Ceftobiprole Activity against Gram-Positive and -Negative Pathogens Collected from the United States in 2006 and 2016

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ABSTRACT Ceftobiprole is an advanced cephalosporin with potent activity against Gram-positive and Gram-negative bacteria that has been approved in many European and non-European countries to treat community- and hospital-acquired pneumonia (excluding ventilator-associated pneumonia). This study reports on the activity of ceftobiprole against a large set of clinical isolates obtained from hospitalized patients in the United States in 2016 that caused serious infections, including pneumonia, bacteremia, and skin and skin structure infections. To assess any potential temporal changes in ceftobiprole activity, the 2016 results were compared to corresponding MIC data from a 2006 U.S. survey that included key target pathogens. Ceftobiprole exhibited potent activity against *Staphylococcus aureus* (including methicillin-resistant *S. aureus* isolates, which were 99.3% susceptible), coagulase-negative staphylococci (100% susceptible), *Enterococcus faecalis* (100% susceptible), *Streptococcus pneumoniae* (99.7% susceptible), and other tested streptococci. Similarly, ceftobiprole was highly active against *Enterobacteriaceae* isolates that did not exhibit an extended-spectrum β -lactamase (ESBL) phenotype, including *Escherichia coli* (99.8% susceptible) and *Klebsiella pneumoniae* (99.6% susceptible). A total of 99.6% of all *Haemophilus influenzae* and *Moraxella catarrhalis* isolates were inhibited at ≤ 1 mg/liter ceftobiprole, and 72.7% of the *Pseudomonas aeruginosa* isolates were susceptible to ceftobiprole. With the exception of decreased cephalosporin susceptibility among *Enterobacteriaceae* isolates, which correlates with an increased prevalence of ESBL-producing isolates, ceftobiprole had similar activities against the isolate sets collected in 2006 and 2016. Therefore, ceftobiprole remains highly active when tested *in vitro* against a large number of current Gram-positive or Gram-negative pathogens that cause serious infections.

KEYWORDS longitudinal, MRSA, surveillance, United States, ceftobiprole, cephalosporin

Ceftobiprole (formerly BAL9141, BAL5788, and RO-63-9141) is an expanded-spectrum parenteral cephalosporin with potent activity against Gram-positive and Gram-negative bacteria (1–3) that has been approved in 17 European countries and 5 non-European countries (Argentina, Canada, Jordan, Peru, and Saudi Arabia) for the treatment of hospital-acquired pneumonia (excluding ventilator-associated pneumonia) and community-acquired pneumonia in adults (4–8). Several features of ceftobiprole make it an attractive therapeutic candidate (5, 6, 9). Unlike most β -lactams, ceftobiprole binds strongly to and maintains excellent activity against the enzyme PBP2A, which confers methicillin (oxacillin) resistance in *Staphylococcus aureus* and coagulase-negative staphylococcal (CoNS) strains (9, 10). Ceftobiprole also exhibits *in vitro* bactericidal activity against methicillin-resistant *S. aureus* (MRSA) strains, with

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kinetics similar to or superior to those of vancomycin and linezolid (11, 12), and displays broad-spectrum *in vitro* antimicrobial activity that is similar to that of ceftipime when tested against *Enterobacteriaceae* and *Pseudomonas aeruginosa* clinical isolates (1–3, 9). Finally, resistance to ceftobiprole develops slowly *in vitro* (9, 12, 13).

Ceftobiprole was recently designated a qualified infectious disease product by the U.S. Food and Drug Administration (FDA) and is undergoing further clinical development to support regulatory filings in the United States. The aim of this study was to examine ceftobiprole susceptibility profiles and antibiograms for 12,001 clinical isolates collected from medical centers in the United States in 2016 as part of the SENTRY Antimicrobial Surveillance Program. In addition, this study compares the results from 2016 to corresponding data generated in 2006.

RESULTS

Activities of ceftobiprole and comparators against Gram-positive bacteria.

