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Timing of Methicillin-resistant *Staphylococcus aureus* (MRSA) Bloodstream Infections among Hospitalized Patients and Its Association with Patient and Prior Healthcare Exposures

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Abstract

Timing of Methicillin-resistant *Staphylococcus aureus* (MRSA) Bloodstream Infections among Hospitalized Patients and Its Association with Patient and Prior Healthcare Exposures

By Katryna Gouin

Background: There have been no significant reductions in hospital-onset MRSA bloodstream infections (BSIs) in recent years. Therefore, we sought to identify patient and healthcare exposures that differ by timing of MRSA BSI among hospitalized patients.

Methods: We estimated the timing of MRSA BSI in adults hospitalized from 2013-2016 in New York using surveillance data from the National Healthcare Safety Network. MRSA events were linked to administrative data to capture patient and healthcare variables. Daily risk was calculated using the number of MRSA events per day and the number of patients remaining in the hospital each day. Among those with MRSA, events were divided into three groups: community-onset (diagnosed on days 1-3), early hospital-onset (days 4-7), late hospital-onset (days 8-30). Univariate and multinomial modeling were performed to identify risk factors for the timing of onset.

Results: The median time to hospital-onset MRSA BSI was 11 days. Of 10,081 (80%) linked events, 19.2% were hospital-onset and 80.8% were community-onset. The daily risk of hospital-onset MRSA BSI was highest for patients with longer length of stay (18.8 events per 100,000 patients on day 28). Patients that were admitted from a skilled nursing facility, had surgery in the previous year, or were on dialysis during hospitalization were more likely to have community-onset vs. early hospital-onset MRSA BSI (aOR=1.74, 95% CI:1.32,2.30, aOR=1.26, 95% CI: 1.02, 1.57, and aOR=1.33, 95% CI: 1.10, 1.61, respectively). Patients with prior inpatient hospitalization or dialysis during hospitalization were less likely to have late hospital-onset vs. early hospital-onset MRSA BSI (aOR=0.79, 95% CI: 0.66, 0.96 and aOR=0.63, 95% CI: 0.49, 0.81).

Conclusion: Using large-scale linkage of surveillance and administrative data, we showed that half of hospital-onset MRSA BSI occurs on or after day 11 of hospitalization. The risk of hospital-onset MRSA BSI is highest with longer length of stay and different healthcare exposures are associated with both community-onset and late hospital-onset MRSA BSI compared to early hospital-onset MRSA BSI. This suggests that length of stay and prior healthcare exposures could be targeted in hospital-based infection prevention.

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Introduction

Antibiotic resistance is one of the most severe threats to public health worldwide. Resistant "superbugs" have the potential to kill 10 million people annually and lead to an additional estimated $100 trillion dollars in costs to the world economy between 2016 and 2050 (1). The Centers for Disease Control and Prevention (CDC) estimates that at least 2 million illnesses, 23,000 deaths, and 8 million extra hospital days in the United States are attributable to antibiotic-resistant bacteria each year (2, 3). Therefore, battling antibiotic resistance is a top public health priority for the CDC and the World Health Organization (WHO). The advances that have been made in longevity and healthcare are now at risk with the impending complications brought on by antibiotic-resistant organisms; infections are exceedingly difficult to treat as new resistant bugs are rapidly emerging (4).

Organisms can have innate resistant to antibiotics or acquire resistance through mutation or exchange of genetic elements. During treatment with antibiotics, bacteria that are susceptible to frontline antibiotics are killed, while resistant organisms survive and reproduce, resulting in the spread of antibiotic resistance (5, 6). Today, there exist many bacterial species that are resistant to multiple classes of antibiotics, known as multidrug-resistant organisms (MDROs). MDROs are increasingly to blame for hospital-acquired infections (HAIs), causing 14% of infections acquired in the healthcare setting (7). Patients with increased susceptibility to HAIs are those with long durations of hospitalization, lowered immunity, severe underlying conditions, and advanced age (8). Invasive device use also increases the risk of acquiring an infection in the hospital, causing central line-associated bloodstream infections, catheter-associated urinary tract

infections, and ventilator-associated pneumonia. Although MDROs present with clinical manifestations that are similar to infections caused by non-resistant pathogens, treating patients with MDRO infections remains a challenge. Consequently, as the armory of antibiotics able to effectively combat antibiotic-resistant organisms diminishes, MDROs continue to be a serious public health threat (9, 10).

The CDC's action plan to fight antibiotic resistance has four tiers: Prevent Infection, Conduct Surveillance, Improve Antibiotic Stewardship, and Develop New Drugs and Diagnostic Tests. Preventing infections reduces the need and administration of antibiotic therapy, thereby reducing the risk of development and spread of drug resistance (3). The CDC tracks antibiotic-resistant HAIs through the National Healthcare Safety Network (NHSN) to identify risk factors for infection and inform strategies to prevent resistant infections. NHSN is the nation's most widely used HAI surveillance system and collects and reports surveillance data from 17,000 medical facilities nationwide, including long- and short-stay acute care hospitals, rehabilitations hospitals, outpatient dialysis centers, ambulatory surgery centers, and skilled nursing facilities (11). The third tier, improving antibiotic stewardship, is the commitment to the safe and appropriate use of antibiotics by determining if antibiotics are necessary and, in situations where antibiotics are indicated, choosing a narrow spectrum antibiotic and prescribing an appropriate duration of treatment that will effectively treat the infection without causing extensive damage to the patient's microbiome. Prudent use of antibiotics is essential in a time when antibiotic use in humans and animals is rampant; half of antibiotic use in humans is unnecessary and poses increased risk for the spread of resistant bacteria.

Finally, new drugs are needed to treat resistant bacteria and improved diagnostic tests are needed to monitor emergent resistance (3).

Staphylococcus aureus is the second leading cause of HAIs, causing 11% of infections in the healthcare setting (12). *S. aureus* colonizes approximately one-third of the population. Its ubiquity in the environment can be attributed to its ability to adapt and develop resistance to antimicrobials. A virulent multidrug-resistant strain of *S. aureus* that is associated with high morbidity and mortality is methicillin-resistant *S. aureus* (MRSA). MRSA is a gram-positive bacterium that is resistant to the beta-lactam class of antibiotics, which consists of most available and widely used antibiotics, including methicillin, amoxicillin, penicillin, oxacillin, and cefoxitin (13). Diagnosis of MRSA infection involves testing the infected area (e.g., abscesses or blood specimen) for *S. aureus*, with additional testing for the susceptibility of the isolate to commonly used antibiotics (14). The first isolation of MRSA in the United States was in 1968 and, until the mid-1990s, MRSA was found predominantly in healthcare settings. By the mid-1990s, MRSA had emerged among individuals in the community with no prior healthcare exposure (15). In 2015, 45% of *S. aureus* HAIs were MRSA (12). Today, there are multiple strains of MRSA in the community as strains evolve to increase transmission potential.

The transmission and persistence of MRSA in the healthcare setting is dependent on its ability to infect patients, survive antimicrobial treatment, and spread to new patients, which are impacted by local adherence to prevention efforts (9). Two percent of the general U.S. population are carriers of MRSA; however, few will develop disease unless they are at increased risk for MRSA infection (16). Risk factors associated with

invasive MRSA infection have been researched extensively and are related to patient immune status and underlying disease severity. Identified risk factors for acquisition of MRSA bloodstream infections in the hospital include prior antibiotic use, multiple co-morbid conditions (17), prior hospitalization, long lengths of stay (8, 17-20), hemodialysis (17, 21), assisted living (22), surgery (17), male sex (23, 24), and African-American race (23, 25). MRSA infections can also be attributed to increased hospital length of stay and increased healthcare costs (18, 19). Individuals at greater risk of contracting MRSA infection in the community include school-aged children, military personnel, athletes, and intravenous drug users (26).

MRSA infections are often categorized into epidemiologic categories based on the location of infection onset. NHSN categorizes MRSA-positive blood cultures obtained on days 1-3 of hospitalization or in the outpatient setting as community-onset (CO), and cultures obtained on or after day 4 of hospitalization as hospital-onset (HO) (27). Identifying a culture as CO however, does not fully explain where MRSA acquisition occurred, because the organism may have been acquired through healthcare contact (28). NHSN attempts to account for this by identifying MRSA-positive blood cultures that occur after hospitalization in the prior month (27). The CDC's Emerging Infections Program (EIP) is an alternative population-level laboratory-based surveillance program that collects information on MRSA in nine states. EIP uses a similar definition for HO infection, but further subsets CO infections into two groups: those with recent contact with the healthcare system as healthcare-associated community-onset (HACO) infections, and those without recent healthcare contacts as community associated (CA). HACO is defined by a history of inpatient hospitalization, surgery, dialysis, or residence in a long-

term care facility in the previous year, or central vascular catheter in place for two days or less prior to culture (29). While classifications of onset exist, the distinction between community and hospital acquisition is difficult to discern; finer resolution of risk factors associated with these onset types would lead to improved prevention of MRSA infection (30, 31).

A study performed by the EIP investigated the incidence of invasive MRSA infections from 2005 to 2011 using U.S. population-based surveillance data. They found that 60% of invasive MRSA infections were HACO and 20% were CA. HO MRSA contributed to 20% of MRSA infections. The majority of HO MRSA infections (71%) were bloodstream infections (BSI), also known as bacteremia. In addition, HO MRSA infections had higher seven-day and in-hospital all-cause mortality compared to CA and HACO MRSA infections (32).

Incidence of HO and CO MRSA BSIs in the U.S. has been decreasing. The CDC estimates that from 2005 to 2016, there was a 7.8% annual decrease in HACO BSIs and a 6.9% annual decrease in CO BSIs. The national incidence of HO MRSA BSIs decreased 17% annually between 2005 and 2012. However, there has been little change in the rates of HO MRSA BSI in recent years (33). This emphasizes the ongoing importance of targeting interventions to prevent the severe consequences of MRSA BSI. An estimated 119,247 *S. aureus* BSIs occurred in 2017 and were associated with 19,832 deaths (33). Furthermore, the 30-day all-cause mortality rate of *S. aureus* BSI is 20% (34). Therefore, interventions to reduce MRSA transmission, improve patient outcomes, and reduce MRSA bacteremia-related mortality are a priority.

The prevalence of MRSA in hospitals poses great risk of infection-related mortality to patients. Healthcare workers are a primary source of MRSA transmission in hospitals. A 2014 meta-analysis of data from hospitals in the U.S. and Europe under non-outbreak conditions estimated that 4.6% of healthcare workers are colonized with MRSA (35). The transmission of MRSA occurs through direct contact with infected skin and wounds or by indirect contact with contaminated shared equipment. MRSA can persist on environmental surfaces for days to months, depending on conditions and surfaces, highlighting the importance of environmental cleaning to reduce transmission (36). Its infection patterns require continued investigation in order to target interventions efficiently and effectively.

Current guidelines indicate the use of standard precautions in the healthcare setting for the prevention of MRSA infections. This entails proper hand hygiene, personal protective equipment as needed, such as gloves, gown, or mask to protect skin, clothing, and mucous membranes, respectively, as well as safe injection practices, environmental cleaning, respiratory hygiene, and aseptic technique. The use of contact precautions may be indicated, including isolation or cohorting of patients with MRSA, wearing gowns or gloves for all interactions with infected or asymptomatically colonized patients, and the use of disposable or dedicated equipment (5). Additional prevention strategies include decolonization with mupirocin nasal ointment and/or bathing with chlorhexidine gluconate, a broad-spectrum antiseptic, which have been successful at reducing MRSA bloodstream infections in randomized controlled trials (5, 37, 38). Supplementary elements that CDC recommends are identifying and reporting patients previously infected

or colonized with MRSA, education of healthcare providers on MRSA infection and prevention, and MRSA surveillance (39).

Healthcare surveillance programs serve to identify outbreaks, evaluate intervention impact, and estimate the burden of HAIs, including MRSA (40). Beginning in 2013, acute care hospitals participating in the Centers for Medicare & Medicaid Services (CMS) Inpatient Quality Reporting were required to report facility-wide inpatient MRSA blood specimen laboratory-identified (Lab ID) events to NHSN. As of January 1, 2015, acute care hospitals are also required to report MRSA Lab ID events from outpatient emergency departments and 24-hour observation locations (41). CMS reduces reimbursements to hospitals with low performance in HAI measures (42, 43).

