

Febrile Seizure Risk Cited

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label was updated to include “convulsion” and “febrile seizure” among adverse reactions that had been reported post vaccination. This wasn’t entirely unexpected, because previous studies had shown that the MMR vaccine is associated with one additional febrile seizure for every 3,000-4,000 doses administered, while Varivax given alone is not associated with an increased risk. Moreover, precensure studies of MMRV demonstrated higher rates of fever and measleslike rash at 5-12 days post vaccination, compared with separate MMR and varicella given on the same day to children aged 12-23 months (*Pediatr. Infect. Dis. J.* 2005;24:665-9).

Now, new interim data presented to ACIP from two studies—one conducted for the CDC by Northern California Kaiser Permanente and the other by Merck—both suggest an increased risk of febrile seizures for the MMRV combination, compared with MMR and varicella vaccines given separately. However, because evaluation is ongoing and the vaccine is not currently in use, ACIP did not discuss withdrawing its 2006 recommendation. Rather, the panel voted simply to add a sentence to its varicella vaccine statement saying, “ACIP does not express a preference for use of combina-

tion MMRV over separate administration of MMR and varicella vaccines.” The move was needed because ACIP’s general vaccine recommendations state that combinations are “preferred” over separate injections whenever possible to minimize the number of injections, Dr. Marin noted.

Dr. Nicola P. Klein, codirector of the Kaiser Permanente Vaccine Study Center, Oakland, Calif., presented data from an analysis that was prompted by surveillance from the eight-site Vaccine Safety Datalink, in which the number of seizures observed among children aged 12-23 months in the 42 days post vaccination first exceeded the expected number sufficient to generate a “signal” during the week of Feb. 11, 2007: Out of 25,779 cumulative doses, there were 59 seizures, compared with the expected 38, for a relative risk of 1.57.

Subsequent investigation indicated a sharp clustering of seizures in days 7-10 following vaccination both with MMRV (45 of 93 total) and with the separate MMR and varicella vaccines given simultaneously (44 of 164). For MMR given alone there was a peak at days 6-10 (11 of 32), and for varicella alone, at days 21-24 (21 of 101). At 7-10 days post

vaccination, the unadjusted rates of seizures per 10,000 population were 9.6 for MMRV, 4.9 for MMR plus V, 3.5 for MMR alone, and 1.5 for varicella alone, Dr. Klein reported.

Subsequent logistic regression analysis showed that the risk of seizures within 7-10 days after MMRV (n = 43,356) was 2.0 times that of MMR plus varicella (314,625), adjusted for age and influenza season. The increased risk with MMRV was not associated

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with sex, Vaccine Safety Datalink site, concomitant vaccines, or seizure temporal trends. The majority of those seizures—92% of the 45 with MMRV and 94% of the 132 with MMR plus V—were febrile. The adjusted odds ratio for just the febrile seizures for MMRV versus MMR plus V was 2.3. There were no differences between the febrile seizure cases in the two vaccine groups in hospitalization rates, first seizure event, or family history of seizures.

The data suggest that for every 10,000 children who receive MMRV instead of separate MMR plus V, there will be approximately five additional seizures 7-10 days after vaccination. From the reverse perspective, there will be approximately one additional seizure 7-10 days post vaccination

for every 2,000 children vaccinated with MMRV instead of the two separate vaccines.

Dr. Klein also reported on two cases of encephalitis out of more than 60,000 MMRV doses administered. Both cases were among those being investigated for seizures, and both occurred 7-10 days after MMRV in late 2006. One was febrile and the other was afebrile. Both had negative clinical work-ups and both survive with residual mild sequelae.

Data from 4- to 6-year-olds receiving their second dose at the Northern California Kaiser Permanente vaccine study center site showed no significant differences in seizure rates between those who received MMRV versus MMR plus V, but there were very few seizures in that age group (two seizures out of 35,185 within 7-10 days of MMRV versus three seizures out of 68,915 for MMR plus V), she noted.

Dr. Patricia Saddier of the epidemiology department at Merck Research Laboratories presented preliminary data from an ongoing postlicensure observational cohort study that was designed in cooperation with the Food and Drug Administration.

The study population includes 14,263 children aged 12-60 months (99% were 12-23 months) who received their first dose of ProQuad in 2006. Historical controls were the identical number of children matched for age, gen-

der, and vaccination date who received MMR plus V in 2005.

A review of medical records yielded 91 unconfirmed seizures, of which 77 were reviewed/adjudicated and 33 were confirmed febrile seizures within 30 days of vaccination. Of those, 14 occurred in the MMRV group for a rate of 1.0/1,000 and 19 in the MMR plus V group, or 1.3/1,000.

