Product Monograph

Including Patient Medication Information

M-M-R® II

(measles, mumps and rubella virus vaccine, live, attenuated, Merck Std.)

Lyophilized powder for injection

0.5 mL for Intramuscular and Subcutaneous Injection

Active Immunizing Agent

ATC code: J07BD52

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Recent Major Label Changes

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Part 1: Healthcare Professional Information

1 Indications

M-M-R® II (measles, mumps and rubella virus vaccine, live, attenuated) is a vaccine indicated for simultaneous vaccination against measles, mumps, and rubella in persons 12 months of age or older (see 4 Dosage And Administration).

1.1 Pediatrics (Less than 1 year old)

- No clinical data are available on safety or efficacy of M-M-R® II in children less than one year of age. Administration to infants under twelve months of age is not recommended.

1.2 Geriatrics

- No data are available to Health Canada; therefore, Health Canada has not authorized an indication for geriatric use.

For other vaccine considerations see the Canadian Immunization Guide.[1]

2 Contraindications

M-M-R® II (measles, mumps and rubella virus vaccine, live, attenuated, Merck Std.) should not be administered to:

- Individuals with a history of history of hypersensitivity to any component of the vaccine including gelatin. For a complete listing, (see 6 Dosage Forms, Strengths, Composition And Packaging).
- Pregnant females. If vaccination of postpubertal females is undertaken, pregnancy should be avoided for one month following vaccination (see 7 Warnings And Precautions, 7.1.1 Pregnancy).
- Individuals with histologic changes, similar to those seen in gestational rubella, have been observed and rubella virus has been recovered from decidua following vaccination of pregnant women with live attenuated rubella vaccine. These vaccines may thus constitute a risk to the fetus.
- Individuals with anaphylactic or anaphylactoid reactions to neomycin. Each dose of reconstituted vaccine contains approximately 25 µg neomycin.
- Individuals with any febrile respiratory illness or other active febrile infection.
- Individuals with active untreated tuberculosis.
- Individuals receiving immunosuppressive therapy with adrenocorticotropic hormone (ACTH), corticosteroids, irradiation, alkylating agents or antimetabolites. This contraindication does not apply to patients who are receiving corticosteroids as replacement therapy, e.g., for Addison's disease.
- Individuals with blood dyscrasias, leukemia, lymphomas of any type, or other malignant neoplasms affecting the bone marrow or lymphatic systems.
- Individuals with primary and acquired immunodeficiency states, including patients who are immunosuppressed in association with AIDS or other clinical manifestation of infection with human

[1] Measles vaccines: Canadian immunization guide - Canada.ca

immunodeficiency viruses; cellular immune deficiencies, hypogammaglobulinemic and dysgammaglobulinemic states. Measles inclusion body encephalitis (MIBE), pneumonitis and death as a direct consequence of disseminated measles vaccine virus infection have been reported in severely immunocompromised individuals inadvertently vaccinated with measles-containing vaccine. M-M-R® II is recommended for asymptomatic HIV-infected individuals. M-M-R® II is not normally recommended for symptomatic HIV-infected individuals because safety and immunogenicity data are not yet available. If there is a known exposure to measles, measles-immune globulin (IG) should be given within 6 days whether or not the individual has been vaccinated, although the efficacy of IG for passive immunoprophylaxis of measles in HIV-infected individuals is uncertain.

- Individuals with a family history of congenital or hereditary immunodeficiency, until the immune competence of the potential vaccine recipient is demonstrated.

4 Dosage and Administration

4.2 Recommended Dose and Dosage Adjustment

The dosage of M-M-R® II is the same for all persons.

For additional information on vaccination and to help control measles and mumps outbreaks, please refer to the National Advisory Committee on Immunization (NACI).[1]

Non-Pregnant Adolescent and Adult Females: Immunization of susceptible non-pregnant adolescent and adult females of childbearing age with live attenuated rubella virus vaccine is indicated if certain precautions are observed (see 7 Warnings And Precautions, 7.1.1 Pregnancy). In view of the importance of protecting this age group against rubella, reasonable precautions in a rubella immunization program include asking females if they are pregnant, excluding those who say they are, and explaining the theoretical risks to the others. Vaccinating susceptible postpubertal females confers individual protection against subsequently acquiring rubella infection during pregnancy, which in turn prevents infection of the fetus and consequent congenital rubella injury.

Women of childbearing age should be advised not to become pregnant for one month after vaccination and should be informed on the reasons for this precaution.

It is recommended, when feasible, that rubella susceptibility be determined by serologic testing prior to immunization. Since serologic testing is expensive and not always accurate, rubella vaccination of a woman who is not known to be pregnant and has no history of vaccination is justifiable without serologic testing. If immune, as evidenced by a specific rubella antibody titer of 1:8 or greater (hemagglutination-inhibition test), vaccination is unnecessary. Congenital malformations do occur in up to seven percent of all live births. Their chance appearance after vaccination could lead to misinterpretation of the cause, particularly if the prior rubella-immune status of vaccinees is unknown.

Postpubertal females should be informed of the frequent occurrence of generally self-limited arthralgia and/or possible arthritis beginning 2 to 4 weeks after vaccination (see 8 Adverse Reactions).

Postpartum Women: It has been found convenient in many instances to vaccinate rubella-susceptible women in the immediate postpartum period (See 7 Warnings And Precautions, 7.1.2 Breastfeeding).

4.3 Reconstitution

Prior to Reconstitution:
Check the appearance of the contents of each vial of vaccine. The content should be a light yellow solid mass ("plug") of powder which fills the bottom of each vial.

To reconstitute, use only the diluent supplied, since it is free of preservatives or other antiviral substances which might inactivate the vaccine.

First withdraw the entire volume of diluent (0.7 mL) into the syringe to be used for reconstitution. Inject all the diluent in the syringe into the vial of lyophilized vaccine and agitate to mix thoroughly. Withdraw the entire contents into a syringe and inject the total volume of restored vaccine intramuscularly or subcutaneously.

Table 1 - Reconstitution

Vial Size	Volume of Diluent to be Added to Vial	Approximate Available Volume	Concentration per Dose
Single-dose	Entire contents (0.7 mL)	0.5 mL	Measles: ≥ 1000 $CCID_{50}$ Mumps: ≥ 5000 $CCID_{50}$ Rubella: ≥ 1000 $CCID_{50}$

4.4 Administration

FOR INTRAMUSCULAR OR SUBCUTANEOUS ADMINISTRATION
After suitably cleansing the immunization site, inject the total volume of the single-dose vial (approximately 0.5 mL) of reconstituted vaccine intramuscularly or subcutaneously, preferably into the outer aspect of the upper arm.

Do not inject M-M-R® II intravascularly. Do not give immune globulin (IG) concurrently with M-M-R® II.

CAUTION: A sterile syringe free of preservatives, antiseptics, and detergents should be used for each injection and/or reconstitution of the vaccine because these substances may inactivate the live virus vaccine. A 25 gauge, 15 mm needle is recommended.

Prior to Administration:
Inspect the reconstituted solution for particulate matter and discoloration. The reconstituted solution should be **clear yellow**. Should complete dissolution not occur within two minutes, do not use and return for reimbursement.

It is important to use a separate sterile syringe and needle for each individual patient to prevent transmission of Hepatitis B and other infectious agents from one person to another.

Use AS SOON AS POSSIBLE after reconstitution. Store reconstituted vaccine in the vaccine vial in a dark place at 2°C to 8°C. Discard if not used within 8 hours.

5 Overdose

Administration of a higher than recommended dose of M-M-R® II was reported rarely and the adverse reaction profile was comparable to that observed with the recommended dose of M-M-R® II.

