Illicit Drug Use and Risk for USA300 Methicillin-Resistant *Staphylococcus aureus* Infections with Bacteremia

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Learning Objectives

Upon completion of this activity, participants will be able to:

- Examine the association of illicit drug use with USA300 MRSA infection, including risk factors for acquisition and transmission.
- Describe characteristics of illicit drug users who acquire MRSA and the changing pattern of risk from 2004 to 2008 in the United States with implications for management and prevention.

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To assess the association of illicit drug use and USA300 methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia, a multicenter study was conducted at 4 Veterans Affairs medical centers during 2004–2008. The study showed that users of illicit drugs were more likely to have USA300 MRSA bacteremia (in contrast to bacteremia caused by other *S. aureus* strains) than were patients who did not use illicit drugs (adjusted relative risk 3.0; 95% confidence interval 1.9–4.4). The association of illicit drug use with USA300 MRSA bacteremia decreased over time (p = 0.23 for trend). Notably, the proportion of patients with USA300 MRSA bacteremia who did not use illicit drugs increased over time. This finding suggests that this strain has spread from users of illicit drugs to other populations.

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Infections caused by community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA) are in-

creasing. Outbreaks have been described in a variety of populations, including sports teams, men who have sex with men, prisoners, and children (*1–10*). The USA300 MRSA clone has been recognized as the most common strain causing CA-MRSA infections (*11*).

CA-MRSA was first reported in illicit drug users in Detroit in 1980 (*12*). The drug-using population has been identified as a reservoir of CA-MRSA (*13*). Because of the repeated injection or inhalation of drugs, the opportunity for a person to cause and spread infection with one's own colonizing strain is multiplied (*13*,*14*). Skin and soft tissue infections are the most common infections in illicit drug users; the USA300 MRSA strain is the cause of up to 75% of these infections (*13–15*). Once this strain colonizes or otherwise infects a person, it can then enter the patient's bloodstream and become a potentially life-threatening bloodstream infection.

If admitted to the hospital, illicit drug–using patients with a USA300 MRSA infection complicated by bacteremia serve as a potential reservoir for transmission to other patient populations. This mechanism may be contributing to the replacement of other MRSA strains typically associated with nosocomial infections by USA300 MRSA and may aid this strain in becoming the predominant isolate causing MRSA infections in both healthcare and community settings (*16*,*17*). The objective of this study was to evaluate the association of illicit drug use with USA300 MRSA bacteremia and whether the association is static or has changed over a 5-year period as the USA300 MRSA epidemic has progressed.

Methods

Study Design and Population

A multicenter retrospective cohort study was conducted by using patients from the population of veterans enrolled from January 2004 through June 2008 at the Veterans Affairs medical centers (VAMCs) in Baltimore, Maryland; Washington, DC; Buffalo, New York; and Richmond, Virginia. Patients who used illicit drugs were compared with those who did not use illicit drugs with respect to having USA300 MRSA bacteremia vs. bacteremia caused by all other types of *S. aureus* (this group includes non-USA300 MRSA and methicillin-susceptible *S. aureus* [MSSA]). Inclusion criteria for patients included in the study were the following: 1) age ≥18 years, 2) enrollment in patient care services at 1 of the 4 VAMCs, 3) a positive blood culture for *S. aureus*, 4) having first known invasive infection caused by *S. aureus*, and 5) having a bacterial isolate from the infection available for testing. We excluded patients from the analysis for whom the infection was found to be polymicrobial, or for whom the bacteremic episode was considered to be clinically insignificant (i.e., the patient did not have clinical symptoms consistent with the presence of infection, such as fever) (*18*). The Institutional Review Boards at all participating sites approved this protocol.

Data Collection and Definitions

Data were collected from patient electronic medical records, which included administrative coding data. An infection control nurse, who was blinded to the outcome of each patient, conducted chart review by using a standardized form. Illicit drug use was defined by International Classification of Diseases, 9th Revision (ICD-9), codes indicating abuse of or dependence on cocaine (ICD-9 codes: 304.21, 304.20, 304.23, 305.61, 305.62, 305.60) or opioids (ICD-9 codes: 304.01, 304.71, 304.00, 305.51, 304.73), designated at any hospitalization up to 1 year prior to the time of the patient's presentation. The electronic medical record of any patient identified as an illicit drug user was further evaluated to determine whether the abuse was by injection.

