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SUPPLEMENT ARTICLE

Twenty-Year Trends in Antimicrobial Susceptibilities Among *Staphylococcus aureus* From the SENTRY Antimicrobial Surveillance Program

Daniel J. Diekema,[1] Michael A. Pfaller,[1,2] Dee Shortridge,[2] Marcus Zervos,[3,4] and Ronald N. Jones[2]

[1]University of Iowa Carver College of Medicine, Iowa City, Iowa; [2]JMI Laboratories, North Liberty, Iowa; [3]Henry Ford Hospital, Detroit, Michigan; [4]Wayne State University School of Medicine, Detroit, Michigan

Background. *Staphylococcus aureus* is among the most common human pathogens, with therapy complicated by the epidemic spread of methicillin-resistant *Staphylococcus aureus* (MRSA).

Methods. The SENTRY Antimicrobial Surveillance Program evaluated the in vitro activity of >20 antimicrobials against 191 460 clinical *S. aureus* isolates collected from 427 centers in 45 countries from 1997 to 2016. Each center contributed isolates and clinical data for consecutive episodes of bacteremia, pneumonia in hospitalized patients, urinary tract infection, and skin and skin structure infection.

Results. Overall, 191 460 *S. aureus* isolates were collected, of which 77 146 (40.3%) were MRSA, varying geographically from 26.8% MRSA in Europe to 47.0% in North America. The highest percentage of MRSA was in nosocomial isolates from patients aged >80 years. Overall, MRSA occurrences 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* bacteremia had a similar trend, with nosocomial and community-onset MRSA rates peaking in 2005–2008 and then declining. Vancomycin activity against *S. aureus* remained stable (minimum inhibitory concentration $[MIC]_{90}$ of 1 mg/L and 100% susceptibility in 2016; no increase over time in isolates with a vancomycin MIC >1 mg/L). Several agents introduced during the surveillance period exhibited in vitro potency against MRSA.

Conclusions. In a large global surveillance program, the rise of MRSA as a proportion of all *S. aureus* peaked a decade ago and has declined since, consistent with some regional surveillance program reports. Vancomycin maintained high activity against *S. aureus*, and several newer agents exhibited excellent in vitro potencies.

Keywords. *Staphylococcus aureus*; antimicrobial resistance; epidemiology.

Staphylococcus aureus is among the most common and devastating human bacterial pathogens, causing 20%–30% of bloodstream and surgical site infections, as well as up to half of bone and joint infections [1–5]. The key to the success of *S. aureus* as a pathogen is its ability to develop antimicrobial resistance. The emergence of penicillinase-producing *S. aureus* strains occurred shortly after the introduction of penicillin for clinical use, and by the 1970s the vast majority of *S. aureus* infections were penicillin resistant [1]. Likewise, methicillin (oxacillin) resistance among *S. aureus* was reported in the early 1960s, after the introduction of methicillin [6]. Since that time, the continued emergence and spread of methicillin-resistant *S. aureus* (MRSA) has complicated the antimicrobial treatment of *S. aureus* [1, 7, 8]. MRSA strains are not only resistant to nearly all beta-lactams, but many have developed resistance to multiple other antimicrobial classes [9].

The epidemiology of MRSA infections has been characterized by sequential "waves" of epidemic clones spreading across geographic regions, nations, and continents [1, 7]. The result has been substantial regional variation in MRSA rates. One recent wave of resistance has been the global increase in community-associated strains of MRSA (CA-MRSA), including the emergence in the 1990s of pulsed-field-type USA300 (clonal complex [CC] 8) in the United States, followed by the spread of this strain across that country, around the world, and into health care (HC) environments [7, 10, 11]. Of note, USA300 and other strains of CA-MRSA are usually resistant to fewer other classes than HC-adapted strains (eg, USA100). Therefore, when they replace older MRSA clones, the result may be reduced rates of resistance to other antibiotic classes among MRSA.

As MRSA has become endemic, the use of vancomycin for therapy of invasive MRSA infections has increased, along with concerns about development of vancomycin resistance among MRSA [12]. Although most MRSA isolates (>99%) remain susceptible to vancomycin, several reports suggest that increased vancomycin minimum inhibitory concentrations (MICs), even within the susceptible range, may predispose to treatment

Correspondence: D. J. Diekema, MD, University of Iowa Carver College of Medicine, 200 Hawkins Drive, Iowa City, IA 52242 (daniel-diekema@uiowa.edu).

