# Timeliness of Childhood Vaccination With the Combination Measles-Mumps-Rubella-Varicella Vaccine vs the Separate Measles-Mumps-Rubella and Varicella Vaccines in the United States

Lara J. Wolfson[1]; Shikha Surati[1]; Elizabeth Richardson[2]; Se Li[1]; Barbara J. Kuter[2]; Zhiwen Liu[1]

[1]Center for Observational and Real-World Evidence; [2]Global Vaccines Medical Affairs, Merck & Co., Inc., Kenilworth, NJ, USA

## BACKGROUND

- Vaccination is a cost-effective public health intervention and can reduce morbidity and mortality associated with infectious diseases, especially in children[1]
- Vaccine refusals, postponements, and delays have been increasingly reported,[2] which has led to variation in vaccine coverage rates and in some cases, epidemic outbreaks
  - Vaccine refusal is defined as refusing to use one or more vaccines
  - Vaccine postponement is defined as acceptance of the vaccine, but deferring to a later visit
  - Vaccine delay (of which vaccine postponement can be a subset) is when a vaccine is received outside of the recommended time frame
- Studies have shown that vaccination rates cannot be solely improved by increasing the number of vaccines during one visit.[3] Parents and healthcare providers have raised concerns about the increased number of injections a child receives per visit.[3] Grouping several antigens into one shot or combination vaccines may be an effective way to increase vaccination rates[1,4]
- A combination measles-mumps-rubella-varicella (MMRV) vaccine was first licensed for use in the United States in 2005.[5] The Advisory Committee on Immunization Practices (ACIP) originally recommended in 2006 that all children receive 2 doses of measles-mumps-rubella (MMR) and varicella (V) vaccines on the same schedule, with the 1st dose at 12-15 months and 2nd dose at 4-6 years, and that MMRV vaccine could be used for each dose[6]
- Post-licensure studies suggested a small increased rate of febrile seizures when MMRV was used as the 1st dose when compared with MMR+V. In 2009, the ACIP revised its guidance to recommend separate injections of MMR+V for the 1st dose unless the parent or caregiver expressed a preference for MMRV[7]

## OBJECTIVE

To evaluate patterns of coverage and product utilization for measles, mumps, rubella, and varicella containing vaccines between 2006-2016.

## METHODS

### Study Design

- This was a retrospective study of health insurance claims data in the MarketScan® Commercial Claims and Encounters Database from 2006-2016. The population was limited to children who are privately insured
- Two cohorts were defined:
  1. Children eligible for vaccination and with continuous enrollment during ages 12-23 months (the "first dose" cohort)
  2. Children eligible for vaccination and with continuous enrollment during ages ≥4 years through 6 years (the "second dose" cohort)
- The type of vaccine and the date of administration were assessed using Current Procedural Terminology (CPT) codes:
  - MMR (M-M-R-II): 90707
  - MMRV (ProQuad®): 90710
  - Varicella (Varivax®): 90716

### Outcome Measures

- Timely vaccine coverage, defined as
  - First dose by age 19 months
  - Second dose by 7th birthday
- Percent of each cohort with postponements of vaccine doses, defined as the interval between the MMR (measles-mumps-rubella) and V (varicella) vaccines, when not given as a combination
- Length of vaccine postponement in each cohort

## RESULTS

- The analysis included 850,779 and 1,403,139 children in the 1st and 2nd dose cohorts, respectively

**Table 1. Baseline Characteristics (number, %)**

| | First Dose Cohort (N=850,779) | Second Dose Cohort (N=1,403,139) |
|---|---|---|
| **Gender** | | |
| Male | 436,963 (51.4) | 717,139 (51.1) |
| Female | 413,816 (48.6) | 686,000 (48.9) |
| **Year of birth** | | |
| 2001 | — | 144,327 (10.3) |
| 2002 | — | 147,925 (10.5) |
| 2003 | — | 140,017 (10.0) |
| 2004 | — | 160,424 (11.4) |
| 2005 | — | 199,953 (14.3) |
| 2006 | 88,153 (10.4) | 185,086 (13.2) |
| 2007 | 94,408 (11.1) | 170,415 (12.1) |
| 2008 | 82,105 (9.7) | 141,456 (10.1) |
| 2009 | 97,798 (11.5) | 113,536 (8.1) |
| 2010 | 108,530 (12.8) | — |
| 2011 | 97,963 (11.5) | — |
| 2012 | 104,449 (12.3) | — |
| 2013 | 89,342 (10.5) | — |
| 2014 | 87,866 (10.3) | — |
| 2015 | 165 (0.0) | — |
| **Region of residence** | | |
| Northeast | 138,776 (16.3) | 196,179 (14.0) |
| North Central | 250,795 (29.5) | 348,996 (24.9) |
| South | 331,992 (39.0) | 561,687 (40.0) |
| West | 123,638 (14.5) | 277,000 (19.7) |
| Other | 5,578 (0.7) | 19,277 (1.4) |
| Unknown | 14,077 (1.7) | 17,834 (1.3) |
| **Health plan type** | | |
| Comprehensive | 7,719 (0.9) | 14,914 (1.1) |
| Exclusive provider organization (EPO) | 15,501 (1.8) | 14,552 (1.0) |
| Health maintenance organization (HMO) | 98,892 (11.6) | 205,075 (14.6) |
| Point-of-service (POS) | 71,549 (8.4) | 97,975 (7.0) |
| Preferred provider organization (PPO) | 527,601 (62.0) | 867,255 (61.8) |
| Point-of-service (POS) with capitation | 3,650 (0.4) | 8,783 (0.6) |
| Consumer directed health plan (CDHP) | 67,185 (7.9) | 103,618 (7.4) |
| High deductible health plan (HDHP) | 44,605 (5.2) | 73,133 (5.2) |

