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Use of Combination Measles, Mumps, Rubella, and Varicella Vaccine

Recommendations of the Advisory Committee on Immunization Practices

DEPARTMENT OF HEALTH AND HUMAN SERVICES
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Use of Combination Measles, Mumps, Rubella, and Varicella Vaccine

Recommendations of the Advisory Committee on Immunization Practices (ACIP)

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Summary

This report presents new recommendations adopted in June 2009 by CDC's Advisory Committee on Immunization Practices (ACIP) regarding use of the combination measles, mumps, rubella, and varicella vaccine (MMRV, ProQuad, Merck & Co., Inc.). MMRV vaccine was licensed in the United States in September 2005 and may be used instead of measles, mumps, rubella vaccine (MMR, M-M-RII, Merck & Co., Inc.) and varicella vaccine (VARIVAX, Merck & Co., Inc.) to implement the recommended 2-dose vaccine schedule for prevention of measles, mumps, rubella, and varicella among children aged 12 months–12 years. At the time of its licensure, use of MMRV vaccine was preferred for both the first and second doses over separate injections of equivalent component vaccines (MMR vaccine and varicella vaccine), which was consistent with ACIP's 2006 general recommendations on use of combination vaccines (CDC. General recommendations on immunization: recommendations of the Advisory Committee on Immunization Practices [ACIP]. MMWR 2006;55;[No. RR-15]). Since July 2007, supplies of MMRV vaccine have been temporarily unavailable as a result of manufacturing constraints unrelated to efficacy or safety. MMRV vaccine is expected to be available again in the United States in May 2010.

In February 2008, on the basis of preliminary data from two studies conducted postlicensure that suggested an increased risk for febrile seizures 5–12 days after vaccination among children aged 12–23 months who had received the first dose of MMRV vaccine compared with children the same age who had received the first dose of MMR vaccine and varicella vaccine administered as separate injections at the same visit, ACIP issued updated recommendations regarding MMRV vaccine use (CDC. Update: recommendations from the Advisory Committee on Immunization Practices [ACIP] regarding administration of combination MMRV vaccine. MMWR 2008;57:258–60). These updated recommendations expressed no preference for use of MMRV vaccine over separate injections of equivalent component vaccines for both the first and second doses.

The final results of the two postlicensure studies indicated that among children aged 12–23 months, one additional febrile seizure occurred 5–12 days after vaccination per 2,300–2,600 children who had received the first dose of MMRV vaccine compared with children who had received the first dose of MMR vaccine and varicella vaccine administered as separate injections at the same visit. Data from postlicensure studies do not suggest that children aged 4–6 years who received the second dose of MMRV vaccine had an increased risk for febrile seizures after vaccination compared with children the same age who received MMR vaccine and varicella vaccine administered as separate injections at the same visit.

In June 2009, after consideration of the postlicensure data and other evidence, ACIP adopted new recommendations regarding use of MMRV vaccine for the first and second doses and identified a personal or family (i.e., sibling or parent) history of seizure as a precaution for use of MMRV vaccine. For the first dose of measles, mumps, rubella, and varicella vaccines at age 12–47 months, either MMR vaccine and varicella vaccine or MMRV vaccine may be used. Providers who are considering administering MMRV vaccine should discuss the benefits and risks of both vaccination options with the parents or caregivers. Unless the parent or caregiver expresses a preference for MMRV vaccine, CDC recommends that MMR vaccine and varicella vaccine should be administered for the first dose in this age group. For

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the second dose of measles, mumps, rubella, and varicella vaccines at any age (15 months–12 years) and for the first dose at age ≥48 months, use of MMRV vaccine generally is preferred over separate injections of its equivalent component vaccines (i.e., MMR vaccine and varicella vaccine). This recommendation is consistent with ACIP's 2009 provisional general recommendations regarding use of combination vaccines (available at http://www.cdc.gov/vaccines/recs/provisional/downloads/combo-vax-Aug2009-508.pdf), which state that use of a combination vaccine generally is preferred over its equivalent component vaccines.

Introduction

To prevent measles, mumps, rubella, and varicella, the Advisory Committee on Immunization Practices (ACIP) recommends a 2-dose vaccine schedule in childhood, with the first dose administered at age 12–15 months and the second dose at age 4–6 years (*1,2*). In September 2005, the combination quadrivalent measles, mumps, rubella, and varicella vaccine (MMRV, ProQuad, Merck & Co., Inc.) was licensed by the Food and Drug Administration for use among children aged 12 months–12 years, and indications for its use were published subsequently (*3*). The availability of MMRV vaccine meant that two vaccination options were available to implement the ACIP recommendation for vaccination of children aged 12 months–12 years: 1) trivalent measles, mumps, rubella vaccine (MMR, M-M-RII, Merck & Co., Inc.) and monovalent varicella vaccine (VARIVAX, Merck & Co., Inc.) administered as two separate injections or 2) combination MMRV vaccine administered as one injection. Consistent with ACIP's 2006 general recommendations on immunization, use of the combination MMRV vaccine was preferred over separate injections of equivalent component vaccines (MMR vaccine and varicella vaccine) (*2,3*). Since July 2007, supplies of MMRV vaccine have been temporarily unavailable as a result of manufacturing constraints unrelated to efficacy or safety (i.e., lower-than-expected yields of bulk varicella-zoster virus in production lots) (*4,5*). MMRV vaccine is expected to be available again in the United States in May 2010.