For the most recent information in the management of a suspected vaccine overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

6 Dosage Forms, Strengths, Composition, and Packaging

To help ensure the traceability of vaccines for patient immunization record-keeping as well as safety monitoring, health professionals should record the time and date of administration, quantity of administered dose (if applicable), anatomical site and route of administration, brand name and generic name of the vaccine, the product lot number and expiry date.

Table 2 – Dosage Forms, Strengths and Composition

Route of Administration	Dosage Form / Strength / Composition	Non-medicinal Ingredients
Intramuscular or Subcutaneous	Lyophilized powder for injection Approximately 0.5 mL dose after reconstitution Measles: ≥ 1000 $CCID_{50}$* Mumps: ≥ 5000 $CCID_{50}$ Rubella: ≥ 1000 $CCID_{50}$ *50% Cell Culture Infectious Dose	Hydrolyzed gelatin / Medium 199 with Hank's salts / Minimum Essential Medium, Eagle / Monosodium L-glutamate monohydrate / Neomycin / Phenol red / Potassium phosphate dibasic (anhydrous) / Potassium phosphate monobasic / Sodium bicarbonate / Sodium phosphate dibasic (anhydrous) / Sodium phosphate monobasic / Sorbitol / Sucrose / Water for injection Manufacturing Process Residuals: Fetal bovine serum / Recombinant human albumin

Dosage Forms:

M-M-R® II (measles, mumps and rubella virus vaccine, live, attenuated, Merck Std.) is supplied as a sterile, lyophilized, light yellow compact crystalline plug in a single-dose vial.

The diluent (STERILE DILUENT For Merck Sharp & Dohme LLC live, attenuated, virus vaccines) is a sterile, clear, colourless fluid supplied separately in a single-dose vial.

After reconstitution, M-M-R® II is a clear yellow liquid.

The vaccine contains no preservative.

The diluent is sterile water for injection.

Packaging

M-M-R® II is supplied in 3 mL single-dose Type I glass vials. Each vial contains one dose of lyophilized vaccine (approximately 0.5 mL when reconstituted as directed).

The diluent (0.7 mL) is supplied separately in 3 mL single-dose Type I glass vials.

The container closure systems of M-M-R® II and the diluent are free of latex.

M-M-R® II is available in packages of 10 single-dose vials. The diluent is also available in packages of 10 single-dose vials.

7 Warnings and Precautions

General

Administer M-M-R® II intramuscularly or subcutaneously; do not give intravascularly.
Severe allergic reactions including anaphylaxis can occur after administration of M-M-R® II (see 8.5 Post-Market Adverse Drug Reactions).

Adequate treatment provisions including epinephrine injection (1:1000) should be available for immediate use in case an anaphylactic or anaphylactoid reaction occurs.

Due caution should be employed in administration of M-M-R® II to persons with individual or family histories of convulsions, a history of cerebral injury or any other condition in which stress due to fever should be avoided. The physician should be alert to the temperature elevation which may occur 5 to 12 days following vaccination (see 8 Adverse Reactions).

Children and young adults who are known to be infected with human immunodeficiency viruses and are not immunosuppressed may be vaccinated. However, the vaccinees who are infected with HIV should be monitored closely for vaccine-preventable diseases because immunization may be less effective than for uninfected persons (see 2 Contraindications).

Excretion of small amounts of the live attenuated rubella virus from the nose or throat has occurred in the majority of susceptible individuals 7 to 28 days after vaccination. There is no confirmed evidence to indicate that such virus is transmitted to susceptible persons who are in contact with the vaccinated individuals. Consequently, transmission, while accepted as a theoretical possibility, is not regarded as a significant risk. However, transmission of the rubella vaccine virus to infants via breast milk has been documented (see 7.1.2 Breastfeeding).

There are no reports of transmission of live attenuated measles or mumps viruses from vaccinees to susceptible contacts.

Although there is a theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD) or its variant (vCJD), no cases of transmission of CJD, vCJD, or viral diseases have ever been identified that were associated with the use of albumin.

As for any vaccine, vaccination with M-M-R® II may not result in protection in 100% of vaccinees.

Hematologic

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 (see 8 Adverse Reactions).

Immune

Immune and Hypersensitivity
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.

According to the National Advisory Committee on Immunization (NACI), "anaphylaxis after measles vaccination is rare. It has been reported both in people with anaphylactic hypersensitivity to eggs and in those with no history of egg allergy. In some of these instances it is hypersensitivity to gelatin that is responsible for the anaphylactic reaction. As well, allergy to other components of the vaccine, such as neomycin, has been hypothesized but not proven.

The minute quantity of egg proteins contained in measles-mumps-rubella vaccines (MMR) seems to be insufficient to cause an allergic reaction in egg-allergic people.

"Several studies have reported uneventful routine MMR immunization in egg-allergic people and in those with positive MMR skin tests, whereas others have reported occasional adverse reactions despite the use of MMR skin testing and graded challenge vaccination. Therefore, the use of skin testing with MMR vaccines in egg-allergic individuals is no longer recommended."

"In view of the cumulative data indicating the safety of MMR immunization in people with a history of anaphylactic hypersensitivity to hens' eggs and the lack of evidence of the predictive value of MMR skin testing, NACI does not recommend routine MMR skin testing or any special precaution in these individuals. As for all vaccines, NACI recommends immunization by personnel with the capability and facilities to manage adverse events following immunization such as anaphylaxis."

Monitoring and Laboratory Tests

It has been reported that live attenuated measles, mumps and rubella virus vaccines given individually may result in a temporary depression of tuberculin skin sensitivity. Therefore, if a tuberculin test is to be done, it should be administered either any time before, simultaneously with, or at least 4 to 6 weeks after M-M-R® II.

Children under treatment for tuberculosis have not experienced exacerbation of the disease when immunized with live measles virus vaccine; no studies have been reported to date on the effect of measles virus vaccines on children with active untreated tuberculosis; however, the vaccine is contraindicated in such cases as a precautionary measure (see 2 Contraindications).

7.1 Special Populations

7.1.1 Pregnancy

Animal reproduction studies have not been conducted with M-M-R® II. The vaccine should not be administered to pregnant females; furthermore, pregnancy should be avoided for one month following vaccination (see 2 contraindications and 8.5 Post-Market Adverse Reactions).

Wild-type rubella infection during pregnancy, especially in the first trimester, can lead to miscarriage, stillbirth, or Congenital Rubella Syndrome (CRS). In an 18-year survey involving over 1200 pregnant women who received rubella vaccine within 3 months before or after conception (of whom 683 received the Wistar RA 27/3 strain), none of the newborns had abnormalities compatible with CRS. Subsequent post-marketing surveillance identified CRS associated with a rubella vaccine strain following inadvertent vaccination of a pregnant female with a measles, mumps, and rubella vaccine. 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. Reports have indicated that contracting of wild-type measles during pregnancy enhances fetal risk. Increased rates of spontaneous abortion, stillbirth, congenital defects and prematurity have been observed subsequent to infection with wild-type 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.

7.1.2 Breastfeeding

Nursing Women

It is not known whether measles or mumps vaccine virus is secreted in human milk. Recent studies have shown that lactating postpartum women immunized with live attenuated rubella vaccine may secrete the virus in breast milk and transmit it to breast-fed infants. In the infants with serological evidence of rubella infection, none exhibited severe disease; however, one exhibited mild clinical illness typical of acquired rubella. Caution should be exercised when M-M-R® II is administered to a nursing woman.

7.1.3 Pediatrics

Pediatric (<12 months)

Based on the data submitted and reviewed by Health Canada, the 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.

8 Adverse reactions

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. Therefore, the frequencies of adverse reactions observed in the clinical trials may not reflect frequencies observed in clinical practice and

should not be compared to frequencies reported in clinical trials of another drug.

