Capsules, Clones, and Curious Events: Pneumococcus under Fire from Polysaccharide Conjugate Vaccine

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(See the article by Byington et al. on pages 21–9)

Many of us had tears in our eyes at the unblinding of data from the sentinel trial of heptavalent pneumococcal conjugate vaccine (PCV7 [Prevnar; Wyeth Lederle Vaccines]) involving ~38,000 infants enrolled in the Northern California Kaiser Permanente medical program [1]. In an intent-to-treat analysis, 49 cases of invasive disease due to Streptococcus pneumoniae serotypes contained in PCV7 occurred in the control group, compared with 3 cases in the PCV7 group. The miracle associated with the Haemophilus influenzae b conjugate vaccine was being recreated with PCV7. By covalently linking protein to polysaccharide, the infant’s immature immune system is tricked into responding to the polysaccharide, which it would not do naturally. Additionally, the protein linkage elicits a T lymphocyte–dependent response, thus stimulating long-lived lymphocyte lines that will respond to a rechallenge with earlier and more vigorous antibody responses. Licensure of PCV7, recommendation for universal vaccination of infants at 2, 4, 6, and 18 months of age, and implementation of a vaccination program came swiftly during the first half of 2000.

Good news poured in of a remarkable reduction in the rates of invasive disease due to vaccine serotypes and to serotypes related to those in the vaccine, as well as a reduction in the rates of “lesser” pneumococcal diseases. First came the results of blinded, controlled trials. Investigators in the Northern California Kaiser Permanente trial observed a 97.4% reduction in the rate of invasive pneumococcal disease (IPD) due to PCV7 serotypes, an 89.1% reduction in the rate of IPD due to any pneumococcal serotype, a 23% reduction in the rate of radiographically confirmed pneumonia, a 7.8% reduction in the rate of physician visits for acute otitis media (AOM), a 5.7% reduction in the rate of antibiotic prescription, and a 24% reduction in the rate of tympanostomy tube placement [1]. Researchers in a Finnish AOM trial recorded a 75% reduction in the rate of invasive pneumococcal disease (IPD) due to vaccine serotypes and a 54% reduction in the rate of AOM due to any S. pneumoniae serotype [2].

Postlicensure studies at Kaiser Permanente through March 2003 showed a 100% reduction in the incidence of IPD due to vaccine serotypes and to PCV7-related serotypes among children <2 years of age [3]. Despite the unthinkable nationwide PCV7 shortages beginning in December 2001, a similar, albeit less dramatic reduction in the rate of IPD has been shown in every regional and population-based study across the United States since the introduction of PCV7 [4–10]. Additionally, PCV7 has been shown to be effective in populations with a higher risk of IPD, such as African Americans, children who attend out-of-home day care centers, children with sickle cell disease or HIV infection, and even many individuals with genetically determined unresponsiveness to pneumococcal polysaccharide. Reductions in the rate of S. pneumoniae AOM that are equivalent or superior to that reported in the prelicensure trial [1] have been found in all US studies [11–13].

Only a minor dampening of spirit has resulted from a recent publication [7] suggesting that part of the explanation of the reduced incidence of IPD during the postlicensure period could be the serendipitous occurrence of milder influenza seasons. On Long Island, during the pre-PCV7 period, 68% of the cases of IPD occurred during the winter. During the post-PCV7 period, 68% of the cases of IPD occurred during the winter. During the post-PCV7 period, there was a 37% reduction in the incidence of IPD across all age groups and a 47% reduction in the rates of hospitalization, emergency department visits, and school absenteeism associated with influenza-like illness [7]. One could postulate, alternatively, that pneumococcus may cause more cases of nonspecific respiratory tract illness than...
was previously thought. By use of an ecologic approach rather than a *S. pneumoniae*-based microbiologic approach to compare the illness burdens during the post- and prelicensure periods, Poehling et al. [14] showed a 10-fold reduction in the rates of pneumonia and invasive disease diagnoses and a 100-fold reduction in the rate of AOM diagnosis, compared with the rates based on microbiologic confirmation. In a blinded, controlled study of a novel 9-valent pneumococcal conjugate vaccine (PCV9) in Israel, PCV9 recipients had significantly fewer cases of nonspecific upper and lower respiratory tract illnesses and used fewer antibiotics for each indication [15].