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failure [13], and some investigators have also reported vancomycin "MIC creep" among MRSA isolates that could result in increased frequency of vancomycin treatment failure [14]. During the same time period, several agents with in vitro activity against MRSA have been introduced [15, 16]. These agents are being used increasingly as alternatives to vancomycin for treating some serious MRSA infections.

To continue to monitor trends in the proportion of *S. aureus* infections due to MRSA, the activity of vancomycin against clinical isolates of MRSA over time, and the activity of other antimicrobial classes and newer agents against *S. aureus*, ongoing prospective surveillance is critical. 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. Strengths of the program include using reference in vitro susceptibility testing methods at a central laboratory, providing consistency over time in MIC determination, and the breadth of the program. We can now report trends in antimicrobial resistance among almost 200 000 *S. aureus* isolates submitted to the SENTRY Program during the 20 years since its inception in 1997.

METHODS

The SENTRY Antimicrobial Surveillance Program is a sentinel surveillance program for tracking antimicrobial occurrences and resistance worldwide via a global network of medical centers. From 1997 to 2016, each participating SENTRY Program center submitted bacterial isolates and clinical data for consecutive episodes of bacteremia (bloodstream infections [BSIs]), pneumonia in hospitalized patients (PIHP), intra-abdominal infections (IAIs), urinary tract infections (UTIs), and skin and skin structure infections (SSSIs). Isolate identification was confirmed at the central reference laboratory using conventional and proteomic methods (*S. aureus* identification was confirmed by the coagulase test from 1997 to 2012 and by matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS) from 2012 to 2016). From 1997 to 2016, the SENTRY Program collected >750 000 clinical isolates from >400 centers worldwide. This report describes results from the 191 460 *S. aureus* isolates collected from 427 SENTRY Program participating centers in North America, Latin America, Europe, and the Asia-Pacific region between January 1997 and December 2016. For designating regional differences within the United States, census division designations were applied [17]. When the sample collection date was ≥3 days after the admission date, we designated the infection episode to be nosocomial (vs community onset).

Antimicrobial Susceptibility Testing

All isolates were tested for susceptibility against >20 antimicrobial agents each year at the central laboratories, using reference broth microdilution methods and interpretive MIC breakpoints, as described by the Clinical and Laboratory Standards Institute (CLSI) [18]. Food and Drug Administration breakpoints were used if CLSI breakpoints were not available, as well as those of the European Committee on Antimicrobial Susceptibility Testing (EUCAST) [19]. Quality control was performed as recommended by the CLSI, and results were all within established ranges [20].

RESULTS

Of the 191 460 *S. aureus* isolates submitted during the 20-year surveillance period, a total of 77 146 (40.3%) were MRSA. The highest rates (%) of MRSA were among nosocomial isolates, those from patients >80 years of age, and those from PIHP or UTI episodes (Table 1). The percentage of 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, the MRSA rate was highest in the Southern census divisions and lowest in the Mountain division (Figure 2). The overall MRSA rate increased from 33.1% in 1997–2000 to a high of 44.2% in 2005–2008, and has since 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 rates peaking in 2005–2008 and then declining (Figure 3).

In vitro susceptibility to penicillin among methicillin-susceptible *S. aureus* (MSSA) increased over time (Table 2). Similarly, several other older antimicrobial agents exhibited increased activity (% susceptible) over time against MRSA (Table 2).

Table 1. Methicillin Resistance by Specimen Source, Health Care Association, and Age (SENTRY Program, 1997–2016)

Variable	No. Tested	% MRSA
Specimen source		
BSI	68 564	37.1
PIHP	34 029	45.6
SSSI	70 757	41.0
UTI	2916	51.9
Health care association		
Community onset	86 366	36.8
Nosocomial	46 086	47.0
Age, y		
≤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; MRSA, methicillin-resistant *Staphylococcus aureus;* PIHP, pneumonia in hospitalized patients; SSSI, skin and skin structure infection; UTI, urinary tract infection; y, years.

