MMRV Vaccine Safety

Contents

Summary

The measles-mumps-rubella-varicella (MMRV) vaccine (ProQuad®, Merck) was licensed in the United States in 2005 for use in children 12 months through 12 years of age. In 2006, the Advisory Committee on Immunization Practices (ACIP) recommended MMRV as an option for both the first and second doses of measles, mumps, rubella, and varicella vaccination. However, post-licensure safety surveillance identified an increased risk of febrile seizures 5–12 days after the first dose in children aged 12–23 months compared to those receiving separate MMR and varicella (MMR + V) vaccines. Based on this finding, ACIP updated its guidance in 2009.

ACIP currently recommends that MMR and varicella vaccines be given separately for the first dose in children 12–47 months; however, MMRV may be used if parents or caregivers request a preference. 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. Use of MMR vaccine and varicella vaccine avoids this increased risk for fever and febrile seizures following MMRV vaccine. Studies of febrile seizures after vaccination with first dose of MMRV vaccine have not been done in older children, but experts agree that this increased risk of fever and febrile seizures during the 5-12 days after first dose vaccination likely also occurs in children aged 24-47 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). First febrile seizures are uncommon after age 4 years (MMRV Questions and Answers for Healthcare Providers | CDC). Either MMRV or MMR + V may be used for the second dose or for children aged 4 years and older (Use of Combination Measles, Mumps, Rubella, and Varicella Vaccine).

Over the past 15+ years and multiple studies, mild fever and rash are the most commonly reported adverse events following MMRV vaccination. The primary safety concern is an increased risk of febrile seizures following the first dose in children aged 12-23 months. This risk

is estimated at 1 additional seizure occurring 5-12 days after vaccination per 2,300-2,600 vaccinated children compared to those receiving MMR + V separately (Use of Combination Measles, Mumps, Rubella, and Varicella Vaccine). These events resolve without long-term consequences (Measles, Mumps, Rubella, Varicella (MMRV) Vaccine Safety | Vaccine Safety | CDC). No increased seizure risk has been observed with the second dose or in children aged 48 months or older.

Several clinical trials have also evaluated the safety of MMRV when administered concomitantly with other routine childhood vaccines, including pneumococcal conjugate vaccine (PCV-7), meningococcal conjugate vaccines (MenACWY, MenC), and DTaP-containing vaccines. These studies found no increase in serious adverse events or clinically meaningful differences in reactogenicity. International surveillance and real-world data from Canada and Europe have confirmed the most common adverse events as mild fever and rash, along with the increased risk of febrile seizure as the only serious adverse event following MMRV vaccination. Although rare cases of encephalitis and death have been reported after MMRV vaccination, no direct link between these events and the vaccine has been established in persons with healthy immune systems.

Cochrane Review

- Di Pietrantonj C, Rivetti A, Marchione P, Debalini MG, Demicheli V. Vaccines for measles, mumps, rubella, and varicella in children. *Cochrane Database Syst Rev*. 2021;11(11):CD004407. Published 2021 Nov 22. doi:10.1002/14651858.CD004407.pub5
    - Authors searched the Cochrane Central Register of Controlled Trials (CENTRAL) (the Cochrane Library 2019, Issue 5), which includes the Cochrane Acute Respiratory Infections Group's Specialised Register, MEDLINE (1966 to 2 May 2019), Embase (1974 to 2 May 2019), the WHO International Clinical Trials Registry Platform (2 May 2019), and ClinicalTrials.gov (2 May 2019).
    - Includes randomized controlled trials (RCTs), controlled clinical trials (CCTs), prospective and retrospective cohort studies (PCS/RCS), case-control studies (CCS), interrupted time-series (ITS) studies, case cross-over (CCO) studies, case-only ecological method (COEM) studies, self-controlled case series (SCCS) studies, person-time cohort (PTC) studies, and case-coverage design/screening methods (CCD/SM) studies, assessing any combined MMR or MMRV / MMR+V vaccine given in any dose, preparation or time schedule compared with no intervention or placebo, on healthy children up to 15 years of age.
    - Seizure: **The analyses provide evidence supporting an association between MMR/MMR+V/MMRV vaccines (Jeryl Lynn strain) and febrile seizures. Febrile seizures normally occur in 2% to 4% of healthy children at least once before the age of 5. The attributable risk febrile seizures vaccine-induced is estimated to be from 1 per 1700 to 1 per 1150 administered doses.**

