Pre– and Post–Conjugate Vaccine Epidemiology of Pneumococcal Serotype 6C Invasive Disease and Carriage within Navajo and White Mountain Apache Communities

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Background. A second-generation 13-valent pneumococcal conjugate vaccine, PCV13, was recently licensed. Although PCV13 includes serotype 6A, the usefulness of that antigen may be limited by the emergence of a new serotype, 6C, which was identified among isolates initially characterized (Quellung reaction) as serotype 6A. The epidemiology of serotype 6C prior to and after 7-valent PCV (PCV7) introduction is incompletely understood.

Methods. We analyzed conventionally serotyped 6A (CS6A) pneumococci from invasive disease case patients of all ages and carriage isolates from children and adults obtained in population-based studies among Navajo and White Mountain Apache communities during 1994–2009. Samples were tested by triplex polymerase chain reaction to resolve serotypes 6C and 6A.

Results. A total of 74 invasive CS6A episodes occurred. All were retyped by polymerase chain reaction; 40 (54.1%) were serotype 6C. The mean annual incidence of serotype 6C invasive disease was 0.3 (95% confidence interval, 0.03–0.9), 0.7 (95% confidence interval, 0.2–1.3), and 1.5 (95% confidence interval, 1.0–2.1) cases per 100,000 population in the years prior to the PCV7 efficacy trial, during the time the PCV7 trial was conducted, and following PCV7 introduction and routine use, respectively (P < .01). In the routine vaccination era, 76% of invasive CS6As were serotype 6C; nearly all cases occurred in adults. The proportion of serotype 6C among CS6A carriage isolates increased from 42% to 61% to 94% in the prevaccine, early vaccine, and routine vaccination eras, respectively.

Conclusion. In the PCV7 routine use era, virtually all serogroup 6 invasive pneumococcal disease and carriage strains among Navajo and White Mountain Apache communities are 6C. Monitoring and evaluation of this and other emerging serotypes among invasive disease and carriage isolates is warranted.

Routine use of 7-valent pneumococcal conjugate vaccine (PCV7) has led to major decreases in overall rates of invasive pneumococcal disease among children; disease due to the 7 vaccine serotypes (4, 6B, 9V, 14, 18C, 19F, and 23F) has been nearly eliminated in the United States [1]. There have been reported increases in rates of invasive disease due to nonvaccine serotypes (ie, serotype replacement), mainly due to serotype 19A [2–4]. In the United States, these rate increases are small relative to the major decreases in vaccine serotype disease that have been achieved. Among certain Native American populations with high underlying rates of pneumococcal disease, the magnitude of the nonvaccine serotype replacement disease has ranged from small among Navajo and White Mountain Apache populations [5, 6] to large among Alaska Natives [4]. The broad diversity of pneumococcal serotypes capable of causing disease has fueled development of sec-
ond-generation pneumococcal conjugate vaccines with increased valency (ie, broader serotype coverage). PCV13 (Pfizer), a new vaccine formulation containing PCV7 serotypes plus serotypes 1, 3, 5, 6A, 7F, and 19A, was licensed in the United States in early March 2010.

Emergence of novel pneumococcal serotypes may present immediate challenges to the effectiveness of PCV13. In 2007, Park et al [7] described the 91st pneumococcal capsular serotype—designated 6C—within a sample of serogroup 6 clinical isolates. These isolates were typed as 6A by standard Quellung reaction, but their capsule-biosynthetic locus differed from that of serotype 6A pneumococci [8], resulting in a single substitution of a galactose unit by a glucose unit in the capsular polysaccharide. Since the discovery of serotype 6C, a small number of studies have described its increasing proportion among carriage and invasive isolates in the PCV7 era, but none have observed long-term surveillance of both carriage and disease before, during and after PCV7 introduction, or a simultaneous control population under observation to address secular changes [9–11].