The two vaccination options are considered to provide the same protection against the four diseases. In MMRV vaccine prelicensure studies conducted among children aged 12–23 months, fever and rash had been reported at a greater rate 0–42 days following vaccination among children who received a first dose of MMRV vaccine (n = 4,497) than among children who received first doses of MMR vaccine and varicella vaccine (n = 2,038) (*6*). In light of these findings, to evaluate if an increased risk for febrile seizures might be associated with the first dose of MMRV vaccine, CDC and Merck initiated separate postlicensure studies. Preliminary data from these two studies presented to ACIP in February 2008 suggested a 2.3-times higher risk for febrile seizures among children aged 12–23 months during the 5–12 or 7–10 days after administration of the first dose of MMRV vaccine compared with administration of the first dose of MMR vaccine and varicella vaccine at the same time (*7*). On the basis of these preliminary data, in February 2008, ACIP issued updated recommendations expressing no preference for use of MMRV vaccine over separate injections of equivalent component vaccines (i.e., MMR vaccine and varicella vaccine) for both the first and second dose (*7*). ACIP also established a workgroup to evaluate postlicensure and other safety data regarding the risk for febrile seizures after MMRV vaccine and formulate policy options for use of MMRV vaccine for consideration by ACIP.

In June 2009, after consideration of final data from the postlicensure studies and other evidence, ACIP adopted new recommendations regarding use of MMRV vaccine. This report provides these recommendations and replaces the 2008 recommendations for the use of MMRV vaccine (*7*).

Methods

The ACIP MMRV Vaccine Safety Workgroup was formed in spring 2008 and included federal and nonfederal experts from diverse backgrounds, including vaccine safety; epidemiology and vaccines related to measles, mumps, rubella, and varicella; statistics and pharmacoepidemiology; clinical pediatric neurology, infectious diseases, and primary care; and vaccinology and vaccine policy. The workgroup also sought input from partner organizations (e.g., the American Academy of Pediatrics and the American Academy of Family Physicians) and from local and state health departments. In addition, members of the CDC Public Health Ethics Committee and members of the Ethics Subcommittee of the Advisory Committee to the CDC Director (http://www.cdc.gov/od/science/phethics) were consulted.

The workgroup reviewed findings from two unpublished (at the time of discussions, June 12, 2008–June 24, 2009) postlicensure studies on MMRV vaccine and risk for febrile seizures; prelicensure MMRV vaccine data; literature regarding MMR vaccine and varicella vaccine immunogenicity, efficacy, effectiveness, and safety; measles, mumps, rubella, and varicella disease burden; the epidemiology of febrile seizures; the medical and psychosocial importance of febrile seizures; and program implementation considerations. The workgroup also reviewed data on provider and parental attitudes regarding multiple injections and the use of MMRV vaccine in the

context of an increased risk for febrile seizures after the first dose of MMRV vaccine.

Each member of the ACIP workgroup provided their individual interpretation of febrile seizure risk data and input on proposed policy options through two surveys that were subsequently discussed and compiled. In June 2009, ACIP discussed the safety evidence for MMRV vaccine and febrile seizure risk and risk-benefit interpretation and approved policy recommendations for the use of MMRV vaccine compared with MMR vaccine and varicella vaccine. CDC provided guidance regarding implementation of these recommendations.

Scientific Evidence Relevant for Decision-Making

Vaccine Safety

Risk for Febrile Seizure After First Dose of MMRV Vaccine

MMR vaccine is associated with an increased risk for febrile seizures during the first 2 weeks after vaccination (*8*) when the peak in replication of the live attenuated measles virus occurs (6–12 days) (*9*). This risk period has been defined variably in clinical and epidemiologic studies as 8–14 days, 7–12 days, or 5–12 days (*8,10,11*).

In the MMRV vaccine prelicensure studies conducted among children aged 12–23 months, two systemic vaccine-related adverse reactions were reported at a significantly greater rate 0–42 days following vaccination in children who received a first dose of MMRV vaccine (n = 4,497) than in children who received first doses of MMR vaccine and varicella vaccine (n = 2,038) (*6*). Fever (reported as abnormal or elevated ≥102°F [≥39°C] oral equivalent) was observed in 21.5% of MMRV vaccine recipients compared with 14.9% of MMR vaccine and varicella vaccine recipients (risk difference [RD]: 6.6%; 95% confidence interval [CI] = 4.6–8.5). Measles-like rash was observed in 3.0% of MMRV vaccine recipients compared with 2.1% of those receiving MMR vaccine and varicella vaccine (RD: 1.0%; CI = 0.1–1.8) (*6*). Both of these adverse events were reported to occur more frequently 5–12 days postvaccination and typically resolved spontaneously without sequelae.

