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Twenty-Year Trends in Antibiotic Susceptibility among *Staphylococcus aureus* from the SENTRY Antimicrobial Surveillance Program

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SENTRY ANTIMICROBIAL SURVEILLANCE

Introduction

- *Staphylococcus aureus* is among the most common and devastating human pathogens
  - *S. aureus* causes 20-30% of bloodstream and surgical site infections, and over half of bone and joint infections
- The emergence and spread of methicillin-resistant *S. aureus* (MRSA) complicates antibiotic treatment
- The epidemiology of MRSA infections has been characterized by an international spread of epidemic clones with highly variable rates of methicillin-resistance across regions, nations, and continents
  - After steady increases in MRSA rates, some regions report declines over the past decade
- Emerging glycopeptide resistance among *S. aureus* isolates is also of concern
  - Vancomycin MIC "creep" reported by some investigators
  - Alternatives to vancomycin now available and increasingly used
- Monitoring rates of antibiotic resistance among *S. aureus* is crucial
- The SENTRY Antimicrobial Surveillance Program has been ongoing for 20 years, collecting consecutive, clinically significant isolates of bacterial pathogens (including *S. aureus*) that cause diseases in North America, Europe, Latin America, and the Asia-Pacific region

Materials and Methods

- From 1997–2016, each SENTRY participating center submitted bacterial isolates and clinical data for consecutive episodes of bacteremia (bloodstream infection, BSI), pneumonia in hospitalized patients (PIHP), intra-abdominal infection (IAI), urinary tract infection (UTI), and skin and skin structure infection (SSSI) each month
- Isolate identification was confirmed at the central reference laboratory (JMI Laboratories, North Liberty, IA) using conventional and proteomic methods
- Susceptibility testing was performed against more than 20 antimicrobial agents at JMI Laboratories, using reference broth microdilution methods and interpretive MIC breakpoints as described by the Clinical and Laboratory Standards Institute (CLSI)
  - Food and Drug Administration breakpoints were used if CLSI breakpoints were not available
- Quality control was performed as recommended by CLSI, and results were all within established ranges
- This report describes antimicrobial susceptibility trends among the 191,462 *S. aureus* isolates collected from >100 SENTRY participating centers in North America, Latin America, Europe, and the Asia-Pacific region between January 1997 and December 2016

Results

- Of the 191,462 *S. aureus* isolates submitted, 77,146 (40.3%) were MRSA (Figure 1)
- Percent MRSA among all *S. aureus* isolates varied geographically, from 26.8% in Europe to 47.0% in North America (Figure 1)
- Within the United States, % MRSA was highest in the Southern divisions and lowest in the Mountain division (Figure 2)
- Overall % MRSA increased from 33.1% in 1997-2000 to a high of 44.2% in 2005–2008, then declined to 42.3% and 39.0% in 2009–2012 and 2013–2016, respectively
  - *S. aureus* BSI isolates had a similar trend, with nosocomial and community-onset % MRSA peaking in 2005–2008 and then declining (Figure 3)

Table 1. Methicillin resistance by specimen source, healthcare association, and age: SENTRY, 1997–2016

Variable	No. tested	% MRSA
Specimen source		
BSI	68,564	37.1
PIHP	34,029	45.6
SSSI	70,757	41.0
UTI	2,916	51.8
Healthcare association		
Community onset	86,366	36.8
Nosocomial	46,087	47.0
Age		
≤10	19,109	37.2
11-20	10,425	33.9
21-30	13,048	37.7
31-40	15,428	38.1
41-50	21,690	38.7
51-60	27,120	40.2
61-70	27,174	41.5
71-80	24,502	45.1
>80	17,371	48.0

Abbreviations: BSI, bloodstream infection; PIHP, pneumonia in hospitalized patients; SSSI, skin and skin structure infection; UTI, urinary tract infection

Table 2. Temporal trend in % susceptibility to selected older antimicrobials among *S. aureus* isolates, stratified by methicillin resistance

Antimicrobial agent	1997–2000	2001–2004	2005–2008	2009–2012	2013–2016	Overall
MSSA						
Penicillin	14	19	20	23	26	21
Erythromycin	73	80	78	73	74	75
Clindamycin	96	96	96	95	96	96
Doxycycline	98	99	98	99	99	99
Tetracycline	93	94	94	94	95	94
Ciprofloxacin	95	93	91	90	90	91
Gentamicin	97	97	97	97	98	97
TMP-SMX	100	98	98	99	99	99
Rifampin	99	99	99	—	—	99
MRSA						
Erythromycin	7	9	12	15	18	13
Clindamycin	23	33	53	63	70	55
Doxycycline	71	84	91	94	96	90
Tetracycline	61	77	83	86	90	83
Ciprofloxacin	10	10	20	25	28	20
Gentamicin	46	65	77	83	89	77
TMP-SMX	72	85	91	96	97	91
Rifampin	78	86	88	—	—	83