An infection was defined as nosocomial if the patient's blood culture was positive for *S. aureus* >48 hours after hospital admission, if the patient was transferred from another healthcare facility, or if the infection was central-line associated. Infections were defined as central-line associated if a primary source was identified (i.e., no other source of infection could be found) and if the patient had a central line in place for 48 hours before the onset of bacteremia (*19*). If the patient had pneumonia, a skin and soft tissue infection, a urinary tract infection, or some other source that could explain the basis for infection, the bacteremia was defined as a secondary infection. Infective endocarditis was defined by using the modified Duke criteria (*20*).

Information on risk factors for MRSA acquisition and infection was also obtained. They included whether the patient had been hospitalized, had surgery, resided in a long-term care facility, or had undergone hemodialysis in the year before infection, as well as if any foreign medical device was present at the time of infection or if the patient had been previously colonized or infected with MRSA. The presence of HIV was assessed, as well as the presence of comorbid conditions to calculate each patient's Charlson score (*21*).

Laboratory Evaluations

All *S. aureus* isolates were sent for testing to the Baltimore VAMC. *S. aureus* was confirmed by standard microbiologic techniques. Any isolate with growth on oxacillin screen agar was defined as MRSA; any isolate without growth on this agar was defined as MSSA. All *S. aureus* isolates were screened for the presence of the Panton-Valentine leukocidin gene (PVL; *luk-F-PV, luk-S-PV*), as previously described (*22*). Further screening for the presence

of the arginine catabolic mobile element gene (ACME; *arc*A) and sequencing of the protein A (*spa*) gene hypervariable region was also performed on MRSA isolates only, as previously described (*23*,*24*). Patient sequences were compared with sequences found in the Ridom *spa* Server (www.ridom.de/spaserver).

USA300 MRSA isolates were identified by using an algorithm previously described (*5*). Any MRSA isolate that tested positive for the genes for PVL and ACME, and was *spa* type motif MBQBLO, was classified as USA300 MRSA. These isolates were confirmed as USA300 MRSA by pulsed-field gel electrophoresis (PFGE) by using a 24% random sample (13/55 suspected USA300 MRSA isolates were tested) (*11*). MRSA isolates that were negative for all 3 genetic factors were classified as non-USA300 MRSA. A 26% random sample of the non-USA300 MRSA isolates was also confirmed by PFGE (27/103 suspected non-USA300 MRSA isolates were tested) (*11*). All MRSA isolates testing positive for at least 1 of the 3 (PVL, ACME, or *spa* type motif MBQBLO) were further characterized by PFGE to determine whether any were the USA300 MRSA strain. If pulsed-field type USA300 by PFGE, the isolates were classified as USA300 MRSA. All other MRSA isolates (non-USA300 MRSA) and MSSA isolates were classified as "all other *S. aureus*." The Fingerprinting II software was used to analyze the electronic images of the gels (Bio-Rad Laboratories, Hercules, CA, USA). The banding patterns of each isolate were compared with the USA PFGE types described by McDougal et al. (*11*); the similarity between isolates was assessed by using the criteria established by Tenover et al. (*25*)

Statistical Analysis

Data were analyzed by using the SAS statistical software package, version 9.1 (SAS Institute Inc., Cary, NC, USA). The Pearson χ^2 or Fisher exact tests were used to compare categorical variables, and the Student *t* test or Wilcoxon signed-rank test was used to compare continuous variables. A p value ≤ 0.05 was considered significant. Unadjusted relative risks (RR) were calculated to estimate the association between illicit drug use and USA300 MRSA bacteremia. Stratified analyses were conducted to test for effect modification and confounding; any variable with a Breslow-Day p value ≤ 0.05 was considered significant, while a 10% difference between the unadjusted and adjusted RR was used to identify confounding. A binomial regression using a log link was fit to estimate the association between illicit drug use and USA300 MRSA bacteremia, adjusting for identified confounders and/or effect modifiers.

