coll. nr.	20221015
datum	07 OKT. 2002
fin. nr.	

Aventis Pasteur MSD

Vaccines for Life

C

[redacted]/320

Brussels, 1 October 2002.

College ter Beoordeling van Geneesmiddelen
Ter attentie van mevr. [redacted]
[redacted]
Kalvermarkt 53
NL - 2500 BE DEN HAAG
Nederland

Betreft:	**M-M-R II poeder voor injectievloeistof - RVG 17672** Uw brief van 1 juli 2002, kenmerk 20012174/[redacted]0110/20213782 **Zaaknummer 20012174005**

Dear Madam,

Please find enclosed the responses to your letter of 1 July concerning the assessment of the report summarising safety data from 01 January 1996 up to 31 December 1999.

As already confirmed during our telephone conversation of 31 July 2002, the above-mentioned document in fact was a Safety Supplement and not a complete PSUR.
From now on, the company will take care no longer to send in any Safety Supplements for assessment by the College; only Periodic Safety Update Reports in line with current requirements will be submitted.

Supplying information that is contained in the last available PSUR edited by Merck &Co solves a substantial part of the deficiency letter. This 5-year PSUR covers the period from 01 January 1996 up to 31 December 2000 and is attached in annex 1 (in 3 volumes).
Additional documentation is supplied in annex 2 "Response to the Netherlands Medicines evaluation Board, PSUR assessment report dated 01-Jul-2002" (volume 3), to reply to questions for which the answers cannot be found in the PSUR of annex 1.

Question 1: You are requested to submit a discussion of the fatal cases

The fatal cases are discussed in **section 9.1 Reports with fatal outcome** (pages 26 to29) of the 5-year PSUR in the time frame of 01-Jan-1996 to 31-Dec-2000, enclosed in **annex 1 .**

AVENTIS PASTEUR MSD s.a.-n.v.
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Question 2: In view of the recent changes in the CCSI as well as some additional information in this PSUR you should submit data, literature and a discussion of the following issues: inadvertently vaccinated immunocompromised patients, thrombocytopenia, Stevens Johnson Syndrome, syncope, irritability, (angioneurotic) oedema, bronchospasm, cough, rhinitis, polyneuropathy, measles inclusion body encephalitis (MIBE), pneumonitis and death from various and in some cases unknown cases (including 'sudden infant death').

- **Inadvertently vaccinated immunocompromised patients:** The information "**Item 2 (a)-** *Review of adverse experiences occurring in immumocompromised hosts vaccinated with MMR-II through July 31,2000"* is enclosed in **annex 2.1**

- **Thrombocytopenia and pneumonitis**: The information "**Item 2(b)-** *Additional information on reports and/or literature as related to the reported adverse experiences of pneumonitis and thrombocytopenia"* is enclosed in **annex 2.2**

- **Steven Johnson syndrome, syncope, irritability, angioneurotic oedema, bronchospasm, cough, rhinitis, polyneuropathy**: The information **"Item 2 (c)-** *Evaluation of reported adverse experience reports of Angioneurotic edema, bronchospasm, cough, irritability, Overdose, Polyneuropathy, rhinitis, Stevens Johnson syndrome and syncope reported in temporal association with the administration of MMR II"* is enclosed in **annex 2.3**

- **Measles inclusion body encephalitis (MIBE):** This subject is discussed in section 9.8 (page 35) of the 5-Year PSUR in the time frame 01-Jan-1996 to 31-dec-2000 enclosed in annex 1. Updated information "**Item 2 (d)** *-Reports of MIBE temporally associated with administration of MMR-II through July 2002"* can be found in **annex 2.4.**

- **Death from various cases, unknown cases, sudden infant death**: A discussion is included in **section 9.1 Reports with fatal outcome** (pages 26 to 29) of the 5-year PSUR in the time frame of 01-Jan-1996 to 31-Dec-2000 that is enclosed in **annex 1.**

Question 3:. You should provide a cumulative overview and detailed discussion of nervous and psychiatric events (including 'autism' and 'infectious meningitis')

- **Nervous and psychiatric events including infectious meningitis:** Updated information is included "**Item 3 (a)**- *Cumulative overview of nervous system reports temporally associated with the administration of MMR-II"* that is enclosed in **annex 2.5.**
  Earlier information was mentioned in section 9.7 Aseptic meningitis (page 33) and section 9.8 Encephalitis (pages 34-35) of the 5-year PSUR in the time frame of 01-Jan-1996 to 31-Dec-2000, enclosed in annex 1.

- **Autism**: Un update of reports until 31-Jul-2002 is given in **" Item 3 (b) "** attached as **annex 2.6.** Former situation was included in section 9.9 Autism (page 35) of the 5-year PSUR in the time frame of 01-Jan-1996 to 31-Dec-2000 that is enclosed in annex 1.
  The manufacturer's assessment leads to conclude that "According to the current scientific knowledge, there is no link between autism and measles-mumps-rubella vaccination."

Question 4: The summary table of spontaneous unlisted events (Appendix 2 Table 1-12 pages) was incomplete. It stopped at Nervous System –hypotonia'. You are requested to submit the missing part of the table to enable a proper safety assessment.

- The **summary table of spontaneous unlisted events** now is included in **Appendix 4-Table 1** (21 pages) of the 5-year PSUR in the time frame of 01-Jan-1996 to 31-Dec-2000, enclosed in **annex 1** (volume 2).

Question 5: You should submit a proper overall safety evaluation, focussing on severe signs or symptoms of measles, mumps, rubella and well-known complication of these diseases (e.g. pancreatitis, myocarditis) and the possibility of vaccine-inducement in these cases.

- This information is contained in **"Item 5-** *Overall safety evaluation focusing on the severe signs and symptoms and well-known complications of measles, mumps and rubella diseases and the possibility of vaccine-inducement in these reports, through July 31, 2000"* and is enclosed in **annex 2.7.**

Question 6: You should provide information on the relevant cases in the litigation in the UK within the next 3 months.

- This information is given in **" Item 6-** *Information on the relevant cases in the litigation in the UK"* that is enclosed in **annex 2.8.**

Question 7: In the next PSUR you should clarify the term 'product exposure'. You are also requested to clarify whether the cases of drug overdose, product misuse, product abnormality, product confusion, product exposure and use of outdated product had any signs or symptoms and you should submit a proper safety evaluation of these cases.

- **Drug overdose:** information can be found in **section 9.3 Overdose** (page 29) of the 5-year PSUR in the time frame of 01-Jan-1996 to 31-Dec-2000, enclosed in **annex 1.**
- **Clarification of terminology, dug abuse and misuse: "Item 7"** enclosed in **annex 2.9** gives further explanation.

Question 8: In the next PSUR you should submit a cumulative review of unwanted effects related to exposure during pregnancy.

- Pregnancy was discussed in **sections 9.5, 9.5.1 and 9.5.2** (pages 29 to 32) of the 5-year PSUR in the time frame of 01-Jan-1996 to 31-Dec-2000 enclosed in **annex 1.**
- Updated information related to exposure during pregnancy is included in **"Item 8"** enclosed in **annex 2.10.**

Question 9: number was omitted in the letter

Question 10: Furthermore you should submit a proposal for a EU birth date and a revised PSUR-cycle

- We propose **29 January 1980** as EU birth date. This is the German registration date of the product and the eldest date of registration of the product in an EEC country.
- Taking into account current EU guidelines on 5-year renewal dates and simultaneous submission of 5-year PSUR, the next 5 year PSUR would be scheduled for submission during the last quarter of 2004.

Question 11: Future PSUR should be in line with all aspects of ICH guidelines E2C, including *registration and marketing authorisation status, specification of total number of reports received during the review period, discussion of clinically relevant cases, literature review.*

- The **registration and marketing status**, discussion of **clinically relevant cases** and **literature review** is contained within the M-M-R-II 5-year PSUR in the time frame of 01-Jan-1996 to 31-Dec-2000 that is enclosed in **annex 1** (volume 1).

Question 12: Furthermore you are requested to mention the RVG number of the product in your letter

- The RVG number **17672** is mentioned on the cover of this letter.
- We like to draw the attention of the College on the fact that the information hereby submitted is also relevant for our duplex registration RVG 18676=17672. Whereas RVG 17672 is registered in name of Merck, Sharp and Dohm with address in Haarlem-the Netherlands, the duplex registration is registered in name of Aventis Pasteur MSD located in Brussels, Belgium.

  As agreed between MSD (the Netherlands), Aventis Pasteur MSD, (Belgium) and the College, Aventis Pasteur MSD in Belgium takes care of the correspondence of the vaccines of which MSD is licence holder. (Product concerned by the same procedure are: Attenuvax RVG 17669, HBVax DNA 10-40 RVG 17461-17600, Meruvax II RVG 17671, M-M-R II RVG 17672, Mumpsvax RVG 17670, Pneumovax 23 RVG 25854-25855, Vaqta adult RVG 20798 and Vaqta Junior RVG 20799).

We believe that we now have replied to all outstanding questions and we will await your assessment of the submitted data.

Please do not hesitate to contact us if you have any queries regarding this documentation.

