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

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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]