Notice to Readers: Licensure of a Combined Live Attenuated Measles, Mumps, Rubella, and Varicella Vaccine

Weekly

December 2, 2005 / 54(47);1212-1214

Please note: *An erratum has been published for this article. To view the erratum, please click here.*

On September 6, 2005, the Food and Drug Administration licensed a combined live attenuated measles, mumps, rubella, and varicella (MMRV) vaccine (ProQuad®, Merck & Co., Inc., Whitehouse Station, New Jersey) for use in children aged 12 months--12 years. The attenuated measles, mumps, and rubella vaccine viruses in ProQuad are identical and of equal titer to those in the measles, mumps, and rubella (MMR) vaccine, MMRII® (Merck). The titer of Oka/Merck varicella-zoster virus is higher in MMRV vaccine than in single antigen varicella vaccine, VARIVAX® (Merck), a minimum of 3.13 $\log_{10}$ plaque-forming units (pfu) versus 1,350 pfu (approximately 1.13 $\log_{10}$), respectively.

Advisory Committee on Immunization Practices (ACIP) current recommendations are that children aged 12 months--12 years receive 2 doses of MMR vaccine at least 1 month apart and 1 dose of varicella vaccine (*1*).* MMRV vaccine can decrease the number of injections received by children when all of the component antigens are indicated for administration. One dose of MMRV vaccine should be administered on or after the first birthday, preferably as soon as the child becomes eligible for vaccination (*2*).

MMRV vaccine was licensed on the basis of equivalence of immunogenicity of the antigenic components rather than clinical efficacy; the efficacy of the individual components of MMRV has been established previously (*3*,*4*). Clinical studies of 7,484 healthy children aged 12--23 months (of whom 5,446 received MMRV vaccine) indicated that those who received 1 dose of MMRV vaccine developed levels of antibody to measles, mumps, rubella, and varicella similar to those of children who received 1 dose of MMR and 1 dose of varicella vaccines concomitantly at separate injection sites. The respective prevalences of detectable antibody (i.e., positive serologic response) using defined cutoff levels among MMRV vaccine recipients were 97.4% (95% confidence interval [CI] = 96.9%--97.9%) for measles (≥255 mIU/mL when compared with the WHO II [66/202] reference immunoglobulin for measles), 95.8% (CI = 95.1%--96.4%) for mumps† (≥10 enzyme-linked immunosorbent assay [ELISA] units/mL), 98.5% (CI = 98.1%--98.8%) for rubella (≥10 IU rubella antibody/mL when compared with the WHO international reference serum for rubella), and 91.2% (CI = 90.3%--92.0%) for varicella (≥5 gpELISA units/mL [a response rate highly correlated with long-term protection]) (*5*).

A subgroup of the children (n = 1,035) who received 1 dose of MMRV vaccine received a second dose of MMRV vaccine approximately 3 months after the first dose. Positive serologic response after 2 doses was 99.4% (CI = 98.6%--99.8%) for measles, 99.9% (CI = 99.4%--100%) for mumps, 98.3% (CI = 97.2%--99.0%) for rubella, and 99.4% (CI = 98.7%--99.8%) for varicella among the children who were seronegative before receipt of the first dose of MMRV vaccine (*5*). The geometric mean titers (GMTs) after the second dose of

MMRV vaccine increased approximately two-fold each for measles, mumps, and rubella and 41-fold for varicella.

To assess the immunogenicity of a second dose of MMRV vaccine at ages 4--6 years, a trial was conducted among 799 healthy children in this age group who had received 1 dose of MMR and 1 dose of varicella vaccine at age ≥12 months and at least 1 month before enrollment in the study (*5*). In that study, subjects were administered either 1) MMRV vaccine and placebo (n = 399), 2) MMR and varicella vaccines (n = 195), or 3) MMR vaccine and placebo (n = 205) concomitantly at separate sites. Recipients of MMRV vaccine had seropositivity rates of 99.2% (CI = 97.6%--99.8%) for measles, 99.5% (CI = 98.0%--99.9%) for mumps, 100% (CI = 99.0%--100.0%) for rubella, and 98.9% (CI = 97.2%--99.7%) for varicella and had postvaccination GMT increases, compared with prevaccination GMTs, of 1.2 for measles, 2.4 for mumps, 3.0 for rubella, and 12.0 for varicella.