Surveillance data from the Centers for Disease Control and Prevention show that the proportion of serotype 6C isolates conventionally typed as serotype 6A increased to 69.1% in 2007 from 16.7% in 1999 [12]. The rate of invasive serotype 6C disease among children aged <5 years increased to 0.61 cases in 2007 from 0.09 cases per 100,000 population in 1999, whereas the rate of invasive serotype 6A disease decreased to 0.06 from 5.05 cases per 100,000 population over the same time period. Although increases in serotype 6C disease are minimal relative to the decreases in serotypes 6B and 6A in the PCV7 era, these data highlight an important phenomenon in the evolution and adaptation of the pneumococcus, one that warrants continued monitoring and evaluation with the introduction and routine use of PCV13.

The issues of novel serotype emergence and effectiveness of new PCVs are particularly important for some Native American communities, where disproportionately high rates of pneumococcal disease and carriage have persisted in spite of high levels of immunization coverage [4–6]. Over the past 12 years, we have conducted a number of population-based studies of pneumococci and established a repository of isolates, collected in the context of a large-scale, cluster-randomized vaccine efficacy trial [13], ongoing laboratory-based active surveillance for invasive disease [6], and a number of household-based studies of nasopharyngeal carriage [14–16]. This longitudinal dataset of both invasive pneumococcal disease and carriage isolates with a contemporaneous control group during the PCV7 introduction period offers a unique opportunity to understand the emergence of serotype 6C. Of the conventionally serotyped 6A (CS6A) isolates in the repository, we tested all invasive isolates and a sample of carriage isolates to assess the prevalence of serotype 6C with use of a polymerase chain reaction (PCR)–based serotyping method. In this report, we describe the epidemiology of serotype 6C pneumococcus among Navajo and White Mountain Apache communities before, during, and after the introduction of PCV7.

METHODS

All CS6A invasive disease isolates, as well as a sample of the CS6A nasopharyngeal carriage isolates, were selected for testing to resolve serotypes 6A and 6C with use of PCR-based serotyping methods. The method of selection from each of the studies is provided below.

Population-based active surveillance for invasive pneumococcal disease. We selected all invasive CS6As identified through the active bacterial surveillance activity from 1994 through 2009.

Nasopharyngeal carriage: pre-PCV era (1998–2000). A total 5177 nasopharyngeal specimens were collected, of which 3544 (68.5%) were positive for pneumococcus. Of these, 469 (13.2%) were CS6A (196 from the PCV7 group and 273 from the group C meningococcal conjugate vaccine [MnCC] group). We restricted selection of CS6A isolates to those obtained from children aged <5 years, and we ensured that eligible individuals/households were represented only once. A total of 217 CS6A specimens (PCV7 group, 102; MnCC group, 115) were eligible for selection. From this list, 50 CS6A isolates from the PCV7 group and 50 CS6A isolates from the MnCC group were randomly selected.

Nasopharyngeal carriage: early vaccine era (2001–2002). Of the 3424 specimens collected, 998 (29.1%) had positive results for pneumococcus. Of these, 84 (8.4%) were CS6A (PCV7 group, 57; MnCC group, 27). We restricted selection of CS6A isolates to those obtained from children aged <10 years (n = 66; PCV7 group, 47; MnCC group, 19). From this list, 25 CS6A isolates from the PCV7 group were randomly selected, and all 19 CS6As from the MnCC group were selected.

Nasopharyngeal carriage: routine vaccine era (2006–2008). A total of 6541 specimens were collected and processed; 2341 (35.8%) were found to have positive results for pneumococcus. Of these, 242 (10.3%) were CS6A. We then restricted selection of CS6A isolates to those obtained from children aged <5 years, and we also ensured that eligible individuals/households were represented only once. From this list (n = 100), a total of 50 CS6A isolates were randomly selected. A random sample of 42 CS6A isolates from children aged ≥5 years and adults was also selected.

