Longitudinal Colonization With *Streptococcus pneumoniae* During the First Year of Life in a Healthy Newborn Cohort

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Background. The objective of this study was to characterize longitudinal colonization with *Streptococcus pneumoniae* during the first year of life within a community newborn infant cohort, and assess the relationship between antibiotic exposure and colonization with antibiotic-resistant organisms.

Methods. During April 2013–February 2014, 326 infants were enrolled from an urban academic hospital well-baby nursery. At ages 4, 8, and 12 months, we collected antibiotic data, other exposure data, and nasopharyngeal cultures for pneumococcal isolation.

Results. Follow-up visits were completed for 211, 158, and 144 infants at ages 4, 8, and 12 months, respectively. By 12 months, 33% of infants attending the visits had ever been exposed to antibiotics, 67% if exposures to maternal antibiotics at birth are included. Pneumococci were isolated at 38/839 (4.5%) visits from 38 infants, including one 13-valent conjugate vaccine (PCV13) serotype (6A). There were 1 (0.3%), 15 (7%), 7 (4%), and 15 (10%) infants who were colonized at 0-, 4-, 8-, and 12-month visits, respectively. By age 12 months, at least 35 (11%) infants had ever been colonized. Sixteen isolates (42%) exhibited nonsusceptibility to at least 1 antibiotic. Infants with recent antibiotic exposure were not more likely to be colonized or to harbor nonsusceptible organisms.

Conclusions. Within a hospital birth cohort followed in the community, pneumococcal colonization and related antibiotic resistance were lower than previously reported, likely associated with PCV13 use. Antibiotic exposure was not associated with subsequent colonization with resistant isolates. The influence of other environmental factors needs further study.

Key words. antibacterial agents; child; cohort studies; drug resistance; *Streptococcus pneumoniae*.

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Infants and young children are at higher risk of invasive infection with *Streptococcus pneumoniae* than the general population and can be reservoirs of antibiotic resistance [1]. US infants receive, on average, >1 course of antibiotics annually [2, 3]. Antibiotic resistance is driven by selective forces related to the spectrum and duration of antibiotic use, especially in ambulatory settings [4], and by close contacts within families and childcare settings that facilitate transmission of resistant organisms [5, 6]. This is important because carriage typically precedes invasive infection [1].

Since the introduction of the 7-valent pneumococcal conjugate vaccine (PCV7) in 2000 and the 13-valent vaccine (PCV13) in 2010, hospital surveillance data reveal that US invasive pneumococcal disease has fallen 90% [7]. Despite this success, there were 30 000 US cases of invasive pneumococcal disease in 2015; 30% of isolates were resistant to at least 1 antibiotic class [8].

Most pneumococcal colonization and invasive disease originates in community settings [1]; few recent data exist regarding community colonization and associated antibiotic susceptibility patterns. Almost sterile before birth, infants become progressively colonized with bacteria and other organisms from their environments; this provides an opportunity to study colonization and associated resistance from a virtual *tabula rasa*. In a pilot study, we enrolled 35 newborns from the well-baby nursery in an urban university-affiliated hospital during June 2011–November 2011, with follow-up visits at 6, 9, and 12 months [9]. Eight (23%) infants were colonized with pneumococci during their first year, at 15 (13%) visits; 11 isolates (73%) were resistant to at least 1 antibiotic class. One isolate was serotype 23F and two isolates were serotype 19A. By 12 months, 14 (40%) infants had ever been exposed to

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antibiotics; 22 (63%) were either exposed directly or had perinatal exposure from maternal antibiotics at delivery.

Our objectives in this study were to characterize longitudinal colonization with *S pneumoniae* within a larger cohort of newborns and to assess the relationship between colonization with antibiotic-resistant pneumococci and infant antibiotic exposure. Secondary objectives were to assess whether household antibiotics and/or infant or household childcare were associated with patterns of pneumococcal colonization and resistance.

METHODS

In this observational cohort study, we enrolled healthy newborns and longitudinally assessed pneumococcal colonization and environmental exposures during their first year of life.

