Ceftaroline Activity against Bacterial Pathogens Frequently Isolated in U.S. Medical Centers: Results from Five Years of the AWARE Surveillance Program

Helio S. Sader, Robert K. Flamm, Jennifer M. Streit, David J. Farrell, Ronald N. Jones

JMI Laboratories, North Liberty, Iowa, USA

A total of 84,704 isolates were collected from 191 medical centers in 2009 to 2013 and tested for susceptibility to ceftaroline and comparator agents by broth microdilution methods. Ceftaroline inhibited all *Staphylococcus aureus* isolates at ≤ 2 $\mu\text{g/ml}$ and was very active against methicillin-resistant strains (MIC at which 90% of the isolates tested are inhibited [MIC₉₀], 1 $\mu\text{g/ml}$; 97.6% susceptible). Among *Streptococcus pneumoniae* isolates, the highest ceftaroline MIC was 0.5 $\mu\text{g/ml}$, and ceftaroline activity against the most common *Enterobacteriaceae* species (MIC₅₀, 0.12 $\mu\text{g/ml}$; 78.9% susceptible) was similar to that of ceftriaxone (MIC₅₀, ≤ 0.25 $\mu\text{g/ml}$; 86.8% susceptible).

Ceftaroline fosamil (Teflaro), the prodrug of ceftaroline, was approved in 2010 by the U.S. Food and Drug Administration (FDA) for the treatment of acute bacterial skin and skin structure infections (ABSSSI) due to susceptible isolates of *Staphylococcus aureus* (including methicillin-susceptible [MSSA] and -resistant [MRSA] isolates), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Klebsiella oxytoca*. Ceftaroline fosamil was also approved for community-acquired bacterial pneumonia (CABP) due to *Streptococcus pneumoniae* (including cases with concurrent bacteremia), *S. aureus* (MSSA only), *Haemophilus influenzae*, *K. pneumoniae*, *K. oxytoca*, and *E. coli* (1–3).

An antimicrobial resistance surveillance program, known as the Assessing Worldwide Antimicrobial Resistance and Evaluation (AWARE) Program, was designed to monitor the activity of ceftaroline and comparator agents (4). This program provides contemporary and longitudinal information on the activity of this agent against relevant pathogens. Previous reports from the AWARE program have provided analyses of ceftaroline activity against bacterial isolates recovered from indicated sites of infections (ABSSSI and CAPB) during the initial years of the program (5, 6) as well as resistant subsets of organisms from indicated species (4, 7, 8). In this report, we summarized the results of 5 years (2009 to 2013) of the AWARE Program in the United States.

A total of 84,704 bacterial isolates were collected from clinical infections, as defined by local clinical criteria. The isolates were collected from January 2009 to December 2013 from 191 medical centers distributed across all nine U.S. census regions, and target numbers of strains for each of the requested bacterial species/genus were predetermined by study protocol. Only isolates deemed clinically relevant by the submitting laboratory were included in the investigation. If multiple isolates of the same organism (species) were collected multiple times during the same infection episode, the investigator was instructed to provide only the first isolate. The isolates were from skin and skin structure infections (27,395; 32.3%), respiratory tract infections (23,931; 28.3%), bloodstream infections (17,685; 20.9%), urinary tract infections (7,814; 9.2%), intra-abdominal infections (1,521; 1.8%), and infections at other sites (6,358; 7.5%). Isolates were sent to the

coordinator laboratory (JMI Laboratories, North Liberty, IA, USA) for reference susceptibility testing. Only one strain per patient infection episode was included in the surveillance.

