Guillain-Barré Syndrome, MCV4 Link Still Unclear

BY MIRIAM E. TUCKER
Senior Writer

ATLANTA — Guillain-Barré syndrome has been reported in 17 recipients of the tetravalent meningococcal conjugate vaccine, but it's unclear whether the association is causal, Dr. Robert L. Davis said at a meeting of the Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices.

The data, also reported the week prior to the meeting in the Oct. 20 issue of CDC's Morbidity and Mortality Weekly Report, suggest an excess risk for Guillain-Barré syndrome (GBS) of about 1.25 cases per million doses of the vaccine. But the limitations of the data collection methods and uncertainty about background rates of GBS prevent any firm conclusions about causation. The additional cases do not affect current CDC recommendations for vaccination, said Dr. Davis, director of the CDC's Immunization Safety Office.

Indeed, a "decision analysis" presented by Dr. Bo-Hyun Cho of the CDC's National Center for Immunization and Respiratory Diseases, suggests that even if the association is real, it is outweighed by the risk of contracting meningococcal disease without the vaccine.

The CDC and the Food and Drug Administration had previously alerted health care providers about a possible association between GBS and the tetravalent meningococcal conjugate vaccine (MCV4), which is marketed as Menactra by Sanofi Pasteur Inc. Five cases were reported in an October 2005 alert, and three cases in an April 2006 notice. Since then, an additional nine cases have been reported to the Vaccine Adverse Event Reporting System (VAERS), bringing to 17 the total number of reported cases since the MCV4 vaccine became available in March 2005.

The onset interval for the 17 cases ranged from 2 to 33 days after vaccination, with a mean of 15.7 days, Dr. Davis said.

Further analysis was restricted to the 15 patients aged 11-19 years, because 94% of MCV4 recipients are in that age range (the other 2 patients were aged 30 and 43 years). A total of 5.9 million doses of MCV4 have been distributed to individuals in that age group.

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Some Guillain-Barré syndrome cases in older adolescents may be a result of *Campylobacter jejuni* infection, Dr. Ban Mishu Allos pointed out at the meeting.

Compared with the observed GBS rate of 0.2 cases per 100,000 person-months for those vaccinated, data from two separate databases (the Healthcare Cost and Utilization Project and the Vaccine Safety Datalink) both yielded an expected background relative risk for GBS of 0.11 per 100,000 person-months.

"There is evidence for a small increased risk of GBS after MCV4. The timing of neurologic symptoms within 1-5 weeks of vaccination among reported cases is of concern," Dr. Davis said.

He added, "Substantial uncertainty exists regarding the risk estimate, using either the HCUS or VSD background incidence rate." Underreporting is assumed with the VAERS, a passive reporting system, but no surges in GBS reports occurred following either of the previous MMWR notices, he said.

The increased risk appears confined to older adolescents, with a relative risk of 0.27 per 100,000 person-months among those aged 11-14 years (based on 1 case out of 2.5 million doses distributed), compared with 2.55 per 100,000 person-months in the 15- to 19-year-old group (14 cases among 3.5 million doses).

Dr. Ban Mishu Allos, an ACIP member from the department of infectious diseases at Vanderbilt University, Nashville, Tenn., noted that many of the older adolescents would likely have received the vaccine before the start of college classes during the summer, which happens to be the season for *Campylobacter jejuni* infection, a frequent antecedent to GBS. The younger teens would be more likely to receive the vaccine at other times of the year as well.

No patient had reported diarrheal prodromes, and none of the four individuals tested for campylobacter were positive. However, the infection is often asymptomatic, and the organism would not be detected in stool by the time GBS symptoms appeared, Dr. Allos remarked.

Dr. Cho's analysis compared the health outcomes of vaccination versus no vaccination in the birth cohort of 11-year-olds, which includes 4,076,600 individuals. Among the assumptions were that the risk for GBS lasts 6 weeks after vaccination, and that an 11-year-old has a life expectancy of 67.7 more years. Parameters included a 5% morbidity rate among adolescents with GBS, which overall carries a favorable prognosis (Lancet 1998;352:635-41).

Meningococcal disease, on the other hand, has a case-fatality rate of 10%. Incidence of disease caused by one of the vaccine's serogroups (A, C, Y, and W-135) is 0.77 per 100,000 unvaccinated individuals, of which the vaccine prevents 93%. With those and other published and unpublished data, Dr. Cho calculated that the vaccine prevents 163 cases of meningococcal disease and 16 deaths due to a vaccine strain for every 3 additional cases of GBS.