The reasons for a higher rate of vaccine-associated fever or measles-like rashes after the first dose of MMRV vaccine are not fully understood but might suggest a more vigorous immune response in response to an increase in measles virus replication. The measles, mumps, and rubella viruses in MMRV vaccine are identical and of equal potency to those in the MMR vaccine, but the potency of the varicella-zoster virus is at least seven times higher than the potency in the monovalent varicella vaccine (a minimum of 3.99 $\log_{10}$ plaque forming units [PFUs] compared with 3.13 $\log_{10}$ PFUs) (*6*). However, the measles geometric mean titers (GMTs) measured 6 weeks after vaccination were higher among children who received the first dose of MMRV vaccine than among children who received the first dose of MMR vaccine and varicella vaccine administered at the same visit, whereas the varicella GMTs were similar (*12*). Statistical modeling indicated that the level of the measles antibody titer after receipt of MMRV vaccine was associated positively with the rate of fever and the rate of measles-like rashes (*13*).

Because of the known association between fever and febrile seizures (*14*), Merck and CDC sponsored separate postlicensure studies among larger populations of vaccinated children than were feasible during prelicensure studies to evaluate if a risk for febrile seizures might be associated with the first dose of MMRV vaccine. These studies assessed the febrile seizure risk in different populations using different methods.

Merck sponsored a postlicensure cohort study among children aged 12–60 months (99% of whom were aged 12–23 months) enrolled in a large managed care organization (MCO) (*11*). All potential cases identified by *International Classification of Diseases, Ninth Revision* (ICD-9) codes for seizure from electronic medical records (779.0 [neonatal seizures], 333.2 [myoclonus], 345 [epilepsy], 780.3 [convulsion], 780.31 [simple febrile convulsion], 780.32 [complex febrile convulsion], and 780.39 [other convulsion]) were adjudicated by an independent committee using the Brighton Collaboration definition for seizure (*15*) and documentation of fever (whether measured or not) in the chart. The study groups included 31,298 children who received a first dose of MMRV vaccine during February 2006–June 2007 and 31,298 children who received a first dose of MMR vaccine and varicella vaccine at the same visit during November 2003–January 2006. The two groups were matched individually by age, sex, and calendar date of vaccination. On the basis of findings on fever from prelicensure trials, the primary period of interest to assess the risk for febrile seizures was 5–12 days after vaccination. Another prespecified period of interest was 0–30 days after vaccination because of the biologic plausibility that the replication of the component viruses of the MMRV vaccine might occur during the month after vaccination. The relative risk (RR) for febrile seizures 5–12 days after vaccination was 2.2 (CI = 1.0–4.7; $p<0.05$) among children who received the first dose of MMRV vaccine (rate: 7.0 per 10,000 vaccinations) compared with children who received the first dose of MMR vaccine and varicella vaccine administered at the same visit (rate: 3.2 per 10,000 vaccinations) (Table). These results suggest that, during the 5–12 day postvaccination period, approximately one additional febrile seizure occurred

TABLE. Summary results from Vaccine Safety Datalink (VSD) and Merck-sponsored studies for febrile seizure after the first dose of measles, mumps, rubella and varicella vaccine (MMRV) compared with the first dose of measles, mumps, rubella vaccine (MMR) and varicella vaccine (V) administered at the same visit — United States, 2009

Characteristic	VSD*	Merck-sponsored†
Age/No. subjects, by vaccine	All aged 12–23 months MMRV: n = 83,107 MMR and V: n= 376,354	99% aged 12–23 months MMRV: n = 31,298 MMR and V: n = 31,298
Postvaccination interval		
Week 1–2	7–10 days§ RR: 2.0 (CI = 1.4–2.9) AR: 4.3 per 10,000 (CI = 2.6–5.6)	5–12 days§ RR: 2.2 (CI = 1.0–4.7) AR: 3.8 per 10,000 (CI = 0.3–7.4)
Week 1–6	0–42 days§ RR: 1.5 (CI = 1.1–1.9) AR: 6.2 per 10,000 (CI = 2.0–9.5)	0–30 days RR: 1.1 (CI = 0.7–1.7) AR: 1.3 per 10,000 (CI = -4.5–7.0)

RR = relative risk; AR = attributable risk; CI = 95% confidence interval.
* **Source:** Klein NP, Fireman B, Yih WK, et al. Measles-mumps-rubella-varicella combination vaccine and the risk of febrile seizures. Pediatrics 2010. In press.
† **Source:** Jacobsen SJ, Ackerson BK, Sy LS, et al. Observational safety study of febrile convulsion following first dose MMRV vaccination in a managed care setting. Vaccine 2009;27:4656–61.
§ Statistically significant at <0.05.

among every 2,600 children vaccinated with a first dose of MMRV vaccine compared with children vaccinated with a first dose of MMR vaccine and varicella vaccine administered at the same visit. During 0–30 days postvaccination, the rate of febrile seizure was 14 per 10,000 vaccinations among MMRV vaccine recipients and 13 per 10,000 vaccinations among MMR vaccine and varicella vaccine recipients; the RR was 1.1 (CI = 0.7–1.7; p=0.66).

