AAC Journals.ASM.org

Activities of Vancomycin, Ceftaroline, and Mupirocin against *Staphylococcus aureus* Isolates Collected in a 2011 National Surveillance Study in the United States

Sandra S. Richter,[a] Daniel J. Diekema,[b] Kristopher P. Heilmann,[b] Cassie L. Dohrn,[b] Emily K. Crispell,[c] Fathollah Riahi,[b] Jennifer S. McDanel,[b] Sarah W. Satola,[c] Gary V. Doern[b]

Cleveland Clinic, Cleveland, Ohio, USA[a]; University of Iowa Carver College of Medicine, Iowa City, Iowa, USA[b]; Emory University, Atlanta, Georgia, USA[c]

Forty-two medical centers from throughout the United States participating in a longitudinal surveillance program were asked to submit 100 consecutive *Staphylococcus aureus* isolates during July to December 2011. Susceptibility testing using CLSI broth microdilution and *mecA* detection by PCR analysis was performed on the 4,131 isolates collected. Methods employing Etest glycopeptide resistance detection (GRD; bioMérieux) and brain heart infusion agar containing 4 μg/ml vancomycin (BHIV) were used to screen methicillin-resistant *S. aureus* (MRSA) isolates for heterogeneous intermediate-level resistance to vancomycin (hVISA). Isolates with positive hVISA screen results were confirmed by population analysis profiling-area under the curve (PAP-AUC) determinations. The genetic relatedness of hVISA, ceftaroline-nonsusceptible, or high-level (HL) mupirocin resistance MRSA isolates was assessed by pulsed-field gel electrophoresis (PFGE). Among 2,093 MRSA isolates, the hVISA screen results were positive with 47 isolates by Etest GRD and 30 isolates by BHIV agar screen. Twenty-five of the GRD- or BHIV screen-positive isolates were confirmed as hVISA by PAP-AUC testing. Results of the current study were compared to results obtained from prior surveillance performed in 2009. The prevalence of hVISA among MRSA isolates was higher in 2011 than in 2009 (1.2% versus 0.4%, $P = 0.003$), especially for isolates with a vancomycin MIC of 2 (45.4% versus 14.3%, $P = 0.01$). The overall rate of ceftaroline susceptibility in the current study was 99.4% (one hVISA isolate had an intermediate ceftaroline MIC). HL mupirocin resistance increased from 2.2% in 2009 to 3.2% in 2011 ($P = 0.006$). Although overall rates of hVISA and HL mupirocin resistance are low, they have increased since 2009.

Staphylococcus aureus is a major pathogen in the health care setting. According to 2009 to 2010 National Healthcare Safety Network data, *S. aureus* is the most common etiology of surgical-site infections and ventilator-associated pneumonia, causing 30% and 24% of cases, respectively (1). Only coagulase-negative staphylococci cause more central line-associated bloodstream infections than *S. aureus* (1).

Testing to detect nasal carriage of *S. aureus* is commonly performed prior to elective cardiothoracic surgery and in intensive care unit (ICU) patients. Positive results are usually followed by contact isolation and/or decolonization with intranasal mupirocin to prevent methicillin-susceptible *S. aureus* (MSSA) and methicillin-resistant *S. aureus* (MRSA) infections (2, 3). Strains with high-level (HL) mupirocin resistance (MIC ≥ 512 μg/ml) have been associated with *mupA* or *mupB* genes encoding altered tRNA synthetases (4, 5). Testing for mupirocin resistance is not commonly performed in clinical laboratories, and most published data come from single-center studies.

Vancomycin continues to be the drug of choice for treating MRSA infections (6, 7). Fortunately, nonsusceptible strains, i.e., strains with vancomycin MICs above the CLSI susceptibility break point (≤2 μg/ml), are rare (8, 9). There are concerns regarding the efficacy of vancomycin therapy for *S. aureus* isolates with heterogeneous intermediate-level resistance to vancomycin (hVISA) that appear susceptible when tested by standard MIC methods (10). The technical difficulty of performing the reference standard test for hVISA, population analysis profiling with area under the curve (PAP-AUC), limits its use to the research setting (11). Commercial "research use only" tests for hVISA detection are not performed routinely in clinical laboratories due to a low positive predictive value (12, 13) and the uncertain clinical implication of hVISA (14, 15). A meta-analysis demonstrated higher glycopeptide treatment failure rates for hVISA but no differences in mortality between patients with hVISA and vancomycin-susceptible MRSA infections (16).

The primary objective of this multicenter study was to determine rates of antimicrobial resistance among clinical isolates of *S. aureus* collected in a United States surveillance program during 2011 and to assess changes since 2009 (17). Monitoring of ceftaroline susceptibility was of particular interest to determine if the anti-MRSA activity of this novel β-lactam would persist following FDA approval in 2010. Methods to detect hVISA and HL mupirocin resistance were included in both study periods (12, 17). In the current study, two different hVISA screening methods, the brain heart infusion agar (BHI) method with vancomycin and the Etest glycopeptide resistance detection (GRD, bioMérieux) method, were compared with PAP-AUC as the reference method. The epidemiology of hVISA strains, ceftaroline-nonsusceptible strains, and strains with HL mupirocin resistance was examined.

