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Post-COVID Rebound in Invasive Pneumococcal Disease Driven by Resurgence of Serotype 4 Among American Indian Individuals in the Southwest United States

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Background. Incidence of invasive pneumococcal disease (IPD) in American Indian (AI) communities in the Southwest United States declined during the COVID-19 pandemic. We estimated the burden and serotype distribution of IPD in the same communities in 2022–2024.

Methods. We conducted active, laboratory-based surveillance for IPD in the Navajo Nation and White Mountain Apache Tribal (WMAT) lands. Isolates were collected and serotyped. Annual incidence rates were calculated and serotype distribution was estimated. The proportion of serotypes covered by available pneumococcal conjugate vaccines (PCV20 and PCV21) were estimated and compared by age group using McNemar χ^2 or exact McNemar tests, as appropriate.

Results. IPD rates increased from 2022 to 2024 to pre-pandemic levels: from 45.9 to 62.1 per 100 000 in the Navajo Nation and 52.9 to 84.4 in the WMAT lands. Among adults in the Navajo Nation, serotype 4 accounted for 28.5% of cases and occurred primarily among younger unvaccinated males. The proportion of cases covered by PCV21 was lower than PCV20 for adults aged 18–49 years (53.2% vs 77.3%; $P < .001$) but higher for adults aged ≥65 years (82.5% vs 65.1%; $P = .03$). In the WMAT lands, no cases of serotype 4 were identified; the proportion of cases covered by PCV21 was the same or higher than for PCV20 across age groups.

Conclusions. In 2 AI communities in the Southwest, IPD rates returned to pre-pandemic levels. In the Navajo Nation, the increase was driven by serotype 4 IPD among younger male unvaccinated adults. These findings can inform vaccine recommendations and highlight the value of surveillance.

Keywords. Indigenous health; invasive pneumococcal disease; serotype 4; comorbidities; adult vaccination.

Streptococcus pneumoniae is a leading cause of severe bacterial infections, including pneumonia and sepsis, in children and adults [1, 2]. In the United States (US), an estimated 27 770 cases and 3230 deaths from invasive pneumococcal disease (IPD) occurred in 2022 [3]. There are >100 serotypes of *S pneumoniae* [4], and safe and effective vaccines are available that protect against serotypes commonly causing disease [5].

American Indian and Alaska Native (AI/AN) populations have high rates of infectious diseases [6], including pneumococcal infections, which are associated with social drivers of health including high household density and lack of running water [7, 8]. IPD rates in AI populations in the Southwest US were higher than the US general population before the 7-valent pneumococcal conjugate vaccine (PCV7) was introduced into the routine childhood immunization schedule in 2000. IPD rates declined with good vaccine uptake, but remained elevated compared to the US general population [9, 10].

Following onset of the coronavirus disease 2019 (COVID-19) pandemic in 2020, Southwest AI populations experienced decreased circulation of respiratory pathogens [11], including *S pneumoniae*, like elsewhere in the US [12–14]. In the Southwest, IPD rates in the Navajo Nation and White

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Mountain Apache Tribal (WMAT) lands declined to the lowest recorded in over 30 years [9]. With easing of COVID-19–related mitigation measures, rates increased but did not reach pre-pandemic levels. While rates for most serotypes decreased, rates of serotype 4 IPD increased among adults in the Navajo Nation [9]. This was notable, as serotype 4 was included in pneumococcal conjugate vaccine formulations (PCV7, 15-valent PCV [PCV15], 20-valent PCV [PCV20]) and the 23-valent pneumococcal polysaccharide vaccine (PPSV23), and was virtually eliminated as a cause of IPD in these populations [9, 10]. A similar increase in serotype 4 IPD was observed in the western states of the Centers for Disease Control and Prevention (CDC) Active Bacterial Core surveillance (ABCs) starting in 2013 [15], and outbreaks of serotype 4 IPD were reported from Alberta, Canada, from 2000 to 2016; both were concentrated among people experiencing homelessness (PEH) and persons with a history of substance use [16, 17]. In 2024, a 21-valent PCV (PCV21) targeting serotypes commonly causing IPD among adults was licensed and included among the recommended pneumococcal vaccines for adults aged ≥50 years and adults aged 19–49 years who have conditions that put them at greater risk of pneumococcal disease; it does not include serotype 4 [5].

The objective of this analysis was to estimate the burden and serotype distribution of IPD in AI individuals in the Navajo Nation and WMAT lands in 2022–2024, and to describe serotype 4 IPD cases in these communities.

METHODS

Study Setting and Population

The Johns Hopkins Center for Indigenous Health (JHCIH) works in collaboration with the Navajo Epidemiology Center, tribal partners, and healthcare facilities serving the Navajo Nation and WMAT to conduct IPD surveillance. The Navajo Nation, located in Arizona, New Mexico, and Utah, spans approximately 27 000 square miles (69 930 square kilometers) and has a population of approximately 243 000 tribal members. The WMAT lands, located in Arizona, cover approximately 2600 square miles (6734 square kilometers) and have a population of approximately 17 000 tribal members. More than 90% of individuals residing in Navajo Nation and WMAT lands identify as AI/AN [18].

Active, population- and laboratory-based surveillance was conducted at 24 Indian Health Service (IHS), tribal, and private facilities located in or near the Navajo Nation and WMAT lands. Cases were identified through regular communications with laboratories. Select laboratories were regularly audited to identify cases not detected in real time. Additionally, cases reported to the Navajo Epidemiology Center by the Arizona and New Mexico health departments, but not identified by JHCIH, were included.

An IPD case was defined as *S pneumoniae* cultured from a normally sterile body site (eg, blood, cerebrospinal fluid, bone) and collected from an AI individual living in or near the Navajo Nation or WMAT lands.

For eligible cases, an isolate was collected, stored at −70°C, and then sent to the CDC Arctic Investigations Program for serotyping. Through 2022, serotyping was performed by slide agglutination and confirmed with the Quellung reaction using commercial group- and type-specific antisera (SSI Diagnostica; Statens Serum Institut, Copenhagen, Denmark). Beginning in 2023, serotypes and antibiotic susceptibility were determined by whole genome sequencing [19]. All serotype 4 isolates from 2010–2022 also underwent whole genome sequencing. Information on demographics, clinical presentation and treatment, and medical history was collected by chart review.

This research was reviewed and approved by the participating tribal communities and the Johns Hopkins Bloomberg School of Public Health Institutional Review Board (IRB; JHU #9505), the Navajo Nation Human Research Review Board (NNR-19.343), and the IHS Phoenix Area IRB (PXR-97.04). A Health Insurance Portability and Accountability Act (HIPAA) waiver was obtained to conduct the chart reviews. This activity was reviewed by the CDC and was conducted consistent with applicable federal law and CDC policy (see 45 Code of Federal Regulations [C.F.R.] part 46; 21 C.F.R. part 56).

