



December 30, 2021

Allison Lucas
Siri & Glimstad LLP
200 Park Avenue, 17th Floor
New York, NY 10166

In reply refer to file: **2019-6073**

Dear Ms. Lucas,

This is in reply to your Freedom of Information Act (FOIA) request dated July 9, 2019, in which you requested "A copy of Merck phase IV (post-licensure) cohort study of 25,000 immunized children designed to detect short term rare adverse events to vaccination with Varivax as cited on page 13 on Merck's Summary for Basis of Approval of Varivax found here: <http://wayback.archive-it.org/7993/20170723031730/https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM142826.pdf>." Your request was received in the Center for Biologics Evaluation and Research (CBER) on July 10, 2019.

Enclosed are the Post Marketing Study records responsive to your request.

We have withheld portions of pages under Exemption (b)(6), 5 U.S.C. § 552(b)(6). That exemption protects information from disclosure when its release would cause a clearly unwarranted invasion of personal privacy. FOIA Exemption 6 is available to protect information in personnel or medical files and similar files. This requires a balancing of the public's right to disclosure against the individual's right to privacy.

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

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

Director, Office of the Executive Secretariat
US Food & Drug Administration
5630 Fishers Lane, Room 1050
Rockville, MD 20857
E-mail: FDAFOIA@fda.hhs.gov

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

If you would like to discuss our response before filing an appeal to attempt to resolve your dispute without going through the appeals process, please contact Katherine Uhl at 301-796-8975.

You may also contact the FDA FOIA Public Liaison for assistance at:

Office of the Executive Secretariat
US Food & Drug Administration
5630 Fishers Lane, Room 1050
Rockville, MD 20857
E-mail: FDAFOIA@fda.hhs.gov

If you are not satisfied with any aspect of the processing and handling of this request, please contact:

Ms. Suzann Burk
Director, Division of Disclosure and Oversight Management
Office of Communication Outreach and Development
Center for Biologics Evaluation and Research (CBER)
U.S. Food and Drug Administration (FDA)
20903 New Hampshire Avenue
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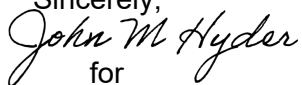
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US Food & Drug Administration
5630 Fishers Lane, Room 1050
Rockville, MD 20857
E-mail: FDAFOIA@fda.hhs.gov

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

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

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

Sincerely,

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

**Report
Protocol 035**

POST-MARKETING STUDY REPORT

VARIVAX®

Post-Marketing Evaluation of Short-Term Safety of Varicella Vaccine

PROTECTION OF HUMAN SUBJECTS:

This study was conducted in conformance with applicable US requirements regarding ethical committee review, informed consent, and other statutes or regulations regarding the protection of the rights and welfare of human subjects participating in biomedical research.

PRODUCT: Varicella Virus Vaccine, [Live Oka/Merck (VARIVAX®)]

PROTOCOL TITLE: Post-Marketing Evaluation of Short-Term Safety of Varicella Vaccine

PROTOCOL NUMBER: #035-00

INVESTIGATOR(S): Steve Black, M.D. (Primary), Henry Shinefield, M.D. (Secondary)

CLINICAL PHASE: Phase IV (Post-Marketing)

DURATION: 2 years

OBJECTIVES:

1. To describe the occurrence of adverse events in at least 25,000 children aged 12 to 23 months in a period (30 days for pediatric outpatient visits and emergency room visits, 60 days for hospitalizations and mortality) immediately after vaccination with VARIVAX®.
2. To compare the rates of specific adverse events in the period post-vaccination with the adverse events rates in three comparison periods of the same time duration:
 - Historical controls randomly selected from the previous year, *i.e.*, before vaccine licensure, using the same calendar days one year prior as the comparison period.
 - The time period 31 - 60 or 31 - 90 days before vaccination in the same individuals who were vaccinated.
 - The time period 91 - 120 or 91 - 150 days after vaccination in the same individuals who were vaccinated.

STUDY STATUS: Completed.

The study was closed on February 5, 1997. A total of 91,740 doses of VARIVAX® were administered in the study period to 89,753 children and adults (34,665 children aged 12 to 23 months, 51,463 individuals 2 to 12 years of age, and 3,625 individuals older than 12 years). This meets Merck's commitment to CBER to study the occurrence of adverse events in at least 25,000 children 12 to 23 months of age.

STUDY DESIGN:

The study proposed to vaccinate at least 25,000 children between the ages of 12 to 23 months who are members of the Kaiser Permanente Medical Care Program (KPMCP) and who meet the eligibility criteria for VARIVAX® vaccination. The process was begun as soon as possible after the date of licensure and the date of product launch (March 17, 1995 and May 1, 1995, respectively).

Study vaccinations were begun on June 1, 1995. Vaccination in the general KPMCP population was begun on May 1, 1995. The study included all persons vaccinated with VARIVAX® between June 1, 1995 and December 31, 1996 through the Kaiser Northern system. Follow-up for adverse events following vaccination was ended on February 5, 1997.

Adverse events were identified through the use of computerized records of pediatric acute care visits, emergency room visits, hospitalizations, and from the mortality data base of the state of California. The principal investigators at KPMCP listed all adverse events, regardless of relationship to vaccination, that occurred among the study population during a post-vaccination period (30 days for pediatric acute care visits and emergency room visits, 60 days for hospitalizations and mortality). The original clinical charts of subjects presenting with adverse events considered by the investigators or the sponsor to be possibly related to vaccine were reviewed by the investigator, as were medical records for any deaths, to assess a possible vaccination effect. All deaths and hospitalizations for neurological events were reported in narrative form to the sponsor. In addition, line summaries of all hospitalizations, regardless of cause were provided to the sponsor. Rates of adverse events following vaccination were compared to the observed rates in the control periods. Relative risks and exact binomial 95% confidence intervals were calculated.

The original protocol focused on evaluating the safety profile of VARIVAX® in children 12 to 23 months of age. At the request of CBER the study was expanded to assess the safety profile of VARIVAX® among vaccinees of all ages. However, rate comparisons using historical controls were conducted only for the original age cohort (12 to 23 months of age) because of the extensive time requirements required for preparation of a randomly selected historical control group. Additionally, comparison of the exposed risk period with the historical control period was not conducted for outpatient visits because computerized records of outpatient visits were not available before vaccine licensure. To avoid potential seasonal biases, historical control periods were created by randomly selecting age-matched controls from the KPMCP database from the calendar year 1994 (before vaccine licensure) and the same calendar days that were used as the risk period following varicella vaccination in 1995 or 1996 were used to form the historical control period in 1994.

INCLUSION CRITERIA:

The vaccine was offered to all children aged 12 to 23 months who were members of KPMCP, who had a negative clinical history of varicella, and who met the eligibility criteria as specified in the package insert. Children were vaccinated in the course of ordinary clinical practice with marketed varicella vaccine over the 1 to 2 year period after licensure of the vaccine. All children 12 to 23 months of age who were vaccinated with VARIVAX® comprised the study population. The study population was later extended to include all vaccinated Kaiser members, regardless of age, in the study population.

DOSAGE:

One 0.5 ml subcutaneous injection of VARIVAX® containing a minimum of 1,350 plaque forming units (PFUs) 30 minutes after reconstitution was injected subcutaneously.

DATA ANALYSIS:

An age-specific rate was calculated for every adverse event (hospitalization, ER visit, outpatient visit) that occurred in the 30 or 60 day period after vaccination. The person-time denominator for each age-specific rate was calculated by multiplying the window period of follow-up for adverse events after vaccination (*i.e.*, 30 or 60 days) by the number of vaccinations in that age category. For the purposes of this analysis, the day 0 (day of vaccination) was included in the risk period for hospitalizations and emergency room visits but not for outpatient visits. Since outpatient visits provide an opportunity for catch-up vaccination, outpatient visits on the day of vaccination are associated with vaccination not because the vaccine causes the visit, but because the visit provides an opportunity for vaccination. Thus inclusion of day 0 in the risk period for outpatient visits creates substantial noise. Comparison of specific adverse event rates in the periods immediately following vaccination were compared with rates of the same events in equal time periods (*i.e.* 30 days versus 30 days, 60 days versus 60 days) in three control periods. The three control periods were:

- Historical controls randomly selected from the previous year, *i.e.*, before vaccine licensure, using the same calendar days one year prior as the comparison period.
- The time period 31 - 60 days or 31 - 90 days before vaccination in the same individuals who were vaccinated.
- The time period 91 - 120 days or 91 - 150 days after vaccination in the same individuals who were vaccinated.

Three control periods were used because each period has advantages and disadvantages. The historical controls have the advantage of not receiving VARIVAX® and of reflecting adverse event experience in the study population before the vaccine had been used. The disadvantage of historical controls is that adverse events with incidence cycles having a periodicity of several years may have differing rates between two consecutive years. Contemporaneous controls would be people who were not vaccinated with VARIVAX® when others were vaccinated. There may be differences in adverse event incidence between those who were vaccinated and those who were not.

Use of the comparison period 31 - 60 days or 31 - 90 days before vaccination in the same individuals who were vaccinated avoids year-to-year fluctuations in adverse event incidence which may occur with the use of historical controls. However, for events whose occurrence would decrease the probability of vaccination within the ensuing 60 days, such as new onset seizures and deaths, the "before" comparison would make the vaccine appear less safe than it actually is. In contrast, events whose occurrence would tend to make vaccination within 60 days more likely because follow-up visits are common, such as certain respiratory illnesses or otitis media, would lead to increased opportunities to vaccinate. This would make the vaccine appear more safe than it actually is, because rates for such events would be artificially elevated in the control period.

The time period 91 - 120 days or 91 - 150 days after vaccination in the same individuals who were vaccinated reduces biases introduced by the "before" control period.

Rate comparisons were estimated using relative risks. The probability of the relative risk occurring by chance alone was calculated using exact p-values. Statistical significance was defined by a p value <0.05. Exact 95% confidence intervals for rate comparisons were also calculated. Since there were approximately 3,213 comparisons conducted, many statistically significant increases in relative risks are expected by chance alone. Consequently, AEs that had one or more rate comparisons that were statistically significantly elevated and had a reasonable possibility of a causal relationship with the vaccine were selected for compilation tables. These tables (Appendix VI) display all rate comparisons across age categories, type of medical service visit, and comparison period for the specific adverse event. Interpretation of the results of these comparisons was made with the recognition of the overall pattern of the comparisons, taking into account biological, clinical and statistical results. Review of medical records of relevant AEs was conducted to add additional information when interpreting rate comparisons.

RESULTS AND DISCUSSION:

The time period for including vaccinated individuals in the study was June 1, 1995 to December 31, 1996, and study follow-up time was closed on February 5, 1997. A total of 91,740 doses of VARIVAX® were administered in the study period to 89,753 children and adults.

Age Distribution of Vaccinees

The following table summarizes the number of vaccinated individuals and number of doses of vaccine stratified by age. There were more doses of vaccine administered than individuals vaccinated among vaccinees older than 13 years because 2 doses of VARIVAX® are recommended for adolescents and adults and 1 dose is recommended for children. Approximately one third of vaccinees were 12 to 23 months of age. The majority of vaccinees were in the 2 to 12 year age category. Approximately 6% of vaccinees were 13 years of age or older.

Table 1
Distribution of Vaccinations by Age

| <i>Age</i> | <i>Number of Individuals</i> | <i>(%)</i> | <i>Number of Vaccinations</i> | <i>(%)</i> |
|----------------|------------------------------|--------------|-------------------------------|--------------|
| 12 - 23 months | 34,665 | 38.6 | 34,665 | 37.8 |
| 2 - 12 years | 51,463 | 57.3 | 51,463 | 56.1 |
| 13 - 17 years | 1,891 | 2.1 | 2,961 | 3.2 |
| 18+ years | 1,734 | 1.9 | 2,651 | 2.9 |
| Total | 89,753 | 100.0 | 91,740 | 100.0 |

Concomitant Vaccination

The following tables (Tables 2 and 3) present the frequency distribution of vaccines given concomitantly with the varicella vaccine among the first 45,000 vaccinees in the study population. In vaccinees of all ages, 60% of doses of VARIVAX® were given alone, the remainder were given concomitantly with at least one other vaccine. Table 2 describes the vaccine combinations given concomitantly with VARIVAX®. Table 3 summarizes the data in Table 2 to describe the proportion of the study population of all ages who were vaccinated with individual vaccines. MMR was the vaccine most commonly used in combination with VARIVAX®.

Table 2
Concomitant Vaccine Combinations with VARIVAX®

| <i>Concomitant Vaccination (including VARIVAX® for all combinations)</i> | <i>No. of Vaccinees</i> | <i>Percent</i> |
|--|-----------------------------|----------------|
| VARIVAX® only | 27,485 | 60.8 |
| Hepatitis B | 2,546 | 5.6 |
| MMR | 2,442 | 5.4 |
| MMR +DTP | 2,117 | 4.7 |
| MMR +aPDT+OPV/IPV | 2,052 | 4.5 |
| MMR +DTP+OPV/IPV | 1,497 | 3.3 |
| aPDT+OPV/IPV | 1,067 | 2.4 |
| MMR +HbOC | 984 | 2.2 |
| Influenza | 588 | 1.3 |
| DTP | 568 | 1.3 |
| aPDT | 588 | 1.3 |
| DTP+OPV/IPV | 462 | 1.0 |
| MMR +Hepatitis B | 241 | 0.5 |
| MMR +aPDT+HepB+OPV/IPV | 230 | 0.5 |
| OPV/IPV | 178 | 0.4 |
| HbOC | 188 | 0.4 |
| MMR +DTP+HepB+OPV/IPV | 160 | 0.4 |
| MMR +aPDT+HbOC | 171 | 0.4 |
| MMR +aPDT+HbOC+OPV/IPV | 187 | 0.4 |
| MMR +aPDT | 123 | 0.3 |
| aPDT+HbOC | 121 | 0.3 |
| Other Combinations | 1,246 | 2.8 |
| TOTAL | 45,241* | 100.0 |

(*) NOT including 2 subjects incorrectly coded as having received a VARIVAX®

(**) OTHER category includes combinations of the following vaccines:

DT, DTP, HEP A, TD, Experimental whole cell DTP, I-TYPH, MENING, MUMPS, R-MUMP, RUBELL, RUBEOL, T, YELLOW, O-TYPH, PNEUMO

Forty-one percent of the 34,665 vaccinated children 12 to 23 months of age, and 82% of 51,463 children 2 to 12 years of age received VARIVAX® without concomitant MMR. The following table presents these numbers.

