Effect of Age on the Risk of Fever and Seizures Following Immunization With Measles-Containing Vaccines in Children

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IMPORTANCE The first dose of live attenuated measles-containing vaccines is associated with an increased risk of febrile seizures 7 to 10 days following immunization among 12- to 23-month-old children. The combination measles, mumps, rubella, and varicella vaccine is associated with a 2-fold increased risk of febrile seizures 7 to 10 days following immunization compared with the separately administered measles, mumps, and rubella and varicella vaccines. It is unknown whether the magnitude of these increased risks depends on age at immunization.

OBJECTIVE To examine the potential modifying effect of age on the risk of fever and seizures following immunization with measles-containing vaccines.

DESIGN, SETTING, AND PARTICIPANTS Retrospective cohort study at 8 Vaccine Safety Datalink sites of a total of 840 348 children 12 to 23 months of age who had received a measles-containing vaccine from 2001 through 2011.

EXPOSURES Any measles-containing vaccines and measles-containing vaccines by type.

MAIN OUTCOMES AND MEASURES Fever and seizure events occurring during a 42-day postimmunization observation period.

RESULTS In the analysis of any measles-containing vaccines, the increased risk of seizures during the 7- to 10-day risk interval, using the remainder of the observation period as the control interval, was significantly greater among older children (relative risk, 6.5; 95% CI, 5.3-8.1; attributable risk, 9.5 excess cases per 10 000 doses; 95% CI, 7.6-11.5) than among younger children (relative risk, 3.4; 95% CI, 3.0-3.9; attributable risk = 4.0 excess cases per 10 000 doses; 95% CI, 3.4-4.6). The relative risk of postimmunization fever was significantly greater among older children than among younger children; however, its attributable risk was not. In the analysis of vaccine type, measles, mumps, rubella, and varicella vaccine was associated with a 1.4-fold increase in the risk of fever and 2-fold increase in the risk of seizures compared with measles, mumps, and rubella vaccine administered with or without varicella vaccine in both younger and older children.

CONCLUSIONS AND RELEVANCE Measles-containing vaccines are associated with a lower increased risk of seizures when administered at 12 to 15 months of age. Findings of this study that focused on safety outcomes highlight the importance of timely immunization of children with the first dose of measles-containing vaccines.
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easles, mumps, and rubella (MMR) and measles, mumps, rubella, and varicella (MMRV) are the 2 live attenuated measles-containing vaccines currently licensed in the United States. These vaccines are effective, immunogenic, and generally well tolerated. MMR, administered as a 2-dose series in the United States, with the first dose administered at 12 to 15 months and the second dose at 4 to 6 years of age. Most children in the United States receive their first dose of a measles-containing vaccine between the ages of 12 and 23 months; approximately 85% of them receive this dose by 19 months of age.

Monitoring the safety of measles-containing vaccines remains an important public health issue. Previous studies have shown that these vaccines administered to children 12 to 23 months of age are associated with an increased risk of fever and febrile seizures 1 to 2 weeks following immunization; however, the exact nature of the relationship between fever and febrile seizures is not entirely understood. It is thought that, during this period, the vaccine virus replication is at its peak and can cause fever, which may in turn induce a seizure event by exceeding a certain threshold.

Postlicensure studies have found that the safety profile of MMRV differs somewhat from that of the separately administered MMR and varicella (MMR+V) vaccines. Among children 12 to 23 months of age, MMRV is associated with a 2-fold increase in the risk of febrile seizures 1 to 2 weeks following immunization compared with MMR+V.

The background risk of febrile seizures is not constant during the second year of life, reaching its highest level at approximately 16 to 18 months of age. It is important to examine the safety of measles-containing vaccines administered at different ages during the second year of life. Currently, it is not known whether the magnitude of increased risk of fever and seizures following immunization with measles-containing vaccines depends on age. The separate examination of fever and seizures could potentially shed light on the underlying immunologic and/or neurologic mechanisms leading to the occurrence of these events following immunization. Using data from the Centers for Disease Control and Prevention–sponsored Vaccine Safety Datalink (VSD), we sought to examine the effect of age at immunization on the increased risk of fever and seizures after measles-containing vaccines administered at 12 to 23 months of age. We evaluated the potential modifying effect of age on the risk of fever and seizures following immunization with (1) any measles-containing vaccines and (2) MMRV compared with MMR administered with or without varicella vaccine (MMR+V). Our hypothesis was that the increased risk of postimmunization fever and seizures following a delayed administration of measles-containing vaccines is greater than that following their timely administration.

