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Authors

Huang, Susan S
Finkelstein, Jonathan A
Lipsitch, Marc

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Modeling Community- and Individual-Level Effects of Child-Care Center Attendance on Pneumococcal Carriage

Susan S. Huang,^{1,4} Jonathan A. Finkelstein,^{1,5} and Marc Lipsitch^{2,3}

¹Department of Ambulatory Care and Prevention, Harvard Medical School and Harvard Pilgrim Health Care, ²Department of Epidemiology and ³Department of Immunology and Infectious Diseases, Harvard School of Public Health, ⁴Channing Laboratory, Brigham and Women's Hospital, and ⁵Division of General Pediatrics, Children's Hospital Boston, Boston, Massachusetts

(See the editorial commentary by Dagan and O'Brien on pages 1223–6)

Background. The prevalence of pneumococcal carriage varies widely across communities. This variation is not fully explained by risk factors at the individual level but may be explained by factors producing effects at both the individual and community levels, such as child-care center (CCC) attendance.

Methods. We developed a transmission model to evaluate whether the combined risks of attending CCCs and associating with playmates who attend CCCs account for a large proportion of the variability in the prevalence of pneumococcal carriage across communities. We based parameters for the model on data from a multicommunity study.

Results. According to our model, differences in the proportion of children who attend CCCs can account for a range of 4%–56% in the prevalence of pneumococcal carriage across communities. Our model, which was based on data collected from 16 Massachusetts communities, predicts that the odds of carriage associated with CCC attendance are 2–3 times the odds associated with no CCC attendance (individual-level effect). The model also predicts that the odds of carriage for nonattendees in a community with CCCs are up to 6 times the odds for children in a community without CCCs (community-level effect). In addition, the mean number of hours spent at CCCs by a single attendee appears to exert effects on pneumococcal carriage that are independent of either the proportion of CCC attendance in the community or the mean number of hours these attendees spend in child care.

Conclusions. We used data from multiple communities to develop a transmission model that explains marked differences in pneumococcal carriage across communities by variations in CCC attendance. This model only accounts for CCC attendance among young children and does not include other known risk factors for pneumococcal carriage.

The annual incidence of invasive pneumococcal disease varies widely across US communities [1–3]. Before the heptavalent conjugate pneumococcal vaccine was available, the annual incidence of invasive disease in US communities was 113–274 cases per 100,000 children aged <2 years and 19–55 cases per 100,000 children aged 2–4 years [2]. Although the vaccine has significantly reduced the incidence of invasive disease [4], variation across communities persists.

Pneumococcal carriage is a known precursor to invasive disease [3, 5]. In children, the prevalence of carriage also varies widely from 14%–52% across communities [6, 7]. The cause of this variation is unknown. Numerous studies have identified individual predictors, including age, number of siblings, child-care center (CCC) attendance, and respiratory tract infection [8–11]. Nevertheless, factors at the individual level do not fully account for marked differences in the prevalence of childhood pneumococcal carriage across communities [3, 12].

Few studies have evaluated community-level predictors of pneumococcal carriage or disease. One study found that census tracts of poor, black populations had an incidence of invasive pneumococcal disease that was higher than that for census tracts of wealthier, white

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Reprints or correspondence: Dr. Susan S. Huang, 181 Longwood Ave., Boston, MA 02115 (sshuang@partners.org).

populations [13]. We recently evaluated census tracts in 16 Massachusetts communities with respect to population size, age distribution, population density, antibiotic use, and disadvantaged socioeconomic status among children. We found that census tracts associated with large household size or disadvantaged socioeconomic status had a risk of pneumococcal carriage that was 2–3 times the risk found in census tracts without those characteristics [14]. However, because census tracts with these characteristics are limited in prevalence, these factors account for only a small etiologic fraction of pneumococcal carriage and are insufficient to explain the marked variation in the prevalence of pneumococcal carriage across US communities.

