Briefing Document: Policy Recommendations for Use of Measles, Mumps, Rubella, and Varicella (MMRV) Vaccine in the United States

Overall Summary:

- **Current ACIP/CDC recommendations** for MMRV vaccine use in the U.S. summary (MMWR, May 2010):
    - The routinely recommended ages for measles, mumps, rubella and varicella vaccination are 12–15 months for the first dose and 4–6 years for the second dose.
        - Both the first and second dose can be administered at other ages provided the minimum age and the interval between doses are respected.
        - For children aged 12 months through 12 years, two vaccination options are available to implement the ACIP recommendation: 1) trivalent measles, mumps, rubella (MMR) vaccine and monovalent varicella vaccine administered as two separate injections or 2) combination MMRV vaccine administered as one injection. MMRV vaccine is licensed for use through 12 years of age.
    - 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 **the second dose** of measles, mumps, rubella, and varicella vaccines at any age through 12 years (i.e., 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.
- The two vaccination options (MMRV vaccine or separate injections of MMR vaccine and varicella vaccine) are considered equivalent in terms of protection against measles, mumps, rubella, and varicella.
- Febrile seizures are a rare event after MMRV vaccination (7-8.5 per 10,000 vaccinations). Compared with separate administration of MMR vaccine and varicella vaccine at the same time, among children aged 12-23 months, an estimated 1 additional febrile seizure occurs per 2,300–2,600 children vaccinated with the first dose MMRV vaccine.
- **MMRV vaccine** accounts for **15.1%** (range by state 5.1%-31.8%, Q1: 10.4%, Q3: 18.3%) of **first dose** measles, mumps, rubella, and varicella vaccination among children 19-35 months of age (National Immunization Survey-Child, 2023) and **~75%** (range by jurisdiction 46%-96%) of **second dose** vaccination (data from 39 jurisdiction Immunization Information Systems, children age 4-6 years by Dec 31, 2024 who received an MMR-containing vaccine, CDC, unpublished data).

Methods

This document was developed based on review of the relevant literature regarding the measles, mumps, rubella, and varicella (MMRV) vaccine licensed in the U.S. (Proquad, Merck &Co., Inc.) for general vaccine safety, association with febrile seizures, and immunogenicity; review of the literature regarding the second MMRV vaccine, available internationally (Priorix-Tetra, GlaxoSmithKline [GSK] Biologicals) for vaccine efficacy/effectiveness; participation in reviewing of the evidence and discussions during the 2008-2009 ACIP MMRV Vaccine Safety Work Group; and CDC analyses (unpublished) on use of MMRV vaccine for the first and second dose vaccination.

MMRV Vaccine Recommendations and Safety Review:

- The currently available MMRV vaccine in the U.S. (Proquad) was **licensed by FDA** in **September 2005** based on **noninferior immunogenicity** of the antigenic components compared with simultaneous administration of MMR vaccine and varicella vaccine. Efficacy of the measles, mumps, rubella, and varicella components of MMRV vaccine was previously established in clinical studies with the monovalent vaccines. As FDA licensure was based on immunogenicity (antibody) comparisons to the individual components (i.e., MMR vaccine and varicella vaccine), studies to evaluate the efficacy of the MMRV combination vaccine were not performed pre-licensure.
    - At the time of licensure, use of MMRV vaccine was preferred for both the first and second dose of measles, mumps, rubella, and varicella vaccination over separate injections of equivalent component vaccines, consistent with the ACIP recommendation on preferred use of combination vaccines.
- In MMRV vaccine pre-licensure clinical trials, two systemic adverse events were reported at a significantly greater rate 0-42 days after vaccination in children aged 12-23 months who received a first dose of MMRV vaccine (n = 4,497) compared with children who received first doses of MMR vaccine and varicella vaccine at the same visit (MMR+varicella) (n = 2,038): fever ≥102°F/≥38.9°C (21.5% vs. 14.9%) and measles-like rash (3.0% vs. 2.1%). Both adverse events were reported to occur more frequently 5–12 days after vaccination and typically resolved spontaneously without sequelae (MMRV/Proquad Package Insert).
- Because of the known association between fever and febrile seizures, CDC (through the Vaccine Safety Datalink [VSD], which routinely monitors vaccine safety by near real-time surveillance), and Merck sponsored separate **post-licensure studies** to understand the risk for febrile seizures that might be associated with MMRV vaccination.
    - Preliminary results from these two studies were presented to ACIP in **February 2008** and 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+varicella vaccines at the same visit.
    - ACIP reviewed these preliminary data on the elevated (but rare, see rates below) risk for febrile seizures after MMRV vaccine, as well as other considerations, such as vaccine availability (MMRV had not been distributed in the U.S. since July 2007 because of manufacturing constraints unrelated to vaccine safety or efficacy and it was not expected to be available again before 2009). In February 2008, ACIP issued updated recommendations, changing from a preferential recommendation for MMRV vaccine, to 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. ACIP also established a Work Group to evaluate post-licensure and other safety data regarding the risk for febrile seizures after MMRV vaccine.