Statistical Analysis

The primary analysis included cases occurring between 1 January 2022 and 31 December 2024 in the Navajo Nation and WMAT lands. Descriptive statistics were used to summarize case characteristics, including proportions for categorical variables and medians and interquartile ranges for continuous variables, separately for each community.

Annual rates and 95% confidence intervals were calculated both overall and by age group for each community. Rate calculations used the number of IPD cases as the numerator and the IHS user population as the denominator [20]. A user is defined as an AI/AN individual who had an inpatient stay, ambulatory medical visit, or dental visit at an IHS facility within the past 3 years. Age-adjusted annual rates were calculated using direct standardization methods and the US population for 2020 as the reference [21]. For comparison and to illustrate trends, previously published rates from 2019 to 2021 were included [9].

Serotype distribution and PCV20 and PCV21 vaccine coverage were described overall and by age group for each community. Serotypes not included in PCV20 or PCV21 were considered non–vaccine type. The proportion of serotypes covered by PCV20 and PCV21 was compared using McNemar χ^2 tests or exact McNemar tests, as appropriate.

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To explore serotype 4 trends, cases occurring between 1 January 2010 (after a decade of serotype 4–containing PCV use) and 31 December 2024 were included. As no cases of serotype 4 occurred in the WMAT lands, the analysis was restricted to the Navajo Nation. Annual rates of all-serotype, vaccine-type, and serotype 4–specific IPD were calculated as described above. Missing serotype data were imputed using the proportion of known serotypes for each year.

To evaluate the case characteristics from the current increase in serotype 4 IPD, cases with available serotypes occurring between 1 January 2019 and 31 December 2024 in the Navajo Nation were included. The characteristics of serotype 4 and non–serotype 4 cases were summarized using descriptive statistics and compared using Wilcoxon rank-sum test for continuous variables and Pearson χ^2 or Fisher exact tests, as appropriate, for categorical variables.

All analyses were conducted in R software (version 4.4.1).

RESULTS

IPD in the Navajo Nation and WMAT Lands, 2022–2024

From 2022 to 2024, 344 and 33 cases of IPD were identified in the Navajo Nation and WMAT lands, respectively (Table 1). In both communities, most cases were identified among adults

Table 1. Characteristics of Invasive Pneumococcal Disease in Navajo Nation and White Mountain Apache Tribal Lands, January 2022–December 2024

Characteristic	Navajo Nation	White Mountain Apache
Total No. of cases	344	33
Age, y, median (IQR)	48.2 (38.2–63.4)	45.2 (40.9–55.1)
Age group		
<5 y	7 (2.0)	0 (0.0)
5–17 y	2 (0.6)	0 (0.0)
18–49 y	174 (50.6)	22 (66.7)
50–64 y	88 (25.6)	7 (21.2)
≥65 y	73 (21.2)	4 (12.1)
Sex		
Female	118 (34.3)	13 (39.4)
Male	226 (65.7)	20 (60.6)
Residence 4 d prior to illness		
Private residence	287 (83.4)	31 (93.9)
Long-term care facility	2 (0.6)	0 (0.0)
Hospital inpatient	1 (0.3)	0 (0.0)
Experiencing homelessness	19 (5.5)	1 (3.0)
Substance abuse treatment center	1 (0.3)	0 (0.0)
Incarcerated	3 (0.9)	0 (0.0)
Unknown	31 (9.0)	1 (3.0)
Body source		
Blood	330 (95.9)	29 (87.9)
Blood and bone	1 (0.3)	0 (0.0)
Blood and CSF	2 (0.6)	0 (0.0)
Blood and joint fluid	2 (0.6)	1 (3.0)
Blood and peritoneal fluid	1 (0.3)	3 (9.1)
Aqueous fluid	1 (0.3)	0 (0.0)
CSF	3 (0.9)	0 (0.0)
Pleural fluid	4 (1.2)	0 (0.0)
Syndrome[a]		
Meningitis	1 (0.3)	0 (0.0)
Pneumonia	268 (77.9)	23 (69.7)
Bacteremia without other focus	6 (1.7)	2 (6.1)
Sepsis	178 (51.7)	16 (48.5)
Concurrent COVID-19 (within 30 d)	22 (6.5)	2 (6.1)
Peritonitis	2 (0.6)	3 (9.1)
Cellulitis	5 (1.5)	0 (0.0)
Osteomyelitis	3 (0.9)	0 (0.0)
Septic arthritis	4 (1.2)	1 (3.0)
Streptococcal toxic shock syndrome	1 (0.3)	0 (0.0)
Missing syndrome data	20 (5.8)	2 (6.1)

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Table 1. Continued

Characteristic	Navajo Nation	White Mountain Apache
Admitted to facility		
Yes	295 (85.8)	28 (84.8)
No	27 (7.8)	4 (12.1)
Unknown	22 (6.4)	1 (3.0)
Length of admission, d, median (IQR)	5.0 (3.0–8.0)	4.0 (3.0–6.2)
Case fatality[b]	37 (12.1)	10 (31.2)
Case fatality[b] among hospitalized patients	29 (10.7)	9 (33.3)
At least 1 chronic medical conditions[c]	263 (76.7)	32 (97.0)
Alcohol abuse	157 (45.8)	26 (78.8)
Asthma	28 (8.2)	3 (9.1)
Cirrhosis/liver failure	50 (14.6)	11 (33.3)
Heart failure/CHF	37 (10.8)	2 (6.1)
Emphysema/COPD	11 (3.2)	2 (6.1)
Diabetes	119 (34.8)	14 (42.4)
Current smoker	63 (18.4)	10 (30.3)
At least 1 immunocompromising conditions[d]	36 (10.6)	2 (6.2)
Immunosuppressed without the presence of an immunocompromising condition[d] (subset of the above)	9 (2.6)	0 (0.0)
Renal failure/dialysis	26 (7.6)	1 (3.0)
Injection drug use	8 (2.3)	0 (0.0)
Risk-based indication for vaccination (excluding age)[e]		
At least 1 risk factor	275 (80.2)	32 (97.0)
At least 2 risk factors	157 (45.8)	23 (69.7)
Received at least 1 dose of pneumococcal vaccine as an adult[f]		
18–49 y	54 (32.5)	17 (81.0)
≥50 y	105 (67.3)	11 (100.0)
Type(s) of vaccine received		
Both PPSV23 and other PCV	59 (17.6)	5 (15.2)
Both PPSV23 and PCV7	1 (0.3)	0 (0.0)
PPSV23 only	79 (23.6)	23 (69.7)
PCV7 only	9 (2.7)	0 (0.0)
Other PCV only	11 (3.3)	0 (0.0)
None	163 (48.7)	4 (12.1)
Unknown vaccination status	13 (3.9)	1 (3.0)
Years since last dose, median (IQR)	7.3 (2.1–11.4)	5.8 (3.4–8.2)

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; CSF, cerebrospinal fluid; d, days; IQR, interquartile range; No., number; PCV, pneumococcal conjugate vaccine; PCV7, 7-valent pneumococcal conjugate vaccine; PPSV23, 23-valent pneumococcal polysaccharide vaccine; y, years.