While useful for the standard reporting of HAIs, surveillance data are often limited in variables that can be collected to ensure compliance and accuracy of reporting. Therefore, the value of surveillance data can be greatly enhanced when they are combined with other data sources. Improvements in meaningful use and clinical practice guidelines have made patient data readily available through electronic medical records and electronic claim submission. Administrative databases can supplement surveillance data by providing claims-level data on patient characteristics, medical history, and previous healthcare exposures in a variety of healthcare settings. The Agency for Healthcare Research and Quality (AHRQ) sets criteria for state inpatient databases in order to standardize variables. However, administrative healthcare data are not collected for research purposes, and thus have limitations when used for studies. Administrative databases may be insufficient to identify HAIs using only the International Classification of Diseases, Ninth and Tenth Revisions Clinical Modification (ICD-9/ICD-10-CM)

diagnosis codes. For example, a MRSA event may be misclassified as a methicillin-susceptible *S. aureus* event or bacteremia may not be identified as the principal diagnosis if the patient has other severe diagnoses. Therefore, surveillance data can be used to identify cases of HAIs and subsequently linked to administrative databases at the patient level to enable access to additional patient, facility, and healthcare data to strengthen epidemiologic studies and answer relevant public health questions.

Few U.S. studies have investigated the epidemiology of the timing of MRSA BSI onset, including the distribution of onset time since hospital admission, risk factors for timing of onset during hospitalization, and how length of stay impacts the daily risk of HO MRSA BSI (44, 45). Variations of these research questions have been addressed in English and Danish studies (46-48). Public Health England found that, in 2007-2008, the median number of days between admission to first positive blood specimen was 7, interquartile range (IQR:0-21), and decreased to 1 (IQR:0-12) in 2016-2017. This was likely because the number of HO BSIs declined faster than CO BSIs, as most prevention interventions were introduced only in hospitals. They also found that the percentage of cases occurring on or after day 7 of hospital admission decreased between 2007 and 2017, from 51.5% to 34.7%. Nonetheless, 34.7% of MRSA BSIs occurred on or after day 7, many of which are likely preventable because of the ample time between admission and onset for prevention measures to be implemented (47). Furthermore, studies that assess the timing of HAIs such as *Clostridioides difficile* (CDI) diagnosis since admission are available, but parallel studies for MRSA are underrepresented (49-51). The risk factors for early and late onset infections have been well described for neonatal sepsis, ventilator-associated pneumonia, and surgical site infections; however, similar studies

have not been performed for adult bacteremia (52-57). In addition, a Danish study found that the risk of all HO bacteremia is lowest during the first 7 days of hospitalization, however this has not been evaluated in U.S. hospitals (46). Comparable studies in the U.S. are needed to answer important questions regarding the timing of HO MRSA BSIs to investigate patterns of infection and evaluate novel approaches to prevention.

Patients with long lengths of hospital stays are a high-risk group for HO MRSA BSIs (20). It is possible that interventions to prevent HO MRSA BSI could be applied to patients according to their duration of hospitalization (e.g., chlorhexidine bathing, which is rarely used outside of intensive care units). This would serve as an efficient way to prevent MRSA BSI, compared to a blanket approach of applying the intervention to all patients at admission and continuing for the duration of each patient's hospital stay. Surgical procedures, illness severity, compromised immunity, and unanticipated complications can extend hospitalization and introduce risk factors for bacteremia. However, the risks for timing of MRSA BSI are not well established. In order to assess how many infections are preventable, a distribution of the time to onset and daily risk of MRSA BSI in U.S. acute care hospitals is needed. Furthermore, the risk factors that distinguish patients infected with MRSA at different times would need to be delineated in order to evaluate the traditional classification of MRSA BSI. This information will serve to better inform clinicians of the window of risk for MRSA BSI and improve targeting of preventative measures based on length of stay, patient characteristics and healthcare exposures and ultimately improve patient outcomes (46).

Thus, the objectives of this study are to:

1. Describe the distribution of time to incident MRSA bloodstream infections for hospital- and community-onset events among hospitalized adults overall and by facility characteristic.
2. Calculate the daily risk of hospital-onset MRSA bloodstream infections for the first 30 days of hospitalization.
3. Identify patient characteristics that are associated with time from hospital admission to MRSA bloodstream infections, among hospitalized patients with MRSA.
4. Determine what healthcare exposures are associated with community-onset vs. early hospital-onset and late hospital-onset vs. early hospital-onset MRSA bloodstream infections.

Methods

Study Design, Population and Data Sources

The study is a retrospective cohort of adult (age ≥18) patients hospitalized in acute care hospitals in New York between 1/1/2013 and 12/31/2016. The NHSN Lab ID event module was used to identify incident MRSA-positive blood cultures, operationalized as MRSA BSI in this study, reported from both inpatient and emergency department/24-hr observation units during the first 365 days of admission. The first MRSA event per hospital admission was included, and observation patients without a subsequent admission were excluded. Events in which the patient had a prior positive MRSA blood culture in the previous 14 days were excluded, per NHSN protocol (27). NHSN facilities were eligible for inclusion if they conducted facility-wide reporting for 12 months of the year, meaning all inpatient units agreed to report any MRSA-positive blood cultures occurring during that calendar year that met NHSN definitions. We excluded MRSA-positive blood cultures reported from specialty and non-acute care hospitals, such as children's hospitals, women's hospitals, critical access hospitals, long-term acute care hospitals, and units with non-representative patients including rehabilitation and psychiatric wards, due to small numbers of MRSA BSIs in these types of facilities and different patient populations to those in short-term acute care hospitals.

To address objectives 2-4, we linked the MRSA BSIs from NHSN to the Statewide Planning and Research Cooperative System (SPARCS). SPARCS is the statewide hospital discharge dataset collected by the New York Department of Health and provides pre-claims data on patient hospitalization characteristics, dates of admission and discharge, procedures, admission source, diagnosis codes, and payer information from

inpatient, ambulatory surgery, emergency, and hospital-based outpatient visits. In order to relate patient and healthcare risk factors in prior and index hospitalizations with the timing of MRSA BSI, the NHSN data were linked at the event level to the SPARCS inpatient database using an exact match of patient date of birth, facility, gender, and NHSN specimen collection date between SPARCS admission date and discharge date, inclusive. NHSN patient events that did not link to SPARCS dataset were excluded from analysis of daily risk and risk factors (i.e., objectives 2-4)

The MRSA BSI events used to address the objectives 1-4 can be visualized in Appendix Figure A1. To describe the timing of MRSA onset overall and for the linked and non-linked events in objective 1, the population was restricted to patients from NHSN data with a MRSA BSI during the first 365 days of hospitalization (N = 13,278). To calculate the daily risk in objective 2, patients at risk of hospital-onset MRSA BSI (length of stay of at least four days) at facilities that reported a MRSA BSI to NHSN in that year were also included in the study population, inclusive of the MRSA BSI events that occurred in the first 30 days of hospitalization (97% of all MRSA BSI). For objectives 3 and 4, the population was limited to linked MRSA BSI events and we excluded events occurring after day 30 (Included N = 10,081).

Outcome Variable

To address objectives 1-2, the outcome of interest is the time (in days) from admission to the collection of a MRSA-positive blood culture, where the date of facility admission is day 1. The onset of MRSA-positive blood cultures obtained in the emergency department (ED) and observation units was considered day 1.

For objectives 1-4, we classified MRSA BSIs into MRSA onset outcome groups by the timing of the MRSA-positive blood culture, per NHSN definitions. CO MRSA BSI was a positive blood culture obtained on the first, second, or third day of hospitalization or in the ED/observation unit. HO MRSA BSI was a positive blood culture obtained on or after day 4 of hospitalization (27). For objectives 3-4, we divided HO MRSA BSIs into two outcome categories: early HO (first positive blood culture occurring in days 4–7 of hospitalization) and late HO (first positive blood culture occurring in days 8–30 of hospitalization).

Potential Factors Associated with Time to MRSA Event

Patient-level factors assessed for an effect on the distribution of time to event for MRSA BSI were patient age, sex, race, ethnicity, payer (Medicare, Medicaid, private), New York residency, socioeconomic status (SES), and comorbid conditions. These patient demographic variables were available in SPARCS. Hospital-level factors assessed were bed size and teaching affiliation, and were available in NHSN. Age was categorized into four groups: 18-44, 45-64, 65-84, and 85+ years. The Clinical Classification Software (CCS) designation was used to describe patient conditions. The CCS is a classification system used to categorize discharge diagnoses and procedure codes that was developed for the Healthcare Cost and Utilization Project (58). The data for the area-level socioeconomic status (SES) indicator was obtained from the United States Census Bureau American Community Survey and linked to the patient zip code. For purposes of this study, low SES zip codes were defined as those zip codes where ≥20% of the residents were below the federal poverty level for 2016. Comorbidity was assessed with

the Gagne Comorbidity Index, an adaption of the Charlson index and Elixhauser comorbidity classification that was developed to predict imminent mortality (59). This index is calculated by addition of scores attributed to 37 diagnoses associated with increased risk of mortality and we used it to adjust for patient acuity (59). The index was calculated using ICD-9-CM and ICD-10-CM diagnosis codes and categorized into four groups: ≤1, 2-3, and ≥4, with higher scores indicating more comorbid conditions. ICD-10-CM codes that correspond to ICD-9-CM codes were added to the Gagne comorbidity index to account for the change in diagnosis coding that took place in October 2015 (Appendix Table A2) (60).

Prior healthcare exposures assessed include inpatient hospitalization, contact with outpatient care, surgical procedures, dialysis, and skilled nursing facility (SNF) stay in the previous year. The linked SPARCS data provided information on prior healthcare exposures in New York. Hospitalizations and surgical procedures in the year prior to the index MRSA hospitalization were identified using the unique patient identifier in SPARCS. Previous hospitalizations were categorized as within 30, 90, 180, and 365 days prior to the index MRSA hospitalization. Procedure codes for each previous hospitalization were assessed for surgical procedures and time from procedure date to index admission was calculated. Surgery during the index hospitalization was assessed by identifying surgical procedure dates that occurred at least 1 day prior to MRSA-positive blood culture. We identified the number of outpatient visits using the number of outpatient claims that occurred within 365 days of the index MRSA BSI hospitalization. Admission from a SNF was determined by assessing the admission source. Dialysis was identified in the index hospitalization by procedure codes indicating dialysis or diagnosis

codes indicating end-stage renal disease, for which renal replacement therapy is indicated. All procedures and diagnosis codes used for dialysis are listed in Appendix Table A2.

We defined healthcare-associated exposure based on CDC EIP classifications (29). Healthcare-associated exposure included any admission from SNF, inpatient hospitalization in the previous year, surgical procedure in the previous year, or dialysis during index hospitalization. We used dialysis during hospitalization as a proxy to indicate exposure to dialysis in the previous year.

Analytic Approach

All analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC). For statistical tests, $p < 0.05$ (two-tailed) were considered statistically significant.

The distribution of time to MRSA BSI was visualized graphically with histograms of the percent of MRSA BSIs versus the day of hospitalization. We described the time to HO MRSA BSIs with the median and interquartile range (IQR). The median time to hospital-onset events was compared across facility characteristics, including bed size and teaching affiliation, using the Wilcoxon rank sum test.

We calculated the daily risk of HO MRSA BSI as the number of incident MRSA BSI each day divided by the number of patients remaining hospitalized each day who had not already experienced an incident MRSA BSI. The number of patients at risk each day is the number of hospitalizations with a length of stay at least that long and without a prior MRSA BSI. Patients who experienced a MRSA BSI were subsequently excluded

from the denominator after their MRSA BSI. We stratified the daily risk of MRSA BSI by age category.

We calculated descriptive statistics on exposures and confounders hypothesized to be associated with the timing of MRSA BSI overall and for each outcome category (CO, early HO, and late HO). Continuous variables (e.g., time from admission to MRSA BSI, age, length of stay, time from previous hospitalization to MRSA BSI) were expressed as the mean with standard deviation (SD) and median with IQR. The Kruskal-Wallis test was used to test for significant differences in non-normally distributed continuous variables. We described categorical variables (e.g., payer, admission source, race, ethnicity) using frequencies and proportions and calculated whether they were independently associated with the three outcome categories using the chi-square (χ^2) or the Fisher exact test, as appropriate.

