# M-M-R™ II

(MEASLES, MUMPS, and RUBELLA VIRUS VACCINE LIVE)

M-M-R™ II (Measles, Mumps, and Rubella Virus Vaccine Live) is a live virus vaccine for immunization against measles (rubeola), mumps and rubella (German measles).

M-M-R II 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 grown in cell cultures of chick embryo; (2) MUMPSVAX™ (Mumps Virus Vaccine Live, MSD), the Jeryl Lynn (B level) strain of mumps virus grown in cell cultures of chick embryo; and (3) MERUVAX™ II (Rubella Virus Vaccine Live, MSD), the Wistar RA 27/3 strain of live attenuated rubella virus grown in human diploid cell (WI-38) culture. The vaccine viruses are the same as those used in the manufacture of ATTENUVAX (Measles Virus Vaccine Live, MSD), MUMPSVAX (Mumps Virus Vaccine Live, MSD) and MERUVAX II (Rubella Virus Vaccine Live, MSD). The three viruses are mixed before being lyophilized. The product contains no preservative.

The reconstituted vaccine is for subcutaneous administration. When reconstituted as directed, the dose for injection is 0.5 mL and contains not less than the equivalent of 1,000 $TCID_{50}$ (tissue culture infectious dose) of the U.S. Reference Measles Virus; 20,000 $TCID_{50}$ of the U.S. Reference Mumps Virus; and 1,000 $TCID_{50}$ of the U.S. Reference Rubella Virus. Each dose contains approximately 25 mcg of neomycin. The product contains no preservative. Sorbitol and hydrolyzed gelatin are added as stabilizers.

## CLINICAL PHARMACOLOGY

Clinical studies of 279 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 percent, mumps neutralizing antibodies in 96 percent, and rubella HI antibodies in 99 percent of susceptible persons.

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[3-9] 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.

Vaccine induced antibody levels following administration of M-M-R II have been shown to persist for over 11 years.

## INDICATIONS AND USAGE

M-M-R II is indicated for simultaneous immunization against measles, mumps, and rubella in persons 15 months of age or older. A second dose of M-M-R II or monovalent measles vaccine is recommended (see Revaccination).

Infants who are less than 15 months of age may fail to respond to the measles component of the vaccine due to presence in the circulation of residual measles antibody of maternal origin, the younger the infant, the lower the likelihood of seroconversion. In geographically isolated or other relatively inaccessible populations for whom immunization programs are logistically difficult, and in population groups in which natural measles infection may occur in a significant proportion of infants before 15 months of age, it may be desirable to give the vaccine to infants at an earlier age. Infants vaccinated under these conditions at less than 12 months of age should be revaccinated after reaching 15 months of age. Most infants 12-14 months of age

respond readily, but a booster on school entry or later may be needed to avoid breakthrough cases in these infants. There is some evidence to suggest that infants immunized at less than one year of age may not develop sustained antibody levels when later reimmunized. The advantage of early protection must be weighed against the chance for failure to respond adequately on reimmunization.

Previously unimmunized children of susceptible pregnant women should receive live attenuated rubella vaccine, because an immunized child will be less likely to acquire natural rubella and introduce the virus into the household.

Individuals planning travel abroad, if not immune, can acquire measles, mumps or rubella and import these diseases to their country. Therefore, prior to International travel, individuals known to be susceptible to one or more of these diseases can receive either a single antigen vaccine (measles, mumps or rubella), or a combined antigen vaccine as appropriate. However, M-M-R II is preferred for persons likely to be susceptible to mumps and rubella as well as measles; and if single-antigen measles vaccine is not readily available, travelers should receive M-M-R II regardless of their immune status to mumps or rubella.

## 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 below and PRECAUTIONS). 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 three months after vaccination and should be informed of the reasons for this precaution.*

It is recommended that rubella susceptibility be determined by serologic testing prior to immunization.** 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 arthritis beginning 2 to 4 weeks after vaccination (see ADVERSE REACTIONS).

## POSTPARTUM WOMEN

It has been found convenient in many instances to vaccinate rubella-susceptible women in the immediate postpartum period (see *Nursing Mothers*).

## REVACCINATION

Children first vaccinated when younger than 12 months of age should be revaccinated at 15 months of age.

A number of national, governmental vaccine authorities, the American Academy of Pediatrics (AAP), and the Immunization Practices Advisory Committee (ACIP), have recommended guidelines for routine measles revaccination and to help control measles outbreaks.