A clinical trial comparing the safety and immunogenicity of M-M-R® II manufactured with recombinant human albumin (rHA) and M-M-R® II manufactured with human serum albumin (HSA) was conducted in 1279 children. Clinical follow-up was obtained for 634/641 (98.9%) subjects who received M-M-R® II with rHA and 632/638 (99.1%) subjects who received M-M-R® II with HSA.

The number and percentage of subjects who reported specific systemic adverse experiences with an incidence of ≥1% in either treatment group during Days 1 to 42 postvaccination are presented by body system and treatment group in Table 3.

Table 3 – Number (%) of Subjects with Specific Systemic Clinical Adverse Experiences (Incidence ≥1% in One or More Treatment Groups) by Body System (Days 1 to 42 Following Vaccination)

	M-M-R® II With rHA (N=641)				M-M-R® II With HSA (N=638)			
	All Adverse Experiences		VR		All Adverse Experiences		VR	
	n	(%)	n	(%)	n	(%)	n	(%)
Number of subjects	641				638			
Number of subjects without follow-up	7				6			
Number of subjects with follow-up	634				632			
Number (%) of subjects with one or more systemic adverse experiences	469	(74.0)			465	(73.6)		
Number (%) of subjects with no systemic adverse experience	165	(26.0)			167	(26.4)		
Ear and Labyrinth Disorders	**11**	**(1.7)**			**7**	**(1.1)**		
Ear pain	7	(1.1)			2	(0.3)		
Eye Disorders	**27**	**(4.3)**			**14**	**(2.2)**	**4**	**(0.6)**
Conjunctivitis	22	(3.5)			10	(1.6)	2	(0.3)
Gastrointestinal Disorders	**99**	**(15.6)**	**8**	**(1.3)**	**110**	**(17.4)**	**14**	**(2.2)**
Constipation	5	(0.8)			7	(1.1)		
Diarrhea NOS	45	(7.1)	4	(0.6)	41	(6.5)	6	(0.9)
Loose stools	8	(1.3)	1	(0.2)	9	(1.4)	2	(0.3)
Teething	11	(1.7)			9	(1.4)		
Vomiting NOS	35	(5.5)	3	(0.5)	41	(6.5)	5	(0.8)
General Disorders and Administration Site Conditions	**158**	**(24.9)**	**61**	**(9.6)**	**149**	**(23.6)**	**69**	**(10.9)**
Pain NOS	10	(1.6)	4	(0.6)	4	(0.6)	2	(0.3)
Pyrexia	144	(22.7)	56	(8.8)	138	(21.8)	63	(10.0)
Immune System Disorders	**6**	**(0.9)**			**8**	**(1.3)**	**1**	**(0.2)**
Hypersensitivity NOS	2	(0.3)			8	(1.3)	1	(0.2)
Infections and Infestations	**279**	**(44.0)**	**15**	**(2.4)**	**256**	**(40.5)**	**17**	**(2.7)**
Croup infectious	8	(1.3)			5	(0.8)		
Ear infection NOS	23	(3.6)	1	(0.2)	18	(2.8)	1	(0.2)
Gastroenteritis NOS	11	(1.7)	1	(0.2)	12	(1.9)		
Nasopharyngitis	80	(12.6)	4	(0.6)	84	(13.3)	5	(0.8)
Otitis media NOS	79	(12.5)	1	(0.2)	65	(10.3)	3	(0.5)
Sinusitis NOS	5	(0.8)			13	(2.1)		
Upper respiratory tract infection NOS	98	(15.5)	3	(0.5)	87	(13.8)	5	(0.8)
Upper respiratory tract infection viral NOS	8	(1.3)			3	(0.5)		

	M-M-R® II With rHA (N=641)				M-M-R® II With HSA (N=638)			
	All Adverse Experiences		VR		All Adverse Experiences		VR	
	n	(%)	n	(%)	n	(%)	n	(%)
Viral infection NOS	25	(3.9)	2	(0.3)	17	(2.7)		
Viral rash NOS	14	(2.2)	3	(0.5)	14	(2.2)	5	(0.8)
Injury, Poisoning and Procedural Complications	**33**	**(5.2)**			**25**	**(4.0)**	**1**	**(0.2)**
Arthropod bite	15	(2.4)			8	(1.3)	1	(0.2)
Metabolism and Nutrition Disorders	**7**	**(1.1)**			**5**	**(0.8)**		
Nervous System Disorders	**7**	**(1.1)**	**1**	**(0.2)**	**6**	**(0.9)**	**3**	**(0.5)**
Psychiatric Disorders	**53**	**(8.4)**	**27**	**(4.3)**	**48**	**(7.6)**	**26**	**(4.1)**
Insomnia	7	(1.1)	1	(0.2)	0	(0.0)		
Irritability	49	(7.7)	27	(4.3)	47	(7.4)	25	(4.0)
Respiratory, Thoracic and Mediastinal Disorders	**109**	**(17.2)**	**4**	**(0.6)**	**121**	**(19.1)**	**11**	**(1.7)**
Cough	41	(6.5)	1	(0.2)	43	(6.8)	1	(0.2)
Nasal congestion	22	(3.5)			30	(4.7)	3	(0.5)
Rhinitis NOS	6	(0.9)			12	(1.9)	1	(0.2)
Rhinorrhoea	41	(6.5)	3	(0.5)	41	(6.5)	4	(0.6)
Wheezing	15	(2.4)	1	(0.2)	12	(1.9)	1	(0.2)
Skin and Subcutaneous Tissue Disorders	**162**	**(25.6)**	**50**	**(7.9)**	**142**	**(22.5)**	**41**	**(6.5)**
Dermatitis diaper	31	(4.9)	1	(0.2)	32	(5.1)	1	(0.2)
Eczema	10	(1.6)			15	(2.4)		
Heat rash	25	(3.9)	4	(0.6)	8	(1.3)	1	(0.2)
Rash morbilliform	20	(3.2)	20	(3.2)	11	(1.7)	10	(1.6)
Rash NOS	53	(8.4)	20	(3.2)	47	(7.4)	19	(3.0)
Urticaria NOS	8	(1.3)	3	(0.5)	8	(1.3)	3	(0.5)

Percentages are calculated based on the number of subjects with follow-up.
Although a subject may have had 2 or more systemic adverse experiences, the subject is counted only once in the overall total.
Adverse experience terms are from MedDRA Version 6.0.
N=Number of subjects vaccinated in each treatment group.
VR=Vaccine-related. Entries in this column refer to the number (%) of subjects with systemic adverse experiences that were determined by the investigator to be possibly, probably, or definitely related to the vaccine.
rHA=Recombinant human albumin.
HSA=Human serum albumin.

Potential undesirable effects

Additional clinical and post marketing data from previous formulations of monovalent and of the combined measles, mumps, and rubella vaccines manufactured by Merck & Co., Inc. without regard to causality or frequency are available and are summarized below. These data were reported based on more than 400 million doses distributed worldwide. Potential undesirable effects already provided in the previous section (related to the clinical experience with M-M-R® II with rHA) are excluded from the data provided below.

Common

Burning and/or stinging of short duration at the injection site.

8.3 Less Common Clinical Trial Adverse Reactions

Other adverse reactions reported at a frequency of uncommon (≥1/1000, <1/100) and rare (≥1/10,000, <1/1000)] are listed below.

Uncommon

Body as a whole
Fever (38.3°C or higher).

Skin
Rash, or measles-like rash, usually minimal but may be generalized. Generally, fever, rash, or both appear between the 5th and the 12th day.

Rare

Arthralgia and/or arthritis
Arthralgia and/or arthritis (usually transient and rarely chronic), and polyneuritis are features of infection with wild-type rubella and vary in frequency and severity with age and sex, being greatest in adult females and least in prepubertal children.