Table 3
Proportion Of Children Vaccinated with VARIVAX® Without Concomitant MMR

| Age | VARIVAX® without MMR | | VARIVAX® with MMR | Total |
|----------------|----------------------|--------|-------------------|--------|
| | % | N | | |
| 12 - 23 months | 41.3 | 14,328 | 20,337 | 34,665 |
| 2 - 12 years | 82.6 | 42,527 | 8,936 | 51,463 |

Acceptance Rate of VARIVAX®:

In order to evaluate varicella vaccine uptake rates and varicella vaccine refusal rates at KPMCP, rates of vaccination with MMR were compared with rates of vaccination with VARIVAX® in the recommended age range for both MMR and VARIVAX®, i.e., 12 to 18 months of age. Both vaccines are recommended to be given at the same visit and uptake of MMR is higher than 95%. Children aged 12 to 18 months who are vaccinated with MMR but not with VARIVAX® represent refusals. The acceptance rate of VARIVAX® by children aged 12 to 18 months who were vaccinated with MMR was 69% in September - November 1996 compared to 57% in September - November 1995. Assessment of the refusal rate for older children was not undertaken because of the added complication of determining susceptibility to varicella before VARIVAX® is offered. A chart review of refusals was not conducted because of logistical considerations.

The following table presents the acceptance rate of VARIVAX® in children aged 12 to 18 months who were vaccinated with MMR during the time period of September through November 1995 and the same period in 1996.

Table 4
Acceptance Rate of VARIVAX®

| Year | Number of children Receiving MMR N | Proportion Receiving VARIVAX® | |
|------|--|-------------------------------|-----|
| | | N | % |
| 1995 | 6,855 | 3,916 | 57% |
| 1996 | 7,493 | 5,150 | 69% |

Person-Time of Follow-up for Safety Evaluation:

Safety data for these vaccinees were collected from emergency room visits and outpatient visits that occurred within 30 days after vaccination and hospitalizations that occurred within 60 days after vaccination. Rates of adverse events in the 30 and 60 day periods immediately post-vaccination were compared with rates of adverse events in equivalent periods of time among randomly selected controls from the year before vaccine licensure, and with adverse event rates that occurred before vaccination (subjects are their own controls) as specified in the study protocol. The person-time of follow-up for adverse events in the risk period and two control periods is shown in Tables 5 and 6. The date selected for data cut-off (February 5, 1997) resulted in less total person-time of follow-up in the control period after vaccination than in the risk period or the control period before vaccination. Among vaccinees aged 13 years or older, there was more person-time of follow-up in the risk period than in the control period before vaccination because no control period before vaccination was used for second dose VARIVAX® vaccinations. There were approximately 7,500 person-years of follow-up for ER visits and outpatients visits and 14,800 person-years of follow-up for hospitalizations and deaths.

The following table presents person-years of follow-up for emergency room utilization and outpatient visits among 89,753 VARIVAX® recipients between June 1, 1995 and February 5, 1997 occurring within 30 days immediately after vaccination and in 30 day control periods before and after vaccination.

Table 5
Person-Years of Follow-up - 30 Days

| <i>Age Group</i> | <i>Risk Period</i> | <i>Control Period 1</i> | <i>Control Period 2</i> |
|------------------|---|---|---|
| | <i>Person-Years (0-30 days after vaccination)</i> | <i>Person-Years (91-120 days after vaccination)</i> | <i>Person-Years (31-60 days before vaccination)</i> |
| 12 - 23 months | 2,847 | 2,528 | 2,847 |
| 2 - 12 years | 4,227 | 3,984 | 4,227 |
| 13 - 17 years | 242 | 140 | 155 |
| 18+ years | 216 | 128 | 142 |
| Total | 7,533 | 6,780 | 7,379 |

The following table presents person-years of follow-up for hospitalizations and deaths among 89,753 VARIVAX® recipients between May 1, 1995 and February 5, 1997 occurring within 60 days immediately after vaccination and in 60 day control periods before and after vaccination.

Table 6
Person-Years of Follow-Up - 60 Days

| Age Group | Risk Period | Control Period 1 | Control Period 2 |
|------------------|---|---|---|
| | Person-Years <i>(0-60 days after vaccination)</i> | Person-Years <i>(91-150 days after vaccination)</i> | Person-Years <i>(31-90 days before vaccination)</i> |
| 12 -23 months | 5,564 | 4,902 | 5,695 |
| 2 - 12 years | 8,435 | 7,814 | 8,454 |
| 13 - 17 years | 431 | 269 | 311 |
| 18+ years | 387 | 249 | 285 |
| Total | 14,817 | 13,233 | 14,744 |

Review of Adverse Events that have appeared in VAERS Reports

No deaths were reported in the 60 days after vaccination among the 89,753 vaccine recipients. No hospitalizations or ER visits were reported for ataxia, encephalitis or anaphylaxis among the vaccine recipients. No outpatient visits for encephalitis or anaphylaxis were observed, and 4 outpatient visits for ataxia were observed. Two outpatient visits for Bell's Palsy, 14 cases of arthritis or arthralgia, and 4 cases of thrombocytopenia occurred among the study subjects in the risk periods following varicella vaccination. The following table presents the number of visits for diagnoses that appeared in the VAERS (vaccine adverse event reporting system) or the Merck spontaneous adverse event reports.

Table 7
Occurrence of Healthcare Visits (6/95-2/97) for Adverse Events that have appeared in VAERS or Merck Spontaneous Reports

| Adverse Event | Observed Number of Visits |
|--------------------------|---|
| Death | 0 |
| Anaphylaxis | 0 |
| Ataxia | 4 Outpatient (1 12-23 mo.s old, 3 2-12 yrs old) |
| Bell's palsy | 2 OP (2-12) |
| Encephalitis | 0 |
| Erythema multiforme | 0 |
| Herpes zoster | 0 |
| Stephen Johnson syndrome | 0 |
| Thrombocytopenia | 4 Outpatient (1 12-23 mo.s old, 3 2-12 yrs old) |

The cases of ataxia, Bell's palsy, and arthritis/arthralgia are described below:

1. Ataxia (Subject (b) (6))

A 110-month-old boy was vaccinated with VARIVAX® on (b) (6). The child had a history of cerebral palsy and brain tumor and was considered to be developmentally delayed. On (b) (6) the child required an emergency room visit as a follow-up to an incident of ataxia. The child was not hospitalized.

Severity: mild Outcome: Partial recovery Related to vaccine: Not related

2. Ataxia (Subject (b) (6))

A 78-month-old girl was vaccinated with VARIVAX® on (b) (6). The child had a history of cerebral degeneration with severe vision and hearing problems. On (b) (6), she presented at the emergency room with ataxia. The child was not hospitalized.

Severity: mild Outcome: Partial recovery Related to vaccine: Not related

3. Ataxia (Subject (b) (6))

A 30-month-old boy was vaccinated with VARIVAX® on (b) (6). The child was also vaccinated with DPT, OPV and MMR on the same date. On (b) (6) the child presented at the emergency room with an episode of ataxia. Inborn error of metabolism was suspected. The child had been recently hospitalized with an episode of acidosis. The child was not hospitalized.

Severity: mild Outcome: Partial recovery Related to vaccine: Not related

4. Ataxia (Subject (b) (6))

A 14-month-old boy was vaccinated with VARIVAX®, DPT and MMR on (b) (6) and developed a rash about 14 days later. The child was seen by a physician who concluded that the rash was probably due to the varicella vaccine. The child's father was concerned that the boy was having trouble walking and the possibility of acute cerebellar ataxia was raised. A careful neurologic examination revealed no other problem. The child was not hospitalized. He was seen in a physician's office about 11 days later (*i.e.*, about 25 days after vaccination) and had a normal neurological examination with no signs of ataxia. The physician considered the prior episode to have been a possible mild acute cerebellar ataxia.

Severity: mild Outcome: Full recovery Related to vaccine: Not related

5. Bell's Palsy (Subject (b) (6))

A 72-month-old girl was vaccinated with VARIVAX® on (b) (6). The child was also vaccinated with influenza vaccine on the same date. The child had symptoms of Bell's Palsy at the time of vaccination. On (b) (6) the child presented at the emergency room for Bell's Palsy.

Severity: mild Outcome: Full recovery Related to vaccine: Not related

6. Bell's Palsy (Subject (b) (6))

A 56-month-old girl was vaccinated with VARIVAX®, DPT, OPV, MMR and hepatitis-B vaccine (#2) on (b) (6) shortly after recovering from a viral illness and possible sinusitis, for which she received amoxicillin. Two days after the vaccination, she was diagnosed as having possible viral stomatitis, on the basis of a painful tongue lesion and cervical adenopathy. Two to three days later (*i.e.*, four to five days post-vaccination) she developed progressive left-sided facial weakness which was subsequently diagnosed as Bell's Palsy by a pediatric neurologist. The child was not hospitalized. At the last report, written 12 days post-vaccination, she had continued to have residual facial weakness associated with mild lower motor neuron seventh cranial nerve weakness on the left side.

Severity: mild Outcome: Partial recovery Related to vaccine: Possible

7. Arthralgia/arthritis 1- Merck Study ID (b) (6)

DOB (46 Year-Old Male)

Date of VARIVAX® First Injection:

Date of VARIVAX® Second Injection:

Event (Arthralgia/Arthritis): (b) (6) (21 days post- vaccination)

Relevant History:

On (b) (6) the patient was hospitalized for removal of a malignant melanoma on his leg. After the surgery, the patient had more than 20 follow-up visits. At one of these follow-up visits, the diagnosis of "Arthritis/Degenerative Joint Disease/Malignant Melanoma" was entered on the patient's medical record. No relationship to vaccine was noted. There was no evidence of serum sickness.

8. Arthralgia/arthritis 2 - Merck ID (b) (6)

DOB (70 Year-Old Male):

Date of VARIVAX® Injection:

Event (Arthralgia/Arthritis): (b) (6) (27 days post-vaccination)

Relevant History:

On (b) (6) the patient was seen in clinic and the diagnosis of "Radiculopathy-lumbar/Degenerative Joint Disease-Knee" was entered on his medical records. The patient had been vaccinated with VARIVAX® at that visit. The patient was seen again in the clinic 27 days later for arthritis/degenerative joint disease of the knee. No relationship to vaccine was indicated. There was no evidence of serum sickness.

9. Arthralgia/arthritis 3 - Merck ID (b) (6)

DOB (26 Year-Old Female):

Date of VARIVAX® Injection:

Event (Arthralgia/Arthritis)

(b) (6)

(3 days post-vaccination)

Relevant History:

In August 1995 the patient had surgery to repair destructive knee lesion/derangement of the medial meniscus. On (b) (6) the patient again had surgery for localized osteoarthritis/excision of semilunar cartilage in the left knee. Six days later the patient was vaccinated with VARIVAX® (b) (6). The patient returned to the clinic on (b) (6) three days after the vaccination complaining about her knee. The diagnosis entered on her medical records was "Degenerative Joint Disease/Meniscus Tear". The Patient had multiple visits for this condition preceding and post vaccination. No relationship to vaccine was indicated. There was no evidence of serum sickness.

10. Arthralgia/arthritis 4 - Merck ID (b) (6)

DOB (16 Year-Old Female):

Date of VARIVAX® Injection:

Event (Arthralgia/Non-Specific):

(b) (6)

(30 days post-vaccination)

Relevant History:

The patient had a history of musculo-skeletal pain, for which she were seen several times in 1995 and 1996. She was seen in clinic on (b) (6) for vaginitis. At that visit, she was vaccinated with VARIVAX®. Thirty days later, on (b) (6) the patient returned to the clinic and the diagnosis entered on her medical records was "Arthralgia, Non-Specific". The patient was later diagnosed as having a minor shoulder joint irregularity. No relationship to vaccine was indicated. There was no evidence of serum sickness.

11. Arthralgia/arthritis 5 - Merck ID (b) (6)

DOB (29 Year-Old Female):

Date of VARIVAX® First Injection:

Date of VARIVAX® Second Injection:

Event (Arthralgia/Arthritis):

(b) (6)

(b) (6) (3 days post-vaccination)

Relevant History:

The patient had a history of shoulder problems. She was seen in clinic on (b) (6) for shoulder sprain. She was seen again on (b) (6) for physical therapy of shoulder. On (b) (6) (b) (6) the patient was again seen in orthopedics for shoulder dislocation. On (b) (6) and (b) (6) the patient was vaccinated with VARIVAX®. Three days after the first vaccination, the patient was seen in orthopedics clinic and corticosteroids were injected into her shoulder. No relationship to vaccine was indicated. There was no evidence of serum sickness.

12. Arthralgia/arthritis 6 & 7 - Merck ID (b) (6)

DOB (16 Year-Old Female):

Date of VARIVAX® First Injection:

Date of VARIVAX® Second Injection:

Event (Arthralgia/Arthritis):

Event (Arthralgia/Arthritis):

(b) (6)

(b) (6) (14 days post-vaccination)

(b) (6) (16 days post-vaccination)

Relevant History:

The patient was seen on (b) (6) for musculo-skeletal pain. On (b) (6) the patient was vaccinated with VARIVAX® (first injection). Nine days later, on (b) (6) the patient returned to the clinic complaining of hip-joint pain. Five days later, the patient was seen in orthopedics clinic and the diagnosis was "Arthritis/Degenerative Joint Disease, Femur/Hip/Pelvis". On (b) (6) patient had a repeat visit to the orthopedic clinic for same condition. Six days later, on (b) (6) he was again seen in the orthopedic clinic and diagnosed as "Overuse Syndrome - Hips". No relationship to vaccine was indicated. There was no evidence of serum sickness.

13. Arthralgia/arthritis 8 - Merck ID (b) (6)

DOB (26 Year-Old Female):

Date of VARIVAX® First Injection:

Date of VARIVAX® Second Injection:

Event (Polyarthritis):

(b) (6)

(b) (6) (17 days post-vaccination)

Relevant History:

The patient was a 26 year-old female who at time of vaccination with VARIVAX® had a history of joint pain in the small joints of her hands and ankles for approximately one year prior to vaccination. The second vaccination was administered on (b) (6). She was seen in the clinic for a rheumatology consultation 17 days later. The patient was diagnosed as being mildly polyarthritic. Additionally, she had positive ANA serology and possibly some nephritis. The symptoms were suggestive of possible lupus. No relationship to vaccine was indicated. There was no evidence of serum sickness.