Within the time frame of 5-12 days post vaccination, there were seven confirmed febrile seizures in the MMRV group (0.5/1,000) versus three with the separate vaccines (0.2/1,000). All of the children with confirmed febrile seizures also received concomitant pneumococcal conjugate vaccine and diphtheria, tetanus, and acellular pertussis vaccines, Dr. Saddier noted.

In a comparison of the two vaccine groups, the relative risk of MMRV versus MMR plus V is 2.3 at days 5-12, and 0.7 for days 5-30 and 0-30. The apparent increased risk at 5-12 days translates to an attributable risk of 0.3/1,000, which is not significant. The final febrile seizure analysis is expected to be completed in July to August 2008, with approximately 30,000 vaccine recipients in each group. The findings will be shared with the FDA, the CDC, and ACIP soon thereafter.

“Merck will continue to collaborate with regulatory and public health authorities and with medical and scientific experts on the interpretation of the febrile seizure data,” Dr. Saddier said. ■

San Diego Measles Outbreak Shows The Effect of Vaccine Exemptions

BY MIRIAM E. TUCKER
Senior Writer

ATLANTA — The recent measles outbreak in San Diego—started by one child who imported the disease from Switzerland—reinforces the ongoing need to maintain high vaccination coverage, Dr. Jane Seward said at the winter meeting of the Centers for Disease Control and Prevention’s Advisory Committee on Immunization Practices.

The unvaccinated 7-year-old boy, who had rash onset 12 days after returning to the United States, infected at least 11 additional children ranging in age from 10 months to 9 years. Four were infected in the pediatrician’s office that the child had visited the day before he was taken to a hospital emergency department for high fever and generalized rash. Another two cases were the boy’s siblings, while five attended his school.

One infant was hospitalized for 2 days for dehydration, and another traveled by plane to Hawaii while infectious, necessitating “quite a response” by public health authorities in that state, Dr. Seward noted.

All cases were unvaccinated, including eight whose parents had claimed personal belief exemptions. In fact, 10% of the 350 children in the index child’s school—kindergarten through 9th grade—were unimmunized because of these sorts of such exemptions, said Dr. Seward, acting deputy director of the CDC’s division of viral diseases, National Center for Immunizations and Res-

piratory Diseases. The other four children were unimmunized because three were less than 12 months of age and therefore too young to be vaccinated and the fourth had received her routine vaccination 6 days after the unrecognized exposure.

At the time of publication in the CDC’s Morbidity and Mortality Weekly Report, the episode had necessitated quarantine of 70 children who lacked evidence of immunity (*MMWR* 2008;57:[early release]1-4).

In the 1950s, 3 million to 4 million cases of measles occurred annually in the United States, causing 4,000 cases of encephalitis, 150,000 respiratory complications, 48,000 hospitalizations, and 450 deaths. Since the implementation of a two-dose immunization schedule in the early 1990s, measles is no longer endemic in the United States. Today, all of the 50 or so U.S. cases reported annually were imported from developed countries including those in Europe and Asia.

There’s good and bad news in the San Diego situation, Dr. Seward said. The bad news is that measles is highly infectious and still poses a threat, unimmunized people are still at risk, and many health care providers are not familiar enough with the disease to ensure appropriate infection-control practices in their offices. But on the upside, there were no cases in immunized children. “The wall of immunity held fast. ... We need to remember we have an ongoing challenge to sustaining high vaccine coverage to maintain our current [measles] elimination status.” ■

Keyboards, Mouses Blamed In School’s Norovirus Hit

An outbreak of norovirus in a District of Columbia elementary school last year was probably transmitted by unclean computer mouses and keyboards.

The Centers for Disease Control and Prevention was notified after 27 students and two staff members experienced symptoms of gastroenteritis (defined as nausea, vomiting, or diarrhea) within a 4-day period.

After inspecting the classrooms, CDC staff administered questionnaires to all staff and students. Results showed that students assigned to one particular first-grade classroom had almost double the risk of gastroenteritis during the 4-day period (relative risk 1.94). The affected classroom was the one that housed the school’s computers, which were shared by students and staff. Foodborne illness was ruled out because no food was served at the school (*MMWR* 2008;56:1340-3).

Environmental samples taken from a computer mouse and keyboard contained norovirus subtype GII. This strain also was found in stool samples from two persons who had been on the site.

At the CDC’s urging, the school cleaned all shared computer surfaces with a bleach solution, and all students and staff were restricted from the school until 72 hours after resolution of their illness to avoid recontamination.

In a commentary, the CDC noted that prior research has shown that norovirus can be transmitted to fomites and that a surrogate marker for norovirus, feline calicivirus, has been shown to survive on computer mouses and keyboards for up to 2 days.

—John R. Bell