Isolates were tested for susceptibility to ceftaroline and multiple comparator agents by reference broth microdilution methods as described by Clinical and Laboratory Standards Institute (CLSI) standard M07-A9 (9), and CLSI interpretations were based on M100-S24 and M45-A2 breakpoints (9, 10). Ceftaroline and comparator agents were tested simultaneously using the same bacterial inoculum and testing reagents. Isolates with positive extended-spectrum β -lactamase (ESBL) screening test results, i.e., MICs of >1 $\mu\text{g/ml}$ for ceftazidime and/or ceftriaxone and/or aztreonam, were categorized as “ESBL phenotype” for the purpose of susceptibility testing result analysis. Although other β -lactamases, such as AmpC and KPC, may also produce an ESBL phenotype, these strains were grouped together because they usually demonstrate resistance to various broad-spectrum β -lactam compounds (10). *K. pneumoniae* isolates with MICs of >1 $\mu\text{g/ml}$ for meropenem or imipenem isolated in 2009, 2010, 2012, and 2013 (all years except 2011) were screened for *bla*_{KPC} by PCR as previously described (11, 12). Streptococcal isolates were tested in Mueller-Hinton broth supplemented with 2.5 to 5% lysed horse blood, and *Haemophilus* species isolates were tested in *Haemophilus* test medium (HTM), whereas all other organisms were tested in cation-adjusted Mueller-Hinton broth. Concurrent testing of quality control (QC) strains ensured proper test conditions.

Received 23 October 2014 Returned for modification 6 January 2015
Accepted 25 January 2015

Accepted manuscript posted online 2 February 2015

Citation Sader HS, Flamm RK, Streit JM, Farrell DJ, Jones RN. 2015. Ceftaroline activity against bacterial pathogens frequently isolated in U.S. medical centers: results from five years of the AWARE surveillance program. Antimicrob Agents Chemother 59:2458–2461. doi:10.1128/AAC.04614-14.

Address correspondence to Helio S. Sader, helio-sader@jmlabs.com.

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doi:10.1128/AAC.04614-14

Staphylococcus aureus and coagulase-negative staphylococci (CoNS) were particularly susceptible to ceftaroline, with MICs at which 90% of the isolates tested were inhibited (MIC₉₀s) of 1 and 0.5 µg/ml, respectively. Ceftaroline inhibited 98.8% of *S. aureus* strains at the susceptible breakpoint of ≤1 µg/ml (Table 1). Rates of susceptibility to levofloxacin and clindamycin were 60.2 and 71.1%, respectively, according to CLSI breakpoints. Rates of susceptibility to daptomycin, linezolid, tigecycline, and vancomycin were >99.9% (data not shown).

The overall methicillin-resistant *S. aureus* (MRSA) rate was 49.7%, varying from a low of 46.0% in 2009 to a high of 50.5% in 2010, with no trend toward increase or decrease during the study period (Table 2). Overall, 97.6% of MRSA isolates (12,514 strains tested) were susceptible to ceftaroline (MIC_{50/90}, 0.5/1 µg/ml; highest MIC, 2 µg/ml [Table 1]). When tested against MSSA, ceftaroline (MIC₅₀ and MIC₉₀, 0.25 µg/ml [Table 1]) was 16-fold more potent than ceftriaxone (MIC₅₀ and MIC₉₀, 4 µg/ml [data not shown]).

Ceftaroline (MIC_{50/90}, ≤0.015/0.12 µg/ml) inhibited all (100.0%) 10,096 *S. pneumoniae* strains at the MIC of ≤0.5 µg/ml, which is the susceptible breakpoint established by the CLSI and U.S. FDA (3, 10), and showed potent activity against ceftriaxone-nonsusceptible (MIC, ≥2 µg/ml) strains (*n* = 952; ceftaroline MIC₅₀ and MIC₉₀, 0.25 µg/ml). When tested against penicillin-resistant (MIC, ≥8 µg/ml) strains (*n* = 117), ceftaroline (MIC_{50/90}, 0.25/0.5 µg/ml [Table 1]) was 8- to 16-fold more potent than ceftriaxone (MIC_{50/90}, 2/8 µg/ml [data not shown]). The overall rate of ceftriaxone-nonsusceptible *S. pneumoniae* was 9.4% and decreased gradually during the study period from 12.7% in 2009 to 6.5% in 2013 (Table 2). Penicillin-nonsusceptible *S. pneumoniae* rates showed a similar trend toward lower rates, varying from 16.0% in 2009 to 7.2% in 2013 (Table 2).