(This work was presented in part as an abstract at the 52nd

Received 2 September 2013 **Returned for modification** 19 October 2013
Accepted 10 November 2013
Published ahead of print 18 November 2013
Address correspondence to Sandra S. Richter, richtes@ccf.org.

doi:10.1128/AAC.01915-13

TABLE 1 MIC frequency distributions for agents against 4,131 clinical isolates of *S. aureus* from 43 U.S. medical centers

Antimicrobial agent	No. of isolates (cumulative %) with indicated MIC (μg/ml)											
	≤0.12	0.25	0.5	1	2	4	8	16	32	≥64	I (%)[a]	R (%)[a]
Ceftaroline	221 (5.4)	1,814 (49.3)	1,323 (81.3)	750 (99.4)	23 (100)						0.6	0
Clindamycin	3512 (85.0)	27 (85.7)	9 (85.9)	0 (85.9)	7 (86.1)	2 (86.1)	4 (86.2)	2 (86.3)	3 (86.3)	565[b] (100)	0.2	13.9[c]
Daptomycin	42 (1.0)	2,414 (59.5)	1,637 (99.1)	34 (99.9)	4 (100)							0.2[d]
Erythromycin	19 (0.5)	564 (14.1)	859 (34.9)	127 (38.0)	14 (38.3)	13 (38.6)	23 (39.2)	73 (41.0)	203 (45.9)	2,236[b] (100)	3.7	61.4
Levofloxacin	705 (17.1)	1,725 (58.8)	141 (62.2)	33 (63.0)	10 (63.3)	560 (76.8)	292 (83.9)	140 (78.3)	81 (89.3)	444 (100)	0.2	37.3
Linezolid	1 (0.02)	2 (0.1)	48 (1.2)	2,424 (59.9)	1,627 (99.3)	28 (99.9)	1 (100)					0.02
Oxacillin	33 (0.8)	519 (13.4)	956 (36.5)	392 (46.0)	127 (49.1)	70 (50.8)	149 (54.4)	254 (60.5)	1,631[e] (100)			51
Tigecycline	3004 (72.7)	980 (96.4)	131 (99.6)	16 (100)								0.4[f]
Tetracycline	743 (18.0)	2,755 (84.7)	346 (93.1)	36 (93.9)	46 (95.0)	28 (95.7)	9 (95.9)	20 (96.4)	44 (97.5)	104 (100)	0.2	4.1
TMP-SMX	3839 (92.9)	108 (95.6)	42 (96.6)	22 (97.1)	8 (97.3)	2 (97.3)	9 (97.6)	10 (97.8)	13 (98.1)	78 (100)		2.7
Vancomycin		1 (0.02)	431 (10.5)	3,658 (99.0)	41 (100)						0	0

[a] Intermediate (I) and resistant (R) categories are those defined by CLSI with the exceptions noted below.
[b] MIC > 32 μg/ml.
[c] An additional 12.7% of isolates were positive for inducible clindamycin resistance.
[d] Nonsusceptible, MIC > 1 μg/ml; intermediate and resistant categories not defined by CLSI.
[e] MIC > 16 μg/ml.
[f] Based on FDA interpretive criterion for susceptibility of ≤0.5 μg/ml.

Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, CA, 10 September 2012 [18]).

MATERIALS AND METHODS

Bacterial isolates. One hundred clinically significant *S. aureus* isolates were requested from medical centers participating in a longitudinal surveillance program tracking antimicrobial resistance in the United States. The *S. aureus* isolates were obtained from different patients during July to December 2011 and then sent to the University of Iowa central laboratory for testing. Details of the surveillance program have been previously published (17). Results of the current study were compared to results obtained from prior surveillance performed in 2009 (17).

Antimicrobial susceptibility testing. Susceptibility to 12 antimicrobial agents was assessed with the Clinical and Laboratory Standards Institute (CLSI) broth microdilution method (19, 20). The endpoint for linezolid MICs was read at 90% inhibition. FDA break points were applied for tigecycline. *Staphylococcus aureus* ATCC 29213, *S. aureus* ATCC BAA-977, and *S. aureus* ATCC BAA1708 were tested for quality control. Screening for *mecA* was performed on all isolates by PCR using modifications (17) of previously published methods (21). Vancomycin MICs were also determined by standard Etest for MRSA isolates (inoculation of Mueller-Hinton agar and reading after 24 h of incubation) in conjunction with the Etest GRD described below. Two methods were used to screen MRSA for hVISA.

Etest GRD. The Etest GRD was used to screen MRSA isolates for hVISA. Mueller-Hinton agar containing 5% sheep blood was inoculated with a 0.5 McFarland suspension of overnight growth followed by GRD strip placement. After 24 and 48 h of incubation in ambient air at 35°C, GRD tests were read. A positive GRD result for hVISA was a vancomycin or teicoplanin MIC of ≥8 μg/ml at 24 or 48 h.

