

Merck: A Long-Lasting Commitment to Pediatric Vaccination

Missed Vaccinations and Declining Vaccination Rates

To halt the spread of SARS-CoV-2 in 2020, global public health efforts included the implementation of restrictions that led to as many as 23 million children missing routine vaccinations.¹ As this unprecedented COVID-19 pandemic evolved, these restrictions, coupled with hesitation from parents to bring their children to doctor's appointments, continued to drive down pediatric vaccination rates.² Compared to 2019, United States measles vaccine orders decreased by more than 20% in 2020-2021.^{2,3} Decreases in vaccines ordered and doses administered are important indicators of and contributors to the vulnerability of communities to outbreaks of vaccine-preventable diseases (VPDs), such as measles.⁴

Now is the time to act. As pandemic-related restrictions loosen in the United States, empowering parents to help protect their children from VPDs is crucial.⁵ Healthcare providers need to emphasize the important role that vaccines play in helping to protect against VPDs so that parents will prioritize getting their children up-to-date on routine vaccinations and adhere to the recommended schedules in the future.^{6,7}

Indications and Usage

ProQuad® (Measles, Mumps, Rubella and Varicella Virus Vaccine Live) is a vaccine indicated for active immunization for the prevention of measles, mumps, rubella, and varicella in children 12 months through 12 years of age.

VARIVAX® (Varicella Virus Vaccine Live) is a vaccine indicated for active immunization for the prevention of varicella in individuals 12 months of age or older.

M-M-R®_{II} (Measles, Mumps, and Rubella Virus Vaccine Live) is indicated for active immunization for the prevention

M-M-R®_{II} (Measles, Mumps, and Rubella Virus Vaccine Live) and ProQuad® (Measles, Mumps, Rubella and Varicella Virus Vaccine Live) Vaccines

As the manufacturer of M-M-R®_{II} (Measles, Mumps, and Rubella Virus Vaccine Live) and ProQuad® (Measles, Mumps, Rubella and Varicella Virus Vaccine Live), Merck is the producer of the first measles-containing vaccine approved by the United States Food and Drug Administration (FDA).⁸⁻¹⁰ M-M-R®_{II} is indicated for active immunization for the prevention of measles, mumps, and rubella in individuals 12 months of age or older; the first dose is recommended at 12 to 15 months and the second dose at 4 to 6 years.⁹ Initially approved for use in the United States in 1978, M-M-R®_{II} was the first vaccine recommended by the United States Centers for Disease Control and Prevention (CDC) to help protect children against measles, mumps, and rubella.^{9,11}

ProQuad® is indicated for active immunization for the prevention of measles, mumps, rubella, and varicella in children 12 months through 12 years of age; the first dose is generally given at 12 to 15 months and the second dose at 4 to 6 years.¹⁰ ProQuad® was initially approved for use in the United States in 2005 and subsequently recommended for use by the CDC.^{10,12,13} The use of a

of measles, mumps, and rubella in individuals 12 months of age or older.

Selected Safety Information

• **Hypersensitivity: ProQuad, M-M-R®_{II}, and VARIVAX** are contraindicated in patients with a history of anaphylactic reaction or hypersensitivity to any component of the vaccine (including gelatin or neomycin) or to a prior dose of measles, mumps, rubella, or varicella-containing vaccine.

Selected Safety Information continues on the next page ►



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combination vaccine can potentially reduce the number of injections required.¹⁴ It is important to note that sometimes combination vaccines can cause slightly more pain or swelling when administered.¹⁴ Additionally, these vaccines do not treat measles, mumps, and rubella or varicella; they are only to help prevent infection.^{9,10}

Vaccine Effectiveness and Safety

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.⁹ 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.⁹ However, a small percentage (1%–5%) of vaccinees may fail to seroconvert after the primary dose.⁹