Ceftaroline demonstrated potent activity against beta-hemolytic streptococci (MIC₅₀ and MIC₉₀, ≤0.015 µg/ml; highest MIC, 0.12 µg/ml; 100.0% susceptible) and viridans group streptococci (MIC_{50/90}, 0.03/0.06 µg/ml; highest MIC, 1 µg/ml) but exhibited limited activity against *Enterococcus faecalis* (MIC_{50/90}, 2/8 µg/ml [Table 1]).

Ceftaroline activity against *Enterobacteriaceae* strains (*n* = 25,139; MIC_{50/90}, 0.12/>32 µg/ml; 78.9% susceptible [Tables 1 and 2]) was similar to those of ceftriaxone (MIC_{50/90}, ≤0.25/8 µg/ml; 86.8% susceptible [data not shown]) and ceftazidime (MIC_{50/90}, 0.12/8 µg/ml; 89.7% susceptible [data not shown]). Non-ESBL-phenotype strains were generally susceptible to ceftaroline (MIC_{50/90}, 0.12/0.25 to 0.5 µg/ml; 95.2 to 97.1% susceptible), whereas ESBL screen-positive strains exhibited elevated ceftaroline MIC values (MIC₅₀, >16 µg/ml [Table 1]). The prevalence of ceftriaxone-nonsusceptible *Enterobacteriaceae* increased from 10.9 to 11.5% in 2009 to 2010 to 13.4 to 14.0% in 2011 to 2013 (Table 2).

ESBL phenotypes were observed in 11.8% of *E. coli* and 15.7% of *K. pneumoniae* isolates overall. Among *E. coli* isolates, the ESBL phenotype rate increased from 9.9% in 2009 to 11.9% in 2010 but showed only minor variations (11.9 to 12.3%) in the following 4 years (2010 to 2013 [Table 2]). In contrast, ESBL phenotype rates increased from 14.5% in 2009 to 17.0% in 2013 among *K. pneumoniae* isolates (Table 2), and all cephalosporins showed limited activity against ESBL-phenotype strains (data not shown).

Among 284 carbapenem-nonsusceptible *K. pneumoniae* iso-

lates screened for *bla*_{KPC}, 266 (93.4%) were positive, and the number of medical centers with KPC-producing strains increased from 9 and 12 in 2009 and 2010, respectively, to 25 and 23 in 2012 and 2013, respectively. Thus, these results indicate that the yearly increase of *K. pneumoniae* with ESBL phenotype and the corresponding increase of meropenem-nonsusceptible strains were mainly due to the dissemination of KPC-producing strains in some geographic regions (Table 2) (11, 12).

Ceftaroline inhibited all (100.0%) *H. influenzae* strains (*n* = 3,906) at MICs of 0.5 µg/ml or less (Table 1). Overall, 25.2% of *H. influenzae* strains were β-lactamase producers, with rates varying from a low of 23.3% in 2012 to a high of 27.8% in 2010 and no trend toward increase or decrease during the study period (Table 2). Ceftaroline was also active against *Haemophilus parainfluenzae* (MIC_{50/90}, ≤0.015/0.03 µg/ml) and *Moraxella catarrhalis* (MIC_{50/90}, 0.06/0.12 µg/ml) strains, independent of β-lactamase production (Table 1).

