High Burden of *Staphylococcus aureus* Among Native American Individuals on the White Mountain Apache Tribal Lands

Catherine G. Sutcliffe,1,2 Lindsey R. Grant,3 Angelina Reid,4 Grace Douglass,4 Laura B. Brown,5 Kamellia Kellywood,6 Robert C. Weatherholtz,7 Robin Hubler,8 Alvaro Quintana,9 Ryan Close,10,11 James B. McAuley,12,13 Mathuram Santosham,14 Katherine L. O’Brien,15 and Laura L. Hammitt16

1Center for American Indian Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA, 2Center for American Indian Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA, 3Center for American Indian Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA, 4Center for American Indian Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA, 5Center for American Indian Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA, 6Center for American Indian Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA, 7Center for American Indian Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA, 8Pfizer Vaccine Medical Development, Scientific and Clinical Affairs, Collegeville, Pennsylvania, USA, 9Pfizer Vaccine Medical Development, Scientific and Clinical Affairs, Collegeville, Pennsylvania, USA, 10Whiteriver Service Unit, Indian Health Service, Whiteriver, Arizona, USA, 11Pfizer Vaccine Medical Development, Scientific and Clinical Affairs, Collegeville, Pennsylvania, USA, 12Whiteriver Service Unit, Indian Health Service, Whiteriver, Arizona, USA, 13Rush Medical College, Rush University, Chicago, Illinois, USA, 14Center for American Indian Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA, 15Center for American Indian Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA, 16Center for American Indian Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA. 

**Background.** This study was done to determine the burden of invasive *Staphylococcus aureus* on the White Mountain Apache Tribal lands.

**Methods.** Active population and laboratory-based surveillance for invasive *S* aureus infections was conducted from May 2016 to April 2018. A case was defined as a Native American individual living on or around the White Mountain Apache Tribal lands with *S* aureus isolated from a normally sterile body site.

**Results.** Fifty-three cases were identified. Most cases were adults (90.6%) and had ≥1 underlying medical condition (86.8%), the most common of which were diabetes (49.1%) and obesity (41.5%). A total of 26.4% cases were categorized as community acquired. Most infections were methicillin-resistant (75.5%). A total of 7.5% of cases required amputation, and 7.7% of cases died within 30 days of initial culture. The incidence of invasive *S aureus* was 156.3 per 100 000 persons. The age-adjusted incidence of invasive methicillin-resistant *S aureus* was 138.2 per 100 000 persons.

**Conclusions.** This community has a disproportionately high burden of invasive methicillin-resistant *S aureus* compared with the general US population. Interventions are urgently needed to reduce the morbidity and mortality associated with these infections.

**Keywords.** invasive bacterial infections; MRSA; Native Americans; surveillance.

In the United States, *Staphylococcus aureus* is a cause of significant morbidity due to both mild infections, such as skin and soft tissue infections, and severe infections, such as pneumonia and necrotizing fasciitis. Infections caused by methicillin-resistant *S aureus* (MRSA) are of particular concern because they are harder to treat and they are no longer limited to healthcare settings [1]. In 2017, there were an estimated 119 247 cases and 19 832 deaths due to *S aureus* bloodstream infections in the United States [2]. *Staphylococcus aureus* and MRSA infections are also associated with significant costs to the healthcare system and to patients and their families [3].

Native American populations experience higher levels of morbidity and mortality from infectious diseases compared with the general population [4, 5], including from invasive bacterial infections [6, 7]. Native Americans may be at higher risk for *S aureus* infections due to the high prevalence of risk factors for *S aureus* [8], such as diabetes and other comorbid health conditions [9]. Although recent studies have evaluated racial disparities in invasive MRSA infections by comparing rates between black and white populations [10, 11], less is known about the burden of disease and potential disparities among Native Americans. From 1996 to 2005, rates of MRSA hospitalization at Indian Health Service (IHS) facilities were increasing across all regions of the United States, with particularly large increases observed in Alaska, the Southern Plains, and the Southwest [12]. The age-adjusted rates of MRSA hospitalization in 2003–2005 were below or comparable to the general US population for most IHS regions [12], but it is unknown whether hospitalization rates continued to increase after 2005. Recent data from
the Navajo Nation and the state of Arizona suggest that Native Americans in the Southwestern United States are currently disproportionately affected by invasive MRSA infections [13, 14].