Ceftobiprole exhibited potent antimicrobial activity when tested against the full set of 2,930 *S. aureus* isolates (MIC₅₀, 0.5 mg/liter; MIC₉₀, 2 mg/liter; 99.7% susceptible at the EUCAST breakpoint of ≤ 2 mg/liter) (Table 1; also see Table S1 in the supplemental material). Ceftobiprole (MIC₅₀, 0.5 mg/liter; MIC₉₀, 0.5 mg/liter) and ceftaroline (MIC₅₀, 0.25 mg/liter; MIC₉₀, 0.25 mg/liter) were the most potent cephalosporins tested against the methicillin-susceptible *S. aureus* (MSSA) isolate subset and were 8- to 16-fold more potent than ceftriaxone (Table S2). All MSSA isolates were susceptible to ceftobiprole, ceftaroline, ceftriaxone, daptomycin, linezolid, tigecycline, and vancomycin at their respective breakpoints (Table S2).

The overall MRSA rate was 43.0% (Table 1). Ceftobiprole (MIC₅₀, 1 mg/liter; MIC₉₀, 2 mg/liter) and ceftaroline (MIC₅₀, 0.5 mg/liter; MIC₉₀, 1 mg/liter) were similarly potent against MRSA isolates (Table 1). Ceftobiprole was 2-fold less potent than linezolid and vancomycin and 4-fold less potent than daptomycin against MRSA isolates, according to MIC₉₀ values. The MRSA isolates also exhibited high levels of resistance against levofloxacin (69.3% resistant). More than 92.8% of MRSA isolates were susceptible to ceftobiprole, ceftaroline, daptomycin, linezolid, tetracycline, tigecycline, trimethoprim-sulfamethoxazole, and vancomycin at their respective breakpoints (Table 1).

The greatest coverage against the full *S. aureus* isolate set was provided by vancomycin, linezolid, and tigecycline (all 100.0% susceptible), daptomycin ($>99.9\%$ susceptible), ceftobiprole (99.7% susceptible), ceftaroline (98.5% susceptible), and trimethoprim-sulfamethoxazole (97.9% susceptible) (Table 1). All isolates were inhibited by ceftobiprole at ≤ 4 mg/liter.

The 439 tested coNS isolates were 100% susceptible to ceftobiprole, using the EUCAST non-species-related breakpoint (14); this isolate set exhibited MIC₅₀ and MIC₉₀ values of 0.5 mg/liter and 1 mg/liter, respectively (Table 1). Ceftaroline (MIC₅₀, ≤ 0.06 mg/liter; MIC₉₀, 0.25 mg/liter) and ceftobiprole (MIC₅₀, 0.12 mg/liter; MIC₉₀, 0.5 mg/liter) were the most potent cephalosporins tested against methicillin-susceptible coNS, with MIC₉₀ values at least 8-fold lower than that of ceftriaxone (MIC₅₀, 2 mg/liter; MIC₉₀, 4 mg/liter) (Table S2).

Compared to the full isolate set, the antibiogram results for the methicillin-resistant coNS (MRCoNS) isolates showed higher resistance rates for all tested drugs except for daptomycin, tigecycline, and vancomycin (all 100.0% susceptible) (Table 1). Ceftaroline (MIC₅₀, 0.25 mg/liter; MIC₉₀, 0.5 mg/liter) and ceftobiprole (MIC₅₀, 1 mg/liter; MIC₉₀, 1 mg/liter) were significantly more potent than ceftriaxone (Table 1), and 100% of the MRCoNS isolates were susceptible to ceftobiprole, using the non-species-related breakpoint (14) (Table 1).