The CDC-sponsored study was conducted through the Vaccine Safety Datalink (VSD),* a collaboration between CDC and eight MCOs that routinely monitors vaccine safety of new vaccines by near real-time surveillance (*16*). Each MCO site prepares data files containing demographic and medical information on their members and ICD-9 codes assigned to medical encounters. Surveillance conducted through VSD assesses the risk for prespecified health outcomes during prespecified periods after vaccination; the 42-day interval postvaccination is used commonly to study a variety of vaccine adverse events. VSD monitoring of MMRV vaccine detected an increased risk for seizure of any etiology in the interval of 42 days postvaccination among children aged 12–23 months after administration of first dose of MMRV vaccine compared with administration of first dose of MMR vaccine (many children also received varicella vaccine) (*17*). 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 of any etiology was observed 7–10 days after vaccination in both groups, with more seizures observed among children who had received MMRV vaccine (p=0.0001) (*18*).

To further evaluate this finding, VSD initiated a cohort study to determine the risk for febrile seizures 7–10 days and 0–42 days postvaccination among 83,107 children aged 12–23 months who received the first dose of MMRV vaccine during January 2006–October 2008 and a cohort of 376,354 children aged 12–23 months who received the first dose of MMR vaccine and varicella vaccine administered at the same visit during January 2000–October 2008. Investigators reviewed medical records of study children to identify those with a clinical diagnosis of febrile seizure within 42 days after vaccination as defined by ICD-9 codes for seizures (345X [epilepsy] and 780.3X [convulsion]). Poisson regression was used to adjust for age, respiratory season, and other covariates. During 7–10 days after vaccination, the unadjusted rate of febrile seizures was 8.5 per 10,000 vaccinations among MMRV vaccine recipients and 4.2 per 10,000 vaccinations among those who received MMR vaccine and varicella vaccine at the same visit (adjusted RR: 2.0; CI = 1.4–2.9; p = 0.0001) (Table). These results suggest that, during the 7–10 day postvaccination period, approximately one additional febrile seizure occurred among every 2,300 children vaccinated with a first dose of MMRV vaccine compared with children vaccinated with a first dose of MMR vaccine and varicella vaccine administered at the same visit. During 0–42 days postvaccination, the RR was 1.5 (CI = 1.1–1.9; p<0.05). An additional VSD analysis of the febrile seizure risk during 0–30 days postvaccination, (the interval used in the Merck-sponsored study) yielded similar findings as those for the 0–42 days postvaccination interval (*18*).

Risk for Febrile Seizure After Second Dose of MMRV Vaccine

Rates for febrile seizures are lower among children aged 4–6 years (the recommended age for the second dose of MMRV vaccine, MMR vaccine, and varicella vaccine) than among children aged 12–15 months (*14*). In prelicensure studies conducted among children who received their second dose in their second year of life and 3 months after their first dose, the second dose of MMRV vaccine was less likely to cause fever

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

than the first dose (*12,13*). Among children aged 4–6 years who received MMRV vaccine for their second dose, the rate of fever was similar to the rate following a second dose of MMR vaccine and varicella vaccine at the same visit (*19*).

Assessing the risk for febrile seizures after the second dose vaccination was not an initial objective of either postlicensure study. In light of findings from first-dose studies, the workgroup requested available data on febrile seizures risk after the second dose from both VSD and Merck. In the data that VSD provided in response to this request, the febrile seizure risk after the second dose was inferred from data among children aged 4–6 years, which is the age when the second dose is routinely recommended. In the data provided by Merck, second-dose subjects were children aged 1–12 years (>95% were aged 4–6 years) who had received MMR vaccine previously, with or without varicella vaccine (for most children in the MMR vaccine and varicella vaccine group, only a second dose of MMR vaccine was administered) (*20*). During 7–10 days following vaccination, the VSD study identified one febrile seizure among 84,653 children aged 4–6 years who received MMRV vaccine and no febrile seizures among 64,663 children the same age who received MMR vaccine and varicella vaccine administered at the same visit (*17*). No febrile seizures occurred during the 5–12 days postvaccination in either group in the Merck-sponsored study (25,212 children received a second dose of MMRV vaccine, and 24,788 received a second dose of MMR vaccine and varicella vaccine at the same visit) (*20*). Therefore, among children aged 4–6 years, postlicensure data do not suggest that children who received MMRV vaccine as a second dose had an increased risk for febrile seizures after vaccination compared with children who received a second dose of MMR vaccine and varicella vaccine at the same visit.

