House Bill 1468- In Opposition
Human Services Committee
67th Legislative Assembly of North Dakota
January 25, 2021

Good afternoon Chairman Weisz, Vice Chair Rohr, and Human Services Committee Members,

My name is Joan Connell. As a pediatrician, I am asking for a Do-Not-Pass decision on House Bill 1468. I am opposed to this piece of legislative, which mandates the conversation shared in the sanctity of the patient-physician relationship for the following reasons:

1. Legislatively mandating that providers give patients a package insert for each vaccine they are receiving will cost human and office resources, unnecessarily and wastefully. The Vaccine Information Statement (VIS) is a document prepared by the Advisory Committee on Childhood Vaccines, which includes two parents of children sustaining injury from vaccines, that contains the most relevant information for a given vaccine, and through federal law, must be provided to each patient/guardian prior to receiving the suggested vaccine. In my office, my nurse will provide this paperwork when the patient family initially is roomed for their visit, providing parents/guardians a chance to look at these statements and ask questions during their appointment. Patients/guardians who have questions and would like additional information are then able to have a discussion with their provider. While I have had a handful of patients' guardians request the vaccine package insert (which I am happy to provide to those who request), the majority of my patients' guardians want and expect me as their provider to cut through the scientific jargon to address their concern. Patients/guardians still uncomfortable with a particular vaccine simply do not agree to its administration. This is one of many discussions that are held during this sanctified period of time during the physician-patient appointment. A package insert is several pages long- the copying and provision of this to each patient/guardian for each vaccine is wasteful, particularly since the patient/guardian already receives a Vaccine Information Statement for each vaccine. Assuming a copy cost of 10 cents/page, and an average package insert length of 10 pages (some are over 40 pages), providing package inserts to the North Dakotans receiving the 689,890 vaccine doses administered in 2020 would cost $689,890- that means $1,380,000 spent on this mandated paperwork per biennium! Here are links to the Measles Mumps and Rubella Vaccine Information Statement https://www.cdc.gov/vaccines/hcp/vis/vis-statements/mmr.pdf and package insert https://www.fda.gov/media/75191/download, with a copy of each found at the bottom of this testimony.
2. Legislatures mandating what providers discuss with their patients/guardians during this very intimate time results in elimination of discussions that may have been more pertinent for that patient during that particular visit. The end result is that both patient and provider are short-changed as neither has accomplished all of the goals of the visit. Here is a link https://brightfutures.aap.org/Bright%20Futures%20Documents/BF4_EarlyChildhoodVisits.pdf to a Bright Futures document that outlines what is to be accomplished during a well check for a 12 month old, covered on pages 503-523, with recommendations for

what is to be covered regarding anticipatory guidance beginning on page 510. As you can see, this is already overwhelming. Mandating additional discussion on vaccine exemption will shortchange patients and providers.

3. The National Vaccine Injury Compensation Program (VICP) https://www.hrsa.gov/vaccine-compensation/index.html is a federal program that has been in place since the 1980s to assure that rare patients who have experienced a serious adverse reaction to immunization are financially compensated. HB 1468's section 1-4's statement about continued liability for manufacturers of immunizations is misleading as patients experiencing adverse events from vaccination would actually pursue compensation through VICP.
4. Mandating provision of information regarding vaccine exemption will potentially undermine confidence in vaccine safety, resulting in decreasing percentages of vaccinated individuals. This compromises everyone's health, particularly the patients who are unable to be vaccinated due to medical conditions or those with history of significant adverse reactions to vaccines, who were unable to complete their vaccine series. Ultimately, this legislation may hurt those you are intending to protect by increasing their risk for infection from the illnesses that result from insufficient vaccination of the rest of the population.

In summary, vaccination saves lives. Patient information about each vaccine is readily available and legally must be provided to patients prior to vaccination. Programs that compensate the rare individual who has a serious reaction to vaccination are already in place and are being utilized. I urge a Do-Not-Pass vote on HB 1468, which adds unnecessary mandates that compromises the patient-physician relationship, increases unnecessary costly paperwork for providers, misleads the rare patient who experiences a vaccine-related adverse event, and has the potential to increase risk of infection from vaccine-preventable diseases for all of us.

