

Are persons with asthma at increased risk of pneumococcal infections, and can we prevent them?

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In this issue of the *Journal of Allergy and Clinical Immunology*, Juhn et al¹ report the association of an increased risk of serious pneumococcal disease, defined as invasive pneumococcal disease or pneumococcal pneumonia, among persons with asthma in a population of residents of Rochester, Minn, studied between 1964 and 1983. Previously, our group reported that persons with asthma had a greater than 2-fold increased risk of invasive pneumococcal disease, using the Active Bacterial Surveillance Core data from the Centers for Disease Control, which identified *Streptococcus pneumoniae* from sterile sites, among both children and adults.² These studies among persons with asthma in 2 very different US populations, and during different study periods, now provide compelling support for adding asthma as a high-risk condition for serious pneumococcal disease. In addition, Almirall et al³ have recently shown that both asthma and inhaled corticosteroids are risk factors for community-acquired pneumonia, although not specific to *Streptococcus pneumoniae*, in a European population-based case-control study among persons age >14 years. What follows is a summary of our current understanding of the data supporting the association of asthma and serious pneumococcal disease, potential mechanisms of host susceptibility to infections, and preventive implications and challenges of our current knowledge.

The available evidence from Juhn et al¹ and Talbot et al⁵ supporting an increased risk of serious pneumococcal disease among persons with asthma comes from observational data. An association between a risk factor (asthma) and a subsequent event (pneumococcal disease) can reflect causal mechanisms; alternatively, such associations could be a result of other unmeasured factors or characteristics that are closely related to asthma (confounders). However, in both cases, “asthma” identifies those at high-risk, and in both of these studies, the results are strikingly consistent.

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These observational investigations are likely to be the extent of the available evidence to support the association between asthma and an increased risk of serious pneumococcal disease. Because human beings cannot ethically be randomized to pneumococcal inoculation, and a prospective study would be labor-consuming and prohibitively costly, these retrospective studies are likely to provide the only answers to the question of whether asthma is a risk factor for invasive pneumococcal disease and pneumonia. Having thus established this association, what we now lack is both an understanding of why persons with asthma have an increased susceptibility to pneumococcal infection, and the efficacy and effectiveness of pneumococcal preventive efforts on both pneumococcal and asthma morbidity among persons with asthma.

So why are persons with asthma at an increased risk for pneumococcal disease? Historically, studies of infections and asthma have centered on the impact of respiratory infections on asthma exacerbations, rather than infection susceptibility. Although more recent investigations provide explanations that lend biologic plausibility to an increased susceptibility to pneumococcal infection among persons with asthma, the exact mechanisms for this increased risk are not known. Persons with asthma have a disrupted airway epithelial physical barrier, increased and aberrant mucous production, and other alterations in innate and adaptive immunity.⁴ There are also genetic factors that affect patterns of immune response to infectious agents that are linked with asthma, and asthma medications may be immunosuppressive, or possibly even enhance immune responses specifically among persons with asthma who are prescribed and compliant with their medications.^{4,5} It is also well recognized that persons with asthma cannot limit viral infections to the upper respiratory tract, and are more likely to experience viremia.⁶ This increased susceptibility has been shown to relate to defective innate immune responses.^{7,8} In addition, persons with asthma have been shown to have increased rates of pneumococcal nasal colonization, as well as hypopharyngeal colonization as neonates before the development of asthma, which provides strong support for a pre-existing defective immune response among persons destined to develop asthma.^{9,10} These data suggest that the increased association of clinically significant pneumococcal infection in asthma is not just an epiphenomenon caused by enhanced airway inflammation rendering persons with asthma more clinically symptomatic from pneumococcal respiratory disease, but that allergic inflammation and asthma are associated with or alter host defenses and in this way render persons with asthma more susceptible to pneumococcal disease. The strongest evidence for this true increased susceptibility to pneumococcal disease among persons with asthma lies in the data supporting an increase in invasive infections—that is, infections outside the respiratory tract, because asthma is a respiratory disease, and respiratory manifestations of a respiratory illness would be expected to be more clinically apparent or severe

in such persons.² This is additionally important, as pneumococcal vaccine is most efficacious for invasive pneumococcal disease.

Although it is imperative for us to understand the mechanisms underlying why persons with asthma are at increased risk for serious pneumococcal disease to identify novel targets for treatment and advance preventive efforts, we do not need these answers now to put these findings into clinical context. With the identification and now confirmation establishing asthma as a risk factor for serious and invasive pneumococcal disease, known immune alterations that provide biological plausibility for increased susceptibility to infections among persons with asthma, we should reconsider whether persons with asthma should be candidates for pneumococcal vaccination.

The next issue is a call for the Advisory Council on Immunization Practices and the Centers for Disease Control to consider the broadening of recommendations for pneumococcal vaccination to include persons with asthma, on the agenda for their most recent meeting. This issue is particularly important in view of the high and rapidly increasing prevalence of asthma in many parts of the world, and in the United States, affecting at least 8% of the population.¹¹⁻¹⁴ Current Advisory Council on Immunization Practices guidelines for pneumococcal vaccination specifically exclude persons with asthma,^{13,14} and guidelines for the management of asthma do not include pneumococcal vaccination as a strategy to prevent infectious complications.¹⁵ However, these have not been easy decisions. Important information that informs policy regarding vaccination strategy is lacking. Is the pneumococcal vaccine efficacious in asthma, and would it be effective and cost-effective in decreasing pneumococcal morbidity and mortality, and possibly asthma-specific morbidity? These questions will only be answered after further study and assessment with pneumococcal vaccine use in persons with asthma. Although we have shown that a majority (85.9%) of the pneumococcal serotypes associated with invasive pneumococcal disease among persons with asthma are included in the currently licensed pneumococcal vaccines, supporting the potential benefit of vaccination, there are scant data that address these other important questions.²

In conclusion, the investigation by Juhn et al¹ provides important and additionally needed evidence of an association between asthma and serious pneumococcal disease. In both the investigations by Juhn et al¹ and Talbot et al,² the increased risk of invasive pneumococcal disease among persons with asthma was similar to the reported risk among persons with other conditions, such as diabetes and chronic obstructive pulmonary disease, a chronic pulmonary disease similarly characterized by chronic airway inflammation, and for which pneumococcal vaccination is currently recommended.^{1,2,13,14} Defining and confirming this association puts asthma on the list of conditions that increase the risk of

serious pneumococcal disease, including invasive pneumococcal disease. As the incidence of asthma continues to climb in the United States and worldwide, the burden of serious pneumococcal disease among persons with asthma will likely increase. Studies of the efficacy and cost-effectiveness of pneumococcal vaccination in persons with asthma on both pneumococcal and asthma morbidity must now be considered, studies most likely to be conducted after the introduction and uptake of recommendations for vaccination among persons with asthma and study of pneumococcal and asthma-specific morbidity outcomes.

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