Results

We identified 300 patients with *S. aureus* bacteremia at the 4 participating sites during the study period. Strains having all 3 genetic factors (PVL, ACME, and *spa* type motif MBQBLO) were classified as USA300 MRSA, and a random sample of these isolates showed 100% sensitivity and specificity by PFGE. Isolates with none of these genetic factors were classified as non-USA300 MRSA, and a random sample of these isolates also showed 100% sensitivity and specificity by PFGE. Isolates with 1 or 2 of the genetic factors were also designated as non-USA300 MRSA; 18% of these isolates were found to be USA300 MRSA by PFGE, resulting in 100% sensitivity and 82% specificity of the laboratory algorithm for identifying USA300 MRSA. Sixty-seven (22%) of the infections were caused by USA300 MRSA, 117 (39%) by non-USA300 MRSA, and 116 (39%) by MSSA.

Patient and infection characteristics of the study population are presented in Tables 1 and 2. Of all patients with *S. aureus* bacteremia, 22 (7%) were illicit drug users, 13 (59%) with injection drugs. The patients had a mean age of 68 years and were almost all male (98%). Infections were classified as nosocomial in 172 (57%) patients, 83 (48%) of which were central-line associated. Sixteen (5%) patients were infected with HIV and 80 (27%) had a previous episode of colonization or infection with MRSA.

Compared with patients who did not use illicit drugs, illicit drug users were younger (mean age 51 vs. 69; $p<0.0001$; Table 3) and more likely to be African American (17% vs. 3%; $p<0.0001$). Illicit drug users were more likely to have HIV (38% vs. 6%; $p<0.0001$) or endocarditis (16% vs. 6%; $p = 0.04$) and less likely to have acquired their infection nosocomially (3% vs. 13%; $p = 0.003$) than patients who did not use illicit drugs. Illicit drug users were significantly more likely to have a bacteremic infection caused by USA300 MRSA than by all other *S. aureus* strains, compared with patients who did not use illicit drugs (RR 3.04, 95% confidence interval [CI] 1.99–4.64; $p<0.0001$; Table 4). Age (mean age 63 vs. 69 years; $p = 0.0004$) and a nosocomial acquisition of infection (RR 0.44, 95% CI 0.29–0.69; $p = 0.0002$) were both negatively associated with USA300 MRSA bacteremia.

Using binomial regression, illicit drug users were significantly more likely to have USA300 MRSA bacteremia compared with patients not using illicit drugs, controlling for year of presentation (adjusted RR [aRR] 3.00, 95% CI 1.88–4.36; $p<0.0001$; Table 5). This result was due to an increase in the proportion of *S. aureus* bacteremic infections caused by the USA300 MRSA strain in patients who did not use illicit drugs over the study period, while the proportion in patients using illicit drugs remained relatively stable after 2004. Stratified by year of presentation (categorized as early [January 1, 2004–March 31, 2006] vs. late [April 1, 2006–June 30, 2008] years of presentation), the association of illicit drug use with USA300 MRSA bacteremia decreased over the study period (RR in early years

Table 1. Isolate and patient characteristics for 300 veterans who had *Staphylococcus aureus* bacteremia at 4 Veterans Affairs medical centers, USA, 2004–2008*

Characteristic	No. (%)
S. aureus isolate characteristics	
USA300 MRSA	67 (22)
All other *S. aureus*	233 (78)
Non-USA300 MRSA	117 (39)
MSSA	116 (39)
Patient characteristics	
Age, y, mean ± SD	68 ± 13
Sex	
M	295 (98)
F	5 (2)
Race	
Black	95 (32)
Other	205 (68)
Year of presentation†	
Late	169 (56)
Early	131 (44)
Charlson score, mean ± SD	4.7 ± 3.0
HIV infection	
Yes	16 (5)
No	284 (95)
Illicit drug use	
Yes	22 (7)
No	278 (93)
History of colonization or infection with MRSA	
Yes	80 (27)
No	220 (73)
Hospitalized in year before infection	
Yes	195 (65)
No	105 (35)
Surgery in year before infection	
Yes	109 (36)
No	191 (64)
Residence in LTCF in year before infection	
Yes	34 (11)
No	266 (89)
Renal failure in year before infection	
Yes	114 (38)
No	186 (62)

*Values are no. (%) except as indicated. MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-susceptible *S. aureus*; LTCF, long-term care facility.
†Year of presentation stratified into 2 periods: early (January 1, 2004–March 31, 2006) and late (April 1, 2006–June 30, 2008).

of presentation 4.63, 95% CI 2.36–9.07; p<0.0001; RR for late years of presentation 2.45, 96% CI 1.38–4.35; p = 0.02). The association of illicit drug use and USA300 MRSA bacteremia weakened over the study period, although the trend was not statistically significant (p = 0.23 for trend over time; Figure).