Serotype 6C identification. CS6A isolates were tested to resolve serotype 6C and 6A with use of a triplex PCR that contained primer pairs specific for cpsA (capsular biosynthetic locus; 160 bp), wci-P serogroup 6 (250 bp), and wci-N beta serotype 6C (727 bp), as described elsewhere [12]. DNA-
Table 1. Comparative Incidence of Pneumococcal Serotype 6A and 6C Invasive Disease among Navajo and White Mountain Apache Persons of All Ages, 1994–2009

| Age group, serotype | Prevaccine period, year | Vaccine introduction period, year |
|---------------------|------------------------|----------------------------------|
|                     | 1994 | 1995 | 1996 | 1997 | 1998 | 1999 | 2000 |
| All ages 6A         | 1    | 1    | 7    | 4    | 4    | 4    | 3    |
| No. of cases        |      |      |      |      |      |      |      |
| Incidence           | 0.4 (0.01–2.3) | 0.4 (0.01–2.3) | 2.8 (1.1–5.8) | 1.6 (0.4–4.1) | 1.6 (0.4–4.1) | 1.6 (0.4–4.2) | 1.2 (0.3–3.6) |
| 6C                  |      |      |      |      |      |      |      |
| No. of cases        | 1    | 1    | 1    | 1    |      |      |      |
| Incidence           | 0.4 (0.01–2.3) | 0.4 (0.01–2.2) | 0.0 (0.0–1.5) | 0.4 (0.01–2.2) | 0.8 (0.1–2.9) | 0.4 (0.01–2.3) | 0.8 (0.1–3.0) |
| Aged <5 years 6A    | 0    | 0    | 0    | 0    | 0    | 0    | 1    |
| No. of cases        |      |      |      |      |      |      |      |
| Incidence           | 0.0 (0.0–10.9) | 3.1 (0.08–17.3) | 13.2 (3.6–33.9) | 3.5 (0.08–19.5) | 10.9 (2.2–31.8) | 3.8 (0.09–20.9) | 0.0 (0.0–14.4) |
| 6C                  | 0    | 0    | 0    | 0    | 0    | 0    | 1    |
| No. of cases        |      |      |      |      |      |      |      |
| Incidence           | 0.0 (0.0–10.9) | 0.0 (0.0–11.4) | 0.0 (0.0–12.1) | 0.0 (0.0–12.9) | 0.0 (0.0–13.3) | 0.0 (0.0–13.9) | 3.9 (0.09–21.8) |
| Aged ≥5 years 6A    | 1    | 0    | 0    | 0    | 0    | 0    | 1    |
| No. of cases        |      |      |      |      |      |      |      |
| Incidence           | 0.5 (0.01–2.6) | 0.0 (0.0–1.7) | 1.4 (0.3–4.0) | 1.4 (0.3–3.9) | 0.5 (0.01–2.5) | 1.4 (0.3–4.0) | 1.4 (0.3–4.1) |
| 6C                  | 0    | 0    | 0    | 0    | 0    | 0    | 1    |
| No. of cases        |      |      |      |      |      |      |      |
| Incidence           | 0.5 (0.01–2.6) | 0.5 (0.01–2.6) | 0.0 (0.0–1.7) | 0.5 (0.01–2.5) | 0.9 (0.1–3.3) | 0.5 (0.01–2.6) | 0.5 (0.01–2.6) |

a No. of cases per 100,000 population (95% confidence interval).
b , by χ² test for trend.

RESULTS

From 1994 through 2009, a total of 74 invasive CS6A isolates among Navajo and White Mountain Apache children and adults were identified by active surveillance. Of these, 40 isolates (54.1%) were identified as serotype 6C. The mean annual incidence of serotype 6C invasive disease was 0.3 (95% confidence interval [CI], 0.03–0.9) cases per 100,000 population in the years prior to the PCV7 efficacy trial (1994–1997), 0.7 (95% CI, 0.2–1.3) cases per 100,000 population during the time the PCV7 trial was conducted (1997–2000), and 1.5 (95% CI, 1.0–2.1) cases per 100,000 population in the years following PCV7 introduction and routine use (2001–2009) (P < .01; Table 1). By contrast, the mean annual incidence of serotype 6A invasive disease during these time periods was 1.3 (95% CI, 0.5–2.3), 1.5 (95% CI, 0.9–2.5), and 0.5 (95% CI, 0.2–0.8) cases per 100,000 population, respectively. In the last 6 years of this analysis (2004–2009), only 3 cases of serotype 6B and 2 cases of serotype 6A invasive disease were identified, compared with 23 cases of serotype 6C invasive disease. All cases of serotype 6B invasive disease occurred among adults in 2004–2005. With the virtual disappearance of serotypes 6A and 6B in the era of routine PCV7 use, serotype 6C is now effectively the only cause of invasive disease.
of serogroup 6 invasive disease among Navajo and White Mountain Apache communities (Figure 1).

