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Describing the impact of COVID-19 hospitalization in invasive Staphylococcus aureus epidemiology including racial/ethnic disparities in iSA incidence, six Emerging Infections Program sites, 2020

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By

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B.A., Anthropology
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Abstract

Describing the impact of COVID-19 hospitalization in invasive Staphylococcus aureus epidemiology including racial/ethnic disparities in iSA incidence, six Emerging Infections Program sites, 2020

By Sydney Resler

Background: Invasive *Staphylococcus aureus* (iSA) infections are frequently associated with healthcare exposures, including recent hospitalization. At various times during the COVID-19 pandemic, a large percent of overall U.S. hospitalizations has been due to COVID-19; therefore, the pandemic may have altered iSA epidemiology. Previous studies described increases in hospital-onset iSA infections during the COVID-19 pandemic, but potential healthcare-related risk factors during COVID-19-associated hospitalization (for example: ICU admission, mechanical ventilation) leading to iSA infection have not been explored. There are also well-documented racial and ethnic disparities in both infections separately, but disparities in persons with COVID-19-associated hospitalizations that later develop iSA are not yet explored.

Methods: Emerging Infections Program surveillance data was used (iSA and COVID-NET) in an overlapping catchment area for March 1, 2020, through December 31, 2020. Odds ratios were calculated for demographics, healthcare, and clinical risk factors to inform a multivariate logistic regression comparing iSA cases with and without a prior COVID-19-associated hospitalization. Additionally, odds ratios were calculated for demographics, healthcare, and clinical risk factors comparing persons with COVID-19-associated hospitalizations with and without subsequent iSA infection. Rates and rate ratios of iSA by racial/ethnic group were calculated for 2019 and 2020, as well as health disparity measures, to see how the pandemic impacted racial/ethnic disparities in iSA infection.

Results: iSA cases with a prior COVID-19-associated hospitalization were more likely to be older, have underlying conditions, die, and be discharged to a LTCF than iSA cases without a prior COVID-19-associated hospitalization. Multivariate regression showed that Black race, Hispanic ethnicity, being ≥65 years old, recent long-term care facility (LTCF) stay, recent long-term acute care hospitalization, and a central venous catheter were associated with iSA cases that had a prior COVID-19-associated hospitalization. Persons with COVID-19-associated hospitalizations that developed iSA were more likely to have underlying conditions, critical care such as ICU admission, die, and be discharged to a LTCF than persons with COVID-19-associated hospitalizations that did not develop iSA. Racial/ethnic disparities in iSA rates appeared to widen during the pandemic.

Conclusions: Racial/ethnic differences exist between iSA cases with and without a prior COVID-19-associated hospitalization. Further research is necessary to explore these findings.

Describing the impact of COVID-19 hospitalization in invasive Staphylococcus aureus epidemiology including racial/ethnic disparities in iSA incidence, six Emerging Infections Program sites, 2020

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Introduction

Invasive *Staphylococcus aureus* (iSA) infections are frequently associated with healthcare exposures, especially recent hospitalization (Jackson et al., 2020; Dantes et al., 2013). Rates of iSA in the United States (U.S.) have previously declined but in more recent years prior to 2020 these declines have slowed (Kourtis et al., 2019). At various times during the COVID-19 pandemic, a large percent of overall U.S. hospitalizations has been due to COVID-19 (Heist et al., 2019). Therefore, the pandemic may have altered iSA epidemiology.

Literature to date about iSA infection and COVID-19 has focused on hospital-onset (HO) iSA; however, most iSA infections are community-onset, particularly arising in patients with prior hospitalization (Dantes et al., 2013; Kourtis et al., 2019; Jackson et al., 2020). Further investigation into modifiable risk factors among patients with prior COVID-19-associated hospitalization may also identify areas of improvement and help prevent some iSA cases and deaths. In addition, comparing rates of iSA during to pre-pandemic can determine whether COVID-19-associated hospitalizations have directly altered existing differences in iSA incidence in different racial or ethnic groups.

There are three objectives of this thesis:

1. Describe the proportion of iSA cases with prior COVID-19-associated hospitalization and characterize COVID-19 and other healthcare risk factors;
2. Describe the proportion of patients with COVID-19-associated hospitalization who subsequently develop iSA infection, during or after discharge from COVID-19 associated hospitalization, and characterize those that developed iSA versus those that did not develop iSA; and
3. Compare rates of iSA among racial/ethnic groups before and during the COVID-19 pandemic to determine if the pandemic contributed to greater racial/ethnic disparities.

Background

iSA, which includes both methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-sensitive *Staphylococcus aureus* (MSSA), is one of the most common causes of infection in healthcare settings (CDC, 2021). CDC categorizes iSA cases into three epidemiologic classifications: HO if iSA culture was obtained on or after day four of hospitalization; healthcare-associated community-onset (HACO) if iSA culture was obtained in an outpatient setting or before day four of hospitalization plus a past-year history of hospitalization, dialysis, surgery, or residing in a long-term care facility (LTCF) or long-term acute care hospital (LTACH), or having a central venous catheter (CVC) in place 2 days prior to SA culture; and community-associated (CA) if neither of the previous definitions fit (CDC, 2022).

COVID-19 hospitalization is associated with secondary infections/Healthcare Associated Infections:

COVID-19 hospitalization has been shown to be associated with secondary infections and healthcare-associated infections. In a study comparing incidence and characteristics of bloodstream infection (BSI) in hospitalized patients in New York before (January 1-February 28, 2020) versus during (March 1-May 1, 2020) a COVID-19 surge, BSI was more likely to be a primary infection pre-COVID, whereas during COVID it was more likely to be a secondary infection. Days of antibiotic therapy and mortality increased, while time from admission to positive BSI culture decreased. The three most common BSI pathogens pre-COVID were MRSA, Streptococci, and *S. pneumoniae*; post-COVID, the top three were Enterococcus, *E. coli*, and MSSA. [Afzal et al, 2021]

Risk factors for healthcare-associated infections among SARS-CoV-2 positive patients in a hospital in the state of Georgia were receipt of cefepime and vancomycin, diabetes or end-stage renal disease, male sex, and people identifying as Black (Kumar et al., 2021).

COVID-19 hospitalization is associated with iSA infection:

Although some studies in the U.S. have shown no statistical significance between pre- and during-COVID rates of iSA infection in specific geographic areas (Madden et al., 2020; Parriott et al., 2021), many studies have identified increases in iSA infection rates, especially those that have larger geographic foci (Baker et al., 2021; Afzal et al, 2021; Cusumano et al., 2020). Some COVID-19 hospital interventions associated with iSA co-infection are antibiotics, mechanical ventilation, central venous catheter (CVC), and corticosteroids (Adalbert et al., 2021). The large numbers of COVID-19 patients receiving these interventions may have contributed to increased iSA rates. Among 148 hospitals in the U.S. between March 1 and December 31, 2020, a model estimated a 44% (95% CI, 10-88%) increase in cases of MRSA bacteremia than expected in the absence of COVID-19 cases; these increases were significantly associated with COVID-19 surges (Baker et al, 2021). Some studies have also shown higher mortality rates among patients co-infected with COVID-19 and iSA compared to those infected with only COVID-19 (Cusumano et al., 2020; Adalbert et al., 2021). On the other hand, some COVID-19 and iSA prevention and control measures overlap. Measures aimed at reducing COVID-19, such as improved handwashing, may have unintentionally also reduced MRSA transmission (Madden et al., 2021).

General iSA and COVID-19 disparities:

There are documented racial/ethnic disparities in both iSA and COVID-19 rates and severity. Black patients have been documented to have higher rates of iSA infections compared to White patients (Gualandi et al, 2018; Jackson et al, 2020), much of which may be explained by socioeconomic factors (See et al., 2017).

In addition, racial and ethnic minorities in the U.S. experience disproportionately high rates of severe COVID-19 outcomes. Hispanic and non-White individuals were more likely to be hospitalized, admitted to the ICU, or die in the hospital than non-Hispanic White individuals, and less likely to be administered monoclonal antibody treatment (mAb) (Acosta, Garg, and Pham, 2021). This could reflect a

number of systemic factors, such as: “limited access to testing and care because of availability constraints, inadequate insurance coverage, and transportation challenges; lack of a primary care provider to recommend treatment; variations in treatment supply and distribution; potential biases in prescribing practices; and limited penetration of messaging in some communities about mAb availability and effectiveness to prevent disease progression…[or] hesitancy about receiving treatment” (Wiltz et al., 2022, 99-100).

Because both infections can be severe, we hypothesize that iSA cases with a prior COVID-19-associated hospitalization will have worse outcomes than iSA cases without a prior COVID-19-associated hospitalization. We also hypothesize that people with COVID-19-associated hospitalization who develop iSA had more interventions and healthcare exposures during their hospitalization than people with a COVID-19-associated hospitalization who do not develop iSA, leading to more opportunities for *S. aureus* exposure. Additionally, since Black individuals are more likely to get iSA and Hispanic and non-White individuals were more likely to experience hospitalization and severe outcomes from COVID-19 compared to non-Hispanic White individuals, we hypothesize that Hispanic Non-Whites could be disproportionately represented in cases of iSA that had a prior COVID-19-associated hospitalization.