BHIV screen. Screening of MRSA for hVISA was performed using a previously published BHI vancomycin (BHIV) screening agar method (22). The BHIV agar was prepared in-house by supplementing BHI agar (Becton, Dickinson and Company) with 4 μg/ml vancomycin (Sigma) and 16 g/liter pancreatic digest of casein (Becton, Dickinson and Company). The BHIV plates were used to screen MRSA isolates for hVISA by inoculation with four 10-μl drops of a 0.5 McFarland suspension. After 24 and 48 h of incubation at 35°C, plates were examined for growth. A positive BHIV screen result for hVISA was defined as growth of two or more colonies from one droplet.

PAP-AUC confirmation of hVISA. PAP-AUC testing was performed as previously described (23, 24) with modifications (12, 22) on isolates with a positive BHIV or GRD test result. A 100-μl volume of serial dilutions of 10^{-6} and 10^{-7} was spiral plated onto BHI agar without vancomycin, and four 10-μl drops of serial dilutions of 10^{-0} to 10^{-5} were plated onto BHI agar plates with vancomycin concentrations of 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 6.0, and 8.0 μg/ml. After 24 and 48 h of incubation at 35°C, $\log_{10}$ values of CFU were plotted against vancomycin concentrations. Isolates with an AUC ratio (isolate AUC divided by hVISA strain Mu3 AUC) of 0.90 or greater were defined as hVISA (11).

PFGE. The genetic relatedness of *mecA*-positive isolates that were also HL mupirocin resistant, ceftaroline nonsusceptible, or hVISA was assessed using standard PFGE methods (25). After digestion of DNA with SmaI (Sigma-Aldrich, St. Louis, MO), restriction fragments were separated by electrophoresis on a Chef DRII apparatus (Bio-Rad Laboratories, Hercules, CA) and analyzed using Bionumerics software (Applied Maths, Kortrijk, Belgium). Dendrogram construction used the unweighted-pair group method. Isolates with a similarity coefficient ≥ 0.8 were assigned to the same PFGE type. This analysis included comparison to PFGE type strains USA100 to USA1200 (26).

Statistical analysis. Differences in resistance rates and demographic characteristics were assessed for statistical significance using Fisher's exact test. Two-tailed *P* values were determined, and values ≤ 0.05 were considered significant.

RESULTS

A total of 4,131 *S. aureus* clinical isolates were collected from 42 U.S. medical centers in 2011. The specimen sources included wounds or abscesses (51%), blood (25%), the lower respiratory tract (12%), tissue (5%), and other normally sterile sites (7%). Data corresponding to patient age and gender and specimen sources in 2011 were similar to those associated with isolates collected in 2009 (17).

Table 1 depicts the MIC distributions for the 4,131 *S. aureus* isolates collected in 2011. A comparison of these distributions for MRSA versus MSSA is found in Table 2. The agents demonstrating the largest differences between MRSA and MSSA in rates of susceptibility were erythromycin (<10% versus 61%) and levofloxacin (36% versus 91%). Ceftaroline, tigecycline, daptomycin, linezolid, vancomycin, tetracycline, and trimethoprim-sulfamethoxazole (TMP-SMX) demonstrated high (>95%) rates of MRSA and MSSA susceptibility.

The 23 isolates with elevated ceftaroline MICs (2 μg/ml) were from patients in every geographic region (14 different centers). These ceftaroline-intermediate isolates were all MRSA and assigned to 12 different PFGE types: USA100 ($n = 7$), USA200 ($n =$

TABLE 2 MIC distributions for agents against methicillin-resistant and methicillin-susceptible *S. aureus*

Antimicrobial agent	MRSA[a] (n = 2,093)				MSSA[b] (n = 2,038)			
	MIC range (μg/ml)	MIC_{50} (μg/ml)	MIC_{90} (μg/ml)	S (%)[c]	MIC range (μg/ml)	MIC_{50} (μg/ml)	MIC_{90} (μg/ml)	S (%)[c]
Ceftaroline	0.06 to 2	0.5	1	98.9	≤0.03 to 1	0.25	0.25	100
Clindamycin	≤0.06 to >32	0.12	>32	76.6	≤0.06 to >32	0.12	0.12	95.4
Daptomycin	≤0.06 to 2	0.25	0.5	99.9	≤0.06 to 2	0.25	0.5	99.9
Erythromycin	0.12 to >32	>32	>32	9.7	≤0.06 to >32	0.5	>32	60.8
Levofloxacin	≤0.12 to >64	4	64	36.0	≤0.03 to >64	0.25	1	90.8
Linezolid	0.25 to 8	1	2	99.9	≤0.12 to 4	1	2	100
Oxacillin	0.25 to >16	>16	>16	0.2	≤0.06 to >16	0.5	1	99.2
Tigecycline	≤0.03 to 1	0.12	0.25	99.3[d]	≤0.03 to 1	0.12	0.25	99.9[d]
Tetracycline	≤0.06 to >64	0.25	0.5	95.9	≤0.06 to >64	0.25	0.5	95.5
TMP-SMX	≤0.03 to >64	0.06	0.12	97.0	≤0.03 to >64	0.06	0.12	97.6
Vancomycin	≤0.25 to 2	1	1	100	0.5 to 2	1	1	100

[a] Methicillin-resistant *S. aureus* (MRSA) isolates were identified by a positive *mecA* PCR result.
[b] Methicillin-susceptible *S. aureus* (MSSA) isolates were identified by a negative *mecA* PCR result.
[c] Susceptibility (S) was determined using CLSI interpretive criteria, with the exceptions noted below.
[d] The FDA interpretive criterion for susceptibility is ≤0.5 μg/ml.