ProQuad[®] (Measles, Mumps, Rubella and Varicella Virus Vaccine Live) can be used either as a two-dose regimen or

as a second dose after primary vaccination with individual MMR and varicella vaccines in the United States.¹⁰ In a clinical trial, 799 healthy 4- to 6-year-old children who had received a primary vaccination with M-M-R[®]_{II} and VARIVAX[®] (Varicella Virus Vaccine Live) at least 1 month prior to study were randomized to receive ProQuad[®] and placebo (n=399), M-M-R[®]_{II} and placebo concomitantly at separate injection sites (n=205), or M-M-R[®]_{II} and VARIVAX[®] concomitantly at separate injection sites (n=195).¹⁰ Strong immune response rates with ProQuad[®] as a second dose in children 4–6 years old were observed six weeks after vaccine dose administration—100%, 99.5%, 100%, and 98.9% for measles, mumps, rubella, and varicella, respectively.¹⁰ Formal studies to evaluate the clinical efficacy of ProQuad[®] have not been performed. The most frequent vaccine-related adverse events reported in ≥5% of subjects vaccinated with ProQuad[®] during clinical trials included injection-site reactions (pain/tenderness/soreness, erythema, and swelling), fever, and irritability.¹⁰

◀ Selected Safety Information (continued)

- **Hypersensitivity (continued):** Use caution when administering **ProQuad** and **M-M-R[®]_{II}** to individuals with anaphylaxis or immediate hypersensitivity to eggs.
- **ProQuad[®] (Measles, Mumps, Rubella and Varicella Virus Vaccine Live), M-M-R[®]_{II} (Measles, Mumps, and Rubella Virus Vaccine Live), and VARIVAX[®] (Varicella Virus Vaccine Live)** are contraindicated in certain individuals, including those with: immunodeficiency or who are immunosuppressed; an active febrile illness; untreated tuberculosis.
- **Pregnancy: ProQuad, M-M-R[®]_{II}, and VARIVAX** are contraindicated for use in pregnant women. Do not administer **ProQuad** or **VARIVAX** to individuals who are planning to become pregnant in the next 3 months. Do not administer **M-M-R[®]_{II}** to individuals who are planning to become pregnant in the next month.
- **Febrile Seizures:** Administration of **ProQuad** (dose 1) to children 12 to 23 months old who have not been previously vaccinated against measles, mumps, rubella, or varicella, nor had a history of the wild-type infections, is associated with higher rates of fever and febrile seizures at 5 to 12 days after vaccination when compared to children vaccinated with a first dose of both **M-M-R[®]_{II}** and **VARIVAX** administered concomitantly.
- **Febrile Seizures:** Use caution when administering **ProQuad** and **M-M-R[®]_{II}** to individuals with a history of febrile seizures.
- **Family History of Immunodeficiency:** Vaccination with **ProQuad, M-M-R[®]_{II}, and VARIVAX** 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.
- **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 a measles, mumps, and rubella-containing vaccine.
- **Varicella Transmission and Precautions:** Advise vaccinees administered **ProQuad** or **VARIVAX** to avoid: close contact with high-risk individuals susceptible to varicella for up to 6 weeks following vaccination since transmission of varicella vaccine virus to susceptible contacts has been reported. Varicella vaccine virus transmission may occur between vaccine recipients and contacts susceptible to varicella including healthy individuals.
- **Immune Globulins and Transfusions:** Immune Globulins and other blood products should not be given concomitantly with **ProQuad, M-M-R[®]_{II}, or VARIVAX.**
- **Use of Salicylates:** Avoid use of salicylates in children and adolescents administered **ProQuad** or **VARIVAX** for 6 weeks following vaccination due to the association of Reye Syndrome with salicylate therapy and wild-type varicella infection.