Chronic arthritis has been associated with wild-type rubella infection and has been related to persistent virus and/or viral antigen isolated from body tissues. Only rarely have vaccine recipients developed chronic joint symptoms.

Following vaccination in children, reactions in joints are uncommon and generally of brief duration. In women, incidence rates for arthritis and arthralgia are generally higher than those seen in children (children: 0–3%; women: 12–20%), and the reactions tend to be more marked and of longer duration. Symptoms may persist for a matter of months or on rare occasions for years. In adolescent girls, the reactions appear to be intermediate in incidence between those seen in children and in adult women. Even in older women (35 to 45 years), these reactions are generally well tolerated and rarely interfere with normal activities.

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

Cardiovascular
Vasculitis.

Digestive
Parotitis, nausea, vomiting, diarrhea.

Hematologic/Lymphatic
Regional lymphadenopathy, thrombocytopenia, purpura.

Hypersensitivity

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

Musculoskeletal
Arthralgia and/or arthritis (usually transient and rarely chronic [see below **Other**]), myalgia.

Nervous/Psychiatric
Febrile convulsions in children, afebrile convulsions or seizures, headache, dizziness, paresthesia, polyneuritis, polyneuropathy, Guillain-Barré syndrome, ataxia, acute disseminated encephalomyelitis (ADEM), transverse myelitis, aseptic meningitis (see below), measles inclusion body encephalitis (MIBE) (see CONTRAINDICATIONS),syncope.

Respiratory System
Pneumonia, pneumonitis (see 2 Contraindications), cough, rhinitis.

Skin
Erythema multiforme, Stevens-Johnson syndrome, Henoch-Schönlein purpura, Acute Hemorrhagic Edema of Infancy, vesiculation at injection site, swelling, pruritus.

Special Senses
Forms of optic neuritis, including retrobulbar neuritis, papillitis, and retinitis; ocular palsies, otitis media, nerve deafness, conjunctivitis.

Urogenital
Epididymitis, orchitis.

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 in healthy individuals (see 2 Contraindications). 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 to 1993.

In a randomized open-label clinical trial, conducted in France and Germany, 752 children 12 months through 18 months of age received M-M-R® II concomitantly administered with VARIVAX at a separate site, by either the intramuscular (n=374) or subcutaneous (n=378) route. In the overall population, 55.3% were male and the median age was 13.2 months. Local and systemic solicited adverse reactions were recorded by parents or guardians using standardized diary cards. Local solicited reactions were recorded for 4 days after vaccination, and systemic solicited adverse reactions were recorded for 42 days after vaccination. In the event that a participant experienced a rash or a mumps-like illness, parents and/or guardians were instructed to contact the investigator for an examination as soon as possible and no later than 72 hours following onset of symptoms. The nature of any rash was characterized by principal investigator either as measles-like, rubella-like, varicella-like or “other”. Study investigators reviewed the diary card with the participant or participant’s legal guardian 42 days after vaccination to ensure consistency with protocol definitions. Table 4 below presents the frequency of solicited adverse reactions based on the final assessment by the study investigators.

Table 4: Proportion of Participants Reporting Solicited Adverse Reactions Following Vaccination with M-M-R® II, Concomitantly Administered with VARIVAX®, by the Intramuscular or Subcutaneous Route

	INTRAMUSCULAR N=374 %	SUBCUTANEOUS N=376 %
Solicited injection-site reactions at MMR injection-site (Days 0 to 4)*		
Erythema[†]	10.4	16.2
Mild	8.8	13.0
Moderate	0.8	3.2
Severe	0	0
Missing	0.8	0
Pain[‡]	7.0	7.2
Mild	5.1	5.9
Moderate	1.9	1.3
Severe	0	0
Swelling[†]	1.9	5.3
Mild	1.1	2.9
Moderate	0.5	1.1
Severe	0	0
Missing	0.3	1.3
Solicited systemic reactions (Days 0 to 42)		
Measles-like rash[§]	2.9	2.7
Rubella-like rash[§]	2.7	2.7
Varicella-like rash[§]	0.5	3.2
Mumps-like illness	0	0.3
Fever (temperature ≥38.0°C)[¶, #]	66.5	66.8
38.0-38.5°C	20.4	22.2
>38.5-39.0°C	17.4	16.6
>39.0-39.5°C	14.2	13.4
>39.5-40.0°C	11.8	11.0
>40.0°C	2.7	3.7
N=total number of participants in the group		

* During the post vaccination monitoring period (0-42 days), 3 participants experienced a varicella-like injection-site rash at the M M R II injection site. All were reported in the subcutaneous group.
† Intensity of injection site reaction: mild or ≤2.5 cm; moderate or >2.5 to ≤5.0 cm; severe or >5.0 cm.
‡ Intensity of pain: mild: awareness of symptom but easily tolerated; moderate: definitely acting like something is wrong; severe: extremely distressed or unable to do usual activities.
§ Testing to distinguish between rash caused by wild-type or vaccine virus was not performed. Reports of measles-, rubella-, and varicella-like rash included 3 reports of measles, 1 report of rubella, and 1 report of varicella, all with onset within 15 days post vaccination.
¶ The percentage of fever is defined within the population who had valid temperature measurements. One participant in IM group and two participants in SC group did not have temperature measurements and were excluded from the denominator; resulting in N=373 and N=374, respectively.
# In the IM Group 92.3% of fevers were documented using the rectal route of measurement and 7.7% of fevers were documented only by the axillary route of measurement. In the SC Group 89.6% of fevers were documented using the rectal route of measurement and 10.4% of fevers were documented only by the axillary route of measurement.

Unsolicited adverse events that occurred within 42 days following vaccination were recorded using diary cards supplemented by medical review. Data on unsolicited adverse events were transcribed into the study database during an on-site visit at day 42. The rates and types of reported adverse events (AEs) across groups were similar and included common clinical events that are often reported in the evaluated populations. Serious adverse events occurred at rates of 0.3% and 1% in the intramuscular and subcutaneous groups, respectively. One moderate intensity case of otitis media occurred in a participant in the subcutaneous group was considered related to the study vaccination.

8.5 Post-Market Adverse Reactions

Subacute Sclerosing Panencephalitis (SSPE)
There have been reports of SSPE in children who did not have a history of infection with wild-type measles but did receive measles vaccine. Some of 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 infection with wild-type measles, 6–22 cases of SSPE per million cases of measles. The results of a retrospective case-controlled study conducted by the Centers 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.

Aseptic Meningitis
Cases of aseptic meningitis have been reported following measles, mumps, and rubella vaccination. A causal relationship between the Urabe strain of mumps vaccine and aseptic meningitis has been shown. Although a temporal association has been observed between the administration of M-M-R® II and rare cases of aseptic meningitis, there is no laboratory-confirmed evidence to link Jeryl Lynn® mumps vaccine to aseptic meningitis.

Encephalitis/encephalopathy
Encephalitis/encephalopathy have been reported approximately once for every 3 million doses of the measles, mumps, and rubella vaccine manufactured by Merck & Co., Inc. Since 1978, post-marketing surveillance indicates that serious adverse events such as encephalitis and encephalopathy continue to be rarely reported. The risk of such serious neurological disorders following live measles virus vaccine administration remains far less than that for encephalitis and encephalopathy with wild-type measles (one per one thousand reported cases).

In severely immunocompromised individuals inadvertently vaccinated with measles-containing vaccine, measles inclusion body encephalitis, pneumonitis, and fatal outcome as a direct consequence of disseminated measles vaccine virus infection have been reported (see 2 Contraindications); disseminated mumps and rubella vaccine virus infection have also been reported.

Panniculitis
Panniculitis has been reported rarely following administration of measles vaccine.
Cases of severe allergic reaction including anaphylaxis have been reported shortly after the administration of M-M-R® II.