- **The ACIP MMRV Vaccine Safety Work Group, the first ever ACIP Work Group established specifically to examine the safety of a vaccine, was formed in spring 2008 and examined several lines of evidence during June 2008-June 2009**.
    - The Work Group reviewed findings from two post-licensure studies on MMRV vaccine and risk for febrile seizures (unpublished at the time of the discussions); pre-licensure 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 Work Group also reviewed data from **focus groups with providers and parents** regarding attitudes on multiple injections and use of MMRV vaccine in the context of an increased risk for febrile seizures after the first dose and had consultations with ethics experts.
        - Summary report from June 2009 ACIP meeting available here (pages 137-165)
    - Post-licensure MMRV vaccine studies reviewed:
        - **VSD study** included children aged 12-23 months: 83,107 received the first dose MMRV vaccine, 376,354 received first dose MMR+varicella vaccines, and found that 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+varicella vaccines at the same visit [adjusted RR: **2.0** (1.4–2.9); p=0.0001].
            - Published report: Klein NP, Fireman B, Yih WK, et al. Measles-mumps-rubella-varicella combination vaccine and the risk of febrile seizures. *Pediatrics*. 2010;126(1):e1-e8. doi:10.1542/peds.2010-0665
        - **Merck study** included children aged 12-60 months (99% aged 12-23 months): 31,298 received first dose MMRV vaccine, 31,298 received first dose MMR+varicella vaccines, and found that 5-12 days after vaccination, the rate of febrile seizures was **7 per 10,000** vaccinations among MMRV vaccine recipients and **3.2 per 10,000** vaccinations among those who received MMR+varicella vaccines at the same visit [RR: **2.2** (1.0–4.7); p <0.05].
            - Published report: 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(34):4656-4661. doi:10.1016/j.vaccine.2009.05.056
        - Consistent results in both studies: **Febrile seizures are a rare event after MMRV vaccination (7-8.5 per 10,000 vaccinations). The ~twofold increased risk for febrile seizures after MMRV vaccine results in an**

estimated 1 additional febrile seizure per 2,300–2,600 children vaccinated with the first dose MMRV vaccine compared with those receiving first dose with MMR+varicella vaccines.

- Of note: the final published results did not differ meaningfully from the unpublished results reviewed by the WG.