Abbreviations: MSSA, methicillin-susceptible *S. aureus*; MRSA, methicillin-resistant *S. aureus*; TMP-SMX, trimethoprim-sulfamethoxazole

Figure 1. Percent MRSA by region

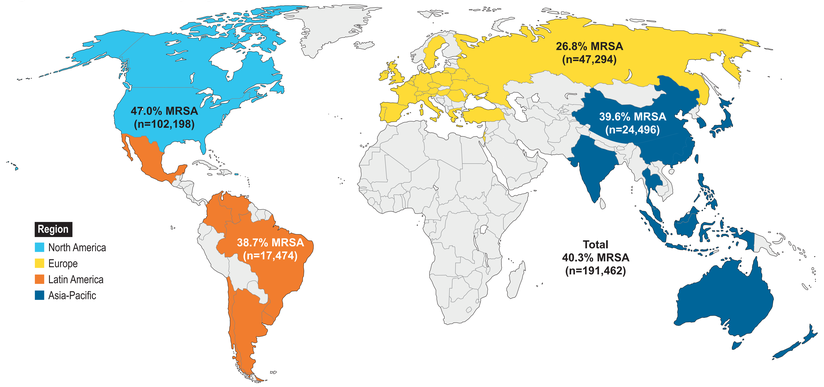


Table 3. Activity of selected antimicrobial agents when tested against *S. aureus*, stratified by methicillin resistance and for isolates with vancomycin MIC ≥2 mg/L

Antimicrobial agent	No. of isolates	MIC_{50}	MIC_{90}	MIC range	CLSI[a] %S	%I	%R
MSSA	**114,300**						
Ceftaroline	58,938	0.25	0.25	≤0.06 — 1	100.0	0.0	0.0
Dalbavancin	92,584	0.06	0.06	≤0.03 — >0.25	>99.9		
Daptomycin	94,022	0.25	0.5	≤0.12 — 4	>99.9		
Delafloxacin	18,033	≤0.004	0.015	≤0.004 — >1	98.1	0.9	0.9
Levofloxacin	103,405	≤0.5	≤0.5	≤0.5 — >4	92.3	0.5	7.1
Linezolid	110,519	1	2	≤0.12 — >8	>99.9		<0.1
Oritavancin	50,013	0.03	0.06	≤0.008 — 0.5	99.7		
QDA	68,250	≤0.5	≤0.5	≤0.5 — >2	99.9	0.1	<0.1
Tedizolid	22,987	0.12	0.12	≤0.008 — 0.5	100.0	0.0	0.0
Teicoplanin	114,285	≤2	≤2	≤2 — >8	>99.9		
Telavancin	46,041	0.03	0.06	≤0.015 — 0.25	>99.9		
Tigecycline	93,850	≤0.12	0.25	≤0.12 — 1	>99.9		
Vancomycin	114,297	1	1	≤0.12 — 4	>99.9	<0.1	0.0
MRSA	**77,146**						
Ceftaroline	40,731	1	1	0.015 — >8	91.6	8.2	0.2
Dalbavancin	66,302	0.06	0.06	≤0.03 — >0.25	>99.9		
Daptomycin	66,380	0.25	0.5	≤0.12 — 4	99.9		
Delafloxacin	10,243	0.12	1	≤0.004 — >1	74.3	12.3	13.4
Levofloxacin	72,075	>4	>4	≤0.5 — >4	23.4	1.7	75.0
Linezolid	75,780	1	2	≤0.25 — >8	99.9		0.1
Oritavancin	35,262	0.03	0.06	≤0.008 — 0.5	99.6		
QDA	46,141	≤0.5	1	≤0.5 — >2	99.5	0.3	0.2
Tedizolid	13,828	0.12	0.12	0.015 — >1	>99.9	0.0	<0.1
Teicoplanin	77,130	≤2	≤2	≤2 — >16	>99.9	<0.1	<0.1
Telavancin	31,000	0.03	0.06	≤0.015 — 0.25	>99.9		
Tigecycline	65,977	≤0.12	0.25	≤0.12 — 4	99.8		
Vancomycin	77,145	1	1	≤0.12 — 4	>99.9	<0.1	0.0
VAN MIC ≥2 mg/L	**5,375**						
Ceftaroline	1,332	0.5	2	0.015 — 2	86.2	13.8	0.0
Dalbavancin	3,318	0.06	0.12	≤0.03 — >0.25	99.5		
Daptomycin	3,479	0.5	1	≤0.12 — 4	98.3		
Delafloxacin	103	0.12	1	≤0.004 — >1	71.8	12.6	15.5
Levofloxacin	4,549	>4	>4	≤0.5 - >4	32.1	1.2	66.7
Linezolid	5,093	1	2	≤0.25 — >8	99.9		0.1
Oritavancin	1,024	0.06	0.12	≤0.008 — 0.5	98.0		
QDA	4,506	≤0.5	1	≤0.5 — >2	98.4	0.7	0.9
Tedizolid	190	0.12	0.25	0.03 — 0.25	100.0		
Teicoplanin	5,374	≤2	4	2 — >16	99.6	0.3	0.1
Telavancin	867	0.06	0.06	≤0.015 — 0.12	100.0		
Tigecycline	3,497	≤0.12	0.5	≤0.12 — 1	98.7		