We hypothesized that, if a dominant source of the variability in pneumococcal carriage across communities exists, it would be highly prevalent and would exert both individual- and community-level effects. We noted elsewhere that CCC attendance is strongly associated with pneumococcal carriage and is very prevalent across communities with diverse socioeconomic characteristics [7]. Nevertheless, CCC attendance has only been evaluated for its direct effect on attendees, despite the fact that CCCs are known foci of increased pneumococcal transmission, from which attendees can spread *Streptococcus pneumoniae* to nonattendees in their community [10, 15, 16].

Mathematical models of transmission estimate the behavior of a small number of variables in a reproducible and controllable setting. They enable separation and evaluation of individual- and community-level effects. Although a simplified version of reality, these models provide an efficient and inexpensive way to evaluate hypotheses that can then be tested in large-scale studies. We developed a transmission model to evaluate whether direct and indirect effects of CCC attendance could account for the wide range of variability in the prevalence of pneumococcal carriage across communities.

METHODS

We defined the direct (individual-level) effect of CCC attendance as the increase in the odds of carriage between CCC attendees and nonattendees in the same community. We defined the indirect (i.e., community-level) effect as the increase in the odds of carriage between CCC nonattendees living in a community in which a fraction of children attend CCCs and children in a hypothetical community in which no children attend CCCs.

We used recently reported data [7] for 742 young children in 16 Massachusetts communities to provide community estimates of the fraction of children attending CCCs, the mean duration (in hours) of CCC attendance per week, rates of antibiotic prescribing, and clearance of pneumococcal carriage in response to antibiotic therapy. In addition, we used these data to estimate transmission rates among CCC attendees and non-

attendees. Study procedures were approved by the institutional review board at Harvard Pilgrim Health Care (Boston).

Model description and assumptions. We designed a mathematical model that represented a single, hypothetical community of young children. Children in the model community have 1 of 2 possible pneumococcal carriage states, either noncolonized or colonized, and the variables X and Y designate the proportion of noncarriers and carriers of pneumococcus, respectively. We assumed that a child could carry only 1 strain of *S. pneumoniae* at a time.

In the general model (figure 1), noncarriers acquire carriage at a rate proportional to the rate of random contact between noncarriers and carriers (contact per week proportional to $X \times Y$). The proportionality constant β incorporates the contact rate and the probability that contact results in transmission. Clearance of pneumococcal carriage occurs spontaneously at rate μ . Additionally, clearance occurs in a fraction of the population of children c for whom antibiotics are prescribed at weekly rate r .

In the extended model (figure 2), the community is divided into 2 subgroups: children attending CCCs (subscript C) and children not attending CCCs (subscript N). X and Y represent the proportion of children within each subgroup who are either not carriers (X_C and X_N) or carriers (Y_C and Y_N), such that $X_C + Y_C = 1$ and $X_N + Y_N = 1$. To obtain their respective community fractions, these proportions are multiplied by the fraction of the community of children in each subgroup. We designated f as the fraction of children in the extended-model community who are attending CCCs.

The extended model assigns different rates for pneumococcal transmission inside CCCs and transmission outside CCCs. The rate constant β_1 was used for transmission outside CCCs; for transmission inside the centers, the rate constant β_2 was used. Because of the intensive interaction among CCC attendees, we expected that $\beta_2 > \beta_1$. Because attendees spend only a portion of their waking hours in CCCs, we included the parameter g , which represents the mean number of waking hours per week that attendees spend in CCCs. On the assumption of 12 waking hours per day for young children, the fraction of waking hours

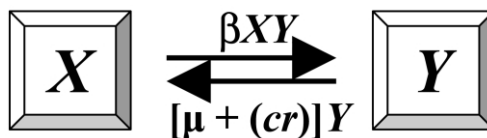


Figure 1. Simplified model of acquisition and clearance of pneumococcal carriage in a community comprised of young children. c , Percentage of children for whom antibiotic therapy results in clearance of carriage; r , percentage of children per week who receive antibiotics; X , proportion of noncarriers; Y , proportion of carriers; β , rate constant for transmission of carriage; μ , spontaneous clearance of carriage per week.

