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The Microbiology of Bloodstream Infection: 20-Year Trends from the SENTRY Antimicrobial Surveillance Program

Short running title: Microbiology of Bloodstream Infection

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Abstract

Bloodstream infection (BSI) organisms were consecutively collected from >200 medical centers in 45 nations between 1997 and 2016. Species identification and susceptibility testing followed Clinical and Laboratory Standards Institute broth microdilution methods at a central laboratory. Clinical data and isolates from 264,901 BSI episodes were collected. The most common pathogen overall was *Staphylococcus aureus* (20.7%), followed by *Escherichia coli* (20.5%), *Klebsiella pneumoniae* (7.7%), *Pseudomonas aeruginosa* (5.3%), and *Enterococcus faecalis* (5.2%). *S. aureus* was the most frequent pathogen overall in the 1997–2004 period, but *E. coli* was the most common after 2005. Pathogen frequency varied by geographic region, hospital-onset or community-onset status, and patient age. The prevalence of *S. aureus* resistant to oxacillin (MRSA) increased until 2005–08, then declined among hospital-onset and community-acquired BSI in all regions. The prevalence of vancomycin-resistant enterococci (VRE) was stable after 2012 (16.4% overall). Daptomycin resistance among *S. aureus* and enterococci (DRE) remained rare (<0.1%). In contrast, the prevalence of multidrug-resistant (MDR) *Enterobacteriaceae* increased from 6.2% in 1997–2000 to 15.8% in 2013–16. MDR rates were highest among non-fermentative Gram-negative bacilli (GNB), and colistin was the only agent with predictable activity against *Acinetobacter baumannii-calcoaceticus* complex (97% susceptible). In conclusion, *S. aureus* and *E. coli* were the predominant causes of BSI worldwide during this 20-year surveillance period. Important resistant phenotypes among Gram-positive pathogens (MRSA, VRE, or DRE) were stable or declining, whereas the prevalence of MDR-GNB increased continuously during the monitored period. MDR-GNB pose the greatest therapeutic challenge among common bacterial BSI pathogens.

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Introduction

Bloodstream infection (BSI) causes significant patient morbidity and mortality worldwide (1). Changing antimicrobial resistance (AMR) rates, pathogen distribution, demographics, and medical care delivery all may affect the epidemiology of BSI; therefore, continuously monitoring trends in the microbiology of BSI pathogens worldwide is very important. Examining microbiological trends can help inform diagnostic approaches, treatment strategies, and prevention programs.

A major concern has been the emergence and global spread of multidrug-resistant (MDR) organisms, including oxacillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* spp. (VRE), and MDR Gram-negative bacilli (GNB), including extended spectrum β-lactamase (ESBL) producers, carbapenem-resistant *Enterobacteriaceae* (CRE), and MDR non-fermenters such as *Pseudomonas aeruginosa* and *Acinetobacter* spp. Several studies have demonstrated the high mortality attributable to BSI due to these MDR organisms (2-5).

The SENTRY Antimicrobial Surveillance Program was established in 1997 to monitor the predominant bacterial pathogens and antimicrobial resistance patterns of organisms isolated from patients with various infection types, including BSI (6). We now report trends in organism distribution and AMR among BSI isolates submitted to the SENTRY Program during the first 20 years of the program, 1997–2016.

68 **Results**

69 Among the 264,901 BSI isolates collected, the most common pathogens overall were *S. aureus* and
70 *Escherichia coli* (together accounting for over 40% of BSIs), followed by *Klebsiella pneumoniae*, *P. aeruginosa*,
71 and *Enterococcus faecalis* (see Table 1). Notably, *E. coli* increased (from 18.7% in 1997–2000, to 24.0% in
72 2013–2016), while *S. aureus* declined (from 22.5% to 18.7%), as an overall proportion of all BSI. This change
73 was accompanied by an increase in the proportion of GNB among the top 10 pathogens causing BSI (from
74 33.5% to 43.4% between 1997–2000 and 2013–2016). *Streptococcus pneumoniae* declined from 4.2% of all
75 BSI in 1997–2000 to less than 2.0% of all BSI in 2009–2016.

