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Authors

HSU, KK
RIFAS-SHIMAN, SL
SHEA, KM
[et al.](#)

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Do Community-Level Predictors of Pneumococcal Carriage Continue to Play a Role in the Conjugate Vaccine Era?

K. K. Hsu¹, S. L. Rifas-Shiman², K. M. Shea³, K. P. Kleinman², G. M. Lee^{2,4}, M. Lakoma², S. I. Pelton¹, J. A. Finkelstein^{2,5}, and S. S. Huang⁶

¹Section of Pediatric Infectious Diseases, Boston University Medical Center, Boston, MA

²Department of Population Medicine, Harvard Pilgrim Health Care Institute and Harvard Medical School, Boston, MA

³Department of Epidemiology, Boston University School of Public Health, Boston, MA

⁴Division of Infectious Diseases & Dept of Laboratory Medicine, Children's Hospital Boston

⁵Division of General Pediatrics, Children's Hospital Boston

⁶Division of Infectious Diseases and Health Policy Research Institute, University of California Irvine School of Medicine, Irvine, CA

Summary

This paper examines whether previously identified community-level factors (high proportion of crowded households and/or persons below the poverty level) remain associated with childhood pneumococcal carriage in the heptavalent pneumococcal conjugate vaccine (PCV7) era. Using logistic regression, individual factors were used to develop base models to which community-level factors were added to evaluate impact on pneumococcal carriage within two pediatric study cohorts from Massachusetts (urban Boston, outside Boston). Six years after introduction of universal childhood PCV7 vaccination, we found no consistent evidence that census tract characteristics (e.g. population size and density, age and race distribution, percent participating in group child care, parental education, percent lacking in-unit plumbing, poverty, and community stability) affected odds of pneumococcal carriage when added to individual predictors (e.g. younger age, current respiratory tract infections, and attendance in group child care). How community-level factors influence carriage continues to change in the era of increasing immunization coverage.

Keywords

Streptococcus pneumoniae; pneumococcal conjugate vaccine; colonization; community risk factors

Introduction

Despite dramatic declines in the incidence of invasive pneumococcal disease (IPD) following universal childhood vaccination with heptavalent pneumococcal conjugate vaccine (PCV7), *Streptococcus pneumoniae* (SP) remains the most common cause of invasive bacterial disease in children. Isolates from IPD are now predominantly non-PCV7

serotypes, though some IPD from PCV7 serotypes continues to exist.^{1,2} In contrast, non-PCV7 serotypes have essentially fully replaced PCV7 serotypes as the dominant carriage serotypes in the nasopharynx (NP).³ In fact, current carriage of non-PCV7 serotypes is at the same level as PCV7 serotype carriage prior to PCV7 vaccine. Since mucosal entry remains the initial step in the pathogenesis of IPD,⁴ understanding risk and protective factors for SP NP mucosal carriage remains critical, particularly as new changes occur in the era of universal 13-valent pneumococcal conjugate vaccination (PCV13).⁵

The complete replacement of pneumococcal serotypes in the NP has raised questions about whether factors previously shown to confer risk or protection for carriage have changed. We have previously reported that individual risk factors of young age, child care attendance, concurrent upper respiratory tract infection, and having young siblings remain associated with increased carriage despite the new dominance of non-PCV7 strains.³ Similarly, recent antibiotic use remains associated with decreased odds of carriage.^{3,6}

In this study we sought to assess whether community-level factors, also associated with carriage in prior studies, continued to predict carriage of non-PCV7 strains. We previously reported that in addition to individual risk factors, living in communities with crowded households and lower incomes independently predicted carriage of PCV7-serotypes, particularly among children who were not in group child care.^{7,8} Here, we examined whether these previously identified community-level factors remain predictive of pneumococcal NP carriage in the PCV7 era, after complete serotype replacement with non-PCV7 strains.³ We particularly examined potential differential effects of community-level factors according to participation in group child care.