Yours sincerely,

[redacted]

Aventis Pasteur MSD

[redacted]

ATTACHMENTS

Volume 1: **Annex 1: 5-Year PSUR with appendixes up to appendix 3- Table 1**

Volume 2: **Annex 1: Appendixes 3- Table 2 up to appendix 8 to the 5-Year PSUR**

Volume 3: **Annex 1: Appendix 9 and addenda to the 5-year PSUR**

Annex 2: Additional documentation annex 2.1 up to annex 2.10

M-M-R II
Poeder voor injectievloeistof

RVG 17672 - Registratiehouder
Merck, Sharp &Dohm –NL-Haarlem

RVG 18676=17672 Registratiehouder
Aventis Pasteur MSD – B- Brussel

Annex 1

Periodic safety Update Report for :

Measles, Mumps and Rubella Virus Vaccine Live, MSD
01-Jan-1996 to 31-Dec-2000
report date : 22-Jan-2001

Volume 1 contains
- Report (37 pages)
- Appendix 1
- Appendix 2
- Appendix 3- Table 1

Volume 2 contains
- Appendix 3- Table 2
- Appendix 4- Table 1
- Appendix 4- Table 2
- Appendix 5
- Appendix 6
- Appendix 7- Table 1
- Appendix 7- Table 2
- Appendix 8

Volume 3 contains
- Appendix 9
- Addendum

M-M-R II
Poeder voor injectievloeistof

RVG 17672 - Registratiehouder
Merck, Sharp & Dohm –NL-Haarlem

RVG 18676=17672 Registratiehouder
Aventis Pasteur MSD – B- Brussel

Annex 2

M-M-R II™ Response to Netherlands Medicines Evaluation Board
PSUR Assessment Report dated 01-Jul-2002
Measles, Mumps and Rubella Virus Vaccine Live, MSD
Signed [redacted], MD
30-Sep-2002

M-M-R II
Poeder voor injectievloeistof

RVG 17672 -	Registratiehouder Merck, Sharp & Dohm –NL-Haarlem
RVG 18676=17672	Registratiehouder Aventis Pasteur MSD – B- Brussel

ANNEX 2.1	Item 2 (a)- Review of adverse experiences occurring in immunocompromised hosts vaccinated with MMR-II through July 31,2000
ANNEX 2.2	Item 2(b)- Additional information on reports and/or literature as related to the reported adverse experiences of pneumonitis and thrombocytopenia
ANNEX 2.3	Item 2 (c)- Evaluation of reported adverse experience reports of Angioneurotic edema, bronchospasm, cough, irritability, Overdose, Polyneuropathy, rhinitis, Stevens Johnson syndrome and syncope reported in temporal association with the administration of MMR II
ANNEX 2.4	Item 2 (d) -Reports of MIBE temporally associated with administration of MMR-II through July 2002
ANNEX 2.5	Item 3 (a)- Cumulative overview of nervous system reports temporally associated with the administration of MMR-II
ANNEX 2.6	Item 3 (b)- Autism
ANNEX 2.7	Item 5- Overall safety evaluation focusing on the severe *signs* and symptoms and well-known complications of measles, mumps and rubella diseases and the possibility of vaccine-inducement in these reports, through July 31, 2002
ANNEX 2.8	Item 6- Information on the relevant cases in the litigation in the UK
ANNEX 2.9	Item 7- Product exposure, drug abuse and misuse
ANNEX 2.10	Item 8- Pregnancy

M-M-R II
Poeder voor injectievloeistof

RVG 17672 - Registratiehouder
Merck, Sharp &Dohm –NL-Haarlem

RVG 18676=17672 Registratiehouder
Aventis Pasteur MSD – B- Brussel

Annex 1

Periodic safety Update Report for :

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- Appendix 5
- Appendix 6
- Appendix 7- Table 1
- Appendix 7- Table 2
- Appendix 8

Volume 3 contains
- Appendix 9
- Addendum

CONFIDENTIAL

Merck Research Laboratories
Worldwide Product Safety & Epidemiology

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

01-Jan-1996 to 31-Dec-2000

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

Date of this Report 22-Jan-2001

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APPENDICES

Appendix 1 Worldwide Market Authorization Status

Appendix 2 Company Core Data Sheet

Appendix 3 Line listings for spontaneous reports

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Table 2 - Reports that have only non-serious ADR terms including at least one that is unlisted

Appendix 4 Period summary tabulations for spontaneous reports

Table 1 - Unlisted ADR terms with the number that were serious and non-serious

Table 2 - Listed ADR terms with the number that were serious and non-serious

Appendix 5 Cumulative summary tabulations for spontaneous reports with ADR terms that are serious and unlisted

Appendix 6 Line listings for study reports that are serious and drug related

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Table 2 - Serious, listed, and drug-related ADR terms

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Addendum Consumer reports where no health care provider has been identified

Line listing of reports that have at least one serious ADR term

Line listing of reports that have only non-serious ADR terms including at least one that is unlisted

Period summary tabulation of reports that have unlisted ADR terms with the number that were serious and non-serious

Period summary tabulation of reports that have listed ADR terms with the number that were serious and non-serious

Cumulative summary tabulations for reports with ADR terms that are serious and unlisted

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 Harmonization (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-1996 to 31-Dec-2000.

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.

B

2. Worldwide Market Authorization Status

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 71 countries (see Appendix 1). Applications are 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 $TCID_{50}$ (tissue culture infectious doses) specification from 20,000 to 100,000 per 0.5 mL dose occurred in February 2000 in order to ensure that expiry titers like release titers consistently exceed 17 times the minimum immunizing dose. The 100,000 $TCID_{50}$ mumps titer is well within the Company's historical experience and meets or exceeds the registered minimum specifications for all countries. 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 IPC 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-1996 to 31-Dec-2000), the following safety-related updates were added to the IPC for measles, mumps, and rubella virus vaccine live [Changes in **BOLD**]. New sections or subsections that were added are also indicated in **bold**.

February 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.

Post-marketing surveillance of the more than [redacted] doses 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.

July 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.

4.2 Changes to Reference Safety Information After the Data Lock-Point

After the data lock-point of this PSUR and as a result of the ongoing review of postmarketing experience data, the Company determined to update the SIDE EFFECTS, Hypersensitivity Section of the measles, mumps, and rubella virus vaccine live CCDS to include the following wording [Changes in **BOLD**]:

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**.

A14
A16

5. Patient Exposure

5.1 Clinical Trials

The [redacted] of patients who were enrolled in [redacted]-sponsored clinical trials between 01-Jan-1996 to 31-Dec-2000 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-1996 to 31-Dec-2000 was approximately [redacted] Approximately, [redacted] patients 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 01-Jan-1996 to 31-Dec-2000. Individual case reports (ICRs) included in this PSUR include spontaneous reports received by Merck & Co., Inc., published individual patient 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 drug-related by the reporting study physician. In keeping with the ICH Harmonized 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 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 report reflects the diagnosis or terminology used by the reporter. The reporter terminology is mapped to a Preferred Term using a Merck-developed dictionary and an autoencoder. Due to evolving dictionary changes and coding guidelines, it is possible that, over time, different Preferred Terms may have been used to identify synonymous reactions. On 20-Oct-97, a new database was implemented and, therefore, the summary tabulations supplied in this report cannot be compared with those in prior reports. Also, some ADR terms that were used in prior PSURs do not appear in the line listings or summary tabulations in this report. The reason that these terms sometimes appear is because, prior to 20-Oct-97, before the new database was implemented, these terms (death, overdose, drug abuse, misuse, and use during pregnancy) were used as ADR terms and reports from non-U.S. countries may still use these as ADR terms. The following changes should be noted:

- Death no longer appears as an ADR term when death is an outcome of a reported ADR. If an ADR resulted in death, then this will be noted in the line listing under recovery status. If death is the only reported term, then the term "unknown cause of death" appears in the line listings and summary tabulations.

- Reports identified as overdose without any other reported ADRs may not be included in the line listings or summary tabulations in this safety update report.

- Reports of use during pregnancy without an ADR or without an adverse pregnancy outcome may not be included in the line listings or summary tabulations in this safety update report.

- Reports of drug abuse or product misuse without an ADR may not be included in the line listings or summary tabulations in this safety update report.

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-98, 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.

The line listings that describe spontaneous reports where a health care provider has been identified are listed in the body system 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 body system. 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 post-marketing clinical trials, compassionate use programs, and from post-marketing 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, drug-related ADR term. Reports are also included if drug relationships were unknown or not provided. Drug relationships are those provided by the reporting investigators. The line listings are in the body system 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 body system. The tabulations are separated as follows:

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

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

In addition, cumulative summary tabulations are provided and include study reports that have a serious, unlisted, drug-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 body system order. A report that contains more than one ADR term is assigned to the primary body system, i.e. the body system 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
-Other

-the country from which the report originated (COUNTRY)

-patient age and sex (AGE, SEX)

-patient's total daily dose of drug 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)

-drug 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 no newly analyzed studies that contained important, new safety information.

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.

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.