Herd immunity due to PCV7 use was documented in a nationwide population-based study published in 2003 [4]. Just as the risk of IPD in adults had been associated with contact with children, PCV7 vaccination of children was now associated with a 32% reduction in the incidence of IPD among adults aged 20–39 years and a 10% reduction among adults aged ≥65 years (the parenting and grandparenting ages, respectively). Herd immunity is undoubtedly the benefit of the vaccine’s effect on respiratory tract carriage. In a controlled trial, Choo et al. [16] showed that PCV7 primes for mucosal memory responses in infants who, when given pure pneumococcal polysaccharide at 13 months of age, have marked increases in local production of IgA (and possibly IgG), compared with unvaccinated controls. Whether because of mucosal response to vaccine and/or mucosal presence of antipneumococcal IgG from serum, PCV7 vaccination decreases the prevalence of carriage of PCV7 *S. pneumoniae* serotypes and vaccine-related serotypes by ∼50%. The dividend is a decreased rate of *S. pneumoniae* transmission to close contacts.

With more than 60 million doses of PCV7 having been distributed by the end of 2004 in the United States, safety data have been reassuring, with acceptable local and systemic reactions and no signals of serious adverse events. Can we be as sanguine about the absence of adverse microbiologic effects? In this issue of *Clinical Infectious Diseases*, Byington et al. [17] report data on IPD due to nonvaccine serogroups of *S. pneumoniae* in children <18 years of age in the intermountain west (IMW) of the United States. They performed a population-based study by retrospectively reviewing the discharge diagnostic codes for all culture-confirmed cases of IPD (including complicated and uncomplicated pneumonia) during the pre-PCV7 period of 1996–2000 and the post-PCV7 period of 2001–2003. Vaccine uptake was estimated to be ∼54% for Utah children <3 years of age during 2001–2003. They also performed serogroup analysis of isolates from children who presented to Primary Children’s Medical Center (Salt Lake City, UT) with IPD during 1997–2003, the only tertiary care referral children’s hospital in the IMW. During the pre-PCV7 period at Primary Children’s Medical Center, 73% of isolates were from serogroups contained in PCV7, rather than the national average of 89%. Byington and colleagues reported a modest (27%) reduction in the overall incidence of IPD across all age groups during the study period, although the incidence of parapneumonic empyema increased from 10.3 to 14.3 cases/100,000 population (P = .01). They also noted a relative reduction in the incidence of IPD classified as occult bacteremia (from 14% during the prevaccine period to 5% during the postvaccine period) and a relative increase in the incidence of empyema (from 16% to 30%); the mean age of children with empyema was higher than that of children with other IPDs. The total number of cases of IPD decreased only slightly from the prevaccine period to the postvaccine period, but the percentage of cases due to serogroups contained in PCV7 decreased from 73% during 1997–2000 to 50% during 2001–2003 (P < .001). The absolute number of isolates of nonvaccine serogroups increased from a mean of 8.75 during 1997–2000 to 26 in 2003. Although nonvaccine serogroups 1 and 3 accounted for 21 (40%) of 53 nonvaccine-serogroup isolates recovered during 2001–2003, an array of 8 nonvaccine serogroups recovered during 2001–2003 only were also found, with only 1–2 isolates recovered per serogroup.

The authors acknowledge several limitations of their study. One involves the identification of *S. pneumoniae* isolates according to serogroup rather than serotype. At least 90 serotypes of *S. pneumoniae* have been determined on the basis of antigenic differences in capsular polysaccharide. (Unencapsulated strains also exist and are of minor apparent importance in flora and in disease, with the noteworthy exception of epidemic conjunctivitis.) In the American system, pneumococcal serotypes were numbered consecutively according to time of first identification. In the Danish system, capsular serotypes were distinguished and then clustered into serogroups of antigenic similarity. For example, Danish serogroup 19 includes serotypes F, A, B, and C, which correspond to serotypes 19, 57, 58, and 59, respectively, in the American system. Vaccination with PCV7 (which includes serogroups 4, 6B, 9V, 14, 18C, 19F, and 23F) leads to protection against vaccine serotypes, as well as variable but substantial protection against vaccine-related serotypes, which are correlated with (but do not necessarily belong to) the serogroups contained in the vaccine. Although the use of serogroups, as in the study by Byington and colleagues, permits less granularity of data, such use might overestimate the efficacy of PCV7 and underestimate the emergence of nonvaccine serotypes.

