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Re-emergence of pneumococcal colonization by vaccine serotype 19F in persons aged ≥5 years after 13-valent pneumococcal conjugate vaccine introduction—Alaska, 2008–2013

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ABSTRACT

Background: The pneumococcal conjugate vaccine (PCV) was introduced in 2001. Widespread PCV use nearly eradicated pneumococcal colonization by vaccine serotypes. Since 2008, however, colonization by PCV-serotype 19F has increased in Alaska residents. We describe the epidemiology of re-emerging serotype 19F colonization.

Methods: We conducted annual cross-sectional colonization surveys from 2008 to 2013. We recruited children aged <5 years at 2 urban clinics and participants of all ages from Region-A (2 villages), Region-B (4 villages), and Region-C (2 villages). We interviewed participants and reviewed their medical records to obtain demographic information and determine PCV status. We obtained nasopharyngeal swab specimens from participants to identify pneumococci and to determine the pneumococcal serotype, antimicrobial resistance, and multilocus sequence type. We used the Cochran-Armitage test to assess for significant trends in colonization across time periods.

Results: Among participants aged <5 years, pneumococcal serotype 19F colonization remained unchanged from 2008–2009 (0.7%) to 2012–2013 (0.5%; *P*-value [*P*] = .54). Serotype 19F colonization increased from 2008–2009 to 2012–2013 among participants aged 5–11 years (0.3% to 3.2%; $P < .01$), participants 12–17 years (0.0% to 2.0%; $P < .01$), and participants aged ≥18 years (0.1% to 0.5%; $P < .01$). During 2012–2013, 85 (93%) of 91 pneumococcal serotype 19F isolates were identified among participants from Region B; the majority of serotype 19F isolates belonged to an antimicrobial nonsusceptibility pattern corresponding to a novel multilocus sequence type 9074.

Conclusions: PCV continues to protect against serotype 19F colonization in vaccinated children aged <5 years. The direct PCV impact on serotype 19F colonization in persons aged 5–11 years and indirect impact in persons aged ≥12 years is waning, possibly because of a newly introduced genotype in Region-B.

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1. Introduction

Nasopharyngeal (NP) pneumococcal colonization is a prerequisite for causing local infections (e.g., otitis media), pneumonia, and invasive diseases (e.g., sepsis) [1]. In addition, pneumococcal transmission can occur from colonized persons to other susceptible persons in the community. Therefore, the 7- and 13-valent pneumococcal conjugate vaccine (PCV7 and PCV13, respectively) can directly protect vaccinated persons against pneumococcal colonization and disease, and indirectly protect others in the community through reduced pneumococcal transmission [2]. Pneumococcal colonization surveys can complement invasive pneumococcal disease (IPD) surveillance data to document the population-level benefits of PCV7 and PCV13 [3].

Following the U.S. Advisory Committee on Immunization Practices (ACIP) recommendations, Alaska introduced PCV7 (protects against pneumococcal serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F) into the routine childhood vaccination schedule in January 2001 and PCV13 (protects against PCV7 serotypes plus serotypes 1, 3, 5, 6A, 7F, and 19A) in April 2010 [4,5]. We previously reported the results of cross-sectional pneumococcal colonization surveys

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we conducted in Alaska from 2008–2012 to describe the impact of PCV13 introduction on the distribution and frequency of colonizing pneumococcal serotypes [6]. We identified that PCV7-serotype colonization among study participants was low during 2008–2009. Following the introduction of PCV13, PCV7-serotype colonization remained low in children <5 years and adults ≥18 years but increased in children age 5–17 years. The increase in PCV7-serotype colonization among children aged 5–17 years was largely attributable to increased colonization by serotype 19F.

During 1995–2000, prior to PCV7 introduction, serotype 19F was the third most frequent cause of IPD among Alaskan children aged <2 years (average annual IPD incidence: 20.8/100,000 persons) [7]. By 2010–2013, the incidence of serotype 19F IPD among persons of all ages in Alaska had declined to 0.2/100,000 persons [8]. Of the 8 PCV7-serotype IPD isolates identified in Alaska during 2010–2013, however, 5 were serotype 19F. We describe the epidemiology of PCV-serotype 19F colonization in Alaska during 2008–2013 to better understand the reasons for the persistence of serotype 19F IPD and for the increases in serotype 19F colonization in the setting of widespread PCV7 and PCV13 use.

2. Methods

2.1. Alaska population

The Alaska population in 2013 was 736,399 including 142,898 (19%) persons who reported American Indian/Alaska Native as their race/ethnicity alone or in combination [9]. The 2013 population in the Anchorage Municipality was 301,324, in Region A was 9875, Region B was 25,822, and Region C was 6711 (Supplementary Fig. 1). The majority of residents in Regions A, B and C were Alaska Native (AN).