We conducted multinomial multivariable logistic regression modeling to identify which of the previous healthcare exposures were associated with timing of MRSA BSI. Multinomial modeling was chosen in order to compare risk of both CO vs. early HO and late HO vs. early HO MRSA BSI by exposures of interest in one model. Adjusted odds ratios were calculated using multinomial multivariable logistic regression for all covariates together. All healthcare exposures of interest (admission from SNF, inpatient hospitalization in the previous year, number of surgical procedures in the previous year, number of outpatient contacts in the previous year, and surgery and dialysis during index hospitalization) were individually assessed for association with timing to MRSA BSI. Other covariates previously described (age category, sex, race, ethnicity, Gagne Comorbidity Index, payer, New York residency, SES) were screened based on univariate

associations, correlation analysis, and clinical significance. Multicollinearity was assessed using condition indices, a measure of interdependence of independent variables, and variance decomposition proportions, the proportion of the variance in the regression that can be attributed to each covariate (61). Adjustment for *a priori* confounders of age category, sex, race, payer, and Gagne Comorbidity Index was performed. Complete case analysis was used in the event of missing values for any variables for regression analyses.

We conducted a sensitivity analysis by forcing all healthcare exposures (admission from SNF, inpatient hospitalization in the previous year, number of surgical procedures in the previous year, number of outpatient contacts in the previous year, and surgery and dialysis during index hospitalization) along with the variables in the parsimonious model (age category, sex, Gagne comorbidity index, and payer) into the model to adjust for residual confounding.

Ethics Approval

The protocol was approved by the Centers for Disease Control and Prevention's Institutional Review Board in accordance with the expedited review process outlined in 45 CFR 46.110(b)(1), category 5. The work was be conducted under data use agreements with SPARCS and NHSN.

Results

Distribution of Time to MRSA Event

To answer the first objective, a total of 13,278 MRSA BSIs reported from 167 hospitals in New York met established study inclusion criteria. The distribution of onset types (CO and HO) and the median time to event overall and by hospital characteristic for all 13,278 MRSA BSIs reported in New York are in Table 1. CO MRSA comprised 78.7% of all MRSA BSIs (N = 10,447) and 84% of the CO BSIs occurred on day 1 (N = 8,790). The CO events are shown in green in Figure 1a. HO MRSA comprised the remaining 21.3% (N = 2,831) of all MRSA BSIs (Table 1).

The mean time to HO MRSA BSI overall was 20 days (SD=28.9) with median of 11 days (IQR: 6-22) (Table 1). Of note, 8.0% of all MRSA BSI occurred between days 4 and 7 (Figure 1b).

Hospital Characteristics

The time to HO MRSA BSI is statistically significantly different by bed size in New York hospitals ($p < 0.0001$), with longer median time to MRSA BSI in hospitals with larger bed size; the median time to onset in hospitals with bed size less than 200 was 8 days (IQR: 5-15), and the median time to onset in hospitals with bed size greater than 1,000 was 15 days (IQR: 8-39) (Table 1). Teaching affiliation was also statistically significantly associated with timing of HO MRSA BSI in New York ($p = 0.02$). The median time to MRSA event in teaching hospitals was 11 days (IQR: 6-22) and 9 days (IQR: 6-17) in non-teaching hospitals.

Data Linkage

For objectives 2-4, 12,826 MRSA BSI occurred between hospitalization days 1 and 30 and 452 events that occurred after day 30 were excluded (3.4%). Percentage of NHSN events that linked to SPARCS varied by hospital (min 0%, median 80%, max 100%, Figure 2). There were 8 hospitals with MRSA events in NHSN that did not successfully link to any hospitalizations in SPARCS, therefore these facilities were dropped from the analysis (number of excluded events = 237, 1.8%, Figure 3). Of the remaining 12,589 MRSA events, 80% (N = 10,081) were successfully linked to SPARCS and used in analysis and 20% were not linked (N = 2,508) (Table 2). Overall, 10,081 linked events from 159 hospitals were included in the analysis and 3,197 MRSA BSIs were excluded from analysis of linked data (based on non-linkage and timing > 30 days). The flowchart in Figure 3 shows how the final linked MRSA cohort was established.

The distribution of MRSA BSI onset types, mean time to onset, patient gender, age, and hospital setting of the linked and non-linked MRSA events are compared in Table 2. The proportion of onset types in the linked and non-linked groups varied slightly ($p = 0.04$); linked events had a smaller proportion of CO MRSA BSI compared to the non-linked events (80.8% vs. 83.1%) and a larger proportion of early HO (8.3% vs. 7.2%) and late HO MRSA BSI (10.9% vs. 9.7%). The time to MRSA event was not statistically significantly different between the linked and non-linked groups for early HO or late HO MRSA BSI. The CO MRSA BSIs (N = 10,230) had statistically significant differences in time to onset between linked and non-linked events; however this difference is not meaningfully different (mean time, 1.2 days for both). There was no significant difference in the distribution of gender between the linked and non-linked

MRSA events. The linked cohort was older (66.9 vs. 63.8, $p < 0.0001$). There was greater success in linking MRSA events reported in the inpatient units compared to the MRSA events reported from the ED/observation units (82% vs. 75%, not shown in table).

Daily Risk

The second objective was to determine the daily risk of HO MRSA BSI for the first 30 days of hospitalization. In the 159 New York facilities with linked MRSA events, a total of 4,728,238 adult hospitalizations were at least 4 days (Appendix Table A1). There were 247 MRSA events occurring on day 4, resulting in the minimum daily risk of 5.2 events per 100,000 patients for patients staying ≥4 days. The maximum daily risk of MRSA BSI occurred on day 28 (18.8 events per 100,000 patients staying ≥28 days). The mean daily risk was 10.2 events per 100,000 patients (SD = 3.1) and the median daily risk was 9.9 events per 100,000 patients (IQR: 8.1-10.9) (Figure 4).

Figure 5 shows the daily risk stratified by age categories: 18-44, 45-64, 65-84, and 85+. The four age categories have similar daily risk of a MRSA BSI for days 4-15 of hospitalization (10 MRSA BSIs per 100,000 patients). On days 20-30, the risk of a MRSA BSI is higher in the two oldest age categories. The 85+ age group experienced the highest daily risk peaking at 52 MRSA BSIs per 100,000 patients on day 22, followed by the 65-84 age group, peaking at 27 MRSA BSIs per 100,000 patients on day 28. The risk remains at 10 MRSA BSIs per 100,000 patients for each day of hospitalization for the two youngest age categories.

Patient Characteristics

The third objective was to determine the patient characteristics associated with CO, early HO, and late HO MRSA BSIs. This was assessed using the linked MRSA BSI cohort (N = 10,081). Table 3 shows the patient characteristics of the linked MRSA BSI cohort by outcome (CO, early HO, and late HO). Overall, the population was 40.5% female and the mean age was 66.9 (SD=17.2), with 59% of patients aged 65 and older. The payer was largely Medicare (68.5%) followed by Medicaid (18.2%). The greatest proportion of MRSA BSIs occurred in whites (60.3%) and blacks (21.0%) and 10.3% of patients were of Spanish or Hispanic ethnicity. MRSA BSIs occurred largely among New York residents (96.3%) and 31.5% of patients lived in areas of low socioeconomic status.

The univariate analysis found that timing of onset differed statistically significantly by race ($p = 0.0004$). Black patients comprised a greater proportion of early (23.1%) and late HO MRSA BSIs (23.9%) than CO MRSA BSIs (20.4%). The distribution of Gagne Comorbidity Index varied by onset: early and late HO MRSA BSI had a higher proportion of Gagne Comorbidity Indexes ≥4, (34.1% and 33.4%, respectively), while CO MRSA BSI had a greater proportion of Gagne scores ≤1 (32.3% vs. 26.8% in early HO and 23.8% in late HO). New York residency differed significantly between the outcome types ($p = 0.0006$). New York residency was more common in CO (96.5%) and early HO MRSA BSI (96.5%), compared to those with late HO MRSA BSI (94.2%).

CO, early HO, and late HO MRSA BSIs did not differ significantly by gender, age, ethnicity, payer, or area-level socioeconomic status (Table 3).

Healthcare Exposures

The fourth specific aim was to identify healthcare exposures that are associated with CO, early HO, and late HO MRSA BSIs and to determine if individuals with early HO MRSA events had previous healthcare exposures that were similar to those experienced by individuals with CO MRSA BSIs. Healthcare exposures in the CO, early HO, and late HO groups in the index hospitalization differed significantly (Table 4): patients with CO MRSA BSI were more likely to be transferred from a SNF (11.8%) compared to patients with early HO (7.1%) and late HO MRSA BSI (8.0%), ($p < 0.0001$). Patients with late HO MRSA BSI were more likely to be in the hospital for elective admission (6.4%) than early HO (3.7%) and CO MRSA BSIs (1.3%), ($p < 0.0001$). In the intensive care unit (ICU), there was a higher incidence of early HO (26.0%) and late HO (27.8%) than CO MRSA BSI (18.0%), ($p < 0.0001$). Patients with CO MRSA BSI were more likely to have septicemia as their CCS category (51.9%), while only 14.9% of early HO and 20.0% of late HO MRSA BSIs were categorized with septicemia. The early HO and late HO BSIs were classified under a chronic disease category, such as congestive heart failure, more frequently (7.1% for early HO and 6.5% for early HO) than CO MRSA BSIs (0.8%) (Table 4).

The patients with different outcome types also differed significantly in the types of procedures they underwent during the index hospitalization. CO and early HO had higher exposure to dialysis (22.0% and 20.0%) than patients with late HO MRSA BSI (14.9%), ($p < 0.0001$). Late HO MRSA BSI patients were more likely to have surgery prior to their MRSA-positive blood culture (21.1%) compared to CO (0.9%) and early HO MRSA BSIs (10.7%), ($p < 0.0001$) (Table 4).

The mean length of stay was significantly different between patients with CO, early HO, and late HO MRSA BSIs. Patients with late HO MRSA events had longer length of stay during index hospitalization (33.1 days, SD = 21.8) compared to early HO (20.6 days, SD = 17.3) and CO MRSA BSIs (15.1 days, SD = 14.1) ($p < 0.0001$) (Table 4).

Late HO MRSA BSI patients were significantly more likely to die during hospitalization where MRSA was diagnosed (35.7%) compared to early HO (26.7%) and CO MRSA BSIs (19.4%), ($p < 0.0001$). Patients with CO MRSA BSI were more likely to be discharged to a skilled nursing or rehabilitation facility (31.7%) or to home (31.9%) than patients with early HO and late HO MRSA BSIs (Table 4).

Healthcare utilization in the previous year varied significantly among patients with different MRSA onset types (Table 5); more patients with CO or early HO (65.0%, 64.4%, respectively) than late HO MRSA BSI (59.8%) had an inpatient hospitalization in the past year ($p = 0.003$). The mean length of stay during a prior hospitalization was 11.6 days (median = 8) and the mean time from previous hospital discharge to MRSA-positive blood culture was 109 days (median = 44); neither was statistically significantly different across the CO, early HO, or late HO MRSA BSIs ($p = 0.72$, $p = 0.09$, respectively).

The number of outpatient contacts in the previous year did not vary significantly among the MRSA BSI outcomes, with 28.7% of CO, 29.2% of early HO, and 26.0% of late HO MRSA BSI having 1-3 outpatients contacts in the previous year ($p = 0.36$). The number of surgical procedures in the previous year did vary significantly among the outcome groups: 15.1% of patients with CO MRSA BSI had 1 surgery in the year prior, while only 12.4% of early HO and 12.0% of late HO MRSA BSI had surgery in the year

prior (p = 0.0006). Using our definition of HACO (inpatient hospitalization/surgery in the previous year, dialysis in current hospitalization, or admission from SNF), we identified 5,836 CO MRSA BSIs (71.6%) that could be classified as HACO MRSA BSIs. The HACO events comprised 57.9% of all MRSA BSIs.

Multivariable multinomial logistic regression was performed to identify previous healthcare exposures that were independently associated with CO and late HO MRSA BSI compared to early HO MRSA BSI (Table 6). There was no evidence of multi-collinearity as no variance decomposition proportions were <0.5 based on collinearity assessment of the fully-adjusted model. Complete case analysis resulted in 16 observations dropped from the analysis due to missing covariates.

In the fully adjusted model controlling for age category, sex, race, Gagne comorbidity index, and payer, patients with admittance from a SNF were 74% more likely to have CO than early HO MRSA BSI (aOR=1.74, 95% CI: 1.32, 2.30). In contrast, admission from SNF was not significantly different between late HO and early HO MRSA BSI (aOR=1.13, 95% CI: 0.80, 1.61).

Patients with inpatient hospitalization in the prior year were not at greater risk of CO than early HO MRSA BSI compared to patients without inpatient hospitalization in the prior year (aOR=1.07, 95% CI: 0.92, 1.25). On the other hand, those with inpatient hospitalization in the prior year were 21% less likely to have late HO than early HO MRSA BSI (aOR=0.79, 95% CI: 0.66,0.96).