Methods

Data Collection

The Emerging Infections Program (EIP) conducts active laboratory- and population-based surveillance for iSA and COVID-19-associated hospitalizations (COVID-NET). An iSA case is defined as when someone who lives in the surveillance area has *S. aureus* isolated from a site that is normally sterile (CDC, 2021). For a COVID-19-associated hospitalization to be included in COVID-NET, the patient had to test positive for SARS-CoV-2 during hospitalization or no more than 14 days before admission (O’Halloran et al., 2023). We included cases with iSA incident specimen collection between March 1,

2020, to December 31, 2020, in the overlapping catchment area of these surveillance systems. The catchment area contains nine counties across six states: California (Alameda, Contra Costa, and San Francisco Counties), Connecticut (New Haven County), Georgia (Fulton County), Minnesota (Hennepin and Ramsey Counties), New York (Monroe County), and Tennessee (Davidson County), covering an estimated 2.69% of the U.S. population.

COVID-NET practiced a sampling schema to develop a representative sample of hospitalized COVID-19 cases and speed up data collection, analysis, and dissemination (O'Halloran et al., 2023). They stratified for sampling by age, site, and hospital admission date by calculating sample sizes for each sampling period, then asking sites to randomly draw samples of cases to reach those sampling sizes (O'Halloran et al., 2023). These randomly sampled cases had their full case report form (CRF) abstracted and sent to CDC, where the data was weighted (O'Halloran et al, 2023). Due to this, the majority of COVID-NET cases do not have more than demographic and outcome information.

Data Analysis

To describe iSA infections with a preceding/concurrent COVID-19-associated hospitalization, we defined iSA cases with prior COVID-19-associated hospitalization as a COVID-19-associated hospitalization (COVID-NET case) where incident iSA culture occurred ≥3 days after the first positive SARS-CoV-2 test and ≥3 days after COVID-NET hospital admission date. We calculated odds ratios to compare iSA cases with a prior COVID-19-associated hospitalization to iSA cases without a prior COVID-19-associated hospitalization using EIP iSA surveillance data (iSA cohort) and similarly compared persons with COVID-19-associated hospitalizations who later develop iSA to people with COVID-19-associated hospitalizations who did not develop iSA (COVIDNet cohort). Fischer's exact test was used for p-value when at least one cell had an expected count of less than five. Chi squares, 95% confidence intervals, and p-values were calculated for all comparisons. The Kruskal-Wallis test was used for age and time

distributions to obtain a p-value for the difference between the medians. A 0.5 correction was applied to create the adjusted odds ratio used when at least one cell had a count of zero. Some iSA cohort analyses were stratified by iSA epidemiologic class: HACO and HO. CA was not included as it is impossible for an iSA case post COVID-19-associated hospitalization to be a CA case. Multivariate logistic regression was done to determine if demographic characteristics, healthcare exposures, and underlying conditions with a univariate p-value cutoff of 0.1 were significantly associated with iSA post-COVID hospitalization vs. iSA without prior COVID-19-associated hospitalization after accounting for other risk factors.

To analyze health disparities, we compared overall rates of iSA infection from a pre-pandemic year (2019) to the first pandemic year (2020) using EIP iSA surveillance data and census data from the same time period (March 1 through December 31). These rates were used to calculate three health disparity measures described by Healthy People 2020: maximal rate difference (MRD), maximal rate ratio (MRR), and summary rate ratio (SRR) (Huang et al., 2022). MRD, an absolute disparity measure, is the difference between the highest and lowest group rates. MRR, a relative disparity measure, is the ratio of the highest to lowest group rates. SRR, also a relative disparity measure, is the directional ratio of the highest group rate in comparison to the average of all other group rates. One cannot assess MRD for significance, but MRR and SRR can be designated as having significant increases or decreases if the difference between the compared numbers is greater than or equal to 0.10 when statistical significance cannot be assessed (National Center for Health Statistics, 2022). The multiracial group was excluded from the calculation of these measures due to possible discrepancy between how multiracial is recorded on the census and hospital intake forms.

Analyses were conducted in SAS version 9.4 (SAS Institute Inc) and Microsoft Excel.

Results

iSA cohort

Of the 3787 iSA cases in the catchment area during March 1, 2020, through December 31, 2020, 146 (3.86%) had a prior COVID-19-associated hospitalization where incident iSA culture occurred ≥3 days after the first positive SARS-CoV-2 test and ≥3 days after COVID-NET hospital admission date. The comparison group—iSA cases without a prior COVID-19-associated hospitalization—encompassed 3473 cases. 168 cases were excluded from the comparison group because they had COVID-19-associated hospitalizations but iSA culture occurred <3 days after the first positive SARS-CoV-2 test and/or <3 days after COVID-NET hospital admission date. Among the 146 cases of iSA with a prior COVID-19-associated hospitalization, there were an average of 45.4 days between first positive SARS-CoV-2 test and iSA culture (median: 18.5; range: 3-244) (Figure 1) and an average of 44 days between hospital admission and iSA culture (median: 18; range: 3-244) (Figure 2).

There were many differences in patient and iSA infection characteristics (Table 1). When compared to iSA cases without a prior COVID-19-associated hospitalization, those with a prior COVID-19-associated hospitalization were more likely to be Hispanic (odds ratio [OR], 2.97; 95% confidence interval [CI], 1.89-4.64; p-value [p] <0.01), older (median age: 67.5 vs 60 years; p<0.01), and have iSA-related diagnoses of pneumonia (OR, 4.21; CI, 2.93-6.06; p<0.01), and/or BSI with no other syndrome (OR, 1.87; CI, 1.33-2.63; p<0.01). They were less likely than iSA cases without a prior COVID-19-associated hospitalization to have iSA-related diagnoses of osteomyelitis (OR, 0.18; CI, 0.07-0.48; p<0.01), endocarditis (OR, 0.28; CI, 0.10-0.77; p<0.01), cellulitis (OR, 0.34; CI, 0.16-0.74; p<0.01), or skin abscess (OR, 0.70; CI, <0.01-1.13; p<0.01). There were also differences in outcomes. iSA cases with prior COVID-19-associated hospitalization were more likely to die during hospitalization (OR, 5.65; CI, 4.02-7.95; p<0.01). If surviving, those with prior COVID-19-associated hospitalization were more likely to be discharged to a LTCF (OR, 2.20; CI, 1.38-3.51; p<0.01) or LTACH (OR, 5.03; CI, 2.05-12.38; p<0.01). Nearly forty-two percent of people with HACO iSA and a prior COVID-19-associated hospitalization were at a

private residence prior to specimen collection, 38% at a LTCF, and 10% at an acute care hospital. Upon discharge, 44% of people with iSA and a prior COVID-19-associated hospitalization went to a private residence, 46% to a LTCF, and 7% to a LTACH. Seventy-six percent of people with iSA without a prior COVID-19 associated hospitalization were at a private residence prior to specimen collection, 15% were at a LTCF, and only 1% were at an acute care hospital. Upon discharge 63% of people with iSA without a prior COVID-19-associated hospitalization went to a private residence, 29% to a LTCF, and 2% to a LTACH. A larger proportion of people were discharged to a LTCF than were located there before specimen collection for both groups, but the proportion is much higher for the iSA group with prior COVID-19-associated hospitalization.

Cases with prior COVID-19-associated hospitalization were more likely to be hospital onset (HO) (OR, 10.39; CI, 7.36-14.67; p<0.01) and less likely to be community-associated (CA) (OR 0.01; CI, <0.01-0.1; p<0.01) or healthcare-associated community onset (HACO) (OR 0.62; CI, 0.44-0.87; p<0.01); however, these numbers, particularly CA, were artificially skewed due to our case definition. Requiring a prior hospitalization in the case skews our sample away from CA and towards healthcare-associated (HO and HACO) by definition.

We stratified by epidemiologic class to see if there were differences within HACO and HO cases by prior COVID-19-associated hospitalization status. HACO iSA cases with a prior COVID-19-associated hospitalization were more likely to have had an acute care hospitalization (OR, 3.91; CI, 1.22-12.57; p=0.01), LTCF stay (OR, 2.27; CI, 1.34-3.84; p<0.01), or LTACH (OR, 6.37; CI, 1.79-22.62; p=0.02) in the year before incident specimen collection (Table 2) and less likely to have had surgery in the year before specimen collection (OR, 0.52; CI, 0.28-0.96; p=0.03) or be on chronic dialysis (OR, 0.40; CI, 0.18-0.89; p=0.02) when compared to HACO-iSA cases without a COVID-19-associated hospitalization. They were also more likely than iSA cases without a prior COVID-19-associated hospitalization to have been at a LTCF (OR, 4.60; CI, 2.57-8.22; p<0.01), acute-care hospital (OR, 14.04; CI, 24.07; p<0.01), or LTACH (OR,

24.07; CI, 5.88-98.50; p<0.01) three days prior to specimen collection versus being at a private residence.

HO iSA cases with prior COVID-19-associated hospitalization were more likely to have underlying chronic pulmonary disease (OR, 1.81; CI, 1.08-3.02; p=0.02), diabetes mellitus (OR, 2.02; CI, 1.26-3.23; p<0.01), at least one underlying condition (OR, 2.67; CI, 1.52-4.70) (Table 3). They were less likely to have underlying intravenous drug use (OR, 0.1; CI, 0.01-1.63; p=0.02). They were also more likely to have stayed at an acute care hospital (OR, 0.55; CI, 0.34-0.90; p=0.02) or have had surgery (OR, 0.25; CI, 0.10-0.65; p<0.01) in the year before specimen collection, or to have had a central vascular catheter in place two days before specimen collection (OR, 1.69; CI, 1.05-2.70; p=0.03).