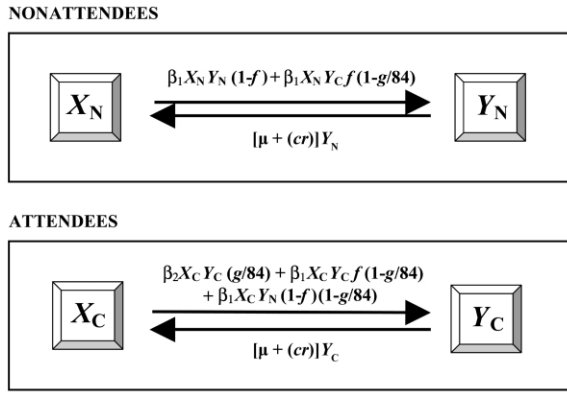


Figure 2. Extended compartmental model of acquisition and clearance of pneumococcal carriage in a community comprised of young children. c , Percentage of children for whom antibiotic therapy results in clearance of carriage; f , fraction of children attending child-care centers (CCCs); g , mean number of hours spent in CCCs; r , percentage of children per week who receive antibiotics; X_C , proportion of noncarriers who are attendees; X_N , proportion of noncarriers who are nonattendees; Y_C , proportion of carriers who are attendees; Y_N , proportion of carriers who are nonattendees; β_1 , rate constant for transmission of carriage outside of CCCs; β_2 , rate constant for transmission of carriage inside of CCCs; μ , spontaneous clearance of carriage per week.

per week spent in CCCs is $g/84$. Inside the CCC ($g/84$), attendees acquire carriage at a rate proportional to β_2 , but outside the CCC ($1 - g/84$), they acquire carriage at a rate proportional to β_1 .

In general, transmission results from child-to-child interactions that occur throughout the entire population of children. For example, noncarrier nonattendees (X_N) interact with carriers (Y_C and Y_N) as follows. During all waking hours (84 h/week), noncarrier nonattendees (X_N) interact with carrier nonattendees (Y_N) according to the equation $\beta_1 X_N Y_N (1-f)$, where $1-f$ is the fraction of nonattendees in the model. During the hours in which attendees are not at the CCC ($1 - g/84$), they rejoin the other children, and noncarrier nonattendees (X_N) can interact with carrier attendees (Y_C) according to the equation $\beta_1 X_N Y_C f$, where the conversion factor f is the fraction of attendees in the model. The conversion factors f and $1-f$ define transmission among subsets of children as a fraction of the total population of children in the model and are found in all transmission terms, except for those that describe transmission that occurs during CCC hours.

Because attendees aggregate in close quarters, our model allows pneumococcal acquisition during CCC hours to occur between carriers and noncarriers as a fraction of those who are at the CCC, as demonstrated by the equation $\beta_2 X_C Y_C (g/84)$. Thus, although attendees can no longer play with nonattendees, the number of playmate contacts for attendees is not reduced: contact occurs between carriers and noncarriers as a fraction of CCC attendees. However, our model did not make this as-

sumption for nonattendees. Instead, we calculated their playmate interactions as a fraction of the entire population of children in the community, effectively suggesting that, during CCC hours, nonattendees have fewer chances of encountering playmates, because the population of potential playmates has decreased.

Model equations. The model is described by the ordinary differential equations

$$dX_N/dt = -dY_N/dt$$

and

$$dX_C/dt = -dY_C/dt.$$

The non-CCC attendance compartment is described by the equations

$$\begin{aligned} dY_N/dt = & \beta_1 X_N Y_N (1-f) + \beta_1 X_N Y_C f (1-g/84) \\ & - \mu Y_N - cr Y_N \end{aligned}$$

and

$$X_N = 1 - Y_N.$$

The CCC attendance compartment is described by the equations

$$\begin{aligned} dY_C/dt = & \beta_2 X_C Y_C (g/84) + \beta_1 X_C Y_C f (1-g/84) \\ & + \beta_1 X_C Y_N (1-f)(1-g/84) - \mu Y_C - r Y_C \end{aligned}$$