Vaccines available for revaccination include monovalent measles vaccine [ATTENUVAX (Measles Virus Vaccine Live, MSD)] and polyvalent vaccines containing measles [e.g., M-M-R II, M-R-VAX(R) II (Measles and Rubella Virus Vaccine Live, MSD), M-M-VAX(R) (Measles and Mumps Virus Vaccine Live, MSD)]. If the prevention of sporadic measles outbreaks is the sole

objective, revaccination with a monovalent measles vaccine should be considered (see appropriate product circular). If concern also exists about immune status regarding mumps or rubella, revaccination with appropriate monovalent or polyvalent vaccine should be considered after consulting the appropriate product circulars. Unnecessary doses of a vaccine are best avoided by ensuring that written documentation of vaccination is preserved and a copy given to each vaccinee's parent or guardian.

## USE WITH OTHER VACCINES

M-M-R II should be given one month before or after administration of other vaccines.
However, other schedules have been used. For example, the AAP has noted that when the patient may not return, some practitioners prefer to administer DTP, OPV, and M-M-R II on a single day. If done, separate sites and syringes should be used for DTP and M-M-R II.[27] The ACIP recommends routine simultaneous administration of M-M-R II, DTP and OPV or inactivated polio vaccine (IPV) to all children ≥ 15 months who are eligible to receive these vaccines on the basis that there are equivalent antibody responses and no clinically significant increases in the frequency of adverse events when DTP, M-M-R II and OPV or IPV are administered either simultaneously at different sites or separately.** Administration of M-M-R II at 15 months followed by DTP and OPV (or IPV) at 18 months remains an acceptable alternative, especially for children with caregivers known to be generally compliant with other health-care recommendations.

## CONTRAINDICATIONS

- Do not give M-M-R II to pregnant females; the possible effects of the vaccine on fetal development are unknown at this time. If vaccination of postpubertal females is undertaken, pregnancy should be avoided for three months following vaccination (see PRECAUTIONS, *Pregnancy*).
- Should not be given within 3 months of an immunoglobulin injection, children with untreated malignant disease or altered immunity and children who have received another live vaccine by injection within 3 weeks.
- Anaphylactic or anaphylactoid reactions to neomycin (each dose of reconstituted vaccine contains approximately 25 mcg of neomycin).
- History of anaphylactic or anaphylactoid reactions to eggs (see HYPERSENSITIVITY TO EGGS).
- Any febrile respiratory illness or other active febrile infection.
- Active untreated tuberculosis.
- Patients receiving immunosuppressive therapy. 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.
- 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.
- Individuals with a family history of congenital or hereditary immunodeficiency, until the immune competence of the potential vaccine recipient is demonstrated.

## 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 should not be vaccinated. Evidence indicates that persons are not at increased risk if they have egg allergies that are not anaphylactic or anaphylactoid in nature. Such persons may be vaccinated in the usual manner. There is no evidence to indicate that persons with allergies to chickens or feathers are at increased risk of reaction to the vaccine.

## PRECAUTIONS

### GENERAL

Adequate treatment provisions including epinephrine, should be available for immediate use should an anaphylactic or anaphylactoid reaction occur.

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 following vaccination (see ADVERSE REACTIONS).

Children and young adults who are known to be infected with human immunodeficiency viruses but without overt clinical manifestations of immunosuppression may be vaccinated; however, the vaccines should be monitored closely for exposure to vaccine-preventable diseases because immunization may be less effective than for uninfected persons. In selected cases confirmation of circulating antibody levels may be indicated to help guide appropriate protective measures, including immunoprophylaxis if immunity has waned to non-protective levels.

Vaccination should be deferred for at least 3 months following blood or plasma transfusions, or administration of human immune serum globulin.

Excretion of small amounts of the live attenuated rubella virus from the nose or throat has occurred in the majority of susceptible individuals 7-28 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 through close personal contact, while accepted as a theoretical possibility, is not regarded as a significant risk.[23] However, transmission of the rubella vaccine virus to infants via breast milk has been documented (see *Nursing Mothers*).

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

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 before or simultaneously with 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 of the effect of measles virus vaccines on untreated tuberculous children.

As for any vaccine, vaccination with M-M-R II may not result in seroconversion in 100% of susceptible persons given the vaccine.

### PREGNANCY

Animal reproduction studies have not been conducted with M-M-R II. It is also not known whether M-M-R II can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Therefore, the vaccine should not be administered to pregnant females; furthermore, pregnancy should be avoided for three months following vaccination (see CONTRAINDICATIONS).

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) Although mumps virus is

capable of infecting the placenta and fetus, there is no good evidence that it causes congenital malformations in humans.

Mumps vaccine virus also has been shown to infect the placenta, but the virus has not been isolated from the fetal tissues from susceptible women who were vaccinated and underwent elective abortions; 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.

## NURSING MOTHERS

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.[34] 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.

## ADVERSE REACTIONS

The adverse reactions associated with the use of M-M-R II are those which have been reported following administration of the monovalent vaccines.

COMMON

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

OCCASIONAL

*Body as a whole:* Fever (101°F [38.3°C] or higher)

*Skin:* Rash, usually minimal but may be generalized.

Generally, fever, rash, or both appear between the 5th and the 12th days.