This study was undertaken to provide current, robust estimates of the incidence of invasive S aureus and MRSA infections among Native Americans on the White Mountain Apache (WMA) Tribal lands in the Southwest United States, with the goal of informing strategies to reduce the burden of disease.

METHODS

Ethics Statement
This study was approved by the White Mountain Apache Tribe and by the Phoenix Area IHS, National IHS, and Johns Hopkins Bloomberg School of Public Health Institutional Review Boards. A Health Insurance Portability and Accountability Act (HIPAA) waiver was obtained to conduct medical chart reviews.

Setting
This study was conducted on the WMA Tribal lands, which cover an area of 2600 square miles in eastern Arizona, United States, with a population of approximately 17 000 Tribal members. The population is served by one main IHS facility that provides inpatient and outpatient care and a smaller IHS outpatient clinic. A private health facility, with inpatient and outpatient services, also serves Tribal members and is located approximately 15 miles from the border of the WMA Tribal lands.

Active Bacterial Surveillance
Active, laboratory and population-based surveillance for invasive S aureus began on May 1, 2016. The Center for American Indian Health at the Johns Hopkins Bloomberg School of Public Health has been conducting active surveillance for Streptococcus pneumoniae, Haemophilus influenzae, and Neisseria meningitidis on the WMA Tribal lands and Navajo Nation for more than 20 years [15]. The protocol and procedures for the surveillance system are modeled on the Active Bacterial Core Surveillance system operated by the Centers for Disease Control and Prevention. Clinical microbiology laboratories at the IHS hospital and private facility serving WMA residents were contacted at least weekly to identify cases of invasive S aureus. Monthly (IHS facility) and quarterly (private facility) audits were also conducted to identify cases that may have been missed. Isolates were sent to the study laboratory in Whiteriver, Arizona where they were confirmed using BBL CHROMagar Staph aureus (Franklin Lakes, NJ). For each case, a chart review was conducted to collect information on case demographics, underlying medical conditions, clinical syndrome, antimicrobial resistance test results, and health outcomes.

Case Definition
A case of invasive S aureus infection was defined as a Native American individual living in a community on or around the WMA Tribal lands with S aureus isolated from a normally sterile body site (eg, blood, cerebrospinal fluid, pleural fluid, synovial fluid, deep tissue). Individuals may have contributed isolates from different body sources on the same day (counted as a single case) or isolates collected on different days. Individuals with isolates collected <7 days after the initial culture were considered part of the same case. Individuals with isolates collected 7–29 days after the initial date of culture were considered persistent cases, and all isolates were considered part of the same case event. For individuals with isolates from a specimen collected at least 30 days after the initial date of culture, the subsequent isolate defined a new case event and was defined as a recurrent case.

Other Definitions
Years 1 and 2 of surveillance were defined as isolates collected between May 1, 2016 and April 30, 2017 and between May 1, 2017 and April 30, 2018, respectively. Infections were defined as (1) hospital-onset (HO) when isolates were obtained from specimens collected >3 days after admission (with day of admission being day 1), (2) healthcare-associated community-onset (HACO) if cases had a healthcare risk factor (dialysis, surgery, hospitalization, or long-term care in the past year, or vascular catheter in the past 2 days) and isolates were obtained from specimens collected before or ≤3 days after hospital admission, or (3) community-associated (CA) for all other cases.

Disease syndromes associated with the invasive S aureus infection were defined based on the physician-reported syndrome in the medical record and the source of the isolate. Cases could have multiple syndromes reported.

Underlying medical conditions were documented based on medical record review (obesity additionally defined as present if body mass index ≥30). The Charlson Index, a measure of comorbidity, was calculated based on underlying conditions and age [16].

Statistical Analysis
Characteristics of cases were described overall and by year of collection, infection type, and antimicrobial resistance. Comparisons were made using Fisher’s exact tests for categorical variables and Wilcoxon rank-sum tests for continuous variables.

Outcomes evaluated included hospitalization during the case event, amputation at or within 30 days after the initial culture, and death within 30 days after the initial culture. Outcomes were compared by year of collection, infection type, and antimicrobial resistance using Fisher’s exact tests.

