Evaluation of Combination Measles-Mumps-Rubella-Varicella Vaccine Introduction in Australia

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IMPORTANCE Incorporating combination vaccines, such as the measles-mumps-rubella-varicella (MMRV) vaccine, into immunization schedules should be evaluated from a benefit-risk perspective. Use of MMRV vaccine poses challenges due to a recognized increased risk of febrile seizures (FSs) when used as the first dose in the second year of life. Conversely, completion by age 2 years of measles, mumps, rubella, and varicella immunization may offer improved disease control.

OBJECTIVE To evaluate the effect on safety and coverage of earlier (age 18 months) scheduling of MMRV vaccine as the second dose of measles-containing vaccine (MCV) in Australia.

DESIGN, SETTING, AND PARTICIPANTS Prospective active sentinel safety surveillance comparing the relative incidence (RI) of FSs in toddlers given MMRV and measles-mumps-rubella (MMR) and a national cohort study of vaccine coverage rates and timeliness before and after MMRV vaccine introduction were conducted. All Australian children aged 11 to 72 months were included in the coverage analysis, and 1471 Australian children aged 11 to 59 months were included in the FS analysis, with a focus on those aged 11 to 23 months.

MAIN OUTCOMES AND MEASURES MMRV vaccine safety, specifically, the RI of FSs after MMRV vaccine at age 18 months, compared with risk following MMR vaccine and vaccine uptake for 2-dose MCV and single-dose varicella vaccine, focusing on timeliness.

RESULTS Of the 1471 children, the median age at first FS was 21 months (interquartile range [IQR], 14-31 months). Three hundred ninety-one children were aged 11 to 23 months and had at least 1 FS included in the analysis; of these, 207 (52.9%) were male. A total of 278 children (71.1%) had received MMR followed by MMRV vaccine, 97 (24.8%) had received MMR vaccine only, and 16 (4.1%) had received neither vaccine. There was no increased risk of FSs (RI, 1.08; 95% CI, 0.55-2.13) in the 5 to 12 days following MMRV vaccine given as the second MCV to toddlers. Febrile seizures occurred after dose 1 of MMR vaccine at a known low increased risk (RI, 2.71; 95% CI, 1.71-4.29). Following program implementation, 2-dose MCV coverage at age 36 months exceeded that obtained at age 60 months in historical cohorts recommended to receive MMR vaccine before school entry, and on-time vaccination increased by 13.5% (from 58.9% to 72.4%). Despite no change in the scheduled age of varicella vaccine, use of MMRV vaccine was associated with a 4.0% increase in 1-dose varicella vaccine coverage.

CONCLUSIONS AND RELEVANCE To our knowledge, this is the first study to provide evidence of the absence of an association between use of MMRV vaccine as the second dose of MCV in toddlers and an increased risk of FSs. Incorporation of MMRV vaccine has facilitated improvements in vaccine coverage that will potentially improve disease control.
S

ome parents and health care workers are finding decision making regarding immunization increasingly complex, presenting a barrier to timely vaccine uptake.1,2 A commonly reported concern is the number of injections given to children.1,2 Combination vaccines reduce the number of injections needed and may improve vaccine acceptance, coverage, and, ultimately, disease control. However, various other factors surrounding use of combination vaccines, including cost-effectiveness, safety, availability, and country- or region-specific disease epidemiology, require consideration.3 In the past decade, several countries have faced challenges in incorporating the combination measles-mumps-rubella-varicella (MMRV) vaccine into their immunization schedules. Although both available MMRV vaccines (Priorix-Tetra [GlaxoSmithKline Biologicals SA] and ProQuad [Merck & Co Inc]) offer the advantage of a single injection against 4 diseases, prelicensure studies showed an increased risk of fever in first-dose recipients aged 12 to 23 months compared with children who received measles-mumps-rubella (MMR) and varicella vaccines separately.4,5 This reaction was presumed to be related to potentiation of the immune response to the measles virus component. Postlicensure studies subsequently reported an approximately 2-fold increased risk of febrile seizures (FSs) following MMRV compared with giving separate MMR and varicella vaccines.6,7 This finding prompted a withdrawal of a preferential recommendation for use of MMRV as the first measles-containing vaccine (MCV) in the United States and Germany.8,9

