Despite PCV7 Results, Vigilance Needed

W hen the 7-valent pneumococcal conjugate vac-
cine 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 dis-
case 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 sug-
gest 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 im-
plementation of the Hib vaccine in the 1990s, invasive Hib disease has virtually disappeared.

In contrast, pneumococcal infection in-
volves multiple serotypes. This alone in-
herently limits the success that the 7-valent pneumococcal conjugate vaccine (PCV7) may achieve because of part of the chang-
ing epidemiology.

Ongoing surveillance is extremely im-
portant now, and will continue to be as we move forward with new vaccines con-
taining 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 infections in Kansas City with data from 2001 through March 2006. They found that the total number of in-
vasive pneumococcal infections in Kansas City have decreased from prevac-
cine years, with the average annual num-
ber of invasive pneumococcal disease cas-
es 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. Sternhoff 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 77% (CID 2006;43:321-5).

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 in-
vasive infections that pediatricians have en-
countered in the past and appears to be the most common invasive infection impact-
ed by PCV7. This entity, which tradition-
ally occurs in infants from 6 to 16 months of age with high fever and no localizing
findings, generally has a benign outcome. Complications, including meningitis, oc-
curred rarely.

Reduction of more virulent diseases
like encephalitis 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 pre-
vaccination cellulitis and empyema were increased threefold from 2003-2004. Antigen analysis of empyema fluid identi-
fied Streptococcus pneumoniae in 27 of 29 cases for whom samples were available, and capular polysaccharide type 1 was confirmed in 18 of those (Pediatr. Infect. Dis. J. 2006;25:359-60).

The authors, Fletcher et al. of the South West of England Invasive Community Ac-
quicale Infection Study Group, concluded that “use of a conjugate vaccine without serotype 1 antigen would have had limit-
ting impact on this morbidity in our region.”

Postvaccine licensure studies have shown a decline in incidence of pneumo-
coccal meningitis cases. In our review, this was less remarkable, with an average of 6.7 cases/year in 1998-2000 and 4.8 cas-
es/year from 2001 through March 2006. This year alone we have treated eight pa-
tients 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 this dis-
ease is notable, because it was hoped that cross-protection with vaccine serotype 19F would occur.

Kaplansky et al. of the U.S. Pediatric Multicenter Pneumococcal Surveillance Group recently examined this issue. In-
vestigators from eight children’s hospitals have been prospectively identifying chil-
dren in their centers with invasive infec-
tions caused by S. pneumoniae for the last 9 years. They found that serotypes 15, 19A, and 33 were the most common nonvac-
cine 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 an antimicrobial resistance is less clear. Schutze et al. not-
ed that 44% of isolates were nonsensi-
tible to penicillin in 1998-2000, not signifi-
cantly different from the 46% seen in the postvaccine era of 2001-2005.

In our institution, 34% of the invasive isolates in 1998-2000 were penicillin non-
susceptible, compared with 42% in 2001 and 48% in 2004. The latter increase was not statistically significant, but it does support data from other studies suggest-
ing that the vaccine’s impact on cases of invasive disease caused by penicillin non-
susceptible pneumococcal strains warrants continued monitoring.

In a study that was funded in part by Wyeth et al. of Kaiser Permanente, Oak-
land, Calif., found that the herd immuni-
ty 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 vac-
cine.

However, they acknowledged, “if serotype replacement increases over time, it is possible that the efficacy of the vac-
cine—both for the vaccinated and nonvac-

Current efforts to develop new multi-
valent pneumococcal conjugate vaccines will pay off in the long run. As we turn our attention to the next phase of develop-
ment, we also must keep in mind and pri-
mance the needs in the developing world.

According to the World Health Organi-
ization, as many as 1 million children un-
der 5 years of age die every year of pneu-
 mococcal pneumonia, meningitis, and sepsis. In populations with high child mor-
tality rates, pneumonia is the leading in-
fected cause of mortality, accounting for about 20%-25% of all deaths in chil-
dren.

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

Phase III studies are ongoing with one prototype that contains 13 serotypes in-
cluding 19A, 1, 3, 5, 6A, and 7F. Investi-
gators 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 pneu-
ococcal 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 oc-
cur. As the epidemiology of pneumococ-
cal infection evolves, it is important for clinicians to continue to stay abreast of data regarding disease incidence, emerging serotypes, bacterial resistance, and future advances.

BY MARY ANNE JACKSON

The largest, documented measles out-
break 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 organi-
izations need to implement more effective policies to protect persons traveling abroad, home-school 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 vac-
cinated for measles; 30 of the patients (88%) were children aged 19 years or younger.

"Concern about adverse events, par-
ticularly related to the possible mis-
conception 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. Park-
er et al. investigators found.

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

Despite having prodromal symp-
toms, 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 rec-
ommended 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 im-
munized, perhaps 90% or less.

"As long as some groups within a giv-
en 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 infec-
tious disease epidemiology at the London School of Hygiene and Tropical Medi-
cine, in a perspective that ran with the ar-