Incidence rates of invasive S aureus were calculated using the IHS User Population from 2016 and 2017 as the denominator for Years 1 and 2, respectively. “Users” are defined as Native Americans receiving services at the IHS facility in the preceding 3 years [17]. For each year, incidence was calculated overall, by
RESULTS

From May 2016 to April 2018, 53 cases of invasive *S aureus* were documented, including 24 in Year 1 and 29 in Year 2. The 53 cases occurred among 48 individuals; 3 individuals had 1 recurrent infection and 1 individual had 2 recurrent infections during the 2-year study period.

Characteristics of Cases and Isolates

Fifty-five isolates were collected from the 53 cases. Isolates were collected from blood (85.5%, 47 of 55), deep tissue (5.5%, 3 of 55), cerebrospinal fluid (3.6%, 2 of 55), bone (3.6%, 2 of 55), and synovial fluid (1.8%, 1 of 55).

The characteristics of cases are presented in Table 1. Most cases were adults (90.6%, 48 of 53; median age, 47.4 years; age range, 5.8–74.2) and had at least 1 underlying condition (86.8%, 46 of 53), with the most common being diabetes (49.1%, 26 of 53), alcoholism (43.4%, 23 of 53), and obesity (41.5%, 22 of 53). The median Charlson index was 2 (range, 0–9). Most cases were categorized as HACO (71.7%, 38 of 53). For HACO cases hospitalized in the year before the case event (n = 36), the median time between the last discharge and the case event was 11.7 weeks (interquartile range [IQR], 2.5–25.3; minimum, maximum: 0.1–47.1). For the HO case (1.9%, 1 of 53), the time between hospital admission and the date of invasive *S aureus* was 7 days. The most common disease syndromes associated with the invasive *S aureus* infection were bloodstream infections with other focus (73.6%, 39 of 53), osteomyelitis (37.7%, 20 of 53), and cellulitis or abscess (30.2%, 16 of 53). Most *S aureus* infections were MRSA (75.5%, 40 of 53). More than half of cases had had prior *S aureus* infections (58.5%, 31 of 53), and most of these prior infections were MRSA (80.6%, 25 of 31). All cases were living in a private residence at the time of the infection. There were no significant differences in the characteristics of cases by year of surveillance.

By type of infection, the HO case differed significantly from the HACO and CA cases: the case was significantly younger, had a lower Charlson Index, and was a surgical site infection (Supplemental Table 1). There were no significant differences in cases by antibiotic susceptibility (Supplemental Table 1).

Outcomes Among Cases

Most cases were hospitalized (88.7%, 47 of 53), and the median duration of hospitalization was 9 days (IQR, 7–20; range, 2–53). For 7.5% (4 of 53) of cases, the *S aureus* infection was associated with or resulted in amputation of toes or feet. Cases requiring amputation (n = 4) were significantly more likely to have diabetes as an underlying condition and osteomyelitis as a disease syndrome (Supplementary Table 2). A total of 7.7% of cases (4 of 52) died a median of 9 days (IQR, 5–15; range, 2–20) after the initial date of culture. Cases who died (n = 4) were significantly more likely to have myocardial infarction as an underlying condition and a bloodstream infection with an implant involved (Supplementary Table 2). No significant differences in outcomes were found by type of infection or antibiotic susceptibility (Supplemental Table 1).

Annual Incidence

The overall incidence of invasive *S aureus* was 156.3 (95% confidence interval [CI], 119.4–204.5) with no significant difference in the incidence by year (Year 1: 141.5 per 100 000 persons; Year 2: 171.1 per 100 000 persons; incidence rate ratio: 1.21; 95% CI, 0.70–2.08). The overall incidence of invasive MRSA was 118.0 per 100 000 persons (95% CI, 86.5–160.8) with no significant difference by year (Year 1: 106.1 per 100 000 persons; Year 2: 129.8 per 100 000 persons; incidence rate ratio: 1.22; 95% CI, 0.66–2.28). The incidence of invasive *S aureus* and MRSA increased with age and was highest among individuals 50–64 years of age (Table 2). By type of infection, the incidence of invasive *S aureus* and MRSA was highest for HACO and lowest for HO. The overall age-adjusted incidence of invasive MRSA was 138.2 per 100 000 persons (Year 1: 125.2; Year 2: 150.9 per 100 000).

