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Changing Epidemiology of Methicillin-Resistant *Staphylococcus aureus* in the Veterans Affairs Healthcare System, 2002-2009

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ABSTRACT

Purpose

The epidemiology of infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA) is changing. Temporal trends and differences between healthcare settings must be described to better predict future risk factors associated with this dangerous bacterial infection.

Methods

A national MRSA-infected cohort was identified from 2002 through 2009 in the Veterans Affairs Healthcare System of the United States: hospital (HOS), long-term care (LTC), and outpatient (OPT). We analyzed within-setting time trends using generalized linear mixed models and between-setting differences with χ^2 and Wilcoxon rank-sum tests.

Results

The incidence of *S. aureus*, methicillin-susceptible *S. aureus*, and MRSA infections increased significantly over time in all three settings based on modeled annual percent changes ($p<0.001$). MRSA incidence rates rose by 14%, 10%, and 37% per year in the HOS, LTC, and OPT settings respectively. Among 56,345 MRSA-infected patients, comorbidity burden was highest among LTC inpatients (n=4,427) and lowest among outpatients (n=7,250), with an average absolute difference in specific comorbidities of +2% and -7% respectively compared to HOS inpatients (n=44,668). Over time, there was a significant ($p\leq0.02$) decrease in previous inpatient admissions and surgeries (all settings); diabetes with complications and surgical site infections (HOS, OPT); median length of stay and inpatient mortality (HOS, LTC). Alternatively, obesity, chronic renal disease, and depression were more common between 2002 and 2009 ($p\leq0.02$).

Conclusions

Over the past eight years, we observed significant changes in the epidemiology of MRSA infections, including decreases in traditional MRSA risk factors, improvements in clinical outcomes, and increases in other patient characteristics that may affect risk.

INTRODUCTION

Over the past decade, substantial shifts in the molecular and clinical epidemiology of methicillin-resistant *Staphylococcus aureus* (MRSA) infections have been reported [1-12]. Although MRSA infections were once predominantly hospital-acquired, this insidious pathogen has evolved and is now pervasive in communities across the United States (U.S.) [2-4]. Ensuing evidence has documented the rise in community-associated MRSA (CA-MRSA) and decline in invasive healthcare-associated MRSA (HA-MRSA), altering the distribution of attributed exposure and onset, strain characteristics, and predominant infection types [1-12]. However, in this era of epidemiologic change, knowledge of trends in patient characteristics is limited.

We therefore sought to describe the underlying patient populations infected with MRSA from diverse healthcare settings of a single source population. Our objectives were to quantify differences in patient demographics, comorbidities, clinical characteristics, and outcomes between healthcare settings and describe within-setting changes over time among hospital inpatients, long-term care inpatients, and outpatients in the national Veterans Affairs (VA) Healthcare System.

METHODS

Study Design and Population. To describe the epidemiology of MRSA from January 1, 2002 through December 31, 2009, we utilized national databases documenting care provided by the VA Healthcare System in the U.S. [13]. This retrospective, observational study identified MRSA-infected adult patients (≥18 years of age) from inpatient settings, consisting of hospital

admissions and long-term care facility admissions, and the outpatient setting. This study was reviewed and approved by the Providence VA Medical Center Institutional Review Board.

Incidence. We assessed changes in MRSA incidence rates over time in the context of *Staphylococcus aureus* (*S. aureus*) infections. Utilizing International Classification of Diseases, 9th Revision (ICD-9) diagnosis codes, we identified *S. aureus* infections (ICD-9 038.11, 038.12, 041.11, 041.12, 482.41, 482.42, V09.0), which were then categorized as methicillin-resistant (038.12, 041.12, 482.42, V09.0), or methicillin-susceptible (MSSA) based on the absence of a MRSA code [10]. The yearly incidence rate was calculated for each setting as the number of *S. aureus*, MSSA, and MRSA-related hospitalizations, long-term care admissions, or outpatient visits per 1,000 admissions or visits.

Characteristics of MRSA-Infected Patients. If patients had more than one MRSA-related admission or visit during the study period, the first encounter was selected for inclusion. Comorbidities were assessed from ICD-9 codes present during the MRSA-related admission/visit and any inpatient admission or visit in the previous year [14, 15]. Previous healthcare exposures, including inpatient admissions and surgeries, were captured in the year prior to the MRSA-related admission/visit. Infection type was categorized as bacteremia (ICD-9 038.11, 038.12, 790.7), endocarditis (421.0), skin and soft tissue infection (ICD-9 681-682, 528.3), surgical site infection (998.5), osteomyelitis (730.0-730.2), and pneumonia (482-486) based on diagnoses present during the MRSA-related admission/visit [10, 15].

