

## Evidence to Guide Measles Immunization Recommendations

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### Purpose

In *AFP Journal Club*, three presenters review an interesting journal article in a conversational manner. These articles involve “hot topics” that affect family physicians or “bust” commonly held medical myths. The presenters give their opinions about the clinical value of the individual study discussed. The opinions reflect the views of the presenters, not those of *AFP* or the AAFP.

### Article

Rowhani-Rahbar A, Fireman B, Lewis E, et al. Effect of age on the risk of fever and seizures following immunization with measles-containing vaccines in children. *JAMA Pediatr.* 2013;167(12):1111-1117.

For more information on evidence-based medicine (EBM) terms, see the EBM Toolkit at <http://www.aafp.org/afp/ebmtoolkit>.

A collection of *AFP Journal Club* published in *AFP* is available at <http://www.aafp.org/afp/jc>.

### Is the risk of fever and seizures after measles immunization dependent on age at administration and/or vaccine type?

*Jill:* Parents often question the administration of vaccines and worry about adverse effects for their children. They especially question attenuated live vaccines, such as the measles, mumps, and rubella (MMR) and varicella vaccines, because they can be associated with bothersome adverse effects. This hesitation often leads them to delay or refuse these vaccines for their children. We counsel parents about the risks of delaying or refusing immunization, usually focusing on the increased susceptibility to the illnesses during vulnerable times in childhood. This study identifies another reason to encourage parents to adhere to the recommended vaccine administration schedule. The 2014 schedule is available at <http://www.aafp.org/patient-care/immunizations/schedules.html>.

### What does this article say?

*Jill:* This retrospective cohort study included 840,348 U.S. children from the Vaccine Safety

Datalink (VSD) database who received measles vaccination between 2001 and 2011. The outcomes of interest were fever and seizure (ascertained by electronic coding data) occurring in the seven- to 10-day postimmunization risk interval when vaccine virus replication is at its peak, compared with these events occurring in the control interval (two to four and 13 to 42 days postimmunization), which were considered to be unrelated to the immunization. During the seven- to 10-day time period, 5,919 children had fever and 519 had a seizure (0.06%). In children who were vaccinated at 12 to 15 months of age, the seizure risk was 0.04%. Regression analysis showed that although the risk of fever and seizure was increased in all children, those who received a measles vaccination at 16 to 23 months of age had a greater increase in seizure risk (relative risk = 6.5; 95% confidence interval, 5.3 to 8.1) than those who received a vaccination at 12 to 15 months of age (relative risk = 3.4; 95% confidence interval, 3.0 to 3.9), conferring an attributable risk of 5.5 additional cases per 10,000 vaccines given (0.055%).

What about the MMR and varicella combination vaccine? Children who received the combination vaccine had a 1.4-fold increase in fever and a twofold increase in seizure compared with children who received the MMR vaccine alone or with a separate varicella vaccination. This equates to approximately nine additional cases of fever (0.09%) and 4.2 to 9.0 additional cases of seizure (0.042% to 0.09%) per 10,000 doses. The increase in the incidence of fever and seizure seen with the MMR and varicella vaccine did not seem to be impacted by age at administration. ▶

## Should we believe this study?

**Mark:** The results certainly make sense. Although the authors of this study didn't distinguish between febrile and afebrile seizures, the vast majority of seizures after immunizations (and in this age group in general) are febrile. The background risk of febrile seizures is highest at 16 to 18 months of age,<sup>1</sup> so anything that increases the risk of fever (like a vaccination) will increase the risk of seizure.

**Jill:** There was no increase in attributable risk of fever based on age at vaccine administration, but children who receive the vaccine after the recommended age (older than 15 months) and get a fever have higher vulnerability to seizure.

**Bob:** It is possible that some of the increased risk is from selection bias. That is, parents who have children with a higher risk of seizures may choose to delay the measles vaccine, thus increasing the seizure rate in that population. This is where randomization would be helpful. However, the number of children needed to allow for an appropriately powered randomized study for an event with such a low incidence would be prohibitive.

**Mark:** This study demonstrates one of the benefits of large, centrally maintained databases like the VSD. We can get a lot of information from a large population very quickly, and the VSD includes data from across the United States. The only concern I can see, and it's a minor one, is that all vaccine recipients in this study were in managed care plans. That probably makes the demographics a little homogeneous, and may have an impact on vaccine exposure rates.

**Bob:** One problem is that the *International Classification of Diseases, Ninth Revision* (ICD-9) codes have been shown to be unreliable when used in research settings to identify a set of patients with a particular disease. This can introduce errors in the data set.<sup>2</sup> Using a limited number of ICD-9 codes to identify patients with a fever or seizure may also lead to missed cases, but that shouldn't vary by age or vaccine status.

## What should the family physician do?

**Mark:** As Bob noted earlier, it's important to emphasize that immunization-related fever and seizures are rare. The baseline risk of seizure after measles vaccination, for example, is only 0.04%, and the attributable risk increases by only 0.05% if given after 15 months of age. We certainly shouldn't discourage vaccination in this age

### Main Points

- Use of the MMR and varicella combination vaccine is associated with a greater risk of fever and seizures in children, compared with the MMR vaccine alone or with a separate varicella vaccination.
- Children who receive a measles vaccination at 16 to 23 months of age have a higher risk of seizures than those who receive the first dose at 12 to 15 months of age.
- Using ICD-9 codes when identifying patients with a particular disease state or outcome can be problematic.

### EBM Points

- Relative risk: the ratio of the probability of an event in an exposed population to the probability in an unexposed population. This calculation is useful in comparisons in which there is a low probability of the event occurring.
- Attributable risk: the difference in the rate of an event between an exposed population and an unexposed population. This is usually calculated in cohort studies.

group based on these data. The benefit of vaccination still outweighs the risk, because the risk of febrile seizures is higher with measles infection.

**Jill:** Nonetheless, encouraging parents to follow the recommended immunization schedule and avoiding the combination vaccine are easy to do. It's certainly worth discussing this increased risk with parents who are proposing alternative immunization schedules, and we probably need to more carefully study the safety of different schedules. The recommended immunization schedule for children is formulated using the best available data to maximize benefit and minimize risk.

**Bob:** Right, and although febrile seizures are benign from a medical perspective, they often cause distress for families, increase health care costs, and propagate "vaccinophobia." Therefore, we need to do what we can to prevent them.

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Author disclosure: No relevant financial affiliations.

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