness				
	102.0	8-12	Upper Respiratory Illness, Lymphadenopathy	<5	≥320	<8	≥512
	103.2	25-35	Irritable, Viral Infection, Non-Specific Rash, Anorexia	<5	≥320	<8	256
	103.0	0-4	Non-Specific Rash, Anorexia	<5	≥320	8	64

8/11/78

Table 7

Maximum Temperatures Reported Among Children Who Received
Combined Live Measles-Rubella (RA 27/3) Virus Vaccine, Lot #62344/C-F022 (Study #514)

Maximum Temperature (°F, Oral)	Total Vaccinees (45 Children)						Initially Seronegatives (32 Children)					
	Days Post Vaccination					No. with Max. Temp.	Days Post Vaccination					No. with Max. Temp.
	0-4	5-12	13-18	19-28	29-42		0-4	5-12	13-18	19-28	29-42	
<99	21 (48.8%)	13 (30.2)	28 (65.1)	25 (59.5)	22 (52.4)	9	17 (56.7)	10 (33.3)	21 (70.0)	18 (62.1)	15 (51.7)	7
99 - 100.9	21 (48.8)	21 (48.8)	14 (32.6)	12 (28.6)	18 (42.9)	20	13 (43.3)	13 (43.3)	9 (30.0)	8 (27.6)	12 (41.4)	14
101 - 102.9	1 (2.3)	8 (18.6)	1 (2.3)	2 (4.8)	2 (4.8)	10		6 (20.0)		2 (6.9)	2 (6.9)	7
103 - 104.6		1 (2.3)		3 (7.1)		4		1 (3.3)		1 (3.4)		2
Not Taken	2	2	2	3	3	2	2	2	2	3	3	2

Case #	Max. Temp.	Days	Clinical Complaint	Serology Measles		Rubella	
(b) (6)	102.7	5-9	Upper Respiratory Illness, Ophthalmopathy, Gastrointestinal Illness	<5	160	32	≥512
	103.0	18-19	Upper Respiratory Illness				
	104.6	22-25	Upper Respiratory Illness, Gastrointestinal Illness	<5	160	8	≥512
	103.0	18-23	Upper Respiratory Illness, Gastrointestinal Illness, Nonspecific Rash, Anorexia	<5	40	<8	≥512
	103.0	10-11	Upper Respiratory Illness	<5	40	<8	≥512
	102.2	10	Upper Respiratory Illness, Gastrointestinal Illness, Irritability, Anorexia	<5	40	≥512	≥512
	102.0	4-6	Upper Respiratory Illness, Myalgia	<5	<5	128	≥512
	102.0	3-10	Irritability	<5	≥320	<8	≥512

6/27/78

Table 8

Maximum Temperatures Reported Among Children Who Received
Combined Live Measles-Rubella (RA 27/3) Virus Vaccine, Lot #62345/C-F023 (Study #514)

Maximum Temperature (°F, Oral)	Total Vaccinees (45 Children)						Initially Seronegatives (33 Children)					
	Days Post Vaccination					No. with Max. Temp.	Days Post Vaccination					No. with Max. Temp.
	0-4	5-12	13-18	19-28	29-42		0-4	5-12	13-18	19-28	29-42	
<99	26 (59.1%)	14 (31.8)	25 (56.8)	21 (47.7)	24 (54.5)	13	22 (66.7)	11 (33.3)	19 (57.6)	17 (51.5)	18 (54.5)	10
99 - 100.9	16 (36.4)	17 (38.6)	16 (36.4)	19 (43.2)	15 (34.1)	13	11 (33.3)	13 (39.4)	11 (33.3)	13 (39.4)	10 (30.3)	10
101 - 102.9	1 (2.3)	5 (11.4)	2 (4.5)	2 (4.5)	4 (9.1)	13		2 (6.1)	2 (6.1)	1 (3.0)	4 (12.1)	8
103 - 104.8		4 (9.1)				4		4 (12.1)				4
105.0		1 (2.3)				1		1 (3.0)				1
Fever - No Temperature	1	3	1	2	1			2	1	2	1	
Not Taken.	1	1	1	1	1							