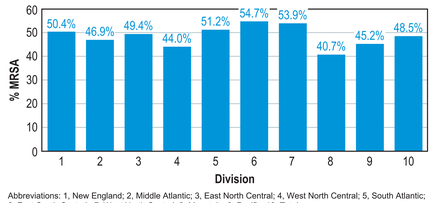
[a] Criteria as published by CLSI 2018.
Abbreviations: MSSA, methicillin-susceptible *S. aureus*; QDA, quinupristin-dalfopristin; MRSA, methicillin-resistant *S. aureus*; VAN, vancomycin

Table 4. Vancomycin MIC distribution of *S. aureus* isolates collected from participating SENTRY centers, 1997–2016

	N	N (cumulative %) at each vancomycin MIC (mg/L): ≤0.12	0.25	0.5	1	2	4	8
MSSA	114,297	49 (0.1)	243 (0.4)	28,862 (25.5)	83,549 (98.6)	1,569 (>99.9)	25 (100.0)	
MRSA	77,145	18 (<0.1)	220 (0.3)	15,807 (20.8)	57,319 (95.1)	3,745 (>99.9)	35 (>99.9)	1 (100.0)
Total	191,442	67 (<0.1)	463 (0.3)	44,669 (23.6)	140,868 (97.2)	5,314 (>99.9)	60 (>99.9)	1 (100.0)

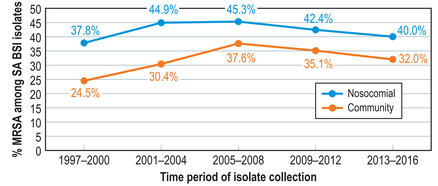
- The highest % MRSA was among nosocomial isolates, those from patients >80 years of age and those from PIHP or UTI episodes (Table 1)
- *In vitro* susceptibility to penicillin among methicillin-susceptible SA (PSSA) increased over time, consistent with reports from some local and regional surveillance (Table 2)
- Several other older antimicrobial agents exhibited increased activity (% susceptible) over time against MRSA, a possible result of epidemic spread of certain MRSA clones (eg, USA300) that are more susceptible to these agents (Table 2)
- Vancomycin activity against *S. aureus* remained stable: overall MIC_{90} = 1 mg/L, 100% susceptible in 2016 (Table 4)
  - No increase over time was observed in % of *S. aureus* (including MRSA) with vancomycin MIC >1 mg/L
- Several agents introduced during the surveillance period exhibited *in vitro* potency against MRSA and isolates with vancomycin MIC >1 mg/L (Table 3)
- Some trending analysis may have limitations due to inconsistent participation of certain countries, especially in the Asia-Pacific and eastern European regions

Figure 2. Methicillin resistance by US census division: SENTRY, 1997–2016



Abbreviations: 1, New England; 2, Middle Atlantic; 3, East North Central; 4, West North Central; 5, South Atlantic; 6, East South Central; 7, West North Central; 8, Mountain; 9, Pacific; 10, Total

Figure 3. 20-year trend in % of *S. aureus* BSI isolates that are MRSA



Conclusions

- In a large global surveillance program, the rise of MRSA as a proportion of all *S. aureus* infections peaked a decade ago, after which the % MRSA has declined
  - This is consistent with some other regional and national surveillance programs
  - Further research is needed to determine factors associated with this decline
- MRSA susceptibility to several older agents has increased over time, possibly associated with the emergence of epidemic clones (eg, USA300) with more favorable co-resistance profiles
- Vancomycin *in vitro* activity against *S. aureus* has been stable over time, and resistance remains rare
- Several agents, including many introduced during the surveillance period, maintain excellent *in vitro* activity against *S. aureus*, including against those isolates with vancomycin MIC >1 mg/L

Acknowledgements

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