Statistical Analyses. Differences in patient demographics, comorbidities, clinical characteristics, and outcomes between healthcare settings were analyzed with χ^2 and Wilcoxon rank-sum tests for categorical and continuous variables respectively. Within healthcare settings, we assessed the significance of temporal trends over the study years using generalized linear mixed models. Due to changes in coding practices, sensitivity analyses were carried out excluding MRSA-infected patients diagnosed in 2009. A p-value of <0.05 was considered statistically significant and all analyses were performed using SAS (SAS Institute Inc., Cary, NC, Version 9.2).

RESULTS

The incidence of *S. aureus*, MSSA, and MRSA infections increased significantly over time in all three settings based on modeled annual percent changes ($p<0.001$). MRSA-related hospitalizations increased from 6.7 in 2002 to 15.9 in 2009, from 8.3 to 15.9 MRSA-related long-term care admissions, and from 0.01 to 0.08 MRSA-related outpatient clinic visits per 1,000 admissions/visits (Fig 1). MRSA incidence rates increased annually by 37% in the outpatient setting, 10% in long-term care, and 14% in hospitals. Similarly, modeled MSSA incidence rates rose each year by 18% in the outpatient setting, 4% in long-term care, and 4% in hospitals. We observed a 4% increase per year in the modeled incidence for *S. aureus*-related long-term care admissions, a 5% increase per year for hospital admissions, and a 21% increase per year for outpatient visits. Sensitivity analyses demonstrated agreement, with the exception of non-significant changes over time in MSSA incidence for the hospital and long-term care settings.

MRSA-infected long-term care inpatients (n=4,427) and outpatients (n=7,250) differed significantly ($p \leq 0.035$) from those hospitalized (n=44,668) on most characteristics assessed including demographics, comorbidities, previous healthcare exposures, and infection type (Table 1). Comorbidity burden was highest among MRSA-infected long-term care inpatients and lowest among outpatients, with an average absolute difference in specific comorbidities of +2% and -7% respectively compared to hospital inpatients. Skin and soft tissue infections were the most commonly reported infection type in each healthcare setting (hospital 31%; long-term care 18%; outpatient 23%), followed by pneumonia among inpatients (hospital 16%; long-term care 16%) and osteomyelitis among outpatients (4%). Endocarditis was reported in less than 1% of the MRSA-infected cohort and site of infection could not be determined from diagnosis codes in 33% of patients (hospital 29%; long-term care 34%; outpatient 56%) [10, 15].

Over time, the median Charlson Comorbidity Index changed significantly only among MRSA-infected outpatients, decreasing from 3 in 2002 to 1 in 2009 ($p=0.034$). Temporal trends within healthcare settings are presented in Table 2. Significant decreases ($p \leq 0.037$) were observed in the modeled annual percent change of MRSA-infected patients with cerebrovascular disease (hospital 0.4%; long-term care 0.8%), diabetes with complications (hospital 0.4%; outpatient 1.7%), dialysis (hospital 0.2%), and peripheral vascular disease (hospital 0.6%; outpatient 1.8%). Inpatient admissions and surgeries in the year prior to the MRSA-related admission/visit were significantly ($p \leq 0.02$) less common over time in all three settings (hospital 2.3% and 1.8%; long-term care 0.9% and 1.3%; outpatient 3.4% and 2.4%). Alternatively, in each healthcare setting, obesity and depression were more commonly reported from 2002 through 2009 in MRSA-

infected patients ($p \leq 0.02$; hospital 1.4% and 1.2%; long-term care 1.2% and 1.7%; outpatient 1.1% and 1.0%).

Non-significant increases were observed in skin and soft tissue infections over the study period in all three settings. Among MRSA-infected long-term care inpatients, infection type was relatively unchanged over time, except for a significant decrease ($p<0.001$) in pneumonia (1.5% modeled annual percent change). Surgical site infections and osteomyelitis decreased significantly each year among hospital inpatients and outpatients (hospital 0.6% and 0.6%; outpatient 0.4% and 1.4%), while pneumonia increased 1.2% per year in the hospital setting. Among MRSA-infected inpatients, annualized decreases in median length of stay (hospital: 11 days in 2002 to 6 days in 2009; long-term care: 52 days to 36 days) and inpatient mortality (hospital 0.9%; long-term care 1.7%) were significant ($p \leq 0.01$). Changes in patient characteristics over time were similar in sensitivity analyses including data from 2002 through 2008.