Case #	Max. Temp.	Days	Clinical Complaint	Serology Measles		Rubella	
(b) (6)	102.2	39	Upper Respiratory Illness, Gastrointestinal Illness, Anorexia	<5	160	<8	≥512
	102.0	5-11	None	<5	40	32	≥512
	105.0	5-7	Upper Respiratory Illness, Otitis, Anorexia	<5	160	<8	256
	104.2	10-11	Upper Respiratory Illness, Gastrointestinal Illness, Headache	<5	160	<8	≥512
	104.8	4-9	Upper Respiratory Illness, Otitis, Irritable, Anorexia	<5	≥320	<8	256
	104.0	8-14	Upper Respiratory Illness, Gastrointestinal Illness, Anorexia	<5	≥320	<8	≥512
	102.4	1	None	<5	80	8	256
	104.0	5-7	Upper Respiratory Illness, Anorexia	<5	160	<8	≥512
	102.0	7-11	Gastrointestinal Illness, Measles-Like Rash	<5	80	<8	≥512

6/27/78

Table 9

Maximum Temperatures Reported Among Children Who Received
Combined Live Measles-Rubella (RA 27/3) Virus Vaccine, Lot # Unknown (Study #514)

Maximum Temperature (°F, Oral)	Total Vaccinees (30 Children)						Initially Seronegatives (28 Children)					
	Days Post Vaccination					No. with Max. Temp.	Days Post Vaccination					No. with Max. Temp.
	0-4	5-12	13-18	19-28	29-42		0-4	5-12	13-18	19-28	29-42	
<99	20 (66.7%)	18 (60.0)	22 (73.3)	19 (63.3)	16 (53.3)	11	18 (64.3)	16 (57.1)	20 (71.4)	17 (60.7)	15 (53.6)	10
99 - 100.9	10 (33.3)	6 (20.0)	7 (23.3)	9 (30.0)	10 (33.3)	9	10 (35.7)	6 (21.4)	7 (25.0)	9 (32.1)	9 (32.1)	8
101 - 102.9		4 (13.3)	1 (3.3)	1 (3.3)	3 (10.0)	7		4 (14.3)	1 (3.6)	1 (3.6)	3 (10.7)	7
103 - 104.0		2 (6.7)		1 (3.3)	1 (3.3)	3		2 (7.1)		1 (3.6)	1 (3.6)	3

Case #	Max. Temp.	Days	Clinical Complaint	Serology Measles		Rubella	
(b) (6)	103.4	21-22	Upper Respiratory Illness, Otitis, Gastrointestinal Illness, Anorexia	<5	160	<8	≥512
	102.1	16-17	Upper Respiratory Illness	<5	10	<8	128
	104.0	6-10	Measles-Like Rash	<5	40	<8	≥512
	103.0	32-36	Bronchitis, Gastrointestinal Illness				
	103.0	7-12	Gastrointestinal Illness, Measles-Like Rash	<5	40	<8	≥512
	102.0	10-11	Gastrointestinal Illness, Anorexia	<5	80	<8	256

6/27/78

Table 10

Clinical Complaints Reported Among Children Who Received
Combined Live Measles-Rubella (RA 27/3) Virus Vaccine, Lot #62343/C-F021 (Study #514)