Clinical Importance of Febrile Seizure

Febrile seizures occur most commonly with the fevers caused by typical childhood illnesses (e.g., middle-ear infections, viral upper respiratory tract infections, and roseola) but can be associated with any condition that results in fever, including vaccination. MMR vaccine is associated with an increased risk for febrile seizures occurring 8–14 days after vaccination among children aged <7 years, resulting in an estimated one additional febrile seizure among every 3,000–4,000 children vaccinated with MMR vaccine compared with children not vaccinated during the preceding 30 days (*8*). Studies have not demonstrated an increased risk for febrile seizures during the 30-day period following varicella vaccination, after controlling for the simultaneous administration of MMR vaccine (*21*).

By age 5 years, approximately one in every 25 children will have had a febrile seizure. Febrile seizures usually occur among children aged 6–59 months; the peak age is 14–18 months (*14*), and approximately 97% of febrile seizures occur in children aged <4 years (*22*). Approximately one third of children with a first febrile seizure will have recurrent febrile seizures (*23*). Parents and caregivers of children who have a first febrile seizure are likely to seek medical attention, which commonly includes a visit to an emergency department.

The prognosis for young children who have febrile seizures generally is excellent (*14*). The majority (>90%) of children who have a febrile seizure will not develop epilepsy; certain factors (e.g., presence of complex features during the seizure [duration of seizure >15 minutes, occurrence of more than a single seizure within 24 hours, and focal features], an initial febrile seizure before age 12 months, delayed developmental milestones, or a pre-existing neurologic disorder) and genetic predisposition (i.e., family history of epilepsy) are associated with future development of epilepsy after a febrile seizure (*14,23*). Children who have a febrile seizure soon after MMR vaccination (within 2 weeks or within 7–21 days, depending on the study) are not more likely to have future epilepsy or neurodevelopment disorders than children who have febrile seizures for other reasons (*8,10*). However, one study indicated that these children might have a slightly higher risk for having another febrile seizure than children who had a febrile seizure for other reasons (RR = 1.19; CI = 1.01–1.41) (*10*). Although data on sequelae of febrile seizures after MMRV vaccine are not available, the findings described for MMR vaccine likely also are applicable to MMRV vaccine.

When a child experiences a febrile seizure, negative effects on family members or caregivers can result, including adverse mental and physical health consequences (*24–27*). Parents and caregivers generally consider febrile seizures to be a more severe adverse event than physicians (*28,29*).

Measles, Mumps, Rubella, and Varicella Disease Burden

The burden of disease for measles, mumps, rubella, and varicella in the United States is very low. Endemic transmission for measles and rubella was declared eliminated in 2000 and 2004, respectively (*30,31*). For mumps, the average reported incidence has been 0.1 per 100,000 population since 1993, except in 2006, when a large outbreak occurred primarily affecting the Midwest (*32*), and during 2009–2010, when an outbreak occurred in a religious community in the Northeast (*33*). During 1995–2005, reported varicella incidence declined approximately 90% (*34*). The very low levels of disease are attributed to high population immunity achieved through the use of MMR vaccine and varicella vaccine. After the elimination of measles was achieved, a number of outbreaks of limited size occurred as a result of importation into primarily

unvaccinated populations; these outbreaks did not extend to the highly 2-dose vaccinated populations (*35*).

Immunogenicity and Efficacy of MMRV Vaccine

MMRV vaccine was licensed on the basis of noninferior immunogenicity of the antigenic components compared with simultaneous administration of MMR vaccine and varicella vaccine (*36*). Formal studies to evaluate the clinical efficacy of MMRV vaccine have not been performed; efficacy of MMRV vaccine was inferred from that of MMR vaccine and varicella vaccine on the basis of noninferior immunogenicity.

Programmatic Considerations

Vaccine Coverage

Among children aged 19–35 months, vaccine coverage with ≥1dose of MMR vaccine and varicella vaccine is high; since 1996, coverage with MMR vaccine has been 90%–93%, and in 2008, coverage with varicella vaccine reached 91%. In 2008, coverage with ≥1 dose of MMR vaccine by state ranged from 85.9% to 95.6%; coverage with ≥1 dose of varicella vaccine by state ranged from 77.0% to 95.3% (*37*). For school-aged children, school-entry requirements have proved to be an effective strategy for achieving and maintaining high vaccine coverage (*38*). All states have school-entry requirements for 2 doses of MMR vaccine, and 46 states have school-entry requirements for 1 dose of varicella vaccine. As of September 2009, a total of 22 states had school-entry requirements for 2 doses of varicella vaccine (CDC, unpublished data, 2009). No data were available on the rate of coverage for 2 doses of varicella vaccine.

Maintaining high vaccination coverage is important for disease control. Combination vaccines reduce the number of injections children receive and have the potential to improve vaccination coverage and timeliness of vaccination. However, evidence is limited about the impact of the use of newer combination vaccines on vaccination coverage. Two studies suggested that receipt of *Haemophilus influenzae* type b (Hib)–hepatitis B (HepB) or pediatric diphtheria and tetanus toxoids and acellular pertussis vaccine (DTaP)-HepB–inactivated poliovirus vaccine (IPV) combination vaccines was associated with 3%–6% increased coverage for DTaP, IPV, Hib, HepB vaccines compared with the coverage among children who did not receive the combination vaccines (*39,40*). Another study did not find increased coverage for the component vaccines when combination Hib-HepB was used, probably because the coverage rates were already high before introduction of the combination vaccine (*41*). No published literature has specifically assessed the impact of MMRV vaccine on coverage for varicella or other vaccines recommended at age 12–15 months. However, several studies have indicated parent and provider preference for fewer injections at one visit (*42–44*).

