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.
Some parents and health care workers are finding decision making regarding immunization increasingly complex, presenting a barrier to timely vaccine uptake. A commonly reported concern is the number of injections given to children. 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. 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. 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. 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. 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, and modeling demonstrated an increased risk of measles outbreaks associated with low 2-dose immunity in younger children. Disease outbreaks arising from measles importations 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, 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, but modeling 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) network 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.

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. 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...
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 MMR vaccine of 18 months (IQR, 18-19 months) and the peak age at FSs shown previously.19 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 this schedule was not consistent with NIP recommendations and occurred rarely.

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.

Table 1. Australian NIP Schedule Before and After Introduction of MMRV From July 1, 2013

<table>
<thead>
<tr>
<th>Age</th>
<th>Before July 1, 2013</th>
<th>After July 1, 2013</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 mo</td>
<td>MMR</td>
<td>MMR</td>
</tr>
<tr>
<td>18 mo</td>
<td>Monovalent varicella</td>
<td>MMRV</td>
</tr>
<tr>
<td>48 mo</td>
<td>MMRV</td>
<td>NA</td>
</tr>
</tbody>
</table>

Abbreviations: MMR, measles-mumps-rubella; MMRV, measles-mumps-rubella-varicella; NA, not applicable; NIP, National Immunisation Program.

*This vaccine was no longer routinely available under NIP after July 1, 2013.

To be eligible to receive the free MMRV vaccine from July 1, 2013, a child must be aged 18 months, have received their 12-month MMR vaccine at least 4 weeks before their 18-month monovalent varicella vaccination, as per the previous NIP schedule. The vaccine used during the study was Priorix-Tetra.

Results

Risk of FSs Following MMRV and MMR 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.1,5 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, and there was a significantly lower risk in the 2 weeks before vaccination. 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. (%)</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. (%)</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.

* Vaccinated between 5 and 12 days before febrile seizure; percentage denotes total children receiving each 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>Unique*</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>Unique*</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>Unique*</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>Unique*</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>Secondary</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>First</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.

* 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>
</thead>
<tbody>
<tr>
<td></td>
<td>Varicella</td>
<td></td>
</tr>
<tr>
<td></td>
<td>24 mo*</td>
<td>36 mo*</td>
</tr>
<tr>
<td>Before MMRV vaccine introduction</td>
<td>85.9*</td>
<td>89.3*</td>
</tr>
<tr>
<td>After MMRV vaccine introduction</td>
<td>89.9*</td>
<td>93.3*</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).

* Only dose, provided as monovalent varicella vaccine before program change and as MMRV vaccine after program change.

* First dose provided as MMR vaccine at age 12 months throughout the study period and assessed at age 18 months for all cohorts combined.

* The second dose of MCV was MMR vaccine before program change and MMRV vaccine after program change.

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to child immunization programs worldwide: introduction of combination MMRV vaccine and bringing forward the scheduled age for provision of the second MCV. Our evaluation demonstrates that MMRV vaccine introduction in Australia has been associated with improved coverage and timeliness of protection against all 4 diseases, with on-time vaccination increasing by 13.5%. This change has been made with no effect on the overall safety profile of the program; use of MMRV vaccine as dose 2 of MCV at the age of 18 months was not associated with an increased risk of FSs.

Global efforts to control measles rely on achieving and maintaining high 2-dose vaccine coverage (preferably >95%) at a country and subnational (district) level.25 Australia was 1 of the first 4 countries in the World Health Organization Western Pacific Region to reach measles elimination status, declared in March 2014.26 However, before 2014 and despite an overall reduction in the incidence of measles, notification rates were highest in infants and children aged 1 to 4 years, outbreaks often involved young children, and measles vaccine coverage for 1 and 2 vaccine doses was suboptimal at 92% nationally.27 This figure also masked smaller areas of lower coverage and lack of timely uptake.26 Within 2.5 years of implementing our compressed schedule at ages 12 and 18 months, we have demonstrated that more children were fully protected against measles at an earlier age. In the United States, which has recently experienced a resurgence of measles,29 MCV dose 2 is recommended at ages 4 to 6 years, and uptake of dose 1 at age 12 months could be more timely. The 2014 US National Immunization Survey estimated that 92% of children aged 19 to 35 months had received 1 dose of MMR vaccine (range, 84%-97%).27

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.28 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 2005.13,16 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.16

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.29 A US assessment showed no increased FS risk when MMRV dose 2 was given at age 4 to 6 years;30 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 1.19,29 Six postmarketing studies6,2,31-34 and a meta-analysis35 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,7 even
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Original Investigation Research

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Critical revision of the manuscript for important intellectual content: Macartney, Gidding, Wang, Dey, Hull, Orr, McRae, Richmond, Crawford, Kynaston, McIntyre, Wood.

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Study supervision: Macartney, Gidding, Richmond, Crawford.

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a low risk has been viewed as concerning. In Australia, an unexpected high rate of FSs occurred from 1 seasonal influenza vaccine brand (Fluvax [Afluria in the United States]) in children younger than 5 years in 2010. Although most FS cases resolved without sequelae, permanent neurologic damage occurred in 2 children.36,37 In the United States, primary care clinicians are reported as being unlikely to recommend MMRV,38 and in Germany, there has been a decline in varicella vaccination uptake.9

Limitations and Strengths

This study has a number of limitations and strengths. Although we showed no statistically significant association between FSs and MMRV vaccine, the point estimate was above 1 and CIs were wide (RI, 1.08; 95% CI, 0.55-2.13), thereby not excluding a very low level of risk. In addition, FS case capture was taken from sentinel pediatric hospital surveillance and may not be representative of all Australian children with FSs. However, each site also functions as a community-based hospital, most children resided nearby and had simple FSs, and our analysis was robust in demonstrating the known association with MCV dose 1. Our ecologic cohort design to assess vaccine coverage changes is subject to unrecognized biases or confounding factors and does not prove that the schedule change was the necessary or only causative factor in improving vaccine uptake. However, no other major programmatic or procedural changes occurred during the study period that would otherwise have increased coverage, and, notably, MCV dose 1 uptake did not change substantially over time. In Australia, all NIP vaccines are commonwealth government procured, and our 8 state and territory health departments undertake oversight program delivery, resulting in more prescriptive use of vaccine combinations and brands than in other countries where vaccine choice is influenced by individual immunization clinicians or insurers. Together with our comprehensive national vaccine register, this control enables accurate evaluation of changes in coverage in response to new vaccine introduction. Although our study primarily reports on 1 brand of MMRV vaccine (Priorix-Tetra), based on first principles, we believe that these results would likely be similar for the other registered MMRV vaccine (ProQuad).

Conclusions

Data from this study help clinicians to better understand the link between measles and varicella virus-containing live vaccines and the risk of FSs—a common but serious early childhood condition that occurs in response to fever from any source. We present a comprehensive evaluation of the incorporation of MMRV vaccine into the Australian NIP, demonstrating an association with improved vaccine uptake and timeliness while maintaining overall program safety. Our findings should help to inform childhood immunization policy decision making regarding use of these vaccines in other countries.