Clinical Complaint	Total Vaccinees (47 Children)						Initially Seronegatives (38 Children)					
	Days Post Vaccination					No. with	Days Post Vaccination					No. with
	0-4	5-12	13-18	19-28	29-42	Complaint	0-4	5-12	13-18	19-28	29-42	Complaint
Injection Site:	2 (4.3%)					2	2 (5.4)					2
Soreness	1					1	1					1
Erythema and Soreness	1					1	1					1
Systemic:												
Lymphadenopathy	1 (2.2)	1 (2.2)				2		1 (2.7)				1
Measles-Like Rash		2 (4.3)				2		1 (2.7)				1
Irritability	5 (10.9)	5 (10.9)	1 (2.2)	3 (6.7)	2 (4.4)	10	5 (13.5)	3 (8.1)		2 (5.4)	1 (2.7)	8
Anorexia	9 (19.6)	13 (28.3)	6 (13.0)	7 (15.6)	8 (17.8)	22	8 (21.6)	12 (32.4)	5 (13.5)	6 (16.2)	5 (13.5)	18
Disturbed Sleep		1 (2.2)		2 (4.4)	2 (4.4)	3		1 (2.7)		2 (5.4)	2 (5.4)	3
Fatigue	2 (4.3)	2 (4.3)	1 (2.2)			4	2 (5.4)	1 (2.7)				3
Myalgia		1 (2.2)	1 (2.2)		1 (2.2)	1		1 (2.7)	1 (2.7)		1 (2.7)	1
Upper Respiratory Illness	19 (41.3)	22 (47.8)	20 (43.5)	16 (35.6)	18 (40.0)	35	16 (43.2)	19 (51.4)	17 (45.9)	13 (35.1)	14 (37.8)	28
Otitis		2 (4.3)	3 (6.5)	1 (2.2)		4		2 (5.4)	3 (8.1)	1 (2.7)		4
Ophthalmopathy	1 (2.2)		2 (4.3)	2 (4.4)		3	1 (2.7)		2 (5.4)	2 (5.4)		3
Gastrointestinal Illness	7 (15.2)	6 (13.0)	4 (8.7)	7 (15.6)	9 (20.0)	19	7 (18.9)	5 (13.5)	3 (8.1)	7 (18.9)	7 (18.9)	15
Nonspecific Rash	4 (8.7)	3 (6.5)	1 (2.2)	4 (8.9)	5 (11.1)	9	3 (8.1)	2 (5.4)	1 (2.7)	4 (10.8)	5 (13.5)	7
Other*	2 (4.3)				1 (2.2)	3	2 (5.4)				1 (2.7)	3
Viral Infection					2 (4.4)	2					1 (2.7)	1
Teething		2 (4.3)	1 (2.2)	3 (6.7)	5 (11.1)	8		2 (5.4)	1 (2.7)	3 (8.1)	5 (13.5)	8
Persons with Complaint:	27 (58.7)	29 (63.0)	25 (54.3)	23 (51.1)	23 (51.1)	40	23 (62.2)	24 (64.9)	20 (54.1)	19 (51.4)	17 (45.9)	32
Persons with No Complaint:	19 (41.3)	17 (37.0)	21 (45.7)	22 (48.9)	22 (48.9)	6	14 (37.8)	13 (35.1)	17 (45.9)	18 (48.6)	20 (54.1)	5
Negative Surveillance	1	1	1	2	2	1	1	1	1	1	1	1

*Includes nosebleed, bruise from venipuncture, and ulcers on tongue.

8/11/78

Table 11

Clinical Complaints Reported Among Children Who Received
Combined Live Measles-Rubella (RA 27/3) Virus Vaccine, Lot #62144/C-F022 (Study #514)

Clinical Complaint	Total Vaccinees (45 Children)						Initially Seronegatives (32 Children)					
	Days Post Vaccination					No. with Complaint	Days Post Vaccination					No. with Complaint
	0-4	5-12	13-18	19-28	29-42		0-4	5-12	13-18	19-28	29-42	
Lymphadenopathy		1 (2.3%)				1		1 (3.3)				1
Measles-Like Rash		3 (7.0)	2 (4.7)			4		2 (6.7)	2 (6.7)			3
Headache	1 (2.3)	3 (7.0)	1 (2.3)		1 (2.3)	4		2 (6.7)				2
Irritability	1 (2.3)	2 (4.7)	1 (2.3)			3	1 (3.3)	1 (3.3)				2
Anorexia	3 (7.0)	4 (9.3)	4 (9.3)	3 (7.0)	3 (7.0)	14	3 (10.0)	2 (6.7)	3 (10.0)	3 (10.0)	1 (3.3)	9
Fatigue	2 (4.7)		1 (2.3)			2	2 (6.7)		1 (3.3)			2
Myalgia	2 (4.7)	3 (7.0)	2 (4.7)	1 (2.3)	1 (2.3)	5	1 (3.3)	2 (6.7)	1 (3.3)	1 (3.3)		3
Upper Respiratory Illness	20 (46.5)	17 (39.5)	16 (37.2)	18 (41.9)	14 (32.6)	32	11 (36.7)	10 (33.3)	11 (36.7)	13 (43.3)	10 (33.3)	21
Otitis		1 (2.3)	1 (2.3)		2 (4.7)	3		1 (3.3)	1 (3.3)		2 (6.7)	3
Ophthalmopathy	2 (4.7)	4 (9.3)	2 (4.7)	1 (2.3)	1 (2.3)	6	2 (6.7)	3 (10.0)	2 (6.7)	1 (3.3)	1 (3.3)	5
Gastrointestinal Illness	5 (11.6)	12 (27.9)	7 (16.3)	10 (23.3)	7 (16.3)	21	3 (10.0)	7 (23.3)	4 (13.3)	7 (23.3)	3 (10.0)	13
Nonspecific Rash	4 (9.3)	7 (16.3)	7 (16.3)	9 (20.9)	5 (11.6)	13	1 (3.3)	3 (10.0)	4 (13.3)	6 (20.0)	2 (6.7)	8
Varicella					1 (2.3)	1						0
Other*	1 (2.3)		1 (2.3)			2			1 (3.3)			1
Teething	2 (4.7)	3 (7.0)	2 (4.7)	1 (2.3)	3 (7.0)	8	1 (3.3)	2 (6.7)	1 (3.3)	1 (3.3)	2 (6.7)	5
Persons with Complaint:	25 (58.1)	30 (69.8)	23 (53.5)	21 (48.8)	20 (46.5)	35	15 (50.0)	19 (63.3)	15 (50.0)	15 (50.0)	12 (40.0)	23
Persons with No Complaint:	18 (41.9)	13 (30.2)	20 (46.5)	22 (51.2)	23 (53.5)	8	15 (50.0)	11 (36.7)	15 (50.0)	15 (50.0)	18 (60.0)	7
Negative Surveillance:	2	2	2	2	2	2	2	2	2	2	2	2