In addition, patients on dialysis during index hospitalization were 33% more likely to be CO than early HO MRSA BSI compared to patients not on dialysis during index hospitalization (aOR=1.33, 95% CI: 1.10, 1.61). Those on dialysis at index

hospitalization were 37% less likely to have late HO than early HO MRSA BSI (aOR= 0.63, 95% CI: 0.49, 0.81).

Surgery during index hospitalization at least 1 day prior to MRSA-positive blood culture (vs. no surgery prior to culture) was associated with 2.29 times higher risk of late HO than early HO (95% CI: 1.75, 2.98).

Patients with one surgical procedure in the year before admission were 26% more likely to be CO than early HO MRSA BSI, compared to patients with no surgical procedures in the previous year (aOR= 1.26, 95% CI: 1.02, 1.57). The number of surgical procedures in the previous year was not significantly different in patients that developed late HO and early HO MRSA BSI.

Having 1-3 or ≥4 outpatient contacts (vs. 0) in the year before admission was not statistically significantly associated with risk of CO vs. early HO MRSA BSI. Patients with 1-3 (vs. 0) outpatient contacts in the previous year had 14% lower odds of late HO than early HO MRSA BSI; however, the estimate did not reach statistical significance (aOR =0.86, 95% CI: 0.70, 1.05).

When all healthcare exposures were forced into the model along with the a priori confounders (age category, sex, race, Gagne comorbidity index, and payer) to conduct the sensitivity analysis, the results did not differ substantially from the individual healthcare exposure adjusted model; direction and magnitude of the estimates did not change (Appendix Table A3). The association between previous inpatient hospitalization and late HO MRSA was no longer statistically significant (aOR=0.85, 95% CI: 0.69, 1.04) and the association between ≥2 surgical procedures and CO became statistically significant (aOR=1.46, 95% CI: 1.02, 2.11).

Discussion

This study addresses several gaps in the epidemiology of MRSA BSI by investigating the timing of MRSA BSI onset. HO infections accounted for 21.3% of MRSA BSIs in New York, and the median time to HO BSI was 11 days. The risk of MRSA BSI on each day of hospitalization was lowest on day 4 and slightly higher among patients with longer lengths of stay. Among MRSA BSIs, higher comorbidity scores were associated with later timing of MRSA BSI. We found that MRSA BSI patients with previous surgery, admission from SNF, and dialysis were more likely to develop CO than early HO. Previous hospitalization and dialysis were associated with lower risk of late HO compared to early HO. Early HO MRSA BSIs were different from CO and late HO in terms of healthcare risk factors, suggesting that early HO may be a combination of true CO and true HO MRSA BSIs.

Timing of MRSA BSI

Hospital length of stay is a key risk factor for HO MRSA BSIs (8, 20). It is useful to understand when HO MRSA BSI occur during hospitalizations in order to determine how future MRSA prevention strategies and clinical trials should target patients based on their predicted length of stay. Public Health England estimated the days between hospital admission and MRSA blood specimen, but they did not distinguish between onset types. They found that the median time to onset decreased from 7 days in 2008 to 1 day in 2017, due to the faster decline in hospital-onset MRSA events than community-onset events that occurred in this period (47). Furthermore, they found that 34.7% of all MRSA BSI occurred on or after day 7 of hospitalization. We found an overall median time to onset of

1 day for each year of the study period, but only 15.2% of all MRSA BSI occurred on or after day 7. This may be related to potential differences in epidemiology of MRSA between the US and England.

This study gives insight into the fraction of MRSA BSIs that are hospital-acquired and potentially preventable during hospitalization. After stratifying all MRSA events from 2013-2016, we found that 50% of HO MRSA BSI occurred on or after day 11. This suggests that up to half of all HO MRSA BSI could be prevented by applying interventions to patients with a length of stay at least 11 days. In our study, we reported the median time to MRSA BSI onset, which is the preferred measure for non-normally distributed data. Older studies of clinically confirmed *S. aureus* BSI reported a shorter mean time to HO event than we observed (16 days vs. 20 days) (45). However, this could be due to different HO definitions; they defined HO as BSI presenting on day 3 or later (45).

To our knowledge, previous studies have not investigated the timing of onset by hospital characteristics, which could be an important indicator for the collection time of MRSA-positive blood culture. We found that the timing of MRSA events varied significantly in New York acute care hospitals by bed size. Hospitals with fewer than 200 beds had the shortest time to HO MRSA infections (median of 7 days) while the hospitals with more than 1000 beds had the longest time to onset (median of 11 days). It is possible that larger hospitals are public and have fewer resources to collect blood cultures on a regular basis, resulting in longer time to eventual MRSA-positive blood culture (62). This suggests that hospitals of different bed sizes should have different length-of-stay-based interventions in order to effectively intervene on their respective patient populations.

In our study, 78.7% of MRSA patients had a positive MRSA blood culture in the first 3 days of their hospitalization (CO), which is consistent with 2011 EIP findings that 80.7% of MRSA bloodstream infections are community onset (32). By applying our definition of previous healthcare exposure to define HACO MRSA BSIs, 71.6% of CO MRSA BSI could be considered HACO. This slightly underestimates the 2011 EIP HACO estimation (74.5% of CO), which may be attributed to our approximation of healthcare exposure: we were only able to identify patients admitted from the SNF and not all SNF exposure in the previous year, included inpatient but not outpatient surgery, and did not include presence of catheter in our analysis (29, 32). Furthermore, differences may be a result of the time periods analyzed and the restriction of our study to New York, whereas the EIP study analyzed surveillance data from nine states (29). However, both data sources show that CO MRSA BSIs represent a large public health burden. This suggests that MRSA BSI prevention initiatives should consider interventions that reduce post-discharge CO BSIs. The Project CLEAR study conducted from 2011 to 2014 is an example of an intervention that could lead to reduction in HACO MRSA BSIs. Huang et al. found that patients colonized with MRSA that received a MRSA decolonization regimen post-discharge for six months experienced a 30% lower risk of MRSA infection than patients that received post-discharge education on hygiene alone (38). Interventions that focus on the prevention of HACO MRSA BSI are critical since many MRSA BSI cases are developing post-discharge, as evidenced by our study.

Daily Risk of Hospital-onset MRSA BSI

Information on the number of people at risk of acquiring a MRSA bloodstream infection for each day of hospitalization could give insight to strategic planning and

application of hospital-infection prevention measures. We found that just 65% of patients stayed in the hospital at least 4 days. Therefore, there is potential to target fewer patients by focusing intervention efforts only on those at risk of hospital-onset infections (i.e., those who stay ≥4 days). These data can be used to inform future clinical trials to improve the cost-effectiveness and feasibility of interventions. For example, the ABATE trial was conducted from 2013-2016 to investigate prevention of HO MRSA clinical cultures in non-ICUs. In the trial, 53 hospitals employed universal decolonization procedures to all patients in general wards starting on their day of admission. Comparing baseline to intervention periods, they found no significant reductions in HO MRSA clinical cultures. However, this did not take into account the patients that would be discharged before risk of HO MRSA BSI (day 4). Therefore, HAI prevention interventions could be improved by only targeting a subset of patients who will remain in the hospital long enough to be at risk of HO infection (63). Furthermore, this type of intervention could also prevent CO MRSA BSI from developing after a hospital stay.

Targeting patients at higher risk of MRSA based on hospital LOS requires daily risk estimates in order to identify when interventions should be applied to have the greatest impact. We found increasing estimated daily risk of MRSA BSI throughout the first 30 days of hospitalization; the lowest risk for a MRSA event was on day 4 (5 MRSA BSIs per 100,000 patients) and highest on day 28 (18.8 MRSA BSIs per 100,000 patients). However, the confidence intervals were wide for late onset times due to fewer patients remaining in the hospital and a small number of MRSA events. Our findings are similar to the daily risk of BSIs from any pathogen evaluated in the Danish healthcare system from 2000-2008, where daily risk was lowest for days 3-7 of hospitalization (10

BSIs per 10,000 bed-days) and slightly higher for days 8-30 (18 BSIs per 10,000 bed-days (46). Our daily risk results provide further evidence that hospital infection prevention should consider patient length of stay when implementing interventions and may focus efforts on patients with higher risk of HO MRSA BSI.

Early vs. Late HO MRSA

The classification of MRSA infections as CO or HO lacks consideration of a wide array of potential differentiating risk factors for infection. Prior studies have suggested potential misclassification of HO MRSA based on the 3-day threshold for community-onset classification (28, 31). The classification of MRSA BSI does not always inform where MRSA prevention strategies could be most effective, necessitating the investigation of characteristics of HO MRSA that occur early in hospitalization. In this study, early HO MRSA BSIs have a combination of healthcare exposures that make them similar to both CO and late HO events.

The distinction between early-onset and late-onset infections is applied for many HAIs, including ventilator-associated pneumonia, sepsis, and surgical site infections. In these HAIs, timing, risk factors, microbiology and outcomes are evaluated (52-57). The cutoff distinguishing early HO and late HO for this analysis was based on the distribution of hospital-onset MRSA events occurring in the first 30 days of hospitalization, the daily risk of hospital-onset events, and the clean designated end at 1 week of hospitalization. There is no predetermined ideal cutoff for early and late hospital-onset infection; however, it may be useful for clinical trials to enroll patient groups that could benefit from hospital-based infection prevention due to their long time to infection onset,

whereas patients with shorter time to onset are less likely to be prevented due to predisposing risk factors.

Patient Characteristics Associated with MRSA Events

Comorbidity indices are useful when using large administrative datasets such as SPARCS to give an overall health status of the patients and adjust for patient acuity in models. Of note, patients with early and late hospital-onset MRSA had similar Gagne scores, which means that these patients had similar morbidity and therefore the timing of hospital-onset cannot only be accounted for by differences in patient acuity, but rather other risks related to patient and healthcare factors. Higher comorbidity among patients with early HO and late HO MRSA BSI than CO MRSA BSI may indicate patients that are more susceptible to opportunistic MRSA infection based on their compromised immune systems and other predisposing clinical conditions (17). Patients afflicted with multiple comorbid conditions may inform a suitable target population to prevent HO MRSA BSIs.

Patient gender, age, ethnicity, payer, and area-level poverty level were not associated with timing of MRSA onset. However, males were more likely to develop MRSA bloodstream infection overall (59.5%) compared to females (40.5%), which is consistent with previous publications (23, 24). In this study, black patients were more likely to have early HO and late HO MRSA events that CO MRSA, which is also consistent with other findings (23, 25). Patients of advanced age are at higher risk of MRSA bloodstream infection due to their increased susceptibility; however, age was not associated with timing of MRSA onset (64). Further analysis may be warranted to

investigate how socioeconomic status is related to the timing of MRSA BSI onset as we had limited access to detailed socioeconomic information in these administrative data.

Healthcare Exposures

We found that 28.9%, 48.3%, and 64.4% of all MRSA events had a hospitalization in the previous 30 days, 90 days, and 365 days. These estimates are lower than those found in a study by Cosgrove et al., which reported 37%, 70%, and 81% of all MRSA bacteremia cases with prior hospitalization in the respective timeframes. The differences in proportions may be a result of different periods and facilities; their study was conducted with 1997-2000 data, which is 16 years prior to our study period, and from one teaching hospital in Boston, whereas our study included 159 hospitals in New York (65). In addition, community-onset and hospital-onset MRSA rates have declined since 2000 as a result of improved hospital infection prevention, so fewer MRSA cases may be associated with a prior hospitalization (33).

Late HO MRSA BSIs were more likely to occur during an elective admission compared to CO and early HO. This is partly expected because CO MRSA BSI cases would likely be admitted because of infection onset. There were more blood cultures obtained in the ICU that were early HO (26.0%) and late HO (27.8%) than CO MRSA (18.0%). There may be a higher prevalence of MRSA in the environment and colonizing healthcare workers in the ICU, plus patients with an ICU stay are sicker than the average patient and are at higher risk of contracting infection, therefore prolonged exposure may increase risk of infection (66, 67).

The length of stay was significantly longer for patients with late HO MRSA bacteremia (33.1 days) compared to early HO (20.6 days) and CO (15.1 days). The prolonged hospitalization may be explained by delayed onset that requires treatment and extended hospital care (20). Patients with late HO MRSA events were more likely to die than patients with early HO (26.7%) and CO MRSA (21.8%). This was possibly because late HO cases were likely more vulnerable at the time of BSI onset than CO and early HO cases.

