

PRODUCT LICENSE APPLICATION

PLA-0002-XXX-CY04 *Val Q*

MERCK & CO., INC.

Measles, Mumps and Rubella Virus Vaccine Live



DCC Volume Sequence No. 157802

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Original  
Application

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**MERCK  
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MANUFACTURING DIVISION

*Division of Merck and Co., Inc.  
West Point, Penna. 19486*

September 26, 1969

Dr. Roderick Murray, Director  
Division of Biologics Standards  
National Institutes of Health  
Bethesda, Maryland 20014

Dear Doctor Murray:

Enclosed is our Application and Report for Measles-Mumps-Rubella Virus Vaccine, Live, Combined, for which we respectfully request a license to market the product.

Samples and protocols for Lot Nos. 59795/92126, 59796/92127, and 61584/96400 are being supplied at this time; the several components in the combined vaccine are noted at the top of each protocol.

A summary of the clinical data is included in this submission, which clearly indicates the safety, purity and efficacy of this combined product.

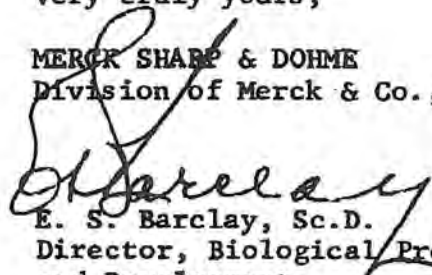
The label, carton, and package circular are in the process of being developed and will be submitted at a later date.

We shall appreciate your early review of this application so that we may determine if there are any areas of omission and possible adjustment to meet the needs of qualifying for a license.

With kindest personal regards,

Very truly yours,

MERCK SHARP & DOHME  
Division of Merck & Co., Inc.

  
E. S. Barclay, Sc.D.  
Director, Biological Production  
and Development

/mb



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MERCK INSTITUTE  
FOR  
THERAPEUTIC RESEARCH  
WEST POINT, PENNSYLVANIA 19486

MAURICE R. HILLEMAN, Ph. D., D. Sc.  
EXECUTIVE DIRECTOR

September 26, 1969

Dr. Roderick Murray, Director  
Division of Biologics Standards  
National Institutes of Health  
Bethesda, Maryland 20014

Dear Doctor Murray:

Very shortly, you will receive from Dr. E. S. Barclay, Summary No. 1 of clinical investigative studies of combined live measles virus vaccine (Moraten line - ATTENUVAX), Jeryl Lynn mumps virus vaccine (MUMPSVAX) and HPV-77 duck rubella virus vaccine (MERUVAX), dated September 26, 1969.

Essentially, this vaccine represents a premixed combined formulation of three previously licensed vaccines. It appears to us that the serologic responses and clinical reactions are within expectation and are acceptable for routine use. I should add that data will be submitted for a second consistency lot of measles-mumps-rubella combined vaccine at a later date (Lot #92126).

Further details relating to the clinical studies are to be found in your file of submissions under DBS-IND 260, in the files of this department, and in the files of the individual clinicians. Any further information you may want will be made available to you upon request.

Kindest regards.

Sincerely yours,



Maurice R. Hilleman, Ph.D.  
Director  
Virus & Cell Biology Research

cc: Dr. Barclay

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NATIONAL INSTITUTE OF HEALTH

SEP 23 10 55 AM '69

Consistency lot prepared by Merck Sharp & Dohme  
Biologics Manufacturing:

59796/92127

Protocols are submitted in Section 4.

4. Serologic Testing

The serologic determinations were made in the laboratories of Virus & Cell Biology Research, Merck Institute, and in the Control Laboratories of the Merck Sharp & Dohme Division of Merck & Co. The testing program was carried out blind.

The hemagglutination-inhibition test was used to determine the measles and rubella antibody responses, and the serum neutralization test was used to measure mumps antibody response.

5. Clinical Studies

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 aspects necessary to permit data analysis.

Subjects in the sampled groups were bled initially and again six weeks later. The sera were tested to define the initial serostatus and the antibody status following vaccination.

Clinical surveillance was by two procedures. In the studies by Dr. Stokes, the observations were made by the mothers, nurses and physicians. In the studies by Dr. Villarejos, observations were made by physicians and nurses with notification of the medical staff by parents and guardians of any significant illness that may have occurred subsequent to vaccination.

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

In the Costa Rican studies, less than one-third of the specimens have been serologically tested. Statistical extrapolation can be made to the total group. It should be pointed out, however, that the remainder of the sera are being tested. In addition, susceptible contacts will be surveyed for possible contact transmission of rubella based on titer rise. These additional data will be reported later.

6. Clinical Study Summaries

Reference 1 - Study 159 - Drs. Joseph Stokes and Robert E. Weibel

The detailed findings for this field-mix vaccine trial are summarized in a published paper, "Combined Live Measles, Mumps and Rubella Virus Vaccines." This paper is included as reference material.

Reference 2 - Study 212 - Drs. Joseph Stokes and Robert E. Weibel

Details of the study plan are given in the clinical test protocol. The findings are self-explanatory. Essentially, we may conclude that the antibody responses were not impaired by combining the three vaccines.

Reference 3 - Study 220 - Dr. Victor Villarejos

Details of the study plan are given in the clinical test protocol. The study was designed to measure the ability of the combined vaccine to elicit antibody response to the three viruses.

Preliminary findings are summarized in the tables and are self-explanatory. The combined vaccine gave satisfactory results in terms of antibody response, and the clinical reactions did not exceed those expected for measles vaccine alone.

7. Vaccine Manufacturing Protocols

Non-Responsive Not Clinical

69-192

Summary No. 1  
of  
Clinical Investigative Studies  
of

Combined Live Measles Virus Vaccine (Moraten Line - ATTENUVAX)

Jeryl Lynn Mumps Virus Vaccine (MUMPSVAX)

HPV-77 Duck Rubella Virus Vaccine (MERUVAX)

for purpose of support for  
a license to manufacture and sell



M. R. Hilleman, Ph.D.

Prepared: September 26, 1969  
Merck Institute for Therapeutic  
Research  
West Point, Pennsylvania

Clinical Investigation of Combined Live Attenuated Measles (Moraten),  
Mumps (Jeryl Lynn) and Rubella (HPV-77 Duck) Vaccine

1. Background

Increasing demands for immunization have made it necessary to simplify the vaccination procedure in order to conserve medical personnel, limit the number of patient visits, and reduce costs. One means toward this end is to combine live measles, mumps and rubella vaccines.

These three vaccines, which have been combined into a premixed and dried product, are licensed. The Moraten measles vaccine was licensed on November 26, 1968 and is sold under the trade name of ATTENUVAX. The Jeryl Lynn mumps vaccine, sold under the trade name of MUMPSVAX, was licensed on December 28, 1967. The HPV-77 rubella duck vaccine was licensed on June 9, 1969 and is sold under the trade name of MERUVAX.

The present submission relates to clinical tests of two lots of the combined vaccine, one of which was experimental (Lot 310) and the other was a consistency lot (Lot 92127).

2. Responsible Investigators

The clinical studies were carried out under the responsibility and overall supervision of Dr. Maurice R. Hilleman, Executive Director, Division of Virus & Cell Biology Research, Merck Institute for Therapeutic Research, West Point, Pa. Dr. Hilleman made arrangements with the responsible physicians in the field, outlined the study plans, and assisted in the collation and analysis of the data.

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

- a) Dr. Joseph Stokes, Jr. and Dr. Robert E. Weibel of the Department of Pediatrics, School of Medicine, University of Pennsylvania, Philadelphia, Pa.
- b) Dr. Victor Villarejos, Program Coordinator, Louisiana State University, International Center for Medical Research and Training, San Jose, Costa Rica

All testing was done under DBS-IND 260.

3. Lot Numbers of Vaccine Tested

Experimental lot  
Lot 310 (C-7358)



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# Combined Live Measles, Mumps, and Rubella Virus Vaccines

Eugene B. Buynak, PhD; Robert E. Weibel, MD; James E. Whitman, Jr., PhD;  
Joseph Stokes, Jr., MD, DSc; and Maurice R. Hilleman, PhD, DSc

Combined trivalent Moraten measles, Jeryl Lynn mumps, and HPV-77 duck embryo rubella vaccine, as well as combined bivalent Moraten measles and Jeryl Lynn mumps vaccine were each administered to children in a single injection. The antibody responses to the three viruses were not significantly altered, and the clinical reactions were no greater than those following measles vaccine given alone. Choice of strain was important, since less favorable results were obtained when the original Enders' measles and Merck C level rubella vaccines were substituted for those mentioned previously. Twenty and forty 50% tissue culture infective doses of Moraten measles and HPV-77 duck rubella viruses, respectively, sufficed to immunize all seronegative persons. All the viruses induced persistent antibody and were sufficiently stable on drying and rehydration to permit use in routine practice. Present evidence indicates that the mumps and rubella vaccines may be given together with the measles vaccine in a single dose without impairing the immune response and without added clinical reaction.

The proliferation of live-virus vaccines in recent years renders it highly desirable to develop methods which will simplify administration, reduce cost, and minimize the number of required contacts of the patient with the physician. Recently, a combined Enders' measles-smallpox vaccine developed by us<sup>1,2</sup> was licensed for general use. Further studies in this area showed the feasibility of administering measles, mumps, and rubella vaccines or of measles

and mumps vaccines in combined dosage forms given in a single injection. In the studies, the Jeryl Lynn strain live attenuated mumps virus vaccine,<sup>3,7</sup> which was licensed for general distribution in January 1968, and the HPV-77<sup>8,10</sup> strain rubella virus vaccine propagated in duck embryo cell culture were employed. The measles virus which was used was either Enders' original Edmonston strain<sup>11</sup> or the new Moraten line<sup>12</sup> of Edmonston virus which was developed here. The latter virus has been shown<sup>13,14</sup> to be so highly attenuated as to cause only minor clinical reaction in susceptible children, though still effecting adequate immunization. The findings relating to the use as single injections of these combined vaccines are the principal subject of this communication.

One essential facet in the development of any monovalent or polyvalent vaccine is the determination of the least quantity of virus required to immunize human beings. The results of such titrations of Enders' measles<sup>1</sup> and of mumps vaccine<sup>4</sup> were reported earlier. Titration findings in similar tests of Moraten measles and of HPV-77 (duck) rubella vaccine are given in this communication. Additionally, data are included relating to the durability of antibody following administration of Moraten compared with other measles vaccines and to the stability of the infectivity of dried and of the rehydrated rubella virus vaccine.

## Methods

The children who were included in the study were from families residing in the Havertown-Springfield suburb of Philadelphia and were vaccinated either in the outpatient clinic of the Lankenau Hospital or in groups in the suburban community. The children ranged in age from 10 months to 13 years with a mean age of 3.8 years and were selected for appro-

From the Division of Virus and Cell Biology Research, Merck Institute for Therapeutic Research, West Point, Pa (Drs. Buynak, Whitman, and Hilleman); and the Department of Pediatrics, School of Medicine, University of Pennsylvania, Philadelphia (Drs. Weibel and Stokes).

Reprint requests to Division of Virus and Cell Biology Research, Merck Institute for Therapeutic Research, West Point, Pa 19486 (Dr. Buynak).

Table 1.—Serologic\* Responses in Initially Seronegative Children Given Experimental or Control Vaccines

| Study No. | Vaccine Kind          | TCID <sub>50</sub> † Per Dose | Homologous Antibody Response |     |        |     |
|-----------|-----------------------|-------------------------------|------------------------------|-----|--------|-----|
|           |                       |                               | Serocconversion              |     | Titer‡ |     |
|           |                       |                               | Rate                         | %   | Range  | GM§ |
| 159       | Trivalent (field mix) | 14,000                        | 28/28                        | 100 | 10-160 | 51  |
|           | Moraten measles       | 6,000                         | 26/28                        | 93  | <1-128 | 8   |
|           | HPV-77 rubella        | 700                           | 28/28                        | 100 | 8-512  | 134 |
| 154       | Bivalent (premix)     | 4,000                         | 37/38                        | 97  | <5-640 | 89  |
|           | Moraten measles       | 3,000                         | 37/38                        | 97  | <1-64  | 7   |
|           | Monovalent (controls) | 4,000                         | 7/7                          | 100 | 20-160 | 54  |
| 92        | Bivalent (premix)     | 9,000                         | 29/29                        | 100 | 2-128  | 7   |
|           | Enders' measles       | 1,600                         | 13/13                        | 100 | 20-640 | 61  |
|           | Jeryl Lynn mumps      | 1,600                         | 10/13                        | 77  | <1-32  | 5   |
|           | Monovalent (controls) | 10,000                        | 29/29                        | 100 | 20-160 | 63  |
|           | Enders' measles       | 9,000                         | 22/22                        | 100 | 1-16   | 6   |
|           | Jeryl Lynn mumps      |                               |                              |     |        |     |

\*Recipients of trivalent vaccine were initially seronegative to all three viruses and those receiving bivalent vaccine were seronegative to the two viruses.

†Fifty percent tissue culture infective dose of virus.

‡For measles vaccine, hemagglutination inhibition (HI) titer determined; for mumps, neutralizing; and for rubella, HI.

§Geometric mean.

Table 2.—Maximal Temperatures and Rash on Days 5 to 12 After Vaccination Among Children Who Received Polyvalent or Monovalent Control Vaccines

| Study No. | Vaccine               | Persons Who Showed Maximum Temperature or Rash, No. (%) |                            |                             |                             |              |
|-----------|-----------------------|---------------------------------------------------------|----------------------------|-----------------------------|-----------------------------|--------------|
|           |                       | Temperature                                             |                            |                             |                             | Measles Rash |
|           |                       | <99.0 F (37.2 C)                                        | 99.0-100.9 F (37.3-38.3 C) | 101.0-102.9 F (38.3-39.4 C) | 103.0-104.5 F (39.4-40.5 C) |              |
| 159       | Trivalent (field mix) | 9 (32.1%)                                               | 15 (53.6%)                 | 4 (14.3%)                   | ...                         | 1 (3.6%)     |
|           | Bivalent (premix)     | 20 (52.6%)                                              | 14 (36.8%)                 | 4 (10.5%)                   | ...                         | 1 (2.6%)     |
|           | Moraten measles       | 5 (71.4%)                                               | 1 (14.3%)                  | 1 (14.3%)                   | ...                         | 1 (14.3%)    |
| 92        | Bivalent (premix)     | 16 (55.2%)                                              | 12 (41.4%)                 | ...                         | 1 (3.4%)                    | ...          |
|           | Enders' measles       | 7 (24.1%)                                               | 3 (23.1%)                  | 8 (61.5%)                   | 2 (15.4%)                   | 4 (30.8%)    |
|           | Jeryl Lynn mumps      | 13 (59.1%)                                              | 8 (27.6%)                  | 8 (27.6%)                   | 6 (20.7%)                   | 1 (3.4%)     |

Table 3.—Titration of Live Moraten Measles Vaccine Lot 254 in Measles-Seronegative Children

| Dilution         | Vaccine | HI† Antibody Titer After Vaccination (No. of Persons) |    |    |    |     |     | No. Responding Per Total | % Responding | Geometric Mean Titer |
|------------------|---------|-------------------------------------------------------|----|----|----|-----|-----|--------------------------|--------------|----------------------|
|                  |         | TCID <sub>50</sub> */Dose                             | 10 | 20 | 40 | 80  | 160 |                          |              |                      |
| 10 <sup>-1</sup> | 2,000   | 1                                                     | 2  | 2  | 1  | 2   | ... | 8/8                      | 100          | 43.6                 |
| 10 <sup>-2</sup> | 200     | 1                                                     | 1  | 2  | 4  | ... | 1   | 9/9                      | 100          | 54.4                 |
| 10 <sup>-3</sup> | 20      | 1                                                     | 2  | 5  | 3  | ... | ... | 11/11                    | 100          | 37.6                 |

\*Fifty percent tissue culture infective dose.

†Hemagglutination inhibition.

private negative history of vaccination or illness with respect to measles, mumps, and rubella. Informed written parental consent was obtained. The monovalent Moraten measles, mumps, and rubella vaccines were prepared as described earlier<sup>9,10,14</sup>; Enders' live, attenuated, Edmonston B measles virus vaccine was from material prepared for commercial distribution (Lyovac Rubeovax). The combined vaccines were either mixed at the field site (field mix) or were mixed prior to lyophilization (premix). Vaccines used in the titrations were diluted in the clinic immediately prior to use, and samples were refrigerated and returned to the laboratory for virus infectivity determinations. The combined vaccines were given subcutaneously in a 1.0-ml dose, and the monovalent vaccines were administered in a 0.5-ml amount. The parents of the children were given a report card for each child for recording temperatures

once daily, plus any other illness, and they were asked to notify one of us (R. E. W.) immediately when any illness occurred.

## Results

**Combined Vaccines.**—Children were given the combined or single measles, mumps, and rubella virus vaccines shown in Table 1. All of the children who received the trivalent vaccine in study 159 developed antibody against measles and rubella viruses, and all but two of the children showed a response to the mumps vaccine. Thus, there was a response against all three viruses in 93% of the initially triple-negative children. The mean antibody titers were of the range expected if these vaccines had been given alone.

The performance of the premixed, bivalent Moraten measles-mumps vaccine (study 154) was equally satisfactory, and the mean titers approximated those which were obtained when the individual vaccines were given alone. The response to the mumps vaccine (study 92) when combined with Enders' rather than Moraten vaccine was somewhat less (77%) than when the mumps vaccine was given alone, while the response to the measles vaccine was unaffected. A similar result was obtained with mumps virus in another study, not recorded here, in which Moraten measles vaccine was combined with mumps vaccine. Such failure appeared related in part to the time interval which elapsed after vaccination before the blood samples were taken, and it appeared that the conventional 28-day period will need to be lengthened to detect the full antibody response to the mumps vaccine. In still another study, the response to rubella vaccine in a trivalent mixture of Moraten measles, mumps, and

Merck C level rubella vaccines was poor. From these data it appeared that not only the virus strain but also the level of attenuation may be important in determining antibody responses when the vaccines are competing against one other in a single combined form. The relative amount of each virus per dose may also be important.

The clinical reactions to the various combined and monovalent vaccines are summarized in Table 2. These are shown for the period of 5 to 12 days following vaccination, which is the critical time period for occurrence of the clinical reactions. The mumps and rubella vaccines given alone cause no discernible clinical reaction in children.<sup>9,7,11,12</sup> Their inclusion with the Moraten measles vaccines did not increase the clinical reaction. Children given Enders' measles vaccine with mumps vaccine showed a greater febrile response than did those receiving the measles



vaccine alone. Whether this is significant or whether it merely reflects the small numbers of children included in the studies remains to be seen.

**Monovalent Moraten Measles Vaccine.**—VACCINE TITRATION.—Twenty-eight children who were initially seronegative for measles and who ranged in age from 1 to 9 years (average: 4 years) were given Moraten measles vaccine in viral doses of the varying amounts shown in Table 3. It is seen that all children developed measles hemagglutination inhibition (HI) antibody after they received Moraten vaccine of varying dosage ranging from 2,000 to 20 fifty percent tissue culture infective doses (TCID<sub>50</sub>). The mean titers of antibody following vaccination were remarkably similar, irrespective of virus dose, considering the sizes of the individual groups. The clinical reactions which were observed were the same as reported heretofore.

**ANTIBODY PERSISTENCE.**—A previous report<sup>14</sup> described a study which was carried out to compare the clinical reactions and serologic responses among groups of 250 to 273 initially seronegative children who were given Enders' original Edmonston measles vaccine, the Moraten-line vaccine, or Schwarz vaccine. The geometric mean antibody titers one month following vaccination were 1:25, 1:16.3, and 1:16.1, respectively, for the three vaccines. Groups of 83 to 92 children were selected at random, and blood samples were taken one year following vaccination. The HI titers of these particular sera taken one month and one year after vaccination were determined, and the findings are shown in the Figure. The antibody levels were retained remarkably well and generally paralleled those found in individuals who have had natural measles. The decline in mean titer was least for Enders' vaccine (1.4-fold or 30.6%) and greatest for Schwarz vaccine (1.9-fold or 47.2%), while that for Moraten was intermediate (1.7-fold or 41.3%).

**Monovalent Rubella Virus Vaccine.**—VACCINE TITRATION.—Fifty-five children who were initially seronegative for rubella and who ranged in age from 3 to 7 years (average: 4.3 years) were given HPV-77 duck rubella vaccine in dosages of virus shown in Table 4. It is seen that 40 TCID<sub>50</sub> sufficed to cause seroconversion in all subjects, and that 12.5 doses were insufficient for this purpose. The geometric mean HI antibody titers were approximately comparable in those virus dosages which were adequate to effect 100% seroconversion. None of the children had a clinical reaction which was referable to the vaccine.



Comparison of measles hemagglutination inhibition (HI) antibody titers of serum samples taken one month and one year after vaccination. All children were initially seronegative for measles. GM signifies geometric mean.

Table 4.—Titration of Live Rubella (HPV-77+5 Duck) Vaccine Lot 267 in Rubella-Seronegative Children

| Vaccine | Dilution           | TCID <sub>50</sub> * /Dose | HI† Antibody Titer After Vaccination (No. of Persons) |     |     |     |    |     |     |     |     |       | No. Responding Per Total | % Responding | Geometric Mean Titer |
|---------|--------------------|----------------------------|-------------------------------------------------------|-----|-----|-----|----|-----|-----|-----|-----|-------|--------------------------|--------------|----------------------|
|         |                    |                            | <8                                                    | 8   | 16  | 32  | 64 | 128 | 256 | 512 |     |       |                          |              |                      |
|         | 10 <sup>0</sup>    | 1,250.0                    | ...                                                   | ... | ... | 3   | 3  | 6   | ... | ... | ... | 12/12 | 100                      |              | 76.1                 |
|         | 10 <sup>-0.5</sup> | 400.0                      | ...                                                   | ... | ... | 2   | 6  | 3   | 2   | ... | ... | 13/13 | 100                      |              | 83.5                 |
|         | 10 <sup>-1.0</sup> | 125.0                      | ...                                                   | ... | 2   | 2   | 2  | 3   | 1   | 1   | ... | 11/11 | 100                      |              | 72.6                 |
|         | 10 <sup>-1.5</sup> | 40.0                       | ...                                                   | ... | ... | 3   | 4  | 1   | ... | ... | ... | 8/8   | 100                      |              | 53.8                 |
|         | 10 <sup>-2.0</sup> | 12.5                       | 5                                                     | ... | ... | ... | 3  | 3   | ... | ... | ... | 6/11  | 54.5                     |              | 11.7                 |

\*Fifty percent tissue culture infective dose.  
†Hemagglutination inhibition.

Table 5.—Stability of Infectivity on Storage of Dried Rubella Vaccine\* Prior to and After Rehydration

| Length of Storage Period | Negative Log <sub>10</sub> Infectivity Titer per 0.1 ml |                 |                 |                  |                                         |                 |                 |  |
|--------------------------|---------------------------------------------------------|-----------------|-----------------|------------------|-----------------------------------------|-----------------|-----------------|--|
|                          | Dried Vaccine, Storage Temperature                      |                 |                 |                  | Rehydrated Vaccine, Storage Temperature |                 |                 |  |
|                          | 39.2 F (4.0 C)                                          | 78.8 F (26.0 C) | 96.8 F (36.0 C) | 132.8 F (56.0 C) | 39.2 F (4.0 C)                          | 78.8 F (26.0 C) | 96.8 F (36.0 C) |  |
| 0                        | 2.6                                                     | 2.6             | 2.6             | 2.6              | 2.6                                     | 2.6             | 2.6             |  |
| 1 hr                     | ...                                                     | ...             | ...             | ...              | 2.5                                     | 2.5             | 2.5             |  |
| 2 hr                     | ...                                                     | ...             | ...             | ...              | 2.7                                     | 2.7             | 2.1             |  |
| 4 hr                     | ...                                                     | ...             | ...             | 2.5              | 2.7                                     | 1.9             | 1.7             |  |
| 6 hr                     | ...                                                     | ...             | ...             | 1.9              | 2.7                                     | 1.7             | 1.9             |  |
| 8 hr                     | ...                                                     | ...             | ...             | 1.7              | 2.7                                     | 1.1             | 1.5             |  |
| 1 day                    | ...                                                     | ...             | 2.7             | 1.5              | 2.7                                     | <0              | <0              |  |
| 3 day                    | ...                                                     | ...             | 2.7             | ...              | ...                                     | ...             | ...             |  |
| 7 day                    | ...                                                     | 2.9             | 2.1             | ...              | ...                                     | ...             | ...             |  |
| 9 day                    | ...                                                     | ...             | 2.3             | ...              | ...                                     | ...             | ...             |  |
| 14 day                   | ...                                                     | 1.9             | 2.1             | ...              | ...                                     | ...             | ...             |  |
| 28 day                   | ...                                                     | 2.7             | ...             | ...              | ...                                     | ...             | ...             |  |
| 42 day                   | ...                                                     | 2.7             | ...             | ...              | ...                                     | ...             | ...             |  |
| 3 mo                     | 2.3                                                     | ...             | ...             | ...              | ...                                     | ...             | ...             |  |
| 6 mo                     | 2.7                                                     | ...             | ...             | ...              | ...                                     | ...             | ...             |  |
| 9 mo                     | 2.7                                                     | ...             | ...             | ...              | ...                                     | ...             | ...             |  |
| 12 mo                    | 2.5                                                     | ...             | ...             | ...              | ...                                     | ...             | ...             |  |
| 15 mo                    | 2.4                                                     | ...             | ...             | ...              | ...                                     | ...             | ...             |  |

\*Live, attenuated, duck, rubella vaccine (HPV-77).

**STORAGE STABILITY OF THE RUBELLA VACCINE.**—Dried HPV-77 lot 267 duck vaccine and rehydrated vaccine of the same lot were stored at various temperatures for the time periods shown in Table 5. The dried vaccine appeared to be stable, at least for the time periods shown, at temperatures of 96.8 F (36.0 C) or lower but the titer was apparently reduced after four hours' storage at 132.8 F (56.0 C). The virus was stable at 39.2 F (4.0 C) for at least one day following rehydration. The titer appeared to be reduced somewhat after two hours storage at 78.8 F (26.0 C) and after one hour at 96.8 F.

## Comment

The antibody responses to vaccination which were obtained in this study show satisfactory immunization of children with combined trivalent Moraten measles, Jeryl Lynn mumps, and HPV-77 duck rubella vaccine and with combined, bivalent Moraten measles and Jeryl Lynn mumps vaccine. The combining of the live viruses produced no apparent suppression in immune responses. Furthermore, the clinical reactions which occurred following administration of the combined vaccines were no greater than were obtained when Moraten measles vaccine was given alone. Though the data are limited and require confirmation in large numbers of children, it would appear that Moraten measles, Jeryl Lynn mumps, and HPV-77 duck rubella vaccines or Moraten measles and Jeryl Lynn mumps vaccines can be formulated into single preparations for administration in a single injection. The infectiousness of each of the three viruses is sufficiently stable on drying and after rehydration to permit routine use in clinical practice. Thus, it may be expected that the mumps and rubella vaccines may be given with the measles vaccine in a single dose without added clinical reaction. The particular strain of virus and level of attenuation used in the combinations may be of considerable importance in modifying serologic and clinical responses, as noted when the Enders' measles and more highly attenuated Merck C level vaccines were substituted for Moraten measles and HPV-77 rubella vaccines. The numbers are small, however, and judgment must be reserved.

It was shown previously in virus titrations<sup>11</sup> in man that 45 TCID<sub>50</sub> of virus sufficed to immunize 100% of the susceptible children when Enders' original Edmonston measles vaccine was used, and that 317 doses of virus were sufficient for mumps vaccine.<sup>7</sup> The present study shows that 20 virus doses were adequate to immunize 100% of the children with Moraten measles virus and that 40 doses of virus were required with the HPV-77 duck rubella vaccine. Thus, only small amounts of virus are actually required for immunization with any one of these vaccines.

Live virus vaccines, to be completely acceptable, ought to provide long-term or lifelong immunity following vaccination, and this seems to be well-established for Enders' measles vaccine. A recent report<sup>18</sup> of follow-up on Jeryl Lynn mumps vaccine has shown durable protection against natural mumps infection through the third mumps year and a persistence of mumps-neutralizing antibody which parallels that in persons who have had natural mumps. The present study revealed that levels of antibody in subjects who received Moraten measles vaccine were still satisfactory one year after vaccination. Studies by Meyer et al<sup>19</sup> and by our group<sup>10</sup> indicate that rubella antibody induced by vaccine virus will also be lasting. It seems probable, therefore, that the technical means are at hand for eventual elimination of these three illnesses from the population of the United

States and possibly also from that of other parts of the world where properly applied.

The following institutions cooperated in this investigation: the Delaware County Children's Day Care Center, Lankenau Hospital, Lansdowne Presbyterian Church, and St. Philomena's Church.

Medical assistance was given by J. Wallace Cleland, MD; J. Ronald Halenda, MD; George Starkweather, MD; and Edward H. Vick, MD.

Technical assistance was given by R. Roehm, D. Morton, J. Haldia, K. Guckert, M. Mages, and M. J. Kim.

Summaries and statistical computations were given by A. McLean, MS, and B. Abbott.

## Generic and Trade Names of Drug

Measles virus vaccine, live, attenuated, Edmonston B—Lyovac Rubrovax, M-Vac, Pfizer-Vax Measles-L.

## References

1. Weibel, R.E., et al: Clinical-Laboratory Experiences With Combined Dried Live Measles-Smallpox Vaccine, *Pediatrics* 37: 913-920 (June) 1966.
2. Kalebic, F., et al: Standardization and Mass Application of Combined Live Measles-Smallpox Vaccine in Upper Volta, *Amer J Epidemiol* 86:93-111 (July) 1967.
3. Buynak, E.B., and Hilleman, M.R.: Live Attenuated Mumps Virus Vaccine: I. Vaccine Development, *Proc Soc Exp Biol Med* 123:768-775 (Dec) 1966.
4. Stokes, J., Jr., et al: Live Attenuated Mumps Virus Vaccine: II. Early Clinical Studies, *Pediatrics* 39:363-371 (March) 1967.
5. Weibel, R.E., et al: Live, Attenuated Mumps-Virus Vaccine: III. Clinical and Serologic Aspects in a Field Evaluation, *New Eng J Med* 276:245-251 (Feb 2) 1967.
6. Hilleman, M. R., et al: Live, Attenuated Mumps-Virus Vaccine: IV. Protective Efficacy as Measured in a Field Evaluation, *New Eng J Med* 276:252-258 (Feb 2) 1967.
7. Hilleman, M.R., et al: Live, Attenuated Mumps-Virus Vaccine, *New Eng J Med* 276:227-232 (Feb 1) 1968.
8. Parkman, P.D., et al: Attenuated Rubella Virus: I. Development and Laboratory Characterization, *New Eng J Med* 275:568-754 (Sept 15) 1966.
9. Meyer, H.M., Jr.; Parkman, P.D.; and Paos, T.C.: Attenuated Rubella Virus: II. Production of an Experimental Live-Virus Vaccine and Clinical Trial, *New Eng J Med* 275:575-580 (Sept 15) 1966.
10. Buynak, E.B., et al: Live Attenuated Rubella Virus Vaccines Prepared in Duck Embryo Cell Culture: I. Development and Clinical Testing *JAMA* 204:195-200 (April 15) 1968.
11. Weibel, R.E., et al: Live Attenuated Rubella Virus Vaccines Prepared in Duck Embryo Cell Culture: II. Clinical Tests in Families and in an Institution, *JAMA* 205:554-558 (Aug 19) 1968.
12. Hilleman, M.R., et al: Live, Attenuated Rubella-Virus Vaccine, *New Eng J Med* 279:300-303 (Aug 8) 1968.
13. Enders, J.F., et al: Studies on an Attenuated Measles-Virus Vaccine: I. Development and Preparation of the Vaccine: Techniques for Assay of Effects of Vaccination, *New Eng J Med* 283:153-164 (July 28) 1960.
14. Hilleman, M.R., et al: Development and Evaluation of the Moraten Measles Virus Vaccine, *JAMA* 205:587-590 (Oct 14) 1968.
15. Krugman, S., et al: Comparison of Two Further Attenuated Live Measles-Virus Vaccines, *Amer J Dis Child*, to be published.
16. Swartz, T., et al: A Comparative Study of Four Live Measles Vaccines in Israel, *Bull WHO*, to be published.
17. Weibel, R., et al: Administration of Enders' Live Measles Virus Vaccine With Human Immune Globulin, *JAMA* 180:1086-1094 (June 30) 1962.
18. Weibel, R.E., et al: Jeryl Lynn Strain Live Mumps Virus Vaccine: Durable Immunity for Three Years Following Vaccination, *JAMA*, to be published.
19. Meyer, H.M., Jr., et al: Clinical Studies With Experimental Live Rubella Virus Vaccine (Strain HPV-77): Evaluation of Vaccine-Induced Immunity, *Amer J Dis Child* 115:648-654 (June) 1968.



Measles-Mumps-Rubella Virus Vaccine, Study 212

Live Measles-Mumps-Rubella Virus Vaccine

Lot 310

Responsible Clinical Investigator:

Joseph Stokes, Jr., M.D., D.Sc.\*

Location:

The Lankenau Hospital Outpatient Department  
Philadelphia, Pa.

Population:

Children residing in the community. 39 children  
with a negative history of measles, mumps and  
rubella were vaccinated with 1.0 ml. of the  
combined vaccine

\* Department of Pediatrics, School of Medicine  
University of Pennsylvania  
Philadelphia, Pa.

9/23/68

# CLINICAL TEST PROTOCOL

Protocol: Mixed Live Virus Vaccines, Study No. 212

Program: Live Virus Vaccines

Purpose: Measure clinical and serologic responses to premix combined live vaccines.

Moraten measles-Jeryl Lynn mumps-rubella (HPV-77+5 Duck)

Jeryl Lynn mumps-rubella (HPV-77+5 Duck)

Materials: 1. Lot 310 (C-7358) Combined live measles-mumps-rubella

## Infectivity of components

Moraten measles  $10^{3.4}$  TCID<sub>50</sub>/1.0 ml dose  
Non-Responsive Not  
Clinical

Jeryl Lynn mumps  $10^{3.7}$  TCID<sub>50</sub>/1.0 ml dose  
Non-Responsive Not Clinical

Rubella (HPV-77+ 5 Duck)  $10^{2.8}$  TCID<sub>50</sub>/1.0 ml dose  
Non-Responsive Not  
Clinical

2. Lot 311 (C-7359) Combined live mumps-rubella

## Infectivity of components

Jeryl Lynn mumps  $10^{3.9}$  TCID<sub>50</sub>/1.0 ml dose  
Non-Responsive Not Clinical

Rubella (HPV-77+ 5 Duck)  $10^{2.9}$  TCID<sub>50</sub>/1.0 ml dose  
Non-Responsive Not  
Clinical

3. Lot 266 (C-6267) live Jeryl Lynn mumps

$10^{3.4}$  TCID<sub>50</sub>/0.5 ml dose  
Non-Responsive Not Clinical

Procedure: 1. Rehydrate all lots with 1.2 ml of sterile distilled water.

2. The dose for:

Lot 310 (measles-mumps-rubella) is 1.0 ml given subcutaneously.

Lot 311 (mumps-rubella) is 1.0 ml given subcutaneously.

Lot 266 (mumps) is 0.5 ml given subcutaneously.

3. Choose:

25-35 subjects likely to be triple-negative to measles, mumps and rubella.

25-35 subjects likely to be double-negative to mumps and rubella.

25 subjects likely to be negative to mumps.

4. Regimen:

| Day     | Activity |                              |                           |                         |
|---------|----------|------------------------------|---------------------------|-------------------------|
|         | Bleed    | Group A                      | Group B                   | Group C                 |
| 0       | 15 ml    | 1.0 ml of Lot 310<br>Me-Mu-R | 1.0 ml of Lot 311<br>Mu-F | 0.5 ml of Lot 266<br>Mu |
| 6 weeks | 15 ml    | ---                          | ---                       | ---                     |

5. Arrange, insofar as possible, to be mutually controlling.

6. Follow:

Clinical: Fever, rash, all other pertinent reactions - 28 days.

Serological: Rubella HI  
Measles HI (neut. when necessary)  
Mumps Neut.

7. Card forms are attached.

NOTE: These vaccines contain neomycin and duck (rubella) or chick embryo (measles, mumps) proteins. Do not use in persons with known sensitivity to these agents.



M. R. Hilleman, Ph.D.

Table 1: Serologic Findings for Children Vaccinated with Combined Measles-Mumps-Rubella Vaccine Lot 310 at Iankenu Hospital Outpatient Clinic from 9/26/68 to 10/10/68 (Study #212)

| Vaccination |                 | Children Initially Seronegative to: |                       |                       |                       |                       |                       |
|-------------|-----------------|-------------------------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|
|             |                 | Measles-Mumps-Rubella               |                       | Measles-Mumps Only    |                       | Measles-Rubella Only  |                       |
| Age (Yrs.)  | Total No. Vacc. | No. Serol. Tested                   | No. Conversions/Total | No. Conversions/Total | No. Conversions/Total | No. Conversions/Total | No. Conversions/Total |
|             |                 |                                     | Measles               | Mumps                 | Measles               | Rubella               | Mumps                 |
| Not Given   | 2               | 2                                   | 1/1                   | 1/1                   |                       |                       | 1/1                   |
| <1          | 2               | 2                                   | 2/2                   | 2/2                   |                       |                       |                       |
| 1           | 31              | 30                                  | 23/23                 | 23/23                 | 1/1                   | 3/3                   | 3/3                   |
| 2           | 3               | 3                                   | 3/3                   | 3/3                   |                       |                       |                       |
| 3           | 1               | 1                                   | 1/1                   | 0/1                   |                       |                       |                       |
| Total       | 39              | 38                                  | 30/30                 | 29/30                 | 1/1                   | 3/3                   | 4/4                   |

Table 2: Distribution of Titers for Children Initially Seronegative to Measles, Mumps and Rubella Who Were Vaccinated with Combined Measles-Mumps-Rubella Vaccine Lot 310 at Iankenu Hospital Outpatient Clinic from 9/26/68 to 10/10/68 (Study #212)

| Measles (HAI)         |                 | Mumps (Neut.)    |                 | Rubella (HAI)    |                 |
|-----------------------|-----------------|------------------|-----------------|------------------|-----------------|
| Post-Vacc. Titer      | No. of Children | Post-Vacc. Titer | No. of Children | Post-Vacc. Titer | No. of Children |
| <5                    | 0               | <1               | 1               | <8               | 0               |
| 5                     | 3               | 1                | 0               | 8                | 7               |
| 10                    | 3               | 2                | 5               | 16               | 5               |
| 20                    | 2               | 4                | 8               | 32               | 7               |
| 40                    | 11              | 8                | 10              | 64               | 7               |
| 80                    | 8               | 16               | 2               | 128              | 2               |
| 160                   | 2               | 32               | 2               | 256              | 2               |
| 320                   | 1               | 64               | 2               | 512              | 0               |
| 640                   | 0               | 128              | 0               | 1024             | 0               |
| Geometric Mean Titer: | 38.2            | 6.5              |                 | 30.6             |                 |



Table 3: Maximum Temperature Recordings for Children Vaccinated with Combined Measles-Mumps-Rubella Vaccine Lot 310 at Lankenau Hospital Outpatient Clinic from 9/26/68 to 10/10/68 (Study #212)

| Maximum Temperature<br>(°F, Oral) | Total Vaccinees       |               |               |               | Children Initially Seronegative to Measles, Mumps and Rubella |               |               |               |
|-----------------------------------|-----------------------|---------------|---------------|---------------|---------------------------------------------------------------|---------------|---------------|---------------|
|                                   | Days Post-Vaccination |               |               |               | Days Post-Vaccination                                         |               |               |               |
|                                   | 1-4                   | 5-12          | 13-18         | 19-28         | 1-4                                                           | 5-12          | 13-18         | 19-28         |
| <99                               | 24<br>(63.2%)*        | 13<br>(33.3%) | 29<br>(74.4%) | 22<br>(56.4%) | 19<br>(65.5%)                                                 | 9<br>(30.0%)  | 21<br>(70.0%) | 17<br>(56.7%) |
| 99-100.9                          | 12<br>(31.6%)         | 21<br>(53.8%) | 9<br>(23.1%)  | 16<br>(41.0%) | 9<br>(31.0%)                                                  | 17<br>(56.7%) | 8<br>(26.7%)  | 12<br>(40.0%) |
| 101-102.9                         | 2<br>(5.3%)           | 5<br>(12.8%)  | 1<br>(2.6%)   | 1<br>(2.6%)   | 1<br>(3.4%)                                                   | 4<br>(13.3%)  | 1<br>(3.3%)   | 1<br>(3.3%)   |
| Not Taken                         | 1                     |               |               |               | 1                                                             |               |               |               |
| Total                             | 39                    | 39            | 39            | 39            | 30                                                            | 30            | 30            | 30            |

\* Percentages based on total temperatures taken during observation period

Measles-Mumps-Rubella Virus Vaccine, Study No. 220

Live Measles-Mumps-Rubella Virus Vaccine

Lot 92127

Responsible Clinical Investigator:

Victor M. Villarejos, M.D., M.P.H. and T.M., Dr. P. H. \*

Location:

Costa Rica

Population:

Children whose families reside in the region near the Panamanian border, Costa Rica. 313 children with a negative history for measles-mumps-rubella were vaccinated with 1.0 ml. of the combined vaccine. 168 guardians and 34 children served as contact controls. All contact controls were serologically tested for rubella HAI antibody. The present summary includes a random sample of 100 of the 313 vaccinees who were serologically tested for measles and rubella HAI antibody and mumps neutralizing antibody.

\* Program Coordinator  
Louisiana State University  
International Center for Medical Research and Training  
San Jose, Costa Rica

February 28, 1969

Clinical Protocol - Study 220

(Dr. V. Villarejos, ICMRT, San Jose, Costa Rica)

Combined: Moraten measles  
Jeryl Lynn mumps  
HPV-77 duck rubella vaccine

3 lots

1. Background.

A combined dried vaccine of above composition has been developed.

The vaccine evokes antibody in essentially all children to all 3 viruses. Measles vaccine causes mild febrile and other reactions in a fraction of the child recipients. The other components of the vaccine cause no significant reaction.

The need is to test the vaccine in triply seronegative children and to measure

- a) antibody responses and
- b) clinical reactions

in triply seronegative children and to measure possible rubella transmission to a token population of susceptible contacts.

2. Vaccines. Combined Measles-Mumps-Rubella

Lot No. 92126 (C-7995)  
          92127 (C-7996)  
          96400 (C-8095)

Rehydrate with 1.2 ml. of distilled water. Dose is 1.0 ml. given subcutaneously.

3. Study plan.

a) Clinical

For each lot of vaccine (3 lots or possibly only 2 lots) select as many children as possible with negative history of measles, mumps and rubella vaccination and previous illness (up to 200 children per lot).

Vaccinate but keep every tenth eligible child as an unvaccinated contact control. Also bleed all mothers in families.

Schedule - Each Lot

| Time<br>Day | Group A<br>(Around 200 children<br>per lot)            | Group B<br>Every 10th child (in<br>families where another<br>child received vaccine) | Group C<br>Mothers    |
|-------------|--------------------------------------------------------|--------------------------------------------------------------------------------------|-----------------------|
| 0           | Bleed 15-20 ml.<br>Vaccinate 1.0 ml.<br>subcutaneously | Bleed 15-20 ml.<br>--                                                                | Bleed 15-20 ml.<br>-- |
| 42-44       | Bleed 15-20 ml.                                        | Bleed 15-20 ml.                                                                      | Bleed 15-20 ml.       |

NOTE: BLEEDINGS ON ALL SUBJECTS

b) Laboratory.

Remove sera from clot and store frozen at  $-20^{\circ}$  C. until shipped in dry ice.

Test all sera by HI or Neut. for all antibodies.

c) Records - as per attached

4. Caution

Vaccines contain chick and duck embryo proteins and neomycin. Vaccines should not be given to persons sensitive to these substances.

  
M. R. Hilleman

Note: To start about April 1, 1969 in Costa Rica, on the border.

NOTE: Record forms  
Bleeding equipment  
Syringes  
Distilled water  
All else,  
to be shipped

Table 4: Clinical Complaints for Children Vaccinated with Combined Measles-Mumps-Rubella Vaccine Lot 310 at Lankenau Hospital Outpatient Clinic from 9/26/68 to 10/10/68 (Study #212)

| Clinical Complaint        | Total Vaccinees       |               |               |               | Children Initially Seronegative to Measles, Mumps and Rubella |               |               |               |
|---------------------------|-----------------------|---------------|---------------|---------------|---------------------------------------------------------------|---------------|---------------|---------------|
|                           | Days Post-Vaccination |               |               |               | Days Post-Vaccination                                         |               |               |               |
|                           | 1-4                   | 5-12          | 13-18         | 19-28         | 1-4                                                           | 5-12          | 13-18         | 19-28         |
| Upper Respiratory Illness | 10<br>(25.6%)         | 9<br>(23.1%)  | 5<br>(12.8%)  | 5<br>(12.8%)  | 8<br>(26.7%)                                                  | 9<br>(30.0%)  | 5<br>(16.7%)  | 3<br>(10.0%)  |
| Otitis                    |                       |               | 1<br>(2.6%)   | 1<br>(2.6%)   |                                                               |               |               | 1<br>(3.3%)   |
| Lymphadenopathy           |                       | 1<br>(2.6%)   |               |               |                                                               |               |               |               |
| Gastrointestinal          | 1<br>(2.6%)           | 3<br>(7.7%)   |               |               | 1<br>(3.3%)                                                   | 2<br>(6.7%)   |               |               |
| Rash (not measles)        | 1<br>(2.6%)           | 3<br>(7.7%)   | 2<br>(5.1%)   | 1<br>(2.6%)   | 1<br>(3.3%)                                                   | 2<br>(6.7%)   | 2<br>(6.7%)   | 1<br>(3.3%)   |
| Irritability              | 2<br>(5.1%)           | 5<br>(12.8%)  | 2<br>(5.1%)   |               | 2<br>(6.7%)                                                   | 3<br>(10.0%)  |               |               |
| Malaise                   | 1<br>(2.6%)           |               |               |               |                                                               |               |               |               |
| Irrelevant                |                       | 2<br>(5.1%)   | 1<br>(2.6%)   | 1<br>(2.6%)   |                                                               | 2<br>(6.7%)   | 1<br>(3.3%)   |               |
| No Complaint              | 25<br>(64.1%)         | 21<br>(53.8%) | 30<br>(76.9%) | 32<br>(82.0%) | 19<br>(63.3%)                                                 | 15<br>(50.0%) | 21<br>(70.0%) | 25<br>(83.3%) |
| Total Subjects            | 39                    | 39            | 39            | 39            | 30                                                            | 30            | 30            | 30            |

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- Not Clinical**



June 14, 1967

# BACKGROUND

## Non-Responsive Not Clinical

Two clinical trials of Moraten have been carried out with Dr. Joseph Stokes in the Philadelphia suburbs. In the studies, Moraten was compared with Pitman-Moore (Schwarz) and Enders' Edmonston (Rubeovax) vaccines.

The findings in the first study are shown below. All the children were proved susceptible and the serologic responses to all vaccines were 100%. The table shows the fever patterns and rash during days 5-12 following vaccine and also the mean HI antibody titers. Moraten performed quite like Pitman-Moore and caused less reaction than Rubeovax.

| Vaccine          | Fever       |            | Rash       | Geom. Mean HI Titer |
|------------------|-------------|------------|------------|---------------------|
|                  | 101-102.9   | 103-104.9  |            |                     |
| Enders' Rubeovax | 13/32 (41%) | 4/32 (12%) | 6/32 (18%) | 1:43                |
| Pitman-Moore     | 2/11 (18%)  | 1/11 (9%)  | 0/11 (0%)  | 1:27                |
| Moraten          | 3/29 (10%)  | 1/29 (3%)  | 2/29 (6%)  | 1:25                |
| Control          | 2/27 (7%)   | 1/27 (4%)  | 0/27 (0%)  | 0                   |

A second larger study has been finished but the serology has not been completed. The data are crude but are reliable since all children had a negative history of measles or measles vaccine. The data shown below are consistent with those for the first trial above.

| Vaccine          | Fever       |            | Rash       |
|------------------|-------------|------------|------------|
|                  | 101-102.9   | 103-104.9  |            |
| Enders' Rubeovax | 11/62 (23%) | 9/62 (19%) | 6/62 (12%) |
| Pitman-Moore     | 6/61 (14%)  | 0/61 (0%)  | 3/61 (7%)  |
| Moraten          | 5/58 (11%)  | 0/58 (0%)  | 3/58 (6%)  |

Further comparative studies need to be made to obtain confirmatory data. Such studies should include clinical observations for fever, rash and other reactions and for serologic responses.

*M. R. Hilleman*  
M. R. Hilleman, Ph.D., Director  
Virus and Cell Biology Research  
Merck Institute for Therapeutic Research  
West Point, Pennsylvania

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A. Introduction.