2), USA300 (n = 1), 3 other PFGE types with two or three isolates (n = 7), and 6 PFGE types with one isolate. Six centers submitted multiple (two to four) isolates with reduced ceftaroline susceptibility, but only one center submitted multiple isolates of the same PFGE type (two USA100 isolates).

The *in vitro* resistance rates for most agents showed little change since 2009. The proportion of MRSA isolates was slightly lower in 2011 (51%) than in 2009 (53%) (P = 0.01). The largest proportional change in resistance rate was seen for high-level (HL) mupirocin resistance. Although HL mupirocin resistance is still uncommon, the HL mupirocin resistance rate increased by approximately 40% both overall (from 2.2% in 2009 to 3.2% in 2011, P = 0.006) and among MRSA isolates only (from 2.8% in 2009 to 4.0% in 2011, P = 0.04). The PFGE analysis of the 84 MRSA isolates with HL mupirocin resistance from 34 centers showed that 50% were USA300 (n = 42), 9.5% were USA100 (n = 8), and 40% were 18 different PFGE types (n = 34) with 1 to 3 isolates assigned to each. Twelve of the 34 centers submitted multiple MRSA isolates with HL mupirocin resistance of the same PFGE type: two or three USA300 isolates from nine centers, five USA300 isolates from one center, and two non-USA PFGE type isolates from two centers.

Screening of the 2,093 MRSA isolates for hVISA yielded positive results for 47 isolates by Etest GRD (teicoplanin MIC of ≥8 μg/ml). The BHIV agar screen for hVISA had positive results for 30 isolates. Both screening tests were positive for 17 isolates, and only one test (GRD or BHIV) was positive for 43 isolates. Twenty-five of the 60 screen-positive isolates were confirmed to be hVISA by PAP-AUC testing. This represents a higher prevalence of hVISA among MRSA in 2011 (1.2%) than in the 2009 surveillance period (0.4%, P = 0.003), especially among MRSA isolates with a vancomycin MIC of 2 (45.4% versus 14.3%, P = 0.01) (12).

Fourteen (56%) of the 25 hVISA isolates were detected by the Etest GRD and BHIV screen agar (Table 3). The GRD screen detected an additional 10 isolates, whereas the BHIV screen agar detected only one more isolate. Twelve hVISA isolates were detected by the GRD screen after 24 h of incubation. The other 12 hVISA isolates detected by the GRD screen required 48 h of incubation. The positive predictive values for the two screening tests were similar (51% for GRD and 50% for BHIV agar). With one exception, all of the isolates with positive hVISA screen and negative PAP-AUC results had a vancomycin MIC of 1 μg/ml. The vancomycin MIC for a majority (56%) of the confirmed hVISA isolates was also 1 μg/ml. Rates of resistance (including intermediate-level resistance) to most agents for the 25 hVISA isolates were higher than those of the 2,046 GRD screen-negative MRSA isolates: for erythromycin, 96.0% versus 90.4%; for clindamycin, 64% versus 23.5%; for levofloxacin, 92.0% versus 63.5%; for trimethoprim-sulfamethoxazole, 8.0% versus 2.8%; for tetracycline, 16% versus 3.8%; for tigecycline, 8.0% versus 0.6%; for linezolid, 0% versus 0.01%; for daptomycin, 4% versus 0.1%; and for ceftaroline, 4% versus 1%. The only hVISA isolate with an elevated ceftaroline MIC (2 μg/ml) was also tigecycline nonsusceptible (MIC, 1 μg/ml).

The proportion of hVISA isolates that were recovered from wounds and abscesses (32%) was smaller than the proportion of GRD-negative isolates (55%, P = 0.03). The proportions of GRD screen-negative and hVISA isolates from blood cultures were similar (24% versus 40%, P = 0.09). Twenty-eight percent of the hVISA isolates were from tissue (n = 2), lower respiratory tract (n = 2), or normally sterile body fluid (not cerebrospinal fluid

TABLE 3 Comparison of Etest GRD and BHIV screen agar for the detection of 25 hVISA isolates[a]

Vancomycin MIC (μg/ml)[b]	No. (%) of MRSA isolates	No. of isolates						
		Etest GRD positive (n = 47)		BHIV agar positive (n = 30)		hVISA[c] (n = 25) initially detected by:		
		hVISA[c]	Not hVISA	hVISA[c]	Not hVISA	BHI + GRD	BHI only	GRD only
0.25	1 (0.05)							
0.5	208 (9.9)				1			
1	1,862 (89)	14	22[d]	5	14[d]	5	0	9
2	22 (1.1)	10	1	10	0	9	1	1
Total	2,093	24	23	15	15	14	1	10

[a] Screening for hVISA was performed on MRSA (*mecA*-positive) isolates only.
[b] Determined by CLSI broth microdilution method.
[c] PAP-AUC ratio ≥ 0.90.
[d] Three isolates with negative PAP-AUC results were positive by BHIV and GRD screen tests.