The clinical emergence of nonvaccine serotypes described by Byington et al. [17] touches a nerve at the center of concern about pneumococcal vaccination. What will be the collateral effect on vaccinees and their contacts of reducing nasopharyngeal colonization with *S. pneumoniae* vaccine serotypes? Will nonvaccine serotypes merely take their place? Will herd effect preclude episodes of colonization?
with vaccine serotypes that boost long-term protection? It is ironic that the effects on colonization that are central to multiple aspects of the success of conjugate vaccines are also the crux of concern. The same concerns arose with the implementation of conjugate H. influenzae b vaccination. In the era of H. influenzae b conjugate vaccines, there has not been significant serotype replacement with non-b strains of H. influenzae in cases of disease or carriage. But H. influenzae b is not pneumococcus. H. influenzae exists as part of the normal flora of the respiratory tract, predominantly in an unencapsulated, nontypeable form. H. influenzae b carriage was not inevitable during early childhood before the H. influenzae b vaccine was licensed; contact largely with non-Haemophilus flora led to accrual of cross-reacting immunity against H. influenzae b in children by the time they were school aged. Encapsulated, invasive H. influenzae has just 6 capsular serotypes. Before licensure of the H. influenzae b conjugate vaccine, the vast majority of cases of invasive H. influenzae disease in the United States were due to isolates with capsular type b.

If only pneumococcus could act more like H. influenzae. Pneumococcus has extensive genetic diversity in encapsulation and pathogenicity. At any point in time, encapsulated S. pneumoniae is present in the nasopharynx of roughly 30%–40% of children and 20%–30% of adults, depending on the methods used for detection, the season, the demographic characteristics of the population under study, and the presence of nonpneumococcal illness. Capsular evasion due to vaccination with PCV7, PCV9, the 11-valent pneumococcal conjugate vaccine, and so on is unlikely to leave “campsites vacant.” Concerns involve the likelihood and effect of acquisition of new S. pneumoniae strains with nonvaccine-serotype polysaccharide capsules (i.e., serotype replacement) and acquisition by virulent vaccine-serotype strains of novel, nonvaccine-serotype capsules (i.e., capsular switching). These events, which are difficult to detect, and their potential effects, which are difficult to predict, should be considered separately.

Serotype replacement denotes a new burden of colonization or disease as a result of vaccination, not merely an increased relative importance concomitant with decreased burdens. In one pre-PCV7 study [18], one-third of individuals who were colonized with pneumococcus had minor density of second serotypes detectable. Whether replacement serotype strains detected during the post-PCV7 period are the result of new acquisitions or of unmasking of strains that were present but less competitive in the presence of vaccine serotypes is difficult to know from studies to date, but a mathematical model for analyzing such events has been proposed [19]. Community-randomized vaccine trials, such as those being performed in an American Indian population in the southwest United States, are best suited to evaluate serotype replacement and unmasking [20]. The magnitude of serotype replacement (or unmasking) on carriage likely depends on multiple factors, most importantly, the preexisting frequency of carriage of nonvaccine serotypes as well as host factors, the environment of transmission, and the extent of PCV7 vaccination.

The current time frame, approaching 5 years after the inauguration of PCV7 vaccination, probably permits the first possible glimpse of S. pneumoniae serotype replacement, although the more definitive picture awaits time and the full implementation of the vaccination program. The potential effect of colonization with nonvaccine S. pneumoniae serotypes depends entirely on whether new serotypes cause disease. Serotype replacement is highly desirable if new serotypes colonize harmlessly and lead to broadened natural immunity in young children. The magnitude of such a positive effect would increase as vaccine penetration increased, permitting transmission of replacement S. pneumoniae serotypes to other vaccinees and contacts. If replacement serotypes were highly virulent, however, the incidence of disease could return to prevaccine levels or worse. The latter seems unlikely, at least if it is caused by replacement or unmasking, because PCV7 serotypes were selected hierarchically on the basis of invasiveness potential, especially with regard to the bloodstream and downstream sites of infection. It is possible, however, that minor existing serotypes or replacement serotypes could overcome the requirement to compete locally and, empowered by density, invade the bloodstream or survive to express an intrinsically different virulence in an area such as the respiratory tract, where noncapsular characteristics have certain cachet.