[a]Syndromes are not mutually exclusive.

[b]Outcome determined by status of patient within 30 days of hospital admission, emergency department visit, or outpatient visit associated with collection of invasive *Streptococcus pneumoniae* isolate. Percentages are among individuals with available data. Data were not available for 37 patients in the Navajo Nation and 1 patient in White Mountain Apache Tribal (WMAT) lands; among those, the WMAT patient and 23 of 37 Navajo Nation patients were hospitalized.

[c]Chronic conditions include alcohol abuse, asthma, liver failure/cirrhosis, heart failure/CHF, emphysema/COPD, diabetes mellitus, and tobacco use.

[d]Immunocompromising conditions include organ transplant, immunodeficiency, HIV/AIDS, and malignancy.

[e]Risk-based indications for vaccination include both chronic and immunocompromising conditions. Age-based indications are not included.

[f]Percentages are among individuals with available data on vaccination status. Vaccination history was unknown for 8 adults aged 18–49 years and 5 aged ≥50 years in the Navajo Nation as well as 1 adult aged 18–49 years in WMAT lands. Pneumococcal vaccine includes both PPSV23 and PCVs.

and presented as pneumonia. Vaccination among adults varied by community, with more adults aged 18–49 years having received at least 1 dose of pneumococcal vaccine in WMAT lands than the Navajo Nation (81.0% vs 32.5%, respectively; $P < .001$). IPD rates (all ages and all serotypes) increased during 2022 to 2024 in both communities to pre-pandemic levels: from 45.9 to 62.1 per 100 000 in the Navajo Nation and 52.9 to 84.4 in the WMAT lands (Supplementary Table 1; see Figure 1 for age-standardized rates). Rates were highest among older adults, with few cases identified among children (none in the WMAT).

Among children in the Navajo Nation with serotype data available (n = 7/9 [77.8%]), serotypes identified included 3 (n = 1 [14.3%]), 19F (n = 1 [14.3%]), 22F (n = 2 [28.6%]), 34 (n = 1 [14.3%]), and 35B (n = 2 [28.6%]). Among adults in the Navajo Nation with serotype data available (n = 274/324 [84.6%]), serotype 4 was the most common (n = 78 [28.5%]), followed by serotype 3 (n = 49 [17.9%]) and serotype 20 (n = 33 [12.0%]) (Figure 2; serotype distribution by age group available in Supplementary Figure 1). Most IPD cases were caused by serotypes included in PCV20 and PCV21; however,

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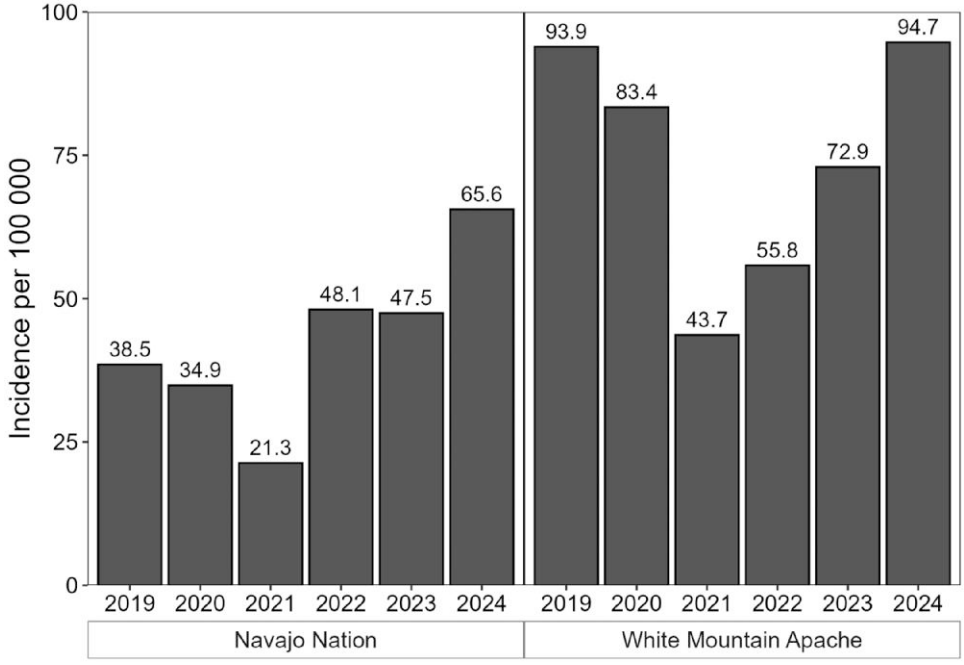

Figure 1 Age-standardized incidence of invasive pneumococcal disease by year, Navajo Nation and White Mountain Apache Tribal lands, January 2019–December 2024.