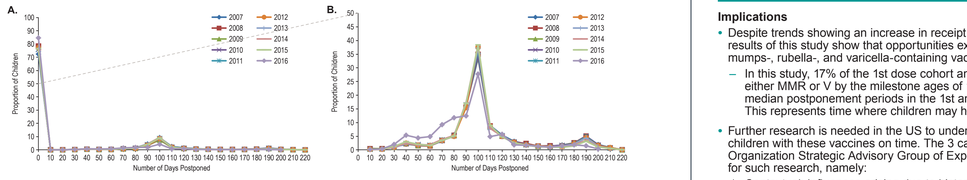
- Of the children in each dose cohort (1st/2nd), 7%/14% received MMRV vaccine, 77%/62% received MMR and/or V, and 17%/24% had no records of receiving any of the vaccines by the milestone age (**Table 2**)
- Of those receiving MMR and/or V vaccines, 9%/21% were missing one of the two vaccines, 70%/65% had both on the same day, and 21%/14% received them on different days with median postponements of 3 months/1 year (1st/2nd dose, respectively)

**Table 2. Timeliness and Delays of Administration of MMRV, MMR, and V (Varicella) Vaccines**

| | First Dose Cohort (N=850,779) | Second Dose Cohort (N=1,403,139) |
|---|---|---|
| **Timely vaccination[a]** | | |
| No MMRV, MMR, or V vaccine administered | 16.6% (16.5%, 16.7%) | 24.4% (24.3%, 24.5%) |
| Received MMRV | 6.7% (6.6%, 6.7%) | 13.8% (13.7%, 13.8%) |
| Received MMR and/or V | 76.7% (76.6%, 76.8%) | 61.7% (61.6%, 61.8%) |
| **Children with postponement of MMR and/or V doses** | | |
| Missing one vaccine | 8.9% (8.8%, 9.0%) | 21.1% (21.0%, 21.2%) |
| Received MMR & V vaccines on same day | 69.7% (69.6%, 69.8%) | 65.3% (65.2%, 65.4%) |
| Received MMR & V vaccines on different days | 21.4% (21.3%, 21.5%) | 13.6% (13.5%, 13.7%) |
| **Length of postponement** | | |
| Median postponement | 3 months/90 days | 1 year/365 days |

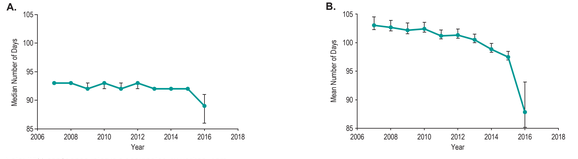
[a]Percent of children receiving the MMRV, MMR, and/or V vaccines by the milestone age (19 months for the first dose cohort and 7 years for the second dose cohort).

**Figure 1. Proportion of Children in the First Dose Cohort by the Number of Days Postponement Between Receiving the MMR and V Vaccines for (A) All Vaccinees and (B) Postponed Vaccinees Only[a]**



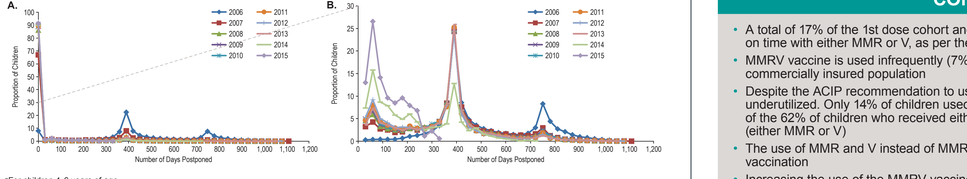

[a]For children 12-18 months of age.

**Figure 2. Time Interval Between the MMR and V Vaccinations for Children in the First Dose Cohort Who Received the Two Vaccines at Different Dates Between 12-18 Months of Age: (A) Median and (B) Mean Days**



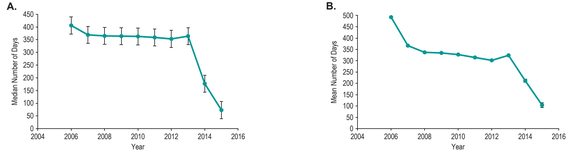

Note: 95% confidence intervals designated by vertical bars.