1. Background.

Mumps, like measles, is deserving of prevention, both the mild ordinary disease and the serious complicated disease. Preventive measures must, however, be effective in the long-term. Delay in time of first appearance can serve no useful purpose and may only result in harm.

To this end, emphasis has been placed on development of a live attenuated mumps vaccine which, like live measles vaccine, might bestow lifelong immunity. Killed vaccines developed to date have provided immunity of only short-term quality, at most two years. Their usefulness has been limited to special circumstances such as, e.g., for protection of adults exposed to or likely to be exposed to mumps.

Non-Responsive Not Clinical

The vaccine was administered initially by the oral route but later, more efficiently, by the intradermal (0.1 ml) or subcutaneous (0.5 ml of 1:5 dilution) route. Children vaccinated dermally often developed erythema measuring 5-30 mm in diameter which was most pronounced at 24 hours and faded within 2-3 days. Apparently, hemagglutination-inhibition titer responses were seen in about 75% of vaccinees. Dermal sensitivity tests appeared more sensitive for detecting an immune response than was the serologic test. Something like 80% responded, and these reactions persisted at least for 18 months post-vaccination.

Reactions to the vaccine were very minor. The quality of each vaccine lot was tested in ten persons. To be acceptable, eight persons were required to show no elevation of temperature and no local reactions of visible intensity during three days post-vaccination.

Vaccination efficacy was appraised in controlled studies in 157 kindergartens in Leningrad. Morbidity rates for mumps were computed for the

following 18-21 month periods in the vaccinated and control groups. The findings were as follow:

| Group      | No. Children | No. Cases | Attack Rate | Efficacy |
|------------|--------------|-----------|-------------|----------|
| Vaccinated | 4,116        | 30        | 0.7%        | > 90%    |
| Control    | 5,567        | 423       | 7.6%        | ---      |

Immunity was found to persist for at least five years. The illness in vaccination "failures" was generally very mild and abortive. Additionally, such illness in vaccine failures was poorly contagious.

During 1956, an additional 30,000 children were vaccinated with similar high efficacy and low reactogenicity results. Subcutaneous inoculation was equally as effective as intradermal.

Non-Responsive Not Clinical

Early results of combination of mumps and measles vaccine in a single dose are excellent and promising.

Immunity to mumps appears evident two weeks post-vaccination.

Non-Responsive Not Clinical

**46 Pages**

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Clinical**



## A. Introduction.

### 1. Background.

Rubella is primarily a disease of childhood of low mortality and of rare serious consequence. Principal complications involve CNS with encephalitis or neuritis or arthritis. Principal import of rubella is in its role in inducing congenital defect in pregnant females who experience infection during the first trimester. About 1 in 5 females who achieve adulthood have no detectable rubella antibody in their sera.

There are clearly 2 needs for rubella vaccine: (a) a live virus vaccine which would afford lifelong immunity against rubella and which would be used in children and (b) a killed virus vaccine which would be used for primarily or booster immunization of newly pregnant women or in persons likely to become pregnant.

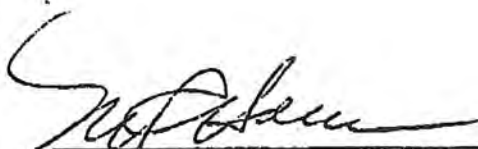
The propagation of rubella virus in cell culture (Parkman, P.D., Buescher, E.L., Artenstein, M.S., Proc. Soc. Exp. Biol. and Med., V. III, 225, 1962; Weller, T.H., Neva, F., Proc. Soc. Exp. Biol. and Med., V. III, 215, 1962) opened the way for vaccine development.

Non-Responsive Not Clinical

The vaccine is judged acceptable for cautious clinical application. The following observations are indicated:

Subcutaneous injection of vaccine in 0.5 ml or 1 ml amounts into rubella seronegative persons excluding persons with leukemia, lymphoma, other generalized malignancies, in persons on therapy which depresses resistance such as steroids, irradiation, alkylating agents and anti-metabolites as for measles virus vaccine. The patients need to be followed daily for 1 month for febrile response, rash, and all detectable signs and symptoms. Throat washings need to be taken at appropriately spaced intervals to permit laboratory tests for virus excretion from the throat. Pre and 28 day post-vaccination sera need to be tested for rubella antibody to establish initial seronegativity and to measure height of serologic response. Individuals need to be followed indefinitely for rubella antibody to measure durability of seropositive status. Initially seronegative persons need to be kept in intimate contact with vaccinees to measure possible spread of the virus from vaccinees to contacts. Depending on

findings and judgment, numbers need to be expanded and tests to measure protection against the natural disease, rubella, need to be carried out.

A handwritten signature in dark ink, appearing to read 'M. Hilleman', is written over a horizontal line.

Maurice R. Hilleman, Ph.D.  
Executive Director  
Virus & Cell Biology Research  
Merck Institute for Therapeutic Research  
West Point, Pennsylvania



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Me & Sharp & Dohme 3  
UNITED STATES GOVERNMENT

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE  
PUBLIC HEALTH SERVICE

# Memorandum

TO : Merck, Sharp and Dohme Files

DATE: November 19, 1969

FROM : Dr. Ruth L. Kirschstein, Chief, LP *RKC*

SUBJECT: Meeting of November 3, 1969

On Monday morning November 3, 1969, Drs. Barclay, Hilleman and Woodhour of Merck, Sharp and Dohme met with Drs. Murray, Meyer, O'Malley and Kirschstein of DBS. During the last portion of the meeting, Drs. Cohen and Hardegree joined the discussion. A number of items were discussed as follows:

Non-Responsive - Not MMR

2. Mumps - Rubella Vaccine - License Application - Three lots have been produced and tested clinically as a 1 ml. dose. The results are shown in Table 1 (attachment 1).

There was no increase in clinical reactions. This vaccine would be primarily for older children who had had measles vaccine already and needed to fill in the gap.



Dr. Meyer raised a question as to whether clinical data are needed concerning the maximum amount of each virus to be present in the combination. At present, the minimum amount is  $10^{3.7}$  of mumps virus and  $10^{3.0}$  of rubella virus. If titers are much higher is there interference? He declared that valuable data would be obtained if a clinical titration study were done but Dr. Hilleman said this would be impossible. Dr. Murray declared that lots of vaccine could be approved for release provided that the amount of each virus present does not exceed the level found to be satisfactory in the clinical trials.

3. Measles-Mumps-Rubella Vaccine - License Application - Three lots have been tested; one by Dr. Stokes in the Philadelphia area and the other two in Costa Rica. The results differ and are shown in Table 2 (attachment 2).

Thus, there is some suppression in the mumps antibody response. Dr. Hilleman is investigating the reason for this and will be testing other lots. He has been considering a 1 ml. dose containing 0.5 ml. of mumps vaccine and 0.25 ml. each of measles and rubella vaccines.

Non-Responsive Not Clinical



The meeting adjourned at 12:30 P.M.

\*

\*

Table 1

|                           | Mumps<br>Virus<br>Titer | Conversion<br>rate | GMT  | Rubella<br>Virus<br>Titer | Rubella<br>Conversion<br>rate | Rubella<br>GMT |
|---------------------------|-------------------------|--------------------|------|---------------------------|-------------------------------|----------------|
| Experimental              | $10^{3.9}$ /ml.         | 30/31              | 1:7  | $10^{2.9}$ /ml.           | 31/31                         | 1:46           |
| First Consistency<br>Lot  | $10^{4.3}$ /ml.         | 60/60              | 1:10 | $10^{3.6}$ /ml.           | 59/60                         | 1:44           |
| Second Consistency<br>Lot | $10^{4.4}$ /ml.         | 43/43              | 1:6  | $10^{3.7}$ /ml.           | 41/43                         | 1:46           |

Table 2

| Site of Study | No. of Children | Measles Virus Titer | Measles Conversion Rate | Measles GMT | Mumps Virus Titer | Mumps Conversion Rate | Mumps GMT | Rubella Virus Titer | Rubella Conversion Rate | Rubella GMT |
|---------------|-----------------|---------------------|-------------------------|-------------|-------------------|-----------------------|-----------|---------------------|-------------------------|-------------|
| Phila.        | 36              | $10^{3.4}$ /dose    | 100%                    | 1:38        | $10^{3.7}$ /dose  | 97%                   | 1:7       | $10^{2.8}$ /dose    | 100%                    | 1:31        |
| Costa Rica    | 52              | $10^{2.8}$ /dose    | 98%                     | 1:62        | $10^{3.9}$ /dose  | 85%                   | 1:3       | $10^{4.1}$ /dose    | 92%                     | 1:36        |
| Costa Rica    | 87              | ---                 | 90%                     | 1:30        | ---               | 87%                   | 1:7       | ---                 | 93%                     | 1:23        |

**MERCK  
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MANUFACTURING DIVISION

*Division of Merck and Co., Inc.  
West Point, Penna. 19486*

002-304 AR  
(Clinical Data)

March 9, 1970

Dr. Roderick Murray, Director  
Division of Biologics Standards  
National Institutes of Health  
Bethesda, Maryland 20014

Dear Doctor Murray:

Reference No. 69-192

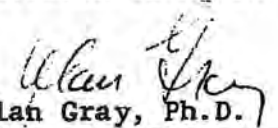
As indicated in Dr. Hilleman's letter of March 4, we are sending three copies of Addendum No. 1 to Summary No. 1 for clinical studies on Measles-Mumps-Rubella Virus Vaccine, Live, Combined, dated March 4, 1970.

This data relates to serology performed on a number of triple negative individuals and shows that the overall seroconversion rate was excellent.

With kindest personal regards,

Very truly yours,

MERCK SHARP & DOHME  
Division of Merck & Co., Inc.

  
Alan Gray, Ph.D.  
Director, Biological Production

/mb



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FOR  
THERAPEUTIC RESEARCH  
WEST POINT, PENNSYLVANIA 19486

MAURICE R. HILLEMAN, Ph. D., D. Sc.  
EXECUTIVE DIRECTOR

March 4, 1970

Dr. Roderick Murray, Director  
Division of Biologics Standards  
National Institutes of Health  
Bethesda, Maryland 20014

Dear Dr. Murray:

Very shortly you will receive from Dr. Alan Gray, Addendum No. 1 to Summary No. 1 of clinical investigative studies of combined live measles virus vaccine (Moraten line - ATTENUVAX), Jeryl Lynn mumps virus vaccine (MUMPSVAX), and HPV-77 duck rubella virus vaccine (MERUVAX), dated March 4, 1970.

The combined mixed vaccine has performed well. The total number of triple negatives vaccinated and the overall seroconversion rates are as follows:

| Lot<br>No. | No. Converted/Total |                  |                  |
|------------|---------------------|------------------|------------------|
|            | Measles             | Mumps            | Rubella          |
| 310        | 30/30               | 29/30            | 30/30            |
| 92126      | 74/82               | 80/82            | 73/82            |
| 92127      | 99/106              | 102/106          | 103/106          |
| 96400      | 69/70               | 67/70            | 66/70            |
| Overall    | 272/288<br>(94%)    | 278/288<br>(96%) | 272/288<br>(94%) |

Further details relating to the clinical studies are to be found in your file of submissions under DBS-IND 260; in the files of this department, and in the files of the individual clinicians. Any further information you may want will be made available to you upon request.

Kindest regards.

Sincerely,



Maurice R. Hilleman, Ph.D.  
Director  
Virus & Cell Biology Research

/bl

cc: Dr. A. Gray

Addendum No. 1

to Summary No. 1

of

Clinical Investigative Studies

of

Combined Live Measles Virus Vaccine (Moraten Line - ATTENUVAX)

Jeryl Lynn Mumps Virus Vaccine (MUMPSVAX)

HPV-77 Duck Rubella Virus Vaccine (MERUVAX)

for purpose of support for  
a license to manufacture and sell.



*M. R. Hilleman*

M. R. Hilleman, Ph.D.

Prepared: March 4, 1970

Merck Institute for Therapeutic Research  
West Point, Pennsylvania

Clinical Investigation of Combined Live Attenuated Measles (Moraten),  
Mumps (Jeryl Lynn), and Rubella (HPV-77) Vaccine

1. The previous submission of 9/26/69 described clinical tests of the above combined product carried out under the clinical direction of Dr. Joseph Stokes, Jr. and Dr. Victor Villarejos.

The present addendum describes further tests under the clinical direction of Dr. Joseph Stokes, Jr. Essentially, the findings in tests of three consistency lots of the combined product are presented. These are Lots 92126, 92127, and 96400.

2. The protocol for Lot 92127 was submitted previously under Reference 4(b). The present submission includes protocols for Lots 92126 and 96400 under References 4(c) and 4(d).
3. The clinical studies were carried out along the lines previously described.
4. The clinical findings for each lot are presented in References 5(a), 5(b), and 5(c). The findings are self-explanatory.
5. It is seen that there was high level seroconversion against all three components in children who were initially seronegative to all three viruses. There did not appear to be significant impairment of antibody responses. The vaccine was safe and did not cause significant untoward effects.

There was one instance of rubella antibody development in a child (#107-2) who was recorded as an unvaccinated contact control in the family of vaccinated child #107-1. Blood typing, CF testing, and review of records did not offer an explanation for the antibody development in the contact control. In discussion with the staff, the most likely explanation is that of mistaken vaccination of child #107-2, who was recorded as unvaccinated.

**38 Pages Removed  
as Non-Responsive  
- Not Clinical**

August 21, 1969

CLINICAL TEST PROTOTOL Study No. 232

Protocol: Live Moraten Measles-Mumps-Rubella (HPV-77+5) Vaccine

Purpose: Establish serologic responses  
Measure possible rubella contact transmission  
Measure reactions

in TRIPLE NEGATIVE CHILDREN

Materials: Lot 96400 (C-8095)

Infectivity of components  
Measles 10<sup>-2.2</sup>/0.1 ml  
Mumps 10<sup>-3.5</sup>/0.1 ml  
Rubella 10<sup>-2.2</sup>/0.1 ml

Lot 92126 (C-7995)

Infectivity of components  
Measles 10<sup>-1.8</sup>  
Mumps 10<sup>-3.4</sup>  
Rubella 10<sup>-2.6</sup>

Lot 92127 (C-7996)

Infectivity of components  
Measles 10<sup>-1.8</sup>  
Mumps 10<sup>-2.9</sup>  
Rubella 10<sup>-3.1</sup>

Procedure:

Rehydrate all lots with 1.2 ml of sterile distilled water.

The dose is 1.0 ml given subcutaneously.

Select children who are negative for vaccination and illness for

Measles  
Mumps  
Rubella

These should be triple-negative serologically.

Target: Vaccinate 100 triple negatives per lot as soon as possible.

Contact controls - (for rubella transmission)  
all mothers - where possible  
1 sibling - where possible (youngest possible -  
care only about rubella seronegativity)

Schedule - Each lot:

| Time<br>Day | Group A                                              | Group B             | Group C             |
|-------------|------------------------------------------------------|---------------------|---------------------|
| 0           | Bleed 15-20 ml<br>Vaccinate 1.0 ml<br>subcutaneously | Bleed 15-20 ml<br>- | Bleed 15-20 ml<br>- |
| 42-44       | Bleed 15-20 ml                                       | Bleed 15-20 ml      | Bleed 15-20 ml      |

Laboratory - Serology for all 3 viruses.

Records: As per attached.

CAUTION: Vaccine contains chick and duck embryo protein and neomycin.  
Do not give to persons sensitive to these substances.

7  
M.R. Hilleman



Reference No. 5(a)

Measles-Mumps-Rubella Virus Vaccine, Study 232

Live Measles-Mumps-Rubella Virus Vaccine  
Lot 92126

Responsible Clinical Investigator:  
Joseph Stokes, Jr., M.D., D.Sc.\*

Location:  
Suburban Philadelphia, Pa.

Population:  
Children residing in the Philadelphia area communities. 101 children with a negative history of measles, mumps, and rubella were vaccinated with 1.0 ml. of the combined vaccine. 83 guardians and 32 children served as contact controls. All contact controls were serologically tested for rubella HI antibody. Vaccinees were serologically tested for measles and rubella HI antibody and mumps neutralizing antibody.

\* Department of Pediatrics, School of Medicine,  
University of Pennsylvania, Philadelphia, Pa.

Table 1: Serologic Findings for Children Vaccinated with Combined Measles-Mumps-Rubella Vaccine  
 Lot 92126 in Suburban Philadelphia from September 11, 1969 to January 31, 1970 (Study 232)

| Age<br>(Yrs.) | Total<br>No.<br>Vacc. | No.<br>Serol.<br>Tested | Children Initially Seronegative to: |                  |                   |         |                   |         |                   |       |                   |              |
|---------------|-----------------------|-------------------------|-------------------------------------|------------------|-------------------|---------|-------------------|---------|-------------------|-------|-------------------|--------------|
|               |                       |                         | Measles-Mumps-Rubella               |                  | Measles-Mumps     |         | Measles-Rubella   |         | Mumps-Rubella     |       | Measles Only      |              |
|               |                       |                         | Conversions/Total                   | Measles          | Conversions/Total | Measles | Conversions/Total | Measles | Conversions/Total | Mumps | Conversions/Total | Rubella Only |
| <1            | 11                    | 11                      | 10/10                               | 47/54            | 9/10              | 10/10   | 1/1               | 2/2     | 1/2               | 2/2   | 1/1               | 1/1          |
| 1             | 59                    | 59                      | 53/54                               | 47/54            | 53/54             | 1/1     | 2/2               | 3/3     | 3/3               | 3/3   | 1/1               | 1/1          |
| 2             | 17                    | 17                      | 9/10                                | 10/10            | 9/10              |         | 3/3               | 3/3     | 2/2               | 2/2   | 1/1               | 1/1          |
| 3             | 9                     | 8                       | 6/6                                 | 6/6              | 6/6               |         |                   |         |                   |       |                   | 1/1          |
| 4             | 5                     | 5                       | 2/2                                 | 2/2              | 2/2               |         |                   |         |                   |       |                   | 1/1          |
| Total         | 101                   | 100                     | 74/82<br>(90.2%)                    | 80/82<br>(97.5%) | 80/82<br>(97.5%)  | 1/1     | 5/5               | 5/5     | 6/7               | 7/7   | 2/2               | 3/3          |

Overall Conversion Rates

|  | Measles          | Mumps            | Rubella          |
|--|------------------|------------------|------------------|
|  | 80/88<br>(90.9%) | 89/92<br>(96.7%) | 88/97<br>(90.7%) |

Table 2: Distribution of Titers of Children Initially Seronegative to Measles, Mumps and Rubella who were Vaccinated with Combined Measles-Mumps-Rubella Vaccine Lot 92126 in Suburban Philadelphia from Sept. 11, 1969 to Jan. 31, 1970 (Study 232)

| Measles (HAI)                 |                    | Mumps (Neut.)       |                    | Rubella (HAI)       |                    |
|-------------------------------|--------------------|---------------------|--------------------|---------------------|--------------------|
| Post-Vacc.<br>Titer           | No. of<br>Children | Post-Vacc.<br>Titer | No. of<br>Children | Post-Vacc.<br>Titer | No. of<br>Children |
| <5                            | 8                  | <1                  | 2                  | <8                  | 9                  |
| 5                             | 2                  | 1                   | 7                  | 8                   | 9                  |
| 10                            | 3                  | 2                   | 12                 | 16                  | 11                 |
| 20                            | 8                  | 4                   | 12                 | 32                  | 12                 |
| 40                            | 10                 | 8                   | 15                 | 64                  | 22                 |
| 80                            | 16                 | 16                  | 15                 | 128                 | 13                 |
| 160                           | 25                 | 32                  | 10                 | 256                 | 4                  |
| 320                           | 7                  | ≥64                 | 9                  | ≥512                | 2                  |
| ≥640                          | 3                  |                     |                    |                     |                    |
| Geometric<br>Mean Titer: 54.4 |                    | 7.9                 |                    | 30.4                |                    |

Table 3: Serologic Findings for Rubella Antibody for Children and Adults Acting as Contact Controls for Combined Measles-Mumps-Rubella Vaccine Lot 92126 (Study 232)

| Age<br>(Yrs.)                | Total<br>No. | Initially Seronegative  |                                  |              |            |       | Pre-Vacc.<br>Sera<br>Only | Total |
|------------------------------|--------------|-------------------------|----------------------------------|--------------|------------|-------|---------------------------|-------|
|                              |              | No.<br>Serol.<br>Tested | No.<br>Initially<br>Seropositive | Paired Sera  |            |       |                           |       |
|                              |              |                         |                                  | No.<br>Conv. | No<br>Rise | Total |                           |       |
| <u>Children</u>              |              |                         |                                  |              |            |       |                           |       |
| 2                            | 7            | 6                       |                                  |              | 6          | 6     |                           | 6     |
| 3                            | 10           | 10                      |                                  |              | 10         | 10    |                           | 10    |
| 4                            | 7            | 7                       | 1                                |              | 6          | 6     |                           | 6     |
| 5                            | 3            | 3                       |                                  |              | 3          | 3     |                           | 3     |
| 6                            | 2            | 2                       | 1                                |              | 1          | 1     |                           | 1     |
| 8                            | 1            | 1                       |                                  |              | 1          | 1     |                           | 1     |
| 9                            | 1            | 1                       |                                  |              | 1          | 1     |                           | 1     |
| 10                           | 1            | 1                       | 1                                |              |            |       |                           |       |
| Total                        | 32           | 31                      | 3                                | 0            | 28         | 28    | 0                         | 28    |
| <u>Adult Female Controls</u> |              |                         |                                  |              |            |       |                           |       |
| 18-29                        | 55           | 53                      | 49                               |              | 4          | 4     |                           | 4     |
| 30-39                        | 23           | 23                      | 23                               |              |            |       |                           |       |
| 40-47                        | 5            | 5                       | 5                                |              |            |       |                           |       |
| Total                        | 83           | 81                      | 77                               | 0            | 4          | 4     | 0                         | 4     |

Table 4: Maximum Temperature Recordings for Children Vaccinated with Combined Measles-Mumps-Rubella Vaccine Lot 92126 and for Their Unvaccinated Contact Controls (Study 232)

| Maximum Temperature (°F, Oral) | Contact Control Children |               |               |               | Total Vaccinees       |               |               |               | Initially Seronegative to Measles-Mumps-Rubella |               |               |               |
|--------------------------------|--------------------------|---------------|---------------|---------------|-----------------------|---------------|---------------|---------------|-------------------------------------------------|---------------|---------------|---------------|
|                                | Days Observed            |               |               |               | Days Post-Vaccination |               |               |               | Days Post-Vaccination                           |               |               |               |
|                                | 1-4                      | 5-12          | 13-18         | 19-28         | 1-4                   | 5-12          | 13-18         | 19-28         | 1-4                                             | 5-12          | 13-18         | 19-28         |
| <99                            | 27<br>(87.1%)            | 23<br>(76.7%) | 25<br>(83.3%) | 23<br>(79.3%) | 68<br>(68.7%)         | 50<br>(50.0%) | 68<br>(69.4%) | 60<br>(61.8%) | 57<br>(69.5%)                                   | 42<br>(51.2%) | 55<br>(67.9%) | 52<br>(65.0%) |
| 99-100.9                       | 4<br>(12.9%)             | 6<br>(20.0%)  | 3<br>(10.0%)  | 4<br>(13.8%)  | 29<br>(29.3%)         | 40<br>(40.0%) | 26<br>(26.5%) | 29<br>(29.9%) | 23<br>(28.0%)                                   | 31<br>(37.8%) | 22<br>(27.2%) | 23<br>(28.8%) |
| 101-102.9                      |                          |               | 2<br>(6.7%)   | 1<br>(3.4%)   | 2<br>(2.0%)           | 7<br>(7.0%)   | 3<br>(3.1%)   | 6<br>(6.2%)   | 2<br>(2.4%)                                     | 6<br>(7.3%)   | 3<br>(3.7%)   | 4<br>(5.0%)   |
| 103-104.9                      |                          | 1<br>(3.3%)   |               | 1<br>(3.4%)   |                       | 3<br>(3.0%)   | 1<br>(1.0%)   | 2<br>(2.1%)   |                                                 | 3<br>(3.6%)   | 1<br>(1.2%)   | 1<br>(1.2%)   |
| Not Taken                      | 1                        | 2             | 2             | 3             | 2                     | 1             | 3             | 4             |                                                 |               | 1             | 2             |
| Total Subjects                 | 32                       | 32            | 32            | 32            | 101                   | 101           | 101           | 101           | 82                                              | 82            | 82            | 82            |

Table 5: Clinical Complaints Recorded for Children Vaccinated with Combined Measles-Mumps-Rubella Vaccine Lot 92126 and for Their Unvaccinated Contact Controls (Study 232)

| Clinical Complaints               | Contact Control Children |               |               |               | Total Vaccinees       |               |               |               | Initially Seronegative to Measles-Mumps-Rubella |               |               |               |
|-----------------------------------|--------------------------|---------------|---------------|---------------|-----------------------|---------------|---------------|---------------|-------------------------------------------------|---------------|---------------|---------------|
|                                   | Days Observed            |               |               |               | Days Post-Vaccination |               |               |               | Days Post-Vaccination                           |               |               |               |
|                                   | 1-4                      | 5-12          | 13-18         | 19-28         | 1-4                   | 5-12          | 13-18         | 19-28         | 1-4                                             | 5-12          | 13-18         | 19-28         |
| Upper Respiratory Illness         |                          | 2<br>(6.4%)   | 3<br>(9.7%)   | 2<br>(6.4%)   | 15<br>(15.0%)         | 20<br>(20.0%) | 12<br>(12.0%) | 14<br>(14.0%) | 13<br>(15.8%)                                   | 16<br>(19.5%) | 10<br>(12.2%) | 9<br>(11.0%)  |
| Otitis                            |                          |               |               |               | 1<br>(1.0%)           | 1<br>(1.0%)   |               | 2<br>(2.0%)   | 1<br>(1.2%)                                     | 1<br>(1.2%)   |               | 1<br>(1.2%)   |
| Swollen Glands                    |                          |               |               |               |                       | 1<br>(1.0%)   |               |               |                                                 | 1<br>(1.2%)   |               |               |
| Conjunctivitis                    |                          |               |               |               |                       | 1<br>(1.0%)   |               |               |                                                 | 1<br>(1.2%)   |               |               |
| Gastrointestinal                  |                          |               |               |               | 11<br>(11.0%)         | 11<br>(11.0%) | 6<br>(6.0%)   | 6<br>(6.0%)   | 9<br>(11.0%)                                    | 10<br>(12.2%) | 6<br>(7.3%)   | 5<br>(6.1%)   |
| Rash                              | 1<br>(3.2%)              | 1<br>(3.2%)   |               |               | 3<br>(3.0%)           | 3<br>(3.0%)   | 2<br>(2.0%)   | 3<br>(3.0%)   | 3<br>(3.6%)                                     | 3<br>(3.6%)   | 2<br>(2.4%)   | 3<br>(3.6%)   |
| Irritability                      |                          |               |               |               | 4<br>(4.0%)           | 6<br>(6.0%)   | 4<br>(4.0%)   | 4<br>(4.0%)   | 4<br>(4.9%)                                     | 5<br>(6.1%)   | 4<br>(4.9%)   | 4<br>(4.9%)   |
| Malaise                           |                          |               |               |               | 1<br>(1.0%)           |               |               |               | 1<br>(1.2%)                                     |               |               |               |
| Irrelevant                        |                          |               |               |               |                       |               |               | 1<br>(1.0%)   |                                                 |               |               | 1<br>(1.2%)   |
| Anorexia                          |                          |               |               |               | 2<br>(2.0%)           | 2<br>(2.0%)   | 1<br>(1.0%)   | 1<br>(1.0%)   | 2<br>(2.4%)                                     | 2<br>(2.4%)   | 1<br>(1.2%)   | 1<br>(1.2%)   |
| Swelling of Face                  |                          |               |               |               |                       | 1<br>(1.0%)   | 1<br>(1.0%)   |               |                                                 | 1<br>(1.2%)   | 1<br>(1.2%)   |               |
| Flush                             |                          |               |               |               |                       |               | 1<br>(1.0%)   |               |                                                 |               | 1<br>(1.2%)   |               |
| Viral Infection                   |                          |               |               |               |                       |               |               | 2<br>(2.0%)   |                                                 |               |               | 2<br>(2.4%)   |
| Measles-like Rash                 |                          |               |               |               |                       | 4<br>(4.0%)   | 1<br>(1.0%)   |               |                                                 | 4<br>(4.9%)   | 1<br>(1.2%)   |               |
| Fatigue                           |                          |               |               |               | 2<br>(2.0%)           | 1<br>(1.0%)   | 1<br>(1.0%)   | 1<br>(1.0%)   | 1<br>(1.2%)                                     |               |               |               |
| Toothache                         |                          |               |               |               | 4<br>(4.0%)           | 2<br>(2.0%)   | 1<br>(1.0%)   | 1<br>(1.0%)   | 3<br>(3.6%)                                     | 1<br>(1.2%)   | 1<br>(1.2%)   | 1<br>(1.2%)   |
| No Complaints                     | 30<br>(96.8%)            | 28<br>(90.3%) | 28<br>(90.3%) | 29<br>(93.5%) | 70<br>(70.0%)         | 64<br>(64.0%) | 76<br>(76.0%) | 71<br>(71.0%) | 57<br>(69.5%)                                   | 52<br>(63.4%) | 61<br>(74.4%) | 60<br>(73.2%) |
| Physician's Surveillance Negative | 1                        | 1             | 1             | 1             | 1                     | 1             | 1             | 1             |                                                 |               |               |               |
| Total Subjects                    | 32                       | 32            | 32            | 32            | 101                   | 101           | 101           | 101           | 82                                              | 82            | 82            | 82            |

Reference No. 5(b)

Measles-Mumps-Rubella Virus Vaccine, Study 232

Live Measles-Mumps-Rubella Virus Vaccine

Lot 92127

Responsible Clinical Investigator:

Joseph Stokes, Jr., M.D., D.Sc.\*

Location:

Suburban Philadelphia, Pa.

Population:

Children residing in the Philadelphia area communities. 101 children with a negative history of measles, mumps, and rubella were vaccinated with 1.0 ml. of the combined vaccine. 77 guardians and 34 children served as contact controls. All contact controls were serologically tested for rubella HI antibody. Vaccinees were serologically tested for measles and rubella HI antibody and mumps neutralizing antibody.

\* Department of Pediatrics, School of Medicine  
University of Pennsylvania, Philadelphia, Pa.



Table 1: Serologic Findings for Children Vaccinated with Combined Measles-Mumps-Rubella Vaccine Lot 92127 in Suburban Philadelphia from September 11, 1969 to January 31, 1970 (Study 232)

| Vaccination |                         | Children Initially Seronegative to: |               |                   |               |                   |         |                   |       |                   |              |                   |       | Seropositive to Measles, Mumps, and Rubella |
|-------------|-------------------------|-------------------------------------|---------------|-------------------|---------------|-------------------|---------|-------------------|-------|-------------------|--------------|-------------------|-------|---------------------------------------------|
| Age (Yrs.)  | Total No. Serol. Tested | Measles-Mumps-Rubella               |               | Measles-Mumps     |               | Measles-Rubella   |         | Mumps-Rubella     |       | Measles Only      |              | Mumps Only        |       |                                             |
|             |                         | Conversions/Total                   |               | Conversions/Total |               | Conversions/Total |         | Conversions/Total |       | Conversions/Total |              | Conversions/Total |       |                                             |
|             |                         | Measles                             | Rubella       | Measles           | Mumps         | Measles           | Rubella | Measles           | Mumps | Measles           | Rubella      | Measles           | Mumps |                                             |
| <1          | 15                      | 14                                  | 8/11          | 11/11             | 11/11         | 1/1               | 1/1     | 1/1               | 1/1   | 2/2               | 7/7          | 2/2               |       | 1                                           |
| 1           | 56                      | 53                                  | 43/45         | 44/45             | 44/45         |                   |         | 2/2               | 2/2   | 2/2               | 7/7          |                   |       |                                             |
| 2           | 17                      | 16                                  | 14/14         | 14/14             | 14/14         |                   |         | 2/2               | 2/2   | 2/2               | 3/3          |                   | 1/1   |                                             |
| 3           | 9                       | 9                                   | 6/6           | 6/6               | 5/6           |                   |         |                   |       |                   |              |                   |       |                                             |
| 4           | 4                       | 4                                   |               |                   |               |                   |         |                   |       |                   |              |                   |       | 1                                           |
| Total       | 101                     | 96                                  | 71/76 (93.4%) | 75/76 (98.7%)     | 74/76 (97.4%) | 1/1               | 1/1     | 5/5               | 5/5   | 11/12 (91.7%)     | 12/12 (100%) | 0                 | 0     |                                             |

Overall Conversion Rates

| Measles       | Mumps         | Rubella       |
|---------------|---------------|---------------|
| 71/76 (93.4%) | 87/89 (97.8%) | 92/94 (97.9%) |

Table 2: Distribution of Titers of Children Initially Seronegative to Measles, Mumps and Rubella who were Vaccinated with Combined Measles-Mumps-Rubella Vaccine Lot 92127 in Suburban Philadelphia from Sept. 11, 1969 to Jan. 31, 1970 (Study 232)

| Measles (HAI)                 |                    | Mumps (Neut.)       |                    | Rubella (HAI)       |                    |
|-------------------------------|--------------------|---------------------|--------------------|---------------------|--------------------|
| Post-Vacc.<br>Titer           | No. of<br>Children | Post-Vacc.<br>Titer | No. of<br>Children | Post-Vacc.<br>Titer | No. of<br>Children |
| <5                            | 5                  | <1                  | 1                  | <8                  | 2                  |
| 5                             | 2                  | 1                   | 6                  | 8                   | 13                 |
| 10                            | 4                  | 2                   | 14                 | 16                  | 6                  |
| 20                            | 4                  | 4                   | 21                 | 32                  | 9                  |
| 40                            | 13                 | 8                   | 5                  | 64                  | 22                 |
| 80                            | 22                 | 16                  | 12                 | 128                 | 14                 |
| 160                           | 17                 | 32                  | 10                 | 256                 | 9                  |
| 320                           | 7                  | 64                  | 7                  | 512                 | 1                  |
| ≥640                          | 2                  | 128                 |                    |                     |                    |
| Geometric<br>Mean Titer: 57.8 |                    | 6.8                 |                    | 45.7                |                    |

Table 3: Serologic Findings for Rubella Antibody for Children and Adults Acting As Contact Controls for Combined Measles-Mumps-Rubella Vaccine Lot 92127 (Study 232)

| Age<br>(Yrs.)         | Total<br>No. | Initially Seronegative  |                              |              |             |    |       | Pre-Vacc.<br>Sera<br>Only | Total |  |
|-----------------------|--------------|-------------------------|------------------------------|--------------|-------------|----|-------|---------------------------|-------|--|
|                       |              | No.<br>Serol.<br>Tested | No.<br>Initially<br>Seropos. | No.<br>Conv. | Paired Sera |    | Total |                           |       |  |
| Children              |              |                         |                              |              |             |    |       |                           |       |  |
| ✓                     | 2            | 1                       | 1                            | 1            | 1           | 1  | 1     |                           | 1     |  |
| 1                     | 1            | 1                       |                              |              |             | 1  | 1     |                           |       |  |
| 2                     | 4            | 4                       |                              |              |             | 3  | 3     |                           |       |  |
| 3                     | 8            | 7                       |                              |              |             | 6  | 7     |                           |       |  |
| 4                     | 8            | 7                       |                              |              |             | 7  | 6     |                           |       |  |
| 5                     | 7            | 6                       |                              |              |             | 2  | 2     |                           |       |  |
| 7                     | 2            | 2                       |                              |              |             | 2  | 2     |                           |       |  |
| 8                     | 2            | 2                       |                              |              |             | 2  | 2     |                           |       |  |
| Total                 | 34           | 30                      | 1                            | 1            | 1           | 28 | 29    | 0                         | 29    |  |
| Adult Female Controls |              |                         |                              |              |             |    |       |                           |       |  |
| 13-19                 | 9            | 9                       | 9                            |              |             | 4  | 4     |                           | 4     |  |
| 20-29                 | 43           | 41                      | 37                           |              |             |    |       |                           |       |  |
| 30-39                 | 22           | 20                      | 20                           |              |             |    |       |                           |       |  |
| 40-41                 | 3            | 3                       | 3                            |              |             |    |       |                           |       |  |
| Total                 | 77           | 73                      | 69                           | 0            | 4           | 4  | 0     | 4                         |       |  |

Table 4: Maximum Temperature Recordings for Children Vaccinated with Combined Measles-Mumps-Rubella Vaccine Lot 92127 and for Their Unvaccinated Contact Controls (Study 232)

| Maximum Temperature<br>(°F, Oral) | Contact Control Children |               |               |               | Total Vaccinees       |               |               |               | Initially Seronegative to Measles-Mumps-Rubella |               |               |               |
|-----------------------------------|--------------------------|---------------|---------------|---------------|-----------------------|---------------|---------------|---------------|-------------------------------------------------|---------------|---------------|---------------|
|                                   | Days Observed            |               |               |               | Days Post-Vaccination |               |               |               | Days Post-Vaccination                           |               |               |               |
|                                   | 1-4                      | 5-12          | 13-18         | 19-28         | 1-4                   | 5-12          | 13-18         | 19-28         | 1-4                                             | 5-12          | 13-18         | 19-28         |
| <99                               | 17<br>(58.6%)            | 16<br>(55.2%) | 18<br>(62.1%) | 18<br>(64.3%) | 55<br>(57.3%)         | 51<br>(54.8%) | 61<br>(66.3%) | 48<br>(52.7%) | 41<br>(54.7%)                                   | 38<br>(52.8%) | 49<br>(69.0%) | 37<br>(51.4%) |
| 99-100.9                          | 10<br>(34.5%)            | 13<br>(44.8%) | 8<br>(27.6%)  | 9<br>(32.1%)  | 35<br>(36.4%)         | 26<br>(28.0%) | 26<br>(28.3%) | 35<br>(38.5%) | 28<br>(37.3%)                                   | 22<br>(30.6%) | 20<br>(28.2%) | 28<br>(38.9%) |
| 101-102.9                         | 2<br>(6.9%)              |               | 3<br>(10.3%)  | 1<br>(3.6%)   | 5<br>(5.2%)           | 13<br>(14.0%) | 3<br>(3.3%)   | 6<br>(6.6%)   | 5<br>(6.7%)                                     | 10<br>(13.9%) | 1<br>(1.4%)   | 5<br>(6.9%)   |
| 103-104.9                         |                          |               |               |               | 1<br>(1.0%)           | 3<br>(3.2%)   | 2<br>(2.2%)   | 2<br>(2.2%)   | 1<br>(1.3%)                                     | 2<br>(2.8%)   | 1<br>(1.4%)   | 2<br>(2.8%)   |
| Not Taken                         | 5                        | 5             | 5             | 6             | 5                     | 8             | 9             | 10            | 1                                               | 4             | 5             | 4             |
| Total Subjects                    | 34                       | 34            | 34            | 34            | 101                   | 101           | 101           | 101           | 76                                              | 76            | 76            | 76            |

Table 5: Clinical Complaints Recorded for Children Vaccinated with Combined Measles-Mumps-Rubella Vaccine Lot 92127 and for Their Unvaccinated Contact Controls (Study 232)

| Clinical Complaints               | Contact Control Children |               |               |               | Total Vaccinees       |               |               |               | Initially Seronegative to Measles-Mumps-Rubella |               |               |               |
|-----------------------------------|--------------------------|---------------|---------------|---------------|-----------------------|---------------|---------------|---------------|-------------------------------------------------|---------------|---------------|---------------|
|                                   | Days Observed            |               |               |               | Days Post-Vaccination |               |               |               | Days Post-Vaccination                           |               |               |               |
|                                   | 1-4                      | 5-12          | 13-18         | 19-28         | 1-4                   | 5-12          | 13-18         | 19-28         | 1-4                                             | 5-12          | 13-18         | 19-28         |
| Upper Respiratory Illness         | 5<br>(16.1%)             | 8<br>(25.8%)  | 3<br>(9.7%)   | 3<br>(9.7%)   | 20<br>(20.6%)         | 30<br>(30.9%) | 14<br>(14.4%) | 16<br>(16.5%) | 15<br>(20.0%)                                   | 24<br>(32.0%) | 10<br>(13.3%) | 14<br>(18.7%) |
| Otitis                            |                          |               | 1<br>(3.2%)   |               | 2<br>(2.1%)           | 3<br>(3.1%)   | 1<br>(1.0%)   | 3<br>(3.1%)   | 2<br>(2.7%)                                     | 3<br>(4.0%)   | 1<br>(1.3%)   | 3<br>(4.0%)   |
| Swollen Glands                    |                          |               | 1<br>(3.2%)   |               |                       | 1<br>(1.0%)   |               |               |                                                 |               |               |               |
| Gastrointestinal                  | 1<br>(3.2%)              | 2<br>(6.4%)   |               |               | 9<br>(9.3%)           | 6<br>(6.2%)   | 3<br>(3.1%)   | 2<br>(2.1%)   | 6<br>(8.0%)                                     | 4<br>(5.3%)   | 3<br>(4.0%)   | 1<br>(1.3%)   |
| Headache                          |                          |               |               | 1<br>(3.2%)   |                       |               |               |               |                                                 |               |               |               |
| Viral Infection                   |                          |               |               | 1<br>(3.2%)   |                       |               |               | 1<br>(1.0%)   |                                                 |               |               |               |
| Conjunctivitis                    |                          |               |               |               |                       |               | 1<br>(1.0%)   | 1<br>(1.0%)   |                                                 |               |               |               |
| Rash                              |                          |               |               |               | 5<br>(5.2%)           | 3<br>(3.1%)   |               | 1<br>(1.0%)   | 5<br>(6.7%)                                     | 2<br>(2.7%)   |               | 1<br>(1.3%)   |
| Irritability                      |                          |               |               |               | 7<br>(7.2%)           | 7<br>(7.2%)   | 3<br>(3.1%)   | 2<br>(2.1%)   | 6<br>(8.0%)                                     | 5<br>(6.7%)   | 1<br>(1.3%)   | 1<br>(1.3%)   |
| Chicken pox                       |                          |               |               |               |                       |               |               | 1<br>(1.0%)   |                                                 |               |               | 1<br>(1.3%)   |
| Irrelevant                        |                          |               |               |               |                       |               | 1<br>(1.0%)   | 3<br>(3.1%)   |                                                 |               |               | 1<br>(1.3%)   |
| Fever                             |                          |               |               |               |                       | 1<br>(1.0%)   | 1<br>(1.0%)   |               |                                                 | 1<br>(1.3%)   | 1<br>(1.3%)   |               |
| Anorexia                          |                          |               |               |               | 1<br>(1.0%)           | 1<br>(1.0%)   |               |               | 1<br>(1.3%)                                     | 1<br>(1.3%)   |               |               |
| Genitourinary Infection           |                          |               |               |               |                       |               | 1<br>(1.0%)   |               |                                                 |               |               |               |
| Flush                             |                          |               |               |               |                       | 1<br>(1.0%)   |               |               |                                                 | 1<br>(1.3%)   |               |               |
| Scarlatina                        |                          |               |               |               |                       |               | 1<br>(1.0%)   |               |                                                 |               | 1<br>(1.3%)   |               |
| Allergy                           |                          |               |               |               |                       |               | 1<br>(1.0%)   |               |                                                 |               | 1<br>(1.3%)   |               |
| Measles-like Rash                 |                          |               |               |               |                       | 3<br>(3.1%)   | 1<br>(1.0%)   |               |                                                 | 3<br>(4.0%)   | 1<br>(1.3%)   |               |
| Teething                          |                          |               |               |               | 3<br>(3.1%)           | 3<br>(3.1%)   | 4<br>(4.1%)   | 1<br>(1.0%)   | 3<br>(4.0%)                                     | 2<br>(2.7%)   | 2<br>(2.7%)   | 1<br>(1.3%)   |
| No Complaints                     | 25<br>(80.6%)            | 22<br>(71.0%) | 27<br>(87.1%) | 27<br>(87.1%) | 62<br>(63.9%)         | 57<br>(58.8%) | 72<br>(74.2%) | 71<br>(73.2%) | 47<br>(62.7%)                                   | 43<br>(57.3%) | 59<br>(78.7%) | 55<br>(73.3%) |
| Negative Physician's Surveillance | 3                        | 3             | 3             | 3             | 4                     | 4             | 4             | 4             | 1                                               | 1             | 1             | 1             |
| Total Subjects                    | 34                       | 34            | 34            | 34            | 101                   | 101           | 101           | 101           | 76                                              | 76            | 76            | 76            |

Reference No. 5(c)

Measles-Mumps-Rubella Virus Vaccine, Study 232

Live Measles-Mumps-Rubella Virus Vaccine

Lot 96400

Responsible Clinical Investigator:

Joseph Stokes, Jr., M.D., D.Sc.\*

Location:

Suburban Philadelphia, Pa.

Population:

Children residing in the Philadelphia area communities. 101 children with a negative history of measles, mumps, and rubella were vaccinated with 1.0 ml. of the combined vaccine. 74 guardians and 40 children served as contact controls. All contact controls were serologically tested for rubella HI antibody. Vaccinees were serologically tested for measles and rubella HI antibody and mumps neutralizing antibody.