Physicians' and Parents' Attitudes on Use of MMRV Vaccine

To better understand attitudes toward use of MMRV vaccine in light of postlicensure findings on febrile seizure risk after the first dose of MMRV vaccine, CDC sponsored a physician survey in 2008 and two parent focus groups in 2009. The physician survey included a nationally representative sample of pediatricians and family physicians (*29,45*). The response rate was 76% for pediatricians (321 of 425) and 71% for family physicians (299 of 424). After being provided with a summary of the findings from the two postlicensure studies of febrile seizure after MMRV vaccination, 59% of pediatricians and 67% of family physicians responded that they would either definitely or probably recommend MMR vaccine and varicella vaccine for the first-dose vaccination for a child aged 12–15 months; 21% and 9%, respectively, would definitely or probably recommend MMRV vaccine; and 20% and 24%, respectively, said they would let the parents decide.[†]

The parent focus groups were conducted in two cities (Kirkland, Washington, and New York City, New York) (*28*). A total of 82 mothers of children aged 7 months–3 years were selected, all of whom reported that they expected their children to receive all or most of the recommended childhood vaccines. Mothers were presented with background materials on febrile seizure risk after the first dose of MMRV vaccine compared with the first dose of MMR vaccine and varicella vaccine. After reviewing and discussing the risks and benefits of both vaccination options, mothers were asked whether they would accept MMRV vaccine for the first-dose vaccination if their pediatrician recommended it; 41% said they would accept vaccination with MMRV vaccine, and 31% said they would refuse. Trust in their pediatrician's judgment was a major factor for mothers' acceptance of MMRV vaccine for their children. Mothers who reported that they would refuse MMRV vaccine said they were unwilling to accept any additional risk over that of MMR vaccine and varicella vaccine, regardless of how small.

[†] Based on response to the following question: "Assuming that your practice has adequate supplies of MMRV, MMR, and varicella vaccines to administer to all your patients, which vaccine(s) would you recommend to a healthy 12–15 month old child?" Answer options were as follows: "1) definitely recommend MMRV, 2) probably recommend MMRV, 3) would let parents choose between MMRV and separate MMR and varicella, 4) probably recommend separate MMR and varicella, and 5) definitely recommend separate MMR and varicella."

Summary and Rationale for MMRV Vaccine Recommendations

Two postlicensure studies (*11,18*) and other related data support the conclusion that use of MMRV vaccine among children aged 12–23 months results in a higher risk for fever and febrile seizures during the 5–12 days after the first dose compared with the use of MMR vaccine and varicella vaccine at the same visit. The approximately twofold increased risk results in an estimated one additional febrile seizure per 2,300–2,600 children vaccinated with the first dose of MMRV vaccine compared with those who receive the first dose with MMR vaccine and varicella vaccine. Although data regarding the risk for febrile seizures after administration of the first dose of MMRV vaccine are available only for children aged 12–23 months, the increased risk for febrile seizures during the 5–12 days postvaccination is likely to be present among children aged ≤47 months because that is the biologic window of vulnerability for febrile seizures in children (approximately 97% of febrile seizures occur in children aged <4 years) (*22*). Compared with no vaccination, MMR vaccine is associated with one additional febrile seizure among every 3,000–4,000 children aged <7 years vaccinated with MMR vaccine (*8*). The risk for febrile seizures during measles illness is higher than the risk after either MMRV vaccine or MMR vaccine (between one in 40 and one in 1,000 children with measles experience a febrile seizure) (*46*).

Results from postlicensure studies do not suggest that children aged 4–6 years who receive the second dose of MMRV vaccine have an increased risk for febrile seizures after vaccination compared with children the same age who receive the second dose of MMR vaccine and varicella vaccine at the same visit (*11,17*). Prelicensure data indicated that the rate of fever after the second dose of MMRV administered to children aged 15–26 months was lower than after the first dose administered to children the same age as either MMRV vaccine or MMR vaccine and varicella vaccine at the same visit (*12*).

The evidence suggests that the two vaccine options (MMRV vaccine or MMR vaccine and varicella vaccine) are equivalent in terms of efficacy, effectiveness, immunogenicity, and burden of disease prevented with the first dose. Evidence to date is not sufficient to demonstrate a clear advantage of either option for the first dose in terms of an impact on program implementation. For the second dose, routine use of MMRV vaccine has the potential to increase second-dose varicella vaccine coverage and thus have a greater impact on controlling varicella disease than MMR vaccine and varicella vaccine, particularly in states that lack school-entry requirements for a second dose of varicella vaccine.