Discussion

In this multicenter study, illicit drug users were more likely to have a bacteremic infection caused by USA300 MRSA than any other type of *S. aureus*, regardless of when the patient's infection occurred. The data were consistent with a decrease in the association over the study period, from a RR of 4.63 in the early years of the study to a RR of 2.45 in the late years of the study.

The finding that the association between illicit drug use and USA300 MRSA bacteremia declined over the study period is clinically important. This illustrates that, although USA300 MRSA infections emerged in drug users, this epidemic is now spreading to other populations. The illicit drug–using population has been recognized as a reservoir for USA300 MRSA (*14*). The spread to other populations observed in this study could be the result of transmission and dissemination of the strains among at-risk patients in the community, as suggested by the fact that 43% of cases of bacteremia were not classified as nosocomial infections in this population. This means that patients who have bacteremia could have acquired the bacteria during a previous healthcare exposure or in the community. In contrast, illicit drug users who are colonized or infected with USA300 MRSA could serve as a reservoir for transmission to other patient populations while hospitalized for their infections (*12–14*,*26*,*27*). Further investigation is warranted.

The increased risk of acquiring an infection caused by USA300 MRSA among illicit drug users found in this study is consistent with the findings of other studies. Gilbert et al. reported that the incidence of USA300 MRSA was higher among high-risk case-patients (defined as including a history of illicit drug use) than low-risk case-patients (*28*).

Table 2. Infection characteristics for 300 veterans who had *Staphylococcus aureus* bacteremia at 4 Veterans Affairs medical centers, USA, 2004–2008

Infection characteristic	Value
Nosocomial infection	
Yes	172 (57)
No	128 (43)
Central line at time of infection	
Yes	83 (28)
No	217 (72)
Permanent hardware at time of infection	
Yes	88 (29)
No	212 (71)
Source of infection	
Primary	126 (42)
Secondary	174 (58)
Infection complicated by endocarditis*	
Yes	38 (13)
No	262 (87)
Infection complicated by pneumonia†	
Yes	45 (15)
No	255 (85)

*Data missing for 4 patients (1%).
†Data missing for 11 patients (4%).

In a study of the New York State Prison System, inmates with drug charges were more likely to have an infection. The USA300 MRSA strain was the predominant clone that caused infections in inmates (*29*). Although our study used different sampling methods and slightly different case definitions than previous studies, the conclusions are the

Table 3. Patient and infection characteristics for 300 veterans with *Staphylococcus aureus* bacteremia and association with illicit drug use at 4 Veterans Affairs medical centers, USA, 2004–2008*

Variable	Used illicit drugs,† n = 22	No illicit drug use,† n = 278	p value‡
Patient characteristics			
Age, y, mean ± SD	51 ± 5	69 ± 12	<0.0001
Sex			
M	20 (7)	275 (93)	0.05
F	2 (40)	3 (60)	
Race			
Black	16 (17)	79 (83)	<0.0001
Other	6 (3)	199 (97)	
Year of presentation§			
Late	10 (6)	159 (94)	0.29
Early	12 (9)	119 (91)	
Charlson score, mean ± SD	5.4 ± 4.1	4.7 ± 2.9	0.28
HIV infection			
Yes	6 (38)	10 (62)	<0.0001
No	16 (6)	268 (94)	
History of colonization or infection with MRSA			
Yes	5 (6)	75 (94)	0.66
No	17 (8)	203 (92)	
Hospitalized in year before infection			
Yes	15 (8)	180 (92)	0.75
No	7 (7)	98 (93)	
Surgery in year before infection			
Yes	1 (1)	108 (99)	<0.0001
No	21 (11)	170 (89)	
Residence in LTCF in year before infection			
Yes	3 (9)	31 (91)	0.73
No	19 (7)	247 (93)	
Renal failure in year before infection			
Yes	14 (8)	172 (92)	0.87
No	8 (7)	106 (93)	
Infection characteristics			
Nosocomial infection			
Yes	6 (3)	166 (97)	0.003
No	16 (13)	112 (87)	
Central line at time of infection			
Yes	5 (6)	78 (94)	0.59
No	17 (8)	200 (92)	
Permanent hardware at time of infection			
Yes	4 (5)	84 (95)	0.33
No	18 (8)	194 (92)	
Source of infection			
Primary	10 (8)	116 (92)	0.73
Secondary	12 (7)	162 (93)	
Infection complicated by endocarditis			
Yes	6 (16)	32 (84)	0.04
No	16 (6)	242 (94)	
Infection complicated by pneumonia			
Yes	3 (7)	42 (93)	1.00
No	19 (7)	236 (93)	