Of the 40 cases of serotype 6C disease, only 4 (10%) occurred among children aged <5 years (1 case each in 2000 and 2002 and 2 cases in 2009). Only 3 cases (7.5%) occurred in children aged <2 years, a stark contrast to serotype 6A invasive disease, for which >40% of case patients were aged <2 years (P = .001). Among individuals aged ≥5 years, the annual incidence of serotype 6C disease increased from 0.3 (95% CI, 0.04–1.1) to 1.5 (95% CI, 1.0–2.1) cases per 100,000 populations in the prevaccine and routine vaccine use eras, respectively (P < .01). By contrast, the annual incidence of serotype 6A disease in this age group decreased from 0.6 (95% CI, 0.2–1.6) to 0.3 (95% CI, 0.08–0.6) cases per 100,000 population during these same time periods, though these differences were not statistically significant.

The clinical characteristics of serotype 6C invasive disease are shown in Table 2. For comparison, the clinical characteristics of serotype 6A invasive disease are also displayed. For both serotypes 6A and 6C, the majority of case patients were male (58.1%) and Navajo (91.9%). Case patients with serotype 6C invasive disease were older (median age, 50.3 vs 37.0 years).

Pneumonia was the most common manifestation of serotype 6C invasive disease (62.5%); all case patients with serotype 6C pneumonia were aged ≥5 years. Among case patients aged ≥5 years, the proportion with pneumonia was higher among those with serotype 6C invasive disease, compared with those with serotype 6A invasive disease (69.4% vs 36.8%; P < .05). Among those case patients with serotype 6C disease for whom the outcome was known, 5 (17.5%) died; 1 was a 9-year-old boy with sepsis, and the remaining deaths were among adults aged ≥75 years, all of whom were diagnosed with bacteremic pneumonia. The mortality rate did not differ between case patients with serotype 6A and serotype 6C invasive disease.

Nasopharyngeal carriage: pre–conjugate vaccine era (1998–2000). Of the 100 CS6A carriage isolates selected for analysis, 3 (3%; 2 from the PCV7 group and 1 from the MnCC group) were nonviable. Of the remaining 97 CS6A isolates, 41 (42%) were identified as 6C. The proportion of serotype 6C was significantly higher in PCV7-randomized communities, compared with MnCC-randomized communities (54% vs 31%; P = .01) (Table 3).

Nasopharyngeal carriage: early vaccine era (2001–2002). Of the 44 CS6A carriage isolates selected for analysis, 3 (6.8%; all from the MnCC group) were nonviable. Of the remaining 41 CS6A isolates, 25 (61%) were identified as 6C. The proportion of serotype 6C remained higher among children living in communities that had been randomized to the PCV7 group.

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Table 1. (Continued.)