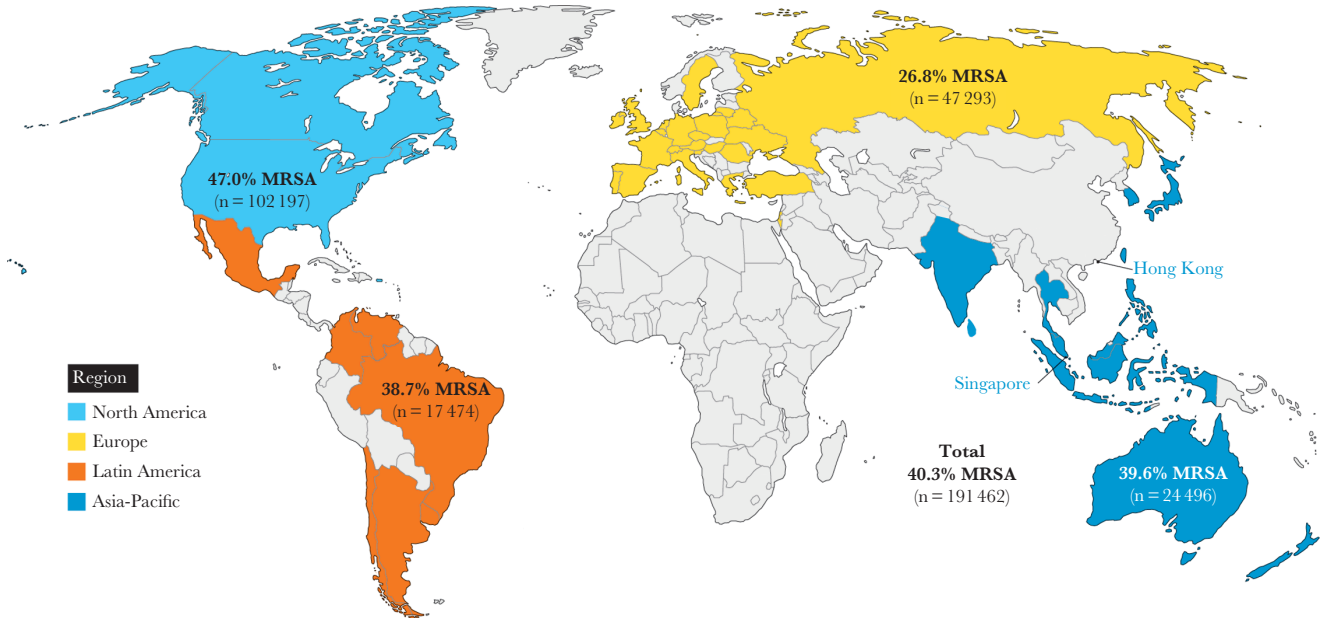

Figure 1. Percent MRSA by region. Abbreviation: MRSA, methicillin-resistant *Staphylococcus aureus*.

Vancomycin activity against *S. aureus* remained stable: overall MIC_{90} at 1 mg/L, with 100% susceptibility in 2016 (Table 3). No increase across time was observed in the percentage of *S. aureus* (including MRSA) with a vancomycin MIC >1 mg/L (<3% overall and <1% during the 2013–2016 time period), and we did not observe a consistent or sustained increase in the percentage of MRSA with a vancomycin MIC of 1 mg/L. Notably, only 1 *S. aureus* isolate with an MIC >4 mg/L (MIC, 8 mg/L) was detected during this 20-year surveillance program using reference MIC methods.

Several agents introduced during the surveillance period exhibited in vitro potency against MRSA and isolates with a vancomycin MIC >1 mg/L (Table 4). For example, >98% of such isolates were susceptible in vitro to daptomycin, dalbavancin, oritavancin, telavancin, linezolid, tedizolid, and tigecycline.

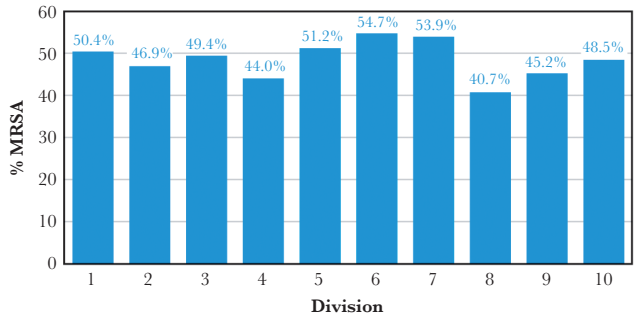

Figure 2. Methicillin resistance by US census division: SENTRY Program, 1997–2016. Abbreviations: MRSA, methicillin-resistant *Staphylococcus aureus*; 1, New England; 2, Middle Atlantic; 3, East North Central; 4, West North Central; 5, South Atlantic; 6, East South Central; 7, West South Central; 8, Mountain; 9, Pacific; 10, Total.