Methods
Study Population
The study was approved by the institutional review boards of all the participating sites. Vaccine Safety Datalink is a collaborative effort between the Centers for Disease Control and Prevention and 10 managed care organizations comprising data on more than 9 million members annually. As the backbone of active surveillance for vaccine safety in the United States, VSD monitors prespecified potential adverse events following immunization using several methods, including a near-real-time system known as rapid cycle analysis. Detailed information on analytic strategies used in rapid cycle analysis can be found elsewhere.

For this study, we used data collected through the VSD-conducted MMRV rapid cycle analysis among children 12 to 23 months of age who were members of 1 of the 8 participating VSD sites and had received their measles-containing vaccine between January 2001 and December 2011. For one of the sites, only data from July 2007 through December 2011 were included since the other portion of data had already been used in another related publication.

Outcomes
The 2 prespecified adverse events following immunization examined in this study were fever and seizures. These 2 outcomes were each investigated separately; hereafter throughout this article, fever and seizures refer to these separate adverse events and not a composite or combined outcome. We identified postimmunization medically attended fever events in the outpatient setting by using International Classification of Diseases, Ninth Revision (ICD-9) code 780.6* as previously described. We identified postimmunization medically attended seizure events in the emergency department or hospital setting by using ICD-9 code 780.3* (convulsion) or 345* (epilepsy) as previously described. All electronically identified seizure events were included in the analyses; we did not distinguish between febrile and afebrile seizures. Data from 2001 to 2008 had been previously used for our earlier study that evaluated the risk of febrile seizures following immunization with MMRV; additional data from 2009 to 2011 were collected for the current study. For both outcomes, we collected data on events during the 42-day postimmunization period to be consistent with earlier studies. Children who had received the corresponding ICD-9 code at any setting during the 42 days prior to their fever or seizure event were excluded to minimize the likelihood of including follow-up visits in the analyses.

Statistical Analysis
The age distribution of measles-containing vaccine recipients was described using prespecified categories of 12 to 13, 14 to 15, 16 to 18, and 19 to 23 months according to the study protocol. We conducted 2 main analyses to examine the effect of age on the risk of fever and seizures following immunization with measles-containing vaccines. In these analyses, 2 age groups of 12 to 15 and 16 to 23 months defined a priori in the protocol were used. The rationale for using these 2 age groups was to reflect the current policy recommendation on immunization with measles-containing vaccines and to enhance power to explore effect modification.

Analysis of Fever and Seizures Following Immunization With Any Measles-Containing Vaccines
Using a risk interval analysis, each child’s follow-up time was partitioned into risk and control intervals during an observa-
Fever/Seizure Risk and Measles-Containing Vaccine

Using a cohort analysis, we compared the incidence of fever and seizures during the 7 to 10 days following immunization with MMRV with that following immunization with MMR±V. To examine the effect of age at immunization, we compared the relative risk of fever and seizures between the age groups of 12 to 15 and 16 to 23 months by adding an age group × vaccine type interaction term to a binomial regression model with an identity link (to provide estimates of increased risk on an additive scale) and reported the results as number of excess cases of fever and seizures per 10,000 doses. We conducted sensitivity analyses by excluding days 0 and 1, 5 and 6, and 11 and 12 following immunization from the control interval. Days 0 and 1 were excluded from the control interval to minimize any potential confounding effect of concomitantly administered inactivated vaccines in causing fever or seizures on those days. Days 5 and 6 and 11 and 12 were excluded from the control interval to minimize the inclusion of days during which some risk of fever or seizures associated with measles-containing vaccine might still be present.