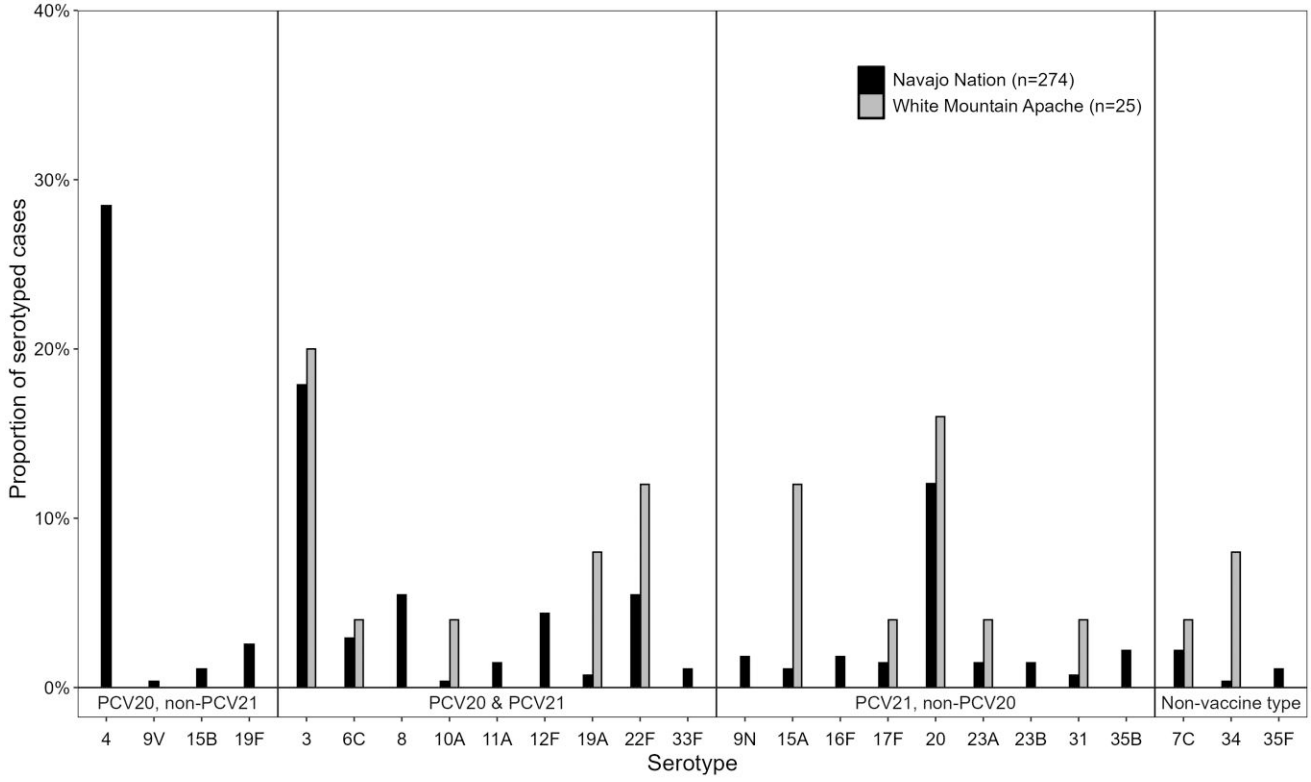

Figure 2. Serotype distribution of invasive pneumococcal disease among adults aged ≥18 years, Navajo Nation and White Mountain Apache Tribal lands, January 2022–December 2024. Abbreviations: PCV20, 20-valent pneumococcal conjugate vaccine; PCV21, 21-valent pneumococcal conjugate vaccine.

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there was variation by age, with a lower proportion of serotypes included in PCV21 than PCV20 among adults aged 18–49 years (53.2% vs 77.3%; $P < .001$), the same proportion among adults aged 50–64 years (68.6%; $P = 1$), and a higher proportion among adults aged ≥65 years (82.5% vs 65.1%; $P = .03$) (Figure 3).

Among adults in the WMAT lands, serotypes 3 (n = 5 [20.0%]), 20 (n = 4 [16.0%]), and 22F (n = 3 [12.0%]) were most common; no cases of serotype 4 were identified (Figure 2). Most IPD cases were caused by serotypes included in PCV20 and PCV21 (Figure 3), with a higher proportion of serotypes included in PCV21 than PCV20 among adults aged 18–49 years (94.1% vs 41.2%; $P = .004$), and similar proportions among adults aged 50–64 years (80.0% vs 80.0%; $P = 1$) and ≥65 years (66.7% vs 33.3%; $P = 1$).

Serotype 4 IPD in the Navajo Nation Among Adults, 2010–2024

All-serotype, PCV20-type, and PCV21-type IPD rates among adults in the Navajo Nation were stable from 2010 to 2019 (Figure 4). As previously reported [9], rates then decreased during the pandemic before increasing and exceeding pre-pandemic levels. The largest increases were observed among adults aged 18–49 years and were driven by increases in serotype 4. Serotype 4 was rare from 2010 to 2019 (Supplementary Figure 2), and then increased to cause 2.6%–4.8% of IPD in 2020–2021 and 22.9%–32.9% in 2022–2024.

Among recent (2019–2024) cases with available serotypes (n = 448), serotype 4 cases (n = 83 [18.5%]) occurred among younger adults (median age, 40 vs 56 years; $P < .001$) and had a different geographic distribution, with nearly half occurring in a single site ($P < .001$) (Table 2). Serotype 4 cases were more likely to present with pneumonia (95.2% vs 78.4%; $P < .001$) and had shorter hospital stays (median: 3 vs 5 days; $P = .002$). Alcohol abuse (68.3% vs 37.7%; $P < .001$), tobacco use (28.0% vs 12.1%; $P < .001$), and injection drug use (6.1% vs 1.1%; $P = .013$) were more common among serotype 4 cases, while diabetes (17.3% vs 46.7%; $P < .001$), malignancy (1.2% vs 8.5%; $P = .02$), immunosuppressive therapy (0% vs 9.4%; $P = .02$), and renal failure/dialysis (2.5% vs 9.6%; $P = .02$) were less common.

Among adults aged 18–49 years and 50–64 years, 77.8% and 80.0% of serotype 4 cases, respectively, had at least 1 risk-based indication for vaccination, with alcohol abuse the most common (Figure 5). However, only 15.9% (n = 10) of adults aged 18–49 years experiencing serotype 4 IPD had received any dose of a pneumococcal vaccine, with the last dose received a median of 6 years before the IPD episode. Vaccination was also low among adults 50–64 years (37.5% [n = 6]) with the last dose received a median of 20 years before the IPD episode. All serotype 4 cases among adults aged ≥65 years (n = 4) had received a dose of pneumococcal vaccine a median of 12 years before the IPD episode.

Most serotype 4 sequence types (STs) from 2010 to 2024 were ST10172 (75/86 [87.2%]) (Supplementary Figure 3). Four of the remaining isolates were single-locus variants of ST10172 (2 differed at the recP allele [ST18763] and 2 at the spi allele [ST19001]). Serotype 4 isolates collected between 2023 and 2024 were susceptible to most antibiotics (Supplementary Table 2) but intermediate resistance to trimethoprim-sulfamethoxazole was detected in 94% (n = 51/54). Other serotypes from this time frame did not exhibit trimethoprim-sulfamethoxazole nonsusceptibility to the same extent (10% intermediate or resistant; n = 15/150).

DISCUSSION

In this study conducted in 2 AI communities in the US Southwest, IPD rates have returned to pre-pandemic levels and are higher than IPD rates for the general US population. Compared to the 2023 IPD rate in the general US population (9.9/100 000) [14], the 2024 age-standardized incidence rates in the Navajo Nation (65.6/100 000) and WMAT (94.7/100 000) remain 7–10 times higher [14]. While few cases occurred among children, cases among adults increased since 2021 when they reached the lowest number recorded since surveillance began in the 1990s [10]. In the Navajo Nation, but not the WMAT, the increase was driven by a surge in serotype 4 IPD primarily among younger male unvaccinated adults. These findings are important for informing vaccine recommendations and practice and highlight the value of surveillance in understanding the local epidemiology of IPD over time.

