# Thimerosal Not Linked to Cognitive Performance

BY ELIZABETH MECHCATIE
*Senior Writer*

A study of 1,047 children found no evidence of a causal association between exposure to ethylmercury from the preservative thimerosal in vaccines during the prenatal, neonatal, or first 7 months of life and neuropsychological outcomes at ages 7-10 years, said the authors.

"The associations that we detected were small, almost equally divided between positive and negative effects, and mostly sex-specific," William W. Thompson, Ph.D., an epidemiologist in the National Center for Immunizations and Respiratory Diseases, at the Centers for Disease Control and Prevention (CDC), and his coauthors wrote in the New England Journal of Medicine.

"The study results were very reassuring," Dr. Anne Schuchat, director of the CDC's National Center for Immunizations and Respiratory Diseases, said during a CDC-sponsored teleconference. "The bulk of the study found very, very similar performance in children who were exposed to high amounts of thimerosal and children exposed to low or no thimerosal and suggests the higher thimerosal content that vaccines had back in the 1990s did not lead to harmful effects in children in performance on standardized testing at ages 7-10."

She noted that parental reports of tics were not associated with any higher exposure of thimerosal but based on evaluator observations during the testing; motor and phonic tics were increased by about twofold among boys with higher thimerosal exposure from birth to 7 months, an association that was not seen in girls. Because of similar findings in two previous studies, this issue is being evaluated further with CDC experts in developmental disability and consultations with outside pediatric neurologists, she said.

This was not an autism study. No measures of autism were included in the testing because the CDC is conducting a separate case-control study of autism and mercury exposure, the results of which are expected in the next year, Dr. Schuchat said.

**Results suggest the higher thimerosal content in vaccines in the 1990s did not lead to harmful effects in children in performance in standardized testing.**

In the cohort study, children enrolled in four HMOs, who were born between January 1993 and March 1997, were administered a wide range of standardized tests that measured 42 neuropsychological outcomes, including speech and language indexes, verbal memory, achievement, fine-motor coordination, visuospatial ability, attention, behavior regulation, tics, and general intellectual functioning, between the ages of 7 and 10 years. Estimates of their exposure to mercury from thimerosal in vaccines and immunoglobulins during the prenatal period, neonatal period (birth to 28 days) and the first 7 months (1-214 days) were based on computerized and personal immunization records, medical records, and parent interviews (N. Engl. J. Med. 2007;357:1281-92).

Between birth and 7 months, the median cumulative exposure to ethylmercury from thimerosal among the children was 112 mcg; 9% of the children were exposed to 62.5 mcg or less of mercury, and 25% had cumulative exposures of 150 mcg or more. (There was no exposure to a thimerosal-containing vaccine or immune globulin during the first 7 months of life in 1.5% of the children.) During the first 28 days, 30% of the children were not exposed to thimerosal and 1.6% had been exposed to more than 12.5 mcg of mercury in hepatitis B and immune globulins. Fewer than 11% of the children had been exposed to thimerosal prenatally when their mothers received vaccinations and immune globulins during pregnancy.

There were "few significant associations" among performance on neuropsychological test results and exposure to mercury in vaccines and immune globulins administered prenatally or up through 7 months of age, the authors reported.

These included a significant association between prenatal exposure to higher ethylmercury levels and a better performance on one measure of language and poorer performance on one measure of attention and executive functioning. Increasing levels of mercury exposure from birth to 7 months were associated with significantly better performance on one measure of fine-motor coordination and on one measure of attention and executive functioning.

Increased mercury exposure during the first 28 days was associated with worse performance on one measure of speech articulation and better performance on one measure of fine-motor coordination. Among the children overall, there was no association between neonatal exposure to mercury from thimerosal and total IQ, while among boys, there was a significant positive association with performance IQ, and among girls, there was a significant negative association with verbal IQ.

"Although the effect sizes were very small, the speech-articulation findings among all children and the lower verbal IQ findings among girls suggest a possible adverse association between neonatal exposure to mercury and language development," the authors said. "Conversely, the finding of higher scores on the performance IQ tests in boys makes it difficult to draw general conclusions about possible effects of neonatal mercury exposure from vaccines and immune globulins on intellectual abilities."

The weight of the evidence in this study does not support a causal association between early exposure to mercury from thimerosal-containing vaccines and immune globulins administered prenatally or during infancy and neuropsychological functioning at the age of 7 to 10 years," they concluded. "The overall pattern of results suggests that the significant associations may have been chance findings stemming from the large number of statistical tests that we performed."