DISCUSSION

Our research uniquely assessed a comprehensive set of patient characteristics in three distinct clinical settings of a nationwide healthcare provider, with a well-defined source population, in the US. From this large, national epidemiologic study, significant increases in MRSA incidence rates were discerned over the past eight years in the VA Healthcare System. Our findings are similar to other national studies that have described rising MRSA incidence rates over the past decade among children and adults in the U.S. and Canada [6, 10, 16]. Unlike the diverse

161 healthcare settings we evaluated, these other studies were restricted to a single clinical setting,
162 specifically hospitals [6, 10, 16].
163
164 In both the hospital and long-term care settings, we observed non-significant declines in MRSA
165 incidence rates between 2008 and 2009. The interaction of several contributing factors may
166 explain these reduced rates. VA infection control policies targeting MRSA were enhanced under
167 a nationwide directive, with full implementation in acute care facilities by December 31, 2007
168 and expansion to other healthcare settings during 2009 [17]. The MRSA Prevention Initiative
169 established active MRSA colonization surveillance and emphasizes contact precautions, hand
170 hygiene, and cultural transformation as components of the overall MRSA prevention bundle,
171 broadening infection control awareness through education [17, 18].
172
173 Additionally, the introduction of new diagnosis codes for MRSA infections may have impacted
174 coding practices. Previously, MRSA could only be coded as a secondary diagnosis (V09.0),
175 however primary ICD-9 codes for MRSA bacterial infection (041.12), MRSA septicemia
176 (038.12), and MRSA pneumonia (482.42) were adopted in 2009. Lastly, shifts in MRSA
177 exposure and onset likely played a role in the recent decline, as CA-MRSA has gained a larger
178 share of MRSA infections with subsequent reductions in HA-MRSA [2-5]. Active laboratory
179 surveillance in 9 U.S. metropolitan areas revealed substantial yearly rate decreases in the
180 incidence of invasive HA-MRSA infections from 2005 through 2008 [5]. We suspect the decline
181 we observed in hospital MRSA incidence was considerably less than the reported HA-MRSA
182 rate drop due to increases in invasive infections requiring inpatient care caused by CA-MRSA
183 [1-5].

As expected, MRSA-infected long-term care inpatients had a higher comorbidity burden than hospital inpatients, and those hospitalized were in poorer health than outpatients. In quantifying differences between healthcare settings, we found most comorbidities differed by several percentage points comparing hospitalized and long-term care inpatients, although this difference was more pronounced between outpatients and hospital inpatients.

In regards to temporal trends among patients infected with MRSA, we observed significant declines in previously established MRSA risk factors, including diabetes with complications [19-21], previous hospitalization [7, 20, 21], previous surgery [23], and dialysis [17, 22, 23]. Also significant over time were increases in obesity and depression. Possible explanations for these increases include changes in the underlying patient population infected with MRSA in the VA Healthcare System, increased awareness and reporting, or the potential for these diseases to affect the risk of developing MRSA infections. Overall, MRSA-infected patients appeared healthier over the study period in each of the three settings and clinical outcomes improved. Our findings are consistent with rising rates of CA-MRSA and the distinct clinical epidemiology of CA-MRSA [2-5, 24].

A considerable limitation in our study and several others [10, 25, 26], is the use of diagnosis codes to identify MRSA infections. Due to the lack of microbiology research databases in U.S. healthcare systems, we are limited to diagnosis codes extracted from administrative data and electronic medical records [10, 13, 25, 26]. Until health informatics advancements are made to

extract and link such data, the only way to ascertain MRSA trends in large populations is with diagnosis codes.