DISCUSSION

This study provides the first population- and laboratory-based estimate of invasive *S aureus* disease among Native Americans on the WMA Tribal lands. The observed age-adjusted incidence of MRSA (138.2 per 100 000 persons) was over 7 times higher than that reported for the general US population in 2015 (18.8 per 100 000 persons) [18]. The incidence was also much higher than that observed among Native Americans on the Navajo Nation (21.2 per 100 000 persons) using the same laboratory-based surveillance system and reported by health facilities to the Arizona Department of Health Services (15.2 per 100 000) over the same time period [13, 14]. Invasive *S aureus* infections led to significant morbidity, including hospitalization, amputation, and death. This represents an important health disparity, the magnitude of which was heretofore unrecognized.

Similar to other communities in the United States, most cases of invasive *S aureus* occurred among adults with underlying health conditions, with diabetes being most common [13, 20]. However, the pattern by age group was different in this community, with the proportion of cases and incidence rates highest among adults 18–64 as opposed to adults 65 years of age and older [13, 18, 20, 21], potentially due to a higher prevalence of
risk factors at younger ages, as has been observed among Native American populations in the United States [22, 23]. The proportion of cases that were MRSA in this study (75.0%) was much higher than in other settings, although direct

Table 1. Characteristics of Cases of Invasive Staphylococcus aureus Disease, May 2016–April 2018

| Characteristic | Year 1 (05/16–04/17) | Year 2 (05/17–04/18) | Total (05/16–04/18) |
|---------------|-----------------------|-----------------------|----------------------|
| Number of cases | 24 (95.8) | 29 (75.9) | 53 (82.8) |
| Demographic Characteristics | | | |
| Male | 15 (62.5) | 20 (69.0) | 35 (66.0) |
| Age | | | |
| <1 year | 0 | 0 | 0 |
| 1–17 years | 2 (8.3) | 310.3 | 5 (9.4) |
| 18–39 years | 6 (25.0) | 9 (31.0) | 15 (28.3) |
| 40–49 years | 5 (20.8) | 6 (20.7) | 11 (20.8) |
| 50–64 years | 10 (41.7) | 10 (34.5) | 20 (37.7) |
| ≥65 years | 1 (4.2) | 1 (3.4) | 2 (3.8) |
| Body mass indexa | | | |
| <25 | 3 (13.6) | 6 (25.0) | 9 (19.6) |
| 25–29 | 7 (31.8) | 8 (33.3) | 15 (32.6) |
| ≥30 | 12 (54.5) | 10 (41.7) | 22 (47.8) |
| Type of infection | | | |
| HO | 0 (0.0) | 1 (3.4) | 1 (1.9) |
| HACO | 15 (62.5) | 23 (79.3) | 38 (71.7) |
| CA | 9 (37.5) | 5 (17.2) | 14 (26.4) |
| Healthcare and Clinical Characteristics | | | |
| Healthcare Exposures | | | |
| Dialysis in past year | 2 (8.3) | 1 (3.4) | 3 (6.7) |
| Surgery in past year | 6 (25.0) | 13 (44.8) | 19 (35.8) |
| Hospitalized in past year | 14 (58.3) | 22 (75.9) | 36 (67.9) |
| Long-term care in past year | 3 (12.5) | 4 (13.8) | 7 (13.2) |
| Vascular catheter in past 2 days | 1 (4.2) | 2 (6.9) | 3 (5.7) |
| Underlying Conditionsb | | | |
| Diabetes | 12 (50.0) | 14 (48.3) | 26 (49.1) |
| Alcoholism | 11 (45.8) | 12 (41.4) | 23 (43.4) |
| Obesity | 12 (50.0) | 10 (34.5) | 22 (41.5) |
| Hypertension | 5 (20.8) | 10 (34.5) | 15 (28.3) |
| Abscess/boil | 4 (16.7) | 3 (10.3) | 7 (13.2) |
| Chronic skin breakdown | 1 (4.2) | 6 (20.7) | 7 (13.2) |
| Chronic renal insufficiency | 2 (8.3) | 4 (13.8) | 6 (11.3) |
| Malignancy | 2 (8.3) | 3 (10.3) | 5 (9.4) |
| Asthma | 3 (12.5) | 2 (6.9) | 5 (9.4) |
| Chronic liver disease | 1 (4.2) | 3 (10.3) | 4 (7.5) |
| Decubitus/pressure ulcer | 0 | 4 (13.8) | 4 (7.5) |
| Chronic pulmonary disease | 1 (4.2) | 2 (6.9) | 3 (5.7) |
| Current smoker | 2 (8.3) | 3 (10.3) | 5 (9.4) |
| Myocardial infarction | 1 (4.2) | 1 (3.4) | 2 (3.9) |
| Atherosclerosis/vascular disease | 1 (4.2) | 1 (3.4) | 2 (3.8) |
| Stroke | 1 (4.2) | 1 (3.4) | 2 (3.8) |
| Congestive heart failure | 0 | 1 (3.4) | 1 (1.9) |
| Dementia | 1 (4.2) | 0 | 1 (1.9) |
| HIV/AIDS | 0 | 0 | 0 |