Study Sampling

Based upon a priori sample size estimation, research nurses enrolled a convenience sample of newborn infants at an urban, university-affiliated hospital in Cleveland, Ohio, from April 2013 through February 2014.

Eligibility criteria included that infants be admitted to the well-baby nursery and had mothers aged ≥ 18 years who understood English and had legal custody. Infants were excluded if they were transferred to neonatal intensive care.

Data Collection

Mothers were interviewed for infant demographic data; gestational age; delivery mode; maternal antibiotic exposure during labor, delivery, and post-delivery; and whether infants received antibiotics after delivery. Additional information collected included whether mothers intended to breastfeed, household member ages and current antibiotic use, household childcare attendance, and household member smoking status [10]. All data regarding antibiotic exposure came from maternal self-report, not health record review. A nasopharyngeal culture for *S pneumoniae* was obtained (Fisher Scientific eSwab) and immediately delivered to the research laboratory in cooled containers, then refrigerated until processing.

At follow-up study visits, scheduled at approximately 4, 8, and 12 months, mothers were asked about interim history since the previous visit, or within the previous 4 months if visits were delayed or missed, including infant nutrition and immunizations, household member ages, infant and household antibiotic use, childcare and hospitalizations, and household smoking. Each follow-up visit included nasopharyngeal cultures. Visits and culture procedures were not altered for concurrent respiratory illness and/or antibiotic treatment.

Data were managed using the Research Electronic Data Capture (REDCap) platform. The University Hospitals of

Cleveland Institutional Review Board approved the study, and parental written informed consent was obtained.

Cultures

Nasopharyngeal swabs were processed for pneumococcal culture, serotyping, and antibiotic susceptibility according to the Clinical and Laboratory Standards Institute Standards for Antimicrobial Susceptibility Testing [9, 11]. Susceptibility results were interpreted according to the 2012 Clinical and Laboratory Standards Institute break points as susceptible, intermediate, or resistant to the following drug classes: penicillins (penicillin, amoxicillin), cephalosporins (ceftriaxone), macrolides (azithromycin), lincosamides (clindamycin), and fluoroquinolones (levofloxacin) [11]. Serotypes were classified as to whether they were PCV7 serotypes (4, 6B, 9V, 14, 18C, 19F, 23F), additional PCV13 serotypes (1, 3, 5, 6A, 7F, 19A), or nonvaccine serotypes.

Antibiotic Exposure

For newborn visits, infants were considered antibiotic-exposed if they received antibiotics after delivery before discharge home from the nursery. For follow-up visits, infants were considered antibiotic-exposed if they received antibiotics since the previous visit, or within the previous 4 months if the visit was delayed or if the previous visit was missed. Household exposures were similarly defined. For sensitivity analysis, we considered whether infants were exposed to antibiotics administered to mothers during delivery, household members had received antibiotics during the previous 4 months, infants had ever received antibiotics, and the number of antibiotic courses received by the infant.

Outcomes

The primary outcome was any antimicrobial drug resistance (AMR), defined as the pneumococcal isolate was intermediate or resistant to at least 1 drug class [12, 13]. Secondary outcomes included pneumococcal colonization and 3 secondary resistance outcomes to reflect definitions used in previous studies: penicillin-resistant (penicillin resistance [PCR], intermediate or resistant to penicillin, amoxicillin, or ceftriaxone) [13], multidrug resistant 1 (MDR1, intermediate or resistant to beta-lactams plus at least 1 other antibiotic class) [14], and multidrug resistant 2 (MDR2, intermediate or resistant to ≥ 3 drug classes) [12–14].

Covariates

Covariates included infant mode and season of birth, gestational age, race, ethnicity, sex, visit, age at visit and within the previous 4 months, infant childcare, any breastfeeding, exclusive breastfeeding, infant overnight hospitalization, immunizations, and household member ages, antibiotic use, childcare, hospitalization, and tobacco smoking.