Analysis of Fever and Seizures by Type of the Measles-Containing Vaccine

Using a cohort analysis, we compared the incidence of fever and seizures during the 7 to 10 days following immunization with MMRV with that following immunization with MMR±V. To examine the effect of age at immunization, we compared the relative risk of fever and seizures between the age groups of 12 to 15 and 16 to 23 months by adding an age group × vaccine type interaction term to a poisson regression model. We additionally compared the attributable risk of fever and seizures between the age groups of 12 to 15 and 16 to 23 months by adding an age group × exposure status interaction term to a binomial regression model with an identity link (to provide estimates of increased risk on an additive scale) and reported the results as number of excess cases of fever and seizures per 10,000 doses. We conducted sensitivity analyses by excluding days 0 and 1, 5 and 6, and 11 and 12 following immunization from the control interval. Days 0 and 1 were excluded from the control interval to minimize any potential confounding effect of concomitantly administered inactivated vaccines in causing fever or seizures on those days. Days 5 and 6 and 11 and 12 were excluded from the control interval to minimize the inclusion of days during which some risk of fever or seizures associated with measles-containing vaccine might still be present.

Results

The study population included 840,348 children 12 to 23 months of age who had received a measles-containing vac-

Discussion

We found that the magnitude of increased risk of seizures following immunization with measles-containing vaccines during the second year of life depends on age. While measles-
containing vaccines administered at 12 to 15 months of age are associated with an increased risk of seizures 7 to 10 days following immunization, their delayed administration at 16 to 23 months of age may result in an even greater increased risk of that adverse event following immunization. The relative risk of fever was significantly greater among children 16 to 23 months of age than among children 12 to 15 months of age; however, no significant difference between the 2 aforementioned age groups in the attributable risk of that adverse event following immunization with measles-containing vaccines was observed.

Table 1. Number of Administered Doses and Fever and Seizure Events Following Immunization With Measles-Containing Vaccines

<table>
<thead>
<tr>
<th>Age, mo</th>
<th>Vaccine Type</th>
<th>Dose, No. (%)</th>
<th>No. of Events</th>
<th>Fever</th>
<th>Seizures</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>0-42 d (n = 18,403)</td>
<td>7-10 d (n = 5,919)</td>
<td>0-42 d (n = 1810)</td>
</tr>
<tr>
<td>12-13</td>
<td>MMR</td>
<td>87,119 (14.9)</td>
<td>1,744</td>
<td>715</td>
<td>183</td>
</tr>
<tr>
<td></td>
<td>MMR+V</td>
<td>422,898 (72.6)</td>
<td>9,173</td>
<td>2,921</td>
<td>703</td>
</tr>
<tr>
<td></td>
<td>MMR only</td>
<td>72,698 (12.5)</td>
<td>1,940</td>
<td>551</td>
<td>99</td>
</tr>
<tr>
<td>14-15</td>
<td>MMR</td>
<td>18,459 (12.7)</td>
<td>447</td>
<td>149</td>
<td>72</td>
</tr>
<tr>
<td></td>
<td>MMR+V</td>
<td>97,538 (66.9)</td>
<td>2,127</td>
<td>632</td>
<td>294</td>
</tr>
<tr>
<td></td>
<td>MMR only</td>
<td>29,839 (20.5)</td>
<td>618</td>
<td>209</td>
<td>73</td>
</tr>
<tr>
<td>16-18</td>
<td>MMR</td>
<td>9,290 (13.1)</td>
<td>211</td>
<td>74</td>
<td>45</td>
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<tr>
<td></td>
<td>MMR+V</td>
<td>41,851 (59.2)</td>
<td>964</td>
<td>293</td>
<td>166</td>
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<tr>
<td></td>
<td>MMR only</td>
<td>19,580 (27.7)</td>
<td>508</td>
<td>155</td>
<td>63</td>
</tr>
<tr>
<td>19-23</td>
<td>MMR</td>
<td>5,509 (13.4)</td>
<td>89</td>
<td>42</td>
<td>23</td>
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<tr>
<td></td>
<td>MMR+V</td>
<td>22,700 (55.3)</td>
<td>346</td>
<td>106</td>
<td>65</td>
</tr>
<tr>
<td></td>
<td>MMR only</td>
<td>12,867 (31.3)</td>
<td>236</td>
<td>72</td>
<td>24</td>
</tr>
<tr>
<td>Total</td>
<td>MMR</td>
<td>120,377 (14.3)</td>
<td>2,491</td>
<td>980</td>
<td>323</td>
</tr>
<tr>
<td></td>
<td>MMR+V</td>
<td>584,987 (69.6)</td>
<td>12,610</td>
<td>3,952</td>
<td>1,228</td>
</tr>
<tr>
<td></td>
<td>MMR only</td>
<td>134,984 (16.1)</td>
<td>3,302</td>
<td>987</td>
<td>259</td>
</tr>
</tbody>
</table>