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Table 1: Serologic Findings for Children Vaccinated with Combined Measles-Mumps-Rubella Vaccine  
 Lot 96400 in Suburban Philadelphia from September 11, 1969 to January 31, 1970 (Study 232)

| Age<br>(Yrs.) | Total<br>No.<br>Vacc. | No.<br>Serol.<br>Tested | Children Initially Seronegative to: |                  |                  |                       |               |       |         |                       |                                     |                 |                 |                       |
|---------------|-----------------------|-------------------------|-------------------------------------|------------------|------------------|-----------------------|---------------|-------|---------|-----------------------|-------------------------------------|-----------------|-----------------|-----------------------|
|               |                       |                         | Measles-Mumps-Rubella               |                  |                  |                       | Measles-Mumps |       |         |                       | Children Initially Seronegative to: |                 |                 |                       |
|               |                       |                         | Measles                             | Mumps            | Rubella          | Conversions/<br>Total | Measles       | Mumps | Rubella | Conversions/<br>Total | Measles                             | Mumps           | Rubella         | Conversions/<br>Total |
| <1            | 9                     | 9                       | 7/8                                 | 8/8              | 7/8              | 45/47                 | 1/1           | 1/1   | 1/1     | 4/5                   | 5/5                                 | 8/8             | 8/8             | 2/2                   |
| 1             | 60                    | 60                      | 47/47                               | 45/47            | 46/47            | 9/9                   |               |       |         | 1/1                   | 1/1                                 | 1/1             | 1/1             | 2/2                   |
| 2             | 13                    | 13                      | 9/9                                 | 8/9              | 9/9              | 3/4                   |               |       |         | 5/5                   | 2/2                                 | 2/2             | 2/2             | 2/2                   |
| 3             | 12                    | 12                      | 4/4                                 | 4/4              | 3/4              | 1/1                   |               |       |         | 1/1                   | 1/1                                 | 1/1             | 1/1             | 1/1                   |
| 4             | 5                     | 5                       | 1/1                                 | 1/1              | 1/1              | 0/1                   |               |       |         |                       |                                     |                 |                 |                       |
| 5             | 1                     | 1                       | 1/1                                 | 1/1              | 0/1              |                       |               |       |         |                       |                                     |                 |                 |                       |
| 6             | 1                     | 1                       |                                     |                  |                  |                       |               |       |         |                       |                                     |                 |                 |                       |
| Total         | 101                   | 101                     | 59/70<br>(84.3%)                    | 67/70<br>(95.7%) | 65/70<br>(92.9%) |                       | 1/1           | 1/1   | 1/1     | 12/12<br>(100%)       | 11/12<br>(91.7%)                    | 12/12<br>(100%) | 12/12<br>(100%) | 5/5                   |

Overall Conversion Rates

|         |                  |       |                  |         |                  |
|---------|------------------|-------|------------------|---------|------------------|
| Measles | 83/84<br>(98.8%) | Mumps | 80/83<br>(96.4%) | Rubella | 94/99<br>(94.9%) |
|---------|------------------|-------|------------------|---------|------------------|



Table 2: Distribution of Titers of Children Initially Seronegative to Measles, Mumps, and Rubella Who Were Vaccinated with Combined Measles-Mumps-Rubella Vaccine Lot 96400 in Suburban Philadelphia from September 11, 1969 to January 31, 1970 (Study 232)

| Measles (HAI)                 |                    | Mumps (Neut.)       |                    | Rubella (HAI)       |                    |
|-------------------------------|--------------------|---------------------|--------------------|---------------------|--------------------|
| Post-Vacc.<br>Titer           | No. of<br>Children | Post-Vacc.<br>Titer | No. of<br>Children | Post-Vacc.<br>Titer | No. of<br>Children |
| <5                            | 1                  | <1                  | 3                  | <8                  | 4                  |
| 5                             |                    | 1                   | 6                  | 8                   | 10                 |
| 10                            | 3                  | 2                   | 16                 | 16                  | 13                 |
| 20                            | 5                  | 4                   | 11                 | 32                  | 15                 |
| 40                            | 16                 | 8                   | 9                  | 64                  | 18                 |
| 80                            | 23                 | 16                  | 11                 | 128                 | 7                  |
| 160                           | 15                 | 32                  | 5                  | 256                 | 3                  |
| 320                           | 6                  | ≥64                 | 9                  | 512                 |                    |
| 640                           |                    |                     |                    |                     |                    |
| ≥2560                         | 1                  |                     |                    |                     |                    |
| Geometric<br>Mean Titer: 73.0 |                    | 6.4                 |                    | 28.4                |                    |

Table 3: Serologic Findings for Rubella Antibody for Children and Adults Acting As Contact Controls for Combined Measles-Mumps-Rubella Vaccine Lot 96400 (Study 232)

| Age (Yrs.)            | Total No. | Initially Seronegative |                            |           |             |                     | Total |
|-----------------------|-----------|------------------------|----------------------------|-----------|-------------|---------------------|-------|
|                       |           | No. Serol. Tested      | No. Initially Seropositive | No. Conv. | Paired Sera | Pre-Vacc. Sera Only |       |
| Children              |           |                        |                            |           |             |                     |       |
| <1                    | 1         | 1                      |                            |           |             |                     | 1     |
| 1                     | 1         | 1                      |                            |           |             |                     | 1     |
| 2                     | 7         | 7                      |                            |           |             |                     | 7     |
| 3                     | 10        | 10                     | 1                          |           |             |                     | 9     |
| 4                     | 7         | 7                      |                            |           |             |                     | 7     |
| 5                     | 4         | 4                      |                            |           |             |                     | 4     |
| 6                     | 1         | 1                      |                            |           |             |                     | 1     |
| 7                     | 4         | 4                      |                            |           |             |                     | 4     |
| 8                     | 2         | 2                      | 1                          |           |             |                     | 1     |
| 9                     | 2         | 2                      | 1                          |           |             |                     | 1     |
| 10                    | 1         | 1                      | 1                          |           |             |                     | 1     |
| Total                 | 40        | 40                     | 4                          | 0         | 36          | 0                   | 36    |
| Adult Female Controls |           |                        |                            |           |             |                     |       |
| 16-19                 | 4         | 4                      | 4                          |           |             |                     |       |
| 20-29                 | 34        | 34                     | 32                         |           |             |                     |       |
| 30-39                 | 26        | 26                     | 26                         |           |             |                     |       |
| 40-44                 | 10        | 10                     | 10                         |           |             |                     |       |
| Total                 | 74        | 74                     | 72                         | 0         | 2           | 0                   | 2     |

Table 4: Maximum Temperature Recordings for Children Vaccinated with Combined Measles-Mumps-Rubella Vaccine Lot 96400 and for Their Unvaccinated Contact Controls  
(Study 232)

| Maximum Temperature<br>(°F, Oral) | Contact Control Children |               |               |               | Total Vaccinees       |               |               |               | Initially Seronegative to Measles-Mumps-Rubella |               |               |               |
|-----------------------------------|--------------------------|---------------|---------------|---------------|-----------------------|---------------|---------------|---------------|-------------------------------------------------|---------------|---------------|---------------|
|                                   | Days Observed            |               |               |               | Days Post-Vaccination |               |               |               | Days Post-Vaccination                           |               |               |               |
|                                   | 1-4                      | 5-12          | 13-18         | 19-28         | 1-4                   | 5-12          | 13-18         | 19-28         | 1-4                                             | 5-12          | 13-18         | 19-28         |
| <99                               | 24<br>(63.2%)            | 18<br>(47.4%) | 21<br>(55.3%) | 21<br>(55.3%) | 60<br>(61.2%)         | 42<br>(42.8%) | 56<br>(58.9%) | 51<br>(53.1%) | 39<br>(56.5%)                                   | 25<br>(36.2%) | 36<br>(54.5%) | 34<br>(50.0%) |
| 99-100.9                          | 12<br>(31.6%)            | 17<br>(44.7%) | 14<br>(36.8%) | 14<br>(36.8%) | 34<br>(34.7%)         | 42<br>(42.8%) | 36<br>(37.9%) | 39<br>(40.6%) | 26<br>(37.7%)                                   | 33<br>(47.8%) | 27<br>(40.9%) | 28<br>(41.2%) |
| 101-102.9                         | 1<br>(2.6%)              | 3<br>(7.9%)   | 3<br>(7.9%)   | 1<br>(2.6%)   | 4<br>(4.1%)           | 12<br>(12.2%) | 3<br>(3.2%)   | 5<br>(5.2%)   | 4<br>(5.8%)                                     | 10<br>(14.5%) | 3<br>(4.5%)   | 5<br>(7.4%)   |
| 103-104.9                         | 1<br>(2.6%)              |               |               | 2<br>(5.3%)   |                       | 2<br>(2.0%)   |               | 1<br>(1.0%)   |                                                 | 1<br>(1.4%)   |               | 1<br>(1.5%)   |
| Not Taken                         | 2                        | 2             | 2             | 2             | 3                     | 3             | 6             | 5             | 1                                               | 1             | 4             | 2             |
| Total Subjects                    | 40                       | 40            | 40            | 40            | 101                   | 101           | 101           | 101           | 70                                              | 70            | 70            | 70            |

Table 5: Clinical Complaints Recorded for Children Vaccinated with Combined Measles-Mumps-Rubella Vaccine Lot 96400 and for Their Unvaccinated Contact Controls (Study 232)

| Clinical Complaints               | Contact Control Children |               |               |               | Total Vaccinees       |               |               |               | Initially Seronegative to Measles-Mumps-Rubella |               |               |               |
|-----------------------------------|--------------------------|---------------|---------------|---------------|-----------------------|---------------|---------------|---------------|-------------------------------------------------|---------------|---------------|---------------|
|                                   | Days Observed            |               |               |               | Days Post-Vaccination |               |               |               | Days Post-Vaccination                           |               |               |               |
|                                   | 1-4                      | 5-12          | 13-18         | 19-28         | 1-4                   | 5-12          | 13-18         | 19-28         | 1-4                                             | 5-12          | 13-18         | 19-28         |
| Upper Respiratory Illness         | 4<br>(10.5%)             | 7<br>(18.4%)  | 5<br>(13.2%)  | 6<br>(15.8%)  | 15<br>(15.2%)         | 22<br>(22.2%) | 10<br>(10.1%) | 13<br>(13.1%) | 13<br>(18.6%)                                   | 16<br>(22.8%) | 8<br>(11.4%)  | 10<br>(14.3%) |
| Otitis                            |                          |               |               | 1<br>(2.6%)   |                       | 2<br>(2.0%)   | 2<br>(2.0%)   | 4<br>(4.0%)   |                                                 | 1<br>(1.4%)   | 2<br>(2.8%)   | 3<br>(4.3%)   |
| Gastrointestinal                  | 2<br>(5.3%)              |               | 1<br>(2.6%)   |               | 1<br>(1.0%)           | 4<br>(4.0%)   | 3<br>(3.0%)   | 3<br>(3.0%)   |                                                 | 4<br>(5.7%)   | 2<br>(2.8%)   | 1<br>(1.4%)   |
| Rash                              | 1<br>(2.6%)              | 1<br>(2.6%)   | 1<br>(2.6%)   | 1<br>(2.6%)   | 2<br>(2.0%)           | 1<br>(1.0%)   | 3<br>(3.0%)   | 1<br>(1.0%)   | 2<br>(2.8%)                                     | 1<br>(1.4%)   | 2<br>(2.8%)   |               |
| Headache                          | 1<br>(2.6%)              |               |               |               |                       | 1<br>(1.0%)   |               | 1<br>(1.0%)   |                                                 |               |               | 1<br>(1.4%)   |
| Irritability                      | 2<br>(5.3%)              |               |               |               | 7<br>(7.1%)           | 8<br>(8.2%)   | 1<br>(1.0%)   | 1<br>(1.0%)   | 5<br>(7.1%)                                     | 7<br>(10.0%)  | 1<br>(1.4%)   |               |
| Anorexia                          | 1<br>(2.6%)              |               |               |               | 1<br>(1.0%)           | 2<br>(2.0%)   |               | 1<br>(1.0%)   | 1<br>(1.4%)                                     | 2<br>(2.8%)   |               | 1<br>(1.4%)   |
| Viral Infection                   |                          |               | 1<br>(2.6%)   |               |                       |               |               | 2<br>(2.0%)   |                                                 |               |               | 2<br>(2.8%)   |
| Fatigue                           |                          | 1<br>(2.6%)   |               |               |                       |               |               |               |                                                 |               |               |               |
| Teething                          |                          | 1<br>(2.6%)   |               |               | 1<br>(1.0%)           | 5<br>(5.0%)   | 3<br>(3.0%)   | 5<br>(5.0%)   | 1<br>(1.4%)                                     | 5<br>(7.1%)   | 2<br>(2.8%)   | 4<br>(5.7%)   |
| Local Reaction - Injection Site   |                          |               |               |               | 2<br>(2.0%)           |               |               |               | 1<br>(1.4%)                                     |               |               |               |
| Malaise                           |                          |               |               |               |                       | 1<br>(1.0%)   |               |               |                                                 | 1<br>(1.4%)   |               |               |
| Chicken Pox                       |                          |               |               |               | 1<br>(1.0%)           |               |               |               | 1<br>(1.4%)                                     |               |               |               |
| Irrelevant                        |                          |               |               |               | 1<br>(1.0%)           |               |               | 2<br>(2.0%)   | 1<br>(1.4%)                                     |               |               | 2<br>(2.8%)   |
| Flush                             |                          |               |               |               |                       | 1<br>(1.0%)   |               |               |                                                 | 1<br>(1.4%)   |               |               |
| Pain                              |                          |               |               |               |                       |               | 1<br>(1.0%)   |               |                                                 |               | 1<br>(1.4%)   |               |
| Measles-like Rash                 |                          |               |               |               |                       | 2<br>(2.0%)   |               |               |                                                 | 2<br>(2.8%)   |               |               |
| Whooping Cough                    |                          |               |               |               | 1<br>(1.0%)           |               |               |               | 1<br>(1.4%)                                     |               |               |               |
| Swollen Glands                    |                          |               |               |               |                       | 2<br>(2.0%)   |               |               |                                                 | 2<br>(2.8%)   |               |               |
| No Complaints                     | 27<br>(71.0%)            | 29<br>(76.3%) | 30<br>(78.9%) | 30<br>(78.9%) | 71<br>(71.7%)         | 62<br>(62.6%) | 81<br>(81.8%) | 69<br>(69.7%) | 47<br>(67.1%)                                   | 40<br>(57.1%) | 56<br>(80.0%) | 48<br>(68.6%) |
| Physician's Surveillance Negative | 2                        | 2             | 2             | 2             | 2                     | 2             | 2             | 2             |                                                 |               |               |               |
| Total Subjects                    | 40                       | 40            | 40            | 40            | 101                   | 101           | 101           | 101           | 70                                              | 70            | 70            | 70            |

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WEST POINT, PENNSYLVANIA 19486

(Clinical Data)

August 7, 1970

Dr. Roderick Murray, Director  
Division of Biologics Standards  
National Institutes of Health  
Bethesda, Maryland 20014

Dear Doctor Murray:

Reference No. 69-192

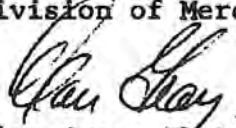
As indicated in Doctor Hilleman's letter to you of August 5, 1970, we are submitting to you three copies of Addendum No. 2 to Summary No. 1 of Clinical Investigative Studies of Combined Live Measles, Mumps, and Rubella Vaccine.

We plan to submit proposed printing for this product shortly. We hope that you have an opportunity to review this data as well as previous prior to our meeting of August 19. We hope at that time to be able to discuss with you any additional requirements that might be required for licensing.

With kindest personal regards,

Sincerely yours,

MERCK SHARP & DOHME  
Division of Merck & Co., Inc.



Alan Gray, Ph.D.  
Director, Biological Production

/jfu



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MERCK INSTITUTE  
FOR  
THERAPEUTIC RESEARCH  
WEST POINT, PENNSYLVANIA 19486

MAURICE R. HILLEMANN, Ph. D., D. Sc.  
EXECUTIVE DIRECTOR

August 5, 1970

Dr. Roderick Murray, Director  
Division of Biologics Standards  
National Institutes of Health  
Bethesda, Maryland 20014

Dear Doctor Murray:

Shortly Dr. A. Gray will send you Addendum No. 2 to Summary No. 1 of clinical investigative studies of combined live measles virus vaccine (Moraten line - ATTENUVAX), Jeryl Lynn mumps virus vaccine (MUMPSVAX), and HPV-77 duck rubella virus vaccine (MERUVAX) dated August 5, 1970.

The present submission summarizes the findings in the rather extensive studies carried out by Dr. Victor Villarejos's associates in Central America. The findings are consistent with those obtained by Drs. Stokes and Weibel in the large-scale trials in Philadelphia.

The seroconversion rates are a bit lower in Central America and the "seroconversions" of rubella among contacts are several. These appear due to endemic rubella and human error, some of which could be detected.

Further details relating to clinical studies of this product are to be found in your file of submissions under DBS-IND 260, in the files of this department, and in the files of the individual clinicians.

Kindest regards.

Sincerely,



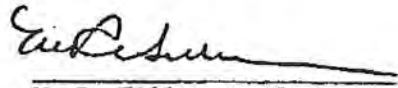
Maurice R. Hilleman, Ph.D.  
Director  
Virus & Cell Biology Research

/b1

Addendum No. 2  
to Summary No. 1  
of  
Clinical Investigative Studies  
of

Combined Live Measles Virus Vaccine (Moraten Line - ATTENUVAX)  
Jeryl Lynn Mumps Virus Vaccine (MUMPSVAX)  
HPV-77 Duck Rubella Virus Vaccine (MERUVAX)

for purpose of support for  
a license to manufacture and sell.

  
M. R. Hilleman, Ph.D.

Prepared: August 5, 1970  
Merck Institute for Therapeutic  
Research, West Point, Penna.

Clinical Investigation of Combined Live Attenuated Measles (Moraten),  
Mumps (Jeryl Lynn), and Rubella (HPV-77 Duck) Vaccine

1. Previous submissions of 9/26/69 and 3/4/70 described clinical tests of the above combined product carried out under the direction of Dr. Joseph Stokes, Jr. and Dr. Victor Villarejos.

The studies by Dr. Stokes were extensive and those by Dr. Villarejos were only token. The present submission relates to a presentation of the extensive studies carried out by Dr. Villarejos.

The findings relate to Lots 92126, 92127, and 96400.

The protocols of these lots were submitted previously under References 4(b), 4(c), and 4(d).

The clinical studies were carried out along the lines previously described.

2. Clinical Study Summaries

Reference 3(a) - Study 220-220B, Dr. Victor Villarejos

Test of Lot 92127. The previous submission (No. 1) described tests of the above vaccine in 100 children. The present report describes the findings in tests of 367 children who were vaccinated. The findings are self-explanatory and we may conclude that the responses to the individual components were not impaired significantly by combination. Further, there were no significant clinical reactions.

There was one unexplained instance of rubella seroconversion in a contact female guardian. It may be noted from Dr. Villarejos's letter (which follows the clinical data in Reference 3(a)) of 11/21/69, that rubella was present in the community at the time the vaccine was given.

Reference 3(b) - Study 220-220B, Dr. Victor Villarejos

Test of Lot 92126. The findings are given in the reference and are self-explanatory. There was no significant impairment of serologic response and no significant clinical reaction.

There were two unexplained instances of rubella seroconversion in contacts--one in a child and one in a mother. As noted in Dr. Villarejos's letter of 11/21/69, rubella was endemic in the community when the vaccine was given.

Reference 3(c) - Study 220B, Dr. Victor Villarejos

Test of Lot 96400. The findings are given in the reference and are self-explanatory. There was no significant impairment of serologic response and no significant clinical reaction.

There were two instances of rubella seroconversion in contacts, both in children. As noted in Dr. Villarejos's letter of 3/2/70, rubella was endemic in the community when the vaccine was given; and, further, it was noted by the clinician that the two children (patients #1194 and #6402) were exposed to rubella prior to vaccination.

Reference 6(a) - Study 220C, Dr. Victor Villarejos

Test of Lot 92126. The findings are given in the reference and are self-explanatory. There was no significant impairment of serologic response and no significant clinical reaction.

There were five instances of rubella seroconversion in contact control children. In one instance, the child (#871) showed a seroconversion to mumps. The remaining four instances are unexplained. There were two additional instances of rubella seroconversion in female guardians. In both instances, there was specimen mix-up. In one case (#128-10), the blood type was O and A. In the other (#163-10), the blood type was O and B. These two cases were eliminated from the study.

Reference 6(b) - Study 220C, Dr. Victor Villarejos

Test of Lot 92127. The findings are given in the reference and are self-explanatory. There was no significant impairment of serologic response and no significant clinical reaction.

There were four instances of rubella seroconversion in contact control children. Child #2281 showed a measles conversion. There were two instances of blood specimen mix-up among vaccinees in a single family (#2132, O-A-O; #2133, A-O-A; these were eliminated from the study). A third member of this same family (#2131) was a rubella-converting control. There was an additional instance of a blood specimen mix-up in another vaccinee (#2352), B-O-O; he was also eliminated from the study.

Reference 6(c) - Study 220C, Dr. Victor Villarejos

Test of Lot 96400. The findings are given in the reference and are self-explanatory. There was no significant impairment of serologic response and no significant clinical reaction.

There were three instances of rubella seroconversion in contact controls, two in children and one in a mother. Of these, child #3523 also showed a rise to measles. There was insufficient serum for retest of the remaining two rubella seroconverters. In addition, one mother (#340-10) also showed a rubella seroconversion. Her blood specimens were mixed, going from B to O. She was eliminated from the study.

3. Reference 7 is included for information purposes. It describes the findings with combined measles, mumps, and rubella vaccines carried out by Smorodintsev et al. in the Soviet Union.

#### 4. Overall Results

The total number of triple negatives now tested is 715. There was a response to measles in 684 (95.7%); to mumps in 680 (95.1%); and to rubella in 670 (93.7%).

The results among triple negatives for each of the vaccine lots tested were as follows:

| <u>Vaccine<br/>Lot</u> | <u>Seroconversions/Triple Negatives</u> |                 |                 |
|------------------------|-----------------------------------------|-----------------|-----------------|
|                        | <u>Measles</u>                          | <u>Mumps</u>    | <u>Rubella</u>  |
| 310                    | 30/30 (100%)                            | 29/30 (96.7%)   | 30/30 (100%)    |
| 92126                  | 223/237 (94.1%)                         | 224/237 (94.5%) | 222/237 (93.7%) |
| 92127                  | 209/221 (94.6%)                         | 207/221 (93.7%) | 209/221 (94.6%) |
| 96400                  | 222/227 (97.8%)                         | 220/227 (96.9%) | 209/227 (92.1%) |



February 28, 1969

Clinical Protocol - Study 220

(Dr. V. Villarejos, ICMRT, San Jose, Costa Rica)

Combined: Moraten measles  
Jeryl Lynn mumps  
HPV-77 duck rubella vaccine

3 lots

1. Background.

A combined dried vaccine of above composition has been developed.

The vaccine evokes antibody in essentially all children to all 3 viruses. Measles vaccine causes mild febrile and other reactions in a fraction of the child recipients. The other components of the vaccine cause no significant reaction.

The need is to test the vaccine in triply seronegative children and to measure

- a) antibody responses and
- b) clinical reactions

in triply seronegative children and to measure possible rubella transmission to a token population of susceptible contacts.

2. Vaccines. Combined Measles-Mumps-Rubella

Lot No. 92126 (C-7995)  
          92127 (C-7996)  
          96400 (C-8095)

Rehydrate with 1.2 ml. of distilled water. Dose is 1.0 ml. given subcutaneously.

3. Study plan.

a) Clinical

For each lot of vaccine (3 lots or possibly only 2 lots) select as many children as possible with negative history of measles, mumps and rubella vaccination and previous illness (up to 200 children per lot).

At the time Study 220 was initiated, lot 96400 was not available. Only lots 92126 and 92127 were used.



Vaccinate but keep every tenth eligible child as an unvaccinated contact control. Also bleed all mothers in families.

Schedule - Each Lot

| Time<br>Day | Group A<br>(Around 200 children<br>per lot)            | Group B<br>Every 10th child (in<br>families where another<br>child received vaccine) | Group C<br>Mothers    |
|-------------|--------------------------------------------------------|--------------------------------------------------------------------------------------|-----------------------|
| 0           | Bleed 15-20 ml.<br>Vaccinate 1.0 ml.<br>subcutaneously | Bleed 15-20 ml.<br>--                                                                | Bleed 15-20 ml.<br>-- |
| 42-44       | Bleed 15-20 ml.                                        | Bleed 15-20 ml.                                                                      | Bleed 15-20 ml.       |

NOTE: BLEEDINGS ON ALL SUBJECTS

b) Laboratory.

Remove sera from clot and store frozen at  $-20^{\circ}$  C. until shipped in dry ice.

Test all sera by HI or Neut. for all antibodies.

c) Records - as per attached

4. Caution

Vaccines contain chick and duck embryo proteins and neomycin. Vaccines should not be given to persons sensitive to these substances.

  
M. R. Hilleman

Note: To start about April 1, 1969 in Costa Rica, on the border.

NOTE: Record forms  
Bleeding equipment  
Syringes  
Distilled water  
All else,  
to be shipped

June 30, 1969

CLINICAL PROTOCOL STUDY 220B

(Dr. Victor Villarejos, ICMRT, San Jose, Costa Rica)

Same protocol as Study 220 of February 28, 1969, attached.

Combined Measles-Mumps-Rubella Virus Vaccine, Lot 61584/96400 (C 8095)

A handwritten signature in dark ink, appearing to read 'M. R. Hilleman', with a long horizontal flourish extending to the right.

M. R. Hilleman

February 28, 1969

Clinical Protocol - Study 220

(Dr. V. Villarejos, ICMRT, San Jose, Costa Rica)

Combined: Moraten measles  
Jeryl Lynn mumps  
HPV-77 duck rubella vaccine

3 lots

1. Background.

A combined dried vaccine of above composition has been developed.

The vaccine evokes antibody in essentially all children to all 3 viruses. Measles vaccine causes mild febrile and other reactions in a fraction of the child recipients. The other components of the vaccine cause no significant reaction.

The need is to test the vaccine in triply seronegative children and to measure

- a) antibody responses and
- b) clinical reactions

in triply seronegative children and to measure possible rubella transmission to a token population of susceptible contacts.

2. Vaccines. Combined Measles-Mumps-Rubella

Lot No. 92126 (C-7995)  
92127 (C-7996)  
96400 (C-8095)

Rehydrate with 1.2 ml. of distilled water. Dose is 1.0 ml. given subcutaneously.

3. Study plan.

a) Clinical

For each lot of vaccine (3 lots or possibly only 2 lots) select as many children as possible with negative history of measles, mumps and rubella vaccination and previous illness (up to 200 children per lot).

Vaccinate but keep every tenth eligible child as an unvaccinated contact control. Also bleed all mothers in families.

Schedule - Each Lot

| Time<br>Day | Group A<br>(Around 200 children<br>per lot)            | Group B<br>Every 10th child (in<br>families where another<br>child received vaccine) | Group C<br>Mothers    |
|-------------|--------------------------------------------------------|--------------------------------------------------------------------------------------|-----------------------|
| 0           | Bleed 15-20 ml.<br>Vaccinate 1.0 ml.<br>subcutaneously | Bleed 15-20 ml.<br>--                                                                | Bleed 15-20 ml.<br>-- |
| 42-44       | Bleed 15-20 ml.                                        | Bleed 15-20 ml.                                                                      | Bleed 15-20 ml.       |

NOTE: BLEEDINGS ON ALL SUBJECTS

b) Laboratory.

Remove sera from clot and store frozen at  $-20^{\circ}$  C. until shipped in dry ice.

Test all sera by HI or Neut. for all antibodies.

c) Records - as per attached

4. Caution

Vaccines contain chick and duck embryo proteins and neomycin. Vaccines should not be given to persons sensitive to these substances.

  
M. R. Hilleman

Note: To start about April 1, 1969 in Costa Rica, on the border.

NOTE: Record forms  
Bleeding equipment  
Syringes  
Distilled water  
All else,  
to be shipped

Reference No. 3(a)

Measles-Mumps-Rubella Virus Vaccine, Study No. 220 - 220B

Live Measles-Mumps-Rubella Virus Vaccine

Lot 92127

Responsible Clinical Investigator:

Victor M. Villarejos, M.D., M.P.H. and T.M., Dr. P.H.\*

Location:

Costa Rica and San Salvador

Population:

Children whose families reside in the region near the Panamanian Border, Costa Rica, and in San Salvador. 367 children with a negative history for measles, mumps, and rubella were vaccinated with 1.0 ml of the combined vaccine. 183 guardians and 36 children served as contact controls. All contact controls were serologically tested for rubella HAI antibody. Vaccinees were serologically tested for measles and rubella HAI antibody and mumps neutralizing antibody.

\* Associate Director  
Louisiana State University  
International Center for Medical Research and Training  
San Jose, Costa Rica

Table 1: Serologic Findings for Children Vaccinated with Combined Measles-Mumps-Rubella Vaccine Lot 92127 in Costa Rica on April 21-30, 1969 and in San Salvador on November 10-12, 1969 (Study 220-2208)

| Vaccination |             |                   | Children Initially Seronegative to: |               |                   |               |       |                   |                 |               |                   |               |               |                   | Initially Seropositive to Measles, Mumps, & Rubella |       |       |
|-------------|-------------|-------------------|-------------------------------------|---------------|-------------------|---------------|-------|-------------------|-----------------|---------------|-------------------|---------------|---------------|-------------------|-----------------------------------------------------|-------|-------|
| Age (Yrs.)  | Total Vacc. | No. Serol. Tested | Measles-Mumps-Rubella               |               |                   | Measles-Mumps |       |                   | Measles-Rubella |               |                   | Mumps-Rubella |               |                   |                                                     |       |       |
|             |             |                   | Measles                             | Mumps         | Conversions/Total | Measles       | Mumps | Conversions/Total | Measles         | Rubella       | Conversions/Total | Mumps         | Rubella       | Conversions/Total |                                                     |       |       |
| 1           | 4           | 3                 | 2/2                                 | 2/2           | 2/2               |               |       | 1/1               | 23/23           | 23/23         | 1/1               | 7/7           | 7/7           |                   |                                                     |       |       |
| 2           | 73          | 67                | 31/31                               | 31/31         | 26/31             | 1/1           | 1/1   | 8/8               | 8/8             | 14/14         | 14/14             | 21/22         | 21/22         | 1/1               | 1/1                                                 | 1/1   | 4/4   |
| 3           | 56          | 53                | 20/22                               | 18/22         | 20/22             |               |       | 14/14             | 13/14           | 20/22         | 20/22             | 17/20         | 17/20         | 2/3               | 2/3                                                 | 2/3   | 7/7   |
| 4           | 72          | 69                | 9/10                                | 9/10          | 10/10             | 1/1           | 0/1   | 5/7               | 5/7             | 5/5           | 5/5               | 20/22         | 20/22         | 4/4               | 4/4                                                 | 10/10 | 19/19 |
| 5           | 67          | 60                | 9/9                                 | 8/9           | 9/9               |               |       | 5/5               | 5/5             | 2/2           | 2/2               | 9/9           | 9/9           | 10/10             | 10/10                                               | 12/12 | 24/24 |
| 6           | 66          | 62                | 5/6                                 | 4/6           | 5/6               | 1/1           | 1/1   | 1/1               | 1/1             | 2/2           | 2/2               | 9/9           | 9/9           | 1/1               | 1/1                                                 | 10/10 | 12/12 |
| 7           | 27          | 27                | 0/1                                 | 1/1           | 1/1               | 1/1           | 1/1   |                   |                 |               |                   |               |               |                   |                                                     |       | 10/10 |
| 8           | 2           | 2                 | 1/1                                 | 1/1           | 1/1               |               |       |                   |                 |               |                   |               |               |                   |                                                     |       |       |
| Total       | 367         | 343               | 77/82 (93.9%)                       | 74/82 (90.2%) | 74/82 (90.2%)     | 3/3           | 2/3   | 58/60 (96.7%)     | 57/60 (95.0%)   | 89/94 (94.7%) | 85/94 (90.4%)     | 4/6           | 19/20 (95.0%) | 66/69 (95.7%)     | 9                                                   | 9     | 9     |

Overall Conversion Rates

| Measles         | Mumps           | Rubella         |
|-----------------|-----------------|-----------------|
| 142/151 (94.0%) | 184/199 (92.5%) | 282/305 (92.5%) |

Table 2: Distribution of Titers of Children Initially Seronegative for Measles, Mumps, and Rubella Who Were Vaccinated with Combined Measles-Mumps-Rubella Vaccine Lot 92127 (Study 220-220B)

| Post-Vacc.<br>Titer      | Measles (HAI)      |                     | Mumps (Neut.)      |                     | Rubella (HAI)      |                     |
|--------------------------|--------------------|---------------------|--------------------|---------------------|--------------------|---------------------|
|                          | No. of<br>Children | Post-Vacc.<br>Titer | No. of<br>Children | Post-Vacc.<br>Titer | No. of<br>Children | Post-Vacc.<br>Titer |
| <5                       | 2                  | <4                  | 3                  | <1                  | 8                  | <8                  |
| 5                        | 0                  | 4                   | 2                  | 1                   | 3                  | 8                   |
| 10                       | 1                  | 8                   | 2                  | 2                   | 17                 | 16                  |
| 20                       | 1                  | 16                  | 4                  | 4                   | 15                 | 32                  |
| 40                       | 6                  | 32                  | 26                 | 8                   | 8                  | 64                  |
| 80                       | 14                 | 64                  | 13                 | 16                  | 6                  | 128                 |
| 160                      | 3                  | 128                 | 2                  | 32                  | 13                 | 256                 |
| 320                      | 2                  | 256                 | 1                  | 64                  | 7                  | 512                 |
| 640                      | 0                  | 512                 | 0                  | 128                 | 5                  |                     |
| Geometric<br>Mean Titer: | 35.6               |                     | 7.4                |                     | 21.0               |                     |



Table 3: Serologic Findings for Rubella Antibody for Children and Adults Acting As Contact Controls for Combined Measles-Mumps-Rubella Vaccine Lot 92127 (Study 220-220B)

| Age<br>(Yrs.)         | Total<br>No. | No.<br>Serol.<br>Tested | No.<br>Initially<br>Seropos. | Initially Seronegative |            |       |
|-----------------------|--------------|-------------------------|------------------------------|------------------------|------------|-------|
|                       |              |                         |                              | No. Showing<br>Rise    | No<br>Rise | Total |
| Children              |              |                         |                              |                        |            |       |
| 1                     | 7            | 7                       |                              |                        | 7          | 7     |
| 2                     | 7            | 7                       |                              |                        | 7          | 7     |
| 3                     | 8            | 8                       |                              |                        | 8          | 8     |
| 4                     | 3            | 3                       |                              |                        | 3          | 3     |
| 5                     | 5            | 5                       | 2                            |                        | 3          | 3     |
| 6                     | 5            | 5                       | 2                            |                        | 3          | 3     |
| 7                     | 1            | 1                       |                              |                        | 1          | 1     |
| Total                 | 36           | 36                      | 4                            | 0                      | 32         | 32    |
| Adult Female Controls |              |                         |                              |                        |            |       |
| 19-29                 | 78           | 77                      | 56                           |                        | 21         | 21    |
| 30-39                 | 69           | 66                      | 50                           | 1                      | 15         | 16    |
| 40-49                 | 33           | 32                      | 28                           |                        | 4          | 4     |
| 54-67                 | 3            | 3                       | 2                            |                        | 1          | 1     |
| Total                 | 183          | 178                     | 136                          | 1                      | 41         | 42    |

Table 4: Clinical Complaints Recorded for Children Vaccinated with Combined Measles-Mumps-Rubella Vaccine Lot 92127 and for Their Unvaccinated Contact Controls (Study 220-820B)

| Clinical Complaints                   | Adult Contact Controls |                |                |                | Contact Control Children |               |               |               | Total Vaccinees       |                |                       |                | Initially Seronegative to Measles, Mumps, & Rubella |               |                       |               |
|---------------------------------------|------------------------|----------------|----------------|----------------|--------------------------|---------------|---------------|---------------|-----------------------|----------------|-----------------------|----------------|-----------------------------------------------------|---------------|-----------------------|---------------|
|                                       | Days Observed          |                | Days Observed  |                | Days Observed            |               | Days Observed |               | Days Post-Vaccination |                | Days Post-Vaccination |                | Days Post-Vaccination                               |               | Days Post-Vaccination |               |
|                                       | 1-4                    | 5-12           | 13-18          | 19-28          | 1-4                      | 5-12          | 13-18         | 19-28         | 1-4                   | 5-12           | 13-18                 | 19-28          | 1-4                                                 | 5-12          | 13-18                 | 19-28         |
| Upper Respiratory Illness             | 3<br>(1.8%)            | 13<br>(7.7%)   | 5<br>(3.0%)    | 5<br>(3.0%)    | 2<br>(5.6%)              | 9<br>(25.0%)  | 6<br>(16.7%)  | 4<br>(11.1%)  | 52<br>(14.2%)         | 74<br>(20.3%)  | 48<br>(13.2%)         | 34<br>(9.3%)   | 10<br>(12.2%)                                       | 16<br>(19.5%) | 9<br>(11.0%)          | 8<br>(9.8%)   |
| Otitis                                | 1<br>(0.6%)            | 6<br>(3.6%)    | 4<br>(2.4%)    | 1<br>(0.6%)    |                          | 1<br>(2.8%)   |               |               | 1<br>(0.3%)           | 6<br>(1.6%)    |                       | 1<br>(0.3%)    |                                                     | 3<br>(3.7%)   |                       |               |
| Swollen Glands                        | 1<br>(0.6%)            | 4<br>(2.4%)    | 3<br>(1.8%)    |                |                          | 2<br>(5.6%)   |               |               |                       | 3<br>(0.8%)    | 2<br>(0.5%)           |                |                                                     | 1<br>(1.2%)   |                       |               |
| Conjunctivitis                        | 2<br>(1.2%)            | 2<br>(1.2%)    |                |                | 1<br>(2.8%)              | 1<br>(2.8%)   | 1<br>(2.8%)   | 1<br>(2.8%)   | 3<br>(0.8%)           | 11<br>(3.0%)   | 4<br>(1.1%)           | 2<br>(0.5%)    | 1<br>(1.2%)                                         | 1<br>(1.2%)   | 1<br>(1.2%)           | 1<br>(1.2%)   |
| Gastrointestinal                      | 5<br>(3.0%)            | 13<br>(7.7%)   | 5<br>(3.0%)    | 4<br>(2.4%)    | 2<br>(5.6%)              | 10<br>(27.8%) | 7<br>(19.4%)  | 5<br>(13.9%)  | 41<br>(11.2%)         | 82<br>(22.5%)  | 34<br>(9.3%)          | 31<br>(8.5%)   | 7<br>(8.5%)                                         | 22<br>(26.8%) | 9<br>(11.0%)          | 8<br>(9.8%)   |
| Rash                                  |                        |                |                |                |                          |               |               |               |                       |                |                       |                |                                                     |               |                       |               |
| Headache                              | 33<br>(19.6%)          | 48<br>(28.6%)  | 16<br>(9.5%)   | 9<br>(5.4%)    | 1<br>(2.8%)              | 2<br>(5.6%)   |               |               | 12<br>(3.3%)          | 14<br>(3.8%)   | 5<br>(1.4%)           | 2<br>(0.5%)    | 1<br>(1.2%)                                         | 4<br>(4.9%)   |                       | 1<br>(1.2%)   |
| Irritability                          | 5<br>(3.0%)            | 9<br>(5.4%)    | 2<br>(1.2%)    | 1<br>(0.6%)    | 2<br>(5.6%)              | 8<br>(22.2%)  | 5<br>(13.9%)  | 6<br>(16.7%)  | 23<br>(6.3%)          | 81<br>(22.2%)  | 40<br>(11.0%)         | 21<br>(5.8%)   | 8<br>(9.8%)                                         | 27<br>(32.9%) | 13<br>(15.9%)         | 8<br>(9.8%)   |
| Malaise                               | 23<br>(13.7%)          | 34<br>(20.2%)  | 13<br>(7.7%)   | 6<br>(3.6%)    | 3<br>(8.3%)              | 6<br>(16.7%)  | 5<br>(13.9%)  | 4<br>(11.1%)  | 52<br>(14.2%)         | 72<br>(19.7%)  | 33<br>(9.0%)          | 20<br>(5.5%)   | 16<br>(19.5%)                                       | 20<br>(24.4%) | 8<br>(9.8%)           | 3<br>(3.7%)   |
| Irrelevant                            | 1<br>(0.6%)            |                |                |                |                          |               |               |               |                       |                |                       |                |                                                     |               |                       |               |
| Fever                                 | 2<br>(1.2%)            | 6<br>(3.6%)    | 1<br>(0.6%)    | 1<br>(0.6%)    | 1<br>(2.8%)              | 5<br>(13.9%)  | 3<br>(8.3%)   | 2<br>(5.6%)   | 18<br>(4.9%)          | 54<br>(14.8%)  | 19<br>(5.2%)          | 4<br>(1.1%)    | 3<br>(3.7%)                                         | 11<br>(13.4%) | 5<br>(6.1%)           |               |
| Anorexia                              | 14<br>(8.3%)           | 20<br>(11.9%)  | 8<br>(4.8%)    | 5<br>(3.0%)    | 4<br>(11.1%)             | 9<br>(25.0%)  | 4<br>(11.1%)  | 2<br>(5.6%)   | 33<br>(9.0%)          | 70<br>(19.2%)  | 30<br>(8.2%)          | 19<br>(5.2%)   | 10<br>(12.2%)                                       | 18<br>(22.0%) | 9<br>(11.0%)          | 6<br>(7.3%)   |
| Exanthema                             |                        |                |                |                |                          | 1<br>(2.8%)   | 1<br>(2.8%)   |               | 1<br>(0.3%)           | 3<br>(0.8%)    | 3<br>(0.8%)           | 4<br>(1.1%)    |                                                     | 1<br>(1.2%)   | 1<br>(1.2%)           | 2<br>(2.4%)   |
| Rubella-like Rash                     |                        |                |                |                |                          |               |               |               |                       |                |                       |                |                                                     |               |                       |               |
| Aggravated Infection - Injection Site |                        |                |                |                |                          |               |               |               |                       |                |                       |                |                                                     |               |                       |               |
| Measles-like Rash                     |                        |                |                |                |                          |               |               |               |                       |                |                       |                |                                                     |               |                       |               |
| No Complaints                         | 113<br>(67.3%)         | 103<br>(61.3%) | 131<br>(78.0%) | 148<br>(88.1%) | 27<br>(75.0%)            | 17<br>(47.2%) | 22<br>(61.1%) | 25<br>(69.4%) | 231<br>(62.9%)        | 165<br>(45.2%) | 251<br>(68.8%)        | 282<br>(77.3%) | 52<br>(63.4%)                                       | 37<br>(45.1%) | 55<br>(67.1%)         | 62<br>(75.6%) |
| Physician's Surveillance Negative     | 15                     | 15             | 15             | 25             |                          |               |               |               |                       | 2              | 2                     | 2              |                                                     |               |                       |               |
| Total Subjects                        | 183                    | 183            | 183            | 183            | 36                       | 36            | 36            | 36            | 367                   | 367            | 367                   | 367            | 82                                                  | 82            | 82                    | 82            |



LOUISIANA STATE UNIVERSITY  
SCHOOL OF MEDICINE  
INTERNATIONAL CENTER FOR MEDICAL RESEARCH  
AND TRAINING

SAN JOSE, COSTA RICA  
APARTADO 5140  
Cable: ICMRT

November 21, 1969

Miss Brenda Abbott  
Virus & Cell Research  
Merck Institute for Therapeutic Research  
West Point, Pennsylvania 19486

Dear Miss Abbott:

The additional information requested in your letter of October 27 and cable of November 20, is as follows:

Study 222

Children: 2014 - 2042 - 2043 - 2282 - 2401. No symptoms were recorded in these children other than fever. Some school children were attending school with elevated temperature and no other complaints. Complaints in smaller children may have been oversseen by unobserving mothers and not reported to visiting nurse.

Study 223

- I.
  1. 15-01 - No symptoms recorded
  2. 15-02 - Rectal temperature
  3. 16-02 - Rectal temperature
  4. 46-01 - Irritability, anorexia, malaise
  5. 52-01 - No symptoms recorded
  6. 103-02 - No symptoms recorded
  7. 104-01 " " "
- II.
  1. 44-02 Attenuated rubella, probably in incubation at time of vaccination.
  2. 61-01 Attenuated rubella, probably in incubation at time of vaccination.

Study 221-B

- I. 1. 30-02 - Pyodermitis
- 2. 36-02 - Chicken-pox
- 3. 109-02 - " "
- 4. 337-03 - " "
- 5. 272-02 - No rash
- 6. 383-04 - Chicken pox
- 7. 442-02 - " "
- II. 1. 54-04 - Asymptomatic
- 2. 120-05 - } Not controlled. Left
- 3. 120-06 - } the community. Were
- 4. 152-04 - } traced for second bloods

Non-Responsive - Not MMR



Further investigation of the communities involved disclosed that indeed low level rubella was present during January to March in San Vito and La Lucha, the areas vaccinated in study 220. The same was true in the provinces of Alajuela and Heredia (Study 221).

It was also possible to contact families of cases 712-15, 5092-95, 8592-93, 5742-44, 6031-33 and ascertain that in each case there had been

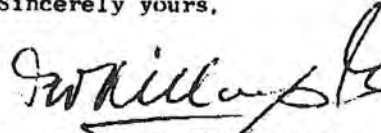
contact with an ouvert case of rubella prior to vaccination.

I am also enclosing copies of the corrected records of [REDACTED] and [REDACTED] which you did not receive.

Hope your records will be now in order.

Best regards,

Sincerely yours,



Dr. Victor M. Villarejos  
Program Coordinator  
LSU-ICMRT

VMV/vl

Encls.

Measles-Mumps-Rubella Virus Vaccine, Study No. 220 - 220B

Live Measles-Mumps-Rubella Virus Vaccine  
Lot 92126

Responsible Clinical Investigator:

Victor M. Villarejos, M.D., M.P.H. and T.M., Dr. P.H. \*

Location:

Costa Rica and San Salvador

Population:

Children whose families reside in the region near the Panamanian Border, Costa Rica, and in San Salvador. 313 children with a negative history for measles, mumps and rubella were vaccinated with 1.0 ml of the combined vaccine. 169 guardians and 31 children served as contact controls. All contact controls were serologically tested for rubella HAI antibody. Vaccinees were serologically tested for measles and rubella HAI antibody and mumps neutralizing antibody.