76 Pathogen frequency varied somewhat over time and by region, hospital- (HO) or community-onset (CO)
77 status, and age (see Tables 1 - 4). However, *S. aureus* and *E. coli* remained predominant, with *S. aureus*
78 representing a larger proportion of BSIs in North and Latin America (24.5% and 20.1% overall, respectively),
79 while *E. coli* was predominant in Europe and the Asia-Pacific region (24.1% and 26.0% overall, respectively).
80 Major decreases in the frequency of *S. aureus* occurred in Latin America (from 21.5% in 1997–2000 to 16.4% in
81 2013–2016) and the Asia-Pacific region (from 20.8% to 13.9%; Table 2). *S. pneumoniae* frequency decreased
82 during the study period especially in Latin America (from 4.0% in 1997-2000 to 0.4% in 2013–2016) and the
83 Asia-Pacific region (from 4.6% to 0.9%). In contrast, *E. coli* and *K. pneumoniae* frequencies increased in all
84 regions, with the greatest increases in Europe and Asia-Pacific regions (Table 2). *Acinetobacter* spp.
85 represented a higher proportion of BSI in Latin America and the Asia-Pacific regions (4.4% and 3.2% overall,
86 respectively) than elsewhere.

87 While *E. coli* and *S. aureus* were the two most common causes of BSI in both HO- and CO-BSI, they
88 were much more predominant for CO-BSI (57.8% vs. 31.3% of HO-BSI). HO-BSI was more often due to non-*E.*
89 *coli* GNB (*P. aeruginosa* and *Acinetobacter* spp.; Table 4).

90 The prevalence of MRSA increased until 2005–2008, then declined in all regions and among HO-BSI
91 and CO-BSI (Figure 1). Of the 56,575 *S. aureus* BSI isolates tested against vancomycin, only one had an MIC in
92 the CLSI non-susceptible category (8 mg/L), and no trend toward an increasing vancomycin MIC over time
93 ("MIC creep") was detected. The occurrence of VRE (vancomycin MIC, >4 mg/L) declined after 2012 and was
94 16.4% overall (see Figure 2). Daptomycin resistance among *S. aureus* and enterococci remained rare (<0.1%).

The frequency of MDR *Enterobacteriaceae* among all *Enterobacteriaceae* isolates increased from 6.2% in 1997–2000 to 15.8% in 2013–2016, and was highest among the HO-BSI (Figure 3). The frequency of MDR among *Enterobacteriaceae* varied by region, with the highest rates observed in Latin America (28.1%). ESBL-phenotype *E. coli*, ESBL-phenotype *Klebsiella* spp., and CRE phenotypes also increased over the surveillance period (Figure 4). MDR rates were highest among the nonfermentative GNB (*P. aeruginosa* at 26.3% and *A. baumannii-calcoaceticus* complex at 70.6%); 48 isolates of *A. baumannii-calcoaceticus* (0.9%) and 9 isolates of *P. aeruginosa* (<0.1%) were pan-drug resistant. Colistin was the only agent with predictable activity against *A. baumannii-calcoaceticus* complex (96.9% susceptible; Table 5).

The antimicrobial activity of selected agents against the 107,617 *Enterobacteriaceae* isolates is outlined in Table 5. Over 95% of these BSI pathogens were susceptible *in vitro* to amikacin, ceftazidime-avibactam, carbapenems, and tigecycline.

Discussion

Many surveillance programs are designed to monitor trends in BSI. However, most programs are limited in scope to specific patient populations, countries, or regions (5, 7-13) and do not confirm the organism identification or susceptibility data at a reference laboratory. The SENTRY Program performs global surveillance, monitoring pathogens from consecutive BSI episodes and testing all isolates at the central reference laboratory (6). Collecting isolates from consecutive episodes allows for the inference of prevalence at each site, providing the opportunity to examine large-scale trends.