1. Frenkel L M, Nielsen K, Garakian A, Jin R, Wolinsky J S and Cherry J D
A search for persistent rubella virus infection in persons with chronic symptoms after rubella and rubella immunization and in patients with juvenile rheumatoid arthritis
Clin Infect Dis 22(2): 287-294, Feb. 1996
The possibility of persistent rubella virus infection after natural rubella or rubella vaccination was studied in children with juvenile rheumatoid arthritis (JRA) and adults with chronic joint or neurologic symptoms. Peripheral blood polymorphonuclear leukocytes, mononuclear cells, and plasma and nasopharyngeal specimens were obtained from 6 subjects aged 1.7-43 yr, including 4 health-care workers with persistent symptoms following rubella immunization; 1 woman aged 22 yr with persistent symptoms after natural rubella infection; 11 children (4 M, 7 F, age 2.5-14 yr) with JRA; 17 healthy seronegative controls (7 M, 10 F, age 1-35 yr) recently vaccinated with RA 27/3 (M-M-R II); and 1 woman control aged 46 yr with acute clinical rubella (control). The 4 health-care workers had symptoms that included weakness, headache, arthralgias, arthritis and, 1 of them, sudden and persistent hearing loss within 1-2 wk of vaccination. In 2 subjects, autism developed within 4 wk of immunization for measles, mumps, and rubella. The rubella virus culture methods used are described. Rubella virus was isolated from blood and/or nasopharynx of 4 of the 18 controls (3 vaccinees and the woman with rubella) but was not recovered from the 7 subjects with persistent symptoms following immunization or natural rubella infection or from the 11 children with JRA. A polymerase chain reaction assay detected rubella virus in the blood from 3 of the 14 controls. These findings do not confirm the results of those who recovered rubella virus from lymphocytes of patients with persistent symptoms after natural rubella or rubella vaccination.

2. Baxter D N
Measles immunization in children with a history of egg allergy
Vaccine 14(2): 131-134, Feb. 1996
This paper reports the outcomes of first-time measles vaccination in 200 children aged up to 9 yr old with a diagnosis of egg allergy, including 20 children who had required hospitalization due to anaphylaxis after eating eggs. Vaccines administered were MEVILIN-L (monovalent, Schwarz strain), MMR-II (Enders attenuated Edmonston strain), IMMRAVAX (trivalent, Schwarz strain), and PLUSERIX (trivalent, Schwarz strain). Of 200 children, 199 were immunized without adverse effects. The first 150 children were given a skin prick test with both undiluted vaccine

and saline, and after 20 min, an intradermal test. If no abnormal reaction occurred, the child was given the full dose of normal vaccine. Of these 150 children, 145 had negative wheal-and-flare reactions after the skin tests; they were vaccinated with no significant immediate reactions. Of the remaining 5 children, 4 had negative intradermal test results and were vaccinated with no immediate reactions. The 5th child, a 15-mo-old baby, was not vaccinated after she developed a 10-mm wheal-and-flare response to the skin prick test with MMR-II, and a 15-mm local reaction within 10 min of the intradermal test, and associated symptoms including urticaria, irritability, hypotension, and diarrhea; 6 wk later, antibody titers were protective for measles, mumps, and rubella. The next group of 50 children were only given the skin prick test, which, if negative, was followed by the vaccine. All of these children had negative results and were vaccinated without significant immediate reactions. The frequency of anaphylaxis was thus 1 of 200 or 0.5%. The authors conclude that a history of egg protein allergy should no longer be considered an absolute contraindication to measles vaccination. However, they recommend continued skin testing before vaccination with egg-derived vaccines to identify children at risk of anaphylaxis.

3. Vasilakis C, Jick H and Derby L E
MMR vaccination and anaphylaxis
Pharmacoepidemiol Drug Safety 5(Suppl. 1): S71-S71, Aug. 1996 (in Soc. Proc.)
The risk of anaphylaxis associated with MMR vaccine or dextran was investigated using a general practice research database. A total of 264,781 subjects were immunized between January 1, 1991, and May 1, 1995; an estimated 92,419 of the MMR vaccines contained dextran for volume replacement. A computer search was performed to find codes indicating systemic reactions within 2 days of the vaccination code. No cases of anaphylaxis, hypotension, or serum sickness were documented. All of the other reported reactions were mild. The authors conclude that MMR vaccine, with or without dextran, does not appear to be a major cause of anaphylaxis or other systemic reactions.

4. Virtanen M, Crasley J, Hanley J, Peltola H, Paunio M and Heinonen O P
Statistical analysis of a double-blind placebo-controlled vaccination trial in twins
Paper presented at the 36th Interscience Conference on Antimicrobial Agents and Chemotherapy, New Orleans, Louisiana, Sept. 15-18, 1996, p. 174
This randomized, double-blind, placebo-controlled, crossover study was conducted to examine adverse reactions of vaccination with MMR in 581 pairs of twins at the onset of the MMR vaccination program in Finland. For the 1st scheduled vaccination, 1 twin was given an injection of MMR while the other was given placebo, and symptoms were recorded daily for 3 wk after each injection. For the 2nd scheduled dose, twins were crossed-over to the alternate treatment, and symptoms were again recorded daily for 3 wk after the injection. Based on McNemar's test for paired analysis of proportions, a statistical analysis was conducted of crude rate differences. Logistic regression analysis was used to combine all 4 observations on each set of twins, as well as to compare other simultaneous factors, nonspecific individual factors, and vaccination as a cause of symptoms. The number of days in which a symptom was present between 6 and 14 days post-injection was considered a symptom score. The symptom score balance (mean difference within a pair of twins) was considered the most sensitive method of detecting the effect of vaccine on a symptom, and was used to analyze genetic factors in monozygotic and heterozygotic twins. The authors note that although statistical analysis clearly reveals no association between vaccine and respiratory symptoms, these symptoms increased after vaccination. They comment on the difficulty of drawing conclusions based on data from uncontrolled studies, and conclude that the simple random clinical trial is the method of choice for studying vaccines.

5. White C J, Stinson D, Stachle B, Cho I, Matthews H, Ngai A, Keller P, Eiden J, Kuter B and the MMRV Vaccine Study Group
Measles, mumps, rubella, and varicella combination vaccine: safety and immunogenicity alone and in combination with other vaccines given to children
Clin Infect Dis 24(5): 925-931, May 1997
To evaluate the effects of the live, attenuated MMRV vaccine given either alone or simultaneously with other pediatric vaccines, 812 healthy children were enrolled in 1 of 2 randomized multicenter studies. In the 1st protocol, 494 children aged 12 mo to 2.5 yr received either MMRV and placebo (group A) or M-M-R II and VARIVAX at 2 separate anatomic sites (group B) subcutaneously in a double-blind fashion on day 0. In the 2nd protocol, 318 children aged 12 mo to 3.5 yr who had completed the primary series of DTwP and OPV vaccines received either MMRV, DTaP, and OPV on day 0 (group A) or M-M-R II, DTaP, and OPV on day 0 and VARIVAX 6 wk later (group B). The varicella vaccine contained about 4000 pfu. Children were followed up for local and systemic reactions for 42 days (for two 42-day periods for group B in the 2nd protocol); blood samples were obtained and exposure surveys were completed 42 days after immunization in all groups and after 84 days in group B in the 2nd protocol. All vaccines used in the studies were well tolerated, with no serious adverse experiences reported. In protocol 1, there were no between-group differences in the incidence of local reactions. There was a higher measles-like/rubella-like rash rate in the MMRV plus placebo group than in the M-M-R II plus VARIVAX group (9.2% vs 3.3%; p=0.013). Irritability and asthenia/fatigue were the most common complaints in both groups. In protocol 2, there were no between-group differences in proportions of subjects with any local reactions or in varicella-like rash rates. Rates of measles-like/rubella-like rash were similar. Asthenia/fatigue was the most common complaint in both groups. Regardless of vaccines or regimens, overall rates of seroconversion for measles, mumps, rubella, and varicella were >95%. In each protocol, the GMT of antibody to varicella was lower among recipients of MMRV than among recipients of VARIVAX as a separate injection: 6.8 vs 12.4 in protocol 1 and 6.9 vs 11.9 in protocol 2 (both p<0.001). In protocol 1, the seroconversion rate for varicella at 6 wk was 97% after MMRV and 100% after VARIVAX as a separate injection (p=0.021). The GMT of antibody to measles was higher after MMRV than after M-M-R II (88.0 vs 69.4; p=0.012). In protocol 2, the seroconversion rate for measles was lower after MMRV than after M-M-R II (95.7% vs 100%; p=0.028). In the 1st yr of follow-up, there were 8 cases of varicella: 7 in protocol 1 (5 after MMRV plus placebo, mean number of lesions 30, range 7-79, with fever in 2 subjects; 2 after M-M-R II plus VARIVAX, with 26 and 5 lesions, respectively, with fever in 1 subject) and 1 in protocol 2 (after MMRV plus DTaP and OPV, with 20 lesions and a reported fever). The authors are from MRL.