\* Associate Director  
Louisiana State University  
International Center for Medical Research and Training  
San Jose, Costa Rica

Table 1: Serologic Findings for Children Vaccinated with Combined Measles-Mumps-Rubella Vaccine Lot 92126 in Costa Rica from 4/8/69 to 4/12/69 and in San Salvador from 11/10/69 to 11/14/69 (Study 220-2208)

| Vaccination |            | Children Initially Seropositive to: |               |               |                   |               |               |                 |                   |               |               |               |                   | Seropositive to Measles, Mumps, and Rubella |       |         |
|-------------|------------|-------------------------------------|---------------|---------------|-------------------|---------------|---------------|-----------------|-------------------|---------------|---------------|---------------|-------------------|---------------------------------------------|-------|---------|
| Age (Yrs.)  | No. Tested | Measles-Mumps-Rubella               |               |               | Measles-Mumps     |               |               | Measles-Rubella |                   |               | Mumps-Rubella |               |                   |                                             |       |         |
|             |            | Measles                             | Mumps         | Rubella       | Conversions/Total | Measles       | Mumps         | Rubella         | Conversions/Total | Measles       | Mumps         | Rubella       | Conversions/Total | Measles                                     | Mumps | Rubella |
| < 1         | 6          | 2/2                                 | 2/2           | 2/2           | 4/6               | 3/3           | 1/1           | 1/1             | 1/1               | 1/1           | 1/1           | 1/1           | 1/1               | 1/1                                         | 1/1   | 1/1     |
| 1           | 55         | 18/18                               | 18/18         | 16/18         | 3/3               | 2/2           | 1/1           | 9/9             | 9/9               | 5/5           | 5/5           | 5/5           | 4/4               | 2/2                                         | 2/2   | 2/2     |
| 2           | 58         | 10/10                               | 7/10          | 10/10         | 1/1               | 1/1           | 1/1           | 13/13           | 13/13             | 16/16         | 16/16         | 13/13         | 3/3               | 7/7                                         | 7/7   | 7/7     |
| 3           | 58         | 10/10                               | 8/10          | 10/10         | 2/2               | 2/2           | 1/1           | 1/1             | 1/1               | 18/19         | 19/19         | 13/13         | 1/1               | 12/12                                       | 12/12 | 12/12   |
| 4           | 55         | 3/4                                 | 4/4           | 4/4           | 5/5               | 5/5           | 2/2           | 2/2             | 2/2               | 13/14         | 14/14         | 2/3           | 1/1               | 8/8                                         | 8/8   | 8/8     |
| 5           | 54         | 6/6                                 | 6/6           | 4/6           | 2/3               | 3/3           | 1/1           | 1/1             | 1/1               | 2/3           | 1/1           | 1/1           | 1/1               | 7/9                                         | 7/9   | 7/9     |
| 6           | 23         |                                     |               |               |                   |               |               |                 |                   |               |               |               |                   | 4/4                                         | 4/4   | 4/4     |
| 7           | 4          |                                     |               |               |                   |               |               |                 |                   |               |               |               |                   | 1/1                                         | 1/1   | 1/1     |
| Total       | 313        | 49/50 (98.0%)                       | 45/50 (90.0%) | 46/50 (92.0%) | 17/20 (85.0%)     | 18/20 (90.0%) | 27/28 (96.4%) | 28/28 (100%)    | 69/72 (95.8%)     | 71/72 (98.6%) | 10/10 (100%)  | 25/30 (83.3%) | 43/43 (100%)      | 19                                          | 19    | 19      |

Overall Conversion Rates

|  | Measles         | Mumps           | Rubella         |
|--|-----------------|-----------------|-----------------|
|  | 103/103 (99.4%) | 157/172 (91.3%) | 186/191 (97.4%) |



Table 2: Distribution of Titers of Children Initially Seronegative to Measles, Mumps, and Rubella Who Were Vaccinated with Combined Measles-Mumps-Rubella Vaccine Lot 92126 (Study 220 and 220B)

| Post-Vacc.<br>Titer      | Measles (HAI)      |                     | Mumps (Neut.)      |                     | Rubella (HAI)      |                     |
|--------------------------|--------------------|---------------------|--------------------|---------------------|--------------------|---------------------|
|                          | No. of<br>Children | Post-Vacc.<br>Titer | No. of<br>Children | Post-Vacc.<br>Titer | No. of<br>Children | Post-Vacc.<br>Titer |
| <5                       |                    | <4                  | 1                  | <1                  | 5                  | <8                  |
| 5                        |                    | 4                   | 2                  | 1                   | 2                  | 8                   |
| 10                       |                    | 8                   | 2                  | 2                   | 20                 | 16                  |
| 20                       | 1                  | 16                  | 1                  | 4                   | 10                 | 32                  |
| 40                       | 2                  | 32                  | 5                  | 8                   | 4                  | 64                  |
| 80                       | 5                  | 64                  | 15                 | 16                  | 4                  | 128                 |
| 160                      | 6                  | 128                 | 6                  | 32                  | 1                  |                     |
| >320                     | 3                  | >256                | 1                  | >64                 | 4                  |                     |
| Geometric<br>Mean Titer: | 59.3               |                     | 3.8                |                     | 34.3               |                     |

Table 3: Serologic Findings for Rubella Antibody for Children and Adults Acting As Contact Controls for Combined Measles-Mumps-Rubella Vaccine Lot 92126 (Study 220 and 220B)

| Age<br>(Yrs.)         | Total<br>No. | No.<br>Serol.<br>Tested | No.<br>Initially<br>Seropos. | Initially Seronegative |         |       |
|-----------------------|--------------|-------------------------|------------------------------|------------------------|---------|-------|
|                       |              |                         |                              | Paired Sera            |         |       |
|                       |              |                         |                              | No. Show Rise          | No Rise | Total |
|                       | Children     |                         |                              |                        |         |       |
| <1                    | 1            | 1                       | 1                            |                        |         |       |
| 1                     | 5            | 2                       |                              |                        | 2       | 2     |
| 2                     | 6            | 6                       |                              |                        | 6       | 6     |
| 3                     | 4            | 4                       |                              |                        | 4       | 4     |
| 4                     | 5            | 5                       | 1                            | 1                      | 3       | 4     |
| 5                     | 7            | 7                       | 3                            |                        | 4       | 4     |
| 6                     | 2            | 1                       |                              |                        | 1       | 1     |
| 7                     | 1            | 1                       | 1                            |                        |         |       |
| Total                 | 31           | 27                      | 6                            | 1                      | 20      | 21    |
| Adult Female Controls |              |                         |                              |                        |         |       |
| 15-19                 | 7            | 7                       | 5                            |                        | 2       | 2     |
| 20-29                 | 72           | 69                      | 53                           | 1                      | 15      | 16    |
| 30-39                 | 68           | 65                      | 53                           |                        | 12      | 12    |
| 40-49                 | 15           | 14                      | 13                           |                        | 1       | 1     |
| 50-59                 | 4            | 4                       | 3                            |                        | 1       | 1     |
| 60-70                 | 2            | 2                       | 1                            |                        | 1       | 1     |
| Total                 | 168          | 161                     | 128                          | 1                      | 32      | 33    |
| Adult Male Controls   |              |                         |                              |                        |         |       |
| Not<br>Given          | 1            | 1                       | 1                            |                        |         |       |

Table 4: Clinical Complaints Recorded for Children Vaccinated with Combined Measles-Mumps-Rubella Vaccine Lot 92126 and for their Unvaccinated Contact Controls (Study 220 and 220b)

| Clinical Complaint                | Adult Contact Controls |                |                |                |  | Contact Control Children |               |               |               |  | Total Vaccines        |                |                |                |  | Initially Seronegative to Measles-Mumps-Rubella |               |               |               |  |
|-----------------------------------|------------------------|----------------|----------------|----------------|--|--------------------------|---------------|---------------|---------------|--|-----------------------|----------------|----------------|----------------|--|-------------------------------------------------|---------------|---------------|---------------|--|
|                                   | Days Observed          |                |                |                |  | Days Observed            |               |               |               |  | Days Post-Vaccination |                |                |                |  | Days Post-Vaccination                           |               |               |               |  |
|                                   | 1-4                    | 5-12           | 13-18          | 19-28          |  | 1-4                      | 5-12          | 13-18         | 19-28         |  | 1-4                   | 5-12           | 13-18          | 19-28          |  | 1-4                                             | 5-12          | 13-18         | 19-28         |  |
| Upper Respiratory Illness         | 6<br>(3.8%)            | 9<br>(5.7%)    | 5<br>(3.1%)    | 2<br>(1.2%)    |  | 3<br>(9.7%)              | 4<br>(12.9%)  | 1<br>(3.2%)   | 2<br>(6.4%)   |  | 24<br>(7.7%)          | 49<br>(15.6%)  | 32<br>(10.2%)  | 24<br>(7.7%)   |  | 2<br>(4.0%)                                     | 9<br>(18.0%)  | 6<br>(12.0%)  | 3<br>(6.0%)   |  |
| Otitis                            | 2<br>(1.2%)            | 2<br>(1.2%)    | 1<br>(0.6%)    |                |  | 1<br>(3.2%)              | 1<br>(3.2%)   | 1<br>(3.2%)   | 1<br>(3.2%)   |  | 6<br>(1.9%)           | 5<br>(1.6%)    | 3<br>(1.0%)    | 1<br>(0.3%)    |  | 2<br>(4.0%)                                     | 1<br>(2.0%)   |               | 1<br>(2.0%)   |  |
| Swollen Glands                    |                        |                |                |                |  |                          |               |               |               |  | 4<br>(1.3%)           | 17<br>(5.4%)   | 2<br>(0.6%)    | 3<br>(1.0%)    |  |                                                 | 6<br>(12.0%)  |               |               |  |
| Conjunctivitis                    |                        | 1<br>(0.6%)    |                |                |  |                          |               |               |               |  | 6<br>(1.9%)           | 4<br>(1.3%)    | 2<br>(0.6%)    | 5<br>(1.6%)    |  |                                                 |               |               |               |  |
| Gastrointestinal                  | 9<br>(5.7%)            | 5<br>(3.1%)    | 2<br>(1.2%)    | 3<br>(1.9%)    |  | 3<br>(9.7%)              | 5<br>(16.1%)  | 5<br>(16.1%)  | 8<br>(25.8%)  |  | 27<br>(8.6%)          | 48<br>(15.3%)  | 29<br>(9.3%)   | 47<br>(15.0%)  |  | 2<br>(4.0%)                                     | 12<br>(24.0%) | 11<br>(22.0%) | 9<br>(18.0%)  |  |
| Local Reaction                    |                        |                |                |                |  |                          |               |               |               |  |                       |                |                |                |  |                                                 |               |               |               |  |
| Headache                          | 13<br>(8.2%)           | 19<br>(11.9%)  | 13<br>(8.2%)   | 6<br>(3.8%)    |  | 3<br>(9.7%)              | 2<br>(6.4%)   |               | 1<br>(3.2%)   |  | 5<br>(1.6%)           | 9<br>(2.9%)    | 2<br>(0.6%)    | 2<br>(0.6%)    |  | 2<br>(4.0%)                                     | 2<br>(4.0%)   | 1<br>(2.0%)   | 2<br>(4.0%)   |  |
| Irritability                      | 2<br>(1.2%)            | 1<br>(0.6%)    | 2<br>(1.2%)    | 1<br>(0.6%)    |  | 4<br>(12.9%)             | 1<br>(3.2%)   |               |               |  | 22<br>(7.0%)          | 34<br>(10.9%)  | 12<br>(3.8%)   | 10<br>(3.2%)   |  | 5<br>(10.0%)                                    | 5<br>(10.0%)  | 3<br>(6.0%)   | 2<br>(4.0%)   |  |
| Malaise                           | 10<br>(6.3%)           | 21<br>(13.2%)  | 15<br>(9.4%)   | 6<br>(3.8%)    |  | 2<br>(6.4%)              | 2<br>(6.4%)   | 2<br>(6.4%)   | 1<br>(3.2%)   |  | 23<br>(7.3%)          | 34<br>(10.9%)  | 13<br>(4.2%)   | 11<br>(3.5%)   |  | 2<br>(4.0%)                                     | 17<br>(34.0%) | 3<br>(6.0%)   | 2<br>(4.0%)   |  |
| Fever                             |                        | 2<br>(1.2%)    | 1<br>(0.6%)    | 1<br>(0.6%)    |  | 2<br>(6.4%)              | 6<br>(19.4%)  | 4<br>(12.9%)  | 8<br>(25.8%)  |  | 21<br>(6.7%)          | 79<br>(25.2%)  | 41<br>(13.1%)  | 27<br>(8.6%)   |  | 4<br>(8.0%)                                     | 22<br>(44.0%) | 10<br>(20.0%) | 2<br>(4.0%)   |  |
| Anorexia                          | 6<br>(3.8%)            | 10<br>(6.3%)   | 10<br>(6.3%)   | 8<br>(5.0%)    |  | 3<br>(9.7%)              | 2<br>(6.4%)   | 5<br>(16.1%)  | 3<br>(9.7%)   |  | 21<br>(6.7%)          | 33<br>(10.5%)  | 24<br>(7.7%)   | 29<br>(9.3%)   |  | 1<br>(2.0%)                                     | 11<br>(22.0%) | 7<br>(14.0%)  | 5<br>(10.0%)  |  |
| Exanthema                         |                        |                |                |                |  |                          |               |               |               |  |                       |                |                |                |  |                                                 |               |               |               |  |
| Rubella-like Rash                 |                        |                |                |                |  |                          |               |               |               |  |                       |                |                |                |  |                                                 |               |               |               |  |
| No Complaints                     | 137<br>(86.2%)         | 124<br>(78.0%) | 136<br>(85.5%) | 146<br>(91.8%) |  | 21<br>(67.7%)            | 16<br>(58.1%) | 21<br>(67.7%) | 15<br>(48.4%) |  | 234<br>(74.8%)        | 152<br>(48.6%) | 210<br>(67.1%) | 204<br>(65.2%) |  | 41<br>(82.0%)                                   | 16<br>(32.0%) | 27<br>(54.0%) | 33<br>(66.0%) |  |
| Physician's Surveillance Negative | 10                     | 10             | 10             | 10             |  |                          |               |               |               |  |                       |                |                |                |  |                                                 |               |               |               |  |
| Total Subjects                    | 169                    | 169            | 169            | 169            |  | 31                       | 31            | 31            | 31            |  | 313                   | 313            | 313            | 313            |  | 50                                              | 50            | 50            | 50            |  |

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AND TRAINING



SAN JOSE, COSTA RICA  
APARTADO 5140  
Cable: ICMRT

November 21, 1969

Miss Brenda Abbott  
Virus & Cell Research  
Merck Institute for Therapeutic Research  
West Point, Pennsylvania 19486

Dear Miss Abbott:

The additional information requested in your letter of October 27 and cable of November 20, is as follows:

Study 222

Children: 2014 - 2042 - 2043 - 2282 - 2401. No symptoms were recorded in these children other than fever. Some school children were attending school with elevated temperature and no other complaints. Complaints in smaller children may have been oversseen by unobserving mothers and not reported to visiting nurse.

Study 223

- I.
  1. 15-01 - No symptoms recorded
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Study 221-B

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  1. 30-02 - Pyodermitis
  2. 36-02 - Chicken-pox
  3. 109-02 - " "
  4. 337-03 - " "
  5. 272-02 - No rash
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  7. 442-02 - " "
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  1. 54-04 - Asymptomatic
  2. 120-05 - } Not controlled. Left
  3. 120-06 - } the community. Were
  4. 152-04 - } traced for second bloods

Non-Responsive - Not MMR



Further investigation of the communities involved disclosed that indeed low level rubella was present during January to March in San Vito and La Lucha, the areas vaccinated in study 220. The same was true in the provinces of Alajuela and Heredia (Study 221).

It was also possible to contact families of cases 712-15, 5092-95, 8592-93, 5742-44, 6031-33 and ascertain that in each case there had been

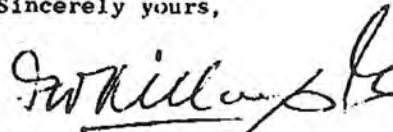
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Hope your records will be now in order.

Best regards,

Sincerely yours,



Dr. Víctor M. Villarejos  
Program Coordinator  
LEU-ICMRT

VMV/v1

Encls.

Measles-Mumps-Rubella Virus Vaccine, Study 220B

Live Measles-Mumps-Rubella Virus Vaccine  
Lot 96400

Responsible Clinical Investigator:

Victor M. Villarejos, M.D., M.P.H. and T.M., Dr. P.H. \*

Location:

San Salvador

Population:

Children whose families reside in San Salvador. 287 children with a negative history for measles, mumps and rubella were vaccinated with 1.0 ml of the combined vaccine. 201 guardians and 44 children served as contact controls. All contact controls were serologically tested for rubella HAI antibody. Vaccinees were serologically tested for measles and rubella HAI antibody and mumps neutralizing antibody.

\* Associate Director  
Louisiana State University  
International Center for Medical Research and Training  
San Jose, Costa Rica



Table 1: Serologic Findings for Children Vaccinated with Combined Measles-Mumps-Rubella Vaccine  
Lot 56400 in San Salvador from November 10, 1959 to December 12, 1959 (Study 220B)

| Age<br>(Yrs.) | Total<br>No.<br>Vaccines | No.<br>Serol.<br>Tested | Children Initially Seronegative to: |                  |                  |                  |                  |                  |                  |         |                 |       |                 |                  | Seropositive<br>to Measles,<br>Mumps, and<br>Rubella |
|---------------|--------------------------|-------------------------|-------------------------------------|------------------|------------------|------------------|------------------|------------------|------------------|---------|-----------------|-------|-----------------|------------------|------------------------------------------------------|
|               |                          |                         | Measles-Mumps-Rubella               |                  | Measles-Rubella  |                  | Mumps-Rubella    |                  | Measles Only     |         | Mumps Only      |       | Rubella Only    |                  |                                                      |
|               |                          |                         | No. Conversions/Total               |                  | No. Conv./Total  |                  | No. Conv./Total  |                  | No. Conv./Total  |         | No. Conv./Total |       | No. Conv./Total |                  |                                                      |
|               |                          |                         | Measles                             | Mumps            | Measles          | Rubella          | Measles          | Rubella          | Measles          | Rubella | Measles         | Mumps | Mumps           | Rubella          |                                                      |
| < 1           | 24                       | 14                      | 10/10                               | 10/10            | 9/10             | 1/1              | 1/1              | 1/2              | 2/2              |         |                 |       |                 | 1/1              |                                                      |
| 1             | 66                       | 37                      | 25/25                               | 25/25            | 22/25            | 5/5              | 5/5              | 5/5              | 4/5              |         |                 |       |                 | 2/2              |                                                      |
| 2             | 53                       | 40                      | 18/19                               | 17/19            | 17/19            | 3/3              | 3/3              | 14/15            | 13/15            |         |                 |       |                 | 2/3              |                                                      |
| 3             | 43                       | 34                      | 5/5                                 | 5/5              | 5/5              | 2/2              | 2/2              | 17/18            | 16/18            |         |                 |       |                 | 7/8              | 1                                                    |
| 4             | 37                       | 29                      | 4/4                                 | 4/4              | 4/4              | 3/3              | 2/3              | 17/17            | 15/17            |         |                 |       |                 | 4/4              | 1                                                    |
| 5             | 34                       | 24                      | 1/1                                 | 0/1              | 1/1              | 1/1              | 1/1              | 11/12            | 12/12            | 1/1     | 2/2             |       |                 | 7/7              | 1                                                    |
| 6             | 22                       | 14                      | 2/2                                 | 2/2              | 2/2              |                  |                  | 5/5              | 5/5              |         | 4/4             |       |                 | 1/2              |                                                      |
| 7             | 8                        | 2                       |                                     |                  |                  | 0/1              | 1/1              |                  |                  |         |                 |       |                 | 1/1              |                                                      |
| Total         | 287                      | 194                     | 65/66<br>(98.5%)                    | 63/66<br>(95.4%) | 60/66<br>(90.9%) | 15/16<br>(93.8%) | 15/16<br>(93.8%) | 70/74<br>(94.6%) | 67/74<br>(90.7%) | 1/1     | 6/6             |       |                 | 25/28<br>(89.3%) | 3                                                    |

Overall Conversion Rate

|                  | Measles            | Mumps              | Rubella |
|------------------|--------------------|--------------------|---------|
| 81/93<br>(87.0%) | 139/146<br>(95.2%) | 167/184<br>(90.8%) |         |

Table 2: Distribution of Titers of Children Initially Seronegative to Measles, Mumps, and Rubella Who Were Vaccinated with Combined Measles-Mumps-Rubella Vaccine Lot 96400 (Study 220B)

| Measles (HAI)            |                    | Mumps (Neut.)       |                    | Rubella (HAI)       |                    |
|--------------------------|--------------------|---------------------|--------------------|---------------------|--------------------|
| Post-Vacc.<br>Titer      | No. of<br>Children | Post-Vacc.<br>Titer | No. of<br>Children | Post-Vacc.<br>Titer | No. of<br>Children |
| < 4                      | 1                  |                     |                    | < 8                 | 6                  |
| 4                        | 1                  | < 1                 | 3                  | 8                   | 11                 |
| 8                        | 0                  | 1                   | 1                  | 16                  | 15                 |
| 16                       | 5                  | 2                   | 17                 | 32                  | 18                 |
| 32                       | 20                 | 4                   | 20                 | 64                  | 12                 |
| 64                       | 13                 | 8                   | 8                  | 128                 | 3                  |
| 128                      | 15                 | 16                  | 11                 | 256                 | 1                  |
| ≥256                     | 11                 | 32                  | 2                  |                     |                    |
|                          |                    | ≥64                 | 4                  |                     |                    |
| Geometric<br>Mean Titer: | 62.0               | 5.3                 |                    | 19.7                |                    |

Table 3: Serologic Findings for Rubella Antibody for Children and Adults Acting As Contact Controls for Combined Measles-Mumps-Rubella Vaccine Lot 96400 (Study 220B)

| Age<br>(Yrs.)         | Total<br>No. | No.<br>Serol.<br>Tested | No.<br>Initially<br>Seropos. | Initially Seronegative |            |       |
|-----------------------|--------------|-------------------------|------------------------------|------------------------|------------|-------|
|                       |              |                         |                              | No. Show.<br>Rise      | No<br>Rise | Total |
| Children              |              |                         |                              |                        |            |       |
| 1                     | 1            | 1                       |                              |                        | 1          | 1     |
| 2                     | 1            | 0                       |                              |                        |            |       |
| 3                     | 3            | 3                       |                              | 1                      | 2          | 3     |
| 4                     | 3            | 3                       |                              | 1                      | 2          | 3     |
| 5                     | 8            | 6                       | 1                            |                        | 5          | 5     |
| 6                     | 13           | 8                       | 2                            |                        | 6          | 6     |
| 7                     | 15           | 14                      | 8                            |                        | 6          | 6     |
| Total                 | 44           | 35                      | 11                           | 2                      | 22         | 24    |
| Adult Female Controls |              |                         |                              |                        |            |       |
| 16-19                 | 16           | 10                      | 5                            |                        | 5          | 5     |
| 20-29                 | 96           | 58                      | 48                           |                        | 10         | 10    |
| 30-39                 | 51           | 31                      | 29                           |                        | 2          | 2     |
| 40-49                 | 23           | 19                      | 18                           |                        | 1          | 1     |
| 50-59                 | 6            | 2                       | 2                            |                        |            |       |
| 60-69                 | 5            | 2                       | 1                            |                        | 1          | 1     |
| 70-79                 | 2            | 2                       | 2                            |                        |            |       |
| Total                 | 199          | 124                     | 105                          | 0                      | 19         | 19    |
| Adult Male Controls   |              |                         |                              |                        |            |       |
| 53-59                 | 2            | 0                       | 0                            | 0                      | 0          | 0     |

Table 4: Clinical Complaints Recorded for Children Vaccinated with Combined Measles-Mumps-Rubella Vaccine Lot 96400 and for Their Unvaccinated Contact Controls (Study 220B)

| Clinical Complaint                     | Contact Control Children |               |               |               | Total Vaccinees       |                |                |                | Initially Seronegative to Measles-Mumps-Rubella |               |               |               |
|----------------------------------------|--------------------------|---------------|---------------|---------------|-----------------------|----------------|----------------|----------------|-------------------------------------------------|---------------|---------------|---------------|
|                                        | Days Observed            |               |               |               | Days Post-Vaccination |                |                |                | Days Post-Vaccination                           |               |               |               |
|                                        | 1-4                      | 5-12          | 13-18         | 19-28         | 1-4                   | 5-12           | 13-18          | 19-28          | 1-4                                             | 5-12          | 13-18         | 19-28         |
| Upper Respiratory Illness              | 10<br>(22.7%)            | 6<br>(14.0%)  | 4<br>(9.3%)   | 4<br>(9.3%)   | 83<br>(30.4%)         | 92<br>(34.3%)  | 42<br>(15.7%)  | 51<br>(19.0%)  | 24<br>(36.4%)                                   | 29<br>(43.9%) | 12<br>(18.2%) | 13<br>(19.7%) |
| Swollen Glands                         |                          |               |               |               |                       |                |                |                |                                                 |               |               |               |
| Conjunctivitis                         | 3<br>(6.8%)              | 1<br>(2.3%)   | 1<br>(2.3%)   | 1<br>(2.3%)   | 8<br>(2.9%)           | 6<br>(2.2%)    | 1<br>(0.4%)    | 1<br>(0.4%)    | 1<br>(1.5%)                                     |               |               | 1<br>(1.5%)   |
| Gastrointestinal                       | 4<br>(9.1%)              | 6<br>(14.0%)  | 1<br>(2.3%)   | 5<br>(11.6%)  | 62<br>(22.7%)         | 49<br>(18.3%)  | 27<br>(10.1%)  | 48<br>(17.9%)  | 18<br>(27.3%)                                   | 16<br>(24.2%) | 9<br>(13.6%)  | 16<br>(24.2%) |
| Arthralgia                             | 1<br>(2.3%)              | 1<br>(2.3%)   |               |               |                       |                |                |                |                                                 |               |               |               |
| Headache                               | 1<br>(2.3%)              | 1<br>(2.3%)   |               |               | 9<br>(3.3%)           | 9<br>(3.4%)    | 1<br>(0.4%)    | 5<br>(1.9%)    | 3<br>(4.5%)                                     | 2<br>(3.0%)   |               |               |
| Irritability                           | 3<br>(6.8%)              | 4<br>(9.3%)   |               |               | 21<br>(7.7%)          | 29<br>(10.8%)  | 7<br>(2.6%)    | 6<br>(2.2%)    | 7<br>(10.6%)                                    | 6<br>(9.1%)   |               | 1<br>(1.5%)   |
| Malaise                                | 1<br>(2.3%)              | 1<br>(2.3%)   | 1<br>(2.3%)   |               | 18<br>(6.6%)          | 17<br>(6.3%)   | 2<br>(0.7%)    | 3<br>(1.1%)    | 4<br>(6.1%)                                     | 5<br>(7.6%)   |               | 1<br>(1.5%)   |
| Rubella                                |                          |               |               |               |                       |                |                |                |                                                 |               |               |               |
| Irrelevant                             |                          |               |               |               |                       |                |                |                |                                                 |               |               |               |
| Fever                                  | 5<br>(11.4%)             | 6<br>(14.0%)  | 4<br>(9.3%)   | 1<br>(2.3%)   | 61<br>(22.3%)         | 58<br>(21.6%)  | 24<br>(9.0%)   | 19<br>(7.1%)   | 14<br>(21.2%)                                   | 19<br>(28.8%) | 9<br>(13.6%)  | 7<br>(10.6%)  |
| Anorexia                               | 1<br>(2.3%)              | 1<br>(2.3%)   | 1<br>(2.3%)   |               | 4<br>(1.5%)           | 13<br>(4.8%)   | 6<br>(2.2%)    | 4<br>(1.5%)    | 1<br>(1.5%)                                     | 6<br>(9.1%)   | 1<br>(1.5%)   |               |
| Musculoskeletal                        |                          |               |               |               |                       |                |                |                |                                                 |               |               |               |
| Allergy                                |                          |               |               |               |                       |                |                |                |                                                 |               |               |               |
| Exanthema                              |                          |               |               |               |                       |                |                |                |                                                 |               |               |               |
| Rubella-like Rash                      | 2<br>(4.5%)              | 2<br>(4.6%)   |               |               | 3<br>(1.1%)           | 5<br>(1.9%)    | 3<br>(1.1%)    | 10<br>(3.7%)   | 2<br>(3.0%)                                     | 3<br>(4.5%)   | 1<br>(1.5%)   | 2<br>(3.0%)   |
| Measles-like Rash                      |                          |               |               |               |                       |                |                |                |                                                 |               |               |               |
| Aggravated Infection at Injection Site |                          |               |               |               |                       |                |                |                |                                                 |               |               |               |
| No Complaints                          | 25<br>(56.8%)            | 28<br>(65.1%) | 32<br>(74.4%) | 34<br>(79.1%) | 127<br>(46.5%)        | 121<br>(45.1%) | 184<br>(68.7%) | 168<br>(62.7%) | 27<br>(40.9%)                                   | 18<br>(27.3%) | 43<br>(65.2%) | 32<br>(48.5%) |
| Physician's Surveillance Negative      |                          | 1             | 1             | 1             | 14                    | 19             | 19             | 19             |                                                 |               |               |               |
| Total Subjects                         | 44                       | 44            | 44            | 44            | 287                   | 287            | 287            | 287            | 66                                              | 66            | 66            | 66            |



LOUISIANA STATE UNIVERSITY  
SCHOOL OF MEDICINE  
INTERNATIONAL CENTER FOR MEDICAL RESEARCH  
AND TRAINING

SAN JOSE, COSTA RICA  
APARTADO 5140  
Cable: ICMRT

March 2, 1970

Miss Brenda Abbott  
Virus & Cell Research  
Merck Institute for Therapeutic Research  
West Point, Pennsylvania 19486

Dear Miss Abbott:

Following your question by telephone this morning we reviewed our records on the three controls which seroconverted. Here is the information:

- 119-04 [REDACTED] Control. Two cases of rubella in the neighborhood prior to vaccination. Exposure probable but not certain.
- 640-02 [REDACTED] Control. Was exposed to rubella. (One case in the same dwelling, prior to vaccination).
- 605-03 [REDACTED] Wrongly reported as control. Was vaccinated on 13/11/69. (This child was originally designated to be a control, therefore the confusion).

Please correct the records accordingly. If there is anything else pending, we will be pleased to help correct this unavoidable small errors.

Kindest regards,

Sincerely yours,

Dr. Victor M. Villarejos  
Associate Director  
LSU-ICMRT

VMV/v1 3/10/70 2:20  
MRH  
qam  
Correspondence

February 28, 1969

Clinical Protocol - Study 220C

(Dr. V. Villarejos, ICMRT, San Jose, Costa Rica)

Combined: Moraten measles  
Jeryl Lynn mumps  
HPV-77 duck rubella vaccine

3 lots

1. Background.

A combined dried vaccine of above composition has been developed.

The vaccine evokes antibody in essentially all children to all 3 viruses. Measles vaccine causes mild febrile and other reactions in a fraction of the child recipients. The other components of the vaccine cause no significant reaction.

The need is to test the vaccine in triply seronegative children and to measure

- a) antibody responses and
- b) clinical reactions

in triply seronegative children and to measure possible rubella transmission to a token population of susceptible contacts.

2. Vaccines. Combined Measles-Mumps-Rubella

Lot No. 92126 (C-7995)  
          92127 (C-7996)  
          96400 (C-8095)

Rehydrate with 1.2 ml. of distilled water. Dose is 1.0 ml. given subcutaneously.

3. Study plan.

a) Clinical

For each lot of vaccine (3 lots or possibly only 2 lots) select as many children as possible with negative history of measles, mumps and rubella vaccination and previous illness (up to 200 children per lot).

Vaccinate but keep every tenth eligible child as an unvaccinated contact control. Also bleed all mothers in families.

Schedule - Each Lot

| Time<br>Day | Group A<br>(Around 200 children<br>per lot)            | Group B<br>Every 10th child (in<br>families where another<br>child received vaccine) | Group C<br>Mothers    |
|-------------|--------------------------------------------------------|--------------------------------------------------------------------------------------|-----------------------|
| 0           | Bleed 15-20 ml.<br>Vaccinate 1.0 ml.<br>subcutaneously | Bleed 15-20 ml.<br>--                                                                | Bleed 15-20 ml.<br>-- |
| 42-44       | Bleed 15-20 ml.                                        | Bleed 15-20 ml.                                                                      | Bleed 15-20 ml.       |

NOTE: BLEEDINGS ON ALL SUBJECTS

b) Laboratory.

Remove sera from clot and store frozen at  $-20^{\circ}$  C. until shipped in dry ice.

Test all sera by HI or Neut. for all antibodies.

c) Records - as per attached

4. Caution

Vaccines contain chick and duck embryo proteins and neomycin. Vaccines should not be given to persons sensitive to these substances.

  
M. R. Hilleman

Note: To start about April 1, 1969 in Costa Rica, on the border.

NOTE: Record forms  
Bleeding equipment  
Syringes  
Distilled water  
All else,  
to be shipped



Reference No. 6(a)

Measles-Mumps-Rubella Virus Vaccine, Study No. 220C

Live Measles-Mumps-Rubella Virus Vaccine

Lot 92126

Responsible Clinical Investigator:

Victor M. Villarejos, M.D., M.P.H. and T.M., Dr. P. H. \*

Location:

Costa Rica

Population:

Children whose families reside in Costa Rica. 235 children with a negative history for measles-mumps and rubella were vaccinated with 1.0 ml of the combined vaccine. 167 guardians and 28 children served as contact controls. All contact controls were serologically tested for rubella HAI antibody. Vaccinees were serologically tested for measles and rubella HAI antibody and mumps neutralizing antibody.

\* Associate Director  
Louisiana State University  
International Center for Medical Research and Training  
San Jose, Costa Rica

Table 1: Serologic Findings for Children Vaccinated with Combined Measles-Mumps-Rubella Vaccine Lot 92126 in Costa Rica on January 12-13, 1970 (Study 220C)

| Age<br>(Yrs.) | Total No.<br>Vaccinees | No.<br>Serol.<br>Tested | Children Initially Seronegative to: |                   |                    |               |             |                  |                  |                  |                  |               |             |                 | Seropositive to<br>Measles, Mumps,<br>and Rubella |     |   |
|---------------|------------------------|-------------------------|-------------------------------------|-------------------|--------------------|---------------|-------------|------------------|------------------|------------------|------------------|---------------|-------------|-----------------|---------------------------------------------------|-----|---|
|               |                        |                         | Measles-Mumps-Rubella               |                   |                    | Measles-Mumps |             |                  | Measles-Rubella  |                  |                  | Mumps-Rubella |             |                 |                                                   |     |   |
|               |                        |                         | Measles                             | Conversions       | Total              | Measles       | Conversions | Total            | Measles          | Conversions      | Total            | Mumps         | Conversions | Total           |                                                   |     |   |
| <1            | 10                     | 9                       | 5/5                                 | 5/5               | 5/5                | 2/2           | 2/2         | 1/1              | 1/1              | 1/1              | 1/1              | 1/1           | 1/1         |                 |                                                   |     |   |
| 1             | 56                     | 52                      | 34/37                               | 35/37             | 36/37              |               |             | 2/2              | 2/2              | 4/4              | 10/13            | 8/8           | 13/13       |                 |                                                   | 3/3 |   |
| 2             | 45                     | 43                      | 28/28                               | 26/28             | 28/28              |               |             | 3/3              | 4/4              | 3/3              | 17/18            | 8/8           | 18/18       |                 |                                                   | 6/6 |   |
| 3             | 90                     | 49                      | 20/21                               | 20/21             | 20/21              |               |             | 4/5              | 4/5              | 3/3              | 15/16            | 8/8           | 14/16       |                 |                                                   | 5/5 |   |
| 4             | 34                     | 34                      | 7/7                                 | 7/7               | 7/7                | 1/1           |             | 1/1              | 1/1              | 1/1              | 2/3              | 2/3           | 3/3         |                 | 2/2                                               | 4/4 |   |
| 5             | 24                     | 23                      | 5/5                                 | 4/5               | 5/5                | 1/1           | 0/1         | 0/1              | 0/1              | 0/1              |                  |               |             |                 |                                                   | 5/5 | 3 |
| 6             | 13                     | 13                      | 1/2                                 | 2/2               | 2/2                |               |             |                  |                  |                  |                  |               |             |                 |                                                   | 2/2 | 1 |
| 7             | 2                      | 2                       |                                     |                   |                    |               |             |                  |                  |                  |                  |               |             |                 |                                                   | 1/1 |   |
| 15            | 1                      | 1                       |                                     |                   |                    |               |             |                  |                  |                  |                  |               |             |                 |                                                   |     |   |
| Total         | 235                    | 226                     | 100/105<br>(95.2%)                  | 99/105<br>(94.3%) | 103/105<br>(98.1%) | 4/4           | 3/4         | 15/17<br>(88.2%) | 16/17<br>(94.1%) | 51/67<br>(76.1%) | 65/67<br>(97.0%) | 1/1           | 2/2         | 26/26<br>(100%) |                                                   |     | 4 |

Overall Conversion Rates

| Measles         | Mumps           | Rubella         |
|-----------------|-----------------|-----------------|
| 120/127 (94.5%) | 165/178 (92.7%) | 210/215 (97.7%) |

Table 2: Distribution of Titers of Children Initially Seronegative to Measles, Mumps, and Rubella Who Were Vaccinated with Combined Measles-Mumps-Rubella Vaccine Lot 92126 (Study 220C)

| Measles (HAI)                 |                    | Mumps (Neut.)       |                    | Rubella (HAI)       |                    |
|-------------------------------|--------------------|---------------------|--------------------|---------------------|--------------------|
| Post-Vacc.<br>Titer           | No. of<br>Children | Post-Vacc.<br>Titer | No. of<br>Children | Post-Vacc.<br>Titer | No. of<br>Children |
| <4                            | 5                  | <1                  | 6                  | <8                  | 2                  |
| 4                             | 1                  | 1                   | 4                  | 8                   | 7                  |
| 8                             | 6                  | 2                   | 19                 | 16                  | 21                 |
| 16                            | 28                 | 4                   | 17                 | 32                  | 40                 |
| 32                            | 39                 | 8                   | 16                 | 64                  | 25                 |
| 64                            | 21                 | 16                  | 16                 | 128                 | 10                 |
| 128                           | 5                  | 32                  | 13                 | 256                 | 0                  |
| ≥256                          | 0                  | ≥64                 | 14                 | ≥512                | 0                  |
| Geometric<br>Mean Titer: 25.1 |                    | 7.9                 |                    | 32.0                |                    |

Table 3: Serologic Findings for Rubella Antibody for Children and Adults Acting as Contact Controls for Combined Measles-Mumps-Rubella Vaccine Lot 92126 (Study 220C)

| Age<br>(Yrs.)         | Total<br>No. | No.<br>Serol.<br>Tested | No.<br>Initially<br>Seropos. | Initially Seronegative |            |       |
|-----------------------|--------------|-------------------------|------------------------------|------------------------|------------|-------|
|                       |              |                         |                              | No. Showing<br>Rise    | No<br>Rise | Total |
| Children              |              |                         |                              |                        |            |       |
| 1                     | 5            | 5                       |                              | 1                      | 4          | 5     |
| 2                     | 4            | 4                       |                              | 1                      | 3          | 4     |
| 3                     | 7            | 6                       |                              | 1                      | 5          | 6     |
| 4                     | 5            | 5                       |                              |                        | 5          | 5     |
| 5                     | 6            | 6                       |                              | 2                      | 4          | 6     |
| 6                     | 1            | 1                       | 1                            |                        |            |       |
| Total                 | 28           | 27                      | 1                            | 5                      | 21         | 26    |
| Adult Female Controls |              |                         |                              |                        |            |       |
| 12-19                 | 13           | 13                      | 7                            |                        | 6          | 6     |
| 20-29                 | 61           | 54                      | 30                           |                        | 24         | 24    |
| 30-39                 | 68           | 65                      | 46                           |                        | 19         | 19    |
| 40-48                 | 16           | 16                      | 11                           |                        | 5          | 5     |
| 52-58                 | 4            | 4                       | 3                            |                        | 1          | 1     |
| 72                    | 1            | 1                       | 1                            |                        |            |       |
| Not<br>Given          | 3            | 2                       | 2                            |                        |            |       |
| Total                 | 166          | 155                     | 100                          | 0                      | 55         | 55    |
| Adult Male Control    |              |                         |                              |                        |            |       |
| 13                    | 1            | 1                       | 0                            | 0                      | 1          | 1     |

Table 4: Clinical Complaints Recorded for Children Vaccinated with Measles-Mumps-Rubella Vaccine Lot 92126 and for Their Unvaccinated Controls (Study 220C)

| Clinical Complaint                | Contact Control Children |               |               |               | Total Vaccinees       |                |                |                | Initially Seronegative to Measles-Mumps-Rubella |               |               |               |
|-----------------------------------|--------------------------|---------------|---------------|---------------|-----------------------|----------------|----------------|----------------|-------------------------------------------------|---------------|---------------|---------------|
|                                   | Days Observed            |               |               |               | Days Post-Vaccination |                |                |                | Days Post-Vaccination                           |               |               |               |
|                                   | 1-4                      | 5-12          | 13-18         | 19-28         | 1-4                   | 5-12           | 13-18          | 19-28          | 1-4                                             | 5-12          | 13-18         | 19-28         |
| Upper Respiratory Illness         | 2<br>(7.1%)              | 4<br>(14.3%)  | 2<br>(7.1%)   | 4<br>(14.3%)  | 18<br>(7.9%)          | 44<br>(19.3%)  | 46<br>(20.2%)  | 32<br>(14.0%)  | 8<br>(7.8%)                                     | 21<br>(20.4%) | 25<br>(24.3%) | 15<br>(14.6%) |
| Otitis                            | 1<br>(3.6%)              | 1<br>(3.6%)   | 1<br>(3.6%)   |               | 2<br>(0.9%)           | 6<br>(2.6%)    | 3<br>(1.3%)    | 2<br>(0.9%)    | 1<br>(1.0%)                                     | 2<br>(1.9%)   | 1<br>(1.0%)   | 1<br>(1.0%)   |
| Lymphadenopathy                   |                          |               |               | 1<br>(3.6%)   | 1<br>(0.4%)           | 2<br>(0.9%)    | 4<br>(1.8%)    | 5<br>(2.2%)    |                                                 |               | 3<br>(2.9%)   | 5<br>(4.9%)   |
| Conjunctivitis                    |                          |               |               |               | 3<br>(1.3%)           | 8<br>(3.5%)    | 7<br>(3.1%)    | 1<br>(0.4%)    |                                                 | 2<br>(1.9%)   | 1<br>(1.0%)   | 1<br>(1.0%)   |
| Gastrointestinal                  |                          |               | 3<br>(10.7%)  | 2<br>(7.1%)   | 14<br>(6.1%)          | 28<br>(12.3%)  | 16<br>(7.0%)   | 13<br>(5.7%)   | 5<br>(4.9%)                                     | 12<br>(11.6%) | 5<br>(4.9%)   | 3<br>(2.9%)   |
| Rash                              |                          | 1<br>(3.6%)   | 1<br>(3.6%)   |               |                       | 1<br>(0.4%)    | 1<br>(0.4%)    | 1<br>(0.4%)    |                                                 | 1<br>(1.0%)   | 1<br>(1.0%)   | 1<br>(1.0%)   |
| Headache                          |                          | 1<br>(3.6%)   | 1<br>(3.6%)   |               |                       | 3<br>(1.3%)    | 2<br>(0.9%)    |                |                                                 | 1<br>(1.0%)   |               |               |
| Irritability                      |                          | 2<br>(7.1%)   | 1<br>(3.6%)   | 1<br>(3.6%)   | 11<br>(4.8%)          | 33<br>(14.5%)  | 18<br>(7.9%)   | 11<br>(4.8%)   | 6<br>(5.8%)                                     | 15<br>(14.6%) | 8<br>(7.8%)   | 4<br>(3.9%)   |
| Malaise                           |                          | 2<br>(7.1%)   | 1<br>(3.6%)   | 1<br>(3.6%)   | 13<br>(5.7%)          | 32<br>(14.0%)  | 20<br>(8.8%)   | 10<br>(4.4%)   | 6<br>(5.8%)                                     | 13<br>(12.6%) | 7<br>(6.8%)   | 5<br>(4.9%)   |
| Measles                           | 1<br>(3.6%)              |               |               |               | 1<br>(0.4%)           | 5<br>(2.2%)    |                |                |                                                 |               |               |               |
| Fever                             | 2<br>(7.1%)              | 2<br>(7.1%)   | 2<br>(7.1%)   | 3<br>(10.7%)  | 3<br>(1.3%)           | 22<br>(9.6%)   | 15<br>(6.6%)   | 14<br>(6.1%)   | 2<br>(1.9%)                                     | 11<br>(10.7%) | 7<br>(6.8%)   | 7<br>(6.8%)   |
| Anorexia                          |                          | 2<br>(7.1%)   | 1<br>(3.6%)   | 1<br>(3.6%)   | 7<br>(3.1%)           | 27<br>(11.8%)  | 18<br>(7.9%)   | 8<br>(3.5%)    | 1<br>(1.0%)                                     | 10<br>(9.7%)  | 6<br>(5.8%)   | 4<br>(3.9%)   |
| Allergy                           |                          | 2<br>(7.1%)   | 2<br>(7.1%)   |               | 1<br>(0.4%)           | 3<br>(1.3%)    | 4<br>(1.8%)    | 2<br>(0.9%)    | 1<br>(1.0%)                                     | 2<br>(1.9%)   | 2<br>(1.9%)   | 1<br>(1.0%)   |
| Exanthema                         |                          |               |               |               | 1<br>(0.4%)           | 6<br>(2.6%)    | 5<br>(2.2%)    | 1<br>(0.4%)    | 1<br>(1.0%)                                     | 2<br>(1.9%)   |               |               |
| Measles-like Rash                 | 1<br>(3.6%)              | 1<br>(3.6%)   | 1<br>(3.6%)   |               | 1<br>(0.4%)           | 1<br>(0.4%)    | 1<br>(0.4%)    | 1<br>(0.4%)    |                                                 |               |               |               |
| Whooping Cough                    |                          |               |               |               |                       | 1<br>(0.4%)    |                |                |                                                 | 1<br>(1.0%)   |               | 1<br>(1.0%)   |
| No Complaint                      | 25<br>(89.3%)            | 19<br>(67.9%) | 20<br>(71.4%) | 20<br>(71.4%) | 187<br>(82.0%)        | 132<br>(57.9%) | 147<br>(64.5%) | 174<br>(76.3%) | 86<br>(83.5%)                                   | 55<br>(53.4%) | 59<br>(57.3%) | 73<br>(70.9%) |
| Physician's Surveillance Negative |                          |               |               |               | 7                     | 7              | 7              | 7              | 2                                               | 2             | 2             | 2             |
| Total Subjects                    | 28                       | 28            | 28            | 28            | 235                   | 235            | 235            | 235            | 105                                             | 105           | 105           | 105           |

Study 220C

Serologic Assay Results for Persons who Served as Contact Controls for Lot 92126 and who Showed Rubella Antibody Rises.

| Patient No. | Status   | Measles |       |       | Mumps |       |       | Rubella |       |       | Blood Type |       |       | Comments                             |
|-------------|----------|---------|-------|-------|-------|-------|-------|---------|-------|-------|------------|-------|-------|--------------------------------------|
|             |          | Pre     | 1 Mo. | 2 Mo. | Pre   | 1 Mo. | 2 Mo. | Pre     | 1 Mo. | 2 Mo. | Pre        | 1 Mo. | 2 Mo. |                                      |
| 513         | Control  | >20     | 80    |       | QNS   | QNS   |       | <8      | 128   |       | O          |       |       | Mumps conversion - Probable Vaccinee |
| 662         | Control  | >20     | >640  |       | QNS   | QNS   |       | <8      | 512   |       | B          |       |       |                                      |
| 871         | Control  | >20     | >640  |       | <2    |       |       | <8      | 512   |       | A          |       |       |                                      |
| ~71         | Control  | <5      | <5    |       | QNS   |       |       | <8      | 64    |       | O          |       |       | Blood mix-up - eliminated from study |
| ~22         | Control  | <5      | <5    |       | QNS   |       |       | <8      | 64    |       | B          |       |       |                                      |
| 128-10      | Guardian |         |       |       |       |       |       | <8      | 16    |       | O          |       |       |                                      |
| 163-10      | Guardian |         |       |       |       |       |       | <8      | 128   |       | O          |       |       | Blood mix-up - eliminated from study |



Measles-Mumps-Rubella Virus Vaccine, Study No. 220C

Live Measles-Mumps-Rubella Virus Vaccine

Lot 92127

Responsible Clinical Investigator:

Victor M. Villarejos, M.D., M.P.H. and T.M., Dr. P. H. \*

Location:

Costa Rica

Population:

Children whose families reside in Costa Rica. 128 children with a negative history for measles-mumps and rubella were vaccinated with 1.0 ml of the combined vaccine. 73 guardians and 11 children served as contact controls. All contact controls were serologically tested for rubella HAI antibody. Vaccinees were serologically tested for measles and rubella HAI antibody and mumps neutralizing antibody.

