(Document 1 of 2)

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Merck Research Laboratories
Worldwide Product Safety & Epidemiology

PERIODIC SAFETY UPDATE REPORT FOR:
Measles, Mumps, and Rubella Virus Vaccine Live, MSD

01-Jan-1999 to 31-Dec-2003

International Birth Date: 15-Sep-1978 (United States)

Date of this Report: **22-Jan-2004**

C

MERCK

TO: SEE ATTACHED LIST

FROM: [redacted]

DATE: 28-February-2004

SUBJECT: Measles, Mumps, and Rubella Virus Vaccine Live Periodic Safety Update Report

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The attached document represents the 5-year Periodic Safety Update Report (PSUR) for M-M-R®II (measles, mumps, and rubella virus vaccine live). This report is in the format proposed by the International Conference for Harmonisation (ICH), Topic E2C. This worldwide document summarizes safety data received by Merck & Co., Inc. from worldwide sources and safety-related updates to the Company Core Data Sheet (CCDS) for measles, mumps, and rubella virus vaccine live between 01-Jan-1999 and 31-Dec-2003.

As with all Merck & Co., Inc. products, the safety profile of measles, mumps, and rubella virus vaccine live is monitored on a continuous basis.

Please submit this PSUR to your regulatory agency only if they require the document.

[redacted]

cc w/o attachment: [redacted]

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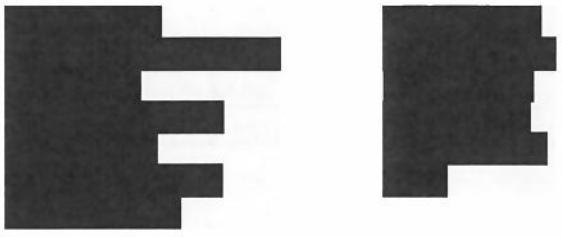
Distribution List – M-M-R®II
Periodic Safety Update Report



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TO: SEE ATTACHED LIST

CC: [redacted]

FROM: [redacted]

SUBJECT: Periodic Safety Update Report for M-M-R®II (measles, mumps, and rubella virus vaccine live): Reporting Period 01-Jan-1999 to 31-Dec-2003

Please acknowledge the receipt of this report by completing this form and returning this form to [redacted] Thank you in advance for your cooperation.

Sincerely,

[redacted]
Merck & Co., Inc., [redacted]
West Point, PA 19486 USA
☎(484) [redacted]
FAX(484) [redacted]

Name_____ Country_____
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I here-by acknowledge receipt of this Periodic Safety Update Report.

_____ _____
(Signature) (Date)

CONFIDENTIAL

Merck Research Laboratories
Worldwide Product Safety & Epidemiology

PERIODIC SAFETY UPDATE REPORT FOR: Measles, Mumps, and Rubella Virus Vaccine Live, MSD

01-Jan-1999 to 31-Dec-2003

International Birth Date: 15-Sep-1978 (United States)

Date of this Report: 22-Jan-2004

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MERCK

MEASLES, MUMPS, AND RUBELLA VIRUS VACCINE LIVE
EXECUTIVE SUMMARY
01-JAN-1999 TO 31-DEC-2003

The attached document represents a 5-year Periodic Safety Update Report (PSUR) for measles, mumps, and rubella virus vaccine live. This report is in the format proposed by the International Conference for Harmonisation (ICH), Topic E2C. This is a worldwide document that summarizes safety data received by Merck & Co., Inc., from worldwide sources, between 01-Jan-1999 to 31-Dec-2003.

Measles, mumps, and rubella virus vaccine live (MSD) is indicated for simultaneous vaccination against measles, mumps, and rubella in individuals 12 months of age or older.

Measles, mumps, and rubella virus vaccine live, was first approved in the United States on 15-Sep-1978 (United States) and is currently registered and approved in 76 countries. Measles, mumps, and rubella virus vaccine live (MSD) is a live virus vaccine for vaccination against measles (rubeola), mumps and rubella (German measles). Measles, mumps, and rubella virus vaccine live (MSD) is a sterile lyophilized preparation of (1) ATTENUVAX™ (Measles Virus Vaccine Live, MSD), a more attenuated line of measles virus derived from Enders' attenuated Edmonston strain and propagated in chick embryo cell culture; (2) MUMPSVAX™ (Mumps Virus Vaccine Live, MSD), the Jeryl Lynn™ (B level) strain of mumps virus propagated in chick embryo cell culture; and (3) MERUVAX II™ (Rubella Virus Vaccine Live, MSD), the Wistar RA 27/3 strain of live attenuated rubella virus propagated in WI-38 human diploid lung fibroblasts.

During the reporting period of this PSUR, the estimated number of marketed measles, mumps, and rubella virus vaccine live doses distributed worldwide between 01-Jan-1999 and 31-Dec-2003 was approximately [redacted]. Approximately [redacted] individuals are estimated to be vaccinated based on the assumptions that each individual received one dose and approximately 10% of the doses distributed were not used. There were approximately [redacted] patients exposed to measles, mumps, and rubella virus vaccine live in Merck-sponsored clinical trials during the reporting period of this PSUR.

Overall, 5,170 spontaneous reports were received from healthcare providers.

There were no new major findings that alter the established overall safety profile of measles, mumps, and rubella virus vaccine live and the overall positive benefit over risk for the product.

During the reporting period of this PSUR, safety-related updates made to the Company Core Data Sheet (CCDS) are discussed in Section 4. Changes to Reference Safety Information). There are no pending safety-related updates.

As with all Merck & Co., Inc. products, the safety profile of measles, mumps, and rubella virus vaccine live is monitored on a continuing basis.

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1. Introduction

This periodic safety update report (PSUR) on measles, mumps, and rubella virus vaccine live, (Merck Sharp & Dohme-MSD) is in the format proposed by the International Conference on Harmonisation (ICH) for Technical Requirements for Registration of Pharmaceuticals for Human Use, Topic E2C. It summarizes the safety data received by Merck & Co., Inc., from worldwide sources, between 01-Jan-1999 and 31-Dec-2003.

Measles, mumps, and rubella virus vaccine live (MSD) is a live virus vaccine for vaccination against measles (rubeola), mumps and rubella (German measles). Measles, mumps, and rubella virus vaccine live (MSD) is a sterile lyophilized preparation of (1) ATTENUVAX™ (Measles Virus Vaccine Live, MSD), a more attenuated line of measles virus derived from Enders' attenuated Edmonston strain and propagated in chick embryo cell culture; (2) MUMPSVAX™ (Mumps Virus Vaccine Live, MSD), the Jeryl Lynn™ (B level) strain of mumps virus propagated in chick embryo cell culture; and (3) MERUVAX II™ (Rubella Virus Vaccine Live, MSD), the Wistar RA 27/3 strain of live attenuated rubella virus propagated in WI-38 human diploid lung fibroblasts.

Measles, mumps, and rubella virus vaccine live (MSD) is indicated for simultaneous vaccination against measles, mumps, and rubella in individuals 12 months of age or older.

2. Worldwide Market Authorization Status

B

At the time of this report, measles, mumps, and rubella virus vaccine live (under the Worldwide Tradename of M-M-R II™) had been registered and approved in 76 countries (see Appendix 1). An application is pending in [redacted] There are no records of any registration being revoked or withdrawn for safety reasons.

3. Update on Regulatory or Manufacturer Actions Taken for Safety Reasons

There have been no regulatory or manufacturer actions related to measles, mumps, and rubella virus vaccine live that resulted in marketing authorization withdrawal or suspension, failure to obtain marketing authorization renewal, restriction on distribution, clinical trial suspension, dosage modification, change in target population, or pharmaceutical changes for safety reasons.

An increase of the mumps virus minimum release specification from 50,000 to 100,000 $TCID_{50}$ (tissue culture infectious doses) per 0.5 mL dose occurred in February 2000 in order to ensure that the product would contain the required mumps potency through expiry. The 100,000 $TCID_{50}$ mumps titer is well within the Company's historical experience and meets or exceeds the registered dose claim (20,000 $TCID_{50}$ per 0.5 mL dose). The safety profile of measles, mumps, and rubella virus vaccine live has been and continues to be closely monitored on a continuing basis.

4. Changes to Reference Safety Information

The International Physicians Circular (IPC) is the Company Core Data Sheet (CCDS) which contains the Company Core Safety Information (CCSI), indications, dosage, pharmacology, and other product information. The CCDS for measles, mumps, and rubella virus vaccine live that was current at the end of the cut-off date is included in Appendix 2.

4.1 Changes to Reference Safety Information During the PSUR Reporting Period

During the reporting period of this PSUR (01-Jan-1999 to 31-Dec-2003), the following safety-related updates were added to the CCDS for measles, mumps, and rubella virus vaccine live [Changes in **BOLD**]. New sections or subsections that were added are also indicated in **BOLD**.

25-Feb-2000

INDICATIONS

M-M-R II is indicated for simultaneous vaccination against measles, mumps, and rubella in **individuals 12 months** of age or older.

There is some evidence to suggest that infants who are born to mothers who had natural measles and who are vaccinated at less than one year of age may not develop sustained antibody levels when later revaccinated. The advantage of early protection must be weighed against the chance for failure to respond adequately on reimmunization.

DOSAGE AND ADMINISTRATION

RECOMMENDED VACCINATION SCHEDULE

Individuals first vaccinated at 12 months of age or older should be revaccinated at 4-6 years of age or 11-12 years of age. Revaccination is intended to seroconvert those who do not respond to the first dose.

MEASLES OUTBREAK SCHEDULE

Infants Between 6-12 Months of Age
Local health authorities may recommend measles vaccination of infants between 6-12 months of age in outbreak situations. This population may fail to respond to the components of the vaccine. Safety and effectiveness of mumps and rubella vaccine in infants less than 12 months of age have not been established. The younger the infant, the lower the likelihood of seroconversion. Such infants should receive a second dose of M-M-R II at 15 months of age followed by revaccination at 4-6 years of age or 11-12 years of age.

POST-EXPOSURE VACCINATION

Vaccination of individuals exposed to natural measles may provide some protection if the vaccine can be administered within 72 hours of exposure. If, however, vaccine is given a

few days before exposure, substantial protection may be afforded. There is no conclusive evidence that vaccination of individuals recently exposed to natural mumps or natural rubella will provide protection.

CONTRAINDICATIONS

Hypersensitivity to any component of the vaccine, including gelatin.

Primary and acquired immunodeficiency states, including patients who are immunosuppressed in association with AIDS or other clinical manifestations of infection with human immunodeficiency viruses; cellular immune deficiencies; and hypogammaglobulinemic and dysgammaglobulinemic states. **Measles inclusion body encephalitis (MIBE), pneumonitis and death as a direct consequence of disseminated measles vaccine virus infection has been reported in severely immunocompromised individuals inadvertently vaccinated with measles-containing vaccine.**

PRECAUTIONS

HYPERSENSITIVITY TO EGGS

Live measles vaccine and live mumps vaccine are produced in chick embryo cell culture. Persons with a history of anaphylactic, anaphylactoid, or other immediate reactions (e.g., hives, swelling of the mouth and throat, difficulty breathing, hypotension, or shock) subsequent to egg ingestion may be at an enhanced risk of immediate-type hypersensitivity reactions after receiving vaccines containing traces of chick embryo antigen. The potential risk to benefit ratio should be carefully evaluated before considering vaccination in such cases. Such individuals may be vaccinated with extreme caution, having adequate treatment on hand should a reaction occur.

THROMBOCYTOPENIA

Individuals with current thrombocytopenia may develop more severe thrombocytopenia following vaccination. In addition, individuals who experienced thrombocytopenia with the first dose of M-M-R II (or its component vaccines) may develop thrombocytopenia with repeat doses. Serologic status may be evaluated to determine whether or not additional doses of vaccine are needed. The potential risk to benefit ratio should be carefully evaluated before considering vaccination in such cases.

PREGNANCY

In counseling women who are inadvertently vaccinated when pregnant or who become pregnant within 3 months of vaccination, the physician should be aware of the following: (1) In a 10 year survey involving over 700 pregnant women who received rubella vaccine within 3 months before or after conception (of whom 189 received the Wistar RA 27/3 strain), none of the newborns had abnormalities compatible with congenital rubella syndrome; **(2) Mumps infection during the first trimester of pregnancy may increase the rate of spontaneous abortion.** Although mumps vaccine virus has been shown to infect the placenta and fetus, there is no evidence that it causes congenital malformations in humans; and (3) Reports have indicated that contracting of natural measles during pregnancy enhances fetal risk. Increased rates of spontaneous abortion,

stillbirth, congenital defects and prematurity have been observed subsequent to natural measles during pregnancy. There are no adequate studies of the attenuated (vaccine) strain of measles virus in pregnancy. However, it would be prudent to assume that the vaccine strain of virus is also capable of inducing adverse fetal effects.

PEDIATRIC USE

Safety and effectiveness of measles vaccine in infants below the age of 6 months have not been established. Safety and effectiveness of mumps and rubella vaccine in infants less than 12 months of age have not been established.

DRUG INTERACTIONS

Administration of immune globulins concurrently with M-M-R II may interfere with the expected immune response. Vaccination should be deferred for 3 months or longer following administration of immune globulin (human) and blood or plasma transfusions.

SIDE EFFECTS

RARE

Body as a whole
Mild local reactions such as erythema, induration and tenderness; sore throat, malaise, **atypical measles, syncope, irritability**

Hypersensitivity
Allergic reactions such as wheal and flare at injection site, anaphylaxis and anaphylactoid reactions, **as well as related phenomena such as angioneurotic edema (including peripheral or facial edema) and bronchial spasm**, urticaria

Nervous/psychiatric
Febrile convulsions in children, afebrile convulsions or seizures, headache, dizziness, paresthesia, polyneuritis, **polyneuropathy**, Guillain-Barre syndrome, ataxia, **measles inclusion body encephalitis (MIBE) (see CONTRAINDICATIONS).** Encephalitis/encephalopathy have been reported approximately once for every 3 million doses. In no case has it been shown that reactions were actually caused by vaccine. The risk of such serious neurological disorders following live measles virus vaccine administration remains far less than that for encephalitis and encephalopathy with natural measles (one per two thousand reported cases).

Respiratory System
Pneumonitis (see CONTRAINDICATIONS), cough, rhinitis

Skin
Erythema multiforme, **Stevens-Johnson syndrome, vesiculation at injection site, swelling**

Other
Death from various, and in some cases unknown, causes has been reported rarely following vaccination with measles, mumps, and rubella vaccines; however, a causal

relationship has not been established. No deaths or permanent sequelae were reported in a published post-marketing surveillance study in Finland involving 1.5 million children and adults who were vaccinated with M-M-R II during 1982-1993. (Note: This update was based on published literature [1]).

Post-marketing surveillance of the more than [redacted] of M-M-R and M-M-R II that have been distributed worldwide over 25 years (1971-1996) indicates that serious adverse events such as encephalitis and encephalopathy continue to be rarely reported.

OVERDOSAGE

Overdose has been reported rarely and was not associated with any serious adverse events.

18-Jul-2000

PRECAUTIONS

OTHER

This product contains albumin, a derivative of human blood. Although there is a theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD), no cases of transmission of CJD or viral diseases have ever been identified that were associated with the use of albumin.

23-Feb-2001

SIDE EFFECTS

RARE

Hypersensitivity

Allergic reactions such as wheal and flare at injection site, anaphylaxis and anaphylactoid reactions, as well as related phenomena such as angioneurotic edema (including peripheral or facial edema) and bronchial spasm, urticaria **in individuals with or without an allergic history**.

03-Apr-2002

DOSAGE AND ADMINISTRATION

RECOMMENDED VACCINATION SCHEDULE

Individuals first vaccinated at 12 **to 15 months** of age or older, **in order to avoid maternal antibody interference,** should be revaccinated at 4-6 years of age **since increased risk of exposure typically occurs around elementary school entry.** Revaccination is intended to seroconvert those who do not respond to the first dose.

[1] Peltola H, et al. The Elimination of Indigenous Measles, Mumps, and Rubella from Finland by a 12-Year, Two Dose Vaccination Program. N. Engl. J. Med. *331*:1397-1402, 1994.

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5. Patient Exposure

5.1 Clinical Trials

The number of patients who were enrolled in [redacted] sponsored clinical trials between 01-Jan-1999 to 31-Dec-2003 and who were treated with measles, mumps, and rubella virus vaccine live was approximately [redacted].

5.2 Market Experience

The estimated number of marketed measles, mumps, and rubella virus vaccine live doses distributed worldwide between 01-Jan-1999 and 31-Dec-2003 was approximately [redacted]. Approximately [redacted] individuals are estimated to be vaccinated based on the assumptions that each patient received one dose and approximately 10% of the doses distributed were not used.