6. Black S, Shinefield H, Ray P, Lewis E, Chen R, Glasser J, Hadler S, Hardy J, Rhodes P, Swint E, Davis R, Thompson R, Mullooly J, Marcy M, Vadheim C, Ward J, Rastogi S and Wise R and the Vaccine Safety Datalink Group
Risk of hospitalization because of aseptic meningitis after measles-mumps-rubella vaccination in one- to two-year-old children: an analysis of the vaccine safety datalink (VSD) project
Pediatr Infect Dis J 16(5): 500-503, May 1997
The level of risk, if any, of hospitalization for aseptic meningitis after Jeryl- Lynn mumps strain MMR was assessed in 1- to 2-yr-old children in the Vaccine Safety Datalink (VSD) population. The VSD project links medical outcome data and vaccine exposure information, as well as demographic and other covariate information from 4 large HMOs that have 500,000 children under age 7 under surveillance. Screening of preliminary automated data from the first 2 yr of the project showed a possible association of aseptic meningitis with receipt of MMR, with an

increased risk of aseptic meningitis 0-14 days after MMR vaccination of 3.61, on the basis of 3 cases of aseptic meningitis. A retrospective 10-yr matched case-control study was therefore conducted of hospitalization data to identify all hospitalized cases of aseptic meningitis in children between 12 and 23 mo of age. Of 93 potential cases of aseptic meningitis identified from automated hospitalization records, 59 were identified as cases of aseptic meningitis by medical record review. The overall rate of aseptic meningitis was 59 cases in an estimated 350,000 person-yr of follow-up time or 16.9 cases per 100,00 person-yr. It is noted that none of the 5 cases of encephalopathy/encephalitis identified had an onset within 30 days of receipt of any vaccine. Case-control analysis showed no increased risk of aseptic meningitis within 8 to 14 days, 14 days, or 30 days after MMR or any other vaccination and no cases of aseptic meningitis within 7 days of any vaccine (odds ratio <=1.0 for all analyses). About 300,000 doses of MMR were given to children aged 12-23 mo during the approximately 350,000 person-yr available for observation in this age group during the study period at the 4 HMOs. One child was hospitalized with aseptic meningitis within 14 days after MMR vaccination (with co-administration of HDTP, OPV, and HBV) and 3 children were hospitalized within 30 days after MMR vaccination (with co-administration of HDTP, OPV, and HBV vaccines in 1 child). The crude rate of disease was 1 case per 300,000 doses within 14 days and 1 case per 100,000 doses within 30 days. The incidence per 100,000 person-yr was 8.7 within 14 days and 12.2 within 30 days. Jeryl-Lynn strain MMR was not followed by hospitalized aseptic meningitis any more often than the upper bounds of these intervals (equivalent to 1 case within the 14-day period per 54,000 doses and 1 case within the 30-day period per 34,000 doses). It is concluded that there is no increased risk of aseptic meningitis after MMR vaccine.

7. Partridge S, Blumberg D A, Marcy S M, Chang S J, Curry E S and Ward J I
Safety and immunogenicity of administering all childhood vaccines for children 12-15 months of age at a single visit
Paper presented at the 35th Annual Meeting of the Infectious Diseases Society of America, San Francisco, California 140, Sept. 13-16, 1997
This study investigated the safety and immunogenicity of administering the 4 vaccines recommended for children aged 12-15 mo at a single visit. A total of 350 toddlers were randomized to 1 of 4 regimens: MMR, varicella, DTP, and Hib vaccines at 1 visit; MMR, varicella DTaP, and Hib vaccines at 1 visit; MMR and varicella vaccines at 1 visit followed by DTP and Hib vaccines 6 wk later; and MMR and varicella vaccines at 1 visit followed by DTaP and Hib vaccines 6 wk later. Antibody levels in groups vaccinated at a single visit were similar to those in groups vaccinated at 2 visits. Antibody levels declined between 6 wk and 12 mo for Hib, diphtheria, tetanus, pertussis, and filamentous hemagglutinin (FHA) but not for measles, mumps, rubella, or varicella. Subjects who received DTaP had significantly higher antibody levels to pertussis and FHA than did those who received DTP. Reaction rates were similar in groups vaccinated at a single visit and in those vaccinated at 2 visits. DTP was associated with significantly more reactions than was DTaP. The frequency of reactions ranged from 2% to 25% in the first 24 hr after vaccination but subsided thereafter. Reactions increased between 9 and 12 days postimmunization. The authors conclude that MMR, varicella, DTP/DTaP, and Hib vaccines can be administered to toddlers at a single visit without adverse outcomes.

8. Davis R L, Marcuse E, Black S, Shinefield H, Givens B, Schwalbe J, Ray P, Thompson R S, Chen R and the Vaccine Safety Datalink Team
MMR2 immunization at 4 to 5 years and 10 to 12 years of age: a comparison of adverse clinical events after immunization in the Vaccine Safety Datalink Project
Pediatrics 100(5): 767-771, Nov. 1997

A multicenter study was conducted to examine the frequency of adverse events after immunization with a second dose of MMR-II vaccine in children 4-6 yr and 10-12 yr of age at 2 large West Coast health maintenance organizations (HMOs). From March 1991 to December 1994, 18,036 children (52% M) at an HMO in Washington state received the MMR-II vaccine at 10-12 yr of age; 8514 children (51% M) at 3 facilities of an HMO in California received the MMR-II vaccine at 4-6 yr of age. Hepatitis B vaccine was given concurrently to 30% of 10- to 12-yr-old children and 10% of 4- to 6-yr-old children. For each group of children, information was collected on the number and type of visits to health care providers for 30 days beginning 3 mo before immunization and for 30 days beginning immediately after immunization. Among children immunized at 10-12 yr, 2101 were seen by health care providers during the period before immunization, and 2907 were seen immediately after immunization. Among children immunized at 4-6 yr, 874 and 523 were seen in the periods before and immediately after immunization, respectively. During the period immediately after immunization, 31 of the visits in the 4- to 6-yr-old group and 68 of those in the 10- to 12-yr-old group were for the conditions of interest, including rash, seizures, and joint pain; older children were almost 50% more likely than younger children to have a visit for one of these diagnoses during the month after vaccination (OR 1.45; 95% confidence interval [CI] 1.00, 2.10). Among children aged 10-12 yr, the number of visits for rash, seizures, and joint pain was significantly greater after than before immunization (OR 1.78; 95% CI 1.07, 2.97); among children aged 4-6 yr, there were significantly fewer visits after than before immunization (OR 0.52; 95% CI 0.28, 0.96). The risks for arthropathy and rash after immunization were greater among older females than among older males. There were no visits for thrombocytopenia or aseptic meningitis. The authors conclude that there is a greater risk for adverse clinical events after MMR-II immunization in 10- to 12-yr-old than in 4- to 6-yr-old children. They suggest that the results of their study may be of interest to the major advisory groups considering the optimal age for administration of the second MMR vaccine.

9. Schwarzer S, Reibel S, Lang A B, Struck M M, Finkel B, Gerike E, Tischer A, Gassner M, Gluck R, Stuck B and Cryz S J Jr
Safety and characterization of the immune response engendered by two combined measles, mumps and rubella vaccines
Vaccine 16(2-3): 298-304, Jan.-Feb. 1998
Two studies were conducted to evaluate immune responses to the MMR-VAX and TRIVIRATEN BERNA vaccines in healthy children. The 1st study was a randomized trial conducted to evaluate the safety and immunogenicity of MMR-VAX and TRIVIRATEN BERNA when administered as primary immunization in 320 children (age 14-24 mo). Each child received a single dose of MMR-VAX (n=147) or TRIVIRATEN BERNA (n=173); blood samples were taken before and 6-9 wk after immunization. Seven children who were seropositive to one of the vaccine components at baseline were excluded from the study. The seroconversion rates against the measles components, as determined by ELISA and plaque reduction neutralization, and against the rubella components, as determined by ELISA and hemagglutination inhibition, were similar for both vaccines (98.2%-100%). The seroconversion rate against the mumps component, as analyzed by ELISA, was higher for MMR-VAX than for TRIVIRATEN BERNA (96.5% vs 38%, $p<0.001$); however, when analyzed by 2 different immunofluorescence systems, the seroconversion rates were similar for the 2 vaccines (100% vs 92%-98.8%, NS). Compared with children who received TRIVIRATEN BERNA, those who received MMR-VAX had significantly higher GMTs for measles and mumps antibody titers and a lower GMT for rubella antibody titers. The group that received MMR-VAX had higher incidences of redness ($p=0.02$) and swelling ($p=0.004$) at the injection site and of fever >38 C

during a 6-wk period after vaccination (p=0.001). In the 2nd study, 13 adolescents (11 F, age 14-16 yr) who had previously received either MMR-VAX (n=8) or TRIVIRATEN BERNA (n=5) were given a booster dose of TRIVIRATEN BERNA. Twenty-eight days after re-immunization, only the 1 subject who had been seronegative at baseline showed a 4-fold or greater rise in measles antibody titer; 9 subjects had a 2-fold or greater rise in proliferative index. The titers for mumps antibodies were higher among subjects who had previously received MMR-VAX than among those who had received TRIVIRATEN BERNA; the difference was significant before re-immunization (p<0.001). The authors conclude that both MMR-VAX and TRIVIRATEN BERNA may be used in a routine 2-dose immunization regimen as part of the effort to eradicate these childhood illnesses.