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Table 1: Serologic Findings for Children Vaccinated with Combined Measles-Mumps-Rubella Vaccine Lot 92127 in Costa Rica on January 14-16, 1970 (Study 220C)

| Age<br>(Yrs.) | Total No.<br>Vaccinees | No.<br>Serol.<br>Tested | Children Initially Seronegative to: |                  |                  |                   |         |         |                   |         |                  |                   |         |         | Seropositive to<br>Measles, Mumps,<br>and Rubella |   |
|---------------|------------------------|-------------------------|-------------------------------------|------------------|------------------|-------------------|---------|---------|-------------------|---------|------------------|-------------------|---------|---------|---------------------------------------------------|---|
|               |                        |                         | Measles-Mumps-Rubella               |                  |                  | Measles-Mumps     |         |         | Measles-Rubella   |         |                  | Mumps-Rubella     |         |         |                                                   |   |
|               |                        |                         | Conversions/Total                   |                  | Rubella          | Conversions/Total |         | Mumps   | Conversions/Total |         | Mumps            | Conversions/Total |         | Rubella |                                                   |   |
|               |                        |                         | Measles                             | Mumps            | Measles          | Mumps             | Measles | Rubella | Measles           | Rubella | Measles          | Rubella           | Measles | Rubella |                                                   |   |
| 1             | 6                      | 4                       | 4/4                                 | 4/4              | 4/4              | 2/2               | 2/2     | 2/2     | 2/2               | 2/2     | 2/2              | 2/2               | 2/2     | 2/2     | 3                                                 |   |
| 2             | 26                     | 25                      | 21/18                               | 17/18            | 16/18            | 1/1               | 1/1     | 2/2     | 2/2               | 2/2     | 2/2              | 2/2               | 2/2     | 2/2     |                                                   |   |
| 3             | 25                     | 24                      | 18/18                               | 16/18            | 18/18            |                   |         | 1/1     | 1/1               | 1/1     | 8/8              | 8/8               | 8/8     | 8/8     |                                                   |   |
| 4             | 20                     | 19                      | 9/10                                | 9/10             | 10/10            |                   |         | 1/1     | 1/1               | 1/1     | 8/8              | 8/8               | 8/8     | 8/8     |                                                   |   |
| 5             | 22                     | 21                      | 8/8                                 | 7/8              | 8/8              | 3/4               | 3/4     | 2/2     | 2/2               | 2/2     | 3/4              | 3/4               | 4/4     | 4/4     |                                                   |   |
| 6             | 14                     | 14                      | 1/1                                 | 1/1              | 1/1              |                   |         | 1/1     | 1/1               | 1/1     | 2/3              | 2/3               | 3/3     | 3/3     |                                                   |   |
| 7             | 1                      | 1                       | 1/1                                 | 1/1              | 1/1              |                   |         |         |                   |         |                  |                   |         |         |                                                   |   |
| Total         | 128                    | 121                     | 61/63<br>(96.8%)                    | 58/63<br>(92.1%) | 61/63<br>(96.8%) | 6/7               | 6/7     | 9/9     | 9/9               | 9/9     | 27/27<br>(92.6%) | 27/27<br>(100%)   | 1/1     | 1/1     | 9/10                                              | 3 |

Overall Conversion Rates

|  | Measles       | Mumps         | Rubella         |
|--|---------------|---------------|-----------------|
|  | 77/80 (96.2%) | 90/98 (91.8%) | 106/109 (97.2%) |

Table 2: Distribution of Titers of Children Initially Seronegative to Measles, Mumps, and Rubella Who Were Vaccinated with Combined Measles-Mumps-Rubella Vaccine Lot 92127 (Study 220C)

| Measles (HAI)                 |                    | Mumps (Neut.)       |                    | Rubella (HAI)       |                    |
|-------------------------------|--------------------|---------------------|--------------------|---------------------|--------------------|
| Post-Vacc.<br>Titer           | No. of<br>Children | Post-Vacc.<br>Titer | No. of<br>Children | Post-Vacc.<br>Titer | No. of<br>Children |
| <4                            | 2                  | <1                  | 5                  | <8                  | 2                  |
| 4                             | 1                  | 1                   | 2                  | 8                   | 2                  |
| 8                             | 6                  | 2                   | 14                 | 16                  | 14                 |
| 16                            | 21                 | 4                   | 12                 | 32                  | 29                 |
| 32                            | 24                 | 8                   | 7                  | 64                  | 15                 |
| 64                            | 8                  | 16                  | 4                  | 128                 | 1                  |
| 128                           | 1                  | 32                  | 11                 | 256                 | 0                  |
| ≥256                          | 0                  | ≥64                 | 8                  | ≥512                | 0                  |
| Geometric<br>Mean Titer: 21.5 |                    | 7.1                 |                    | 28.4                |                    |

Table 3: Serologic Findings for Rubella Antibody for Children and Adults Acting As Contact Controls for Combined Measles-Mumps-Rubella Vaccine Lot 92127 (Study 220C)

| Age<br>(Yrs.)         | Total<br>No. | No.<br>Serol.<br>Tested | No.<br>Initially<br>Seropos. | Initially Seronegative |            |       |
|-----------------------|--------------|-------------------------|------------------------------|------------------------|------------|-------|
|                       |              |                         |                              | No. Show.<br>Rise      | No<br>Rise | Total |
| Children              |              |                         |                              |                        |            |       |
| 1                     | 1            | 1                       |                              |                        | 1          | 1     |
| 2                     | 2            | 2                       |                              | 2                      |            | 2     |
| 3                     | 3            | 3                       |                              |                        | 3          | 3     |
| 4                     | 2            | 2                       | 1                            |                        | 1          | 1     |
| 5                     | 2            | 2                       |                              | 1                      | 1          | 2     |
| 6                     | 1            | 1                       |                              | 1                      |            | 1     |
| Total                 | 11           | 11                      | 1                            | 4                      | 6          | 10    |
| Adult Female Controls |              |                         |                              |                        |            |       |
| 11-15                 | 5            | 5                       | 2                            |                        | 3          | 3     |
| 21-29                 | 22           | 20                      | 10                           |                        | 10         | 10    |
| 30-39                 | 33           | 33                      | 22                           |                        | 11         | 11    |
| 41-49                 | 11           | 11                      | 6                            |                        | 5          | 5     |
| 80                    | 1            | 1                       | 1                            |                        |            |       |
| Not<br>Given          | 1            | 1                       | 1                            |                        |            |       |
| Total                 | 73           | 71                      | 42                           | 0                      | 29         | 29    |

Table 4: Clinical Complaints Recorded for Children Vaccinated with Measles-Mumps-Rubella Vaccine Lot 92127 and for Their Unvaccinated Controls (Study 220C)

| Clinical Complaint        | Contact Control Children |              |              |              | Total Vaccinees       |               |               |               | Initially Seronegative to Measles-Mumps-Rubella |               |               |               |
|---------------------------|--------------------------|--------------|--------------|--------------|-----------------------|---------------|---------------|---------------|-------------------------------------------------|---------------|---------------|---------------|
|                           | Days Observed            |              |              |              | Days Post-Vaccination |               |               |               | Days Post-Vaccination                           |               |               |               |
|                           | 1-4                      | 5-12         | 13-18        | 19-28        | 1-4                   | 5-12          | 13-18         | 19-28         | 1-4                                             | 5-12          | 13-18         | 19-28         |
| Upper Respiratory Illness |                          | 6<br>(54.5%) | 5<br>(45.5%) | 2<br>(18.2%) | 8<br>(6.2%)           | 57<br>(44.5%) | 48<br>(37.5%) | 28<br>(21.9%) | 4<br>(6.3%)                                     | 33<br>(52.4%) | 29<br>(46.0%) | 16<br>(25.7%) |
| Otitis                    |                          | 1<br>(9.1%)  | 1<br>(9.1%)  |              |                       | 10<br>(3.1%)  | 11<br>(1.6%)  | 3<br>(2.3%)   |                                                 | 2<br>(3.2%)   | 1<br>(1.6%)   | 2<br>(3.2%)   |
| Lymphadenopathy           |                          |              | 1<br>(9.1%)  |              |                       | 21<br>(7.8%)  | 10<br>(8.6%)  | 7<br>(5.5%)   |                                                 | 5<br>(7.9%)   | 5<br>(7.9%)   | 5<br>(7.9%)   |
| Conjunctivitis            |                          | 1<br>(9.1%)  | 1<br>(9.1%)  |              | 3<br>(2.3%)           | 13<br>(16.4%) | 9<br>(7.8%)   | 8<br>(4.7%)   | 3<br>(4.8%)                                     | 10<br>(15.9%) | 6<br>(9.5%)   | 4<br>(6.3%)   |
| Gastrointestinal          | 1<br>(9.1%)              | 1<br>(9.1%)  | 1<br>(9.1%)  | 2<br>(18.2%) | 5<br>(3.9%)           | 4<br>(10.2%)  | 9<br>(7.0%)   | 1<br>(0.8%)   | 2<br>(3.2%)                                     | 6<br>(9.5%)   | 6<br>(9.5%)   | 3<br>(4.8%)   |
| Headache                  |                          | 3<br>(27.3%) | 1<br>(9.1%)  | 2<br>(18.2%) | 9<br>(7.0%)           | 39<br>(30.5%) | 23<br>(18.0%) | 8<br>(6.2%)   | 4<br>(6.3%)                                     | 26<br>(41.3%) | 17<br>(27.0%) | 4<br>(6.3%)   |
| Irritability              | 2<br>(18.2%)             | 3<br>(27.3%) | 1<br>(9.1%)  | 1<br>(9.1%)  | 12<br>(9.4%)          | 27<br>(21.1%) | 6<br>(4.7%)   | 5<br>(3.9%)   | 7<br>(11.1%)                                    | 16<br>(25.4%) | 6<br>(9.5%)   | 5<br>(7.9%)   |
| Malaise                   | 3<br>(27.3%)             | 3<br>(27.3%) | 1<br>(9.1%)  | 3<br>(27.3%) | 4<br>(3.1%)           | 21<br>(16.4%) | 16<br>(12.5%) | 18<br>(14.1%) | 3<br>(4.8%)                                     | 16<br>(25.4%) | 8<br>(12.7%)  | 8<br>(12.7%)  |
| Fever                     | 1<br>(9.1%)              | 1<br>(9.1%)  | 3<br>(27.3%) |              | 5<br>(3.9%)           | 14<br>(10.9%) | 7<br>(5.5%)   | 5<br>(3.9%)   | 4<br>(6.3%)                                     | 10<br>(15.9%) | 5<br>(7.9%)   | 5<br>(7.9%)   |
| Anorexia                  | 1<br>(9.1%)              | 1<br>(9.1%)  | 1<br>(9.1%)  |              | 2<br>(1.6%)           | 1<br>(0.8%)   | 2<br>(1.6%)   | 3<br>(2.3%)   | 2<br>(3.2%)                                     | 1<br>(1.6%)   | 5<br>(7.9%)   | 1<br>(1.6%)   |
| Allergy                   |                          |              |              |              | 103<br>(80.5%)        | 39<br>(30.5%) | 54<br>(42.2%) | 65<br>(50.8%) | 49<br>(77.8%)                                   | 12<br>(19.0%) | 19<br>(30.2%) | 28<br>(44.4%) |
| Exanthema                 |                          | 4<br>(36.4%) | 4<br>(36.4%) | 6<br>(54.5%) |                       |               |               |               |                                                 |               |               |               |
| No Complaint              | 7<br>(63.6%)             |              |              |              |                       |               |               |               |                                                 |               |               |               |
| Total Subjects            | 11                       | 11           | 11           | 11           | 128                   | 128           | 128           | 128           | 63                                              | 63            | 63            | 63            |

Study 220C

Serologic Assay Results for Persons who Served as Contact Controls for Lot 92127 and who Showed Rubella Antibody Rises, and for Vaccinees with Serum Specimen Mix-up.

| Patient No. | Status  | Measles |       |       | Mumps |       |       | Rubella |       |       | Blood Type |       |       | Comments                               |
|-------------|---------|---------|-------|-------|-------|-------|-------|---------|-------|-------|------------|-------|-------|----------------------------------------|
|             |         | Pre     | 1 Mo. | 2 Mo. | Pre   | 1 Mo. | 2 Mo. | Pre     | 1 Mo. | 2 Mo. | Pre        | 1 Mo. | 2 Mo. |                                        |
|             |         |         |       |       |       |       |       |         |       |       |            |       |       |                                        |
| 2012        | Control | >20     | 320   |       | QNS   | 8     |       | <8      | 8     |       | AB         | AB    |       | Measles Conversion - Probable Vaccinee |
| 2131        | Control | QNS     | <5    |       | QNS   | 64    |       | <8      | 128   |       | A          | A     |       |                                        |
| 2281        | Control | <5      | 80    |       | 4     | 8     |       | <8      | 128   |       | A          | A     |       |                                        |
| 2421        | Control | <5      | <5    |       | QNS   | >128  |       | <8      | 32    |       | A          | A     |       | Blood Mix-up - eliminated from study   |
| 2132        | Vacc.   | <4      | <4    | 64    | 4     | >64   | 64    | <8      | 64    | 32    | O          | A     | O     |                                        |
| 2133        | Vacc.   | <4      | 64    | 4     | 4     | 16    | >64   | <8      | 16    | 64    | A          | O     | A     |                                        |
| 2352        | Vacc.   | <4      | <4    | <4    | 1     | 1     | <4    | <8      | 32    | 64    | B          | O     | O     | Blood Mix-up - eliminated from study   |

Reference No. 6(c)

Measles-Mumps-Rubella Virus Vaccine, Study No. 220C

Live Measles-Mumps-Rubella Virus Vaccine  
Lot 96400

Responsible Clinical Investigator:

Victor M. Villarejos, M.D., M.P.H. and T.M., Dr. P. H. \*

Location:

Costa Rica

Population:

Children whose families reside in Costa Rica. 226 children with a negative history for measles-mumps and rubella were vaccinated with 1.0 ml of the combined vaccine. 128 guardians and 25 children served as contact controls. All contact controls were serologically tested for rubella HAI antibody. Vaccinees were serologically tested for measles and rubella HAI antibody and mumps neutralizing antibody.

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Table 1: Serologic Findings for Children Vaccinated with Combined Measles-Mumps-Rubella Vaccine Lot 956400 in Costa Rica on January 15-21, 1970 (Study 2200)

| Age<br>(Yrs.) | Total No.<br>Vaccinees | No.<br>Serol.<br>Tested | Children Initially Seronegative to: |                  |                  |                   |       |       |                   |         |                  |                   |                  |       | Seropositive<br>to Measles,<br>Mumps & Rubella |                   |         |                  |         |
|---------------|------------------------|-------------------------|-------------------------------------|------------------|------------------|-------------------|-------|-------|-------------------|---------|------------------|-------------------|------------------|-------|------------------------------------------------|-------------------|---------|------------------|---------|
|               |                        |                         | Measles-Mumps-Rubella               |                  |                  | Measles-Mumps     |       |       | Measles-Rubella   |         |                  | Mumps-Rubella     |                  |       |                                                |                   |         |                  |         |
|               |                        |                         | Conversions/Total                   |                  | Rubella          | Conversions/Total |       | Mumps | Conversions/Total |         | Rubella          | Conversions/Total |                  | Mumps |                                                | Conversions/Total |         |                  |         |
|               |                        |                         | Measles                             | Mumps            |                  | Measles           | Mumps |       | Measles           | Rubella |                  | Measles           | Rubella          |       |                                                | Measles           | Rubella | Measles          | Rubella |
| <1            | 11                     | 10                      | 9/9                                 | 9/9              | 8/9              |                   |       |       |                   |         |                  | 1/1               | 1/1              |       |                                                |                   |         |                  |         |
| 1             | 40                     | 36                      | 24/25                               | 25/25            | 22/25            |                   |       |       |                   | 4/4     | 4/4              | 7/7               | 6/7              |       |                                                |                   |         |                  |         |
| 2             | 50                     | 46                      | 30/30                               | 29/30            | 26/30            |                   |       |       | 2/2               | 2/2     | 2/2              | 9/9               | 9/9              |       | 1/1                                            |                   |         | 2/2              |         |
| 3             | 44                     | 44                      | 14/15                               | 15/15            | 15/15            |                   |       |       |                   | 4/4     | 3/4              | 23/23             | 21/23            |       |                                                |                   |         | 2/2              |         |
| 4             | 35                     | 34                      | 7/8                                 | 8/8              | 8/8              |                   |       |       | 2/2               | 2/2     | 2/2              | 15/16             | 16/16            |       |                                                |                   |         | 4/6              |         |
| 5             | 22                     | 22                      | 2/2                                 | 2/2              | 2/2              |                   |       |       | 2/2               | 2/2     | 1/2              | 7/7               | 6/7              |       |                                                | 1/1               |         | 7/7              |         |
| 6             | 23                     | 22                      | 1/1                                 | 1/1              | 1/1              |                   |       |       | 2/2               | 2/2     |                  | 6/6               | 4/6              |       |                                                | 3/3               |         | 9/9              |         |
| 8             | 1                      | 1                       | 1/1                                 | 1/1              | 1/1              |                   |       |       |                   |         |                  |                   |                  |       |                                                |                   |         |                  |         |
| Total         | 226                    | 215                     | 89/91<br>(96.7%)                    | 90/91<br>(98.9%) | 83/91<br>(91.2%) |                   |       |       | 4/6               | 5/6     | 12/14<br>(85.7%) | 68/69<br>(98.6%)  | 63/69<br>(91.3%) |       | 2/1                                            |                   |         | 24/26<br>(92.3%) | 4.      |

Overall Conversion Rates

|  | Measles         | Mumps           | Rubella         |
|--|-----------------|-----------------|-----------------|
|  | 107/112 (95.5%) | 168/170 (98.8%) | 182/200 (91.0%) |



Table 2: Distribution of Titers of Children Initially Seronegative to Measles, Mumps, and Rubella Who Were Vaccinated with Combined Measles-Mumps-Rubella Vaccine Lot 96400 (Study 220C)

| Measles (HAI)            |                    | Mumps (Neut.)       |                    | Rubella (HAI)       |                    |
|--------------------------|--------------------|---------------------|--------------------|---------------------|--------------------|
| Post-Vacc.<br>Titer      | No. of<br>Children | Post-Vacc.<br>Titer | No. of<br>Children | Post-Vacc.<br>Titer | No. of<br>Children |
| <4                       | 3                  | <1                  | 1                  | <8                  | 8                  |
| 4                        | 7                  | 1                   | 2                  | 8                   | 9                  |
| 8                        | 16                 | 2                   | 22                 | 16                  | 31                 |
| 16                       | 24                 | 4                   | 15                 | 32                  | 22                 |
| 32                       | 29                 | 8                   | 19                 | 64                  | 17                 |
| 64                       | 7                  | 16                  | 11                 | 128                 | 3                  |
| 128                      | 4                  | 32                  | 12                 | 256                 | 1                  |
| ≥256                     | 1                  | ≥64                 | 9                  | ≥512                | 0                  |
| Geometric<br>Mean Titer: | 18.2               | 7.6                 |                    | 19.8                |                    |

Table 3: Serologic Findings for Rubella Antibody for Children and Adults Acting As Contact Controls for Combined Measles-Mumps-Rubella Vaccine Lot 96400 (Study 220C)

| Age<br>(Yrs.)         | Total<br>No. | No.<br>Serol.<br>Tested | No.<br>Initially<br>Seropos. | Initially Seronegative |            |       |
|-----------------------|--------------|-------------------------|------------------------------|------------------------|------------|-------|
|                       |              |                         |                              | No.Show.<br>Rise       | No<br>Rise | Total |
| Children              |              |                         |                              |                        |            |       |
| 1                     | 4            | 4                       |                              |                        | 4          | 4     |
| 2                     | 4            | 4                       |                              | 1                      | 3          | 4     |
| 3                     | 5            | 5                       |                              |                        | 5          | 5     |
| 4                     | 9            | 9                       |                              |                        | 9          | 9     |
| 5                     | 2            | 2                       |                              | 1                      | 1          | 2     |
| 6                     | 1            | 1                       |                              |                        | 1          | 1     |
| Total                 | 25           | 25                      | 0                            | 2                      | 23         | 25    |
| Adult Female Controls |              |                         |                              |                        |            |       |
| 16-19                 | 4            | 4                       | 1                            |                        | 3          | 3     |
| 20-29                 | 53           | 50                      | 22                           | 1                      | 27         | 28    |
| 30-39                 | 44           | 41                      | 24                           |                        | 17         | 17    |
| 40-49                 | 20           | 18                      | 13                           |                        | 5          | 5     |
| 51-56                 | 4            | 4                       | 2                            |                        | 2          | 2     |
| 65                    | 1            | 1                       | 1                            |                        |            |       |
| 70                    | 1            | 1                       | 1                            |                        |            |       |
| Not<br>Given          | 1            | 1                       |                              |                        | 1          | 1     |
| Total                 | 128          | 120                     | 64                           | 1                      | 55         | 56    |

Table 4: Clinical Complaints Recorded for Children Vaccinated with Measles-Mumps-Rubella Vaccine Lot 96400 and for Their Unvaccinated Controls (Study 220C)

| Clinical Complaint                | Contact Control Children |               |               |               | Total Vaccinees       |                |                |                | Initially Seronegative to Measles-Mumps-Rubella |               |               |               |
|-----------------------------------|--------------------------|---------------|---------------|---------------|-----------------------|----------------|----------------|----------------|-------------------------------------------------|---------------|---------------|---------------|
|                                   | Days Observed            |               |               |               | Days Post-Vaccination |                |                |                | Days Post-Vaccination                           |               |               |               |
|                                   | 1-4                      | 5-12          | 13-18         | 19-28         | 1-4                   | 5-12           | 13-18          | 19-28          | 1-4                                             | 5-12          | 13-18         | 19-28         |
| Upper Respiratory Illness         | 1<br>(4.0%)              | 3<br>(12.0%)  | 1<br>(4.0%)   | 3<br>(12.0%)  | 13<br>(6.7%)          | 19<br>(8.5%)   | 14<br>(6.2%)   | 19<br>(8.5%)   | 4<br>(4.4%)                                     | 5<br>(5.5%)   | 3<br>(3.3%)   | 8<br>(8.8%)   |
| Otitis                            | 1<br>(4.0%)              |               |               |               | 1<br>(0.4%)           |                | 1<br>(0.4%)    |                |                                                 |               |               |               |
| Typhoid                           |                          |               |               |               | 1<br>(0.4%)           |                |                |                |                                                 |               |               |               |
| Lymphadenopathy                   |                          |               |               | 1<br>(4.0%)   | 4<br>(1.8%)           | 3<br>(0.9%)    |                | 2<br>(0.9%)    |                                                 |               |               |               |
| Conjunctivitis                    | 1<br>(4.0%)              | 1<br>(4.0%)   |               |               | 4<br>(1.8%)           | 1<br>(0.4%)    |                | 1<br>(0.4%)    | 1<br>(1.1%)                                     | 2<br>(2.2%)   |               | 1<br>(1.1%)   |
| Gastrointestinal                  | 1<br>(4.0%)              | 1<br>(4.0%)   | 1<br>(4.0%)   | 2<br>(8.0%)   | 20<br>(8.9%)          | 38<br>(17.0%)  | 17<br>(7.6%)   | 10<br>(4.5%)   | 13<br>(14.3%)                                   | 20<br>(22.0%) | 9<br>(9.9%)   | 7<br>(7.7%)   |
| Headache                          |                          |               |               |               | 5<br>(2.2%)           | 9<br>(4.0%)    | 6<br>(2.7%)    | 2<br>(0.9%)    | 2<br>(2.2%)                                     | 4<br>(4.4%)   | 2<br>(2.2%)   | 1<br>(1.1%)   |
| Irritability                      | 1<br>(4.0%)              | 1<br>(4.0%)   | 1<br>(4.0%)   | 1<br>(4.0%)   | 6<br>(2.7%)           | 14<br>(6.2%)   | 2<br>(0.9%)    | 3<br>(1.3%)    | 3<br>(3.3%)                                     | 6<br>(6.6%)   | 1<br>(1.1%)   | 1<br>(1.1%)   |
| Malaise                           |                          |               | 1<br>(4.0%)   |               | 6<br>(2.7%)           | 11<br>(4.9%)   | 4<br>(1.8%)    | 6<br>(2.7%)    | 4<br>(4.4%)                                     | 7<br>(7.7%)   | 2<br>(2.2%)   | 5<br>(5.5%)   |
| Measles                           |                          |               |               |               | 1<br>(0.4%)           |                |                |                |                                                 |               |               |               |
| Fever                             | 1<br>(4.0%)              | 3<br>(12.0%)  | 2<br>(8.0%)   | 5<br>(20.0%)  | 12<br>(5.1%)          | 49<br>(21.9%)  | 19<br>(8.5%)   | 32<br>(14.3%)  | 8<br>(8.8%)                                     | 23<br>(25.3%) | 6<br>(6.6%)   | 13<br>(14.3%) |
| Anorexia                          |                          |               |               |               | 11<br>(4.9%)          | 19<br>(8.5%)   | 7<br>(3.1%)    | 4<br>(1.8%)    | 6<br>(6.6%)                                     | 12<br>(13.2%) | 6<br>(6.6%)   | 2<br>(2.2%)   |
| Allergy                           |                          |               |               |               | 1<br>(0.4%)           | 1<br>(0.4%)    |                | 1<br>(0.4%)    |                                                 |               |               | 1<br>(1.1%)   |
| Exanthema                         |                          |               |               |               | 1<br>(0.4%)           | 1<br>(0.4%)    | 1<br>(0.4%)    | 2<br>(0.9%)    |                                                 |               |               | 1<br>(1.1%)   |
| Measles-like Rash                 |                          |               | 1<br>(4.0%)   |               |                       |                |                |                |                                                 |               |               |               |
| No Complaint                      | 22<br>(88.0%)            | 19<br>(76.0%) | 21<br>(84.0%) | 14<br>(56.0%) | 166<br>(74.1%)        | 120<br>(53.6%) | 172<br>(76.8%) | 164<br>(73.2%) | 61<br>(67.0%)                                   | 43<br>(47.3%) | 71<br>(78.0%) | 64<br>(70.3%) |
| Physician's Surveillance Negative |                          |               |               |               | 2                     | 2              | 2              | 2              |                                                 |               |               |               |
| Total Subjects                    | 25                       | 25            | 25            | 25            | 226                   | 226            | 226            | 226            | 91                                              | 91            | 91            | 91            |

Study 220C

Serologic Assay Results for Persons who Served as Contact Controls for Lot 96400 and who Showed Rubella Antibody Rises.

| Patient No. | Status   | Measles |       |       | Mumps |       |       | Rubella |       |       | Blood Type |       |       | Comments                                      |
|-------------|----------|---------|-------|-------|-------|-------|-------|---------|-------|-------|------------|-------|-------|-----------------------------------------------|
|             |          | Pre     | 1 Mo. | 2 Mo. | Pre   | 1 Mo. | 2 Mo. | Pre     | 1 Mo. | 2 Mo. | Pre        | 1 Mo. | 2 Mo. |                                               |
| 2471        | Control  | >20     | 80    |       | QNS   | 32    |       | <8      | 128   |       | QNS        | QNS   |       | Insufficient sera for retesting               |
| 334-10      | Guardian | >20     | QNS   |       | <2    | QNS   |       | <8      | 16    |       | 0          | QNS   |       | Insufficient sera for retesting               |
| 10-10       | Guardian |         |       |       |       |       |       | <8      | 256   |       | B          | 0     |       | Blood specimen mix-up - eliminated from study |
| 3523        | Control  | <5      | 10    |       | QNS   | QNS   |       | <8      | 256   |       | 0          | 0     |       | Measles conversion - probable vaccinee        |

## Experience with Live Rubella Virus Vaccine Combined with Live Vaccines against Measles and Mumps\*

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*Vaccination of pre-school children in the 1-7-years age-group for the specific prophylaxis of mumps and rubella is often difficult to arrange because of the already large number of inoculations given to these children. Combined vaccines to protect against measles, mumps and rubella should therefore be a valuable development. The existence of effective live vaccines for each of these 3 diseases makes possible the production of a single preparation suitable for subcutaneous inoculation.*

*Tests on vaccine strains of measles (Leningrad-16), mumps (Leningrad-3) and rubella (Leningrad-8) viruses in various combinations have established that divalent or trivalent vaccines remain clinically harmless, highly immunogenic and epidemiologically effective. Single subcutaneous administrations of live measles vaccine combined with mumps or rubella vaccines or both, when given to children aged 1-8 years, brought about a high percentage of serological conversions and an increase in antibodies to a level comparable with that achieved with the corresponding monovalent vaccines. Morbidity from the 3 diseases was reduced among those vaccinated with the trivalent vaccine by 10 or more times, i.e., by about the same factor as when monovalent or divalent vaccines were used.*

Success in the prevention and treatment of scarlet fever and in vaccination against pertussis, together with favourable prospects for the rapid eradication of diphtheria, poliomyelitis and measles, has, in recent years, substantially increased the relative epidemiological importance of rubella.

The rubella virus causes mass infections among children of pre-school age and not infrequently attacks pregnant women, resulting in multiple foetal defects. Specific prophylaxis by means of a live vaccine is needed urgently because of the lack of effective measures to limit contacts between rubella cases and healthy persons.

The possibility of active immunization against rubella arises from the achievements in mass immu-

nization against measles which provide a safe basis for the study of combined vaccination against such infections as rubella and epidemic parotitis.

Reports of highly promising results from combined vaccination against measles and mumps have been published elsewhere (Smorodintsev et al., 1967; Nasibov, 1965; Šikina et al., 1965).

The present communication summarizes the results obtained in the study of live rubella virus vaccine combined with live vaccines against measles and mumps.

### MATERIALS AND METHODS

The live rubella virus vaccine was prepared in primary rabbit tissue-culture from the Leningrad-8 strain obtained after 23 passages in the same culture.

Live vaccines against measles from the Leningrad-16 strain and against mumps from the Leningrad-3 (L-3) strain were prepared in primary guinea-pig kidney tissue-culture using the vaccine strains obtained after 16 serial passages in the same culture.

The programme of combined vaccination involved susceptible children aged between 1 and 7 years in nurseries and kindergartens. The children were vac-

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culated simultaneously with 0.5 ml of di- or trivalent vaccine containing from 500 TCID<sub>50</sub> to 1000 TCID<sub>50</sub> of rubella, measles or mumps virus with homologous monovalent vaccines as controls.

The concentration of rubella virus in the vaccines was determined by virus titration in continuous rabbit kidney culture (RK<sub>13</sub>) and the results were evaluated by the cytopathogenic effect of the virus and by interference with vesicular stomatitis virus. The concentration of mumps virus was determined by titration in a monolayer culture of chick embryo fibroblasts with the help of fowl erythrocyte haemadsorption tests to detect infection.

The biological activity of the viruses contained in di- or trivalent vaccine was estimated by use of tissue-cultures optimal for each component after the cross-exclusion of heterologous viruses with highly active homologous immune sera applied in doses of 16-32 neutralizing units.

The effectiveness of the rubella virus vaccine from the Leningrad-8 strain was studied by means of clinical, immunological and virological examination of the vaccinated healthy children. All vaccine recipients were regularly observed by a physician and temperatures were taken twice a day for 3 weeks after the start of the vaccination programme. Virological examinations of blood, urine or throat swabs obtained from vaccinated or contact groups of

children were also carried out to investigate the possible spread of the vaccine virus from vaccinated persons to susceptible contacts after intimate, prolonged exposure.

The immunogenic properties of the live rubella virus vaccine combined with live measles and mumps vaccine were evaluated by means of serological tests using paired sera obtained before and a month after the vaccination.

The immunogenicity of the vaccine strains of measles and rubella viruses was determined by titrating the sera with a titre of 1:2 in haemagglutination-inhibition tests using 4-8 units of the rubella virus (the Leningrad-8 strain) and measles virus (the Leningrad-16 strain) antigens. The immunogenic activity of the mumps virus was estimated in virus-neutralization tests using 100 TCID<sub>50</sub> per ml of the virus in monolayer chicken fibroblast tissue-culture. The results of the neutralization tests were read after 4-5 days of incubation at 35°C-36°C on the basis of the haemadsorption reaction with a 1% suspension of fowl erythrocytes.

The epidemiological effectiveness of the combined vaccine was evaluated by comparing the rate of morbidity among institutionalized children vaccinated with monovalent or combined vaccines and those in unvaccinated control groups during natural rubella, measles or epidemic parotitis outbreaks.

TABLE 1  
CLINICAL, IMMUNOLOGICAL AND VIROLOGICAL FINDINGS AMONG 875 CHILDREN: 357 VACCINATED WITH LIVE RUBELLA VIRUS VACCINE AND 520 UNVACCINATED CONTACTS

| Group      | No. of children in nurseries and kindergartens | Clinical findings                          |                                             |                           | Virus in throat secretions on indicated days after vaccination <sup>a</sup> |      |      |      |      |      |      |      |      |      | Virus recovery from : |       | Reciprocal HI & antibody titre |               |
|------------|------------------------------------------------|--------------------------------------------|---------------------------------------------|---------------------------|-----------------------------------------------------------------------------|------|------|------|------|------|------|------|------|------|-----------------------|-------|--------------------------------|---------------|
|            |                                                | No. of children showing a temperature rise | No. of children with lymph node enlargement | No. of children with rash | 4                                                                           | 6    | 8    | 10   | 12   | 14   | 16   | 18   | 20   | 22   | Blood                 | Urine | Prior to vaccination           | After 30 days |
|            |                                                |                                            |                                             |                           |                                                                             |      |      |      |      |      |      |      |      |      |                       |       |                                |               |
| Vaccinated | 30                                             | 1                                          | 0                                           | 0                         |                                                                             |      |      |      |      |      |      |      |      |      | —                     | —     | <4                             | 8             |
|            | 55                                             | 2                                          | 0                                           | 0                         | 0/0                                                                         | 0/0  | 0/2  | 0/2  | 0/1  | 0/0  | 0/0  | 0/0  | 0/0  | 0/0  | —                     | —     | <4                             | 16            |
|            | 75                                             | 0                                          | 0                                           | 0                         |                                                                             |      |      |      |      |      |      |      |      |      | —                     | —     | <4                             | 32            |
|            | 60                                             | 2                                          | 0                                           | 0                         | 0/0                                                                         | 0/0  | 5/1  | 4/1  | 5/2  | 0/0  | 4/0  | 5/0  | 4/0  | 0/0  | —                     | —     | <4                             | 64            |
|            | 77                                             | 0                                          | 0                                           | 0                         | 0/0                                                                         | 7/0  | 0/3  | 0/2  | 0/2  | 7/0  | 0/0  | 0/0  | 0/0  | 0/0  | —                     | —     | <4                             | 128           |
|            | 24                                             | 0                                          | 0                                           | 0                         |                                                                             |      |      |      |      |      |      |      |      |      | —                     | —     | <4                             | 256           |
| Contact    | 220                                            | 4                                          | —                                           | —                         | 32/0                                                                        | 30/0 | 25/0 | 31/0 | 30/0 | 25/0 | 25/0 | 28/0 | 32/0 | 31/0 | —                     | —     | <4                             | <4            |

<sup>a</sup> Number of children in a group/number of virus recoveries.

<sup>b</sup> Haemagglutination-inhibition.

TABLE 2  
RATE OF DEVELOPMENT AND PERSISTENCE OF VIRUS-NEUTRALIZING, HAEMAGGLUTINATION-INHIBITING OR COMPLEMENT-FIXING ANTIBODIES IN CHILDREN IMMUNIZED BY LIVE RUBELLA VIRUS VACCINE AND IN CHILDREN WITH A PREVIOUS HISTORY OF RUBELLA

| Antibody level after 1, 8 or 9 months as determined by the following tests : |                                        |         |          |                      |                                        |                              |          |                      |                                        |                     |          |          |                      |      |
|------------------------------------------------------------------------------|----------------------------------------|---------|----------|----------------------|----------------------------------------|------------------------------|----------|----------------------|----------------------------------------|---------------------|----------|----------|----------------------|------|
| Group and serum No.                                                          | Virus-neutralization                   |         |          |                      |                                        | Haemagglutination-inhibition |          |                      |                                        | Complement-fixation |          |          |                      |      |
|                                                                              | Pre-vaccination or at onset of illness | 1 month | 9 months | Geometric mean titre | Pre-vaccination or at onset of illness | 1 month                      | 9 months | Geometric mean titre | Pre-vaccination or at onset of illness | 1 month             | 8 months | 9 months | Geometric mean titre |      |
| Vaccinated                                                                   | 1                                      | <4      | 64       | 128                  | 64                                     | <4                           | 64       | 128                  | 128                                    | <4                  | 16       | 16       | <4                   | 22.8 |
|                                                                              | 2                                      | <4      | 128      | 64                   | 64                                     | <4                           | 128      | 128                  | 128                                    | <4                  | 8        | 32       | <4                   |      |
|                                                                              | 3                                      | <4      | 32       | 64                   | 64                                     | <4                           | 256      | 128                  | 256                                    | <4                  | 16       | 8        | 4                    |      |
|                                                                              | 4                                      | <4      | 16       | 32                   | 32                                     | <4                           | 64       | 64                   | 64                                     | <4                  | 8        | 16       | 4                    |      |
|                                                                              | 5                                      | <4      | 64       | 64                   | 64                                     | <4                           | 128      | 128                  | 128                                    | <4                  | 8        | 16       | <8                   |      |
|                                                                              | 6                                      | <4      | 16       | 32                   | 32                                     | <4                           | 256      | 128                  | 128                                    | <4                  | 16       | 32       | 4                    |      |
| Control                                                                      | 7                                      | <4      | 64       | 64                   | 128                                    | <4                           | 64       | 128                  | 128                                    | <4                  | 8        | 16       | <4                   | 22.8 |
|                                                                              | 8                                      | <4      | 32       | 64                   | 64                                     | <4                           | 128      | 64                   | 128                                    | <4                  | 16       | 32       | <4                   |      |
|                                                                              | 9                                      | <4      | 64       | 32                   | 64                                     | <4                           | 256      | 128                  | 256                                    | <4                  | 8        | 16       | <4                   |      |
|                                                                              | 10                                     | <4      | 64       | 32                   | 64                                     | <4                           | 32       | 64                   | 64                                     | <4                  | 4        | 16       | 4                    |      |
|                                                                              | 11                                     | <4      | 64       | 128                  | 256                                    | <4                           | 128      | 256                  | 256                                    | <4                  | 8        | 32       | <8                   |      |



## RESULTS

No post-vaccination signs or symptoms (rise in temperature, rash, catarrhal symptoms, enlargement of the regional nodes or changes in blood or urine) were detected among 355 children given a single subcutaneous injection of the live rubella virus vaccine.

The reproduction of the vaccine strain in the body of the recipients was shown by the recovery of rubella virus from throat discharges in 6 out of 20 children in the study 7-12 days after vaccination; all vaccinated children developed specific antibodies 30 days after vaccination. The attenuated rubella virus strain was not transmitted to susceptible children of the control group who were in close and prolonged contact with the vaccinees. This was confirmed by the lack of any clinical reactions or detectable virus in the upper respiratory tracts of the contacts and also by absence of specific immunological changes in the latter (Table 1).

Injection of the live vaccine against rubella into susceptible children was followed by 100% seroconversion of virus-neutralizing and haemagglutination-inhibiting antibodies. No difference was found between the rate of development and titres of the

antibodies after vaccination and in natural infections (Table 2).

Mean geometric antibody titres in vaccinees and in children with a previous history of rubella determined in haemagglutination-inhibition tests were significantly higher than those obtained in neutralization reactions (1:138 and 1:91 in vaccinees compared with 1:147 and 1:97 in convalescents).

Concentrations of complement-fixing antibodies were significantly lower than concentrations of the virus-neutralizing antibodies in both vaccinated and convalescent children. Complement-fixing antibody titres were not higher than 1:8-1:16 in the majority of vaccinees or convalescent children.

Titres of virus-neutralizing and haemagglutination-inhibiting antibodies were maximal 4 weeks after the injection of the live vaccine or recovery from natural infection and remained at the same levels during 6-9 months of observation; complement-fixing antibodies were completely lacking by the end of the ninth month in the same children.

The isolated large-scale use of the live monovalent rubella virus vaccine for vaccination of children aged 1-7 years is rather difficult to arrange because of the large number of inoculations already given to children in this age-group. Accordingly, it was

TABLE 3  
SEROLOGICAL FINDINGS AMONG CHILDREN GIVEN MONOVALENT OR COMBINED VACCINES  
AGAINST MUMPS, MEASLES AND RUBELLA

| Antigen against | Serological test <sup>a</sup> | Vaccine against:           | No. of children observed | No. of children with antibody rise |      | Geometric mean antibody titre |
|-----------------|-------------------------------|----------------------------|--------------------------|------------------------------------|------|-------------------------------|
|                 |                               |                            |                          | Total                              | %    |                               |
| Mumps           | N                             | Mumps                      | 200                      | 198                                | 99.0 | 36.0                          |
|                 |                               | Mumps and measles          | 124                      | 114                                | 92.0 | 24.2                          |
|                 |                               | Mumps and rubella          | 122                      | 116                                | 95.0 | 22.0                          |
|                 |                               | Mumps, measles and rubella | 99                       | 91                                 | 91.9 | 21.1                          |
| Measles         | HI                            | Measles                    | 85                       | 83                                 | 96.9 | 56                            |
|                 |                               | Measles and mumps          | 138                      | 121                                | 88.0 | 32                            |
|                 |                               | Measles and rubella        | 46                       | 42                                 | 91.3 | 49                            |
|                 |                               | Measles, mumps and rubella | 88                       | 80                                 | 90.9 | 42                            |
| Rubella         | HI                            | Rubella                    | 239                      | 229                                | 95.8 | 194                           |
|                 |                               | Rubella and mumps          | 122                      | 116                                | 94.3 | 126                           |
|                 |                               | Rubella and measles        | 75                       | 72                                 | 96.0 | 120                           |
|                 |                               | Rubella, mumps and measles | 99                       | 90                                 | 90.9 | 112                           |

<sup>a</sup> N = virus-neutralization; HI = haemagglutination-inhibition.

considered reasonable to investigate the possibility of using the rubella virus vaccine in combination with the more essential vaccines against measles and mumps.

A study of combined vaccination against rubella, measles and mumps has shown that the maintenance of high immunogenic activity is quite impossible when simultaneous injections of  $\gamma$ -globulin are used to suppress clinical reactions to the live measles virus vaccine. The latter must involve a properly attenuated variant of the virus of the Leningrad-16 type.

Immunological changes produced by a single subcutaneous injection of di- or trivalent vaccine were studied and correlated with seroconversion findings obtained with homologous monovalent vaccines. The proportion of children showing a rise in specific antibodies after injection of mono-, di- or trivalent vaccines ranged from 89.0% to 98.0% (Table 3).

Conclusive evidence of the high immunogenic activity of the live rubella virus vaccines, both monovalent and combined, might be provided by observations on the morbidity rate among vaccinees during outbreaks of natural infection.

Table 4 shows that coefficients of effectiveness of the live rubella virus vaccine, monovalent or combined, ranged from 95.0% to 100%, suggesting a high activity in the rubella virus vaccine strain used. This is additional evidence that it would be sound practice to use rubella virus vaccine in combination with live vaccines against measles and mumps.

TABLE 4  
EPIDEMIOLOGICAL EFFECTIVENESS OF LIVE RUBELLA VIRUS VACCINE, MONOVALENT OR COMBINED WITH LIVE VACCINES AGAINST MUMPS AND MEASLES, DURING OUTBREAKS OF RUBELLA

| Groups of children | Vaccine against rubella combined with vaccines against: | Children in contact |              | Coefficient of effectiveness (%) |
|--------------------|---------------------------------------------------------|---------------------|--------------|----------------------------------|
|                    |                                                         | Total No.           | No. of cases |                                  |
| Vaccinated         | Mumps                                                   | 115                 | 1            | 98.3                             |
| Unvaccinated       | —                                                       | 121                 | 10           |                                  |
| Vaccinated         | Measles                                                 | 150                 | 0            | 100.0                            |
| Unvaccinated       | —                                                       | 112                 | 50           |                                  |
| Vaccinated         | Mumps and measles                                       | 138                 | 2            | 98.8                             |
| Unvaccinated       | —                                                       | 180                 | 44           |                                  |
| Vaccinated         | Rubella only                                            | 170                 | 0            | 100.0                            |
| Unvaccinated       | —                                                       | 215                 | 47           |                                  |

The coefficient of morbidity in the control group of children exceeded morbidity rates among the recipients of the monovalent mumps or measles vaccines by 97%-99% and by 91%-97% for the recipients of the combined vaccine (Tables 5 and 6).

TABLE 5  
EPIDEMIOLOGICAL EFFECTIVENESS OF LIVE MUMPS VIRUS VACCINE, MONOVALENT OR COMBINED WITH LIVE VACCINES AGAINST MEASLES AND RUBELLA, DURING OUTBREAKS OF MUMPS

| Groups of children | Mumps virus vaccine combined with vaccines against : | Children in contact |              |           | Coefficient of effectiveness (%) |
|--------------------|------------------------------------------------------|---------------------|--------------|-----------|----------------------------------|
|                    |                                                      | Total No.           | No. of cases |           |                                  |
|                    |                                                      |                     | Total        | Per 1 000 |                                  |
| Vaccinated         | Measles                                              | 6 340               | 4            | 0.6       | 98.0                             |
| Unvaccinated       | —                                                    | 4 375               | 122          | 29.3      |                                  |
| Vaccinated         | Rubella                                              | 793                 | 1            | 1.3       | 97.8                             |
| Unvaccinated       | —                                                    | 654                 | 26           | 59.6      |                                  |
| Vaccinated         | Measles and rubella                                  | 597                 | 4            | 6.7       | 91.6                             |
| Unvaccinated       | —                                                    | 603                 | 46           | 76.0      |                                  |
| Vaccinated         | Mumps only                                           | 10 570              | 5            | 0.5       | 99.2                             |
| Unvaccinated       | —                                                    | 6 720               | 430          | 65.1      |                                  |

TABLE 6  
EPIDEMIOLOGICAL EFFECTIVENESS OF LIVE MEASLES  
VIRUS VACCINE, MONOVALENT OR COMBINED WITH  
LIVE VACCINES AGAINST MUMPS AND RUBELLA,  
DURING OUTBREAKS OF MEASLES

| Groups of children | Measles virus vaccine combined with vaccines against: | Children in contact |              | Coefficient of effectiveness (%) |
|--------------------|-------------------------------------------------------|---------------------|--------------|----------------------------------|
|                    |                                                       | Total No.           | No. of cases |                                  |
| Vaccinated         | Mumps                                                 | 269                 | 1            | 97.0                             |
| Unvaccinated       | —                                                     | 211                 | 38           |                                  |
| Vaccinated         | Rubella                                               | 99                  | 1            | 98.0                             |
| Unvaccinated       | —                                                     | 115                 | 23           |                                  |
| Vaccinated         | Mumps and rubella                                     | 124                 | 3            | 97.0                             |
| Unvaccinated       | —                                                     | 150                 | 35           |                                  |
| Vaccinated         | Measles only                                          | 340                 | 1            | 97.4                             |
| Unvaccinated       | —                                                     | 321                 | 39           |                                  |

The results obtained thus offer favourable prospects for the combined use of the live rubella virus vaccine with live vaccines against measles and mumps.

#### DISCUSSION

It seems quite reasonable to attempt to control widespread contagious infections of childhood by means of combined vaccination with live vaccines against rubella, measles and mumps and the results of trials are promising. The mild reactogenicity of the live measles virus vaccine from the Leningrad-16 strain (30%–40% transient febrile reactions of mild or moderate intensity) was unaffected by simultaneous injection of non-reactogenic live vaccines against mumps (Nasibov, 1965).

Fairly high immunogenic activity of monovalent live vaccines against measles mumps and rubella (seroconversion over 90% with minimal virus doses) was also retained under conditions of combined vaccination. Some decrease in the immunogenic activity of the mumps and rubella components was observed in children responding with fever to the measles component of the triple vaccine but there was no distinct influence on the efficacy of combined immunization. When vaccine febrile reactions were absent, the immunogenic activity of the trivalent vaccine was similar to that of the control monovalent preparations.

Epidemiological observations have demonstrated a sharp decrease in the incidence of mumps among children protected by single subcutaneous injections of measles-mumps vaccine compared with an unvaccinated control group. The live mumps-measles vaccine remained highly immunogenic when in combination with the live rubella virus vaccine. Rubella infections were completely prevented by the injection of both triple and single vaccines.

The results of the USSR programme of controlled vaccination with live measles virus vaccine from the Leningrad-16 strain offer favourable prospects for mass prophylaxis against epidemic parotitis and rubella. The effective live vaccines against mumps and rubella developed by the present authors can be successfully used in combination with measles vaccine in a single injection. The use of this triple vaccine against measles mumps and rubella might provide a safe basis for the limiting and eradication not only of measles but also of mumps and rubella, which are also highly hazardous, mass contagious infections of childhood.

The practical realization of this goal requires the speedy manufacture of the mumps-measles vaccine, the components of which have been carefully studied in the USSR, and also the production of rubella virus vaccine to be included in the trivalent vaccine.

#### RÉSUMÉ

##### RÉSULTATS OBTENUS PAR L'ADMINISTRATION D'UN VACCIN VIVANT CONTRE LA RUBÉOLE ASSOCIÉ À DES VACCINS VIVANTS CONTRE LA ROUGEOLE ET LES OREILLONS

Des perspectives particulièrement intéressantes sont offertes à la prophylaxie de masse des infections virales de l'enfance par la vaccination sous-cutanée associant des vaccins vivants contre la rougeole (souche Leningrad-16), contre les oreillons (souche Leningrad-3) et contre la

rubéole (souche Leningrad-8) mis au point en URSS par A. Smorodintsev et ses collaborateurs.

Le vaccin antirougeoleux vivant issu de la souche Leningrad-16 provoque chez les enfants vaccinés environ 30 à 40% de réactions fébriles transitoires d'une intensité

faible à moyenne. L'injection sous-cutanée de vaccins monovalents vivants contre la rubéole et contre les oreillons ne s'accompagne d'aucune manifestation clinique. L'association dans une préparation bivalente ou trivalente du vaccin vivant contre la rougeole et des vaccins vivants contre la rubéole ou les oreillons n'aggrave pas les réactions cliniques propres au vaccin anti-rougeoleux seul.

Chacun des trois vaccins vivants a régulièrement (95,8-98,0%) amené la séroconversion chez les enfants âgés de 1 à 8 ans qui ont été soumis à l'essai, même lorsque la dose inoculée n'avait qu'une teneur minimale

en virus-vaccin. L'intensité et la régularité des réactions sérologiques sont restées à un niveau élevé lorsque ces vaccins ont été administrés en association bivalente ou trivalente.

Le vaccin trivalent a entraîné une forte diminution de la morbidité parmi les enfants immunisés, avec un coefficient d'efficacité épidémiologique comparable à celui des préparations monovalentes correspondantes (plus de 90%). L'efficacité du vaccin double antirougeoleux-antioreillon a été confirmée dans des cas où les enfants vaccinés vivaient dans des collectivités atteintes par des épidémies d'oreillons et de rougeole.

#### REFERENCES

- Nasibov, M. N. (1965) [Results of combined immunization against measles and mumps by use of live vaccines] In: [Live measles vaccine], Leningrad, Leningrad Pasteur Institute of Epidemiology and Microbiology vol. 28, pp. 424-432.
- Sikina, E. S., Taras, L. Ju., Tregubova, T. V., Matjusina, N. V., Luzjanina, T. Ja., Mikuckaja, B. A., Nasibov, M. N. & Smorodintsev, A. A. (1965) [Serological and epidemiological data on the combined immunization against measles and mumps]. In: [Live measles vaccine], Leningrad, Leningrad Pasteur Institute of Epidemiology and Microbiology, vol. 28, pp. 291-301.
- Smorodintsev, A. A., Kljačko, N. S., Nasibov, M. N. & Sikina, E. S. (1967) Experience with live mumps vaccine in the USSR. In: *Proceedings of the First International Conference on Vaccines against Viral and Rickettsial Diseases of Man, Washington, 1966*, pp. 422-429.

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September 8, 1970

License Applications currently filed by Merck, Sharp and Dohme

Merck, Sharp and Dohme Files

1. On August 19, 1970, Drs. Hilleman, Gray, Woodhour, and Peck of Merck, Sharp and Dohme met with Drs. Murray, Parkman, Meyer, Cohen, and Kirschstein of DBS to discuss the status of license applications currently on file and future plans for production of vaccines.