Although a vaccination strategy that would result in the fewest adverse events might be preferred, maximizing choice based on parent or caregiver and physician preference also is an important ethical principle. The decision-making process must include provision of specific information to parents and caregivers about the risk for febrile seizures associated with receipt of the first dose of MMRV vaccine compared with the first dose of MMR vaccine and varicella vaccine.

Use of MMRV vaccine has the benefit of requiring one less injection than the alternative of MMR vaccine and varicella vaccine. The risk for a febrile seizure after the first dose of MMRV vaccine, although low, is higher than after MMR vaccine and varicella vaccine administered as separate injections, and use of MMR vaccine and varicella vaccine avoids this increased risk. Children who have febrile seizures generally have an excellent prognosis. However, first febrile seizures often require a medical visit to an emergency department and are distressing for parents and caregivers. Therefore, parents might prefer to avoid the small increased risk for fever and febrile seizures after the first dose of MMRV vaccine compared with the first dose of MMR vaccine and varicella vaccine administered as separate injections. Given the balance of risks and benefits of a first dose of MMRV vaccine compared with a first dose of MMR vaccine and varicella vaccine, and the importance of individual values and preferences in weighing these risks and benefits, decisions should be made by providers and parents or caregivers on a case-by-case basis.

Recommendations for Use of MMRV Vaccine

ACIP recommendations for use of MMRV vaccine have been summarized (Box). The routinely recommended ages for measles, mumps, rubella, and varicella vaccination continue to be 12–15 months for the first dose and 4–6 years for the second dose.

MMRV vaccine may be administered simultaneously with other vaccines recommended for children aged 12–15 months and 4–6 years. If simultaneous administration is not possible, MMRV vaccine may be administered at any time before or after an inactivated vaccine but at least 28 days before or after another live, attenuated vaccine, except varicella vaccine, for which a minimum interval of 3 months is recommended. Guidance on administration of MMRV vaccine in special situations (e.g., administration of antibody-containing products or tuberculosis screening and skin test reactivity) has been published previously (*47*).

BOX. Summary of recommendations for measles, mumps, rubella and varicella (MMRV) vaccine use

- The routinely recommended ages for measles, mumps, rubella and varicella vaccination continue to be age 12–15 months for the first dose and age 4–6 years for the second dose.
- For the first dose of measles, mumps, rubella, and varicella vaccines at age 12–47 months, either measles, mumps, and rubella (MMR) vaccine and varicella vaccine or MMRV vaccine may be used. Providers who are considering administering MMRV vaccine should discuss the benefits and risks of both vaccination options with the parents or caregivers. Unless the parent or caregiver expresses a preference for MMRV vaccine, CDC recommends that MMR vaccine and varicella vaccine should be administered for the first dose in this age group.
- For the second dose of measles, mumps, rubella, and varicella vaccines at any age (15 months–12 years) and for the first dose at age ≥48 months, use of MMRV vaccine generally is preferred over separate injections of its equivalent component vaccines (i.e., MMR vaccine and varicella vaccine). Considerations should include provider assessment, patient preference, and the potential for adverse events.
- A personal or family (i.e., sibling or parent) history of seizures of any etiology is a precaution for MMRV vaccination. Children with a personal or family history of seizures of any etiology generally should be vaccinated with MMR vaccine and varicella vaccine.

First Dose at Age 12–47 Months

The routinely recommended age for the first dose of measles, mumps, rubella, and varicella vaccines is age 12–15 months; children not vaccinated according to the routine schedule may receive the first dose of MMRV vaccine up to age 12 years. For the first dose of measles, mumps, rubella, and varicella vaccines at age 12–47 months, either MMR vaccine and varicella vaccine or MMRV vaccine may be used. Providers who are considering administering MMRV vaccine should discuss the benefits and risks of both vaccination options with the parents or caregivers. Unless the parent or caregiver expresses a preference for MMRV vaccine, CDC recommends that MMR vaccine and varicella vaccine should be administered for the first dose in this age group.

The discussion with parents or caregivers should focus on helping them understand the risks and benefits using tools including the Vaccine Information Statements. Compared with use of MMR vaccine and varicella vaccine at the same visit, use of MMRV vaccine results in one fewer injection but is associated with a higher risk for fever and febrile seizures 5–12 days after the first dose among children aged 12–23 months (approximately one extra febrile seizure for every 2,300–2,600 MMRV vaccine doses). Use of MMR vaccine and varicella vaccine avoids this increased risk for fever and febrile seizures following MMRV vaccine.

The 47-month cutoff was selected on the basis of the epidemiology of febrile seizures. Approximately 97% of febrile seizures occur in children aged ≤47 months.