10. Peltola H, Patja A, Leinikki P, Valle M, Davidkin I and Paunio M
No evidence for measles, mumps, and rubella-associated inflammatory bowel disease or autism in a 14-year prospective study
Lancet 351(9112): 1327-1328, May 2, 1998 (in Research Letters)
Because of concern raised by a recent paper by Wakefield et al suggesting a causal link between measles-mumps-rubella vaccine and a syndrome of chronic bowel inflammatory disease and autism, the authors examined data from a long-term measles-mumps- rubella vaccination program in Finland. With this program, launched in 1982, all children are vaccinated twice, at age 14-18 mo and at age 6 yr; further vaccinations are carried out among military recruits and some nursing schools. Only one type of vaccine (M-M-R or VIRIVAC) has been used since the beginning of the project. Adverse events temporally related to administration of the vaccine were reported prospectively to the National Public Health Institute. Vaccinees who developed GI symptoms or signs lasting 24 hr or longer at any time after vaccination were followed by checking hospital records or interviewing public health nurses. By the end of 1996, about 3 million doses of vaccine had been delivered by the Institute. Thirty- one children developed GI symptoms after vaccination, all but one after the first dose. These illnesses were mild, and probably sometimes caused by concomitant infections. Four children had received concomitant Hib conjugate vaccine. Twenty of the children were admitted to the hospital. The mean interval between the reported event and the health check was 9 yr 3 mo. Diarrhea, frequently with vomiting, was the most common symptom (55%, n=17). The time from vaccination to onset of symptoms varied from 20 hr to 15 days. Symptoms usually subsided within a week, except in one 1-yr-old boy in whom diarrhea lasted 6 wk; this child was healthy when checked 6 yr later. Most CNS signs and symptoms were the type that would be expected in conjunction with acute GI disease (febrile seizures in 5 and headache in 2). One child developed ataxia that subsided quickly. No child developed an autistic disorder. An autosomal recessive disease, hyperornithaemic gyrate atrophy, was diagnosed in 1 girl 8 years after vaccination. Two others developed bacterial meningitis 1 and 7 days after vaccination, respectively. The authors conclude that more than a decade of monitoring to detect severe adverse events associated with measles-mumps-rubella vaccine failed to uncover any evidence to support the hypothesis that it causes pervasive developmental disorder or inflammatory bowel disease. This study was funded partly by a grant from Merck Research Laboratories.

11. Andrews R M, Kempe A E, Sinn K K and Herceg A
Vaccinating children with a history of serious reactions after vaccination or of egg allergy
Med J Aust 168(10): 491-494, May 18, 1998
This paper describes the results of a 2-yr retrospective study on a special clinic vaccination program established to provide close medical supervision for children who had a serious adverse event after a previous vaccination or who had a history of egg allergy and required immunization

with M-M-R. Ninety-one children (male: female ratio, 1.2:1, age 2 mo-15 yr, median age 14 mo) attended over the 2 yr including 53 with a previous serious adverse vaccination event, 35 with egg allergy, 1 with seizure associated with meningitis, 1 with subdural hemorrhage in infancy and 1 with a possible allergy to DTPw vaccine. Of the 53 children referred for previous adverse vaccination events, all but one occurred after DTPw vaccination, with persistent screaming (>3 hr) the most frequent reaction; 29 of these children (55%) reacted after the 1st dose, 15 (28%) after the 2nd, 6 (11%) after the 3rd, and 3 (6%) after the 4th. Three additional children received their first dose of pertussis vaccine at the clinic. Forty- seven of the 53 were revaccinated with DTPw or monovalent pertussis, 4 with CDT, 1 with tetanus toxoid and 1 with typhoid vaccine. Hib, OPV and MMR were also provided if appropriate. None of the 35 children referred due to egg allergy had experienced anaphylaxis after egg or were considered severely allergic; all were vaccinated with MMR at the clinic. The children were observed after vaccination for 1 hr (3 children), 2 hr (88 children), 3 hr (16 children), 4 hr (2 children) and 6 hr (1 child); no adverse events were recorded during these time periods. In particular, there were no post-discharge adverse event reports in children vaccinated with the MMR vaccine or in those children referred because of persistent screaming, 19 having received whole-cell pertussis and 1 having received CDT. Only 1 child (age 6 mo) had a serious adverse event (hypotonic-hyporesponsive episode lasting several minutes) 8 hr after vaccination with DTPw, OPV and Hib at the clinic. The child had been referred to the clinic for similar episodes after prior vaccinations with these vaccines. The episode occurred at home, and the child recovered spontaneously. No further episodes occurred in this child upon subsequent vaccination with MMR at 12 mo or with DTPw and Hib (4th dose) at 18 mo. Mild reactions occurred in 2 other children: the 1st child (age 2 mo) screamed persistently for an unspecified duration after DTPw, OPV and Hib vaccination and the 2nd child (16 mo) had a high temperature (unspecified) after receiving DTPw (3rd dose) and Hib. The authors conclude that the vaccination clinic program successfully improved vaccination coverage by vaccinating children who may otherwise have remained unvaccinated or incompletely vaccinated due to histories of serious vaccination reactions.

12. 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-Barré 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-Barré 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-Barré 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-Barré syndrome varied from 80 days to years. There was no accumulation of Guillain-Barré 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 suggests that there is no causal relationship between MMR vaccination and Guillain-Barré syndrome.

13. Taylor B, Miller E, Farrington C P, Petropoulos M C, Favot-Mayaud I, Li J and Waight P A

Autism and measles, mumps, and rubella vaccine: no epidemiological evidence for a causal association

Lancet 353(9169): 2026-2029, June 12, 1999

The authors undertook a population- based study in the North East Thames region of the U.K. to investigate trends in the incidence of autistic disorders before and after the introduction of measles-mumps-rubella vaccine in Oct. 1988 and to determine if there might be any causal link with immunization. Clustering of onsets within defined postvaccination periods was investigated by the case-series method, a method which is valid for rare chronic disorders of acute onset. Two analyses were done for each combination of endpoint and risk period: the first covered only the triple-antigen vaccine, and the 2nd analysis also included single- antigen measles and mumps-rubella vaccines. Autism was identified in 498 children born since 1979 (typical or core autism [CA] in 261, atypical autism [AA] in 166, and Asperger's syndrome [AS] in 71). Diagnosis could be confirmed by ICDA criteria (10th revision) in 293. The number of cases by year of birth showed a steady rise peaking in the early to mid 1990s, followed by a sharp decline that was most pronounced for cases of CA and AA. There was a significant upward trend over the period 1979-92 for CA and AA (test for zero trend, $p<0.001$), but there was no evidence of a sudden "step-up" in 1987, the first birth cohort that would have been eligible for vaccination in the 2nd yr of life. A total of 389 children with CA, AA, or AS were born after 1987; 336 (86.4%) of these had received measles-mumps- rubella vaccine by the end of the 2nd year of life, and a further 17 (4.4%) were vaccinated after this age. The measles-mumps-rubella vaccine coverage in the 389 study cases did not differ significantly from that in the same birth cohorts in the study region as a whole. Trends in the incidence of autism by birth cohort since 1987 were not temporally associated with changes in vaccine coverage. For age at parental concern, no significant clustering was seen for cases of CA or AA, with the exception of a single interval within 6 mo ($p=0.03$), but this may have been due to difficulty in defining the precise age of onset. Regression was recorded for 29% of CA cases, 18% of AA, and 6% of AS. Of those diagnosed at age 18 mo or older (n=356), 233 received the vaccine before this age, 64 never received the vaccine, and 59 received it at age 18 mo or older. There were no differences in age at diagnosis between those vaccinated before or after 18 mo of age and those never vaccinated ($p=0.41$) and no interaction between these vaccine categories and year of birth ($p=0.29$). These results were consistent with an increase in the incidence of autism in recent birth cohorts. However, the authors do not feel that the increasing incidence of autism was related to the introduction of measles-mumps- rubella vaccine or to vaccine coverage, and hope that these results will help restore confidence in the vaccine. [Editors note: Usage of the term "MMR" in the original article appeared to be as an abbreviation rather than as the Merck trademark.]

14. DeStefano F, Gu D and Kramarz P and the Vaccine Safety Datalink Team

Infant vaccinations and risk of asthma in childhood

Pharmacoepidemiol Drug Safety 8(Suppl. 2): S101-S101, Aug. 1999 (in Soc. Proc.)

The authors studied the relationship between infant vaccinations and the development of asthma, through the analysis of data from the Vaccine Safety Datalink (VSD), a collaborative project between the Centers for Disease Control (CDC) and four large health maintenance organizations (HMOs). The authors identified all children who were enrolled in the HMOs from birth during 1991 through 1996. A total of 116,496 children were analyzed, of whom 11,134 (10%) developed asthma. The risk ratio of asthma associated with the DTP vaccine was 0.96. Administration of OPV was highly correlated with DTP; children who received OPV or DTP vaccine had a risk ratio of developing asthma of 1.16 relative to children who received neither

vaccine. For MMR vaccine the risk ratio was 1.00 (0.92-1.08). The authors concluded that these results do not support the hypothesis that DTP or MMR vaccine may increase children's risk of developing asthma.

15. DSouza R M, Campbell-Lloyd S, Isaacs D, Gold M, Burgess M, Turnbull F and OBrien 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.