The healthcare risk factors for CO and HO MRSA bacteremia have been researched extensively (17-22). This study adds to the body of knowledge by investigating whether there are differences in prior healthcare exposures that are associated with the timing of MRSA onset. There was greater likelihood of CO than early HO MRSA BSI among patients admitted from the SNF (74%), with one prior surgery in the past year (26%), and dialysis during hospitalization (33%). Patients with CO BSI may have acquired MRSA in the SNF, during a previous surgical procedure, or in a dialysis clinic prior to developing infection (17, 22, 68).

Patients with inpatient hospitalization in the previous year and dialysis during hospitalization were less likely to develop late HO than early HO (21% and 33%, respectively). This reflects healthcare exposures that result in shorter time to HO MRSA BSI and may indicate a need for different intervention approaches for patients with a shorter window for infection prevention. In contrast, previous inpatient hospitalization was not associated with CO compared to early HO MRSA BSI, suggesting that early HO may share similar exposures with CO BSI, and some early HO BSI may have

experienced the onset of symptoms in the community with a delayed diagnosis upon admission to hospital.

Overall, we found evidence that early HO MRSA BSIs have healthcare exposures that are different from CO and late HO BSI. This is applicable in the hospital setting to identify patient clusters that are at risk of shorter and longer time to hospital-onset based on their healthcare exposures, so that more strategic infection prevention strategies can be applied. This information may also be useful when evaluating intervention effectiveness; patients at high-risk of earlier onset would not be expected to experience a reduced rate of infection compared to patients with later-onset infections if both patient groups are given equivalent interventions (i.e., same number of chlorhexidine baths). Thus, hospital interventions can focus resources to effectively reduce hospital-onset MRSA infections.

Limitations

This study has several limitations. The NHSN database only captures MRSA-positive blood cultures and does not record clinical data. However, patients who had a blood culture performed likely had symptoms of an infection that prompted testing. It is also unclear if blood cultures were positive because of contamination from MRSA skin colonization, although MRSA blood cultures are reported to have high specificity (69). Additionally, we do not have access to data on MRSA strain type, which would be able to further differentiate CO, early HO, and late HO MRSA cultures.

We achieved 80% linkage of NHSN MRSA BSIs to their respective hospital claims in the SPARCS dataset, which is lower than a previous study linking NHSN surgical site infections to SPARCS (88%). However, their study had the advantage of a linking on procedure date whereas our study could not link on specimen collection date since it is not available in SPARCS (70). We had lower success in linking CO BSIs than HO BSIs that can be attributed to the lower linkage success of MRSA events reported from the ED/observation units to the outpatient SPARCS data because these patients were likely admitted and may not have an outpatient record. There is evidence of selection bias because the linked cohort was slightly older than the non-linked MRSA BSIs (66.9 vs. 63.8). The older patients may represent patients with higher acuity and increased healthcare utilization (64).

Importantly, this study is limited to healthcare exposure data available in the SPARCS database, therefore we may be missing prior healthcare exposures. For example, information on a prior SNF stay was only available if the patient was transferred directly from a SNF to the hospital. Any SNF stay in previous year that

resulted in discharge to the community with a subsequent hospital admission was not included. Additionally, SPARCS only captures hospital-based outpatient care. Therefore, outpatient exposures occurring outside of a hospital network in clinics, urgent care, and dialysis facilities are not captured. Other identified risk factors for invasive MRSA infection that may be involved in the timing of MRSA infection are not captured in administrative data (e.g., there is incomplete reporting on vascular and urinary catheterization and enteral feedings). In addition, antibiotic use and MRSA infections at non-blood body sites in the year preceding BSI were not available in either the SPARCS or NHSN data (17). These exposures may be able to further illuminate the relationship between CO, early HO, and late HO.

Patients living outside of New York that experience their MRSA hospitalization encounter in a New York hospital may be missing information on prior hospitalizations, surgeries, and outpatient care outside of New York. However, this is unlikely to impact the validity of our results as only 4% of MRSA BSIs were in non-New York residents.

In this analysis, dialysis during the index hospitalization was used as a proxy to measure dialysis use in the previous year, which is part of the EIP definition of prior healthcare exposure related to HACO events. However, dialysis during index hospitalization may not reflect the patient's prior exposure, since patients with sepsis or other events at or during hospitalization may experience acute kidney injury and require renal replacement therapy during hospitalization (71). The proportion of early and late hospital-onset MRSA patients undergoing dialysis (18.5% and 14.3%, respectively) is higher than estimates of chronic dialysis in hospital-onset MRSA patients in the 2014 EIP surveillance study (7.3%) (72); suggesting we may have overestimated the number of

patients on chronic dialysis. We adjusted for illness severity using the Gagne Comorbidity Index, which only accounts for comorbidity in the index hospitalization; it does not reflect the patient health status throughout care and may not adjust fully for the patient susceptibility to MRSA, which would affect a patient's date of MRSA-positive blood culture during their hospitalization. The adoption of ICD-10-CM coding in October 2015 occurred in the middle of the study period from 2013-2016, which may have impacted disease coding and ability to capture diagnosis-related indices in the study. ICD-10-CM codes that link to ICD-9-CM codes were added to the Gagne comorbidity index and dialysis diagnosis and procedure codes to account for the change in diagnosis coding that took place (59, 61, 73). While additional analyses showed ICD-10-CM and ICD-9-CM distribution of variable indices did not differ, the change in coding may have affected variable classification.

The daily risk for MRSA bloodstream infections was estimated by pooling all hospital MRSA events and inpatient populations for the years 2013 to 2016. However, patient disease severity and preventative measures for HAIs likely differed among hospitals in New York and within hospitals over the 4-year period. Therefore, it may be useful to investigate the daily risk at the hospital-level instead of at the state-level and assess the daily risk by ICU vs. non-ICU, because ICUs may employ different interventions than other hospital units. Furthermore, rehabilitation and psychiatric hospital units that were excluded from NHSN data could not be identified in SPARCS; therefore, the number of patients in the daily risk denominator may be an overestimate, resulting in a more conservative estimate of daily risk.

Strengths

Hospital surveillance data are the gold standard for identifying healthcare-associated infections because they provide a more systematic measure of incident infection than diagnosis-based claims data. Therefore, the National Healthcare Safety Network (NHSN) was used to identify MRSA-positive blood culture events reported to the surveillance patient safety database. The use of surveillance data lends a strength to this study over other studies that identify MRSA infections though ICD-9-CM codes, which can result in misclassification of HAIs and low sensitivity (74). The high linkage of events from NHSN to SPARCS enabled for analysis of a rich set of potential risk factors for timing of MRSA BSI without putting additional strain on hospital workers conducting surveillance, making the inclusion of administrative data an effective research strategy.

There were 167 acute care hospitals with varying patient populations included in this analysis. This makes the findings more generalizable than a less representative single-hospital analysis. Furthermore, while the study was limited to New York hospitals, New York has a relatively heterogeneous population so the study findings may be more generalizable to institutions in other states. The large sample size of 10,081 MRSA events allowed for identification of patient and healthcare exposures that are potential risk factors for the timing of community-onset, early hospital-onset, and late hospital-onset MRSA bloodstream infection with precise estimates and detection of differences between the onset groups for each exposure.

Future Directions

Future analysis may perform multilevel modeling to evaluate how hospital characteristics interact with patient and prior healthcare exposures to affect the time to onset of MRSA bloodstream infections. It would also be beneficial to quantify the burden reduction of targeted interventions based on length of stay compared to targeting all admitted patients. Specific analysis could produce Receiver Operating Characteristic (ROC) curve and Area Under the Curve (AUC) statistics to identify the day of hospitalization that interventions could be applied to minimize the number of patients intervened on. This would serve to reduce the burden on healthcare workers and lower costs associated with the intervention, while still targeting most of the disease burden. It would also be useful to calculate the incremental benefit of using length of stay information to target interventions compared to only targeting based on other risk factors. Emergency admission, recent nursing home stay (e.g., by linking to Medicare data, which is the primary payer for nursing home care), and MRSA infections in the previous year (which is available in patient electronic health records and in other electronic health datasets) could be evaluated risk factors that may be synergistic with length of stay-based interventions.

Conclusion

This study fills a gap in epidemiology research on MRSA BSI by investigating the timing of MRSA onset. In order to assess how many infections are potentially preventable from developing during hospitalization, this study identified the distribution of the time to onset and daily risk of MRSA bacteremia in New York hospitals. HO MRSA BSIs accounted for 21.3% of MRSA BSI in New York, which represents a substantial proportion of MRSA infections that could potentially be avoided with hospital-based interventions such as bathing patients with antiseptic solution and MRSA decolonization (37, 63). Furthermore, this analysis found that the risk of HO MRSA BSI is slightly higher among patients with longer lengths of stay. This study also identified risk factors related to patient characteristics, index hospitalization, and previous healthcare exposures that distinguished patients who experienced MRSA BSIs at different times in relation to their admission to the hospital. Admission from a SNF and number of previous surgical procedures in the year before admission does not affect the timing of HO MRSA BSI; however they are associated with CO MRSA BSI. Previous hospitalization, dialysis, and surgery are healthcare exposures that are associated with different timing of HO MRSA BSI. Novel strategies that address these different risk factors in addition to long lengths of stay could prevent a large portion of HO and HACO MRSA BSI. This study serves to better inform clinicians of the window of risk for MRSA BSI and improve targeting of preventative measures based on length of stay, patient characteristics and healthcare exposures that will ultimately improve patient outcomes.

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Tables and Figures

Table 1. Time to methicillin-resistant *Staphylococcus aureus* (MRSA) bloodstream infections (BSIs) overall and by hospital characteristics in New York hospitals reporting to NHSN, 2013-2016 for the first 365 days of hospitalization (N=13,278)

	Number of MRSA BSI	Time to Onset Median (IQR)	p
All MRSA BSI	13,278	1 (1-2)	
Community-onset Days 1-3 N (%)	10,447 (78.7)	1 (1-1)	
Hospital-onset Days 4-365 N (%)	2,831 (21.3)	11 (6-22)	
Hospital-onset Only: by Hospital Characteristic (N=145)			
Bed size N(%)			<0.0001
<200 (N=58)	378 (13.3)	8 (5-15)	
201-500 (N=67)	1,294 (45.7)	10 (6-21)	
501-1000 (N=19)	996 (35.2)	12 (6-24)	
>1000 (N=1)	163 (5.8)	15 (8-39)	
Teaching Affiliation N(%)			0.02
Teaching (N=104)	2,520 (89.0)	11 (6-22)	
Non-Teaching (N=41)	311 (11.0)	9 (6-17)	

IQR: interquartile range

Table 2. Comparison of the linked vs. non-linked MRSA BSIs in New York hospitals for the first 30 days of hospitalization, 2013-2016 (N = 12,589)

Characteristic	Linked	Not Linked	Total N	p
Onset Type: N (%)				
Community (1-3)	8,147 (80.8)	2,083 (83.1)	10,230	0.04
Early Hospital (4-7)	832 (8.3)	181 (7.2)	1,013	
Late Hospital (8-30)	1,102 (10.9)	244 (9.7)	1,346	
Time to Event, days: mean (SD)				
Community (Days 1-3)	1.21 (0.52)	1.18 (0.49)		0.02
Early Hospital (Days 4-7)	5.3 (1.1)	5.4 (1.1)		0.28
Late Hospital (Days 8-30)	15.2 (6.2)	15.8 (6.2)		0.20
Gender: N (%)[1]				
Female	4,085 (40.5)	1,054 (42.1)	5,139	0.15
Male	5,996 (59.5)	1,450 (57.9)	7,446	
Age, years mean (SD)	66.9 (17.2)	63.8 (17.7)		<0.0001
Setting: N (%)				
Inpatient	7,615 (75.5)	1,700 (67.8)	9,315	<0.0001
ED/Observation Unit	2,466 (24.5)	808 (32.2)	3,274	
Total	10,081 (80)	2,508 (20)	12,589	

SD: standard deviation; ED: emergency department; MRSA: methicillin-resistant *Staphylococcus aureus*; BSIs: bloodstream infections

[1] Gender is missing for 4 events

Table 3. Characteristics among patients with MRSA BSI in New York, 2013-16, overall and stratified by type of onset (community-onset, early hospital-onset, and late hospital-onset) (N= 10,081)