and

$$X_C = 1 - Y_C.$$

Model parameters. To model carriage across communities with varying CCC attendance, we obtained data for several model parameters (β_1 , β_2 , f , g , r , and c) from a multicommunity study [7]. Nasopharyngeal cultures were performed for 742 children <7 years of age from 16 Massachusetts communities during sick-child or well-child physician visits in the spring of 2001. Communities were selected on the basis of the population size, the proportion of nonwhite individuals in the population, and the proportion of the population insured by Medicaid. Individual predictors of pneumococcal carriage were collected through questionnaires and medical record review. Although some children had received the conjugate pneumococcal vaccine, the overall prevalence of carriage among vaccinated children was not statistically significantly different from that among unvaccinated children at the time of sampling, likely because some children had not completed the vaccination series and

Table 1. Summary of the parameters used in a model to determine the association between child-care center (CCC) attendance and the risk of pneumococcal carriage.

Parameter	Variable	Estimated value (range)
Rate constant for transmission of carriage outside CCCs	β_1	0.23
Rate constant for transmission of carriage inside CCCs	β_2	0.82
Mean duration of carriage, weeks	$1/\mu$	5 (1–10)
Proportion of children attending CCCs	f	0.44 (0.24–0.65)
Mean hours per week spent in CCCs	g	19.8 (11–28)
Percentage of children per week who receive antibiotics	r	4.6 (2.8–6.6)
Percentage of children for whom antibiotic therapy results in clearance of carriage	c	22

because sampling had occurred shortly after the vaccine was licensed for use.

Clearance of pneumococcal colonization (c) was estimated to have occurred in 22% of the children receiving antibiotics. This percentage was based on the proportional decrement in the point prevalences of carriage for children who were and children who were not receiving antibiotics. To estimate the rate constants for transmission of carriage, we assumed that community pneumococcal transmission was at equilibrium and set the model equations equal to 0, solving for β_1 and β_2 by use of summary statistical values for f , g , c , and r derived from multicommunity data [7]. The duration of carriage was based on published data [11]. Unless otherwise specified, all models were run using values specified in table 1.

We solved the models at equilibrium using the multicommunity summary statistical values as starting values for X_N , Y_N , X_C , and Y_C . By adding parallel equations that represent a single child who does not contribute to the force of infection, we were able to calculate the effect of both community- and in-

dividual-level child care on a given child whose CCC participation might differ from the community average.

RESULTS

We solved for the prevalence of *S. pneumoniae* carriage at equilibrium while varying the fraction of attendees f in the model community and the mean number of hours per week g of CCC attendance (figure 3). The model predicted that, at equilibrium, children in communities with progressively higher fractions of attendees will have progressively higher prevalences of pneumococcal carriage. As f and g increased, total community pneumococcal carriage increased from 4% to 56%. Of note, as f increased from 0 to 1 (when $g = 19.8$), CCC attendance increased the prevalence of pneumococcal carriage not only among attendees (from 14% to 42%) but also among nonattendees (from 4% to 25%).

We distinguished between the direct effect that CCC attendance had on carriage and the indirect effect that living in a community where other children attend CCCs had on carriage. We refer to these effects as individual-level and community-level effects, respectively. Three ORs were determined. First, we calculated the OR for the odds of pneumococcal carriage among attendees versus the odds of carriage among nonattendees in the same community (direct OR). This is the traditional measurement of the effect of CCC attendance on the odds of pneumococcal carriage that is used in epidemiological studies. Second, we calculated the OR for the odds of carriage among nonattendees in a community where a fraction of children attend CCCs versus the odds of carriage among children in a community where no children attend CCCs (indirect OR). Finally, we calculated the OR for the overall odds of pneumococcal carriage in a community where a fraction of children f attend CCCs versus the odds of carriage in a community where no children attend CCCs (total OR) (figure 4). These direct, indirect, and total effects parallel those described elsewhere for vaccine efficacy and herd immunity [17].