Major findings from the first two decades of SENTRY Program BSI surveillance include: (1) the predominance of *S. aureus* and *E. coli* as BSI pathogens worldwide, (2) the decline in proportion of BSI due to important resistant Gram-positive pathogens (MRSA, VRE, DRE) during the second decade of surveillance, and (3) the ongoing increase in GNB and in MDR-GNB as a proportion of all BSI worldwide.

Population-based BSI surveillance is consistent with our findings regarding the prominence of *S. aureus* and *E. coli* as BSI pathogens. Laupland (10) has reviewed population-based BSI surveillance programs from various regions, noting that *E. coli* and *S. aureus* were the two most common BSI pathogens with estimated incidence rates of 35 and 25 per 100,000, respectively. By comparison, the next most common BSI cause was *S. pneumoniae*, at 10 cases/100,000 (10). SENTRY surveillance suggests that *E. coli* has become slightly more prominent over the past two decades in comparison with *S. aureus*, while the proportion of BSI caused by *S. pneumoniae* has declined. The reasons for these trends are not yet understood, but may be related to changes in health care delivery, emergence and global spread of the *E. coli* sequence type 131 clone (14), increased focus on *S. aureus* disease prevention in community (15) and health care (16, 17) settings, and the introduction of pneumococcal conjugate vaccines (18). Whatever the reasons, our findings suggest that priority should be given to developing novel prevention approaches for these two important BSI pathogens, including continued research and development of vaccine candidates (19, 20).

For the first decade of SENTRY BSI surveillance, important resistant phenotypes among Gram-positive pathogens (MRSA and VRE) were stable or increasing. Somewhat surprisingly, the proportion of *S. aureus* and *Enterococcus* spp. BSI due to MRSA and VRE, respectively, declined over the past 5-10 years of the surveillance period. The decline in MRSA we report is consistent with other regional and national surveillance programs that observed reductions in MRSA infections, or in the proportion of *S. aureus* that are MRSA, during

the decade of the 2000s (7-9, 17, 21). Although this decline has coincided with an increased emphasis on hospital infection prevention practices worldwide, the reasons for it are unclear and likely to be complex and multifactorial (22-26). We discuss this in more detail in a recent report on overall *S. aureus* infections at all anatomic infection sites in the SENTRY Program (27). We also observed that the percent of vancomycin resistance among enterococci has stabilized and begun to decline. Given the fact that VRE BSI is an almost exclusively health care-associated infection, it seems likely that a decline in VRE as a proportion of all enterococcal infections is related to improved hospital infection prevention, and coincides with general reductions in health care-associated infections (28). Finally, only one BSI isolate of *S. aureus* with vancomycin resistance (MIC = 8 mg/L) was detected across two decades of surveillance, and daptomycin-resistance among indicated *S. aureus* and *Enterococcus* spp. (MIC, >1 mg/L) has remained extremely uncommon.

In contrast to resistance trends among Gram-positive pathogens, SENTRY surveillance finds that GNB are increasing as a proportion of all BSI and that important GNB resistance phenotypes have increased over the past two decades. Our findings support reports of the emergence and spread of ESBL (5, 14, 29, 30) and carbapenemase (31-33) enzymes worldwide. While some of these enzymes have disseminated globally, e.g., CTX-M, KPC (14, 31, 32), regional (and even local) variation is prevalence is substantial (33). This increases the importance of developing regional surveillance and prevention collaborations in an attempt to interrupt transmission in communities and across health care networks (34, 35). Beyond *Enterobacteriaceae*, the most resistant GNB in our surveillance were the non-fermenters *P. aeruginosa* and *Acinetobacter* spp. These are the species among which the pan-drug resistant GNB are most likely to be detected (36) and for which new drug development is increasingly critical (37, 38).

The 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. In addition, not all sentinel medical centers participated for each year of the 20-year surveillance program. As participating centers leave the program, additional centers from that region are 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 in this report, e.g., Africa. Finally, we do not present our molecular or sequencing data in this report to investigate some of the trends noted.