When controlling for other factors, several variables were significantly associated with having a prior COVID-19-associated hospitalization. This includes patient characteristics such as being at least 65 years old (OR, 1.80; CI 1.23-2.65; p<0.01), Hispanic (OR, 4.53; CI: 2.77-7.42; p<0.01), and Black or African American (OR, 1.61; CI: 1.04-2.51; p=0.03). Healthcare exposures of significance were having stayed in a LTCF in the year prior (OR, 25.1; CI: 1.67-3.76; p<0.01), having stayed in a LTACH in the year prior (OR, 7.52; CI: 2.14-26.39, p<0.01), and having a CVC in the two days prior to iSA specimen collection (OR, 5.20; CI: 3.42-7.89; p<0.01). iSA cases who had surgery in the year prior (OR, 0.39; CI: 0.22-0.66; p<0.01) and chronic dialysis (OR, 0.18; CI 0.09-0.36; p<0.01) were significantly less likely to have a prior COVID-19-associated hospitalization.

COVID-NET cohort

Of the 44,087 COVID-19-associated hospitalizations in the catchment area, 146 (0.3%) developed iSA ≥3 days after the first positive SARS-CoV-2 test and ≥3 days after COVID-NET hospital admission date. Due to sampling, 10,392 COVID-19-associated hospitalizations without iSA and 40 COVID-19-associated hospitalizations with iSA had full case report forms.

Patient characteristics differed between our two comparison groups. When compared to COVID-19-associated hospitalizations without subsequent iSA infection, those who later developed iSA were more likely to be older (median age: 67 vs. 63 years; p=0.04), male (OR, 1.41; CI, 1.02-1.97; p=0.04), and have more than one type of insurance (OR, 2.42; CI, 1.06-5.52; p=0.04) (Table 4, Table 5). COVID-19-associated hospitalizations who later developed iSA when compared to those who did not develop iSA were more likely to be homeless or reside at a shelter, alcohol/drug treatment facility, corrections facility, or psychiatric facility (noted in the table as "homeless/shelter/facility") (OR, 6.20; CI, 2.12-18.13; p<0.01) or reside at a LTCF (OR, 2.96; CI, 1.51-5.81; p<0.01) at time of hospitalization. COVID-19-associated hospitalizations with iSA were more likely to have a pre-existing medical condition (OR, 4.80; CI, 1.48-15.59; p<0.01) (Table 6). The underlying conditions most associated with people with COVID-19-associated hospitalization with iSA versus without iSA were hypertension (OR, 3.20; CI, 1.60-6.42; p<0.01), chronic liver disease (OR, 3.90; CI, 1.52-10.01; p=0.01), asthma/COPD/reactive airway disease/emphysema (OR, 3.29; CI, 1.75-6.17; p<0.01), and diabetes mellitus (OR, 3.13; CI, 1.67-5.86; p<0.01).

Healthcare exposures during COVID-19-associated hospitalization also differed between groups. COVID-19-associated hospitalizations who developed iSA were more likely to be admitted to the ICU (OR, 4.19; CI, 2.22-7.89; p<0.01) and for longer (median 18 days vs 6 days, p<0.01), and have at least one critical care intervention (OR, 2.64; CI, 1.32-5.29; p<0.01) (Table 7). Critical care interventions that were more commonly used with COVID-19-associated hospitalized patients with iSA compared to those without iSA were invasive mechanical ventilation (OR, 7.03; CI, 3.77-13.11; p<0.01), BiPAP/CPAP/high flow nasal cannula (OR, 3.56; CI, 1.91-6.62; p<0.01), ECMO (OR, 12.77; CI, 3.84-42.48; p<0.01), vasopressor (OR, 6.19; CI, 3.32-11.55; p<0.01), systemic steroids (OR, 2.12; CI, 1.14-3.95; p<0.01), and renal replacement therapy or dialysis (OR, 3.55; CI, 1.38-9.11; p=0.01).

Outcomes were worse for people with COVID-19-associated hospitalization who developed iSA. This group was more likely to be discharged from COVID-19-associated hospitalization with acute respiratory distress syndrome (ARDS) (OR, 4.14; CI, 1.96-8.73; p<0.01), sepsis (OR, 3.10; CI, 1.60-6.03; p<0.01), or acute renal failure (OR, 2.83; CI, 1.46-5.51; p<0.01) than those who did not develop iSA. They were also more likely to die during COVID-19-associated hospitalization (OR, 4.39; CI, 3.06-6.30; p<0.01). Among those surviving, persons with COVID-19-associated hospitalizations who developed iSA were more likely to be released into homelessness, a shelter or facility (OR, 31.57; CI, 8.42-118.47; p<0.01), LTCF (OR, 15.20; CI, 5.56-41.56; p<0.01), or against medical advice (OR, 14.51; CI, 1.70-126.72; p=0.02) than a private residence when compared to people with COVID-19-associated hospitalizations who did not develop iSA. Fifty-five percent of people with COVID-19-associated hospitalizations with iSA were admitted from a private residence, whereas only 17.86% were discharged to a private residence. This pre-post hospitalization change is much less stark for the COVID-19-associated hospitalizations without iSA: 81.32% admitted from private residence to 76.22% discharged to private residence. Twenty percent of people with COVID-19-associated hospitalizations that developed iSA were admitted from a long-term or assisted care facility, and 57.14% were discharged to a long-term or assisted care facility. Again, the percentages for long-term or assisted care among persons with COVID-19-associated hospitalizations that did not develop iSA were much more similar, but still showed an increase: 9.46% admitted, 15.81% discharged.

Among the antiviral treatments investigated, monoclonal antibody/immunomodulators (OR, 3.14; CI, 1.22-8.04; p=0.03) and convalescent plasma (OR, 3.21; CI, 1.56-6.58; p<0.01) were more commonly prescribed to people with COVID-19-associated hospitalizations who developed iSA.

Health Disparity Analysis

American Indian people had the highest rates of iSA both before (195.72 per 100,000 population) and during (203.24) the COVID-19 pandemic (Table 10). The next lowest rates were among the Asian or Pacific Islander population: 20.81 before and 19.59 during. People who identified as multiracial had the lowest (9.63 before; 6.10 during); however, these numbers could be skewed due to possible differences in self-identifying as multiracial (such as on the census) and hospital intake forms marking multiracial for a patient. Rates decreased among White people (RR, 0.90; CI 0.85-0.97) and among all races/ethnicities (RR, 0.92; CI, 0.88-0.97) from before to during the pandemic. There was no significant change for Hispanic (RR, 0.87; CI 0.76-1.00), Black (RR, 1.01; 0.92-1.11), American Indian (RR, 1.04; CI 0.71-1.52), Asian or Pacific Islander (RR, 0.94; CI 0.80-1.11), and Multiracial (RR, 0.63; CI 0.34-1.17) people. Overall and by epidemiologic class, American Indian people had the highest rates of all racial/ethnic groups while Multiracial had the lowest rates, followed by Asian or Pacific Islander.

The MRD for pre-pandemic was 174.92 and was 183.65 for during the pandemic (Table 11). The MRR increased from 9.41 pre-pandemic to 10.38 during-pandemic, and summary rate ratio increased from 4.10 pre-pandemic to 4.34 during-pandemic. When breaking down by epidemiologic class, CA MRR decreased from 16.15 to 13.06 and CA SRR decreased from 5.78 to 5.05 (Table 15). HACO MRR increased from 5.92 to 9.64, and HACO SRR increased from 3.19 to 4.08. HO MRR increased from 6.76 to 7.74 and SRR from 3.70 to 3.94.

Discussion

iSA cohort

iSA cases with a prior COVID-19-associated hospitalization were older and more likely to be Hispanic versus White when compared to iSA cases without a prior COVID-19-associated hospitalization. Rates of death and discharge location show that iSA cases with prior COVID-19-associated hospitalization saw worse outcomes when compared to iSA cases without prior COVID-19-associated

hospitalization. Some iSA infection types are associated with prior COVID-19-associated hospitalization, and some are associated with not having a prior COVID-19-associated hospitalization. All are classically associated with iSA in general; the ones that are associated with prior COVID-19-associated hospitalization are BSI and pneumonia. The pneumonia may be due to the respiratory nature of both pneumonia and COVID-19. Hospital interventions such as mechanical ventilation (associated with pneumonia) and central lines (associated with BSI), which we saw as significant healthcare exposures in the COVID-NET cohort analysis, may also explain higher proportions of iSA pneumonia and BSI in patient with prior COVID-19-associated hospitalization.

Our case definition excluded CA and some HO and HACO cases from our COVID-hospitalization study population, so the overrepresentation of hospital-associated (HO and HACO) cases is exaggerated. It is interesting to note that HACO iSA cases with prior COVID-19-associated hospitalization saw no significant differences in underlying conditions when compared to HACO iSA cases without prior COVID-19-associated hospitalization, yet HO iSA cases with prior COVID-19-associated hospitalization had higher rates of chronic pulmonary disease, diabetes, and at least one underlying condition. This is consistent with existing literature claiming that chronic pulmonary diseases and diabetes are associated with more severe COVID-19 illness (Gulsen et al., 2021; Lippi and Henry, 2020; Diedisheim et al., 2021; Targher et al, 2020; Zhou et al., 2020). These cases may be HO because they have more severe illness from COVID-19 and thus were never discharged from a hospital like HACO cases would be. However, the multivariable regression shows that no underlying medical conditions were significant when adjusting for other factors.