Before July 2013, MMRV vaccine was not used in Australia. Two doses of MMR vaccine were scheduled on the National Immunisation Program (NIP) and spaced 3 years apart at ages 12 months and 4 years, similar to the US and UK schedules. However, data from the national Australian Childhood Immunisation Register (ACIR) in 2012 showed that vaccine uptake was suboptimal; approximately 92% of children had received 2 MCVs by age 5 years,10 and modeling demonstrated an increased risk of measles outbreaks associated with low 2-dose immunity in younger children. Disease outbreaks arising from measles importations11,12 demonstrated the need to improve 2-dose coverage at all ages, but especially in the young. A single dose of monovalent varicella vaccine had been scheduled under NIP at age 18 months since November 2005,13 but coverage by age 2 years was only 86%, although it increased to 92% by 5 years. Declines in varicella-related morbidity and mortality had occurred,14-17 but modeling18 suggested that improved 1-dose coverage was needed to decrease the risk of shifting disease to older age groups where higher disease severity occurs.

To address these challenges, the decision was made to include MMRV vaccine on the Australian NIP at age 18 months as the second MCV dose from July 2013 onward, as reported in Table 1. The risk-benefit assessment that underpinned this change was based on 2 hypotheses: (1) higher and earlier population-level vaccine coverage of 2 doses of MCV and 1 dose of varicella vaccine would be achieved by bringing forward the scheduled age for the second MCV dose to 18 months and replacing MMR with MMRV vaccine, and (2) when used as the second instead of the first dose of MCV, MMRV vaccine would not be associated with an increased risk of FSs, even though it would be provided to children aged 18 months, when the incidence of FSs peaks. The vaccine safety and evaluation plan for MMRV vaccine introduction included active, prospective sentinel FS surveillance using the Paediatric Active Enhanced Disease Surveillance (PAEDS) network19,20 and analysis of vaccine uptake using the ACIR. We aim to present the findings of this evaluation, examining the effect of the program change on (1) vaccine safety, specifically, the risk of MCV-associated FS and (2) vaccine uptake and timeliness.

### Key Points

#### Question
What is the effect of introduction of combination measles-mumps-rubella-varicella vaccine at age 18 months as the second dose of measles-containing vaccine on vaccine coverage and risk of vaccine-associated febrile seizures in Australia?

#### Findings
A national cohort study of vaccine coverage before and after measles-mumps-rubella-varicella vaccine introduction showed improvement in uptake and timeliness for all 4 vaccine components. Despite the peak incidence of all-cause febrile seizures occurring at age 18 months and a known increased risk of febrile seizures following the first dose, in a self-controlled case series analysis including 1471 children, use of measles-mumps-rubella-varicella vaccine at 18 months was not associated with an increased risk of febrile seizures.

#### Meaning
Measles-mumps-rubella-varicella combination vaccine was safely incorporated into the Australian National Immunisation Program schedule and improved population-level protection against these serious viral diseases.

### Methods

#### Febrile Seizure Risk Associated With Measles- and Varicella-Containing Vaccine Exposure

#### Data Sources
Active, prospective sentinel FS surveillance was conducted from May 1, 2013 (2 months before MMRV vaccine introduction), to June 30, 2014, by the PAEDS Network at 5 Australian tertiary pediatric hospitals, as previously described.19,21 At each site, emergency department and inpatient databases were scanned daily by PAEDS surveillance nurses to ascertain possible FS presentations in all children younger than 5 years. Periodic review of all International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification–coded FS encounters (code R56.0) was also conducted to capture additional cases. Clinical and demographic data were collected from the medical records and caregiver interviews, and all FS diagnoses were confirmed. All children had immunization records obtained from the ACIR, both at FS presentation and at study end (to identify all vaccine exposures).

#### Study Population and Exclusion Criteria
In Australia, the timing of vaccine administration is highly associated with NIP-recommended schedule points. Therefore, our analysis cohort was restricted to children who were...
Results

Risk of FSs Following MMRV and MMR Vaccines

During the study analysis period, 1668 unique FS episodes were identified in 1471 children younger than 5 years. Of these children, 1335 (90.8%) had only 1 episode and 136 (9.2%) had 2 or more episodes separated by at least 7 days. The median age at the time of the first FS was 21 months (interquartile range [IQR], 14–31 months), similar to the median age at receipt of MMRV vaccine in 18 months (IQR, 18–19 months) and the peak age at FSs shown previously. After restriction to age 11 to 23 months and the recommended vaccine sequence, there were 465 FS episodes in 391 children. Ten children with 12 FSs (10 of 401 cases [2.4%]) were excluded because the recommended schedule was not followed (only 4 had MMRV as dose 1, which was an insufficient sample to analyze FS risk). Of the 391 children included, 278 (71.1%) had received MMR followed by MMRV vaccine, 97 (24.8%) had received MMR vaccine only, and

The primary analysis included children who had both first and subsequent FS episodes (considered unique episodes), in which the subsequent FS was separated by at least 7 days from a previous episode. Two sensitivity analyses were conducted: (1) adjustment for age using finer intervals (1-month age groups) and (2) restriction of the analysis to first FS episodes.