*MRSA, methicillin-resistant *S. aureus*; LTCF, long-term care facility.
†Values are no. (%) except as indicated.
‡Calculated by using Pearson χ^2 or Fisher exact tests for categorical variables, Student *t* test or Wilcoxon signed-rank test for continuous variables.
§Year of presentation stratified into 2 periods: early (January 1, 2004–March 31, 2006) and late (April 1, 2006–June 30, 2008).

Table 4. Patient and infection characteristics for 300 veterans with *Staphylococcus aureus* bacteremia and association with USA300 MRSA at 4 Veterans Affairs medical centers, USA, 2004–2008*

Variable	USA300 MRSA bacteremia,† n = 67	Bacteremia due to all other *S. aureus,*† n = 233	p value‡
Patient characteristics			
Age, y, mean ± SD	63 ± 12	69 ± 13	0.0004
Sex			
M	65 (22)	230 (78)	0.31
F	2 (40)	3 (60)	
Race			
Black	34 (36)	61 (64)	0.0001
Other	33 (16)	172 (84)	
Year of presentation§			
Late	45 (27)	124 (73)	0.04
Early	22 (17)	109 (83)	
Charlson score, mean ± SD	5.2 ± 3.6	4.6 ± 2.8	0.19
HIV infection			
Yes	5 (31)	11 (69)	0.36
No	62 (22)	222 (78)	
Illicit drug use			
Yes	13 (59)	9 (41)	<0.0001
No	54 (19)	224 (81)	
History of colonization or infection with MRSA*			
Yes	21 (26)	59 (74)	0.33
No	46 (21)	174 (79)	
Hospitalized in year before infection			
Yes	40 (21)	155 (79)	0.30
No	27 (26)	78 (74)	
Surgery in year before infection			
Yes	17 (16)	92 (84)	0.03
No	50 (26)	141 (74)	
Residence in LTCF in year before infection			
Yes	10 (29)	24 (71)	0.29
No	57 (21)	209 (79)	
Renal failure in year before infection			
Yes	42 (23)	144 (77)	0.90
No	25 (22)	89 (78)	
Infection characteristics			
Nosocomial infection			
Yes	25 (15)	147 (85)	0.0002
No	42 (33)	86 (67)	
Central line at time of infection			
Yes	11 (13)	72 (87)	0.02
No	56 (26)	161 (74)	
Permanent hardware at time of infection			
Yes	20 (33)	68 (77)	0.92
No	48 (28)	126 (72)	
Source of infection			
Primary	19 (15)	107 (85)	0.01
Secondary	48 (28)	126 (72)	
Infection complicated by endocarditis			
Yes	9 (24)	29 (76)	0.83
No	57 (22)	201 (78)	
Infection complicated by pneumonia			
Yes	8 (18)	37 (82)	0.40
No	57 (23)	186 (77)	

*MRSA, methicillin-resistant *S. aureus*, LTCF, long-term care facility.
†Values are no. (%) except as indicated.
‡Calculated by using Pearson χ^2 or Fisher exact tests for categorical variables, Student *t* test or Wilcoxon signed-rank test for continuous variables.
§Year of presentation stratified into 2 periods: early (January 1, 2004–March 31, 2006) and late (April 1, 2006–June 30, 2008).

Table 5. Independent risk factors for USA300 MRSA bacteremia among 300 veterans at 4 Veterans Affairs medical centers, USA, 2004–2008*

Variable	Adjusted RR (95% CI)	p value
Illicit drug use	3.00 (1.88–4.36)	<0.0001
Late year of presentation†	1.56 (1.03–2.48)	0.04

*MRSA, methicillin-resistant *Staphylococcus aureus*; RR, relative risk; CI, confidence interval.
†Year of presentation stratified into 2 periods: early (January 1, 2004–March 31, 2006) and late (April 1, 2006–June 30, 2008).

same. Illicit drug users are at increased risk for an infection caused by USA300 MRSA compared with persons who do not use illicit drugs.