Prior healthcare exposures did not suffer the same fate. Chronic dialysis and surgery, known risk factors for iSA, was not significantly associated with COVID-19-associated hospitalization. Past year LTACH and LTCF stays, and ≥ 2 days CVC placement, were associated with COVID-19-associated hospitalization. LTCF and LTACH are locations where people vulnerable to both COVID-19 and iSA live—

often elderly people with underlying condition(s)—and many cases early in the pandemic were in LTCFs (Yen et al., 2020; Lai et al., 2020; Thompson et al., 2020). CVC is an intervention related to COVID-19 care (Scoppettuolo et al., 2020). Additionally, the cancellation of non-essential surgical procedures early in the pandemic reduced the number of people in hospitals and could have impacted the healthcare exposures leading to iSA infection with and without a prior COVID-19-associated hospitalization (WHO, 2021; COVIDSurg Collaborative, 2020).

COVID-NET cohort

iSA was uncommon following COVID-19-associated hospitalization. This coincides with other research, including a study across two New York City hospitals which found that only 1.57% of patients hospitalized for COVID-19 between March and May 2020 were identified as having *S. aureus* bacteremia (Cusumano et al., 2020). People with COVID-19-associated hospitalization with iSA were older, had poorer health at baseline, and had more complicated hospitalizations as evidenced by statistically significant associations with nearly every intervention examined. Additionally, people with COVID-19-associated hospitalizations with iSA had poorer outcomes such as death, more severe discharge diagnoses such as ARDS and sepsis, and being discharged to long-term care following hospitalization. The differences between residence at time of hospitalization and discharge location is particularly important to note. A greater percent of COVID-19-associated hospitalizations with iSA moved from entering the hospital from a private residence to discharging into a LTCF than did COVID-19-associated hospitalizations without iSA, suggesting that having both infections leads to more long-lasting complications that need continued care.

The increased rates of monoclonal antibody/immunomodulator treatment and convalescent plasma in the people with COVID-19-associated hospitalizations that developed iSA (versus those that did not) hint that these patients may have been sicker, warranting the medication.

One difference between the results from the iSA and COVID-NET cohorts is race/ethnicity. Hispanic ethnicity is significantly associated with iSA cases with prior COVID-19-associated hospitalization versus iSA cases without prior COVID-19-associated hospitalization, while there are no significant racial/ethnic differences between people with COVID-19-associated hospitalizations with and without iSA. This suggests that while there may be disparities in who is exposed to and develops severe illness from COVID-19, once in the hospital (for COVID-19) there is no difference in care between racial/ethnic groups that would lead to the introduction of iSA.

Health disparity analysis

Overall rates of iSA decreased from pre-pandemic to during-pandemic, as did rates of CA and HACO. HO rates for all races/ethnicities did increase, but not significantly so. The white population is the only racial/ethnic group (excluding multiracial) that saw a significant change as rates decreased in the overall and HACO-stratified groups. Although not significant, the trends between the different epidemiologic classes are interesting to note: CA saw nearly all declines whereas HACO and HO saw nearly all increases across all racial/ethnic groups during the pandemic. One group that does stand out in all strata is American Indian: although not statistically significant, they had the largest rate increase for overall, HACO, and HO.

The overall MRD shows that the difference between the largest and smallest iSA rates widened during the pandemic. The overall MRR and SRR increased significantly, again showing a widening of disparity between the groups with the highest and lowest rates. This supports our hypothesis that racial/ethnic disparities in iSA may have been negatively impacted by the COVID-19 pandemic. Stratifying these measures by epidemiologic class highlights differences between them: all measures for CA decreased from pre- to during-pandemic, whereas all measures increased for HACO and HO. This follows the trends of the rates and rate ratios.

Strengths

One strength of this study is its catchment area. It is random and only catches 2.6% of the U.S. population, so it may not be representative; however, this study was not limited to a single hospital or hospital system and includes multiple geographic areas. Additionally, this study expanded beyond HO iSA.

Limitations

A major limitation of this study is small sample size and missingness. This is especially true for the COVID-NET cohort due to the COVID-NET sampling schema leaving a limited number of full case report forms. Case report forms also changed regularly during the surveillance period. Small numbers lead to low power—too low to do any modeling and control for confounders. Thus, some variables and relationships were not able to be explored. Small numbers were also a limitation in the health disparities analysis. When stratifying by any epidemiologic class, the number of cases for Multiracial was below 10 and had to be suppressed, as were American Indian numbers for HO iSA cases.

Additionally, the impact of COVID-19 on iSA may have changed over time, which would not be captured in this analysis. The way healthcare utilization changed early in the pandemic (e.g., limiting surgical procedures and time in hospital) may have changed the "normal" epidemiology of iSA. The impact of COVID-19 on iSA is also underestimated by limiting to cases with prior hospitalization.

Another limitation is timing, which especially comes into play in the COVID-NET cohort analysis. For many healthcare interventions and antiviral treatments, the timeline of care compared to iSA culture is not known. Due to this, it is difficult to say whether the development of iSA is an outcome of receiving further care—the healthcare exposures introduced the pathogen, thus naming those interventions as a risk factor for developing iSA—or if iSA causes worsening health in COVID-19-hospitalized patients, thus leading to the need for more intensive care and medication.

Recommendations

These analyses could be used to inform healthcare policy and future research. Although the COVID-NET cohort numbers in this dataset were too small to conduct a multivariable regression, such an analysis as more years of data become available would help illuminate the factors at play leading to worse outcomes. Further research should also be conducted to investigation potential reasons for disparate iSA rates among racial/ethnic groups.

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Appendix: Figures and Tables

iSA cohort

Figure 1: Days between first SARS-CoV-2 test and iSA culture, six Emerging Infections Program sites, 2020 (N=146)

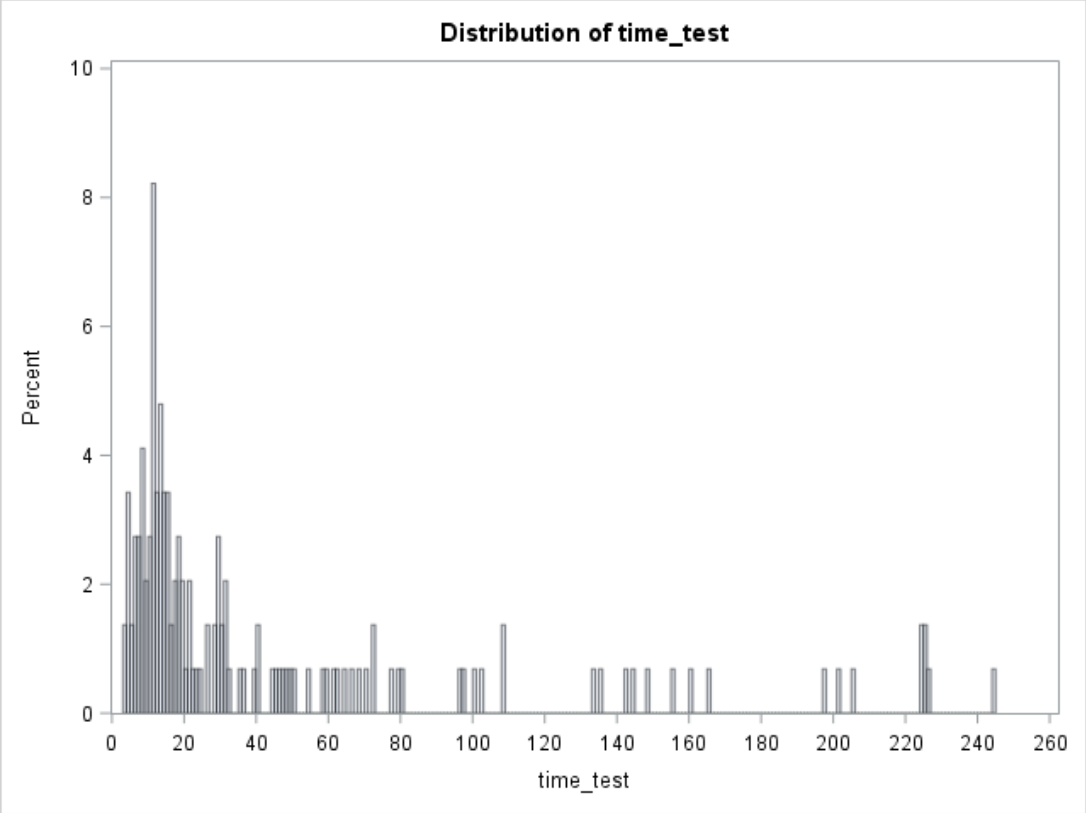

Figure 2: Days between COVID-19 hospital admission and iSA culture, six EIP sites, March 1-December 31, 2020 (N=146)

