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Update: Recommendations from the Advisory Committee on Immunization Practices (ACIP) Regarding Administration of Combination MMRV Vaccine

On February 27, 2008, new information was presented to the Advisory Committee on Immunization Practices (ACIP) regarding the risk for febrile seizures among children aged 12--23 months after administration of the combination measles, mumps, rubella, and varicella (MMRV) vaccine (ProQuad®, Merck & Co., Inc., Whitehouse Station, New Jersey). This report summarizes current knowledge regarding the risk for febrile seizures after MMRV vaccination and presents updated ACIP recommendations that were issued after presentation of the new information. These updated recommendations remove ACIP's previous preference for administering combination MMRV vaccine over separate injections of equivalent component vaccines (i.e., measles, mumps, and rubella [MMR] vaccine and varicella vaccine).

The combination tetravalent MMRV vaccine was licensed by the Food and Drug Administration (FDA) on September 6, 2005, for use in children aged 12 months--12 years (*1*). MMRV vaccine can be used in place of trivalent MMR vaccine and monovalent varicella vaccine to implement the recommended 2-dose vaccine policies for prevention of measles, mumps, rubella, and varicella (*1*,*2*). The first vaccine dose is recommended at age 12--15 months and the second at age 4--6 years.

In MMRV vaccine prelicensure studies, an increased rate of fever was observed 5--12 and 0--42 days after the first vaccine dose, compared with administration of MMR vaccine and varicella vaccine at the same visit (*3*,*4*). Because of the known association between fever and febrile seizures (*5*), CDC and Merck initiated postlicensure studies to better understand the risk for febrile seizures that might be associated with MMRV vaccination.

The Vaccine Safety Datalink (VSD),* which routinely monitors vaccine safety by near real-time surveillance using computerized patient data, detected a signal of increased risk for seizures of any etiology among children aged 12--23 months after administration of MMRV vaccine compared with administration of MMR vaccine (many children also received varicella vaccine). When children who received MMRV vaccine were compared with children who received MMR vaccine and varicella vaccine administered at the same visit, statistically significant clustering of seizures was observed 7--10 days after vaccination in both groups. Once the signal was detected, a VSD study was initiated that evaluated the risk for febrile seizures 7--10 days after vaccination among 43,353 children aged 12--23 months who received MMRV vaccine and 314,599 children aged 12--23 months who received MMR vaccine and varicella vaccine administered at the same visit. Medical records were reviewed to validate the diagnosis, and a multivariate logistic regression was used to adjust for age and influenza season.

The preliminary results indicated a rate of febrile seizure of nine per 10,000 vaccinations among MMRV vaccine recipients compared with four per 10,000 vaccinations among MMR vaccine and varicella vaccine recipients (adjusted odds ratio = 2.3; 95% confidence interval [CI] = 1.6--3.2; p<0.0001). These results suggest that, in the 7--10 day postvaccination period, approximately one additional febrile seizure would occur among every 2,000 children vaccinated with MMRV vaccine, compared with children vaccinated with MMR vaccine and varicella vaccine administered at the same visit. Of the 166 children who experienced febrile seizures after vaccination and had hospitalization information available, 26 (16%) were hospitalized. No child who had a febrile seizure died.

At the ACIP meeting, representatives from Merck presented interim results of an ongoing postlicensure study being conducted among children aged 12--60 months (99% of the children were aged 12--23 months). All potential cases of febrile seizure were reviewed using Brighton Collaboration guidelines (*6*). This interim analysis found a 2.3 times (CI = 0.6--9.0) higher relative risk for confirmed febrile seizures 5--12 days after MMRV vaccination (14,263 children; rate = five per 10,000 vaccinations) when compared with a historic control group of children (matched on age, sex, and date of vaccination) vaccinated with MMR vaccine and varicella vaccine at the same visit (14,263 children; rate = two per 10,000 vaccinations). Although the relative risk was not statistically significant, it was similar to the adjusted odds ratio reported by the VSD study for the 7--10 days after vaccination. The Merck study also evaluated the risk for febrile seizures during the 0--30 days after vaccination. This risk was not significantly different (relative risk = 0.7; CI = 0.4--1.5) for children who received MMRV vaccine (10 per 10,000) compared with those who received MMR vaccine and varicella vaccine at the same visit (13 per 10,000). The Merck results are considered interim; approximately half of the final sample size needed to investigate the risk for febrile seizures was available for this analysis.