Similar to other research using diagnosis codes, we could only determine site of infection in two-thirds of the cohort [10]. This may explain the absence of significant increases in MRSA skin and soft tissue infections over time. Three of the MRSA diagnosis codes await validation as they were recently implemented (038.12, 041.12, 482.42). The original MRSA diagnosis code (V09.0) has suboptimal sensitivity but a high positive predictive value, indicating underascertainment [10, 27, 28]. It is important to note that coding accuracy in VA databases is reportedly higher than other healthcare systems [29, 30]. Further, sensitivity has been found to increase with greater numbers of available diagnosis code entries, which is relatively high in the VA databases (13 entries per admission plus 5 per bed section, 10 per outpatient visit) [10, 13, 27, 28]. The generalizability of the findings should be interpreted in the context of our source population, comprising 5.5 million patients treated annually by the VA Healthcare System, which is the largest integrated healthcare system in the country.

In conclusion, MRSA incidence rates rose significantly over the past eight years in the VA Healthcare System. We observed significant changes in the epidemiology of MRSA infections among hospital inpatients, long-term care inpatients, and outpatients from the same source population. Over time, MRSA-infected patients appeared healthier, with fewer exposures to MRSA risk factors and improved clinical outcomes, suggesting CA-MRSA has gained considerable ground in the VA Healthcare System nationally.

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TABLES

Table 1. Demographics, comorbidities, clinical characteristics, and outcomes by healthcare setting among MRSA-infected patients in the Veterans Affairs Healthcare System

Covariates	Hospital N = 44,668	Long-term care[a] N = 4,427	Outpatient clinic[a] N = 7,250
Median age, y (IQR)	63 (55-76)	68 (58-79)	60 (52-72)
Male	43,337 (97.0)	4,305 (97.2)[NS]	6,711 (92.6)
Race			
White	33,445 (74.9)	3,462 (78.2)	5,206 (71.8)
African American	8,758 (19.6)	709 (16.0)	1,175 (16.2)
Hispanic	2,417 (5.4)	187 (4.2)	301 (4.2)
Region of facility			
North	5,297 (11.9)	749 (16.9)	874 (12.0)
South	18,887 (42.3)	1,333 (30.1)	3,275 (45.2)
Midwest	9,537 (21.3)	1,309 (29.6)	1,462 (20.2)
West	10,947 (24.5)	1,036 (23.4)	1,639 (22.6)
Admitted from home	38,155 (85.4)	1,471 (33.2)	--
Median Charlson Comorbidity Index (IQR)	3 (1-5)	3 (2-6)	1 (0-3)
Comorbidities			
Amputation	3,321 (7.4)	503 (11.4)	322 (4.4)
Cancer	9,943 (22.3)	1,110 (25.1)	1,056 (14.6)

Cerebrovascular disease	7,441 (16.7)	960 (21.7)	631 (8.7)
Chronic renal disease	9,438 (21.1)	921 (20.8)[NS]	775 (10.7)
Chronic respiratory disease	15,925 (35.7)	1,688 (38.1)	1,683 (23.2)
Congestive heart failure	10,588 (23.7)	1,127 (25.5)	796 (11.0)
Depression	15,219 (34.1)	1,813 (41.0)	2,322 (32.0)
Diabetes	19,092 (42.7)	1,965 (44.4)	2,503 (34.5)
Diabetes with complications	9,238 (20.7)	1,032 (23.3)	1,010 (13.9)
Dialysis	1,517 (3.4)	142 (3.2)[NS]	87 (1.2)
Hypertension	31,925 (71.5)	3,304 (74.6)	4,474 (61.7)
Obesity	6,945 (15.5)	597 (13.5)	1,292 (17.8)
Paralysis	3,130 (7.0)	310 (7.0)[NS]	177 (2.4)
Peripheral vascular disease	9,320 (20.9)	1,136 (25.7)	919 (12.7)
Previous healthcare exposures			
Inpatient admission	27,408 (61.4)	3,630 (82.0)	2,211 (30.5)
Surgery	9,214 (20.6)	1,493 (33.7)	694 (9.6)
Infection type			
Bacteremia	6,650 (14.9)	591 (13.4)	191 (2.6)
Skin and soft tissue	13,892 (31.1)	805 (18.2)	1,656 (22.8)
Surgical site infection	2,803 (6.3)	343 (7.8)	186 (2.6)
Osteomyelitis	4,022 (9.0)	524 (11.8)	255 (3.5)
Pneumonia	7,149 (16.0)	696 (15.7)[NS]	141 (1.9)
Outcomes			
Inpatient mortality	2,701 (6.0)	1,006 (22.7)	--

Follow-up MRSA admission	27,731 (62.1)	2,236 (50.5)	2,427 (33.5)
Median length of stay, d (IQR)	7 (4-15)	45 (21-105)	--

Data are no. (%), unless otherwise indicated. MRSA, methicillin-resistant *Staphylococcus aureus*; IQR, interquartile range; NS, non-significant.