Vaccine Information Statement

MMR Vaccine (Measles, Mumps, and Rubella): What You Need to Know

Many Vaccine Information Statements are available in Spanish and other languages. See www.immunize.org/vis
Hojas de información sobre vacunas están disponibles en español y en muchos otros idiomas. Visite www.immunize.org/vis

1. **Why get vaccinated?**

MMR vaccine can prevent **measles**, **mumps**, and **rubella.**

- • **MEASLES (M)** can cause fever, cough, runny nose, and red, watery eyes, commonly followed by a rash that covers the whole body. It can lead to seizures (often associated with fever), ear infections, diarrhea, and pneumonia. Rarely, measles can cause brain damage or death.
- • **MUMPS (M)** can cause fever, headache, muscle aches, tiredness, loss of appetite, and swollen and tender salivary glands under the ears. It can lead to deafness, swelling of the brain and/or spinal cord covering, painful swelling of the testicles or ovaries, and, very rarely, death.

- • **RUBELLA (R)** can cause fever, sore throat, rash, headache, and eye irritation. It can cause arthritis in up to half of teenage and adult women. If a woman gets rubella while she is pregnant, she could have a miscarriage or her baby could be born with serious birth defects.

Most people who are vaccinated with MMR will be protected for life. Vaccines and high rates of vaccination have made these diseases much less common in the United States.

2. MMR vaccine

Children need 2 doses of MMR vaccine, usually:
- • First dose at 12 through 15 months of age
- • Second dose at 4 through 6 years of age

Infants who will be traveling outside the United States when they are between 6 and 11 months of age should get a dose of MMR vaccine before travel. The child should still get 2 doses at the recommended ages for long-lasting protection.

Older children, **adolescents**, and **adults** also need 1 or 2 doses of MMR vaccine if they are not already immune to measles, mumps, and rubella. Your health care provider can help you determine how many doses you need.

A third dose of MMR might be recommended in certain mumps outbreak situations.

MMR vaccine may be given at the same time as other vaccines. Children 12 months through 12 years of age might receive MMR vaccine together with varicella vaccine in a single shot, known as MMRV. Your health care provider can give you more information.

3. Talk with your health care provider

Tell your vaccine provider if the person getting the vaccine:
- • Has had an **allergic reaction after a previous dose of MMR or MMRV vaccine**, or has any **severe, life-threatening allergies.**
- • Is **pregnant**, or thinks she might be pregnant.
- • Has a **weakened immune system**, or has a **parent, brother, or sister with a history of hereditary or congenital immune system problems.**
- • Has ever had a **condition that makes him or her bruise or bleed easily.**
- • Has recently **had a blood transfusion or received other blood products**.
- • Has **tuberculosis.**
- • Has **gotten any other vaccines in the past 4 weeks.**

In some cases, your health care provider may decide to postpone MMR vaccination to a future visit.

People with minor illnesses, such as a cold, may be vaccinated. People who are moderately or severely ill should usually wait until they recover before getting MMR vaccine.

Your health care provider can give you more information.

4. Risks of a vaccine reaction

- • Soreness, redness, or rash where the shot is given and rash all over the body can happen after MMR vaccine.
- • Fever or swelling of the glands in the cheeks or neck sometimes occur after MMR vaccine.
- • More serious reactions happen rarely. These can include seizures (often associated with fever), temporary pain and stiffness in the joints (mostly in teenage or adult women), pneumonia, swelling of the brain and/or spinal cord covering, or temporary low platelet count which can cause unusual bleeding or bruising.
- • In people with serious immune system problems, this vaccine may cause an infection which may be life-threatening. People with serious immune system problems should not get MMR vaccine.

People sometimes faint after medical procedures, including vaccination. Tell your provider if you feel dizzy or have vision changes or ringing in the ears.

As with any medicine, there is a very remote chance of a vaccine causing a severe allergic reaction, other serious injury, or death.

5. What if there is a serious problem?

An allergic reaction could occur after the vaccinated person leaves the clinic. If you see signs of a severe allergic reaction (hives, swelling of the face and throat, difficulty breathing, a fast heartbeat, dizziness, or weakness), call **9-1-1** and get the person to the nearest hospital.