14. Arthralgia/arthritis 9 - Merck ID (b) (6)

DOB (4 Year-Old Male): (b) (6)
Date of VARIVAX® Injection: (b) (6)
Event (Arthralgia/Arthritis): (b) (6) (25 days post-vaccination)

Relevant History:

The child experienced a fall on April 3, 1996. He refused to walk, probably due to discomfort from a contusion or groin pull. The child was seen in clinic on (b) (6). At each visit the diagnosis was recorded as transient synovitis. The condition resolved April 22. The child began to walk again. The child was completely well at a visit on (b) (6). No relationship to vaccine was indicated. There was no evidence serum sickness.

15. Arthralgia/arthritis 10 - Merck ID (b) (6)

DOB (4 Year-Old Female): (b) (6)
Date of VARIVAX® Injection: (b) (6)
Event (Juvenile Rheumatoid Arthritis): (b) (6) (7 days post-vaccination)

Relevant History:

In August of 1995 it was suspected that this patient might have juvenile rheumatoid arthritis. She was seen in clinic on (b) (6) and in a pediatric orthopedic clinic on (b) (6). (b) (6) Additional clinic visits were made on (b) (6). She was diagnosed with "Juvenile Rheumatoid Arthritis". She was vaccinated with VARIVAX® on (b) (6). (b) (6) The vaccination was administered at a clinic visit at which she was seen for conjunctivitis and pharyngitis. Seven days later, on (b) (6) the patient was seen again for juvenile rheumatoid arthritis. The patient was seen on (b) (6) and (b) (6) of the following year (1996) for arthritis. No relationship to vaccine was indicated. There was no evidence of serum sickness.

16. Arthralgia/arthritis 11- Merck ID (b) (6)

DOB (3 Year-Old Female): (b) (6)
Date of VARIVAX® Injection: (b) (6)
Event (Arthralgia/Arthritis): (b) (6) (7 days post-vaccination)

Relevant History:

The patient was seen in clinic several times for multiple complaints of musculo-skeletal pain, knee swelling and arthritis. She was diagnosed as having juvenile rheumatoid arthritis in August 1995. She was seen 7 days after immunization with VARIVAX® in the physical therapy department (b) (6). The diagnosis was entered as "Rheumatoid Arthritis/Knee/Thigh Injury". No relationship to vaccine was indicated. There was no evidence of serum sickness.

17. Arthralgia/arthritis 12 - Merck ID (b) (6)

DOB (2 Year-Old Female):

Date of VARIVAX® Injection:

Event (Arthralgia/Arthritis):

(b) (6)

(7 days post-vaccination)

Relevant History:

Prior to vaccination with VARIVAX® the patient was seen more than 20 times in the clinic for juvenile rheumatoid arthritis. The patient was vaccinated on (b) (6) following a visit for arthritis. Seven days after the immunization on (b) (6) the patient was seen in the orthopedics clinic for juvenile rheumatoid arthritis. No relationship to vaccine was indicated. There was no evidence of serum sickness.

18. Arthralgia/arthritis 13 - Merck ID (b) (6)

DOB (3 Year-Old Female):

Date of VARIVAX® Injection:

Event (Arthralgia/Arthritis):

(b) (6)

(b) (6) (24 days post-vaccination)

Relevant History:

The patient was immunized with VARIVAX® during a routine physical. She was seen in clinic 21 days later for acute pharyngitis. On (b) (6) 24 days post-vaccination the patient was seen in the emergency room with an oral rash. There was no mention of joint pain or fever. Her medical record was erroneously coding with a diagnosis of "Arthralgia/Arthritis".

19. Arthralgia/arthritis 14 - Merck ID (b) (6)

DOB (2 Year-Old Male):

Date of VARIVAX® Injection:

Event (Arthralgia/Arthritis)

(b) (6)

(b) (6) (14 days post- vaccination)

Relevant History:

The patient's father was seen in the emergency room for his arthritis/bursitis. The father's diagnosis was erroneously entered on the son's medical record. The error has been corrected.

Rate comparisons indicating a statistically significant rate increase in adverse events after VARIVAX®

The complete line listing of all diagnosis categories, regardless of relationship to vaccine, for outpatient visits, ER visits, and hospitalizations is shown in Appendix II. The Appendix is organized into 4 age categories (II-1 = 12 to 23 months, II-2 = 2 to 12 years, II-3 = 13 to 17 years, II-4 = 18 or older). These categories were further divided into hospitalizations, ER visits and outpatient visits. Rates of the events in 30 or 60 day periods were calculated for both the risk and

control period. Rate comparisons between risk and control periods by means of the relative risk are outlined in the appendices. The opportunity for type I statistical error is very large in this analysis because of multiple comparisons. There were 365 rate comparisons for hospitalizations, 390 comparisons for emergency room visits, and 1,408 comparisons for outpatient visits. This resulted in 2,163 rate comparisons.

A list of adverse event comparisons that had statistically significantly elevated (*i.e.*, $p < 0.05$) relative risk estimates is presented in Appendix III. There were 68 rate comparisons that were significantly elevated out of a total of 2,163 calculated relative risks. Several of these adverse events were clearly not vaccine related because the onset of the adverse event preceded the date of vaccination, *i.e.*, congenital anomaly and congenital heart disease.

Adverse events that had one or more rate comparisons that were statistically significantly elevated and had a reasonable possibility of a causal relationship with the vaccine based on biological and clinical plausibility were selected for compilation tables.

Composite tables of rate comparisons for adverse events of interest or potential concern are found in Appendix VI, and are discussed below.

Rate comparisons which were statistically significantly elevated were confounded by concomitant vaccination with MMR and DTP, vaccines which are known to cause fever, febrile seizures, and possibly other adverse events. To control for concomitant MMR vaccination, rate comparisons which were significantly elevated were stratified on concomitant MMR use. Results were not adjusted or stratified on DTP use since this information was not available at the time of preparation of this report. However, some adverse reactions to DTP, such as fever and febrile seizures, are known to occur within 4 to 5 days following DTP vaccination. Analyses for adverse events that remained significantly elevated among recipients of VARIVAX® without concomitant MMR were further analyzed excluding the first 4 days of the risk period.

1. **Febrile Illness:** Febrile illness rate comparisons for hospitalizations (compared to the historical control period), emergency room visits (compared to the before and after control periods), and outpatient visits (compared to the after control period) were significantly elevated among vaccinated children 12 to 23 months of age. The following table on the following page summarizes rate comparisons of febrile illness which were significantly elevated ($P < 0.05$). Table VI-1 in Appendix VI summarizes all rate comparisons for febrile illness (including rate comparisons that were not significantly elevated).

Table 8. Significantly Elevated Rate Comparisons for Febrile Illness

| Age at Vaccination | Type of Visit | Comparison Period | Cases in Risk Period | No. of Vaccinees | Relative Risk Estimate | 95% CI | P-Value |
|-----------------------|---------------|-------------------|----------------------|------------------|------------------------|--------------------|---------|
| 12 - 23 Months | | | | | | | |
| All subjects | Hospital | Historical | 5 | 34,665 | ∞ | 1.23 - ∞ | 0.031 |
| Without MMR† | Hospital | Historical | 1 | 14,328 | ∞ | (0.13 - ∞) | 0.293 |
| All subjects | ER | Before | 52 | 34,665 | 2.00 | (1.26 - 3.25) | 0.003 |
| Without MMR | ER | Before | 18 | 14,328 | 1.50 | (0.72 - 3.20) | 0.281 |
| All subjects | ER | After | 52 | 34,665 | 2.57 | (1.52 - 4.49) | <0.001 |
| Without MMR | ER | After | 18 | 14,328 | 1.95 | (0.86 - 4.75) | 0.113 |
| All subjects | ER | Historical | 52 | 34,665 | 1.53 | (0.99 - 2.38) | 0.053 |
| Without MMR† | ER | Historical | 18 | 14,328 | 1.27 | (0.70 - 2.23) | 0.416 |
| All subjects | Out Pat | After | 179 | 34,665 | 1.75 | (1.37 - 2.25) | <0.001 |
| Without MMR | Out Pat | After | 66 | 14,328 | 1.48 | (1.00 - 2.21) | 0.049 |
| No MMR, 4-30 days | Out Pat | After | 59 | 14,328 | 1.47 | (0.99 - 2.22) | 0.057 |
| 2 - 12 Years | | | | | | | |
| All subjects | Out Pat | After | 72 | 51,463 | 1.56 | (1.08 - 2.28) | 0.018 |
| Without MMR | Out Pat | After | 68 | 42,527 | 1.59 | (1.08 - 2.37) | 0.018 |
| No MMR, 4-30 days | Out Pat | After | 62 | 42,527 | 1.62 | (1.09 - 2.43) | 0.016 |

† This relative risk may be biased in favor of VARIVAX®, since some of the historical controls may have received MMR during the historical control period.

Out of the 5 hospitalizations for febrile illness among children 12 to 23 months of age, only one child had received VARIVAX® without concomitant MMR vaccine. Among 1 year-old children vaccinated with VARIVAX® without concomitant MMR, the rate of hospitalizations for febrile illness within 60 days of vaccination was 0.42 per 1,000 person-years compared to 0.0 in the historical control period. An unbiased stratified analysis by MMR use compared to the historical controls was not feasible because of the difficulty in ascertaining MMR experience in the historical control period. However, the relative risk of hospitalizations for febrile illness after vaccination compared with the rate in the historical control period was indeterminate, or ∞ , because of the division by 0 (95% CI = 0.13- ∞ , exact p=0.293). This relative risk, however, may be biased in favor of the vaccine, since some of the historical controls may have received MMR during the historical control period. However, the stratification by concomitant MMR use indicates that VARIVAX® in the absence of MMR receipt is not associated with an increase in hospitalizations for febrile illness. The same results were found for emergency room visits for febrile illness, which were no longer significantly elevated after removing subjects with concomitant MMR.

However, the rate comparison of outpatient visits for febrile illness compared to the after control period remained significantly elevated among subjects vaccinated with VARIVAX® without concomitant MMR who were 12-23 months of age (RR = 1.48, p=0.049) and 2-12 years of age (RR = 1.59, p=0.018). Rate comparisons of outpatient visits for febrile illness

were not elevated compared to the before comparison period. Rates of outpatient visits for febrile illness were not adjusted for concomitant DTP use, a vaccine that is known to be associated with febrile reactions.

Most febrile reactions to DTP have been reported to occur within 5 days of vaccination (reference 1) while febrile reactions to MMR have been reported to peak at day 10 after vaccination (reference 2), which reflects the incubation period of wild-type measles virus. The incubation period for wild-type varicella disease ranges between 10 and 21 days but is usually between 14 and 17 days after infection (reference 3). Potential febrile reactions to the Oka/Merck strain varicella virus could thus be expected to occur mostly after day 10. To evaluate the impact of concomitant DTP vaccination, we eliminated the first 4 days of the risk period from the rate comparison and adjusted the person-time of the risk period to reflect the shorter follow-up period. Reduction of the risk period to 4 to 60 days following vaccination resulted in the rate comparison for outpatients compared to the after control period becoming marginally significant among 1 year-olds, but remaining significantly elevated in children 2-12 months of age. This suggests there may be a possible increase in outpatient visits for febrile illness among children vaccinated with VARIVAX®. However, frequency of these visits was low - 4.6 per 1,000 vaccinated children 12 to 23 months of age and 1.6 per 1,000 vaccinated children 2 to 12 years of age.

2. Febrile Seizures: All rate comparisons for febrile seizures are shown in Appendix VI (Table VI-2), and significantly elevated relative risks are shown in the table on the following page. Increased risks of febrile seizure were observed for hospitalizations in the 1 year age group compared to the after and historical control periods. Rate comparisons relative to the before control period for hospitalizations, as well as all rate comparisons for emergency room and outpatient visits were not elevated. There were 21 children who were hospitalized for febrile seizures in the 60 days following VARIVAX® receipt, and 19 had received MMR concomitant with VARIVAX®. After stratification on concomitant MMR use, the rate comparison for hospitalizations relative to the after comparison period was no longer significantly elevated among children who received VARIVAX® without concomitant MMR, (RR= 0.58, 95% CI = 0.07 - 3.92, p-value = 0.586). The rate of hospitalizations for febrile seizures in 12 to 23 month old children who received VARIVAX® without concomitant MMR was 0.85 per 1,000 person-years compared to 1.23 per 1,000 person-years among the historical controls. The relative risk was 0.70 (exact 95% CI = 0.10 - 3.1, exact p value = 0.700), although this estimate may be somewhat biased in favor of VARIVAX® because some of the historical controls may have received MMR in the historical control period. Hence, no rate comparisons appeared to be significantly elevated among subjects who were vaccinated with VARIVAX® without concomitant MMR vaccine.). It should be born in mind that concomitant vaccination with MMR could be a marker for vaccination with several other vaccines simultaneously.

Table 9. Significantly Elevated Rate Comparisons for Febrile Seizures

| Age at Vaccination | Type of Visit | Comparison Period | Cases in Risk Period | No. of Vaccinees | Relative Risk Estimate | 95% CI | P-Value |
|-----------------------|---------------|-------------------|----------------------|------------------|------------------------|---------------|---------|
| 12 - 23 Months | | | | | | | |
| All subjects | Hospital | After | 21 | 34,665 | 2.27 | (1.03 - 5.45) | 0.043 |
| Without MMR | Hospital | After | 2 | 14,328 | 0.58 | (0.07 - 3.92) | 0.586 |
| All subjects | Hospital | Historical | 21 | 34,665 | 3.02 | (1.32 - 7.63) | 0.008 |
| Without MMR† | Hospital | Historical | 2 | 14,328 | 0.70 | (0.10 - 3.1) | 0.700 |

† This relative risk may be biased in favor of VARIVAX®, since some of the historical controls may have received MMR during the historical control period.

3. **Afebrile Seizures:** None of the rate comparisons for afebrile seizures was statistically significantly elevated (Table VI-3, Appendix VI).

4. **Seizures, Type Unknown:** All rate comparisons for seizures of unknown type are shown in Table VI-4, Appendix VI, and significantly elevated relative risks are shown in the table below. The rate of outpatient visits for seizures of unspecified type was statistically significantly elevated relative to the after control period among children 2-12 years of age. However, among children vaccinated with VARIVAX® without concomitant MMR, the relative risk was 0.84 (p=0.629).

Table 10. Significantly Elevated Rate Comparisons for Seizures, Type Unknown

| Age at Vaccination | Type of Visit | Comparison Period | Cases in Risk Period | No. of Vaccinees | Relative Risk Estimate | 95% CI | P-Value |
|-----------------------|---------------|-------------------|----------------------|------------------|------------------------|---------------|---------|
| 12 - 23 Months | | | | | | | |
| All subjects | Hospital | After | 21 | 34,665 | 1.59 | (1.02 - 2.52) | 0.041 |
| Without MMR | Hospital | After | 2 | 14,328 | 0.84 | (0.42 - 1.69) | 0.629 |

† This relative risk may be biased in favor of VARIVAX®, since some of the historical controls may have received MMR during the historical control period.