Selected Safety Information continues on the next page ►

Certain people should not receive the M-M-R_{II}® or ProQuad® vaccines, including individuals with a hypersensitivity to any component of the vaccine, including gelatin; those who have experienced a hypersensitivity reaction to a previous dose of M-M-R_{II}® or measles, mumps, and rubella and/or varicella-containing vaccine; those with a history of anaphylaxis to neomycin; those who are immunodeficient or immunosuppressed due to a disease or medical therapy; individuals with a moderate or severe febrile illness; those with active tuberculosis that is not treated; or those who are pregnant or plan to get pregnant soon.^{9,10}

Concern of Outbreaks in VPDs

In recent years, measles outbreaks have been documented in communities across the United States.¹⁶ In 2019, 1,282 measles cases were reported, the highest number of cases in the United States in nearly 30 years.¹⁵

The number of first- and second-dose measles-containing vaccines given in 2020 was lower than in 2019, further increasing the concern and risk for outbreaks.^{4,16} As children interact in a world redefined by COVID-19, we all have the responsibility to continue to educate and encourage parents to stay on track and/or update their children's vaccination schedules aiming to help reduce the chances for outbreaks of measles or other VPDs.^{2,4,16}

Efforts to Increase Childhood Vaccination

Although COVID-19 continues to be a public health concern, it is important to follow and maintain childhood vaccination schedules to help protect against outbreaks of

VPDs.^{2,6} While acknowledging parents' concerns regarding COVID-19 infection risks, facilitating communication, outreach and empowering them to help protect against VPDs is an important goal to address the overall health and well-being of their children, as well as to help protect the communities where they live.^{4,17}

Conclusions

For years, M-M-R_{II}® and ProQuad® vaccines have been available to help protect children from these VPDs.^{6,10,18,19} Although the pandemic has caused delays in vaccination, helping to improve vaccination rates and continuing to emphasize adherence to the CDC-recommended vaccination schedules can have an impact on helping to prevent outbreaks.^{1,6,17} It is important to reinforce to parents and caregivers of babies and young children to schedule and keep appointments for appropriate vaccinations and thus contribute to the efforts to help prevent outbreaks of VPDs.^{6,20}

REFERENCES

1. COVID-19 pandemic leads to major backsliding on childhood vaccinations, new WHO, UNICEF data shows. UNICEF website. Published July 15, 2021. Accessed March 29, 2022. <https://www.who.int/news/item/15-07-2021-covid-19-pandemic-leads-to-major-backsliding-on-childhood-vaccinations-new-who-unicef-data-shows>
2. Santoli JM, Lindley MC, DeSilva MB, et al. Effects of the COVID-19 pandemic on routine pediatric vaccine ordering and administration - United States, 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69(19):591-593. doi:10.15585/mmwr.mm6919e2
3. Childhood vaccination toolkit for clinicians. Centers for Disease Control and Prevention website. Reviewed May 6, 2022. Accessed June 24, 2022. <https://www.cdc.gov/vaccines/hcp/childhood-vaccination-toolkit.html>

◀ Selected Safety Information (continued)

- **Adverse Events:** The following have been reported for ProQuad® (Measles, Mumps, Rubella and Varicella Virus Vaccine Live), M-M-R_{II}® (Measles, Mumps, and Rubella Virus Vaccine Live), and VARIVAX® (Varicella Virus Vaccine Live): fever, injection-site reactions (pain/tenderness/soreness, erythema, and swelling); irritability; and rash on the body or at the injection site. Systemic vaccine-related adverse events that were reported at a significantly greater rate in recipients of ProQuad than in recipients of the component vaccines administered concomitantly were fever and measles-like rash.
- **VARIVAX Dose-related Adverse Events:** In a clinical trial involving children who received 2 doses of VARIVAX 3 months apart, the incidence of injection-site clinical complaints observed in the first 4 days following vaccination was slightly higher post-dose 2 (overall incidence 25.4%) than post-dose 1 (overall incidence 21.7%), whereas the incidence of systemic clinical complaints in the 42-day follow-up period was lower post-dose 2 (66.3%) than post-dose 1 (85.8%).