For other signs that concern you, call your health care provider.

Adverse reactions should be reported to the Vaccine Adverse Event Reporting System (VAERS). Your health care provider will usually file this report, or you can do it yourself. Visit the VAERS website at **www.vaers.hhs.gov** or call **1-800-822-7967**. *VAERS is only for reporting reactions, and VAERS staff do not give medical advice.*

6. The National Vaccine Injury Compensation Program

The National Vaccine Injury Compensation Program (VICP) is a federal program that was created to compensate people who may have been injured by certain vaccines. Visit the VICP website at **www.hrsa.gov/vaccinecompensation** or call **1-800-338-2382** to learn about the program and about filing a claim. There is a time limit to file a claim for compensation.

7. How can I learn more?

- • Ask your health care provider.
- • Call your local or state health department.
- • Contact the Centers for Disease Control and Prevention (CDC):
  - • - Call **1-800-232-4636** (**1-800-CDC-INFO**) or
  - • - Visit CDC's website at **www.cdc.gov/vaccines**

Vaccine Information Statement (Interim)
MMR Vaccine
8/15/2019
42 U.S.C. § 300aa-26

Department of Health and Human Services
Centers for Disease Control and Prevention
Vaccine Package Insert

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use M-M-R II safely and effectively. See full prescribing information for M-M-R II.

M-M-R® II (Measles, Mumps, and Rubella Virus Vaccine Live) Suspension for subcutaneous injection
Initial U.S. Approval: 1978

----------INDICATIONS AND USAGE----------

M-M-RII is a vaccine indicated for active immunization for the prevention of measles, mumps, and rubella in individuals 12 months of age and older. (1)

---------- DOSAGE AND ADMINISTRATION ----------

Administer a 0.5-mL dose of M-M-R II subcutaneously. (2.1)

- The first dose is administered at 12 to 15 months of age. (2.1)
- The second dose is administered at 4 to 6 years of age. (2.1)

---------- DOSAGE FORMS AND STRENGTHS ----------

Suspension for injection (0.5-mL dose) supplied as a lyophilized vaccine to be reconstituted using accompanying sterile diluent. (3)

----------CONTRAINDICATIONS ----------

- Hypersensitivity to any component of the vaccine. (4.1)
- Immunosuppression. (4.2)
- Moderate or severe febrile illness. (4.3)
- Active untreated tuberculosis. (4.4)
- Pregnancy. (4.5, 8.1)

---------- WARNINGS AND PRECAUTIONS----------

• Use caution when administering M-M-R II to individuals with a history of febrile seizures. (5.1)

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• Use caution when administering M-M-R II to individuals with anaphylaxis or immediate hypersensitivity following egg ingestion. (5.2)

• Use caution when administering M-M-R II to individuals with a history of thrombocytopenia. (5.3)

• Evaluate individuals for immune competence prior to administration of M-M-R II if there is a family history of congenital or hereditary immunodeficiency. (5.4)

• Immune Globulins (IG) and other blood products should not be given concurrently with M-M-R II. (5.5, 7.2)

---------- ADVERSE REACTIONS ----------

See full prescribing information for adverse reactions occurring during clinical trials or the post-marketing period. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., at 1-877- 888-4231 or VAERS at 1-800-822-7967 or www.vaers.hhs.gov.

----------DRUG INTERACTIONS----------

• Administration of immune globulins and other blood products concurrently with M-M-RII vaccine may interfere with the expected immune response. (7.2)

• M-M-R II vaccination may result in a temporary depression of purified protein derivative (PPD) tuberculin skin sensitivity. (7.3)

---------- USE IN SPECIFIC POPULATIONS ----------

• Pregnancy: Do not administer M-M-R II to females who are pregnant. Pregnancy should be avoided for 1 month following vaccination with M-M-R II. (4.5, 8.1, 17)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: XX/20XX

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FULL PRESCRIBING INFORMATION 1 INDICATIONS AND USAGE

M-M-R® II is a vaccine indicated for active immunization for the prevention of measles, mumps, and rubella in individuals 12 months of age and older.