Neither the VSD study nor the Merck study assessed the risk for febrile seizures after MMRV vaccine administered as a second dose at age 4--6 years. However, previous studies have determined that the second dose of MMRV vaccine is less likely to cause fever than the first dose (*3*), and rates of febrile seizure are lower in the general population of children aged 4--6 years than in the population aged 12--15 months (*5*).

Febrile seizures are not uncommon in young children and generally have an excellent prognosis (*7*), although they often are distressing to parents and other family members. Approximately one in 25 (4%) young children will have at least one febrile seizure, usually at age 6--59 months; the peak age for febrile seizures is 14--18 months (*5,7*). Febrile seizures occur most commonly with the fevers caused by typical childhood illnesses, such as middle ear infections, viral upper respiratory tract infections, and roseola, but can be associated with any condition that results in fever. Febrile seizures can occur after certain vaccinations, although rarely. MMR vaccination has been associated previously with febrile seizures occurring 8--14 days later; approximately one additional febrile seizure occurs among every 3,000--4,000 children vaccinated with MMR vaccine, compared with children not vaccinated during the preceding 30 days (*8*).

Availability of MMRV vaccine currently is limited in the United States because of manufacturing constraints unrelated to vaccine safety or efficacy (*9*). MMRV vaccine is not expected to be widely available before 2009; however, some clinics might have MMRV vaccine in stock.

Consistent with ACIP General Recommendations on Immunization (*10*), the 2007 ACIP recommendations for prevention of varicella included a preference for use of combination MMRV vaccine over separate injections of equivalent component vaccines (i.e., MMR vaccine and varicella vaccine) (*2*). At its February 27, 2008, meeting, ACIP considered the preliminary results from the VSD and Merck studies, which suggested an increased risk for febrile seizures after the first dose of MMRV vaccine. Given the availability of alternative options for vaccination against measles, mumps, rubella, and varicella and the limited supply of MMRV vaccine, ACIP voted to change the preference language for MMRV vaccine to read as follows: "Combination MMRV vaccine is approved for use among healthy children aged 12 months--12 years. MMRV vaccine is indicated for simultaneous vaccination against measles, mumps, rubella, and varicella. ACIP does not express a preference for use of MMRV vaccine over separate injections of equivalent component vaccines (i.e., MMR vaccine and varicella vaccine)." ACIP also recommended establishing a work group to conduct in-depth evaluation of the findings regarding the increased risk for febrile seizures after the first dose of MMRV vaccine

to present for consideration of future policy options. CDC, FDA, and ACIP will communicate updates and implement further necessary actions based on these evaluations.

Clinically significant adverse events that follow vaccination should be reported to the Vaccine Adverse Event Reporting System (VAERS). Guidance about how to obtain and complete a VAERS form is available at http://www.vaers.hhs.gov or by telephone, 800-822-7967. Additional information on MMRV vaccine and febrile seizures is available at http://www.cdc.gov/od/science/iso/vsd/mmrv.htm and http://www.fda.gov/cber/label/proquadlbinfo.htm.

Reported by: *NP Klein, MD, PhD, Kaiser Permanente Vaccine Study Center, Oakland, California, and Vaccine Safety Datalink Rapid Cycle Analysis Team. WK Yih, PhD, Dept of Ambulatory Care and Prevention, Harvard Medical School and Harvard Pilgrim Health Care, Boston, Massachusetts, and Vaccine Safety Datalink Rapid Cycle Analysis Team. M Marin, MD, AO Jumaan, PhD, JF Seward, MBBS, Div of Viral Diseases, National Center for Immunization and Respiratory Diseases; K Broder, MD, J Iskander, MD, Immunization Safety Office; DE Snider Jr, MD, Office of the Chief Science Officer, CDC.*

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* Additional information available at http://www.cdc.gov/od/science/iso/vsd.

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