Abbreviations: MMR, measles, mumps, and rubella vaccine; MMRV, measles, mumps, rubella, and varicella vaccine; V, varicella vaccine.

Table 2. Increased Risk of Fever and Seizure Events 7 to 10 Days Following Immunization
With Measles-Containing Vaccines During the Second Year of Life by Age

<table>
<thead>
<tr>
<th>Type of Analysis</th>
<th>Age, mo</th>
<th>Fever</th>
<th>Seizures</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Excess Cases* (95% CI)</td>
<td>IRR (95% CI)</td>
</tr>
<tr>
<td>Any measles-containing vaccine (risk-interval analysis)</td>
<td>12-15</td>
<td>4.4 (4.3 to 4.6)</td>
<td>52.0 (49.9 to 54.0)</td>
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<tr>
<td></td>
<td>16-23</td>
<td>5.9 (5.4 to 6.5)</td>
<td>47.4 (43.0 to 51.8)</td>
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<tr>
<td>P value for interaction</td>
<td>&lt;.01</td>
<td>.07</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>MMRV vs MMR+V vaccine (cohort analysis)</td>
<td>12-15</td>
<td>1.4 (1.3 to 1.5)</td>
<td>8.9 (3.2 to 15.2)</td>
</tr>
<tr>
<td></td>
<td>16-23</td>
<td>1.4 (1.1 to 1.7)</td>
<td>9.4 (5.1 to 24.0)</td>
</tr>
<tr>
<td>P value for interaction</td>
<td>.90</td>
<td>.95</td>
<td>.94</td>
</tr>
</tbody>
</table>

Abbreviations: IRR, incidence rate ratio; MMR, measles, mumps, and rubella vaccine; MMRV, measles, mumps, rubella, and varicella vaccine; V, varicella vaccine. *Per 10,000 doses.
Febrile seizures have been shown to occur following immunization with a small number of other childhood vaccines including whole-cell pertussis-containing vaccines and concomitantly administered inactivated influenza vaccine and 13-valent pneumococcal conjugate vaccine. They are the most common neurologic adverse events following immunization with measles-containing vaccines. Nonetheless, the increased risk is overall small regardless of age; medically attended febrile seizures following immunization with measles-containing vaccines are not common events. For instance, it is known that the incidence of postimmunization febrile seizures is several-fold lower than that following natural infection with measles virus. Despite the excellent prognosis, when a child sustains a febrile seizure, negative effects on family members can result; many parents and caregivers consider febrile seizures as frightening events and seek medical attention including a visit to an emergency department. Previous studies have reported that the incidence of febrile seizures among all children 12 to 23 months of age is approximately 10 to 20 cases per 1000 person-years. In our study, the incidence of seizures during the control interval, shown in Figure 1B, was consistent with previously reported age-specific febrile seizures background rates. Similar to previous studies that found the background risk of febrile seizures to be at its highest level at approximately 16 to 18 months of age, we found that the incidence of seizures reached its peak at around 16 to 18 months of age during the control interval. The attributable risk of postimmunization seizures following any measles-containing vaccines was significantly greater among children 16 to 23 months of age than those 12 to 15 months of age in our study. This was the function of the higher incidence of seizures during the control interval, as well as higher relative risk of seizures, among older children compared with younger children. These findings collectively suggest that the administration of measles-containing vaccines at the age of highest vulnerability to febrile seizures may result in an even greater increased risk of those adverse events following immunization.