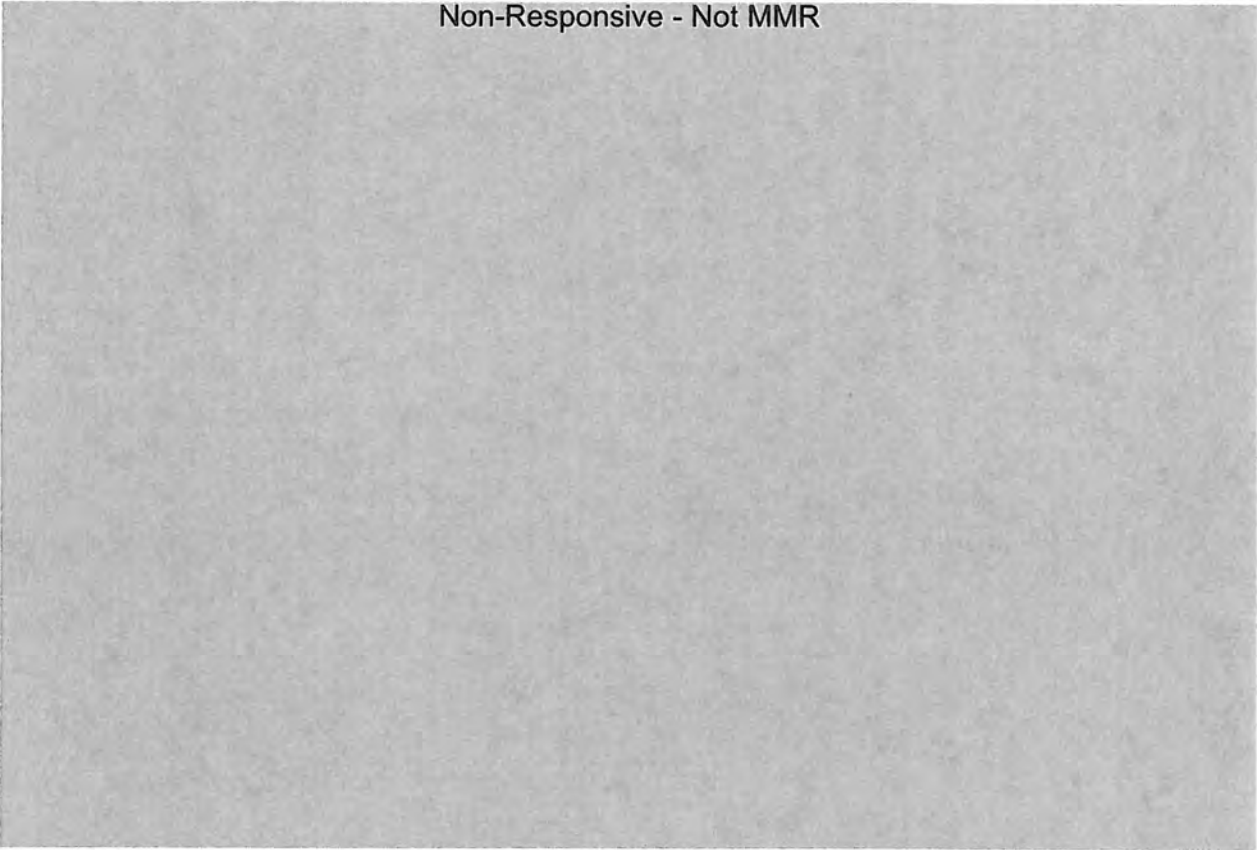
2. Dr. Hilleman opened the meeting by discussing the new rules governing IND's which require a 30 day waiting period before proceeding with the clinical studies. Dr. Murray indicated that DBS had had such a gentlemen's agreement with manufacturers for quite some time. He also stated that the new regulations will require a waiting period between the completion of phase 2 clinical studies and initiation of phase 3 studies.

3. Dr. Hilleman brought the group up to date concerning the clinical studies of the Measles-Mumps-Rubella combined vaccine for which a completed license application has been submitted. Three consistency lots have been prepared and studied in about 600 triple negative children. Conversion rates were between 94-100% for the measles component, 93.7 to 96.9% for the mumps component, and 92-100% for the rubella component. Dr. Krugman will also do a study on triple negatives. He has already done a study with the measles-rubella combined vaccine and has found 98% conversion with GMT's as expected and no significant depression of either GMT. However, although the license application for Measles-Rubella has been submitted, the clinical data has not yet been sent. Thus far 379 double negatives have received this vaccine with 97% conversion for measles and 93% conversion for rubella.

Non-Responsive - Not MMR

Page 2 - Merck, Sharp and Dohme Files

Non-Responsive - Not MMR



8. The meeting adjourned at 3:00 P.M.

cc: Dr. Murray  
Dr. Parkman  
Dr. Meyer  
Dr. Cohen  
Dr. Hardegree  
Dr. O'Malley  
Dr. Wagner

LP:RLKirschstein:ek:9/8/70



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- Not Clinical**

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LICENSING & INVESTIGATIONS

# MERCK SHARP & DOHME

DIVISION OF MERCK & CO., INC.

WEST POINT, PENNSYLVANIA 19486

November 4, 1970

Dr. Roderick Murray, Director  
Division of Biologics Standards  
National Institutes of Health  
Bethesda, Maryland 20014

Dear Doctor Murray:                      Reference No. 69-192

As indicated in Dr. Hilleman's letter of November 3, we are submitting three copies of Addendum No. 3 to Summary No. 1 of Clinical Investigative Studies of Combined Live Measles, Mumps and Rubella Vaccine.

We would appreciate your making this information a part of our license application.

With kindest personal regards,

Sincerely yours,

MERCK SHARP & DOHME  
Division of Merck & Co., Inc.

*Alan Gray /mb*

Alan Gray, Ph.D.  
Director, Biological Production

/mb

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Nov 9 4 25 PM '70

MERCK INSTITUTE  
FOR  
THERAPEUTIC RESEARCH  
WEST POINT, PENNSYLVANIA 19486

MAURICE R. HILLEMANN, Ph.D., D.Sc.  
EXECUTIVE DIRECTOR

November 3, 1970

Dr. Roderick Murray, Director  
Division of Biologics Standards  
National Institutes of Health  
Bethesda, Maryland 20014

Dear Dr. Murray:

Sometime past, it was suggested to us that an independent test of triple measles-mumps-rubella vaccine be carried out. Such trial was performed by Dr. Saul Krugman with the results as given in the attached letter. The findings are highly satisfactory.

Dr. Alan Gray will send the data to you shortly as part of the official submission in support of licensing this product.

Kindest regards.

Sincerely yours,

  
Maurice R. Hilleman, Ph.D.  
Director  
Virus & Cell Biology Research

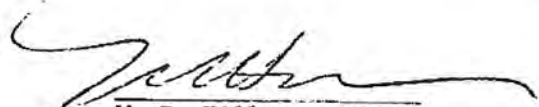
/b1  
Attachment

cc: Dr. Gray

Addendum No. 3  
to Summary No. 1  
of  
Clinical Investigative Studies  
of

Combined Live Measles Virus Vaccine (Moraten Line - ATTENUVAX)  
Jeryl Lynn Mumps Virus Vaccine (MUMPSVAX)  
HPV-77 Duck Rubella Virus Vaccine (MERUVAX)

for purpose of support for  
a license to manufacture and sell.



M. R. Hilleman, Ph.D.

Prepared: November 3, 1970  
Merck Institute for Therapeutic  
Research, West Point, Pa.

Clinical Investigation of Combined Live Attenuated Measles (Moraten),  
Mumps (Jeryl Lynn), and Rubella (HPV-77 Duck) Vaccine

The present report deals with a clinical investigation of combined Measles (Moraten) - Mumps (Jeryl Lynn) - Rubella (HPV-77 + 5 duck) vaccine carried out in children under the direction of Dr. Saul Krugman, Department of Pediatrics, School of Medicine, New York University, New York 10016. The vaccine used was consistency lot 61584/96400 (C-8095).

The findings are presented in the attached report.



NEW YORK UNIVERSITY

School of Medicine  
550 FIRST AVENUE, NEW YORK, N.Y. 10016

Office of the Chairman  
Department of Pediatrics

October 29th, 1970

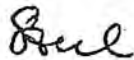
Maurice R. Hilleman, Ph.D.  
Director  
Virus & Cell Biology Research  
Merck Institute  
West Point, Pennsylvania 19486

Dear Maurice,

Enclosed is a copy of the report of our evaluation  
of combined measles-mumps-rubella vaccine No. 61584/  
96400 (C-8095). The results are very impressive.

With best wishes.

Sincerely,



Saul Krugman, M.D.  
Professor and Chairman

Encl. - 2

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# Evaluation of Combined Measles-Rubella-Mumps Vaccine

Lot No. 96400 C-8095.

This study was conducted at the New York Foundling Hospital in collaboration with Dr. Vincent Fontana and Dr. Gloria Muriel. It was designed to evaluate the antigenic effect of combined live measles-rubella-mumps vaccine when administered to infants with no detectable antibody for the three viruses. There were 41 triple - negative susceptible infants available for study. An additional 12 infants had detectable levels of mumps neutralizing antibody.

A sample of blood was obtained immediately before and seven or more weeks after inoculation of vaccine. Measles and rubella hemagglutination inhibition (HI) antibody tests were performed in the NYU Pediatric Infectious Disease Laboratories. Aliquots of the paired serum specimens were coded and sent to Dr. Hilleman's laboratory to be tested for the presence of mumps neutralizing antibody.

Results. The results of antibody studies in the 41 triple-negative infants are listed in Table 1. All 41 infants developed measles and <sup>mumps \*</sup>~~rubella~~ antibody; only one of 41 infants failed to develop rubella antibody.

The results of studies in 12 infants who were not triple-negative are shown in Table 2. All seronegative infants responded with the development of measles and rubella HI antibody.

The vaccine was well tolerated by all infants. The usual febrile response associated with measles vaccination was observed.

\* corrected by Dr. S. Krugman by phone, November 2, 1970

Conclusion. Combined live measles-rubella-mumps vaccine, lot No. 96400 C-805 was immunogenic for triple - negative infants. No evidence of interference was observed.

Saul Krugman, M.D.  
Professor and Chairman  
Department of Pediatrics  
New York University  
School of Medicine

Table 1. Combined Live Measles-Rubella-Mumps Vaccine: Antibody Response of 41 Seronegative Infants.

| No.   | Name | Age<br>(mos.) | Measles HI |       | Rubella HI |      | Mumps | Neut |
|-------|------|---------------|------------|-------|------------|------|-------|------|
|       |      |               | Pre        | Post  | Pre        | Post | Pre   | Post |
| 1.    |      | 17            | <4         | 256   | <8         | <8   | <2    | 8    |
| 2.    |      | 12            | <4         | 1024  | <8         | 32   | <2    | 2    |
| 3.    |      | 20            | <4         | 512   | <8         | 512  | <2    | 32   |
| 4.    |      | 20            | <4         | 1024  | <8         | 32   | <2    | 4    |
| 5.    |      | 12            | <4         | 256   | <8         | 8    | <2    | 64   |
| 6.    |      | 17            | <4         | 512   | <2         | 4    | <2    | 4    |
| 7.    |      | 14            | <4         | 512   | <2         | 8    | <2    | 128  |
| 8.    |      | 21            | <4         | 512   | <8         | 16   | <2    | 128  |
| 9.    |      | 14            | <4         | 1024  | <8         | 16   | <2    | 32   |
| 10.   |      | 17            | <4         | >1024 | <8         | 64   | <2    | 8    |
| 11.   |      | 16            | <4         | 256   | <8         | 16   | <2    | 64   |
| 12.   |      | 14            | <4         | 256   | <8         | 16   | <2    | 2    |
| 13.   |      | 11            | <4         | 512   | <8         | 16   | <2    | 8    |
| 14.   |      | 20            | <4         | 1024  | <8         | 64   | <2    | 4    |
| 15.   |      | 17            | <4         | 256   | <8         | 32   | <2    | 32   |
| 16.   |      | 13            | <4         | 256   | <8         | 32   | <2    | 64   |
| 17.   |      | 18            | <4         | 512   | <8         | 8    | <2    | 16   |
| 18.   |      | 19            | <4         | 512   | <8         | 16   | <2    | 16   |
| 19.   |      | 14            | <4         | >1024 | <8         | 32   | <2    | 4    |
| 20.   |      | 15            | <4         | 512   | <8         | 64   | <2    | 32   |
| 21.   |      | 13            | <4         | 512   | <8         | 32   | <2    | 16   |
| 22.   |      | 12            | <4         | 512   | <8         | 32   | <2    | 2    |
| 23.   |      | 14            | <4         | 256   | <8         | 32   | <4    | 4    |
| 24.   |      | 12            | <4         | 512   | <8         | 32   | <2    | 32   |
| 25.   |      | 12            | <4         | 256   | <8         | 16   | <2    | 4    |
| 26.   |      | 12            | <4         | 128   | <8         | 16   | <2    | 16   |
| 27.   |      | 14            | <4         | 256   | <8         | 32   | <2    | 4    |
| 28.   |      | 12            | <4         | 128   | <8         | 32   | <2    | 8    |
| 29.   |      | 12            | <4         | 512   | <8         | 128  | <2    | 4    |
| 30.   |      | 13            | <4         | 512   | <8         | 8    | <2    | 32   |
| 31.   |      | 12            | <4         | >512  | <8         | 64   | <2    | 64   |
| 32.   |      | 12            | <4         | 256   | <8         | 32   | <2    | 128  |
| 33.   |      | 12            | <4         | 512   | <8         | 64   | <8    | 32   |
| 34.   |      | 12            | <4         | 256   | <8         | 16   | <2    | 16   |
| 35.   |      | 17            | <4         | 256   | <8         | 64   | <2    | 64   |
| 36.   |      | 16            | <4         | 256   | <8         | 64   | <2    | 8    |
| 37.   |      | 24            | <4         | 512   | <8         | 32   | <4    | 32   |
| → 38. |      | 24            | <4         | >1024 | <8         | <2   | <2    | 8    |
| 39.   |      | 25            | <4         | 256   | <8         | 64   | <2    | 128  |
| 40.   |      | 15            | <4         | 256   | <8         | 64   | <2    | 16   |
| 41.   |      | 16            | <4         | 256   | <8         | 128  | <2    | 256  |

Table 2. Combined Live Measles-Rubella-Mumps Vaccine: Antibody Response of 12 Infants Who Were Seronegative for Measles and Rubella and Seropositive for Mumps.

| No. | Name | Age<br>(mos.) | Measles HI |       | Rubella HI |      | Mumps | Neut |
|-----|------|---------------|------------|-------|------------|------|-------|------|
|     |      |               | Pre        | Post  | Pre        | Post | Pre   | Post |
| 1.  |      | 17            | <4         | 256   | <8         | 16   | 8     | 4    |
| 2.  |      | 13            | <4         | 512   | <8         | 32   | 4     | <8   |
| 3.  |      | 19            | <4         | 512   | <8         | 8    | 2     | 4    |
| 4.  |      | 14            | <4         | >1024 | <8         | 128  | 32    | 256  |
| 5.  |      | 9             | <4         | >1024 | <8         | 256  | 2     | 2    |
| 6.  |      | 13            | <4         | 256   | <8         | 64   | 4     | 4    |
| 7.  |      | 24            | <4         | 256   | <8         | 8    | 512   | 512  |
| 8.  |      | 12            | <4         | 256   | <8         | 8    | 2     | 16   |
| 9.  |      | 28            | <4         | 512   | <8         | 32   | 4     | 2    |
| 10. |      | 26            | <4         | 256   | <8         | 8    | 2     | 128  |
| 11. |      | 14            | <4         | 1024  | <8         | 512  | 4     | 8    |
| 12. |      | 16            | <4         | 512   | <8         | 32   | 4     | 8    |

Table 3: Summary

|                                                  | Virus        |              |              |
|--------------------------------------------------|--------------|--------------|--------------|
|                                                  | Measles      | Rubella      | Mumps        |
| <u>Triple Seronegatives</u>                      |              |              |              |
| Seroconversions/Total:                           | 41/41 (100%) | 39/41 (95%)  | 41/41 (100%) |
| Geometric Mean Titer :                           | 411.0        | 25.7         | 16.8         |
| <u>Double Seronegatives</u><br>(measles-rubella) |              |              |              |
| Seroconversions/Total:                           | 12/12 (100%) | 12/12 (100%) | —            |
| Geometric Mean Titer :                           | 456.1        | 33.9         |              |

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WEST POINT, PENNSYLVANIA 19486

MAURICE R. HILLEMAN, Ph. D., D. Sc.  
EXECUTIVE DIRECTOR

January 15, 1971

Dr. Roderick Murray, Director  
Division of Biologics Standards  
National Institutes of Health  
Bethesda, Maryland 20014

Dear Doctor Murray:

Enclosed is a manuscript titled "Trivalent Combined Measles-Mumps-Rubella (M-M-R®) Vaccine. Findings in Clinical-Laboratory Studies." This paper describes the development and clinical evaluation of a new combined triple vaccine. It should be of importance in simplifying the routine immunization. It is being sent to you for information purpose.

Kindest regards.

Sincerely yours,



Maurice R. Hilleman, Ph.D.  
Director  
Virus & Cell Biology Research

/mmh

Enclosure



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TRIVALENT COMBINED MEASLES-MUMPS-RUBELLA (M-M-R®) VACCINE

Findings in Clinical-Laboratory Studies

by

\*Joseph Stokes, Jr, MD, DSc

\*Robert E. Weibel, MD

\*\*Victor M. Villarejos, MD, Dr PH

\*\*Jorge A. Arguedas G, MD, MPH

\*\*\*Eugene B. Buynak, PhD

\*\*\*Maurice R. Hilleman, PhD, DSc

from the

\*Department of Pediatrics  
School of Medicine  
University of Pennsylvania  
Philadelphia, Pennsylvania;

\*\*Louisiana State University  
International Center for Medical  
Research and Training  
San Jose, Costa Rica;

and

\*\*\*Division of Virus and Cell Biology Research  
Merck Institute for Therapeutic Research  
West Point, Pennsylvania

Reprint requests to Division of Virus and Cell Biology Research, Merck  
Institute for Therapeutic Research, West Point, Pa. 19486 (Dr. Hilleman).

SYNOPSIS-ABSTRACT

Four lots of combined trivalent Moraten measles, Jeryl Lynn mumps, HPV-77 duck rubella vaccine (M-M-R®) were administered to a total of 715 children, 7 months to 7 years of age, who were initially without antibody against any of the three viruses. Overall, 96% of the children developed measles hemagglutination-inhibiting, 95% developed mumps neutralizing, and 94% developed rubella hemagglutination-inhibiting antibodies. The geometric mean antibody titers against each of the 3 viruses were essentially the same in tests in children given the trivalent vaccine as in tests of the corresponding monovalent vaccines. The most important clinical reaction to the trivalent vaccine was mild fever in a portion of the children such as is expected following administration of Moraten measles vaccine alone. Joint involvement was notably absent during the 28 day follow-up. The combined measles-mumps-rubella vaccine provides a simple means for immunizing against all three of these diseases without impairment of antibody response and without significant increase in clinical reaction.

The past decade has seen the development and licensing, for general use, of three new live virus vaccines: measles, mumps and rubella. Such progress makes it desirable to evolve combined forms of the vaccines that will simplify administration, reduce costs, and minimize the required number of contacts of the patient with the physician. A recent report (1) from our laboratories described the preparation and clinical testing in small groups of children of combined measles-mumps-rubella vaccine and measles-mumps vaccine. Another report (2) described the development and large-scale clinical testing of a combined mumps-rubella vaccine which has been licensed for general distribution under the name of BIAVAX®. The present paper describes the large-scale clinical testing of a combined trivalent live measles [Moraten line (3)], mumps [Jeryl Lynn strain (4)], and rubella [HPV-77 duck (5)] vaccine, all components of which are presently licensed products. The combined vaccines were premixed prior to filling and lyophilization.

#### METHODS

Design of the Clinical Studies. Three clinical studies were carried out. The first was a pilot study in a small number of children in families residing in the Havertown-Springfield suburb of Philadelphia. The children included in the pilot study were 11 months to 3 years of age with a mean age of 1.1 years. The children were selected for negative prior history of vaccination or illness with respect to rubella, mumps, and measles. Immunizations were carried out in

the Outpatient Department of Lankenau Hospital and informed written parental consent was obtained. The time period for the vaccinations was September 26 to October 10, 1968. Lot 310 of combined vaccine was used and the dose was 1.0 ml given subcutaneously. All subjects were bled immediately prior to vaccination and again 6 to 9 weeks later. The sera were stored frozen at  $-20^{\circ}\text{C}$  until tested up to 2 months later for measles, mumps and rubella antibodies. Clinical observations were made by the mothers, nurses and physicians. The parents of the children were given a report card for each child for recording temperatures once daily for 28 days, plus any other illness, and they were asked to notify one of us (REW) immediately when any illness occurred. The second study was a large-scale field trial carried out in a similar way in suburban Philadelphia during the time period September 11, 1969 to January 31, 1970. Three lots of vaccine were used; numbers 92126, 92127 and 96400. The children were 10 months to 6 years of age and the mean age was 1.5 years. The third study was a large-scale field trial of trivalent lots 92126, 92127 and 96400 of vaccine carried out among children whose families resided in rural areas in Costa Rica and San Salvador. The time period of the studies was October 10, 1969 to January 21, 1970, and the children were 7 months to 7 years of age, with a mean age of 3.0 years. In these studies, clinical observations for follow-up purpose were made by physicians who saw the children on alternate days for 28 days following vaccination. Further, parents and guardians of the children were instructed to

notify the medical staff of any significant illness that occurred during the 28 day period subsequent to vaccination. Parental cooperation was excellent. Vaccines. The measles virus vaccine was the Moraten line measles virus (3) marketed as a single vaccine under the trade name of ATTENUVAX®. The mumps virus was the Jeryl Lynn strain (4) attenuated by passage in embryonated hens' eggs and chick embryo cell culture and marketed under the trade name of MUMPSVAX®. The rubella virus vaccine was the HPV-77 strain passaged 5 times in cell culture of duck embryo (5) and marketed as a single vaccine under the trade name of MERUVAX®. Lot 310 of combined measles-mumps-rubella vaccine used in the pilot study was prepared in the Research Laboratories of the Merck Institute for Therapeutic Research. Lots 92126, 92127 and 96400 of the combined vaccine were prepared in the Biological Production Laboratories of Merck Sharp & Dohme. The individual components of the combined vaccine contained a minimum of 1000 50% tissue culture infectivity doses (TCID<sub>50</sub>) each of measles and rubella virus and 5000 TCID<sub>50</sub> of mumps vaccine virus, within the titration variability range of the assay procedures. Serologic Testing. The sera were assayed for titer of measles and rubella hemagglutination-inhibiting (HI) antibody and for mumps neutralizing (neut.) antibody in our laboratories (Merck Institute and the Biologics Control Laboratories of Merck Sharp & Dohme) according to procedures described earlier (3-5).

#### RESULTS

Pilot Study (Havertown-Springfield). A total of 30 children who

were initially seronegative to measles, mumps and rubella viruses were given 1.0 ml of lot 310 of the combined vaccine by the subcutaneous route. Tables 1 and 2 summarize the antibody responses against the three viruses. All 30 children (100%) developed measles and rubella HI antibody and 29 (97%) developed mumps neutralizing antibody in the titer distribution pattern shown in Table 1. The geometric mean antibody titers were 1:38.2, 1:6.5, and 30.6 respectively, against the measles, mumps and rubella viruses (Table 2). The clinical findings in the 30 children during the 28 day period of follow-up are shown in Tables 3 and 4. There was somewhat more fever (Table 3) for the 5-12 day period following vaccination, which is the critical time period of occurrence for measles reaction, than during the preceding or following periods. Upper respiratory illness (Table 4) was commonly present during the total observation period. There were no other remarkable complaints.

Large-Scale Field Studies. A total of 685 children who resided in suburban Philadelphia or in the Costa Rica-San Salvador area and who were initially without antibody against measles, mumps or rubella virus were given 1.0 ml of lot 92126, 92127 or 96400 of trivalent vaccine by the subcutaneous route. Table 2 summarizes the antibody responses which were obtained against the three viruses. From 90 to 99% of the children responded serologically to the measles component of the vaccine, with a titer of 1:5 to 1:2560. The geometric mean antibody titers against measles among recipients of the individual vaccine lots ranged from 1:28.6 to 1:73.0. The overall seroconversion rate for measles, including the children who received lot 310 in the



pilot study, was 96% and the geometric mean titer was 1:38.5. From 91 to 99% of the children in the field study developed neutralizing antibody against the mumps component of the vaccine, with a titer of 1:1 to 128. The geometric mean antibody titers among recipients of the individual vaccine lots ranged from 1:6.3 to 1:7.9. The overall seroconversion rate for mumps, including the children who received lot 310, was 95% and the geometric mean titer was 1:6.8. Eighty-nine to 97% of the children in the field trials developed HI antibody against rubella virus, with a titer of 1:8 to 1:512. The geometric mean antibody titers among recipients of the individual vaccine lots ranged from 1:19.8 to 1:45.7. The overall seroconversion rate for rubella, including the children in the pilot study, was 94% and the mean titer was 1:27.8.

The clinical findings among 228 children given vaccine in the Havertown-Springfield field trial, compared with 106 unvaccinated sibling controls, are given in Tables 5 and 6. There was slightly more fever (Table 5) during the 5-12 day period among the vaccinees than during the periods before or after and than observed in the unvaccinated controls. The fifth to twelfth days after vaccination is the critical time period for occurrence of the expected low incidence of febrile reaction following Moraten measles virus vaccine (3). The miscellaneous clinical findings among the children in the Havertown-Springfield study (Table 6) were not remarkable. However, there was somewhat greater occurrence of upper respiratory illness, among the vaccinees than the controls. The similar miscellaneous clinical findings recorded among the children in the Costa Rica-San Salvador

trial are given in Table 7. There was a slightly greater occurrence of lymphadenopathy, upper respiratory illness, irritability, and malaise among the vaccinated children than among the controls but the significance of the difference is doubtful.

Comparison, in Simultaneous Tests, of Antibody Levels Following Combined or Single Vaccines. A portion of the serologic tests reported in the sections above were carried out in the Biologics Control Laboratories of Merck Sharp & Dohme and a portion were carried out in our laboratories in the Merck Institute. In spite of standardization of test procedures, 2-fold lower titer values were commonly reported from the Control Laboratories compared with the Merck Institute. These differences did not affect the seroconversion rates of the individual children but did reflect substantial differences in geometric mean antibody titers following vaccination.

The question of whether combination of the 3 vaccines does or does not cause detectable suppression of the height of antibody response was, therefore, studied further. The paired sera from initially seronegative children who had received trivalent vaccine (present study) or who had been given monovalent Moraten measles, Jeryl Lynn mumps or HPV-77 duck rubella vaccine in previous investigations (3-5) were tested simultaneously in our laboratories in the Merck Institute. Sera from 24 or 25 children per vaccine group were selected blindly and at random for the comparisons. Table 8 summarizes the composition of the populations and presents the geometric mean antibody titers for the children in the 4 groups. Table 9 shows the distribution of the individual titer values which

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were measured. The titer distribution and the geometric mean titer obtained against each virus given alone or in combined vaccine were not significantly different. There was no indication for suppression of the antibody responses by administering the vaccines in combination.

#### COMMENT

The antibody responses to vaccination which were obtained in this study show satisfactory immunization of children with combined trivalent Moraten measles, Jeryl Lynn mumps and HPV-77 duck rubella virus vaccine. The percentages of the 715 initially triple seronegative children who showed a demonstrable antibody response was 96% for measles, 95% for mumps and 94% for rubella. There was no detectable suppression of the height of antibody titer following combined vaccine compared with the monovalent vaccines. Dr. S. Krugman et al. (6) obtained similar results with trivalent vaccine lot 96400 in independent clinical-laboratory investigations carried out at the New York Foundling Hospital. Smorodintsev et al. (7) have also reported satisfactory results of tests of a trivalent combined measles-mumps-rubella vaccine prepared in the U.S.S.R.

HPV-77 duck and Jeryl Lynn mumps vaccines cause remarkably little, if any, clinical reaction in children (3, 5). Moraten measles vaccine may cause mild febrile reactions, rash and generalized malaise in a portion of recipients of the preparation. There was no apparent alteration of the clinical reactivity by the combined administration of the three vaccines in a single dose. The reactions noted were not unlike those expected from Moraten measles vaccine given alone.

Especially important was the lack of arthritis/arthralgia which are prominent features of natural rubella, particularly in adults. The lack of joint involvement in children given the combined vaccine was consistent with the previous total experience by our laboratories (unpublished) in studies of monovalent HPV-77 duck rubella vaccine. In these studies, among 15,339 children aged 1 to 12 years who were vaccinated, only 7 or 0.05% were observed to have any arthritis or arthralgic manifestations during the 28 day follow-up. The time period of observation for such signs was adequate since these manifestations are most often evident within the 28 day time period (8) if they are going to occur at all.

The large majority of children in the U.S.A. have been vaccinated against measles and a sizable portion have been given mumps and rubella vaccines. It is estimated by us, based on vaccine distribution, that about 41 million children have received measles vaccine, 7 million mumps vaccine, and 21 million rubella vaccine. The combined triple vaccine provides a simple, safe and effective immunization procedure using a single vaccine dose against three important diseases in children who have not yet been immunized. The combined vaccine may be of special importance in providing immunization against the three diseases in children who might be difficult to reach on more than one occasion.

Indexing terms: MEASLES-MUMPS-RUBELLA VACCINE, IMMUNOGENS, COMBINED LIVE VACCINES, MEASLES, MUMPS, RUBELLA.

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# References

1. Buynak, EB, Weibel, RE, Whitman, JE, Jr, Stokes, J, Jr, Hilleman, MR: Combined live measles, mumps, and rubella virus vaccine. JAMA 207:2259-2262, 1969.
2. Weibel, RE, Stokes, J, Jr, Villarejos, VM, Arguedas G, JA, Buynak, EB, Hilleman, MR: Combined live rubella-mumps virus vaccine (BIAVAX®). Findings in clinical-laboratory studies. JAMA, In Press.
3. Hilleman, MR, Buynak, EB, Weibel, RE, Stokes, J, Jr, Whitman, JE, Jr, Leagus, MB: Development and evaluation of the Moraten measles virus vaccine. JAMA 206:587-590, 1968.
4. Weibel, RE, Stokes, J, Jr, Buynak, EB, Whitman, JE, Jr, Hilleman, MR: Live, attenuated mumps-virus vaccine. 3. Clinical and serologic aspects in a field evaluation. New Eng J Med 276: 245-251, 1967.
5. Weibel, RE, Stokes, J, Jr, Buynak, EB, Whitman, JE, Jr, Leagus, MB, Hilleman, MR: Live attenuated rubella virus vaccines prepared in duck embryo cell culture. II. Clinical tests in families and in an institution. JAMA 205:554-558, 1968.
6. Krugman, S, Muriel, G, Fontana, VJ: Combined live measles, mumps, rubella vaccine: Immunologic response. Submitted for publication.
7. Smorodintsev, AA, Nasibov, MN, Jakovleva, NV: Experience with live rubella virus vaccine combined with live vaccines against measles and mumps. Bull WHO 42:283-289, 1970.

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8. Weibel, RE, Stokes, J, Jr, Buynak, EB, Hilleman, MR:  
Rubella vaccination in adult females. New Eng J Med 280:682-685,  
1969.



TABLE 1.--Distribution of Serum Antibody Titers  
Following Vaccination Among 30 Triple Seronegative Children  
Given Lot 310 of Trivalent Measles-Mumps-Rubella  
Vaccine (Havertown-Springfield).

| Measles (HI)* |                 | Mumps (Neut)* |                 | Rubella (HI)* |                 |
|---------------|-----------------|---------------|-----------------|---------------|-----------------|
| Titer         | No. of Children | Titer         | No. of Children | Titer         | No. of Children |
| <5            | 0               | <1            | 1               | <8            | 0               |
| 5             | 3               | 1             | 0               | 8             | 7               |
| 10            | 3               | 2             | 5               | 16            | 5               |
| 20            | 2               | 4             | 8               | 32            | 7               |
| 40            | 11              | 8             | 10              | 64            | 7               |
| 80            | 8               | 16            | 2               | 128           | 2               |
| 160           | 2               | 32            | 2               | 256           | 2               |
| 320           | 1               | 64            | 2               | 512           | 0               |
| 640           | 0               | 128           | 0               | 1024          | 0               |
| Geometric     |                 |               |                 |               |                 |
| Mean: 38.2    |                 | 6.5           |                 | 30.6          |                 |

\*HI = Hemagglutination-inhibition

Neut = Serum neutralization

Trivalent Measles-Mumps-Rubella Vaccine  
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TABLE 2.—Summary of Serologic Response in Triple Seronegative Children Given Four Lots of Trivalent Measles-Mumps-Rubella Vaccine (Suburban Philadelphia and Costa Rica-San Salvador).

| Study Location          | Vaccine Lot No. | Antibody Responses |     |                       |               |         |                       |               |     |                       |     |        |      |
|-------------------------|-----------------|--------------------|-----|-----------------------|---------------|---------|-----------------------|---------------|-----|-----------------------|-----|--------|------|
|                         |                 | Measles (HI)*      |     |                       | Mumps (Neut)* |         |                       | Rubella (HI)* |     |                       |     |        |      |
|                         |                 | Conversion         |     | Titer                 | Conversion    |         | Titer                 | Conversion    |     | Titer                 |     |        |      |
|                         |                 | Rate               | %   | Range GM <sup>†</sup> | Rate          | %       | Range GM <sup>†</sup> | Rate          | %   | Range GM <sup>†</sup> |     |        |      |
| <u>Pilot study:</u>     |                 |                    |     |                       |               |         |                       |               |     |                       |     |        |      |
| Havertown-Springfield   | 310             | 30/30              | 100 | 5-320                 | 38.2          | 29/30   | 97                    | <1-64         | 6.5 | 30/30                 | 100 | 8-256  | 30.6 |
| <u>Field studies:</u>   |                 |                    |     |                       |               |         |                       |               |     |                       |     |        |      |
| Suburban Philadelphia   | 92126           | 74/82              | 90  | <5-640                | 54.4          | 80/82   | 98                    | <1-64         | 7.9 | 73/82                 | 89  | <8-512 | 30.4 |
| "                       | 92127           | 71/76              | 93  | <5-640                | 57.8          | 75/76   | 99                    | <1-64         | 6.8 | 74/76                 | 97  | <8-512 | 45.7 |
| "                       | 96400           | 69/70              | 99  | <5-2560               | 73.0          | 67/70   | 96                    | <1-64         | 6.4 | 66/70                 | 94  | <8-256 | 28.4 |
| Costa Rica-San Salvador | 92126           | 149/155            | 96  | <5-320                | 33.1          | 144/155 | 93                    | <1-64         | 6.3 | 149/155               | 96  | <8-128 | 32.7 |
| "                       | 92127           | 138/145            | 95  | <5-320                | 28.6          | 132/145 | 91                    | <1-128        | 7.3 | 135/145               | 93  | <8-128 | 23.9 |
| "                       | 96400           | 153/157            | 97  | <4-256                | 30.5          | 153/157 | 97                    | <1-64         | 6.6 | 143/157               | 91  | <8-256 | 19.8 |
| Total<br>(All Lots)     |                 | 684/715            | 96  | <4-2560               | 38.5          | 680/715 | 95                    | <1-128        | 6.8 | 670/715               | 94  | <8-512 | 27.8 |

\*HI = Hemagglutination-inhibition test; Neut. = neutralization test.

<sup>†</sup>GM = Geometric mean titer.

TABLE 3.—Occurrence of Fever, According to Time After  
Vaccination Among 30 Triple Seronegative  
Children Given Lot 310 of Trivalent Measles-Mumps-Rubella Vaccine  
(Havertown-Springfield).

| Days After<br>Vaccination |    | Maximum Oral Temperature |    |                              |   |                               |   |              |
|---------------------------|----|--------------------------|----|------------------------------|---|-------------------------------|---|--------------|
|                           |    | <99°F<br>(37.2°C)        |    | 99-100.9°F<br>(37.2-38.29°C) |   | 101-102.9°F<br>(38.3-39.39°C) |   | Not<br>Taken |
|                           |    | No.                      | %  | No.                          | % | No.                           | % |              |
| 1-4                       | 19 | 65.5                     | 9  | 31.0                         | 1 | 3.4                           | 1 |              |
| 5-12                      | 9  | 30.0                     | 17 | 56.7                         | 4 | 13.3                          |   |              |
| 13-18                     | 21 | 70.0                     | 8  | 26.7                         | 1 | 3.3                           |   |              |
| 19-28                     | 17 | 56.7                     | 12 | 40.0                         | 1 | 3.3                           |   |              |

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TABLE 4. Miscellaneous Clinical Complaints Following  
Vaccination, Among 30 Triple Seronegative Children  
Given Lot 310 of Trivalent Measles-Mumps-Rubella Vaccine  
(Havertown-Springfield)

| Complaint                 | Days Following Vaccination |           |           |           |
|---------------------------|----------------------------|-----------|-----------|-----------|
|                           | No. (%)                    |           |           |           |
|                           | 1-4                        | 5-12      | 13-18     | 19-28     |
| Upper respiratory illness | 8 (26.7)                   | 9 (30.0)  | 5 (16.7)  | 3 (10.0)  |
| Otitis                    |                            |           |           | 1 (3.3)   |
| Gastroenteritis           | 1 (3.3)                    | 2 (6.7)   |           |           |
| Rash (heat and diaper)    | 1 (3.3)                    | 2 (6.7)   | 2 (6.7)   | 1 (3.3)   |
| Irritability              | 2 (6.7)                    | 3 (10.0)  | 2 (6.7)   |           |
| Teething                  |                            | 2 (6.7)   | 1 (3.3)   |           |
| No complaint              | 19 (63.3)                  | 15 (50.0) | 21 (70.0) | 25 (83.3) |

TABLE 5.—Occurrence of Fever, According to Time after Vaccination, Among 228 Triple Seronegative Children, Who Received 3 Lots of Trivalent Measles-Mumps-Rubella Vaccine and Among 106 Unvaccinated Controls (Suburban Philadelphia).

| Maximum<br>Oral<br>Temperature | Vaccinated Children (228) |                |                |                | Control Children (106) |               |               |               |
|--------------------------------|---------------------------|----------------|----------------|----------------|------------------------|---------------|---------------|---------------|
|                                | Days after Vaccination    |                |                |                | Days Observed          |               |               |               |
|                                | 1-4                       | 5-12           | 13-18          | 19-28          | 1-4                    | 5-12          | 13-18         | 19-28         |
| <99°F<br>(<37.2°C)             | 137<br>(60.6%)            | 105<br>(47.1%) | 140<br>(64.2%) | 123<br>(55.9%) | 68<br>(69.4%)          | 57<br>(58.8%) | 64<br>(66.0%) | 62<br>(65.3%) |
| 99-100.9°F<br>(37.2-38.29°C)   | 77<br>(34.1%)             | 86<br>(38.6%)  | 69<br>(31.7%)  | 79<br>(35.9%)  | 26<br>(26.5%)          | 36<br>(37.1%) | 25<br>(25.8%) | 27<br>(28.4%) |
| 101-102.9°F<br>(38.3-39.39°C)  | 11<br>(4.9%)              | 26<br>(11.7%)  | 7<br>(3.2%)    | 14<br>(6.4%)   | 3<br>(3.1%)            | 3<br>(3.1%)   | 8<br>(8.2%)   | 3<br>(3.2%)   |
| 103-104.9°F<br>(39.4-40.5°C)   | 1<br>(0.4%)               | 6<br>(2.7%)    | 2<br>(0.9%)    | 4<br>(1.8%)    | 1<br>(1.0%)            | 1<br>(1.0%)   |               | 3<br>(3.2%)   |
| Not Taken                      | 2                         | 5              | 10             | 8              | 8                      | 9             | 9             | 11            |

TABLE 6.--Miscellaneous Clinical Complaints Among Triple Seronegative Children Given Trivalent Vaccine Compared with Unvaccinated Controls (Suburban Philadelphia).

| Complaint                  | Vaccinated Children (228) |            |            |            |           | Contact Controls (106) |           |           |     |      |
|----------------------------|---------------------------|------------|------------|------------|-----------|------------------------|-----------|-----------|-----|------|
|                            | Days Post-Vaccination     |            |            |            |           | Days Post-Vaccination  |           |           |     |      |
|                            | 1-4                       | 5-12       | 13-18      | 19-28      | 1-4       | 5-12                   | 13-18     | 19-28     | 1-4 | 5-12 |
| Conjunctivitis             |                           | 1 (0.4)    |            |            |           |                        |           |           |     |      |
| Otitis                     | 3 (1.3%)                  | 5 (2.2)    | 3 (1.3)    | 7 (3.1)    |           |                        | 1 (0.9)   | 1 (0.9)   |     |      |
| Upper respiratory illness  | 41 (18.0)                 | 56 (24.6)  | 28 (12.3)  | 33 (14.5)  | 9 (8.5)   | 17 (16.0)              | 11 (10.4) | 11 (10.4) |     |      |
| Lymphadenopathy            |                           | 3 (1.3)    |            |            |           |                        | 1 (0.9)   |           |     |      |
| Gastroenteritis            | 15 (6.6)                  | 18 (7.9)   | 11 (4.8)   | 7 (3.1)    | 3 (2.8)   | 2 (1.9)                | 1 (0.9)   |           |     |      |
| Rash (non-measles)         | 10 (4.4)                  | 6 (2.6)    | 4 (1.8)    | 4 (1.8)    | 2 (1.9)   | 2 (1.9)                | 1 (0.9)   | 1 (0.9)   |     |      |
| Local reaction - inj. site | 1 (0.4)                   |            |            |            |           |                        |           |           |     |      |
| Headache                   |                           |            |            | 1 (0.4)    | 1 (0.9)   |                        |           |           |     |      |
| Irritability               | 15 (6.6)                  | 17 (7.5)   | 6 (2.6)    | 5 (2.2)    | 2 (1.9)   |                        |           |           |     |      |
| Malaise                    | 1 (0.4)                   | 1 (0.4)    |            |            |           |                        |           |           |     |      |
| Anorexia                   | 4 (1.8)                   | 5 (2.2)    | 1 (0.4)    | 2 (0.9)    | 1 (0.9)   |                        |           |           |     |      |
| Measles-like rash          |                           | 9 (3.9)    | 2 (0.9)    |            |           |                        |           |           |     |      |
| Fatigue                    | 1 (0.4)                   |            |            |            |           |                        |           | 1 (0.9)   |     |      |
| Unrelated illness          | 10 (4.4)                  | 12 (5.3)   | 11 (4.8)   | 15 (6.6)   |           |                        | 1 (0.9)   | 1 (0.9)   |     |      |
| No complaints              | 152 (66.7)                | 136 (59.6) | 177 (77.6) | 164 (71.9) | 88 (83.0) | 85 (80.2)              | 91 (85.8) | 92 (86.8) |     |      |



TABLE 7.---Miscellaneous Clinical Complaints Among Triple Seronegative Children Given Trivalent Vaccine Compared with Unvaccinated Controls (Costa Rica-San Salvador).

| Complaint                 | Vaccinated Children (457) |            |            |            |            | Contact Controls (175) |            |            |            |            |
|---------------------------|---------------------------|------------|------------|------------|------------|------------------------|------------|------------|------------|------------|
|                           | Days Post-Vaccination     |            |            |            |            | Days Post-Vaccination  |            |            |            |            |
|                           | 1-4                       | 5-12       | 13-18      | 19-28      | 1-4        | 5-12                   | 13-18      | 19-28      | 1-4        | 5-12       |
| Conjunctivitis            | 5 (1.1%)                  | 15 (3.3)   | 8 (1.8)    | 8 (1.8)    | 5 (2.9)    | 4 (2.3)                | 3 (1.7)    | 2 (1.1)    | 5 (2.9)    | 4 (2.3)    |
| Otitis                    | 3 (0.7)                   | 8 (1.8)    | 2 (0.4)    | 3 (0.7)    | 2 (1.1)    | 3 (1.7)                | 1 (0.6)    | 1 (0.6)    | 2 (1.1)    | 3 (1.7)    |
| Upper respiratory illness | 52 (11.4)                 | 113 (24.7) | 84 (18.4)  | 63 (13.8)  | 18 (10.3)  | 32 (18.3)              | 19 (10.9)  | 19 (10.9)  | 18 (10.3)  | 32 (18.3)  |
| Lymphadenopathy           |                           | 12 (2.6)   | 8 (1.8)    | 11 (2.4)   | 1 (0.6)    | 3 (1.7)                | 2 (1.1)    | 3 (1.7)    | 1 (0.6)    | 3 (1.7)    |
| Gastroenteritis           | 47 (10.3)                 | 88 (19.3)  | 49 (10.7)  | 46 (10.1)  | 11 (6.3)   | 24 (13.7)              | 18 (10.3)  | 24 (13.7)  | 11 (6.3)   | 24 (13.7)  |
| Natural measles           |                           |            |            |            | 1 (0.6)    | 1 (0.6)                |            |            | 1 (0.6)    | 1 (0.6)    |
| Fever                     | 24 (5.3)                  | 102 (22.3) | 45 (9.8)   | 37 (8.1)   | 12 (6.9)   | 23 (13.1)              | 18 (10.3)  | 22 (12.6)  | 12 (6.9)   | 23 (13.1)  |
| Headache                  | 7 (1.5)                   | 15 (3.3)   | 3 (0.7)    | 3 (0.7)    | 5 (2.9)    | 6 (3.4)                | 1 (0.6)    | 2 (1.1)    | 5 (2.9)    | 6 (3.4)    |
| Irritability              | 28 (6.1)                  | 85 (18.6)  | 42 (9.2)   | 20 (4.4)   | 12 (6.9)   | 19 (10.9)              | 7 (4.0)    | 10 (5.7)   | 12 (6.9)   | 19 (10.9)  |
| Malaise                   | 39 (8.5)                  | 68 (14.9)  | 26 (5.7)   | 21 (4.6)   | 9 (5.1)    | 15 (8.6)               | 11 (6.3)   | 9 (5.1)    | 9 (5.1)    | 15 (8.6)   |
| Anorexia                  | 23 (5.0)                  | 67 (14.7)  | 35 (7.7)   | 22 (4.8)   | 9 (5.1)    | 16 (9.1)               | 12 (6.9)   | 8 (4.6)    | 9 (5.1)    | 16 (9.1)   |
| Measles-like rash         |                           | 1 (0.2)    | 1 (0.2)    | 4 (0.9)    | 1 (0.6)    | 2 (1.1)                | 1 (0.6)    | 1 (0.6)    | 1 (0.6)    | 2 (1.1)    |
| Exanthema                 | 1 (0.2)                   | 4 (0.9)    | 3 (0.7)    | 2 (0.4)    | 2 (1.1)    | 2 (1.1)                |            | 1 (0.6)    | 2 (1.1)    | 2 (1.1)    |
| Rubella-like rash         | 2 (0.4)                   | 3 (0.7)    | 1 (0.2)    | 2 (0.4)    | 1 (0.6)    | 1 (0.6)                |            |            | 1 (0.6)    | 1 (0.6)    |
| Arthralgia                |                           |            |            |            |            |                        |            |            |            |            |
| Unrelated illness         | 3 (0.7)                   | 11 (2.4)   | 6 (1.3)    | 6 (1.3)    |            | 2 (1.1)                | 3 (1.7)    |            |            | 2 (1.1)    |
| No complaints             | 318 (69.6)                | 183 (40.0) | 276 (60.4) | 294 (64.3) | 127 (72.6) | 106 (60.6)             | 121 (69.1) | 115 (65.7) | 127 (72.6) | 106 (60.6) |



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TABLE 8.--Antibody Responses Among Initially Seronegative Children Vaccinated with Trivalent  
Compared with Monovalent Vaccines.

| Study<br>No.<br>(Ref.) | Vaccine                            | Vaccinees |                |             | Level of Antibody Response |                  |                |                  |                |
|------------------------|------------------------------------|-----------|----------------|-------------|----------------------------|------------------|----------------|------------------|----------------|
|                        |                                    | No.       | Age Range      | Mean<br>Age | Measles (HI)               |                  | Mumps (Neut)   |                  | Rubella (HI)   |
|                        |                                    |           |                |             | Titer<br>Range             | G.M.T.*<br>Range | Titer<br>Range | G.M.T.*<br>Range | Titer<br>Range |
| 232                    | Combined measles-<br>mumps-rubella | 24        | 11 mos.-3 yrs. | 1.4 yrs.    | 5-320                      | 95.1             | 1-128          | 15.1             | 8-512 52.3     |
| 97<br>(3)              | Moraten measles                    | 25        | 11 mos.-4 yrs. | 2.2 yrs.    | 20-640                     | 80.0             |                |                  |                |
| 71<br>(4)              | Jeryl Lynn mumps                   | 25        | 2-5 yrs.       | 4.3 yrs.    |                            |                  | 2-256          | 8.7              |                |
| 153<br>(5)             | Rubella<br>(HPV-77 + 5 Duck)       | 25        | 11 mos.-5 yrs. | 1.5 yrs.    |                            |                  |                |                  | 8-256 69.6     |

\*Reciprocal of geometric mean antibody titer.

TABLE 9.—Distribution of Individual Antibody Titers in Sera  
from Initially Seronegative Children Given Trivalent  
or Monovalent Vaccine.

| Combined<br>Measles-Mumps-Rubella<br>Vaccine |     |       |     |         |     | Monovalent Vaccines |     |       |     |         |     |
|----------------------------------------------|-----|-------|-----|---------|-----|---------------------|-----|-------|-----|---------|-----|
| Measles                                      |     | Mumps |     | Rubella |     | Measles             |     | Mumps |     | Rubella |     |
| Titer*                                       | No. | Titer | No. | Titer   | No. | Titer               | No. | Titer | No. | Titer   | No. |
| 5                                            | 2   | 1     | 1   | 8       | 4   | 5                   | 0   | 1     | 0   | 8       | 1   |
| 10                                           | 0   | 2     | 0   | 16      | 3   | 10                  | 0   | 2     | 5   | 16      | 1   |
| 20                                           | 0   | 4     | 8   | 32      | 2   | 20                  | 1   | 4     | 5   | 32      | 5   |
| 40                                           | 2   | 8     | 1   | 64      | 7   | 40                  | 9   | 8     | 5   | 64      | 7   |
| 80                                           | 9   | 16    | 5   | 128     | 4   | 80                  | 8   | 16    | 5   | 128     | 9   |
| 160                                          | 6   | 32    | 3   | 256     | 3   | 160                 | 4   | 32    | 4   | 256     | 2   |
| 320                                          | 5   | 64    | 2   | 512     | 1   | 320                 | 2   | 64    | 0   | 512     | 0   |
| 640                                          | 0   | 128   | 4   | 1024    | 0   | 640                 | 1   | 128   | 0   | 1024    | 0   |
| 1280                                         | 0   | 256   | 0   | 2048    | 0   | 1280                | 0   | 256   | 1   | 2048    | 0   |

\*Reciprocal of serum dilution.