- **Concomitant Vaccines With ProQuad®:** ProQuad may be administered concomitantly with diphtheria and tetanus toxoids and acellular pertussis vaccine adsorbed (DTaP), *Haemophilus influenzae* type b conjugate (meningococcal protein conjugate) and hepatitis B (recombinant) vaccine. It may also be administered concomitantly with pneumococcal 7-valent conjugate vaccine and/or hepatitis A vaccine (inactivated) at separate injection sites.
- **Concomitant Vaccines With VARIVAX:** VARIVAX can be administered with other live viral vaccines. If not given concurrently, at least 1 month should elapse between a dose of a live attenuated measles virus-containing vaccine and a dose of VARIVAX. In children, at least 3 months should elapse between administration of 2 doses of a live attenuated varicella virus-containing vaccine.
- **Tuberculin Testing :** If a tuberculin test is to be done with M-M-R_{II}® and ProQuad, it should be administered either any time before, simultaneously with, or at least 4 to 6 weeks after vaccination.

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4. Ackerson BK, Sy LS, Glenn SC, et al. Pediatric vaccination during the COVID-19 pandemic. *Pediatrics*. 2021;148(1):e2020047092. doi:10.1542/peds.2020-047092
5. Domestic travel during COVID-19. Centers for Disease Control and Prevention. Updated May 3, 2022. Accessed June 22, 2022. <https://www.cdc.gov/coronavirus/2019-ncov/travelers/travel-during-covid19.html>
6. Catch up on well-child visits and recommended vaccinations. Centers for Disease Control and Prevention. Reviewed August 1, 2022. Accessed July 6, 2022. <https://www.cdc.gov/vaccines/parents/visit/vaccination-during-COVID-19.html>
7. Recommended Vaccinations for Infants and Children, Parent-Friendly Version. Centers for Disease Control and Prevention. Last Reviewed February 17, 2022. Accessed July 20, 2022. <https://www.cdc.gov/vaccines/schedules/easy-to-read/child-easyread.html>
8. Measles, mumps and rubella virus vaccine live. United States Food and Drug Administration. Updated on December 14, 2020. Accessed June 22, 2022. <https://www.fda.gov/vaccines-blood-biologics/vaccines/measles-mumps-and-rubella-virus-vaccine-live>
9. M-M-R-II. Prescribing information. Merck; 2020. Accessed August 3, 2022. https://www.merck.com/product/usa/pi_circulars/m/mmr_ii/mmr_ii_pi.pdf
10. ProQuad. Prescribing Information. Merck; 2021. Accessed August 3, 2022. https://www.merck.com/product/usa/pi_circulars/p/proquad/proquad_pi_4171.pdf
11. Routine measles, mumps, and rubella vaccination. Centers for Disease Control and Prevention website. Reviewed January 26, 2021. Accessed July 1, 2022. <https://www.cdc.gov/vaccines/vpd/mmr/hcp/recommendations.html>
12. Notice to Readers: Licensure of a Combined Live Attenuated Measles, Mumps, Rubella, and Varicella Vaccine. Centers for Disease Control and Prevention. *Morbidity and Mortality Weekly Report (MMWR)*. December 2, 2005. Accessed July 20, 2022. <https://www.cdc.gov/mmwr/preview/mmwrhtml/mm5447a4.htm>
13. Use of Combination Measles, Mumps, Rubella, and Varicella Vaccine: Recommendations of the Advisory Committee on Immunization Practices (ACIP). Centers for Disease Control and Prevention. *Morbidity and Mortality Weekly Report (MMWR)*. May 7, 2010. Accessed July 20, 2022. <https://www.cdc.gov/mmwr/preview/mmwrhtml/rr5903a1.htm>
14. Combination vaccines. Centers for Disease Control and Prevention. Reviewed August 1, 2019. Accessed June 22, 2022. <https://www.cdc.gov/vaccines/parents/why-vaccinate/combo-combination-vaccines.html#:~:text=Combining%20vaccines%20into%20fewer%20shots,fewer%20delays%20in%20disease%20protection>
15. Measles cases and outbreaks. Centers for Disease Control and Prevention. Reviewed August 9, 2022. Accessed June 22, 2022. <https://www.cdc.gov/measles/cases-outbreaks.html>
16. Global progress against measles threatened amidst COVID-19 pandemic. World Health Organization. Published November 10, 2021. Accessed August 3, 2022. <https://www.who.int/news/item/10-11-2021-global-progress-against-measles-threatened-amidst-covid-19-pandemic>
17. Marotta S, McNally VV. Increasing vaccine confidence through parent education and empowerment using clear and comprehensible communication. *Acad Pediatr*. 2021;21(4S):S30-S31. doi:10.1016/j.acap.2021.01.016
18. Kuter B, Brown M, Wiedmann R, Hartzel J, Musey L. Safety and immunogenicity of M-M-R-III (combination measles-mumps-rubella vaccine) in clinical trials of healthy children conducted between 1988 and 2009. *Pediatric Infectious Disease Journal*. 2016;35(9). Accessed March 7, 2022. https://journals.lww.com/pidj/Fulltext/2016/09000/Safety_and_Immunogenicity_of_M_M_R_III_Combination.18.aspx
19. September 6, 2005 Approval Letter - ProQuad. Department of Health and Human Services. Food and Drug Administration. September 6, 2005. Accessed July 20, 2022. <http://wayback.archive-it.org/7993/20170723150912/https://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm123799.htm>
20. Guidance on providing pediatric well-care during COVID-19. American Academy of Pediatrics. Updated July 19, 2022. Accessed August 3, 2022. <https://www.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections/clinical-guidance/guidance-on-providing-pediatric-well-care-during-covid-19/>