Methods

We performed a secondary analysis of data from two studies examining NP colonization with SP (any SP, not limited to non-PCV7 serotypes) in young children <7 years during sick and well-child clinic visits. One study was conducted in 8 Massachusetts communities outside of Boston,³ and, a parallel study was conducted at a single site in urban Boston, both during the 2006-2007 winter respiratory virus season. Details of the 8 Massachusetts communities outside of Boston have previously been described. The 8 Massachusetts pediatric practices which participated from the 8 Massachusetts communities, were selected because they were among the largest of the previously participating pediatric practices in a cluster-randomized trial of a community-level intervention to promote judicious antibiotic-prescribing for children.^{9,10} These 8 communities were originally chosen on the basis of evidence that few children crossed community boundaries for pediatric care. Because these two study cohorts were drawn from very different populations served by very different pediatric practices, analysis of the cohorts was conducted separately. Data collection and microbiologic processing were conducted using identical protocols as previously described.¹¹ In brief, adult caregivers consented to a survey of possible individual- and household-level predictors of pneumococcal carriage and collection of a swab of their child's NP by trained study staff. This survey included individual and household-level questions about race/ethnicity, income and education level. Medical records were subsequently reviewed for pneumococcal vaccination history. NP samples were processed within 24 hours and all pneumococcal isolates underwent serotyping as previously described.^{10,11}

In addition to individual-level risk factors, community level risk factors were evaluated to understand the contribution of population level factors above and beyond individual characteristics. Previously evaluated community-level predictors⁷ were obtained from the U.S. Census for the census tract of residence of each individual child by geocoding street

addresses obtained from the medical record. U.S. census tracts are a defined geographic area, usually with 2,500 to 8,000 persons, designed to be homogeneous with respect to population characteristics, economic status, and living conditions.¹² Census tract variables included population size, density, age and race distribution, use of child-care facilities, education, percent lacking in-unit plumbing, poverty, and community stability. All census tract variables were dichotomized around the median value for the studied cohorts, for consistent analysis between the two cohorts. Each census tract variable was also analyzed as a continuous variable and using breakpoints initially established via recursive partitioning in the prior study.⁷ Because the objective was to examine the contribution of community-level risk factors above and beyond individual- or household-level risk factors, our base models to which community-level factors were added, included individual- and household-level factors such as race/ethnicity, parent educational level (< college graduation, or college graduation) and household income, regardless of whether those factors were significant after adjustment for other factors within the base model. Likewise, individual PCV7 vaccine exposure, defined as having received at least 1 dose of PCV7, was kept within base models because of its impact on select non-PCV7 serotypes, some of which cross-react with antibodies in PCV7.¹³ In each cohort, adjusted associations between census tract variables and outcomes were evaluated by adding one census tract variable at a time to each cohort's base model, then removing it and replacing with another census tract variable. Specific stratification by child care participation was performed in both cohorts, as had been performed previously.⁷ All models were generalized linear mixed models that accounted for clustering by census tracts.

Two models were developed – one for the site in urban Boston and another for the 8 communities outside of Boston. Analyses were performed using SAS, version 9.2 (SAS Institute, Cary, NC). All study procedures were approved by the Harvard Pilgrim Health Care and Boston University Medical Center Institutional Review Boards.

Results

Individual characteristics of the two study populations are shown in Table 1. Overall, >95% of the study population had received at least one dose of PCV7. Both cohorts of children reported equivalent proportions of child care participation and exposure to smokers within the home. Subjects in urban Boston were predominantly black, non-Hispanic (64%) and had a median household income of <\$35,000. Those from communities outside Boston were predominantly white, non-Hispanic (84%) with a higher median income (between \$50,000 and \$74,000). Fewer urban Boston children had an upper respiratory tract infection, current or recent antibiotic exposure, or siblings under the age of 6 years, compared with children outside Boston. Urban Boston families also reported lower levels of parental education.

Of 543 children from urban Boston, 92% received 1 dose of PCV7 vaccine. Twenty-two percent (121 children) carried pneumococci, of which 93% were non-PCV7 serotypes (11% 19A, 11% 6A, 10% 35B, 9% 15 B/C, 7% 11A, 6% 15A, 6% NT). In the base model, individual-level predictors for pneumococcal carriage included young age, respiratory tract infection, and group child care (Table 2). Race/ethnicity, recent antibiotic use, and receipt of at least 1 PCV7 dose were not found to be significant individual level predictors of pneumococcal carriage.

Of 794 children from the 8 communities outside of Boston, 99% received 1 dose of PCV7 vaccine. Thirty percent (241 children) carried pneumococci, of which 96% were non-PCV7 serotypes (16% 19A, 11% 15 B/C, 10% 6C, 9% 35B, 9% 35B, 9% 11A, 7% 23A, 6% 23B). Of note, overall pneumococcal carriage rates differed between urban Boston and outside Boston cohorts (22 vs. 30%, $p = 0.0011$). Consistent with results from the urban Boston

children, base model individual-level predictors for pneumococcal carriage included young age, respiratory tract infection, and group child care, but not race/ethnicity or PCV7 vaccine exposure (1 dose of PCV7), (Table 2). However, in contrast to children from urban Boston, recent antibiotic use was additionally found to be protective against carriage.