Patient Characteristic	Overall		Community (days 1-3)		Early Hospital (days 4-7)		Late Hospital (days 8 -30)		
	N	%	N	%	N	%	N	%	p
Total	10081	100	8147	80.8	847	8.3	1102	10.9	
Female	4085	40.5	3276	40.2	334	40.1	475	43.1	0.18
Age (mean, SD)	66.9	17.2	66.7	17.2	67.5	17.0	67.9	17.2	0.07
Age Category									
18-44	1122	11.1	917	11.3	86	10.3	119	10.8	0.12
45-64	3010	29.9	2480	30.4	237	28.5	293	26.6	
65-84	4328	42.9	3449	42.3	374	45.0	505	45.8	
≥85	1621	16.1	1301	16.0	135	16.2	185	16.8	
Race									
White	6083	60.3	5010	61.5	470	56.5	603	54.7	0.0004
Black	2113	21.0	1658	20.4	192	23.1	263	23.9	
Asian[1]	291	2.9	233	2.9	24	2.9	32	3.1	
Other Race	1594	15.8	1246	15.3	146	17.6	202	18.3	
Ethnicity[2]									
Spanish/Hispanic Origin	1000	10.3	809	9.9	90	10.8	101	9.2	0.52
Not of Spanish/Hispanic Origin	8696	89.7	7031	86.3	712	85.6	953	86.5	
Gagne Comorbidity Index (Continuous)	2.6	1.9	2.5	1.9	2.8	1.9	2.9	1.9	<0.0001
Gagne Comorbidity Index Category									
≤1	3113	30.9	2628	32.3	223	26.8	262	23.8	<0.0001
2-3	4030	40.0	3233	39.7	325	39.1	472	42.8	
≥4	2938	29.1	2286	28.1	284	34.1	368	33.4	
Payer of Majority of Bill[3]									
Medicare	6905	68.5	5582	68.5	561	67.4	762	69.2	0.3
Medicaid	1834	18.2	1482	18.2	149	17.9	203	18.4	
Private Health Insurance	1043	10.4	853	10.5	90	10.8	100	9.1	
Other	283	2.8	215	2.6	31	3.7	37	3.4	
New York Resident	9704	96.3	7863	96.5	803	96.5	1038	94.2	0.0006
Low SES zip code resident[4,5]	3035	31.5	2428	31.1	269	33.8	338	32.7	0.20

[1] Chinese, Pacific Islander, Asian Indian, Other Asian

[2] Ethnicity missing for 385 events

[3] Pay of Majority of Bill missing for 16 events

[4] Resident in Zip code with at least 20% of residents below poverty level

[5] Poverty Level missing for 430 events

Table 4. Index hospitalization characteristics among patients with MRSA BSI in New York, 2013-16, overall and stratified by type of onset (community-onset, early hospital-onset, and late hospital-onset) (N= 10,081)

Hospitalization Characteristic	Overall		CO (days 1-3)		Early HO (days 4-7)		Late HO (days 8 -30)		
	N	%	N	%	N	%	N	%	p
Total	10081	100	8147	80.8	847	8.3	1102	10.9	
Admission Source[1]									
Home	7649	78.5	6123	78.3	669	81.3	857	78.4	<0.0001
Transfer from SNF	1066	10.9	920	11.8	58	7.05	88	8.0	
Transfer from Hospital	549	5.6	400	5.1	58	7.05	91	8.3	
Transfer from Other Facility[2]	478	4.9	382	4.9	38	4.6	58	5.3	
Type of Admission[3]									
Emergency/Urgent/Trauma	9631	97.9	7800	98.7	800	96.3	1031	93.6	<0.0001
Elective	206	2.1	104	1.3	31	3.7	71	6.4	
Diagnosed in Intensive Care Unit (ICU)									
ICU	1992	19.8	1470	18.0	216	26.0	306	27.8	<0.0001
Non-ICU	8089	80.2	6677	82.0	616	74.0	796	72.3	
Clinical Classification Software Category									
Septicemia (except labor)	4560	45.2	4230	51.9	164	14.9	166	20.0	<0.0001
Complication of device; implant or graft	1521	15.1	1395	17.1	50	4.5	76	9.1	
Complications of surgical procedures/medical care	476	4.7	427	5.2	88	2.5	21	2.5	
Skin and subcutaneous tissue infections	237	2.4	227	2.8	6	0.5	4	0.5	
Congestive heart failure; non-hypertensive	195	1.9	63	0.8	78	7.1	54	6.5	
Other	2844	28.2	1596	19.6	699	63.4	489	58.8	
Dialysis during hospitalization	2120	21.0	1790	22.0	166	20.0	164	14.9	<0.0001
Surgery prior to MRSA blood culture	392	3.9	71	0.9	89	10.7	232	21.1	<0.0001
Discharge Status[4]									
SNF	3107	30.9	2572	31.7	236	28.4	299	27.1	<0.0001
Died	2194	21.8	1579	19.4	222	26.7	393	35.7	
Home	3025	30.1	2591	31.9	215	25.8	219	19.9	
Hospice	418	4.2	303	3.7	53	6.4	62	5.6	
Short Stay Acute Care Hospital	572	5.7	485	6.0	40	4.8	47	4.3	
Other Facility[5]	486	4.8	373	4.6	53	6.4	60	5.4	
Other[6]	258	2.6	223	2.7	13	1.6	22	2.0	
Length of Stay until Sample Collection									
Mean (SD)	3.1	(4.9)	1.2	(0.5)	5.3	(1.1)	15.2	(6.2)	<0.0001
Median (IQR)	1	(1-2)	1	(1-1)	5	(4-6)	13	(10-19)	
Total Hospitalization Length of Stay (LOS)									
Mean (SD)	17.5	(16)	15.1	(14)	20.6	(17)	33.1	(22)	<0.0001
Median (IQR)	13	(8-22)	12	(7-18)	17	(11-25)	28	(20-41)	

SNF, skilled nursing facility; [1] Admission Source missing for 339 events, [2] Transferred from another type of healthcare facility such as a clinic, ambulatory surgery center, hospice, or other facility that doesn't include SNF, or different hospital, [3] Type of Admission not available for 244 events, [4] Discharge status missing for 21 events, [5] Rehab Facility, Long-Term Care Facility, Cancer Center, Other, [6] Left against medical advice, Court/Law Enforcement

Table 5. Prior healthcare exposures among patients with MRSA BSI in New York, 2013-16, overall and stratified by type of onset (community-onset, early hospital-onset, and late hospital-onset) (N= 10,081)

Healthcare Exposure	Overall		Community-Onset (days 1-3)		Early Hospital-Onset (days 4-7)		Late Hospital-Onset (days 8 -30)		
	N	%	N	%	N	%	N	%	p
Recent Hospitalization[1]									
prior 30 days	2909	28.9	2287	28.1	251	30.2	371	33.7	0.0004
prior 90 days	4866	48.3	3931	48.3	406	48.8	529	48.0	0.94
prior 180 days	5818	57.7	4742	58.2	483	58.1	593	53.8	0.02
prior 365 days	6492	64.4	5297	65.0	536	64.4	659	59.8	0.003
Number of Outpatient Visits[1] mean (SD)									
prior 30 days	0.4	(1.2)	0.4	(1.2)	0.5	(1.3)	0.5	(1.4)	0.22
prior 90 days	1.1	(3.0)	1.1	(3.0)	1.1	(3.0)	1.2	(3.3)	0.31
prior 180 days	2.0	(5.3)	2.0	(5.1)	2.0	(5.1)	2.3	(6.3)	0.21
prior 365 days	3.7	(9.3)	3.6	(9.2)	3.5	(8.1)	4.0	(10.7)	0.52
Number of Outpatient Visit in Previous Year[1]									
0	4718	46.8	3800	46.6	378	45.4	540	49.0	0.36
1-3	2871	28.5	2341	28.7	243	29.2	287	26.0	
4+	2492	24.7	2006	24.6	211	25.4	275	25.0	
Number of Surgical Procedures in Previous Year[1]									
0	8100	80.4	6478	79.5	693	83.3	929	84.3	0.0006
1	1465	14.5	1230	15.1	103	12.4	132	12.0	
2+	516	5.1	439	5.4	36	4.3	41	3.7	
Admitted from Skilled Nursing Facility	1066	10.9	920	11.8	58	7.1	88	8.0	<0.0001
Healthcare Exposure in Previous Year[2]	7148	70.9	5836	71.6	583	70.1	729	66.2	0.0007
Previous Hospitalization LOS[3,4]									
Mean (SD)	11.6	(13.9)	11.5	(13.8)	10.8	(11.4)	12.4	(16.4)	0.72
Median (IQR)	8	(5-14)	8	(5-14)	7	(5-13)	8	4-14	
Days from Previous Hospital Discharge to Positive MRSA Blood Culture[3,4]									
Mean (SD)	109	(175)	109	(175)	105	(164)	113	(187)	0.09
Median (IQR)	44	(17-119)	45	(16-120)	45	(17-116)	42	(22-107)	

[1] Prior to admission date of MRSA hospitalization

[2] Inpatient hospitalization or surgery in previous 365 days, dialysis during hospitalization, or admission from a skilled nursing facility

[3] Day of previous discharge overlaps with index admission for 2 individuals

[4] Among those with hospitalization in prior 365 days

Table 6. Comparison of risk factors for community-onset and late hospital-onset MRSA BSI compared to early hospital-onset MRSA BSI

	Community-onset (Days 1-3) vs. Early-onset (Days 4-7)		Late hospital onset (Days 8-30) vs. Early-onset (Days 4-7)	
Factor	**aOR[1]**	**(95% CI)**	**aOR[1]**	**(95% CI)**
Admitted from SNF Yes vs. No	1.74	(1.32, 2.30)*	1.13	(0.80,1.61)
Inpatient hospitalization[2] Any vs. None	1.07	(0.92, 1.25)	0.79	(0.66, 0.96)*
Dialysis[3] Yes vs. No	1.33	(1.10, 1.61)*	0.63	(0.49, 0.81)*
Surgery[3,4] Yes vs. No	0.07	(0.05, 0.10)*	2.29	(1.75, 2.98)*
Number of Surgical Procedures in Previous Year[2]				
1 vs. 0	1.26	(1.02, 1.57)*	0.96	(0.73, 1.27)
2≤ vs. 0	1.27	(0.90, 1.80)	0.85	(0.54, 1.35)
Number of Outpatient Visits[2]				
1-3 vs. 0	0.97	(0.82, 1.13)	0.86	(0.70, 1.05)
4≤ vs. 0	0.96	(0.81, 1.14)	0.98	(0.79, 1.21)

Note. aOR, adjusted odds ratio; CI, confidence interval; MRSA, methicillin-resistant *S. aureus*

[1] Multivariable model adjusted for age category, sex, race, Gagne Comorbidity Index, and payer

[2] In the year prior to current admission date

[3] During index hospitalization

[4] Prior to MRSA-positive blood culture

* indicates statistical significance at $p < 0.05$

Figure 1a. Distribution of time from hospital admission to incident methicillin-resistant *S. aureus* (MRSA) bloodstream infections (BSIs) in New York hospitals reporting to NHSN, 2013-2016 (N = 13,278 BSI) – subset of BSIs on days 1-30

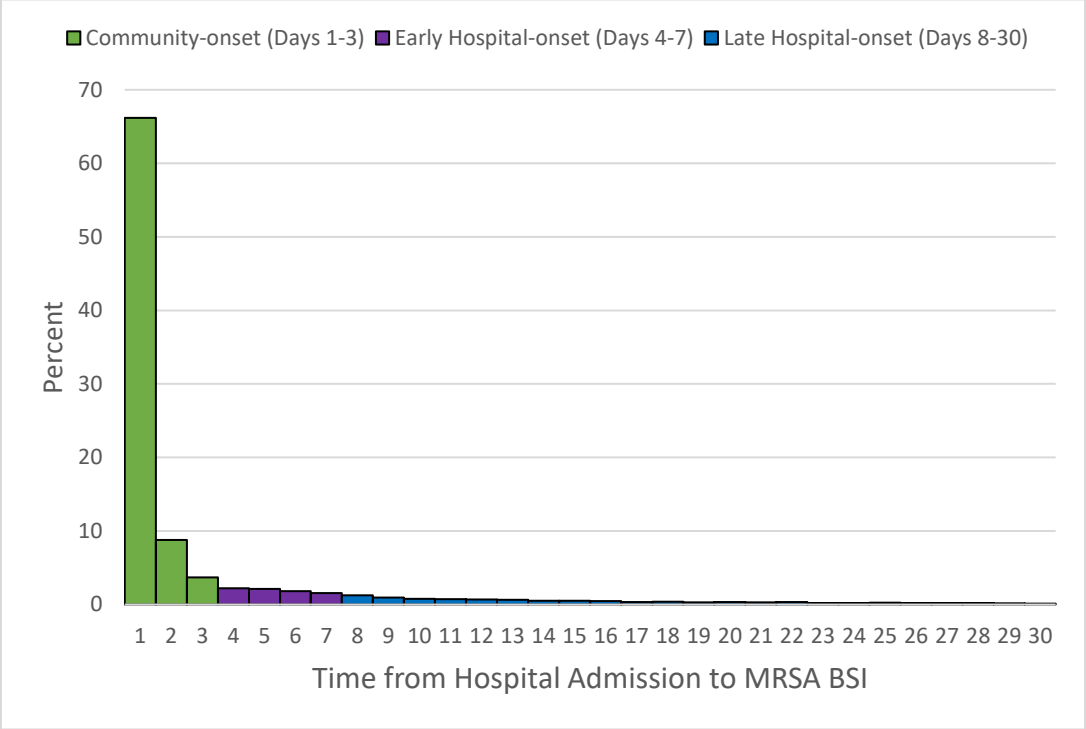


Figure 1b. Distribution of time from hospital admission to incident hospital-onset methicillin-resistant *S. aureus* (MRSA) bloodstream infections (BSIs) in New York hospitals reporting to NHSN, 2013-2016 (N=2,379 BSI) – subset of Figure 1a days 4-30

