AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy®

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

Daniel J. Diekema,[a] Po-Ren Hsueh,[b] Rodrigo E. Mendes,[c] Michael A. Pfaller,[a,c] Kenneth V. Rolston,[d] Helio S. Sader,[c] Ronald N. Jones[c]

[a]University of Iowa, Iowa City, Iowa, USA
[b]National Taiwan University Hospital, National Taiwan University College of Medicine, Taipei, Taiwan
[c]JMI Laboratories, North Liberty, Iowa, USA
[d]The University of Texas MD Anderson Cancer Center, Houston, Texas, USA

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 frequently isolated pathogen overall in the 1997-to-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* isolates resistant to oxacillin (ORSA) increased until 2005 to 2008 and 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 to 2000 to 15.8% in 2013 to 2016. MDR rates were highest among nonfermentative Gram-negative bacilli (GNB), and colistin was the only agent with predictable activity against *Acinetobacter baumannii-Acinetobacter 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 represent the greatest therapeutic challenge among common bacterial BSI pathogens.

KEYWORDS antimicrobial resistance, bloodstream infection, surveillance

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* (ORSA), vancomycin-resistant *Enterococcus* spp. (VRE), and MDR Gram-negative bacilli (GNB) (including extended-spectrum-β-lactamase [ESBL] producers), carbapenem-resistant *Enterobacteriaceae* (CRE), and MDR nonfermenters such as *Pseudomonas aeruginosa* and *Acineto-*

TABLE 1 Rank order of pathogens causing bloodstream infection worldwide in the SENTRY Program by 4-year period

Rank	Pathogen (%) during:					
	1997–2000	2001–2004	2005–2008	2009–2012	2013–2016	All yrs
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)

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

bacter 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 the 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 to 2016).

RESULTS

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

Pathogen frequency varied somewhat over time and by region, hospital-onset (HO) or community-onset (CO) status, and age (see Tables 1, 2, 3, and 4). However, *S. aureus* and *E. coli* remained predominant, with *S. aureus* representing a larger proportion of BSIs in North and Latin America (24.5% and 20.1% overall, respectively), while *E. coli* was predominant in Europe and the Asia-Pacific region (24.1% and 26.0% overall, respec-

TABLE 2 Rank order and frequency of most common organisms causing bloodstream infections in the 1997-to-2000 and 2013-to-2016 time periods stratified by region

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

[a]Rank order based on the 2013-to-2016 time period.
[b]*Acinetobacter baumannii-Acinetobacter calcoaceticus* species complex.

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

Rank	Pathogen (%) for patients aged:					
	<1 yr	1–5 yrs	6–18 yrs	19–49 yrs	50–64 yrs	>64 yrs
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)

tively). Major decreases in the frequency of *S. aureus* detection occurred in Latin America (from 21.5% in 1997 to 2000 to 16.4% in 2013 to 2016) and the Asia-Pacific region (from 20.8% to 13.9%; Table 2). *S. pneumoniae* frequency decreased during the study period, especially in Latin America (from 4.0% in 1997 to 2000 to 0.4% in 2013 to 2016) and the Asia-Pacific region (from 4.6% to 0.9%). In contrast, *E. coli* and *K. pneumoniae* frequencies increased in all regions, with the greatest increases in Europe and the Asia-Pacific regions (Table 2). *Acinetobacter* spp. represented higher proportions of BSI in Latin America and the Asia-Pacific regions (4.4% and 3.2% overall, respectively) than elsewhere.

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

The prevalence of ORSA increased until 2005 to 2008 and then declined in all regions and among HO-BSI and CO-BSI (Fig. 1). Of the 56,575 *S. aureus* BSI isolates tested against vancomycin, only 1 had a vancomycin MIC in the CLSI nonsusceptible category (8 mg/liter), and no trend toward an increase in the vancomycin MIC over time ("MIC creep") was detected. The proportion of VRE (vancomycin MIC, >4 mg/liter) declined after 2012 and was 16.4% overall (see Fig. 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 to 2000 to 15.8% in 2013 to 2016 and was highest among the HO-BSI isolates (Fig. 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 (Fig. 4). MDR rates were highest among the nonfermentative GNB (*P. aeruginosa* at 26.3% and *Acinetobacter baumannii-Acinetobacter calcoaceticus* complex at 70.6%); 48 isolates of *Acinetobacter baumannii-Acinetobacter calcoaceticus* (0.9%) and 9 isolates of *P. aeruginosa* (<0.1%) were pan-drug resistant. Colistin was the only