[a] For all covariates, differed significantly compared to MRSA-infected hospitalized patients ($p \leq 0.035$), unless otherwise indicated (NS). Determined from χ^2 or Wilcoxon Rank-Sum tests as appropriate.

Table 2. Temporal trends in demographics, comorbidities, clinical characteristics, and outcomes by healthcare setting among MRSA-infected patients in the Veterans Affairs Healthcare System

Covariates	Hospital N = 44,668			Long-term care N = 4,427			Outpatient clinic N = 7,250		
	2002	2009	↓↑[a]	2002	2009	↓↑[a]	2002	2009	↓↑[a]
Median age, y	67	63	NS	71	66	↓	70	60	↓
Male	97.7	96.4	↓	97.6	96.2	NS	95.5	92.8	NS
White	77.3	72.3	NS	81.0	75.0	↓	78.3	71.3	↓
Hispanic	5.4	5.4	NS	5.0	5.0	NS	3.0	4.4	NS
Admitted from home	80.5	87.1	↑	28.0	39.5	↑	--	--	--
Median Charlson Comorbidity Index	3	3	NS	3	4	NS	3	1	↓
Comorbidities									
Amputation	9.1	6.6	↓	13.1	11.2	NS	12.6	3.4	↓
Cancer	24.3	22.4	NS	24.9	26.4	NS	20.2	13.8	NS
Cerebrovascular disease	19.7	16.7	↓	24.5	20.5	↓	11.1	8.0	NS
Chronic renal disease	19.1	23.3	↑	13.3	26.7	↑	10.6	11.1	NS
Chronic respiratory disease	37.9	33.7	NS	42.3	37.8	NS	33.3	22.8	NS

Congestive heart failure	26.5	22.5	NS	27.3	26.9	NS	19.2	9.6	↓
Depression	28.8	37.1	↑	36.1	45.9	↑	26.8	35.2	↑
Diabetes	42.7	43.6	NS	43.2	47.2	NS	42.4	33.1	↓
Diabetes with complications	23.1	20.3	↓	22.8	24.0	NS	22.7	12.6	↓
Dialysis	4.7	3.2	↓	4.0	3.6	NS	1.5	1.1	NS
Hypertension	66.3	75.5	↑	67.2	80.0	↑	66.7	61.9	NS
Obesity	10.0	18.7	↑	9.3	18.6	↑	12.1	19.2	↑
Paralysis	9.0	6.3	↓	9.3	6.7	NS	4.5	2.2	↓
Peripheral vascular disease	25.5	19.7	↓	24.0	27.6	NS	23.7	10.7	↓
Previous healthcare exposures									
Inpatient admission	72.7	56.9	↓	84.3	78.3	↓	52.5	28.9	↓
Surgery	29.6	17.5	↓	38.7	27.9	↓	28.8	8.1	↓
Infection type									
Bacteremia	18.0	15.1	↓	10.9	12.2	NS	2.5	3.0	NS
Skin and soft tissue	22.9	32.0	NS	15.0	16.2	NS	15.2	21.0	NS
Surgical site infection	8.7	5.5	↓	8.8	7.2	NS	5.1	1.4	↓
Osteomyelitis	11.4	8.4	↓	9.5	10.3	NS	12.6	2.2	↓
Pneumonia	19.8	11.3	↓	20.7	9.0	↓	2.0	2.2	NS

Outcomes									
Inpatient mortality	9.9	4.1	↓	28.7	17.4	↓	--	--	--
Follow-up MRSA admission	68.3	46.2	↓	54.2	32.9	NS	62.1	21.9	↓
Median length of stay, d	11	6	↓	52	36	↓	--	--	--

Data are %, unless otherwise indicated. MRSA, methicillin-resistant *Staphylococcus aureus*; NS, non-significant.

[a] Increased (↑) or decreased (↓) significantly over time ($p \leq 0.037$), unless otherwise indicated (NS), as determined from generalized linear mixed models.