- ITP: ITP can happen after natural measles infection. The analyses provide evidence supporting an association between ***MMR*** vaccination and ITP. However, the risk of ITP after vaccination is smaller than after natural infection with these viruses. Natural infection of ITP occur in 5 cases per 100,000 (1 case per 20,000) per year. The attributable risk is estimated about 1 case of ITP per 40,000 administered MMR doses. The overall meta-analysis estimate of association between MMR vaccination and ITP in children aged 9 to 23 months was RR 4.21 (95% CI 2.28 to 7.78). There was no statistical evidence in children aged 4 to 6 years (RR 3.06, 95% CI 0.42 to 22.30), and **no statistical evidence of association between MMRV vaccination and ITP in children aged 9 to 23 months (RR 2.87, 95% CI 0.78 to 10.56).** The latter two results came from one study (db-O'Leary 2012).

General safety

- Klopfer SO, Stek JE, Petrecz M, et al. Analysis of safety data in children after receiving two doses of ProQuad® (MMRV). *Vaccine*. 2014;32(52):7154-7160. doi:10.1016/j.vaccine.2014.08.067
  - Safety data from five clinical studies were combined for all children who were scheduled to receive two doses of MMRV ~3-6 months apart. All vaccinated children were followed for safety following each dose of MMRV.
  - Of 3112 children who received a first dose of MMRV, 2780 (89.3%) received a second dose of MMRV. Overall, 70.5% and 57.7% of children reported ≥1 adverse experiences following first and second doses of MMRV, respectively**. Injection-site redness** was statistically significantly higher postdose 2 than postdose 1, while **injection-site pain/tenderness** was statistically significantly higher postdose 1 compared to postdose 2. **Rashes** were statistically significantly lower postdose 2 compared to postdose 1. **Ten febrile seizures** (8 postdose 1, 2 postdose 2) were reported following MMRV vaccination. **The incidence of febrile seizures postdose 1 of MMRV was 0.26% (8/3019) compared to 0.07% (2/2695) postdose 2 of MMRV.**
  - Author's conclusions: administration of two doses of MMRV has an acceptable safety profile in children 12 to 23 months of age. There is a small increase in the risk of febrile seizures following the first dose of MMRV as compared to the component vaccines, but the risk for any individual child is relatively low.
- Klein NP, Lewis E, Fireman B, et al. Safety of measles-containing vaccines in 1-year-old children. *Pediatrics*. 2015;135(2):e321-e329. doi:10.1542/peds.2014-1822
  - Study children were aged 12 to 23 months in the Vaccine Safety Datalink from 2000 to 2012. Nine study outcomes were investigated**: 7 main outcomes (anaphylaxis, ITP, ataxia, arthritis, meningitis/encephalitis, acute disseminated encephalomyelitis, and Kawasaki disease), seizure, and fever.** Comparing MMRV with MMR + V, relative risk was estimated by using stratified exact binomial tests. Secondary analyses examined post-MMRV or MMR + V risk versus comparison