6. Presentation of Individual Case Histories

Description of the Data Presented

This Periodic Safety Update Report (PSUR) covers the period from 01-Jan-1999 to 31-Dec-2003. Individual case reports (ICRs) included in this PSUR include spontaneous reports received by Merck & Co., Inc., published individual case reports of suspected adverse drug reactions (ADRs) identified by the Company during the period covered by this PSUR, and reports of serious adverse events occurring in clinical studies and considered possibly, probably, or definitely vaccine-related by the reporting study physician. In keeping with the ICH Harmonised Tripartite Guideline, Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs (ICH E2C), throughout this report, these reports are referred to as ADR reports. The use of this term, however, does not imply, necessarily, that the reported events occurred due to an effect of measles, mumps, and rubella virus vaccine live, either in the opinion of the Company, or in the opinion of the reporter, or in fact. The data described in this document include reports in which measles, mumps, and rubella virus vaccine live was considered the primary suspect therapy.

References for the published individual patient case reports are included in Appendix 9.

The ADR terminology used in this PSUR reflects the diagnosis or terminology used by the reporter. The reporter terminology has been mapped to a Preferred Term using the Medical Dictionary for Regulatory Activities (MedDRA) and an autoencoder developed by Merck. On 08-Apr-2002, the Company implemented use of MedDRA for ADR reports. All prior reports in the database have been mapped to MedDRA, version 4.1. The terminology that displays in the line listings and summary tabulations of this PSUR is based on version 6.1 of MedDRA, which was the version of MedDRA that was in use at the time the PSUR line listings and summary tabulations were generated. However, the terminology that displays in appended CIOMS-I forms is based on the version of MedDRA that was in use at the time of individual case report data entry. Due to the mapping of the historic data, changes in MedDRA versions, and evolving coding guidelines and conventions, it is possible that, over time, different Preferred Terms may have been used to identify synonymous reactions. With the transition to MedDRA, the Preferred Terms are now organized into 26 System Organ Class groups versus the 15 Body Systems into which Preferred Terms were previously organized. Therefore, with the transition to MedDRA, the summary tabulations supplied in this PSUR may not be able to be compared with those in prior PSURs. In addition, the ADR Preferred Terms tabulated in the line listings and summary tabulations of this PSUR use British spellings. However, American spellings of ADR Preferred Terms are used throughout the discussions in Sections 1 through 10 of this PSUR.

For new spontaneous reports and follow-up information entered into the WAES database on or after 18-Apr-2003, all medical events with onset or worsening after initiation of the primary suspect therapy which did not prompt the contact with the Company and for which there is no implicit or explicit expression of possible drug causality by the reporter, are captured as abstracted events. Abstracted events are adverse events that are not related to the spontaneously reported adverse experience. Previously, these events were described in ADR narratives as "incidental findings." If a subject/patient experiences a medical event while on therapy with a Merck product and this event is mentioned in a report, the event is considered an abstracted event if the following conditions are met:

- The event is not the focus of the report.
- The reporter does not link the event with the current/suspect therapy or any other Merck product -i.e., there is no implication of association with a Merck product.

Abstracted Events are coded and included as adverse experiences in tabulations, but are referred to as abstracted ADRs throughout this PSUR. The numbers of events in these tabulations, therefore, may be larger than comparable numbers in similar reporting periods in prior PSURs because of this change in coding procedures.

For purposes of this report, a serious reaction is defined as one that: results in death, or is life-threatening, or results in a persistent or significant disability/incapacity, or results in or prolongs hospitalization, or is a congenital anomaly, or is a cancer, or is the result of an overdose (accidental or intentional). Since 01-Apr-1998, a serious report could also include any report with an "important medical event" (i.e., required medical or surgical intervention to prevent one of the aforementioned outcomes).

Spontaneous Reports

Reports on marketed products that were reported spontaneously are presented separately from study reports. Per the general principles of ICH E2C, all adverse experiences from spontaneous reports are assumed to be ADRs unless indicated otherwise by the reporting health care provider. Spontaneous reports also include reports from the literature and from government agencies. Only those reports where a health care provider was identified as a reporting source are included in the line listings and summary tabulations in Appendixes 3, 4, and 5. These reports may have been reported by health care providers or they may have initially been reported by consumers and follow-up was received from health care providers. Spontaneous reports, where the only information provided was from consumers, are attached as an addendum and are not further discussed.

The line listings that describe spontaneous reports where a health care provider has been identified are listed in the system organ class of the most important ADR term as determined by a Merck reviewer and are separated as follows:

Appendix 3, Table 1 - Line listing of reports that have at least one serious ADR term

Appendix 3, Table 2 - Line listing of reports that have only non-serious ADR terms including one that is unlisted

Reports that have only non-serious, listed ADRs do not appear in the line listings.

The period summary tabulations for spontaneous reports are organized by ADR term and categorized by system organ class. The tabulations are separated as follows:

Appendix 4, Table 1 - Period summary tabulation of ADR terms that are unlisted with the number of serious and non-serious reactions for each term

Appendix 4, Table 2 - Period summary tabulation of ADR terms that are listed with the number of serious and non-serious reactions for each term

In addition, a cumulative summary tabulation (Appendix 5) is provided and includes ADR terms that are serious and unlisted.

It is important to emphasize that the spontaneous reporting system is a voluntary system of reporting. Therefore, despite attempts to obtain follow-up information per Standard Operating Procedures, the data are not necessarily complete and may include reports with unsubstantiated diagnoses and incomplete information, irrespective of whether the reports originated from a health care provider or consumer.

Study Reports

Study reports include cases from Merck-sponsored investigational clinical trials, from postmarketing clinical trials, compassionate use programs, and from postmarketing surveillance (PMS) studies conducted anywhere in the world. Cases from retrospective and prospective studies that are described in the literature are classified as PMS studies.

The line listings that describe study reports (Appendix 6) include any report that had at least one serious, vaccine-related ADR term. Reports are also included if vaccine relationships were unknown or not provided. Vaccine relationships are those provided by the reporting investigators. The line listings are in the system organ class of the most important ADR term as determined by a Merck reviewer.

The period summary tabulations for study reports are organized by ADR term and categorized by system organ class. The tabulations are separated as follows:

Appendix 7, Table 1 Period summary tabulation of ADR terms that are serious, unlisted, and vaccine-related

Appendix 7, Table 2 Period summary tabulation of ADR terms that are serious, listed and vaccine-related

In addition, cumulative summary tabulations are provided and include study reports that have a serious, unlisted, vaccine-related ADR term (Appendix 8).

Description of Data Tables

The line listings of reports from spontaneous notifications, from studies or compassionate use, from literature, and from regulatory authorities are in order of system organ class. A report that contains more than one ADR term is assigned to the primary system organ class i.e., system organ class of the most clinically significant ADR term as determined by a Merck reviewer. Other ADR terms in the report are listed with it. The listings include the following information:

- the Merck identification number of the report (WAES NO)

- the primary reporting source (SOURCE)

    - Physician
    - Other health care provider (HCP) i.e., physician's assistant, nurse, dentist, veterinarian

  - Pharmacist
  - Consumer
  - Lawyer
  - Company representative
  - Agency

- the country from which the report originated (COUNTRY)

- patient age and sex (AGE, SEX)

- patient's total daily dose of vaccine at the time of the initial ADR (DOSE)

- the start date of therapy (THER START)

- the stop date of therapy (THER STOP)

- the date of onset of the ADR (ONSET)

- vaccine relationship provided by the investigator for study reports (DR)

  - (Y) yes (definite, probable, possible)
  - (N) no (probably not, definitely not)
  - (U) unknown or blank

- serious (SER)-(Y) yes, -(N) no

- ADR term (with the notation # for any that are a worsening of a pre-existing condition)

- outcome from the ADR (RECOVERED/RESOLVED, RECOVERED/RESOLVED WITH SEQUELAE, RECOVERING/RESOLVING, NOT RECOVERED/NOT RESOLVING, FATAL, UNKNOWN)

All cases submitted individually on an expedited basis to one or more regulatory authorities have been marked with an asterisk beside the Merck reference number.

7. Studies

7.1 Newly Analyzed Studies

During the reporting period of this PSUR, there were 3 newly analyzed studies that contained important, new safety information for measles, mumps, and rubella virus vaccine live. These 3 protocols are briefly summarized below.

7.1.1 Protocol 006

Title: A Randomized Double-Blind Comparison Of M-M-R™ Ii And Priorix™ In Infants 12 To 24 Months Of Age

Objectives: The primary objective of this study was to examine the differences in mumps virus strain specificity of virus neutralizing antibody responses elicited by immunization with M-M-R™ II (Trademark of Merck & Co., Inc., Whitehouse Station, New Jersey, U.S.A.) and PRIORIX™ (Trademark of GlaxoSmithKline, Rixensart, Belgium). Secondary objectives were: (1) To compare the safety and tolerability of M-M-R™ II and PRIORIX™. (2) To summarize the geometric mean titers and seroconversion rates (as measured by ELISA) for measles, mumps, and rubella for both M-M-R™ II and PRIORIX™. (3) If differences in neutralization of JL-2 are observed in M-M-R™ II and PRIORIX™ sera, to explore whether these differences are reproducible using wild-type mumps isolates that are genotypically similar to JL-2. (4) To compare the mumps virus neutralization titers induced against the Merck Jeryl Lynn™ strain by M-M-R™ II and PRIORIX™. (5) To identify any mumps strains that are less susceptible to PRIORIX™ sera, purify them, grow them out in culture, and probe them to identify regions of difference, particularly regions in the HN gene segments.

Safety Findings: The following table is a summary of clinical adverse experiences. Laboratory data were not collected in this study; therefore, no laboratory adverse experiences were reported.

A total of 5 subjects (3 recipients of M-M-R™ II and 2 recipients of PRIORIX™) reported non-vaccine-related serious adverse experiences. No subject reported vaccine-related serious adverse experiences. No enrolled subjects died during the study period. Overall, the safety profiles for recipients of M-M-R™ II and PRIORIX™ were found to be comparable. The proportion of subjects with vaccine-related injection-site adverse experiences were 4.7 and 4.8% in the 2 treatment groups, respectively. The total proportions of injection-site adverse experiences, including non-vaccine-related incidents, were 5.9 and 4.8% for the 2 treatment groups, respectively. The 95% confidence interval on the risk difference included zero, indicating no evidence of an overall difference in injection-site adverse experiences between the groups. The incidence rates of measles/rubella-like rash were 2.4 and 4.8% for the 2 treatment groups, respectively. The 95% confidence interval on the risk difference included zero, suggesting no evidence of a difference in rash rates. No incidents of mumps-like symptoms were reported during the study period. The percentages of subjects with elevated temperatures (≥102°F [≥38.9°] rectal equivalent or abnormal) within 6 weeks postvaccination were 51.8 and 56.0% for the 2 treatment groups, respectively. These differences were not statistically significant. There was one report of febrile seizure in a recipient of M-M-R™ II that was determined to be not vaccine related.

Clinical Adverse Experience Summary

Number (%) of subjects:	M-M-R™ II N=85		PRIORIX™ N=84	
	n	(%)	n	(%)
With no adverse experience	15	(17.6)	16	(19.0)
With one or more adverse experiences	70	(82.4)	68	(81.0)
Injection-site adverse experiences	5	(5.9)	4	(4.8)
Systemic adverse experiences	69	(81.2)	66	(78.6)
With rash	8	(9.4)	7	(8.3)
With maximum temperatures, rectal equivalent, ≥102°F (38.9°C) or abnormal	44	(51.8)	47	(56.0)
With vaccine-related adverse experiences†	23	(27.1)	22	(26.2)
Injection-site adverse experiences	4	(4.7)	4	(4.8)
Systemic adverse experiences	19	(22.4)	18	(21.4)
With serious adverse experiences	3	(3.5)	2	(2.4)
With serious vaccine-related adverse experiences‡	0	(0.0)	0	(0.0)
Who died‡	0	(0.0)	0	(0.0)
Discontinued due to an adverse experience‡	0	(0.0)	0	(0.0)
Discontinued due to a vaccine-related adverse experience‡	0	(0.0)	0	(0.0)
Discontinued due to a serious adverse experience‡	0	(0.0)	0	(0.0)
Discontinued due to a serious vaccine-related adverse experience‡	0	(0.0)	0	(0.0)

† Determined by the investigator to be possibly, probably, or definitely related to the study vaccine.
‡ At any time during study.
Percentages are calculated based on the number of subjects with follow-up after any visit.
Risk differences planned for injection-site adverse experiences, systemic clinical adverse experiences, and occurrence of any adverse experience.

Conclusion: In healthy children, 12 to 24 months of age, vaccinated with M-M-R™ II or PRIORIX™: (1) M-M-R™ II and PRIORIX™ induce similar levels of mumps-specific neutralizing antibodies to various mumps strains (wild-type strains Lo-1, Merck Jeryl Lynn™, Tennessee, and Barnes, as well as vaccine virus substrain Jeryl Lynn™ JL-2), in terms of geometric mean titers (GMTs) and seroconversion rates (SCRs) at 42 days postvaccination. Although differences were not statistically significant, neutralizing antibody titers tended to be consistently numerically higher in subjects vaccinated with M-M-R™II than in those immunized with PRIORIX™ with respect to GMTs; (2) M-M-R™ II and PRIORIX™ elicit comparable SCRs and GMTs for measles, mumps, and rubella by ELISA; (3) M-M-R™ II and PRIORIX™ are generally well tolerated and display similar safety and tolerability profiles.

7.1.2 Protocol 007-02

Title: A Study of M-M-R®II at Mumps Expiry Potency in Healthy Children 12 to 18 Months of Age

Objectives: (1) To demonstrate a similar immune response to mumps virus by neutralization among subjects receiving M-M-R®II containing an expiry dose of mumps virus concomitantly with VARIVAX™ in comparison to subjects receiving M-M-R®II containing a release dose of mumps virus concomitantly with VARIVAX™ and (2) To demonstrate an adequate immune response by mumps virus neutralization among subjects receiving M-M-R®II containing an expiry dose of mumps concomitantly with VARIVAX™.

Safety Findings: The following table is a summary of clinical adverse experiences. Safety data based on laboratory adverse experiences were not collected in this study; therefore, no laboratory adverse experiences were reported. A total of 25 subjects reported serious adverse experiences

during the 42 days postvaccination safety follow-up. Only 1 subject reported a vaccine-related serious adverse experience. The incident was reported as a febrile seizure occurring 19 days postvaccination and lasting 1 day with no sequelae noted. No enrolled subjects died during the study period or were discontinued from the study due to an adverse experience. No subjects reported a vaccine-related serious adverse experience during the 1-year persistence follow-up period. In general, the safety profiles of M-M-R®II containing a mumps virus potency of no more than 3.8 $\log_{10}$ $TCID_{50}$ mumps virus potency and M-M-R®II containing a mumps virus potency of no more than 4.1 $\log_{10}$ $TCID_{50}$ mumps virus potency were comparable to the safety profile of M-M-R®II containing a dose of mumps virus (4.8 $\log_{10}$ $TCID_{50}$ mumps virus potency) within the current release range. Incidence rates of injection-site adverse experiences and systemic adverse experiences were comparable among the 3 treatment groups. The proportion of subjects with elevated temperatures (defined as maximum temperature [oral equivalent] ≥102°F [38.9°C] or abnormal) between Days 0 to 42 postvaccination were 30.3%, 30.5%, and 31.2% for the 3.8, 4.1, and 4.8 $\log_{10}$ $TCID_{50}$ Mumps-Virus-Potency groups, respectively.

