Modeling the Association between Pneumococcal Carriage and Child-Care Center Attendance

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(See the article by Huang et al. on pages 1215–22)

Child-care centers (CCCs) are the main venues for out-of-home care for preschool children in Western nations [1, 2]. The number of children attending such facilities is increasing, such that in the United States, >13 million children <5 years of age attend some form of out-of-home CCC [2]. Children attending CCCs are at increased risk for infectious diseases, the most common of which are respiratory infections [2–4]. The increased rate of infection among CCC attendees not only results in significant morbidity among the children but also has a significant economic impact resulting from work loss and the cost of medical care. These costs are estimated to be $1.8 billion annually in the United States alone [4].

There is no doubt that Streptococcus pneumoniae is an important cause of morbidity and mortality in all populations [5]. Pneumococcal nasopharyngeal carriage is important for 2 fundamental reasons: it is a precondition for the development of disease, and it is this condition, rather than pneumococcal disease, that results in person-to-person pneumococcal transmission. Crowded conditions facilitate this transmission directly (by increasing the frequency of contact) and indirectly (by increasing the prevalence of other respiratory infections that facilitate pneumococcal colonization and transmission).

CCCs are efficient catalysts for the spread of pneumococcal carriage, because they impose a major risk factor for pneumococcal colonization (i.e., crowding) on the very population—young children—at greatest risk for pneumococcal colonization and subsequent disease. Among young children in CCCs, the combination of increased biological susceptibility to pneumococcal carriage, high rates of viral infection, and poor hygienic behavior are responsible for pneumococcal carriage rates of >90% in some studies [6–10]. Furthermore, frequent antibiotic use in CCCs contributes to theirunique role in the promotion of carriage of antibiotic-resistant S. pneumoniae and the resultant increased morbidity associated with these strains [10, 11]. It is no surprise, then, that CCC attendance by children <6 years of age was independently associated with invasive disease in household adult contacts aged 18–64 years [25]. Thus, the role of CCCs in the transmission of S. pneumoniae to the community, as well as the resulting increase in morbidity, is clear and well documented.

In this issue of Clinical Infectious Diseases, Huang et al. [26] have moved our understanding of the dynamics of pneumococcal carriage a step forward by quantitatively estimating the role of CCCs on the community-wide prevalence of pneumococcal carriage. They constructed a mathematical model based on the hypothesis that, if CCCs are a dominant source of variability in the prevalence of pneumococcal carriage across communities, the presence and characteristics of...
CCGs would be associated with the prevalence of carriage not only among individuals attending CCGs (i.e., the direct effect) but also among children in the same community who are not attending CCGs (i.e., the indirect effect), because of pneumococcal transmission from CCC attendees to contacts not attending CCGs.

The parameters used in this relatively complex transmission model were based on summary data from 16 distinct communities in Massachusetts and included simple parameters, such as transmission rate within CCGs, transmission rate outside of CCGs, and fraction of children attending CCGs, and more-complex parameters, such as mean hours per week in CCGs, weekly rate of antibiotic prescribing, and antibiotic-induced clearance of carriage. The extended model strongly suggested that indirect effects substantially determined the variability in the prevalence of pneumococcal carriage across communities. Although the direct OR for carriage (i.e., the effect of attending a CCC) remained constant (range, 2–3) regardless of the variability in CCC attendance between the communities, the risk of pneumococcal carriage for children not attending CCGs was up to 6 times the risk for children in a community without a CCC as the proportion of attendees in the community increased (the indirect OR). Furthermore, both direct and indirect ORs are not only a function of the number of community children in CCGs, but they are also a function of the mean number of hours that children spend in CCGs in their specific communities. In communities without CCGs, the model predicted that transmission is barely maintained, resulting in a prevalence of carriage of ~4%.

Huang et al. [26] point out that their model has the following limitations: (1) it does not account for any known pneumococcal risk factors other than CCC attendance; (2) it restricts the modeling population to young children; (3) it does not explain or model the factors in CCGs that contribute to pneumococcal carriage; (4) it assumes that the mean duration of carriage is a fixed value; (5) it assumes that children mix randomly within compartments (i.e., within CCGs and within communities) rather than live in distinct families and attend discrete CCGs; (6) it does not account for antibiotic-resistant strains, which would be differentially selected by antibiotic use; and (7) the model parameters are not based on a truly random community sample of children. Several additional limitations should be mentioned. First, the model does not take into account crowding within the community [27], which further affects transmission outside of CCGs. It is logical to assume that community crowding may account for an increased rate of transmission. Second, the model does not account for the potential differences in the serotype-specific duration of carriage. The prevalent serotypes might differ across communities or CCGs and might be associated with different durations of carriage [28]. Third, the model does not include a potentially important parameter that accounts for variability in antibiotics use per se and the rate in which antibiotics from a given class are used. Oral cephalosporins and long-acting macrolides were shown to account for a greater selection of carried antibiotic-resistant and multidrug-resistant S. pneumoniae than were penicillins (i.e., amoxicillin) and thus may contribute to higher prevalence of pneumococcal carriage, compared with other agents [29]. Fourth, the model does not consider the density of colonization, which would be expected to affect the transmissibility of pneumococci from person to person. Newly implemented vaccination approaches using conjugate pneumococcal vaccine may affect the density of carriage, in addition to the rate of carriage acquisition, the serotype distribution, and the duration of carriage [30].