RARE

*Body as a whole:* Mild local reactions such as erythema, induration and tenderness; sore throat, malaise.

*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, urticaria.

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

*Nervous/psychiatric:* Febrile convulsions in children, afebrile convulsions or seizures, headache, dizziness, paresthesia, polyneuritis, Guillain-Barre syndrome, ataxia, acute disseminated encephalomyelitis (ADEM), transverse myelitis. 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).

*Skin:* Erythema multiforme, pruritus

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

*Urogenital:* Orchitis

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 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, 6-22 cases of SSPE per million cases of measles. The results of a retrospective case-controlled study conducted by the Center for Disease Control suggest that the overall effect of measles vaccine has been to protect against SSPE by preventing measles with its inherent higher risk of SSPE.

Local reactions characterized by marked swelling, redness and vesiculation at the injection site of attenuated live measles virus vaccines, and systemic reactions including atypical measles, have occurred in persons who received killed measles vaccine previously. M-M-R II was not given under this condition in clinical trials. Rarely, more severe reactions that require hospitalization, including prolonged high fevers and extensive local reactions, have been reported. Panniculitis has been reported rarely following administration of measles vaccine.
Arthralgia and/or arthritis (usually transient and rarely chronic), and polyneuritis are features of natural 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 natural 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 (35-45 years), these reactions are generally well tolerated and rarely interfere with normal activities. Such reactions occur much less frequently after revaccination than primary vaccination.

## DOSAGE AND ADMINISTRATION

### FOR SUBCUTANEOUS ADMINISTRATION
**Do not inject intravenously**
The dosage of vaccine is the same for all persons. Inject the total volume of the single dose vial (about 0.5 mL) of reconstituted vaccine subcutaneously, preferably into the outer aspect of upper arm. **Do not give immune globulin (IG) concurrently with M-M-R II.**

During shipment, to insure that there is no loss of potency, the vaccine must be maintained at a temperature of 10°C (50°F) or less.

Before reconstitution, store M-M-R II at 2-8°C (35.6- 46.4°F). **Protect from light.**

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, 5/8" needle is recommended.
To reconstitute, use only the diluent supplied, since it is free of preservatives or other antiviral substances which might inactivate the vaccine.

### SINGLE DOSE VIAL
First withdraw the entire volume of diluent 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 subcutaneously.

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.
Each dose contains not less than the equivalent of 1,000 $TCID_{50}$ (tissue culture infectious dose) of the U.S. Reference Measles Virus; 20,000 $TCID_{50}$ of the U.S. Reference Mumps Virus; and 1,000 $TCID_{50}$ of the U.S. Reference Rubella Virus.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. M-M-R II when reconstituted, is clear yellow.

## HOW SUPPLIED

M-M-R II is supplied as a single-dose vial of lyophilized vaccine and a vial of diluent.

## STORAGE

Shelf life: 24 months.

Before reconstitution, store M-M-R II at 2-8°C (35.6-46.4°F). **Do not freeze. Protect from light.** M-M-R II retains at least 8 times the minimum immunizing dose even after 6 weeks at 22°C or 1 week at 37°C. Storage at temperatures above 2 to 8°C cannot be recommended due to the difficulty in monitoring the exact temperature and monitoring repeated exposures to time out of refrigeration.

It is recommended that the vaccine be used as soon as possible after reconstitution. Protect vaccine from light at all times, since such exposure may inactivate the virus. Store reconstituted vaccine in the vaccine vial in a dark place at 2-8°C (35.6-46.4°F) and discard if not used within 8 hours.

*NOTE: The Immunization Practices Advisory Committee (ACIP) has recommended "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."[23]

**NOTE: The Immunization Practices Advisory Committee (ACIP) has stated "When practical, and when reliable laboratory services are available, potential vaccinees of childbearing age can have serologic tests to determine susceptibility to rubella. However, routinely performing serologic tests for all females of childbearing age to determine susceptibility so that vaccine is given only to proven susceptibles is expensive and has been ineffective in some areas. Accordingly, the ACIP believes that rubella vaccination of a woman who is not known to be pregnant and has no history of vaccination is justifiable without serologic testing."

***NOTE: A primary difference among these recommendations is the timing of revaccination: the ACIP recommends routine revaccination at entry into kindergarten or first grade, whereas the AAP recommends routine revaccination at entrance to middle school or junior high school. In addition, some public health jurisdictions mandate the age for revaccination. The complete text of applicable guidelines should be consulted. 25, 26

****NOTE: The ACIP recommends administering M-M-R II concomitantly with the fourth dose of DTP and the third dose of OPV to children 15 months of age or older providing that 6 months have elapsed since DTP-3; or, if fewer than three DTPs have been received, at least 6 weeks have elapsed since the last dose of DTP and OPV.

Pada proses pembuatannya bersinggungan dengan bahan bersumber babi

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