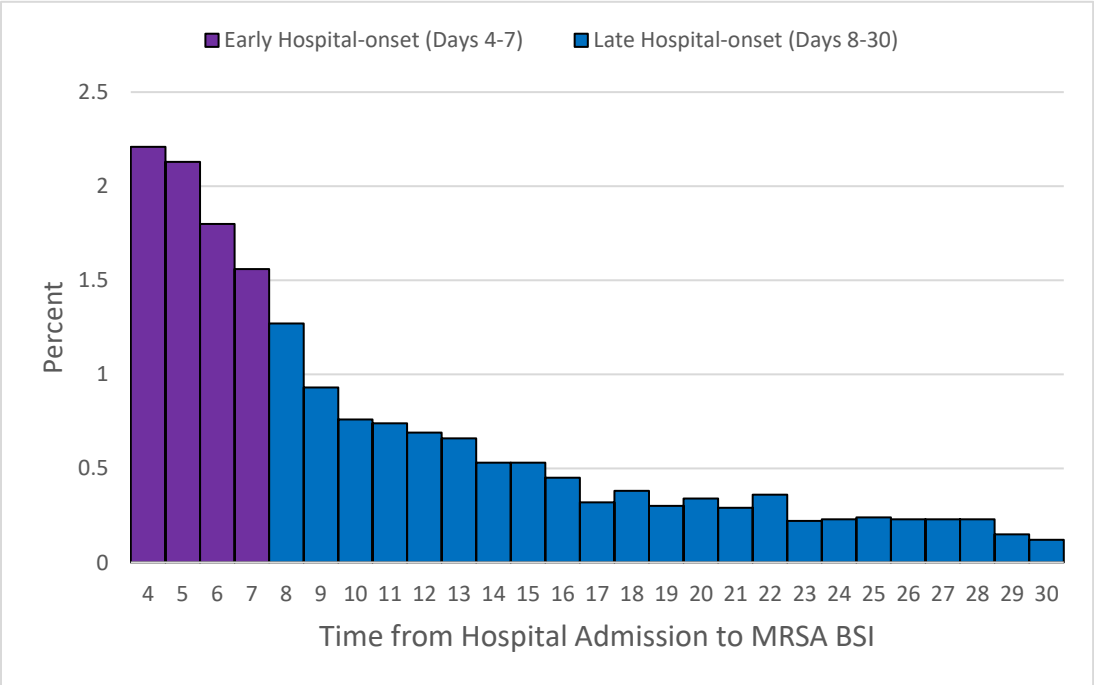


Figure 2. Histogram of the distribution of percent linkage of MRSA-positive blood cultures in hospitals (Facilities N = 167, MRSA cultures = 12,826)

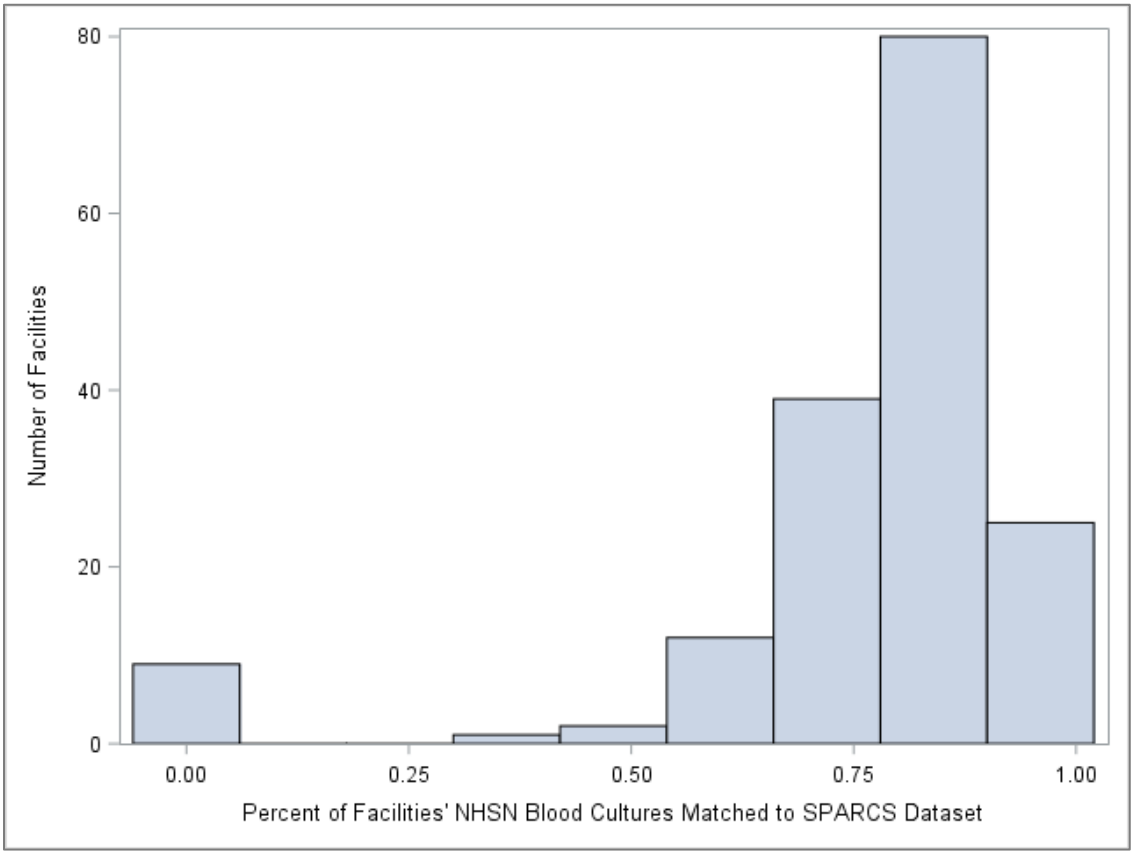


Figure 3. Flowchart of study population inclusion and linkage results between NHSN MRSA bloodstream infections and the SPARCS administrative database. Initial N=13,278 MRSA BSI, Final N=10,081 MRSA BSI

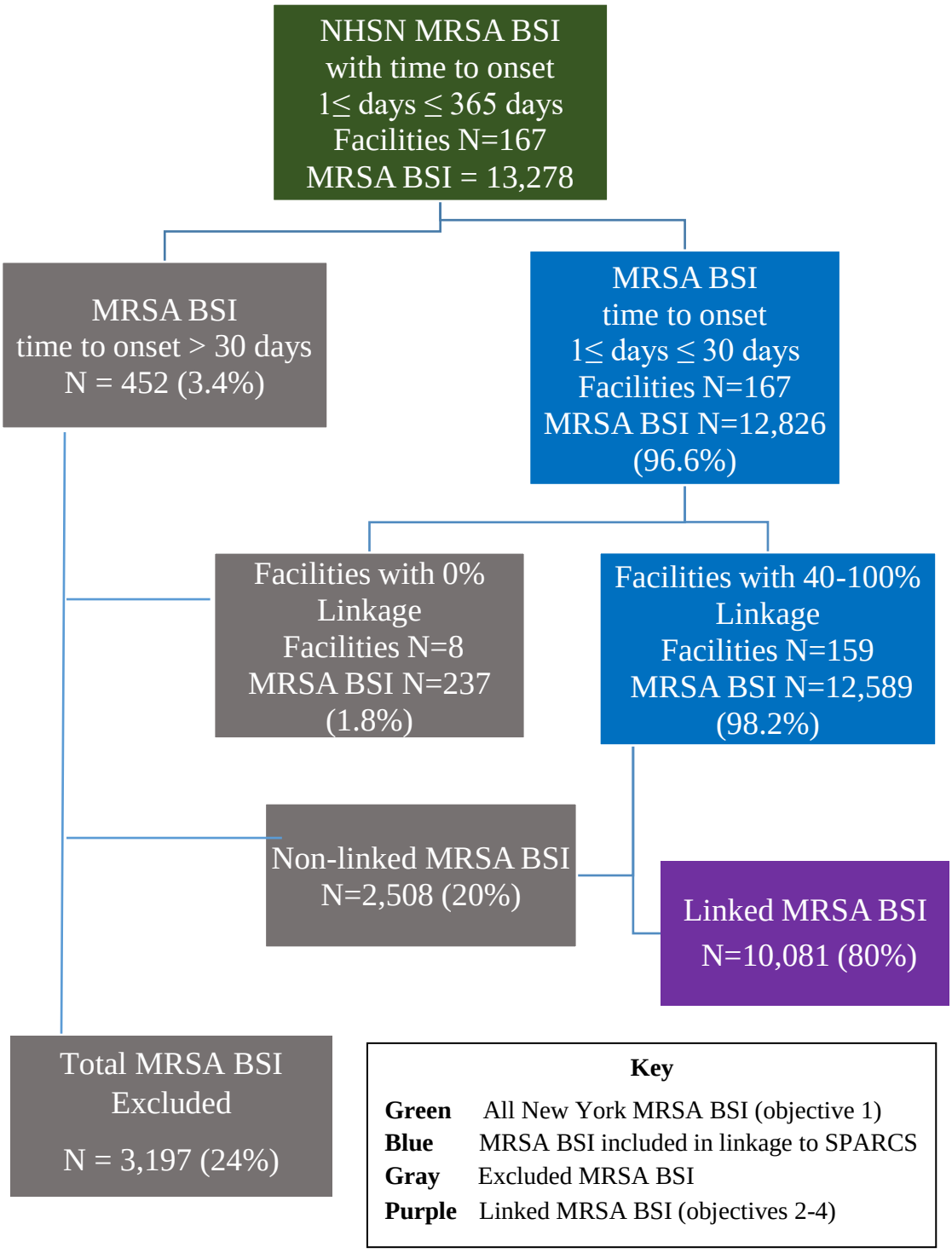


Figure 4. Risk of hospital-onset MRSA bloodstream infections in New York hospitals by days since admission in 2013-2016, lines 95% confidence intervals