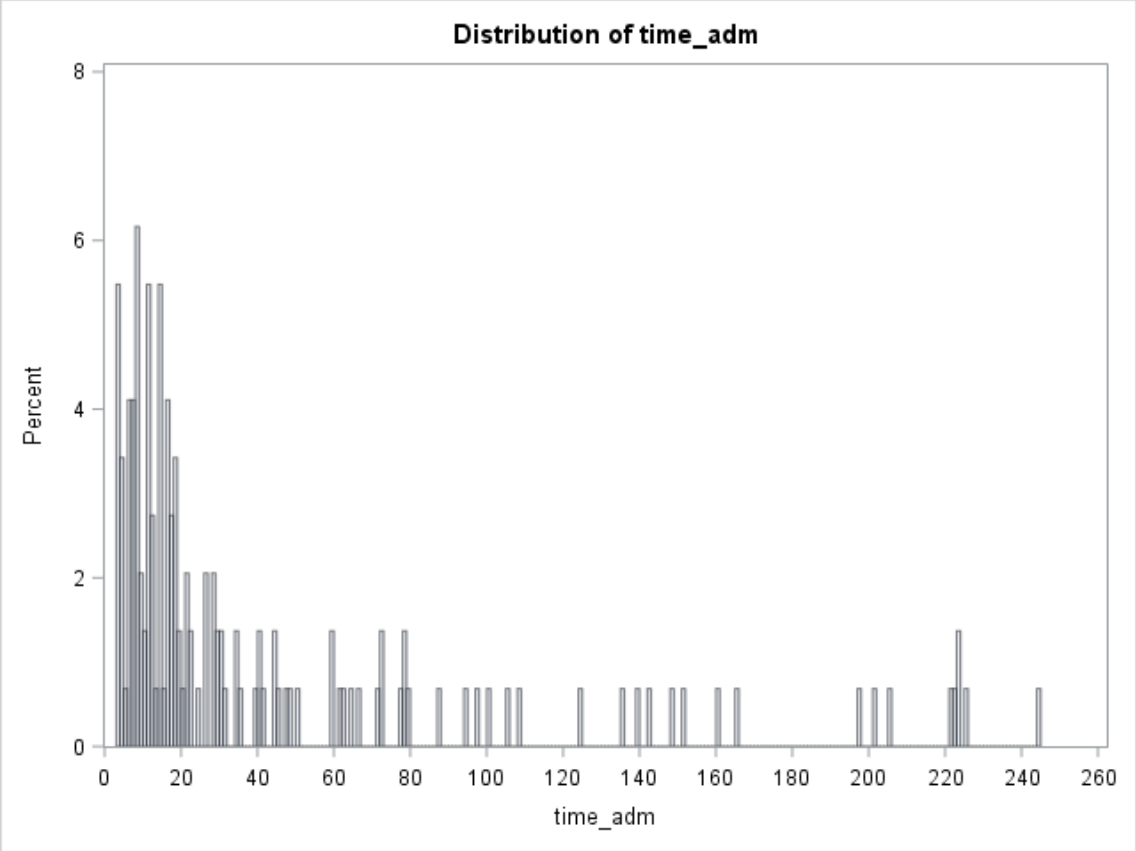

Figure 3: Multivariate regression of demographic and epidemiologic characteristics associated with prior COVID-19 associated hospitalization among iSA cases, six EIP sites, March 1-December 31, 2020

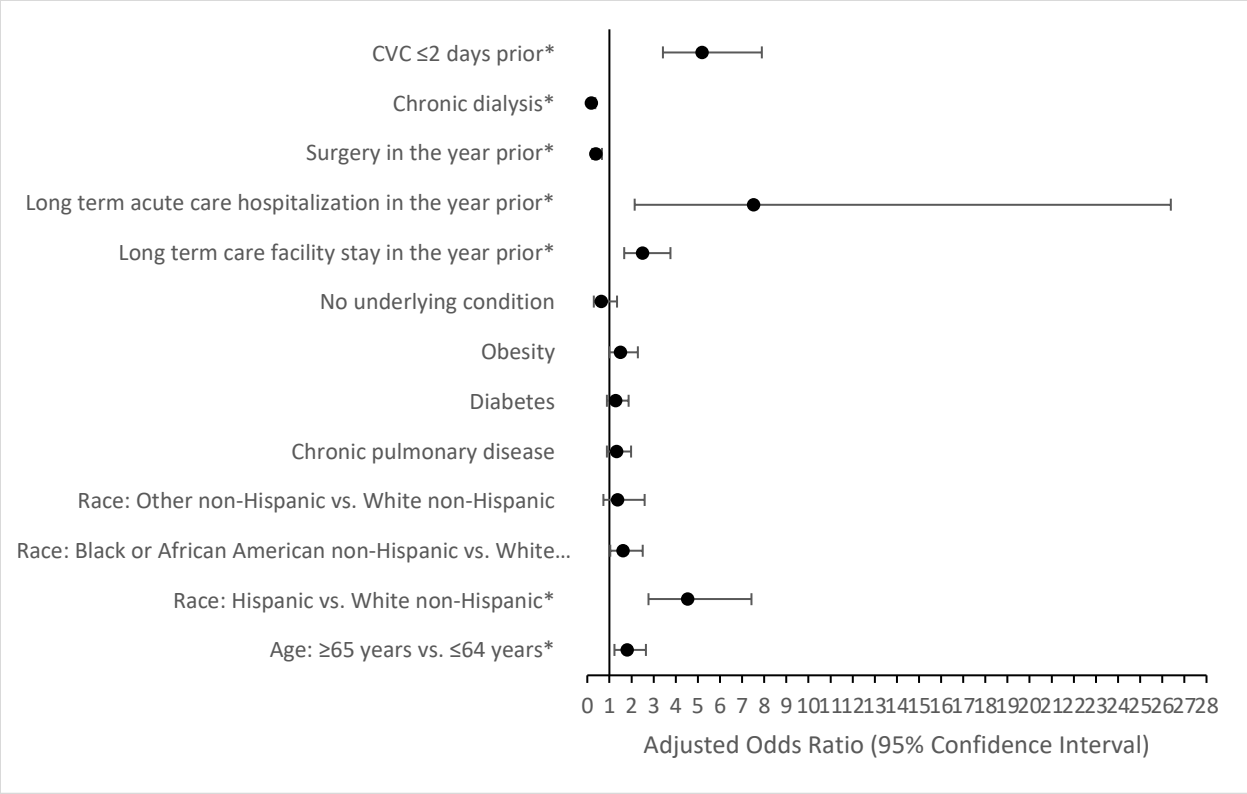

Table 1: Invasive *S. aureus* demographics by prior COVID-19 associated hospitalization status, six EIP sites, March 1-December 31, 2020

	iSA, COVID-19 No. (%) (N=146)	**iSA, No COVID-19 No. (%) (N=3473)**	**OR**	**95% CI**	**P**
Race/Ethnicity					
White, not Hispanic	61 (41.78)	1873 (53.93)		Referent	
Black/African American, not Hispanic	37 (25.34)	823 (23.70)	1.38	0.91-2.09	0.1
Asian, not Hispanic	9 (6.16)	228 (6.56)	1.21	0.59-2.47	0.6
American Indian or Alaska Native, non-Hispanic	3 (2.05)	47 (1.35)	1.96	0.59-6.47	0.3
Native Hawaiian or Other Pacific Islander, non-Hispanic	0 (0.0)	31 (0.89)	<0.01	<0.01->999	0.9
Hispanic, any race	31 (21.23)	321 (9.24)	2.97	1.89-4.64	<0.01
Multiple races, not Hispanic	1 (0.68)	16 (0.46)	1.92	0.25-14.70	0.5
Unknown race, not known to be Hispanic[1]	4 (2.74)	134 (3.86)	0.92	0.33-2.56	0.5
Age median (range)	67.5 (14-96)	60 (0-104)			<0.01
Sex[2]					
Male	87 (59.59)	2219 (64.04)			
Female	59 (40.41)	1246 (35.96)	1.21	0.86-1.69	0.3

Outcome[3]					
Died	65 (44.52)	431 (12.43)	5.65	4.02-7.95	<0.01
Survived	81 (55.48)	3036 (87.57)			
Discharge location after iSA acute-care hospitalization among patients who survived[4]					
Private residence	36 (44.44)	1902 (62.88)		Referent	
Long term care facility	37 (45.68)	887 (29.32)	2.20	1.38-3.51	<0.01
Long term acute care hospital	6 (7.41)	63 (2.08)	5.03	2.05-12.38	<0.01
Other	0 (0.0)	88 (2.91)	<0.01	<0.01->999	0.9
Resistance status					
MRSA	57 (39.04)	1204 (34.68)	0.83	0.59-1.16	0.3
MSSA	89 (60.96)	2268 (65.32)			
Epidemiologic class					
Community-associated (CA)	0 (0.0)	1213 (34.93)	0.01	<0.01-0.1	<0.01
Healthcare-associated, community-onset (HACO)	60 (41.10)	1839 (52.95)	0.62	0.44-0.87	<0.01
Hospital-onset (HO)	86 (58.90)	421 (12.12)	10.39	7.36-14.67	<0.01
Syndrome					
Bloodstream Infection					
Bloodstream infection with other syndrome	69 (50.36)	1944 (65.48)	0.54	0.38-0.75	<0.01
Bloodstream infection with no other syndrome	68 (49.64)	1025 (34.52)	1.87	1.33-2.63	<0.01
Pneumonia	48 (32.88)	362 (10.42)	4.21	2.93-6.06	<0.01
Osteomyelitis	4 (2.74)	474 (13.65)	0.18	0.07-0.48	<0.01
Endocarditis	4 (2.74)	314 (9.04)	0.28	0.10-0.77	<0.01
Cellulitis	7 (4.79)	444 (12.78)	0.34	0.16-0.74	<0.01
Surgical wound	1 (0.68)	54 (1.55)	0.44	0.06-3.18	0.7
Decubitus/pressure ulcer	5 (3.42)	66 (1.90)	1.83	0.73-4.61	0.2
Skin abscess	0 (0.0)	161 (4.64)	0.70	<0.01-1.13	<0.01
Other ulcer or wound	4 (2.74)	132 (3.80)	0.71	0.26-1.95	0.5
Traumatic wound	0 (0.0)	43 (1.24)	0.27	0.02-4.39	0.4

[1]Of cases with unknown race, 3 COVID-19 cases and 67 non-COVID-19 cases had unknown ethnicity
[2]Excludes 8 iSA no COVID-19 cases with unknown sex
[3]Excludes 6 iSA no COVID-19 cases with unknown outcome
[4]Excludes 2 iSA COVID-19 and 533 iSA no COVID-19 cases with unknown discharge location
[5]Excludes 9 iSA COVID-19 and 504 iSA no COVID-19 cases with unknown bloodstream infection