TABLE 4 Rank order of pathogens causing BSI worldwide submitted to the SENTRY Program, 1997–2016, by community or hospital onset

Rank	Pathogen (%)	
	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)

[a]*Acinetobacter baumannii-Acinetobacter calcoaceticus* species complex.
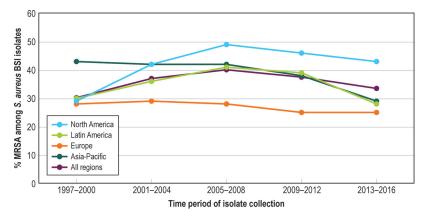
FIG 1 Twenty-year trend in percent methicillin-resistant *S. aureus* (MRSA) among all *S. aureus* blood-stream infections, SENTRY, 1997 to 2016.

agent with predictable activity against *Acinetobacter baumannii-Acinetobacter 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, the scope of most programs is limited to specific patient populations, countries, or regions (5, 7–13) and the programs 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 inference of rates of prevalence at each site, providing the opportunity to examine large-scale trends.

Major findings from the first 2 decades of SENTRY Program BSI surveillance include (i) the predominance of *S. aureus* and *E. coli* as BSI pathogens worldwide, (ii) the decline in the proportion of BSI due to important resistant Gram-positive pathogens (ORSA, VRE, daptomycin resistance among *S. aureus* and enterococci [DRE]) during the second decade of surveillance, and (iii) the ongoing increase in the detection of GNB and in MDR-GNB as a proportion of all causes of 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
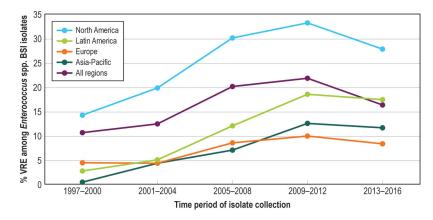

FIG 2 Twenty-year trend in percent vancomycin-resistant enterococci (VRE) among *Enterococcus* sp. bloodstream infections, SENTRY, 1997 to 2016.
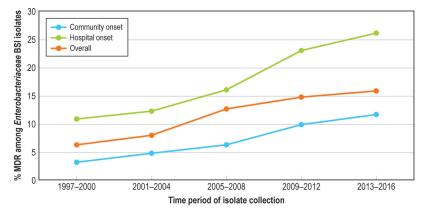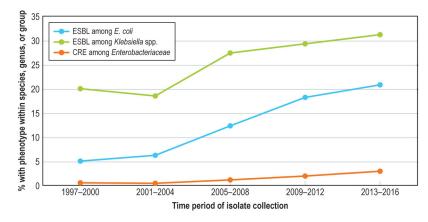
FIG 3 Twenty-year trend in percent multidrug resistance (MDR) among *Enterobacteriaceae* bloodstream infection, by community-onset versus hospital-onset infection, SENTRY, 1997 to 2016.

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 than *S. aureus* over the past 2 decades, 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, the proportions of important resistant phenotypes among Gram-positive pathogens (ORSA and VRE) were stable or increasing. Somewhat surprisingly, the proportions of *S. aureus* BSI and *Enterococcus* sp. BSI due to ORSA and VRE, respectively, declined over the past 5 to 10 years of the surveillance period. The decline in the proportion of ORSA that we report is consistent with other regional and national surveillance programs that observed reductions in ORSA infections, or in the proportion of *S. aureus* that are ORSA, 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

FIG 4 Twenty-year trend in percent extended-spectrum-β-lactamase (ESBL)-resistant and carbapenem-resistant *Enterobacteriaceae* (CRE) among selected *Enterobacteriaceae*, SENTRY, 1997 to 2016.