DISCUSSION

Although many antimicrobial resistance surveillance programs exist, most are limited to a single country or region [4, 21–23] and focus exclusively on 1 infection site or type (eg, bloodstream infections, nosocomial infections). Moreover, many programs gather susceptibility data from participating sites but do not confirm susceptibility or organism identification results. The SENTRY Program is a large global surveillance program that monitors pathogens from consecutive episodes of infection at multiple body sites, providing a very large number of isolates tested by a central monitoring reference laboratory [24]. The consecutive nature of SENTRY Program collection allows for the inference of prevalence at each site and, to some degree, for that region. These strengths provide the opportunity to examine on a large scale the trends that have been reported from various geographic areas.

The major trend noted in our 20-year *S. aureus* surveillance was that the rise of MRSA as a proportion of all *S. aureus* infections peaked a decade ago, after which the MRSA rates have declined. This is consistent with several other regional and national surveillance programs that observed reductions in MRSA infections, or in the proportion of *S. aureus* that are MRSA, beginning during 2000–2010 in the United States [2, 21], the United Kingdom [25], and Europe [22]. This decline coincided with increased focus on infection prevention in medical centers generally, and MRSA in particular in some health systems [26]. However, the fact that the decline occurred in all surveillance regions and among both community-onset and hospital-onset infections suggests that factors other than health care facility infection control interventions may be responsible,

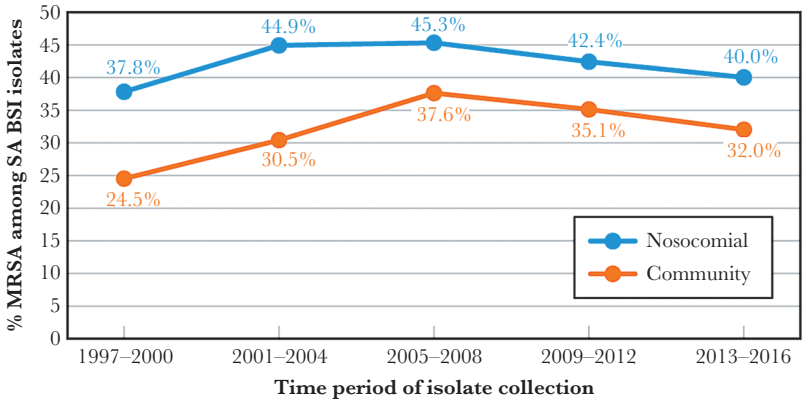

Figure 3. SENTRY Program 20-year trends in percentage of *Staphylococcus aureus* BSI isolates that are MRSA. Abbreviations: BSI, bloodstream infection; MRSA, methicillin-resistant *Staphylococcus aureus*.

including bacterial factors associated with the continued evolution of this common human pathogen (eg, the rise and fall of successful MRSA clones across human populations). Regional variation in antibiotic prescribing and socioeconomic factors may also be associated with MRSA infection rates, as recently described by Andreatos and colleagues [27]. Ongoing surveillance and further research are required to detect future waves of resistance among *S. aureus* and to help determine in more detail what factors may be associated with MRSA epidemics, as well as with periods of decline in MRSA incidence or prevalence [28].

The susceptibility of MRSA isolates to several older antimicrobial agents has also increased across the last 2 decades, a possible result of the epidemic spread of MRSA clones (eg, USA300) that are more susceptible to these agents [1, 7, 11]. This favorable trend provides options for MRSA therapy from among well-established older agents (eg, clindamycin, trimethoprim-sulfamethoxazole, tetracyclines) [29]. However, for serious invasive MRSA infections, including bacteremia, vancomycin remains the most commonly used antimicrobial for treatment, despite concerns about efficacy [29], the emergence of resistance [12], and the MIC creep phenomenon [14]. Regarding the emergence of resistance and MIC creep, results from this large longitudinal study are reassuring: we find no evidence to support MIC creep, consistent with a recently published meta-analysis [14], and confirm that >99.9% of both MRSA and MSSA isolates have vancomycin MICs of ≤2 mg/L.

Table 2. Temporal Trend in Percent Susceptibility to Selected Older Antimicrobials Among *S. aureus* Isolates, Stratified by Methicillin Resistance (SENTRY Program, 1997–2016)

	% Susceptible by Time Interval					
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: MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *S. aureus*; TMP-SMX, trimethoprim-sulfamethoxazole.

Table 3. Vancomycin MIC Distributions of *S. aureus* Isolates Collected From Participating SENTRY Program Centers, 1997–2016

		No. (Cumulative %) at Each Vancomycin MIC, mg/L						
	No.	≤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)	1569 (>99.9)	25 (100.0)	
MRSA	77 145	18 (<0.1)	220 (0.3)	15 807 (20.8)	57 319 (95.1)	3745 (>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)	5314 (>99.9)	60 (>99.9)	1 (100.0)

Abbreviations: MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *S. aureus*.