Analytical Approach

Descriptive statistics were generated for infant characteristics; infant and household antibiotics and other exposures; and pneumococcal isolates, serotypes, and antimicrobial susceptibilities. Analyses were performed using Stata, with a type 1 error of 0.05 and controlled for data clustering by infant. χ^2 and t tests were used to compare characteristics of infants attending visits vs those with missing visits. Mixed-effects logistic regression was used for multivariable analysis. Multivariable models for each outcome all included infant antibiotic use and infant childcare during the previous 4 months. Additional covariates were included in the final model if they had bivariable association with the outcome of interest and of removing them changed the primary association of interest by >10%. Akaike and Bayesian information criteria were used to help assess model fit.

Sample Size

We estimated antibiotic exposure of at least 33% during the first year [2]. Recent estimates of nasopharyngeal pneumococcal colonization among young children ranged from 25% to 37%, with 20%–65% of strains nonsusceptible to antibiotics [14–16]. In published observational studies, odds ratios (ORs) for resistant vs nonresistant colonization or infection with respiratory bacteria for antibiotic-exposed vs antibiotic-unexposed children ranged from 2.4 to 7.5 [17, 18]. Power calculations were performed using PASS2008 (NCSS Kaysville, UT), assuming a type 1 error of 0.05. With 326 infants, 4 time points, and approximately 10% lost to follow-up, with 33% infants antibiotic-exposed, we would have 86% power to detect an OR for resistance of 2.0 for exposed vs unexposed infants.

RESULTS

Of 326 enrolled infants, most were black (85%) and non-Hispanic (97%), reflecting the population served by the hospital. Eighty-four (26%) infants were born by cesarean section compared with 29% for this hospital and 26% for the state [19]. During delivery, 155 mothers (47%) received antibiotics: 89% of mothers undergoing cesarean section and 33% of mothers with vaginal deliveries. Two infants (0.6%) received antibiotics after delivery. If exposures to maternal antibiotics during delivery are considered, 48% of infants were exposed to antibiotics either during or shortly after birth.

Of the 326 enrolled infants, 211, 158, and 144 were evaluated at 4-month, 8-month, and 12-month visits, respectively. Table 1 summarizes infant and household exposure questionnaire results at each visit. Infants lost to follow-up at each visit did not differ from those attending each visit according to gestational age, sex, birth season, race, or ethnicity. At 4-, 8-, and 12-months, 10%, 16%, and 21% of infants had recently been antibiotic-exposed. By the 12-month visit, 33% of infants attending the visit had ever been exposed to antibiotics; 67% if exposed to maternal antibiotics at birth is included. All infants were up-to-date with pneumococcal immunization at each visit.

Table 2 shows infant colonization with *S pneumoniae* and associated antibacterial resistance at each visit, stratified by recent antibiotic exposure. One infant in the nursery, 15 (7.2%) attending the 4-month visit, 7 (4.5%) the 8-month visit, and 15 (10.4%) the 12-month visit were colonized with pneumococci. By 1 year, at least 1 in 5 infants had ever been colonized. One PCV13 vaccine strain was isolated, serotype 6A, at 12 months, resistant to azithromycin. Similar to the pilot, colonization was dynamic; while 3 infants were colonized at more than 1 visit, no infant was colonized with the same serotype at a subsequent visit.

No colonized infant had experienced recent antibiotic exposure until the 12-month visit, when 3 of 12 colonized infants had received antibiotics.

In unadjusted analysis (Supplementary Table A.1), there was no relationship between pneumococcal colonization and recent infant antibiotic exposure, the infant's ever receiving antibiotics, or the number of antibiotic courses ever received. If maternal antibiotics during delivery are included, antibiotic exposure within the previous 4 months was associated with decreased odds of pneumococcal colonization; this result depended on only 1 nonexposed infant colonized during the nursery visit.

Antimicrobial Drug Resistance

Of the 38 pneumococcal isolates, 16 expressed any AMR, 1 (100%), 7 (47%), 3 (43%), and 5 (33%) at the nursery, 4-month, 8-month, and 12-month visits, respectively. None of the infants with isolates expressing AMR had been exposed to antibiotics within the previous 4 months, even when considering maternal antibiotic exposure during delivery.

Seven isolates expressed PCR, 1 in the nursery, 3 at 4 months, 1 at 8 months, and 2 at 12 months. Five isolates expressed MDR1, 3 at the 4-month visit and 2 at the 12-month visit. No isolate expressed MDR2.