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

Organism/antimicrobial agent (no. tested)	MIC$_{50}$ (mg/liter)	MIC$_{90}$ (mg/liter)	CLSI[a] %S	%I	%R	EUCAST[a] %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
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
Acinetobacter baumannii-Acinetobacter 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			
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			

(Continued on next page)

TABLE 5 (Continued)

Organism/antimicrobial agent (no. tested)	MIC$_{50}$ (mg/liter)	MIC$_{90}$ (mg/liter)	CLSI[a]			EUCAST[a]		
			%S	%I	%R	%S	%I	%R
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. S, sensitive; I, intermediate; R, resistant.
[b]Breakpoints from FDA package insert (42).
[c]Dilution range did not extend far enough to determine whether the data represented intermediate or resistant status, so only the susceptible percentage is displayed.
[d]Intermediate data interpreted as susceptible-dose dependent.

recent report on overall *S. aureus* infections at all anatomic infection sites in the SENTRY Program (27). We also observed that the percentage of vancomycin resistance among enterococci stabilized and has 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 the rates of health care-associated infections (28). Finally, only one *S. aureus* BSI isolate with vancomycin resistance (MIC = 8 mg/liter) was detected across 2 decades of surveillance, and daptomycin resistance among indicated *S. aureus* and *Enterococcus* spp. (MIC, >1 mg/liter) has remained extremely uncommon.

In contrast to the resistance trends seen among Gram-positive pathogens, SENTRY surveillance revealed that detection of GNB is increasing as a proportion of all BSI causes and that the proportion of important GNB resistance phenotypes has increased over the past 2 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, e.g., CTX-M and KPC (14, 31, 32), have disseminated globally, rates of regional (and even local) variations in prevalence are 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 nonfermenters *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 in 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 robust and broadly representative samples from as many countries and regions as possible. Furthermore, regions of the world with limited resources for clinical laboratory support, e.g., Africa, are also underrepresented or not represented in this report. Finally, while we have investigated some of the trends noted, we do not present our molecular or sequencing data in this report.

Nonetheless, the duration and global scope of the SENTRY Program provide 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 between 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, the proportion of MDR GNB is increasing worldwide. Improved diagnostic, therapeutic, and preventive approaches are urgently needed for these pathogens. Ongoing global surveillance

remains important to help inform 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, IA, 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 United States 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 a "hospital-onset" episode.

Resistance phenotypes. VRE was defined on the basis of a vancomycin MIC of >4 mg/liter (nonsusceptible per CLSI and resistant per the 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. The ESBL phenotype was defined as *E. coli*, *P. mirabilis*, and *Klebsiella* spp. with an aztreonam, ceftazidime, or ceftriaxone MIC of ≥ 2 mg/liter. 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.

REFERENCES

1. McNamara JF, Righi E, Wright H, Hartel GF, Harris PNA, Paterson DL. 2018. Long-term morbidity and mortality following bloodstream infection: a systematic literature review. J Infect 77:1–8. https://doi.org/10.1016/j.jinf.2018.03.005.

2. Cosgrove SE, Sakoulas G, Perencevich EN, Schwaber MJ, Karchmer AW, Carmeli Y. 2003. Comparison of mortality associated with methicillin-resistant and methicillin-susceptible *Staphylococcus aureus* bacteremia: a meta-analysis. Clin Infect Dis 36:53–59. https://doi.org/10.1086/345476.

3. Edmond MB, Ober JF, Dawson JD, Weinbaum DL, Wenzel RP. 1996. Vancomycin-resistant enterococcal bacteremia: natural history and attributable mortality. Clin Infect Dis 23:1234–1239. https://doi.org/10.1093/clinids/23.6.1234.

4. Falagas ME, Tansarli GS, Karageorgopoulos DE, Vardakas KZ. 2014. Deaths attributable to carbapenem-resistant *Enterobacteriaceae* infec-

tions. Emerg Infect Dis 20:1170–1175. https://doi.org/10.3201/eid2007.121004.

5. Stewardson AJ, Allignol A, Beyersmann J, Graves N, Schumacher M, Meyer R, Tacconelli E, De Angelis G, Farina C, Pezzoli F, Bertrand X, Gbaguidi-Haore H, Edgeworth J, Tosas O, Martinez JA, Ayala-Blanco MP, Pan A, Zoncada A, Marwick CA, Nathwani D, Seifert H, Hos N, Hagel S, Pletz M, Harbarth S; TIMBER Study Group. 2016. The health and economic burden of bloodstream infections caused by antimicrobial-susceptible and non-susceptible Enterobacteriaceae and Staphylococcus aureus in European hospitals, 2010 and 2011: a multicentre retrospective cohort study. Euro Surveill 21(33):pii=30319. https://doi.org/10.2807/1560-7917.ES.2016.21.33.30319.