intervals; risk and comparison intervals were then contrasted for MMRV versus MMR+V.
    - Authors evaluated 123,200 MMRV and 584,987 MMR + V doses**. Comparing MMRV with MMR + V, risks for the 7 main outcomes were not significantly different.** Several outcomes had few or zero postvaccination events. **Comparing risk versus comparison intervals, ITP risk was higher after MMRV (odds ratio [OR]: 11.3 [95% confidence interval (CI): 1.9 to 68.2]) and MMR + V (OR: 10 [95% CI: 4.5 to 22.5]) and ataxia risk was lower after both vaccines (MMRV OR: 0.8 [95% CI: 0.5 to 1]; MMR + V OR: 0.8 [95% CI: 0.7 to 0.9]). Compared with MMR + V, MMRV increased risk of seizure and fever 7 to 10 days after vaccination.**
    - Author's conclusions: This study did not identify any new safety concerns comparing MMRV with MMR + V or after either the MMRV or the MMR + V vaccine. This study provides reassurance that these outcomes are unlikely after either vaccine.
- Ma SJ, Li X, Xiong YQ, Yao AL, Chen Q. Combination Measles-Mumps-Rubella-Varicella Vaccine in Healthy Children: A Systematic Review and Meta-analysis of Immunogenicity and Safety. *Medicine (Baltimore)*. 2015;94(44):e1721. doi:10.1097/MD.0000000000001721
    - Authors searched PubMed, Embase, BIOSIS Previews, Web of Science, Cochrane Library, and other databases through September 9, 2014. Eligible randomized controlled trials (RCTs) were selected and collected independently by 2 reviewers. Meta-analysis was conducted using Stata 12.0 and RevMan 5.3.
    - Incidences of any serious adverse events (SAEs) were around 1% in all the groups; only about one-tenth of the events were considered to be related to vaccination studied. About half of the related SAEs were febrile seizures. The incidence of related febrile seizure was under 0.8% in MMRV groups and under 0.5‰ in MMR + V/MMR groups. No statistical difference was found between groups with no evidence of heterogeneity**. No related fatal SAE was reported in any studies included.**
    - **Well tolerated safety profiles were demonstrated except higher incidence of fever (relative risks 1.12–1.60) and measles/rubella-like rash (relative risks 1.44–1.45) in MMRV groups.**
    - Author's conclusions: MMRV had comparable immunogenicity and overall safety profiles to MMR + V/MMR in healthy children based on current evidence.
- Woo EJ, Winiecki SK, Arya D, Beeler J. Adverse Events After MMR or MMRV Vaccine in Infants Under Nine Months Old. *Pediatr Infect Dis J*. 2016;35(8):e253-e257. doi:10.1097/INF.0000000000001201
    - The Vaccine Adverse Event Reporting System was searched for reports of measles, mumps and rubella vaccine (MMR) or measles, mumps, rubella and varicella vaccine (MMRV) vaccination in children less than 9 months of age. A clinical assessment of each report was conducted and the frequency, range, onset time and severity of adverse events was summarized.