Clinical Adverse Experience Summary

	Treatment Groups of M-M-R®II					
	3.8 $\log_{10}$ $TCID_{50}$/dose Mumps Virus Potency† (N=663)		4.1 $\log_{10}$ $TCID_{50}$/dose Mumps Virus Potency† (N=662)		4.8 $\log_{10}$ $TCID_{50}$/dose Mumps Virus Potency‡ (N=672)	
	n	(%)	n	(%)	n	(%)
Number of subjects	663		662		672	
Subjects without follow-up	32		26		29	
Subjects with follow-up	631		636		643	
Number (%) of subjects:						
with no adverse experience	91	(14.4)	105	(16.5)	92	(14.3)
with one or more adverse experiences	540	(85.6)	531	(83.5)	551	(85.7)
injection-site adverse experiences	253	(40.1)	239	(37.6)	260	(40.4)
systemic adverse experiences	489	(77.5)	488	(76.7)	497	(77.3)
with vaccine-related§ adverse experiences	347	(55.0)	313	(49.2)	337	(52.4)
injection-site adverse experiences	251	(39.8)	237	(37.3)	258	(40.1)
systemic adverse experiences	181	(28.7)	148	(23.3)	150	(23.3)
with serious adverse experiences	10	(1.6)	6	(0.9)	9	(1.4)
with serious vaccine-related adverse experiences	0	(0.0)	1	(0.2)	0	(0.0)
who died	0	(0.0)	0	(0.0)	0	(0.0)
discontinued due to an adverse experience	0	(0.0)	0	(0.0)	0	(0.0)
discontinued due to a vaccine-related adverse experience	0	(0.0)	0	(0.0)	0	(0.0)
discontinued due to a serious adverse experience	0	(0.0)	0	(0.0)	0	(0.0)
discontinued due to a serious vaccine-related adverse experience	0	(0.0)	0	(0.0)	0	(0.0)

† Two sublots of M-M-R®II derived from the same parent lot as the control lot of M-M-R®II were aged to target mumps virus potencies with a 95% upper confidence bound of no more than 3.7 and 4.0 $\log_{10}$ $TCID_{50}$/dose. After reassignment of the mumps house standard (HS) potency to 4.3 $\log_{10}$ $TCID_{50}$/0.1mL, the 95% upper confidence bound values were no more than 3.8 and 4.1 $\log_{10}$ $TCID_{50}$, respectively. Final mumps virus potencies (95% upper confidence bound) were 3.76 (3.79) and 4.04 (4.08) $\log_{10}$ $TCID_{50}$, respectively.

‡ The mumps virus potency of 4.8 $\log_{10}$ $TCID_{50}$/dose is the point estimate for the control group and is representative of a mumps potency within the release range for M-M-R®II.

§ Determined by the investigator to be possibly, probably, or definitely related to the vaccine.

Conclusion:

A safety and immunogenicity study was conducted in healthy children 12 to 18 months of age. From this study, one can conclude that the expiry dose of mumps virus in M-M-R®II is no less than 4.1 $\log_{10}$ $TCID_{50}$ based on the following study results: (1) M-M-R®II with a mumps expiry dose of 4.1 $\log_{10}$ $TCID_{50}$ is highly immunogenic and induces an acceptable mumps-specific neutralizing antibody SCR that is comparable to that induced by M-M-R®II containing a release mumps virus potency of 4.8 $\log_{10}$ $TCID_{50}$. M-M-R®II with a mumps expiry dose of 3.8 $\log_{10}$

$TCID_{50}$ does not induce an acceptable mumps-specific neutralizing antibody SCR nor is it comparable to that induced by M-M-R®II containing a release mumps virus potency of 4.8 log_{10} $TCID_{50}$. (2) M-M-R®II with a mumps expiry dose of 4.1 log_{10} $TCID_{50}$ induces comparable SCRs for measles-, mumps-, and rubella-specific antibodies by ELISA as M-M-R®II containing a release mumps virus potency of 4.8 log_{10} $TCID_{50}$. Comparable SCRs to measles and rubella by ELISA were demonstrated for M-M-R®II with a mumps expiry dose of 3.8 log_{10} $TCID_{50}$ when compared with the current release mumps virus potency of 4.8 log_{10} $TCID_{50}$, but was not achieved for mumps. (3) Among subjects who seroconverted by ELISA, antibody to measles, mumps, and rubella persists for at least 1 year (the maximum time period evaluated in this study) with any of the 3 formulations of M-M-R®II evaluated. (4) M-M-R®II with a mumps expiry dose of 3.8 log_{10} $TCID_{50}$ or 4.1 log_{10} $TCID_{50}$, or M-M-R®II with a release dose of 4.8 log_{10} $TCID_{50}$ is generally well tolerated.

7.1.3 Protocol 009

Title: A Comparison Of The Safety, Tolerability, And Immunogenicity Of M-M-R™$_{II}$ Manufactured With Recombinant Human Albumin (rHA) Versus M-M-R™$_{II}$ Manufactured With Pooled-Donor Human Serum Albumin (HSA) In Healthy Children 12 To 18 Months Of Age

Objectives: (1) To demonstrate that the antibody response rates to measles, mumps, and rubella among children who receive M-M-R™$_{II}$[†] (Measles, Mumps, and Rubella Virus Vaccine Live) manufactured with rHA will be similar to the antibody response rates among children who receive M-M-R™$_{II}$ manufactured with HSA. (2) To demonstrate that M-M-R™$_{II}$ manufactured with rHA will induce acceptable antibody response rates to measles, mumps, and rubella. (3) To demonstrate that M-M-R™$_{II}$ manufactured with rHA will be generally well tolerated.

Safety Findings: Clinical adverse experiences reported during the 42 days postvaccination are summarized in the following table. The 2 treatment groups were generally comparable in terms of the incidence rates of serious adverse experiences, systemic adverse experiences, and adverse experiences of special interest. Although injection-site reactions were reported by a significantly greater proportion of subjects who received M-M-R™$_{II}$ with rHA (35.8%) than subjects who received M-M-R™$_{II}$ with HSA (29.7%), the incidence rates were within the range observed in previous clinical trials in which M-M-R™$_{II}$ had been administered. The majority of local reactions were reported as pain at the injection site and were mostly of mild intensity and short duration (<48 hours). The 6.1% difference in incidence rates of injection-site reactions could be attributable, at least in part, to variability between vaccine lots, which has been observed in recipients of M-M-R™$_{II}$ in previous clinical trials. A total of 8 subjects (3 recipients of M-M-R™$_{II}$ with rHA and 5 recipients of M-M-R™$_{II}$ with HSA) experienced serious adverse experiences, but none was assessed to be related to the study vaccine. No subjects were discontinued from the study because of an adverse experience.

[†] M-M-R $_{II}$ is a trademark of Merck & Co., Inc., Whitehouse Station, New Jersey, U.S.A.

Summary of Overall Clinical Adverse Experiences and Adverse Experiences of Special Interest (Days 1 to 42 Following Vaccination)

	M-M-R™$_{II}$ With rHA (N=641)		M-M-R™$_{II}$ With HSA (N=638)		Risk Difference ([M-M-R™$_{II}$ With rHA] - [M-M-R™$_{II}$ With HSA]) Percentage Points (95% Confidence Interval)[†]
	n	(%)	n	(%)	
Number of subjects:	641		638		
without follow-up	7		6		
with follow-up	634		632		
Number (%) of subjects:					
with no adverse experience	114	(18.0)	126	(20.0)	-2.0 (-6.4, 2.3)
with one or more adverse experiences	520	(82.0)	504	(80.0)	2.0 (-2.3, 6.4)
injection-site adverse experiences	227	(35.8)	187	(29.7)	6.1 (0.9, 11.3)
systemic adverse experiences	469	(74.0)	463	(73.5)	0.5 (-4.4, 5.3)
with vaccine-related adverse experiences[‡]	308	(48.6)	274	(43.5)	5.1 (-0.4, 10.6)
injection-site adverse experiences	226	(35.6)	186	(29.5)	6.1 (1.0, 11.3)
systemic adverse experiences	139	(21.9)	147	(23.3)	-1.4 (-6.0, 3.2)
with serious adverse experiences	3	(0.5)	5	(0.8)	-0.3 (-1.4, 0.7)
with serious vaccine-related adverse experiences[‡]	0	(0.0)	0	(0.0)	0.0 (-0.6, 0.6)
discontinuations due to adverse experiences	0	(0.0)	0	(0.0)	
with no adverse experiences of special interest[§]	547	(86.3)	545	(86.2)	0.1 (-3.7, 3.9)
with one or more adverse experiences of special interest[§]	87	(13.7)	87	(13.8)	0.0 (-3.9, 3.8)
urticaria	8	(1.3)	8	(1.3)	-0.0 (-1.4, 1.4)
angioedema	1	(0.2)	0	(0.0)	0.2 (-0.4, 0.9)
non-injection site rash	63	(9.9)	62	(9.8)	0.1 (-3.2, 3.4)
wheezing	19	(3.0)	18	(2.8)	0.1 (-1.8, 2.1)
collapse or shock-like state (onset within 48 hours of vaccination)	0	(0.0)	0	(0.0)	0.0 (-0.6, 0.6)
unexpected serious adverse experience that was potentially an allergic reaction	0	(0.0)	0	(0.0)	0.0 (-0.6, 0.6)

[†] Risk differences and confidence intervals are based on the pooled incidence rates across study centers.
[‡] Determined by the investigator to be possibly, probably, or definitely related to the study vaccine.
[§] Adverse experiences of special interest included urticaria, angioedema, non-injection site rash (this included maculopapular and generalized erythematous rashes but excluded eczematous and other simple, localized rashes), wheezing, collapse or shock-like state (onset within 48 hours of vaccination), and any unexpected serious adverse experiences that were potentially allergic reactions.
Percentages were calculated based on the number of subjects with follow-up.
N=Number of subjects vaccinated in each treatment group.
rHA=Recombinant human albumin.
HSA=Human serum albumin.

There was no statistically significant difference between the 2 treatment groups with respect to the proportion of subjects who experienced elevated temperatures (≥102°F [38.9°C], oral equivalent) during the 42 days postvaccination (17.6% of the recipients of M-M-R™$_{II}$ with rHA and 14.6% of the recipients of M-M-R™$_{II}$ with HSA [risk difference=3.0 percentage points, p-value=0.159]). No subjects in either treatment group developed antibodies to albumin. Similar proportions of subjects in both treatment groups (13.7% of the recipients of M-M-R™$_{II}$ with rHA and 13.8% of the recipients of M-M-R™$_{II}$ with HSA) reported 1 or more adverse experiences of special interest, with the most commonly reported adverse experience of special interest being non-injection-site rash. The number and proportion of adverse experiences of special interest considered to be vaccine-related appeared comparable between the 2 treatment groups.

Conclusion: This safety and immunogenicity study was conducted in healthy, 12- to 18-month-old children who were vaccinated with a single dose of either an investigational formulation of M-M-R™$_{II}$ with rHA or M-M-R™$_{II}$ with HSA, which is the currently licensed product. In conclusion, this clinical trial supports the replacement of HSA with rHA in the manufacturing of

the viral bulks for M-M-R™$_{II}$ based on the following study results: (1) M-M-R™$_{II}$ with rHA induced acceptable antibody response rates for measles, mumps, and rubella that are similar to those induced by M-M-R™$_{II}$ with HSA. (2) M-M-R™$_{II}$ with rHA was generally well tolerated and had safety and tolerability profiles comparable with those of M-M-R™$_{II}$ with HSA, the currently licensed vaccine. (3) No subjects had detectable anti-albumin antibodies in their serum at baseline or 42 days postvaccination.

7.2 Targeted New Safety Studies

During the reporting period of this PSUR, there were no targeted safety studies that were initiated, ongoing, or have been completed but not yet analyzed for measles, mumps, and rubella virus vaccine live.

7.3 Published Safety Studies

During the reporting period of this PSUR, there were 16 published safety studies that described new and potentially important safety information. These 16 published safety studies identified involved the following: neurologic disorders (5), vaccination safety and adverse events (3), allergic reactions or anaphylaxis (3), egg allergy (3), live viral vaccines in patients with a chromosomal syndrome (1), and inflammatory bowel disease (1).

1. Makela A, Nuorti J P and Peltola H
Neurologic disorders after measles-mumps-rubella vaccination
Pediatrics 110(5): 957-963, Nov. 2002

This retrospective study linked data from a hospital discharge register with data from a vaccination register to assess whether an association existed between MMR-II vaccination and autism, aseptic meningitis, or encephalitis among 535,544 children (age 1-7 yr) in Finland. The children included in the analysis were vaccinated between November 1982 and June 1986. The numbers of events associated with aseptic meningitis and encephalitis reported within the 3-mo postvaccination risk interval period were compared with the expected numbers of events estimated from the occurrence of aseptic meningitis and encephalitis during the subsequent 3-mo intervals. The 3-mo interval allowed for the incubation periods of all 3 viruses and ensured an adequate follow-up time for both aseptic meningitis and encephalitis. Changes in the overall number of hospitalizations for autism after vaccination were evaluated for the entire study period. Hospitalizations for inflammatory bowel disease were investigated in children with autism. Of the 535,544 children vaccinated, 352 were hospitalized for autism, 161 for aseptic meningitis, and 199 for encephalitis. Of the 352 children hospitalized for autism, 309 were hospitalized after MMR-II vaccination, 43 were vaccinated after their 1st hospitalization, and 31 were hospitalized but not vaccinated. None were hospitalized for inflammatory bowel disease. The time interval between MMR-II vaccination and hospitalization ranged from 3 days to 12 yr and 5 mo. Of the 161 children with aseptic meningitis, 10 (8 M, 2 F, age 15-85 mo) were hospitalized within 3 mo of MMR-II vaccination; the time from vaccination to hospitalization ranged from 2 days to 1 mo and 29 days. In 110 children, the time interval from vaccination to hospitalization exceeded 3 mo. Forty-one children were vaccinated after hospitalization. Of the 199 children with encephalitis, 9 (7 M, 2 F, age 15-82 mo) were hospitalized within 3 mo of MMR-II vaccination; the time from vaccination to hospitalization ranged from 2 days to 2 mo and 22 days. In 110 children, the time interval from vaccination to hospitalization exceeded 3 mo. Eighty children were vaccinated after hospitalization. During the study period, no increased

occurrences of either aseptic meningitis or encephalitis were observed within the designated 3-mo postvaccination risk period. In fact, the incidences of aseptic meningitis and encephalitis in children age 1-7 yr decreased by 24% and by 35%, respectively. In Finland, children diagnosed with autism are admitted to the hospital for extensive neurobiological examinations, treatment, and rehabilitation; thus a significant clustering of admissions for autism after vaccination would have been detected. No clustering of hospitalizations for autism were observed in this study. On the basis of these results, the authors did not identify any associations between MMR-II vaccination and autism, aseptic meningitis, or encephalitis.

2. Patja A, Paunio M, Kinnunen E, Junttila O, Hovi T and Peltola H
Risk of Guillain-Barre syndrome after measles-mumps-rubella vaccination
J Pediatr 138(2): 250-254, Feb. 2001

The authors performed an active retrospective study that linked data from the national hospital discharge register with individual vaccination records of patients hospitalized for Guillain Barre syndrome (GBS) in Finland between November 1982 and December 1986 to determine the risk of GBS after MMR vaccination. During the study period, 900,000 doses of M-M-R-II were administered to roughly 630,000 people. Of the 189 individuals hospitalized for GBS during this time, 20 children aged 1- 12 yr (9 M, 11 F) and 4 men aged 21-25 yr had been vaccinated. None of the 20 children had onset of symptoms within 6 wk of vaccination. The shortest duration of time between vaccination and onset of symptoms was 80 days in a 5-yr-old boy who had gastroenteritis, a respiratory tract infection, and otitis media 1 mo before the onset of symptoms. In 13 children, the duration ranged from 10 mo to 3 yr and 10 mo. The remaining 6 children did not receive the vaccine until after diagnosis; MMR vaccine did not cause recurrence of GBS in these children. Of the 14 children who received vaccine before GBS, 11 were revaccinated after recovery and had no relapses. Of the total 24 patients with GBS, 20 had had a respiratory or GI tract infection before onset of GBS. Laboratory tests indicated that cytomegalovirus infection may have been responsible for GBS in 2 patients; respiratory syncytial virus was isolated from a child receiving artificial respiration. One 18-mo-old girl who developed GBS in 1985 still had severe sensory polyneuropathy in November 1999. The authors conclude that there is an absence of evidence to suggest that MMR vaccination causes GBS.

3. Patja A, Paunio M and Peltola H
Neurological events following MMR vaccination
Clin Infect Dis 31(1): 324-324, July 2000 (in Soc. Proc.)

The incidence of neurological events associated with childhood vaccination against measles, mumps and rubella was determined prospectively using data from 14 yr of follow-up in Finland. During surveillance of adverse events related to measles-mumps-rubella vaccination since 1982, a total of 8 cases of encephalitis or meningitis were attributed to the vaccine. Of the 4 encephalitis cases, only 1 was confirmed to be due to measles virus, which was isolated from a child with acute lymphoblastic leukemia at 54 days after vaccination. One case of encephalitis was caused by Herpes simplex; the other 2 cases had undetermined etiology. Of the 4 meningitis cases, 2 were caused by bacteria (Haemophilus influenzae and meningococcus); the other 2 were probably due to viral infection, but since symptoms developed within 2 days after vaccination, they were considered not to be caused by vaccine virus. The authors note that about 3 million doses of measles-mumps-rubella vaccine were administered during the 14-yr period; thus, the 3 cases of encephalitis that were considered possibly related to the vaccine represented an incidence of only 0.1/100,000 doses for all 3 components of the vaccine. Since the incidence of

encephalitis associated with natural measles, mumps, and rubella is 35, 150, and 12.5 per 100.000 cases, respectively, this represents about a 2000-fold difference. The authors mention that meningitis, which has an incidence of 1/1000 cases of clinical mumps, did not appear to be causally related to measles-mumps-rubella vaccine in any case in this survey. They conclude that neurological events after administration of this vaccine are rare and that the risks are dwarfed by the incidence of natural sequelae of these diseases.