Nonetheless, the duration and global scope of the SENTRY Program provides important insights into trends in pathogen frequency and antimicrobial resistance trends among BSI pathogens. While *E. coli* and *S. aureus* remain the major causes of BSI worldwide, there is an important divergence in the antimicrobial resistance challenges posed by Gram-positive and Gram-negative bacterial causes of BSI. While the most important resistance phenotypes among Gram-positive BSI pathogens are stable or declining as a proportion of reported infections, MDR GNB are increasing worldwide. Improved diagnostic, therapeutic, and preventive approaches to these pathogens are urgently needed. Ongoing global surveillance remains important to help inform the development, implementation and follow-up of these approaches.

Materials and Methods

Organism collection. SENTRY is a sentinel surveillance program for tracking antimicrobial resistance worldwide via a global network of medical centers. Each participating SENTRY Program center submitted bacterial isolates and clinical data for consecutive unique episodes of BSI each month during the surveillance period (one isolate per patient, from any acute care setting). Isolate identification was confirmed at the central reference laboratory (JMI Laboratories, North Liberty, Iowa, USA) using conventional and proteomic methods. This report describes the organism distribution and antimicrobial susceptibility trends among the 264,901 BSI isolates collected from 238 SENTRY participating centers in North America (72 centers in the US and Canada), Latin America (18 centers in 7 countries), Europe (65 centers in 23 countries), and the Asia-Pacific region (83 centers in 12 countries) between January 1997 and December 2016. When the sample collection date was 3 or more days after the admission date, we designated the BSI episode to be "hospital-onset."

Resistance phenotypes. VRE was defined as vancomycin MIC at >4 mg/L (nonsusceptible per CLSI and resistant per European Committee on Antimicrobial Susceptibility Testing [EUCAST]). CRE was defined as resistance to meropenem, imipenem (not applied for *Proteus mirabilis* or indole-positive *Proteeae*), and/or doripenem. ESBL phenotype was defined as *E. coli*, *P. mirabilis*, and *Klebsiella* spp. with aztreonam, ceftazidime, or ceftriaxone MIC of ≥2 mg/L. MDR among GNB was defined using CDC criteria (nonsusceptibility to at least one drug in ≥ 3 of the following antibiotic classes: broad-spectrum cephalosporins, carbapenems, broad-spectrum penicillin combined with a β-lactamase-inhibitor, fluoroquinolones, aminoglycosides, glycylcyclines (for *Enterobacteriaceae* only), and the polymyxins (36). Pan-drug resistance was defined as nonsusceptibility to a drug in all antibiotic classes.

Susceptibility methods. Susceptibility testing was performed against more than 20 antimicrobial agents, using reference broth microdilution methods and interpretive MIC breakpoints as described by CLSI (39, 40) and EUCAST (41). FDA breakpoints were used if CLSI breakpoints were not available. Quality control was performed as recommended by CLSI, and results were all within established ranges.

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Transparency Declaration

JMI Laboratories has been contracted to perform services in 2018 for Achaogen, Actelion, Allecra Therapeutics, AmpliPhi Biosciences, API, Astellas Pharma, AstraZeneca, Basilea Pharmaceutica, Bayer AG, BD, Biomodels, Cardeas Pharma Corp., CEM-102 Pharma, Cempra, Cidara Therapeutics, Inc., CorMedix, CSA Biotech, Cutanea Life Sciences, Inc., Debiopharm Group, Dipexium Pharmaceuticals, Inc., Entasis Therapeutics, Inc., Fortress Biotech, Fox Chase Chemical Diversity Centre, Inc., Geom Therapeutics, Inc., GSK, Laboratory Specialists, Inc., Medpace, Melinta Therapeutics, Inc., Merck & Co., Inc., Micromyx, MicuRx Pharmaceuticals, Inc., Motif Bio, N8 Medical, Inc., Nabriva Therapeutics, Inc., Nexcida Therapeutics, Inc., Novartis, Paratek Pharmaceuticals, Inc., Pfizer, Polyphor, Rempex, Scynexis, Shionogi, Spero Therapeutics, Symbal Therapeutics, Synlogic, TenNor Therapeutics, TGV Therapeutics, The Medicines Company, Theravance Biopharma, ThermoFisher Scientific, VenatoRx Pharmaceuticals, Inc., Wockhardt, Zavante Therapeutics, Inc. There are no speakers' bureaus or stock options to declare.

