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

Daniel J. Diekema,1 Michael A. Pfaffer,1,4 Dee Shortridge,2 Marcos Zervos,3,4 and Ronald N. Jones2

1University of Iowa Carver College of Medicine, Iowa City, Iowa; 2JMI Laboratories, North Liberty, Iowa; 3Henry Ford Hospital, Detroit, Michigan; 4Wayne 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]0 ≤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.
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 | 2,916 | 51.9 |
| Health care association | | |
| Community onset | 86,386 | 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 | 27,124 | 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.
Vancomycin activity against *S. aureus* remained stable: overall MIC₉₀ 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.

**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.
including bacterial factors associated with the continued evolution of this common human pathogen (e.g., 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 (e.g., 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 (e.g., 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)

| Antimicrobial Agent | % Susceptible by Time Interval |
|---------------------|-------------------------------|
|                     | 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        | —         | 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        | 89        | 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 |
|------------|----------------------------------------------|
|            | ≤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) | 3 415 (>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)

| Antimicrobial Agent | No. of Isolates | MIC<sub>50</sub> | MIC<sub>90</sub> | MIC Range | %S | %I | %R |
|---------------------|-----------------|-----------------|-----------------|------------|----|----|----|
| **MSSA**            | 114 300         |                 |                 |            |    |    |    |
| Ceftaroline         | 58 038          | 0.25            | 0.25            | ≤0.06–1    | 100 | 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  | 0  |
| Levofloxacin        | 103 405         | ≤0.5            | ≤0.5            | ≤0.5–4     | 92.3 | 0  | 0  |
| 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  | <0.1 |
| Tedizolid           | 22 987          | 0.12            | 0.12            | ≤0.008–0.5 | 100.0 | 0  | 0  |
| Telavancin          | 66 380          | 0.25            | 0.5             | ≤0.12–4   | >99.9 |    |    |
| Tigecycline         | 77 145          | 1               | 1               | ≤0.12–4   | >99.9 | <0.1 | 0  |

**MRSA**

| Antimicrobial Agent | No. of Isolates | MIC<sub>50</sub> | MIC<sub>90</sub> | MIC Range | %S | %I | %R |
|---------------------|-----------------|-----------------|-----------------|------------|----|----|----|
| 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 |    |    |
| 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 |
| Telavancin          | 77 130          | ≤2              | ≤2              | ≤2–16     | >99.9 | <0.1 | <0.1 |
| Tigecycline         | 65 977          | ≤0.12           | 0.25            | ≤0.12–4   | 99.9 |    |    |
| Vancomycin          | 77 144          | 1               | 1               | ≤0.12–4   | >99.9 | <0.1 | 0.0 |

**Vancomycin (MIC ≥2 mg/L)**

| Antimicrobial Agent | No. of Isolates | MIC<sub>50</sub> | MIC<sub>90</sub> | MIC Range | %S | %I | %R |
|---------------------|-----------------|-----------------|-----------------|------------|----|----|----|
| 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 |    |    |
| Oritavancin         | 1024            | 0.06            | 0.12            | ≤0.008–0.5 | 98.8 |    |    |
| 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 |    |    |
| Telavancin          | 5374            | ≤2              | 4               | 2–16      | 99.6 | 0.3 | 0.1 |
| Tigecycline         | 3497            | ≤0.12           | 0.5             | ≤0.12–1   | 96.7 |    |    |

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.

*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, ceftriaxone, 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. With the caveat that laboratory confirmation of susceptibility is required given the limitations of phenotypic detection of penicillin resistance in S. aureus, our findings serve as a reminder that penicillin may be an option for a non-trivial number of serious S. aureus infections.

The S. aureus surveillance data we present in this report have limitations. As a sentinel network that collects pathogens from selected 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.

Acknowledgments

The authors thank all participants of the SENTRY Program for their work in providing isolates.

Financial support. D.J.D. receives research funding from bioMerieux, Inc. Funding for the manuscript was provided by JMI Laboratories.