Second Dose at Any Age and First Dose at Age ≥48 Months

Although the routinely recommended age for the second dose of measles, mumps, rubella, and varicella vaccines is 4–6 years, the second dose may be administered before age 4 years, provided ≥3 months have elapsed since the first dose. MMRV vaccine is licensed for use among children through age 12 years. For the second dose of measles, mumps, rubella, and varicella vaccines at any age (15 months–12 years) and for the first dose at age ≥48 months, use of MMRV vaccine generally is preferred over separate injections of its equivalent component vaccines (i.e., MMR vaccine and varicella vaccine). Considerations should include provider assessment (i.e., the number of injections, vaccine availability, likelihood of improved coverage, likelihood of patient return, and storage and cost considerations), patient preference, and the potential for adverse events. This recommendation is consistent with ACIP's 2009 provisional general recommendations on combination vaccines (*48*).

Other MMRV Vaccine-Related Guidance

New Precaution for MMRV Vaccine Use

A personal or family (i.e., sibling or parent) history of seizures of any etiology is a precaution[§] for MMRV vaccination. Studies suggest that children who have a personal or family history of febrile seizures or family history of epilepsy are at increased risk for febrile seizures compared with children without such histories (*10,49*). Children with a personal or family history of seizures of any etiology generally should be vaccinated with MMR vaccine and varicella vaccine because the risks for using MMRV vaccine in this group of children generally outweigh the benefits.

Contraindications and Precautions for MMRV Vaccine Use

Contraindications for use of MMRV vaccine include

- history of anaphylactic reaction to neomycin;
- allergic reaction to gelatin, other component of the vaccine, or after previous vaccination with MMRV vaccine, varicella vaccine or MMR vaccine;
- altered immunity (i.e., blood dyscrasias, leukemia, lymphomas of any type, or other malignant neoplasms affecting the bone marrow or lymphatic system);
- primary or acquired immunodeficiency including HIV infections/AIDS, cellular immune deficiencies, hypogammaglobulinemia, and dysgammaglobulinemia;
- family history of congenital or hereditary immunodeficiencies, unless the immune competence of the potential vaccine recipient has been demonstrated;
- systemic immunosuppressive therapy, including oral steroids ≥2 mg/kg of body weight or ≥20 mg/day of prednisone or equivalent for persons who weigh >10 kg, when administered for ≥2 weeks); and
- pregnancy.

Precautions for use of MMRV vaccine include

- recent (≤11 months) receipt of antibody-containing blood product (specific interval depends on dose administered);
- history of thrombocytopenia or thrombocytopenic purpura;
- moderate or severe acute illness with or without fever; and
- a personal or family (i.e., sibling or parent) history of seizures of any etiology.

Use of Antipyretics for Prevention of Febrile Seizures

Studies have not demonstrated that antipyretics (e.g., acetaminophen or ibuprofen) prevent febrile seizures (*50*). Vaccination with either MMR vaccine or MMRV vaccine can cause fever and, rarely, febrile seizures. Most fevers and febrile seizures after administration of a measles-containing vaccine occur 5–12 days after vaccination with the first dose. Parents and caregivers should be counseled about the possibility of fever after receipt of a measles-containing vaccine and educated on timing and measures to control it. Guidance on diagnosis and management of febrile seizures has been published previously (*14,50*).

Reporting of Adverse Events after Vaccination

Clinically significant adverse events that follow vaccination should be reported to the Vaccine Adverse Event Reporting System (VAERS) at http://vaers.hhs.gov/esub/index. Reports can be filed securely online, by mail, or by fax. A VAERS form can be downloaded from the VAERS website or requested by sending an e-mail message to info@vaers.org, by calling telephone 1-800-822-7967, or by sending a faxed request to 1-877-721-0366. Additional information on VAERS or vaccine safety is available at http://vaers.hhs.gov/about/index or by calling telephone 1-800-822-7967.

National Vaccine Injury Compensation Program

The National Vaccine Injury Compensation Program (VICP), established by the National Childhood Vaccine Injury Act of 1986 (as amended), provides a mechanism through which compensation can be paid on behalf of a person determined to have been injured or to have died as a result of receiving a vaccine covered by VICP. The Vaccine Injury Table lists the vaccines covered by VICP and the injuries and conditions (including death) for which compensation might be paid. If the injury or condition is not on the table, or does not occur within the specified time period on the table, persons must prove that the vaccine caused the injury or condition.

Persons of all ages who receive a VICP-covered vaccine might be eligible to file a claim. MMRV vaccine, MMR vaccine and varicella vaccine are covered under VICP.

[§] A precaution is a condition in a recipient that might increase the risk for a serious adverse reaction or that might compromise the ability of the vaccine to produce immunity (e.g., administering measles vaccine to a person with passive immunity to measles from a blood transfusion). A person might experience a more severe reaction to the vaccine than would have otherwise been expected; however, the risk for this happening is less than expected with a contraindication. In general, vaccinations should be deferred when a precaution is present. However, a vaccination might be indicated in the presence of a precaution because the benefit of protection from the vaccine outweighs the risk for an adverse reaction. (CDC. ACIP general recommendations on immunization. MMWR 2006;55[No. RR-15]).

Additional information about VICP is available at http://www.hrsa.gov/vaccinecompensation or by calling telephone 1-800-338-2382.

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