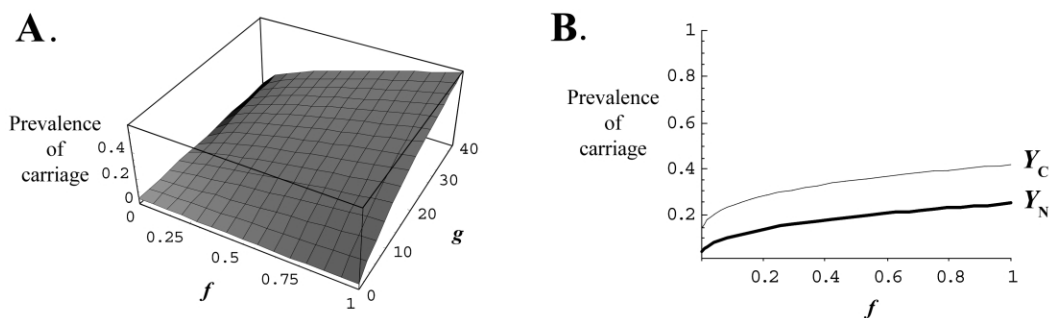
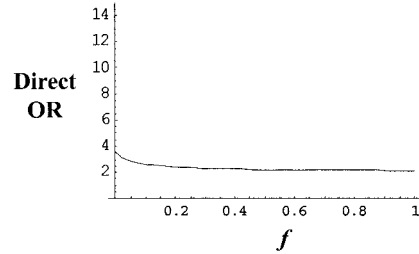
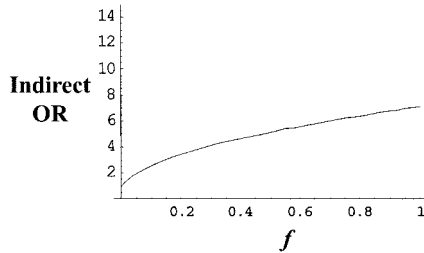


Figure 3. A, Equilibrium prevalence of pneumococcal carriage as a function of the fraction of children f in the community attending child-care centers (CCC) and the mean number of hours per week g that attendees spend in CCCs. B, Equilibrium prevalence of pneumococcal carriage among attendees (Y_C) and nonattendees (Y_N) as a function of f . The value g was fixed at 19.8 h/week, which was the mean number of hours spent in CCCs in our multicommunity dataset. As f increases, the prevalence of carriage increases not only among attendees, but also among nonattendees.

A. INDIVIDUAL EFFECT



B. COMMUNITY EFFECT



C. TOTAL EFFECT

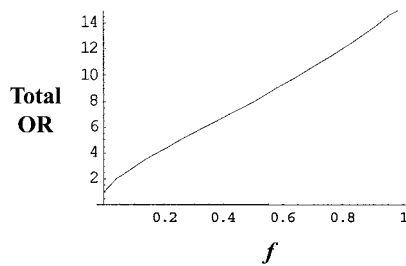


Figure 4. Effects of child-care center (CCC) attendance on pneumococcal carriage. *A*, Individual-level effect of CCC attendance: direct OR for the odds of carriage among CCC attendees versus the odds of carriage among nonattendees in the same community. The direct OR is dependent on the fraction of children f in the community who are attendees and the mean number of hours per week g that attendees spend in CCCs (fixed at 19.8 h/week in this simulation). *B*, Community-level effect of CCC attendance: indirect OR for the odds of carriage among nonattendees living in a community with attendees versus the odds of carriage among nonattendees in a hypothetical community in which there are no attendees. *C*, Total effect of CCC attendance: total OR for the overall odds of carriage in a community with attendees versus the odds of carriage in a community without attendees.

In our model, the direct OR for carriage was consistent over a large range of values for f in the 16 Massachusetts communities. Across this range (0.24–0.65), the direct OR was 2.2–2.4. However, the indirect OR was highly dependent on f . In a community where 24%–65% of the children attend CCCs, the odds of pneumococcal carriage for nonattendees were 3.7–5.8 times the odds of carriage in a community with no CCC attendees. Naturally, the total OR was even higher. Given $f = 0.44$ in the multicommunity cohort, the total OR of carriage was 7.3.

