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# Invasive Pneumococcal Disease

## The Target Is Moving

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**T**HE HEPTAVALENT PNEUMOCOCCAL CONJUGATE VACCINE (PCV7) that has been recommended since the year 2000 for all US children younger than 2 years has been a towering success. Childhood PCV7 vaccination has resulted in much greater reductions in invasive disease in young children, as well as older children and adults through herd immunity, than had been anticipated.<sup>1-4</sup> From 2001 through 2005, Active Bacterial Core surveillance of the Centers for Disease Control and Prevention showed that the US burden of invasive pneumococcal disease decreased by more than 100 000 cases, including about 2000 cases of meningitis and 25 000 cases of pneumonia with bacteremia. Invasive disease occurred in 188 per 100 000 US children younger than 2 years before PCV7 licensure. In 2005, 5 years after PCV7 licensure, rates of invasive disease decreased 81% to 36 per 100 000 children.<sup>5</sup> The success of this vaccine is underscored by the recent recommendation of the World Health Organization to include PCV7 in national immunization programs worldwide.<sup>6</sup>

In this issue of *JAMA*, Singleton and colleagues<sup>7</sup> report increases in invasive pneumococcal disease in Alaska Native children despite high PCV7 coverage. Alaska Native children and adults experience excessive invasive pneumococcal disease, and before PCV7 introduction (1995-2000), rates of pneumococcal disease were 403.2 per 100 000 children younger than 2 years. Following PCV7 introduction (2001-2003), these rates decreased by 67% to 134 per 100 000 children. However, Alaska Native children experienced a significant increase in invasive pneumococcal disease more recently (2004-2006), to 244.6 per 100 000 children. The benefit of PCV7 among non-Native Alaska children has essentially been the same as among the general US population, and, as yet, there has been no resurgence of invasive disease.

See also p 1784.

The efficacy of the vaccine has remained excellent and sustained. Alaska Native children have a 95% rate reduction in invasive pneumococcal disease caused by PCV7 serotypes (4, 6B, 9V, 14, 18C, 19F, and 23F). The authors further report that the manifestations and severity of invasive pneumococcal disease remained largely constant, although the proportion of pneumococcal disease with empyema or bacteremia-associated pneumonia has increased, and the proportion with bacteremia without focus has decreased.<sup>7</sup>

Increased rates of invasive pneumococcal disease in Alaska Native children are explained by a changing prevalence of pathogenic bacterial serotypes, or "serotype replacement." Singleton et al report a 140% increase in invasive pneumococcal disease caused by nonvaccine serotypes in Alaska Native children since introduction of PCV7. The majority of invasive disease occurring in children younger than 2 years in 2004-2006 was caused by serotypes 3, 6A, 7F, and 19A, with nearly 30% caused by serotype 19A. Notably, replacement serotypes causing disease also included some not represented in the 23-valent pneumococcal polysaccharide vaccine used primarily in adults. Increases in disease were consistent with patterns of pneumococcal nasopharyngeal colonization in this population, with a reported increase in serotype 19A colonization from less than 0.5% to 15%.<sup>7</sup> This study is the first to show that pneumococcal serotype replacement has resulted in increased rates of invasive disease from the nadir in this highly vaccinated population of US children.

For reasons that are not understood, Alaska Native children have a 2- to 3-fold higher prevalence of pneumococcal disease than the prevalence in the US population overall. Revising the vaccine strategy to better protect these vulnerable Alaska Native children and adults from invasive pneumococcal disease is an important public health goal. It is also important to consider whether the experience of this subpopulation of US children is an early manifestation of a changing

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pneumococcal epidemiology that is occurring much more widely. Surveillance of pneumococcal nasopharyngeal carriage has shown widespread changes in colonization patterns and marked increases in nonvaccine serotypes such as 19A.<sup>8-12</sup> These studies are informative given that nasopharyngeal colonization with a particular serotype is a necessary precondition for invasive disease with that serotype. Vaccination with pneumococcal protein-conjugate vaccines results in a significant reduction of colonization with vaccine serotypes, and this correlates with protection from serotype-specific invasive disease. Increased nasopharyngeal colonization with virulent, nonvaccine serotypes reasonably predicts increased risk of invasive disease. The findings of Singleton et al reinforce the widely held expert opinion that pneumococcal serotype replacement will ultimately erode PCV7 effectiveness in all vaccinated populations.

The effects of increasing rates of pneumococcal disease on routine clinical practice are potentially great. Since PCV7 introduction, the use of blood cultures in the evaluation of febrile children younger than 36 months has decreased<sup>13</sup> as rates of pneumococcal bacteremia have decreased in vaccinated populations.<sup>5</sup> The positive predictive value of a blood culture will increase as the pretest likelihood of bacteremia increases. If local rates of invasive pneumococcal disease increase, the utility of the blood culture will logically increase and it may be important to once again revise clinical practice in the evaluation of febrile children. This is just one example of how early awareness of local increases in pneumococcal invasive disease may be important for practicing clinicians.

The potential occurrence and consequences of serotype replacement were anticipated long before the licensure of PCV7 and the recommendation for universal vaccination of US children. The work of Singleton et al underscores the importance of postlicensure surveillance studies. Ongoing surveillance of invasive pneumococcal disease,<sup>1,4,14-18</sup> as well as nasopharyngeal colonization studies,<sup>8-12,19</sup> have identified several serotypes including 19A as a threat to the spectacular success of childhood pneumococcal vaccination programs long before this first confirmation that serotype replacement is causing increased invasive disease in vaccinated children. A 13-valent pneumococcal conjugate vaccine that includes serotype 19A is in phase 3 clinical trials.<sup>20</sup> Data from these surveillance studies will be critically important in the design and distribution of new pneumococcal protein conjugate vaccines. Continued serotype replacement may necessitate revision or expansion of protein-conjugate vaccines every 5 to 10 years, until successful development of a vaccine that provides immunity to all pneumococcal serotypes. Virulent pneumococcal serotypes not covered in the 23-valent polysaccharide vaccine widely used in adult patients may emerge, another reminder that childhood vaccination policy has tremendous health implications for the entire population.

Pneumococcal serotype replacement is occurring in a subpopulation of highly vaccinated, especially vulnerable US children. Although the efficacy of PCV7 remains high, chang-

ing pneumococcal serotype prevalence is causing increased rates of invasive disease. Surveillance of pneumococcal colonization and disease is important to public health and is informing vaccine redesign. The target is moving. An adaptable vaccine strategy must also move to protect children worldwide and defend the idea that humankind will ultimately be free of pneumococcal disease.

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