Potential conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Chambers HF, Deleo FR. Waves of resistance: Staphylococcus aureus in the antibiotic era. Nat Rev Microbiol. 2009;7:629–41.
2. Kleven RS, Morrison MA, Nadle J, et al; Active Bacterial Core surveillance (ABCs) MRSA Investigators. Invasive methicillin-resistant Staphylococcus aureus infections in the United States. JAMA 2007;298:1763–71.
3. Rubin RJ, Harrington CA, Poon A, et al. The economic impact of Staphylococcus aureus infection in New York City hospitals. Emerg Infect Dis 1999;5:9–17.
4. Sievert DM, Ricks P, Edwards JR, et al; National Healthcare Safety Network (NHSN) Team and Participating NHSN Facilities. 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 2013;34:1–14.
5. Weiner LM, Webb AK, Limbago B, et al; 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, 2011–2014. Infect Control Hosp Epidemiol 2016;37:1288–301.
6. Barber M. Methicillin-resistant staphylococci. J Clin Pathol 1961;14:385–93.
7. Chatterjee SS, Otto M. Improved understanding of factors driving methicillin-resistant Staphylococcus aureus epidemic waves. Clin Epidemiol 2013;5:205–17.
8. Lowy FD. Staphylococcus aureus infections. N Engl J Med 1998;339:520–32.
9. Diekema DJ, Pfaller MA, Turndije I, et al; Sentry Participants Group. Genetic relatedness of multidrug-resistant, methicillin (oxacillin)-resistant Staphylococcus aureus bloodstream isolates from SENTRY Antimicrobial Resistance Surveillance Centers worldwide, 1998. Microb Drug Resist 2000;6:213–21.
10. Van De Griend P, Herwaldt LA, Alvis B, et al. Community-associated methicillin-resistant Staphylococcus aureus, Iowa, USA, 2004. Emerg Infect Dis 2004;10:1110–2.
11. Diekema DJ, Richter SS, Heilmann KP, et al; Sentry Participants Group. Genetic relatedness of multidrug-resistant, methicillin (oxacillin)-resistant Staphylococcus aureus bloodstream isolates from SENTRY Antimicrobial Resistance Surveillance Centers worldwide, 1998. Microb Drug Resist 2000;6:213–21.
12. Limbago BM, Kallen AJ, Zhu W, et al. Report of the 15th vancomycin-resistant Staphylococcus aureus isolate from the United States. J Clin Microbiol 2014;52:998–1002.
13. Lodise TP, Graves J, Evans A, et al. Relationship between vancomycin MIC and failure among patients with methicillin-resistant Staphylococcus aureus bacteremia treated with vancomycin. Antimicrob Agents Chemother 2008;52:3315–20.
14. Diaz R, Afreixo V, Ramalheira E, et al. Evaluation of vancomycin MIC creep in methicillin-resistant Staphylococcus aureus infections: a systematic review and meta-analysis. Clin Microbiol Infect 2018;24:97–104.
15. Pfaller MA, Sader HS, Flamm RK, et al; Oritavancin in vitro activity against gram-positive organisms from European and United States medical centers: results from the SENTRY Antimicrobial Surveillance Program for 2010–2014. Diagn Microbiol Infect Dis 2018;91:199–204.
16. Sader HS, Mendes RE, Streit JM, Flamm RK. Antimicrobial susceptibility trends among Staphylococcus aureus from U. S. hospitals: results from 7 years of the cfazidime (AWARe) surveillance program (2010–2016). Antimicrob Agents Chemother 2017;61:e01043.
17. US Census Bureau. Census regions and divisions of the United States. 2015. https://www2.census.gov/geo/pdfs/maps-data/maps/reference/us_regdiv.pdf. Accessed 14 July 2018.
18. CLSI. \textit{M07Ed11E}; Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically: Approved Standard. 11th ed. Wayne, PA: Clinical and Laboratory Standards Institute, 2018.