- Pre-licensure data indicated that the rate of fever after the second dose of MMRV vaccine 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+varicella vaccines at the same visit. 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+varicella vaccines at the same visit [temperature reported as elevated (≥102°F, oral equivalent) or abnormal: MMRV: 2.5%, MMR+varicella vaccines: 4.1%].
  - VSD and Merck's post-licensure studies also examined the risk for febrile seizures after the second dose. Results from both studies suggested that children aged 4–6 years who receive the second dose of MMRV vaccine had no increased risk for febrile seizures after vaccination compared with children the same age who receive the second dose of MMR+varicella vaccines at the same visit.
    - 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+varicella vaccines.
    - No febrile seizures occurred during the 5–12 days postvaccination in either group in the Merck's sponsored study, 25,212 children received a second dose of MMRV vaccine, and 24,788 received a second dose of MMR+varicella vaccines.
- Febrile seizures can occur with any condition that causes a fever. Children who have febrile seizures generally have an excellent prognosis. Typically, febrile seizures are resolved spontaneously without sequelae. However, first febrile seizures often require a medical visit to an emergency department and can be distressing for parents and caregivers.
  - Maximizing choice based on parent or caregiver and physician preference is an important ethical principle. 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.
- In **June 2009**, considering the safety and other evidence (e.g., use of MMRV vaccine has the benefit of requiring one less injection than the alternative of MMR+varicella vaccines, epidemiology of febrile seizures, parent and provider input), ACIP recommended:
  - For the first dose of measles, mumps, rubella and varicella vaccination among children aged 12-47 months, either MMRV vaccine or separate injections of MMR vaccine and varicella vaccine can be used. Providers who

are considering administering MMRV vaccine as the first dose to young children should discuss the benefits and risks of both vaccination options with the parents or caregivers.

        - For the first dose at age ≥48 months and the second dose at any age (15 months-12 years) MMRV vaccine is preferred over the component MMR vaccine and varicella vaccine.

    - At the time of the publication of the recommendations in the MMWR, CDC provided guidance regarding implementation of the recommendation for the first dose among young children that **unless the parent or caregiver expresses a preference for the MMRV vaccine, CDC recommends that MMR vaccine and varicella vaccine should be administered for the first dose among children aged 12–47 months.**

- Safety data post-licensure has continued to be closely and regularly monitored. A summary of reports received to the Vaccine Adverse Event Reporting System (VAERS) after administration of MMRV vaccine in the U.S. during 2006-2020 was recently published.
    - Approximately 35.5 million MMRV vaccine doses were distributed; 13,325 reports were received (37.6 reports/100,000 doses distributed) with 3.3% classified as serious (1.3 reports/100,000 doses distributed). The most common adverse health events after MMRV vaccine were injection site reactions (27%), rash (20%), and fever (14%). **No new or unexpected adverse event was disproportionally reported,** no new or unexpected safety findings were detected for MMRV vaccine given as recommended, reinforcing the favorable safety profile of the vaccine.

Immunogenicity and Effectiveness of MMRV Vaccine:

- **Immunogenicity** after the first dose of MMRV vaccine vs. MMR+varicella vaccines in children aged 12 to 23 months was assessed in 4 randomized clinical trials (5446 received MMRV, 2038 received MMR+varicella concomitantly at separate injection sites). Children enrolled in these trials had no history of disease, no known recent exposure, and no vaccination history for varicella, measles, mumps, and rubella. The end points assessed were response rates and geometric mean titers (GMTs).
    - Response rates and GMTs were similar and met the pre-established criteria for non-inferiority (lower bound of the 95% CI for the difference in measles, mumps, and rubella seroconversion rates >-5.0%, lower bound of the 95% CI for the difference in varicella seroprotection rates was either >-15% [one study] or >-10.0% [three studies]) (Table).
    - Work Group assessment during the 2008-2009 deliberations: **given the non-inferior immunogenicity, effectiveness was assumed to be equal.**

Table. Summary of combined immunogenicity results 6 weeks after administration of a single dose of ProQuad (varicella virus potency ≥3.97 log10 PFU) or M-M-R II and VARIVAX