16. Johnson C E, Darbari A, Darbari D S, Nalin D, Whitwell J, Chui L W, Cleves M A and Kumar M L

Measles vaccine immunogenicity and antibody persistence in 12 vs 15-month old infants

Vaccine 18(22): 2411-2415, May 8, 2000

This study was conducted to evaluate the seroconversion rates and antibody persistence in infants vaccinated with measles vaccine at either 12 or 15 mo of age. The mothers of all infants had reported receiving measles vaccine in childhood. Forty-seven 15-mo-old infants received

measles vaccine; 23 of these had received ATTENUVAX during participation in a previous study and the other 24 received subcutaneous M-M-R-II during participation in the current study. Forty-seven 12-mo-old infants were given subcutaneous M-M-R- II. Serum samples were taken after 4 wk and antibody titers were measured using an enzyme immunoassay (EIA) and a microneutralization assay (NT). In addition, 36 infants were followed up for 9 to 39 mo to determine antibody persistence. One 15-mo-old infant was excluded from analyses because he did not respond to the first dose of M-M-R- II; he subsequently had normal seroconversion after a 2nd vaccine dose. The proportion of infants who developed seropositivity at 4 wk was similar in the 2 age groups. At 4 wk, 41 of forty-seven 12-mo-old infants were seropositive by EIA (87%, 95% CI 74%-95%) compared with 45 of forty-six 15-mo-old infants (98%, CI 88%-100%; p=0.174). Two 12-mo-old infants had ambiguous results. The proportion of 12-mo-old infants who were seropositive by NT was 94% (CI 82%-99%) while the proportion of 15-mo-old infants was 98% (CI 88%-100%; p=0.317). Nineteen 12-mo old infants (40%) and seventeen 15-mo old infants (37%) were followed up for a mean of 20.3 mo. All children remained positive for measles antibody by both EIA and NT. There was no statistically significant decrease in the median NT or EIA titers during the follow-up. There were few reported adverse events, and all were transient and mild; there were no statistically significant differences between age groups in the incidence of adverse events. The authors conclude that 12- and 15-mo-old infants born to mothers with vaccine-induced immunity had similar antibody response to measles vaccine, but that further studies with larger sample sizes are needed to settle the issue of maternal antibody and its effect on primary vaccine failure.

17. Sarno M J, Blase E, Galindo N, Ramirez R, Schirmer C L and Trujillo-Juarez D F
Clinical immunogenicity of measles, mumps and rubella vaccine delivered by the Injex jet injector: comparison with standard syringe injection
Pediatr Infect Dis J 19(9): 839-842, Sept. 2000

A single- blind study was performed to evaluate the immunogenicity of M-M-R-II vaccine delivered subcutaneously via the Injex jet injector in comparison with needle syringe administration. A total of 40 adolescents (22 M, 18 F, age 9-14 yr, mean 11.1 yr) from Tijuana, Mexico were injected bilaterally with vaccine and with the buffer used for reconstitution. Blood samples were obtained before immunization and at 1, 2, and 12 wk postvaccination. Pain of injection was evaluated using the visual analog pain scale. Adverse events were recorded during the first 15 days after immunization. Twelve subjects had previously received measles vaccinations; 1 had previously received measles-mumps-rubella vaccine at 12 mo of age. Five subjects who received the vaccine via the Injex jet injector and 3 who received the vaccine via needle syringe were lost to follow-up by wk 12 of the study because of refusal to give blood samples. By wk 12, antibody titers against measles had increased in all of the subjects (100% response rate). One subject in the Injex group and 1 subject in the needle syringe group failed to respond to the mumps vaccine (95% response rate); 1 subject in the Injex group failed to respond to the rubella vaccine. Immune response to measles seemed to decrease by wk 12; antibody titers to mumps and rubella increased continuously during the follow-up period. There was no significant difference between injection devices with respect to the percentage of subjects responding by >200% over baseline by wk 1 and 2 postvaccination. Similarly, there was no significant difference between injection devices with respect to geometric mean antibody ratios at any time point postvaccination. Injection site soreness was reported by 1 subject after injection with the Injex and by 5 subjects injected with the needle syringe. Bleeding was observed in 3 subjects after injection with the needle syringe. Malaise was reported by 2 subjects and fever was reported by 1 subject during the 15-day follow- up; all 3 had received the vaccine via the needle syringe. There was no significant difference between injector types with respect to

injection pain scores. The authors conclude that both delivery methods resulted in equivalent immunogenicity and that the Injex jet injector is a safe alternative to needle syringe administration of the M-M-R II vaccine in healthy adolescents.

18. 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
BACKGROUND: Several disorders have been attributed to measles-mumps-rubella (MMR) vaccination during the past decade. The aim of this prospective follow-up study was to identify serious adverse events causally related to MMR vaccination. METHODS: When the MMR vaccination program was launched in Finland in 1982, a countrywide surveillance system was set up to detect serious adverse events associated with MMR. To obtain detailed case histories vaccinees' clinical charts were reviewed. Serum samples were analyzed to trace concurrent infections. SETTING: All hospitals and health centers in Finland from 1982 through 1996. RESULTS: Immunization of 1.8 million individuals and consumption of almost 3 million vaccine doses by the end of 1996 gave rise to 173 potentially serious reactions claimed to have been caused by MMR vaccination. In all, 77 neurologic, 73 allergic and 22 miscellaneous reactions and 1 death were reported, febrile seizure being the most common event. However, 45% of these events proved to be probably caused or contributed by some other factor, giving an incidence of serious adverse events with possible or indeterminate causal relation with MMR vaccination of 5.3 per 100,000 vaccinees or 3.2 per 100,000 vaccine doses. CONCLUSIONS: Causality between immunization and a subsequent untoward event cannot be estimated solely on the basis of a temporal relation. Comprehensive analysis of the reported adverse reactions established that serious events causally related to MMR vaccine are rare and greatly outweighed by the risks of natural MMR diseases.

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 IPC 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 that were received by Merck & Co., Inc., from worldwide sources, between 01-Jan-1996 to 31-Dec-2000.

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 Reports with Fatal Outcome

During the reporting period for this PSUR, 24 spontaneous reports of death in patients treated with measles, mumps, and rubella virus vaccine live were received from health care professionals, regulatory agencies, or published literature articles. In addition, 7 reports of fatal outcomes were identified as meeting the criteria for inclusion in this PSUR (see Section 6); however, upon internal review, it was determined that 6 of these reports (WAES [redacted]) had a consumer as a primary source and 1 report (WAES [redacted] identified from a literature article by D. Dlugos (See Appendix 9) concerned a 22-year-old male who was vaccinated with M-M-R™ in 1974. These reports will be updated in the WAES database, but these updates are not reflected in the attached appendices.

The remaining 24 reports were about 12 males, 11 females, and 1 report had no specified gender, ranging in age from 1 to 28 years with an average age of 5. The interval between vaccination and death for 21 reports was 10 days or less in 76%, 31 to 41 days in 10%, and 14% of deaths occurred after more than one year. Four of these 24 reports were identified from published literature articles. The remaining 20 reports were reported by health care professionals, including regulatory agencies from the following countries: United States (10), United Kingdom (4), Germany (3), Denmark (1), France (1), and Sweden (1).

These 24 reports are summarized by causes of death in the table below. In addition, the Company received 23 use-during-pregnancy reports in which the pregnancy resulted in an elective abortion (12), spontaneous abortion (8), ectopic pregnancy (1), or fetal death (2). As per Company procedures, these reports are coded with a serious criterion of "died". These 23 reports are included in Section 9.5, Use During Pregnancy.

Table 9.1.1
Summary of Causes of Death in Reports with Fatal Outcomes

Cause	Number of Reports
Cancer	1
Cardiovascular	3
Hematologic	2
Infection	6
Miscellaneous	3
Sudden Infant Death Syndrome	3
Unknown Cause	6

C
D

[redacted]

Cancer

There was 1 death that was related to cancer. WAES [redacted] concerned a 27- or 28-year-old male Asian immigrant from [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. The fatal outcome was reported not to be associated with vaccination.

Cardiovascular

There were 3 deaths related to the cardiovascular system. WAES [redacted] concerned a 16-month-old female, with a history of aortic valve stenosis and left heart insufficiency, who died of aortic valve sclerosis, mitral valve sclerosis and heart failure 3 hours post vaccination. The reporter did not consider the event related to therapy with measles, mumps, and rubella vaccine. WAES [redacted] concerned a 13-month-old female who died of cardiorespiratory arrest and status epilepticus 8 days after receiving a first dose of measles, mumps, and rubella vaccine. WAES [redacted] concerned an 11-year-old obese male, who died of pneumococcal sepsis and circulatory failure 1 day after receiving a first dose of measles, mumps, and rubella vaccine.

[redacted]

Hematologic

There were 2 reports of hematologic events in patients treated with measles, mumps, and rubella virus vaccine live. WAES [redacted] concerned a 6-year-old male, who had no adverse experience after the first dose of measles, mumps, and rubella vaccine, developed idiopathic thrombocytopenic purpura (ITP) approximately 2 years following the second dose. Subsequently, the patient died of a second case of ITP approximately 3 years and 9 months after vaccination. Conflicting information has been received from the mother and physician regarding the first onset date of ITP. The patient's mother and two siblings tested positive for Von Willebrand's disease. WAES [redacted] concerned a 15-month-old female who had a roseola type virus and was vaccinated 1 week after recovery. The patient had a viral syndrome which developed into encephalitis and aplastic anemia. Subsequently, the patient was diagnosed with Dubowitz Syndrome and died 5 months later.

[redacted]

Infection

There were 6 reports of death related to infection. WAES [redacted] concerned a patient with measles inclusion body encephalitis and is discussed in Section 9.8, Encephalitis.