19. European Committee on Antimicrobial Susceptibility Testing. Breakpoint tables for interpretation of MICs and zone diameters. Version 8.0. 2018. http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/v_8.0_Breakpoint_Tables.pdf. Accessed January 2018.
20. CLSI. *M100Ed28E*. Performance Standards for Antimicrobial Susceptibility Testing: 28th Informational Supplement. Wayne, PA: Clinical and Laboratory Standards Institute; 2018.
21. Burton DC, Edwards JR, Horan TC, et al. Methicillin-resistant *Staphylococcus aureus* central line-associated bloodstream infections in US intensive care units, 1997-2007. JAMA 2009; 301:727–36.
22. Gagliotti C, Balode A, Baquero F, et al. *Escherichia coli* and *Staphylococcus aureus*: bad news and good news from the European Antimicrobial Resistance Surveillance Network (EARS-Net, formerly EARSS), 2002 to 2009. Euro Surveill 2011; 16:19819.
23. Kallen AJ, Mu Y, Bulens S, et al; Active Bacterial Core surveillance (ABCs) MRSA Investigators of the Emerging Infections Program. Health care-associated invasive MRSA infections, 2005-2008. JAMA 2010; 304:641–8.
24. Diekema DJ, Pfaller MA, Schmitz FJ, et al. Survey of infections due to *Staphylococcus* species: frequency of occurrence and antimicrobial susceptibility of isolates collected in the United States, Canada, Latin America, Europe, and the Western Pacific region for the SENTRY Antimicrobial Surveillance Program, 1997–1999. Clin Infect Dis 2001; 32(Suppl 2):S114–32.
25. Johnson AP, Davies J, Guy R, et al. Mandatory surveillance of methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia in England: the first 10 years. J Antimicrob Chemother 2012; 67:802–9.
26. Jain R, Kravovic SM, Evans ME, et al. Veterans Affairs initiative to prevent methicillin-resistant *Staphylococcus aureus* infections. N Engl J Med 2011; 364:1419–30.
27. Maronis GA, Buerrett S, Andreatos N, et al. Association of BRAF mutations with survival and recurrence in surgically treated patients with metastatic colorectal liver cancer. JAMA Surg 2018; 153:e180996.
28. Perencevich EN, Diekema DJ. Decline in invasive MRSA infection: where to go from here? JAMA 2010; 304:687–9.
29. Liu C, Bayer A, Cosgrove SE, et al; Infectious Diseases Society of America. 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 2011; 52:e18–55.
30. Chabot MR, Stefan MS, Friderici J, et al. Reappearance and treatment of penicillin-susceptible *Staphylococcus aureus* in a tertiary medical centre. J Antimicrob Chemother 2015; 70:3353–6.
31. Cheng MP, René P, Cheng AP, Lee TC. Back to the future: penicillin-susceptible *Staphylococcus aureus*. Am J Med 2016; 129:1331–3.
32. Crane JK. Resurgence of penicillin-susceptible *Staphylococcus aureus* at a hospital in New York State, USA. J Antimicrob Chemother 2014; 69:280–1.
33. Jokinen E, Laine J, Huttunen R, et al. Trends in incidence and resistance patterns of *Staphylococcus aureus* bacteremia. Infect Dis 2018; 50:52–8.
34. Kanjilal S, Sater MRA, Thayer M, et al. Trends in antibiotic susceptibility in *Staphylococcus aureus* in Boston, Massachusetts, from 2000 to 2014. J Clin Microbiol 2018; 56:e01160.
35. Richter SS, Doern GV, Heilmann KP, et al. Detection and prevalence of penicillin-susceptible *Staphylococcus aureus* in the United States in 2013. J Clin Microbiol 2016; 54:812–4.
36. Shah MD, Wardlow LC, Stevenson KB, Coe KE, Reed EE. Clinical outcomes with penicillin versus alternative beta-lactams in the treatment of penicillin-susceptible *Staphylococcus aureus* bacteremia. Pharmacotherapy. In press.