2 DOSAGE AND ADMINISTRATION For subcutaneous use only.

2.1 Dose and Schedule

Each 0.5 mL dose is administered subcutaneously.

The first dose is administered at 12 to 15 months of age. A second dose is administered at 4 to 6 years of age.

The second dose may be administered prior to 4 years of age, provided that there is a minimum interval of one month between the doses of measles, mumps and rubella virus vaccine, live {1-2}.

Children who received an initial dose of measles, mumps and rubella vaccine prior to their first birthday should receive additional doses of vaccine at 12-15 months of age and at 4-6 years of age to complete the vaccination series *[see Clinical Studies (14.2)]*.

For post-exposure prophylaxis for measles, administer a dose of M-M-R II vaccine within 72 hours after exposure.

2.2 Preparation and Administration

Use a sterile syringe free of preservatives, antiseptics, and detergents for each injection and/or reconstitution of the vaccine because these substances may inactivate the live virus vaccine. To reconstitute, use only the diluent supplied with the vaccine since it is free of preservatives or other antiviral substances which might inactivate the vaccine.

Withdraw the entire volume of the supplied diluent from its vial and inject into lyophilized vaccine vial. Agitate to dissolve completely. Discard if the lyophilized vaccine cannot be dissolved.

Withdraw the entire volume of the reconstituted vaccine and inject subcutaneously into the outer aspect of the upper arm (deltoid region) or into the higher anterolateral area of the thigh.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Visually inspect the vaccine before and after reconstitution prior to administration. Before reconstitution, the lyophilized vaccine is a light yellow compact crystalline plug, when reconstituted, is a clear yellow liquid. Discard if particulate matter or discoloration are observed in the reconstituted vaccine.

To minimize loss of potency, administer M-M-R II as soon as possible after reconstitution. If not used immediately, the reconstituted vaccine may be stored between 36°F to 46°F (2°C to 8°C), protected from light, for up to 8 hours. Discard reconstituted vaccine if it is not used within 8 hours.

3 DOSAGE FORMS AND STRENGTHS

M-M-R II vaccine is a suspension for injection supplied as a single dose vial of lyophilized vaccine to be reconstituted using the accompanying sterile diluent *[see Dosage and Administration (2.2) and How Supplied/Storage and Handling (16)]*. A single dose after reconstitution is 0.5 mL.

4 CONTRAINDICATIONS

4.1 Hypersensitivity

Do not administer M-M-R II vaccine to individuals with a history of hypersensitivity to any component of the vaccine (including gelatin) {3} or who have experienced a hypersensitivity reaction following administration of a previous dose of M-M-R II vaccine or any other measles, mumps and rubella-containing vaccine. Do not administer M-M-R II vaccine to individuals with a history of anaphylaxis to neomycin *[see Description (11)].*

4.2 Immunosuppression

Do not administer M-M-R II vaccine to individuals who are immunodeficient or immunosuppressed due to disease or medical therapy. Measles inclusion body encephalitis {4} (MIBE), pneumonitis {5} and death as a direct consequence of disseminated measles vaccine virus infection have been reported in immunocompromised individuals inadvertently vaccinated with measles-containing vaccine. In this population, disseminated mumps and rubella vaccine virus infection have also been reported.

4.3 Moderate or Severe Febrile Illness

Do not administer M-M-R II vaccine to individuals with an active febrile illness with fever >101.3◦F (>38.5◦C).

4.4 Active Untreated Tuberculosis

Do not administer M-M-R II vaccine to individuals with active untreated tuberculosis (TB). **4.5 Pregnancy**

Do not administer M-M-R II to individuals who are pregnant or who are planning on becoming pregnant within the next month *[see Use in Specific Populations (8.1) and Patient Counseling Information (17)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Febrile Seizure

There is a risk of fever and associated febrile seizure in the first 2 weeks following immunization with M-M-R II vaccine. For children who have experienced a previous febrile seizure (from any cause) and those with a family history of febrile seizures there is a small increase in risk of febrile seizure following receipt of M-M-R II vaccine *[see Adverse Reactions (6)]*.

5.2 Hypersensitivity to Eggs

Individuals 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 M-M-R II vaccine. The potential risks and known benefits should be evaluated before considering vaccination in these individuals.