**Figure 3. Proportion of Children in the Second Dose Cohort by the Number of Days Postponement Between Receiving the MMR and V Vaccines for (A) All Vaccinees and (B) Postponed Vaccinees Only[a]**




[a]For children 4-6 years of age.

**Figure 4. Time Interval Between the MMR and V Vaccinations for Children in the Second Dose Cohort Who Received the Two Vaccines at Different Dates Between 4 and 6 Years of Age: (A) Median and (B) Mean Days**




## DISCUSSION

### Implications

- Despite trends showing an increase in receipt of MMR and V vaccines from 2006-2016 in the US,[8] the results of this study show that opportunities exist to improve timely vaccine administration of measles-, mumps-, rubella-, and varicella-containing vaccines in the US
  - In this study, 17% of the 1st dose cohort and 24% of the 2nd dose cohort were not vaccinated with either MMR or V by the milestone ages of 19 months and 7 years, respectively. Furthermore, the median postponement periods in the 1st and 2nd dose cohorts were 3 months and 1 year, respectively. This represents time where children may have been under-vaccinated and potentially unprotected
- Further research is needed in the US to understand the reasons why parents are not vaccinating their children with these vaccines on time. The 3 categories of vaccine hesitancy identified by the World Health Organization Strategic Advisory Group of Experts on Immunization (SAGE)[9] may be a useful framework for such research, namely:
  1. Contextual: Influences arising due to historic, socio-cultural, environmental, health system/institutional, economic, or political factors
  2. Individuals and group: Influences arising from personal perception of the vaccine or influences of the social/peer environment
  3. Vaccine-/vaccination-specific influences: Directly related to vaccine or vaccination

### Limitations

- The individuals identified in the claims database were from a population of privately insured individuals and therefore, these results may not be generalizable to populations that differ from those in the database
- Several limitations inherent to administrative claims data apply to this study:
  1. Vaccines that were not submitted for insurance reimbursement or received outside the network were not captured
  2. Vaccine administration was based on CPT codes rather than on medical chart review, so there was the potential for misclassification of vaccine doses
  3. We imputed the date of birth using ICD-9 codes for live births, which might lead to inaccuracies. However, this method has been validated in a previous study and misclassification of birth date is unlikely to be correlated with individual vaccination status[10]

## CONCLUSIONS

- A total of 17% of the 1st dose cohort and 24% of the 2nd dose cohort were not vaccinated on time with either MMR or V, as per the ACIP vaccination recommendations
- MMRV vaccine is used infrequently (7% of vaccinees) as the 1st dose vaccine in this commercially insured population
- Despite the ACIP recommendation to use MMRV for the 2nd dose, this vaccine is underutilized. Only 14% of children used the MMRV for the 2nd dose. Furthermore, 21% of the 62% of children who received either the MMR or V vaccine were missing one dose (either MMR or V)
- The use of MMR and V instead of MMRV may result in postponed or missed 2nd dose vaccination
- Increasing the use of the MMRV vaccine for the second dose between 4-6 years of age has the potential to improve vaccine compliance and coverage and to reduce the number of physician office visits
- For both 1st and 2nd doses, there is a noticeable reduction in the postponement between vaccine doses in more recent years

**References**

1. Kurosky SK, et al. *Vaccine.* 2016;34(3):387-394.
2. Larson HJ, et al. *Vaccine.* 2014;32(19):2150-2159.
3. Maman K, et al. *Hum Vaccin Immunother.* 2015;11(9):2132-2141.
4. Marshall GS, et al. *Pediatr Infect Dis J.* 2007;26(6):496-500.
5. Merck & Co., Inc. ProQuad® Prescribing Information. July 2018.
6. Marin M, et al. *MMWR Recomm Rep.* 2010;59(RR-3);1-12.
7. Robinson CL, et al. *MMWR Morb Mortal Wkly Rep.* 2016;67(5):156-157.
8. Centers for Disease Control and Prevention. Evaluating Vaccination Coverage Trends with the National Immunization Survey (NIS)-Child, 2012-2016, United States. November 1, 2017. Available at: https://www.cdc.gov/vaccines/imz-managers/coverage/childvaxview/pubs-presentations/NIS-vax-trends-2012-2016.html. Accessed March 1, 2018.
9. WHO Strategic Advisory Group of Experts on Immunization. Report of the SAGE Working Group on Vaccine Hesitancy. Available at: http://www.who.int/immunization/sage/meetings/2014/october/SAGE_working_group_revised_report_vaccine_hesitancy.pdf?ua=1. Accessed August 14, 2018.
10. Gebremeskel BG, et al. *J Pediatric Infect Dis Soc.* 2016;5(4):473-475.

https://bit.ly/2o5IVZh

Presented at IDWeek 2018; San Francisco, CA, USA; October 3-7, 2018.