  - After excluding 346 reports because they were duplicates or because they contained insufficient information about the child's age or vaccine(s), authors retained 204 reports in the analysis, including 35 (17%) that were serious. **Among the 169 nonserious reports, more than half (88; 52%) described a vaccination error without any adverse event per se. Other nonserious reports described fever, injection reactions and gastrointestinal symptoms**. **Serious adverse events included developmental disorders, fever and fussiness. There were 44 reports of fever, but only 4 cases began 5-12 days after immunization, the peak risk window. The vast majority of fever reports listed concomitant vaccines, such as diphtheria and tetanus toxoids, acellular or whole-cell pertussis vaccine.**
  - Author's conclusions: This review did not identify any major safety concerns. These findings may facilitate discussions about the risks and benefits of vaccinating infants who are potentially exposed to this life-threatening disease.
- Safety Surveillance of Varicella Vaccines in the Vaccine Adverse Event Reporting System, United States, 2006–2020 - PMC
  - US VAERS reports received after administration of VAR and MMRV during 2006-2020 were identified. Reports were analyzed by vaccine type, age, seriousness, most common adverse events (AEs), and concomitant vaccines. Medical records of selected reports of AEs of special interest were reviewed and empirical Bayesian data mining to identify disproportionally reported AEs was conducted.
  - During 2006-2020, approximately 132.8 million VAR doses were distributed; 40 684 reports were received in VAERS (30.6/100 000 doses distributed), with 4.1% classified as serious (1.3/100 000 doses distributed). Approximately 35.5 million MMRV doses were distributed; 13 325 reports were received (37.6/100 000 doses distributed) with 3.3% classified as serious (1.3/100 000 doses distributed). The most common adverse health events after both VAR and MMRV were injection site reactions (31% and 27%), rash (28% and 20%), and fever (12% and 14%), respectively. Vaccination errors accounted for 23% of reports after VAR administration and 41% after MMRV administration, but ≥95% of them did not describe an adverse health event. AEs associated with evidence of vaccine strain varicella-zoster virus (vVZV) infection included meningitis, encephalitis, herpes zoster, and 6 deaths (all in immunocompromised persons with contraindications for vaccination). **No new or unexpected AE was disproportionally reported**.
  - Author's conclusions: No new or unexpected safety findings were detected for VAR and MMRV given as recommended, reinforcing the favorable safety profiles of these vaccines. Providers should obtain specimens for viral testing and strain-typing for serious AEs if they consider vVZV as the possible causative agent.
- Vittrup DM, Charabi S, Jensen A, Stensballe LG. A systematic review and meta-analysis of adverse events following measles-containing vaccines in infants less than 12 months of age. *Vaccine*. 2025;47:126687. doi:10.1016/j.vaccine.2024.126687

- EMBASE and PubMed were searched in February 2021, and the search was updated in February 2024. With the exception of case reports, we included all English-written original studies published >1985 that contained frequency measures on adverse events (AEs) within 56 days following MCV1 in infants <12 months of age. We identified all common AEs and their frequencies and combined these across studies in a meta-analysis. The effect of measles strain and vaccine valency was also evaluated.
- 24 studies were included in the analysis: 18 randomized controlled trials (RCTs), three interventional studies, and three observational studies. Only one RCT was placebo-controlled. Commonly reported AEs were injection site reactions, fever, rash, gastrointestinal symptoms, respiratory tract symptoms, conjunctivitis, and symptoms related to the general condition of the infant**. The frequency of any AE was generally <10 %; however, the placebo-controlled trial showed no difference between MCV1 and placebo-injected infants. Edmonston B strains and measles-mumps-rubella-varicella vaccine (MMRV) were associated with a higher rate of high fever >39 °C.**
- Most AEs occurred in <10 % of infants receiving MCV1 at < 12 months of age. The placebo-controlled trial suggested no excess reactogenicity following early MCV. Measles strain and vaccine valency may affect AE risks, but other factors such as socioeconomic status, race, and setting could also explain this finding, as these were not equally distributed between studies. Caution is advised when interpreting findings from studies without a placebo group.

Febrile convulsion/febrile seizure

- 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
  - Children ages 12–60 months who received a first dose of MMRV in February 2006–June 2007 in a managed care organization were included in the study. Subjects were optimally matched on age, sex, and calendar date of vaccination to children who received MMR + V concomitantly in November 2003–January 2006, before MMRV licensure. Potential cases of febrile convulsion were identified through administrative data and adjudicated by expert panel, according to pre-specified criteria.
  - During the 30 days post-vaccination, there were 128 and 94 potential convulsion cases among the 31,298 children in the MMRV and MMR+V cohorts, respectively. After review of available medical charts and adjudication, there were 84 cases of confirmed febrile convulsion, 44 (1.41/1000) and 40 (1.28/1000) in the MMRV and MMR+V cohorts, respectively (RR=1.10, 95% CI=0.72, 1.69). In days 5-12 following vaccination, a pre-specified period of