6. Diekema DJ, Pfaller MA, Jones RN, Doern GV, Kugler KC, Beach ML, Sader HS. 2000. Trends in antimicrobial susceptibility of bacterial pathogens isolated from patients with bloodstream infections in the USA, Canada

and Latin America. SENTRY Participants Group. Int J Antimicrob Agents 13:257–271. https://doi.org/10.1016/S0924-8579(99)00131-4.

7. Burton DC, Edwards JR, Horan TC, Jernigan JA, Fridkin SK. 2009. Methicillin-resistant *Staphylococcus aureus* central line-associated blood-stream infections in US intensive care units, 1997–2007. JAMA 301:727–736. https://doi.org/10.1001/jama.2009.153.

8. Gagliotti C, Balode A, Baquero F, Degener J, Grundmann H, Gur D, Jarlier V, Kahlmeter G, Monen J, Monnet DL, Rossolini GM, Suetens C, Weist K, Heuer O; EARS-Net Participants (Disease Specific Contact Points for AMR). 2011. 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 16(33):pii=19819. https://doi.org/10.2807/ese.16.11.19819-en.

9. Johnson AP, Davies J, Guy R, Abernethy J, Sheridan E, Pearson A, Duckworth G. 2012. Mandatory surveillance of methicillin-resistant *Staphylococcus aureus* (MRSA) bacteraemia in England: the first 10 years. J Antimicrob Chemother 67:802–809. https://doi.org/10.1093/jac/dkr561.

10. Laupland KB. 2013. Incidence of bloodstream infection: a review of population-based studies. Clin Microbiol Infect 19:492–500. https://doi.org/10.1111/1469-0691.12144.

11. Skogberg K, Lyytikainen O, Ollgren J, Nuorti JP, Ruutu P. 2012. Population-based burden of bloodstream infections in Finland. Clin Microbiol Infect 18:E170–E176. https://doi.org/10.1111/j.1469-0691.2012.03845.x.

12. Weiner LM, Webb AK, Limbago B, Dudeck MA, Patel J, Kallen AJ, Edwards JR, Sievert DM. 2016. 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 37:1288–1301. https://doi.org/10.1017/ice.2016.174.

13. Wilson J, Elgohari S, Livermore DM, Cookson B, Johnson A, Lamagni T, Chronias A, Sheridan E. 2011. Trends among pathogens reported as causing bacteraemia in England, 2004–2008. Clin Microbiol Infect 17:451–458. https://doi.org/10.1111/j.1469-0691.2010.03262.x.

14. Nicolas-Chanoine MH, Blanco J, Leflon-Guibout V, Demarty R, Alonso MP, Canica MM, Park YJ, Lavigne JP, Pitout J, Johnson JR. 2008. Intercontinental emergence of *Escherichia coli* clone O25:H4-ST131 producing CTX-M-15. J Antimicrob Chemother 61:273–281. https://doi.org/10.1093/jac/dkm464.

15. Knox J, Uhlemann AC, Lowy FD. 2015. *Staphylococcus aureus* infections: transmission within households and the community. Trends Microbiol 23:437–444. https://doi.org/10.1016/j.tim.2015.03.007.

16. Kallen AJ, Mu Y, Bulens S, Reingold A, Petit S, Gershman K, Ray SM, Harrison LH, Lynfield R, Dumyati G, Townes JM, Schaffner W, Patel PR, Fridkin SK. 2010. Health care-associated invasive MRSA infections, 2005–2008. JAMA 304:641–648. https://doi.org/10.1001/jama.2010.1115.

17. Klevens RM, Morrison MA, Nadle J, Petit S, Gershman K, Ray S, Harrison LH, Lynfield R, Dumyati G, Townes JM, Craig AS, Zell ER, Fosheim GE, McDougal LK, Carey RB, Fridkin SK. 2007. Invasive methicillin-resistant *Staphylococcus aureus* infections in the United States. JAMA 298:1763–1771. https://doi.org/10.1001/jama.298.15.1763.