* Includes soreness at site of venipuncture and ulcers on tongue.

6/27/78

Table 12

Clinical Complaints Reported Among Children Who Received
Combined Live Measles-Rubella (RA 27/3) Virus Vaccine, Lot #62345/C-F023 (Study #514)

Clinical Complaint	Total Vaccinees (45 Children)						Initially Seronegatives (33 Children)					
	Days Post Vaccination					No. with	Days Post Vaccination					No. with
	0-4	5-12	13-18	19-28	29-42	Complaint	0-4	5-12	13-18	19-28	29-42	Complaint
Injection Site:	1 (2.3%)					1	1 (3.0)					1
Soreness	1					1	1					1
Systemic:												
Measles-Like Rash		4 (9.1)	1 (2.3)			4		3 (9.1)	1 (3.0)			3
Headache	1 (2.3)	2 (4.5)	1 (2.3)	2 (4.5)		2	1 (3.0)	2 (6.1)	1 (3.0)	2 (6.1)		2
Irritability	1 (2.3)	2 (4.5)	1 (2.3)		1 (2.3)	4		2 (6.1)	1 (3.0)		1 (3.0)	3
Anorexia	6 (13.6)	11 (25.0)	3 (6.8)	6 (13.6)	9 (20.5)	17	5 (15.2)	9 (27.3)	2 (6.1)	4 (12.1)	6 (18.2)	13
Fatigue		1 (2.3)				1		1 (3.0)				1
Myalgia			1 (2.3)		1 (2.3)	1			1 (3.0)		1 (3.0)	1
Upper Respiratory Illness	14 (31.8)	25 (56.8)	20 (45.5)	24 (54.5)	19 (43.2)	38	10 (30.3)	19 (57.6)	14 (42.4)	18 (54.5)	13 (39.4)	29
Otitis	1 (2.3)	4 (9.1)	3 (6.8)	2 (4.5)	2 (4.5)	6		3 (9.1)	2 (6.1)	2 (6.1)	1 (3.0)	5
Ophthalmopathy	1 (2.3)	3 (6.8)	1 (2.3)			3	1 (3.0)	1 (3.0)	1 (3.0)			1
Gastrointestinal Illness	7 (15.9)	12 (27.3)	7 (15.9)	5 (11.4)	10 (22.7)	23	5 (15.2)	9 (27.3)	4 (12.1)	3 (9.1)	7 (21.2)	15
Nonspecific Rash	4 (9.1)	5 (11.4)	3 (6.8)	3 (6.8)	3 (6.8)	11	2 (6.1)	3 (9.1)	2 (6.1)	2 (6.1)	3 (9.1)	8
Teething	1 (2.3)	1 (2.3)		2 (4.5)	2 (4.5)	5		1 (3.0)		2 (6.1)	2 (6.1)	4
Persons with Complaint:	22 (50.0)	32 (72.7)	26 (59.1)	27 (61.4)	25 (56.8)	41	16 (48.5)	25 (75.8)	19 (57.6)	21 (63.6)	19 (57.6)	31
Persons with No Complaint:	22 (50.0)	12 (27.3)	18 (40.9)	17 (38.6)	19 (43.2)	3	17 (51.5)	8 (24.2)	14 (42.4)	12 (36.4)	14 (42.4)	2
Negative Surveillance	1	1	1	1	1	1						