interest, the respective numbers were 22 (0.70/1000) and 10 (0.32/1000) (RR=2.20, 95% CI=1.04, 4.65).
    - **These data suggest that the risk of febrile convulsion is increased in days 5-12 following vaccination with MMRV as compared to MMR+V given separately during the same visit, when post-vaccination fever and rash are also increased in clinical trials.**
- 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
    - Using 2000–2008 Vaccine Safety Datalink data, authors assessed seizures and fever visits among children aged 12 to 23 months after MMRV and separate MMR + varicella vaccines. Authors compared seizure risk after MMRV vaccine to that after MMR + varicella vaccines by using Poisson regression as well as with supplementary regressions that incorporated chart-review results and self-controlled analyses.
    - MMRV vaccine recipients (83 107) were compared with recipients of MMR + varicella vaccines (376 354). Seizure and fever significantly clustered 7 to 10 days after vaccination with all measles-containing vaccines but not after varicella vaccination alone. Seizure risk during days 7 to 10 was higher after MMRV than after MMR + varicella vaccination (relative risk: 1.98 [95% confidence interval: 1.43–2.73]). Supplementary analyses yielded similar results. The excess risk for febrile seizures 7 to 10 days after MMRV compared with separate MMR + varicella vaccination was 4.3 per 10 000 doses (95% confidence interval: 2.6–5.6).
    - **Among 12- to 23-month-olds who received their first dose of measles-containing vaccine, fever and seizure were elevated 7 to 10 days after vaccination. Vaccination with MMRV results in 1 additional febrile seizure for every 2300 doses given instead of separate MMR + varicella vaccines.**
- Klein NP, Lewis E, Baxter R, et al. Measles-containing vaccines and febrile seizures in children age 4 to 6 years. *Pediatrics*. 2012;129(5):809-814. doi:10.1542/peds.2011-3198
    - Among 4- to 6-year-old Vaccine Safety Datalink members, authors identified seizures in the emergency department and hospital from 2000 to 2008 and outpatient visits for fever from 2006 to 2008 during days 7 to 10 and 0 to 42 after MMRV and MMR + V. Incorporating medical record reviews, we assessed seizure risk after MMRV and MMR + V.
    - From 2006 through 2008, 86 750 children received MMRV; from 2000 through 2008, 67 438 received same-day MMR + V. Seizures were rare throughout days 0 to 42 without peaking during days 7 to 10. There was 1 febrile seizure 7 to 10 days after MMRV and 0 after MMR + V. Febrile seizure risk was 1 per 86 750 MMRV doses (95% confidence interval, 1 per 3 426 441, 1 per 15 570) and 0 per 67 438 MMR + V doses (1 per 18 282).

    - **This study provides reassurance that MMRV and MMR + V were not associated with increased risk of febrile seizures among 4- to 6-year-olds. We can rule out with 95% confidence a risk greater than 1 febrile seizure per 15 500 MMRV doses and 1 per 18 000 MMR + V doses.**
- Ma SJ, Xiong YQ, Jiang LN, Chen Q. Risk of febrile seizure after measles-mumps-rubella-varicella vaccine: A systematic review and meta-analysis. *Vaccine*. 2015;33(31):3636-3649. doi:10.1016/j.vaccine.2015.06.009
    - PubMed, Embase, BIOSIS Previews, Scopus, Web of Science, Cochrane Library and other databases were searched through 12 December 2014.
    - A total of thirty-nine studies were included. Thirty-one published or unpublished clinical trials involving about 40,000 subjects did not show significant differences in incidence of febrile seizure or vaccine related febrile seizure between MMRV and MMR with or without varicella vaccine after any doses, in the risk windows of 0-28, 0-42 or 0-56 days and 7-10 days. In addition, these studies showed that the receipt of concomitant use of MMRV and other pediatric vaccines was not a significant predictor of febrile seizure. Eight post-marketing observations involving more than 3,200,000 subjects were included. **No evidence suggested elevated risk of febrile seizure associated with MMRV vaccine among children aged 4-6 years old during 7-10 days or 0-42 days after vaccination. However, an approximately 2-fold increase in risk of seizure or febrile seizure during 7-10 days or 5-12 days after MMRV vaccination was found among children aged 10-24 months, although the highest incidence of seizure was still lower than 2.95%.**
    - First MMRV vaccine dose in children aged 10-24 months was associated with an elevated risk of seizure or febrile seizure.