Measles- and Varicella-Containing Vaccine Uptake

Data Sources

The ACIR is a nearly complete electronic population register. It includes approximately 99% of all children registered with the national public health insurance scheme, Medicare, that covers all citizens, permanent residents, and select visa holders. During the study period, the ACIR recorded receipt of all vaccines provided up to age 7 years. Doses recorded on the ACIR (renamed the Australian Immunisation Register [AIR] from November 2016 and including all aged persons) are linked to financial incentives for families and health care professionals, providing a basis for complete reporting.

Study Population and Outcome

The study outcome was immunization coverage of consecutive, 3-month national cohorts of children born between January 1, 2009, and December 31, 2012, who had reached the ages of 24, 36, 48, and 72 months, respectively, for receipt of MMR, varicella, and/or MMRV vaccine by December 2015 (Table 1).

Statistical Analysis

Coverage estimates for receipt of a second MCV dose and single varicella vaccine dose, either on time (within 30 days of the recommended age) or at scheduled assessments dates, were compared between the pre-MMRV and post-MMRV periods. Data were analyzed in SAS, version 9.3 (SAS Institute Inc); Stata, version 12 (StataCorp); and Excel 2007 (Microsoft Corp).

Ethical Approval

Each PAEDS hospital obtained ethical approval to conduct the FS safety study: Sydney Children’s Hospital Network Human Research Ethics Committee; Princess Margaret Hospital Human Research Ethics Committee; Women’s and Children’s Hospital Network Human Research Ethics Committee; QLD Children’s Health Services (Royal Children’s Hospital) Human Research Ethics Committee; and the Royal Children’s Hospital Human Research Ethics Committee (Melbourne). Specific ethics approval was not required for vaccine coverage analysis, as we conducted our study using deidentified ACIR data supplied by the Australian Government Department of Human Services for the purposes of program evaluation.

Study Outcomes

The main study outcome was the RI of FS in the 5 to 12 days after the first and second MCV doses compared with nonrisk periods (baseline) within the same person. An additional risk period of 13 to 30 days after each MCV was also included to identify any longer-term risk.

Statistical Analysis

Relative incidences were calculated using the self-controlled case series (SCCS) method of analysis. The SCCS method requires FS cases only and compares the FS rate during biologically plausible, predetermined risk periods with nonrisk periods (baseline) within the same person using conditional Poisson regression models; thus, all fixed confounders (eg, sex) are automatically adjusted for. Because age is a strong predictor of FS and is time varying, all models were adjusted for the effect of age (using 3 age groupings in the base case: 11-14, 15-18, and 19-23 months). We removed the −1 to −13-day period before vaccination from the baseline time because it may be associated with a lower FS risk (an FS occurrence may delay receipt of scheduled vaccines).

The primary analysis included children who had both first and subsequent FS episodes (considered unique episodes), in which the subsequent FS was separated by at least 7 days from a previous episode. Two sensitivity analyses were conducted: (1) adjustment for age using finer intervals (1-month age groups) and (2) restriction of the analysis to first FS episodes.
16 (4.1%) had received neither vaccine. Further data are provided in Table 2.

Table 3 provides the results of the primary and sensitivity self-controlled case series analyses. In the primary analysis, which adjusted for age using 3 age groups, there was no significantly increased risk of FSs within the 5- to 12-day risk period following MMRV, the prevaccination period, or the 13- to 30-day postvaccination period. The RI of FSs was raised in the 5 to 12 days following MMRV, the prevaccination period, or the 13- to 30-day postvaccination period. The results of the sensitivity analyses were similar to those of the primary analyses.