The postvaccination GMTs for measles, mumps, rubella, and varicella among MMRV vaccine recipients were comparable to that of the group vaccinated with MMR and varicella vaccines. Likewise, the GMTs were similar for measles, mumps, and rubella among the MMRV vaccine recipients and the group vaccinated with MMR vaccine and placebo (*5*).

Concomitant administration of MMRV with other vaccines was assessed among 1,913 healthy children aged 12--15 months. A group concomitantly administered at separate sites MMRV vaccine, diphtheria and tetanus toxoids and acellular pertussis adsorbed (DTaP) vaccine, *Haemophilus influenzae* type b conjugate (meningococcal protein conjugate) (Hib) vaccine, and hepatitis B (recombinant) (HepB) vaccine (n = 949) was compared with 1) a group receiving MMRV at the initial visit, followed by DTaP, Hib, and HepB vaccines administered concomitantly 6 weeks later (n = 485), and 2) a group receiving MMR and varicella vaccines concomitantly (n = 479) (*5*). Seroconversion rates and antibody titers were comparable for the measles, mumps, rubella, and varicella components for all three groups; the Hib and HepB seroconversion rates for the two groups that received those vaccines also were comparable.

The safety profile of MMRV vaccine without concomitant administration of other vaccines was studied in healthy children aged 12--23 months who were monitored for 42 days postvaccination. Rates of most local and systemic adverse events for children vaccinated with MMRV (n = 4,497 recipients) were comparable to rates for MMR and varicella vaccines administered concomitantly (n = 2,038 recipients). Two systemic vaccine-related adverse events were reported at significantly greater rates among MMRV vaccine recipients; fever of ≥102°F (≥38.9°C) was observed in 21.5% of MMRV recipients versus 14.9% of MMR and varicella vaccine recipients, and measles-like rash was observed in 3.0% of recipients of MMRV vaccine recipients versus 2.1% of those administered MMR and varicella vaccines (*5*). Both of these adverse events were reported to occur more frequently during day 5 through day 12 postvaccination and typically resolved spontaneously without sequelae. Rash at the injection site was the only local vaccine-related adverse event reported more commonly among MMRV recipients (2.3%) than among MMR and varicella vaccine recipients (1.5%). Among 2,108 healthy children aged 12--23 months who received MMRV vaccine and were followed for up to 1 year, two cases of herpes zoster were reported; both cases were unremarkable and resolved without sequelae. In two studies of 1,035 vaccinees aged 12--23 months who received 2 doses of MMRV vaccine, the rates of adverse events after the second dose were generally similar or lower than those observed with the first dose (*5*).

Indications and Usage

1. MMRV vaccine is indicated for simultaneous vaccination against measles, mumps, rubella, and varicella among children aged 12 months--12 years; MMRV is not indicated for persons outside of this age group. Use of licensed combination vaccines, such as MMRV vaccine, is preferred over separate injection of equivalent component vaccines (*6*). MMRV vaccine can reduce the number of injections when administered to children aged 12 months--12 years for whom 1) the first dose of MMR and varicella vaccines is indicated and 2) the second dose of MMR and either the first or second dose (e.g., during a varicella outbreak) of varicella vaccine is indicated. MMRV vaccine is administered subcutaneously as a single 0.5-mL dose.

2. MMRV vaccine may be used whenever any components of the combination vaccine are indicated and the other components are not contraindicated. Using combination vaccines containing some antigens not indicated at the time of administration might be justified when 1) products that contain only the needed antigens are not readily available or would result in extra injections and 2) potential benefits to the child outweigh the risk of adverse events associated with the extra antigen(s).

3. At least 1 month should elapse between a dose of measles-containing vaccine, such as MMR vaccine, and a dose of MMRV vaccine. Should a second dose of varicella vaccine be indicated for children aged 12 months--12 years (e.g., during a varicella outbreak), at least 3 months should elapse between administration of any 2

doses of varicella-containing vaccine, including single antigen varicella vaccine or MMRV vaccine.