5. **"Rule-Out Sepsis":** This category consists mainly of outpatient visits, generally prompted by fever, to rule out sepsis and which indicate no sepsis is present. The rate of outpatient visits for "rule-out sepsis" was statistically significantly elevated in the risk period compared to "before" and "after" control periods for both 1 year-olds and 2 to 12 year-olds (Table VI-5, Appendix VI). Such visits are typically prompted by fever and the physician is faced with determining whether the fever is associated with significant bacteremia. Similar findings have been observed following injection with MMR alone in other studies where an increased risk of negative "rule out sepsis" evaluations prompted by fever was observed. Among children vaccinated with VARIVAX® without concomitant MMR, the outpatient visits for "rule-out sepsis" were no longer statistically significantly elevated compared to the before comparison

period among 1 year-olds, but remained statistically significantly elevated for children 2-12 years of age and for 1 year-old children when compared to the after control period. Exclusion of the first 4 days of the risk period to reduce the number of febrile reactions related to DTP administration did not substantially influence the rate comparisons. The frequency of visits to rule out sepsis was low - 0.66 per 1,000 vaccinated children 1 year of age, and 0.23 per 1,000 vaccinated children 2-12 years of age. These results suggest that vaccination with the varicella vaccine may be associated with fever leading to "rule-out sepsis" outpatient visits in less than 0.1% of vaccine recipients 1 year of age and less than 0.5% of vaccine recipients 2-12 years of age. The following table presents significantly elevated rate comparisons for "rule-out sepsis" outpatient visits

Table 11. Significantly Elevated Rate Comparisons for "Rule-Out Sepsis"

| Age at Vaccination | Type of Visit | Comparison Period | Cases in Risk Period | No. of Vaccinees | Relative Risk Estimate | 95% CI | P-Value |
|-----------------------|---------------|-------------------|----------------------|------------------|------------------------|----------------|---------|
| 12 - 23 Months | | | | | | | |
| All subjects | Outpat | Before | 23 | 34,665 | 3.40 | (1.50 - 8.53) | 0.002 |
| Without MMR | Outpat | Before | 11 | 14,328 | 2.28 | (0.80 - 7.27) | 0.126 |
| No MMR, 4-30 days | Outpat | Before | 11 | 14,328 | 2.54 | (0.89 - 8.11) | 0.081 |
| All subjects | Outpat | After | 23 | 34,665 | 3.52 | (1.49 - 9.47) | 0.003 |
| Without MMR | Outpat | After | 11 | 14,328 | 4.93 | (1.23 - 32.74) | 0.021 |
| No MMR, 4-30 days | Outpat | After | 11 | 14,328 | 5.50 | (1.37 - 36.51) | 0.013 |
| 2 - 12 Years | | | | | | | |
| All subjects | Outpat | Before | 12 | 51,463 | 6.21 | (1.57 - 40.88) | 0.006 |
| Without MMR | Outpat | Before | 11 | 42,527 | 5.69 | (1.41 - 37.79) | 0.011 |
| No MMR, 4-30 days | Outpat | Before | 10 | 42,527 | 5.77 | (1.41-38.71) | 0.012 |
| All subjects | Outpat | After | 12 | 51,463 | 5.85 | (1.48 - 38.52) | 0.008 |
| Without MMR | Outpat | After | 11 | 42,527 | 10.32 | (1.76 - 224.1) | 0.005 |
| No MMR, 4-30 days | Outpat | After | 10 | 42,527 | 10.46 | (1.76 - 229.1) | 0.005 |

6. Varicella: All rate comparisons for varicella are shown in Appendix VI (Table VI-6), and significantly elevated relative risks are shown in the table below. Elevated rate comparisons relative to the before comparison group are expected since children who visited a healthcare facility because of varicella disease in the before comparison period are no longer eligible for vaccination. Similarly, elevated rate comparisons relative to the after control period are to be expected since the vaccine is not expected to be as effective for protection against varicella exposures that occur before or only a few days after vaccination as it is for exposures occurring more than sixty days after vaccination.

When compared to the before comparison period, emergency room visits for varicella were statistically significantly elevated in the 2 to 12 year age group. Such elevated rate comparisons were to be expected, especially since it is unclear whether the cause of the varicella was wild-type of vaccine varicella virus. There were 6 emergency room visits for

varicella within 30 days after vaccination among the 51,463 vaccinated children 2-12 years of age, a rate of 0.17 per 1,000 vaccine recipients in this age category.

The rate of outpatient visits for varicella among both 1 year-old infants and children 2-12 years of age relative to the before and after control period were statistically significantly elevated. These estimates were not affected substantially by stratification on concomitant MMR administration, or by excluding the first 4 days of the risk period. The occurrence of outpatient visits for varicella may result from varicella-like rash (which occurs in 3 to 4% of children postvaccination according to the package circular), wild-type varicella disease in the 30 days following vaccination, or varicella disease. Outpatient visits for varicella were rare - 0.63 per 1,000 vaccine recipients among 1 year-olds and 0.68 per 1,000 children 2-12 years of age.

Table 12. Significantly Elevated Rate Comparisons for Varicella

| Age at Vaccination | Type of Visit | Comparison Period | Cases in Risk Period | No. of Vaccinees | Relative Risk Estimate | 95% CI | P-Value |
|-----------------------|---------------|-------------------|----------------------|------------------|------------------------|----------------|---------|
| 12 - 23 Months | | | | | | | |
| All subjects | Out Pat | Before | 22 | 34,665 | 3.79 | (1.59 - 10.24) | 0.002 |
| Without MMR | Out Pat | Before | 11 | 14,328 | 2.84 | (0.93 - 10.33) | 0.067 |
| All subjects | Out Pat | After | 22 | 34,665 | 10.11 | (2.77 - 63.71) | <0.001 |
| Without MMR | Out Pat | After | 11 | 14,328 | 4.93 | (1.23 - 32.74) | 0.021 |
| No MMR, 4-30 days | Out Pat | After | 10 | 14,328 | 5.00 | (1.22 - 33.53) | 0.023 |
| 2 - 12 Years | | | | | | | |
| All subjects | ER | Before | 6 | 51,463 | ∞ | (1.54 - ∞) | 0.016 |
| Without MMR | ER | Before | 5 | 42,527 | ∞ | (1.22 - ∞) | 0.031 |
| All subjects | Out Pat | Before | 35 | 51,463 | 12.07 | (4.14 - 49.49) | <0.001 |
| Without MMR | Out Pat | Before | 29 | 42,527 | 10.00 | (3.38 - 41.35) | <0.001 |
| All subjects | Out Pat | After | 35 | 51,463 | 8.53 | (3.28 - 28.17) | <0.001 |
| Without MMR | Out Pat | After | 29 | 42,527 | 13.60 | (3.82 - 84.65) | <0.001 |

7. **Rash:** Appendix VI, Table VI-7. The rate of emergency room and outpatient visits for rash were statistically significantly elevated relative to the after control periods among 1 year-old infants. However, among 1 year-old infants who had received VARIVAX® without MMR[®], the relative risks were no longer statistically significantly elevated (RR=0.87 and 0.83 respectively).

8. **Allergic Reactions and Hives:** Among 1 year-old children who received VARIVAX®, the rate of outpatient visits for allergic reactions including hives (Table VI -8) was significantly elevated relative to the after (RR=1.27, p=0.036) but not the before comparison period (RR=1.03). However, among children who had received VARIVAX® without concomitant MMR, the relative risk was no longer statistically significantly elevated (RR=0.85, p=0.378). Similarly, the rate of outpatient visits for allergic rhinitis among 1 year-old children (Table VI-9) was statistically significantly elevated relative to the before comparison period (RR=3.72,

$p=0.005$) but not the after control period ($RR=1.27$, $p=0.516$). However, among infants who had received VARIVAX® without concomitant MMR, the relative risk compared to the before comparison period was no longer statistically significantly elevated ($RR=3.10$, $p=0.082$). It should be born in mind that concomitant vaccination with MMR could be a marker for vaccination with several other vaccines.

The rate of emergency room visits for hives was elevated among children 2 to 12 years of age compared to the after control period ($RR=3.46$, $p=0.045$), but not the before control period ($RR=1.83$, 95% CI=0.68-5.36, $p=0.238$) (Table VI-10). Among children who had received VARIVAX® without concomitant MMR, the relative risk was borderline statistically significant ($RR=3.33$, 95% CI = 0.98 - 14.84, $p=0.053$). In contrast, the rate of emergency room visits for allergic reaction not including angioedema was statistically significantly lower than the rate in the before comparison period among 2-12 year-old children ($RR=0.14$, 95% CI = 0.01 - 0.92, $p=0.039$).

The following table presents significantly elevated rate comparisons for allergic reactions. The compilation tables containing all rate comparisons for these adverse events are shown in Tables VI-8 to VI-10 in Appendix VI.

Table 13. Significantly Elevated Rate Comparisons for Allergic Reactions

| Age at Vaccination | Type of Visit | Comparison Period | Cases in Risk Period | No. of Vaccinees | Relative Risk Estimate | 95% CI | P-Value |
|--|---------------|-------------------|----------------------|------------------|------------------------|----------------|---------|
| 12 - 23 Months | | | | | | | |
| Allergic Reaction including Hives | | | | | | | |
| All subjects | Outpat | After | 180 | 34,665 | 1.27 | (1.02 - 1.60) | 0.036 |
| Without MMR | Outpat | After | 62 | 14,328 | 0.85 | (0.60 - 1.21) | 0.378 |
| Allergic Rhinitis | | | | | | | |
| All subjects | Outpat | Before | 18 | 34,665 | 3.72 | (1.44 - 11.24) | 0.005 |
| Without MMR | Outpat | Before | 9 | 14,328 | 3.10 | (0.88 - 14.21) | 0.082 |
| 2 - 12 years | | | | | | | |
| Hives | | | | | | | |
| All subjects | ER | After | 11 | 51,463 | 3.46 | (1.02 - 15.42) | 0.045 |
| Without MMR | ER | After | 11 | 42,527 | 3.33 | (0.98 - 14.84) | 0.053 |

9. Epilepsy: Rate comparisons of emergency room visits for epilepsy among 1 year-olds in comparison with before and historical control periods were significantly elevated, while the relative risk estimate for the after control period as well as outpatient visits were not significantly elevated. Among children 12 to 23 months of age who were vaccinated with VARIVAX® without concomitant MMR®, the relative risk for emergency room visits remained elevated, but no longer significantly elevated ($RR= \infty$, 95% CI = 0.90 - ∞ , $p=0.063$). Elevated comparisons with the before control period are consistent with delay in vaccination of children with active epilepsy, or delay in vaccination to evaluate whether the child has an evolving neurological disorder. Elevated comparisons with the after control periods and historical control periods are consistent

with increased opportunity to vaccinate a child undergoing frequent care for epilepsy. Because the automated databases do not specifically describe the type of visit (e.g. follow-up visits or case management) the principal investigators reviewed the charts of all 24 cases of outpatient visits for epilepsy among 1 year-olds. All were either case management, follow-up visits, or neurology consultations. None of the visits were the first care for acute episodes of epilepsy. Four out of the 6 children who had visits to an emergency room for epilepsy in the 30 days following varicella vaccination had a diagnosis of seizures or epilepsy prior to VARIVAX® as identified by prior healthcare facility visits for these diagnoses.

The following table presents significantly elevated rate comparisons for epilepsy. The compilation tables containing all rate comparisons for these adverse events are shown in Table VI-11 in Appendix VI.

Table 14. Significantly Elevated Rate Comparisons for Epilepsy

| Age at Vaccination | Type of Visit | Comparison Period | Cases in Risk Period | No. of Vaccinees | Relative Risk Estimate | 95% CI | P-Value |
|-----------------------|---------------|-------------------|----------------------|------------------|------------------------|--------------------|---------|
| 12 - 23 Months | | | | | | | |
| All subjects | ER | Before | 6 | 34,665 | ∞ | (1.54 - ∞) | 0.016 |
| Without MMR | ER | Before | 4 | 14,328 | ∞ | (0.90 - ∞) | 0.063 |
| All subjects | ER | Historical | 6 | 34,665 | ∞ | (1.54 - ∞) | 0.016 |
| Without MMR† | ER | Historical | 4 | 14,328 | ∞ | (0.90 - ∞) | 0.063 |

† This relative risk may be biased in favor of VARIVAX®, since some of the historical controls may have received MMR during the historical control period.

10. Soft Tissue Disease: Table VI -12. The rate of outpatient visits for soft tissue disease was statistically significantly elevated relative to the before control period among 1 year-old infants (RR=7.24, 95% CI = (1.12 - 164.4, p-value=0.035). After stratification on MMR use, this rate comparison was no longer statistically significantly elevated (RR= ∞ , 95% CI = (0.30 - ∞ , p-value 0.242).

12. Elective Procedures: Among the 1 year of age and 2-12 years of age comparison groups, higher rates of elective procedures in the hospital within 60 days following vaccination are observed. Most elective procedures are scheduled during routine care visits, where there is the opportunity for vaccination. Therefore, we would expect a higher rate of routine care visits and immunizations to precede hospital visits for elective procedures. The same line of reasoning applies to the comparison of hospitalization rates with historical controls.

13. Acute Gastroenteritis: The rate of acute gastroenteritis among one year-olds was significantly increased following vaccination compared to historical controls for both hospitalizations and emergency room visits. The principal investigators believe this result is due to year to year variation in the seasonality of acute gastroenteritis. Among one year-olds, there was a reported increased risk of emergency room visits for acute

gastroenteritis when compared with the 91 -120 period after vaccination, but this does not appear in the 31-60 day before vaccination control interval. This may be due to seasonal variation within the study time period.