5.3 Thrombocytopenia

Transient thrombocytopenia has been reported within 4-6 weeks following vaccination with measles, mumps and rubella vaccine. Carefully evaluate the potential risk and benefit of vaccination in children with thrombocytopenia or in those who experienced thrombocytopenia after vaccination with a previous dose of measles, mumps, and rubella vaccine {6-8} *[see Adverse Reactions (6)]*.

5.4 Family History of Immunodeficiency

Vaccination should be deferred in individuals with a family history of congenital or hereditary immunodeficiency until the individual's immune status has been evaluated and the individual has been found to be immunocompetent.

5.5 Immune Globulins and Transfusions

Immune Globulins (IG) and other blood products should not be given concurrently with M-M-R II *[see Drug Interactions (7.2)]*. These products may contain antibodies that interfere with vaccine virus replication and decrease the expected immune response.

The Advisory Committee on Immunization Practices (ACIP) has specific recommendations for intervals between administration of antibody containing products and live virus vaccines.

6 ADVERSE REACTIONS

The following adverse reactions include those identified during clinical trials or reported during post-approval use of M-M-R II vaccine or its individual components.

Body as a Whole

Panniculitis; atypical measles; fever; syncope; headache; dizziness; malaise; irritability.

Cardiovascular System

Vasculitis.

Digestive System

Pancreatitis; diarrhea; vomiting; parotitis; nausea.

Hematologic and Lymphatic Systems

Thrombocytopenia; purpura; regional lymphadenopathy; leukocytosis.

Immune System

Anaphylaxis, anaphylactoid reactions, angioedema (including peripheral or facial edema) and bronchial spasm.
Musculoskeletal System

Arthritis; arthralgia; myalgia.

3

Nervous System

Encephalitis; encephalopathy; measles inclusion body encephalitis (MIBE) subacute sclerosing panencephalitis (SSPE); Guillain-Barré Syndrome (GBS); acute disseminated encephalomyelitis (ADEM); transverse myelitis; febrile convulsions; afebrile convulsions or seizures; ataxia; polyneuritis; polyneuropathy; ocular palsies; paresthesia.

Respiratory System

Pneumonia; pneumonitis; sore throat; cough; rhinitis.

Skin

Stevens-Johnson syndrome; acute hemorrhagic edema of infancy; Henoch-Schönlein purpura; erythema multiforme; urticaria; rash; measles-like rash; pruritus; injection site reactions (pain, erythema, swelling and vesiculation).
Special Senses — Ear

Nerve deafness; otitis media.

Special Senses — Eye

Retinitis; optic neuritis; papillitis; conjunctivitis.

Urogenital System

Epididymitis; orchitis.

7 DRUG INTERACTIONS

7.1 Corticosteroids and Immunosuppressive Drugs

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 *[see Contraindications (4.2)].*

7.2 Immune Globulins and Transfusions

Administration of immune globulins and other blood products concurrently with M-M-R II vaccine may interfere with the expected immune response {9-11} *[see Warnings and Precautions (5.5)].* The ACIP has specific recommendations for intervals between administration of antibody containing products and live virus vaccines.

7.3 Tuberculin Skin Testing

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.

7.4 Use with Other Live Viral Vaccines

M-M-R II vaccine can be administered concurrently with other live viral vaccines. If not given concurrently, M-M-R II vaccine should be given one month before or one month after administration of other live viral vaccines to avoid potential for immune interference.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary
M-M-R II vaccine is contraindicated for use in pregnant women because infection during pregnancy

with the wild-type viruses has been associated with maternal and fetal adverse outcomes.
Increased rates of spontaneous abortion, stillbirth, premature delivery and congenital defects have been observed following infection with wild-type measles during pregnancy. {12,13} Wild-type mumps

infection during the first trimester of pregnancy may increase the rate of spontaneous abortion.
Infection with wild-type rubella during pregnancy can lead to miscarriage or stillbirth. If rubella infection occurs during the first trimester of pregnancy, it can result in severe congenital defects, Congenital Rubella Syndrome (CRS). Congenital Rubella Syndrome in the infant includes but is not limited to eye manifestations (cataracts, glaucoma, retinitis), congenital heart defects, hearing loss, microcephaly, and intellectual disabilities. M-M-R II vaccine contains live attenuated measles, mumps and rubella viruses. It is not known whether M-M-R II vaccine can cause fetal harm when administered to pregnant woman. There are no adequate and well-controlled studies of M-M-R II vaccine administration to pregnant

women.