4. Plesner A M, Juul Hansen F, Taudorf K, Holme Nielsen L, Brenner Larsen C and Pedersen E

Gait disturbance interpreted as cerebellar ataxia after MMR vaccination at 15 months of age: a follow-up study

Acta Paediatr 89(1): 58-63, Jan. 2000

The authors report on 41 infants (29 M, 12 F) with "gait disturbance" following M-M-R vaccination at age 15 mo; long-term follow-up data are presented for 26 cases. Reports were identified from a search of 550 adverse event notifications sent to the Statens Serum Institut in Denmark during the 10-yr period after the inclusion of M-M-R in their childhood vaccination program (1987-1996). A total of 0.8 notifications per 10,000 vaccinees was recorded (533,000 doses total). During this period, about the same number of M-M-R doses (scheduled boosters) was administered to 12-yr-old children; none was associated with any reports of "gait disturbance." Twenty-eight of 41 cases of "gait disturbance" were not further classified by the doctor. Of the remaining cases, 2 were interpreted as dizziness, 6 as encephalitis, 2 as reactive arthritis, 1 as convulsions, and 2 as cerebellar ataxia. A pediatric neurologist found signs and symptoms of "gait disturbance" to be consistent with cerebellar ataxia, which the authors postulate may be due to an immune reaction in the immature brain. The adverse reaction was more prevalent in males than in females (3:1). Thirty-two parents filled in a questionnaire during a 1996 nationwide survey of adverse events to all vaccines, and 26 (63%) agreed to participate in a follow up in 1997. All parents wrote that their child had been walking steadily before the vaccination. Sixteen children had eye symptoms, and some had trouble keeping the head upright. Six parents commented that their child had memory, concentration, and/or language problems. According to the mother of one child with encephalitis symptoms, the child stopped talking for 2.5 yr after the episode. The majority of parents reported that the time from vaccination until onset of symptoms was 8-14 days, and that the duration of symptoms was a median of 1-2 wk (range, 1 day-4+ mo). Seven (19%) had symptoms of short duration (1 day in 5 cases), 1/3 had symptoms lasting 1-2 wk, and 1/3 had symptoms lasting a month or longer. Eleven children (34%) were hospitalized. None of the 26 children who attended the clinical follow-up examination 1-10 yr after vaccination still had a gait disturbance, although 15 had "soft" neurological signs, and 6 had additional neuropsychological complaints. The 11 children who had fully normal examinations had had a significantly shorter duration of symptoms (median 10 days, range 1-30 days) than did the 15 children with lingering neurological and/or neuropsychological complaints (median, 30 days; range 3-120 days; P=0.002). A prospective follow-up or case-control study, perhaps in a Nordic population, would be the model of choice to better characterize the clinical diagnosis of cerebellar ataxia and the exact incidence of this adverse event. The authors note that although the introduction of M-M-R vaccination has saved the lives of many children, doctors and health officials must weigh knowledge of adverse events against the benefits of vaccination.

5. Patja A, Kinnunen E, Junttila O and Peltola H
MMR vaccination and Guillain-Barre Syndrome
Clin Infect Dis 27(4): 1054-1054, Oct. 1998 (in Soc. Proc.)

The association between MMR vaccination and Guillain-Barre syndrome was investigated in a study of about 450,000 vaccinees for whom 900,000 doses of MMR vaccine was used in Finland between 1982 and 1986. MMR vaccine was administered routinely to children at the age of 14-18 mo and 6 yr. Since 1986, MMR vaccine was also routinely given to recruits of the Defense Forces. The hospital register was utilized to identify all Guillain-Barre syndrome patients in Finland during that time period. Timing of MMR vaccination was defined according to the patient's medical records kept in health care (immunization) centers. A total of 189 patients were hospitalized for Guillain-Barre syndrome. Twenty-one patients were among those for whom MMR vaccination was scheduled; 20 were vaccinated. Time interval between immunization with MMR vaccine and onset of Guillain-Barre syndrome varied from 80 days to years. There was no accumulation of Guillain-Barre syndrome at any time point during the almost 4-yr period post-immunization with MMR vaccine. The authors note that although a valid control group was not feasible (because almost all subjects in the target groups were immunized), this information strongly suggest that there is no causal relationship between MMR vaccination and Guillain-Barre syndrome.

6. Patja A, Davidkin I, Kurki T, Kallio M J T, Valle M and Peltola H
Serious adverse events after measles-mumps-rubella vaccination during a fourteen-year prospective follow-up
Pediatr Infect Dis J 19(12): 1127-1134, Dec. 2000

The incidence of serious adverse events after MMR vaccination was determined prospectively using data from 14 yr of follow-up (1982-1996) in Finland, where MMR II was the primary vaccine administered. A total of 2,990,000 doses were administered to 1.8 million vaccinees (57% M, 43% F, age 13 mo-23 yr) by the end of 1996. Of the 437 vaccinees who reported adverse events during the 14- yr period, 169 had 173 adverse reactions that were considered potentially serious. All events were analyzed, with the exception of a possible anaphylactic reaction in a 6-yr-old child, whose medical records were not obtained. Paired sera were available for 83 children; a single sample was available for 19. Eighty-one percent of adverse events occurred after the 1st vaccine dose. However, 63% of anaphylactic reactions occurred after the 2nd dose. Overall, 77 neurologic reactions, 73 allergic reactions, 22 miscellaneous reactions, and 1 death due to aspiration of vomit caused by acute gastritis were reported. Neurologic reactions included febrile seizures in 52 cases, epilepsy in 3, undefined seizures in 4, encephalitis in 4, meningitis in 4, Guillain-Barre syndrome in 2, transient gait disturbances in 5, and confusion during fever in 3. Allergic reactions included anaphylaxis in 30 cases, urticaria in 30, asthma-like symptoms in 10, Henoch-Schonlein purpura in 2, and Stevens-Johnson syndrome in 1. Miscellaneous reactions included pneumonia in 12 cases, otitis media in 2, orchitis in 4, diabetes mellitus in 3, and polydipsia and polyuria in 1. Forty-five percent of all serious adverse reactions were proved to be probably caused or contributed by some factor other than MMR. Therefore, the incidence of serious adverse events with a possible or unknown causal relation with MMR vaccination was 3.2 per 100,000 vaccine doses or 5.3 per 100,000 vaccinees. No cases of autism were associated with MMR vaccination during the 14-yr follow-up. In addition, there were no reports of ulcerative colitis, Crohn's disease, or any other chronic GI disorder. The authors

conclude that serious adverse events occur rarely with MMR vaccine and that these events are outweighed by the risks of natural infection.

7. Virtanen M, Peltola H, Paunio M and Heinonen O P
Day-to-day reactogenicity and the healthy vaccinee effect of measles-mumps-rubella vaccination
Pediatrics [serial online] 106(5, Part 1): E62.1-E62.6, Nov. 2000 [cited Pediatrics 106(5, Part 1): 1128-1128]. Available from: http://www.pediatrics.org/cgi/content/full/106/5/e62
A randomized double-blind placebo-controlled crossover study was conducted in Finland to evaluate the incidence of true adverse reactions to MMR vaccine in 581 pairs of twins (age 14 mo-6 yr). Early results of the study were published previously; this article presents an analysis of the day-to-day symptoms and signs in 2 age groups with or without previous measles vaccination. For each pair of twins, one child received 1 dose of MMR vaccine followed by 1 dose of placebo 3 wk later; the other twin received the placebo dose, followed by the MMR dose 3 wk later. Among the 230 pairs of 1-yr-old twins, 3 pairs (1.3%) had been previously vaccinated against measles. Among the 351 pairs of twins aged 2 yr or more, 313 (89%) had been vaccinated against measles; 42 additional children in this age group had experienced natural measles. Systemic MMR-related events, defined as any symptom or sign (except those affecting the respiratory or gastrointestinal tracts) occurring during postvaccination days 6-14, peaked on day 10 regardless of whether the MMR vaccine was the 1st or 2nd injection received. Overall, 6% of vaccinees had adverse events attributable to the MMR vaccine. The frequency of respiratory signs and symptoms increased by 15% to 20% during the first 10 days postinjection, and did not decline thereafter; this occurred after both the MMR and placebo injections. The most common systemic sign observed with MMR vaccination was fever. Among children aged 14 to 18 mo, fever of 38.5°C or higher occurred more frequently after the MMR vaccine than after placebo (odds ratio: 3.28, 95% CI: 2.23-4.82; $p<0.001$); among 6-yr-old children, there was no difference in the incidence of fever after MMR vaccine and placebo. In children 14-18 mo of age, the incidences of rash ($p=0.07$), arthralgia ($p=0.07$), conjunctivitis ($p=0.0008$), staying in bed ($p=0.0008$), drowsiness ($p=0.002$), and irritability ($p=0.0001$) were or tended to be higher after MMR vaccination than after placebo. The incidence of vaccine-attributable reactions was 15-fold higher in younger than in older vaccinees; previously vaccinated children had 16-fold fewer symptoms and signs than did children not previously vaccinated. Among 6-yr-old children, arthralgia was the only symptom associated with MMR vaccination. The authors conclude that the MMR vaccine was virtually nonreactogenic in children 6 yr of age, of whom more than 95% had either already received measles vaccine or had experienced the disease. They also note that, although administration of the vaccine or placebo was avoided during infection, there was a steady increase in respiratory symptoms and signs for 7-9 days postinjection; they suggest that since 15%-20% is the usual frequency of such symptoms and signs in children, this observation can be explained by the healthy vaccinee effect.

8. D'Souza R M, Campbell-Lloyd S, Isaacs D, Gold M, Burgess M, Turnbull F and O'Brien E
Adverse events following immunisation associated with the 1998 Australian Measles Control Campaign
Commun Dis Intell 24(2): 27-33, Feb. 17, 2000

The authors report adverse events (AEs) following immunization of 1.7 million school children with MMR-II during the Australian Measles Control Campaign (MCC) from August to November 1998. Of 124 AEs reported in children aged 4-13 yr within 30 days of vaccination, 35

with missing onset dates or uncertain causality were excluded; 46 were categorized as certainly caused by MMR-II, 23 as probably associated with MMR-II, and 20 as possibly associated with MMR-II. The overall AE rate (per 100,000 doses administered) was 5.24. The most common AE was syncopal fit (23.6%; rate 1.24), followed by allergic reaction (rate 0.65); 57% of the reactions occurred <1 hr after vaccination. No deaths and 1 anaphylactic reaction were reported (rate 0.06). Nineteen children were seen by a doctor, 13 were seen in the emergency department (ED), and 14 were hospitalized (after syncope in 3, seizure in 1, hyperventilation in 4, fever in 2, anaphylactoid reactions in 2, local reaction in 1, and other in 1); 79 children recovered (outcome unknown in 9). One anaphylactic reaction and 12 allergic and 6 anaphylactoid reactions were classified as certainly due to MMR-II; except for 4 allergic reactions, all occurred <1 hr after vaccination and all children recovered. Adrenaline was given to 13 children. Rates for allergic and anaphylactoid reactions were 0.65 and 0.35, respectively, for an overall rate of 1.06 for any immediate allergic-type reaction. Afebrile seizure was reported in 4 children (rate 0.24), febrile seizure in 1 (rate 0.06), and encephalopathy in 1 (rate 0.06); the rate for any seizure was 0.30. Afebrile seizure occurred 12, 15, and 28 days, respectively, after MMR-II in 3 children; seizure onset was <24 hr for the child with febrile seizure and for one 7-yr-old child with a 20-min afebrile seizure. A 10-yr-old boy with viral infection 2 wk before vaccination had a focal seizure 15 days after MMR-II, followed by facial puffiness 3 days later possibly related to the mumps component; he received anticonvulsants and recovered. A 6-yr- old girl with a seizure 28 days after MMR-II was diagnosed with juvenile absence seizures; her symptoms are under control with anticonvulsants. Transient encephalopathy in an 8-yr-old boy 4 days after MMR-II was possibly related to MMR-II. There were 2 cases of arthralgia (rate 0.12) 5 and 14 days, respectively, after MMR-II, and 1 case of arthritis (rate 0.06). Four parotitis reactions were reported. There were 5 local reactions (rate 0.3), 2 of which were severe, and 1 case of lymphadenitis. Other reactions included measles- (2) and rubella-like illness (4), hallucinations (7-yr-old boy, full recovery), and encephalopathy (possibly triggered by MMR-II viremia 7 days after vaccination in an 8-yr-old boy with familial hemiplegic migraine, with recovery). The authors state that the benefits of this MCC far outweigh the incidence of serious AEs associated with immunization.

9. Bohlke K, Davis R L, Marcy S M, Braun M M, DeStefano F, Black S B, Mullooly J P and Thompson R S for the Vaccine Safety Datalink Team
Risk of anaphylaxis after vaccination of children and adolescents
Pediatrics 112(4): 815-820, Oct. 2003

This study was conducted to quantify the risks to children and adolescents (age 0-17 yr) of developing an anaphylactic reaction after immunizations that included the following vaccines: Hib; HBV; measles-mumps-rubella; DT; DTP; DTP-Hib; and OPV. The children were all enrolled in 1 of 4 West Coast HMOs that participated in the Centers for Disease Control and Prevention's Vaccine Safety Datalink (VSD) Project. In this study, vaccine-associated anaphylaxis was restricted to days 0 to 2 after vaccination and was defined by one of the following diagnostic descriptions: anaphylactic shock; adverse reactions from bacterial vaccines; adverse reactions from other vaccines and biological substances; and unspecified allergies. A search of the VSD Project for the period 1991-1997 examined a total of 7,644,049 vaccine doses and identified 5 potential cases of vaccine-associated anaphylaxis among children age 7 wk to 17 yr, for a risk of 0.65 cases/million doses. Overall, the observed risks of anaphylaxis after vaccination were as follows: HBV, 1.1 cases/million doses; Hib, 1.3 cases/million doses; and measles-mumps-rubella, 3.5 cases/million doses. Patient [redacted] was a 16-mo-old child with a history of asthma and eczema who developed erythema, wheezing, tachycardia, and rash within 1 hr of

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receiving a measles-mumps-rubella vaccination. The child was diagnosed with an adverse reaction to a vaccine and/or to a biological substance, and recovered following treatment with albuterol and diphenhydramine elixir. Patient [redacted] was a 7-wk-old infant who developed cyanosis, dyspnea, petechial lesions, and tachycardia within 2 hr of receiving HBV, OPV, and DTP-HIB vaccinations. The infant was diagnosed with an adverse reaction to a bacterial vaccine, and recovered following treatment with acetaminophen. Patient [redacted] was a 17-yr-old adolescent who developed facial flushing, nausea, lightheadedness, shortness of breath, and leg numbness within 1 hr of receiving measles-mumps-rubella and DT vaccinations. The adolescent was diagnosed with anaphylactic shock, and recovered following treatment with IV hydrocortisone (no dosage details), epinephrine, diphenhydramine, and D5W. Patient [redacted] was a 10-mo-old infant with a history of asthma who developed rash, wheezing, and swollen lips within 2 days of receiving HBV, DTP-HIB, and OPV vaccinations. The infant was diagnosed with anaphylactic shock, and recovered following treatment with IM dexamethasone (no dosage details), epinephrine, albuterol, and hydroxyzine. Patient [redacted] was a 19-mo-old child who developed pruritus, swollen lips, urticaria, and slight stridor within 5-10 min of receiving measles-mumps-rubella, DTP, OPV, and Hib vaccinations. The child was diagnosed with an unspecified allergy, and recovered following treatment with epinephrine and diphenhydramine. The authors conclude that even though vaccine-associated anaphylaxis is a rare occurrence, health care providers should be prepared to provide immediate treatment if needed.