14. Alopecia: The rate comparison of outpatient visits for alopecia among children 2 to 12 years of age was elevated relative to the after control period (Table 15), and borderline significantly elevated for the before comparison period (RR=4.14, 95% CI = 0.96 - 28.52, p-value = 0.058). However, the rate comparisons for other age groups were not significantly elevated, and there were no hospitalizations or emergency visits for this diagnostic category (Table VI-13, Appendix VI). Among children 2 to 12 years of age vaccinated with VARIVAX® without concomitant MMR, the relative risk compared to the after control period remained significantly elevated. After exclusion of the first 4 days after vaccination to reduce potential confounding by DTP, the relative risk was elevated but no longer statistically significant (p=0.062). There were a total of 8 cases per 51,463 vaccine recipients (0.016%) of outpatient visits for alopecia among children 2 to 12 years of age, and the small number of visits is indicated in the wide 95% confidence intervals. Further evaluation of the impact of potential confounding by concomitant vaccination with recombinant hepatitis B vaccine, DTP (since the potential association with DTP may not occur in the first 4 days after vaccination for alopecia), and concomitant medications (e.g. heparin, ethionamide, cytotoxic medications, and some hormonal therapies, reference 4) needs to be undertaken.

Table 15. Significantly Elevated Rate Comparisons for Alopecia

| Age at Vaccination | Type of Visit | Comparison Period | Cases in Risk Period | No. of Vaccinees | Relative Risk Estimate | 95% CI | P-Value |
|---------------------|---------------|-------------------|----------------------|------------------|------------------------|-----------------|---------|
| 2 - 12 Years | | | | | | | |
| All subjects | Out Pat | After | 8 | 51,463 | 7.80 | (1.25 - 174.47) | 0.024 |
| Without MMR | Out Pat | After | 7 | 42,527 | 6.57 | (1.02 - 149.14) | 0.048 |
| No MMR, 4-30 days | Out Pat | After | 6 | 42,527 | 6.28 | (0.93-145.43) | 0.062 |

15. Arthritis/Arthralgia: Visits of arthritis/arthralgia were evaluated by medical chart review to assess whether any cases of serum sickness could be identified in the risk periods following varicella vaccination. There were 14 outpatient visits for arthritis or arthralgia in the risk periods among the study population. There were no hospitalizations or emergency room visits for arthritis or arthralgia. The medical charts of these cases were reviewed to identify possible cases of serum sickness. There were no cases of serum sickness and none of the cases were related to the vaccine in the opinion of the principal investigators (Dr. Shinefield). An outline of these cases is given on page 19 of this report.

CONCLUSIONS:

A total of 91,740 doses of VARIVAX® were administered in the study period to 89,753 children, adolescents, and adults (34,665 children 12 to 23 months of age). The report of the Principal Investigators is attached in Appendix I. No deaths were reported in the 60 days after vaccination among the 89,753 vaccine recipients. No hospitalizations, ER visits, or outpatient visits were

observed for encephalitis or anaphylaxis among the vaccine recipients. Four children had outpatient visits for mild ataxia in the risk period, which were judged not related to the vaccine by the principal investigators (Drs. Black and Shinefield). Two children had outpatient visits for mild cases of Bell's Palsy. One of these cases, in a 56-month-old girl vaccinated with VARIVAX®, DPT, OPV, MMR and hepatitis-B vaccine (#2) concomitantly, was considered possibly related to vaccination.

Rate comparisons were performed for three control periods: (1) Historical control children who were randomly selected from the year before vaccine licensure and were vaccinated with routine pediatric vaccines excluding VARIVAX® (historical controls), (2) the same vaccinees in a specified time window ending 31 days prior to the date of vaccination ("before" control period), and (3) the same vaccinees in a specified time window beginning 91 days after vaccination ("after" control period).

Overall, a review of all the significantly elevated relative risks identified by this study suggested a favorable safety profile of the vaccine (Appendix III). Rate comparisons that were significantly elevated and had a feasible relationship to the vaccine were scrutinized in more depth, as is reported below.

Febrile illness rate comparisons for hospitalizations (compared to the historical control period), emergency room visits (compared to the before and after control periods), and outpatient visits (compared to the after control period) were significantly elevated among vaccinated children 12 to 23 months of age (Table 8). Out of the 5 hospitalizations for febrile illness among children 12 to 23 months of age, only one child had received VARIVAX® without concomitant MMR vaccine. The rate of hospitalizations for febrile illness within 60 days of vaccination among vaccine recipients without concomitant MMR was 0.42 per 1,000 person-years compared to 0.0 in the historical control period. The stratification by concomitant MMR use suggests that VARIVAX® in the absence of MMR receipt is not associated with an increase in hospitalizations for febrile illness. Similar results were found for emergency room visits for febrile illness, which were no longer significantly elevated after removing subjects with concomitant MMR.

However, the rate comparison of outpatient visits for febrile illness compared to the after control period remained significantly elevated among subjects vaccinated with VARIVAX® without concomitant MMR. Exclusion of the first 4 days of follow-up from the risk period, when febrile reactions to DTP are most frequent, resulted in a borderline significantly elevated risk for outpatient visits for 1 year-olds, while for 2-12 year-olds the relative risk remained significantly elevated. This suggests the vaccine may be associated with an increase in outpatient visits for febrile illness (0.46% vaccine recipients 1 year of age and 0.14% of vaccine recipients 2-12 years of age).

Relative risk comparisons of hospitalizations for febrile seizures compared to after and historical control periods were elevated among children 12 to 23 months of age. Rate comparisons for emergency room visits and outpatient visits were not elevated. There were 21 children who were hospitalized for febrile seizures in the 60 days following VARIVAX® receipt, and 19 had received MMR concomitant with VARIVAX®. After stratification on concomitant MMR[®] use, the rate comparison for hospitalizations relative to the after comparison period was no longer significantly elevated among children who received VARIVAX® without concomitant MMR (RR= 0.58, 95% CI = 0.07 - 3.92, p-value = 0.586). The rate of hospitalizations for febrile seizures in 12 to 23

month old children who received VARIVAX® without concomitant MMR was 0.85 per 1,000 person-years compared to 1.23 per 1,000 person-years among the historical controls. Hence, no rate comparisons appeared to be significantly elevated among subjects who were vaccinated with VARIVAX® without concomitant MMR vaccine.). Concomitant vaccination with MMR could be a marker for vaccination with several other vaccines simultaneous to MMR.

The rate of outpatient visits for "rule-out sepsis" was statistically significantly elevated for both 1 year-olds and 2 to 12 year-olds (Table 11). Such visits are generally prompted by fever without a source to rule out sepsis. Among children vaccinated with VARIVAX® without concomitant MMR, the relative risks were no longer statistically significantly elevated for outpatient visits among 1 year-olds, but remained statistically significantly elevated for children 2-12 years of age. Exclusion of the first 4 days of the risk period to reduce the number of febrile reactions related to DTP administration did not substantially influence the rate comparisons. These results suggest that vaccination with the varicella vaccine may be associated with fever leading to "rule-out sepsis" outpatient visits in less than 0.1% of vaccine recipients 1 year of age and less than 0.5% of vaccine recipients 2-12 years of age.

The rate of emergency room and outpatient visits for rash were statistically significantly elevated relative to the after control periods among 1 year-old infants. However, among 1 year-old infants who had received VARIVAX® without MMR, the relative risks were no longer statistically significantly elevated (RR=0.87, p=0.844 and 0.83, p=0.052 respectively).

Rate comparisons for allergic reactions were not significantly elevated in subjects who were vaccinated with VARIVAX® without concomitant MMR (Table 13).

Rate comparisons of emergency room visits for epilepsy among 1 year-olds in comparison with before and historical control periods were significantly elevated, while the relative risk estimate for the after control period as well as hospitalizations and outpatient visits were not significantly elevated. Among children 12 to 23 months of age who were vaccinated with VARIVAX® without concomitant MMR, the relative risk for emergency room visits remained elevated, but no longer significantly elevated (RR= ∞ , 95% CI = 0.90 - ∞ , p=0.063). Elevated comparisons with the before control period are consistent with delay in vaccination of children with active epilepsy, or delay in vaccination to evaluate whether the child has an evolving neurological disorder. Elevated comparisons with the after control periods and historical control periods are consistent with increased opportunity to vaccinate a child undergoing frequent care for epilepsy. Because the automated databases do not specifically describe the type of visit (e.g. follow-up visits or case management) the principal investigators reviewed the charts of all 24 cases of outpatient visits for epilepsy among 1 year-olds. All were either case management, follow-up visits, or neurology consultations. None of the visits were the first care for acute episodes of epilepsy. Four out of the 6 children who had visits to an emergency room for epilepsy in the 30 days following varicella vaccination had a diagnosis of seizures or epilepsy prior to VARIVAX® as identified by prior healthcare facility visits for these diagnoses.

The rate comparison of outpatient visits for alopecia among children 2 to 12 years of age was elevated relative to the after control period. After removal of children with concomitant MMR

from the analysis, the relative risk compared to the after control period remained significantly elevated. After exclusion of the first 4 days after vaccination to reduce potential confounding by DTP, the relative risk was elevated but no longer statistically significant ($p=0.062$). There were a total of 8 cases per 51,463 vaccine recipients (0.016%) of outpatient visits for alopecia among children 2 to 12 years of age, and the small number of visits is indicated in the wide 95% confidence intervals. Further evaluation of the impact of potential confounding by concomitant vaccination with recombinant hepatitis B vaccine, DTP, and concomitant medications needs to be undertaken. There were no spontaneous reports to Merck of alopecia following VARIVAX® as of June 25, 1997 among the over 3,000 spontaneous reports and 6 million doses of VARIVAX® distributed.

A medical chart review of all visits in the 30 or 60 day periods following vaccination for arthritis or arthralgia identified 14 cases of arthritis or arthralgia from outpatient visits. None were related to the vaccine and the principal investigators suggested there were no cases of serum sickness identified. None of the rate comparisons for arthritis or arthralgia were significantly elevated.

The data suggest that no serious adverse events associated with VARIVAX® vaccination were identified among the 89,753 vaccinees in this study. These data confirm the overall favorable safety profile of VARIVAX®.

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1. Waight PA, Pollock TM, Miller E, Coleman EM. Pyrexia after diphtheria/tetanus/pertussis and diphtheria/tetanus vaccines. *Arch Dis Child* 1983; 58(11): 921-23.
2. Peltola H, Heinonen OP. Frequency of true adverse reactions to measles-mumps-rubella vaccine. *Lancet* 1986; 4:939-942.
3. Harrison's Principles of Internal Medicine, 13th Edition. Isselbacher KJ et al. (editors). Chapter 144 (Varicella-Zoster Virus Infections). 1994; 787. McGraw Hill Publishers.
4. Harrison's Principles of Internal Medicine, 9th Edition. Isselbacher KJ et al. (editors). Chapter 171-1 (Clinical Manifestations of Adverse Reactions to Drugs). 1980; page 386. McGraw Hill Publishers.

PUBLICATIONS:

1. Abstract presented at Society for Pediatric Research, May 10 -11, 1996, Washington, DC:

SAFETY OF VARICELLA VACCINE: RESULTS OF POST-MARKETING SURVEILLANCE IN 32,947 RECIPIENTS OF VARIVAX® (MSD).

S. Black, H. Shinefield, P. Ray, N. Lewis, J. Hansen at Kaiser Permanente Pediatric Vaccine Study Center (KPVSC), Oakland, CA and P. Coplan, H. Guess, and R.G. Sharrar at Merck Research Laboratories, West Point, PA.

2. Oral presentations of the safety of the varicella vaccine as assessed by post-marketing studies were presented by Paul Coplan to the FDA (January 1997), the Advisory Committee on Immunization Practices at the CDC (October 1996), the American Public Health Association Meeting (November 1996, New York City), the Society for Epidemiological Research meeting (June 1997, Edmonton, Canada), the CDC National Immunization Program in Atlanta, the National Immunization Program Annual Meeting (May 1997, Detroit, MI), and the National Consultants' Meeting for VARIVAX® organized by Merck Vaccine Division (November 1996, Palm Springs, FL).
3. Abstract presented to 36th Interscience Conference on Antimicrobial Agents and Chemotherapy, September 15-18, New Orleans.

POST-MARKETING SURVEILLANCE IN 44,369 RECIPIENTS OF VARIVAX® ((MSD).
S. Black, H. Shinefield, P. Ray, N. Lewis, at Kaiser Permanente Pediatric Vaccine Study Center (KPVSC), Oakland, CA and P. Coplan, H. Guess, and R.G. Sharrar at Merck Research Laboratories, West Point, PA.

POST-MARKETING STUDY REPORT

VARIVAX®

Post-Marketing Evaluation of Short-Term Safety of Varicella Vaccine

PROTECTION OF HUMAN SUBJECTS:

This study was conducted in conformance with applicable US requirements regarding ethical committee review, informed consent, and other statutes or regulations regarding the protection of the rights and welfare of human subjects participating in biomedical research.

PRODUCT: Varicella Virus Vaccine, [Live Oka/Merck (VARIVAX®)]

PROTOCOL TITLE: Post-Marketing Evaluation of Short-Term Safety of Varicella Vaccine

PROTOCOL NUMBER: #035-00

INVESTIGATOR(S): Steve Black, M.D. (Primary), Henry Shinefield, M.D. (Secondary)

CLINICAL PHASE: Phase IV (Post-Marketing)

DURATION: 2 years

OBJECTIVES:

1. To describe the occurrence of adverse events in at least 25,000 children aged 12 to 23 months in a period (30 days for pediatric outpatient visits and emergency room visits, 60 days for hospitalizations and mortality) immediately after vaccination with VARIVAX®.
2. To compare the rates of specific adverse events in the period post-vaccination with the adverse events rates in three comparison periods of the same time duration:
 - Historical controls randomly selected from the previous year, *i.e.*, before vaccine licensure, using the same calendar days one year prior as the comparison period.
 - The time period 31 - 60 or 31 - 90 days before vaccination in the same individuals who were vaccinated.
 - The time period 91 - 120 or 91 - 150 days after vaccination in the same individuals who were vaccinated.

STUDY STATUS: Completed.

The study was closed on February 5, 1997. A total of 91,740 doses of VARIVAX® were administered in the study period to 89,753 children and adults (34,665 children aged 12 to 23 months, 51,463 individuals 2 to 12 years of age, and 3,625 individuals older than 12 years). This meets Merck's commitment to CBER to study the occurrence of adverse events in at least 25,000 children 12 to 23 months of age.

The previous annual report to CBER provided a detailed analysis describing the occurrence of adverse events in the 30 or 60 days after vaccination and comparing the rates of specific adverse events in the period post-vaccination with the adverse events rates in three comparison periods.

