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COMMENTARY

Deconstructing Pneumococcal Progression from Colonization to Disease

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ABSTRACT Despite advances in treatment and prevention, the pneumococcus continues to be a dominant cause of severe pneumonia and sepsis and of otitis media, sinusitis, and nonbacteremic pneumonia. Lewnard and colleagues (Infect Immun 86: e00727-17, 2018, https://doi.org/10.1128/IAI.00727-17) used a unique data set of nasopharyngeal and middle ear fluid samples to provide further insight into the progression of nasopharyngeal pneumococcal colonization to disease. They report the comparative rate of progression from colonization to otitis media by serotype, providing insight into how conjugate vaccines that do not reduce the overall prevalence of pneumococci in the nasopharynx dramatically impact the incidence of acute and complex otitis media.

KEYWORDS nontypeable *Haemophilus influenzae*, *Streptococcus pneumoniae*, invasive capacity, otitis media

From a historical perspective, the pneumococcus has perhaps been the most deadly of human pathogens. From its early biology of division into three serotypes (I, II, and III), it established itself as the dominant pathogen in pneumonia. Over the last century, it has evolved into more than 90 serotypes and continues today to be a dominant cause of severe pneumonia and sepsis, of otitis media (OM), and of sinusitis and nonbacteremic pneumonia. Despite the advances in treatment and prevention, it remains a major foe causing mortality in both young and old throughout the globe.

Nearly all humans are colonized at some point during childhood with a pneumococcus, and yet relatively few develop disease. The article by Lewnard and colleagues in this issue of *Infection and Immunity* expands our insight into the nuances of the capacity of pneumococci to progress from colonization to middle ear pathogen (1). The combination of clinical investigation with cutting edge modeling approaches uses data collected from sentinel studies of acute otitis media (AOM) in Israel and demonstrates the value of new approaches and new collaborations. We already know from studies correlating pneumococcal serotypes found in the blood, cerebrospinal fluid, or middle ear with those recovered from the nasopharynx in afflicted individuals that virtually all pneumococcal disease syndromes begin with nasopharyngeal acquisition (2). As well, concurrent viral infection appears to be critical, an idea supported by both epidemiological studies demonstrating increased incidence of disease during seasonal respiratory syncytial virus and influenza virus circulation and mechanistic identification of increased pneumococcal density in the nasopharynx in the presence of viral respiratory infection (3). In addition, cocolonization with pneumococcus and other respiratory pathobionts (specifically, nontypeable *Haemophilus influenzae* and *Moraxella catarrhalis*) increases the likelihood of development of otitis media, suggesting that changes in virulence result from such interactions (4). As well, several studies have suggested that disease is most likely to occur shortly after pneumococcal acquisition, suggesting that the risk of progression from colonization to disease changes during persistent carriage (5).

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Lewnard and colleagues provide further insights into the progression of nasopharyngeal pneumococcal colonization to disease using an invaluable collection of colonization and middle ear fluid samples from a 10-year prospective study of the incidence and microbiology of severe otitis media requiring tympanocentesis as part of clinical management. Their first observation is that the diversity of pneumococcal serotypes found in nasopharyngeal colonization exceeds that of serotypes recovered from the middle ear, further clarifying that each serotype and its accompanying genome have unique capacities to progress to pneumococcal otitis media, with the result being that a limited number of serotypes cause a disproportionate amount of disease. The implication is that progression to disease following pneumococcal acquisition differs by serotype and, potentially, by strain. Second, the article by Lewnard and colleagues further clarifies what had been a dilemma to me. Several previous analyses of the invasive capacity of pneumococci according to serotype for otitis media had come to the conclusion that, unlike those causing invasive disease, there was little difference among the serotypes in their ability to ascend from the nasopharynx to the middle ear (6, 7). As a consequence of the availability of a unique and extensive database of nasopharyngeal and middle ear specimens, we now have a clear picture of the magnitude of the differences between the highest and lowest progression rates and a critical but heretofore missing piece explaining how conjugate vaccines that do not reduce the prevalence of pneumococci in the nasopharynx dramatically impact the incidence of acute and complex otitis media. The 100-fold difference between the progressors with the highest rates, many of them conjugate vaccine serotypes, and those with the lowest rates, many of which are now prominent colonizers of the nasopharynx, provides insight into the mechanisms leading to disease reduction, albeit it still leaves us to delve further into the molecular mechanisms that account for such differences.

The third observation focuses on the interaction between pneumococci and nontypeable *Haemophilus influenzae* in the nasopharynx and middle ear. In children colonized with both *Streptococcus pneumoniae* and nontypeable *Haemophilus influenzae*, rather than approximating the reduced diversity of serotypes recovered from the middle ear compared to the nasopharynx as reported for single-species carriage, the diversity of middle ear serotypes more closely approximated that in the nasopharynx when dual carriage is present. The authors concluded that polymicrobial interaction in the nasopharynx resulted in these observations. They reported that many pneumococcal serotypes demonstrate lower rates of progression to pneumococcal otitis when the nasopharynx is cocolonized with nontypeable *Haemophilus influenzae*. This observation is consistent with previous reports that when both nontypeable *Haemophilus influenzae* and *Streptococcus pneumoniae* are present in the nasopharynx, nontypeable haemophilus is found in the middle ear in nearly 75% of cases (8, 9). Mechanistic animal modeling has suggested that cocolonization with nontypeable *Haemophilus influenzae* and *Streptococcus pneumoniae* increases neutrophil recruitment and promotes pneumococcal clearance, a potential mechanism that would decrease the likelihood of progression to disease (10). Alternatively, neuraminidase-producing strains of *S. pneumoniae* may desialylate the lipopolysaccharide of *Haemophilus* spp., making such strains more susceptible to complement and killing. The *in vivo* observations reported by Lewnard and colleagues serve to identify which mechanisms dominate in young children and, with the large database, whether important differences among serotypes are likely.

Epidemiologic studies deconstructing the progression from colonization to disease, such as that by Lewnard and colleagues, will be invaluable in different geographies and in different populations. The introduction of pneumococcal conjugate vaccine in the United States has resulted in a dramatic shift in the epidemiology of pneumococcal disease such that the disease incidence in adults ≥65 years of age now exceeds that in children (11). Disease in adults is increasingly concentrated in those over 65 years of age or those with comorbidity or both, potentially reflecting a different rate of progression from colonization to disease in these at-risk populations (12). Weinberger

reported that the invasiveness of individual serotypes (disease incidence divided by carriage prevalence) had similar rank orders across age groups, with some exceptions (13). However, I would speculate that invasiveness for the less invasive serotypes varies with increasing age and comorbidity, with higher progression rates in older adults and those with comorbidity. Large epidemiologic studies of pneumococcal carriage and pneumonia in adults, using methods similar to that used by Lewnard and colleagues, could potentially provide further insight into the vulnerability of these individuals as well as identify those serotypes most likely to cause disease following acquisition and enable new strategies for prevention.

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