Ceftaroline represents a new class of cephalosporin with anti-MRSA activity. Favorable features of ceftaroline include avid binding to penicillin-binding proteins 2a and 2x of MRSA and penicillin-resistant *S. pneumoniae*, respectively, and lack of antagonism with other agents used in combination (4, 13, 14). Numerous published studies confirm the potent activity of ceftaroline against *S. aureus* and *S. pneumoniae*, including multi-drug-resistant strains, such as *S. aureus* with decreased susceptibility to linezolid, daptomycin, or vancomycin and emerging *S. pneumoniae* serotypes 19A, 35B, and 6C (7, 8, 15). The data presented here provide further documentation of the excellent activity of ceftaroline when tested against significant collections of contemporary U.S. isolates. We evaluated ceftaroline activity against 25,192 *S. aureus* and 10,096 *S. pneumoniae* contemporary clinical isolates collected from 191 U.S. medical centers distributed throughout all nine census regions, and ceftaroline was active against 98.8% of *S. aureus* and all (100.0%) of the *S. pneumoniae* isolates at the respective susceptible breakpoints. It is important to note that all ceftaroline-nonsusceptible *S. aureus* (all MRSA) isolates exhibited ceftaroline MIC values only 1 doubling dilution higher than the susceptible breakpoint (i.e., 2 µg/ml, intermediate), and no ceftaroline-resistant *S. aureus* isolate was detected during these 5 years of surveillance in the United States. Furthermore, Monte Carlo simulations using ceftaroline pharmacokinetic and pharmacodynamic properties have indicated that target attainment rates (stasis or 1 log₁₀ CFU/g bacterial cell kill) remained >95% up to an MIC of 2 µg/ml, suggesting clinical efficacy in treating ABSSSI against strains up to this MIC (16).

Ceftaroline also demonstrated potent and consistent (2009 to 2013) *in vitro* activity against large collections of beta-hemolytic streptococci (*n* = 5,679; MIC₉₀, ≤0.015 µg/ml), viridans group streptococci (*n* = 2,332; MIC₉₀, 0.06 µg/ml), coagulase-negative staphylococci (CoNS) (*n* = 3,379; MIC₉₀, 0.5 µg/ml), *H. influenzae* (*n* = 3,906; MIC₉₀, 0.03 µg/ml), *M. catarrhalis* (*n* = 1,511; MIC₉₀, 0.12 µg/ml), and non-ESBL-phenotype strains of *Enterobacteriaceae* (*n* = 15,151; MIC₉₀, 0.25 to 0.5 µg/ml). These results are similar to those of previous publications and indicate that ceftaroline *in vitro* activity against key bacterial species remained stable since its approval for clinical use in the United States in 2010 (17). These results, coupled with the documented efficacy of ceftaroline fosamil in the treatment of serious infections (1, 2, 18), make this agent particularly attractive in the initial

TABLE 1 Summary of cefaroline activity tested against 84,704 bacterial isolates from U.S. medical centers (2009 to 2013)