TABLE 4 Comparison of vancomycin MICs determined by Etest and the CLSI broth microdilution method for 2,093 MRSA isolates

Vancomycin MIC (μg/ml)[a]	No. of MRSA isolates	No. isolates with indicated Etest vancomycin MIC (μg/ml)						
		≤0.5	0.75	1	1.5	2	3	4
0.25	1	1	0	0	0	0	0	0
0.5	208	9	18	72	106	3	0	0
1	1,862	7	35	391	1,278	150	1	0
2	22	0	0	1	8	10	2	1
Total	2,093	17	53	464	1,392	163	3	1

[a] Determined by CLSI broth microdilution method.

[CSF]) ($n = 3$) sources. The percentage of hVISA isolates from patients aged ≥65 years was higher than that of GRD-negative isolates (68% versus 22%, $P < 0.0001$).

The 25 hVISA isolates were received from 17 medical centers in eight geographic regions of the United States. The PFGE analysis of hVISA isolates revealed 16 different PFGE types. Five hVISA isolates had USA300 PFGE patterns, and six isolates were USA100. The other 14 hVISA isolates had unique PFGE profiles. Five centers submitted multiple hVISA isolates (two hVISA isolates from two centers, three hVISA isolates from one center, and four hVISA isolates from one center). Only two centers submitted multiple hVISA isolates with the same PFGE type (USA300).

A comparison of the vancomycin MICs determined by broth microdilution to those determined by standard Etest for MRSA is shown in Table 4. The majority (61%) of isolates had MICs of 1.5 μg/ml by Etest and 1.0 μg/ml by broth microdilution. Twenty-three of the 25 hVISA isolates had an Etest MIC of 2 μg/ml or greater. Two hVISA isolates had an Etest MIC of 1.5 μg/ml.

DISCUSSION

Although we observed higher rates of hVISA among MRSA isolates in 2011 (1.2%) than in 2009 (0.4%), prospective clinical-outcome studies are needed to justify routine screening for this low-prevalence phenotype. A recent review summarized 43 reports from throughout the world representing different study designs and testing algorithms for hVISA (16). The hVISA rates ranged from 0 to 73.7%, and combining these diverse studies yielded an overall prevalence of 1.3% (16). Our report is unique in providing longitudinal surveillance for hVISA in the United States. The hVISA isolates were more clonal (20% USA300 and 24% USA100) in 2011 than in 2009, when only one isolate from each of these major PFGE types was detected (12).

Since only Etest GRD- or BHIV agar-positive isolates were tested by the gold standard (PAP-AUC), the current study did not assess the hVISA sensitivity of either screening test. The sensitivity of the Etest GRD has been reported as 70% to 77% after 24 h of incubation and 93% to 94% after 48 h of incubation (14). Better detection of hVISA by Etest GRD after the longer incubation time was also noted in the current study. The BHIV agar and GRD Etest methods had similar hVISA detection rates for isolates with a vancomycin MIC of 2 μg/ml, but only 36% of hVISA isolates with a vancomycin MIC of 1 μg/ml were detected using BHIV agar. A previous study reporting a higher sensitivity of BHIV in comparison to Etest GRD may be partially explained by limiting testing to isolates with a vancomycin MIC of 2 μg/ml (22). Our higher prevalence of hVISA among isolates with a vancomycin MIC of 2 μg/ml (45%) compared to 1 μg/ml (0.8%) supports restricting routine hVISA screening to isolates with the higher MIC.

A recent study demonstrated high variability when the results of vancomycin MIC determinations derived from automated systems were compared to those obtained by broth microdilution, with the Phoenix system having the greatest tendency to underestimate a vancomycin MIC of 2 μg/ml (27). However, the results of most automated systems were within the 1 $\log_2$ dilution variability expected with an MIC test.

It has been suggested that clinical laboratories should determine vancomycin MICs using Etest (27, 28). The Etest is more expensive and labor-intensive than automated systems, and our data show variability for this method as well. The most common Etest MIC of 1.5 μg/ml occurred for 67% of the MRSA isolates and usually correlated with broth microdilution MICs of 1 but also represented 36% of the isolates with a broth microdilution MIC of 2 (Table 4). A recent review (7) affirmed Infectious Diseases Society of America (IDSA) guidance to use clinical response for deciding whether to discontinue vancomycin therapy for patients with MRSA isolates with a MIC of 2 μg/ml (6).