A summary of the findings is presented in this paragraph. No deaths were reported in the 60 days after vaccination among the 89,753 vaccine recipients. No hospitalizations, ER visits, or outpatient visits were observed for encephalitis or anaphylaxis among the vaccine recipients. Overall, a review of all the significantly elevated relative risks identified by this study suggested a

favorable safety profile of the vaccine. Rate comparisons that were significantly elevated and had a feasible relationship to the vaccine were scrutinized in more depth, as is reported below. After adjustment for concomitant vaccination with other routine pediatric vaccines, there appeared to be an increase in outpatient visits for febrile illness (0.46% vaccine recipients 1 year of age and 0.14% of vaccine recipients 2-12 years of age). In addition, there was a suggestion that vaccination with the varicella vaccine may be associated with fever leading to "rule-out sepsis" outpatient visits in less than 0.1% of vaccine recipients 1 year of age and less than 0.5% of vaccine recipients 2-12 years of age. The data suggest that no serious adverse events associated with VARIVAX® vaccination were identified among the 89,753 children, adolescents and adults in this study. These data confirm the overall favorable safety profile of VARIVAX®.

However, the rate comparison of outpatient visits for alopecia among children 2 to 12 years of age was elevated relative to the after control period. There were a total of 8 cases per 51,463 vaccine recipients (0.016%) of outpatient visits for alopecia among children 2 to 12 years of age. The previous annual report stated that further evaluation of the elevated rate of alopecia needed to be undertaken. This report describes the findings of the further evaluation.

Alopecia: The rate comparison of outpatient visits for alopecia among children 2 to 12 years of age was elevated relative to the after control period (Table 1), and borderline significantly elevated for the before comparison period (RR=4.14, 95% CI = 0.96 - 28.52, p-value = 0.058). However, the rate comparisons for other age groups were not significantly elevated, and there were no hospitalizations or emergency visits for this diagnostic category. Among children 2 to 12 years of age vaccinated with VARIVAX® without concomitant MMR, the relative risk compared to the after control period remained significantly elevated.

Table 1. Significantly Elevated Rate Comparisons for Alopecia

| Age at Vaccination | Type of Visit | Comparison Period | Cases in Risk Period | No. of Vaccinees | Relative Risk | 95% CI | P-Value |
|-----------------------|----------------------|-------------------|----------------------|------------------|---------------|-----------------|---------|
| 2 - 12 Years | | | | | | | |
| All subjects | Out Pat [†] | After | 8 | 51,463 | 7.80 | (1.25 - 174.47) | 0.024 |
| Without MMR | Out Pat | After | 7 | 42,527 | 6.57 | (1.02 - 149.14) | 0.048 |
| All subjects | Out Pat | Before | 8 | 51,463 | 4.14 | (0.96 - 28.52) | 0.058 |
| 12 - 23 Months | | | | | | | |
| All subjects | Out Pat | After | | 34,665 | ∞ | (0.05 - ∞) | 0.521 |
| All subjects | Out Pat | Before | | 34,665 | 1.03 | (0.03 - 40.34) | 0.983 |

† Outpatient Visits

There were a total of 8 cases per 51,463 vaccine recipients of outpatient visits for alopecia among children 2 to 12 years of age that occurred within 30 days after vaccination. A review of the medical charts of these 8 cases indicated that the onset of alopecia predated vaccination in 7 children, and only 1 case was a new onset of alopecia (Table 2). After removal of the 7 cases with prior onset of alopecia, the relative risks were no longer elevated.

Table 2. Date of Alopecia Diagnoses Compared to Date of VARIVAX®

| Case # | Age (yrs) | Date of Injection | Date of Alopecia Dx | Interval (days) | Onset Predates Vaccination |
|--------|-----------|-------------------|----------------------|-----------------|----------------------------|
| 1 | 8.42 | 10/26/95 | 10/26/95 | 0 | Yes |
| 2 | 3.77 | 7/14/95 | 7/14/95 | 0 | Yes |
| 3 | 4.27 | 5/30/96 | 5/30/96 | 0 | Yes |
| 4 | 3.31 | 11/20/95 | 11/20/95 | 0 | Yes |
| 5 | 4.19 | 2/6/96 | 2/6/96 | 0 | Yes |
| 6 | 2.99 | 12/11/95 | 12/11/95 | 0 | Yes |
| 7 | 2.01 | 12/6/95 | Predates vaccination | 2 | Yes |
| 8 | 2.19 | 12/4/95 | 12/12/95 | 8 | No [†] |

† Probable new onset alopecia.

CONCLUSIONS:

A total of 91,740 doses of VARIVAX® were administered in the study period to 89,753 children, adolescents, and adults (34,665 children 12 to 23 months of age). No deaths were reported in the 60 days after vaccination among the 89,753 vaccine recipients. No hospitalizations, ER visits, or outpatient visits were observed for encephalitis or anaphylaxis among the vaccine recipients.

There were a total of 8 cases per 51,463 vaccine recipients of outpatient visits for alopecia among children 2 to 12 years of age that occurred within 30 days after vaccination. A review of the medical charts of these 8 cases indicated that the onset of alopecia predated vaccination in 7 children, and only 1 case was a new onset of alopecia (Table 2). After removal of the 7 cases with prior onset of alopecia, the relative risks were no longer elevated.

The data suggest that no serious adverse events associated with VARIVAX® vaccination were identified among the 89,753 vaccinees in this study. These data confirm the overall favorable safety profile of VARIVAX®.

PUBLICATIONS, ORAL PRESENTATIONS and POSTERS:

1. "Evaluation of the Varicella Vaccine Safety in over 89,000 Vaccine Recipients and Long-Term Effectiveness Using a Retrospective Healthcare Database". P Coplan. Drug Information Association Workshop: Advanced Applications and Case Studies in Retrospective Healthcare Databases. January 13-15, 1998, Washington, D.C.
2. "Post-Marketing Safety of Varicella Vaccine among 44,369 Vaccinees". P. Coplan, S. Black, HA Guess, Shinefield H, Sharrar RG, Ray P, Lewis N, and Hansen J. *Society for Epidemiologic Research*, Abstract 302, June 12-14, 1997, Edmonton, Canada.
3. Invited presentation for a workshop entitled "Varicella in Child Care Center Attendees: What is the role of varicella immunization?" on the effectiveness of the varicella vaccine in 10 day care centers in North Carolina. National Immunization Conference, May 19-22, 1997, Detroit, MI.
4. Invited presentation for a workshop entitled "How do we know vaccines are safe?" on the post marketing safety study of the varicella vaccine. National Immunization Conference, May 19-22, 1997, Detroit, MI.
5. Presentation to CBER, U.S. Food and Drug Administration: "First Annual Report on Post-Licensure Studies of the Varicella Vaccine" January 24, 1997, Rockville, MD
6. "Results of the VARIVAX® post-marketing special studies" P Coplan. Seminar for the National Immunization Program, Centers for Disease Control, Atlanta, GA, October 1, 1996.
7. "Varicella Incidence Rate among Individuals 15-19 Years Of Age: Shift in the Age Distribution of Chickenpox?". P Coplan, H Guess at Merck Research Laboratories (MSD), Blue Bell, PA and S Black, H Shinefield, P Ray, N Lewis at Kaiser Permanente Vaccine Study Center, Oakland, CA. Oral presentation at *36th Interscience Conference on Antimicrobial Agents and Chemotherapy*, [Abstract K160] September 15-18, 1996, New Orleans, LA.
8. Post-Marketing Surveillance In 44,369 Recipients Of Varivax (MSD). S. Black, H. Shinefield, P. Ray, N. Lewis, at Kaiser Permanente Pediatric Vaccine Study

Center (KPVSC), Oakland, CA and P. Coplan, H. Guess, and R.G. Sharrar at Merck Research Laboratories, West Point, PA. *36th Interscience Conference on Antimicrobial Agents and Chemotherapy*, [Abstract H128] September 15-18, 1996, New Orleans, LA.

9. "Safety Of Varicella Vaccine: Results Of Post-Marketing Surveillance In 32,947 Recipients Of Varivax (MSD)". S. Black, H. Shinefield, P. Ray, N. Lewis, J. Hansen at Kaiser Permanente Pediatric Vaccine Study Center (KPVSC), Oakland, CA and P. Coplan, H. Guess, and R.G. Sharrar at Merck Research Laboratories, West Point, PA. Presented at *Society for Pediatric Research Conference*, May 10 - 11, 1996, Washington, DC.

POST-MARKETING STUDY REPORT

VARIVAX[®]

Post-Marketing Evaluation of Short-Term Safety of Varicella Vaccine

PROTECTION OF HUMAN SUBJECTS:

This study was conducted in conformance with applicable US requirements regarding ethical committee review, informed consent, and other statutes or regulations regarding the protection of the rights and welfare of human subjects participating in biomedical research.

PRODUCT: Varicella Virus Vaccine, [Live Oka/Merck (VARIVAX®)]

PROTOCOL TITLE: Post-Marketing Evaluation of Short-Term Safety of Varicella Vaccine

PROTOCOL NUMBER: #035-00

INVESTIGATOR(S): Steve Black, M.D. (Primary), Henry Shinefield, M.D. (Secondary)

CLINICAL PHASE: Phase IV (Post-Marketing)

DURATION: 2 years

OBJECTIVES:

1. To describe the occurrence of adverse events in at least 25,000 children aged 12 to 23 months in a period (30 days for pediatric outpatient visits and emergency room visits, 60 days for hospitalizations and mortality) immediately after vaccination with VARIVAX®.
2. To compare the rates of specific adverse events in the period post-vaccination with the adverse events rates in three comparison periods of the same time duration:
 - Historical controls randomly selected from the previous year, *i.e.*, before vaccine licensure, using the same calendar days one year prior as the comparison period.
 - The time period 31 - 60 or 31 - 90 days before vaccination in the same individuals who were vaccinated.
 - The time period 91 - 120 or 91 - 150 days after vaccination in the same individuals who were vaccinated.

STUDY STATUS: Completed.

Post Marketing Evaluation of the Safety and Effectiveness of Varicella Vaccine

Authors

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ABSTRACT

Background

The Oka strain of live attenuated varicella virus was licensed for use in healthy children in the United States in March, 1995. We report here on a post marketing evaluation of the short-term safety of this vaccine within Kaiser Permanente.

Methods

Following licensure, varicella vaccination was introduced into the preventive care program of KPMCP. Potential adverse events following vaccination with varicella vaccine were identified from automated clinical databases of hospitalizations, emergency room visits, and clinic visits. Deaths were identified from automated clinical databases at Kaiser as well as from the State death records for California. Rates of diagnosis-specific events in the risk periods were compared with the rates in self control (before and after vaccination) and a historical control periods. A relative risk (RR) was calculated for each diagnostic-specific event occurring in the risk periods.

Results

During the study period of April 1, 1995, to December 31, 1996, a total of 89,753 adults and children received 91,740 doses of varicella vaccine. A total of 3,200 relative risks were calculated and of these 5 hospital, 9 emergency visit, and 30 outpatient diagnostic categories demonstrated a RR with a p-value <0.05 in at least one age group or at least one control period. The p-value for these tests was not adjusted for multiple comparisons. Of these categories, 14 demonstrated an increased risk either in more than one age group or against more than one comparison group. These categories included elective procedures, febrile seizure, febrile illness, well child visits, acute gastroenteritis, varicella, congenital anomaly, "rule out sepsis", trauma, viral syndrome, apnea, back pain, congenital valvular heart disease, and vision evaluation for glasses. Of these, the outcomes of elective procedure, congenital anomaly, congenital valvular heart disease, well child and vision evaluation for glasses were judged not to have a biologically plausible association with vaccination. A second diagnostic grouping included febrile illness, viral illness, febrile seizure and "rule out sepsis". In an analysis of these events which adjusted for the concomitant administration of M-M-R_{II}® vaccine, none of the associations were

statistically associated with receipt of varicella vaccine except the diagnostic categories of “rule out sepsis”. The diagnostic category of “rule out sepsis” still had a RR=1.95 with $p=0.02$. None of the children in the “rule out sepsis” category had positive bacteriologic cultures from blood or any other normally sterile site. Because of the large number of gastroenteritis cases, a random sample of 100 exposed and 100 unexposed cases were reviewed. From this review, no consistent time association or clustering of any of these events was seen in the exposed follow-up time interval. Only gastroenteritis and negative evaluations for sepsis were felt to be possibly associated with receipt of varicella vaccine. Although there was a statistically significant increased risk over the entire 30 day-period, there was no clustering of these events within the 30 day window.

Conclusion

We conclude that in this study population of 89,753 children and adults vaccinated with the varicella vaccine (Oka strain, Merck), no serious vaccine-related adverse events were identified. Rates of varicella-like rash and of breakthrough cases were both low and consistent with the rates observed in prelicensure studies.

INTRODUCTION

Varicella is a common childhood disease which infects more than 90% of children before ten years of age. In the vast majority of children, this infection is mild and self-limited. Prior to the introduction of the varicella vaccine, however, varicella infection in healthy children was responsible for an estimated 100 deaths each year as well as encephalitis, cerebellar ataxia, pneumonia, hepatitis and secondary infection.¹ According to the Centers for Disease Control, varicella is still the leading cause of vaccine-preventable deaths among children in the U.S.²

The Oka strain, live attenuated varicella vaccine, was developed by Takahashi in Japan and was licensed for use in healthy children in the United States in March, 1995. The varicella vaccine has also been recommended for routine use in children by the Advisory Committee on Immunization Practices (ACIP) and the American Academy of Pediatrics. Between April 1995 when the vaccine was licensed and December 1996, a total of 91,740 doses of the Merck Varivax® brand varicella vaccine were given to children and adults within the Northern California Kaiser Permanente Medical Care Program as part of routine preventive care.

We report here on an evaluation of the short-term safety of this vaccine as assessed by rates of medical events resulting in hospitalization, emergency room visits, outpatient utilization and deaths within Kaiser Permanente. In addition, the long-term effectiveness of the vaccine is assessed by serial semi-annual telephone interviews in a 15-year cohort study. The post-marketing surveillance program within Kaiser Permanente also includes periodic cross-sectional surveys to assess any changes in age-specific varicella incidence within our program. These results will be reported separately.³

METHODS

The Northern California Kaiser Permanente Medical Care Program (KPMCP) provides pre-paid medical care for 2.5 million people at 31 medical centers in Northern California. The population of Kaiser Permanente is racially and ethnically similar to the population of the communities which it serves. Based upon surveys conducted within the program, members of Kaiser Permanente are 52% white, 21% Hispanic, 11% Black, 14% Asian and 2% other.

Beginning in April, 1995, varicella vaccination was introduced into the preventive care program of KPMCP. The vaccine was recommended for routine use in children between the ages of one and two years as well as for older children and adults without a history or serological evidence of prior varicella infection.