Organism ^a	Total no. of isolates	No. of isolates (cumulative %) inhibited at ceftriaxone MIC (μg/ml) of:											MIC ₅₀	MIC ₉₀	
		≤0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16			>16
<i>Staphylococcus aureus</i>	25,192	4 (0.0)	9 (0.1)	64 (0.3)	1,193 (5.0)	11,035 (48.8)	6,931 (76.4)	5,656 (98.8)	300 (100.0)					0.5	1
MSSA	12,678	4 (0.0)	9 (0.1)	64 (0.6)	1,183 (9.9)	10,832 (95.4)	583 (>99.9)	3 (100.0)						0.25	0.25
MRSA	12,514				10 (0.1)	203 (1.7)	6,348 (52.4)	5,653 (97.6)	300 (100.0)					0.5	1
Coagulase- negative staphylococci	3,379	32 (0.9)	90 (3.6)	683 (23.8)	513 (39.0)	1,184 (74.0)	788 (97.4)	79 (99.7)	10 (100.0)					0.25	0.5
<i>Streptococcus pneumoniae</i>	10,096	6,186 (61.3)	902 (70.2)	916 (79.3)	1,441 (93.6)	573 (99.2)	78 (100.0)							≤0.015	0.12
Penicillin S (MIC, ≤2 μg/ml)	8,937	6,186 (69.2)	902 (79.3)	907 (89.5)	907 (99.6)	33 (>99.9)	2 (100.0)							≤0.015	0.12
Penicillin I (MIC, 4 μg/ml)	1,042			8 (0.8)	531 (51.7)	467 (96.5)	36 (100.0)							0.12	0.25
Penicillin R (MIC, ≥8 μg/ml)	117			1 (0.9)	3 (3.4)	73 (65.8)	40 (100.0)							0.25	0.5
Ceftriaxone non-S (MIC, ≥2 μg/ml)	952	1 (0.1)	3 (0.4)	5 (0.8)	365 (39.3)	501 (91.9)	77 (100.0)							0.25	0.25
Viridans group streptococci	2,332	1,136 (48.7)	747 (80.7)	250 (91.5)	91 (95.4)	49 (97.5)	43 (99.3)	16 (100.0)						0.03	0.06
Beta-hemolytic streptococci	5,679	5,162 (90.9)	497 (99.6)	19 (>99.9)	1 (100.0)									≤0.015	≤0.015
<i>Streptococcus pyogenes</i>	2,166	2,155 (99.5)	8 (99.9)	2 (100.0)	1 (100.0)									≤0.015	≤0.015
<i>Streptococcus agalactiae</i>	2,873	2,465 (85.8)	405 (99.9)	3 (100.0)										0.03	0.03
<i>Enterococcus faecalis</i>	2,315				3 (0.1)	12 (0.6)	49 (2.8)	582 (27.9)	1,092 (75.1)	229 (85.0)	305 (98.1)	31 (99.5)	12 (100.0)	2	8
<i>Enterobacteriaceae</i>	25,139	139 (0.6)	1,251 (5.5)	6,443 (31.2)	6,578 (57.3)	3,259 (70.3)	2,161 (78.9)	1,294 (84.0)	453 (85.8)	301 (87.0)	273 (88.1)	303 (89.3)	2,684 (100.0)	0.12	>16
<i>Escherichia coli</i>	8,287	76 (0.9)	744 (9.9)	2,645 (41.8)	2,164 (67.9)	902 (78.8)	480 (84.6)	223 (87.3)	86 (88.3)	55 (89.0)	60 (89.7)	58 (90.4)	794 (100.0)	0.12	16
Non-ESBL phenotype	7,306	76 (1.0)	744 (11.2)	2,643 (47.4)	2,151 (76.8)	882 (88.9)	461 (95.2)	212 (98.1)	72 (99.1)	35 (99.6)	16 (99.8)	10 (99.9)	4 (100.0)	0.12	0.5
ESBL phenotype	981			2 (0.2)	13 (1.5)	90 (3.6)	11 (5.5)	11 (6.6)	14 (8.1)	20 (10.1)	44 (14.6)	48 (19.5)	790 (100.0)	>16	>16
<i>Klebsiella</i> spp.	7,381	34 (0.5)	263 (4.0)	2,198 (33.8)	2,110 (62.4)	963 (75.4)	514 (82.4)	207 (85.2)	60 (86.0)	55 (87.6)	51 (88.3)	51 (88.3)	866 (100.0)	0.12	>16
Non-ESBL phenotype	6,298	34 (0.5)	263 (4.7)	2,197 (39.6)	2,107 (73.1)	962 (88.3)	508 (96.4)	187 (99.4)	21 (99.7)	10 (99.9)	3 (99.9)	3 (100.0)	3 (100.0)	0.12	0.5
ESBL phenotype	1,083			1 (0.1)	3 (0.4)	1 (0.5)	6 (1.0)	20 (2.9)	39 (6.5)	50 (11.1)	52 (15.9)	48 (20.3)	863 (100.0)	>16	>16