Changes in Measles- and Varicella-Containing Vaccine Uptake
As reported in Table 4, within 2.5 years following MMRV introduction, 2-dose MCV coverage increased to 93.8% at age 36 months, which exceeded the most recent preprogram historical coverage level of 92% at age 60 months (1 year after the previous age 48-month schedule point). Coverage with varicella-containing vaccine, consistently recommended at 18 months and assessed at age 24 months, increased by 4% after the change (Table 4). Overall, on-time immunization with the second MCV (defined as vaccine receipt within 30 days of the recommended age) improved by 13.5% (from 58.9% to 72.4%) (Figure). During this time, there was virtually no change in the coverage of MMR dose 1 (recommended at age 12 months and measured at age 18 months), which increased by only 0.5% (Table 4).

Discussion
We present a comprehensive evaluation of the effect of 2 simultaneous changes to the Australian NIP that are relevant

Table 2. Characteristics of Febrile Seizures in 391 Children Aged 11 to 23 Months in SCCS Analysis

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Febrile Seizure</th>
<th>First Episode</th>
<th>Unique Episodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Febrile seizures, No.</td>
<td>391</td>
<td>465</td>
<td></td>
</tr>
<tr>
<td>Male, No. (%)</td>
<td>207 (52.9)</td>
<td>249 (53.5)</td>
<td></td>
</tr>
<tr>
<td>No MCV, No. (%)</td>
<td>16 (4.1)</td>
<td>22 (4.7)</td>
<td></td>
</tr>
<tr>
<td>MMR during risk period, No. (%)a</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>23 (6.1)</td>
<td>24 (5.4)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>352 (93.9)</td>
<td>419 (94.6)</td>
<td></td>
</tr>
<tr>
<td>MMRV during risk period, No. (%)b</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>7 (2.5)</td>
<td>9 (2.7)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>271 (97.5)</td>
<td>319 (97.3)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: MCV, measles-containing vaccine; MMR, measles-mumps-rubella; MMRV, measles-mumps-rubella-varicella; SCCS, self-controlled case series.

a Vaccinated between 5 and 12 days before febrile seizure; percentage denotes total children receiving each vaccine.
b Includes only children who received a previous MMR vaccine.

Table 3. FS Risk Following Dose 1 of MMR and a Subsequent Dose of MMRV in Young Children

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Method for Age Control</th>
<th>FS Episode</th>
<th>Vaccine</th>
<th>RI 1 to 13 d (95% CI)</th>
<th>P Value</th>
<th>RI 5 to 12 d (95% CI)</th>
<th>P Value</th>
<th>RI 13 to 30 d (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>11-14, 15-18, and 19-23 mo</td>
<td>Uniquea</td>
<td>MMR</td>
<td>0.41 (0.18-0.94)</td>
<td>.04</td>
<td>2.71 (1.71-4.29)</td>
<td>&lt;.001</td>
<td>0.89 (0.54-1.48)</td>
<td>.66</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>MMRV</td>
<td>1.26 (0.77-2.07)</td>
<td>.36</td>
<td>1.08 (0.55-2.13)</td>
<td>.82</td>
<td>1.08 (0.67-1.74)</td>
<td>.74</td>
</tr>
<tr>
<td>Secondary</td>
<td>1-mo intervals</td>
<td>Uniquea</td>
<td>MMR</td>
<td>0.42 (0.18-0.97)</td>
<td>.04</td>
<td>2.57 (1.56-4.23)</td>
<td>&lt;.001</td>
<td>0.83 (0.49-1.40)</td>
<td>.48</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>MMRV</td>
<td>1.25 (0.74-2.14)</td>
<td>.40</td>
<td>1.17 (0.57-2.40)</td>
<td>.67</td>
<td>1.10 (0.66-1.83)</td>
<td>.72</td>
</tr>
<tr>
<td></td>
<td>11-14, 15-18, and 19-23 mo</td>
<td>First</td>
<td>MMR</td>
<td>0.37 (0.15-0.92)</td>
<td>.03</td>
<td>2.85 (1.78-4.56)</td>
<td>&lt;.001</td>
<td>0.82 (0.47-1.43)</td>
<td>.48</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>MMRV</td>
<td>1.37 (0.81-2.33)</td>
<td>.24</td>
<td>1.06 (0.49-2.27)</td>
<td>.89</td>
<td>1.21 (0.73-2.01)</td>
<td>.73</td>
</tr>
</tbody>
</table>

Abbreviations: FS, febrile seizure; MMR, measles-mumps-rubella; MMRV, measles-mumps-rubella-varicella; RI, relative incidence.

a First FS episode or multiple FS episodes, with the episodes separated by at least 7 days.