Table 2: Selected underlying conditions, healthcare exposures, and location 3 days prior to onset of healthcare-associated community-onset iSA by prior COVID-19 hospitalization status

HACO	**iSA, COVID-19 (n=60)**	**iSA, No COVID-19 (n=1839)**	**OR**	**95% CI**	**p**
Underlying Conditions					

Burn/surgical wound	0 (0.0)	54 (2.94)	0.27	0.02-4.44	0.4
Chronic pulmonary disease	13 (21.67)	373 (20.28)	1.09	0.58-2.03	0.8
Chronic kidney disease	18 (30.00)	772 (41.98)	0.59	0.34-1.04	0.06
Decubitus/pressure ulcer	6 (10.00)	134 (7.29)	1.41	0.60-3.35	0.4
Diabetes mellitus	27 (45.00)	830 (45.13)	0.99	0.59-1.67	1.0
Hemiplegia	0 (0.0)	31 (1.69)	0.47	0.03-7.85	0.6
Intravenous drug use	4 (6.67)	159 (8.65)	0.75	0.27-2.11	0.6
Obesity or morbid obesity	13 (21.67)	329 (17.89)	1.27	0.68-2.37	0.5
Other chronic ulcer or chronic wound	7 (11.67)	223 (12.13)	0.96	0.43-2.13	0.9
Paraplegia	1 (1.67)	45 (2.45)	0.68	0.09-4.99	1.0
Pregnancy	0 (0.0)	6 (0.33)	2.33	0.13-41.85	1.0
Unknown	0 (0.0)	7 (0.38)	2.02	0.11-35.76	1.0
At least one of the above underlying conditions	47 (78.33)	1414 (76.89)	1.09	0.58-2.03	0.8
No underlying condition	2 (3.33)	144 (7.83)	0.41	0.10-1.68	0.3
Exposures					
Healthcare facility stay in the year before incident specimen collection					
Acute care hospitalization[1]	57 (95.00)	1520 (82.92)	3.91	1.22-12.57	0.01
Long term care facility residence[2]	25 (41.67)	438 (23.92)	2.27	1.34-3.84	<0.01
Long term acute care hospitalization[3]	3 (5.00)	15 (0.82)	6.37	1.79-22.62	0.02
Surgery in the year before the date on incident specimen collection[2]	13 (21.67)	639 (34.90)	0.52	0.28-0.96	0.03
Chronic dialysis[4]	7 (11.67)	455 (24.77)	0.40	0.18-0.89	0.02
Peritoneal	0 (0.00)	30 (6.59)	0.93	0.05-16.67	1.0
Hemodialysis[5]	7 (100.00)	421 (92.53)	1.23	0.07-21.95	1.0
AV fistula/graft	3 (42.86)	212 (50.12)	0.75	0.17-3.38	1.0
CVC	5 (71.43)	210 (49.88)	2.51	0.48-13.09	0.4
Unknown type of dialysis[6]	0 (0.0)	4 (0.88)	6.69	0.33-135.64	1.0
Central vascular catheter in place at any time in the 2 calendar days before incident specimen collection[7]	8 (13.33)	366 (19.93)	0.62	0.29-1.31	0.2
CVC in place >2 calendar days	5 (62.50)	301 (82.24)	0.36	0.08-1.54	0.2
ICU 2 days before DISC[8]	0 (0.0)	32 (1.74)	0.46	0.03-7.57	0.6
Location 3 days prior to specimen collection[9]					
Private residence	25 (41.67)	1404 (76.35)		Referent	
Long-term care facility	23 (38.33)	281 (15.28)	4.60	2.57-8.22	<0.01
Acute-care hospital (inpatient)	6 (10.00)	24 (1.31)	14.04	5.28-37.34	<0.01
Long-term acute care hospital	3 (5.00)	7 (0.38)	24.07	5.88-98.50	<0.01
Homeless	3 (5.00)	109 (5.93)	1.55	0.46-5.20	0.5

Incarcerated	0 (0.0)	5 (0.27)	<0.01	<0.01->999	1.0

[1]Excludes 6 iSA no COVID-19 cases with unknown hospitalization in the past year
[2]Excludes 8 iSA no COVID-19 cases with unknown hospitalization in the past year
[3]Excludes 9 iSA no COVID-19 cases with unknown hospitalization in the past year
[4]Excludes 2 iSA no COVID-19 cases with unknown chronic dialysis history
[5]Excludes 6 iSA no COVID-19 cases with unknown hemodialysis type
[6]Excludes 4 iSA no COVID-19 cases with unknown type of chronic dialysis
[7]Excludes 3 iSA no COVID-19 cases with unknown CVC history
[8]Excludes 5 iSA no COVID-19 case with unknown ICU status 2 days before DISC
[9]Excludes 9 iSA no COVID-19 cases with other or unknown location prior to specimen collection

Table 3: Selected clinical characteristics, healthcare exposures, and location 3 days prior to onset of hospital-onset invasive *S. aureus* by prior COVID-19 hospitalization status

HO	**iSA, COVID-19 (n=86)**	**iSA, No COVID-19 (n=421)**	**OR**	**95% CI**	**P**
Underlying Conditions					
Burn/surgical wound	0 (0.0)	5 (1.19)	0.44	0.02-7.99	0.6
Chronic pulmonary disease	27 (31.40)	85 (20.19)	1.81	1.08-3.02	0.02
Chronic kidney disease	20 (23.26)	114 (27.08)	0.82	0.47-1.41	0.5
Decubitus/pressure ulcer	4 (4.65)	21 (4.99)	0.92	0.31-2.78	0.9
Diabetes mellitus	42 (48.84)	135 (32.07)	2.02	1.26-3.23	<0.01
Hemiplegia	0 (0.0)	3 (0.71)	0.69	0.04-13.50	1.0
Intravenous drug use	0 (0.0)	23 (5.46)	0.1	0.01-1.63	0.02
Obesity or morbid obesity	23 (26.74)	74 (17.58)	1.71	1.0-2.94	0.07
Other chronic ulcer or chronic wound	3 (3.49)	31 (7.36)	0.45	0.14-1.52	0.2
Paraplegia	0 (0.0)	1 (0.24)	1.62	0.07-40.11	1.0
Pregnancy	0 (0.0)	0			
Unknown	0 (0.0)	4 (0.95)	0.54	0.03-10.05	1.0
At least one of the above underlying conditions	69 (80.23)	254 (60.33)	2.67	1.52-4.70	<0.01
No underlying condition	9 (10.47)	60 (14.25)	0.70	0.33-1.48	0.4
Exposures					
Healthcare facility stay in the year before incident specimen collection					
Acute care hospitalization	28 (32.56)	196 (46.56)	0.55	0.34-0.90	0.02
Long term care facility residence[1]	19 (22.09)	59 (14.05)	1.74	0.97-3.10	0.06
Long term acute care hospitalization[1]	1 (1.16)	1 (0.24)	4.93	0.31-79.58	0.2
Surgery in the year before the date on incident specimen collection[1]	5 (5.81)	82 (19.52)	0.25	0.10-0.65	<0.01
Chronic dialysis[1]	4 (4.65)	45 (10.71)	0.41	0.14-1.16	0.08
Peritoneal	0 (0.0)	1 (2.22)	3.30	0.12-93.41	1.0

Hemodialysis	4 (100)	44 (97.78)	0.30	0.01-8.60	1.0
AV fistula/graft	2 (50.00)	16 (36.36)	1.75	0.22-13.65	0.6
CVC	2 (50.00)	30 (68.18)	0.47	0.06-3.66	0.6
Central vascular catheter in place at any time in the 2 calendar days before incident specimen collection[1]	38 (44.19)	134 (31.90)	1.69	1.05-2.7	0.03
CVC in place for >2 calendar days	31 (81.58)	112 (83.58)	0.87	0.34-2.22	0.8
	31 (36.05)	112 (26.60)	1.56	0.95-2.54	0.08
ICU two days before DISC[2]	26 (30.59)	289 (68.81)	0.20	0.12-0.33	<0.01

[1]Excludes 1 iSA no COVID-19 case with unknown hospitalization in the past year, chronic dialysis history, and/or CVC history

[2]Excludes 1 iSA COVID-19 and 1 iSA no COVID-19 with unknown ICU status 2 days before DISC

COVID-NET cohort

Table 4: COVID-NET cases by race/ethnicity, age, sex

	COVID-19 hospitalization, iSA (N=146) No. (%)	**COVID-19 hospitalization, no iSA (N=44087) No. (%)**	**OR**	**95% CI**	**P-value**
Race/Ethnicity[1]					
White, not Hispanic	61 (41.78)	17807 (40.40)		Referent	
Hispanic, any race	32 (21.92)	10183 (23.10)	0.92	0.60-1.41	0.7
Black/African American, not Hispanic	37 (25.34)	10427 (23.65)	1.04	0.69-1.56	0.9
Asian, not Hispanic	9 (6.16)	3115 (7.07)	0.84	0.42-1.70	0.6
American Indian or Alaska Native, not Hispanic	3 (2.05)	568 (1.29)	1.54	0.48-4.93	0.5
Multiple Races, not Hispanic	0 (0.0)	225 (0.51)	<0.01	<0.01->999	1.0
Unknown race and ethnicity	4 (2.74)	1762 (4.00)	0.66	0.24-1.83	0.4
Age median (range)	67 (14-96)	63 (1->100)			0.04
Sex					
Male	87 (59.6)	22512 (51.2)	1.41	1.02-1.97	0.04
Female	59 (40.4)	21575 (48.9)			