◀ Selected Safety Information (continued)

- **Tuberculin Testing (continued):** With **VARIVAX® (Varicella Virus Vaccine Live)**, tuberculin testing may be performed before the vaccine is administered or at least 4 weeks following vaccination.
- **Additional M-M-R®_{II} (Measles, Mumps, and Rubella Virus Vaccine Live) Precautions:** Additional adverse reactions, which have been reported without regard to causality, include febrile convulsions, arthritis, thrombocytopenia, anaphylaxis, anaphylactoid reactions, arthritis, encephalitis and encephalopathy in their diverse clinical presentations.
- **Additional VARIVAX Precautions:** It is not known if varicella vaccine virus is excreted in human milk. A boost in antibody levels has been observed in vaccinees following exposure to wild-type varicella, which could account for the apparent long-term persistence of antibody levels in studies. The duration of protection from varicella infection after vaccination is unknown.
- **Efficacy:** Vaccination with **ProQuad® (Measles, Mumps, Rubella and Varicella Virus Vaccine Live)**, **VARIVAX**, or **M-M-R®_{II}** may not result in protection in 100% of vaccinees.

Dosage and Administration

ProQuad:

- Each 0.5 mL dose of **ProQuad** is administered subcutaneously.

- At least 1 month should elapse between a dose of a measles-containing vaccine such as **M-M-R®_{II}** and a dose of **ProQuad**. At least 3 months should elapse between a dose of varicella-containing vaccine and **ProQuad**.

VARIVAX:

- Each 0.5 mL dose is administered subcutaneously.
 - The first dose is administered at 12 to 15 months of age.
 - The second dose is administered at 4 to 6 years of age.
 - There should be a minimum interval of 3 months between doses.
 - 12 months to 12 years of age: If a second dose is administered, there should be a minimum interval of 3 months between doses.
 - Adolescents (≥13 years of age) and Adults: 2 doses, to be administered with a minimum interval of 4 weeks between doses.

M-M-R®_{II}:

- The dose for any age is 0.5 mL administered subcutaneously.
- The recommended age for primary vaccination is 12 to 15 months and the second dose should be given at 4 to 6 years of age.

Before administering VARIVAX® (Varicella Virus Vaccine Live), M-M-R®_{II} (Measles, Mumps, and Rubella Virus Vaccine Live), or ProQuad® (Measles, Mumps, Rubella and Varicella Virus Vaccine Live), please read the accompanying Prescribing Information. The Patient Information also is available for VARIVAX, M-M-R®_{II}, and ProQuad.

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