Different factors may explain the effect of age on the risk of postimmunization fever and seizures observed in this study. Previous studies have suggested that measles-containing vaccines result in stronger immune responses among children older than 15 months compared with those 12 to 15 months of age. In addition, immunologic responses following immunization with measles-containing vaccines have been shown to be positively correlated with the rate of fever and measles-like rashes among children 12 to 23 months of age. It is conceivable that 16- to 23-month-old children are capable of mounting a more rigorous immunologic response to the measles component of these vaccines than 12- to 15-month-old children, resulting in their being susceptible to an even greater increased risk of febrile seizures 7 to 10 days following immunization. Alternative explanations for our findings may include differential underlying medical conditions or health-seeking behaviors between children who received their immunization on a timely basis and those who received it with a delay. Specifically, parents of children susceptible to seizures might have delayed receipt of a vaccine known to cause seizures; such children might have also been more likely to develop seizures following the receipt of these vaccines. We did not evaluate the potential contribution of such differences between younger and older children to our findings in this study.

We found no evidence that the 2-fold increased risk of seizures 7 to 10 days following immunization with MMRV compared with MMR±V is modified by age. However, the attributable risk of seizures 7 to 10 days following immunization with MMRV, using MMR±V as the reference, was not the same across the age groups; there appeared to be a greater number of excess seizure cases per 10 000 doses among 16- to 23-month-old children compared with 12- to 15-month-old children. This observed difference was a reflection of the variation by age in the incidence of seizures 7 to 10 days following immunization with MMR±V. Therefore, the same 2-fold increased risk following immunization with MMRV resulted in different numbers of excess cases per 10 000 doses across the age groups.

This study was subject to potential limitations. We exclusively used ICD-9 codes for the identification of fever events, and also seizures without a distinction between febrile and afebrile events, because of the large number of outcomes that would have made medical record reviews cost prohibitive. All
cases identified prior to October 2008 included in this study arose from our previous study of febrile seizures following immunization with MMRV. Medical record reviews conducted in that study found 87% of all electronically identified seizure events in the emergency department or hospital settings occurring within 42 days following immunization with measles-containing vaccines to be febrile seizures. There is no reason to believe that the risk of febrile seizures varies in relation to the time since immunization with measles-containing vaccines; therefore, it is unlikely that potential inclusion of a relatively small number of febrile seizure events could explain the observed differences. We did not examine health care encounters for the evidence of fever-inducing illnesses that could have potentially served as time-varying confounders. However, we do not believe that such illnesses had preferentially occurred within the risk interval of interest as opposed to other periods following immunization in this study. We did not include information on concomitantly administered vaccines in our analyses. However, results of our previous study found that the receipt of concomitant vaccines was not a significant predictor of seizures. Furthermore, our sensitivity analysis in the current study that excluded days 0 and 1 from the control interval in an attempt to remove any potential effect of concomitantly administered vaccines in causing fever or seizures during those days did not materially change the results.

The findings of this large study provide new insights into the effect of age on the risk of fever and seizures following immunization with measles-containing vaccines in the second year of life. Previously, Vestergaard et al sought to determine subgroups of children who were particularly susceptible to developing febrile seizures following immunization with MMR. They assessed the potential modifying effect of several characteristics, but not age, among all children born in Denmark from 1991 through 1998. We were able to assess the effect of age since children in our study had received their vaccines at varying ages during the second year of life. Vaccines are typically recommended at an age that maximizes the likelihood of vaccine-induced protection and minimizes the risk of morbidity and mortality that would occur by delaying immunization. The safety profile of vaccines at different ages is another important consideration in immunization policy decision making. Our findings are of direct relevance to the recommended childhood immunization schedule; they support the timely immunization of children with the first dose of measles-containing vaccines in accordance with current recommendations.

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REFERENCES