| Early routine use period, year | Routine use period, year |
|-------------------------------|-------------------------|
| 2001 2002 | 2003 2004 | 2005 2006 | 2007 2008 | 2009 2010 |
| 2 4 | 2 1 | 0 0 | 1 0 | 0 0 |
| 0.8 (0.1–3.0) | 1.7 (0.4–4.3) | 0.8 (0.1–2.9) | 0.4 (0.01–2.3) | 0.0 (0.0–1.5) | 0.4 (0.01–2.4) | 0.0 (0.0–1.5) | 0.0 (0.0–1.5) |
| 3 2 | 4 6 | 1 2 | 3 2 | 9 |
| 1.2 (0.3–3.7) | 0.8 (0.1–3.0) | 1.7 (0.4–4.2) | 2.5 (0.9–5.4) | 0.4 (0.01–2.3) | 0.8 (0.1–3.0) | 1.3 (0.3–3.8) | 0.8 (0.1–3.0) | 3.7 (1.7–6.9) |
| 1 0 | 0 0 | 0 1 | 0 0 | 0 0 |
| 4.1 (0.1–22.8) | 0.0 (0.0–14.7) | 8.1 (0.9–29.3) | 0.0 (0.0–15.1) | 0.0 (0.0–15.3) | 0.0 (0.0–15.5) | 4.3 (0.1–23.7) | 0.0 (0.0–14.9) | 0.0 (0.0–14.5) |
| 0 0 | 0 0 | 1 |
| 0.0 (0.0–15.1) | 0.0 (0.0–14.7) | 4.1 (0.1–22.9) | 0.0 (0.0–15.3) | 0.0 (0.0–15.5) | 0.0 (0.0–15.7) | 0.0 (0.0–14.9) | 7.9 (0.9–28.5) |
| 0 4 | 0 |
| 0.0 (0.0–1.7) | 1.9 (0.5–4.7) | 0.0 (0.0–1.7) | 0.5 (0.01–2.6) | 0.0 (0.0–1.7) | 0.0 (0.0–1.7) | 0.0 (0.0–1.8) | 0.0 (0.0–1.7) | 0.0 (0.0–1.7) |
| 3 2 | 4 5 | 1 |
| 1.4 (0.3–4.1) | 0.9 (0.1–3.3) | 1.9 (0.5–4.7) | 2.3 (0.7–5.3) | 0.5 (0.01–2.5) | 0.9 (0.1–3.3) | 1.5 (0.3–4.2) | 0.9 (0.1–3.4) | 3.2 (1.3–6.6) |
for the preceding trial than among children living in communities that had been randomized to the MnCC group (72% vs 44%), though this did not reach statistical significance ($P = .07$) (Table 3).

**Nasopharyngeal carriage: routine vaccine era (2006–2008).** Of the 50 CS6A carriage isolates from children aged <5 years selected, 47 (94%) were identified as 6C (Table 3). Of the 42 CS6A isolates from children aged ≥5 years and adults, all (100%) were identified as serotype 6C. There were no longer any differences in the prevalence of 6C according to the community of randomization during the preceding PCV7 trial.

**DISCUSSION**

Since the first reports detailing the identification and characterization of the novel pneumococcal serotype 6C [17, 18], a number of epidemiologic studies have described the prevalence, clinical characteristics, and antibiotic-resistance profile of this serotype among cases of invasive disease [10–12, 19, 20]. Three studies have described the epidemiology of serotype 6C carriage [9, 20, 21]. Only 1 study has evaluated changes in serotype 6C prevalence among both disease and carriage isolates in the pre- and post–PCV7 introduction eras [22]. Longitudinal studies of this novel serotype are critical, because its emergence and dissemination may be related to the introduction and widespread use of PCV7 in the past decade.

To our knowledge, this is the only study of serotype 6C that describes the epidemiology of both invasive disease and carriage over a prolonged period. This 15-year period of observation spans the years prior to, during, and after the introduction and widespread use of PCV7. Moreover, the invasive pneumococcal disease data and 2 of these carriage studies in which serotype 6C was identified were conducted in the context of a group-randomized efficacy trial of PCV7 [14, 23]. Data from these randomized, controlled, community-based studies provide a rare insight into the dynamics between community-wide vaccine introduction and emergence of novel pneumococcal serotypes, such as serotype 6C. Although previous ecological analyses have shown that serotype 6C was identified more commonly following PCV7 use, our analysis of clinical trial data more strongly suggest a link between PCV7 introduction and emergence of this serotype. Findings from this study bear relevance for future disease prevention strategies, particularly as pneumococcal vaccines with broader serotype coverage (eg, PCV13) are introduced in routine immunization programs.

Population-based active laboratory surveillance data indicate that the incidence of serotype 6C invasive disease has increased from the pre-PCV7 to the routine PCV7 use eras. It should be noted, however, that these rate increases are minimal relative to the substantial decreases of serotypes 6B and 6A invasive disease during the same time periods.