[1]Excludes 2 COVID-19 no iSA cases with missing race/ethnicity

Table 5: Patient residence at time of COVID-19 hospitalization and insurance type by iSA status (sampled population)

	COVID-19 hospitalization, iSA (N=40) No. (%)	COVID-19 hospitalization, No iSA (N=10392) No. (%)	OR	95% CI	P-value
Residence at time of hospitalization[1]					
Private residence, with and without services	22 (55.00)	8254 (79.83)		Referent	
Homeless/shelter/facility[2]	4 (10.00)	242 (2.34)	6.20	2.12-18.13	<0.01
Long term or assisted care[3]	14 (35.00)	1772 (17.14)	2.96	1.51-5.81	<0.01
Hospice	0 (0.0)	5 (0.05)	<0.01	<0.01->999	1.0
Hospitalized at birth	0 (0.0)	14 (0.14)	<0.01	<0.01->999	1.0
Type of insurance[4]					
Private	8 (20.00)	2856 (27.98)		Referent	
Medicare	8 (20.00)	1168 (11.44)	2.45	0.92-6.53	0.07
Medicaid	3 (7.50)	1934 (18.95)	0.55	0.15-2.09	0.4
Uninsured	2 (5.00)	755 (7.40)	0.95	0.20-4.46	0.9
Other	0 (0.0)	586 (5.74)	<0.01	<0.01->999	1.0
Multiple (2+)	19 (47.50)	2809 (27.52)	2.42	1.06-5.53	0.04

[1]Excludes 52 COVID-19 no iSA cases with unknown or other discharge location
[2]Homeless/shelter, alcohol/drug abuse treatment, corrections facility, or psychiatric facility
[3]Nursing home/skilled nursing facility, assisted living/residential care, long-term acute care hospital, group/retirement home, rehabilitation facility, or other long term care facility
[4]Excludes 284 COVID-19 no iSA cases with unknown insurance

Table 6: Underlying medical conditions of COVID-19 hospitalized patients by iSA status (sampled)

	COVID-19 hospitalization, iSA (N=40) No. (%)	COVID-19 hospitalization, no iSA (N= 10392) No. (%)	OR	95% CI	P-value
Any pre-existing medical condition[1]	37 (92.50)	7965 (71.97)	4.80	1.48-15.59	<0.01
Any underlying respiratory condition[2]	27 (67.50)	4412 (42.75)	2.78	1.43-5.40	<0.01
Asthma/COPD/Reactive airway disease/Emphysema[3]	17 (42.50)	1895 (18.34)	3.29	1.75-6.17	<0.01
Other chronic lung disease[3]	8 (20.00)	1174 (11.36)	1.95	0.90-4.24	0.1
Diabetes mellitus[3]	23 (57.50)	3120 (30.20)	3.13	1.67-5.86	<0.01
Any respiratory condition OR diabetes[2]	32 (80.00)	5782 (55.70)	3.18	1.46-6.91	<0.01
Any blood disorder/hemoglobinopathy[3]	2 (5.00)	296 (2.86)	1.78	0.43-7.43	0.3
Cardiomyopathy/heart failure[3]	6 (15.00)	989 (9.57)	1.67	0.70-3.98	0.3
Myocardial infarction (MI)[3]	2 (5.00)	426 (4.12)	1.22	0.29-5.09	0.7
Peripheral artery disease/vascular disease[3]	3 (7.50)	242 (2.34)	3.38	1.04-11.04	0.07
Cerebral vascular accident (CVA)/stroke/transient ischemic attack (TIA)[3]	4 (10.00)	749 (7.25)	1.42	0.50-4.00	0.53
Other cardiovascular disease[2]	15 (37.50)	2346 (22.60)	2.05	1.08-3.90	0.04

Dementia/Alzheimer's disease[3]	4 (10.00)	798 (7.72)	1.33	0.47-3.74	0.5
Plegias/paralysis/quadriplegia[3]	0 (0.0)	142 (1.37)	0.88	0.05-14.43	1.0
Epilepsy/seizure/seizure disorder[3]	1 (2.50)	419 (4.06)	0.61	0.08-4.43	1.0
Cerebral palsy/developmental delay/Edward's syndrome/Down syndrome/neural tube defects[3]	1 (2.50)	314 (3.04)	0.82	0.11-5.97	1.0
Multiple sclerosis[3]	0 (0.0)	46 (0.45)	2.73	0.17-45.08	1.0
Neuropathy[3]	4 (10.00)	424 (4.10)	2.60	0.92-7.33	0.08
Other neurologic disorder[2]	3 (7.50)	414 (4.01)	1.94	0.60-6.33	0.2
HIV/AIDS[3]	0 (0.0)	94 (0.91)	1.34	0.08-21.91	1.0
Solid organ malignancy[3]	1 (2.50)	253 (2.45)	1.02	0.14-7.46	1.0
Leukemia/lymphoma/Hodgkins/ Non-Hodgkins/multiple myeloma[3]	0 (0.0)	96 (0.93)	1.31	0.08-21.45	1.0
Transplant, hematopoietic stem call[3]	0 (0.0)	11 (0.11)	11.08	0.62-191.21	1.0
Transplant, solid organ[3]	1 (2.50)	100 (0.97)	2.62	0.36-19.28	0.3
Immunosuppressive therapy[3]	0 (0.0)	204 (1.97)	0.61	0.04-9.98	1.0
Steroid therapy[3]	0 (0.0)	222 (2.15)	0.56	0.04-9.79	1.0
Other immunocompromised condition[2]	1 (2.50)	317 (3.05)	0.81	0.11-5.94	0.8
Dialysis[3]	3 (7.50)	241 (2.33)	3.40	1.04-11.09	0.07
Chronic kidney disease/chronic renal insufficiency/end stage renal disease/glomerulonephritis/ nephrotic syndrome[3]	11 (27.50)	1391 (13.46)	2.44	1.22-4.89	<0.01
Crohn's disease/ulcerative colitis[3]	0 (0.0)	84 (0.81)	1.50	0.09-24.55	1.0
Alcoholic hepatitis/autoimmune hepatitis/chronic liver disease/cirrhosis/hepatitis B chronic/hepatitis C chronic/non-alcoholic fatty liver disease[3]	5 (12.50)	365 (3.53)	3.90	1.52-10.01	0.01
Any rheumatologic condition[3]	0 (0.0)	423 (4.09)	0.29	0.02-4.71	0.4
Hypertension[3]	29 (72.50)	4658 (45.14)	3.20	1.60-6.42	<0.01
Feeding tube dependent[4]	0 (0.0)	94 (1.99)	0.83	0.05-13.68	1.0
Trach dependent/vent dependent[5]	0 (0.0)	31 (0.66)	2.53	0.15-42.24	1.0
Wheelchair dependent[6]	1 (3.45)	188 (3.93)	0.87	0.12-6.45	1.0

[1]Excludes 72 COVID-19 no iSA cases with unknown pre-existing condition status

[2]Excludes 12 COVID-19 no iSA cases with unknown underlying medical condition specifics

[3]Excludes 60 COVID-19 no iSA cases with unknown underlying medical conditions specifics

[4]Excludes 11 COVID-19 iSA and 5,673 COVID-19 no iSA cases with unknown feeding tube dependence

[5]Excludes 11 COVID-19 iSA and 5,668 COVID-19 no iSA cases with unknown trach/vent dependence

[6]Excludes 11 COVID-19 iSA and 5,612 COVID-19 no iSA cases with unknown wheelchair dependence

Table 7: Selected healthcare exposures or risk factors during COVID-19 hospitalization by iSA status (sampled population)

	COVID-19 hospitalization, iSA (N=40) No. (%)	**COVID-19 hospitalization, no iSA (N=10392) No (%)**	**OR**	**95% CI**	**P-value**

ICU and other interventions					
ICU admission[1]	24 (60.00)	2723 (26.38)	4.19	2.22-7.89	<0.01
Number of days in ICU median (range)[2]	18 (0-151)	6 (0-127)			<0.01
Invasive mechanical ventilation[3]	21 (52.50)	1402 (13.58)	7.03	3.77-13.11	<0.01
BiPAP/CPAP/high flow nasal cannula[4]	20 (50.00)	2269 (21.99)	3.55	1.91-6.60	<0.01
BiPAP/CPAP/HFNC without IMV[5]	3 (7.5)	1209 (13.55)	0.61	0.19-1.98	0.6
ECMO[6]	3 (7.50)	65 (0.63)	12.77	3.84-42.48	<0.01
Vasopressor use[7]	19 (47.50)	1315 (12.78)	6.17	3.31-11.52	<0.01
Systemic steroids[8]	21 (52.50)	3535 (32.62)	2.12	1.14-3.95	<0.01
Renal replacement therapy or dialysis[9]	5 (12.50)	400 (3.88)	3.54	1.38-9.09	<0.01
At least one of the above[10]	29 (72.50)	5125 (49.98)	2.64	1.32-5.29	<0.01
Discharge summary					
Acute respiratory distress syndrome (ARDS)[11]	9 (22.50)	677 (6.55)	4.14	1.96-8.73	<0.01
Sepsis[12]	13 (32.50)	1387 (13.43)	3.10	1.60-6.03	<0.01
Acute renal failure[11]	13 (32.50)	1500 (14.52)	2.83	1.46-5.51	<0.01
Acute respiratory failure[11]	19 (47.50)	3788 (34.44)	1.58	0.84-2.91	0.2
Disseminated intravascular coagulation (DIC)[11]	0 (0.0)	2 (0.02)	51.00	2.41-1079.15	1.0