Census tract data from the two study populations are shown in Table 3. There were marked differences in census tract characteristics between the urban Boston and outside Boston study participants, particularly in terms of population density, proportions of non-white residents, levels of adult education, levels of in-unit plumbing, and measures of poverty. However, census tracts of subjects in urban Boston and outside Boston had similar overall levels of household size, proportions of households with children <6 years, and proportions of households with children <6 years reporting both parents working.

Census tract measures did not significantly modify odds of carriage in overall models of urban Boston or outside Boston cohorts when using median values as breakpoints (Table 4), nor when using prior breakpoints from the 2004 study,⁷ nor when analyzing census tract measures as continuous variables. However, a number of significant interactions were identified between group child care exposure and census tract measures particularly in the urban Boston cohort. Therefore we further analyzed community models stratified by group child care exposure, and found differences between the two cohorts. These differences were not attributable to individual differences in socio-economic status, as household income distribution did not differ between those in child care and those not in child care. In the urban Boston cohort, and only among those who attend group child care, increased odds for pneumococcal carriage was seen in children who lived in census tracts characterized by markers of lower socioeconomic status (e.g. more adults with less than a high school education, or four out of five census tract measures of increased poverty, or more members who relocated homes). In contrast, measures of increased poverty were significantly protective against pneumococcal carriage in children who did not attend group child care (Table 4). Living in census tracts with more adults with less than high school education appeared marginally protective against SP colonization in the outside Boston cohort, but no other census tract measures showed effect modification according to group child care exposure.

Discussion

Community-level factors were previously shown to have independent effects on childhood NP pneumococcal carriage during the pre-PCV7 era.⁷ Therefore we re-evaluated whether community-level factors continue to have an impact on pneumococcal carriage beyond individual factors in the era of widespread use of PCV7, after complete serotype replacement with non-PCV7 strains. Because of differential findings by child care participation in previous analyses,^{7,8} we looked for differential effects of community-level factors among child care participants versus non-participants.

In the cohorts studied here where 90% of the study population had received at least one dose of PCV7, risk for carriage of primarily non-PCV7 serotypes (younger age, concomitant upper respiratory tract illness, and group child care), appear to have remained relatively constant in our two demographically different cohorts of Massachusetts pediatric patients – those residing outside of urban Boston (who tended to live in families with higher levels of parental education and income), and those in urban Boston (who tended to be non-white, with lower levels of parental education and income). Consistency of these individual-level risk factors for pneumococcal carriage was demonstrated despite noticeable differences in the overall rates of carriage and the proportion of children in each cohort who had current respiratory infection or recent antibiotic use.

Similar to what was found prior to widespread introduction of pneumococcal conjugate vaccine,⁷ no community-level measures of population size, population density, age distribution, race, child care, education, hygiene, poverty, or stability were found to be significant predictors of pneumococcal colonization in overall models (not stratified by child care) controlling for significant individual-level risk factors for pneumococcal colonization, as well as individual- and household-level race, education, household income, and PCV7 vaccination (Table 4).

While overall models identified no impact from community variables, we then examined whether living in census tracts with larger average household size, or in socioeconomically disadvantaged communities, which had previously been associated with an excess risk (2- to 3-fold increased odds) of SP carriage in the pre-PCV7 era in child care attendees, still continued to confer excess risk.⁷ In this PCV7 era follow-up study, we were no longer able to demonstrate consistent linkages with childhood pneumococcal carriage among children attending or not attending group child care in the outside Boston cohort. It is possible that widespread use of PCV7 has reduced the impact of community-level sociodemographic characteristics and essentially “leveled the playing field,” so to speak; alternatively, non-PCV7 serotypes now occupying the NP niche may not be as affected by community variables compared to previous serotypes.

In the urban Boston cohort the results were more puzzling. It appeared that living in socioeconomically disadvantaged census tracts was protective against non-PCV7 serotype pneumococcal carriage in those unexposed to group child care, but in those exposed to group child care, the opposite effect was seen (increased risk of carriage). Since there is no known mechanism that would explain this finding, we consider it only hypothesis generating for further analyses in other cohorts. An alternative explanation is that the finding from this model, regarding community-level factors, represents a spurious association (Type 1 error) with pneumococcal carriage. It is also important to point out that both the individual and community-level variables assessed here represent markers or proxies for biological risk factors; we do not assert a particular mechanism by which they affect carriage directly.