From the cases identified to date, it appears that serotype 6C invasive disease primarily affects adults and is less common among infants and young children [12]. It is unlikely that this can be explained by age-related differences in exposure; CS6A is the most commonly carried serotype among children aged <5 years [16], and data from the current study strongly suggest that these isolates are, in fact, serotype 6C. Although it is not uncommon for specific pneumococcal serotypes to frequently colonize the nasopharynx but be infrequent causes of invasive disease [24], it is possible that serotype 6C clones with increased invasive potential and increasing abundance in the carriage reservoir are circulating in these communities and may still
Table 2. Clinical Characteristics of Serotype 6A and 6C Invasive Disease Cases among Navajo and White Mountain Apache Children and Adults, 1994–2009

| Characteristic       | No. or proportion (%) of cases | Serotype 6A (n = 34) | Serotype 6C (n = 40) | Total (n = 74) |
|----------------------|--------------------------------|----------------------|----------------------|----------------|
| Male sex             |                                | 18 (52.9)            | 25 (62.5)            | 43 (58.1)      |
| Age, years           |                                |                      |                      |                |
| 0–1                  |                                | 14 (41.2)            | 3 (7.5)              | 17 (23.0)      |
| 2–4                  |                                | 1 (2.9)              | 1 (2.5)              | 2 (2.7)        |
| 5–17                 |                                | 1 (2.9)              | 2 (5.0)              | 3 (4.1)        |
| 18–39                |                                | 5 (14.7)             | 8 (20.0)             | 13 (17.6)      |
| 40–64                |                                | 8 (23.5)             | 14 (35.0)            | 22 (29.7)      |
| >65                  |                                | 5 (14.7)             | 12 (30.0)            | 17 (23.0)      |
| Isolate source<sup>a</sup> |                             |                      |                      |                |
| Blood                |                                | 31 (91.2)            | 39 (97.5)            | 70 (94.6)      |
| CSF                  |                                | 3 (8.8)              | 0 (0.0)              | 3 (4.1)        |
| Other                |                                | 2 (5.9)              | 1 (2.5)              | 3 (4.1)        |
| Outcome<sup>b</sup>, all ages |                          |                      |                      |                |
| Died                 |                                | 4 (16.7)             | 7 (18.4)             | 11 (17.7)      |
| Survived with neurological sequelae |                    | 1 (4.2)              | 2 (5.3)              | 3 (4.8)        |
| Survived with no sequelae |                           | 19 (79.2)            | 29 (76.3)            | 48 (77.4)      |
| Unknown              |                                | 10 (29.4)            | 2 (5.0)              | 12 (16.2)      |
| Syndrome<sup>c</sup>, by age group |                        |                      |                      |                |
| Aged <5 years        |                                |                      |                      |                |
| Pneumonia            |                                | 5/15 (33.3)          | 0/4 (0.0)            | 5 (26.3)       |
| Meningitis           |                                | 3/15 (20.0)          | 2/4 (50.0)           | 5 (26.3)       |
| Sepsis               |                                | 2/15 (13.3)          | 0/4 (0.0)            | 2 (10.5)       |
| Bacteremia without other focus |                   | 6/15 (40.0)          | 2/4 (50.0)           | 8 (42.1)       |
| Peritonitis          |                                | 0/15 (0.0)           | 0/4 (0.0)            | 0 (0.0)        |
| Other                |                                | 0/15 (0.0)           | 0/4 (0.0)            | 0 (0.0)        |
| Aged ≥5 years        |                                |                      |                      |                |
| Pneumonia            |                                | 7/19 (36.8)          | 25/36 (69.4)         | 32/55 (58.2)   |
| Meningitis           |                                | 1/19 (5.3)           | 3/36 (8.3)           | 4/55 (7.3)     |
| Sepsis               |                                | 4/19 (21.1)          | 4/36 (11.1)          | 8/55 (14.5)    |
| Bacteremia without other focus |                   | 6/19 (31.6)          | 4/36 (11.1)          | 10/55 (18.2)   |
| Peritonitis          |                                | 0/19 (0.0)           | 4/36 (11.1)          | 4/55 (7.3)     |
| Other                |                                | 2/19 (10.5)          | 1/36 (2.8)           | 3/55 (5.5)     |
| Outcome<sup>b</sup>, by age group |                        |                      |                      |                |
| Aged <5 years        |                                |                      |                      |                |
| Died                 |                                | 1/15 (10.0)          | 0/4 (0.0)            | 1/19 (7.1)     |
| Survived with neurological sequelae |                    | 0/15 (0.0)           | 0/4 (0.0)            | 0/19 (0.0)     |
| Survived with no sequelae |                           | 9/15 (90.0)          | 4/4 (100.0)          | 13/19 (92.9)   |
| Unknown              |                                | 5/15 (33.3)          | 0/4 (0.0)            | 5/19 (26.3)    |
| Aged ≥5 years        |                                |                      |                      |                |
| Died                 |                                | 3/19 (16.8)          | 7/36 (20.6)          | 10/55 (18.2)   |
| Survived with neurological sequelae |                    | 1/19 (7.1)           | 2/36 (5.9)           | 3/55 (6.3)     |
| Survived with no sequelae |                           | 10/19 (52.6)         | 25/36 (73.5)         | 35/55 (62.9)   |
| Unknown              |                                | 5/19 (26.3)          | 2/36 (5.6)           | 7/55 (12.7)    |