Pregnancy
A cumulative assessment of post-marketing reports for M-M-R® II vaccine from licensure 01 April 1978 through 31 December 2018, identified 796 reports of inadvertent administration of M-M-R® II vaccine occurring 30 days before or at any time during pregnancy with known pregnancy outcomes. Of the prospectively followed pregnancies for which the timing of M-M-R® II vaccination was known, 425 women received M-M-R® II vaccine during the 30 days prior to conception through the second trimester. The outcomes for these 425 prospectively followed pregnancies included 16 infants with major birth defects, 4 cases of fetal death and 50 cases of miscarriage; however, no abnormalities compatible with congenital rubella syndrome (CRS) were identified.
The US Centers for Disease Control and Prevention (CDC) established the Vaccine in Pregnancy registry (1971-1989) of women who had received rubella vaccines within 3 months before or after conception. Data on 1221 inadvertently vaccinated pregnant women demonstrated no evidence of an increase in fetal abnormalities or cases of CRS in the enrolled women.
Subsequent post-marketing surveillance identified CRS associated with a rubella vaccine strain following inadvertent vaccination of a pregnant woman with a measles, mumps, and rubella vaccine.

Skin
Skin granuloma associated with vaccine derived rubella virus.

9 Drug Interactions

9.2 Drug Interactions Overview
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.

9.4 Drug-Drug Interactions
M-M-R® II vaccine should not be administered to individuals receiving immunosuppressive therapy, including high dose corticosteroids. Vaccination with M-M-R® II vaccine can result in disseminated disease due to measles vaccine in individuals on immunosuppressive drugs.

Administration of immune globulins and other blood products concurrently with M-M-R® II vaccine may interfere with the expected immune response. There are specific recommendations for intervals between administration of antibody containing products and live virus vaccines.

It has been reported that live attenuated measles, mumps and rubella virus vaccines given individually may result in a temporary depression of tuberculin skin sensitivity. Therefore, if a tuberculin skin test with tuberculin purified protein derivative (PPD) is to be done, it should be administered before, simultaneously with, or at least 4 to 6 weeks after vaccination with M-M-R® II vaccine.

Use with other Vaccines:
M-M-R® II should be given concomitantly, or one month before or after administration of other live attenuated viral vaccines.

M-M-R® II has been administered concurrently with other vaccines (i.e., live attenuated varicella, DTaP [or DTwP], IPV [or OPV], Hib with or without Hepatitis B vaccine) using separate injection sites and syringes. No impairment of immune response to individual tested vaccine antigens was demonstrated. The type, frequency, and severity of adverse experiences observed with M-M-R® II were similar to those seen when each vaccine was given alone.

In combined clinical studies involving 1107 children 12 to 36 months of age, 680 received varicella vaccine (Oka/Merck) and M-M-R® II concomitantly at separate sites and 427 received the vaccines six weeks apart. Seroconversion rates and antibody levels were comparable between the two groups at approximately six weeks postvaccination to each of the virus vaccine components. No differences were noted in adverse reactions reported in those who received varicella vaccine (Oka/Merck) concomitantly with M-M-R® II at separate sites and those who received varicella vaccine (Oka/Merck) and M-M-R® II at different times.

In a clinical study involving 609 children 12 months to 23 months of age, 305 received varicella vaccine (Oka/Merck), M-M-R® II, and Tetramune (*Haemophilus influenzae* type b, diphtheria, tetanus, and pertussis vaccines) concomitantly at separate sites and 304 received M-M-R® II and Tetramune given concomitantly at separate sites followed by varicella vaccine (Oka/Merck) 6 weeks later. At six weeks postvaccination, seroconversion rates for measles, mumps, rubella, and varicella were similar between the two groups. Compared to prevaccination GMTs, the six-week postvaccination boost in GMTs for *Haemophilus influenzae* type b, diphtheria, tetanus and pertussis was similar between the two groups. GMTs for all antigens were similar except for varicella which was lower when varicella vaccine (Oka/Merck) was administered concomitantly with M-M-R® II and Tetramune but within the range of GMTs seen in previous clinical experience when varicella vaccine (Oka/Merck) was administered alone. At 1 year postvaccination, GMTs for measles, mumps, rubella, varicella and *Haemophilus influenzae* type b were similar between the two groups. All three vaccines were well tolerated regardless of whether they were administered concomitantly at separate sites or 6 weeks apart. There were no clinically important differences in reaction rates when the three vaccines were administered concomitantly versus 6 weeks apart.

9.5 Drug-Food Interactions
Interactions with food have not been established.

10 Clinical Pharmacology

M-M-R® II is a live, attenuated vaccine for immunization against measles, mumps, and rubella.

Following vaccination, antibodies associated with protection can be measured by neutralization assays,

HI, or ELISA (enzyme linked immunosorbent assay) tests. Neutralizing and ELISA antibodies to measles, mumps, and rubella viruses are still detectable in most individuals 11 to 13 years after primary vaccination.

10.1 Mechanism of Action

M-M-R® II vaccination induces antibodies to measles, mumps, and rubella associated with protection which can be measured by neutralization assays, hemagglutination-inhibition (HI) assays, or enzyme linked immunosorbent assay (ELISA) tests. Results from efficacy studies or effectiveness studies that were previously conducted for the component vaccines of M-M-R® II were used to define levels of serum antibodies that correlated with protection against measles, mumps, and rubella.

10.2 Pharmacodynamics

Pharmacotherapeutic group: Vaccines, Viral Vaccine; ATC code: J07BD52

10.3 Pharmacokinetics

Duration of Effect

The duration of protection from measles, mumps, and rubella infection after vaccination with M-M-R® II is unknown (see 10 Clinical Pharmacology).

10.4 Immunogenicity

Clinical studies of 284 triple seronegative children, 11 months to 7 years of age, demonstrated that M M R® II is highly immunogenic and generally well tolerated. In these studies, a single injection of the vaccine induced measles hemagglutination-inhibition (HI) antibodies in 95%, mumps neutralizing antibodies in 96%, and rubella HI antibodies in 99% of susceptible persons. However, a small percentage (1–5%) of vaccinees may fail to seroconvert after the primary dose.

The RA 27/3 rubella strain in M M R® II elicits higher immediate post-vaccination HI, complement-fixing and neutralizing antibody levels than other strains of rubella vaccine and has been shown to induce a broader profile of circulating antibodies including anti-theta and anti iota precipitating antibodies. The RA 27/3 rubella strain immunologically simulates natural infection more closely than other rubella vaccine viruses. The increased levels and broader profile of antibodies produced by RA 27/3 strain rubella virus vaccine appear to correlate with greater resistance to subclinical reinfection with the wild virus, and provide greater confidence for lasting immunity.

11 Storage, Stability, and Disposal

During shipment, to ensure that there is no loss of potency, M-M-R® II must be maintained at a temperature between -50°C and +8°C. Use of dry ice may subject M-M-R® II to temperatures colder than -50°C.

Before reconstitution, M-M-R® II should be stored refrigerated at a temperature of 2°C to 8°C. The vaccine may also be stored in a freezer at temperatures above -50°C; if subsequently transferred to a refrigerator, the vaccine may be placed back in the freezer.

M-M-R® II can be administered provided total (cumulative multiple excursions) time out of

refrigeration (prior to reconstitution, at temperatures between 8°C and 25°C) does not exceed 6 hours. These are not, however, recommendations for storage.

Protect the vaccine from light at all times, since such exposure may inactivate the viruses.

Before reconstitution, store the vial of lyophilized vaccine at 2°C to 8°C or colder (above -50°C). The diluent should be stored in the refrigerator with the lyophilized vaccine or separately at room temperature. Refrigeration of the diluent is not needed. Store at 2°C to 27°C. Do not freeze the diluent.

