Rethinking Replacement and Resistance

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(See the article by Dagan et al., on pages 776–85.)

Before 2000, the year in which the 7-valent pneumococcal conjugate vaccine (PCV7; Prevnar, Wyeth) was introduced into the US infant immunization schedule, most antibiotic-resistant strains of Streptococcus pneumoniae belonged to serotypes included in PCV7. During just the first 3 years after vaccine introduction, we observed profound reductions in the incidence of invasive pneumococcal disease (e.g., bacteremia and meningitis) caused by vaccine serotypes and their associated antibiotic-resistant strains, not only among vaccinated children but also among persons too young [1] and too old [2] to receive the vaccine. The dramatic success of PCV7 in reducing pneumococcal disease in wealthy countries [3–6]—and the potential benefits to poor countries [7, 8]—have led to World Health Organization recommendations for the global introduction of conjugate vaccines [9] and to extraordinary efforts to finance vaccine purchase and delivery to the poorest countries of the world [10].

At the same time we were heralding the benefits of PCV7, we were alert to the unintended consequence of serotype replacement. This phenomenon, demonstrated convincingly in randomized, controlled trials [11], occurs when serotypes not included in a conjugate vaccine colonize the nasopharynx and “replace” the vaccine serotypes whose colonization is prevented by the vaccine. The net effect is that PCV7 does not reduce the overall prevalence of nasopharyngeal colonization. PCV7 serotypes are, on average, better suited to causing invasive disease than non-PCV7 serotypes [12, 13]; therefore, vaccine-induced elimination of PCV7 serotypes from the nasopharynx leads to a net reduction in invasive disease and antibiotic resistance. Of all the serotypes, serotype 19A may come closest to having certain characteristics that make it a successful replacement serotype. First, serotype 19A has relatively high propensities for colonizing the nasopharynx (to maximize transmissibility) and for causing invasive disease. Second, serotype 19A was associated with antibiotic resistance even before the introduction of PCV7; therefore, when exposed to antibiotics prescribed for upper respiratory tract infections, it had a selective advantage over other, more susceptible serotypes. Finally, PCV7 has no efficacy against serotype 19A.

Increases in the incidence of serotype 19A associated with otitis [14], mastoiditis [15], and invasive disease [16–18] have been described in multiple US settings since 2000, making it impossible to ignore the temporal association between the introduction of PCV7 and the emergence of serotype 19A. It seemed safe to assume that PCV7 had caused replacement with serotype 19A. There were hints, however, that we might have been presumptuous in attributing the rise of serotype 19A exclusively to the use of PCV7. In multiple studies conducted before PCV7 introduction, serotype 19A was identified as an antibiotic-resistant serotype, not only in the United States [19] but in other parts of the world as well [20, 21]. Until now, the strongest evidence against PCV7-induced serotype replacement was that the incidence of serotype 19A seemed to be increasing in Korea [22], France, and Belgium [23] before the introduction of PCV7. The article by Dagan et al. [24] in this issue of the Journal pushes us to question our assumptions about serotype replacement even more forcefully.

The authors describe the emergence of serotype 19A as a cause of otitis media among Bedouin children in southern Israel who, along with their Jewish counterparts, had not received PCV7. During 1999–2006, the proportion of otitis media cases among Bedouin children caused by serotype 19A increased from ~8% to 14%. Among Jewish children over the same time period, the prevalence of serotype 19A varied between 8% and 14% without a clear upward or downward trend. These findings are not particularly striking until one examines the susceptibility patterns and clones of serotype 19A strains in these 2 groups. A stable 38% of serotype 19A strains causing otitis in Jewish children from 2002 to 2006 were resis-
tant to penicillin, with very few isolates resistant to macrolides or multiple agents. In contrast, the Bedouin population experienced a dramatic increase in the prevalence of 2 multidrug-resistant pneumococcal clones (ST-276 and ST-2928) of serotype 19A over the same time period. Why the difference?

One hypothesis is that Bedouin children may have had greater exposure to antibiotics than Jewish children. In fact, in the 20% of both populations for whom data were available, modest reductions in overall antibiotic use, including amoxicillin and cefalosporins, were observed. Azithromycin prescriptions, on the other hand, increased markedly in both groups—antibiotic replacement, so to speak. This is important for 2 reasons. First, azithromycin may promote macrolide resistance better than other macrolides because of its long half-life and low extracellular concentrations [25]. Macrolide resistance often travels with other resistance determinants, so it is plausible that the dramatic increase in multidrug resistance can be attributed to increased azithromycin use. Second, azithromycin use increased dramatically in the United States after its licensure in 1991 at the same time that overall antibiotic use was declining [26] and the prevalence of multidrug-resistant *S. pneumoniae* was increasing [27]. This pattern suggests that the appearance of multidrug-resistant serotype 19A in the United States and southern Israel may somehow have been a response to the introduction and increased use of azithromycin. However, if Bedouin and Jewish children both experienced important increases in azithromycin use, why were the increases in multidrug-resistant serotype 19A confined to the Bedouin population? A careful look at differences between these populations may shed light on this question.

One important difference relates to seasonal patterns of antibiotic use. Antibiotic prescribing among Jewish children declines substantially in warm months and is accompanied by reductions in antibiotic resistance, whereas, among Bedouins, antibiotic prescribing and the prevalence of antibiotic resistance are more consistent year-round [28]. This more stable antibiotic pressure may force strains colonizing Bedouin children to maintain multidrug-resistance determinants despite the fitness costs required to do so [29]. There are also important socioeconomic disparities to consider. According to Dagan et al., Jews and Bedouins live side by side without intermingling. Bedouins have lower family incomes, but their birth rates and family sizes are more than double those of their Jewish counterparts. If living conditions among Bedouins favor more intense transmission, this may be sufficient to overcome any growth costs paid by the organism to sustain multiple resistance determinants [30]. Similar relationships between socioeconomic factors and pneumococcal colonization and transmission have been described in other settings [18, 31–34].

Is the emergence of serotype 19A in the PCV7 era entirely attributable to antibiotic use, and is the introduction of PCV7 pure coincidence? It is hard to imagine that increases in serotype 19A causing otitis and invasive disease are not in some way related to the introduction of PCV7, and evidence of increased genetic diversity within serotype 19A, including some antibiotic-susceptible clones, suggests that a serotype-specific selection process is at work [16]. But Dagan et al.’s study reminds us to consider how other important factors, such as antibiotics, contribute to well-documented trends in individual pneumococcal serotypes in the absence of PCV7 [35–37]. It is a cautionary note to resist the temptation to attribute all increases in nonvaccine serotypes to the introduction of PCV7, as biologically plausible as that relationship may be. As we prepare for the availability of pneumococcal conjugate vaccines with expanded valency and as the introduction of conjugate vaccine moves forward among vulnerable populations of the world’s poor, Dagan et al. remind us that vaccines do not cause antibiotic resistance, antibiotics do.

### References

14. Pichichero ME, Casey JR. Emergence of a multiresistant serotype 19A pneumococcal strain not included in the 7-valent conjugate