Table 4. Activity of Selected Antimicrobial Agents When Tested Against *S. aureus*, Stratified by Methicillin Resistance and for Isolates With Vancomycin MIC at >1 mg/L (SENTRY Program, 1997–2016)

					CLSI[a]		
Antimicrobial Agent	No. of Isolates	MIC_{50}	MIC_{90}	MIC Range	%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		
Quinupristin-dalfopristin	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	65 302	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		
Quinupristin-dalfopristin	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
Vancomycin (MIC ≥2 mg/L)	5375						
Ceftaroline	1332	0.5	2	0.015–2	86.2	13.8	0.0
Dalbavancin	3318	0.06	0.12	≤0.03–>0.25	99.5		
Daptomycin	3479	0.5	1	≤0.12–4	98.3		
Delafloxacin	103	0.12	1	≤0.004–>1	71.8	12.6	15.5
Levofloxacin	4549	>4	>4	≤0.5–>4	32.1	1.2	66.7
Linezolid	5093	1	2	≤0.25–>8	99.9		0.1
Oritavancin	1024	0.06	0.12	≤0.008–0.5	98.0		
Quinupristin-dalfopristin	4506	≤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	5374	≤2	4	2–>16	99.6	0.3	0.1
Telavancin	867	0.06	0.06	≤0.015–0.12	100.0		
Tigecycline	3497	≤0.12	0.5	≤0.12–1	98.7		

Abbreviations: CLSI, Clinical and Laboratory Standards Institute; I, intermediate; MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *S. aureus;* R, resistance; S, susceptible.

[a]Criteria as published by CLSI 2018.

Several newer alternatives to vancomycin among other antimicrobial classes were introduced during the 20-year time period of this surveillance program, providing an expanded armamentarium against MRSA. Although the number of isolates tested against these agents varies based upon when they were added to our surveillance, ceftaroline, daptomycin, dalbavancin, oritavancin, telavancin, linezolid, tedizolid, and tigecycline all exhibit good in vitro activity against *S. aureus*, including isolates with vancomycin MICs of 2 mg/L or greater. More experience will be required to demonstrate the efficacy of some of these agents in clinical settings, in which vancomycin remains a default choice (eg, invasive and high-inoculum MRSA infections, including bacteremia and endocarditis).

Among MSSA isolates, which still cause the majority of *S. aureus* infections, rates of susceptibility to non-beta-lactam agents remain stable and high. Of particular interest, penicillin susceptibility among MSSA isolates has steadily increased, from 14% in 1997–2000 to 26% in 2013–2016. Other investigators have noted similar findings, from single centers to national surveillance programs [30–35]. With the caveat that laboratory confirmation of susceptibility is required given the limitations of phenotypic detection of penicillin resistance in *S. aureus* [35], our findings serve as a reminder that penicillin may be an option for a non-trivial number of serious *S. aureus* infections [36].

The *S. aureus* surveillance data we present in this report have limitations. As a sentinel network that collects pathogens from select medical centers, the SENTRY Program does not provide population-based information about the incidence of infections in a given region. For example, it is possible for the proportion of *S. aureus* isolates that are MRSA to be falling while overall infection rates due to *S. aureus* or MRSA are increasing. In addition, not all sentinel medical centers participated in each year of the 20-year surveillance program. As participating centers leave the program, additional centers from that region may be added, with the goal of maintaining a robust and broadly representative sample from as many countries and regions as possible. Furthermore, regions of the world with limited resources for clinical laboratory support are also underrepresented or not represented (eg, Africa) in this report. Finally, we do not present molecular typing or sequencing data in this report to investigate some of the trends noted (eg, emergence over time of various epidemic clones of MRSA).

Nonetheless, the 2-decade surveillance period and international scope of this study provide important insights into trends in antimicrobial resistance among *S. aureus*, most of which do not fit neatly into a narrative of relentless increases in resistance. The proportion of clinical *S. aureus* isolates represented by MRSA has been declining for the past decade, resistance to several older drug classes among MRSA has been decreasing, vancomycin in vitro activity remains stable, and penicillin susceptibility among MSSA isolates has been increasing. Meanwhile, the number of available options for treatment of MRSA infections has expanded with the release of several new compounds with excellent in vitro activity. Despite these favorable findings, MRSA remains a common and devastating pathogen that is frequently refractory to therapy and for which improved prevention and treatment approaches are needed. Ongoing surveillance is important to help inform the development of these approaches.

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