ID CONSULT

Serotype 19A Disease Doesn't Outweigh PCV7 Benefit

The emergence of pneumococcal "replacement" serotype 19A should not lead us to view the seven-valent pneumococcal conjugate vaccine in anything other than an overwhelmingly positive light.

Since the introduction of PCV7 (Prevnar) in the United States in 2000, there has been concern that *Streptococcus pneumoniae* serotypes other than the seven included in the vaccine (4, 6B, 9V, 14, 18C, 19F, and 23F) could become more prevalent. Now, several recent reports—including one from our group at Boston University—have documented both the relative and absolute increase in the nonvaccine serotype 19A in particular, along with an associated increase in antimicrobial resistance among these isolates.

BY STEPHEN I. PELTON, M.D.

This emergence suggests that we may need to shift our treatment approach to both invasive pneumococcal disease and noninvasive respiratory tract disease. It also underscores the need for continued surveillance. However, it should *not* lessen our enthusiasm for immunizing children with PCV7, nor should it lead us to relinquish our embrace of a vaccine that continues to provide enormous benefit for both child and adult health.

Indeed, the most recent data from the Centers for Disease Control and Prevention show that the overall rate of invasive pneumococcal disease (IPD) in the United States dropped by 43%, from 24/100,000 in 1998-1999 to 13/100,000 in 2004 to 14/100,000 in 2005. Between 1998-1999 and 2005, PCV7 prevented approximately 34,900 cases of IPD caused by vaccine serotypes and 24,000 cases overall. The declines in IPD were significant in all age groups, ranging from 17% among 50- to 64-year-olds to 77% among children younger than 5 years of age, Tamara Pilishvili of the CDC reported in October of this year at the annual meeting of the Infectious Diseases Society of America (IDSA).

These data are impressive. Nonetheless, we do need to be attentive to "replacement disease" in general and serotype 19A specifically, particularly when it comes to pneumococcal disease in the most vulnerable patients: those with developing immune systems (infants), those with underlying immune system abnormalities, and those with chronic conditions that put them at increased risk for complicated pneumococcal infections.

Here in Massachusetts, surveillance identified 467 cases of IPD in residents younger than 18 years of age. Annual incidence rates were stable between 2002 and 2006, ranging from 15.9 to 18.6 per 100,000 children younger than 5 years of age. Compared with the pre-PCV7 era (1990-1991), when the annual IPD rate was about 56.9/100,000 in that age group, these numbers represent a major decline of about 70% (MMWR 2007;56:1077-80).

Of 353 isolates available for serotyping during 2001-2006, 27% (97) were serotype 19A. Both the number and proportion of cases caused by that serotype increased from 10% (6) during 2001-2002 to 41% (33) during 2005-2006, while there were no significant changes in the proportions of IPD caused by other PCV7 or PCV7-related serotypes or by non-PCV7 serotypes. Since 2005-2006, 19A has become the most common serotype isolated. The majority of these isolates were nonsusceptible to penicillin, and during 2001-2006 there were significant increases in the proportion that were nonsusceptible to amoxicillin, ceftriaxone, or three or more classes of antimicrobials (multidrug resistant). It was of concern that 14 of 94 (15%) 19A isolates were highly resistant to ceftriaxone. We could not identify any clinical or demographic factor that characterized individuals who developed highly ceftriaxone-resistant 19A IPD.

Similar data from the U.S. Pediatric Multicenter Pneumococcal Surveillance Group were reported at IDSA by Dr. Sheldon L. Kaplan of Baylor College of Medicine, Houston. In eight U.S. children's hospitals, 19A has been the most common serotype causing invasive disease each year since 2003, accounting for 46% of all cases in 2006. Since 2000, penicillin nonsusceptibility and resistance increased—from 38% and 0%, respectively, in 2000, to 75% and 34% in 2006. No 19A isolates were ceftriaxone nonsusceptible or resistant in 2000; in 2006, those numbers had risen to 19% and 3%, respectively.

And the 19A story extends beyond invasive disease. In the widely publicized report last month by Dr. Michael E. Pichichero and Dr. Janet R. Casey, nine children with acute otitis media (AOM) were found to be infected with a 19A pneumococcal serotype that was resistant to all antibiotics approved by the Food and Drug Administration for use in children with the infection. Four of the children were ultimately treated with tympanostomy tube insertion, and the other five with levofloxacin (JAMA 2007;298:1772-8).

Although antimicrobial-resistant 19A has clearly taken hold in the PCV7 era, there is evidence that the vaccine is only one of several reasons for its emergence. In another IDSA abstract, Dr. Eunhwa Choi of Seoul (Republic of Korea) National University Medical College reported that increases in the proportion of 19A among clinical isolates of invasive disease occurred over a 15-year period prior to the introduction of PCV7 in Korea. In children under 5 years of age, 19A increased from 0% in 1991-1994 to 8% in 1995-1997, and to 20%-26% in 2001-2006. All of the 19A isolates were multidrug resistant.