The detection of higher rates of HL mupirocin resistance (3.2% overall, 4% of MRSA isolates) in 2011 was not unexpected. In 2005 to 2006, the CDC detected HL mupirocin resistance in 2.3% of invasive MRSA using a lower break point of >128 (29). A Canadian surveillance program observed an increase in HL mupirocin resistance among MRSA isolates from 1995 to 1999 (1.6%) to 2000 to 2004 (7.0%) (30). A single-center surgical intensive care unit (SICU) study found 13.2% of 302 MRSA isolates from nares to be HL mupirocin resistant (31). Screening of 1,089 patients with community-onset cutaneous infections detected only 2.1% colonized with an *S. aureus* isolate with HL mupirocin resistance (32).

The prevalence of isolates with HL mupirocin resistance that were USA300 (50%) and USA100 (9.5%) did not exceed the overall distribution of these PFGE types among all MRSA isolates in 2009 (17). The detection of a new genetic variant, *mupB*, in strains with HL mupirocin resistance is interesting, and studies to determine prevalence are needed (4). A recent randomized prospective study demonstrating the greatest reduction in infection rates among those universally decolonized with intranasal mupirocin suggests that the use of this drug and resistant populations are likely to increase (33).

The continued nearly uniform activity of ceftaroline (99.4% susceptibility) since FDA approval is encouraging. A dominant clone was not detected among the MRSA isolates with intermediate-level resistance to ceftaroline. Good activity of ceftaroline (MIC ≤ 1 μg/ml) was noted for 96% of hVISA and all daptomycin-nonsusceptible isolates. The only ceftaroline-resistant isolates (MICs of ≥4 μg/ml) that have been described previously in the literature were from four patients in Athens, Greece, during 2008 (34). These four isolates were represented by a single clone (34).

In conclusion, the primary changes noted in U.S. surveillance during 2011 were increased rates of HL mupirocin resistance and hVISA compared to 2009. More hVISA isolates were detected by the Etest GRD than by the BHIV agar method. Both hVISA screening methods require PAP-AUC confirmation. Ceftaroline remained active against MRSA and hVISA isolates. Continued surveillance for resistant *S. aureus* populations is important to direct prevention and treatment strategies.

ACKNOWLEDGMENTS

We thank the participating medical centers for providing the isolates of *S. aureus* characterized in this study.

G.V.D. has received research funding from Abbott Laboratories, Schering-Plough, Bayer Pharmaceutical, Merck, Shionogi, Cubist, and AstraZeneca. He has been on the speakers' bureaus of Abbott Laboratories, Aventis, Astra-Zeneca, Forest Laboratories, Pfizer, Astellas, and Schering-Plough. D.J.D. has received research funding from Merck, Pfizer, Schering-Plough, Astellas, and bioMérieux. S.S.R. has received research funding from bioMérieux, Forest Laboratories, Nanosphere, and Pocared.

K.P.H., C.L.D., E.K.C., F.R., J.S.M., and S.W.S. declare that we have no conflicts of interest.

Financial support for this project was provided by Forest Laboratories, Inc. (New York, NY). Scientific Therapeutics Information, Inc. (Springfield, NJ), provided editorial assistance funded by Forest Laboratories for the manuscript.