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352 Table 1 Rank order (%) of pathogens causing bloodstream infection worldwide, by 4-year period in the SENTRY Program

Rank	1997–2000	2001–2004	2005–2008	2009–2012	2013–2016	All years
1	*S. aureus* (22.5)	*S. aureus* (22.7)	*E. coli* (20.0)	*E. coli* (21.3)	*E. coli* (24.0)	*S. aureus* (20.7)
2	*E. coli* (18.7)	*E. coli* (20.2)	*S. aureus* (19.4)	*S. aureus* (18.8)	*S. aureus* (18.7)	*E. coli* (20.5)
3	*K. pneumoniae* (6.8)	*K. pneumoniae* (6.6)	*K. pneumoniae* (7.8)	*K. pneumoniae* (8.5)	*K. pneumoniae* (9.9)	*K. pneumoniae* (7.7)
4	*P. aeruginosa* (5.1)	*E. faecalis* (5.6)	*P. aeruginosa* (5.4)	*E. faecalis* (5.3)	*P. aeruginosa* (5.4)	*P. aeruginosa* (5.3)
5	*E. faecalis* (5.0)	*P. aeruginosa* (5.4)	*E. faecalis* (5.1)	*P. aeruginosa* (5.2)	*E. faecalis* (5.0)	*E. faecalis* (5.2)
6	*S. epidermidis* (4.8)	*S. epidermidis* (3.9)	*S. epidermidis* (3.4)	*E. faecium* (3.8)	*S. epidermidis* (4.1)	*S. epidermidis* (3.8)
7	*S. pneumoniae* (4.2)	*S. pneumoniae* (3.5)	*E. cloacae* (3.3)	*S. epidermidis* (3.1)	*E. faecium* (3.4)	*E. cloacae* (2.9)
8	*E. cloacae* (2.9)	*E. cloacae* (3.1)	*E. faecium* (3.1)	*E. cloacae* (2.8)	*E. cloacae* (2.1)	*S. pneumoniae* (2.8)
9	*E. faecium* (1.7)	*E. faecium* (2.2)	*A. baumannii*[a] (2.4)	*A. baumannii* (2.4)	*A. baumannii* (2.0)	*E. faecium* (2.8)
10	*S. agalactiae* (1.5)	*P. mirabilis* (1.7)	*S. pneumoniae* (2.2)	*S. pneumoniae* (1.9)	*S. pneumoniae* (1.9)	*A. baumannii* (2.0)

353 [a] *Acinetobacter baumannii-calcoaceticus* species complex.

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Table 2. Rank order and frequency (%) of most common organisms causing bloodstream infections in the 1997–2000 and 2013–2016 time periods stratified by region