**NOTE.** CSF, cerebrospinal fluid.

<sup>a</sup> Multiple isolate sources were possible.

<sup>b</sup> Data were not collected over the entire surveillance period. The reported proportion is among cases with known outcome.

<sup>c</sup> Multiple syndromes are possible; other syndromic presentations included arthritis (6A), cellulitis (6A), and surgical site infection (6C).
emerge as important causes of disease, especially in younger age groups. The likelihood of this scenario might be increased by the high clonal diversity of this serotype [12], because specific clone(s) may prove especially adaptable.

We previously described the impact of routine, community-wide use of PCV7 on the epidemiology of pneumococcal carriage, namely, a rapid decrease and near elimination of vaccine types, offset by an increased prevalence of nonvaccine types, in the nasopharynx of both immunized and nonimmunized individuals [14, 15, 23]. The findings of the present study indicate that serotype 6C carriage, though likely present prior to the introduction of PCV7, increased in prevalence as immunization coverage in these communities increased. It is tempting to speculate that the observed increases in serotype 6C carriage filled an ecological void created by the elimination of serotypes 6B and 6A and other serotypes through routine, community-wide use of PCV7.

The near disappearance of serotype 6A invasive disease in the routine PCV7 era demonstrates that the serotype 6B antigen in the vaccine confers remarkable cross-protective immunity to serotype 6A. Evidence of cross-protection can be gleaned from both population-based and laboratory-based studies. In several population-based assessments of PCV7 (which contains serotypes 6B and 19F but not the related serotypes 6A and 19A), cross-protection against serotype 6A [25–27] but not serotype 19A disease was demonstrated [2, 28]. In laboratory studies of opsonophagocytic activity, serum of PCV7 (children) and PS-23 (adults) vaccine recipients demonstrated cross-protection against serotype 6A but not serotype 6C [29]. Whether the 6A antigen in PCV13 will protect against serotype 6C is uncertain. The utilization of both population- and laboratory-based methods will be critical in the evaluation of PCV13 effectiveness against disease due to serotype 6C, as well as other potentially cross-reactive vaccine serotypes.

In summary, we have described the clinical and epidemiologic characteristics of serotype 6C among Navajo and White Mountain Apache communities, populations known to be at increased risk for pneumococcal disease and carriage. Serotype 6C invasive disease primarily affects adults and is associated with high rates of mortality in these communities. Although disease rates remain low, serotype 6C is now virtually the only serogroup 6 serotype among invasive isolates in these communities; serotypes 6A and 6B have essentially been eliminated. Although it is not known whether disease due to serotype 6C or other novel serotypes will become more prevalent in these communities, the epidemiology of pneumococcal serotypes has changed considerably since the introduction of PCV7. Further changes are likely; a putative pneumococcal serotype 6D was recently described [30]. Maintenance of population-based active laboratory surveillance activities is essential for the control and prevention of pneumococcal disease.

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