6/27/78

Table 13

Clinical Complaints Reported Among Children Who Received
Combined Live Measles-Rubella (RA 27/3) Virus Vaccine, Lot # Unknown (Study #514)

Clinical Complaint	Total Vaccinees (30 Children)						Initially Seronegatives (28 Children)					
	Days Post Vaccination					No. with Complaint	Days Post Vaccination					No. with Complaint
	0-4	5-12	13-18	19-28	29-42		0-4	5-12	13-18	19-28	29-42	
Injection Site:	2 (6.7%)					2	2 (7.1)					2
Erythema	1					1	1					1
Soreness	1					1	1					1
Systemic:												
Lymphadenopathy		1 (3.3)				1		1 (3.6)				1
Measles-Like Rash		4 (13.3)	2 (6.7)			4		4 (14.3)	2 (7.1)			4
Headache		1 (3.3)				1		1 (3.6)				1
Irritability	2 (6.7)	2 (6.7)	1 (3.3)	1 (3.3)	2 (6.7)	4	2 (7.1)	2 (7.1)	1 (3.6)	1 (3.6)	2 (7.1)	4
Anorexia	1 (3.3)	3 (10.0)	2 (6.7)	5 (16.7)	5 (16.7)	9	1 (3.6)	2 (7.1)	2 (7.1)	4 (14.3)	4 (14.3)	8
Fatigue				1 (3.3)	1 (3.3)	1				1 (3.6)	1 (3.6)	1
Upper Respiratory Illness	18 (60.0)	14 (46.7)	11 (36.7)	13 (43.3)	19 (63.3)	26	18 (64.3)	13 (46.4)	11 (39.3)	12 (42.9)	18 (64.3)	24
Lower Respiratory Illness					1 (3.3)	1					1 (3.6)	1
Otitis				1 (3.3)		1				1 (3.6)		1
Ophthalmopathy	1 (3.3)	2 (6.7)	2 (6.7)			3	1 (3.6)	2 (7.1)	2 (7.1)			3
Gastrointestinal Illness	3 (10.0)	6 (20.0)	3 (10.0)	5 (16.7)	5 (16.7)	14	3 (10.7)	5 (17.9)	3 (10.7)	5 (17.9)	5 (17.9)	13
Nonspecific Rash	1 (3.3)	1 (3.3)	1 (3.3)		3 (10.0)	5	1 (3.6)	1 (3.6)	1 (3.6)		3 (10.7)	5
Bell's Palsy				1 (3.3)		1				1 (3.6)		1
Teething	2 (6.7)		3 (10.0)	3 (10.0)	1 (3.3)	7	2 (7.1)		3 (10.7)	3 (10.7)	1 (3.6)	7
Persons with Complaint:	21 (70.0)	20 (66.7)	13 (43.3)	17 (56.7)	22 (73.3)	28	21 (75.0)	18 (64.3)	13 (46.4)	16 (57.1)	20 (71.4)	26
Persons with No Complaint:	9 (30.0)	10 (33.3)	17 (56.7)	13 (43.3)	8 (26.7)	2	7 (25.0)	10 (35.7)	15 (53.6)	12 (42.9)	8 (28.6)	2

6/27/78

MEMO

To File Location Date 8/14/78

From T. Schofield Location

Subject Statistical Analysis - Study #514

Significant differences in seroconversion rates for measles and rubella and clinical reaction rates among vaccinees receiving three lots of combined measles-rubella (RA 27/3) vaccine were investigated. Lots of vaccine were:

Lot #62343/C-F021
Lot #62344/C-F022
Lot #62345/C-F023

No significant differences exist among the three lots for any of these rates.

The groups (lots) were investigated for statistical differences in post-vaccination titer among vaccinees who were initially seronegative to both measles and rubella by the HI test. Multivariate analysis of variance was run in conjunction with the Kruskal-Wallis k-sample test on the individual components. No significant differences could be determined among the three lots of vaccine.

T.S.