Reconstituted Solutions
To maintain the potency, it is imperative that only the STERILE DILUENT For Merck Sharp & Dohme LLC. live, attenuated, virus vaccines (Sterile Water) be used for reconstitution and injection.

Use AS SOON AS POSSIBLE after reconstitution. Store reconstituted vaccine in the vaccine vial in a dark place at 2°C to 8°C. Discard if not used within 8 hours.

12 Special Handling Instructions

Discard if reconstituted vaccine is not used within 8 hours. Do not refreeze reconstituted vaccine.

Part 2: Scientific Information

13 Pharmaceutical Information

Drug Substance

Proper name: measles, mumps, and rubella virus vaccine, live, attenuated, Merck Std.

Product Characteristics: M-M-R® II with rHA (recombinant human albumin) is a sterile lyophilized preparation combining three viruses: (1) Measles Virus Live, a more attenuated line of measles virus, derived from Enders' attenuated Edmonston strain and grown in cell cultures of chick embryo, (2) Mumps Virus Live, the attenuated Jeryl Lynn® strain of mumps virus grown in cell cultures of chick embryo, and (3) Rubella Virus Live, the Wistar RA 27/3 strain of live attenuated rubella virus grown in human diploid cell (WI-38) culture. When the lyophilized vaccine is reconstituted as directed, the product contains not less than 1000 $CCID_{50}$ (cell culture infectivity dose) measles virus, 5000 $CCID_{50}$ mumps virus, and 1000 $CCID_{50}$ rubella virus (minimum potencies at expiry, 8 hours post-reconstitution). The product is intended for single-dose administration and contains no preservative. Sterile diluent is provided for reconstitution.

14 Clinical Trials

14.1.Clinical Trials by Indication

The original trivalent measles, mumps and rubella vaccine, M-M-R®, was first licensed in the United States in 1971 and in Canada in 1972. This formulation contained the HPV 77 DE strain of live rubella virus, also used in the monovalent rubella virus vaccine (MERUVAX®). In developing M-M-R® II, the rubella component of M-M-R® (HPV 77 DE) was exchanged with the Wistar RA 27/3 attenuated rubella strain. M-M-R® was subsequently discontinued, and M-M-R® II (Wistar RA 27/3) was licensed in the United States in 1978 and in Canada in 1979. The Wistar RA 27/3 attenuated rubella strain is cultured in human diploid fibroblasts and was developed by Plotkin in 1965. Comparative studies using the 2 rubella vaccine virus strains showed that RA 27/3 induced stronger rubella-specific immune responses, was associated with lower incidence of adverse experiences, and was associated with lower incidence of breakthrough infection after exposure with wild type rubella virus. Since 1978, the Wistar RA 27/3 strain has been used in place of the HPV 77 DE strain and is the only rubella strain used in all rubella containing vaccines licensed by Merck Sharp & Dohme LLC.

From 1975 to 1978, 7 studies involving approximately 2,000 subjects (8 months to 27 years of age), were conducted to support the licensure of M-M-R® II in many parts of the world, including Canada. These studies compared the immunogenicity, safety, and tolerability of different combinations of measles, mumps, and rubella live virus vaccines. A summary of 6 out of the 7 studies is included in Table 5.

The seventh study, Protocol 484, compared the immunogenicity and clinical tolerability of M-M-R® II Lot 621/C D763 or M-M-R®. One hundred fifty-five (155) subjects 13 months to 27 years of age were enrolled. Of the children with available antibody results, seroconversion was observed in 98% (30/31) of those receiving HPV 77 DE containing vaccine and in 100% (47/47) of those receiving RA 27/3 containing vaccine.

The most frequent systemic reactions reported in the original study summaries were upper respiratory illness (32%), gastrointestinal illness (23%), irritability (17%), and anorexia (17%). Measles like rash

occurred in 5% of subjects immunized with trivalent vaccine containing the RA 27/3 rubella strain. Seroconversion rates observed at 6 weeks postvaccination among this triple seronegative population were 95% for measles, 96% for mumps, and 99% for rubella.

Table 5 – Summary of Immunogenicity Results in Children Initially Seronegative to Measles, Mumps, and Rubella Who Received Trivalent Measles, Mumps and Rubella Vaccine Containing the RA 27/3 Rubella Strain

					Antibody Responses among Triple Seronegative Subjects								
					Measles (HI)			Mumps (Neut)			Rubella (Neut)		
Study No.	Lot No.	Range	Mean (Year)	N	Observed Response		GMT	No. Converting/ No. Seronegative		GMT	No. Converting/ No. Seronegative		GMT
442	621	10 m to 7 y	3.7	199	100%	(23/23)	99	96%	(22/23)	7	100%	(23/23)	149
443	621	11 m to 8 y	1.7	105[1]	94%	(65/69)[1]	56	96%	(66/69)[1]	8	100%	(69/69)[1]	133
459	60664	14 m to 4 y	1.5	59	93%	(13/14)	62	93%	(13/14)	17	100%	(14/14)	269
467	621	11 m to 7 y	1.9	137[2]	95%	(55/58)[2]	71	98%	(57/58)[2]	7	100%	(58/58)[2]	146
511	60664	8 m to 11 y	3.3	50	82%	(9/11)	20	91%	(10/11)	5	100%	(11/11)	226
	60665	11 m to 7 y	3.3	50	80%	(4/5)	25	80%	(4/5)	11	100%	(5/5)	169
	60666	11 m to 11 y	4.2	50	100%	(2/2)	28	100%	(2/2)	8	100%	(2/2)	256
513	60664	12 m to 7 y	1.6	58	94%	(30/32)	74	94%	(30/32)	16	100%	(32/32)	250
	60665	12 m to 4 y	1.6	58	97%	(35/36)	72	97%	(35/36)	23	97%	(35/36)	307
	60666	11 m to 4 y	1.5	59	97%	(33/34)	66	97%	(33/34)	27	97%	(33/34)	256
				Totals	95%	(269/284)	63	96%	(272/284)	11	99%	(282/284)	179

HI = Hemagglutination-inhibition.
Neut = Neutralizing.
y = Years.
m = Months.
N = Number vaccinated.
Observed Response = number converted/number initially seronegative.
[1] Three of these subjects were immunized with a 1.0 mL dose of trivalent vaccine containing RA 27/3 strains, 1 subject was triple seronegative prior to immunization and is included in this table.
[2] Twenty subjects were immunized with a 1.0 mL dose of trivalent vaccine containing RA 27/3 strains, 9 subjects were triple seronegative prior to immunization and are included in this table.

Protocol 009 (M-M-R® II [measles, mumps and rubella virus vaccine, live, attenuated, Merck Std.] with rHA replacement study) was designed to (1) demonstrate that the antibody response rates to measles, mumps, and rubella among children who received M-M-R® II manufactured with rHA will be similar to the antibody response rates among children who receive M-M-R® II manufactured with HSA; (2) to demonstrate that M-M-R® II manufactured with rHA will induce acceptable antibody response rates to measles, mumps, and rubella; and (3) to demonstrate that M-M-R® II with rHA will be generally well tolerated. This was a double blind (using in house blinding procedures), randomized, comparative multicenter study of 1282 healthy children at 12 to 18 months of age. Eligible subjects were randomized to receive either an investigational formulation of M-M-R® II manufactured with rHA or currently licensed M-M-R® II manufactured with HSA. In order to determine if any rHA manufacturing residual would elicit an immune reaction, certain adverse experiences of special interest (AESI) that are indicative of hypersensitivity reaction were prespecified in the protocol and prompted for on the Vaccination Report Card (VRC). The incidence of injection site adverse experiences, temperature ≥38.9 °C ([≥102.0 °F], oral equivalent or abnormal), non injection site rashes, other local and systemic adverse experiences were reported for the 42 days (6 weeks) following vaccination. Serum samples were obtained from each subject immediately prior to the vaccination on Day 0, and 6 weeks postvaccination.