In a report (WAES [redacted]) identified from a published literature article by J. Beeler (See Appendix 9), a 4-year-old male developed thrombocytopenic purpura after vaccination and subsequently, experienced an acute onset of *Escherichia coli* infection complicated by pseudomembranous colitis. The patient died 7 days post vaccination. WAES [redacted] identified from a published literature article by M. Masurekar, et al (See Appendix 9), concerned a 21-year-old HIV infected male patient, who was diagnosed with Pneumocystis carinii pneumonia (PCP) 1 month after vaccination with a third booster dose of measles, mumps, and rubella. One (1) year later the patient was treated for presumed measles pneumonia (later confirmed as the vaccine strain) and subsequently, died of cytomegalovirus (CMV) encephalitis with pulmonary measles and mycobacterium avium complex (MAC) 69 days later. WAES [redacted] identified from a published literature article by E. Peronne, et al (See Appendix 9), concerned a 10-year-old male who died of meningoencephalitis, not due to "acute viral infections

[redacted]

by common virus as vaccinal measles or mumps virus", 14 days after receiving the second dose of vaccine. WAES [redacted] concerned a 5-year-old female who died of encephalitis 10 days after receiving a second dose of measles, mumps, and rubella vaccine. PCR results were negative for rubella and positive IgG titers against measles virus. WAES [redacted] concerned a 13-month-old patient who was diagnosed with erythrophagocytic lymphohistiocytosis and subsequently, died 5 months post vaccination. An autopsy revealed a giant cell pneumonitis. It was also noted that "measles RNA (presumably) was detected in the lung tissue."

Sudden Infant Death Syndrome

There were 3 deaths related to the Sudden Infant Death Syndrome (SIDS). WAES [redacted] concerned an 18-month-old female who died of SIDS 9 days after receiving a first dose of measles, mumps, and rubella vaccine. The reporter felt that the cause of death was not related to therapy with vaccination. WAES [redacted] concerned a 15-month-old female who experienced a fever upon arriving home. Six hours post-vaccination, the patient was found unresponsive in bed and subsequently, the patient died. Postmortem did not show any evidence of any previously existing natural disease to account for the child's death and thus the cause of death was not ascertained. WAES [redacted] concerned a 14-month-old female who experienced a fever and rash 1 week after vaccination and was subsequently found cyanotic and unresponsive. The cause of death was reported by the patient's parents as Sudden Infant Death Syndrome.

Unknown Cause

In 6 reports, the cause of death was either unknown or not reported to the Company. WAES [redacted] concerned a 17-month-old male who died 4 hours following vaccination of his first dose. The medical examiner made a preliminary statement that the case is consistent with SIDS. WAES [redacted] concerned a 15-month-old female who became febrile 8 days after the administration of a first dose of measles, mumps, and rubella vaccine. The patient received antibiotic therapy and was subsequently treated again 47 days later. Approximately 1 year post vaccination the patient developed hepatitis, liver dysfunction, and received 3 liver transplants. The patient died 5 months later. WAES [redacted] concerned a healthy 15-month-old female who died 8 days post vaccination. The reporter did not think that the death was due to vaccination. A narrowing at the coronary ostium was noted on an otherwise normal autopsy. Information (WAES [redacted]) was received from an agency concerning a 15-month-old male born of consanguineous parents with a history of febrile seizures associated with apneic spells, who died 9 days post vaccination. The cause of death was a probable seizure; however, no clear anatomic cause of death was found. WAES [redacted] concerned a 15-month-old female who developed diarrhea 6 days following vaccination with a first dose of measles, mumps, and rubella. The patient died the same day. Information (WAES [redacted]) was received from a health authority concerning a 13-year-old male who had a seizure and died 1 month post vaccination.

Miscellaneous

WAES [redacted] concerned a 16-month-old male, with a history of convulsions, who died of asphyxiation 3 days post vaccination. The reporter felt that death was not related to vaccination with measles, mumps, and rubella vaccine. WAES [redacted] concerned a 13-month-old female who died of seizures 10 days after receiving vaccination. WAES [redacted] concerned a 12-month-old male, with a history of gastroesophageal reflux, negative viral serology for CMV,

influenza, rickettsiae, mycoplasma, HIV, respiratory syncytial virus, echovirus, Coxsackie and EBV, who died of cranial trauma 9 days post vaccination.

Comment

Most of these patients died of their underlying disease(s) or other concurrent illnesses. In the remainder of the cases, 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.

9.2 Drug Interactions

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

9.3 Overdose

During the reporting period for this PSUR, there were five (5) reports of overdose with measles, mumps, and rubella virus vaccine live. Of those reports, four (4) were identified from the same source with no adverse event reported (WAES [redacted]).

[redacted] each concerned a patient no more than 5-years-old who was reported to have experienced an overdose at 10 times the regular dose.

WAES [redacted] concerned 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 the age of 12-15 months). Following the two injections, the patient felt some pain when sitting but had no other symptoms. Subsequently, the patient's soreness at the injection site resolved. No further information is available.

9.4 Abuse

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

9.5 Use During Pregnancy

A prospective report of exposure during pregnancy is defined as a report where 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 where the Company first learned of the exposure after the outcome of the pregnancy was known.

During the reporting period for this PSUR, 309 spontaneous reports of exposure to measles, mumps, and rubella virus vaccine live during conception and pregnancy were identified.

These analyses include both reports from healthcare providers (i.e., spontaneous reports) and reports from consumers.

9.5.1 Pregnancy Reports with No Known Outcomes

One hundred ninety-eight (198) reports describe exposures to measles, mumps, and rubella virus vaccine live during pregnancy where the outcomes of the pregnancies were not reported. Three (3) of these reports were identified as full-term delivery and 1 report was identified as premature delivery; however, no information was received as to the outcome.

9.5.2 Pregnancy Reports with Known Outcomes

Table 9.5.2.1 Reports With Known Pregnancy Outcomes

OUTCOME	Number of RETROSPECTIVE Reports	Number of PROSPECTIVE Reports
Elective Abortion	7	5
Spontaneous Abortion	4	4
Fetal Death	2	0
Ectopic Pregnancy	0	1
Live Births	52	37
Total	**65**	**47**

Elective Abortion

Twelve (12) reports describe patients who underwent elective abortions. No medical indications were reported for these elective terminations.

Spontaneous Abortion

Eight (8) reports describe patients who experienced spontaneous abortions. Timing of abortion was reported in 5 of the reports; all occurred in the first trimester. No complications were reported.

Fetal Death

Two (2) reports describe patients who experienced fetal death that occurred in the 2nd trimester of pregnancy. There were no reported malformations of the fetuses. One (1) death was attributed to "missed spontaneous rupture of membranes" at 6 months gestation. The other cause of death, at 18 weeks gestation, was unknown.

Ectopic Pregnancy

One (1) report described a patient who experienced an ectopic pregnancy.

Live Births

There were 88 reports that identified live births: 2 reports describe patients who experienced premature birth or labor, 79 reports describe the delivery of normal newborns, and 7 reports describe congenital anomalies or other events.

Premature Birth or Labor

Two (2) reports describe patients who experienced premature birth or labor. One newborn required neonatal resuscitation, recovered and subsequently was discharged from the hospital. The second report noted no congenital anomalies.

Normal Newborns

Seventy-nine (79) reports describe the delivery of normal newborns. Of these reports, seventy-three (73) were first trimester (0-13 weeks) exposure; four (4) were second trimester (14-27 weeks) exposure and 2 were third trimester exposure (28-42 weeks). Of the 73 first trimester reports, thirty-three (33) reports were from one WAES report [redacted]) identified from a surveillance system from the [redacted].

Congenital Anomalies and Other Events

Table 9.5.2.2 Prospective Reports of Congenital Anomalies or Other Events

Anomaly or Event	Outcome	Timing of Vaccination	Comment
Down's Syndrome	Liveborn	Fifth week of pregnancy	Physician felt Down's syndrome was not associated with the vaccine

Table 9.5.2.3 Retrospective Reports of Congenital Anomalies or Other Events

Anomaly or Event	Outcome	Timing of Vaccination	Comment
Microcephaly and mental retardation	Liveborn	Conception	Full term infant
Transposition of the great arteries	Liveborn	Approximately five weeks prior to pregnancy	An expert in teratology was not in favor of a relation between the vaccine and the anomaly
Possible omphalocele or gastroschisis	Liveborn	Five weeks prior to LMP	Full term infant
Fetal Distress	Liveborn	Five days after LMP	It was noted that the fetal distress was not linked to the vaccination
Monocular blindness, mental retardation, sterility, seizure disorder, fever, rash, diarrhea	Liveborn	4.5 months pregnant	Full term infant
Prolonged gestation syndrome (Clifford I), neonatal sepsis, C-reactive protein increased, drug exposure via mother	Liveborn	Approximately six months pregnant	Infant discharged as healthy and recovered

Comment

In the pregnancy reports with known outcomes, 1 prospective and 6 retrospective reports of congenital anomalies or other events have been received during this reporting period. Given the relatively small number of reports with known outcomes available to date, these findings should be viewed with caution as there is not sufficient power to detect an increased risk of rare disorders or birth defects. 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.

9.6 Gelatin Allergy

Since measles, mumps, and rubella virus vaccine live was introduced, there have been 5 total reports of allergy to gelatin. During the reporting period for this PSUR, there have been 4 reports identified. A summary of those 4 cases follows.

WAES [redacted] concerned a 6-year-old male with no history or family history of atopic disease. The patient was vaccinated with measles, mumps, and rubella virus vaccine live and inactivated tick-borne encephalitis vaccine [redacted] According to the physician's opinion, the reaction was defined as Type I allergy to gelatin/polygeline. The reporter felt that these experiences were possibly related to therapy with measles-mumps-rubella vaccine.