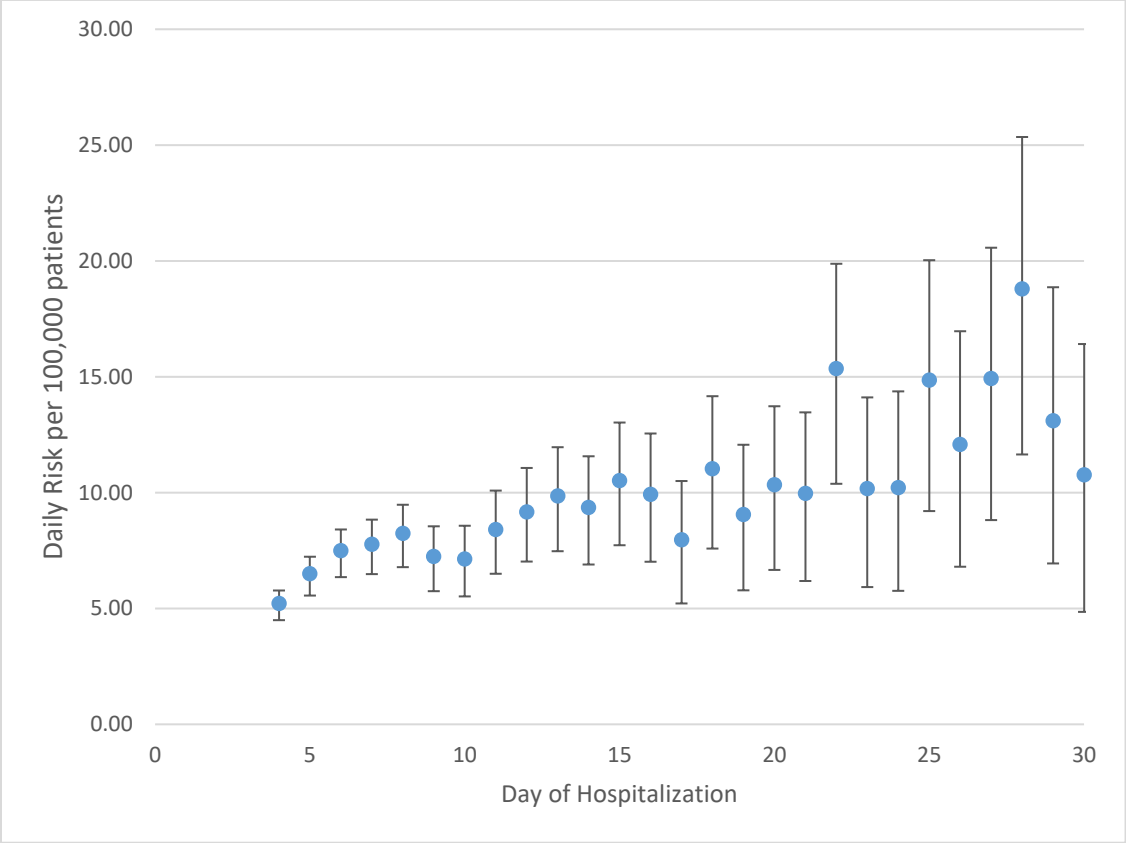
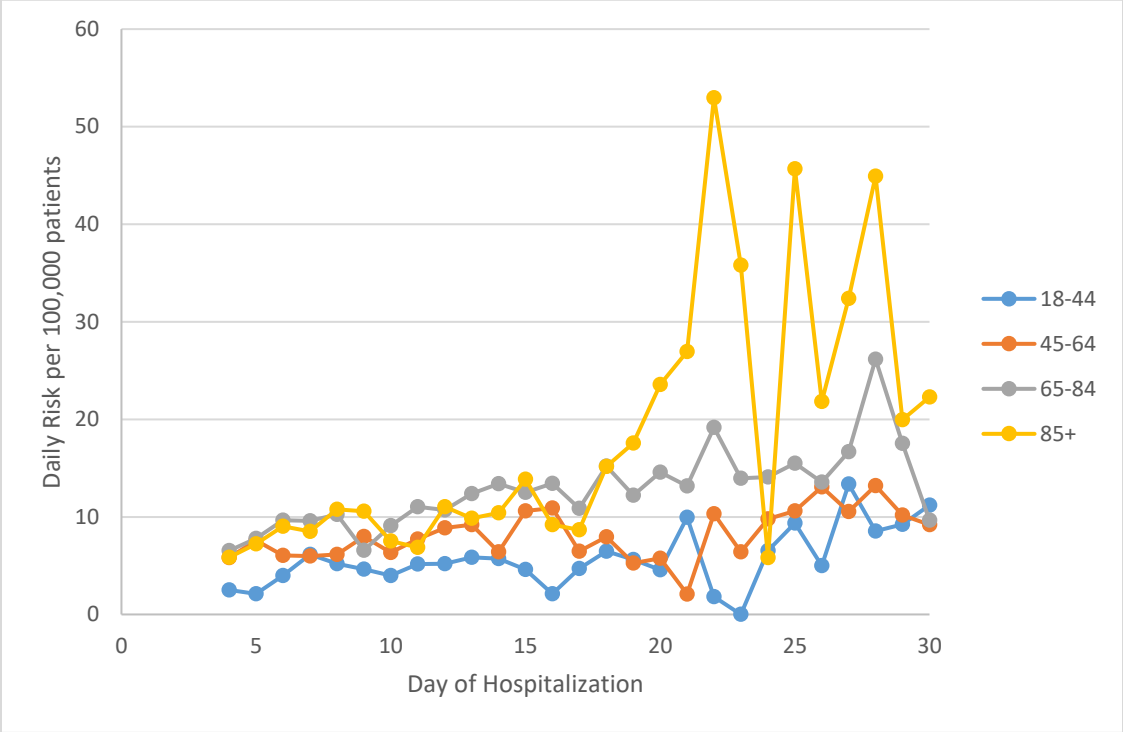


Figure 5. Risk of hospital-onset MRSA bloodstream infections in New York hospitals by days since admission in 2013-2016, stratified by age category



Appendix

Table A1. Daily risk of hospital-onset MRSA bloodstream infections (BSIs) in New York hospitals in 2013-2016

Day of Hospitalization	Number of MRSA BSI	Number of Patients Hospitalized on Day X	Daily Risk of MRSA BSI (per 100,000 hospitalizations)
1	0	7,240,621	0
2	0	7,083,881	0
3	0	6,155,678	0
4	247	4,728,238	5.22
5	224	3,446,449	6.50
6	198	2,642,055	7.49
7	163	2,097,391	7.77
8	140	1,697,603	8.25
9	100	1,379,839	7.25
10	82	1,147,633	7.15
11	82	974,981	8.41
12	77	839,469	9.17
13	72	730,667	9.85
14	60	640,633	9.37
15	59	560,455	10.53
16	48	483,613	9.93
17	34	426,419	7.97
18	42	380,646	11.03
19	31	342,275	9.06
20	32	309,220	10.35
21	28	280,711	9.97
22	39	253,873	15.36
23	23	226,096	10.17
24	21	205,374	10.23
25	28	188,495	14.85
26	21	173,878	12.08
27	24	160,697	14.93
28	28	148,917	18.80
29	18	137,278	13.11
30	13	120,639	10.78

Table A2. ICD-9-CM and ICD-10-CM codes used to identify dialysis exposure and calculate the Gagne Comorbidity Index (59, 73)

	ICD-9-CM	ICD-10-CM
Dialysis Exposure		
Dialysis	39.95, 54.98	3E1M39Z, 5A1D70Z, 5A1D80Z, 5A1D90Z
End Stage Renal Disease	V45.11, 585.6	Z99.2, N18.6
Gagne Comorbidity Index		
Alcohol Abuse	291.1, 291.2, 291.5, 291.8, 291.9, 303.9-303.93, 305.0-305.03, V11.3	F10.x, E52, G62.1, I42.6, K29.2x, K70.0, K70.3x, K70.9, T51.x, Z71.4x, Z65.8
Any tumor	140.x–171.x, 174.x–195.x, 200.x–208.x, 273.0, 273.3, V104.6	C00.x-C26.x, C30.x–C34.x, C37.x-C41.x, C43.x, C45.x–C58.x, C60.x– C75.x, C76.x, C81.x-94.3x, C94.8x, C95.x, C96.0-C96.4, C96.9, C96.A, C96.Z, D45, D89, Z85.46
Cardiac arrhythmias	426.10, 426.11, 426.13, 426.2-426.4, 426.50-426.53, 426.6-426.8, 427.0, 427.2, 427.31, 427.6, 427.9, 785.0, V45.0, V53.3	I44.0, I44.1, I44.3x-145.2, I45.4-I45.8x, I45.9, I47.x–I49.x, R00.0, R00.1, R00.8, T82.1x, Z45.0x, Z95.0, Z95.810, Z95.818, Z95.9
Chronic pulmonary disease	415.0, 416.8, 416.9, 491.x–494.x, 496.x	I26.0x, I27.2-I27.9, J40.x-J47.x, J60.x–J67.x, J68.4, J70.1, J70.3
Coagulopathy	286.0-286.9, 287.1, 287.3–287.5	D65.x-D68.x, D69.1, D69.3–D69.6
Complicated diabetes	250.4–250.73, 250.90-250.93	E10.2x–E10.8, E11.2x–E11.8, E12.2x– E12.8, E13.2x–E13.8x
Congestive heart failure	402.01, 402.11, 402.91, 425.x, 428.x, 429.3	A18.84, I09.9, I11.0, I13.0, I13.2, I25.5, I42.x, I43.x, I50.x, I51.7, P29.0
Deficiency anemia	280.1–281.9, 285.9	D50.1-D50.9, D51.x–D53.x, D64.9
Dementia	290.x, 331.0, 331.1, 331.2	F01.x–F03.x, F05, G30.x, G31.01, G31.09, G31.1
Fluid and electrolyte disorders	276.x	E22.2, E86.x, E87.x
Hemiplegia	342.x, 344.x	G04.1, G11.4, G80.1, G80.2, G81.x, G82.x, G83.x
HIV/AIDS	042.x–044.x	B20.x
Hypertension	401.1, 401.9, 402.10, 402.90, 404.10, 404.90, 405.11, 405.19, 405.91, 405.99	I10.x, I11.x–I13.x, I15.x, N26.2
Liver disease	070.32, 070.33, 070.54, 456.0, 456.1, 456.20, 456.21, 571.0, 571.2, 571.3, 571.40-571.49, 571.5,	B18.x, I85.x, I86.4, K70.x, K71.1, K71.3–K71.5, K71.7, K72.1x, K72.9.x, K73.x-K74.x,

	571.6, 571.8, 571.9, 572.3, 572.8, V42.7	K75.4, K75.81, K76.0, , K76.2–K76.9, Z48.23, Z94.4
Metastatic cancer	196.x–199.x	C45.9, C77.x-C80.x
Peripheral vascular disease	440.x, 441.2, 441.4, 441.7, 441.9, 443.1–443.9, 447.1, 557.1, 557.9, V43.4	E08.51, E08.52, E09.51, E09.52, E10.51, E10.52, E11.51, E13.51, E13.52, I67.0, I70.x, I71.x, I73.1, I73.8x, I73.9, I77.1, I77.71- I77.74, I177.79, I79.x, K55.1, K55.8, K55.9, Z95.82x, Z95.9
Psychosis	295.x-298.99, 299.1, 299.11	F20.x, F22-25.x, F28.x, F29.x, F30.x-F33.x, F34.8, F34.9, F39.x, F44.89, F84.3
Pulmonary circulation disorders	416.x, 417.9	I26.x, I27.x, I28.0, I28.8, I28.9
Renal failure	403.11, 403.91, 404.12, 404.92, 585.x, 586.x, V42.0, V45.1, V56.0, V56.8	I12.0, I13.x, N03.2–N03.7, N05.2– N05.7, N18.x, N19.x, N25.0, Z39.32, Z48.22, Z49.0x, Z49.31, Z91.15, Z94.0, Z99.2
Weight loss	260.x–263.x	E40.x-E46.x, E64.0, R63.4, R64

Table A3. Sensitivity analysis: comparison of risk factors for community-onset and late hospital-onset MRSA BSI compared to early hospital-onset MRSA BSI, adjusted for all healthcare exposures

	Community onset (Days 1-3) vs. Early-onset (Days 4-7)		Late hospital onset (Days 8-30) vs. Early-onset (Days 4-7)	
Factor	**Full Model[1]**	**(95% CI)**	**Full Model[1]**	**(95% CI)**
Admitted from SNF Yes vs. No	1.66	(1.26, 2.21)*	1.22	(0.86, 1.74)
Inpatient hospitalization[2] Any vs. None	0.93	(0.79, 1.10)	0.85	(0.69, 1.04)
Dialysis[3] Yes vs. No	1.29	(1.06, 1.57)*	0.64	(0.50, 0.83)*
Surgery[3,4] Yes vs. No	0.07	(0.05, 0.10)*	2.28	(1.74, 2.98)*
Number of Surgical Procedures[2]				
1 vs. 0	1.41	(1.12, 1.78)*	1.01	(0.75, 1.36)
≥2 vs. 0	1.46	(1.02, 2.11)*	0.90	(0.56, 1.45)
Number of Outpatient Visits[2]				
1-3 vs. 0	0.90	(0.76, 1.08)	0.87	(0.70, 1.09)
≥4 vs. 0	0.91	(0.76, 1.10)	0.95	(0.75,1.20)

Note. CI, confidence interval; MRSA, methicillin-resistant *S. aureus*;
[1] Fully adjusted models for all variables in table in addition to age category, sex, Gagne comorbidity index, and payer
[2] In the year prior to current admission date
[3] During index hospitalization
[4] Prior to MRSA-positive blood culture
* indicates statistical significance at $p < 0.05$

Figure A1. Flow chart of the populations included within each study objective