Ceftobiprole also displayed potent antimicrobial activity against 347 *Enterococcus faecalis* isolates (MIC₅₀, 0.5 mg/liter; MIC₉₀, 2 mg/liter; 100.0% susceptible using the EUCAST non-species-related breakpoint [14]) (Table 1). All *E. faecalis* isolates were susceptible to ampicillin, daptomycin, linezolid, and tigecycline (Table 1). A total of 3.7% of *E. faecalis* strains were resistant to vancomycin. *Enterococcus faecium* isolate testing revealed 65.5% overall resistance to vancomycin (Table S2). Like ampicillin, ceftobiprole displayed limited activity against *E. faecium* isolates (MIC₅₀, >4 mg/liter),

TABLE 1 Activities of ceftobiprole and comparator antimicrobial agents against Gram-positive cocci collected in 2016

Species or group and antimicrobial agent	MIC (mg/liter)			CLSI criteria ^a			EUCAST criteria ^a		
	MIC ₅₀	MIC ₉₀	MIC range	% S	% I	% R	% S	% I	% R
<i>Staphylococcus aureus</i> (n = 2,930)									
Ceftobiprole	0.5	2	≤0.03 to 4				99.7		0.3
Ceftaroline	0.25	1	≤0.06 to 4	98.5	1.5	<0.1	98.5		1.5 ^b
Ceftriaxone	4	>8	0.5 to >8	57.0		43.0			
Clindamycin	≤0.25	>2	≤0.25 to >2	85.3	0.2	14.5	85.2	0.1	14.7
Daptomycin	0.25	0.5	≤0.12 to 2	>99.9			>99.9		<0.1
Erythromycin	4	>8	≤0.06 to >8	43.3	6.9	49.7	44.0	2.9	53.1
Levofloxacin	0.25	>4	≤0.03 to >4	62.6	1.8	35.5	62.6		37.4
Linezolid	1	1	≤0.12 to 4	100.0		0.0	100.0		0.0
Oxacillin	0.5	>2	≤0.25 to >2	57.0		43.0	57.0		43.0
Tetracycline	≤0.5	≤0.5	≤0.5 to >8	96.3	0.6	3.1	94.0	1.2	4.8
Tigecycline	0.06	0.12	≤0.015 to 0.5	100.0 ^c			100.0		0.0
Trimethoprim-sulfamethoxazole	≤0.5	≤0.5	≤0.5 to >4	97.9		2.1	97.9	0.1	2.0
Vancomycin	0.5	1	0.25 to 2	100.0	0.0	0.0	100.0		0.0
MRSA (n = 1,260)									
Ceftobiprole	1	2	0.25 to 4				99.3		0.7
Ceftaroline	0.5	1	0.25 to 4	96.4	3.5	0.1	96.4		3.6 ^b
Ceftriaxone	>8	>8	4 to >8	0.0		100.0			
Clindamycin	≤0.25	>2	≤0.25 to >2	71.0	0.3	28.7	71.0	0.0	29.0
Daptomycin	0.5	0.5	≤0.12 to 2	99.9			99.9		0.1
Erythromycin	>8	>8	≤0.06 to >8	11.1	4.7	84.2	11.7	1.6	86.7