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MAURICE R. HILLEMAN, Ph.D., D.Sc.  
VICE PRESIDENT

January 29, 1971

Dr. Harry Meyer, Chief  
Laboratory of Viral Immunology  
Division of Biologics Standards  
National Institutes of Health  
Bethesda, Maryland 20014

Dear Harry:

Nice seeing you. Sorry we didn't have more time.

The enclosed letter was sent to Dr. Murray.

You might want the enclosed table on mean rubella titers.

You may also want the vaccine titer range tables sent you earlier, also enclosed.

Also, I am sending you copies of the 3 papers for publication.

We will be getting the contact seroconversion and arthritis/arthralgia information to you soon. Also we will ship the vaccines to you.

Kindest regards to you and Barbara.

Sincerely yours,



Maurice R. Hilleman, Ph.D.  
Director, Virus & Cell Biology Research  
Merck Institute for Therapeutic Research

MERCK SHARP & DOHME

RESEARCH LABORATORIES

DIVISION OF MERCK & CO., INC. WEST POINT, PENNSYLVANIA 19486 • TELEPHONE (215) 699-5311

MAURICE R. HILLEMAN, PH. D., D. SC.  
VICE PRESIDENT

January 28, 1971

Dr. Roderick Murray, Director  
Division of Biologics Standards  
National Institutes of Health  
Bethesda, Maryland 20014

Dear Doctor Murray:

It was good of you and your staff to spend so much time with us during our visit last Wednesday.

For the record--

1. Measles-mumps-rubella and measles-rubella. We are getting together the contact serology data plus the arthritis/arthralgia surveillance information for Dr. Meyer. This will be sent soon.

We feel that the 715 triple negatives and 375 double negatives, respectively, are adequate to answer definitively all questions of safety and efficacy. We hope for concurrence so that we may enter the market with these new products soon.

Non-Responsive - Not MMR

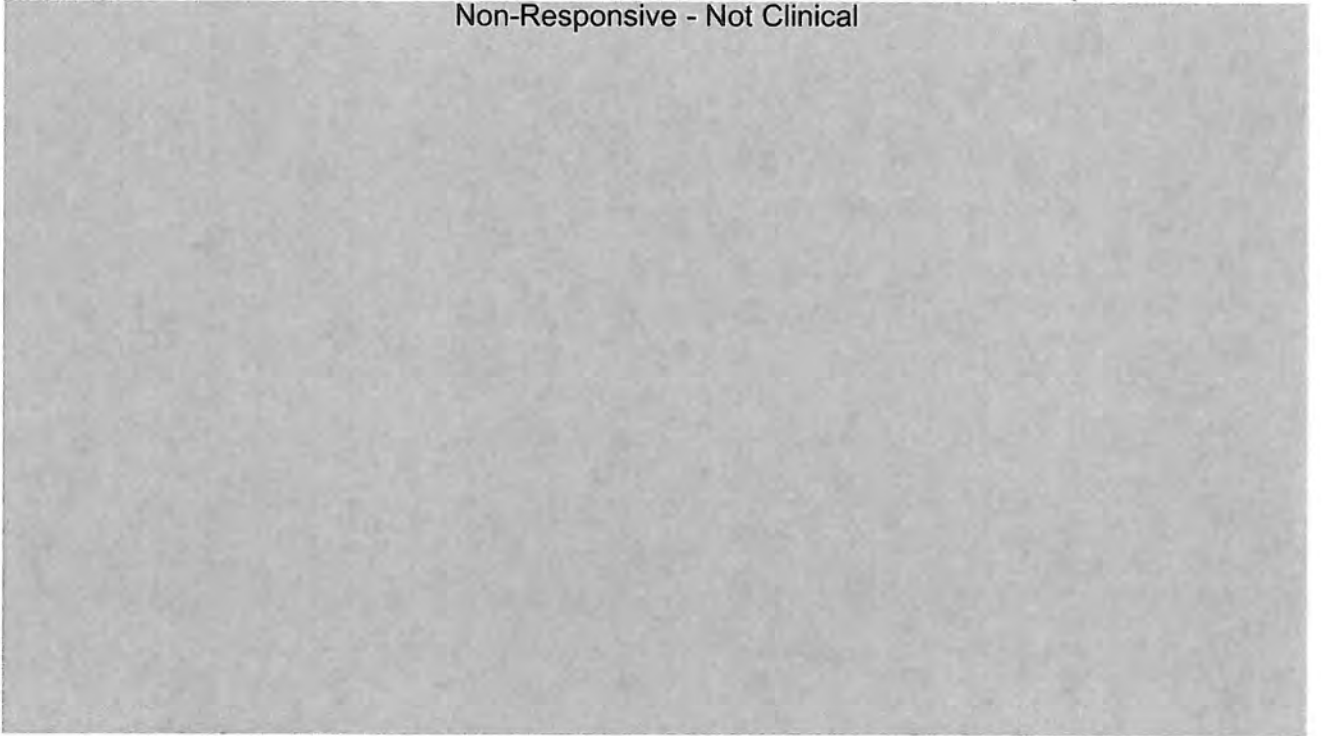


Dr. Roderick Murray

-2-

January 29, 1971

Non-Responsive - Not Clinical

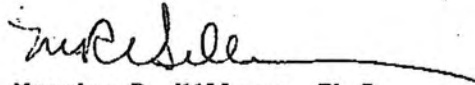


6. Arthritis/arthralgia - statement.

It is hoped that you will review the current arthritis/arthralgia statement in all our licensed and to-be-licensed products containing HPV-77 duck rubella vaccine. The occurrence is clearly stated. We will be pleased to consider alternative statements.

Kind regards.

Sincerely yours,



Maurice R. Hilleman, Ph.D.  
Director, Virus & Cell Biology Research  
Merck Institute for Therapeutic Research

enc. - 4 extra copies of  
letter

Antibody Titers in Direct Comparison Studies in Children  
Receiving Combined or Corresponding Monovalent Vaccines.

| Vaccine<br>(Combined or<br>Single) | No.<br>Children | Mean<br>Antibody Titer* |       |         |
|------------------------------------|-----------------|-------------------------|-------|---------|
|                                    |                 | Measles                 | Mumps | Rubella |
| Measles-mumps-rubella              | 24              | 95                      | 15    | 52      |
| Measles                            | 25              | 80                      |       |         |
| Mumps                              | 25              |                         | 9     |         |
| Rubella                            | 25              |                         |       | 70      |
| Measles-rubella                    | 25              | 103                     |       | 50      |
| Measles                            | 24              | 85                      |       |         |
| Rubella                            | 25              |                         |       | 68      |

\*Mean titers between corresponding combined or monovalent vaccines were not statistically different.

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Table 1

## Dose-Response Results for Combined Live Measles-Mumps-Rubella Vaccines

| Vaccine Lot #                                 | Component                   | Infectivity Titer/1 ml. dose                                | TCID <sub>50</sub> /1.0 ml. | Seroconversions Among Double Negatives               |
|-----------------------------------------------|-----------------------------|-------------------------------------------------------------|-----------------------------|------------------------------------------------------|
| 311                                           | Mumps<br>Rubella            | 10 <sup>3.9</sup><br>10 <sup>2.9</sup>                      | 7900<br>790                 | 30/31 = 96.8%<br>31/31 = 100%                        |
| 92123                                         | Mumps<br>Rubella            | 10 <sup>4.5</sup><br>10 <sup>3.8</sup>                      | 32000<br>6300               | 133/140 = 95.0%<br>133/140 = 95.0%                   |
| 92124                                         | Mumps<br>Rubella            | 10 <sup>4.6</sup><br>10 <sup>3.9</sup>                      | 40000<br>7900               | 95/100 = 95.0%<br>94/100 = 94.0%                     |
| 96399                                         | Mumps<br>Rubella            | 10 <sup>4.7</sup><br>10 <sup>3.1</sup>                      | 50000<br>1300               | 139/144 = 96.5%<br>132/144 = 91.7%                   |
| 310                                           | Measles<br>Mumps<br>Rubella | 10 <sup>3.4</sup><br>10 <sup>3.7</sup><br>10 <sup>2.8</sup> | 2500<br>5000<br>630         | 30/30 = 100%<br>29/30 = 96.7%<br>30/30 = 100%        |
| 92126                                         | Measles<br>Mumps<br>Rubella | 10 <sup>2.8</sup><br>10 <sup>4.4</sup><br>10 <sup>3.6</sup> | 630<br>25000<br>4000        | 74/82 = 90.2%<br>80/82 = 97.6%<br>73/82 = 89.0%      |
| 92127                                         | Measles<br>Mumps<br>Rubella | 10 <sup>2.8</sup><br>10 <sup>4.0</sup><br>10 <sup>4.0</sup> | 630<br>10000<br>10000       | 99/106 = 93.4%<br>102/106 = 96.2%<br>103/106 = 97.2% |
| 96400                                         | Measles<br>Mumps<br>Rubella | 10 <sup>3.2</sup><br>10 <sup>4.5</sup><br>10 <sup>3.2</sup> | 1600<br>32000<br>1600       | 69/70 = 98.6%<br>67/70 = 95.7%<br>66/70 = 94.3%      |
| 284                                           | Measles<br>Mumps            | 10 <sup>3.9</sup><br>10 <sup>3.8</sup>                      | 7900<br>6300                | 37/38 = 97.4%<br>37/38 = 97.4%                       |
| <u>Field Mix</u>                              |                             |                                                             |                             |                                                      |
| 254                                           | Measles                     | 10 <sup>4.1</sup>                                           | 14000                       | 28/28 = 100%                                         |
| 253                                           | Mumps                       | 10 <sup>3.8</sup>                                           | 6300                        | 26/28 = 92.8%                                        |
| 267                                           | Rubella                     | 10 <sup>2.8</sup>                                           | 630                         | 28/28 = 100%                                         |
| <u>Additional Information on 0.5 ml. dose</u> |                             |                                                             |                             |                                                      |
| 92123                                         | Mumps<br>Rubella            | 10 <sup>4.2</sup><br>10 <sup>3.5</sup>                      | 16000<br>3100               | 131/138 = 94.9%<br>126/138 = 91.3%                   |
| 92124                                         | Mumps<br>Rubella            | 10 <sup>4.3</sup><br>10 <sup>3.6</sup>                      | 20000<br>4000               | 145/159 = 91.2%<br>142/159 = 89.3%                   |
| 96399                                         | Mumps<br>Rubella            | 10 <sup>4.4</sup><br>10 <sup>2.8</sup>                      | 25000<br>630                | 119/122 = 97.5%<br>114/122 = 93.4%                   |

Table 2

Summary - Titer Ranges Measles-Mumps-Rubella Components

| Vaccine Lot No.                        | Infectivity Titer (Doses) of Virus/1.0 ml. Dose |                               |                             |
|----------------------------------------|-------------------------------------------------|-------------------------------|-----------------------------|
|                                        | Measles (Attenuvax)                             | Mumps (Mumpsvax)              | Rubella (Meruvax)           |
| 311                                    |                                                 | 3.9 (7,900)                   | 2.9 (790)                   |
| 92123                                  |                                                 | 4.5 (32,000)                  | 3.8 (6,300)                 |
| 92124                                  |                                                 | 4.6 (40,000)                  | 3.9 (7,900)                 |
| 96399                                  |                                                 | 4.7 (50,000)                  | 3.1 (1,300)                 |
| 310                                    | 3.4 (2,500)                                     | 3.7 (5,000)                   | 2.8 (630)                   |
| 92126                                  | 2.8 (630)                                       | 4.4 (25,000)                  | 3.6 (4,000)                 |
| 92127                                  | 2.8 (630)                                       | 4.0 (10,000)                  | 4.0 (10,000)                |
| 96400                                  | 3.2 (1,600)                                     | 4.5 (32,000)                  | 3.2 (1,600)                 |
| 284                                    | 3.9 (7,900)                                     | 3.8 (6,300)                   |                             |
| Field Mix                              | 4.1 (14,000)<br>(Lot #254)                      | 3.8 (6,300)<br>(Lot #253)     | 2.8 (630)<br>(Lot #267)     |
| Additional Information on 0.5 ml. Dose |                                                 |                               |                             |
| 92123                                  |                                                 | 4.2 (16,000)                  | 3.5 (3,100)                 |
| 92124                                  |                                                 | 4.3 (20,000)                  | 3.6 (4,000)                 |
| 96399                                  |                                                 | 4.4 (25,000)                  | 2.8 (630)                   |
| Range/dose                             | 2.8 - 4.1<br>(630 - 14,000)                     | 3.7 - 4.7<br>(5,000 - 50,000) | 2.8 - 4.0<br>(630 - 10,000) |

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COMBINED LIVE RUBELLA (HPV-77 DUCK)-MUMPS (JERYL LYNN)

VIRUS VACCINE (BIAVAX<sup>®</sup>)

Findings in Clinical-Laboratory Studies

by

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SYNOPSIS-ABSTRACT

Four lots of combined bivalent HPV-77 duck rubella-Jeryl Lynn mumps vaccine (Biavax<sup>®</sup>) were administered to a total of 415 children 7 mos. to 7 years of age who were initially without antibody against either virus. Overall, 94% of the children developed rubella hemagglutination-inhibition antibodies and 96% developed mumps neutralizing antibodies. The geometric mean antibody titers were 1:35.9 and 1:6.8, respectively. The antibody responses approximated those obtained in previous studies when the individual vaccines were given alone. Clinical reactions including joint involvement and fever, were notably absent among the children during the 28 day follow-up. The combined rubella-mumps vaccine provides a simple means for immunizing against both these diseases without impairment of immune response and without significant clinical reaction.



The evolution of increasing numbers of new vaccines renders it desirable to develop combined forms of the vaccines which will simplify administration, reduce costs, and minimize the number of contacts of the patient with the physician. A recent report (1) from our laboratories described the preparation and clinical testing of combined measles-mumps-rubella and measles-mumps vaccines. Excellent antibody responses were obtained without added clinical reaction. The present report describes the development and clinical testing of live rubella (HPV-77 duck) (2-4) vaccine combined with mumps (Jeryl Lynn) (5-7) virus vaccine. The individual components in the vaccine were premixed prior to filling and lyophilization. This particular combination has considerable significance in the U.S.A. in view of the widespread use of measles vaccine and in the large reservoir, to date, of children who have not received either rubella or mumps virus vaccines. The combined rubella-mumps vaccine has been licensed recently for general use under the name of Biavax<sup>®</sup>.

Methods. Design of the clinical studies. Two clinical studies were carried out. The first was a pilot study in a small number of children in families residing in Havertown-Springfield suburb of Philadelphia. The second was a large-scale field study carried out in Costa Rica. The children included in the pilot study were 10 mos. to 5 years of age with a mean age of 2.0 years and were selected for prior negative history of vaccination or illness with respect to rubella and mumps. The immunizations were carried out in the Outpatient Department of Lankenau Hospital and informed written parental consent was

obtained. The time period for the vaccinations was 9/26/68 to 10/10/68. The vaccine dose was 1.0 ml given subcutaneously. All subjects were bled immediately prior to vaccination and again 6 to 8 weeks later. The sera were stored frozen at  $-20^{\circ}\text{C}$  until tested up to 2 months later for rubella and mumps antibody. Clinical observations were made by the mothers, nurses and physicians. The parents of the children were given a report card for each child for recording temperatures once daily for 28 days, plus any other illness, and they were asked to notify one of us (R.E.W.) immediately when any illness occurred. The large-scale field study, with minor modification to meet the local situation, was carried out in a similar way among children whose families resided in the semi-rural areas around San Jose, Costa Rica. The time periods for the studies were 3/15/69 to 4/15/69 for lots 92123 and 92124 of vaccine and 8/14/69 to 8/18/69 for lot 96399 of vaccine. The children were 7 mos. to 7 years of age with a mean age of 3.4 years. In these studies, clinical observations and follow-ups were made by physicians and nurses who saw the children on alternate days for 28 days following vaccination. Further, parents and guardians of the children were instructed to notify the medical staff of any significant illness that occurred during the 28 day period subsequent to vaccination. Parental cooperation was excellent. Vaccines. The rubella virus vaccine was the HPV-77 strain passaged 5 times in cell cultures of duck embryo (2-4) and marketed as a single vaccine under the trade name of Meruvax<sup>®</sup>. The mumps virus vaccine was the Jeryl Lynn strain (5-7) attenuated by passage in embryonated hens' eggs and chick embryo cell culture



and marketed under the trade name of Mumps<sup>®</sup>vax. Lot 311 of combined rubella-mumps vaccine used in the pilot study was prepared in the research laboratories of the Merck Institute for Therapeutic Research. Lots 92123, 92124, and 96399 of the combined vaccine were prepared in the Biological Production Laboratories of Merck, Sharp & Dohme. The individual components of the combined vaccine contained a minimum of 1000 50% tissue culture infective doses (TCID<sub>50</sub>) of rubella vaccine virus and 5000 TCID<sub>50</sub> of mumps vaccine virus. Serologic testing. The sera were assayed for titer of rubella hemagglutination-inhibiting (HI) antibody and for mumps neutralizing (neut.) antibody in our laboratories (Merck Institute) according to procedures described earlier (2, 8).

#### RESULTS

Pilot Study (Havertown). A total of 31 children who were initially seronegative to both rubella and mumps viruses were given 1.0 ml of lot 311 of the combined vaccine by the subcutaneous route. Tables 1 and 2 summarize the antibody responses against the two viruses. All 31 children developed rubella HI antibody in the titer distribution pattern shown in Table 1 and the geometric mean titer was 1:45.8. Thirty of the 31 children, 97%, developed mumps neutralizing antibody and the mean titer was 1:7.0.

The clinical findings in the 31 children during the 28 day period of follow-up are shown in Tables 3 and 4. There was slightly more fever (Table 3) for the 5-12 day period following vaccination, which is the critical time period for occurrence of clinical reactions, than during the preceding or following periods. Low grade fever was

commonly noted for all time periods of the study and it is doubtful whether the fever was due to the vaccination since upper respiratory illnesses were prevalent in the group during the time period of the study. Nonrubelliform rash, gastroenteritis and irritability were the only other complaints noted during the follow-up and these were of such low frequency as to be of questionable relevance to the vaccine.

Large-Scale Field Study.—A total of 384 children who were initially without antibody against either rubella or mumps virus were given 1.0 ml of lot 92123, 92124, or 96399 of combined vaccine by the subcutaneous route. Table 2 summarizes the antibody responses which were obtained against the 2 viruses. From 92 to 95% of the children responded serologically to the rubella component of the vaccine with a titer of 1:8 to 1:512. The geometric mean antibody titers among recipients of the individual vaccine lots ranged from 1:28.5 to 1:40.8. The overall seroconversion rate for rubella including the children who received lot 311 was 94% and the geometric mean titer was 1:35.9. From 95 to 97% of the children developed antibody against the mumps component of the vaccine with a titer of 1:1 to 1:128. The geometric mean antibody titers among recipients of the individual vaccine lots ranged from 1:5.0 to 1:9.0. The overall seroconversion rate for mumps, including the children who received lot 311 was 96% and the geometric mean titer was 1:6.8.

The clinical findings among the children in the large-scale field study during the 28 day follow-up are summarized in Table 5. A group of 87 children who did not receive vaccine and who were siblings of

the vaccinees served as controls. The clinical findings were not remarkable and there was no substantial difference between the vaccinated and control groups. Further breakdown to the 4 time periods (not shown here) such as were used in Table 4 did not show any significant pattern of occurrence of symptoms or signs according to time.

#### COMMENT

The antibody responses to vaccination which were obtained in this study show satisfactory immunization of children with combined bivalent HPV-77 duck rubella and Jeryl Lynn mumps virus vaccine. The percentages of children who showed a demonstrable antibody response was 94% for rubella and 96% for mumps. These are not significantly different from those recorded earlier (2-7) when the vaccines were given alone. The overall geometric mean antibody titers were 1:35.9 and 1:6.8, respectively and these are roughly in the same range as previously recorded (2-7) for the vaccines given alone. The correlation with the earlier test results is remarkable, considering the degree of variation which is inherent in the antibody assay systems. It is evident, therefore, that the combining of the live viruses produced no apparent suppression or increase in immune responses.

The HPV-77 duck and Jeryl Lynn mumps virus vaccines cause remarkably little, if any, clinical reaction in children (2-7). Such lack of reactivity was not altered by combined administration of the 2 vaccines in a single dose. Especially important was the lack of fever and the arthritis/arthritis which are prominent features of the natural disease. The lack of joint involvement for the combined vaccine in

children was consistent with previous total experience by our laboratories (unpublished) in studies of HPV-77 duck rubella vaccine. In these studies, among 15,339 children aged 1 to 12 who were vaccinated, only 7 or 0.05% were noted to have any arthritis or arthralgic manifestations during the 28 day follow-up. The time period for observation for such signs was adequate since such manifestations are most often evident within the 28 day time period (9) if they are going to occur at all.

The large majority of children in the U.S.A. have been vaccinated against measles. It is estimated by us, based on vaccine distribution, that about 22 million children have received rubella vaccine and 7 million have been given mumps vaccine. The combined vaccine provides a simple, safe and effective means for providing immunization against these 2 important diseases in the remaining children through use of a single vaccine dose.

Indexing terms: RUBELLA-MUMPS, VACCINES, IMMUNOGENS, COMBINED LIVE VACCINES, RUBELLA, MUMPS.

Bivalent Rubella    mps Vaccine -  
Weibel, et al.

#### ACKNOWLEDGMENT

Medical assistance was given by George A. Starkweather, MD, Edward H. Vick, MD, Alvaro Gutierrez D., MD, and Oscar Vargas N., MD. Technical and nursing assistance was given by R. Roehm, BS, J. Haldis, BS, J. Orzeck, BS, B. Traupman, BS, J. Calvo T., A. Bitzer, RN, J. Munzinger, RN, E. Najar, M. Aguilar, M. Mendoza and A. Castro. Summaries and statistical computations were made by A. McLean, MS and B. Abbott, BS.

#### References

1. Buynak, EB, Weibel, RE, Whitman, JE, Jr, Stokes, J, Jr, Hilleman, MR: Combined live measles, mumps, and rubella virus vaccines. JAMA 207:2259-2262, 1969.
2. Buynak, EB, Hilleman, MR, Weibel, RE, Stokes, J, Jr: Live attenuated rubella virus vaccines prepared in duck embryo cell culture. I. Development and clinical testing. JAMA 204:195-200, 1968.
3. Weibel, RE, Stokes, J, Jr, Buynak, EB, Whitman, JE, Jr, Leagus, MB, Hilleman, MR: Live attenuated rubella virus vaccines prepared in duck embryo cell culture. II. Clinical tests in families and in an institution. JAMA 205:554-558, 1968.
4. Hilleman, MR, Buynak, EB, Whitman, JE, Jr, Weibel, RE, Stokes, J, Jr: Live attenuated rubella virus vaccines. Experiences with duck embryo cell preparations. Amer J Dis Child 118:166-171, 1969.
5. Weibel, RE, Stokes, J, Jr, Buynak, EB, Whitman, JE, Jr, Hilleman, MR: Live, attenuated mumps-virus vaccine. 3. Clinical and serologic aspects in a field evaluation. New Eng J Med 276:245-251, 1967.
6. Hilleman, MR, Weibel, RE, Buynak, EB, Stokes, J, Jr, Whitman, JE, Jr: Live, attenuated mumps-virus vaccine. 4. Protective efficacy as measured in a field evaluation. New Eng J Med 276:252-258, 1967.
7. Hilleman, MR, Buynak, EB, Weibel, RE, Stokes, J, Jr: Live, attenuated mumps-virus vaccine. New Eng J Med 278:227-232, 1968.

Bivalent Rubella-Mu Vaccine -  
Weibel, et al.

8. Buynak, EB, Whitman, JE, Jr, Roehm, RR, Morton, DH, Lampson, GP, Hilleman, MR: Comparison of neutralization and hemagglutination-inhibition techniques for measuring mumps antibody. Proc Soc Exp Biol Med 125:1068-1071, 1967.

9. Weibel, RE, Stokes, J, Jr, Buynak, EB, Hilleman, MR: Rubella vaccination in adult females. New Eng J Med 280:682-685, 1969.



Table 1.--Distribution of Serum  
Antibody Titers Following Vaccin-  
ation Among 31 Double Seronegative  
Children Given Lot 311 of Bivalent  
Rubella-Mumps Vaccine (Havertown)

| Rubella (HI)*          |                    | Mumps (Neut)* |                    |
|------------------------|--------------------|---------------|--------------------|
| Titer                  | No. of<br>Children | Titer         | No. of<br>Children |
| < 8                    | 0                  | < 1           | 1                  |
| 8                      | 2                  | 1             | 3                  |
| 16                     | 4                  | 2             | 2                  |
| 32                     | 9                  | 4             | 9                  |
| 64                     | 11                 | 8             | 4                  |
| 128                    | 3                  | 16            | 8                  |
| 256                    | 1                  | 32            | 1                  |
| 512                    | 1                  | 64            | 3                  |
| 1024                   | 0                  | 128           | 0                  |
| Geometric<br>Mean 45.8 |                    | 7.0           |                    |

\*HI = Hemagglutination-inhibition;

Neut = Serum neutralization.

Table 2.--Summary of Serologic Responses in Double-Seronegative Children Given Four Lots of Bivalent Rubella-Mumps Vaccine (Havertown-Costa Rica)

| Vaccine<br>Lot<br>No. | Antibody Responses |     |        |      |               |    |        |     |
|-----------------------|--------------------|-----|--------|------|---------------|----|--------|-----|
|                       | Rubella (HI)*      |     |        |      | Mumps (Neut)* |    |        |     |
|                       | Conversion         |     | Titer  |      | Conversion    |    | Titer  |     |
|                       | Rate               | %   | Range  | GM†  | Rate          | %  | Range  | GM† |
| 311                   | 31/31              | 100 | <8-512 | 45.8 | 30/31         | 97 | <1-64  | 7.0 |
| 92123                 | 133/140            | 95  | <8-256 | 40.8 | 133/140       | 95 | <1-128 | 6.2 |
| 92124                 | 94/100             | 94  | <8-256 | 38.6 | 95/100        | 95 | <1-64  | 5.0 |
| 96399                 | 132/144            | 92  | <8-512 | 28.5 | 139/144       | 97 | <1-64  | 9.0 |
| Total all lots        | 390/415            | 94  | <8-512 | 35.9 | 397/415       | 96 | <1-128 | 6.8 |

\*HI = Hemagglutination-inhibition; Neut = Serum neutralization.

†Geometric mean titer.

Bivalent Rubella mps Vaccine -  
Weibel, et al.

Table 3.—Occurrence of Fever, According to Time After  
Vaccination Among 31 Double Seronegative Children  
Given Lot 311 of Bivalent Rubella-Mumps  
Vaccine (Havertown)

| Days after<br>Vaccination | Maximum Oral Temperature |      |                            |      |                             |     |
|---------------------------|--------------------------|------|----------------------------|------|-----------------------------|-----|
|                           | <99F<br>(<37.2C)         |      | 99-100.9F<br>(37.2-38.29C) |      | 101-102.9F<br>(38.3-39.39C) |     |
|                           | No.                      | %    | No.                        | %    | No.                         | %   |
| 1-4                       | 19                       | 61.3 | 12                         | 38.7 | 0                           | 0   |
| 5-12                      | 12                       | 38.7 | 16                         | 51.6 | 3                           | 9.7 |
| 13-18                     | 17                       | 54.8 | 14                         | 45.2 | 0                           | 0   |
| 19-28                     | 15                       | 48.4 | 14                         | 45.2 | 2                           | 6.4 |

Table 4.--Miscellaneous Clinical Complaints Following  
Vaccination, Among 31 Double Seronegative Children  
Given Lot 311 of Bivalent Rubella-Mumps Vaccine  
(Havertown)

| Complaint                 | Days Following Vaccination |           |           |           |
|---------------------------|----------------------------|-----------|-----------|-----------|
|                           | No. (%)                    |           |           |           |
|                           | 1-4                        | 5-12      | 13-18     | 19-28     |
| Upper respiratory illness | 3 (9.7)                    | 6 (19.4)  | 3 (9.7)   | 9 (29.0)  |
| Nonrubelliform rash       | 0 (0.0)                    | 1 (3.2)   | 1 (3.2)   | 1 (3.2)   |
| Gastroenteritis           | 0 (0.0)                    | 1 (3.2)   | 0 (0.0)   | 1 (3.2)   |
| Irritability              | 1 (3.2)                    | 3 (9.7)   | 1 (3.2)   | 0 (0.0)   |
| No complaint              | 27 (87.1)                  | 22 (71.0) | 26 (83.9) | 21 (67.7) |

Table 5.--Miscellaneous Clinical Complaints  
Within 28 Days Following Vaccination Among  
384 Double Seronegative Children Who Re-  
ceived 3 Lots of Bivalent Rubella-Mumps  
Vaccine or Were Unvaccinated Controls  
(Costa Rica)

| Complaint                        | Vaccinated<br>Children |      | Contact<br>Controls |      |
|----------------------------------|------------------------|------|---------------------|------|
|                                  | No.                    | %    | No.                 | %    |
| Conjunctivitis                   | 18                     | 4.7  | 5                   | 5.7  |
| Otitis                           | 5                      | 1.3  | 3                   | 3.4  |
| Upper respiratory<br>illness     | 55                     | 14.3 | 11                  | 12.6 |
| Lymphadenopathy                  | 21                     | 5.5  | 4                   | 4.6  |
| Nonrubelliform<br>rash-Exanthema | 7                      | 1.8  | 0                   | 0    |
| Gastroenteritis                  | 29                     | 7.6  | 9                   | 10.3 |
| Headache                         | 22                     | 5.7  | 10                  | 11.5 |
| Irritability                     | 56                     | 14.6 | 21                  | 24.1 |
| Malaise                          | 63                     | 16.4 | 13                  | 14.9 |
| Anorexia                         | 95                     | 24.7 | 22                  | 25.3 |
| Fever                            | 39                     | 10.2 | 15                  | 17.2 |
| Varicella                        | 7                      | 1.8  | 0                   | 0    |
| Pertussis                        | 0                      | 0    | 1                   | 1.1  |
| "Allergy"                        | 2                      | 0.5  | 0                   | 0    |
| No complaint                     | 208                    | 54.2 | 41                  | 47.1 |

TRIVALENT COMBINED MEASLES-MUMPS-RUBELLA (M-M-R®) VACCINE

Findings in Clinical-Laboratory Studies

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Reprint requests to Division of Virus and Cell Biology Research, Merck  
Institute for Therapeutic Research, West Point, Pa. 19486 (Dr. Hilleman).

FOR COPY - SEE LETTER ADDRESSED  
TO DR. MURRAY DATED JAN. 15. 1971

MERCK SHARP & DOHME

RESEARCH LABORATORIES

DIVISION OF MERCK & CO., INC. WEST POINT, PENNSYLVANIA 19486 • TELEPHONE (215) 699-5311

MAURICE R. HILLEMAN, Ph. D., D. Sc.  
VICE PRESIDENT

February 3, 1971

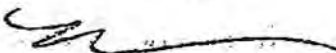
Dr. Harry Meyer  
Chief  
Laboratory of Viral Immunology  
Division of Biologics Standards  
National Institutes of Health  
Bethesda, Maryland 20014

Dear Harry:

The data you asked for on combined vaccines, viz., rubella responses in contact controls and arthritic/arthralgic observations, are being sent down as official submissions. Meantime, in view of the urgency, we are sending you a copy of submission. Please let me know if you need more information.

Kindest regards.

Sincerely yours,



Maurice R. Hilleman, Ph.D.  
Director  
Virus & Cell Biology Research  
Merck Institute for Therapeutic Research

/b1

Enclosure



At the time of the last discussion in Washington on January 27, 1971, the need was expressed for added information relating to the clinical trials of the various combined measles, mumps, and rubella vaccines. Thus, a) a summary of information on the antibody responses to rubella in contacts, b) the kind of clinical observation for arthritis, and c) copies of recently prepared papers for publication are being submitted for review.

a) Rubella antibody responses in contact controls. Tables 1, 2, and 3 show the contact responses for mumps-rubella, measles-mumps-rubella, and measles-rubella combined, respectively. The tables are self-explanatory and the interpretation for each case is given. Several points are to be made.

(1) There was only one response in the Philadelphia studies. If this were a real phenomenon, then we should see just as much in Philadelphia as in other studies.

(2) The Costa Rican studies were carried out carefully, but in the field where less optimal conditions prevailed than in Philadelphia. Also, natural rubella of low endemicity was present in the area for some of the studies at the time that the vaccine was being given.

For mumps-rubella, Table 1, there were adequate explanations for all 3 children who responded.

For measles-mumps-rubella, Table 2, there were 20 responses among controls. Eight of these were associated with evident specimen, child, etc. mix-up. Four were associated with known exposure to rubella or with known presence of rubella in the community. Six were unexplained responses and 2 had insufficient sera for retest. This is about par for the course. In view of detectable errors, it should be reasonable to expect undetectable errors also.

For measles-rubella, Table 3, there was one unexplained response among the 3 controls.

Conclusion: The studies showed a total of 26 rubella responses among 602 contact controls who were initially seronegative for rubella. Most were explainable as specimen or record mix-up, or as natural disease. There were a few instances in which the rises could not be explained from the available data. This was true also for rubella vaccine given alone. The fact that errors did occur and that rubella was endemic in Costa Rica makes it likely that the several unexplained rises were due to similar circumstance. Contact transmission, if real, should be a general phenomenon and not limited to a particular location or investigator. The fact that contact rise was essentially nonexistent in Philadelphia supports the view that contact transmission,

from vaccinee to contact, if it ever occurs at all, is an extremely rare event. One may conclude also that certainly combination of rubella with measles or mumps vaccines does not detectably enhance the theoretical risk for contact transmission.

b) Arthritis-arthralgia. The children in the Philadelphia studies were observed by the parents for 6-9 weeks post-vaccination with instructions to call the physician if anything untoward at all occurred. Additionally, the first 28 days were covered by a parent's report card. Finally, the parents were queried by Dr. Weibel at the time of the second bleeding (6-9 weeks) asking whether any problems at all had been observed. There were no arthritic/arthralgic symptoms or signs reported.

In the Costa Rican studies, the physicians and nurses saw the children on alternate days for 28 days. The children were bled at about 6 weeks and the parents were queried at that time. Finally, the parents were asked to report in any significant problem which developed during the time period.

Conclusion: There were no arthritic/arthralgic manifestations noted in the children in these studies during the 6-9 weeks follow-up. The children were young, 7 months to 8 years, and this is an age group in whom it might be expected that joint manifestations would be least or nonexistent. Most important, perhaps, is the fact that the combined vaccines are targeted for use in the very young children who would be unlikely to show symptoms even with a truly arthritigenic vaccine.

Table 1

Detailed Serologic Findings for Contact Controls Who Showed a Rise in Rubella HI Titer

## Combined Mumps-Rubella Vaccine

| Study No.            | Subject No. | Child or Guardian | HI Titer 1 |      | HI Titer 2 |      | CF Titer |      | Interpretation                                                                                                                                                                                                                                                                                                          |
|----------------------|-------------|-------------------|------------|------|------------|------|----------|------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                      |             |                   | Pre        | Post | Pre        | Post | Pre      | Post |                                                                                                                                                                                                                                                                                                                         |
| 221B<br>(Costa Rica) | 2143        | child             | <8         | 128  | <8         | 128  | <5       | <5   | Probable vaccinee.<br>This child also showed a mumps antibody rise (<2,8) while his "vaccinee" sibling (#2142) responded to neither mumps nor rubella.<br><br>There was insufficient sera for a mumps test; however, his vaccinee sibling, child #3993, failed to show an antibody response to either mumps or rubella. |
|                      | 3892        | child             | <8         | 64   | <8         | 64   | <5       | <5   |                                                                                                                                                                                                                                                                                                                         |
| 221B                 | 3371        | guardian          | <8         | 16   | <8         | 8    | N.D.     | N.D. | Blood type inconsistency (AB→A)                                                                                                                                                                                                                                                                                         |

Table 2

Detailed Serologic Findings for Contact Controls Who Showed a Rise in Rubella HI Titer

Combined Measles-Mumps-Rubella Vaccine

| Study No.                                             | Subject No. | Child or Guardian | HI Titer 1 |      | HI Titer 2 |      | CF Titer |        | Interpretation                                                                     |
|-------------------------------------------------------|-------------|-------------------|------------|------|------------|------|----------|--------|------------------------------------------------------------------------------------|
|                                                       |             |                   | Pre        | Post | Pre        | Post | Pre      | Post   |                                                                                    |
| 232<br>(Philadelphia)<br>220-<br>220B<br>(Costa Rica) | 107-2       | child             | <8         | 64   | <8         | 64   | <5       | <5     | Unexplained rise.                                                                  |
|                                                       | 71-3        | child             | <8         | 128  | <8         | 128  | <5       | AC@1:5 | Rubella was present in the community at the time of vaccination.                   |
|                                                       | 509-2       | guardian          | <8         | 128  | <8         | 128  | AC@5     | AC@10  | Rubella was present in the community.                                              |
| 220B<br>(Costa Rica)                                  | 859-2       | guardian          | <8         | 256  | <8         | 256  | <5       | <5     | Rubella was present in the community.                                              |
|                                                       | 119-4       | child             | <8         | 16   |            |      | <5       | <5     | Exposure to rubella. Also, possible specimen mix-up since mumps titers were 4, <2. |
|                                                       | 640-2       | child             | <8         | 64   | <8         | 128  | <5       | <5     | Exposure to rubella.                                                               |
| 220C<br>(Costa Rica)                                  | 51-3        | child             | <8         | 64   | <8         | 128  | <5       | <5     | Unexplained rise.                                                                  |
|                                                       | 66-2        | child             | <8         | 64   | <8         | 512  | <5       | <5     | Unexplained rise.                                                                  |
|                                                       | 87-1        | child             | <8         | 32   | <8         | 512  | <5       | <5     | Probable vaccinee. Child also showed a mumps antibody rise (<2,8).                 |
|                                                       | 90-1        | child             | <8         | 32   | <8         | 64   | <5       | <5     | Unexplained rise.                                                                  |
|                                                       | 92-2        | child             | <8         | 32   | <8         | 64   | <5       | <5     | Unexplained rise.                                                                  |

(continued ...)

## Detailed Serologic Findings for Contact Controls Who Showed a Rise in Rubella HI Titer

## Combined Measles-Mumps-Rubella Vaccine

| Study No.            | Subject No. | Child or Guardian | HI Titer 1 |      | HI Titer 2 |      | CF Titer |      | Interpretation                                                                                                   |
|----------------------|-------------|-------------------|------------|------|------------|------|----------|------|------------------------------------------------------------------------------------------------------------------|
|                      |             |                   | Pre        | Post | Pre        | Post | Pre      | Post |                                                                                                                  |
| 220C<br>(Costa Rica) | 128-10      | guardian          | <8         | 16   |            |      |          |      | Blood type inconsistency (O+A).                                                                                  |
|                      | 163-10      | guardian          | <8         | 32   |            |      |          |      | Blood type inconsistency (O+B).                                                                                  |
|                      | 201-2       | child             | <8         | 8    | <8         | 8    | <5       | <5   | Unexplained rise.                                                                                                |
|                      | 213-1       | child             | <8         | 64   | <8         | 128  | <5       | <5   | Unexplained rise. However, blood type inconsistency among sibling vaccinees #2132 and #2133 (O+A+O) and (A+O+A). |
|                      | 228-1       | child             | <8         | 32   | <8         | 128  | <5       | <5   | Probable vaccinee. Child also showed a rise in measles antibody titer (<5,80).                                   |
|                      | 242-1       | child             | <8         | 16   | <8         | 32   | <5       | <5   | Unexplained rise.                                                                                                |
|                      | 247-1       | child             | <8         | 128  | <8         | 32   | N.D.     | N.D. | Insufficient sera for CF test and blood typing.                                                                  |
|                      | 334-10      | guardian          | <8         | 16   |            |      |          |      | Insufficient sera for additional testing.                                                                        |
|                      | 340-10      | guardian          | <8         | 256  |            |      |          |      | Blood type inconsistency (B+O).                                                                                  |
|                      | 352-3       | child             | <8         | 256  |            |      | <5       | <5   | Probable vaccinee. Child also showed a rise in measles antibody titer (<5,10).                                   |



Table 3

Detailed Serologic Findings for Contact Controls Who Showed a Rise in Rubella HI Titer

## Combined Measles-Rubella Vaccine

| Study No.           | Subject No. | Child or Guardian | HI Titer 1 |      | HI Titer 2 |      | CF Titer |      | Interpretation                                                                                                                                                |
|---------------------|-------------|-------------------|------------|------|------------|------|----------|------|---------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                     |             |                   | Pre        | Post | Pre        | Post | Pre      | Post |                                                                                                                                                               |
| 243<br>(Costa Rica) | 64-1        | child             | <8         | 8    | <8         | 8    | AC@5     | <5   | Probable vaccinee<br>This child also showed a measles antibody response (<4,16) while his "vaccinee" sibling (#642) responded to neither measles nor rubella. |
|                     | 24-2        | child             | <8         | 64   | <8         | 64   | <5       | <5   | Unexplained rise.                                                                                                                                             |
| 243                 | 81-10       | guardian          | <8         | 32   | <8         | 32   | <5       | 5    | Natural disease on basis of CF rise.                                                                                                                          |

Table 4

## Clinical Surveillance Techniques Used in Combined Vaccine Clinical Trials

| Investigator(s)<br>(Location)                      | Clinical Trial                                                                                                             | Clinical Surveillance                                                                                                                                                                                                                                                                                                                                                                                     |
|----------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Stokes and Weibel<br>(Philadelphia and<br>Suburbs) | Mumps-Rubella Study 212<br>Measles-Mumps-Rubella Study 212<br>Measles-Mumps-Rubella Study 232<br>Measles-Rubella Study 244 | Temperature recordings and clinical observations were recorded by the parents on a daily basis for 28 days following vaccination. In addition, parents were instructed to notify the physician if any unusual clinical complaints occurred during the 6-9 week interval between bleedings. Finally, the parents were questioned about clinical complaints at the time of the second bleeding (6-9 weeks). |
| Villarejos<br>(Costa Rica and<br>San Salvador)     | Measles-Mumps-Rubella Study 220,<br>220B, 220C<br>Mumps-Rubella Study 221, 221B<br>Measles-Rubella Study 243               | Clinical observations were made by a physician and nurses who saw the children on alternate days for 28 days following vaccination. In addition, parents and guardians were instructed to notify the medical staff of any significant illness that occurred for the 6-week duration of the study, and they were questioned about clinical complaints at the time of the 6-week bleeding.                  |



MERCK SHARP & JOHME

RESEARCH LABORATORIES

DIVISION OF MERCK & CO., INC. WEST POINT, PENNSYLVANIA 19486 • TELEPHONE (215) 699-5311

MAURICE R. HILLEMAN, Ph. D., D. Sc.  
VICE PRESIDENT

February 2, 1971

Dr. Harry Meyer, Chief  
Laboratory of Viral Immunology  
Division of Biologics Standards  
National Institutes of Health  
Bethesda, Maryland 20014

Dear Harry:

Hope Hopps asked for the titer values on the individual  
paired sera we had sent to you.

These are enclosed. A carbon copy is being sent to Hope  
directly in response to her query.

Kindest regards and all good wishes.

Sincerely yours,

Maurice R. Hilleman, Ph.D.  
Director, Virus & Cell Biology Research  
Merck Institute for Therapeutic Research

enc.

Mrs. Hope Hopps

- Study 97 samples sent to Meyer

| <u>Fl #</u> | <u>pre</u> | <u>post (Crude antigen)</u> |
|-------------|------------|-----------------------------|
| A-55        | <5         | 10                          |
| A-43        | <5         | 10                          |
| B-1         | <5         | 20                          |
| B-34        | <5         | 40                          |
| B-55        | <5         | 20                          |
| B-91        | <5         | 20                          |
| C-25        | <5         | 10                          |
| D-37        | <5         | 10                          |
| D-10        | <5         | 20                          |
| E-46        | <5         | 20                          |
| F-108       | <5         | 40                          |
| F-91        | <5         | 160                         |
| G-79        | <5         | 10                          |
| G-16        | <5         | 10                          |
| H-31        | <5         | 10                          |
| H-22        | <5         | 10                          |
| I-73        | <5         | 20                          |
| I-49        | <5         | 20                          |
| I-37        | <5         | 20                          |
| I-25        | <5         | 10                          |
| I-4         | <5         | 20                          |
| J-13        | <5         | 10                          |
| L-31        | <5         | 20                          |
| L-28        | <5         | 5                           |
| L-22        | <5         | 20                          |
| L-16        | <5         | 10                          |
| L-7         | <5         | 10                          |
| L-1         | <5         | 10                          |
| B-73        | <5         | 20                          |
| D-25        | <5         | 20                          |
| E-4         | <5         | 10                          |
| F-55        | <5         | 20                          |
| G-7         | <5         | 20                          |
| G-52        | <5         | 5                           |
| I-46        | <5         | 10                          |
| G.H.T =     |            | 15.2                        |

Reginald Rivers

Study 232 Samples sent to Meyer

| Date   | measles |      | mumps |      | rubella |      |
|--------|---------|------|-------|------|---------|------|
|        | pre     | post | pre   | post | pre     | post |
| 20/1   | <5      | 160  | <1    | 4    | <8      | 32   |
| 21/1   | <5      | 320  | <1    | 4    | <8      | 64   |
| 102/1  | <5      | 80   | <1    | 2    | <8      | 32   |
| 103/1  | <5      | 160  | <1    | 16   | <8      | 64   |
| 109/1  | <5      | 10   | <1    | 2    | <8      | 8    |
| 110/1  | <5      | 80   | <1    | 4    | <8      | 16   |
| 111/1  | <5      | 40   | <1    | 32   | <8      | 64   |
| 114/1  | <5      | 160  | <1    | 32   | <8      | 128  |
| 117/1  | <5      | 160  | <1    | 64   | <8      | 32   |
| 120/1  | <5      | 80   | <1    | 4    | <8      | 256  |
| 120/2  | <5      | 80   | <1    | 16   | <8      | 64   |
| 122/1  | <5      | 20   | <1    | 8    | <8      | 32   |
| 123/1  | <5      | 160  | <1    | 2    | <8      | 16   |
| 124/2  | <5      | 160  | <1    | 8    | <8      | 256  |
| 147/1  | <5      | 160  | <1    | 32   | <8      | 16   |
| 150/1  | <5      | 320  | <1    | 4    | <8      | 128  |
| 151/1  | <5      | 80   | <1    | 8    | <8      | 512  |
| 155/1  | <5      | 160  | <1    | 4    | <8      | 16   |
| 161/1  | <5      | 80   | <1    | 2    | <8      | 16   |
| 157/1  | <5      | 320  | <1    | 32   | <8      | 128  |
| 158/1  | <5      | 80   | <1    | 4    | <8      | 64   |
| 160/1  | <5      | 10   | <1    | 16   | <8      | 64   |
| 161/1  | <5      | 10   | <1    | 64   | <8      | 64   |
| 165/1  | <5      | 20   | <1    | 32   | <8      | 64   |
| 167/1  | <5      | 80   | <2    | 64   | <8      | 64   |
| 170/1  | <5      | 80   | <1    | 4    | <8      | 64   |
| 171/1  | <5      | 40   | <1    | 64   | <8      | 128  |
| 173/1  | <5      | 40   | <1    | 4    | <8      | 64   |
| 95/1   | <5      | 40   | <1    | 16   | <8      | 64   |
| 96/1   | <5      | 320  | <1    | 8    | <8      | 16   |
| 97/1   | <5      | 160  | <1    | 8    | <8      | 16   |
| 140/1  | <5      | 160  | <1    | 16   | <8      | 64   |
| 142/1  | <5      | 80   | <1    | 4    | <8      | 64   |
| 144/1  | <5      | 40   | <1    | 8    | <8      | 32   |
| 214/1  | <5      | 80   | <1    | 4    | <8      | 128  |
| G.M.T. |         | 80.0 |       | 9.4  |         | 52.5 |

Study 244 samples sent to Mugh

Biognat Results

| Pt #  | measles |       | Rubella |      |
|-------|---------|-------|---------|------|
|       | pre     | post  | pre     | post |
| 2/1   | <5      | 160   | <8      | 16   |
| 3/1   | <5      | 80    | <8      | 64   |
| 4/1   | <5      | 80    | <8      | 32   |
| 6/1   | <5      | 80    | <8      | 256  |
| 7/1   | <5      | 80    | <8      | 64   |
| 8/1   | <5      | 160   | <8      | 128  |
| 9/1   | <5      | 40    | <8      | 16   |
| 10/1  | <5      | 80    | <8      | 64   |
| 12/1  | <5      | 80    | <8      | 256  |
| 13/1  | <5      | 320   | <8      | 128  |
| 14/1  | <5      | 320   | <8      | 128  |
| 15/1  | <5      | 160   | <8      | 64   |
| 16/1  | <5      | 160   | <8      | 32   |
| 17/1  | <5      | 640   | <8      | 32   |
| 19/1  | <5      | 160   | <8      | 512  |
| 28/1  | <5      | 80    | <8      | 64   |
| 29/1  | <5      | 640   | <8      | 128  |
| 30/1  | <5      | 80    | <8      | 32   |
| 31/1  | <5      | 160   | <8      | 64   |
| 33/1  | <5      | 320   | <8      | 128  |
| 35/1  | <5      | 160   | <8      | 16   |
| 39/1  | <5      | 160   | <8      | 64   |
| 40/1  | <5      | 320   | <8      | 32   |
| 55/1  | <5      | 160   | <8      | 128  |
| 56/1  | <5      | 160   | <8      | 256  |
| 58/2  | <5      | 160   | <8      | 256  |
| 59/1  | <5      | 160   | <8      | 256  |
| 65/1  | <5      | 160   | <8      | 512  |
| 66/1  | <5      | 40    | <8      | 64   |
| 69/1  | <5      | 320   | <8      | 16   |
| 109/1 | <5      | 160   | <8      | 32   |
| 110/1 | <5      | 160   | <8      | 512  |
| 111/1 | <5      | 320   | <8      | 16   |
| 119/1 | <5      | 640   | <8      | 16   |
| 120/1 | <5      | 160   | <8      | 64   |
|       | G.M.T.  | 160.0 |         | 73.5 |

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Not Clinical**

# MERCK SHARP & DOHME

DIVISION OF MERCK & CO., INC.

