Editorial

Developing the Right Pneumococcal Vaccine for the Time and Place

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William Schaffner, the quotable Chairman of the Department of Preventative Medicine at Vanderbilt once said, “Sometimes, the crystal ball is a little bit cloudy and the influenza virus fakes us out so that the virus in the vaccine isn’t an exact match for the virus circulating in the community.” The continuous genetic drift and the occasional genetic shift in circulating influenza strains resulting in immune escape make life difficult for influenza vaccine developers. *Streptococcus pneumoniae* is another ubiquitous pathogen with significant serotype diversity that may be undergoing antigenic shifts driven by vaccination as well.¹

In the current issue of *AJTMH*, Moore and others² describe a new real-time polymerase chain reaction (PCR) assay to detect and classify *S. pneumoniae* isolates causing invasive infection in relation to the pneumococcal serotypes included in the 13-valent polysaccharide-protein conjugate vaccine (PCV-13, Prevnar 13, Wyeth Lederle, Madison, NJ). The authors then use this assay to analyze isolates causing invasive pneumococcal disease (IPD) from 10,799 blood cultures and 353 cerebrospinal fluid (CSF) samples from a single hospital in Vientienne, Laos. In addition to finding an improved sensitivity using this assay in the CSF samples, the authors found that only 33% of isolates were serotypes included in the PCV-7 Prevnar vaccine (4, 6B, 9V, 14, 18C, 19F, and 23F). Although in North America, before the introduction of PCV-7, > 80% of IPD isolates were serotypes represented in the PCV-7 vaccine, surveillance studies around the world have shown that the epidemiology seen in Laos is not an anomaly. The Global Alliance for Vaccines and Immunizations’ Pneumococcal Vaccines Accelerated Development and Introduction Plan (PneumoADIP) recently showed that in a surveillance project involving 15 resource limited nations, PCV-7 serotypes ranged from 6% to 79% of isolates,³ while another recent study in Thailand found that 69% of isolates were PCV-7 serotypes.⁴ Thus, the benefits of this vaccine, designed for North America and western Europe, may not extend to the rest of the world.

In western nations the PCV-7 has been shown to significantly reduce the incidence of invasive pneumococcal disease, (~45% from 1999 to 2004 as noted in a United States based surveillance program), and decrease the incidence of antibiotic-resistant pneumococcal infections.⁵ Similar benefits were seen with the introduction of the *Hemophilus influenzae* Type B vaccine (Hib) in the early 1990s.⁶ Although significant capsular diversity exists for *H. influenzae*, no significant increase in non-b serotype disease has occurred.^{6–9} This is in contrast to pneumococcal disease, where studies showed that as nasopharyngeal colonization of vaccine serotypes is decreased, colonization with non-vaccine serotypes increases.¹⁰ Rates of IPD from serotype 19A, a non-PCV-7 serotype, have significantly increased across all age groups since the PCV-7 was intro-

duced.¹¹ This was most notably seen in the < 5 year old age group in the United States, where serotype 19A caused 2.5% of IPD cases in 1999, but 36% of cases in 2005 (in absolute numbers ~250% increase).¹¹ This serotype is unfortunately also increasingly associated with multi-drug resistance, and a full 60% of isolates were penicillin resistant in this United States based study, with similar results seen worldwide. Selection for this serotype by the PCV-7 vaccine is likely playing some role in the increasing prevalence of this serotype, and as a vaccine replacement serotype, it may be more harmful than its predecessors. In Laos, Moore and others² found that the most common causes of IPD are serotypes 1 and 5, neither of which is in the PCV-7 vaccine. Widespread use of the PCV-7 vaccine could lead to directional selection favoring these two invasive serotypes. Thus, although significant benefits have been associated with PCV-7 vaccination, there are also potential risks, which need to be weighed on a region-by-region basis.

The PCV-13 vaccine was recently approved by the U.S. Food and Drug Administration. This protein-conjugate vaccine includes the serotypes found in PCV-7 plus 1, 3, 5, 6A, 7F, and 19A, which would have included 76% of the identified Laotian IPD causing isolates.² Therefore, the epidemiology of Laotian IPD suggests that there would be significantly greater public health benefit to the use of PCV-13 over PCV-7. However, this expanded repertoire may run up against the same issues seen after the introduction of the PCV-7, where a significant early public health benefit occurred but waned over time as non-vaccine serotypes colonized the population. Perhaps the broader efficacy of the PCV-13 will provide a deeper and more lasting public health benefit, but it is likely that over time non-vaccine serotypes will still fill in the void. The lasting efficacy of these vaccines depends upon the presumption that these new arrivals will be less invasive than their predecessors.

Serotype drift occurring after a vaccination campaign may result in the increased prevalence of non-vaccine serotypes, some of which may be invasive strains. Matching the administered vaccine to the predominant circulating serotypes in a region requires background knowledge of the epidemiology, similar to influenza. Thus, just as for influenza, disease surveillance is essential for a pneumococcal vaccination program. An active population-based surveillance system with serotype identification and genotypic evaluation of well-characterized cases will allow public health researchers to compare rates of IPD to those of other investigators in other settings. Such a system would also allow the tracking of serotypes and strains that have evolved selective advantages and are not affected by previous vaccination. The fragility of the pneumococcus and the resulting difficulty in isolation of this pathogen suggest that the use of a molecular approach to typing pneumococcal isolates may be more efficacious than standard isolation and serotyping approaches. Molecular typing assays, such as the real-time PCR typing assay developed by Moore and others,² address this need and should be used when possible.

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Shifts seen in the serotypes associated with IPD can be used to direct the vaccine manufacturers to change their product to fit the local and temporal epidemiology, and guide other organizations when implementing vaccination programs.

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