Abbreviations: AIDS, acquired immune deficiency syndrome; CA, community-associated; HACO, healthcare-associated community-onset; HIV, human immunodeficiency virus; HO, hospital-onset; MRSA, methicillin-resistant Staphylococcus aureus; SA, Staphylococcus aureus.

aAmong cases ≥18 years of age.
bMultiple categories per case are possible.
cDefined as SA isolated from blood.

Two additional cases died at 33 and 34 days after the date of culture; for one case, the vital status after 30 days was unknown.
| Category | No. SA Cases | No. MRSA Cases | Population* | Incidence of SA\(^b\) (95% CI) | Incidence of MRSA\(^b\) (95% CI) | No. SA Cases | No. MRSA Cases | Population* | Incidence of SA\(^b\) (95% CI) | Incidence of MRSA\(^b\) (95% CI) |
|----------|-------------|----------------|--------------|-------------------------------|-------------------------------|-------------|----------------|--------------|-------------------------------|-------------------------------|
| Overall  | 24          | 18             | 16 965       | 14.15 (94.8–211.1)            | 106.1 (66.9–168.4)           | 29          | 22             | 16 948       | 171.1 (118.9–246.2)            | 129.8 (85.5–197.1)           |
| Age (Years) | | | | | | | | | | |
| <1       | 0           | 0              | 323          | 0                             | 0                             | 0           | 0              | 339          | 0                             | 0                             |
| 1–17     | 2           | 2              | 5709         | 35.0 (8.8–140.1)              | 35.0 (8.8–140.1)             | 3           | 2              | 5720         | 52.5 (16.9–162.6)              | 35.0 (8.8–139.8)             |
| 18–39    | 6           | 5              | 5597         | 107.2 (48.2–238.6)            | 89.3 (372–214.6)             | 9           | 7              | 5465         | 164.7 (85.7–316.3)             | 128.1 (61.1–268.6)           |
| 40–49    | 5           | 3              | 1651         | 302.8 (126.1–727.6)           | 181.7 (58.6–563.4)           | 6           | 5              | 1795         | 334.3 (150.4–743.1)            | 278.6 (116.1–668.4)          |
| 50–64    | 10          | 7              | 2477         | 403.7 (217–750.3)             | 282.6 (592.8)                | 10          | 7              | 2383         | 419.6 (226.1–778.9)            | 293.8 (140.2–615.5)          |
| ≥65      | 1           | 1              | 1208         | 82.8 (11.7–587.7)             | 82.8 (11.7–587.7)            | 1           | 1              | 1246         | 80.3 (11.3–569.3)              | 80.3 (11.3–569.3)            |
| Type of Infection | | | | | | | | | | |
| CA       | 9           | 6              | 16 965       | 53.1 (276–102.0)              | 35.4 (15.9–78.7)             | 5           | 3              | 16 948       | 29.5 (12.3–70.9)               | 17.7 (5.7–54.9)              |
| HACO     | 15          | 15             | 16 965       | 88.4 (53.3–146.7)             | 88.4 (53.3–146.7)            | 23          | 18             | 16 948       | 135.7 (9.0–204.2)              | 106.2 (66.9–168.5)           |
| HO       | 0           | 0              | 16 965       | 0                             | 0                             | 0           | 0              | 16 948       | 5.9 (0.8–41.9)                 | 5.9 (0.8–41.9)               |
| Antibiotic Resistance | | | | | | | | | | |
| MSSA     | n/a         | 16 965         | 35.4 (15.9–78.7) | n/a | 7 | n/a | 16 948 | 41.3 (19.7–86.6) | n/a |
| MRSA     | 18          | n/a            | 16 965       | 106.1 (66.9–168.4)            | n/a                          | 22          | 16 948         | 129.8 (85.5–197.1)            | n/a                          |