In the above analyses, we held fixed the mean weekly du-

ration g of CCC attendance at 19.8 h/week. In figure 5, we show the effects that varying f and g have on the direct OR. The direct OR for carriage increased in a nonlinear fashion as g , the mean number of hours attendees spend in CCCs, increased. The direct OR associated with attending CCCs was 2.3 in a community in which $g = 20$ h; 3.3, when $g = 30$ h; and 5.0, when $g = 40$ h. Figure 5 also shows the effect of varying both f and g on the total OR.

We varied the number of hours per week a specific child spends in CCCs separately from the community mean and found that each factor substantially increased the risk of pneumococcal carriage. In a community ($f = 0.44$) in which attendees spend a mean of 20 h/week in CCCs, a child who spends 20 h/week in CCCs would have a direct OR of 2.3. However, children who attend CCCs full time (40 h/week) would be predicted to have a direct OR of 3.4. We tested this predicted association between an increasing prevalence of pneumococcal carriage and increasing weekly hours at CCCs with data from the 16 Massachusetts communities. We performed a similar multivariate regression analysis of individual risk factors for pneumococcal carriage, replacing the binomial variable of CCC attendance with a categorical variable that divided weekly CCC attendance into 10-h increments [7]. The estimates of the multivariate analysis (table 2) paralleled the predictions of the model.

Our model assumed that the number of playmate contacts for nonattendees was less than that for attendees during hours in which the CCC was open. If it was assumed that nonattendees maintain their number of playmate contacts during hours in which the CCC is open because they seek regular contact with the remaining nonattendees, the model still generated similar qualitative and quantitative results.

Finally, in models of infectious diseases transmission, R_0 represents the number of secondary cases generated by a single infectious individual. This term is useful for describing the outbreak potential of an infectious agent. When $R_0 > 1$, infection is propagated; when $R_0 = 1$, the rate of infection is barely maintained; and when $R_0 < 1$, infection dissipates. Our model estimated that $R_0 = 1.1$ in communities without CCCs ($f = 0$).

DISCUSSION

Most epidemiologic studies of infectious diseases limit risk factor analyses to individual-level predictors. Nevertheless, the contagiousness of infectious diseases suggests that transmission is associated with risk factors related to both an individual and the individual's close contacts [18–21]. We evaluated individual- and community-level effects of attending CCCs on pneumococcal carriage and demonstrated how ecological effects can explain large variations in the prevalence of carriage across communities.