Studies performed outside of the United States

Canada

- Seo CY, Rashid M, Harris T, Stapleton J, Deeks SL. Assessing safety of Ontario's publicly funded MMR and MMRV immunization programs, 2012 to 2016. *Paediatr Child Health*. 2019;25(6):358-364. Published 2019 Apr 8. doi:10.1093/pch/pxz037
    - Reports of AEFIs were extracted from the provincial surveillance database on May 9, 2017. Events were grouped by provincial surveillance definitions. Reporting rates were calculated using provincial population estimates or net doses distributed as the denominator. A serious AEFI is defined as an AEFI that resulted in an in-patient hospitalization or death.
    - Overall, 289 AEFIs were reported following administration of MMR (n=246) or MMRV (n=43) vaccines, for annualized reporting rates of 16.6 and 8.8 reports per 100,000 distributed doses, respectively. The highest age-specific reporting rate was in children aged 1 to 3 years for MMR (7.7 per 100,000 population) and

children aged 4 to 9 years for MMRV (0.8 per 100,000 population). Systemic reactions were the most frequently reported event category, while rash was the most frequently reported event for both vaccines. There were 22 serious AEFIs, 19 following MMR and 3 following MMRV (1.3 and 0.6 per 100,000 doses distributed, respectively).
    - Authors found a low reporting rate of adverse events following MMR and MMRV vaccines in Ontario. No safety concerns were identified.

Germany

- Schäfer W, Reinders T, Schink T. Second dose of measles-mumps-rubella-varicella vaccine (MMRV) and the risk of febrile convulsions. *Vaccine*. 2022;40(14):2168-2172. doi:10.1016/j.vaccine.2022.02.072
    - A retrospective cohort study using claims data from the German Pharmacoepidemiological Research database (GePaRD) was performed in children born between January 1st, 2004 and October 31st, 2015 who received two doses of MMRV, MMR + V or MMR. Cases were defined as hospitalization with a diagnosis of febrile convulsions (FC) without neurological conditions coded as main discharge diagnosis. Unadjusted and adjusted odds ratios (OR) with 95% confidence intervals (CIs) were calculated to compare the risk of FC. Stratified analyses were performed to examine potential effect modification by age, sex, history of FC or type of first dose vaccine.
    - In the first 30 days after second dose vaccination, 464 FCs were observed in a cohort of 528,639 children with a median age of 17 months. After adjustment for potential confounders, the adjusted OR for FC in the 30 days after vaccination was 1.25 (95% CI 0.67–2.30) for MMRV compared to MMR + V and 1.04 (0.82–1.32) for MMRV compared to MMR. History of FC was the most important risk factor with an OR of 36.26 (29.30–44.89). We found no effect modification by age, sex, history of FC, or type of first dose vaccine.
    - Author's conclusions: Use of MMRV at second dose is not associated with an increased risk of FC compared to MMR + V or MMR, irrespective of age, sex, history of FC, or type of first dose vaccine.

Italy

- Stefanizzi P, Stella P, Ancona D, et al. Adverse Events Following Measles-Mumps-Rubella-Varicella Vaccination and the Case of Seizures: A Post Marketing Active Surveillance in Puglia Italian Region, 2017-2018. *Vaccines (Basel)*. 2019;7(4):140. Published 2019 Oct 7. doi:10.3390/vaccines7040140
    - In the Puglia Region launched, from May 2017 to November 2018, a post-marketing active surveillance program of adverse events following MMRV immunization (AEFIs). Immunized children (second year of life) were enrolled on

a voluntary basis, AEFIs diaries were used, and their parents were interviewed 25 days after the immunization.