	Frequency of species (%) in the first (1997–2000) and last (2013–2016) time period for each region							
	North America		Latin America		Europe		Asia-Pacific	
Rank[a]	1997-2000	2013-2016	1997-2000	2013-2016	1997-2000	2013-2016	1997-2000	2013-2016
1	*S. aureus*		*E. coli*		*E. coli*		*E. coli*	
	25.3	24.3	17.2	18.3	21.0	27.0	21.6	33.7
2	*E. coli*		*S. aureus*		*S. aureus*		*S. aureus*	
	17.5	19.8	21.5	16.4	18.2	16.9	20.8	13.9
3	*K. pneumoniae*		*K. pneumoniae*		*K. pneumoniae*		*K. pneumoniae*	
	6.5	8.6	9.2	13.6	5.8	10.1	7.6	13.5
4	*E. faecalis*		*P. aeruginosa*		*P. aeruginosa*		*P. aeruginosa*	
	6.2	5.4	6.5	7.1	5.9	5.8	4.8	5.7
5	*P. aeruginosa*		*E. cloacae*		*E. faecalis*		*E. cloacae*	
	4.5	4.8	3.6	5.9	4.6	5.4	3.4	3.0
6	*S. epidermidis*		*A. baumannii*[b]		*S. epidermidis*		*E. faecalis*	
	3.3	4.6	3.2	5.5	7.8	4.1	3.4	2.9
7	*E. faecium*		*S. epidermidis*		*E. faecium*		*A. baumannii*[b]	
	2.3	3.4	4.6	5.4	1.5	4.0	2.1	2.7
8	*E. cloacae*		*E. faecalis*		*E. cloacae*		*E. faecium*	
	2.8	3.1	2.2	5.0	2.7	2.6	1.1	2.6
9	*S. pneumoniae*		*S. marcescens*		*A. baumannii*[b]		*S. epidermidis*	
	4.8	2.4	1.5	*3.3*	1.8	2.4	4.8	2.5
10	*S. agalactiae*		*E. faecium*		*P. mirabilis*		*S. agalactiae*	
	2.0	2.2	0.3	2.4	1.8	2.3	1.2	1.9

[a] Rank order based on the 2013–2016 time period.

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359 [b] *Acinetobacter baumannii-calcoaceticus* species complex.

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360 Table 3. Rank order of pathogens causing bloodstream infection worldwide, by age group, submitted to the SENTRY Program, 1997–2016

Rank	<1 year	1–5 years	6–18 years	19–49 years	50–64 years	>64 years
1	*S. aureus* (16.4)	*S. aureus* (15.9)	*S. aureus* (26.4)	*S. aureus* (24.9)	*S. aureus* (23.1)	*E. coli* (26.6)
2	*E. coli* (13.7)	*S. pneumoniae* (11.4)	*E. coli* (12.6)	*E. coli* (18.1)	*E. coli* (19.9)	*S. aureus* (20.1)
3	*K. pneumoniae* (8.6)	*E. coli* (9.2)	*P. aeruginosa* (6.6)	*K. pneumoniae* (7.3)	*K. pneumoniae* (8.6)	*K. pneumoniae* (8.0)
4	*E. faecalis* (6.9)	*K. pneumoniae* (7.9)	*K. pneumoniae* (6.5)	*P. aeruginosa* (5.4)	*P. aeruginosa* (5.9)	*E. faecalis* (5.9)
5	*S. epidermidis* (6.3)	*P. aeruginosa* (5.7)	*S. epidermidis* (5.1)	*E. faecalis* (4.8)	*E. faecalis* (5.3)	*P. aeruginosa* (5.4)

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362 Table 4. Rank order (%) of pathogens causing BSI worldwide, by community or hospital onset, submitted to the SENTRY Program, 1997–2016

Rank	**Community onset** (*n* = 102,638)	**Hospital onset** (*n* = 103,945)
1	*E. coli* (26.6)	*S. aureus* (21.3)
2	*S. aureus* (22.4)	*E. coli* (15.6)
3	*K. pneumoniae* (7.2)	*K. pneumoniae* (8.8)
4	*S. pneumoniae* (5.2)	*P. aeruginosa* (7.4)
5	*E. faecalis* (4.7)	*E. faecalis* (6.4)
6	*P. aeruginosa* (3.7)	*S. epidermidis* (4.8)
7	*E. cloacae* (2.4)	*E. faecium* (4.3)
8	*S. agalactiae* (2.3)	*E. cloacae* (4.0)
9	*S. epidermidis* (2.2)	*A. baumannii*[a] (3.2)
10	*P. mirabilis* (2.0)	*S. marcescens* (2.1)

363 [a] *Acinetobacter baumannii-calcoaceticus* species complex.