All pregnancies have a risk of birth defect, loss or other adverse outcomes. In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Available data suggest the rates of major birth defects and miscarriage in women who received M-M-R II vaccine within 30 days prior to pregnancy or during pregnancy are consistent with estimated background rates *(see Data)*.
Data

Human Data

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 whom 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. No abnormalities compatible with congenital rubella syndrome have been identified in patients who received M-M-R II vaccine. Rubella vaccine virus can cross the placenta, leading to asymptomatic infection of the fetus. Mumps vaccine virus has also been shown to infect the placenta {14}, but there is no evidence that it causes congenital malformations or disease in the fetus or infant.

The 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 Congenital Rubella Syndrome (CRS) in the enrolled women {15}.

8.2 Lactation

Risk Summary
It is not known whether measles or mumps vaccine virus is secreted in human milk. Studies have

shown that lactating postpartum women vaccinated with live attenuated rubella vaccine may secrete the virus in breast milk and transmit it to breast-fed infants. {16,17} In the breast-fed infants with serological evidence of rubella virus vaccine strain antibodies, none exhibited severe disease; however, one exhibited mild clinical illness typical of acquired rubella. {18,19}

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for M-M-R II, and any potential adverse effects on the breastfed child from M-M-R II or from the underlying maternal condition. For preventive vaccines, the underlying maternal condition is susceptibility to disease prevented by the vaccine.

8.4 Pediatric Use

M-M-R II vaccine is not approved for individuals less than 12 months of age. Safety and effectiveness of measles vaccine in infants below the age of 6 months have not been established *[see Clinical Studies (14)]*. Safety and effectiveness of mumps and rubella vaccine in infants less than 12 months of age have not been established.

8.5 Geriatric Use

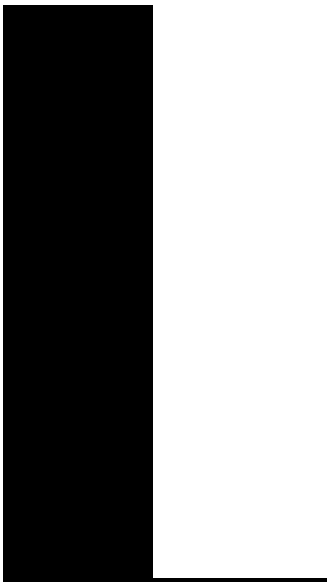
Clinical studies of M-M-R II did not include sufficient numbers of seronegative subjects aged 65 and over to determine whether they respond differently from younger subjects.

11 DESCRIPTION

M-M-R II vaccine is a sterile lyophilized preparation of (1) Measles Virus Vaccine Live, an attenuated line of measles virus, derived from Enders' attenuated Edmonston strain and propagated in chick embryo cell culture; (2) Mumps Virus Vaccine Live, the Jeryl LynnTM (B level) strain of mumps virus propagated in chick embryo cell culture; and (3) Rubella Virus Vaccine Live, the Wistar RA 27/3 strain of live attenuated rubella virus propagated in WI-38 human diploid lung fibroblasts. {20,21} The cells, virus pools, recombinant human serum albumin and fetal bovine serum used in manufacturing are tested and determined to be free of adventitious agents.

After reconstitution, each 0.5 mL dose contains not less than 3.0 $\log_{10}$ $TCID_{50}$ (tissue culture infectious doses) of measles virus; 4.1 $\log_{10}$ $TCID_{50}$ of mumps virus; and 3.0 $\log_{10}$ $TCID_{50}$ of rubella virus.

Each dose is calculated to contain sorbitol (14.5 mg), sucrose (1.9 mg), hydrolyzed gelatin (14.5 mg), recombinant human albumin (≤0.3 mg), fetal bovine serum (<1 ppm), approximately 25 mcg of neomycin and other buffer and media ingredients. The product contains no preservative.



