BY MARY ANNE JACKSON, M.D.

ID CONSULT

Despite PCV7 Results, Vigilance Needed

When the 7-valent pneumococcal conjugate vaccine was first introduced in 2000, many of us had high hopes that it would bring with it a new era in which we could leave invasive pneumococcal disease out of the equation and not have to worry that we might be missing a case of meningitis.

Indeed, the vaccine has resulted in an impressive overall reduction in pediatric invasive pneumococcal infection.

Unfortunately, emerging data now suggest that rates of invasive disease caused by nonvaccine serotypes are rising and that the overall disease reduction seen in the first 5 years since licensure of the vaccine may have leveled off.

With *Haemophilus influenzae* type b (Hib), all invasive disease was caused by a single strain. Following the universal implementation of the Hib vaccine in the 1990s, invasive Hib disease has virtually disappeared.

In contrast, pneumococcal infection involves multiple serotypes. This alone inherently limits the success that the 7-valent pneumococcal conjugate vaccine (PCV7) may have and explains part of the changing epidemiology.

Ongoing surveillance is extremely important now, and will continue to be as we move forward with new vaccines containing additional serotypes.

Here at Children's Mercy Hospital, my colleagues Dr. Douglas S. Swanson and Dr. Christopher J. Harrison compared data from patients with invasive pneumococcal disease in the pre-PCV7 era of 1998-2000 with data from 2001 through March 2006. They found that the total number of invasive pneumococcal infections in Kansas City children has decreased from prevaccine years, with the average annual number of invasive pneumococcal disease cases declining by about 50%, from 43 cases/year during 1998-2000 to 21 cases/year from 2001 through March 2006. This is remarkable and consistent with data from other pediatric hospitals.

Steenhoff et al. recently compared data on pneumococcal bacteremia from the pre-PCV7 era in Philadelphia with data from 2001 through May 2005, and found that the incidence decreased by 57% (CID 2006;42:907-14).

Schutze et al. similarly noted a decrease in disease incidence of invasive disease in Arkansas from a high of 5.78/100,000 population to 3.02/100,000 population in the postvaccine era (Pediatr. Infect. Dis. J. 2004;23:1125-9).

Occult pneumococcal bacteremia has been by far the most common of the invasive infections that pediatricians have encountered in the past and appears to be the most common invasive infection impacted by PCV7. This entity, which traditionally occurs in infants from 6 to 36 months of age with high fever and no localizing findings, generally has a benign outcome. Complications, including meningitis, occur rarely.

Reduction of more virulent diseases like empyema and meningitis with PCV7 has been clearly demonstrated. However, data suggest that pneumococcus continues to play an important role in complicated pneumonia with empyema.

In a study from the United Kingdom published earlier this summer, locally presenting pleural empyema cases in children increased threefold during 2003-2004. Antigen analysis of empyema fluid identified *Streptococcus pneumoniae* in 27 of 29 cases for whom samples were available, and capsular polysaccharide type 1 was confirmed in 18 of those (Pediatr. Infect. Dis. J. 2006;25:559-60).

The authors, Fletcher et al. of the South West of England Invasive Community Acquired Infection Study Group, concluded that "use of a conjugate vaccine without serotype 1 antigen would have had limited impact on this morbidity in our region."

Postvaccine licensure studies have shown a decline in incidence of pneumococcal meningitis cases. In our review, this was less remarkable, with an average of 6.7 cases/year in 1998-2000 and 4.8 cases/year from 2001 through March 2006. This year alone we have treated eight patients with pneumococcal meningitis.

Serotype replacement is a major issue. In our institution since 2001, only 2 of the 20 isolates that have been serotyped are vaccine-specific serotypes. The apparent failure of the vaccine to impact 19A disease is notable, because it was hoped that cross-protection with vaccine serotype 19F would occur.

Kaplan et al. of the U.S. Pediatric Multicenter Pneumococcal Surveillance Group recently examined this issue. Investigators from eight children's hospitals have been prospectively identifying children in their centers with invasive infections caused by *S. pneumoniae* for the last 9 years. They found that serotypes 15, 19A, and 33 were the most common nonvaccine serotypes and accounted for almost half of nonvaccine isolates recovered from vaccinated patients in the postvaccine era (Pediatrics 2004;113:443-9).

The vaccine's impact on antimicrobial resistance is less clear. Schutze et al. noted that 44% of isolates were nonsusceptible to penicillin in 1998-2000, not significantly different from the 46% seen in the postvaccine era of 2001-2003.