364 **Table 5** Activity of antimicrobial agents when tested against *Staphylococcus aureus*, *Enterobacteriaceae*,
365 and *Acinetobacter baumannii-calcoaceticus* species complex submitted to the SENTRY Program, 1997–
366 2016

	MIC_{50}	MIC_{90}	CLSI[a]			EUCAST[a]		
Organism/antimicrobial agent (no. tested)	**(mg/L)**		**%S**	**%I**	**%R**	**%S**	**%I**	**%R**
Staphylococcus aureus (56,579)								
Ceftaroline (16,658)	0.25	1	96.2	3.7	0.1	96.2	3.7	0.1
Ceftobiprole (23,214)	0.5	2				99.4		0.6
Dalbavancin (36,161)	0.06	0.06	>99.9 [b]			99.7		0.3
Daptomycin (37,814)	0.25	0.5	99.9			99.9		0.1
Linezolid (53,595)	2	2	>99.9		<0.1	>99.9		<0.1
Teicoplanin (56,570)	≤2	≤2	>99.9 [c]			98.8		1.2
Tigecycline (37,085)	≤0.12	0.25	99.8 [b]			99.8		0.2
Vancomycin (56,575)	1	1	99.9	0.1	0.0	99.9		0.1
Enterobacteriaceae (107,617)								
Amikacin (107,561)	≤4	≤4	97.4	1.3	1.3	95.5	2.0	2.6
Ampicillin-sulbactam (74,048)	16	>16	49.4	17.1	33.5	49.4		50.6
Aztreonam (107,580)	≤0.12	16	86.5	1.6	11.9	84.0	2.5	13.5
Cefepime (107,581)	≤0.5	4	89.3	3.0 [d]	7.7	87.5	3.3	9.1
Ceftazidime-avibactam (31,672)	0.12	0.25	99.7		0.3	99.7		0.3
Ceftriaxone (107,575)	≤0.25	>8	83.5	0.8	15.7	83.5	0.8	15.7
Ciprofloxacin (107,567)	≤0.5	>2	80.9	1.7	17.5	76.6	1.9	21.5
Colistin (54,476)	≤0.5	>4				88.0		12.0
Doxycycline (59,912)	2	>8	66.5	9.1	24.5			
Gentamicin (107,561)	≤2	>8	87.9	1.1	11.0	86.7	1.2	12.1
Imipenem (107,322)	≤0.5	1	95.2	3.1	1.7	98.3	1.1	0.6
Levofloxacin (107,571)	≤0.5	>4	82.5	2.4	15.1	79.2	2.3	18.5
Meropenem (107,529)	≤0.12	≤0.12	98.8	0.2	1.0	99.0	0.3	0.7
Minocycline (56,100)	2	>8	77.2	8.5	14.3			
Piperacillin-tazobactam (107,301)	2	16	90.0	4.4	5.6	86.8	3.2	10.0