Levofloxacin	4	>4	0.06 to >4	27.8	2.9	69.3	27.8		72.2
Linezolid	1	1	0.25 to 4	100.0		0.0	100.0		0.0
Tetracycline	≤0.5	1	≤0.5 to >8	95.7	0.6	3.7	92.8	2.1	5.2
Tigecycline	0.06	0.12	≤0.015 to 0.5	100.0 ^c			100.0		0.0
Trimethoprim-sulfamethoxazole	≤0.5	≤0.5	≤0.5 to >4	95.8		4.2	95.8	0.2	4.0
Vancomycin	0.5	1	0.25 to 2	100.0	0.0	0.0	100.0		0.0
CoNS (n = 439) ^d									
Ceftobiprole	0.5	1	≤0.03 to 4				100.0 ^e		0.0
Ceftaroline	0.25	0.5	≤0.06 to 2						
Ceftriaxone	8	>8	0.5 to >8	39.9		60.1			
Clindamycin	≤0.25	>2	≤0.25 to >2	70.2	0.9	28.9	69.2	0.9	29.8
Daptomycin	0.25	0.5	≤0.12 to 1	100.0			100.0		0.0
Erythromycin	>8	>8	≤0.06 to >8	39.2	3.6	57.2	40.3	1.4	58.3
Levofloxacin	0.25	>4	≤0.03 to >4	60.4	1.6	38.0	60.4		39.6
Linezolid	0.5	1	≤0.12 to >8	97.7		2.3	97.7		2.3
Oxacillin	2	>2	≤0.25 to >2	39.9		60.1	42.8		57.2
Tetracycline	≤0.5	>8	≤0.5 to >8	85.6	0.5	13.9	83.6	1.4	15.0
Tigecycline	0.06	0.12	≤0.015 to 0.5				100.0		0.0
Trimethoprim-sulfamethoxazole	≤0.5	>4	≤0.5 to >4	70.2		29.8	70.2	19.4	10.5
Vancomycin	1	2	≤0.12 to 2	100.0	0.0	0.0	100.0		0.0
MRCoNS (n = 264)									
Ceftobiprole	1	1	0.12 to 4				100.0 ^e		0.0
Ceftaroline	0.25	0.5	≤0.06 to 2						
Ceftriaxone	>8	>8	1 to >8	0.0		100.0			
Clindamycin	≤0.25	>2	≤0.25 to >2	56.8	1.1	42.0	56.1	0.8	43.2
Daptomycin	0.5	0.5	≤0.12 to 1	100.0			100.0		0.0
Erythromycin	>8	>8	≤0.06 to >8	24.6	5.3	70.1	26.5	2.3	71.2
Levofloxacin	4	>4	0.06 to >4	39.8	2.3	58.0	39.8		60.2
Linezolid	0.5	1	≤0.12 to >8	96.2		3.8	96.2		3.8
Oxacillin	>2	>2	0.5 to >2	0.0		100.0	4.9		95.1
Tetracycline	≤0.5	>8	≤0.5 to >8	79.5	0.4	20.1	77.3	1.5	21.2
Tigecycline	0.12	0.25	0.03 to 0.5				100.0		0.0
Trimethoprim-sulfamethoxazole	1	>4	≤0.5 to >4	56.8		43.2	56.8	29.2	14.0
Vancomycin	1	2	0.25 to 2	100.0	0.0	0.0	100.0		0.0
<i>Enterococcus faecalis</i> (n = 347)									
Ceftobiprole	0.5	2	≤0.03 to 4				100.0 ^e		0.0
Ampicillin	1	2	≤0.5 to 4	100.0		0.0	100.0	0.0	0.0
Ceftaroline	2	8	≤0.06 to >8						
Daptomycin	1	1	≤0.25 to 2	100.0					