During the pre- and postlicensure periods, surveillance for serotype replacement or unmasking has been fixed on detectable events that are most likely (AOM) and serious (bloodstream infection). In the first Finnish study by Eskola et al. [2], which involved prelicensure clinical trials of PCV7, serotype replacement was already documented in patients with AOM. Although replacement of PCV7 S. pneumoniae serotypes with nonvaccine serotypes in nasopharyngeal colonization and AOM has been documented in every study since licensure of PCV7 in the United States, it has not occurred to an extent that renders PCV7 noneffective for reducing the number of cases of pneumococcal AOM, especially those associated with increased severity, an increased number complications, or penicillin-nonsusceptible strains. Typanocentesis studies in children with AOM during the PCV7 era show a shift to more penicillin-susceptible, nonvaccine S. pneumoniae serotypes, as well as to β-lactam-resistant, nontypeable H. influenzae [11, 12]. One postlicensure nasopharyngeal colonization study from Boston, Massachusetts, showed a reduction in the prevalence of carriage of S. pneumoniae vaccine serotypes (from 22% to 2%) and an increase in the prevalence of nonvaccine serotype carriage (from 7% to 16%) between the pre- and postlicensure periods, respec-
tively, with no change in the proportion of infecting isolates resistant to antibiotics [21]—fair warning that reducing antibiotic use remains a priority. Serotype replacement was not observed in persons with invasive disease in the population-based Northern California studies, in which PCV7 serotypes accounted for 89% of the cases of IPD during the prevaccine period and in which 90% and 74% of infants received 3 doses of vaccine by 1 year of age in 2001 and 2002, respectively [3]. There are recurring themes in studies of IPD during the postlicensure period: protection is best against serotype 14, least against type 19, and best against bloodstream invasive disease. There are signals in some other studies (all of which involved populations with a lower rate of vaccination than that for California) of minor replacement of nonvaccine serotypes in persons with IPD, especially in populations in which nonvaccine serotypes were prevalent before PCV7 licensure and pneumonia is a common invasive disease. There are mixed messages about the age group(s) in which serogroup changes may be occurring. The Pediatric Multicenter Pneumococcal Surveillance Group, comprised of 8 children’s hospitals in the United States, showed increases of 28% and 66% in the number of invasive isolates from nonvaccine serogroups that were recovered during 2001 and 2002, respectively, in children ≈24 months of age, compared with the mean number recovered during 1994–2000. Isolates from just 3 serogroups (15, 3, and 33) accounted for >50% of 65 nonvaccine-serogroup isolates recovered in 2002; the remaining nonvaccine-serogroup isolates were from <15 serogroups [5]. At Arkansas Children’s Hospital in Little Rock, although the number of cases S. pneumoniae bacteremia decreased, the number of cases of S. pneumoniae pneumonia increased, with nonvaccine serogroups responsible for 1 case of pneumonia in 1998–2000 and 17 cases in 2001–2003 (76% of the cases were due to serogroups 1, 5, and 12) [6]. In Massachusetts children <5 years of age, the annual incidence of nonmeningitis IPD due to non-PCV7 serogroups increased from 2.9 cases/100,000 children in 1990–1991 to 5.8 cases/100,000 children in 2001–2003 (P = .04) [8]. In a Tennessee Active Bacterial Core (ABC) surveillance study, rates of IPD due to PCV7 serotypes decreased across all age groups from 1999 to 2002. The incidence of IPD due to non-PCV7 serotypes increased modestly but significantly (from 1.8 to 2.8 cases/100,000 children; P = .03) exclusively in children ≥2 years of age and without nonvaccine-serotype clustering [9]. Although ABC surveillance performed by the CDC through 2001 documented herd immunity among adults and showed no significant increase in the incidence of IPD due to nonvaccine serotypes [4], preliminary data through 2003 for adults with HIV/AIDS suggest that the incidence has significantly increased [22]. Capsular switching is a more sinister event than serotype replacement. It is a measure of the plasticity of pneumococcus. As part of a quorum-sensing mechanism, S. pneumoniae can acquire new traits