- There were 2540 children enrolled; 2149/2540 (84.6%) completed the post-vaccination follow-up. Of these, 992 AEFIs were registered with a reporting rate of 46.2 × 100 doses: 883/992 (89.0%) AEFIs were not serious, while 109/992 (11.0%) were serious. For serious AEFIs, the evaluation of causality assessment was performed using the algorithm proposed by the World Health Organisation (WHO): 82/109 consistent causal associations to MMRV immunization were detected (reporting rate of consistent AEFIs: 3.8 × 100 follow-up). All serious AEFIs consistently associated with immunization resulted completely resolved at the follow-up. The reporting rate of seizure consistently associated with immunization was 0.05 × 100, lower than data previous published in the literature that did not report the causality assessment.
- Author's conclusion: Because no emerging signals were detected, data from the active surveillance program confirmed the safety profile of the MMRV vaccine.

Clinical Trial data

- Reisinger KS, Brown ML, Xu J, et al. A combination measles, mumps, rubella, and varicella vaccine (ProQuad) given to 4- to 6-year-old healthy children vaccinated previously with M-M-RII and Varivax [published correction appears in Pediatrics. 2006 Jun;117(6):2338]. *Pediatrics*. 2006;117(2):265-272. doi:10.1542/peds.2005-0092
  - Four- to 6-year-old children who had been immunized previously with M-M-RII and Varivax were assigned randomly to receive either ProQuad and placebo (*N* = 399), M-M-RII and placebo (*N* = 195), or M-M-RII and Varivax (*N* = 205) and were then monitored for safety and immunogenicity. **ProQuad was generally well tolerated.** Similarity (noninferiority) was demonstrated in postvaccination antibody responses to measles, mumps, and rubella between recipients of ProQuad and all recipients of M-M-RII and in responses to varicella between recipients of ProQuad and recipients of Varivax. Postvaccination seropositivity rates for antibodies against all 4 viruses were nearly 100% in all 3 groups. Small fold increases were observed for measles, mumps, and rubella antibody titers. In contrast, substantial boosts in varicella antibody titers were observed among recipients of a second dose of varicella vaccine, administered as ProQuad or Varivax.
  - ProQuad may be used in place of a second dose of M-M-RII or second doses of M-M-RII and Varivax for 4- to 6-year-old children.
- Shinefield H, Black S, Thear M, et al. Safety and immunogenicity of a measles, mumps, rubella and varicella vaccine given with combined Haemophilus influenzae type b conjugate/hepatitis B vaccines and combined diphtheria-tetanus-acellular pertussis vaccines. *Pediatr Infect Dis J*. 2006;25(4):287-292. doi:10.1097/01.inf.0000207857.10947.1f
  - In this open, multicenter trial, 1915 healthy children ages 12-15 months were randomized into 3 groups: group 1, MMRV, combined Haemophilus influenzae

type b conjugate-hepatitis B vaccines (Hib/HepB) and combined diphtheria-tetanus-acellular pertussis vaccines (DTaP) concomitantly; group 2, MMRV followed by Hib/HepB and DTaP 42 days later; group 3, MMR and varicella vaccine followed by Hib/HepB and DTaP 42 days later.

- Antibody responses to measles, mumps, rubella, varicella, Hib, HepB, diphtheria and tetanus were similar between groups 1 and 2 (all >95%, except varicella, 89.7% in group 1 and 90.9% in group 2). Pertussis toxin and filamentous hemagglutinin responses were significantly lower in group 1 than in group 2 (group 1, 74.1 and 67.1%; group 2, 90.4 and 86.8%, respectively). An exploratory analysis suggested that the difference in pertussis toxin and filamentous hemagglutinin responses was likely the result of study design rather than interference among vaccine components because the groups differed in age of receipt of DTaP (group 1, approximately 12 months; group 2, approximately 13.5 months). When the groups were matched for age, sample size was sufficient for comparison only in children > or =13.5 months old. Pertussis toxin and filamentous hemagglutinin responses were similar in these children. **The safety profiles for each vaccination regimen were comparable.**
- Concomitant administration of MMRV, Hib/HepB and DTaP is well-tolerated.