Dr. Schuchat said that chance alone could explain these significant findings since a large number (378) of individual statistical comparisons were performed.

The authors disclosed some financial ties to vaccine manufacturers; Dr. Thompson is a former employee of Merck & Co.

Thimerosal has been removed from childhood vaccines, except for flu vaccines. ■

# Otitis Media 'Superbug' Holds Implications for Adults and Kids

BY KATE JOHNSON
*Montreal Bureau*

A strain of *Streptococcus pneumoniae* that is resistant to all antibiotics approved to treat acute otitis media in children has been identified as an otopathogen, according to the findings of a study.

The multidrug-resistant serotype 19A strain is not included in the pneumococcal 7-valent conjugate vaccine (PCV-7), reported Dr. Michael E. Pichichero and Dr. Janet R. Casey, from the University of Rochester Medical Center and Legacy Pediatrics, a private practice involved in the study (JAMA 2007;298:1772-8).

Children with the serotype 19A strain "represented a small subset of those in our practice, but the results are worrisome, especially since there are no new antibiotics in the pipeline for ear infections in children," said Dr. Pichichero in a statement.

"While it appears that the overall decrease in invasive pneumococcal disease still outweighs the increase in serotype 19A, it is clear that surveillance needs to continue for this important pathogen, both for strain type and antibiotic resistance," commented Dr. Elizabeth Bancroft, from the Los Angeles County Department of Public Health, in an editorial in the same issue of the journal (JAMA 2007;298:1803-4).

The prospective study included 212 children from the authors' clinic who underwent tympanocentesis for acute otitis media (AOM) during one of three respiratory seasons: September 2003–June 2004, September 2004–June 2005, and September 2005–June 2006. All children had been previously immunized with the PCV-7 vaccine.

From the tympanocentesis procedures, a pathogen was identified in 162 cases: nontypable *Haemophilus influenzae* (n = 94); *S. pneumoniae* (n = 59); and other (n = 9). Serotyping of the 59 *S. pneumoniae* pathogens revealed 9 that belonged to serotype 19A, which is resistant to all antibiotics approved by the Food and Drug Administration for the treatment of AOM in children.

Infections caused by the serotype 19A strain "continued to produce symptoms and signs of AOM until aggressive therapy was provided—either surgery or levofloxacin, an antibiotic unapproved for children," the authors noted.

While the incidence was the same, with two cases each in the 2003-2004 and 2004-2005 seasons, it increased to five cases in the 2005-2006 season. None of the first four cases was treated with effective antibiotics "because we did not perform antibiotic susceptibility testing (or serotyping) contemporaneously as we did in 2005-2006," they wrote. The first four cases were referred to an otolaryngologist for tympanostomy tube insertion, "and all continued with drainage from their tubes for 1-4 weeks despite use of antibiotic otic drops."

The five cases from the 2005-2006 season all recovered fully after treatment with levofloxacin.

"Our approach has been to use levofloxacin only for children in whom we have performed tympanocentesis and isolated a 19A serotype organism that is susceptible only to that drug," according to the authors. But, they cautioned that "this information is shared with concern that some providers and the public will interpret this finding as an indication to begin using levofloxacin or other fluoroquinolones in difficult-to-treat cases of AOM, sinusitis, or other pneumococcal infections. This could lead to disastrous results." The authors suggested that "an expanded pneumococcal conjugate vaccine to include additional serotypes may be needed sooner than previously thought," noting that U.S. trials are underway of a vaccine containing 13 serotypes, including 19A.

**The results are worrisome since there are no new antibiotics in the pipeline for ear infections in children.**

**DR. PICHICHERO**

"In the near future" more primary care providers may need to become trained to perform tympanocentesis in order to avoid the excessive use of fluoroquinolones in children.

While *S. pneumoniae* serotype 19A carries direct implications for children's health, its existence and treatment also has important implications for adults, said Dr. Keith Klugman, professor of infectious diseases at Emory University in Atlanta. "Strains that circulate among children are an important source of pneumococcal infections in adults," he said. The fact that this new strain requires fluoroquinolone treatment in children, poses a potential threat to adults.

Both Dr. Pichichero and Dr. Carey report that they have received support for otitis media trials from Ortho-McNeil, maker of levofloxacin, and that they have received compensation for consulting, speaking, and conducting clinical trials of antibiotics and vaccines from multiple companies, including Wyeth, which has a 13-valent pneumococcal conjugate vaccine in phase III trials. ■