in a process called transformation. Experimentally as well as during colonization or infection in humans, an S. pneumoniae strain can acquire a cassette of DNA that encodes production of a serotypically different capsule. Although genotype correlates with serotype, a single serotype can include multiple genotypes, and a single genotype can transform to a new serotype. If donors of nonvaccineserotype S. pneumoniae increase because of replacement and if virulent antibiotic-resistant strains persist under selective pressure, successful major antibiotic-resistant clones with nonvaccine capsular serotypes could emerge in a single step. In a study of S. pneumoniae isolates from the nasopharynx and middle ear fluid of children from Israel and Costa Rica, Porat et al. [23] found the successful, resistant, international SpainT3 clone to predominate among penicillin-nonsusceptible isolates of serotype 11A. If capsular switching, although seemingly rare at present, is documented more frequently, it could have significant implications for the long-term effectiveness of polysaccharide conjugate vaccines. Is the IMW experience reported by Byington and colleagues an early warning of serotype replacement, or is it merely a curious event? In the years leading up to PCV7 licensure, Byington et al. [24] reported an increase in the rate of pneumococcal empyema from 1 to 5 cases/100,000 children in the same hospital featured in their current report [17]. The increase was associated with a single clone of serotype 1 (50% of cases), outpatient treatment with certain antibiotics, use of ibuprofen, and varicella infection (ORs of 3.3–14, by logistic regression analysis; P < .0001) [24]. In the current report by Byington et al. [17], the population-based incidence of bacteremia and pneumonia decreased in the PCV7 era, but the incidence of S. pneumoniae parapneumonic empyema continued to increase (from 10.3 cases/100,000 children in 1996–2000 to 14.3 cases/100,000 children in 2001–2003; P = .01), as did the incidence of IPD due to nonvaccine serogroups (from a mean of 8.75 cases/year during the pre-PCV7 period to 26 cases during 2003). Serogroup I isolates (all of which had sequence type 227) accounted for 24% of the nonvaccine-serogroup isolates observed in the post-PCV7 period, serogroup 3 isolates (for which multilocus sequence typing data were not reported) accounted for 22%, and 13 other nonvaccine serogroups accounted for the 25 remaining isolates. Three nonvaccine serogroups disappeared and 8 nonvaccine serogroups appeared between the pre- and post-PCV7 periods. Previously determined secular trends in the prevalence of all risk factors for empyema in this population likely have continued or increased (except, we hope, the prevalence of varicella infection). A shift in the referral pattern away from uncomplicated bacteremia and toward complicated pneumonia could explain these findings. Additionally, the IMW area had
a curious explosion of cases of rheumatic fever in the late 1990s that did not extend across the country. In that instance, large family size was the most definable risk factor, which also could facilitate transmissibility of nonvaccine-serotype S. pneumoniae. It is likely, however, that the IMW experience, as well as other reports coming in, are examples that, in a conducive setting, superadaptable (recognizable by clonal dominance) or insurgent nonvaccine-serotype strains can cause disease. The respiratory tract is the likely to be the first site affected. Will serotype replacement bloodstream infections follow? We need to monitor this carefully. Surveillance systems are in place.

We do not want the battle between humans and the pneumococci to be over ever, because we would have lost. Should the strategic next move(s) involve follow-up vaccination of children with 23-valent pneumococcal polysaccharide vaccine at 5 years of age (renegade serogroups to date are covered by this vaccine), addition of capsular types to conjugate vaccines, and/or development of pneumococcal surface protein vaccines, such as PspA and PsaA, or other highly conserved surface proteins? Eviction of pneumococcus from the flora of the nasopharynx is a foolish goal. Rather, a stealth attack, a silver bullet, or a velvet harpoon—to render defenseless the ‘bad guys’ and to assist the ‘good guys’—should be the goal.

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References