4. Simultaneous administration of the most widely used live and inactivated vaccines have produced seroconversion rates and rates of adverse reactions similar to those observed when the vaccines are administered separately (*7*). Therefore, MMRV may be administered simultaneously with other vaccines recommended at ages 12 month--12 years, although data are absent or limited for the concomitant use of MMRV vaccine with DTaP, inactivated polio, pneumococcal conjugate, influenza, and hepatitis A vaccines.

5. MMRV vaccine must be stored frozen at an average temperature ≤5°F (≤-15°C) for up to 18 months. Adequacy of the freezer should be checked before obtaining or storing MMRV vaccine. Unlike single antigen varicella vaccine, MMRV vaccine cannot be stored at refrigerator temperature. Once reconstituted, the vaccine should be used immediately to minimize loss of potency and should be discarded if not used within 30 minutes. The diluent should be stored separately at room temperature or in the refrigerator.

6. MMRV vaccine should not be administered as a substitute for the component vaccines when vaccinating children with human immunodeficiency virus (HIV) infection until revised recommendations can be considered for the use of MMRV vaccine in this population; current recommendations for vaccination of HIV-infected children with MMR and varicella vaccines are available (*3*,*8*).

ACIP recommendations for MMR and varicella vaccines have been previously published (*3*,*4*,*8*,*9*) and are applicable for the respective components of MMRV vaccine. Additional information regarding ProQuad is available from the package insert (*5*) provided by the manufacturer (http://www.merck.com).

References

1. CDC. Recommended childhood and adolescent immunization schedule---United States, 2005. MMWR 2005;53:Q1--3.
2. CDC. Preventable measles among U.S. residents, 2001--2004. MMWR 2005;54:817--20.
3. CDC. Measles, mumps, and rubella---vaccine use and strategies for elimination of measles, rubella, and congenital rubella syndrome and control of mumps: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 1998;47(No. RR-8).
4. CDC. Prevention of varicella: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 1996;45 (No. RR-11).
5. Merck & Co., Inc. ProQuad® [measles, mumps, rubella and varicella (Oka/Merck) virus vaccine live] prescribing information. Whitehouse Station, NJ: Merck & Co., Inc.; 2005.
6. CDC. Combination vaccines for childhood immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP), the American Academy of Pediatrics (AAP), and the American Academy of Family Physicians (AAFP). MMWR 1999;48(No. RR-5).
7. CDC. General recommendations on immunizations: recommendations of the Advisory Committee on Immunization Practices (ACIP) and the American Academy of Family Physicians (AAFP). MMWR 2002;51 (No. RR-2):5.
8. Advisory Committee on Immunization Practices (ACIP). Prevention of varicella---provisional updated ACIP recommendations for varicella vaccine use. Atlanta, GA: US Department of Health and Human Services, Advisory Committee on Immunization Practices; 2005. Available at http://wwwdev.cdc.gov/nip/vaccine/varicella/varicella_acip_recs.pdf.
9. CDC. Prevention of varicella: updated recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 1999;48(No. RR-6).

* During a varicella outbreak, a second dose of varicella vaccine may be administered to persons who previously received 1 dose of varicella vaccine to provide additional protection from varicella disease, if the appropriate vaccination interval (3 months for persons aged 12 months--12 years) has elapsed since the first dose.

† Two separate assays, one based on wild type and one on vaccine type strains, were used to assess mumps immune response rates; the data presented here are the lower values obtained; more detailed information is contained in the package insert.

Use of trade names and commercial sources is for identification only and does not imply endorsement by the U.S. Department of Health and Human Services.

References to non-CDC sites on the Internet are provided as a service to *MMWR* readers and do not constitute or imply endorsement of these organizations or their programs by CDC or the U.S. Department of Health and Human Services. CDC is not responsible for the content of pages found at these sites. URL addresses listed in *MMWR* were current as of the date of publication.

Date last reviewed: 12/1/2005