[1]Excludes 128 COVID-19 no iSA cases with unknown ICU admission
[2]Excludes 16 COVID-19 iSA and 7789 COVID-19 no iSA cases with unknown length of ICU stay
[3]Excludes 130 COVID-19 no iSA cases with unknown IMV use
[4]Excludes 80 COVID-19 no iSA cases with unknown BiPAP/CPAP/HFNC use
[5]Excludes 83 COVID-19 no iSA cases with unknown BiPAP/CPAP/HFNC or IMV use
[6]Excludes 87 COVID-19 no iSA cases with unknown ECMO use
[7]Excludes 100 COVID-19 no iSA cases with unknown vasopressor use
[8]Excludes 81 COVID-19 no iSA cases with unknown systemic steroid use
[9]Excludes 73 COVID-19 no iSA cases with unknown renal replacement therapy/dialysis use
[10]Excludes 137 COVID-19 no iSA cases with unknown intervention use
[11]Excludes 62 COVID-19 no iSA cases with unknown ARDS, acute renal failure, acute respiratory failure, and/or DIC diagnosis
[12]Excludes 65 COVID-19 no iSA cases with unknown sepsis diagnosis

Table 8: Outcomes of hospitalized COVID-19 cases by iSA status

	COVID-19 hospitalization, iSA (N=140) No. (%)	**COVID-19 hospitalization, No iSA (N=44087) No. (%)**	**OR**	**95% CI**	**P-value**
Died during hospitalization[1]	48 (38.40)	4504 (12.44)	4.39	3.06-6.30	<0.01
Alive[1]	77 (61.60)	31700 (87.56)			

Discharge location among patients who survived[1]					
Private residence with or without services	5 (17.86)	7854 (76.22)		Referent	
Homeless/shelter/facility[3]	4 (14.29)	199 (1.93)	31.57	8.42-118.47	<0.01
Any long term or assisted care[4]	16 (57.14)	1653 (16.04)	15.20	5.56-41.56	<0.01
Hospice	0 (0.0)	162 (1.57)	<0.01	<0.01->999	1.0
Against medical advice	1 (3.57)	111 (1.08)	14.51	1.64-122.12	0.02
Discharged to another hospital	0 (0.0)	20 (0.19)	<0.01	<0.01->999	1.0

[1]Excludes 15 COVID-19 iSA and 7883 COVID-19 no iSA cases with unknown outcome
[2]Excludes 14 COVID-19 iSA and 21,701 COVID-19 no iSA cases with unknown or other discharge location
[3]Homeless/shelter, alcohol/drug abuse treatment, corrections facility, or psychiatric facility
[4]Nursing home/skilled nursing facility, assisted living/residential care, long-term acute care hospital, group/retirement home, rehabilitation facility, or other long term care facility

Table 9: Antiviral treatment of hospitalized COVID-19 patients by iSA status (sampled)

	COVID-19 hospitalization, iSA (N=40) No. (%)	**COVID-19 hospitalization, no iSA (N=10392) No. (%)**	**OR**	**95% CI**	**P-value**
Any treatment[1]	25 (62.50)	5873 (56.88)	1.26	0.67-2.40	0.5
Monoclonal antibody/ immunomodulator treatment[2,3]	5 (12.50)	450 (4.36)	3.14	1.22-8.04	0.03
Monoclonal antibody/ immunomodulator treatment[2] – unknown[4]	1 (2.50)	111 (1.07)	2.37	0.32-17.44	0.4
Convalescent plasma[3]	10 (25.00)	973 (9.42)	3.21	1.56-6.58	<0.01
Convalescent plasma – unknown[4]	0 (0.0)	4 (0.04)	28.50	1.51-538.03	1.0
Remdesivir[3]	13 (32.50)	2800 (27.11)	1.29	0.67-2.51	0.4
Remdesivir – unknown[4]	0 (0.0)	65 (0.63)	1.95	0.12-31.99	1.0
Unknown[5]	0 (0.0)	4 (0.04)	28.50	1.51-538.03	1.0

[1]Excludes 67 COVID-19 no iSA cases with unknown treatment information
[2]Included: anakinra, infliximab, Jakafi, sarilumab, tocilizumab
[3]Excludes 62 COVID-19 no iSA cases with unknown MAB, remdesivir, and/or convalescent plasma treatment information
[4]These cases were listed as being a part of a randomized control trial for the treatment in question so whether they received the treatment or placebo is unknown
[5]These were listed as an unspecified randomized control trial that may have included a remdesivir, immunomodulator, or convalescent plasma

Health disparities analysis

Table 10: Rates of iSA by race/ethnicity per 100,000 population, 2019 (pre-COVID-19 pandemic) vs 2020 (COVID-19 pandemic), six Emerging Infections Program sites, March 1-December 31, 2020

Race/Ethnicity	2019 No. (Rate/100,000)	2020 No. (Rate/100,000)	Rate Ratio	95% CI
Hispanic	416 (31.56)	364 (27.54)	0.87	0.76-1.00
White, not Hispanic	2256 (51.03)	2008 (45.97)	0.90	0.85-0.97
Black, not Hispanic	892 (62.66)	902 (63.17)	1.01	0.92-1.11
American Indian, not Hispanic	53 (195.72)	54 (203.24)	1.04	0.71-1.52
Asian or Pacific Islander, not Hispanic	295 (20.81)	282 (19.59)	0.94	0.80-1.11
Multiracial, not Hispanic	26 (9.63)	17 (6.10)	0.63	0.34-1.17
All races/ethnicities	3938 (44.36)	3627 (40.63)	0.92	0.88-0.97

Excludes 189 cases with unknown race/ethnicity

Table 11: Health disparity measures, iSA rates overall (excluding multiracial)

Health Disparity Measure	2019	2020	Change
Maximal rate difference (MRD)	174.92	183.65	-
Maximal rate ratio (MRR)	9.41	10.38	Increase
Summary rate ratio (SRR)	4.10	4.34	Increase

Table 12: Rates of CA iSA by race/ethnicity per 100,000 population, 2019 (pre-COVID-19 pandemic) vs 2020 (COVID-19 pandemic)

Race/Ethnicity	2019 No. (Rate/100,000)	2020 No. (Rate/100,000)	Rate Ratio	95% CI
Hispanic	161 (12.21)	128 (9.68)	0.79	0.63-1.00
White, not Hispanic	826 (18.69)	736 (16.85)	0.90	0.82-1.00
Black, not Hispanic	217 (15.24)	210 (14.71)	0.96	0.80-1.17
American Indian, not Hispanic	29 (107.09)	20 (75.27)	0.70	0.39-1.24
Asian or Pacific Islander, not Hispanic	94 (6.63)	83 (5.76)	0.87	0.65-1.17
Multiracial, not Hispanic	*	*	*	*
All races/ethnicities	1331 (14.99)	1183 (13.35)	0.89	0.82-0.96

*= suppressed, n less than 10

Excludes 74 CA cases with unknown race/ethnicity

Table 13: Rates of HACO iSA by race/ethnicity per 100,000 population, 2019 (pre-COVID-19 pandemic) vs 2020 (COVID-19 pandemic)

Race/Ethnicity	2019 No. (Rate/100,000)	2020 No. (Rate/100,000)	Rate Ratio	95% CI
Hispanic	208 (15.78)	187 (14.15)	0.90	0.82-1.21
White, not Hispanic	1165 (26.35)	1010 (23.12)	0.88	0.81-0.95
Black, not Hispanic	554 (38.92)	550 (38.52)	0.99	0.88-1.11
American Indian, not Hispanic	19 (70.17)	29 (109.15)	1.56	0.87-2.82

Asian or Pacific Islander, not Hispanic	168 (11.85)	163 (11.32)	0.96	0.77-1.19
Multiracial, not Hispanic	17 (6.30)	*	*	*
All races/ethnicities	2131 (24.01)	1945 (21.95)	0.91	0.86-0.97

*= suppressed, n less than 10

Excludes 82 HACO cases with unknown race/ethnicity

Table 14: Rates of HO iSA by race/ethnicity per 100,000 population, 2019 (pre-COVID-19 pandemic) vs 2020 (COVID-19 pandemic)

Race/Ethnicity	**2019 No. (Rate/100,000)**	**2020 No. (Rate/100,000)**	**Rate Ratio**	**95% CI**
Hispanic	45 (3.41)	48 (3.63)	1.06	0.71-1.60
White, not Hispanic	256 (5.79)	259 (5.93)	1.02	0.86-1.22
Black, not Hispanic	119 (8.36)	142 (9.95)	1.19	0.93-1.52
American Indian, not Hispanic	*	*	*	*
Asian or Pacific Islander, not Hispanic	31 (2.19)	35 (2.43)	1.11	0.68-1.81
Multiracial, not Hispanic	*	*	*	*
All races/ethnicities	460 (5.18)	494 (5.57)	1.08	0.95-1.22

*= suppressed, n less than 10

Excludes 20 HO cases with unknown race/ethnicity

Table 15: Health disparity measures stratified by epi class

	CA			**HACO**			**HO**		
Measure	**2019**	**2020**	**Change**	**2019**	**2020**	**Change**	**2019**	**2020**	**Change**
MRD	100.46	69.51	-	58.32	97.82	-	12.59	16.39	-
MRR	16.15	13.06	Decrease	5.92	9.64	Increase	6.76	7.74	Increase
SRR	5.78	5.05	Decrease	3.19	4.08	Increase	3.70	3.94	Increase