Vaccination: A Novel Approach to Reduce Antibiotic Resistance

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(See the article by Talbot et al. on pages 641–8)

The state of Tennessee has had, for the past 2 decades, the greatest burden of antibiotic-resistant pneumococci isolated in the United States, culminating, in 1999, in rates of penicillin resistance as high as 60% among blood isolates from young children <2 years of age [1]. It is not just the proportion of penicillin-nonsusceptible strains isolated from blood that is remarkable, but also the degree of resistance that is due, at least in part, to the occurrence of a pneumococcal clone named for the state (Tennessee 23F-4) [2]. The type strain of this clone has a cefotaxime MIC of 32 µg/mL—one of the most cephalosporin-resistant pneumococci ever described [2, 3]—and was originally isolated from the blood and CSF of a child in Memphis, Tennessee, whose cefotaxime therapy failed [4].

The situation in Tennessee is all now changing, perhaps partly because of improvements in empirical antimicrobial prescribing, although more likely, as argued by Talbot and colleagues [1], because of the introduction of pneumococcal conjugate vaccine (PCV). Since the introduction of the vaccine in 1999, the proportion of resistant strains has fallen dramatically, not only in immunized children, but also in nonimmunized older children and adults. Although the fall in the proportion of antibiotic-resistant strains among children (from 59.8% to 30.4%) is dramatic, it is not as dramatic as the reduction in invasive disease due to vaccine serotypes among children of the same age (from 106.3 to 13.8 cases per 100,000). Although the exact numbers cannot be calculated from the data presented, it is of concern that the proportion of resistant strains among residual conjugate-vaccine serotypes likely remains high, and selection of resistance in those and other serotypes is certainly continuing. The emergence of resistance in nonvaccine serotypes has been documented in the absence of conjugate vaccine selection in isolates from middle-ear specimens from Israeli toddlers [5], and previously rare vaccine serotypes, such as 35B, have also emerged as important antibiotic-resistant clones in the United States [6]. The data from Tennessee [1] provide some evidence for the low-level emergence of nonvaccine serotypes.

Current models of the progression of antimicrobial resistance in the United States [7] suggest a continuous increase in antimicrobial resistance in the absence of a novel intervention, such as use of PCV, and the data from Tennessee clearly demonstrate the impact of such an intervention. Rapid reductions in resistance of this magnitude cannot be shown in resistance models to be due to changes in prescribing behavior alone [8]. How has the introduction of PCV had such a dramatic impact on antimicrobial resistance? The reasons are several.

PCV interrupts the transmission of antibiotic-resistant strains by blocking the acquisition of vaccine type pneumococci that are resistant to antibiotics. The emergence of antimicrobial resistance in the pneumococcus has taken place almost exclusively among pneumococcal serotypes commonly carried by children, suggesting that selection is favored by the long periods of time that these serotypes are carried by young infants [9]. The first evidence that PCV was able to interrupt the acquisition of antibiotic-resistant strains came from a study of vaccination with 1 or 2 doses of a now discontinued—at the time, investigational—7-valent vaccine conjugated to Neisseria meningitidis outer membrane protein that was given to toddlers in Israel [10]. The incidence of antibiotic-resistant vaccine-type strains was reduced to 4% among the vaccinated children, compared with an incidence of 14%...
among the control subjects \( (P = .04) \) [10]. The first evidence that such an effect on antibiotic-resistant strains could be achieved in young infants with the CRM197 conjugated vaccine was demonstrated in Africa, where the rate of carriage of penicillin-resistant pneumococci was reduced from 41% to 21% \( (P = .0002) \) among recipients of 9-valent CRM197 conjugate vaccine who were immunized during infancy [11]. The study showed that a reduced rate of acquisition of resistant strains could be demonstrated at 9 months of age among children who were immunized at 6, 10, and 14 weeks of age. Of importance for developing countries was the observation that the incidence of trimethoprim-sulfamethoxazole–resistant pneumococci also decreased among immunized children, from 35% to 23% \( (P = .003) \). Recent studies in Israel that used the same vaccine have also demonstrated the efficacy of this vaccine in reducing the percentage of resistant isolates among vaccinated toddlers attending day care centers [12]. This study demonstrated reductions in the incidence of isolates with penicillin, erythromycin, and trimethoprim-sulfamethoxazole, as well as in the incidence of pneumococci categorized as resistant to at least 1, 2, or 3 classes of drugs.