The primary endpoints used to assess immunogenicity 6 weeks postvaccination were the antibody response rates for measles, mumps, and rubella, defined as the proportion of subjects who developed

serum antibody levels >120 mIU/mL for measles, >10.0 ELISA antibody units/mL for mumps, or >10.0 IU/mL for rubella. The primary analysis of the response rate to measles, mumps, and rubella were based on a per protocol subject population, which included subjects without protocol violations who had a valid baseline and week 6 titer values for analysis, and whose baseline measles antibody titers were <120 mIU/mL, whose baseline mumps antibody titers were <10.0 ELISA antibody units/mL, and whose baseline rubella antibody titers were <10.0 IU/mL. Both the primary immunogenicity hypotheses of similarity to the control group and for acceptability of antibody responses in recipients of M-M-R® II with rHA were satisfied for measles, mumps, and rubella. The 2 sided 90% confidence intervals on the differences in estimated antibody response rates to measles, mumps, and rubella between recipients of M-M-R® II with rHA and recipients of M-M-R® II with HSA all excluded a decrease of 5 percentage points or more and thus support a conclusion of similarity between the 2 treatment groups for each antigen. The lower bounds of the 2 sided 95% CI for each of the 3 antibody response rates in recipients of M-M-R® II with rHA were all greater than 90%, supporting the conclusion of acceptable antibody response rates. Measles, mumps, and rubella GMTs measured 6 weeks postvaccination were comparable between the two treatment groups. Summaries of the immunogenicity results measured in the 2 treatment groups are provided in tables 6 (non inferiority analysis) and 7 (acceptability analysis).

Table 6 – Statistical Analysis of Similarity of Measles, Mumps, and Rubella Antibody Responses in Initially Seronegative Subjects (Per-Protocol Analysis)

		M-M-R® II With rHA (N=641)		M-M-R® II With HSA (N=638)		Estimated Difference[†‡] (Percentage Points) (90% CI)[‡]	Similarity Conclusion
Antibody (ELISA)	Parameter	n	Estimated Response[†]	n	Estimated Response[†]		
Measles	% ≥120 mIU/mL	531	98.3%	498	98.8%	-0.5% (-1.9%, 0.8%)	Similar[§]
Mumps	% ≥10.0 ELISA antibody units/mL	563	99.4%	533	97.9%	1.5% (0.4%, 2.8%)	Similar[§]
Rubella	% ≥10.0 IU/mL	572	99.6%	543	99.6%	0.0% (-0.8%, 0.8%)	Similar[§]

[†] Responses and their difference were based on a statistical analysis model adjusting for study centers.

[‡] [M-M-R® II with rHA] - [M-M-R® II with HSA].

[§] A lower bound of 90% confidence interval (CI) on the difference excluding a decrease of 5 percentage points or more implies the difference is statistically significantly less than the prespecified clinically relevant decrease of 5 percentage points and allows for a conclusion of similarity (non-inferiority). The associated 1-sided p-value for each test is <0.001 (a p-value ≤0.05 implies that the difference is statistically significantly less than the prespecified difference of 5 percentage points).

N=Number of subjects vaccinated in each treatment group.

n=Number of subjects initially seronegative for measles, mumps, and rubella contributing to the per-protocol analyses.

rHA=Recombinant human albumin.

HSA=Human serum albumin.

ELISA=Enzyme-linked immunosorbent assay.

Table 7 – Statistical Analysis of Acceptability of Measles, Mumps, and Rubella Responses in Initially Seronegative Subjects (Per-Protocol Analysis)

Antibody (ELISA)	Parameter	M-M-R® II With rHA (N=641)		Acceptability Conclusion
		n	Observed Response (95% CI)†	
Measles	% ≥120 mIU/mL	531	98.3% (96.8%, 99.2%)	Acceptable†
Mumps	% ≥10.0 ELISA antibody units/mL	563	99.5% (98.5%, 99.9%)	Acceptable†
Rubella	% ≥10 IU/mL	572	99.7% (98.7%, 100%)	Acceptable†

† The lower bound of the 95% confidence interval (CI) being >90% implies that the value of the parameter is statistically significantly greater than the prespecified acceptability criterion (90%) and allows for a conclusion of acceptability.

N=Number of subjects vaccinated in treatment group.

n=Number of subjects initially seronegative for measles, mumps, and rubella contributing to the per-protocol analyses.

rHA=Recombinant human albumin.

ELISA=Enzyme-linked immunosorbent assay.

For safety evaluation, one or more adverse experiences occurred in 520 (82.0%) recipients of

M-M-R® II with rHA and in 506 (80.1%) recipients of M-M-R® II with HSA. One or more vaccine-related adverse experiences occurred in 308 (48.6%) recipients of M-M-R® II with rHA and in 276 (43.7%) recipients of M-M-R® II with HSA. Two-hundred twenty-six (35.6%) recipients of M-M-R® II with rHA compared with 187 (29.6%) recipients of M-M-R® II with HSA reported injection-site adverse experiences that were vaccine related. Vaccine related systemic adverse experiences were reported for 139 (21.9%) recipients of M-M-R® II with rHA compared to 149 (23.6%) recipients of M-M-R® II with HSA. Only 8 subjects (3 recipients of M-M-R® II with rHA and 5 recipients of M-M-R® II with HSA) experienced a serious adverse experience during the safety follow up period. None of these 8 serious adverse experiences was determined by the investigator to be vaccine related (see 8 Adverse Reactions). No subjects died during the study and no subjects were discontinued from the study due to an adverse experience.

The two treatment groups were generally comparable in terms of the incidence rates of adverse experiences, although a significantly higher proportion of subjects who received M-M-R® II with rHA reported an injection site adverse experience compared with those who received M-M-R® II with HSA. The incidence rates of these local reactions were found to be within the historical ranges observed in previous M-M-R® II studies and are thought to be related to variability between lots. Moreover, incidence rates of potential hypersensitivity reactions (AESI) were well balanced between the 2 treatment groups and no subjects in either treatment group had detectable antibody to albumin at baseline or 6 weeks postvaccination.

Overall, the study supports the replacement of HSA with rHA in the manufacturing of viral bulks for M-M-R® II based on the following similar seroconversion rates for measles, mumps, and rubella induced by M-M-R® II manufactured with rHA compared with M-M-R® II manufactured with HSA. M-M-R® II with rHA is generally well tolerated and has safety and tolerability profiles comparable to those of M-M-R® II with HSA, the currently licensed vaccine.

In an open label clinical trial 752 children 12 through 18 months of age received M-M-R® II either intramuscularly (n=374) or subcutaneously (n=378), concomitantly with VARIVAX. Antibody responses to measles, mumps, and rubella viruses were measured by ELISAs using sera obtained 6 weeks

postvaccination. For anti-measles virus, anti-mumps virus and anti-rubella virus, seroresponse rates were defined as the percentage of children seronegative at baseline who achieved antibody titers above the respective seroresponse threshold for each assay 6 weeks post vaccination. Seroresponse thresholds were defined as 255 mIU/mL, 10 EU/mL, and 10 IU/mL for anti-measles virus, anti-mumps virus, and anti-rubella virus antibodies, respectively. For each vaccine antigen at least 89% of enrolled children were seronegative at baseline. In a prespecified primary analysis, seroresponse rates to measles, mumps and rubella viruses were noninferior for the intramuscular group compared to the subcutaneous group (the lower bound of the 95% confidence interval for the difference in seroresponse rates [intramuscular group minus subcutaneous group] was > -10%).