FIGURE

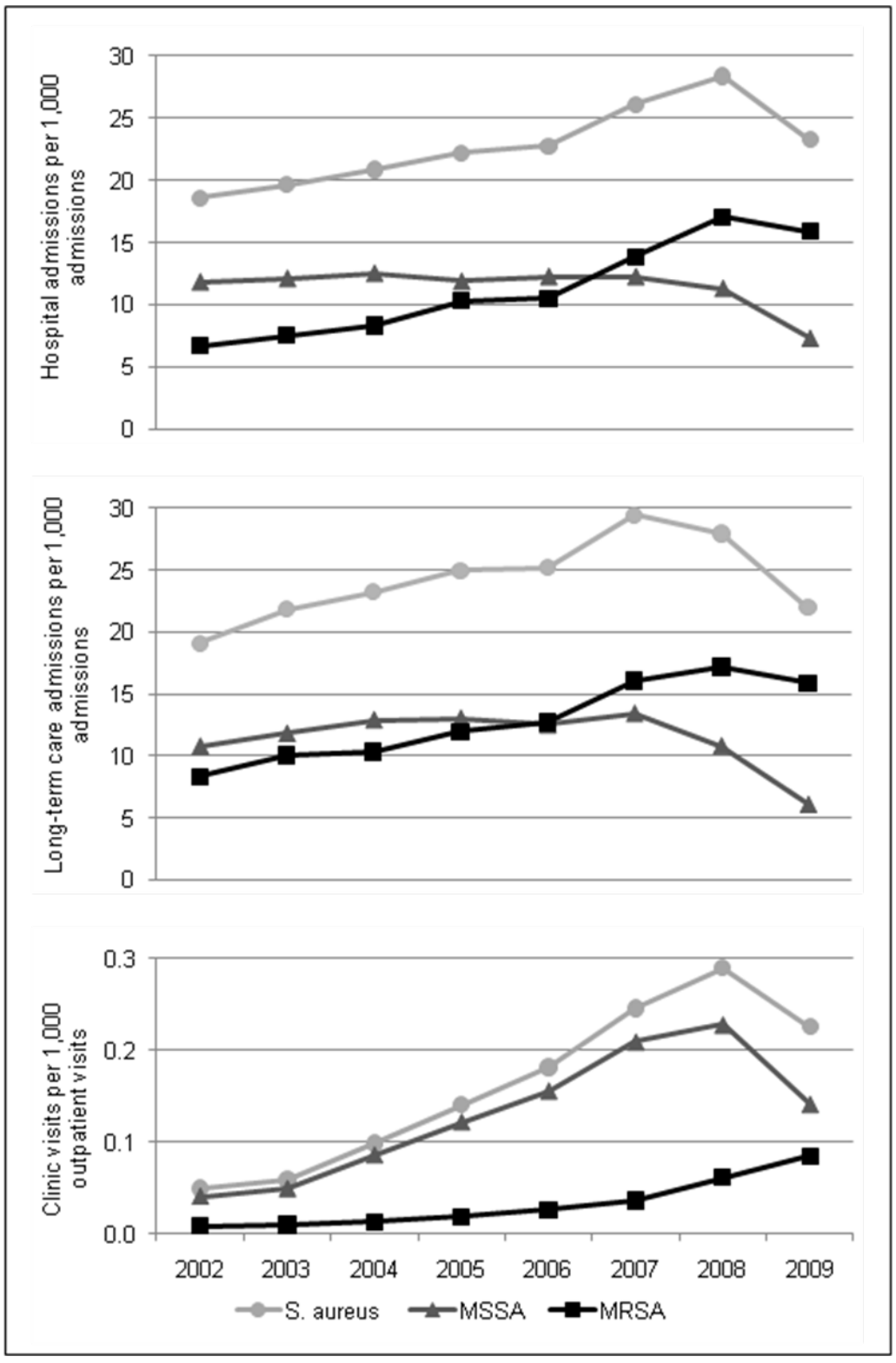
Hospital admissions per 1,000 admissions
30
25
20
15
10
5
0
Long-term care admissions per 1,000 admissions
30
25
20
15
10
5
0
Clinic visits per 1,000 outpatient visits
0.3
0.2
0.1
0.0
2002
2003
2004
2005
2006
2007
2008
2009
S. aureus
MSSA
MRSA

Fig 1 Incidence of *Staphylococcus aureus* (*S. aureus*), methicillin-susceptible *S. aureus* (MSSA), and methicillin-resistant *S. aureus* (MRSA) hospital admissions, long-term care admissions, and outpatient clinic visits per 1,000 admissions or visits in the Veterans Affairs Healthcare System, 2002-2009