Multivariable Analyses

In multivariable analysis (Table 3), *S pneumoniae* colonization was not significantly associated with recent antibiotic exposure. Age (OR, 1.12 per month; 95% confidence interval [CI], 1.05–1.20; $P = .001$), Hispanic ethnicity (OR, 4.62; 95% CI, 1.50–14.22; $P = .008$), and recent infant childcare (OR, 3.16; 95% CI, 1.40–7.12; $P = .006$) were associated with increased odds of colonization. The odds of AMR were lower with non-white race (OR, 0.17; 95% CI, 0.06–0.46; $P < .001$) and borderline significantly higher for recent infant childcare (OR, 3.07; 95% CI, 0.95–9.94; $P = .061$). Odds of PCR were increased with recent infant childcare (OR, 5.24; 95% CI, 1.03–26.61; $P = .046$) and borderline lower for non-white race (OR, 0.20; 95% CI, 0.04–1.08; $P = .061$). Odds of MDR1 were associated with recent infant childcare (OR, 11.83; 95% CI, 2.08–67.24; $P = .005$) and non-white race (OR, 0.10; 95% CI, 0.02–0.55; $P = .008$).

Table 1. Infant Exposures to Antibiotics Over the First Year of Life

Characteristic	Nursery N = 326	Visit 2 N = 211	Visit 3 N = 158	Visit 4 N = 144
Age, mean (SD, range), y	NA	4.2 (0.9, 2.2–7.1)	8.2 (1.3, 6.1–12.4)	13.4 (1.8, 10.4–19)
Infant, N (%) ^a				
Antibiotics				
Yes	2 (0.6)	20 (9.5)	25 (15.8)	30 (20.8)
Yes, including maternal antibiotics during delivery	156 (47.8)	...	...	...
No	324	189	132	114
Missing	0	2	1	0
Ever antibiotics (visit cohort)				
Yes	2 (0.6)	22 (10.4)	36 (22.8)	48 (33.3)
No	324	189	122	96
Yes, including maternal antibiotics at delivery	156 (47.8)	116 (55.0)	94 (5)	96 (66.7)
Childcare				
Yes	NA	45 (21.3)	45 (28.5)	49 (34.0)
No	...	164	112	95
Missing	...	2	1	0
Hospitalization				
Yes	326 (100)	22 (10.4)	10 (6.3)	11 (7.6)
No	0	187	147	132
Missing	0	2	1	1
Breastfeeding, any				
Yes	224 (68.7)	49 (23.2)	20 (12.7)	11 (7.6)
No	100	160	137	133
Missing	2	2	1	0
Breastfeeding, exclusive				
Yes	111 (34.0)	24 (11.4)	11 (7.0)	10 (7.0)
No	215	185	146	134
Missing	0	2	1	0
Household ^a (other than infant)				
Antibiotics				
Yes	193 (59.2)	33 (15.6)	17 (10.8)	9 (6.2)
No	133	174	140	133
Unknown	0	4	1	1
Childcare				
Yes	65 (19.9)	38 (18.0)	26 (16.5)	27 (18.7)
No	261	170	129	117
Unknown	0	3	3	0
Hospitalization				
Yes	326 (100)	7 (3.3)	5 (3.2)	13 (9.0)
No	0	202	152	131
Unknown	0	2	1	0
Smoking				
Yes	158 (48.5)	92 (43.6)	64 (40.5)	63 (43.7)
No	166	116	93	81
Unknown	1	3	1	0
Any household member age <2 y				
Yes	42 (12.9)	22 (10.4)	12 (7.6)	13 (9.0)
No	284	186	145	128
Unknown	0	3	1	3
Any household member age <5 y				
Yes	154 (47.2)	84 (39.8)	56 (35.4)	56 (38.9)
No	172	124	101	85
Unknown	0	3	1	3
Infant or household antibiotics				
Yes	193 (59.2)	48 (22.7)	35 (22.1)	37 (25.7)
No	133	161	122	107
Unknown	0	2	1	0

Abbreviation: NA, not applicable.