The association between illicit drug use and USA300 MRSA bacteremia could be explained by the fact that *S. aureus* infections are a common complication of drug use. Drug users are colonized with *S. aureus* more often than persons who do not use drugs (*13*,*14*). Colonization is a main risk factor for infection; the patient is usually infected with his own colonizing strain. In addition, invasive infections can occur from transfer of the colonizing strain directly into the patient's bloodstream (*13*,*14*). If USA300 MRSA is the colonizing strain, the frequent inhalation or injection of drugs could transfer this strain into the bloodstream to cause a life-threatening invasive infection.

Our study has some limitations. First, data regarding illicit drug use at the various VAMCs is based on self-report. Information regarding drug use is of a sensitive nature and, therefore, subject to recall bias. Also, to locate in the patient's electronic medical record whether the drugs were injected depended on whether the healthcare professional specifically asked and made note of this, a situation which is prone to information bias. Second, the ICD-9 codes used to define illicit drug use are imperfect measurements because they are used for insurance billing, rather than clinical purposes. Also, if any illicit drug–using patients were not hospitalized in the year before enrollment, or if drug-using patients did not report drug use during the hospitalization of interest, drug use would have been misclassified. In addition, using ICD-9 codes to define drug use up to 1 year before admission may not accurately measure current patterns of drug use in patients; the result would be a differential misclassification of exposure and could overestimate or underestimate the true association. Third, the study population was comprised only of veterans. The use of such a distinct population could reduce the generalizability of these findings. However, the relationship of illicit drug use with USA300 MRSA among veterans would likely not differ from the relationship among nonveterans, so the results should still be generalizable. Finally, USA300 MRSA isolates could have been misclassified with the use of our laboratory algorithm; however, the validation of isolates by PFGE, which showed a high sensitivity and specificity, makes this unlikely.

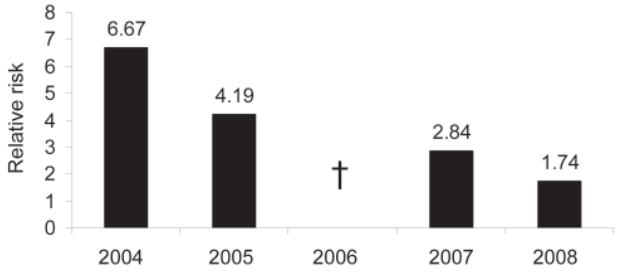

Figure. Association between illicit drug use and USA300 methicillin-resistant *Staphylococcus aureus* bacteremia among 300 veterans at 4 Veterans Affairs medical centers, USA, 2004–2008 (generalized linear model p value for trend over time = 0.23). †No illicit drug users had a bacteremic infection caused by USA300 MRSA in 2006.

This study has several strengths. First, the use of more than 1 study site helped improve the generalizability of these findings. For example, we evaluated whether any of the associations observed may have been due to differences between the 4 VAMCs (this analysis was in response to a finding that patients from the Buffalo VAMC were less likely to be illicit drug users and less likely to have an infection due to USA300 MRSA). After excluding all patients from the Buffalo VAMC from the analysis, we found no difference from the results of the entire cohort (data not shown); therefore, we chose to present the combined data. Additionally, the electronic medical record system used throughout the Veterans Health Administration is known to be a valuable asset because of the completeness of data and for the amount of time it has stored information. The use of this system for chart review helped decrease selection and information bias. Finally, the findings of this study are strengthened because we could provide molecular typing data for each of the isolates.

In conclusion, the data from this study showed that illicit drug users are more likely to acquire a bacteremic infection caused by USA300 MRSA than by all other *S. aureus* strains. The decrease observed in the association of illicit drug use and USA300 MRSA bacteremia over the study period suggests that the USA300 MRSA epidemic is now spreading from illicit drug users to other patient populations. Focusing infection control efforts on high-risk groups such as illicit drug users might slow the progression of the USA300 MRSA epidemic in areas of the country where the association between illicit drug use and USA300 is still high.

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