REFERENCES

1. **Sievert DM, Ricks P, Edwards JR, Schneider A, Patel J, Srinivasan A, Kallen A, Limbago B, Fridkin S.** 2013. Antimicrobial resistant pathogens associated with healthcare-associated infections: summary of data reported to the national healthcare safety network at the Centers for Disease Control and Prevention, 2009–2010. Infect. Control Hosp. Epidemiol. **34:**1–14. http://dx.doi.org/10.1086/668770.
2. **Bode L, Kluytmans J, Wertheim H, Bogaers D, Vandenbroucke C, Roosendaal R, Troelstra A, Box A, Voss A, van der Tweel I, van Belkum A, Verbrough H, Vos M.** 2010. Preventing surgical site infections in nasal carriers of *Staphylococcus aureus*. N. Engl. J. Med. **362:**9–17. http://dx.doi.org/10.1056/NEJMoa0808939.
3. **Robicsek A, Beaumont JL, Thomson RB, Govindarajan G, Peterson LR.** 2009. Topical therapy for methicillin-resistant *Staphylococcus aureus* colonization: impact on infection risk. Infect. Control Hosp. Epidemiol. **30:**623–632. http://dx.doi.org/10.1086/597550.
4. **Seah C, Alexander DC, Louie L, Simor A, Low DE, Longtin J, Melano RG.** 2012. MupB, a new high-level mupirocin resistance mechanism in *Staphylococcus aureus*. Antimicrob. Agents Chemother. **56:**1916–1920. http://dx.doi.org/10.1128/AAC.05325-11.
5. **Patel JB, Gorwitz RJ, Jernigan JA.** 2009. Mupirocin resistance. Clin. Infect. Dis. **49:**935–941. http://dx.doi.org/10.1086/605495.
6. **Liu C, Bayer A, Cosgrove SE, Daum RS, Fridkin SK, Gorwitz RJ, Kaplan SL, Karchmar AW, Levine DP, Murray BE, Rybak MJ, Talan DA, Chambers HF.** 2011. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children. Clin. Infect. Dis. **52:**1–38. http://dx.doi.org/10.1093/cid/ciq146.
7. **van Hal SJ, Foler VG.** 2013. Is it time to replace vancomycin in the treatment of methicillin-resistant *Staphylococcus aureus* infections? Clin. Infect. Dis. **56:**1779–1787. http://dx.doi.org/10.1093/cid/cit178.
8. **CDC.** 2013. Health-associated infections. CDC, Atlanta, GA. www.cdc.gov/HAI/settings/lab/vrsa_lab_search_containment.html.
9. **Melo-Christino J, Resina C, Manuel V, Lito L, Ramirez M.** 21 June 2013. First case of infection with vancomycin-resistant *Staphylococcus aureus* in Europe. Lancet http://dx.doi.org/10.1016/S0140-6736(13)61219-2.
10. **Hiramatsu K.** 2001. Vancomycin-resistant *Staphylococcus aureus*: a new model of antibiotic resistance. Lancet Infect. Dis. **1:**147–155. http://dx.doi.org/10.1016/S1473-3099(01)00091-3.
11. **Wootton M, Howe RA, Hillman R, Walsh TR, Bennett PM, MacGowan AP.** 2001. A modified population analysis profile (PAP) method to detect hetero-resistance to vancomycin in *Staphylococcus aureus* in a UK hospital. J. Antimicrob. Chemother. **47:**399–404. http://dx.doi.org/10.1093/jac/47.4.399.
12. **Richter SS, Satola SW, Crispell E, Heilmann KP, Dohrn CL, Riahi F, Costello A, Diekema DJ, Doern GV.** 2011. Detection of *Staphylococcus aureus* with heterogeneous intermediate-level resistance to vancomycin (hVISA) in the United States. J. Clin. Microbiol. **49:**4203–4207. http://dx.doi.org/10.1128/JCM.01152-11.
13. **van Hal SJ, Wehrhahn MC, Barbagiannakos T, Mercer J, Chen D, Paterson DL, Gosbell IB.** 2011. Performance of various testing methodologies for detection of heteroresistant vancomycin-intermediate *Staphylococcus aureus* bloodstream isolates. J. Clin. Microbiol. **49:**1489–1494. http://dx.doi.org/10.1128/JCM.02302-10.
14. **Howden BP, Davies JK, Johnson PDR, Stinear TP, Grayson ML.** 2010. Reduced vancomycin resistance in *Staphylococcus aureus*, including vancomycin-intermediate and heterogeneous vancomycin-intermediate strains: resistance mechanisms, laboratory detection, and clinical implications. Clin. Microbiol. Rev. **23:**99–139. http://dx.doi.org/10.1128/CMR.00042-09.
15. **Horne KC, Howden BP, Grabsch EA, Graham M, Ward PB, Xie S, Mayall BC, Johnson PDR, Grayson ML.** 2009. Prospective comparison of the clinical impacts of heterogeneous vancomycin-intermediate methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-susceptible MRSA. Antimicrob. Agents Chemother. **53:**3447–3452. http://dx.doi.org/10.1128/AAC.01365-08.
16. **van Hal SJ, Paterson Dl.** 2011. Systematic review and meta-analysis of the signficance of heterogeneous vancomycin-intermediate *Staphylococcus aureus* isolates. Antimicrob. Agents Chemother. **55:**405–410. http://dx.doi.org/10.1128/AAC.01133-10.
17. **Richter SS, Heilmann KP, Dohrn CL, Riahi F, Costello AJ, Kroeger JS, Biek D, Critchley IA, Diekema DJ, Doern GV.** 2011. Activity of ceftaroline and epidemiologic characterization of *Staphylococcus aureus* from 43 medical centers in the United States, 2009. Antimicrob. Agents Chemother. **55:**4154–4160. http://dx.doi.org/10.1128/AAC.00315-11.
18. **Richter SS, Diekema DJ, Heilmann KP, Dohrn CL, Crispell EK, Riahi F, McDanel JS, Satola SW, Doern GV.** 2012. Abstr. 52nd Intersci. Conf. Antimicrob. Agents Chemother., San Francisco, CA, 10 September 2012, abstr C2-126.
19. **Clinical and Laboratory Standards Institute.** 2012. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; approved standard—8th ed. CLSI document M7-A9. CLSI, Wayne, PA.
20. **Clinical and Laboratory Standards Institute.** 2013. Performance standards for antimicrobial susceptibility testing; 23rd informational supplement. CLSI document M100-S23. CLSI, Wayne, PA.
21. **Oliveira DC, de Lencastré H.** 2002. Multiplex PCR strategy for rapid identification of structural types and variants of the *mec* element in methicillin-resistant *Staphylococcus aureus*. Antimicrob. Agents Chemother. **46:**2155–2161. http://dx.doi.org/10.1128/AAC.46.7.2155-2161.2002.
22. **Satola SW, Farley MM, Anderson KF, Patel JB.** 2011. Comparison of detection methods for heteroresistant vancomycin-intermediate *Staphylococcus aureus* with the population analysis profile method as the reference method. J. Clin. Microbiol. **49:**177–183. http://dx.doi.org/10.1128/JCM.01128-10.
23. **Pfeltz RF, Schmidt JL, Wilkinson BJ.** 2001. A microdilution plating method for population analysis of antibiotic-resistant staphylococci. Microb. Drug Resist. **7:**289–295. http://dx.doi.org/10.1089/10766290152652846.
24. **Satola SW, Caliendo AM, Farley MM, Patel JB, Burd EM.** 2009. Lack of heteroresistance among *Staphylococcus aureus* isolates with vancomycin MICs of 2 micrograms per milliliter by automated testing. J. Clin. Microbiol. **47:**2680–2681. http://dx.doi.org/10.1128/JCM.01184-09.
25. **Pfaller MA, Caliendo AM, Versalovic J.** 2010. Chromosomal restriction fragment analysis by pulsed-field gel electrophoresis: application to molecular epidemiology, p 12.4.5.1–12.4.5.7127. *In* Garcia LS, Isenberg HD (ed), Clinical microbiology procedures handbook, 3rd ed. ASM Press, Washington, DC.
26. **McDougal LK, Steward CD, Killgore GE, Chaitram JM, McAllister SK, Tenover FC.** 2003. Pulsed-field gel electrophoresis typing of oxacillin-resistant *Staphylococcus aureus* isolates from the United States: establishing a national database. J. Clin. Microbiol. **41:**5113–5120. http://dx.doi.org/10.1128/JCM.41.11.5113-5120.2003.
27. **Rybak MJ, Vidaillac C, Sader HS, Rhomberg PR, Salimnia H, Briski LE, Wanger A, Jones RN.** 2013. Evaluation of vancomycin susceptibility testing for methicillin-resistant *Staphylococcus aureus*: comparison of Etest and three automated testing methods. J. Clin. Microbiol. **51:**2077–2081. http://dx.doi.org/10.1128/JCM.00448-13.
28. **van Hal SJ, Lodise TP, Paterson DL.** 2012. The clinical significance of vancomycin minimium inhibitory concentration in *Staphylococcus aureus* infections: a systematic review and meta-analysis. Clin. Infect. Dis. **54:**755–771. http://dx.doi.org/10.1093/cid/cir935.
29. **Limbago B, Fosheim GF, Schoonover V, Crane CE, Nadle J, Petit S, Heltzel D, Ray SM, Harrison LH, Lynfield R, Dumyati G, Townes JM, Schaffner W, Mu Y, Fridkin SK.** 2009. Characterization of methicillin-resistant *Staphylococcus aureus* isolates collected in 2005 and 2006 from

