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Experimental Model for Studies of Pneumococcal Colonization in Older Adults

Pneumococci are major contributors to morbidity and mortality globally, being a major cause of community-acquired pneumonia, with or without septicemia, and bacterial meningitis, especially after the introduction of the Hib vaccine globally (1). The ecological niche for pneumococci is regarded to be the nasopharynx of young and healthy children and has been shown to carry pneumococci in the upper respiratory tract in up to 60% of cases (2, 3). Pneumococcal colonization is believed to be a prerequisite for acquiring severe invasive pneumococcal diseases (IPD) (4). Young children and the elderly belong to the risk groups for getting IPD; hence, pneumococcal conjugated vaccines (PCVs) were introduced into childhood vaccination programs in many countries, leading to a dramatic decrease of IPD in vaccinated children (5–8). However, some studies have shown that nasopharyngeal colonization rates in children have remained the same after PCV introduction because of an increase of nonvaccine types, that is, serotype replacement with nonvaccine strains (7, 9).

Several studies show that nasopharyngeal colonization decreases with age and that it is lower in adults than in children (10). Also, it has been suggested that adults might be less susceptible to pneumococcal colonization. More knowledge is needed on why age influences colonization, which immune responses are evoked by pneumococcal colonization, especially in the elderly population, and to what extent a prior colonization might protect against recolonization. These issues are being addressed in this issue of the *Journal* in the study by Adler and colleagues (pp. 604–613) (11). Previous experimental model systems in humans with pneumococcal challenge have studied immune responses in younger adults (12), but here, Adler and colleagues are the first to challenge healthy older adults from 50 to 84 years of age, thus also including the risk group of the elderly above 65 years of age. In total, 64 adults were challenged with a pneumococcal strain of serotype 6B, originally isolated from the nasopharynx of a child (13). The authors determined colonization rates by culture of nasal washes and humoral immune responses by anticapsular and antiprotein IgG levels. They found that colonization could be successfully established in 39% of the adults, though higher in the age group of 50 to 59 years (47%) than in those greater than or equal to 70 years of age (21%), suggesting that this model can be used for studies of pneumococcal colonization in all age groups. The authors conclude that colonization rates are similar between younger and older adults, but a larger study might be needed to clarify this issue, especially because only 14 participants were included in the 70- to 80-year-old group. In addition, only one pneumococcal strain was used in the study, and we know that there might be differences between strains of different serotypes in, for example, the ability to colonize, the length of carriage, and the pathogenicity. Moreover, pneumococci interact with other microbes in the respiratory microbiota, both other bacteria and viruses, which might affect colonization rates, and it has been shown that heterogenicity in the nasopharyngeal microbiome promotes pneumococcal colonization (14). One can speculate that the elderly might have more frequently undergone antibiotic treatment and that this could have reduced the diversity of the bacterial microbiome of the upper respiratory tract, as has been suggested previously (15). The expression of specific receptors of the nasopharyngeal epithelium that recognize pneumococcal proteins important for bacterial adhesion may also differ between individuals and influence colonization rates. Previously it has been described that aging and chronic inflammation were associated with enhanced expression levels in the lungs of receptors such as the pIgR (polymeric immunoglobulin receptor) (16). pIgR has been shown to interact with pneumococcal proteins such as PspC (CbpA), and hence this increased interaction might promote pneumococcal adhesion to epithelial and endothelial cells and disease development (17, 18). The current study opens possibilities to address these questions in a larger human experimental study including more participants, other pneumococcal serotypes, and data on the microbial nasopharyngeal flora and individual immune responses.

Interestingly, they observed that prior vaccination with 23-valent pneumococcal polysaccharide vaccine (PPV23) did not affect colonization rates in older adults. There are few data on the effect of

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PPV23 on colonization; however, some studies show that PCVs might confer short protection, whereas other studies do not see an effect on colonization rates after PCV introduction, such as in Sweden, because of a massive serotype replacement by nonvaccine serotypes (7). PPV23 and PCVs target only a limited number of the 100 pneumococcal capsular polysaccharides described so far, and hence they do not protect against the whole pneumococcal population circulating in the society. Thus, development of vaccines on the basis of conserved pneumococcal proteins has been suggested. Importantly, Adler and colleagues analyzed antibody levels against 27 pneumococcal proteins and observed increased antiprotein antibody levels to several pneumococcal proteins, such as the adhesin PspC, PspA, PiuA, PcpA, PsaA, and the pilus protein RrgA (19, 20), in participants that were colonized but not in the noncolonized group. Several of these proteins have been suggested as vaccine candidates in protein-based vaccines. Potentially, pneumococcal colonization might influence protection by evoking antibodies to these proteins in older adults, but this remains to be studied. Surprisingly, though, and also in contrast to what was found previously for younger adults, the authors did not observe an increase in the antibody response (IgG) to the 6B capsule after colonization and rather a drop in noncolonized participants. Moreover, a rechallenge was performed 1 year later on the 16 participants that showed a limited protection to reacquisition of the same pneumococcal strain as opposed to what has been found in younger adults. These findings are interesting but need to be confirmed in a larger study and by using other pneumococcal strains and serotypes because the antibody response might be influenced by the serotype.

Pneumococcal diseases are human specific and need to be studied in humans, if possible. This study in older adults with no adverse effects shows the potential of using this experimental model system in all age groups. This is highly needed to explain mechanisms for carriage in different age groups. Possibly such models could also be used in vaccine studies and to analyze the efficacy of vaccines as a complement to large clinical studies of IPD. ■

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