The proportions of children achieving antibody titers above the seroresponse thresholds for measles, mumps, and rubella viruses were as follows: 94.3%, 97.7%, and 98.1%, respectively, in the intramuscular group and 96.1%, 98.1%, and 98.1%, respectively, in the subcutaneous group.

15 Microbiology

No microbiological information is required for this drug product.

16 Non-Clinical Toxicology

Carcinogenicity: M-M-R® II has not been evaluated for its carcinogenic potential.

Genotoxicity: M-M-R® II has not been evaluated for its genotoxicity potential.

Reproductive and Developmental Toxicology: M-M-R® II has not been evaluated for its potential to impair fertility. It is also not known whether M-M-R® II can cause harm to the fetus when administered to a pregnant woman (see 7 Warnings And Precautions, 7.1.1 Pregnancy).

Patient Medication Information

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

M-M-R® II

(measles, mumps and rubella virus vaccine, live, attenuated, Merck Std.)

This Patient Medication Information is written for the person who will be taking **M-M-R® II**. This may be you or a person you are caring for. Read this information carefully. Keep it as you may need to read it again.

This Patient Medication Information is a summary. It will not tell you everything about this medication. If you have more questions about this medication or want more information about **M-M-R® II**, talk to a healthcare professional.

What M-M-R® II is used for:

M-M-R® II is an injectable live virus vaccine to help prevent measles , mumps, and rubella .

How M-M-R® II works:

Your doctor has recommended or administered M-M-R® II to help protect you or your child against measles, mumps, and rubella. The vaccine can be administered to persons 12 months of age or older.

- Measles is a serious disease that is very easily passed from one person to another. It causes a high fever, cough, and a rash and lasts for 1 to 2 weeks. One out of every 10 children who catch measles will also have an ear infection or pneumonia. On rare occasions, measles can also cause an infection of the brain that could lead to seizures, hearing loss, mental retardation, and even death. Babies and adults who catch measles are often much sicker for a longer time or are more likely to die than elementary school children and teenagers who catch measles.
- Mumps is easily passed from one person to another and causes fever, headache, and swollen, painful glands under the jaw (salivary glands). It can sometimes be a very serious disease and usually lasts for several days. Mumps can cause a mild inflammation of the coverings of the brain and spinal cord (meningitis) in about 1 person in every 10 who catch it. About 1 out of every 4 teenage or adult males with mumps will have a painful swelling of the testicles for several days (this does not usually affect their ability to father children). Teenagers and adults, especially males, who catch mumps are often much sicker and more likely to suffer longer than children do.
- Rubella is usually a mild disease that causes a mild fever, swollen glands in the neck, pain and swelling in the joints, and a rash that lasts for a short time but is very dangerous if a pregnant woman catches it. Women who catch rubella when they are pregnant can have babies who are stillborn, or have heart disease, blindness, deafness, or problems with learning.

The ingredients in M-M-R® II are:

Medicinal ingredient: The medicinal ingredient is an injectable live attenuated virus vaccine to help prevent measles, mumps and rubella virus.

Non-medicinal ingredients: M-M-R® II contains neomycin, gelatin and recombinant human albumin as

inactive ingredients. Tell your doctor if you or your child has ever had an allergic reaction to these ingredients.

For a full listing of nonmedicinal ingredients see Part 1 of the product monograph.

M-M-R® II comes in the following dosage forms:

- a box of 10 single-dose vials of lyophilized vaccine, and
- a box of 10 vials (0.7 mL) of sterile diluent.

Do not use M-M-R® II if the recipient:

- is allergic to any of its components (including neomycin)
- is pregnant (in addition, pregnancy should be avoided for 1 month after vaccination)
- has a fever
- has active untreated tuberculosis
- is taking medications to suppress their immune system (other than corticosteroid replacement)
- has a blood disorder or any type of cancer that affects their immune system
- has an immune deficiency as a result of a disease or a treatment

To help avoid side effects and ensure proper use, talk to your healthcare professional before your child gets M-M-R® II. Talk about any health conditions or problems you or your child may have, including if:

- you or your child has or has had any medical problems, and about any allergies (especially to neomycin).
- you or your child has a history of convulsions or a brain injury, or a low blood platelet count.

Use in children

M-M-R® II should be used in children 12 months of age or older. However, your doctor may recommend that M-M-R® II be given to infants who are less than 12 months of age in special situations.

Use in pregnancy

M-M-R® II should not be administered to pregnant women. Women of child-bearing age should take the necessary precautions to avoid pregnancy for 1 month following vaccination.

Use in breastfeeding

Tell your doctor if you are breastfeeding or intend to breastfeed. Your doctor will decide if you should receive M-M-R® II**.**

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with M-M-R® II:

- Administration of immunoglobulins with M-M-R® II may interfere with immune response.

- Tell your doctor if your child has received blood or plasma transfusions or administration of human serum globulin within the last 3 months.

How to take M-M-R® II:

M-M-R® II will be given to your child by a healthcare professional in a healthcare setting.

Usual dose:

- M-M-R® II is given to persons 12 months of age or older. The dose of the vaccine is the same for everyone.
- For persons vaccinated at 12 months of age or older, a second dose of the vaccine is recommended at a later date which will be decided by your doctor.
- Children first vaccinated at less than 12 months of age should receive two additional doses after reaching 12 months of age.
- Non-pregnant adolescent and adult females of childbearing age who are susceptible to rubella can be vaccinated with M-M-R® II (or live attenuated rubella virus vaccine) if certain precautions are observed (see Use in Pregnancy). It has been found convenient in many instances to vaccinate women who are susceptible to rubella in the immediate post-partum period.

See your doctor for more details.

Overdose:

If you think you, or a person you are caring for, have taken too much M-M-R® II, contact a healthcare professional, hospital emergency department, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

Missed Dose:

Your doctor will decide when to give the missed dose.

Possible side effects from using M-M-R® II?

These are not all the possible side effects you may have when taking M-M-R® II. If you experience any side effects not listed here, tell your healthcare professional.

Any vaccine may have unintended or undesirable effects, so-called side effects. The most common is burning and/or stinging at the injection site for a short time. Transient joint pain and/or swelling have occurred more frequently in adult females; sometimes these symptoms may be chronic. Occasionally, fever and rash may occur. Rarely, unusual bleeding or bruising under the skin, and swelling of the testicles may occur.

Other side effects may also occur rarely and some of these may be serious. These include allergic reactions, seizures, and inflammation of the nervous system (brain and/or spinal cord).

Your doctor has a more complete list of side effects.

Tell your doctor promptly about any of these or any other unusual symptoms. If the condition persists or worsens, seek medical attention.

If you or your child have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Suspected Side Effects for Vaccines

For the general public: Should you experience a side effect following immunization, please report it to your healthcare professional.

Should you require information related to the management of the side effect, please contact your healthcare professional. The Public Health Agency of Canada, Health Canada and Merck Canada Inc. cannot provide medical advice.

For healthcare professionals: If a patient experiences a side effect following immunization, please complete the Adverse Events Following Immunization (AEFI) Form appropriate for your province/territory (https://www.canada.ca/en/public-health/services/immunization/reporting-adverse-events-following-immunization/form.html) and send it to your local Health Unit.

Storage:

Vial of powder: Store at 2°C to 8°C. The vaccine may also be stored in a freezer at temperatures above -50°C; if subsequently transferred to a refrigerator, the vaccine may be placed back in the freezer. Keep the vial in the outer carton in order to protect from light.

Diluent: The diluent may be stored in the refrigerator with the lyophilized vaccine or separately at room temperature. Refrigeration of the diluent is not needed. Store at 2°C to 27°C.

All vaccines must be discarded after the expiration date.

Keep out of reach and sight of children.

If you want more information about M-M-R® II:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes the Patient Medication Information by visiting the Health Canada Product Database website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website www.merck.ca, or by calling 1-800-567-2594.

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