2.2. Alaska PCV immunization schedule

The State of Alaska recommendations for PCV follow ACIP guidelines for primary, booster, or catch-up doses for children and adults [4,5,10–12]. The recommended immunization schedule included PCV7 from January 1, 2008 to March 31, 2010, and switched to PCV13 from April 1, 2010 to December 31, 2013; however, all remaining doses of PCV7 after April 1, 2010 were used first before implementing PCV13.

2.3. Pneumococcal colonization survey data collection

We conducted annual cross-sectional pneumococcal colonization surveys from 2008 to 2013. We enrolled a convenience sample of children aged 3–59 months presenting for sick or well-child visits to two urban pediatric clinics in Anchorage, Alaska; we aimed to enroll 450 children/year between the two clinics. We also enrolled a convenience sample of all willing participants regardless of age from eight AN villages (minimum–maximum population/village in 2013: 229–783) located in 3 in rural Alaskan Regions (Fig. 1). We visited each study site at the same time of the year between January and May. We interviewed each participant to obtain demographic and household information and reviewed their medical records to determine their PCV vaccination status. For each participant, we inserted a nylon fiber flocked swab (Copan Diagnostics, Corona, CA) through the nares to swab the posterior NP. We placed the NP swab specimen into tubes containing transport medium with skim milk-tryptone-glucoseglycerin (STGG). The STGG tubes were then maintained in an ice cooler for transport to our laboratory in Anchorage, Alaska.

The colonization survey was approved by the Centers for Disease Control and Prevention and Alaska Area Institutional Review Boards. We obtained tribal approval to conduct our study from each of the rural villages. We obtained informed consent from participants aged ≥8 years and from the parent/guardian of participants aged <18 years. We additionally obtained written assent from children aged 7–17 years.

2.4. Invasive pneumococcal disease surveillance

IPD is a reportable disease in Alaska. In partnership with the State of Alaska, we conducted IPD surveillance through all 23 clinical laboratories in Alaska. At the time of initiating this present study, we had available to us surveillance data for 2008–2015. For surveillance, a case of IPD was defined as the isolation of *Streptococcus pneumoniae* from a normally sterile body site, such as blood or cerebrospinal fluid, in a resident of Alaska. Clinical laboratories forwarded invasive pneumococcal isolates to our laboratory for *S. pneumoniae* confirmation, serotype determination, and antimicrobial susceptibility testing. Upon confirmation of a clinical pneumococcal isolate, our research nurses or local infection control practitioners then reviewed the patient's medical record to obtain case demographic information and clinical information, including the underlying comorbid medical conditions, the presenting clinical syndrome, and whether the person survived the illness. We determined patients' pneumococcal vaccination status by reviewing the medical records and by cross-referencing their names with the statewide centralized vaccine registry.

2.5. Laboratory methods

We thawed the STGG tubes and plated 50 Âμl of the specimen onto trypticase soy agar supplemented with 5% sheep blood containing 10 μg/mL of gentamicin (BAP), and incubated the plates at 37 °C in 5% CO2 for 18–24 h. We then identified *S. pneumoniae* on the plates by evaluation colony morphology, susceptibility to optochin, and bile solubility. We did not systematically evaluate for colonization by multiple pneumococcal serotypes. When morphologically distinct colonies were observed, however, those colonies were subcultured onto separate BAP. From 2008 to 2010, we determined the pneumococcal serotype by latex agglutination and confirmed with the Quellung reaction. Beginning in 2011, we determined the serotype by using an algorithm that combined microbiologic, serologic, and sequential multiplex polymerase chain reaction (PCR) techniques as previously described [13]. Briefly, we determined the pneumococcal serotype by using a series of six sequential multiplex PCR assays that included primers for a total of 42 serotypes/serogroups. We grouped primers representing the most prevalent serotypes from the previous year into the initial three PCR assays. The first PCR assay included a primer for the cps gene. Isolates lacking the cps gene or isolates whose serotype could not be resolved by the series of multiplex PCR assays underwent further testing by latex agglutination and the Quellung reaction. Isolates where the serotype could not be resolved by latex agglutination and the Quellung reaction were classified as nontypeable. We used the Etest (bioMérieux Clinical Diagnostics) to assess colonizing pneumococcal isolates for nonsusceptibility to tetracycline (minimum inhibitory concentration [MIC] >2 mcg/mL), cotrimoxazole (MIC >0.5 mcg/mL), erythromycin (MIC ≥0.5 mcg/mL), ceftriaxone (MIC >0.5 mcg/mL), and penicillin (MIC >0.064 mcg/mL).

For IPD surveillance isolates, we confirmed the presence of *S. pneumoniae* by evaluating colony morphology, susceptibility to optochin, and bile solubility. Pneumococcal serotype was determined by the Quellung reaction.

We determined the genotype of pneumococcal isolates by multi-locus sequence typing (MLST). We performed MLST testing as previously described [14], with modifications [15]. Sequence

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