10. Pool V, Braun M M, Kelso J M, Mootrey G, Chen R T, Yunginger J W, Jacobson R M, Gargiullo P M and the VAERS Team

Prevalence of anti-gelatin IgE antibodies in people with anaphylaxis after measles-mumps-rubella vaccine in the United States

Pediatrics [serial online] 110(6): E71.1-E71.9, Dec. 2002 [cited Pediatrics 110(6):]. Available from: http://www.pediatrics.org/cgi/content/full/110/6/e71]

This retrospective case-control study in the USA used data from the Vaccine Adverse Event Reporting System (VAERS) to compare the levels of anti-gelatin IgE antibodies and the profiles of self-reported allergies in patients who reported anaphylactic reactions following the administration of measles virus-containing vaccines (including MMR-II and unspecified measles-mumps-rubella vaccine) with those in healthy controls who did not report anaphylactic reactions following vaccinations. It also reviewed the reporting trends for selected hypersensitivity adverse events following measles-mumps-rubella or varicella vaccinations during the time periods before and after the introduction into the USA immunization schedule of gelatin-containing DTaP vaccines. A total of 57 patients were recruited into the study; 34 had histories of drug, environmental, and food allergies. Twenty-two patients (9 M, 13 F, age 15 mo-33 yr) provided serum samples for IgE analysis; 27 others also provided serum samples in addition to acting as a comparison group. A retrospective analysis of the data revealed significantly higher levels of anti-gelatin IgE antibodies among patients than among controls. Six (27%) of the patients tested positive for anti-gelatin IgE antibodies, but none of the controls did. The rate of anaphylactic reactions following measles virus- containing vaccinations that were reported to VAERS between 1991 and 1997 was 1.8/1 million doses distributed. There was no extensive increase in the number of reported allergic events following immunization with gelatin-containing measles-mumps-rubella or varicella vaccines after the introduction into the USA immunization schedule of gelatin-containing DTaP vaccines. The case reports of 7 patients (4 M, 3 F, age 15 mo-23 yr) who developed anaphylaxis following administration of a measles-containing vaccine are described. On the basis of these results, the authors conclude that anaphylactic reactions to measles-mumps-rubella or MMR-II vaccines occur rarely in the USA

and at the same rate as they do in other countries. In approximately 25% of the patients who report anaphylaxis, the hypersensitivity can be attributed to the gelatin in the vaccine. Consequently, these patients may be at a high risk of developing anaphylaxis to subsequent doses of other gelatin-containing vaccines and should undergo allergy evaluations prior to other immunizations.

11. Patja A, Makinen-Kiljunen S, Davidkin I, Paunio M and Peltola H
Allergic reactions to measles-mumps-rubella vaccination
Pediatrics [serial online] 107(2): E27.1-E27.7, Feb. 2001 [cited Pediatrics 107(2): 398-398]. Available from: http://www.pediatrics.org/cgi/content/full/107/2/e27

Serum samples from 36 individuals (age 14 mo-23 yr, median age 5 yr 11 mo) who developed anaphylaxis, asthmatic symptoms, Henoch-Schonlein purpura, or urticaria with or without angioedema following M-M-R vaccination were analyzed by RAST and immunospot methods to identify the true allergenic vaccine component. Seventy-three presumably allergic reactions were collected from a prospective follow up of serious adverse events after M-M-R vaccination during a 14-yr period (Nov. 1982-Dec. 1996) in Finland, where M-M-RII has been the only vaccine in general use (2,990,000 doses distributed). Serum samples were available for analysis in 36. Twenty-five of 36 reactions occurred after the first dose of M-M-R, and 10 after the second (data not available for one). Twenty reactions occurred within 1 hr (17 within 10 min). Seven children (19.4%) had received other vaccines simultaneously, and 10 had concurrent infections (27.8%). Two vaccine lots, two types of gelatin (pork, beef), egg, neomycin, human albumin, and hydrolyzed collagen were tested; the porcine gelatin currently used by the manufacturer was not available for testing. Ten children were found to be allergic to gelatin, and 7 had persistent allergic symptoms possibly due to foods (gelatin ingredients or cross-reactive antigens). All 10 had distinct binding of IgE to gelatin. Tests were rated as "strong positive" in 4 and "weak positive" in 6. Two of the 10 showed reactivity against hydrolyzed collagen. Nine subjects also had egg-specific IgE binding and 8 had chicken-specific IgE binding. One 20-yr-old woman had anaphylaxis 9 hr after vaccination, shortly after eating chicken. All subjects recovered uneventfully. To correlate RAST and positive immunospot results with later allergic symptoms, vaccinees with gelatin-specific IgE or their parents were interviewed in May 2000, which was as long as 17 yr 5 mo after the original episode. Only 2 of the 10 reported no allergic symptoms. Among the other 8, one developed an anaphylactic reaction to chicken 1 yr after M-M-R vaccination. Four reported frequent GI symptoms, and 3 reported angioedema or blistering of the mouth or throat that they associated with food, especially chicken, egg, fish, or pudding. Two patients reported persistent atopic eczema. Three patients were revaccinated with M-M-R 4 yr 5 mo-14 yr after the first dose. One developed cough and sneezing after the 2nd dose; the other 2 had no symptoms. During the period 1992-1996, 2570 doses of egg-protein-free measles-mumps- rubella vaccine were given to egg-allergic individuals; there were no reports of allergic reactions with this vaccine. Mechanisms were debated regarding how gelatin allergy develops in children <1 yr of age. This study shows the rarity of severe allergic reactions induced by M-M-R, and supports current recommendations for vaccination of egg-allergic individuals. More research is needed to characterize the allergenic role of gelatin.

12. Dimitriou A N D, Syrigou E K S, Tapranzi P T, Manousakis M M, Baka G B, Zanikou S Z, Psarros P P and Saxoni Papageorgiou P S P
Administration of measles-mumps-rubella vaccine (MMR) in egg-allergic children
Allergy 57(Suppl. 73): 209-209, 2002 (in Soc. Proc.)

The safety of measles-mumps-rubella vaccine was assessed in 114 children (72 M, 42 F, mean age 24.8 mo) with allergy to egg proteins. Before vaccination with a 0.5-ml SC dose, subjects underwent a skin prick test and radioallergosorbent test (RAST) with egg and a skin prick test and/or intradermal test with measles-mumps-rubella vaccine, diluted in normal saline at a 1:10 and 1:100 ratio, respectively. Ten (8.77%) children had positive skin test results with measles-mumps-rubella vaccine. Only 1 (0.87%) of the 114 subjects had an immediate adverse reaction to the vaccine, manifesting as mild generalized urticaria; this child had a had a positive intradermal test with the vaccine. Thus, the positive predictive value of skin testing with measles-mumps-rubella vaccine was very low (10%). The authors conclude that children with egg allergy can be safely immunized with measles-mumps-rubella vaccine without any extra precautions.

13. Atanaskovic-Markovic M and Nestorovic B
MMR vaccination of children allergic to eggs
Allergy 57(Suppl. 73): 177-178, 2002 (in Soc. Proc.)

A study was conducted in 104 Yugoslavian children with suspected severe allergy to eggs to determine if they were at greater risk for anaphylactic reactions to measles + mumps + rubella vaccine than were children without the allergy. The children were monitored over a 5-yr period. The children received skin prick tests with ovalbumin and measles + mumps + rubella vaccine. If both skin prick tests were negative, the vaccine was administered in a single dose of 0.5 ml. If either test was positive, the vaccine was administered in increasing doses of 0.05 ml every 15 min. Positive skin tests for the egg and measles + mumps + rubella vaccine were seen in 14 children (13.5%). No systemic reactions were seen after vaccination of any child with positive skin tests. Minor reactions after vaccination were seen in 7 children who had positive skin tests to egg and vaccine. Positive skin tests for the egg were found in 90 children (86.5%); however, none of these children had a reaction after vaccination. Positive skin tests to measles + mumps + rubella vaccine were seen in 8 children (7.7%), but none of these children had a reaction following vaccination. A positive skin test to the vaccine, but not to the egg was seen in 1 child (0.9%). The authors conclude that children with allergic reactions to eggs are not at higher risk for anaphylactic reactions following measles + mumps + rubella vaccine than are children without the allergy.

14. Chow W C, Kwan E Y W and Lau Y L
MMR vaccination of children allergic to egg
Paper presented at The 23rd International Congress of Pediatrics, The 2nd International Congress on Pediatric Nursing, Beijing, China 104-104, Sept. 9-14, 2001

A retrospective study was conducted in Hong Kong to document any association between established egg allergy and anaphylactic reaction to MMR vaccine in 146 patients (79 M, 67 F) admitted to the hospital for MMR vaccination. A total of 96 patients had a history of egg allergy; most of the patients did not know if they were allergic to egg white or to egg yolk. Seven of the 96 patients had had an anaphylactic reaction to an egg component; the other patients had had

minor reactions such as rash or urticaria. All 146 patients were given MMR vaccine. None of the patients developed an anaphylactic reaction; 2 patients developed a non-specific rash soon after injection. All patients were discharged on the day of injection. No deaths were reported. The authors conclude that MMR vaccination is safe, and that egg allergy should not delay vaccination with MMR. They note that children with mild egg allergy can be safely vaccinated without any additional precautions; however, all vaccination should be carried out in a setting equipped to deal with anaphylactic reactions.

15. Perez E E, Bokszczanin A, McDonald-McGinn D, Zackai E H and Sullivan K E
Safety of live viral vaccines in patients with chromosome 22q11.2 deletion syndrome (DiGeorge syndrome/velocardiofacial syndrome).
Pediatrics [serial online] 112(4): e325-e327, Oct. 2003 [cited Pediatrics 112(4): 969-970]. Accessed 14-Oct-2003. Available from: http://www.pediatrics.org/cgi/content/full/112/4/e325

This retrospective study was conducted to evaluate the incidence of adverse effects following the administration of live viral vaccines in 59 children (age 2.5-7 yr) with chromosome 22q11.2 deletion syndrome (DiGeorge Syndrome/Velocardiofacial Syndrome). The vaccines studied were varicella and measles-mumps-rubella virus. The consequences of withholding vaccination were also evaluated. The study population was comprised of 174 patients with chromosome 22q11.2 deletion syndrome who were seen at the Children s Hospital of Philadelphia between 1994 and 2002. Some of the patients were vaccinated prior to the diagnosis of chromosome 22q11.2 deletion syndrome. Of the 174 directed mailings sent out, 59 responses were received and were included in the final analysis. Fifty-two of the 59 children were vaccinated with a measles-mumps-rubella vaccine. Only 12 (23%) children experienced adverse effects: fever (n=11), rash (n=3), and constitutional symptoms (n=4). Thirty-two of the 59 children were vaccinated with a varicella vaccine. Only 3 (9%) children experienced adverse effects: fever (n=3). A total of 63% of the unvaccinated children developed chickenpox, but none developed a natural measles, mumps, or rubella disease. T-cell counts were similar among vaccinated children, regardless of the presence of adverse effects. The incidences of adverse effects following measles-mumps-rubella and varicella vaccinations among children with chromosome 22q11.2 deletion syndrome were similar to those among children in the general population. On the basis of these results, the authors conclude that this cohort of children with chromosome 22q11.2 deletion syndrome tolerated live viral vaccines without significant adverse events.

16. Davis R L, Kramarz P, Bohlke K, Destefano F and Chen R T
A case-control study of MMR and other measles-containing vaccines and inflammatory bowel disease: results from the Vaccine Safety Datalink study
Paper presented at the 40th Interscience Conference on Antimicrobial Agents and Chemotherapy, Toronto, Canada 250-250, Sept. 17, 2000

Recent studies have linked measles vaccine and inflammatory bowel disease (IBD), but these studies have been questioned on methodological grounds. Therefore, the authors conducted a case-control study within the CDC's Vaccine Safety Datalink Project to assess whether measles-containing vaccine triggered the onset of IBD and whether vaccine receipt or the timing of vaccination was associated with the disease. Automated records identified persons with ICD-9 codes specific for Crohn's disease and ulcerative colitis. Cases were born between 1958 and 1989, enrolled from birth until disease onset, and matched to 3 controls by gender and birth yr. There were 155 cases of IBD, including 80 cases of Crohn's disease and 73 cases of ulcerative colitis. Ninety-two percent of cases and 94% of controls had received MMR vaccine or other

measles-containing vaccine; 8% of cases and 6% of controls were never vaccinated. Past vaccination with MMR did not increase the risk for Crohn's disease (relative risk [RR] 0.34; 95% confidence interval [CI] 0.06-1.78), ulcerative colitis (RR 0.83, 95% CI 0.19-3.70), or IBD (RR 0.53, 95% CI 0.18-1.53). Risk for IBD was not increased in children vaccinated at <12 mo or 12-18 mo of age, but children vaccinated with MMR at >18 mo of age were at decreased risk, compared with children who were never vaccinated (RR 0.16, 95% CI 0.04-0.68). There was no increased risk for development of symptoms of IBD, Crohn's disease, or ulcerative colitis in the 2, 4, 6, or 12 mo following vaccination with MMR or other measles-containing vaccine. In conclusion, this large, population-based study showed that MMR or other measles-containing vaccine did not increase the risk for IBD or trigger its onset.

8. Other Information

8.1 Late-Breaking Information

There was no important or new late-breaking information that would alter the currently known safety profile as described in the current CCDS for measles, mumps, and rubella virus vaccine live.

9. Overall Safety Evaluation

The data presented in this PSUR represent the marketed and clinical study experience with measles, mumps, and rubella virus vaccine live for reports that meet the criteria described in Section 6, Presentation of Individual Case Histories, that were received by Merck & Co., Inc., from worldwide sources, between 01-Jan-1999 to 31-Dec-2003.

Most of the ADRs reported during the period of this PSUR are either already listed or represent situations for which conclusions cannot be drawn. Those events, which are unlisted, have been reviewed against cumulative data and relevant safety-related issues are summarized in this section.

9.1 Summary Tabulation of Reports

During the reporting period of this PSUR, there were a total of 5,170 reports with ADRs spontaneously received from healthcare providers for measles, mumps, and rubella virus vaccine live. A total of 22 serious, vaccine-related study reports were received during the reporting period and no study reports were serious and unlisted.

Table 9.1.1 is a summary tabulation of the number of spontaneous reports of ADRs for measles, mumps, and rubella virus vaccine live (presented by System Organ Class), which were received during the reporting period of this PSUR and from Market Introduction (International Birthdate for measles, mumps, and rubella virus vaccine live is 15-Sep-1978, in the United States) to 31-Dec-2003.

Table 9.1.1
Measles, Mumps, and Rubella Virus Vaccine Live
Summary Tabulation of Reports From Healthcare Providers by System Organ Class*

System Organ Class	Number of Reports Received From 01-Jan-1999 to 31-Dec-2003	% *of Reports*	Number of Reports Received From Market Introduction to 31-Dec-2003	% *of Reports*
Blood and lymphatic system disorders	337	7	924	8
Cardiac disorders	39	1	108	1
Congenital, familial and genetic disorders	10	<1	25	<1
Ear and labyrinth disorders	51	1	132	1
Endocrine disorders	4	<1	6	<1
Eye disorders	144	3	341	3
Gastrointestinal disorders	365	7	822	7
General disorders and administration site conditions	2,751	53	6,187	53
Hepatobiliary disorders	9	<1	47	<1
Immune system disorders	112	2	255	2
Infections and infestations	666	13	1,895	16
Injury, poisoning and procedural complications	1,340	26	2,436	21
Investigations	193	4	364	3
Metabolism and nutrition disorders	92	2	214	2
Musculoskeletal and connective tissue disorders	233	5	669	6
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	9	<1	19	<1
Nervous system disorders	947	18	2,112	18
Pregnancy, puerperium and perinatal conditions	29	1	122	1
Psychiatric disorders	253	5	493	4
Renal and urinary disorders	16	<1	43	<1
Reproductive system and breast disorders	16	<1	54	<1
Respiratory, thoracic and mediastinal disorders	330	6	627	5
Skin and subcutaneous tissue disorders	1,429	28	3,374	29
Social circumstances	5	<1	9	<1
Surgical and medical procedures	2	<1	32	<1
Vascular disorders	107	2	247	2
DISTINCT NUMBER OF REPORTS	**5,170**	—	**11,738**	—

*A single patient report may include ADRs in one or more System Organ Classes. Therefore, the sum of reports from all System Organ Classes can be greater than the total distinct number of reports received. Percentages are the number of reports in the System Organ Class per total number of distinct reports in the given column.

Comment

Review of Table 9.1.1 reveals that the percentages of ADR reports by System Organ Class for the reporting period of this PSUR are generally consistent with those percentages from Market Introduction.

Table 9.1.2 is a summary tabulation of the number and percent of spontaneous reports of unlisted serious and nonserious ADRs from healthcare providers for measles, mumps, and rubella virus vaccine live (presented by SOC), which were received during the reporting period of this PSUR and from Market Introduction to 31-Dec-2003.