18. Rosen JB, Thomas AR, Lexau CA, Reingold A, Hadler JL, Harrison LH, Bennett NM, Schaffner W, Farley MM, Beall BW, Moore MR; CDC Emerging Infections Program Network. 2011. Geographic variation in invasive pneumococcal disease following pneumococcal conjugate vaccine introduction in the United States. Clin Infect Dis 53:137–143. https://doi.org/10.1093/cid/cir326.

19. Giersing BK, Dastgheyb SS, Modjarrad K, Moorthy V. 2016. Status of vaccine research and development of vaccines for *Staphylococcus aureus*. Vaccine 34:2962–2966. https://doi.org/10.1016/j.vaccine.2016.03.110.

20. Huttner A, Hatz C, van den Dobbelsteen G, Abbanat D, Hornacek A, Frolich R, Dreyer AM, Martin P, Davies T, Fae K, van den Nieuwenhof I, Thoelen S, de Valliere S, Kuhn A, Bernasconi E, Viereck V, Kavvadias T, Kling K, Ryu G, Hulder T, Groger S, Scheiner D, Alaimo C, Harbarth S, Poolman J, Fonck VG. 2017. Safety, immunogenicity, and preliminary clinical efficacy of a vaccine against extraintestinal pathogenic *Escherichia coli* in women with a history of recurrent urinary tract infection: a randomised, single-blind, placebo-controlled phase 1b trial. Lancet Infect Dis 17:528–537. https://doi.org/10.1016/S1473-3099(17)30108-1.

21. Sader HS, Mendes RE, Streit JM, Flamm RK. 2017. Antimicrobial suscep-

tibility trends among Staphylococcus aureus from U.S. hospitals: results from 7 years of the ceftaroline (AWARE) surveillance program (2010–2016). Antimicrob Agents Chemother 61:e01043-17. https://doi.org/10.1128/AAC.01043-17.

22. Chambers HF, Deleo FR. 2009. Waves of resistance: *Staphylococcus aureus* in the antibiotic era. Nat Rev Microbiol 7:629–641. https://doi.org/10.1038/nrmicro2200.

23. Chatterjee SS, Otto M. 2013. Improved understanding of factors driving methicillin-resistant *Staphylococcus aureus* epidemic waves. Clin Epidemiol 5:205–217. https://doi.org/10.2147/CLEP.S37071.

24. Perencevich EN, Diekema DJ. 2010. Decline in invasive MRSA infection: where to go from here? JAMA 304:687–689. https://doi.org/10.1001/jama.2010.1125.

25. Planet PJ. 2017. Life after USA300: the rise and fall of a superbug. J Infect Dis 215:S71–S77. https://doi.org/10.1093/infdis/jiw444.

26. Rolain JM, Abat C, Brouqui P, Raoult D. 2015. Worldwide decrease in methicillin-resistant *Staphylococcus aureus*: do we understand something? Clin Microbiol Infect 21:515–517. https://doi.org/10.1016/j.cmi.2015.04.017.

27. Diekema DJ, Pfaller MA, Shortridge D, Zervos M, Jones RN. 2019. Twenty-year trends in antimicrobial susceptibilities among *Staphylococcus aureus* from the SENTRY Antimicrobial Surveillance Program. Open Forum Infect Dis 6:S47–S53. https://doi.org/10.1093/ofid/ofy270.

28. Magill SS, O'Leary E, Janelle SJ, Thompson DL, Dumyati G, Nadle J, Wilson LE, Kainer MA, Lynfield R, Greissman S, Ray SM, Beldavs Z, Gross C, Bamberg W, Sievers M, Concannon C, Buhr N, Warnke L, Maloney M, Ocampo V, Brooks J, Oyewumi T, Sharmin S, Richards K, Rainbow J, Samper M, Hancock EB, Leaptrot D, Scalise E, Badrun F, Phelps R, Edwards JR; Emerging Infections Program Hospital Prevalence Survey Team. 2018. Changes in prevalence of health care-associated infections in U.S. hospitals. N Engl J Med 379:1732–1744. https://doi.org/10.1056/NEJMoa1801550.

29. Castanheira M, Mendes RE, Jones RN, Sader HS. 2016. Changes in the frequencies of beta-lactamase genes among *Enterobacteriaceae* isolates in U.S. hospitals, 2012 to 2014: activity of ceftazidime-avibactam tested against beta-lactamase-producing isolates. Antimicrob Agents Chemother 60:4770–4777. https://doi.org/10.1128/AAC.00540-16.