patients with invasive disease: a population-based analysis. J. Clin. Microbiol. **47:**1344–1351. http://dx.doi.org/10.1128/JCM.02264-08.

30. **Simor AE, Stuart TL, Louie L, Watt C, Ofner-Agostini M, Gravel D, Mulvey M, Loeb M, McGeer A, Bryce E, Matlow A, Canadian Nosocomial Infection Surveillance Program.** 2007. Mupirocin-resistant, methicillin-resistant *Staphylococcus aureus* strains in Canadian hospitals. Antimicrob. Agents Chemother. **51:**3880–3886. http://dx.doi.org/10.1128/AAC.00846-07.
31. **Jones JC, Rogers TJ, Brookmeyer P, Dunne WM, Storch GA, Coopersmith CM, Fraser VJ, Warren DK.** 2007. Mupirocin resistance in patients colonized with methicillin-resistant *Staphylococcus aureus* in a surgical intensive care unit. Clin. Infect. Dis. **45:**541–547. http://dx.doi.org/10.1086/520663.
32. **Fritz SA, Hogan PG, Camins BC, Ainsworth AJ, Patrick C, Martin MS, Krauss MJ, Rodriguez M, Burnham CA.** 2013. Mupirocin and chlorhexidine resistance in *Staphylococcus aureus* in patients with community-onset skin and soft tissue infections. Antimicrob. Agents Chemother. **57:**559–568. http://dx.doi.org/10.1128/AAC.01633-12.
33. **Huang SS, Septimus E, Kleinman K, Moody J, Hickok J, Avery TR, Lankiewicz J, Gombosev A, Terpstra L, Hartford F, Hayden MK, Jernigan JA, Weinstein RA, Fraser VJ, Haffenreffer K, Cui E, Kaganov RE, Lolans K, Perlin JB, Platt R.** 29 May 2013. Targeted versus universal decolonization to prevent ICU infection. N. Engl. J. Med. http://dx.doi.org/10.1056/NEJMoa1207290.
34. **Mendes RE, Tsakris A, Sader HS, Jones RN, Biek D, McGhee P, Appelbaum PC, Kosowska-Shick K.** 2012. Characterization of methicillin-resistant *Staphylococcus aureus* displaying increased MICs of ceftaroline. J. Antimicrob. Chemother. **67:**1321–1324. http://dx.doi.org/10.1093/jac/dks069.