<i>Klebsiella pneumoniae</i>	5,833	31 (0.5)	220 (4.3)	1,952 (37.8)	1,689 (66.7)	536 (75.9)	320 (81.4)	162 (84.2)	53 (85.1)	51 (86.0)	47 (86.8)	36 (87.4)	736 (100.0)	0.12	>16
<i>Klebsiella oxytoca</i>	1,548	3 (0.2)	43 (3.0)	246 (18.9)	421 (46.1)	427 (73.6)	194 (86.2)	45 (89.1)	7 (89.5)	9 (90.1)	8 (90.6)	15 (91.6)	130 (100.0)	0.25	4
<i>Proteus mirabilis</i>	1,883	2 (0.1)	35 (2.0)	650 (36.5)	771 (77.4)	184 (87.2)	97 (92.4)	37 (94.3)	17 (95.2)	8 (95.6)	4 (95.9)	14 (96.6)	64 (100.0)	0.12	0.5
Non-ESBL phenotype	1,547	2 (0.1)	29 (2.0)	584 (39.8)	649 (81.7)	161 (92.1)	77 (97.1)	29 (99.0)	13 (99.8)	1 (99.9)	1 (100.0)	1 (100.0)	1 (100.0)	0.12	0.25
ESBL phenotype	80													>16	>16
<i>Enterobacter cloacae</i>	2,465	12 (0.5)	35 (1.9)	112 (6.5)	622 (31.7)	695 (99.9)	309 (72.4)	95 (76.3)	39 (77.8)	25 (78.9)	33 (80.2)	13 (26.3)	59 (100.0)	>16	>16
<i>Enterobacter aerogenes</i>	894	3 (0.3)	21 (2.7)	309 (37.2)	268 (67.2)	58 (73.7)	32 (77.3)	17 (79.2)	11 (80.4)	11 (81.7)	9 (82.7)	22 (85.1)	133 (100.0)	0.12	>16
<i>Morganella morganii</i>	911	8 (0.9)	74 (9.0)	253 (36.8)	182 (56.8)	74 (64.9)	57 (71.1)	26 (74.0)	24 (76.6)	22 (79.0)	23 (81.6)	23 (84.1)	145 (100.0)	0.12	>16
<i>Citrobacter koseri</i>	514	3 (0.6)	7 (1.9)	156 (32.3)	251 (81.1)	31 (87.2)	41 (95.1)	13 (97.7)	2 (98.1)	2 (98.4)	1 (98.6)	1 (98.8)	6 (100.0)	0.12	0.5
<i>Citrobacter freundii</i>	574		1 (0.2)	11 (2.1)	146 (27.5)	211 (64.3)	61 (74.9)	9 (76.5)	4 (77.2)	5 (78.0)	6 (79.1)	18 (82.2)	102 (100.0)	0.25	>16
<i>Serratia marcescens</i>	1,378	3 (0.4)	1 (0.1)	1 (0.1)	3 (0.4)	71 (5.5)	467 (39.4)	541 (78.7)	134 (88.4)	47 (91.8)	45 (95.1)	24 (96.8)	44 (100.0)	1	4
<i>Proteus vulgaris</i>	305	3 (1.0)	7 (3.3)	7 (3.3)	8 (5.9)	41 (19.3)	50 (35.7)	53 (53.1)	30 (63.0)	25 (71.1)	14 (75.7)	17 (81.3)	57 (100.0)	1	>16
<i>Providencia</i> spp.	547	1 (0.2)	67 (12.4)	101 (30.9)	53 (40.6)	29 (45.9)	53 (55.6)	73 (68.9)	46 (77.3)	41 (84.8)	23 (89.0)	23 (93.2)	37 (100.0)	0.5	16
<i>Pseudomonas aeruginosa</i>	4,115					4 (0.1)	19 (0.6)	46 (1.7)	104 (4.2)	260 (10.5)	781 (29.5)	1,150 (57.4)	1,751 (100.0)	16	>16
<i>Acinetobacter baumannii</i>	632						3 (0.5)	19 (3.5)	72 (14.9)	86 (28.5)	63 (38.4)	17 (41.1)	372 (100.0)	>16	>16
<i>Haemophilus influenzae</i>	3,906	3,403 (87.1)	386 (97.0)	87 (99.2)	22 (99.8)	6 (99.9)	2 (100.0)							≤0.015	0.03
β-Lactamase negative	2,921	2,701 (92.5)	202 (99.4)	16 (99.9)	2 (100.0)									≤0.015	≤0.015
β-Lactamase positive	985	702 (71.3)	184 (89.9)	71 (97.2)	20 (99.2)	6 (99.8)	2 (100.0)							≤0.015	0.06
<i>Haemophilus parainfluenzae</i>	408	354 (86.8)	29 (93.9)	10 (96.3)	8 (98.3)	2 (98.8)	3 (99.5)	1 (99.8)	1 (100.0)					≤0.015	0.03
<i>Moraxella catarrhalis</i>	1,511	185 (12.2)	379 (37.3)	481 (69.2)	354 (92.6)	100 (99.2)	10 (99.9)	2 (100.0)						0.06	0.12