In conclusion, in a highly vaccinated population 6 years after universal childhood vaccination with PCV7 was begun, living in census tracts with larger households, or that are socioeconomically disadvantaged, no longer consistently confers increased odds of childhood non-PCV7 serotype pneumococcal carriage above individual or household predictors of pneumococcal carriage, even in children not participating in group child care. The finding that some community-level variables impact carriage rates differentially (with associations seen only in some child care exposure groups, and only in some communities) bears further study.

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Table 1

Characteristics of Massachusetts children who provided nasopharyngeal specimens, 2006-07*

	Urban Boston (n=543)		Outside Boston (n=794)	
	n	%	n	%
Age (months)				
0-6	65	12.0	57	7.2
6-24	223	41.1	348	43.8
24-36	86	15.8	105	13.2
36	169	31.1	284	35.8
Sex				
Male	268	49.4	430	54.2
Female	275	50.6	364	45.8
Race/ethnicity				
Black non-hispanic	347	63.9	43	5.4
Hispanic	111	20.4	54	6.8
Other non-hispanic	38	7.0	34	4.3
White non-hispanic	47	8.7	663	83.5
Current respiratory tract infection[†] (survey only)	252	46.4	527	66.4
Current antibiotic use[‡] (chart only)	8	1.5	47	5.9
<i>Antibiotic use within 2 months (survey only)</i>	79	14.6	298	37.5
Pneumococcal vaccination (PCV7) doses[§] (chart only)				
0	42	7.7	11	1.4
1	53	9.8	53	6.7
>1	448	82.5	729	91.9
Child-care participant	274	50.5	409	51.5
Number of siblings aged <6 years				
0	353	65.0	420	52.9
1	158	29.1	297	37.4
>1	32	5.9	77	9.7
Smoking in home[¶]	108	20.1	145	19.6
Breastfed for >2 months	307	56.5	410	52.0
Education				
Less than high school grad	78	14.4	26	3.3
High school grad	219	40.3	111	14.0
Some college	140	25.8	195	24.6
College grad or more	106	19.5	462	58.2
Household income				
<35K	408	75.1	125	15.7
35-49K	85	15.7	100	12.6

	Urban Boston (n=543)		Outside Boston (n=794)	
	n	%	n	%
50-74K	30	5.5	150	18.9
75-99K	11	2.0	137	17.3
>100K	9	1.7	282	35.5
Nasopharyngeal carriage of SP	121	22.3	241	30.4

* Numbers vary because of missing data (participants excluded from analysis cohort if missing values for variables in multivariate model).

† Includes runny nose, sore throat, cough, bronchitis, ear pain/infection, sinus pain

‡ Reflects the antibiotic status on the day of the swab, prior to being seen by the physician

§ Doses of PCV7 completed 30 days prior to the swab date

¶ Defined as an affirmative response to the question, “Does anyone in the child’s home smoke cigarettes?”

Table 2

Base models analyzing individual- and household-level factors associated with SP carriage, prior to addition of community-level variables.

	Urban Boston (n=543)*				Outside Boston (n=794)*			
	aOR**	LCL	UCL	p-value	aOR**	LCL	UCL	p-value
Age in months (v. 36 months)								
0<6	2.72	1.17	6.35	0.02	2.81	1.34	5.89	0.01
6<24	1.85	1.01	3.39	0.05	2.73	1.76	4.24	<.0001
24<36	1.24	0.60	2.58	0.56	2.19	1.25	3.82	0.01
Race/ethnicity (v. white)								
Black non-Hispanic	0.85	0.39	1.86	0.69	0.53	0.22	1.23	0.14
Hispanic	0.79	0.33	1.90	0.59	1.35	0.69	2.63	0.38
Other non-Hispanic	1.67	0.58	4.87	0.34	0.53	0.20	1.39	0.20
Current respiratory tract infection[†] (survey only)	3.14	1.98	4.99	<.0001	2.17	1.47	3.20	<.0001
Antibiotic use within 2 months (survey only)	0.92	0.50	1.70	0.78	0.52	0.36	0.74	0.00
Child-care participant	2.86	1.66	4.92	0.00	2.45	1.63	3.67	<.0001
Number of siblings aged <6 years (v. >1)								
0	0.61	0.25	1.47	0.26	0.58	0.33	1.01	0.06
1	0.69	0.27	1.75	0.43	0.72	0.41	1.27	0.26
College grad v. <CG	1.39	0.77	2.50	0.27	1.10	0.76	1.58	0.62
Household income (v. >=35K)								
<35K	1.38	0.79	2.42	0.26	1.06	0.62	1.79	0.84
No PCV7 doses (v. >=1) (chart only)	1.15	0.50	2.65	0.74	0.95	0.22	4.09	0.95

* GLIMMIX used to adjust for clustering by census tract number. Multivariable adjusted odds ratios (aOR) presented with lower and upper 95% confidence limits (LCL and UCL).