Table 9.1.2
Measles, Mumps, and Rubella Virus Vaccine Live
Summary Tabulation of Reports of Unlisted Serious/Nonserious ADRs
From Healthcare Providers by System Organ Class*

System Organ Class	Number of Reports Received From 01-Jan-1999 to 31-Dec-2003		Number of Reports Received From Market Introduction to 31-Dec-2003	
	Reports With Serious, Unlisted ADRs (%)	Reports With Nonserious, Unlisted ADRs (%)	Reports With Serious, Unlisted ADRs (%)	Reports With Nonserious, Unlisted ADRs (%)
Blood and lymphatic system disorders	37 (4)	15 (1)	76 (5)	73 (1)
Cardiac disorders	27 (3)	12 (<1)	62 (4)	46 (1)
Congenital, familial and genetic disorders	9 (1)	1 (<1)	21 (1)	4 (<1)
Ear and labyrinth disorders	16 (2)	28 (1)	24 (2)	64 (1)
Endocrine disorders	1 (<1)	3 (<1)	2 (<1)	4 (< 1)
Eye disorders	43 (5)	53 (2)	69 (5)	182 (3)
Gastrointestinal disorders	49 (5)	93 (3)	85 (6)	221 (3)
General disorders and administration site conditions	146 (16)	1,388 (48)	271 (18)	2,999 (46)
Hepatobiliary disorders	7 (1)	2 (<1)	29 (2)	18 (<1)
Immune system disorders	9 (1)	5 (<1)	16 (1)	33 (1)
Infections and infestations	163 (18)	217 (8)	288 (19)	584 (9)
Injury, poisoning and procedural complications	14 (2)	1,326 (46)	33 (2)	2,402 (37)
Investigations	20 (2)	144 (5)	49 (3)	277 (4)
Metabolism and nutrition disorders	51 (6)	41 (1)	92 (6)	127 (2)
Musculoskeletal and connective tissue disorders	49 (5)	76 (3)	78 (5)	211 (3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	6 (1)	3 (<1)	12 (1)	8 (<1)
Nervous system disorders	317 (36)	117 (4)	449 (30)	329 (5)
Pregnancy, puerperium and perinatal conditions	25 (3)	6 (<1)	41 (3)	49 (1)
Psychiatric disorders	65 (7)	125 (4)	83 (6)	252 (4)
Renal and urinary disorders	9 (1)	7 (<1)	22 (1)	23 (<1)
Reproductive system and breast disorders	7 (1)	5 (<1)	10 (1)	26 (<1)
Respiratory, thoracic and mediastinal disorders	111 (12)	139 (5)	166 (11)	309 (5)
Skin and subcutaneous tissue disorders	105 (12)	498 (17)	160 (11)	956 (15)
Social circumstances	4 (<1)	1 (<1)	7 (<1)	2 (<1)
Surgical and medical procedures	2 (<1)	0 (0)	19 (1)	13 (<1)
Vascular disorders	47 (5)	61 (2)	70 (5)	180 (3)
DISTINCT NUMBER OF REPORTS	**891**	**2,866**	**1,509**	**6,488**

* A single patient report may include serious and nonserious, listed and unlisted ADRs in one or more System Organ Classes. Therefore, the sum of reports from all System Organ Classes, and the sum of serious and nonserious, listed and unlisted reports, can be greater than the total distinct number of reports received. Percentages are the number of reports in the System Organ Class per total number of distinct reports in the given column.

Comment

Review of Table 9.1.2 reveals that the majority of reports with unlisted ADRs were nonserious. The distribution of reports received during the period of this PSUR remained reasonably consistent with the percentages of total reports received from Market Introduction.

Table 9.1.3 is a summary tabulation of the number and percent of spontaneous reports of listed serious and non-serious ADRs from healthcare providers for measles, mumps, and rubella virus vaccine live (presented by System Organ Class), which were received during the reporting period of this PSUR and from Market Introduction to 31-Dec-2003.

Table 9.1.3
Measles, Mumps, and Rubella Virus Vaccine Live
Summary Tabulation of Reports of Listed Serious/Nonserious ADRs
From Healthcare Providers by System Organ Class*

System Organ Class	Number of Reports Received From 01-Jan-1999 to 31-Dec-2003		Number of Reports Received From Market Introduction to 31-Dec-2003	
	Reports With Serious, Listed ADRs (%)	Reports With Nonserious, Listed ADRs (%)	Reports With Serious, Listed ADRs (%)	Reports With Nonserious, Listed ADRs (%)
Blood and lymphatic system disorders	126 (14)	173 (8)	247 (15)	593 (9)
Cardiac disorders	0 (0)	0 (0)	0 (0)	0 (0)
Congenital, familial and genetic disorders	0 (0)	0 (0)	0 (0)	0 (0)
Ear and labyrinth disorders	7 (1)	1 (<1)	30 (2)	15 (<1)
Endocrine disorders	0 (0)	0 (0)	0 (0)	0 (0)
Eye disorders	17 (2)	33 (2)	24 (1)	92 (1)
Gastrointestinal disorders	85 (9)	170 (8)	129 (8)	446 (7)
General disorders and administration site conditions	308 (34)	1,177 (54)	525 (31)	3,081 (49)
Hepatobiliary disorders	0 (0)	0 (0)	0 (0)	0 (0)
Immune system disorders	67 (7)	31 (1)	100 (6)	127 (2)
Infections and infestations	56 (6)	288 (13)	109 (6)	1,081 (17)
Injury, poisoning and procedural complications	1 (<1)	0 (0)	1 (<1)	0 (0)
Investigations	6 (1)	25 (1)	9 (1)	33 (1)
Metabolism and nutrition disorders	0 (0)	0 (0)	0 (0)	0 (0)
Musculoskeletal and connective tissue disorders	34 (4)	104 (5)	82 (5)	383 (6)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0 (0)	0 (0)	0 (0)	0 (0)
Nervous system disorders	427 (47)	191 (9)	799 (48)	770 (12)
Pregnancy, puerperium and perinatal conditions	0 (0)	0 (0)	4 (<1)	51 (1)
Psychiatric disorders	11 (1)	71 (3)	19 (1)	187 (3)
Renal and urinary disorders	0 (0)	0 (0)	0 (0)	0 (0)
Reproductive system and breast disorders	1 (<1)	4 (<1)	3 (<1)	17 (<1)
Respiratory, thoracic and mediastinal disorders	36 (4)	91 (4)	45 (3)	187 (3)
Skin and subcutaneous tissue disorders	168 (18)	776 (36)	280 (17)	2,247 (36)
Social circumstances	0 (0)	0 (0)	0 (0)	0 (0)
Surgical and medical procedures	0 (0)	0 (0)	0 (0)	0 (0)
Vascular disorders	0 (0)	0 (0)	0 (0)	0 (0)
DISTINCT NUMBER OF REPORTS	**916**	**2,168**	**1,679**	**6,262**

* A single patient report may include serious and nonserious, listed and unlisted ADRs in one or more System Organ Classes. Therefore, the sum of reports from all system organ classes, and the sum of serious and nonserious, listed and unlisted reports, can be greater than the total distinct number of reports received. Percentages are the number of reports in the System Organ Class per total number of distinct reports in the given column.

Comment

Review of Table 9.1.3 reveals that the majority of reported listed ADRs were nonserious. There were no substantial increases in percentages of reports with listed ADRs by System Organ Class in the time frame of this PSUR, as compared to the overall percentages of reports with listed ADRs from Market Introduction.

9.2 Reports with Fatal Outcomes

During the reporting period for this PSUR, 62 spontaneous reports involving fatal outcomes in patients treated with measles, mumps, and rubella virus vaccine live were received from health care professionals, regulatory agencies, or published literature articles. Of these 62 reports, the Company received 25 use-during-pregnancy reports in which the pregnancy resulted in an elective abortion (5), spontaneous abortion (17), intra-uterine death (2), and twin pregnancy with foetal loss and retention of one foetus (1). Per Company policy, these reports are recorded as adverse events with a fatal outcome. These 25 reports are discussed in Section 9.6, Use During Pregnancy. The remaining 37 reports are summarized in the Table 9.2.1 below.

The remaining 37 reports involved 18 males, 18 females, and 1 report had no specified gender, ranging in age from 12 months to 28 years with an average age of 6 years. Three of these 37 reports were identified from published literature articles. The remaining 34 reports were received from the following countries: United States (15), United Kingdom (6), Sweden (6), Norway, (2), Germany (1), Denmark (1), France (1), China (1), and Malta (1).

Table 9.2.1
Measles, Mumps, and Rubella Virus Vaccine Live
Reports of Fatal Outcomes
01-Jan-1999 to 31-Dec-2003

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WAES No:	Age/Gender	Reported Cause of Death	Comment
[redacted]	12 m / F	Seizure	Information was received from a health care professional concerning a 12-month-old female who was vaccinated IM with one dose of measles, mumps, and rubella virus vaccine live. Concomitant vaccinations included hepatitis A vaccine and "Meningitec." Subsequently, the patient experienced convulsions and died. The cause of death was seizure.
[redacted]	5 y / F	Encephalomyelitis, Encephalopathy NOS, Multi-organ failure	Information was received from a physician concerning a normal, healthy 5-year-old Caucasian female who was vaccinated with a second dose of measles, mumps, and rubella virus vaccine live. Concomitant vaccinations included acellular diphtheria toxoid/pertussis vaccine/tetanus, oral poliovirus vaccine, and a tuberculin tine test. No concurrent conditions or past medical history. Approximately 1-week post vaccination, the patient was given a dose of cefixime for the treatment of pharyngitis and "redness in the ear." Eight hours later, the patient developed a fever of 107°F which progressed to grand mal seizures. The patient was diagnosed with acute disseminated encephalomyelitis. Subsequently, the patient went into a coma, had organ failure, life support was discontinued, and she died. The reported cause of death was encephalitis.

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WAES No:	Age/Gender	Reported Cause of Death	Comment
[redacted]	28 y / M	T-cell lymphoma NOS	Information was received from a physician concerning a 27- or 28-year-old male Asian immigrant [redacted] who died of Natural Killer Cell Lymphoma approximately 1 to 2 months after receiving a first dose of measles, mumps, and rubella virus vaccine live.
[redacted]	18 m / Unk	Lymphohistiocytosis, Pneumonitis NOS	Information was received from a health care professional concerning a patient who was vaccinated with measles, mumps, and rubella virus vaccine live at approximately 13-months-old. Subsequently, at 18-months-old, the patient died with a diagnosis of erythrophagocytic lymphohistiocytosis. Autopsy revealed a "giant cell pneumonitis".
[redacted]	11 y / M	Cardiac failure congestive, Cardiovascular disorder NOS, Malaise, Obesity, Pneumococcal infection NOS	Information was received from a health care professional concerning an 11-year-old obese male patient with a "metabolic disorder" and history of adipositas who was vaccinated with measles, mumps, and rubella virus vaccine live. Concomitant vaccinations that same day included a first dose of diphtheria toxoid (+) poliovirus vaccine (+) tetanus toxoid IM in the upper arm. The patient became severely ill, was hospitalized, and subsequently died. An autopsy revealed pneumococcal sepsis. The patient died of circulatory failure, furthered by a cardiac insufficiency caused by extreme adipositas (100 kg body-weight).
[redacted]	13 y / M	Death NOS	Information was received from a health authority concerning a 13-year-old male who was vaccinated with measles, mumps, and rubella virus vaccine live. The patient collapsed and died from an unknown cause (sudden death). The patient took no other drug within the past three months.
[redacted]	13 m / M	Aspiration, Gastritis NOS	Information received from a published literature article concerning a healthy 13-month-old male who died during his sleep 8 days after vaccination with measles, mumps, and rubella virus vaccine live. Forensic autopsy disclosed the cause of death as aspiration of vomit caused by acute gastritis.
[redacted]	14 m / F	Multi-organ failure	Information was received from a physician concerning a 14-month-old female with failure to thrive and possible immunodeficiency who was vaccinated with measles, mumps, and rubella virus vaccine live. Subsequently, the patient experienced encephalitis, seizures, and combined immune deficiency which required hospitalization. The patient continued to deteriorate and eventually developed pneumonitis, hepatitis, and multiple organ failure which prolonged hospitalization. The cause of death was multiple organ failure.
[redacted]	18 m / M	Bacterial sepsis	Information was received from a health professional concerning an 18-month-old male who was vaccinated with measles, mumps, and rubella virus vaccine live. [redacted] He had overwhelming sepsis with DIC. He was ventilated and the next day, the ventilator was switched off and the patient died. The cause of death was sepsis.

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WAES No:	Age/Gender	Reported Cause of Death	Comment
[redacted]	15 m / F	Cardio-respiratory arrest	Information was received from a company representative concerning a 15-month-old white female with reactive airway disease was vaccinated with measles, mumps, and rubella virus vaccine live. Concomitant therapy included varicella virus vaccine live and streptococcus pneumoniae vaccine. [redacted] the patient experienced an unexplained cardiorespiratory arrest and died. The cause of death was later reported as unknown.
[redacted]	12 m / M	Cardio-respiratory arrest	Information was received from CBER concerning a 12-month-old male with gastroenteritis and chronic obstructive airway disease and a history of prematurity who was vaccinated subcutaneously in the right leg with measles, mumps, and rubella virus vaccine live. Concomitant vaccine therapy included varicella virus vaccine live, streptococcus pneumoniae vaccine, and haemophilus b conjugate vaccine. Other concomitant medication included albuterol and fluticasone propionate. Subsequently, the patient died of cardiopulmonary arrest of unknown etiology.
[redacted]	12 m / F	Bacterial sepsis, Cardiac arrest, Dehydration, Erythema multiforme minor, Fever, Lethargy, Measles, Meningitis meningococcal, Shock, Vomiting NOS	Information was received from a physician concerning a 12-month-old Asian female with a past history of allergies, eczema, and a hematoma on the forehead, who received measles, mumps, and rubella virus vaccine live, varicella virus vaccine live, and streptococcus pneumoniae vaccine. [redacted] The physician confirmed that the child did eat a different type of fish and wondered if the child may have contracted a Vibrio infection from ingesting infected raw fish.

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WAES No:	Age/Gender	Reported Cause of Death	Comment
[redacted]	5 y / F	Yellow fever	Information was received from the physician of a published literature article concerning a 5-year-old white female with a history of low birth weight, diarrhea, bronchitis during childhood and aseptic meningitis 3 months before the current illness, who was vaccinated with measles, mumps, and rubella virus vaccine live and a separate vaccine of yellow fever virus vaccine live. [redacted] The cause of death was yellow fever. It was concluded that the vaccine virus was the probable cause of fatal infections, which closely resembled wild-type yellow fever.
[redacted]	11 y / F	Death NOS	Information was received from a newspaper reporter concerning an 11-year-old female who was vaccinated with a first dose of measles, mumps, and rubella virus vaccine live at age 1 and at age 5 was vaccinated with a second dose of measles, mumps, and rubella virus vaccine live. [redacted] The brain biopsy tissue confirmed that the child was infected with wild type measles virus. Subsequently, the patient died.
[redacted]	25 y / M	Death NOS	Information was received from a physician concerning a 25-year-old male with no known allergies or psychiatric history and a history of varicella, who was vaccinated with measles, mumps, and rubella virus vaccine live. Concomitant therapy included hepatitis B vaccine recombinant (yeast). [redacted] Follow-up information indicated that there is no connection between the vaccinations and the death.

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WAES No:	Age/Gender	Reported Cause of Death	Comment
[redacted]	14 m / M	Acute respiratory distress syndrome, Cyanosis NOS, Encephalopathy NOS, Fever, Neurological examination abnormality, Viral infection NOS	Information was received from a health professional concerning a 14-month-old male with a history of varicella, who was vaccinated with measles, mumps, and rubella virus vaccine live. [redacted] The first diagnosis was infectious pneumopathy associated with an infectious or hypoxic encephalopathy. He died a few days later. The diagnosis was acute respiratory distress syndrome, probably secondary to an infectious pulmonary pathology, from probable viral origin. The exact cause of death was not specified. No autopsy was performed.
[redacted]	7 y / M	Subacute sclerosing panencephalitis	Information was received from a physician concerning a 7-year-old male who was vaccinated with measles, mumps, and rubella virus vaccine live. The patient presented with a history of recent psychomotor retardation without any associated history or signs of an infectious or neoplastic process. Investigations concluded that the etiology lay in a subacute sclerosing panencephalitic process attributable to measles, mumps, and rubella virus vaccine live. [redacted] the patient died. The reporter felt that subacute sclerosing panencephalitic process was related to therapy with measles, mumps, and rubella virus vaccine live.
[redacted]	18 m / F	Sudden infant death syndrome	Information was received from a health authority concerning an 18-month-old [redacted] who was vaccinated with the first dose of measles, mumps, and rubella virus vaccine live. After vaccination, the patient developed a common cold with fever. [redacted] Follow-up information indicated that an autopsy had been done and the result showed no abnormalities.