Although formal CCGs are not common in large parts of the world where the rates of pneumococcal disease and mortality are highest, the living and child-care arrangements in these developing regions are often de facto CCGs. Thus, the hypotheses and inferences from the study by Huang et al. [26] may well extend to settings around the world where pneumococcal disease is most burdensome. This model provides an additional rationale and biological basis for making critical decisions about the potential benefits of conjugate pneumococcal vaccine use in epidemiological settings where colonization and disease burden are high. The model would suggest that any vaccination regimen that can impact colonization among the vaccinees will substantially reduce the colonization risk among persons who find themselves in crowded child-care settings and persons who have no direct contact with these settings.

Mathematical models are never perfect. In fact, they are always wrong, because no model can mimic the complexities of real life. However, models are invaluable tools for disentangling the relative importance and behavior of a small number of variables in a reproducible and controlled manner. In the present case, the model enables us to separate and evaluate the individual- and community-level effects of CCGs on pneumococcal colonization among children in communities. The main purpose of the model is to direct our thinking by helping to clarify that various observations about colonization rates and factors affecting colonization are not just a cluster of facts but likely fit a clear hypothesis. Given the evidence reviewed above for the role of CCGs in the spread of pneumococcal disease in communities, the model helps tie together the evidence and thereby adds an important dimension to our understanding of the epidemiology of pneumococcal carriage and disease.

The main hypothesis generated from the model is that CCGs are key factors for promoting variability in pneumococcal carriage among individuals and across communities. Estimating the community-level attributable risk for carriage associated with CCC attendance is a novel project. What are the implications of such a project? First, it is important to validate the hypothesis by carefully comparing the
attributable community-level risks associated with CCC attendance to other risk factors for a high carriage rate of \textit{S. pneumoniae}, in general, and antibiotic-resistant \textit{S. pneumoniae}, in particular, in specific communities. These include environmental factors (e.g., degree of crowding, number of siblings per household, poor hygienic conditions, burden of other respiratory illnesses, and smoke exposure), antibiotic use factors, and potential genetic factors, among others. In some developed nations (e.g., the United States, France, Iceland, and Israel), communities with relatively high pneumococcal carriage rates usually have high antibiotic-resistance rates and high rates of CCC attendance. At the other end of the spectrum are countries in which CCC attendance is less common or is initiated at a later age (e.g., Finland, Denmark, and The Netherlands), where the rates of \textit{S. pneumoniae} carriage and antibiotic resistance are much lower than those in other developed nations. However, the latter countries may also have fewer children per family, less crowding, and lower levels of antibiotic use. Studies are therefore needed to confirm that most of the variability in the prevalence of carriage is accounted for by CCC attendance.

Understanding the community-level attributable risks associated with CCC attendance has important implications for pneumococcal conjugate vaccine programs. CCC attendees are considered to be at risk for invasive pneumococcal disease, even those \( \geq 2 \) years of age [28]. The American Academy of Pediatrics’ Committee on Infectious Diseases states that “the relative merits of the conjugate 7-valent pneumococcal vaccine or 23-valent nonconjugated polysaccharide vaccine given as a single dose in children 24 months of age or older have not been studied. … Either the 7-valent conjugate vaccine or the 23-valent nonconjugate vaccine can be used for elective administration to children 24–59 months of age who are at moderate risk” [31]. Use of conjugate pneumococcal vaccine clearly reduces the risk of acquiring vaccine-serotype strains and antibiotic-resistant strains of \textit{S. pneumoniae} among CCC attendees [11, 32] and their close contacts [33]. Use of plain polysaccharide vaccines does not have an effect on preventing pneumococcal carriage in infants and toddlers [34]. Recent data from the United States [35] strongly suggest that the degree of indirect protection against invasive \textit{S. pneumoniae} disease and antibiotic-resistant \textit{S. pneumoniae} infection—that is, the number of cases prevented in unvaccinated individuals from a vaccinated community (also referred to as herd immunity)—is at least as high as the degree of direct protection for vaccinated children, resulting in an impressive decrease in the number of cases of disease in all age groups. Understanding the important role of CCCs in the transmission of carriage of \textit{S. pneumoniae} and antibiotic-resistant \textit{S. pneumoniae} among nonattendees of CCCs clearly increases the incentive to vaccinate CCC attendees, even if the latter are 24–36 months of age or older, and increases the preference for administration of conjugate vaccines (at least for the first dose) instead of the wider-spectrum but nonconjugated 23-valent polysaccharide vaccine.

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References

17. Black S, Shirefield H, Elvin L, Schwable J. Pneumococcal epidemiology in childhood in...