The published literature consistently reports ORs of 2–3 for

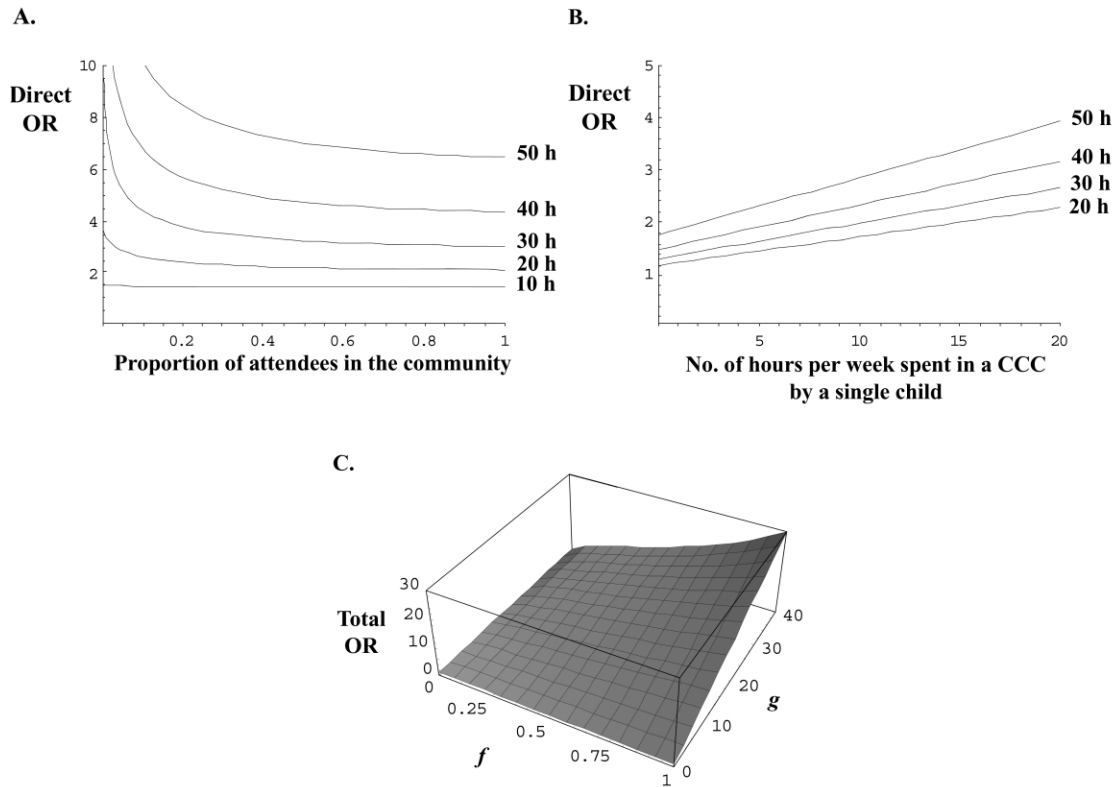


Figure 5. Relationship between ORs for pneumococcal carriage and the number of hours spent in a child-care center (CCC). *A*, Relationship between the mean number of hours per week that CCC attendees in the community spend in CCCs, the proportion of attendees in the community, and the direct OR for pneumococcal carriage. *B*, Relationship between the mean number of hours per week that attendees spend in CCCs, the number of hours per week that a given child spends in CCCs, and the direct OR of pneumococcal carriage. *C*, Total OR for CCC-associated pneumococcal carriage, displayed as the OR for the overall odds of carriage in a community as a function of the fraction of attendees f in the community and the mean number of hours per week g spent in CCCs versus the odds of carriage in a community without CCCs.

the CCC-associated risk of pneumococcal carriage [6, 22, 23] but widely varying estimates for the prevalence of carriage. In our model, the direct OR was similarly consistent (range, 2.2–2.4) across communities with varying fractions of children attending CCCs. The model provided an explanation for this stability. As more children attended CCCs, the prevalence of carriage increased for both attendees and nonattendees because of playmate interactions between and within groups. Because the prevalence of carriage increased among both groups, the direct OR remained relatively constant (range, 2–3). Nevertheless, evaluations limited to individual-level effects may miss the full effect that CCC attendance has on pneumococcal carriage.

Our model suggested that indirect (i.e., community-level) effects can be substantial. Whereas the direct OR remained constant (range, 2–3), the prevalence of carriage among nonattendees increased as the proportion of attendees increased. This occurred because a progressively higher proportion of a nonattendee’s playmates were attendees. This increase in prevalence among nonattendees was revealed by the indirect OR,

which was as high as 6 when actual multicomunity data were used in the model.

Our transmission model further demonstrated that pneumococcal carriage is independently affected by the mean number of hours that attendees spend in CCCs. Carriage among nonattendees was 4%–25%, on the basis of both the proportion of playmates who were attendees and the mean number of hours per week these playmates spent in CCCs. Overall, our model suggests that CCC attendance may account for variations of 4%–56% in the prevalence of pneumococcal carriage across communities. This range in prevalence closely resembles that reported in the literature [6, 7]. This suggests that the effect of CCC attendance alone may have the potential to explain the variation in carriage across communities. In fact, the model predicted that transmission would barely be maintained in a community devoid of CCCs ($R_0 = 1.1$; prevalence, 4%). Although such communities may be quite rare in the United States, the model’s prediction that lack of CCCs would result in minimal pneumococcal carriage further supports the idea

Table 2. Results of multicomcommunity multivariate analysis and the mathematical model for determining the odds of pneumococcal carriage associated with child-care center (CCC) attendance.