^aSince previous visit or within previous 4 months if visit was missed or delayed.

Table 2. *Streptococcus pneumoniae* Colonization and Associated Antibacterial Resistance During the First Year of Life, Stratified by Antibiotic Exposure During the Previous 4 Months

Pneumococcal Isolates	Nursery		4 Months		8 Months		12 Months	
Infant Antibiotic ^a	Antibiotic	No Antibiotic	Antibiotic	No Antibiotic	Antibiotic	No Antibiotic	Antibiotic	No Antibiotic
N ^b	2	324	20	189	25	132	30	114
Pneumococcus	0	1	0	15	0	7	3	12
Serotypes (N = 1 unless specified)	NA	38	...	11A, 15A, 15C (3) 16F, 22F, 23A, 23B, 35B (3), 9N (2), NT	NA	11A, 15B (2), 22F, 23B(2), 33	7C, 9N, 11A	6A ^{PCV13} , 15A, 15C, 23A, 23B(4), 35B(2), 7C, NT
AMR ^c	0	1	0	7	0	3	0	5
PCR ^c	0	1	0	3	0	1	0	2
MDR1 ^c	0	0	0	3	0	0	0	2
MDR2 ^c	0	0	0	0	0	0	0	0
Infant or household antibiotic ^{a,d}	Antibiotic	No Antibiotic	Antibiotic	No Antibiotic	Antibiotic	No Antibiotic	Antibiotic	No Antibiotic
N	193	133	48	161	35	122	37	107
Pneumococcus	0	1	1	14	1	6	4	11
AMR ^c	0	1	0	7	0	3	1	4
PCR ^c	0	1	0	3	0	1	0	2
MDR1 ^c	0	0	0	3	0	0	0	2
MDR2 ^c	0	0	0	0	0	0	0	0

Abbreviations: AMR, any antimicrobial drug resistance; MDR1, resistance to beta-lactam plus at least 1 additional drug class; MDR2, resistance to at least 3 drug classes; NA, not applicable; PCR, penicillin resistance; PCV13, pneumococcal conjugate vaccine 13-valent strain (1,3,4,5,6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F).

^aSince previous visit or within previous 4 months if visit was missed or delayed.

^bNot including infants or household with missing antibiotic exposure data.

^cIntermediate or resistant.

^dIncluding maternal antibiotics received during delivery.

The presence of additional young children in the home was not associated with colonization or resistance (data not shown).

DISCUSSION

Almost half of mothers received antibiotics during delivery; this is higher than in our pilot study (34%) and in a recent New Hampshire cohort (33%) but lower than a recent New York City cohort (59%) [9, 20, 21]. At least one-third of infants

had been exposed to antibiotic treatment by age 1 year, around half the rate in our pilot study and one-third to two-thirds of previously reported rates for similarly aged children [9, 22, 23]. Supplementary Table A.2 shows previous study results regarding pneumococcal colonization and associated antibiotic resistance in young children in community settings; these studies used culture techniques that were comparable to ours. In a 2001 Massachusetts sample [24], 10% of children were colonized with *S pneumoniae*; one-third of isolates were resistant

Table 3. Multivariable Analysis Results

Outcome	Characteristic	Odds Ratio	95% Confidence Interval	P Value
<i>Streptococcus pneumoniae</i> colonization	Infant			
	Antibiotics	0.39	0.11–1.40	.148
	Childcare	3.16	1.40–7.12	.006
	Age (months)	1.12	1.05–1.20	.001
	Hispanic ethnicity	4.62	1.50–14.22	.008
<i>S pneumoniae</i> colonization with any AMR	Infant			
	Antibiotics	No infant with AMR was antibiotic-exposed within previous 4 months		
	Childcare	3.07	0.95–9.94	.061
	Age (months)	1.09	0.91–1.30	.336
	Race (non-white)	0.17	0.06–0.46	<.001
<i>S pneumoniae</i> colonization with PCR	Infant			
	Antibiotics	No infant with PCR was antibiotic-exposed within previous 4 months		
	Childcare	5.24	1.03–26.61	.046
	Non-white race	0.20	0.04–1.08	.061
<i>S pneumoniae</i> colonization with intermediate or MDR1	Infant			
	Antibiotics	No infant with MDR1 was antibiotic-exposed within previous 4 months		
	Childcare	11.83	2.08–67.24	.005
	Race (non-white)	0.10	0.02–0.55	.008