An increase in serotype 4 IPD was also reported in other parts of the US [5], Canada, and Europe. CDC reported an upsurge of serotype 4 IPD in ABCs sites in New Mexico, Colorado, and California from 2010 to 2022, with cases primarily occurring among PEH [15, 16]. In 2019–2020, Alaska reported an increase in serotype 4 cases compared to 2011–2018, particularly among AN individuals and PEH [22]. In 2022–2023, El Paso County, Colorado, reported a cluster of serotype 4 cases among PEH [23]. Over the same time frame, Alberta reported an increase in serotype 4 cases, primarily among PEH and people who inject drugs, use alcohol, and smoke [24]. A post-pandemic surge in Calgary, Alberta, was reported to be predominantly due to serotype 4 [25], and across Canada in 2021–2022, serotype 4 was the most common serotype, particularly among adults 18–49 years old [26]. In Europe, pre-pandemic outbreaks of serotype 4 were observed in shipyard workers in Northern Ireland in 2015, Norway and Finland in 2019, and France in 2020 [27]. Since the pandemic, more generalized increases in serotype 4 were observed in Belgium [28], the Netherlands [29, 30], Germany [31], Spain [32], and the United Kingdom [33], all primarily among younger adults.

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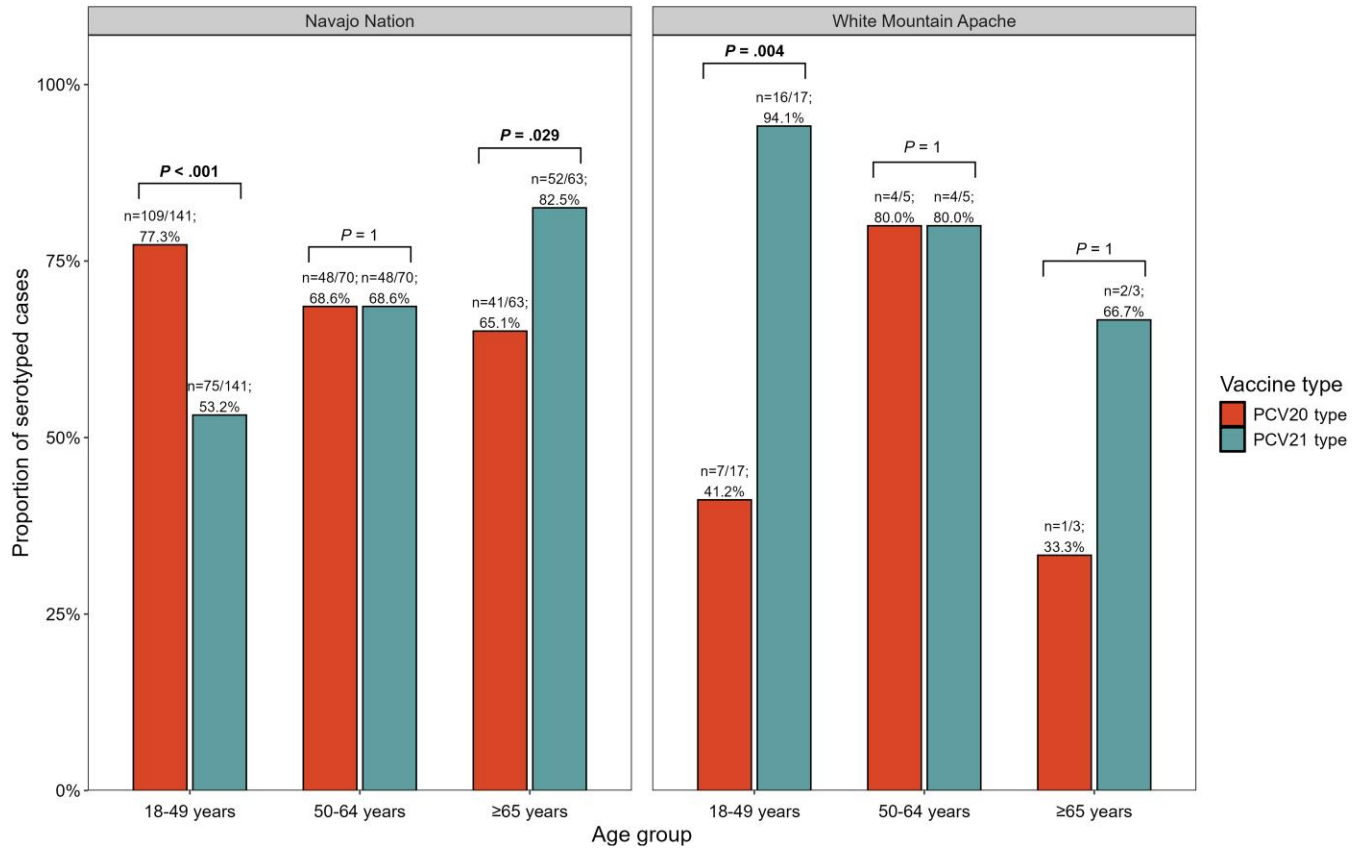

Figure 3. Proportion of invasive pneumococcal disease among adults aged ≥18 years caused by vaccine serotypes, Navajo Nation and White Mountain Apache Tribal lands, January 2022–December 2024. *P* values were computed using either McNemar χ^2 tests or exact McNemar tests as appropriate. Abbreviations: PCV20, 20-valent pneumococcal conjugate vaccine; PCV21, 21-valent pneumococcal conjugate vaccine.