Model, factor	OR (95% CI)	P
Multicomcommunity		
Duration of CCC attendance		
0 h/week	1	
<4 h/week	1.32 (0.4–3.9)	.6
4–10 h/week	1.97 (1.0–3.8)	.04
11–20 h/week	1.87 (1.0–3.6)	.06
21–30 h/week	2.18 (1.1–4.3)	.03
31–40 h/week	2.38 (1.3–4.5)	.008
>40 h/week	6.16 (2.6–14.9)	<.0001
Recent antibiotic use	0.71	.12
No. of siblings in the household		
0	1	
1	1.61	.02
>1	2.59	.002
Age		
<5 months	1	
5–23 months	4.48	<.001
24–35 months	2.80	.02
≥36 months	3.54	.004
AOM/URI	2.48	<.0001
Breastfed for >2 months	0.91	.02
Mathematical		
Duration of CCC attendance		
0 h/week	1	
2 h/week	1.3	
7 h/week	1.5	
15 h/week	2.0	
25 h/week	2.5	
35 h/week	3.1	
45 h/week	3.6	

NOTE. AOM, acute otitis media; URI, upper respiratory tract infection.

that CCCs may be a dominant source of pneumococcal transmission.

Finally, our transmission model predicted that an individual's risk of carriage is quantitatively affected by the hours spent in CCCs. We subsequently validated this finding using data from a cohort of 742 children. Previously published studies have evaluated the effects of CCC attendance in an all-or-none fashion [7, 24–26]. We suggest that quantification of the weekly hours spent in CCCs provides an additional level of detail that may explain high and low prevalences of pneumococcal carriage.

We submit that CCC attendance is a key factor in producing both individual- and community-level variability in the prevalence of pneumococcal carriage. Our transmission model supports a high degree of association between CCC attendance and carriage, and CCC attendance is sufficiently common among

children to result in a high attributable risk for carriage. This model used actual data from a multicomcommunity study to derive parameters and to describe multilevel effects of CCC attendance as an explanation of variability in the prevalence of pneumococcal carriage across communities. By specifically evaluating the range of parameter estimates derived from data from the 16 communities, we provided rational estimates of how the prevalence of *S. pneumoniae* carriage can vary according to differences in CCC attendance alone. Estimates of the prevalence and individual-level risk of pneumococcal carriage resulting from this model are similar to those in published reports, although, to our knowledge, the community-level risks of CCC attendance are described here for the first time.

This model has several limitations. It did not account for any known pneumococcal risk factors other than CCC attendance, although it limited its scope to young children. With regard to CCC attendance, it evaluated the intensity of community and individual exposure to CCCs and estimated an elevated transmission rate between attendees, but it did not attempt to explain or model the factors at CCCs that contribute to pneumococcal carriage. It assumed that the duration of carriage was a fixed value, and it assumed that children mix randomly within compartments (i.e., CCC and non-CCC groups), rather than live in distinct families and attend discrete CCCs. It also did not account for antibiotic-resistant strains of *S. pneumoniae*, which would be differentially selected by antibiotic use. In addition, the parameters of the model were not based on data for a truly random community sample of children. However, sampling of data from physician visits avoided the clustering bias associated with child-care or classroom settings in which clonal strains might be disseminated. Although we did not exclude children who presented for sick-child physician visits, we believe that the frequency of both routine and illness-related visits during the early years of life permits an approximate cross-sectional view of children in a community. Finally, despite the use of multicomcommunity data, the number of children in the individual communities who provided swab samples was insufficient to test the community-level conclusions derived from the model. Additional multicomcommunity studies would be needed to validate our predictions of the indirect association between CCC attendance and pneumococcal carriage, as well as the ability of this association to account for variations in the prevalence of carriage.

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Potential conflicts of interest. All authors: no conflicts.

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