Abbreviations: AMR, any antimicrobial drug resistance; MDR1, resistance to beta-lactam plus at least 1 additional drug class; PCR, penicillin resistance.

to at least 1 antibiotic class. In 2010–2013, 34% of an Atlanta cohort were colonized, with 19% resistant [15]. In 2013–2014, children in St. Louis, Missouri, had a similar colonization rate, but 65% resistance [16]. Only the Massachusetts group found a relationship between antibiotic exposure and antibiotic-resistant colonization. These previous cross-sectional studies did not consider antibiotic use prior to the study periods [15, 16, 25].

One-quarter of infants were born via cesarean section, similar to US trends [26]. Most received antibiotics during delivery; however, half of mothers who received antibiotics delivered vaginally. If transplacental exposure to maternal antibiotics during delivery is considered, early antibiotic exposure was 67% and highly correlated with caesarean section.

Pneumococcal colonization was 7%–10%, lower than the 10%–40% found previously, including in our pilot study, likely a consequence of PCV13. Serotypes were similar to those found by Lee et al in 2014 [27]. Future studies should monitor serotype replacement, particularly for serotypes 15A/B/C and 35B, which are associated with antibiotic-resistant infections in other countries [28].

While the prevalence of AMR was similar to that in previous studies (33%–50%) [9, 12, 14–16, 24], only 1 PCV-13 serotype was isolated (3% isolates) compared with 20% in our pilot study 2 years previously. This is consistent with the rapid decline in infections with antibiotic-resistant pneumococci after PCV13 introduction [12].

Recent antibiotic exposure was not associated with colonization or resistance in multivariable analysis. No infant with AMR had received antibiotic treatment within the previous 4 months.

Infant childcare was consistently associated with increased odds of colonization and associated resistance, with ORs between 3 and 11. This is similar to some, but not all, previous studies showing increased pneumococcal colonization and associated resistance among children attending childcare [15, 24, 27].

Hispanic ethnicity was associated with >4 time increased odds of pneumococcal colonization; only 2.8% of the study population was of Hispanic ethnicity. Though of borderline statistical significance for PCR, the point estimates for non-white race suggested persistently lower odds of 80%–90% across all resistance outcomes. The underlying mechanisms of these differences are unknown; they may result, at least in part, from unmeasured confounding or moderating characteristics.

Limitations of this study include that it describes infants enrolled in 1 geographic locale; results cannot necessarily be generalized to other populations. It is reassuring that our cesarean section and intrapartum antibiotic rates were similar to those in other US cohorts [9, 19–21]. Our immunization level, while higher than the 2014 rate for the United States (84%) and for Ohio (89%), is consistent with the 99.5% rate for 2014 central Ohio cities [29, 30]. Our results may be different than those from infants with respiratory infections.

We do not have data on infants whose mothers declined enrollment. Our power was lower than anticipated due to high loss to follow-up and unexpectedly low prevalence of pneumococcal colonization and associated antibiotic resistance. The proportion lost to follow-up is similar to that in other longitudinal studies [31]. It is reassuring that the infants lost to follow-up had characteristics similar to those with complete study results. Antibiotic exposure was ascertained by maternal report; parent report has been shown to have excellent sensitivity and specificity for identifying child medication exposures [32, 33].

In conclusion, within our cohort, infant colonization with *S pneumoniae*, pneumococcal antibiotic nonsusceptibility, and colonization with PCV13 strains were lower than reported previously and lower than found in our pilot study, evidence for PCV13 effectiveness. Recent antibiotic exposure was not associated with an increased risk of colonization with an organism expressing antibiotic resistance. Infant childcare continues to be a risk factor for colonization with antibiotic-resistant organisms [6].

Supplementary Data

Supplementary materials are available at *Journal of the Pediatric Infectious Diseases Society* online.

Notes

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Potential conflicts of interest. All authors: No reported conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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