Abbreviations: CA, community-associated; CI, confidence interval; HACO, healthcare-associated community-onset; HO, hospital-onset; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*; n/a, not applicable; SA, *Staphylococcus aureus*.

\(^a\)Indian Health Service User Population from 2016 (Year 1) and 2017 (Year 2).

\(^b\)Per 100 000 person.
comparisons are limited by differing case definitions. In 5 large US hospitals, 42.9% of *S. aureus* bacteremia isolates from 2008 to 2011 were MRSA [24]. Among Native Americans on Navajo Nation in 2016–2017, 32.7% of invasive cases were MRSA [13]. In a Native American community in the Midwestern United States in 1997, 55.4% of *S. aureus* infections, including noninvasive infections, were MRSA [25], and at all IHS facilities in 2005, 52% of *S. aureus*-associated hospitalizations were characterized as MRSA [12]. Reasons for the high proportion of MRSA in this population are unknown but might reflect different patterns of strain circulation or antibiotic prescription practices in the community.

Reasons for the high burden of disease observed in this community are unknown, but they are likely due to both host and environmental factors. High rates of *S. aureus* infections have been found in indigenous communities around the world, including those in Australia [26], New Zealand [26], and Canada [27]. In Australia, rates of *S. aureus* bacteremia as high as 172 per 100,000 persons were observed in some indigenous communities compared with 65 per 100,000 in the general population [26]. Other socially disadvantaged populations, including African American populations in the United States [10], are also at increased risk for *S. aureus* infections. In the United States in 2013, rates of invasive MRSA were 39.93 per 100,000 persons among African American individuals compared with 19.78 per 100,000 persons among white individuals. A recent study comparing rates of CA invasive MRSA by ethnicity found that most of the increased burden among African American populations was due to differences in socioeconomic status [11]. The proportion of the population living at 100% below the federal poverty level is similarly high for reservation-based communities in the Southwest United States [28], so although low socioeconomic status may be a contributor, it does not explain the large difference in rates between Native American communities in this region [13, 14]. Given the prevalence of prior documented *S. aureus* and MRSA infections among cases, it is clear that exposure to *S. aureus* and MRSA is common in this community. *Staphylococcus aureus* carriage is the greatest single risk factor for infection [29], and data are needed to determine the prevalence of *S. aureus* and MRSA colonization across age groups in this population. Additional studies are also needed to characterize the strains circulating in this community and how they differ from those in other regions across the United States. This information would help to understand whether these factors are contributing to the burden of *S. aureus* and MRSA disease observed in this study.

This study had several limitations. First, due to the large proportion of cases that were HACO and MRSA, our ability to evaluate differences in the characteristics of cases by infection type and antibiotic resistance was limited. Second, it is possible that cases were missed and that the incidence reported was underestimated. However, efforts were made to minimize missed cases, including audits of the participating laboratories; therefore, this is unlikely to have significantly impacted the study results. Third, a definitive link between the *S. aureus* infection and death could not be established, because cause of death was not available for any case.

**CONCLUSIONS**

These findings have important implications for the public health and medical communities in this region. Reservation-based Native American populations are not adequately represented in national laboratory-based surveillance systems, leading to an underrecognition of disease burden in these settings. Robust, population-based, laboratory-based surveillance for invasive disease in high-risk populations should be prioritized. Interventions are urgently needed to reduce the morbidity and mortality due to *S. aureus*. Addressing this health disparity will require a multipronged approach; additional research priorities should include establishing community *S. aureus* and MRSA colonization prevalence, exploring the potential role for targeted decolonization as a strategy to prevent infection in this community [30], developing culturally determined outreach initiatives to promote prevention, early recognition, and appropriate treatment of *S. aureus* infections, and developing effective vaccines or other interventions to modify the immune response and prevent invasive disease.

**Supplementary Data**

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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