Within KPMCP, all immunizations, diagnoses and procedure codes for all hospitalizations, emergency room visits, clinic visits, visits to specialists, as well as emergency visits to outside providers are available for reporting and analysis. For the purposes of the analyses performed in this study, potential adverse events following vaccination with varicella vaccine were identified from the automated clinical databases. Deaths were identified from automated clinical databases at Kaiser as well as from the State death records for California. The risk period for the identification of adverse events following vaccination was defined as a 30-day period immediately following vaccination for events resulting in clinic or outpatient visits. For hospitalizations or death, the risk period was 60 days following vaccination. The risk period for follow-up of events following vaccination began on the day of vaccination (Day 0) for deaths, hospitalizations, and for emergency room visits. The day after vaccination (Day 1) was used as

the start of the risk period for outpatient clinic visits, except allergic reactions where the risk period began on Day 0.

The rates of diagnosis-specific events in the 30- and 60-day risk periods were compared with diagnosis-specific event rates in control periods. The expected rate of events was obtained by using control comparison groups or periods.

Three control periods were used for hospital and emergency comparisons whereas data was only available for the two self control periods for the clinic data. The first control period was a historical cohort comparison with the rates of the same events in an equivalent 30- or 60-day period following routine pediatric vaccination in children who were one to two years old during the year prior to the onset of the post marketing study. These children were individually matched to the varicella-vaccinated children on birth date and sex as well as on date of receipt of M-M-R[®] vaccine in the control children. The two other control periods were two distinct follow-up time periods in the vaccinees: the "before" control periods and the post-vaccine or "after" control periods. The "before" control periods were 30 day windows defined as 60-90 days prior to receipt of the varicella vaccine for clinic and emergency visits and 60 day windows defined as 60-120 days prior to vaccine for hospitalization and deaths. The "after" control periods were 30 day windows defined as 31-61 days after the receipt of the varicella vaccine for clinic and emergency visits and 60 day windows defined as 31-91 days following vaccine for hospitalization and deaths. All events that occurred in the risk periods following vaccination were reviewed by one of the two principal investigators to evaluate whether there was a possible association with vaccine and to classify severity. Any events felt to be possibly associated with vaccination and all allergic reactions, all deaths, all seizures, and those neurologic events which

resulted in hospitalization within the risk period were reported to the Vaccine Adverse Events Reporting System (VAERS) through the manufacturer.

The occurrence of at least one diagnosis-specific event in the risk period triggered the calculation of relative risks for that event. The relative risks compared the diagnosis-specific rates of events within the risk periods with the rates of the same diagnostic event in the appropriate control comparison periods. This method has been used previously to evaluate the safety of vaccines.^{4,5,6} Exact midpoint binomial confidence intervals and p-values were calculated for this comparison.^{7,8} For the before and after control periods, separate analyses were performed for the one year old, 2-12 year old, 13-17 year old and over 18 year old age groups. Because a single episode of care could have resulted in medical utilization at more than one site, it was not possible to combine the analyses of utilization into one table. Relative risks were calculated for diagnosis-specific events in the outpatient, emergency room, and hospital setting. Relative risks were calculated for approximately 3,200 separate diagnostic events. The criterion for a statistically significantly elevated relative risk was maintained at a p-value of $p < 0.05$ in spite of the multiple comparisons. As a result, the potential for type I errors was large. In reviewing the results of these multiple comparisons, any events with a significantly elevated risk (*i.e.*, $p < 0.05$) following vaccination and for which there was biologic plausibility of vaccine causation were flagged for more intensive follow-up using two methods: first, the corresponding medical records of cases in the risk period were reviewed by one of the two principal investigators; second, the overall pattern of association of the diagnosis-specific event was examined epidemiologically to evaluate whether there was a consistent pattern of significantly elevated relative risks for that event across all age groups, control comparison periods, and healthcare settings.

To evaluate long-term effectiveness and rates of breakthrough cases and zoster, a cohort of 9,316 children vaccinated with varicella vaccine between ages one to two years old was randomly identified from the set of vaccinees in the first six months of the safety study. Parents of these children were contacted and asked to participate in a long-term follow-up study during which telephone interviews with the parents would be conducted every six months for fifteen years. Specific instructions regarding the diagnosis of varicella or zoster were not given to parents.

A total of 7,585 children whose parents consented to participate in the 15-year study comprise the long-term follow-up cohort. Parents of these children are interviewed semi-annually regarding any varicella- or zoster-like rash or disease in the vaccinated child or in any other family member. In addition, parents in this study have been given a toll-free telephone number to report any varicella or zoster cases as they occur.

For the purposes of this analysis, cases that occurred within 42 days of vaccination were considered either as vaccine-induced rashes, or as wild-type varicella. Cases that occurred at 42 days or more following vaccination were classified as breakthrough cases. Person-time for the annual incidence rates of varicella was calculated from the product of the sample size and the 6 month period in which the occurrence of varicella was asked about minus the first 6 weeks of follow-up time. Cases of varicella that occurred ≤ 42 or > 42 days of vaccination were not censored to allow for the possibility of a recurrence of varicella. The case definition of zoster required physician diagnosis to confirm parental report of zoster, because mild breakthrough varicella or varicella-like rash after vaccination could be misdiagnosed as zoster by untrained parents. The zoster rates observed in this study cohort were compared with population-based rates of physician-diagnosed zoster among unvaccinated children.

RESULTS

During the study period of April 1, 1995, to December 31, 1996, a total of 89,753 members of Kaiser Permanente Northern California received at least one dose of varicella vaccine and formed the study population. The age distribution of this study population is shown in Table 1.

Short-Term Safety Study

As a new vaccine, varicella was often given alone as part of a "catch-up" program in children and adults. Overall, 60.8% of vaccine doses was given alone, but 22.6% was given with measles-mumps-rubella vaccine (M-M-R_{II}®, Merck), 12.9% with either OPV or IPV, 10.7% with DTP, 7.7% with DTaP, 7.0% with hepatitis B vaccine and 3.7% with Hib vaccine (HibTITER®, Wyeth-Lederle). In the one-to-two-year-old age group, 65% of children received M-M-R_{II}® concomitantly. During the study period, there was only one death within 60 days of vaccination. This occurred in a child with respiratory failure resulting from bronchiolitis, which was not considered to be related to vaccination. Overall, there were 852 hospitalizations, 2,082 emergency visits, and 22,699 outpatient visits within the risk periods following vaccination. In the comparison of rates, approximately 3,200 relative risks were calculated and of these a total of 5 hospital diagnostic categories, 9 emergency visit diagnostic categories, and 30 outpatient diagnostic categories demonstrated at least one relative risk with a p-value <0.05 in one or more age groups and in comparisons with one or more control periods. The p-value for these tests was not adjusted, and hence did not take into account the large number of multiple comparisons being performed. For each of these diagnostic categories, the diagnosis, the age groups in which the association was seen, the relative risk, p-value and the relevant comparison group(s) are shown in

Table 2 for hospital and emergency utilization and in Table 3 for outpatient clinic visits. Of these categories, only 14 demonstrated an increased risk either in more than one age group or against more than one comparison group. These categories included elective procedures, febrile seizure, febrile illness, well child visits, acute gastroenteritis, varicella, congenital anomaly, "rule out sepsis", trauma, viral syndrome, apnea, back pain, congenital valvular heart disease, and vision evaluation for glasses. Of these, the outcomes of elective procedure (elective PE tube placement, elective hernia repair), congenital anomaly, congenital valvular heart disease, well child visits and vision evaluation for glasses were judged not to have a biologically plausible association with vaccination. A second category was the group of febrile illness, viral illness, febrile seizure and "rule out sepsis". All of these categories could reasonably be expected to be associated with a febrile reaction following vaccination. Since the rate of febrile reaction following varicella vaccine alone was known to be quite low from clinical trials, an analysis was conducted which took into account other vaccines given concomitantly with varicella vaccine. In an analysis of these events which adjusted for the concomitant administration of M-M-R[®] II vaccine, the associations of febrile seizure, febrile illness and viral syndrome were no longer statistically associated with receipt of varicella vaccine. The outpatient diagnostic category of "rule out sepsis" still had a RR=1.95 with p=0.02. The cause of the febrile illness leading to diagnostic evaluation for sepsis is not known. However, it should be noted that none of the children in the "rule out sepsis" category had positive bacteriologic cultures from blood or any other normally sterile site and all recovered from this episode.

For all the other outcomes, including trauma, gastroenteritis, apnea and back pain, medical record reviews of cases during risk and control comparison follow-up time were conducted. For all the outcomes, except gastroenteritis, all records were reviewed. For gastroenteritis, due to the large

number of cases in the risk and comparison follow-up periods, a random sample of 100 exposed and 100 unexposed cases were reviewed. From this review, no consistent time association or clustering of any of these events was seen in the exposed follow-up time interval. In addition, for trauma, apnea and back pain, a non-vaccine etiology was identified in all cases as well. Thus, following completion of chart review, only gastroenteritis and negative evaluations for sepsis were felt to be possibly associated with receipt of varicella vaccine. For both of these outcomes, although there was a statistically significant increased risk over the entire 30 day-period, there was no clustering of these events within the 30 day window.

Long-Term Effectiveness Study

In the long-term follow-up study, results of the first two sets of telephone interviews are shown in Table 4A and Table 4B. The follow-up rate for cohort participants was 99.9%. During the first 28 months of the study, a total of 335 cases of varicella-like rash occurred in these children for a breakthrough rate of 2.5% per year. Of these, only eight were classified as extensive (≥ 300 lesions). Twenty-three cases of zoster have been reported by parents during telephone interviews. Of these possible cases of zoster, ten had been seen by a physician and two of these were clinically confirmed as compatible with zoster. In one additional case, the child had been seen by a physician outside the HMO and the parent was unable to provide the name of the physician for follow-up to confirm the diagnosis. The remaining children had not been seen by a physician at the time of illness. Consequently, there were only two cases of physician-diagnosed herpes zoster out of 13,596 person-years of follow-up for a rate of 1.5 cases per 10,000 person-years of follow-up (95% CI = 0.18 to 5.3). The expected rate of herpes zoster among children 12-23 months of age after wild-type varicella infection is approximately 11 per

10,000 person-years.⁹ This estimate of the expected rate of herpes zoster after wild-type varicella is based on cases ascertained by physician diagnosis of zoster.

DISCUSSION

The Oka strain varicella vaccine underwent the longest prelicensure evaluation of any vaccine in US history. Prelicensure concerns were related to the safety and long-term effectiveness of this vaccine. Prelicensure evaluations of the varicella vaccine in more than 10,000 individuals demonstrated that the vaccine was generally well tolerated. Reported adverse effects included fever reported in 5% of recipients and varicella-like rash in approximately 1.5-3% of recipients.¹⁰

In this evaluation of possible rare medical events associated with vaccination, no serious vaccine-related adverse events were identified.. Despite the extremely large number of comparisons conducted and the statistical likelihood that false positive associations would occur in some of the comparisons, the number of positive associations observed was extremely low. Of note, is that events such as cerebellar ataxia, reported to occur in 1:4,000 children following wild type varicella, were not seen following varicella vaccination in this study¹¹. Similarly, no cases of new onset of encephalopathy were identified following vaccination. Seizures were seen during the follow-up periods, but there was no increased risk of this event following vaccination when results were adjusted for concomitant administration of other vaccines. In addition, there was no consistent association of anaphylaxis or hives with receipt of vaccine. In this study, we identified an increased risk of gastroenteritis following receipt of varicella vaccine. For this outcome, there was no time clustering of cases within the 30 day window, making a true physiologic association less likely. Long-term follow-up of vaccinees in pre-licensure studies

for up to five years in this country have shown that the vaccine provides long-term protection in the setting of circulating wild type varicella virus and breakthrough varicella rates ranged from 0.3% to 2.2% per year with a cumulative breakthrough rate of 5.5% (95% CI = 4.0% to 7.0%) at 5 years after vaccination¹². Although these results are reassuring, as part of the post marketing evaluation of varicella vaccine, we have placed surveillance systems to detect any vaccine-induced change in the age specific incidence of varicella and to assess the vaccine's long-term effectiveness in the post marketing setting where boosting from exposure to wild type virus may decrease. In addition, the impact of the vaccination program on the incidence of zoster will be assessed. To date, the rate of "breakthrough cases" following varicella has been low and concordant with the rates observed in pre-licensure studies.

We conclude that in this study population of 89,753 children and adults, the varicella vaccine (Oka strain, Merck) was well tolerated. Rates of varicella-like rash and of breakthrough cases are both low and consistent with the rates observed in prelicensure studies. Studies of the long-term effectiveness of varicella vaccine are ongoing.

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- ⁴ Griffin MR, Ray WA, Mortimer, EA, et al. Risk of seizures after Measles-Mumps-Rubella immunization. *Pediatrics* 1991; 88: 881-885.
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- ⁹ Guess HA, Broughton DD, Melton LJ, Kurland LT. Epidemiology of herpes-zoster in children and adolescents: a population-based study. *Pediatrics* 1985; 76: 512-517.
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- ¹¹ Guess HA, Broughton DD, Melton LJ, Kurland LT. Population-based studies of varicella complications. *Pediatrics* 1986; 78 (suppl): 723-727.
- ¹² Chan CY, Li S, Bird S, Matthews H, Carfagno P, Kutzler D, Stinson D, Meechan C, Kuter B, Sadoff J, and VARIVAX Study Group. Effectiveness and Antibody Persistence after VARIVAX [Varicella Virus Vaccine Live (Oka/Merck)] in Healthy Children: an Interim 5-Year Report of the Long-Term (10-Year) Follow-Up Studies. *38th Interscience Conference on Antimicrobial Agents and Chemotherapy*, [Abstract 32H] September 24-27, 1998, San Diego, CA..