These data are subject to many limitations and should be considered preliminary. But they do suggest that "the period of risk of vaccine-attributable GBS is small and short [compared with] the prolonged benefit of meningococcal disease prevention," Dr. Cho said.

Dr. Michael D. Decker, vice president of Scientific Affairs at Sanofi-Pasteur, said his company is supporting a study to further investigate the issue over a 2-year period in the 11- to 17-year-old population in an HMO database of over 100 million covered lives. "We believe there is enough power to clarify the association," he said in an interview.

The CDC also is continuing to evaluate the issue. ■

Clinicians are requested to report adverse events related to the MCV4 vaccine by going to www.vaers.hhs.gov, sending a fax to 877-721-0366, or calling 800-822-7967. A Vaccine Information Statement and fact sheet with information on the vaccine and reported GBS cases are available at www.cdc.gov/nip/publications/vis/default.htm, and an updated fact sheet for health care workers is available at www.cdc.gov/nip/vacsafe/concerns/gbs/menactra.htm.

Christine Kilgore contributed to this report.

Intussusception Rates With Rotateq Are Lower Than Expected

BY MIRIAM E. TUCKER
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ATLANTA — No major safety issues have arisen thus far with the new rotavirus vaccine, Penina Haber said at a meeting of the Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices.

In fact, rates of intussusception—the complication that resulted in the 1999 withdrawal from the market of the old rotavirus vaccine (Wyeth-Ayerst's RotaShield)—are actually lower with Merck's Rotateq than would be expected in the general population, said Ms. Haber, an epidemiologist with the CDC's Immunization Safety Office.

The CDC is monitoring Rotateq for gastrointestinal-related adverse events as well as any other unexpected problems via the passive Vaccine Adverse Event Reporting System (VAERS). Should any safety "signals" arise, the active surveillance system known as the Vaccine Safety Datalink (VSD), comprising eight large HMOs (covering 3% of the U.S. population), will be utilized to investigate further.

The CDC is now using VAERS and VSD to monitor safety for all new vaccines, with researchers from the CDC and the Food and Drug Administration reviewing all reports sent to VAERS on a daily basis, Robert L. Davis, director of the CDC's Immunization Safety Office, said during a joint presentation with Ms. Haber on vaccine safety.

From March 1, 2006, through Oct. 23, 2006, VAERS received a total of 189 adverse event reports following receipt of Rotateq, from a background of 1,786,476 doses distributed as of Sept. 30, 2006. Of the 189 reports, 48% were associated with receipt of Rotateq alone, and the rest were in combination with other vaccines. Children aged 2-3 months accounted for 57% of the reports, while 5% were for children under 2 months of age. (The vaccine is recommended at ages 2, 4, and 6 months.) Fifty-five percent of reports were of events occurring within 2 days of vaccination, while another 5% occurred within 7 days.

Among the most frequent adverse events following receipt of Rotateq in children up to 12 months of age were diarrhea (24% vs. 3% following all other vaccines), vomiting (22% vs. 5%), GI hemorrhage (7% vs. 0%), and melena (6% vs. 1%). A total of 30 (16%) of the reports were of serious events, including 6 cases of intussusception. Four occurred after dose 1 and two after the second dose, at an interval of 2-32 days following vaccination.

Calculated from the VSD background intussusception rate of 2.98 per 10,000 person-years, the expected number of cases within a 21-day period would be 30.7. In contrast, just four cases were observed within 21 days of Rotateq receipt. If an underreporting rate of 47% is assumed (Am. J. Epidemiol. 2001;154:1006-12), the number of intussusceptions associated with Rotateq would still be significantly lower than expected, Ms. Haber said.

Excluding the intussusception cases, there were 19 reports of hematochezia following Rotateq. During the same time period, hematochezia was reported in 4 children receiving other vaccines in 2,248 VAERS reports. Most of the hematochezia cases occurred within 3 days of vaccination, and none was serious. In addition to the approximately 96,000 infants born each year who are surveilled in VSD and will be followed for adverse events after administration of Rotateq, about 45,000 infants will provide additional data to Merck in a phase 4 study, she noted. ■