WAES [redacted] concerned a 16-month-old male who was vaccinated with measles, mumps, and rubella virus vaccine live in the leg. Subsequently, the patient developed a severe local reaction at the injection site. [redacted]

WAES [redacted] concerned an 11-year-old female with asthma-like bronchitis and an allergy to acarids. Previous vaccination history included one exposure to measles, mumps, and rubella virus vaccine live and three exposures to diptheria toxoid (+) pertussis vaccine (+) tetanus toxoid and inactivated poliovirus vaccine. The patient was vaccinated with a second dose of measles, mumps, and rubella virus vaccine live and a dose of diphtheria toxoid (+) inactivated poliovirus vaccine (+) tetanus toxoid. Some minutes post-vaccination, the patient developed syncope and an erythematous rash over the trunk which lasted for 10 minutes. [redacted]

[redacted] The patient recovered spontaneously, [redacted]

[redacted] concerned a 16-month-old male who was vaccinated with one dose of measles, mumps, and rubella virus vaccine live in one arm and one dose of varicella virus vaccine live in the other arm. Within five minutes of vaccination, the patient developed a local reaction at the measles, mumps, and rubella virus vaccine live injection site described as a twenty-five cent urticarial lesion. There were no other symptoms. The patient was treated with diphenhydramine HCl with resolution symptoms in less than 1 hour. There was no reaction to varicella virus vaccine live. [redacted] It was noted that two months later, the patient was vaccinated with Hib and had a similar reaction.

Comment

Of the 4 reports, one may be classified as some type of immediate systemic hypersensitivity reaction (WAES [redacted]), two as localized injection site reactions (WAES [redacted] and [redacted]), and one as a syncopal reaction (WAES [redacted]. It is explicitly stated that three of the four patients recovered, and recovery is implied in the remaining case. The Contraindications Section of the CCDS for measles, mumps, and rubella virus vaccine live includes hypersensitivity to any component of the vaccine, including gelatin. The estimated number of marketed measles, mumps, and rubella virus vaccine live doses distributed worldwide between 01-Jan-1996 to 31-Dec-2000 was approximately [redacted]. Approximately [redacted] patients 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. Severe allergic reactions to gelatin contained within this product would seem to be an exceedingly rare occurrence. The Company will continue to monitor all adverse experiences as part of its ongoing evaluation of the safety of this product.

9.7 <u>Aseptic Meningitis</u>

From market introduction to 31-Dec-2000, a total of 55 spontaneous reports of meningitis (reported as aseptic meningitis, cerebrospinal fluid abnormality, infectious meningitis, infectious meningoencephalitis, meningismus, meningitis, meningococcal meningitis, and/or viral meningitis) have been received from healthcare professionals, including regulatory agencies.

Twenty-seven (27) of these reports were received during the reporting period of this PSUR (01-Jan-1996 to 31-Dec-2000). The reports were about 19 males, 6 females, and in 2 reports no gender was specified. Ages ranged from 1 to 16 years with an average age of 5 years. The onset occurred from 0 to 833 days post vaccination, with a median onset of 7 days. Six (6)* of the 27 reports were identified from published literature articles; 4 of these reports were from the same source. One (1) report was identified from a Swedish newspaper. The remaining 21 reports were spontaneously reported by health care professionals, including regulatory agencies from the following countries: France (7), Austria (4), Germany (4), Denmark (2), United Kingdom (1), United States (2), and Sweden (1).

* WAES Reports: [redacted] (See Appendix 9)

C

Comment

Even though measles, mumps, and rubella virus vaccine live has been used extensively, only a very small number of cases of aseptic meningitis have been reported following vaccination. Although a causal relationship between the Urabe strain of mumps vaccine and aseptic meningitis has been shown, there are no data to link Jeryl Lynn mumps vaccine to aseptic meningitis.

9.8 Encephalitis

From market introduction to 31-Dec-2000, a total of 105 spontaneous reports of encephalitis (reported as encephalitis, encephalomyelitis, encephalopathy—and/or subacute sclerosing panencephalitis) have been received from healthcare professionals, including regulatory agencies.

Fifty-one (51) of these reports were received during the reporting period of this PSUR (01-Jan-1996 to 31-Dec-2000). The reports were about 24 males, 20 females, and in 7 reports no gender was specified. Ages ranged from 1 to 43 years with an average age of 5. The onset occurred from 0 to 493 days post vaccination, with a median onset of 8 days. Fifteen (15)** of the 51 reports were identified from published literature articles; two sources reported 5 and 3 cases, respectively. The remaining 36 reports were spontaneously reported by health care professionals, including regulatory agencies from the following countries: United States (9), Denmark (7), France (5), United Kingdom (4), Germany (3), Sweden (3), Canada (1), Australia (1), Austria (1), Italy (1), and Switzerland (1). [redacted]

During the reporting period of this PSUR, there were 4 reports of encephalitis that resulted in a fatal outcome. Three (3) of these 4 reports (WAES [redacted]) are included in Section 9.1, Death. The remaining report (WAES [redacted] is discussed below under measles inclusion body encephalitis.

During the reporting period of this PSUR, there were 2 reports of subacute sclerosing panencephalitis (SSPE) identified. Information (WAES [redacted]) was received from a published literature article by S Park (See Appendix 9) concerning a 9-year-old female twin who had received measles, mumps, and rubella vaccination at 1- and 5-years of age. The patient probably contracted wild measles at the age of one year. WAES [redacted] concerned a 5-year-old male, with hemophilia A and no previous history of measles, who received measles, mumps, and rubella vaccine and 16 months post vaccination experienced SSPE. In WAES [redacted], the polymerase chain reaction (PCR) was positive for measles virus in the cerebrospinal fluid; however, as no brain biopsy was available, there was no sequencing of various parts of the virus to further identify the virus.

Comment

The Side Effects Section of the CCDS for measles, mumps, and rubella virus vaccine live states: There have been reports of subacute sclerosing panencephalitis (SSPE) in children who did not have a history of natural measles but did receive measles vaccine. Some of

** WAES Reports: [redacted] (See Appendix 9)

these cases may have resulted from unrecognized measles in the first year of life or possibly from the measles vaccination. Based on estimated nationwide measles vaccine distribution, the association of SSPE cases to measles vaccination is about one case per million vaccine doses distributed. This is far less than the association with natural measles, 6 to 22 cases of SSPE per million cases of measles. The results of a retrospective case-controlled study conducted by the Center for Disease Control and Prevention suggest that the overall effect of measles vaccine has been to protect against SSPE by preventing measles with its inherent higher risk of SSPE.

During the reporting period of this PSUR, there was 1 report (WAES [redacted]) of measles inclusion body encephalitis (MIBE) identified. Information initially received from a health care professional and subsequently from a published article and a paper presented by Bitnun, et al (see Appendix 9), indicated that a previously healthy 21-month-old patient, with no history of measles exposure nor evidence, at the time, of immune deficiency was vaccinated with one dose of measles, mumps, and rubella vaccine. Approximately 8.5 months following vaccination, the patient was diagnosed with measles inclusion body encephalitis and subsequently died. Immunological studies found that the patient had a profound deficiency of CD8+ cells and dysgammaglobulinemia.

Comment

The Contraindications Section of the CCDS states that measles, mumps, and rubella virus vaccine live is contraindicated in 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.

Comment

The Side Effects Section of the CCDS for measles, mumps, and rubella virus vaccine live states: Post-marketing surveillance of the more than [redacted] doses 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. The Company will continue to monitor all adverse experiences as part of its ongoing evaluation of the safety of this product.

9.9 Autism

Since measles, mumps, and rubella virus vaccine, live was introduced, there have been 64 total reports of autism from health care professionals (54 spontaneous, 10 literature). Eighty percent (51/64) of these reports occurred during the period of this PSUR. These reports were most probably stimulated by a 1998 article in the Lancet[1] which in turn stimulated numerous contrary publications[2,3,4,5,6,7], much press coverage and litigation, as well as parallel influx of consumer reports (63 total, 75% of which originated in the United Kingdom).

9.10 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 supports the adequacy of 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.

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[1] Wakefield AJ, Murch SH, Anthony A, et al. Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children. Lancet. 1998;351:637-641.

[2] Dales, L., S.J. Hammer, and N.J. Smith. Time trends in autism and in MMR immunization coverage in California. JAMA 2001;285:1183-1185.

[3] DeStefano, F., and R.T. Chen. Negative association between MMR and autism. Lancet 353:1987-1989, 1999.

[4] Kaye, J.A., M. Melero-Montes, and H. Jick. Mumps, measles, and rubella vaccine and incidence of autism recorded by general practitioners: a time trend analysis. Brit. Med. J. 322:460-463, 2001.

[5] Miller, D., J. Wadsworth, J. Diamond, and E. Ross. Measles vaccination and neurological events. Lancet 349:730-731, 1997.

[6] Peltola, H., A. Patja, P. Leinikki, et al. No evidence for measles, mumps, and rubella vaccine-associated inflammatory bowel disease or autism in a 14-year prospective study. Lancet 351:1327-1328, 1998.

[7] Taylor, B., E. Miller, C.P. Farrington, et al. Autism and measles, mumps, and rubella vaccine: no epidemiological evidence for a causal association. Lancet 353:2026-2029, 1999.