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WAES No:	Age/Gender	Reported Cause of Death	Comment
[redacted]	2 y / M	Chromosomal abnormality NOS (Wolf-Hirschhorn syndrome)	Information was received from a health authority concerning a 2-year-old male with Wolf-Hirschhorn syndrome, a disease with a defection in chromosome No. 4 and epilepsy, who was vaccinated with measles, mumps, and rubella virus vaccine live. Concomitant therapy included oral sulfamethoxazole/ trimethoprim, valproate sodium 4 ml/d, and valproic acid. Two days later, the boy was found dead [redacted] It was reported that 35% of children with Wolf-Hirschhorn syndrome will die before the age of 2 years. An autopsy was performed and there was no indication for any other explanation for his death than the Wolf-Hirschhorn syndrome.
[redacted]	18 m / F	Sepsis NOS	Information was received from a journalist concerning an 18-month-old female (also reported as male) with a history of coli infection of urinary tract at 2 months of age and frequent outpatient visits and hospitalizations due to various infections especially upper respiratory and otitis media, who was vaccinated with a 0.5 ml dose of measles, mumps, and rubella virus vaccine live. The patient was previously vaccinated against BCG, diptheria, tetanus x3, and polio 1 and 2 without reactions. [redacted] The patient received intensive treatment with hydrocortisone sodium succinate and cefuroxime sodium, but the patient subsequently died.
[redacted]	18 m / M	Pneumonia NOS	Information was received from a journalist concerning an 18-month-old previously healthy male who was vaccinated with a 0.5 ml dose of measles, mumps, and rubella virus vaccine live. [redacted] The autopsy showed inflammation of the lungs and respiratory system. The reporter felt that pneumonia was not related to therapy with measles, mumps, and rubella virus vaccine live.

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WAES No:	Age/Gender	Reported Cause of Death	Comment
[redacted]	18 m / M	Sepsis NOS	Information was received from a journalist concerning a healthy 18-month-old male who was vaccinated with measles, mumps, and rubella virus vaccine live. [redacted] No results were reported from the autopsy. Further information received reported that the investigations pointed at sepsis and that there is not causal relationship to the vaccine.
[redacted]	1 y / F	Sepsis NOS	Information was received from a journalist concerning a 1-year-old female who was vaccinated with measles, mumps, and rubella virus vaccine live. Subsequently, the patient died. The diagnosis was reported as sepsis. The patient's death was assessed as not related to the vaccination with measles, mumps, and rubella virus vaccine live.
[redacted]	18 m / F	Intracranial haemorrhage NOS, Thrombocytopenia	Information was received from a journalist concerning an 18-month-old female who was vaccinated with a 0.5 ml dose of measles, mumps, and rubella virus vaccine live. Low platelet counts were measured. Her condition deteriorated and she was referred to the hospital for further investigation. [redacted] The girl died shortly thereafter due to the large intracerebral hemorrhage. The report was assessed as possibly related to vaccination with measles, mumps, and rubella virus vaccine live.
[redacted]	25 m / M	Sudden infant death syndrome	Information was received from a health authority concerning a 25-month-old male with a history of 2 episodes of uncomplicated fever convulsions who was vaccinated with measles, mumps, and rubella virus vaccine live. There was no concomitant medication. [redacted] The autopsy showed no certain cause of death and the cause of death was classified as borderline SIDS.

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WAES No:	Age/Gender	Reported Cause of Death	Comment
[redacted]	Unk / F	Death NOS	Information was received from a physician concerning a female adult patient who was vaccinated with a dose of measles, mumps, and rubella virus vaccine live, while in the hospital. Concomitant therapy included a dose of tetanus toxoid. The physician "heard" that the patient "may have had a serious adverse event" and requested information regarding measles, mumps, and rubella virus vaccine live, encephalitis, and coma. He reported that she went on to develop encephalitis and later died.
[redacted]	Unk / M	Death NOS	Information was received from a physician concerning a male who was vaccinated with a dose of measles, mumps, and rubella virus vaccine live. At the time of vaccination, the "patient had an unknown immune deficiency." Following vaccination, the patient developed a "morbilliform rash and fever," got better, then developed "another morbilliform rash and fever for 3-4 days, then a serious illness." The patient had been diagnosed with "hematophagocytic syndrome" and Epstein-Barr virus was found. The patient was hospitalized and subsequently died (cause unknown).
[redacted]	12 y / F	Brain compression	Information was received from a health authority concerning a 12-year-old female who was vaccinated with a dose of measles, mumps, and rubella virus vaccine live. It was noted that the patient had a history of "intern hydrocephalus and signs of meningioencephalitis," but the onset of these is unclear. There was no concomitant medication. [redacted] The results of autopsy showed, "big, swollen, fluid-filled and slightly asymmetric brain with thick membrane and compressed under side. The content of the stomach has been found in the airpathways.
[redacted]	18 y / M	Meningitis bacterial NOS	Information was received from a health professional concerning an 18-year-old male patient who was vaccinated with a dose of measles, mumps, and rubella virus vaccine live. Concomitant therapy included hepatitis A vaccine (inactive), hepatitis B virus vaccine rHBsAg (yeast), pneumococcal vaccine 23 polyvalent (MSD), tuberculin purified protein derivative, influenza virus vaccine, and meningococcal polysaccharide vaccine. The patient presented with an acute onset of a rash on his feet that spread to his face over a few hours, a 3-day history of a cough, and sore throat. [redacted] The autopsy showed that the cause of death was Neisseria Meningitidis Septicemia (Meningococcemia). It was confirmed that the patient was positive for serogroup C Meningococcal infection.

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WAES No:	Age/Gender	Reported Cause of Death	Comment
[redacted]	Unk / M	Airways obstruction	Information was received from an internet news site concerning a male infant, born prematurely at 28 weeks and suffers from a rare stomach disorder, who was vaccinated with a dose of measles, mumps, and rubella virus vaccine live. Secondary suspect therapy included poliovirus vaccine inactivated (unspecified). [redacted] The coroner recorded a verdict of accidental death after the patient "inhaled some gastric contents".
[redacted]	Unk / M	Subacute sclerosing panencephalitis	Information was received from a newspaper article concerning a male patient, who was vaccinated with a dose of measles, mumps, and rubella virus vaccine live. It was reported that over the eighteen months following vaccination, the patient developed subacute sclerosing panencephalitis and lost the ability to do everything. It was reported that the patient died at 18 years of age from subacute sclerosing panencephalitis.
[redacted]	22 y / F	Lupus-like syndrome, Pulmonary haemorrhage	Information was received from a newspaper article concerning a 22-year-old female Army reservist, with no history of skin problems or immune system problems, who was vaccinated with a dose of measles, mumps, and rubella virus vaccine live. Additional suspect therapies included vaccination on the same day with hepatitis B vaccine, smallpox vaccine, anthrax vaccine and typhoid vaccine (unspecified). Subsequently, she became ill with aches and fever resembling the cold that other members of her unit had. When the symptoms worsened, they resembled lupus. The patient died of a complicated illness, diagnosed as 'like lupus'". It was noted that she eventually died from bleeding in her lungs. The Army said two civilian medical panels looked into the case and agreed that the death was "probably" or "possibly" an adverse reaction to vaccines, though they did not single out one.
[redacted]	34 m / F	Malignant neoplasm of parotid gland	Information was received from a physician concerning a 34-month-old Asian girl who was vaccinated with measles, mumps, and rubella virus vaccine live. [redacted] girl died due to parvicellular malignant tumour in right parotid gland. The reporting physician felt the girl's parvicellular malignant tumour in right gland region was definitely not related to the vaccination with measles, mumps, and rubella virus vaccine live.

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WAES No:	Age/Gender	Reported Cause of Death	Comment
[redacted]	15 m / F	Aplastic anaemia	Information was received from a physician concerning a 15-month-old female who was vaccinated with measles, mumps, and rubella virus vaccine live and became ill 10 days later. The patient had a viral syndrome which developed into encephalitis and the patient was hospitalized. The child then developed aplastic anemia and was diagnosed with Dubowitz Syndrome. The patient was noted as having "a long stormy course" and had a reoccurrence of aplastic anemia. Subsequently, the patient died at age 20 months.
[redacted]	13 m / F	Cardio-respiratory arrest, Gastrointestinal bleeding, Status epilepticus	Information was received from a physician concerning a 13-month-old Caucasian female who was vaccinated with measles, mumps, and rubella virus vaccine live. [redacted] later that day, the patient died. The cause of death was cardiorespiratory arrest and status epilepticus. An autopsy did show some mucus and blood in her gastrointestinal tract. The pathologist reported that the patient had died from hemorrhagic gastroenteritis with secondary disseminated intravascular coagulation.
[redacted]	15 m / F	Death NOS	Information was received from another pharmaceutical company concerning a 15-month-old female patient who was vaccinated with measles, mumps, and rubella virus vaccine live. Concomitant vaccinations that same day included a dose of haemophilus B conjugate vaccine and a dose of aluminum potassium sulfate (+) diphtheria toxoid (+) pertussis vaccine (+) tetanus toxoid. Six days post-vaccination, the patient presented with diarrhea and that evening, the patient died. An autopsy was performed, but the results were not yet received.

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WAES No:	Age/Gender	Reported Cause of Death	Comment
[redacted]	10 y / M	Encephalitis infection NOS, Fever, Grand mal convulsion	A published literature article was received concerning a 10-year-old male patient who was vaccinated with the second dose of measles, mumps, and rubella virus vaccine live. Concomitant vaccinations administered included diphtheria toxoid (+) poliovirus vaccine (+) tetanus toxoid. The patient presented with "drowsiness and cephalalgia. [redacted] Despite resuscitation attempts, he developed an irreversible coma and died 4 days later. Diagnosis of meningoencephalitis was made. An autopsy was not planned. The reporter felt there was no causal relationship between the patient's adverse experiences and measles, mumps, and rubella virus vaccine live.

Comment

Of the 37 reports of fatal outcome, 29 reports indicate that the patients died of their underlying disease(s) or other concurrent illnesses. Two reports of fatal outcome were due to sudden infant death syndrome (SIDS). In the 6 remaining reports, a relationship between measles, mumps, and rubella virus vaccine live and these deaths could not be established. No new safety issues with fatal outcomes were identified during the ongoing monitoring of the safety of measles, mumps, and rubella virus vaccine live. The Company will continue to monitor all adverse experiences as part of its ongoing evaluation of the safety of this product.

9.3 Drug Interactions

During the reporting period for this PSUR, no reports of drug interaction with measles, mumps, and rubella virus vaccine live were identified.

9.4 Overdose

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During the reporting period for this PSUR, there were 31 reports of overdose with measles, mumps, and rubella virus vaccine live out of approximately [redacted] doses distributed. None of these reports involved fatal outcomes. One of the 31 reports is not a report of overdose involving measles, mumps, and rubella virus vaccine live. This report (WAES [redacted]) that involved dilantin overdose and toxicity was mapped to the MedDRA preferred term of 'drug toxicity' and is not considered further. For the purposes of this analysis, accidental exposures to measles, mumps, and rubella virus vaccine live are evaluated as 'overdoses'. The remaining reports involved reports of 'accidental exposure' (29) and 'accidental overdose (1). Of those

reports of 'accidental exposure, 24 reports (WAES [redacted] involved the vaccine inadvertently being splashed into the eye during administration of the vaccine. Two of the 24 reports (WAES [redacted]) also involved inadvertent exposure to vaccine during pregnancy (see Section 9.6 Use During Pregnancy). There were 2 reports (WAES [redacted] which involved the vaccine inadvertently being splashed into the health professional's mouth during administration of the vaccine and 1 report (WAES [redacted]) involved a nurse who inhaled some of the measles, mumps, and rubella virus vaccine live before it was reconstituted. One report (WAES [redacted] involved the mother of the patient inadvertently being splashed (site not specified) while her son was being vaccinated. One report (WAES [redacted] involved secondary exposure when a patient was vaccinated with measles, mumps, and rubella virus vaccine live and subsequently, the patient's mother who was 8 months pregnant, experienced a higher than normal rubella titer. The 1 report of accidental overdose (WAES [redacted]) involved a 4-year-old male who was accidentally given 2 injections of measles-mumps-rubella vaccine, one immediately after the other. (The patient had previously received his first injection of measles-mumps-rubella vaccine at 12-15 months). Following the 2 injections of measles-mumps-rubella vaccine, the patient felt some pain when sitting, but had no other symptoms. Subsequently, the patient's soreness at the injection site resolved.

Twenty-two of the 29 reports of 'accidental exposure' had no adverse event reported and 7 reports of 'accidental exposure' with adverse events of: eye feels funny (WAES [redacted], eyes burning and eyes itching (WAES [redacted]), eye abrasion (WAES [redacted], dryness in the eye (WAES [redacted]), pain burning and slight redness (WAES [redacted]), eyes felt numb (WAES [redacted]), and higher than normal rubella titer (WAES [redacted]) .

The Company will continue to monitor all reports of overdose with measles, mumps, and rubella virus vaccine live.

9.5 Drug Abuse and Misuse

During the reporting period for this PSUR, there were no reports of drug abuse and 1,031 spontaneous reports of product misuse (medication error) with measles, mumps, and rubella virus vaccine live from health care providers were identified which consisted of the following: drug maladministration (716*); inappropriate schedule of drug administration (95*); drug administered via inappropriate route (83*); medication error (no other term specified) (71); expired drug used (60*); inappropriate dose of drug administered (6*); wrong drug administered (3*); inappropriate dilution of vaccine (2*); improper formulation of drug administered (1).

The term 'Drug Abuse' is herein interpreted in the context of *use that is illegal or addictive*, though it is acknowledged that this has limited utility when applied to vaccines, as contrasted with pharmaceuticals.

* For 4 patients, 2 medication errors were reported for each and there was 1 patient who had 3 medication errors reported.

The term 'Misuse' is herein interpreted in the context of *use that deviates from what is recommended*, i.e., what is described in the CCDS or the package circular (Prescribing Information). Misuse is applied broadly to conditions of shipping, storage and administration, including doses given when contraindicated, at an inappropriate age, too soon or too late, by an incorrect route, etc. In MedDRA, 'Misuse' maps to the preferred terms of 'Medication Error', which includes such lower level terms as *expired drug, wrong drug administered, wrong patient, inappropriate schedule, expired drug, vaccine not stored properly*, etc.

Conclusion

The Company will continue to monitor reports of product misuse as part of the ongoing safety evaluation of measles, mumps, and rubella virus vaccine live.

9.6 Use During Pregnancy

9.6.1 New Reports of Pregnancy Exposures Between 01-Jan-1999 and 31-Dec-2003

During the reporting period of this PSUR, the Company received a total of 292 spontaneous reports of maternal exposure to measles, mumps, and rubella virus vaccine live during pregnancy. Two-hundred fifty-three (253) of the reports were prospective and the remaining 39 were retrospective reports.

A prospective report of exposure during pregnancy is defined as a report for which the Company first learned of the exposure during the pregnancy and the outcome of the pregnancy may be subsequently reported.

A retrospective report of exposure during pregnancy is defined as a report for which the Company first learned of the exposure after the outcome of the pregnancy was known. The pregnancy outcomes of these 292 reports are presented in Table 9.6.1.

Table 9.6.1
New Reports Received
Summary of Pregnancy Exposures
01-Jan-1999 to 31-Dec-2003

	Total Reports of Pregnancy Exposure	Live Births	Elective Abortions	Spontaneous Abortions	Abortion (Not specified)	Fetal Death	Outcome Unknown
Prospective Reports	253	33	3	6	1		210
Retrospective Reports	39	24 [a,b]	2	11		2	

[a] One report of limb hypoplasia congenital
[b] One report of microcephaly and mental retardation

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9.6.1.1 Prospective Reports

The pregnancy outcomes of the 253 prospective reports of exposure to measles, mumps, and rubella virus vaccine live during pregnancy were: 33 live births, 3 elective abortions, 6 spontaneous abortions, and 1 abortion (not specified). The pregnancy outcomes of the remaining 210 reports are unknown.

9.6.1.2 Retrospective Reports

The pregnancy outcomes of the 39 retrospective reports of exposure to measles, mumps, and rubella virus vaccine live during pregnancy were: 24 live births, 2 elective abortions, 11 spontaneous abortions, and 2 fetal (intra-uterine) deaths.

