The Challenge of Preventing Invasive Pneumococcal Disease in Children With Comorbid Illnesses

Stephen I. Pelton
Boston University, Schools of Medicine and School of Public Health, Massachusetts

(See the Major Article by Ladhani et al on pages 517–25.)

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In the current issue of Clinical Infectious Diseases, Ladhani and colleagues at Public Health England report on invasive pneumococcal disease (IPD) in children aged 5–15 years with comorbid illness [1]. Often this age group is thought of as low risk, but the authors demonstrate that disease is not evenly distributed and children with comorbid illnesses are disproportionately represented. Twenty-nine percent of children with IPD had a comorbid condition; these illnesses can be divided into 3 groups: immunocompromised children, those with chronic respiratory conditions, and those characterized as “others” with comorbidities such as diabetes, neurologic conditions, heart, kidney, or liver disease. Combined, there is a 22-fold greater risk of IPD compared to age-matched healthy peers. Children with comorbidities also had excess overall mortality, although not all deaths were considered infection related. Our own studies [2], from insurance claims databases in the United States, also identify that children with comorbid conditions remain at increased risk for IPD despite >92% uptake of 3 doses of 7-valent pneumococcal conjugate vaccine (PCV7) in the United States, with the greatest risk among those with immunocompromising conditions compared to those with “at risk” conditions as defined by the Advisory Committee on Immunization Practices and the American Academy of Pediatrics [3].

The outcome of IPD in children with comorbid conditions as reported by Ladhani et al provides a mixed picture [1]. Mortality is increased, yet complications of pneumonia are reduced. Although this may appear inconsistent, it likely reflects the spectrum of comorbidity. In children without splenic function, most notably those with sickle cell anemia, IPD has consistently been severe (often clinically indistinguishable from meningococcemia), with case fatality rates possibly explaining the observed increase in mortality. In contrast, complications were less frequent in bacteremic pneumonia. Although there are likely multiple explanations for this observation, the increased susceptibility to infection and the potential for rapid progression among some children with underlying conditions often leads to increased vigilance by parents and physicians and a lower threshold for intervention as a contributing factor to improved outcomes.

Children with comorbid illness were found to have a decline in disease due to PCV7 serotypes following its introduction; however, despite the decline, these serotypes were more frequent in children with comorbid illnesses than in healthy children. This observation is consistent with Whitney and colleagues’ report of 96% (95% confidence interval [CI], 93%–98%) effectiveness in healthy children and 81% (95% CI, 57%–92%) effectiveness in those with coexisting conditions [4]. However, with increasing penetration of vaccine over time, herd immunity will protect these children against the serotypes within PCV vaccines. The challenge is that a large proportion of disease in children with comorbidity is due to serotypes not within the 13-valent PCV (PCV13), and further reductions in disease burden may not be achieved with limited-valency conjugate vaccines. Traditionally most non-PVC13 serotypes are considered of low invasive capacity and are less prevalent causes of IPD. Why these serotypes are found more frequently in children with comorbidity is a critical question in furthering our understanding of pneumococcal disease and for developing strategies for prevention. It is predictable that children with congenital and acquired immunologic deficiencies...
are at greater risk for less virulence serotypes; however, the biologic rationale in those with chronic respiratory disease or “other” comorbidities are less clear. Is the pattern of colonization different in these children? Is the respiratory environment more or less “friendly” for specific serotypes? Is the event per colonization risk higher in such children? Is local immune function compromised beyond our current capacity to measure these differences? Our studies find that these children are at increased risk for both pneumococcal and all-cause pneumonia as well as IPD [2], and that the excess burden of pneumonia far exceeds that of IPD. The combined burden of IPD and pneumonia emphasizes the need to expand prevention efforts in this population beyond the current 13 serotypes.

The use of 23-valent pneumococcal polysaccharide vaccine (PPV23) in children with comorbid conditions was limited despite 2006 UK guidelines for its use in children >5 years of age with at-risk and high-risk conditions. The limited penetration of PPV23 is consistent with a lack of clarity as to who should administer the vaccine between the general practitioner and the pediatrician as well as an uncertainty about its effectiveness. Studies clearly demonstrate an age-related antibody response that appears to mature for all serotypes before 6 years of age [5]. Recent studies of immunogenicity of PPV23 after 2 doses of PCV7 in UK children aged 2–16 years report 1- to 2-fold increases in antibody to the non-PCV7 serotypes after completion of this regimen with few children achieving a protective antibody concentration (>0.35 µg/mL) [6]. Furthermore, effectiveness data are controversial, with modest evidence to support up to a 50% reduction in IPD due to serotypes unique to PPV23 and less confidence in its impact on nonbacterial pneumonia. The presence of comorbidity adds an additional level of uncertainty, as Vila-Corcoles et al reported little or null effect for PPV23 against pneumococcal pneumonia in adults with chronic pulmonary diseases [7].

Ladhani and colleagues’ observation that nonvaccine serotypes are a more prevalent cause of IPD in children with chronic diseases may have global implications. Will nonvaccine serotypes emerge as prevalent pathogens in children with human immunodeficiency virus, malnutrition, chronic respiratory diseases, vitamin deficiency, and so on, in developing and emerging nations? Will the anticipated success of limited-valency PCVs be mitigated by high burdens of disease due to nonvaccine serotypes in this population? These unknowns can only be answered by ongoing global surveillance of pneumococcal disease. The burden of pneumococcal disease and its devastating mortality rates can only partially be reduced with the current conjugate vaccines. A commitment to develop next-generation vaccines that will broaden protection is needed to protect the most vulnerable children.

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**References**