Replacement Pneumococcal Disease in Perspective

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(See the article by Bender et al. on pages 1346–52)

Bender et al. [1] describe 33 patients with pneumococcal necrotizing pneumonia who were admitted to Primary Children’s Medical Center (Salt Lake City, Utah) from January 2001 through March 2006. One-third of all hospitalized cases of pneumococcal pneumonia in the period after the introduction of 7-valent pneumococcal conjugate vaccine (PCV-7) were complicated by radiographic evidence of necrosis (evidence of necrotic lung, lung abscess, or pneumatocele), compared with 13% of cases before 2001. This group has also reported an increase in pediatric parapneumonic empyema beginning the same year [2]. The number of cases of parapneumonic empyema among children also increased in Spain and France during the period following the introduction of PCV-7. At Primary Children’s Medical Center, 88% of cases of necrotizing pneumonia and 86% of cases of parapneumonic empyema identified from January 2001 through March 2006 were due to nonvaccine serotypes. These reports represent the latest part of the changing ecology of pneumococcal disease in association with the universal vaccination of infants with PCV-7.

PCV-7 was introduced in 2000 for universal vaccination of infants <2 years of age and selected vaccination of high-risk toddlers 2–5 years of age. At that time, the 7 serotypes incorporated into this vaccine and their “cross reactive” serotypes were the cause of >85% of cases of invasive pneumococcal disease (IPD) in children in North America. Following the introduction of PCV-7, a rapid decrease in the incidence of IPD occurred as a result of the direct effect of vaccination. A decrease in the incidence of IPD in children <5 years of age of ~70% was apparent within 2 years after introduction of PCV-7 in Massachusetts [3]. The populations with a reduction in the incidence of disease included high-risk groups, such as Alaskan native children, children with sickle cell disease, and children with HIV infection [4, 5]. In addition to the prevention of IPD in vaccinated children, a dramatic shift in the pneumococcal serotypes found in the nasopharynx of asymptomatic children was observed, with a progressive decrease in carriage of vaccine serotypes and an increase in the carriage of nonvaccine serotypes [6]. By 2007, 96% of pneumococci recovered from colonized children were nonvaccine serotypes [7]. The reduction in exposure of unvaccinated children and adults to vaccine serotypes resulted in substantial decreases in the incidence of IPD among unvaccinated children, infants too young to be fully vaccinated, and adults of all ages, including those >65 years of age [8,9]. The herd effect was estimated to prevent ~20,000 cases in unvaccinated individuals annually.

One of the consequences of the dramatic shift in serotypes circulating in the pediatric community has been increases in the incidence of disease due to infection with nonvaccine serotypes—so-called “replacement disease.” Although the increase in disease incidence among children <5 years of age has been modest (~11 cases per 100,000 children), compared with the decrease in the incidence of vaccine serotype–related disease (~80 cases per 100,000 children), concerns for high-risk populations, specific clinical syndromes, and emerging multidrug resistance warrant ongoing surveillance and require clinical attention [10]. A near doubling in the incidence of IPD due to infection with nonvaccine serotypes has been reported among Alaskan native children, threatening to return incidence rates of pneumococcal disease to near pre–vaccine era levels [5]. Although such increases in disease due to infection with nonvaccine serotypes are currently isolated to this high-risk population, whether additional high-risk groups, such as children with sickle cell disease or HIV infection or young infants, are at disproportionate risk requires further surveillance.

Specific clinical issues have emerged as a consequence of both the increase in the incidence of disease due to infection with nonvaccine serotypes of pneumococci and
the increasing acquisition of resistance to antimicrobial agents among these strains. An increasing number of cases of pleural empyema have been occurring among children living in the 5-state area of the intermountain West (Utah, Idaho, Wyoming, Nevada, and Montana) due to serotypes 1, 3, and 19A; there has also been an increase in the incidence of necrotizing pneumonia due to serotype 3 and serogroup 19, as reported by Bender et al. [1]. It is not surprising that serotype 3 has been linked with cases of complicated pneumonia, because it was the most common serotype isolated (accounting for 16% of isolates) from patients with cases of pneumococcal empyema at Boston City Hospital (Boston, MA) during selected years from 1947 through 1974 [11]. It was also prominent in all types of focal pneumococcal infections. As discussed by Bender et al. [1], Kaplan et al. [12] have reported an increase in the incidence of bacteremia due to serotype 3 at 8 children’s hospitals subsequent to the introduction of PCV-7. Mastoiditis and recalcitrant acute otitis media due to multidrug-resistant serotype 19A have been reported by Kaplan et al. [12] and Pichichero et al. [13], respectively. Kaplan et al. [12] observed an increase in cases of mastoiditis beginning in the period 2003–2004. The cases were characterized by coalescent mastoiditis requiring surgical intervention and intravenous antibiotic therapy. Antimicrobial susceptibility testing of isolates from these cases demonstrated resistance to penicillin, ampicillin, ceftriaxone and other cephalosporins, macrolides, and trimethoprim-sulfamethoxazole and susceptibility to vancomycin, linezolid, and quinolones, such as levofloxacin. Recalcitrant acute otitis media due to multidrug-resistant 19A was reported in 9 children in Rochester, New York. Treatment required drainage, most often with ventilation tubes, and targeted antimicrobial therapy, including off-label use of levofloxacin in some of the cases. Even with aggressive management, several children had otitis through the tympanostomy tube that was slow to resolve.

Cyclic patterns of disease caused by infection with various pneumococcal serotypes have been observed previously, and in the past, variations appeared to be independent of each other. In the current era, there is no doubt that the reduction in carriage of vaccine serotypes has been permissive for nasopharyngeal colonization with nonvaccine serotype pneumococcal isolates. However, there is more to the picture, because the incidence of empyema associated with serotype 1 has increased in the previous decade in the United Kingdom in the absence of vaccine pressure and antimicrobial resistance; in addition, antibiotic-resistant serotype 19A has increased as a cause of IPD in South Korea and of acute otitis media in Israeli Bedouins during the same period without universal vaccination with PCV-7. These variations in serotype distribution by time and geographic location remain without obvious biologic explanations.

I finish 2 clear lessons from the changes in the ecology of pneumococcal disease following the introduction of universal vaccination in the United States with PCV-7. First, antimicrobial resistance has continued to evolve among those serotypes that are commonly found in the nasopharynx, and further efforts to improve diagnosis of bacterial respiratory tract illness and judicious use of antimicrobial therapy are necessary to reduce selective pressure, which fosters the expansion of drug-resistant clones. Second, ongoing surveillance of IPD and respiratory tract infection is necessary. In 1977, Dr. Maxwell Finland wrote that, to be successful, pneumococcal vaccines must contain antigens against the specific pneumococcal types that are occurring or that can be expected to occur in the population [11]. The success of the first-generation PCV-7 both encourages us that the morbidity and mortality of pneumococcal disease can be substantially reduced worldwide and informs us that second-generation vaccines must incorporate additional serotypes, identify through surveillance, as non-vaccine serotypes emerge as important pathogens in the community.

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