WEST POINT, PENNSYLVANIA 19486

February 9, 1971

Dr. Roderick Murray, Director  
Division of Biologics Standards  
National Institutes of Health  
Bethesda, Maryland 20014

Dear Doctor Murray:

Reference No. 69-192

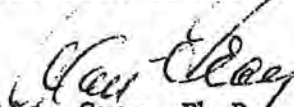
As indicated in Dr. Hilleman's letter of February 4, 1971 we are submitting Addendum No. 4 to Summary No. 1 of Clinical Investigative Studies of Combined Live Measles Virus Vaccine (Moraten Line - ATTENUVAX) Jeryl Lynn Mumps Virus Vaccine (MUMPSVAX) HPV-77 Duck Rubella Virus Vaccine (MERUVAX).

Please make this information a part of our license application for Measles, Mumps and Rubella Virus Vaccine, Live - Reference No. 69-192.

With kindest personal regards,

Sincerely yours,

MERCK SHARP & DOHME  
Division of Merck & Co., Inc.

  
Alan Gray, Ph.D.  
Director, Biological Production

/mb

**RECEIVED**  
FEB 17 1971  
**RECEIVED**  
LICENSING & INVESTIGATIONS

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MERCK SHARP & DOHME

RESEARCH LABORATORIES

DIVISION OF MERCK & CO., INC. WEST POINT, PENNSYLVANIA 19486 • TELEPHONE (215) 699-5311

MAURICE R. HILLEMAN, Ph. D., D. Sc.  
VICE PRESIDENT

February 4, 1971

Dr. Roderick Murray  
Director  
Division of Biologics Standards  
National Institutes of Health  
Bethesda, Maryland 20014

Dear Dr. Murray:

Shortly, Dr. Alan Gray will send you the following:

1. Addendum No. 1 to Summary No. 1 of Clinical Investigative Studies of Combined Live Attenuated Measles Virus Vaccine (Moraten Line - ATTENUVAX) HPV-77 Duck Rubella Virus Vaccine (MERUVAX)
2. Addendum No. 3 to Summary No. 1 of Clinical Investigative Studies of Combined Live Jeryl Lynn Mumps Virus Vaccine (MUMPSVAX) HPV-77 Duck Rubella Virus Vaccine (MERUVAX)
- ③. Addendum No. 4 to Summary No. 1 of Clinical Investigative Studies of Combined Live Measles Virus Vaccine (Moraten Line - ATTENUVAX) Jeryl Lynn Mumps Virus Vaccine (MUMPSVAX) HPV-77 Duck Rubella Virus Vaccine (MERUVAX)

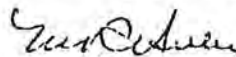
Copies are enclosed for your immediate use.

These submissions relate to the combined measles-mumps-rubella vaccines. They deal with antibody responses to rubella in contact controls, clinical observation for arthritic/arthralgic manifestations, and recent papers submitted for publication.

We do hope these will be of help to you in your considerations for licensure.

Kindest regards.

Sincerely yours,



Maurice R. Hilleman, Ph.D.  
Director  
Virus & Cell Biology Research  
Merck Institute for Therapeutic Research

/b1  
Enclosures

cc: Dr. A. Gray

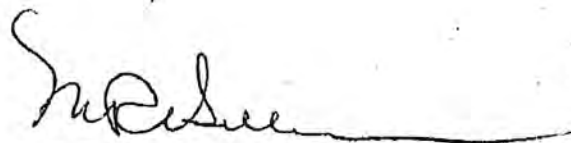
Addendum No. 4  
to  
Summary No. 1  
of  
Clinical Investigative Studies  
of

Combined Live Measles Virus Vaccine (Moraten Line - ATTENUVAX)

Jeryl Lynn Mumps Virus Vaccine (MUMPSVAX)

HPV-77 Duck Rubella Virus Vaccine (MERUVAX)

for purpose of support for  
a license to manufacture and sell.



Maurice R. Hilleman, Ph.D.

Prepared: February 3, 1971  
Merck Institute for Therapeutic Research  
West Point, Pennsylvania

At the time of the last discussion in Washington on January 27, 1971, the need was expressed for added information relating to the clinical trials of the various combined measles, mumps, and rubella vaccines. Thus, a) a summary of information on the antibody responses to rubella in contacts, b) the kind of clinical observation for arthritis, and c) copies of recently prepared papers for publication are being submitted for review.

a) Rubella antibody responses in contact controls. Tables 1, 2, and 3 show the contact responses for mumps-rubella, measles-mumps-rubella, and measles-rubella combined, respectively. The tables are self-explanatory and the interpretation for each case is given. Several points are to be made.

(1) There was only one response in the Philadelphia studies. If this were a real phenomenon, then we should see just as much in Philadelphia as in other studies.

(2) The Costa Rican studies were carried out carefully, but in the field where less optimal conditions prevailed than in Philadelphia. Also, natural rubella of low endemicity was present in the area for some of the studies at the time that the vaccine was being given.

For mumps-rubella, Table 1, there were adequate explanations for all 3 children who responded.

For measles-mumps-rubella, Table 2, there were 20 responses among controls. Eight of these were associated with evident specimen, child, etc. mix-up. Four were associated with known exposure to rubella or with known presence of rubella in the community. Six were unexplained responses and 2 had insufficient sera for retest. This is about par for the course. In view of detectable errors, it should be reasonable to expect undetectable errors also.

For measles-rubella, Table 3, there was one unexplained response among the 3 controls.

Conclusion: The studies showed a total of 26 rubella responses among 602 contact controls who were initially seronegative for rubella. Most were explainable as specimen or record mix-up, or as natural disease. There were a few instances in which the rises could not be explained from the available data. This was true also for rubella vaccine given alone. The fact that errors did occur and that rubella was endemic in Costa Rica makes it likely that the several unexplained rises were due to similar circumstance. Contact transmission, if real, should be a general phenomenon and not limited to a particular location or investigator. The fact that contact rise was essentially nonexistent in Philadelphia supports the view that contact transmission,

from vaccinee to contact, if it ever occurs at all, is an extremely rare event. One may conclude also that certainly combination of rubella with measles or mumps vaccines does not detectably enhance the theoretical risk for contact transmission.

b) Arthritis-arthralgia. The children in the Philadelphia studies were observed by the parents for 6-9 weeks post-vaccination with instructions to call the physician if anything untoward at all occurred. Additionally, the first 28 days were covered by a parent's report card. Finally, the parents were queried by Dr. Weibel at the time of the second bleeding (6-9 weeks) asking whether any problems at all had been observed. There were no arthritic/arthralgic symptoms or signs reported.

In the Costa Rican studies, the physicians and nurses saw the children on alternate days for 28 days. The children were bled at about 6 weeks and the parents were queried at that time. Finally, the parents were asked to report in any significant problem which developed during the time period.

Conclusion: There were no arthritic/arthralgic manifestations noted in the children in these studies during the 6-9 weeks follow-up. The children were young, 7 months to 8 years, and this is an age group in whom it might be expected that joint manifestations would be least or nonexistent. Most important, perhaps, is the fact that the combined vaccines are targeted for use in the very young children who would be unlikely to show symptoms even with a truly arthritigenic vaccine.

Table 1

Detailed Serologic Findings for Contact Controls Who Showed a Rise in Rubella HI Titer

Combined Mumps-Rubella Vaccine

| Study No.            | Subject No. | Child or Guardian | HI Titer 1 |      | HI Titer 2 |      | CF Titer |      | Interpretation                                                                                                                                            |
|----------------------|-------------|-------------------|------------|------|------------|------|----------|------|-----------------------------------------------------------------------------------------------------------------------------------------------------------|
|                      |             |                   | Pre        | Post | Pre        | Post | Pre      | Post |                                                                                                                                                           |
| 221B<br>(Costa Rica) | 2143        | child             | <8         | 128  | <8         | 128  | <5       | <5   | Probable vaccinee.<br>This child also showed a mumps antibody rise (<2,8) while his "vaccinee" sibling (#2142) responded to neither mumps nor rubella.    |
|                      | 3892        | child             | <8         | 64   | <8         | 64   | <5       | <5   |                                                                                                                                                           |
| 221B                 | 3371        | guardian          | <8         | 16   | <8         | 8    | N.D.     | N.D. | There was insufficient sera for a mumps test; however, his vaccinee sibling, child #3993, failed to show an antibody response to either mumps or rubella. |
| 221B                 |             |                   |            |      |            |      |          |      | Blood type inconsistency (AB→A)                                                                                                                           |

Table 2

## Detailed Serologic Findings for Contact Controls Who Showed a Rise in Rubella HI Titer

## Combined Measles-Mumps-Rubella Vaccine

| Study No.                                             | Subject No. | Child or Guardian | HI Titer 1 |      | HI Titer 2 |      | CF Titer |        | Interpretation                                                                     |
|-------------------------------------------------------|-------------|-------------------|------------|------|------------|------|----------|--------|------------------------------------------------------------------------------------|
|                                                       |             |                   | Pre        | Post | Pre        | Post | Pre      | Post   |                                                                                    |
| 232<br>(Philadelphia)<br>220-<br>220B<br>(Costa Rica) | 107-2       | child             | <8         | 64   | <8         | 64   | <5       | <5     | Unexplained rise.                                                                  |
|                                                       | 71-3        | child             | <8         | 128  | <8         | 128  | <5       | AC@1:5 | Rubella was present in the community at the time of vaccination.                   |
|                                                       | 509-2       | guardian          | <8         | 128  | <8         | 128  | AC@5     | AC@10  | Rubella was present in the community.                                              |
| 220B<br>(Costa Rica)                                  | 859-2       | guardian          | <8         | 256  | <8         | 256  | <5       | <5     | Rubella was present in the community.                                              |
|                                                       | 119-4       | child             | <8         | 16   | <8         |      | <5       | <5     | Exposure to rubella. Also, possible specimen mix-up since mumps titers were 4, <2. |
|                                                       | 640-2       | child             | <8         | 64   | <8         | 128  | <5       | <5     | Exposure to rubella.                                                               |
| 220C<br>(Costa Rica)                                  | 51-3        | child             | <8         | 64   | <8         | 128  | <5       | <5     | Unexplained rise.                                                                  |
|                                                       | 66-2        | child             | <8         | 64   | <8         | 512  | <5       | <5     | Unexplained rise.                                                                  |
|                                                       | 87-1        | child             | <8         | 32   | <8         | 512  | <5       | <5     | Probable vaccinee. Child also showed a mumps antibody rise (<2,8).                 |
|                                                       | 90-1        | child             | <8         | 32   | <8         | 64   | <5       | <5     | Unexplained rise.                                                                  |
|                                                       | 92-2        | child             | <8         | 32   | <8         | 64   | <5       | <5     | Unexplained rise.                                                                  |

(continued ...)



## Detailed Serologic Findings for Contact Controls Who Showed a Rise in Rubella HI Titer

## Combined Measles-Mumps-Rubella Vaccine

| Study No.            | Subject No. | Child or Guardian | HI Titer 1 |      | HI Titer 2 |      | CF Titer |      | Interpretation                                                                                                   |
|----------------------|-------------|-------------------|------------|------|------------|------|----------|------|------------------------------------------------------------------------------------------------------------------|
|                      |             |                   | Pre        | Post | Pre        | Post | Pre      | Post |                                                                                                                  |
| 220C<br>(Costa Rica) | 128-10      | guardian          | <8         | 16   |            |      |          |      | Blood type inconsistency (O+A).                                                                                  |
|                      | 163-10      | guardian          | <8         | 32   |            |      |          |      | Blood type inconsistency (O+B).                                                                                  |
|                      | 201-2       | child             | <8         | 8    | <8         | 8    | <5       | <5   | Unexplained rise.                                                                                                |
|                      | 213-1       | child             | <8         | 64   | <8         | 128  | <5       | <5   | Unexplained rise. However, blood type inconsistency among sibling vaccinees #2132 and #2133 (O+A+O) and (A+O+A). |
|                      | 228-1       | child             | <8         | 32   | <8         | 128  | <5       | <5   | Probable vaccinee. Child also showed a rise in measles antibody titer (<5,80).                                   |
|                      | 242-1       | child             | <8         | 16   | <8         | 32   | <5       | <5   | Unexplained rise.                                                                                                |
|                      | 247-1       | child             | <8         | 128  | <8         | 32   | N.D.     | N.D. | Insufficient sera for CF test and blood typing.                                                                  |
|                      | 334-10      | guardian          | <8         | 16   |            |      |          |      | Insufficient sera for additional testing.                                                                        |
|                      | 340-10      | guardian          | <8         | 256  |            |      |          |      | Blood type inconsistency (B+O).                                                                                  |
|                      | 352-3       | child             | <8         | 256  |            |      | <5       | <5   | Probable vaccinee. Child also showed a rise in measles antibody titer (<5,10).                                   |



Table 3

Detailed Serologic Findings for Contact Controls Who Showed a Rise in Rubella HI Titer

## Combined Measles-Rubella Vaccine

| Study No.           | Subject No. | Child or Guardian | HI Titer 1 |      | HI Titer 2 |      | CF Titer |      | Interpretation                                                                                                                                                |
|---------------------|-------------|-------------------|------------|------|------------|------|----------|------|---------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                     |             |                   | Pre        | Post | Pre        | Post | Pre      | Post |                                                                                                                                                               |
| 243<br>(Costa Rica) | 64-1        | child             | <8         | 8    | <8         | 8    | AC@5     | <5   | Probable vaccinee<br>This child also showed a measles antibody response (<4,16) while his "vaccinee" sibling (#642) responded to neither measles nor rubella. |
|                     | 24-2        | child             | <8         | 64   | <8         | 64   | <5       | <5   |                                                                                                                                                               |
| 243                 | 81-10       | guardian          | <8         | 32   | <8         | 32   | <5       | 5    | Unexplained rise.<br>Natural disease on basis of CF rise.                                                                                                     |

Table 4

## Clinical Surveillance Techniques Used in Combined Vaccine Clinical Trials

| Investigator(s)<br>(Location)                      | Clinical Trial                                                                                                             | Clinical Surveillance                                                                                                                                                                                                                                                                                                                                                                                     |
|----------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Stokes and Weibel<br>(Philadelphia and<br>Suburbs) | Mumps-Rubella Study 212<br>Measles-Mumps-Rubella Study 212<br>Measles-Mumps-Rubella Study 232<br>Measles-Rubella Study 244 | Temperature recordings and clinical observations were recorded by the parents on a daily basis for 28 days following vaccination. In addition, parents were instructed to notify the physician if any unusual clinical complaints occurred during the 6-9 week interval between bleedings. Finally, the parents were questioned about clinical complaints at the time of the second bleeding (6-9 weeks). |
| Villarejos<br>(Costa Rica and<br>San Salvador)     | Measles-Mumps-Rubella Study 220,<br>220B, 220C<br>Mumps-Rubella Study 221, 221B<br>Measles-Rubella Study 243               | Clinical observations were made by a physician and nurses who saw the children on alternate days for 28 days following vaccination. In addition, parents and guardians were instructed to notify the medical staff of any significant illness that occurred for the 6-week duration of the study, and they were questioned about clinical complaints at the time of the 6-week bleeding.                  |

TRIVALENT COMBINED MEASLES-MUMPS-RUBELLA (M-M-R®) VACCINE

Findings in Clinical-Laboratory Studies

by

\*Joseph Stokes, Jr, MD, DSc

\*Robert E. Weibel, MD

\*\*Victor M. Villarejos, MD, Dr PH

\*\*Jorge A. Arguedas G, MD, MPH

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and

\*\*\*Division of Virus and Cell Biology Research  
Merck Institute for Therapeutic Research  
West Point, Pennsylvania

Reprint requests to Division of Virus and Cell Biology Research, Merck  
Institute for Therapeutic Research, West Point, Pa. 19486 (Dr. Hilleman).

For Copy - SEE LETTER ADDRESSED  
TO DR. MURRAY DATED JAN. 15, 1971

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MERCK SHARP & DOHME

RESEARCH LABORATORIES

DIVISION OF MERCK & CO., INC. WEST POINT, PENNSYLVANIA 19486 • TELEPHONE (215) 699-5311

MAURICE R. HILLEMAN, Ph. D., D. Sc.  
VICE PRESIDENT

April 15, 1971

Dr. Roderick Murray, Director  
Division of Biologics Standards  
National Institutes of Health  
Bethesda, Maryland 20014

Dear Doctor Murray:

Shortly Dr. A. Gray will send you:

1. Addendum No. 5 to Summary No. 1 of clinical investigative studies of combined live measles virus vaccine (Moraten line - ATTENUVAX), Jeryl Lynn mumps virus vaccine (MUMPSVAX), and HPV-77 duck rubella virus vaccine (MERUVAX), and
2. Addendum No. 2 to Summary No. 1 of clinical investigative studies of combined live measles virus vaccine (Moraten line - ATTENUVAX) and HPV-77 duck rubella virus vaccine (MERUVAX).

Copies are enclosed for your immediate use.

These submissions summarize clinical findings with multiple dose preparations of the combined products. The studies were conducted by Dr. Victor Villarejos in Costa Rica. The findings are highly satisfactory.

Kindest regards.

Sincerely yours,



Maurice R. Hilleman, Ph.D.  
Director, Virus & Cell Biology Research  
Merck Institute for Therapeutic Research

MRH:b1

Enclosures

cc: Dr. A. Gray

Addendum No. 5  
to  
Summary No. 1  
of  
Clinical Investigative Studies  
of

Combined Live Attenuated Measles Virus Vaccine (Moraten Line - ATTENUVAX)

Jeryl Lynn Mumps Virus Vaccine (MUMPSVAX)

HPV-77 Duck Rubella Virus Vaccine (MERUVAX)

for purpose of support for  
a license to manufacture and sell.



Maurice R. Hilleman, Ph.D.

Prepared: April 14, 1971  
Merck Institute for Therapeutic Research  
West Point, Pennsylvania

Clinical Investigation of Combined Live Attenuated Measles (Moraten),  
Mumps (Jeryl Lynn), and Rubella (HPV-77) Vaccine

Previous submissions have described clinical trials with single dose preparations of combined measles-mumps-rubella vaccine. The present submission describes a clinical test of a multiple dose preparation of the combined product.

The clinical trial was conducted by Dr. Victor M. Villarejos in San Jose, Costa Rica.

A 1.0 ml dose of vaccine lot 12238 (C-8685) was given subcutaneously via jet gun. A 13 mm spacer was used.

The clinical test protocol, study findings, and vaccine manufacturing protocol are presented in Reference 8. The study was designed to measure the ability of the multiple dose preparation to elicit antibody responses to all three viruses and to measure clinical reactions.

It is seen that there was a high level of seroconversion against all three components. Clinical reactions did not exceed those expected for measles vaccine alone.



Measles-Mumps-Rubella Virus Vaccine, Study 253

Live Measles-Mumps-Rubella Virus Vaccine

Lot 12238

Responsible Clinical Investigator:

Victor M. Villarejos, M.D., M.P.H. and T.M., Dr. P.H.\*

Location:

San Jose, Costa Rica

Population:

Children whose families reside in and around San Jose, Costa Rica. 117 children with negative histories for measles, mumps, and rubella were vaccinated with 1.0 ml of the Combined Live Measles-Mumps-Rubella Virus Vaccine Lot 12238 by jet gun. All vaccinees were followed for clinical and serologic responses.

\* Associate Director  
Louisiana State University  
International Center for Medical  
Research and Training  
San Jose, Costa Rica

June 16, 1970

Clinical Protocol - Study #253

(Dr. V. Villarejos, ICMRT, San Jose, Costa Rica)

Combined: Moraten Measles  
Jeryl Lynn Mumps  
HPV-77 Duck Rubella

1. Purpose

To test the multiple dose preparation of measles-mumps-rubella virus vaccine in susceptible children and ascertain clinical reactions and serologic responses.

2. Background

A combined vaccine of above composition has been developed.

The vaccine evokes antibody in essentially all children to all three viruses. Measles vaccine causes mild febrile and other reactions in a fraction of the child recipients. The other components of the vaccine cause no significant reaction.

The need is to test the multiple dose preparation in triply seronegative children and to measure

- a) antibody responses and
- b) clinical reactions

to establish efficacy and safety.

3. Vaccine

Combined Measles-Mumps-Rubella

Multiple dose preparation

Lot #12238 (C-8685)

Rehydrate with 27.5 ml of distilled water.

Dose is 1.0 ml given subcutaneously via jet gun.

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

Keep dried vaccine at 4° C. in transport.

Keep on ice after rehydration. Discard after 4 hours.

Sterilize jet gun parts by boiling. Be sure to flush out water by firing several times with vaccine.

4. Study Plan

A. Clinical

Select as many children as possible with negative history of measles, mumps and rubella vaccination and previous illness. (Up to 50 children).

Vaccinate:

1.0 ml subcutaneously via jet gun.

Schedule:

| Time<br>Day | Activity                                           |
|-------------|----------------------------------------------------|
|             | Up to 50 Susceptible Children                      |
| 0           | Bleed 20 ml<br><br>Vaccinate 1.0 ml subcutaneously |
| 42-44       | Bleed 20 ml                                        |

B. Laboratory

Remove sera from clot and store frozen at  $-20^{\circ}$  C until shipped in dry ice.

Test all sera by HI or neut. for mumps and rubella antibodies.

C. Records

As per attached.

5. Caution

Vaccines contain chick and duck embryo protein and neomycin. Vaccines should not be given to persons sensitive to these substances.

*M. R. Hilleman*

M. R. Hilleman

Table 1

Serologic Findings for Children Vaccinated with Combined Measles-Mumps-Rubella Vaccine Lot 12238 in Costa Rica from July 29-31, 1970 (Study #253)

| Vaccination |                  |                   | Initially Seronegative to: |               |               |                   |         |       |                   |         |               |                   |                                |                              |                                |
|-------------|------------------|-------------------|----------------------------|---------------|---------------|-------------------|---------|-------|-------------------|---------|---------------|-------------------|--------------------------------|------------------------------|--------------------------------|
| Age (Yrs.)  | Total No. Vacci. | No. Serol. Tested | Measles-Mumps-Rubella      |               |               | Measles-Mumps     |         |       | Measles-Rubella   |         | Mumps-Rubella |                   | Measles Only Conversions/Total | Mumps Only Conversions/Total | Rubella Only Conversions/Total |
|             |                  |                   | Measles                    | Mumps         | Rubella       | Conversions/Total | Measles | Mumps | Conversions/Total | Measles | Rubella       | Conversions/Total |                                |                              |                                |
| <1          | 13               | 13                | 10/10                      | 10/10         | 10/10         |                   |         |       | 1/1               | 1/1     | 2/2           | 2/2               |                                |                              | 1/1                            |
| 1           | 30               | 30                | 26/26                      | 26/26         | 24/26         |                   |         |       | 1/1               | 1/1     | 2/2           | 1/2               |                                |                              | 3/4                            |
| 2           | 21               | 21                | 12/12                      | 12/12         | 12/12         |                   |         |       |                   |         | 5/5           | 5/5               |                                |                              | 1/1                            |
| 3           | 16               | 16                | 6/6                        | 5/6           | 6/6           |                   |         |       | 2/2               | 2/2     | 7/7           | 7/7               |                                | 1/1                          | 3/3                            |
| 4           | 18               | 18                | 3/4                        | 4/4           | 4/4           | 1/1               | 1/1     |       | 3/3               | 2/3     | 6/6           | 6/6               |                                | 1/1                          | 5/5                            |
| 5           | 9                | 9                 |                            |               |               |                   |         |       | 1/1               |         | 3/4           | 4/4               |                                |                              | 6/6                            |
| 6           | 10               | 10                | 1/1                        | 1/1           | 0/1           |                   |         |       | 1/1               | 1/1     | 2/2           | 2/2               |                                |                              |                                |
| Total       | 117              | 117               | 58/59 (98.3%)              | 58/59 (98.3%) | 56/59 (94.9%) | 1/1               | 1/1     | 1/1   | 8/8               | 7/8     | 27/28         | 27/28             | 0                              | 1/1                          | 19/20                          |

## Overall Conversion Rates

|  | Measles       | Mumps         | Rubella         |
|--|---------------|---------------|-----------------|
|  | 67/68 (98.5%) | 87/89 (97.8%) | 109/115 (94.8%) |

Table 2

Distribution of Titers of Children Initially Seronegative to Measles, Mumps, and Rubella Who Were Vaccinated with Combined Measles-Mumps-Rubella Vaccine Lot 12238 in Costa Rica from July 29-31, 1970 (Study #253)

| Measles (HI)*               |                 | Mumps (Neut.)* |                 | Rubella (HI)* |                 |
|-----------------------------|-----------------|----------------|-----------------|---------------|-----------------|
| Titer                       | No. of Children | Titer          | No. of Children | Titer         | No. of Children |
| <5                          | 1               | <1             | 1               | <8            | 3               |
| 5                           | 0               | 1              | 6               | 8             | 6               |
| 10                          | 0               | 2              | 9               | 16            | 17              |
| 20                          | 1               | 4              | 8               | 32            | 21              |
| 40                          | 4               | 8              | 12              | 64            | 10              |
| 80                          | 25              | 16             | 13              | 128           | 2               |
| 160                         | 24              | 32             | 4               |               |                 |
| 320                         | 4               | 64             | 6               |               |                 |
| 640                         | 0               | 128            | 0               |               |                 |
| Geometric Mean Titer: 100.8 |                 | 7.3            |                 | 22.5          |                 |

\* HI = Hemagglutination-inhibition  
Neut. = Serum neutralization

Table 3

Clinical Complaints Recorded for Children Vaccinated with  
Combined Measles-Mumps-Rubella Vaccine Lot 12238 (Study #253)

| Clinical Complaint        | Total Vaccinees       |               |                |                | Initially Seronegative to Measles-Mumps-Rubella |               |               |               |
|---------------------------|-----------------------|---------------|----------------|----------------|-------------------------------------------------|---------------|---------------|---------------|
|                           | Days Post-Vaccination |               |                |                | Days Post-Vaccination                           |               |               |               |
|                           | 1-4                   | 5-12          | 13-18          | 19-28          | 1-4                                             | 5-12          | 13-18         | 19-28         |
| Upper Respiratory Illness |                       | 4<br>(3.4%)   | 2<br>(1.7%)    | 3<br>(2.6%)    |                                                 | 3<br>(5.1%)   | 1<br>(1.7%)   | 3<br>(5.1%)   |
| Otitis                    | 1<br>(0.9%)           | 5<br>(4.3%)   |                |                | 1<br>(1.7%)                                     | 1<br>(1.7%)   |               |               |
| Swollen Glands            |                       | 1<br>(0.9%)   |                |                |                                                 |               |               |               |
| Conjunctivitis            | 1<br>(0.9%)           | 1<br>(0.9%)   |                |                |                                                 |               |               |               |
| Gastrointestinal          | 2<br>(1.7%)           | 7<br>(6.0%)   | 3<br>(2.6%)    | 2<br>(1.7%)    | 1<br>(1.7%)                                     | 5<br>(8.5%)   | 3<br>(5.1%)   | 2<br>(3.4%)   |
| Headache                  |                       | 1<br>(0.9%)   |                |                |                                                 | 1<br>(1.7%)   |               |               |
| Irritability              | 4<br>(3.4%)           | 23<br>(19.7%) | 4<br>(3.4%)    | 10<br>(8.5%)   | 4<br>(6.8%)                                     | 16<br>(27.1%) | 3<br>(5.1%)   | 6<br>(10.2%)  |
| Malaise                   | 4<br>(3.4%)           | 23<br>(19.7%) | 4<br>(3.4%)    | 10<br>(8.5%)   | 4<br>(6.8%)                                     | 16<br>(27.1%) | 3<br>(5.1%)   | 6<br>(10.2%)  |
| Irrelevant                |                       | 1<br>(0.9%)   |                |                |                                                 | 1<br>(1.7%)   |               |               |
| Fever                     | 3<br>(2.6%)           | 20<br>(17.1%) | 3<br>(2.6%)    | 6<br>(5.1%)    | 3<br>(5.1%)                                     | 13<br>(22.0%) | 2<br>(3.4%)   | 4<br>(6.8%)   |
| Anorexia                  | 6<br>(5.1%)           | 22<br>(18.8%) | 4<br>(3.4%)    | 8<br>(6.8%)    | 5<br>(8.5%)                                     | 16<br>(27.1%) | 3<br>(5.1%)   | 5<br>(8.5%)   |
| Allergy                   |                       | 2<br>(1.7%)   | 2<br>(1.7%)    |                |                                                 | 2<br>(3.4%)   | 2<br>(3.4%)   |               |
| No Complaints             | 108<br>(92.3%)        | 83<br>(70.9%) | 110<br>(94.0%) | 106<br>(90.6%) | 53<br>(89.8%)                                   | 39<br>(66.1%) | 53<br>(89.8%) | 52<br>(88.1%) |
| Total Subjects            | 117                   | 117           | 117            | 117            | 59                                              | 59            | 59            | 59            |

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Table 1

Serologic Findings for Children Vaccinated with Combined Measles-Mumps-Rubella Vaccine Lot 92127 in Santiago and San Bernardo, Chile from April 28, 1970 to June 24, 1970 (Study 246)

| Vaccination   |                       |                         | Children Initially Seronegative to: |                  |                   |       |                   |         |                   |         |                   |         |                   |       | Seropositive<br>to Measles,<br>Mumps, and<br>Rubella |                   |       |
|---------------|-----------------------|-------------------------|-------------------------------------|------------------|-------------------|-------|-------------------|---------|-------------------|---------|-------------------|---------|-------------------|-------|------------------------------------------------------|-------------------|-------|
| Age<br>(Yrs.) | Total<br>No.<br>Vacc. | No.<br>Serol.<br>Tested | Measles-Mumps-Rubella               |                  | Measles-Mumps     |       | Measles-Rubella   |         | Mumps-Rubella     |         | Measles Only      |         | Mumps Only        |       |                                                      | Rubella Only      |       |
|               |                       |                         | Conversions/Total                   |                  | Conversions/Total |       | Conversions/Total |         | Conversions/Total |         | Conversions/Total |         | Conversions/Total |       |                                                      | Conversions/Total |       |
|               |                       |                         | Measles                             | Mumps            | Measles           | Mumps | Measles           | Rubella | Measles           | Rubella | Measles           | Rubella | Measles           | Total |                                                      | Mumps             | Total |
| 0             | 17                    | 15                      | 11/11                               | 10/11            | 10/11             | 1/1   | 2/2               | 2/2     | 1/1               | 1/1     | 1/1               |         |                   |       |                                                      |                   |       |
| 1             | 74                    | 71                      | 44/44                               | 42/44            | 41/44             | 5/5   | 9/9               | 8/9     | 6/5               | 6/6     | 2/2               |         |                   |       |                                                      | 1/1               |       |
| 2             | 14                    | 14                      | 7/7                                 | 6/7              | 7/7               | 1/1   | 3/3               | 3/3     | 1/1               | 1/1     | 1/1               |         |                   | 2/2   |                                                      |                   |       |
| 3             | 5                     | 5                       | 2/2                                 | 2/2              | 2/2               |       | 1/1               | 1/1     | 1/1               | 1/1     |                   |         |                   | 1/1   |                                                      |                   |       |
| Total         | 110                   | 105                     | 64/64<br>(100%)                     | 60/64<br>(93.8%) | 60/64<br>(93.8%)  | 7/8   | 15/15             | 14/15   | 8/8               | 8/8     | 3/3               |         |                   | 3/3   |                                                      | 1/1               | 3     |

## Overall Conversion Rates

| Measles |         | Mumps |         | Rubella |         |
|---------|---------|-------|---------|---------|---------|
| 89/90   | (98.9%) | 78/83 | (94.0%) | 83/88   | (94.3%) |

Table 2

Distribution of Titers of Children Initially Seronegative to Measles, Mumps, and Rubella Who Were Vaccinated with Combined Measles-Mumps-Rubella Vaccine Lot 92127 in Santiago and San Bernardo, Chile from April 28, 1970 to June 24, 1970 (Study 246)

| Measles (HAI)                 |                    | Mumps (Neut.)       |                    | Rubella (HAI)       |                    |
|-------------------------------|--------------------|---------------------|--------------------|---------------------|--------------------|
| Post-Vacc.<br>Titer           | No. of<br>Children | Post-Vacc.<br>Titer | No. of<br>Children | Post-Vacc.<br>Titer | No. of<br>Children |
| 20                            | 8                  | <2                  | 4                  | <8                  | 4                  |
| 40                            | 12                 | 2                   | 8                  | 8                   | 1                  |
| 80                            | 26                 | 4                   | 11                 | 16                  | 11                 |
| 160                           | 12                 | 8                   | 14                 | 32                  | 15                 |
| ≥320                          | 6                  | 16                  | 8                  | 64                  | 20                 |
|                               |                    | 32                  | 9                  | 128                 | 11                 |
|                               |                    | ≥64                 | 10                 | 256                 | 2                  |
| Geometric<br>Mean Titer: 76.6 |                    | 9.6                 |                    | 37.6                |                    |

Table 3

Serologic Findings for Rubella Antibody for Children  
and Adults Acting as Contact Controls for Combined  
Measles-Mumps-Rubella Vaccine Lot 92127 (Study 246)

| Age<br>(Yrs.)         | Total<br>No. | No.<br>Serol.<br>Tested | No.<br>Initially<br>Seropos. | Initially Seronegative<br>Paired Sera |            |       |
|-----------------------|--------------|-------------------------|------------------------------|---------------------------------------|------------|-------|
|                       |              |                         |                              | No.<br>Conv.                          | No<br>Rise | Total |
| Children              |              |                         |                              |                                       |            |       |
| 1                     | 3            | 3                       | 1                            |                                       | 2          | 2     |
| 2                     | 2            | 2                       |                              |                                       | 2          | 2     |
| 4                     | 1            | 1                       |                              | 1                                     |            | 1     |
| Total                 | 6            | 6                       | 1                            | 1                                     | 4          | 5     |
| Adult Female Controls |              |                         |                              |                                       |            |       |
| 17-19                 | 10           | 10                      | 10                           |                                       |            |       |
| 20-29                 | 65           | 63                      | 58                           | 1                                     | 4          | 5     |
| 30-39                 | 23           | 21                      | 20                           |                                       | 1          | 1     |
| 40-49                 | 8            | 8                       | 8                            |                                       |            |       |
| 57                    | 1            | 1                       | 1                            |                                       |            |       |
| 65                    | 1            | 1                       | 1                            |                                       |            |       |
| Total                 | 108          | 104                     | 98                           | 1                                     | 5          | 6     |

Table 4

Clinical Complaints Recorded for Children Vaccinated with Combined Measles-Mumps-Rubella Vaccine Lot 92127 and for Their Unvaccinated Contact Controls (Study 246)

| Clinical Complaints       | Contact Control Children |              |             |             | Total Vaccinees       |               |               |               | Initially Seronegative to Measles-Mumps-Rubella Days Post-Vaccination |               |               |               |
|---------------------------|--------------------------|--------------|-------------|-------------|-----------------------|---------------|---------------|---------------|-----------------------------------------------------------------------|---------------|---------------|---------------|
|                           | Days Observed            |              |             |             | Days Post-Vaccination |               |               |               | Days Post-Vaccination                                                 |               |               |               |
|                           | 1-4                      | 5-12         | 13-18       | 19-28       | 1-4                   | 5-12          | 13-18         | 19-28         | 1-4                                                                   | 5-12          | 13-18         | 19-28         |
| Upper Respiratory Illness | 2<br>(33.3%)             | 2<br>(33.3%) |             |             | 36<br>(32.7%)         | 48<br>(43.6%) | 18<br>(16.4%) | 13<br>(11.8%) | 21<br>(32.8%)                                                         | 29<br>(45.3%) | 9<br>(14.1%)  | 8<br>(12.5%)  |
| Conjunctivitis            |                          |              |             |             | 2<br>(1.8%)           | 3<br>(2.7%)   | 2<br>(1.8%)   |               | 1<br>(1.6%)                                                           | 2<br>(3.1%)   | 1<br>(1.6%)   |               |
| Gastrointestinal          |                          |              |             |             | 4<br>(3.6%)           | 6<br>(5.5%)   |               |               | 4<br>(6.2%)                                                           | 4<br>(6.2%)   |               |               |
| Headache                  |                          |              |             |             | 5<br>(4.5%)           | 2<br>(1.8%)   |               |               | 1<br>(1.6%)                                                           | 1<br>(1.6%)   |               |               |
| Irritability              |                          |              |             |             | 11<br>(10.0%)         | 9<br>(8.2%)   | 1<br>(0.9%)   | 1<br>(0.9%)   | 7<br>(10.9%)                                                          | 6<br>(9.4%)   |               |               |
| Malaise                   |                          |              |             |             | 10<br>(9.1%)          | 3<br>(2.7%)   | 2<br>(1.8%)   | 1<br>(0.9%)   | 4<br>(6.2%)                                                           | 2<br>(3.1%)   | 1<br>(1.6%)   |               |
| Measles                   |                          |              |             |             |                       | 1<br>(0.9%)   |               |               |                                                                       |               |               |               |
| Anorexia                  |                          |              |             |             | 10<br>(9.1%)          | 12<br>(10.9%) | 5<br>(4.5%)   | 3<br>(2.7%)   | 6<br>(9.4%)                                                           | 6<br>(9.4%)   | 3<br>(4.7%)   | 2<br>(3.1%)   |
| Exanthema                 |                          |              |             |             | 1<br>(0.9%)           | 2<br>(1.8%)   | 1<br>(0.9%)   |               | 1<br>(1.6%)                                                           | 1<br>(1.6%)   |               |               |
| No Complaints             | 4<br>(66.7%)             | 4<br>(66.7%) | 6<br>(100%) | 6<br>(100%) | 62<br>(56.4%)         | 55<br>(50.0%) | 87<br>(79.1%) | 94<br>(85.5%) | 36<br>(56.2%)                                                         | 32<br>(50.0%) | 51<br>(79.7%) | 53<br>(82.8%) |
| Total Subjects            | 6                        | 6            | 6           | 6           | 110                   | 110           | 110           | 110           | 64                                                                    | 64            | 64            | 64            |

Table 1.  
Serologic Findings for Children Vaccinated with Combined Measles-Mumps-Rubella Vaccine Lot 96400  
in Santiago and San Bernardo, Chile from May 6, 1970 to July 15, 1970 (Study 246)

| Vaccination   |              | Children Initially Seronegative to: |                       |                   |                 |                       |                   | Seropositive<br>to Measles,<br>Mumps, and<br>Rubella |                                       |
|---------------|--------------|-------------------------------------|-----------------------|-------------------|-----------------|-----------------------|-------------------|------------------------------------------------------|---------------------------------------|
|               |              | Measles-Mumps-Rubella               |                       | Measles-Mumps     |                 | Measles-Rubella       |                   | Mumps Only                                           |                                       |
| Age<br>(Yrs.) | No.<br>Vacc. | No.<br>Serol.<br>Tested             | Conversions/<br>Total | Measles/<br>Total | Mumps/<br>Total | Conversions/<br>Total | Rubella/<br>Total | Conversions/<br>Total                                | Rubella Only<br>Conversions/<br>Total |
| <1            | 17           | 15                                  | 10/10                 | 10/10             | 2/2             | 2/2                   | 1/1               | 2/2                                                  |                                       |
| 1             | 46           | 42                                  | 22/22                 | 22/22             | 4/4             | 2/2                   | 7/7               | 2/2                                                  | 1/1                                   |
| 2             | 8            | 8                                   | 5/5                   | 5/5               |                 |                       | 1/1               | 1/1                                                  |                                       |
| 3             | 2            | 2                                   |                       |                   | 1/1             |                       |                   | 1/1                                                  |                                       |
| 4             | 2            | 2                                   |                       |                   |                 |                       |                   |                                                      | 1/1                                   |
| 5             | 2            | 2                                   |                       |                   | 1/1             |                       |                   |                                                      |                                       |
| 11            | 1            | 0                                   |                       |                   |                 |                       | 0/1               |                                                      |                                       |
| Total         | 78           | 71                                  | 37/37<br>(100%)       | 37/37<br>(100%)   | 8/8             | 8/8                   | 10/10             | 6/6                                                  | 5/5                                   |
|               |              |                                     |                       |                   |                 |                       | 9/10              | 2/2                                                  | 2/2                                   |
|               |              |                                     |                       |                   |                 |                       |                   |                                                      | 1                                     |

Overall Conversion Rates

|  | Measles         | Mumps           | Rubella          |
|--|-----------------|-----------------|------------------|
|  | 60/60<br>(100%) | 53/53<br>(100%) | 53/55<br>(96.4%) |

Table 2

Distribution of Titers of Children Initially Seronegative to Measles, Mumps, and Rubella Who Were Vaccinated with Combined Measles-Mumps-Rubella Vaccine Lot 96400 in Santiago and San Bernardo, Chile from May 6, 1970 to July 15, 1970 (Study 246)

| Measles (HAI)                 |                    | Mumps (Neut.)       |                    | Rubella (HAI)       |                    |
|-------------------------------|--------------------|---------------------|--------------------|---------------------|--------------------|
| Post-Vacc.<br>Titer           | No. of<br>Children | Post-Vacc.<br>Titer | No. of<br>Children | Post-Vacc.<br>Titer | No. of<br>Children |
| 10                            | 1                  | 2                   | 4                  | 8                   | 2                  |
| 20                            | 2                  | 4                   | 9                  | 16                  | 6                  |
| 40                            | 12                 | 8                   | 5                  | 32                  | 6                  |
| 80                            | 8                  | 16                  | 5                  | 64                  | 14                 |
| 160                           | 10                 | 32                  | 5                  | 128                 | 8                  |
| ≥320                          | 4                  | ≥64                 | 9                  | 256                 | 1                  |
| Geometric<br>Mean Titer: 78.5 |                    | 12.8                |                    | 49.2                |                    |

Table 3

Serologic Findings for Rubella Antibody for Children  
and Adults Acting as Contact Controls for Combined  
Measles-Mumps-Rubella Vaccine Lot 96400 (Study 246)

| Age<br>(Yrs.)         | Total<br>No. | No.<br>Serol<br>Tested | No.<br>Initially<br>Seropos. | Initially Seronegative |            |       |                           |       |
|-----------------------|--------------|------------------------|------------------------------|------------------------|------------|-------|---------------------------|-------|
|                       |              |                        |                              | Paired Sera            |            |       | Pre-Vacc.<br>Sera<br>Only | Total |
|                       |              |                        |                              | No.<br>Conv.           | No<br>Rise | Total |                           |       |
| Children              |              |                        |                              |                        |            |       |                           |       |
| 2                     | 2            | 2                      |                              |                        | 2          | 2     |                           | 2     |
| 3                     | 1            | 1                      |                              |                        |            |       | 1                         | 1     |
| Total                 | 3            | 3                      | 0                            | 0                      | 2          | 2     | 1                         | 3     |
| Adult Female Controls |              |                        |                              |                        |            |       |                           |       |
| 16-19                 | 9            | 9                      | 9                            |                        |            |       |                           |       |
| 20-29                 | 46           | 46                     | 41                           | 2                      | 3          | 5     |                           | 5     |
| 30-39                 | 14           | 14                     | 13                           |                        | 1          | 1     |                           | 1     |
| 40-47                 | 3            | 3                      | 3                            |                        |            |       |                           |       |
| 58                    | 1            | 1                      | 1                            |                        |            |       |                           |       |
| 67                    | 1            | 1                      | 1                            |                        |            |       |                           |       |
| 70                    | 1            | 1                      | 1                            |                        |            |       |                           |       |
| Total                 | 75           | 75                     | 69                           | 2                      | 4          | 6     | 0                         | 6     |



Table

Clinical Complaints Recorded for Children Vaccinated with Combined Measles-Mumps-Rubella Vaccine Lot 96400 and for Their Unvaccinated Contact Controls (Study 246)

| Clinical Complaints       | Contact Control Children |              |              |             | Total Vaccinees       |               |               |               | Initially Seronegative to Measles-Mumps-Rubella |               |               |               |
|---------------------------|--------------------------|--------------|--------------|-------------|-----------------------|---------------|---------------|---------------|-------------------------------------------------|---------------|---------------|---------------|
|                           | Days Observed            |              |              |             | Days Post-Vaccination |               |               |               | Days Post-Vaccination                           |               |               |               |
|                           | 1-4                      | 5-12         | 13-18        | 19-28       | 1-4                   | 5-12          | 13-18         | 19-28         | 1-4                                             | 5-12          | 13-18         | 19-28         |
| Upper Respiratory Illness | 1<br>(33.3%)             | 1<br>(33.3%) | 1<br>(33.3%) |             | 31<br>(39.7%)         | 32<br>(41.0%) | 7<br>(9.0%)   | 5<br>(6.4%)   | 12<br>(32.4%)                                   | 16<br>(43.2%) | 6<br>(16.2%)  | 2<br>(5.4%)   |
| Otitis                    |                          |              |              |             |                       | 1<br>(1.3%)   |               |               |                                                 |               |               |               |
| Swollen Glands            |                          |              |              |             | 1<br>(1.3%)           | 1<br>(1.3%)   |               |               |                                                 |               |               |               |
| Conjunctivitis            | 1<br>(33.3%)             | 1<br>(33.3%) |              |             |                       |               |               |               |                                                 |               |               |               |
| Gastrointestinal          |                          |              |              |             |                       | 2<br>(2.6%)   | 1<br>(1.3%)   | 3<br>(3.8%)   |                                                 | 2<br>(5.4%)   | 1<br>(2.7%)   | 2<br>(5.4%)   |
| Headache                  |                          |              |              |             | 3<br>(3.8%)           | 1<br>(1.3%)   |               |               |                                                 |               |               |               |
| Irritability              | 1<br>(33.3%)             | 1<br>(33.3%) |              |             | 5<br>(6.4%)           | 3<br>(3.8%)   |               |               | 1<br>(2.7%)                                     | 1<br>(2.7%)   |               |               |
| Malaise                   | 2<br>(66.7%)             | 2<br>(66.7%) |              |             | 8<br>(10.3%)          | 3<br>(3.8%)   |               |               | 2<br>(5.4%)                                     | 1<br>(2.7%)   |               |               |
| Anorexia                  |                          |              |              |             | 1<br>(1.3%)           | 5<br>(6.4%)   | 1<br>(1.3%)   | 1<br>(1.3%)   |                                                 | 2<br>(5.4%)   | 1<br>(2.7%)   | 1<br>(2.7%)   |
| Exanthema                 |                          |              |              |             | 1<br>(1.3%)           | 1<br>(1.3%)   |               |               | 1<br>(2.7%)                                     | 1<br>(2.7%)   |               |               |
| No Complaints             | 1<br>(33.3%)             | 1<br>(33.3%) | 2<br>(66.7%) | 3<br>(100%) | 46<br>(59.0%)         | 44<br>(56.4%) | 70<br>(89.7%) | 71<br>(91.0%) | 25<br>(67.6%)                                   | 20<br>(54.1%) | 30<br>(81.1%) | 33<br>(89.2%) |
| Total Subjects            | 3                        | 3            | 3            | 3           | 78                    | 78            | 78            | 78            | 37                                              | 37            | 37            | 37            |

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as Non-Responsive  
- Not Clinical**