12 CLINICAL PHARMACOLOGY

12.1 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 *[see Clinical Studies (14)].*

12.6 Persistence of Antibody Responses After Vaccination

Neutralizing and ELISA antibodies to measles, mumps, and rubella viruses are still detectable in 95-100%, 74-91%, and 90-100% of individuals respectively, 11 to 13 years after primary vaccination. {22-28}

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

M-M-R II vaccine has not been evaluated for carcinogenic or mutagenic potential or impairment of fertility.

14 CLINICAL STUDIES

14.1 Clinical Efficacy

Efficacy of measles, mumps, and rubella vaccines was established in a series of double-blind controlled trials. {29-34} These studies also established that seroconversion in response to vaccination against measles, mumps and rubella paralleled protection. {35-38}

14.2 Immunogenicity

Clinical studies enrolling 284 triple seronegative children, 11 months to 7 years of age, demonstrated that M-M-R II vaccine is immunogenic. In these studies, a single injection of the vaccine induced measles HI antibodies in 95%, mumps neutralizing antibodies in 96%, and rubella HI antibodies in 99% of susceptible individuals.

A study of 6-month-old and 15-month-old infants born to mothers vaccinated with a measles vaccine in childhood, demonstrated that, following infant and toddler vaccination with Measles Virus Vaccine, Live (previously US-licensed, manufactured by Merck), 74% of the 6-month-old infants developed detectable neutralizing antibody titers while 100% of the 15-month-old infants vaccinated with Measles Virus Vaccine, Live or M-M-R II vaccine developed neutralizing antibodies {39}. When the 6-month-old infants of immunized mothers were revaccinated at 15 months with M-M-R II vaccine, they developed antibody titers similar to those of toddlers who were vaccinated previously at 15-months of age.

15 REFERENCES

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16 HOW SUPPLIED/STORAGE AND HANDLING

No. 4681 – M-M-R II vaccine is supplied as follows:
(1) a box of 10 single-dose vials of lyophilized vaccine (package A), NDC 0006-4681-00
(2) a box of 10 vials of diluent (package B)
Exposure to light may inactivate the vaccine viruses.
To maintain potency, M-M-R II must be stored between -58°F and +46°F (-50°C to +8°C). Use of

dry ice may subject M-M-R II to temperatures colder than -58°F (-50°C).
Before reconstitution, refrigerate the lyophilized vaccine at 36°F to 46°F (2°C to 8°C).
Store accompanying diluent in the refrigerator (36°F to 46°F, 2°C to 8°C) or at room temperature (68°F

to 77°F, 20°C to 25°C). **Do not freeze the diluent**.
Administer M-M-R II vaccine as soon as possible after reconstitution. If not administered immediately,

reconstituted vaccine may be stored between 36°F to 46°F (2°C to 8°C), protected from light, for up to 8 hours. Discard reconstituted vaccine if it is not used within 8 hours.

For information regarding the product or questions regarding storage conditions, call 1-800-MERCK-90 (1-800-637-2590).

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PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Package Insert).

Discuss the following with the patient:

- Provide the required vaccine information to the patient, parent, or guardian.
- Inform the patient, parent, or guardian of the benefits and risks associated with vaccination.
- Question the patient, parent, or guardian about reactions to a previous dose of M-M-R II vaccine or other measles-, mumps-, or rubella-containing vaccines.
- Question females of reproductive potential regarding the possibility of pregnancy. Inform female patients to avoid pregnancy for 1 month following vaccination *[see Contraindications (4.5) and Use in Specific Populations (8.1)]*.
- Inform the patient, parent, or guardian that vaccination with M-M-R II may not offer 100% protection from measles, mumps, and rubella infection.
- Instruct patients, parents, or guardians to report any adverse reactions to their health-care provider. The U.S. Department of Health and Human Services has established a Vaccine Adverse Event Reporting System (VAERS) to accept all reports of suspected adverse events after the administration of any vaccine, including but not limited to the reporting of events required by the National Childhood Vaccine Injury Act of 1986. For information or a copy of the vaccine reporting form, call the VAERS toll-free number at 1-800-822-7967, or report online at https://www.vaers.hhs.gov.

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