Group	Antigen	n	Observed Response Rate (95% CI)	Observed GMT (95% CI)
ProQuad (N=5446*)	Varicella	4381	91.2% (90.3%, 92.0%)	15.5 (15.0, 15.9)
	Measles	4733	97.4% (96.9%, 97.9%)	3124.9 (3038.9, 3213.3)
	Mumps (OD cutoff)†	973	98.8% (97.9%, 99.4%)	105.3 (98.0, 113.1)
	Mumps (wild-type ELISA)†	3735	95.8% (95.1%, 96.4%)	93.1 (90.2, 96.0)
	Rubella	4773	98.5% (98.1%, 98.8%)	91.8 (89.6, 94.1)
M-M-R II + VARIVAX (N=2038*)	Varicella	1417	94.1% (92.8%, 95.3%)	16.6 (15.9, 17.4)
	Measles	1516	98.2% (97.4%, 98.8%)	2239.6 (2138.3, 2345.6)
	Mumps (OD cutoff)†	501	99.4% (98.3%, 99.9%)	87.5 (79.7, 96.0)
	Mumps (wild-type ELISA)†	1017	98.0% (97.0%, 98.8%)	90.8 (86.2, 95.7)
	Rubella	1528	98.5% (97.7%, 99.0%)	102.2 (97.8, 106.7)

*Combined numbers from 4 trials with ProQuad with the varicella zoster potency similar to that in the licensed product; children aged 12 to 23 months

†The mumps antibody response was assessed by a vaccine-strain ELISA in 2 studies (serostatus was based on the OD cutoff) and by a wild-type ELISA in 2 studies.

n = Number of per-protocol subjects with evaluable serology.

CI = Confidence interval.

GMT = Geometric mean titer.

ELISA = Enzyme-linked immunosorbent assay.

PFU = Plaque-forming units.

OD = Optical density.

- No specific post-licensure vaccine effectiveness (VE) estimates are available for the MMRV vaccine used in the U.S.
    - MMRV vaccine was licensed in the US in September 2005 and in July 2007 became temporarily unavailable due to manufacturing constraints unrelated to efficacy or safety. MMRV vaccine became available again in the U.S. in 2012; however, with measles and rubella being eliminated in the U.S., mumps at low levels (and outbreaks occurring primarily in young adults), and the number of cases of varicella declining 90% by 2010, there were not enough cases of disease or outbreaks in children to assess vaccine effectiveness in the U.S.
    - **Vaccinated persons continue to have very low rates of disease for measles, mumps, rubella and varicella in the U.S**, including in ages where MMRV is used (data provided in references). There have been no reports to CDC indicating concern for lower MMRV vaccine effectiveness compared to use of the separate component vaccines, consistent with the immunogenicity results seen in the clinical trials.

MMRV vaccine in international settings

- The second MMRV vaccine available globally (Priorix-Tetra) was also licensed based on non-inferior immunogenicity. Note there are important differences in the varicella-zoster virus (VZV) antigen content between Priorix-Tetra and Proquad (less VZV antigen in Priorix-Tetra).
    - Post-licensure, a **randomized, controlled trial** was conducted in 10 European countries that reported on **efficacy against varicella**
        - 2,279 children aged 12-22 months received 2 doses of MMRV vaccine, 42 days apart; mean follow-up 36 months.
        - Two dose MMRV vaccine efficacy against all varicella: 94.9% (92.4–96.6); against moderate to severe varicella: 99.5% (97.5–99.9).
            - Prymula R, Bergsaker MR, Esposito S, et al. Protection against varicella with two doses of combined measles-mumps-rubella-varicella vaccine versus one dose of monovalent varicella vaccine: a multicentre, observer-blind, randomised, controlled trial - PubMed. *Lancet*. 2014;383(9925):1313-1324.
        - A continuation of the study above a median follow-up of 9.8 years reported
            - Two dose MMRV vaccine efficacy against all varicella: 95.4% (94.0–96.4); against moderate or severe varicella: 99.1% (97.9–99.6).
                - Povey M, Henry O, Bergsaker MR et al. Protection against varicella with two doses of combined measles-mumps-rubella-varicella vaccine or one dose of monovalent varicella vaccine: 10-year follow-up of a phase 3 multicentre, observer-blind, randomised, controlled trial. *Lancet Infect Dis* 2019;19: 287–97.