Table 4. One-Dose Varicella Vaccine and 2-Dose MCV Coverage Assessed at Ages Before and After MMRV Vaccine Introduction

<table>
<thead>
<tr>
<th>Timing</th>
<th>Vaccine Antigen and Age Assessed</th>
<th>MMR or MMRV</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Varicella</td>
<td>MMR or MMRV</td>
</tr>
<tr>
<td></td>
<td>24 moa</td>
<td>36 moa</td>
</tr>
<tr>
<td>Before MMRV vaccine introduction</td>
<td>85.9a</td>
<td>89.3a</td>
</tr>
<tr>
<td>After MMRV vaccine introduction</td>
<td>89.9b</td>
<td>93.3b</td>
</tr>
</tbody>
</table>

Abbreviations: MCV, measles-containing vaccine; MMR, measles-mumps-rubella; MMRV, measles-mumps-rubella-varicella; NA, not applicable; NC, not calculated (due to cohort not yet reaching this age).

a Only dose, provided as monovalent varicella vaccine before program change and as MMRV vaccine after program change.
b First dose provided as MMRV vaccine at age 12 months throughout the study period and assessed at age 18 months for all cohorts combined.
c The second dose of MCV was MMRV vaccine before program change and MMRV vaccine after program change.
d Cohort born January 1 to June 30, 2011.
e Cohort born January 1 to June 30, 2010.
f Cohort born January 1 to June 30, 2009.
g Cohort born January 1 to June 30, 2008.
h Cohort born July 1 to December 3, 2012.
Each country needs to assess its own unique disease epidemiology, immunization program characteristics, and barriers to vaccine uptake to determine the optimal timing of MCV doses. However, for children in whom vaccination is delayed whether due to missed opportunities, access issues, or vaccine hesitancy, earlier scheduled measles vaccination offers more opportunities to provide catch-up vaccination, particularly before school entry. One potential downside of earlier second-dose vaccination is the potential for waning immunity.

Modeling the effect of this schedule change on population immunity to measles in Australia was sensitive to assumptions regarding the extent of waning of vaccine-derived immunity. Waning immunity may also be an issue for the less-efficacious mumps component of the vaccine; ongoing disease surveillance will be important to monitor for this potential outcome and, if needed, adjust policy recommendations accordingly. However, several European countries, Canadian provinces, and low- to middle-income countries under the Expanded Program on Immunization use a similarly compressed MCV schedule.

Australia has had a 1-dose varicella vaccination program for children aged 18 months since late 2005. We show that MMRV introduction has rapidly been associated with improvements in the absolute level and timeliness of coverage against varicella over that achieved with the single-antigen vaccine. While our study design cannot confirm a direct cause-and-effect relationship, reasons for this increase in coverage may include (1) reduced prior attendance at the 18-month schedule point due to parental (and clinician) perceptions of varicella as a mild disease for which an appointment for the immunization was not considered sufficiently important (no other vaccine was recommended at this schedule point between 2003 and 2016); (2) increased encouragement for children to attend the 18-month immunization visit due to the inclusion of other antigens, particularly measles, in the vaccine; and/or (3) reduction of the overall number of scheduled injections, which was appealing to caregivers and clinicians. Although a routine 2-dose varicella immunization schedule, as adopted in the United States in 2007, would offer improved protection against varicella, the addition of a second varicella dose was previously rejected for NIP inclusion in Australia on the basis of inadequate incremental cost-effectiveness.

To our knowledge, this study is the first to demonstrate that administration of MMRV vaccine as dose 2 of the MCV at age 18 months is not associated with an increased risk of FSs despite peak FS incidence at this age. A US assessment showed no increased FS risk when MMRV dose 2 was given at age 4 to 6 years; however, overall FS incidence is much lower in that age group. These results are also consistent with those of the previous PAEDS study showing no increased risk of FSs after monovalent varicella vaccine at age 18 months and confirming the well-described fold increase in FSs after MCV dose 1. Six postmarketing studies and a meta-analysis have consistently shown a 2-fold increase in FS risk in the risk window of approximately 5 to 12 days after MCV dose 1 in toddlers compared with giving MMR or MMR and the varicella vaccine separately. Although this finding equates to a relatively low absolute excess of 4.3 FSs per 10 000 doses, even
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