Table 1. Age Distribution of the Study Population, June '95 - December '96

| Age | Dose 1 | Dose 2 | Total |
|----------|--------|--------|--------|
| 12-23 mo | 34,665 | --- | 34,665 |
| 2-12 yrs | 51,463 | --- | 51,463 |
| ≥13yrs | 3,625 | 1,987 | 5,612 |
| Total | 89,753 | 1,987 | 91,740 |

Table 2. Hospital and ER Outcomes by Diagnostic Category with at Least One Elevated Relative Risk¹ Following Vaccination with Varivax® Compared To Comparison Periods²

| Hospitalizations | Age Group (yrs) | Control Period | Setting | Risk Period N ³ | Control Period N | RR | 95% C.I. | P Value |
|------------------------------|-----------------|-------------------|---------|----------------------------|------------------|------|---------------|---------|
| Acute Gastroenteritis | 1 yr | 91-120 Days After | ER | 92 | 48 | 1.70 | (1.20, 2.43) | <.01 |
| | | historical | H | 33 | 18 | 1.84 | (1.04, 3.34) | 0.04 |
| | | historical | ER | 92 | 62 | 1.48 | (1.08, 2.06) | 0.02 |
| Elective procedure | 1 yr | 91-150 Days After | H | 131 | 79 | 1.44 | (1.09, 1.90) | 0.01 |
| | | historical | H | 131 | 85 | 1.55 | (1.18, 2.04) | <.01 |
| | 2-12 yrs | 31-90 Days Before | H | 129 | 90 | 1.44 | (1.10, 1.88) | 0.01 |
| Epilepsy | 1 yr | historical | ER | 6 | 0 | - | (1.54,) | 0.02 |
| Febrile Illness | 1 yr | 91-120 Days After | ER | 52 | 18 | 2.57 | (1.52, 4.49) | <.01 |
| | | 31-60 Days Before | ER | 52 | 26 | 2.00 | (1.26, 3.25) | <.01 |
| | | historical | H | 5 | 0 | - | (1.23,) | 0.03 |
| Hives | 2-12 yrs | 91-120 Days After | ER | 11 | 3 | 3.46 | (1.02, 15.42) | 0.05 |
| Rash | 1 yr | 91-120 Days After | ER | 20 | 7 | 2.54 | (1.10, 6.45) | 0.03 |
| Seizure, Febrile | 1 yr | 91-150 Days After | H | 21 | 8 | 2.27 | (1.03, 5.45) | 0.04 |
| | | historical | H | 21 | 7 | 3.02 | (1.32, 7.63) | <.01 |
| Trauma | 2-12 yrs | 91-120 Days After | ER | 427 | 321 | 1.18 | (1.02, 1.36) | 0.02 |
| URI | 2-12 yrs | 91-150 Days After | H | 5 | 0 | - | (1.13,) | 0.04 |
| Varicella | 2-12 yrs | 31-60 Days Before | ER | 6 | 0 | - | (1.54,) | 0.02 |
| Varicella w & w/o Cellulitis | 2-12 yrs | 31-60 Days Before | ER | 6 | 0 | - | (1.54,) | 0.02 |
| Viral Syndrome | 1 yr | 91-120 Days After | ER | 105 | 54 | 1.73 | (1.25, 2.41) | <.01 |
| Well Child/Reassurance/FU | 2-12 yrs | 91-120 Days After | ER | 25 | 9 | 2.62 | (1.25, 5.91) | 0.01 |
| | | 31-60 Days Before | ER | 25 | 12 | 2.08 | (1.06, 4.29) | 0.03 |

¹ Elevated relative risk determined by a p-value <0.05 without adjusting the p-value for the 61 diagnostic categories for which hospital visits were made and 58 emergency room diagnostic categories, and comparisons with two or three control periods for each diagnostic category.

² Relative risks for age groups or comparison groups (i.e., "before", "after" or "historical" control periods) that were not significantly elevated are not shown in this table because of space limitations.

³ 0 - 60 days following hospitalizations and 0 - 30 days following ER visits.

Table 3. Clinic Visit Outcomes With One or More Elevated Relative Risks¹ Following Vaccination With Varivax® Compared To Comparison Periods²

| Diagnostic Category | Age Group | Control Period | 0 – 30 Days N | Control Period N | RR | 95% C.I. | P Value |
|--------------------------------|-----------|-------------------|------------------|---------------------|-------|----------------|---------|
| Acute Gastroenteritis | 1 yr | 91-120 Days After | 983 | 790 | 1.14 | (1.04, 1.26) | 0.01 |
| Abcess | 1 yr | 31-60 Days Before | 78 | 55 | 1.47 | (1.04, 2.08) | 0.03 |
| Allergic React w or w/o Hives | 1 yr | 91-120 Days After | 180 | 130 | 1.27 | (1.02, 1.60) | 0.04 |
| Allergic React (inc. Hives) | 1 yr | 91-120 Days After | 180 | 130 | 1.27 | (1.02, 1.60) | 0.04 |
| Allergic Rhinitis | 1 yr | 31-60 Days Before | 18 | 5 | 3.72 | (1.44, 11.24) | 0.01 |
| Alopecia | 2-12 yrs | 91-120 Days After | 8 | 1 | 7.80 | (1.25, 174.47) | 0.02 |
| Apnea | 2-12 yrs | 91-120 Days After | 41 | 22 | 1.82 | (1.09, 3.10) | 0.02 |
| | | 31-60 Days Before | 41 | 16 | 2.65 | (1.51, 4.85) | <.01 |
| Attention Def. Dis. | 2-12 yrs | 31-60 Days Before | 71 | 50 | 1.47 | (1.02, 2.12) | 0.04 |
| Back Pain | 2-12 yrs | 91-120 Days After | 25 | 8 | 3.05 | (1.41, 7.19) | <.01 |
| | | 31-60 Days Before | 25 | 11 | 2.35 | (1.17, 4.97) | 0.02 |
| Congenital Anomaly | 1 yr | 91-120 Days After | 143 | 101 | 1.30 | (1.01, 1.68) | 0.04 |
| | 2-12 yrs | 91-120 Days After | 135 | 88 | 1.50 | (1.14, 1.96) | <.01 |
| | 2-12 yrs | 31-60 Days Before | 135 | 79 | 1.77 | (1.34, 2.34) | <.01 |
| Congenital Heart Disease | 2-12 yrs | 91-120 Days After | 46 | 26 | 1.72 | (1.07, 2.82) | 0.03 |
| | | 31-60 Days Before | 46 | 27 | 1.76 | (1.10, 2.87) | 0.02 |
| Elective Surgery | 1 yr | 31-60 Days Before | 40 | 16 | 2.59 | (1.46, 4.74) | <.01 |
| | 2-12 yrs | 91-120 Days After | 52 | 25 | 2.03 | (1.27, 3.31) | <.01 |
| Febrile Illness | 1 yr | 91-120 Days After | 179 | 94 | 1.75 | (1.37, 2.25) | <.01 |
| | 2-12 yrs | 91-120 Days After | 72 | 45 | 1.56 | (1.08, 2.28) | 0.02 |
| Healthcare Class | 1 yr | 31-60 Days Before | 10 | 2 | 5.17 | (1.26, 34.70) | 0.02 |
| | 2-12 yrs | 31-60 Days Before | 12 | 2 | 6.21 | (1.57, 40.88) | 0.01 |
| Heart Murmur | 2-12 yrs | 91-120 Days After | 20 | 7 | 2.79 | (1.21, 7.08) | 0.02 |
| Metatarsus Adductus | 2-12 yrs | 91-120 Days After | 9 | 1 | 8.77 | (1.44, 193.96) | 0.03 |
| Neurological, General Disorder | 2-12 yrs | 31-60 Days Before | 5 | 0 | - | (1.26,) | 0.03 |
| Otitis Externa | 2-12 yrs | 91-120 Days After | 129 | 90 | 1.40 | (1.07, 1.83) | 0.01 |
| Phimosis | 2-12 yrs | 31-60 Days Before | 11 | 3 | 3.79 | (1.12, 16.93) | 0.03 |
| Pneumonia | 1 yr | 31-60 Days Before | 81 | 59 | 1.42 | (1.02, 1.99) | 0.04 |
| Rash | 1 yr | 91-120 Days After | 555 | 432 | 1.18 | (1.04, 1.34) | 0.01 |
| R/O Sepsis | 1 yr | 91-120 Days After | 23 | 6 | 3.52 | (1.49, 9.47) | <.01 |
| | | 31-60 Days Before | 23 | 7 | 3.40 | (1.50, 8.53) | <.01 |
| | 2-12 yrs | 91-120 Days After | 12 | 2 | 5.85 | (1.48, 38.52) | 0.01 |
| | | 31-60 Days Before | 12 | 2 | 6.32 | (1.57, 40.88) | 0.01 |
| Seizures | 1 yr | 91-120 Days After | 52 | 30 | 1.36 | (1.02, 2.52) | 0.04 |
| Soft Tissue Disease | 1 yr | 31-60 Days Before | 7 | 1 | 7.24 | (1.12, 164.44) | 0.04 |
| Tonsillitis | 2-12 yrs | 91-120 Days After | 35 | 18 | 1.90 | (1.08, 3.42) | 0.03 |
| Trauma | 2-12 yrs | 91-120 Days After | 496 | 421 | 1.15 | (1.01, 1.31) | 0.04 |
| | 12-17 yrs | 91-120 Days After | 76 | 27 | 1.68 | (1.09, 2.64) | 0.02 |
| Valvular Heart Disease | 2-12 yrs | 91-120 Days After | 16 | 1 | 15.60 | (2.81, 330.40) | <.01 |
| | | 31-60 Days Before | 16 | 5 | 3.31 | (1.26, 10.10) | 0.01 |
| Varicella | 1 yr | 91-120 Days After | 22 | 2 | 10.11 | (2.77, 63.71) | <.01 |
| | | 31-60 Days Before | 22 | 6 | 3.79 | (1.59, 10.24) | <.01 |
| | 2-12 yrs | 91-120 Days After | 35 | 4 | 8.53 | (3.28, 28.17) | <.01 |
| | | 31-60 Days Before | 35 | 3 | 12.07 | (4.14, 49.49) | <.01 |
| Viral Syndrome | 1 yr | 91-120 Days After | 1470 | 1030 | 1.31 | (1.21, 1.42) | <.01 |
| | | 31-60 Days Before | 1470 | 1386 | 1.10 | (1.02, 1.18) | 0.01 |
| Vision Problem | 2-12 yrs | 91-120 Days After | 549 | 345 | 1.55 | (1.36, 1.78) | <.01 |
| | | 31-60 Days Before | 549 | 287 | 1.98 | (1.72, 2.28) | <.01 |

¹ Elevated relative risk determined by a p-value <0.05 without adjusting the p-value for the 221 diagnostic categories for which outpatient clinic visits were made, and comparisons with two or three control periods for each diagnostic category.

² Relative risks for age groups or comparison groups (i.e., "before" or "after" control periods) that were not significantly elevated are not shown in this table because of space limitations.

Table 4a. Incidence of Varicella¹ Six Weeks Or More After Vaccination In Children Aged 12-23 Months As Reported 6 to 24 Months Post-Vaccination

| Interval Post-vaccination (months) | Number of Cases | Person-Years of Follow-up Time | Rate per 1000 Person-Years | 95% CI |
|--|--------------------|-----------------------------------|-------------------------------|--------------|
| 0-6 | 58 | 2,870 | 20.2 | (15.5, 26.2) |
| 7-12 | 116 | 3,723 | 31.2 | (25.9, 37.4) |
| 13-18 | 85 | 3,790 | 22.4 | (18.1, 27.8) |
| 19-24 | 76 | 3,213 | 23.7 | (18.8, 29.7) |
| Cumulative | 335 | 13,596 | 24.6 | (22.1, 27.4) |

¹ Defined as any parent-reported chickenpox with onset of symptoms occurring at >6 weeks post- vaccination.

Table 4b: Parent-Reported Incidence of Varicella¹ at 6 to 24 Months Post-Vaccination Among 7,545 Children Vaccinated at 12 - 23 Months of Age

| Varicella Cases | | Person-Years | Rate /1000 | 95% CI |
|----------------------|----------|--------------|------------|-------------|
| <i>Lesions</i> | <i>N</i> | | P-Years | |
| <i>Any (≥1)</i> | 335 | 13,596 | 24.6 | 22.1 - 27.4 |
| <i>≥ 50 lesions</i> | 48 | 13,596 | 3.5 | 2.6 - 4.7 |
| <i>≥ 300 lesions</i> | 8 | 13,596 | 0.6 | 0.2 - 1.2 |

¹ Defined as any parent-reported chickenpox with onset of symptoms occurring at >6 weeks post-vaccination.

PUBLICATIONS, ORAL PRESENTATIONS and POSTERS of PROTOCOL 035:

1. "An Analytical Algorithm to Distinguish Vaccine-Related Adverse Events from Usual Medical Events in Vaccine Post-Marketing Safety Studies Using Computerized Databases." Coplan PM, Black S, Shinefield H, Ray P, Lewis N, Hansen J, Sharrar RG, Guess HA. International Biometrics Conference, December 14-18, 1998, Cape Town, South Africa.
2. "Evaluation of the Varicella Vaccine (Varivax®) Safety in 89,753 Vaccine Recipients and Long-Term Effectiveness Using a Retrospective Healthcare Database". PM Coplan, S Black, H Shinefield, P Ray, N Lewis, J Hansen, H Guess. *14th International Conference on Pharmacoepidemiology*, August 16-19, 1998, Berlin, Germany.
3. "Evaluation of the Varicella Vaccine Safety in over 89,000 Vaccine Recipients and Long-Term Effectiveness Using a Retrospective Healthcare Database". P Coplan. Drug Information Association Workshop: Advanced Applications and Case Studies in Retrospective Healthcare Databases. January 13-15, 1998, Washington, D.C.
4. "Post-Marketing Safety of Varicella Vaccine among 44,369 Vaccinees". P Coplan, S. Black, HA Guess, H Shinefield, RG Sharrar, P Ray, N Lewis, and J Hansen. *Society for Epidemiologic Research*, Abstract 302, June 12-14, 1997, Edmonton, Canada.
5. Invited presentation for a workshop entitled "Varicella in Child Care Center Attendees: What is the Role of Varicella Immunization?" on the effectiveness of the varicella vaccine in 10 day care centers in North Carolina. National Immunization Conference, May 19-22, 1997, Detroit, MI.
6. Invited presentation for a workshop entitled "How Do We Know Vaccines Are Safe?" on the post marketing safety study of the varicella vaccine. National Immunization Conference, May 19-22, 1997, Detroit, MI.
7. Presentation to CBER, U.S. Food and Drug Administration: "First Annual Report on Post-Licensure Studies of the Varicella Vaccine" January 24, 1997, Rockville, MD
8. "Results of the VARIVAX® Post-marketing Special Studies" P Coplan. Seminar for the National Immunization Program, Centers for Disease Control, Atlanta, GA, October 1, 1996.

9. "Varicella Incidence Rate Among Individuals 15-19 Years Of Age: Shift in the Age Distribution of Chickenpox?". P Coplan, H Guess at Merck Research Laboratories, Blue Bell, PA and S Black, H Shinefield, P Ray, N Lewis at Kaiser Permanente Vaccine Study Center, Oakland, CA. Oral presentation at *36th Interscience Conference on Antimicrobial Agents and Chemotherapy*, [Abstract K160] September 15-18, 1996, New Orleans, LA.
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