References:

- CDC/ACIP Recommendations for MMRV use:
    - Current Recommendations: Use of Combination Measles, Mumps, Rubella, and Varicella Vaccine Recommendations of the Advisory Committee on Immunization Practices; Published May 7, 2010. https://www.cdc.gov/mmwr/pdf/rr/rr5903.pdf
    - Webpage with all MMRV recommendations: https://www.cdc.gov/acip-recs/hcp/vaccine-specific/mmrv.html
    - Summary from June 2009 ACIP meeting where Evidence to Recommendation framework from the MMRV Vaccine Work Group were presented and discussed: Advisory Committee on Immunization Practices (ACIP) summary report : June 24-26, 2009, Atlanta, Georgia (pages 137-165)
- The published reports of the two post-licensure studies on MMRV vaccine and febrile seizure among children 12-23 months of age examined by ACIP in 2008-2009
    - Klein NP, Fireman B, Yih WK, et al. Measles-mumps-rubella-varicella combination vaccine and the risk of febrile seizures. *Pediatrics*. 2010;126(1):e1-e8. doi:10.1542/peds.2010-0665

    - 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(34):4656-4661. doi:10.1016/j.vaccine.2009.05.056
- Study that examined MMRV vaccine and febrile seizures in children 4-6 years of age
    - Klein NP, Lewis E, Baxter R, et al. Measles-containing vaccines and febrile seizures in children age 4 to 6 years - PubMed. *Pediatrics*. 2012;129(5):809-14.
- MMRV (Proquad, Merck) package insert (Package Insert - Frozen Formulation - ProQuad)
    - Merck added febrile seizures to the PI in Feb 2008 in the section of post-marketing experience (under Nervous system disorders), Approved Products > February 27, 2008 Approval Letter - ProQuad
    - Addition of "additional safety data after a first or second dose of ProQuad®" approved in October 29, 2009, Approved Products > October 29, 2009 Approval Letter - ProQuad
- MMRV (Priorix-Tetra, GSK) randomized clinical trials
    - Prymula R, Bergsaker MR, Esposito S, et al. Protection against varicella with two doses of combined measles-mumps-rubella-varicella vaccine versus one dose of monovalent varicella vaccine: a multicentre, observer-blind, randomised, controlled trial - PubMed. *Lancet*. 2014;383(9925):1313-1324.
    - Povey M, Henry O, Bergsaker MR et al. Protection against varicella with two doses of combined measles-mumps-rubella-varicella vaccine or one dose of monovalent varicella vaccine: 10-year follow-up of a phase 3 multicentre, observer-blind, randomised, controlled trial. *Lancet Infect Dis* 2019;19: 287–97.
- Current/recent epidemiology of measles, mumps, rubella, and varicella (including very low rates among vaccinated individuals): Note for diseases eliminated in the US (measles and rubella), recent U.S. studies to examine vaccine effectiveness are not possible.
    - **Measles**: Measles Cases and Outbreaks: CDC Website: https://www.cdc.gov/measles/data-research/index.html
    - **Mumps**: Tappe J, et al. Characteristics of reported mumps cases in the United Stats: 2018-2023. Vaccine 2024;42(25):
    - **Rubella**: Rubella in the United States: https://www.cdc.gov/rubella/vaccine-impact/index.html
    - **Varicella**: Shapiro E and Marin M. The effectiveness of varicella vaccine: 25 years of post-licensure experience in the United States. *The Journal of Infectious Diseases* 2022: 226 (4): S425–S430; Marin M, Leung J, Anderson TC, Lopez A. Monitoring Varicella Vaccine Impact on Varicella Incidence in the United States: Surveillance Challenges and Changing Epidemiology, 1995–2019. *The Journal of Infectious Diseases* 2022: 226 (4): S392-399.