9.6.2 Congenital Anomalies

During the reporting period of the PSUR, in all of the new reports of exposure to measles, mumps, and rubella virus vaccine live during pregnancy, there were no prospective reports of congenital anomalies and 2 retrospective reports of congenital anomalies. In the first retrospective report (WAES [redacted], information was received concerning a 22-year-old female who was vaccinated with the first dose of dose of measles virus vaccine live (+) mumps virus vaccine live (+) rubella virus vaccine live (second generation) one month before the beginning of her pregnancy. At 29 weeks gestation, an echography was performed and a congenital anomaly (i.e., a pathology of the fetus' lower limbs) was observed. At 40 weeks gestation, the patient gave birth by Cesarean to a male with an "ectromelia consisting of hypoplasia of the fibula." The male infant was evaluated: Apgar score test = 9/10, weight = 4,270 g, height = 50 cm, and cranial perimeter = 37 cm. The second retrospective report (WAES [redacted] concerned a 23-year-old female who was vaccinated with one dose of measles virus vaccine live (+) mumps virus vaccine live (+) rubella virus vaccine live (second generation). Subsequently the patient learned that she became pregnant at approximately the time of vaccination. The patient gave birth to a female who was diagnosed with microcephaly as an infant and with mental retardation. The infant sought unspecified medical treatment. The microcephaly and mental retardation were considered disabling adverse events.

Comment

In the pregnancy reports with known outcomes, 2 retrospective reports of congenital anomalies have been received during the reporting period. It is not known whether measles, mumps, and rubella virus vaccine live can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Therefore, the vaccine should not be administered to pregnant females; furthermore, pregnancy should be avoided for three months following vaccination. During the reporting period of this PSUR, the CCDS has been updated to include text stating that exposure to mumps infection during the first trimester of pregnancy may increase the rate of spontaneous abortion.

9.6.3 Previously Identified Reports

During the reporting period of this PSUR, follow-up information was received concerning the outcomes of 24 previously identified reports in which women were exposed to measles, mumps,

and rubella virus vaccine live during pregnancy and in which the pregnancy outcomes were unknown at the time of previous PSURs (prospective reports). In the 24 reports with follow-up information, 20 pregnancies resulted in normal healthy newborns, 2 reports involved patients who were lost to follow-up, 1 report involved a patient who underwent an elective abortion, and 1 report involved a congenital anomaly. This report (WAES [redacted]) involving a congenital anomaly concerned a patient who gave birth to a female with Down's syndrome (Trisomy 21). The physician felt that Down's syndrome was not associated with the vaccine.

Table 9.6.3

Summary of Pregnancy Exposures from Previously Identified Reports (Follow-up Information Received) 01-Jan-1999 to 31-Dec-2003

	Total Reports of Pregnancy Exposure	Live Births	Elective Abortions	Lost to Follow-Up
Prospective Reports	24	21 [a]	1	2

[a] One report of Down's syndrome (Trisomy 21)

Comment

Merck & Co., Inc. will continue efforts to obtain outcome information for all reports of exposure to measles, mumps, and rubella virus vaccine live during pregnancy.

9.6.4 Use During Lactation

During the reporting period of this PSUR, 3 reports of exposure during lactation involving measles, mumps, and rubella virus vaccine were identified. In 1 report (WAES [redacted]), a mother was vaccinated with measles virus vaccine live (+) mumps virus vaccine live (+) rubella virus vaccine live (second generation). Her 11-month-old baby was breastfeeding when the mother was vaccinated. Approximately 14 days post-vaccination, her child broke out in a fine rash along with a high fever. Subsequently, the patient recovered from fine rash and fever. The reporting nurse felt that fine rash and fever were related to therapy with measles-mumps-rubella vaccine. The second report (WAES [redacted]) concerned a 30-year-old female who was vaccinated with measles virus vaccine live (+) mumps virus vaccine live (+) rubella virus vaccine live (second generation). The physician reported that the patient had been breastfeeding her 4 month old son. No adverse events were reported. In the third report (WAES [redacted]), the male infant "broke out with a measles like rash" after breast feeding.

Comment

The Company will continue to monitor all reports of exposure during pregnancy and lactation as part of its ongoing evaluation of the safety of measles, mumps, and rubella virus vaccine.

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9.7 Neutropenia

From market introduction to 31-Dec-2003, there were a total of 16 marketed reports of neutropenia following the administration of measles, mumps, and rubella virus vaccine live. Eight of the 16 reports were from the United States, 3 from France, 2 each from Sweden and United Kingdom, and 1 from Norway. These reports occurred in 7 females and 9 males for a female to male ratio of 0.77:1.0. The patient age ranged from 12 months to 11 years, with a median age of 1.3 years. The time to onset of neutropenia from last dose of measles, mumps, and rubella virus vaccine live ranged from 3 days to 95 days, with a median time to onset of 17 days. Recovery status for the adverse experience of neutropenia was unknown in 8 reports, the other 8 reports indicated that the patient had recovered. The total number of doses distributed of measles, mumps, and rubella virus vaccine live from market introduction to 31-Dec-2003 was approximately [redacted].

Table 9.7.1 presents the total number of neutropenia reports and measles, mumps, and rubella virus vaccine live doses distributed, with the adverse experience reporting rate calculated per 100 million of measles, mumps, and rubella virus vaccine live doses distributed.

Table 9.7.1
Reporting Rates of Neutropenia After Vaccination with Measles, Mumps, and Rubella Virus Vaccine Live Per 100 Million Doses Distributed

Number of Neutropenia Reports	Number of M-M-R ®II Doses Distributed	Reporting Rate per 100 Million Doses Distributed
16	[redacted]	[redacted]

Table 9.7.2 presents the number of neutropenia reports by year of reporting.

Table 9.7.2
Number of Neutropenia WAES Reports by Year of Reporting

Year of Report*	Number of Reports
1978	0
1979	0
1980	0
1981	0
1982	0
1983	0
1984	0
1985	1
1986	0
1987	0
1988	0
1989	0
1990	0
1991	1
1992	2
1993	1
1994	0

Year of Report*	Number of Reports
1995	2
1996	2
1997	1
1998	0
1999	1
2000	1
2001	2
2002	2
2003	0
Total	**16**

* Year of the report was determined by the first two digits of the WAES numbers.

Conclusion

This analysis demonstrates that there have been a very small number of reported adverse experiences of neutropenia following the administration of measles, mumps, and rubella virus vaccine live. As of 31-Dec-2003, there have been more than [redacted] measles, mumps, and rubella virus vaccine live doses distributed. Because of the limitations inherent in post-marketing surveillance, it is difficult to determine the causality of post-marketing reports based on a descriptive epidemiologic analysis of the reports. This analysis neither supports nor refutes a possible association between the administration of measles, mumps, and rubella virus vaccine live and the onset of neutropenia; however, the very small number of reported cases in light of the large number of doses distributed, suggests that a causal association is unlikely. The Company will continue to monitor all reports of neutropenia as part of its ongoing evaluation of the safety of measles, mumps, and rubella virus vaccine live.

9.8 Sudden Death

From market introduction to 31-Dec-2003, there were a total of 11 reports of sudden infant death syndrome. The 11 reports of sudden infant death syndrome temporally associated with the administration of measles, mumps, and rubella virus vaccine live were reported from United States (5), Norway (2), Canada (1), Germany (1), Sweden (1), and United Kingdom (1). These reports occurred in 6 males and 5 females for a male to female ratio of 0.83: 1.0. The age range of patients was 14 months to 24 months, with a median age of 16 months. Nine reports occurred after the first birthday and two occurred after the second birthday.

In the 11 reports, the patient had been vaccinated with one dose of measles, mumps, and rubella virus vaccine live. The time to onset of sudden infant death from the last dose was known in 10 reports and approximated in 1 of the 11 reports, the time to onset of the sudden infant death ranged from 1 day to 24 days, with a median time to onset of 8 days.

In 5 of the 11 reports, the patient had a past medical history or concurrent condition that was clinically significant. These histories included febrile convulsions (3 reports) premature birth twin, respiratory tract infection NOS, and protrusion of tongue (1 report). In one report a concurrent condition of bronchitis and pneumonia viral NOS was reported, and in the fifth report the patient had a medical history of febrile convulsion along with a history of a concurrent condition of a specific drug allergy.

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The total number of doses distributed of measles, mumps, and rubella virus vaccine live from market introduction to 31-Dec-2003 was approximately [redacted].

Table 9.8.1 presents the total number of sudden infant death syndrome reports and measles, mumps, and rubella virus vaccine live doses distributed.

Table 9.8.1
Reporting Rates of Sudden Infant Death Syndrome After Vaccination with Measles, Mumps, and Rubella Virus Vaccine Live Per 100 Million Doses Distributed

Number of Sudden Infant Death Syndrome Reports	Number of M-M-R ®II Doses Distributed	Reporting Rate per 100 Million Doses Distributed
11	[redacted]	[redacted]

Table 9.8.2 presents the number of sudden infant death syndrome reports by year of reporting.

Table 9.8.2
Number of Sudden Infant Death Syndrome WAES Reports by Year of Reporting

Year of Report*	Number of Reports
1978	0
1979	0
1980	0
1981	0
1982	0
1983	0
1984	0
1985	0
1986	0
1987	0
1988	1
1989	0
1990	2
1991	1
1992	0
1993	0
1994	2
1995	0
1996	0
1997	2
1998	1
1999	0
2000	0
2001	0
2002	2
2003	0
Total	**11**

* Year of the report was determined by the first two digits of the WAES numbers.

Conclusion

This analysis demonstrates that there have been a small number of reports of sudden infant death syndrome following the administration of measles, mumps, and rubella virus vaccine live. An analysis of these data shows that the cases are distributed over a wide period of time and that the reporting rate for the sudden infant death syndrome of 2 adverse event reports per [redacted] doses distributed is very low and in temporal association with the administration of measles, mumps, and rubella virus vaccine live. The Company will continue to monitor all reports of sudden infant death syndrome as part of its ongoing evaluation of the safety of measles, mumps, and rubella virus vaccine live.

9.9 Cough

From market introduction to 31-Dec-2003, there were a total of 194 marketed reports of cough following the administration of measles, mumps, and rubella virus vaccine live. To capture all reports of cough, the following terms are included: cough and productive cough.

Table 9.9.1 lists the total number of adverse event reports of cough reported during this time period. Note that 60 reports (30.9%) were considered serious. Since there were [redacted] doses distributed worldwide, the overall reporting rate was 43 adverse event reports per [redacted] distributed.

Table 9.9.1
Total Number of Adverse Event Reports Of Cough and
Total Number of Serious and Non-Serious Adverse Experiences

Total Number	Serious	Non-serious	Total
AE Reports	60	134	194

Table 9.9.2 lists the number of cough reports by year of the report. The number of reports varied from 0 to 35 reports per year with a mean of 7.5 reports per year.

Table 9.9.2
Number of Cough WAES Reports by Year of Reporting

Year of Report*	Number of Reports
1978	0
1979	0
1980	0
1981	0
1982	1
1983	2
1984	2
1985	1
1986	2
1987	0
1988	7
1989	9
1990	5
1991	4
1992	3

Year of Report*	Number of Reports
1993	7
1994	6
1995	11
1996	12
1997	10
1998	14
1999	9
2000	10
2001	35
2002	30
2003	14
Total	**194**

* Year of the report was determined by the first two digits of the WAES numbers.

Table 9.9.3 lists the country of origin of the cough reports. Most of the reports are from the United States.

Table 9.9.3
Cough Reports by Country of Origin

Country	Number of Reports
Australia	3
Belgium	2
Canada	1
China	1
Denmark	16
Finland	10
France	18
Germany	18
Japan	2
New Zealand	12
Norway	2
Sweden	6
United Kingdom	10
United States	93
Total	**194**

Table 9.9.4 lists the distribution of cough reports by age groups. Most of the reports occur in the age group of 1 to 4 years of age, and 5 to 9 years of age, as these are the age groups to receive the vaccine as recommended in the prescribing information. The female to male ratio is 1.23:1.00.

Table 9.9.4
Distribution of Cough Reports by Age Group

Age	Male	Female	Unknown	Total
<1	0	2	1	3
1-4	68	76	2	146
5-9	11	7	0	18
10>	3	15	0	18
Unknown	1	2	6	9
Total	**83**	**102**	**9**	**194**

The most frequently reported adverse events in addition to cough (195) included, pyrexia (137), rash NOS (71), rhinorrhea (33), rash morbilliform (25), vomiting NOS (22), nasopharyngitis (21), conjunctivitis NOS (19), rhinitis NOS (19), general symptom NOS (17), irritability (16), lymphadenopathy (16), urticaria NOS (14), asthenia (12), febrile convulsion (12), and diarrhea NOS (12).

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Cough appears to be associated with other symptoms compatible with viral infection, or with mild measles, perhaps secondary to the vaccination with measles, mumps, and rubella virus vaccine live. The Company will continue to monitor all reports of cough as part of its ongoing evaluation of the safety of measles, mumps, and rubella virus vaccine live.

9.10 Syncope

From market introduction to 31-Dec-2003, there were a total of 387 marketed reports of syncope following the administration of measles, mumps, and rubella virus vaccine live. To capture all reports of syncope, the following terms are included: syncope, syncope vasovagal, and dizziness.

Table 9.10.1 lists the total number of adverse event reports of syncope reported during this time period. Note that 77 reports (20%) were considered serious. Since there were [redacted] doses distributed, the overall reporting rate was 9 adverse event reports per [redacted] doses distributed.

Table 9.10.1
Total Number of Adverse Event Reports Of Syncope

Total Number	Serious	Non-serious	Total
AE Reports	77	310	387

Table 9.10.2 lists the number of syncope reports by year of the report. The number of reports varied from 0 to 74 reports per year with a mean of 14.9 reports per year.

Table 9.10.2
Syncope Reports by Year of the Report

Year of Report*	Number of Reports
1978	0
1979	0
1980	0
1981	1
1982	0
1983	3
1984	1
1985	3
1986	0
1987	0
1988	0
1989	36
1990	21
1991	23
1992	16
1993	42
1994	48
1995	15
1996	15
1997	12
1998	12
1999	14
2000	74
2001	16
2002	23
2003	12
Total	**387**

* Year of the report was determined by the first two digits of the WAES numbers.

Table 9.10.3 lists the country of origin of the syncope reports. Most of the reports are from the United States.

Table 9.10.3
Syncope Reports by Country of Origin

Country	Number of Reports
Australia	65
Austria	1
Belgium	1
Canada	4
Denmark	14
Finland	4
France	13
Germany	15
Ireland	3
Italy	1
New Zealand	26

Country	Number of Reports
Norway	3
Sweden	6
United Kingdom	16
United States	215
Total	**387.**

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Table 9.10.4 lists the distribution of syncope reports by age groups. Most of the reports occur in the age groups of 10 to 14 years of age and 15 to 19 years of age. The female to male ratio is 1.28:1.0

Table 9.10.4
Distribution of Syncope Reports by Age Group

Age	Male	Female	Unknown	Total
1-4	21	11	0	32
5-9	9	15	0	24
10-14	50	60	0	110
15-19	19	23	1	43
20-24	1	2	0	3
25-29	2	7	0	9
30-34	1	5	0	6
35-39	0	5	0	5
40-44	0	2	0	2
Unknown	2	4	147	153
Total	**105**	**134**	**148**	**387**

The most frequently reported adverse events in addition to syncope (231) included, dizziness (131), vasovagal attack (41), nausea (40), headache NOS (37), malaise (26), vomiting NOS (26), pallor (23), flushing (21), pyrexia (21), asthenia (19), convulsions NOS (18), abdominal pain NOS (14), and sweating increased (14).

Conclusion

The reporting rate of syncope of 9 reports per [redacted] doses in temporal association of measles, mumps, and rubella virus vaccine live is very low. The recommended route of administration for the measles, mumps, and rubella virus vaccine live vaccination is the subcutaneous route. This may have an affect on the age groups where the higher number of syncope episodes were reported (in the age range of 10 to 19 years of age as reported in Table 9.10.4) the patient may become syncopal in relation to receiving the vaccination in a subcutaneous injection. The Company will continue to monitor all reports of syncope as part of its ongoing evaluation of the safety of measles, mumps, and rubella virus vaccine live.

9.11 Consumer Reports

Line listings, period summary tabulations and cumulative summary tabulations of consumer reports for measles, mumps, and rubella virus vaccine live, for which no information has been received from a health care professional, are listed in Addendum 1. In all cases, attempts have been made to obtain medical follow-up. Review of these reports raises no additional safety concerns.

10. Overall Conclusion

Examination of the data contained within this PSUR supports the conclusion that measles, mumps, and rubella virus vaccine live is generally well tolerated. Analysis of these data is consistent with the current CCDS in terms of product safety.

As with all Merck & Co., Inc. products, the safety profile of measles, mumps, and rubella virus vaccine live is closely monitored on a continuing basis.