To date, data from 2 randomized trials have documented another way in which conjugate vaccine may reduce antimicrobial resistance indirectly: through its impact on antibiotic use. In a study of nearly 40,000 recipients of 7-valent CRM197 conjugate vaccine and control subjects in northern California, there was a 5.4% reduction in the number of antibiotic prescriptions and a 12.6% reduction in the use of “second-line antibiotics” among children who received the conjugate vaccine. Between the time the first dose was administered and the age of 3.5 years, use of the vaccine prevented 35 antibiotic prescriptions per 100 fully vaccinated children in the trial [13]. Reductions in the number of days that patients received antibiotic therapy have also been documented among day-care attendees in Israel who received the 9-valent conjugate vaccine [14]. The impact of the vaccine on acquisition of carriage has led to herd immunity, which was most dramatically illustrated by the effectiveness data on antimicrobial resistance reported by the Centers for Disease Control and Prevention (CDC; Atlanta, GA) in the United States [15], as well as by Talbot and colleagues [1]. There is direct evidence of herd immunity in a randomized trial, also from Israel, in which the younger siblings of day-care center attendees were less likely to have carriage of antibiotic-resistant pneumococci if their older sibling had been vaccinated, compared with the younger siblings of nonvaccinated day-care center attendees [16].

Direct experimental evidence of the impact of conjugate vaccine on antibiotic-resistant invasive disease is also now available from the large randomized trial of 9-valent conjugate vaccine in Soweto, South Africa [17]. In that study, the vaccine reduced the number of cases of invasive pneumococcal disease due to penicillin-resistant pneumococci by 67% (95% CI, 19%–88%), and there was a 56% reduction (95% CI, 16%–78%) in the number of trimethoprim-sulfamethoxazole-resistant blood isolates in vaccinees, compared with control subjects. Overall, there was a 56% reduction (95% CI, 21%–77%) in the number of isolates of any antibiotic-resistant pneumococci from blood or CSF obtained from recipients of the vaccine, despite a high burden of HIV disease among vaccine recipients in that study [17].

Ongoing surveillance by the CDC, which includes documentation of the molecular fingerprint of pneumococcal isolates from children by use of PFGE and multi-locus sequence typing, will enable surveillance for the emergence of resistance in new pneumococcal lineages. There are 2 likely scenarios for this emergence. One is the emergence of resistance in lineages of nonvaccine serotypes. The other is the continued dissemination of existing resistant clones of vaccine serotypes that may switch their capsular genes to those of nonvaccine serotypes. In a small study from Pittsburgh conducted after the introduction of the vaccine, there was no evidence of capsular switching detected in nonvaccine types isolated from middle-ear specimens from immunized children [18]. Although capsular switching has been documented in the laboratory, the likelihood of detecting the actual switch in vivo is low [19]. However, once a switch has occurred, continued antibiotic-selective pressure may allow for the rapid selection of such strains.

In conclusion, vaccination with PCV is a novel approach to reduction of the burden of antibiotic resistance in the pneumococcus. The effect of the vaccine has extended beyond immunized children to reduce the carriage of resistant strains among family members and adults. Although capsular switching has not yet been documented as a consequence of immunization in a vaccinated child, surveillance is required to document the further evolution of antimicrobial resistance after the introduction of the vaccine. Lower levels of antimicrobial resistance may allow the reevaluation of the effectiveness of certain classes of antibiotics. The vaccine has also contributed to the reduction in antibiotic use, but continued restraint in antibiotic use—for example, in the proposed use of fluoroquinolones to treat children—is required to reduce the selective pressure for resistance among residual vaccine serotypes and nonvaccine-type pneumococcal strains.

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References