^a Abbreviations: S, susceptible; I, intermediate; R, resistant; ESBL, extended-spectrum β-lactamase.

TABLE 2 Yearly frequency of selected resistance phenotypes

Resistance phenotype	Frequency (%)					
	2009	2010	2011	2012	2013	Overall
MRSA	46.0	50.5	49.7	47.3	49.9	49.7
Ceftaroline-NS ^a <i>S. aureus</i>	1.6	0.8	1.2	1.3	1.3	1.2
Ceftriaxone-NS <i>S. pneumoniae</i> (MIC, ≥ 2 μ g/ml)	12.7	10.6	11.6	9.2	6.5	9.4
Penicillin-NS <i>S. pneumoniae</i> (MIC, ≥ 4 μ g/ml)	16.0	14.6	14.8	10.2	7.2	11.5
Ceftriaxone-NS <i>Enterobacteriaceae</i>	10.9	11.5	14.0	13.8	13.4	13.2
ESBL-phenotype <i>E. coli</i>	9.9	11.9	12.1	11.9	12.3	11.8
ESBL-phenotype <i>K. pneumoniae</i>	14.5	12.3	15.5	16.0	17.0	15.7
Meropenem-NS <i>K. pneumoniae</i>	5.4	4.1	5.1	6.2	6.8	5.9
β -Lactamase-positive <i>H. influenzae</i>	23.7	27.8	27.0	23.3	23.8	25.2

^a NS, nonsusceptible.

management of CABP and ABSSI patients requiring hospitalization.

ACKNOWLEDGMENTS

This study performed at JMI Laboratories was supported in part by an Educational/Research Grant from Forest/Cerexa, and JMI Laboratories received compensation fees for services in relation to preparing the manuscript, which was funded by the sponsor.

We thank all AWARE participants for providing bacterial isolates for this surveillance program.

This study was supported by Cerexa, Inc., a wholly owned subsidiary of Forest Laboratories, Inc. Forest Laboratories, Inc., was involved in the design and decision to present these results. Forest Laboratories, Inc., had no involvement in the collection, analysis, and interpretation of data. JMI Laboratories, Inc., has also received research and educational grants in 2012 to 2014 from Achaogen, Actelion, Affinium, American Proficiency Institute (API), AmpliPhi Bio, Anacor, Astellas, AstraZeneca, Basilea, BioVersys, Cardeas, Cempra, Cubist, Daiichi, Dipexium, Durata, Fedora, Furiex, Genentech, GlaxoSmithKline, Janssen, Johnson & Johnson, Medpace, Meiji Seika Kaisha, Melinta, Merck, Methylgene, Nabriva, Nanosphere, Novartis, Pfizer, Polyphor, Rempex, Roche, Seachaid, Shionogi, Synthes, The Medicines Co., Theravance, ThermoFisher, Venatorx, Vertex, and Waterloo. Some JMI employees are advisors/consultants for Astellas, Cubist, Pfizer, Cempra, Cerexa-Forest, and Theravance. In regards to speakers bureaus and stock options, there are none to declare.

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