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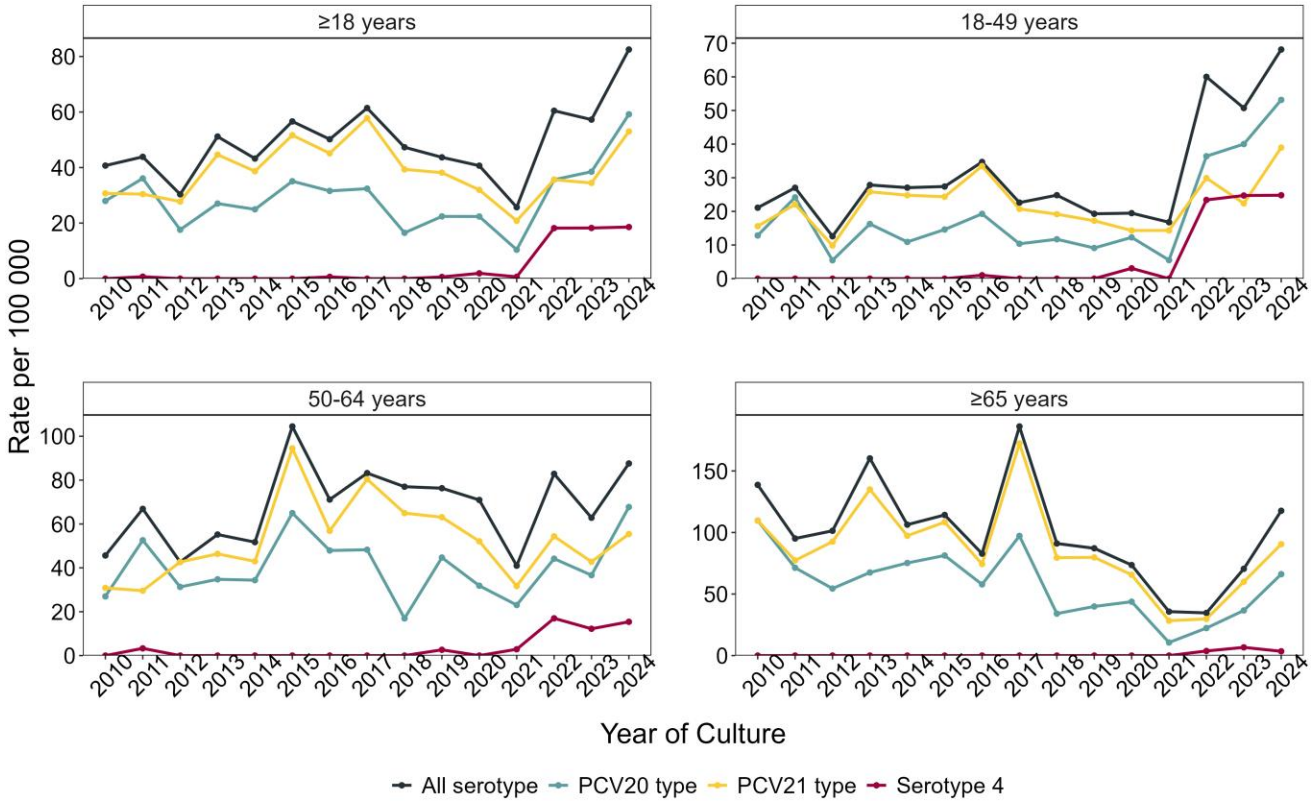

Figure 4. Incidence of invasive pneumococcal disease among adults, Navajo Nation, January 2010–December 2024. Abbreviations: PCV20, 20-valent pneumococcal conjugate vaccine; PCV21, 21-valent pneumococcal conjugate vaccine.

Before the surge, the 2 cases in 2011 in the Navajo Nation were ST205, consistent with one of the STs associated with outbreaks in Europe [27]. Starting in 2019, ST10172 was predominant in the Navajo Nation, aligning with the emergence and expansion of ST10172 in the western US [15, 16]. During 2021–2022, ST10172 was the most common lineage of serotype 4 IPD that ABCs detected among PEH [16]. Genomic analysis found that serotype 4 isolates exhibited high clustering, particularly by geography (isolates from Colorado and New Mexico were predominantly ST10172, whereas isolates from California were predominantly ST695) and among PEH [34]. In contrast, the uptick in serotype 4 IPD in Alberta was primarily ST244, with some ST205 and ST695. STs were available from some post-pandemic studies in Europe, with ST801 common in Belgium (also ST15063, ST205, ST1022, ST13753) [28], ST15063 common in the Netherlands [30], and ST801 and ST15063 common in the United Kingdom [33]. Further work to characterize the serotype 4 isolates since this surveillance platform's establishment will show how the pathogen has changed over time and the relationships between serotype 4 isolates found in different settings.

Consistent with the uptick in the Navajo Nation, the increase in serotype 4 IPD observed in many other settings was primarily among vulnerable populations characterized by younger age and exposure to factors including poverty, crowded or unstable living conditions, and poor access to water and healthcare [15, 16, 22–24], which are associated with increased risk of pneumococcal disease [35]. These conditions create an environment conducive to circulation of pathogens and progression to severe disease once infected, thus contributing to the overall higher rates of pneumococcal disease in these communities, and potentially to a surge in disease if a novel or successful pathogen is introduced.

The available genomic data suggest that changes in the pathogen may have played a role in the recent surge in serotype 4 IPD, with emergence of new STs in several geographic areas. The dominant type in the Navajo Nation, ST10172, was first observed in the ABCs program in 2013 and suspected to be a recent emergence of a serotype switch variant [15]. Further work is needed to understand the characteristics of this new ST, particularly if its features lead to higher virulence. The predominance of disease among younger adult males suggests that a potential immunity gap in this group may have also played a role. Serotype 4 was included in all licensed pneumococcal vaccines; however, younger adults may be too old to have received PCV7 when introduced in 2000 and currently too young for

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Table 2. Characteristics of Cases of Invasive Pneumococcal Disease Among Adults Aged ≥18 Years, Serotype 4 Versus Non–Serotype 4, Navajo Nation, January 2019–December 2024

Characteristic	Non–Serotype 4	Serotype 4	*P* Value[a]
Total No.	365	83	
Age, y, median (IQR)	56 (44–68)	40 (33–49)	<.001
Age group			
18–49 y	131 (35.9)	63 (75.9)	<.001
50–64 y	121 (33.2)	16 (19.3)	
≥65 y	113 (31.0)	4 (4.8)	
Sex			
Female	138 (37.8)	23 (27.7)	.084
Male	227 (62.2)	60 (72.3)	
Site			
A	57 (15.6)	16 (19.3)	<.001
B	6 (1.6)	1 (1.2)	
C	42 (11.5)	11 (13.3)	
D	92 (25.2)	41 (49.4)	
E	13 (3.6)	3 (3.6)	
F	99 (27.1)	7 (8.4)	
G	44 (12.1)	4 (4.8)	
H	1 (0.3)	0 (0.0)	
I	11 (3.0)	0 (0.0)	
Clinical syndromes[b]			
Meningitis	2 (0.5)	0 (0.0)	>.9
Pneumonia	286 (78.4)	79 (95.2)	<.001
Bacteremia without focus	6 (1.6)	1 (1.2)	>.9
Sepsis	196 (53.7)	46 (55.4)	.8
Concurrent COVID-19 (within 30 d)	31 (10.9)	3 (3.9)	.061
Peritonitis	4 (1.1)	0 (0.0)	>.9
Cellulitis	7 (1.9)	1 (1.2)	>.9
Osteomyelitis	1 (0.3)	1 (1.2)	.3
Septic arthritis	3 (0.8)	0 (0.0)	>.9
Streptococcal toxic shock syndrome	2 (0.5)	0 (0.0)	>.9
Data unavailable	4 (1.1)	0 (0.0)	>.9
Hospitalized			
Yes	320 (87.7)	77 (92.8)	.12
No	44 (12.1)	5 (6.0)	
Unknown	1 (0.3)	1 (1.2)	
Number of days hospitalized, median (IQR)	5.0 (3.0–8.0)	3.0 (2.0–6.0)	.002
Case fatality, overall[c]	56 (16.6)	5 (6.9)	.036
Case fatality among hospitalized patients[c]	44 (14.8)	5 (7.4)	.1
Residence 4 d prior to illness			
Private residence	327 (89.6)	69 (83.1)	.003
Long-term care facility	1 (0.3)	0 (0.0)	
Hospital inpatient	1 (0.3)	0 (0.0)	
Experiencing homelessness	9 (2.5)	7 (8.4)	
Substance abuse treatment center	1 (0.3)	1 (1.2)	
Incarcerated	0 (0.0)	3 (3.6)	
Unknown	26 (7.1)	3 (3.6)	
At least 1 chronic medical conditions[d]	287 (79.1)	63 (76.8)	.7
Alcohol abuse	137 (37.7)	56 (68.3)	<.001
Asthma	35 (9.6)	7 (8.6)	.8
Cirrhosis/liver failure	54 (14.9)	6 (7.3)	.069
Heart failure/CHF	41 (11.3)	6 (7.3)	.3
Emphysema/COPD	15 (4.1)	2 (2.4)	.7
Diabetes	169 (46.7)	14 (17.3)	<.001
Current smoker	44 (12.1)	23 (28.0)	<.001