** Odds ratios adjusted for age, race/ethnicity, current respiratory tract infection, recent antibiotic use, child care participation (in the overall model), education, household income, and PCV7 vaccine dose.

[†] Includes runny nose, sore throat, cough, bronchitis, ear pain/infection, sinus pain.

Table 3

Census tract data for study participants.

Census tract variables	Median*	Urban Boston (n=543)		Outside Boston (n=794)	
		> median		> median	
Measures of population size		N	%	N	%
Persons in 1,000s	4.92	235	43	433	55
Children aged <6 years in 100s	3.91	230	42	444	56
Average household size	2.58	289	53	384	48
Measures of population density					
Persons/square mile (2.59 km ²)	3568.75	500	92	169	21
Children aged <6 years/square mile	260.95	503	93	165	21
% living in crowded housing	2.10%	481	89	186	23
Measures of age distribution					
% of persons aged <6 years	8.30%	279	51	391	49
% of households with children aged <18 years	37.10%	276	51	391	49
Measures of race					
% White	88.75%	40	7	628	79
% Black	2.75%	492	91	176	22
% Hispanic	3.09%	481	89	182	23
Measure of child care					
% of children aged <6 years with both parents working	63.07%	260	48	404	51
Measure of education					
% of adults with less than high school education	15.88%	414	76	253	32
Measure of hygiene					
% lacking plumbing in unit	0.52%	389	72	279	35
Measures of poverty					
% of children aged <6 years in poverty	9.40%	417	77	253	32
% of persons in poverty	8.28%	446	82	222	28
Median household income (\$)	46307.00	128	24	543	68
% unemployed aged >16 years, seeking job	4.43%	409	75	259	33
% owner-occupied housing	61.59%	82	15	587	74
Measures of community stability					
% of community flux [‡]	60.39%	157	29	511	64
% of county flux [§]	11.79%	244	45	425	54

* Proportion above and below medians established by combining urban and outside Boston cohorts

[‡] Census tract members, expressed as percentage, who relocated their homes between 1996 and 2000.[§] Census tract members, expressed as percentage, who relocated from outside the county between 1996 and 2000

	Overall										No Child Care						Child Care							
	Urban Boston (n=543)					Outside Boston (n=794)					Urban Boston (n=269)			Outside Boston (n=385)			Urban Boston (n=274)			Outside Boston (n=409)				
	aOR	LCL	UCL	p-val	aOR	LCL	UCL	p-val	aOR	LCL	UCL	p-val	aOR	LCL	UCL	p-val	aOR	LCL	UCL	p-val	aOR	LCL	UCL	p-val
Census tract variables																								
% unemployed aged >16 years, seeking job	1.2	0.7	2.0	0.56	0.9	0.6	1.4	0.78	0.3	0.1	1.0	0.05	1.2	0.7	2.3	0.48	2.4	1.0	5.6	0.04	0.8	0.5	1.3	0.36
Lower % owner-occupied housing	1.1	2.2	0.6	0.70	1.0	1.5	0.7	0.99	0.5	1.1	0.2	0.09	1.3	2.5	0.7	0.42	3.7	12.7	1.1	0.04	0.9	1.6	0.5	0.75
Measures of community stability																								
% of community flux‡	1.0	0.6	1.6	0.96	1.0	0.7	1.5	0.82	3.3	1.2	9.2	0.03	0.8	0.4	1.4	0.41	0.5	0.2	1.0	0.06	1.2	0.7	2.0	0.44
% of county flux§	1.1	0.7	1.7	0.66	1.2	0.8	1.6	0.33	1.0	0.4	2.7	0.98	1.4	0.8	2.4	0.23	1.3	0.7	2.4	0.35	1.1	0.7	1.8	0.58

* Base model shown in Table 2: odds ratios adjusted for age, race/ethnicity, current respiratory tract infection, recent antibiotic use, child care participation (in the overall model), education, household income, and PCV7 vaccine dose.