Given these data, vancomycin remains first-line therapy for all suspected cases of pneumococcal meningitis, as well as for those who are severely ill. For the more common respiratory infections, we now need to consider serotype 19A as a potential etiology in a child who does not respond to traditional antibiotic therapy in 48-72 hours. In the case of AOM, tympanocentesis to identify the specific pathogen is the preferred approach. When that is not possible, a nasopharyngeal swab for identification of *S. pneumoniae* 19A is acceptable to identify children at risk for infection due to this multidrug resistant pathogen.

While waiting for the results in a child with respiratory tract infection who is well enough to be managed as an outpatient, ceftriaxone in doses of 75-100 mg/kg once per day, given either intramuscularly or intravenously for a minimum of 3 days is appropriate. Whether this will work depends on the level of resistance. If cultures reveal *S. pneumoniae* 19A and either the minimum inhibitory concentration is above 6-8 mg/mL or the child fails to respond to ceftriaxone, an alternative approach is necessary.

In that setting, I would use levofloxacin (the only fluoroquinolone available in a suspension). The American Academy of Pediatrics' recent guidelines on the use of fluoroquinolones in children (Pediatrics 2006;118:1287-92) did not specifically address this particular clinical scenario, but I agree with Dr. Pichichero and Dr. Casey that AOM caused by multidrug-resistant 19A *S. pneumoniae* is an appropriate off-label use once you have documentation that 19A is the likely pathogen. If the child can't tolerate levofloxacin or has a contraindication to a quinolone, surgical drainage of the ear with tube placement is the only remaining option.

Future vaccines may address the 19A problem. GlaxoSmithKline's 10-valent Synflorix will contain a 19F capsular polysaccharide that results in some functional activity against serotype 19A. Wyeth's 13-valent conjugate pneumococcal vaccine will actually contain serotype 19A capsular polysaccharide. Both vaccines are in phase III clinical trials and could be licensed in 2009-2010. While I don't expect IPD to ever completely disappear from the planet, these second-generation vaccines could further reduce the number of cases of IPD in children and potentially adults.

I am on the advisory board for both the GSK and Wyeth pneumococcal vaccine programs. I also have an investigator-initiated grant from Wyeth for statewide surveillance. I have no current relationship with the makers of levofloxacin. ■

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Campylobacter Incidence Drops, Yet Is High in Young Children

BY DOUG BRUNK
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SAN DIEGO — Cases of *Campylobacter* infections in the United States declined by an average of 30% between 1996 and 2006, according to an epidemiologist from the Centers for Disease Control and Prevention.

However, the incidence remains highest among children under 5 years of age, and males have a higher incidence compared with females in all age groups except ages 20-29 years.

Those are key findings from an analysis of data from the Foodborne Diseases Active Surveillance Network (FoodNet), which began tracking *Campylobacter* infections in 1996, reported the CDC's Mary E. Patrick during a poster session at the annual meeting of the Infectious Diseases Society of America. The FoodNet project is a partnership involving the CDC, the U.S. Department of Agriculture–Food Safety Inspection Service, the U.S. Food and Drug Administration, and designated FoodNet sites in 10 states.

Ms. Patrick and her associates calculated gender- and age-specific incidence rates of *Campylobacter* infections that were reported by FoodNet sites between 1996 and 2006, and compared the changes in rates over the time period.

In 2006, the rates of *Campylobacter* infections were higher among males (14 per 100,000 persons) than among females (11 per 100,000 persons). The overall crude rate of laboratory-confirmed *Campylobacter* infections in 2006 was 13 per 100,000 U.S. residents. From baseline to 2006, the incidence declined 30% overall.

The largest decline by age group, 47%, was observed in adults aged 20-29 years, followed by children less than 1 year of age at 41%, adults aged 30-39 years at 40%, and children aged 1-4 years at 30%, reported Ms. Patrick.

Among infants less than 1 year of age, the rate of *Campylobacter* infections in 2006 was 37 per 100,000 persons and the rate among children aged 1-4 years was 23 per 100,000 persons. These rates were significantly higher compared with any other age group. In fact, the lowest 2006 rate, 7 per 100,000 persons, was found not among adults but in children and adolescents aged 10-14 years.

"Obviously infants are not consuming the main sources of *Campylobacter* such as chicken," Ms. Patrick said in an interview. "We're thinking that there is a lot of cross-contamination from sources such as raw chicken juices in the kitchen. You can reduce the risk of cross-contamination by separating raw and cooked products, and making sure that you wash your hands, utensils, and cutting boards before and after contact with raw poultry."

The 10 states with FoodNet sites are California, Colorado, Connecticut, Georgia, Maryland, Minnesota, New Mexico, New York, Oregon, and Tennessee. ■