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Table 2. Continued

Characteristic	Non–Serotype 4	Serotype 4	*P* Value[a]
At least 1 immunocompromising conditions[e]	42 (11.7)	5 (6.1)	.14
Immunosuppressed without the presence of an immunocompromising condition[e] (subset of the above)	17 (4.7)	0 (0.0)	.052
Renal failure/dialysis	35 (9.6)	2 (2.5)	.035
Injection drug use	4 (1.1)	5 (6.1)	.013
≥1 risk-based indications for vaccination (not including age)[f]	301 (82.7)	63 (76.8)	.2
≥2 risk-based indications for vaccination (not including age)[f]	172 (47.3)	39 (47.6)	>.9
Received at least 1 dose of pneumococcal vaccine[g]			
18–49 y	46 (36.8)	10 (16.4)	.006
≥50 y	174 (77.0)	10 (52.6)	.026
Type(s) of vaccine received[h]			
Both PPSV23 and other PCV	92 (25.2)	3 (3.6)	<.001
Both PPSV23 and PCV7	4 (1.1)	0 (0.0)	
PPSV23 only	110 (30.1)	15 (18.1)	
PCV7 only	1 (0.3)	1 (1.2)	
Other PCV only	12 (3.3)	1 (1.2)	
Unknown vaccine received	1 (0.3)	0 (0.0)	
None	131 (35.9)	60 (72.3)	
Unknown vaccination status	14 (3.8)	3 (3.6)	
Years since last dose, median (IQR)	6 (2–10)	9 (4–17)	.023

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; d, days; IQR, interquartile range; No., number; PCV, pneumococcal conjugate vaccine; PCV7, 7-valent pneumococcal conjugate vaccine; PPSV23, 23-valent pneumococcal polysaccharide vaccine; y, years.

[a]Wilcoxon rank-sum test; Pearson χ^2 test; Fisher exact test.

[b]Syndromes are not mutually exclusive.

[c]Outcome determined by status of patient within 30 days of hospital discharge, emergency department visit, or outpatient visit associated with collection of invasive *Streptococcus pneumoniae* isolate. Percentages are among individuals with available data. Data were not available for 11 serotype 4 cases (n = 9/11 hospitalized) and 27 non–serotype 4 cases (n = 22/27 hospitalized).

[d]Chronic conditions include alcohol abuse, asthma, liver failure/cirrhosis, heart failure/CHF, emphysema/COPD, diabetes mellitus, and tobacco use.

[e]Immunocompromising conditions include organ transplant, immunodeficiency, HIV/AIDS, and malignancy.

[f]Risk-based indications for vaccination include both chronic and immunocompromising conditions. Age-based indications are not included.

[g]Percentages are among individuals with available data on vaccination status. Vaccination history was unknown for 6 adults aged 18–49 years and 8 aged ≥50 years within the non–serotype 4 category as well as 2 adults aged 18–49 years and 1 aged ≥50 years who had a serotype 4 isolate.

[h]Among serotype 4 cases, adults aged 18–49 years accounted for PPSV23 only, n = 7; PPVS23 and other PCV, n = 2; other PCV only, n = 1. Adults aged 50–64 years received PPSV23 only, n = 5; PCV7 only, n = 1. Adults aged ≥65 years received PPSV23 only, n = 3; PPVS23 and other PCV, n = 1.

age-based recommendations for older adults [5, 36]. While many IPD cases in the Navajo Nation were vaccine-eligible based on risk conditions, only a small proportion were vaccinated. Reasons for not being vaccinated are unknown in this study but may include lack of engagement in the healthcare system, which is more common among younger men [37], missed opportunities at clinic visits potentially from gaps in provider knowledge about risk factor–based pneumococcal vaccine recommendations [38], or low uptake of the vaccine when offered. All of these factors may have played a role in the observed increases of serotype 4 IPD, with emergence or introduction of a novel strain into a vulnerable and susceptible population and subsequent transmission within these communities. Increases in these disadvantaged communities may serve as an early warning signal for the general population, as observed in Canada with serotype 4 rising to become the most common serotype nationwide in 2021–2022 [26].

The increase in serotype 4 IPD has implications for vaccine policy and recommendations. The surge among younger unvaccinated adults highlights the importance of promoting vaccine uptake and addressing barriers to vaccination. This could include messaging tailored to younger adults and using platforms that reach these age groups as well as healthcare provider education, materials to decrease missed vaccination opportunities, and ensuring accessible healthcare services. The surge in serotype 4 highlights the importance of understanding circulating serotypes to optimize vaccine product recommendations. While serotype 4 is included in PCV15 and PCV20, it is not included in PCV21 [5]. The Advisory Committee on Immunization Practices recommendations for adults available at the time of this writing suggested that PCV20 alone or PCV15 in combination with PPSV23 would provide broader protection in areas where serotype 4 causes a high proportion (≥30%) of disease [5]. The current findings suggest that even in those areas, the optimal product may vary by age group, with older adults (eg, ≥65 years) receiving broader protection from PCV21 and younger adults from PCV15 (followed by PPSV23) or PCV20. Belgium may provide a helpful model given its recent age stratification of adult pneumococcal vaccine recommendations, with PCV20 recommended for adults