30. McDanel J, Schweizer M, Crabb V, Nelson R, Samore M, Khader K, Blevins AE, Diekema D, Chiang HY, Nair R, Perencevich E. 2017. Incidence of extended-spectrum beta-lactamase (ESBL)-producing *Escherichia coli* and *Klebsiella* infections in the United States: a systematic literature review. Infect Control Hosp Epidemiol 38:1209–1215. https://doi.org/10.1017/ice.2017.156.

31. Jacob JT, Klein E, Laxminarayan R, Beldavs Z, Lynfield R, Kallen AJ, Ricks P, Edwards J, Srinivasan A, Fridkin S, Rasheed KJ, Lonsway D, Bulens S, Herrera R, McDonald LC, Patel J, Limbago B, Bell M, Cardo D. 2013. Vital signs: carbapenem-resistant *Enterobacteriaceae*. MMWR Morb Mortal Wkly Rep 62:165–170.

32. Tangden T, Giske CG. 2015. Global dissemination of extensively drug-resistant carbapenemase-producing *Enterobacteriaceae*: clinical perspectives on detection, treatment and infection control. J Intern Med 277:501–512. https://doi.org/10.1111/joim.12342.

33. van Duin D, Doi Y. 2017. The global epidemiology of carbapenemase-producing *Enterobacteriaceae*. Virulence 8:460–469. https://doi.org/10.1080/21505594.2016.1222343.

34. Ray MJ, Lin MY, Tang AS, Arwady MA, Lavin MA, Runningdeer E, Jovanov D, Trick WE. 2018. Regional spread of an outbreak of carbapenem-resistant *Enterobacteriaceae* through an ego network of healthcare facilities. Clin Infect Dis 67:407–410. https://doi.org/10.1093/cid/ciy084.

35. Slayton RB, Toth D, Lee BY, Tanner W, Bartsch SM, Khader K, Wong K, Brown K, McKinnell JA, Ray W, Miller LG, Rubin M, Kim DS, Adler F, Cao C, Avery L, Stone NT, Kallen A, Samore M, Huang SS, Fridkin S, Jernigan JA. 2015. Vital signs: estimated effects of a coordinated approach for action to reduce antibiotic-resistant infections in health care facilities - United States. MMWR Morb Mortal Wkly Rep 64:826–831. https://doi.org/10.15585/mmwr.mm6430a4.

36. Magiorakos AP, Srinivasan A, Carey RB, Carmeli Y, Falagas ME, Giske CG, Harbarth S, Hindler JF, Kahlmeter G, Olsson-Liljequist B, Paterson DL, Rice LB, Stelling J, Struelens MJ, Vatopoulos A, Weber JT, Monnet DL. 2012. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. Clin Microbiol Infect 18:268–281. https://doi.org/10.1111/j.1469-0691.2011.03570.x.

37. Isler B, Doi Y, Bonomo RA, Paterson DL. 2019. New treatment options

against carbapenem-resistant Acinetobacter baumannii infections. Antimicrob Agents Chemother 63:e01110.

38. Perez F, Hujer AM, Hujer KM, Decker BK, Rather PN, Bonomo RA. 2007. Global challenge of multidrug-resistant *Acinetobacter baumannii*. Antimicrob Agents Chemother 51:3471–3484. https://doi.org/10.1128/AAC .01464-06.

39. CLSI. 2018. M07Ed11E. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; approved standard: 11th ed. Clinical and Laboratory Standards Institute, Wayne, PA.

40. CLSI. 2017. M100-S27. Performance standards for antimicrobial susceptibility testing: 27th informational supplement. Clinical and Laboratory Standards Institute, Wayne, PA.

41. EUCAST. 2017. Breakpoint tables for interpretation of MIC's and zone diameters. Version 7.1, March 2017. http://www.eucast.org/fileadmin/ src/media/PDFs/EUCAST_files/Breakpoint_tables/v_7.1_Breakpoint _Tables.pdf. Accessed March 2017.

42. EUCAST. 2018. Package insert, Allergan USA, Inc. https://www.allergan .com/assets/pdf/dalvance_pi. Accessed 22 August 2018.