- Leonardi M, Bromberg K, Baxter R, et al. Immunogenicity and safety of MMRV and PCV-7 administered concomitantly in healthy children. *Pediatrics*. 2011;128(6):e1387-e1394. doi:10.1542/peds.2010-2132
  - Healthy 12- to 15-month-old children who lacked vaccination and clinical histories for measles, mumps, rubella, varicella, and zoster but had written documentation of receipt of a 3-dose primary series of PCV-7 were randomly assigned in a 2:1:1 ratio to receive either the MMRV and PCV-7 (group 1), PCV-7 followed 6 weeks later by MMRV (group 2), or MMRV followed 6 weeks later by PCV-7 (group 3). The primary safety analysis was 56 days (28 days after each visit). Immunogenicity was evaluated 6 weeks after each vaccination.
  - A total of 1027 children were enrolled (group 1: 510; group 2: 258; group 3: 259). For all 3 groups, the antibody response rate was ≥96.8% for measles, mumps, and rubella, ≥88.0% for varicella-zoster virus, and ≥98.3% for all of the 7 Streptococcus pneumoniae serotypes. The immune responses to all antigens present in MMRV and PCV-7 were similar whether administered concomitantly or sequentially. **The incidence of local and systemic adverse experiences (AEs) was comparable between group 1 and groups 2 and 3 combined. No vaccine-related serious AEs were reported.**
  - Concomitant administration of the MMRV and PCV-7 is highly immunogenic and **generally well tolerated**. Similar immune responses between the groups support concomitant administration of the MMRV and PCV-7 to healthy children 12 to 15 months of age.

- Klein NP, Shepard J, Bedell L, Odrljin T, Dull P. Immunogenicity and safety of a quadrivalent meningococcal conjugate vaccine administered concomitantly with measles, mumps, rubella, varicella vaccine in healthy toddlers. *Vaccine*. 2012;30(26):3929-3936. doi:10.1016/j.vaccine.2012.03.080
    - Should be noted that for this study, because of a shortage of ProQuad during part of the study, MMR+V was used. When "MMRV" is used in this paper, it includes subjects vaccinated with MMRV *or* MMR+V.
    - Two age groups were concurrently enrolled: 7- to 9-month-old infants who received 2 doses of MenACWY-CRM at 7-9 and 12 months and were randomized 1:1 to receive MenACWY-CRM with or without MMRV at 12 months, and 12-month-old infants who received MMRV only at 12 months. Using predefined non-inferiority criteria, immune responses to the antigens in MMRV were compared between those who did and did not receive MenACWY-CRM; immune responses to MenACWY-CRM as measured by the percentage of subjects with human serum bactericidal activity (hSBA) titers ≥ 8, were compared between those who did and did not receive concomitant MMRV. Adequacy of the immune response to 2 doses of MenACWY-CRM administered at 7-9 and 12 months was also assessed. Local and systemic reactions, adverse events resulting in withdrawal or requiring medical attention and serious adverse events were monitored.
    - Concomitant administration of MMRV with MenACWY-CRM did not affect the immune response to either vaccine. The 2-dose series of MenACWY-CRM induced adequate immune response to all 4 serogroups. **No increased reactogenicity was observed with MenACWY-CRM+MMRV compared with MMRV alone, and there were no study-related serious adverse events.**
    - Concomitant administration of MenACWY-CRM with MMRV vaccinations at 12 months was well-tolerated, without safety concerns. Robust immune responses to all components of both vaccines were produced and all criteria for non-inferiority were met, supporting the use of a 2-dose regimen of MenACWY-CRM in this age group.