In our institution, 34% of the invasive isolates in 1998-2000 were penicillin nonsusceptible, compared with 42% in 2001 through March 2006. The latter finding was not statistically significant, but it does support data from other studies suggesting that the vaccine's impact on cases of invasive disease caused by penicillin nonsusceptible pneumococcal strains warrants continued monitoring.

In a study that was funded in part by Wyeth et al. of Kaiser Permanente, Oakland, Calif., found that the herd immunity conferred by individuals vaccinated with PCV7 resulted in significant savings in cost per life-year saved during the first 5 years following introduction of the vaccine.

However, they acknowledged, "if serotype replacement increases over time, it is possible that the efficacy of the vaccine—both for the vaccinated and nonvaccinated populations—could decline in the future" (Pediatr. Infect. Dis. J. 2006;25:494-501).

Current efforts to develop new multivalent pneumococcal conjugate vaccines will pay off in the long run. As we turn our attention to the next phase of development, we also must keep in mind and prioritize the needs in the developing world.

According to the World Health Organization, as many as 1 million children under 5 years of age die every year of pneumococcal pneumonia, meningitis, and sepsis. In populations with high child mortality rates, pneumonia is the leading infectious cause of mortality, accounting for about 20%-25% of all deaths in children.

Clinical trials now underway in Africa and elsewhere are utilizing conjugate pneumococcal vaccines containing between 7 and 13 serotypes. While serotype replacement could eventually occur in the developing world as well, the immediate impact in reducing disease and death would be enormous and undeniably worthwhile.

Phase III studies are ongoing with one prototype that contains 13 serotypes including 19A, 1, 3, 5, 6A, and 7V. Investigators estimate that in the United States, the 13-valent vaccine will cover around 60% of the remaining disease in children and expand coverage for strains prevalent in developing countries.

Despite the success of conjugate pneumococcal vaccine, it is clear that it will not be associated with the type of triumph we achieved with the Hib vaccine.

For the near future at least, we will need to remain vigilant when evaluating febrile children, understanding the clinical setting in which pneumococcal infection may occur. As the epidemiology of pneumococcal infection evolves, it is important for clinicians to continue to stay abreast of data regarding disease incidence, emerging serotypes, bacterial resistance, and future advances. ■

DR. JACKSON *is chief of pediatric infectious diseases at Children's Mercy Hospital, Kansas City, and professor of pediatrics at the University of Missouri–Kansas City.*

Vaccine Refusal Triggered 2005 Measles Outbreak in Indiana

BY MITCHEL L. ZOLER
Philadelphia Bureau

The largest, documented measles outbreak to hit the United States in a decade infected 34 people in Indiana last year.

The vast majority of the infected were children whose parents had objected to immunization.

The Indiana outbreak "shows that states, localities, and health care organizations need to implement more effective policies to protect persons traveling abroad, home-schooled children, and health care workers against measles and other vaccine-preventable diseases," wrote Amy A. Parker of the Centers for Disease Control and Prevention in Atlanta, and her associates.

The CDC team found that all but two of the 34 infections were in people who had never been vaccinated for measles; 30 of the patients (88%) were children aged 19 years or younger.

"Concern about adverse events, particularly related to media reports of a putative association between vaccinations and autism and of the dangers of thimerosal, appeared to play a major role in the decision of these families to decline vaccination," Dr. Parker and her coinvestigators found.

'As long as some groups ... respond to spurious claims about the risks of the vaccine by refusing to vaccinate their infants, further outbreaks will occur.'

The index patient was an unvaccinated 17-year-old girl who returned to her community after a church-mission trip to a Romanian orphanage, where she became infected.

Despite having prodromal symptoms, she attended a large gathering of church members the day after she got home. Eighteen patients were infected at the meeting (N. Engl. J. Med. 2006;355:447-55).

A school survey in 2004-2005 indicated that 98% of kindergartners and 98% of sixth graders in Indiana had received the recommended two doses of measles vaccine. But church officials estimated that a much smaller percentage of the 500 people who attended the Indiana meeting had been immunized, perhaps 90% or less.

"As long as some groups within a given community respond to spurious claims about the risks of the vaccine by refusing to vaccinate their infants, further outbreaks will occur," commented Dr. E. Kim Mulholland, a professor of infectious disease epidemiology at the London School of Hygiene and Tropical Medicine, in a perspective that ran with the article (N. Engl. J. Med. 2006;355:440-3). ■