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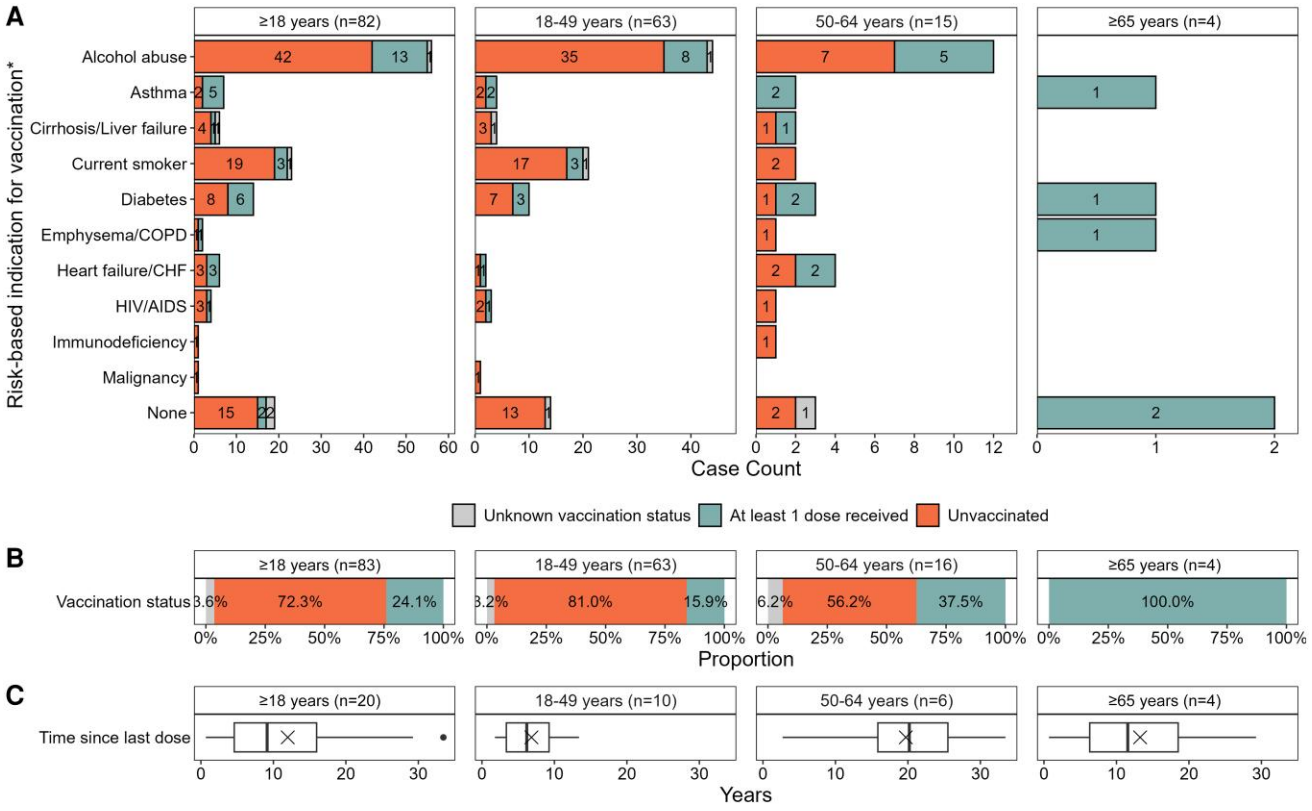

Figure 5. Risk-based indications for pneumococcal vaccination (*A*), vaccination status (*B*), and time since last dose of pneumococcal vaccine (*C*) among adults aged ≥18 years with serotype 4 invasive pneumococcal disease, Navajo Nation, January 2019–December 2024. *Risk-based indications for pneumococcal vaccination are not mutually exclusive and include alcohol abuse, asthma, liver failure/cirrhosis, heart failure/congestive heart failure (CHF), emphysema/chronic obstructive pulmonary disease (COPD), diabetes mellitus, tobacco use, organ transplant, immunodeficiency, immunosuppressive therapy, human immunodeficiency virus (HIV)/AIDS, and malignancy. Age-based indications are not included. Panel *C* shows horizontal boxplots where the box denotes the interquartile range, the vertical line denotes the median, and the "X" denotes the mean.

aged 18–49 years with risk conditions [39]. The findings also highlight geographic variation even for similar communities, as serotype 4 was not found in the WMAT lands. While we do not have population level adult pneumococcal vaccine coverage data for the Navajo Nation and WMAT, a higher proportion of younger adults with IPD in WMAT lands had previously received a serotype 4–containing pneumococcal vaccine, suggesting that higher vaccine uptake may have prevented circulation of serotype 4 in this community. Given ongoing circulation of serotype 4 in the western US, there is no single vaccine that provides optimal protection for all communities and age groups. The findings from this study may also suggest that 1 dose of pneumococcal vaccine may not be sufficient to confer lifelong protection against IPD, as 16%–100% of adults with serotype 4 IPD across age groups had received a dose of pneumococcal vaccine a median of 6–20 years prior to their illness. This is consistent with findings from other pediatric and adult studies. A small study in rural Alaska found that 36% of adults with chronic diseases receiving PPSV23 a mean of 7.4 years prior had similar antibody levels to unvaccinated adults [40]. A pooled analysis of pediatric carriage studies found that overall vaccine efficacy of PCV against PCV7-type carriage was maintained 5 years after the last dose, but that the rate at which efficacy waned varied by serotype, with some serotypes, including serotype 4, projected to have 0% efficacy within 4–6 years [41]. These findings suggest that adults with risk conditions or in communities with a high burden of disease may benefit from a booster dose of PCV as they age and from combination vaccination regimens (eg, PCV15 or PCV20 plus PCV21), at least until vaccines are available that protect against all leading serotypes.

In summary, IPD rates in 2 AI communities in the Southwest increased since the COVID-19 pandemic and remain higher than in the US general population. Increases in 1 community were driven by serotype 4, primarily among younger male unvaccinated adults, a finding observed in other western states, Canada, and European countries, with implications for vaccine recommendations and policies. Maintaining a long-standing IPD surveillance platform in these communities has provided critical insight into the high IPD burden, impact of vaccine

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introduction, and now the changing epidemiology of IPD. Given its broad utility and timely data, continued bacterial surveillance should be prioritized in these communities.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online (http://jid.oxfordjournals.org/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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Data availability. Participant data collected on tribal lands are owned by the participating Tribal Nations. Data can be made available upon request to the corresponding authors if consistent with the IRB-approved protocol and if the disclosure is approved by the participating Tribes.

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