Organism/antimicrobial agent (no. tested)	MIC_{50} (mg/L)	MIC_{90} (mg/L)	CLSI[a] %S	CLSI[a] %I	CLSI[a] %R	EUCAST[a] %S	EUCAST[a] %I	EUCAST[a] %R
Tetracycline (107,577)	≤4	>8	64.0	2.8	33.2			
Tigecycline (68,141)	0.25	1	98.4[b]	1.4	0.2	94.9	3.5	1.6
Tobramycin (107,579)	0.5	>8	86.4	3.1	10.5	83.6	2.8	13.6
Trimethoprim-sulfamethoxazole (107,571)	≤0.5	>1	74.7		25.3	74.7[c]		
P. aeruginosa (14,562)								
Amikacin (14,559)	≤4	16	90.0	2.4	7.6	86.1	4.0	10.0
Aztreonam (14,558)	8	>16	66.7	13.9	19.4	1.7	78.9	19.4
Cefepime (14,559)	4	>16	79.9	10.0	10.1	79.9		20.1
Ceftazidime (14,557)	≤2	>16	77.7	4.9	17.4	77.7		22.3
Ceftazidime-avibactam (3,911)	2	8	93.4		6.6	93.4		6.6
Ciprofloxacin (14,559)	≤0.5	>2	74.8	3.0	22.2	71.0		29.0
Colistin (7,107)	1	2	99.3		0.7	99.3		0.7
Doripenem (9,112)	0.5	>4	78.9	8.0	13.1	71.5	7.3	21.1
Gentamicin ((14,557)	≤2	>8	79.8	2.8	17.4	79.8		20.2
Imipenem (14,534)	1	>8	75.3	4.7	20.0	80.0	7.2	12.7
Levofloxacin (14,557)	≤0.5	>4	72.9	4.1	23.0	66.2		33.8
Meropenem (14,556)	0.5	>8	77.5	6.2	16.3	77.5	11.8	10.8
Piperacillin-tazobactam (14,549)	8	>64	73.8	11.3	14.9	73.8		26.2
Polymyxin B (8,855)	≤1	2	99.6	0.4	<0.1			
Tobramycin (14,558)	0.5	>8	82.8	0.7	16.6	82.8		17.2
A. baumannii-calcoaceticus complex (5,333)								
Amikacin (5,332)	>32	>32	45.7	4.2	50.1	42.6	3.1	54.3
Ampicillin-sulbactam (4,056)	>16	>16	36.5	11.8	51.7			
Cefepime (5,332)	>16	>16	35.5	11.1	53.4			
Ceftazidime (5,332)	>16	>16	32.8	5.8	61.5			
Ciprofloxacin (5,332)	>2	>2	32.4	0.6	67.0	32.4		67.6
Colistin (3,124)	≤0.5	2	96.9		3.1	96.9		3.1
Doxycycline (3,238)	≤1	>8	67.4	1.5	31.1			

Organism/antimicrobial agent (no. tested)	MIC_{50} (mg/L)	MIC_{90} (mg/L)	CLSI[a] %S	CLSI[a] %I	CLSI[a] %R	EUCAST[a] %S	EUCAST[a] %I	EUCAST[a] %R
Gentamicin (5,324)	>8	>8	39.0	5.4	55.6	39.0		61.0
Imipenem (5,333)	2	>8	55.3	3.1	41.6	55.3	5.9	38.8
Levofloxacin (5,332)	>4	>4	34.6	8.3	57.1	32.3	1.1	66.7
Meropenem (5,326)	2	>8	52.0	4.1	43.8	52.0	8.9	39.1
Minocycline (3,098)	≤1	>8	81.5	8.4	10.1			
Piperacillin-tazobactam (5,320)	>64	>64	30.8	9.4	59.8			
Tetracycline (5,178)	8	>8	42.4	13.2	44.4			
Tigecycline (3,688)	0.5	2						
Tobramycin (5,330)	4	>8	52.4	3.2	44.4	52.4		47.6
Trimethoprim-sulfamethoxazole (5,331)	>1	>1	41.7		58.3	41.7 [c]		

[a] Criteria as published by CLSI (40) and EUCAST (41), the latter for comparison only.

[b] Breakpoints from FDA Package Insert (42).

[c] Dilution range did not extend high enough to determine between intermediate and resistant so only susceptible percentage is displayed.

[d] Intermediate interpreted as susceptible-dose dependent.

373 Figure 1 Twenty-year trend in percent MRSA among all *S. aureus* bloodstream infection, SENTRY 1997–
374 2016

375

376 MRSA, methicillin-resistant *S. aureus*.

377

Figure 2. Twenty-year trend in percent VRE among *Enterococcus* spp. bloodstream infection, SENTRY 1997–2016

VRE, vancomycin-resistant enterococci.

383 Figure 3. Twenty-year trend in percent MDR among *Enterobacteriaceae* bloodstream infection, by
384 community-onset versus hospital-onset infection, SENTRY 1997–2016
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386 MDR, multidrug resistance.
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388 Figure 4. Twenty-year trend in percent ESBL and CRE among selected *Enterobacteriaceae*, SENTRY 1997–
389 2016

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391 ESBL, extended-spectrum β-lactamase; CRE, carbapenem-resistant *Enterobacteriaceae*.