(Continued on next page)

TABLE 1 (Continued)

Species or group and antimicrobial agent	MIC (mg/liter)			CLSI criteria ^a			EUCAST criteria ^a		
	MIC ₅₀	MIC ₉₀	MIC range	% S	% I	% R	% S	% I	% R
Levofloxacin	1	>4	≤0.03 to >4	76.1	0.3	23.6	76.4		23.6 ^f
Linezolid	1	1	0.25 to 2	100.0	0.0	0.0	100.0		0.0
Teicoplanin	≤0.5	≤0.5	≤0.5 to >16	96.3	0.0	3.7	96.0		4.0
Tigecycline	0.06	0.12	≤0.015 to 0.12	100.0 ^c			100.0	0.0	0.0
Vancomycin	1	2	0.25 to >16	96.3	0.0	3.7	96.3		3.7
<i>Streptococcus pneumoniae</i> (n = 698)									
Ceftobiprole	0.015	0.5	0.002 to 1				99.7		0.3
Ceftaroline	≤0.008	0.12	≤0.008 to 0.5	100.0 ^g			99.7		0.3
Ceftriaxone	0.03	1	≤0.015 to >2	86.2	11.6	2.2 ^h	86.2	13.5	0.3
				97.8	1.9	0.3 ^g			
Clindamycin	≤0.25	>2	≤0.25 to >2	85.0	0.4	14.6	85.4		14.6
Erythromycin	0.06	>32	≤0.015 to >32	53.3	0.9	45.8	53.3	0.9	45.8
Levofloxacin	1	1	0.25 to >4	99.0	0.1	0.9	99.0		1.0
Linezolid	1	2	0.25 to 2	100.0			100.0	0.0	0.0
Penicillin	0.015	2	≤0.004 to 8	64.2	23.9	11.9 ⁱ	64.2		35.8 ^h
				64.2		35.8 ^j	64.2	32.8	3.0 ^g
				97.0	2.9	0.1 ^k			
Tetracycline	≤0.25	>8	≤0.25 to >8	79.7	0.3	20.1	79.7	0.3	20.1
Trimethoprim-sulfamethoxazole	0.25	>4	≤0.12 to >4	72.3	10.5	17.2	78.2	4.6	17.2
VGS (n = 127) ^j									
Ceftobiprole	0.06	0.25	0.004 to >2						
Ceftaroline	0.015	0.06	≤0.008 to 0.5						
Ceftriaxone	0.12	0.5	≤0.015 to >2	94.5	2.4	3.1	91.3		8.7
Clindamycin	≤0.25	>2	≤0.25 to >2	82.7	1.6	15.7	84.3		15.7
Daptomycin	0.25	1	≤0.06 to 1	100.0					
Erythromycin	0.03	>32	≤0.015 to >32	53.5	1.6	44.9			
Levofloxacin	1	2	0.25 to >4	92.9	0.0	7.1			
Linezolid	1	1	0.12 to 2	100.0					
Meropenem	0.03	0.5	≤0.008 to >1	95.3			100.0		0.0
Penicillin	0.06	1	≤0.004 to 8	74.0	22.8	3.1	83.5	13.4	3.1
Tetracycline	1	>8	≤0.25 to >8	56.7	4.7	38.6			
BHS (n = 585) ^m									
Ceftobiprole	0.015	0.03	0.002 to 0.12				100.0 ^e		0.0
Ceftaroline	≤0.008	0.015	≤0.008 to 0.03	100.0			100.0		0.0
Ceftriaxone	0.03	0.06	≤0.015 to 0.12	100.0			100.0		0.0
Clindamycin	≤0.25	>2	≤0.25 to >2	83.2	0.5	16.2	83.8		16.2
Daptomycin	≤0.06	0.25	≤0.06 to 1	100.0			100.0		0.0
Erythromycin	0.03	>32	≤0.015 to >32	67.3	0.7	32.0	67.3	0.7	32.0
Levofloxacin	0.5	1	0.12 to >4	99.8	0.0	0.2	99.8		0.2
Linezolid	1	1	0.25 to 2	100.0			100.0	0.0	0.0
Meropenem	≤0.008	0.06	≤0.008 to 0.12	100.0			100.0		0.0
Penicillin	0.015	0.06	≤0.004 to 0.12	100.0			100.0		0.0
Tetracycline	0.5	>8	≤0.25 to >8	53.4	1.4	45.2	52.2	1.2	46.6
Vancomycin	0.25	0.5	0.12 to 1	100.0			100.0		0.0

^aCriteria were published by CLSI (22) and EUCAST (14). S, susceptible; I, intermediate; R, resistant.^bUsing pneumonia breakpoints.^cBreakpoints from FDA website, revised December 2017 (23).^dOrganisms included *Staphylococcus auricularis* (n = 1), *Staphylococcus capitis* (n = 31), *Staphylococcus caprae* (n = 3), *Staphylococcus cohnii* (n = 3), *Staphylococcus epidermidis* (n = 251), *Staphylococcus haemolyticus* (n = 20), *Staphylococcus hominis* (n = 44), *Staphylococcus intermedius* (n = 2), *Staphylococcus lugdunensis* (n = 42), *Staphylococcus pettenkoferi* (n = 9), *Staphylococcus pseudintermedius* (n = 3), *Staphylococcus saprophyticus* (n = 13), *Staphylococcus schleiferi* (n = 5), *Staphylococcus simulans* (n = 5), *Staphylococcus warneri* (n = 6), and CoNS not identified to the species level (n = 1).^eUsing the pharmacokinetic/pharmacodynamic (non-species-related) breakpoint based on the standard dose (EUCAST [14]).^fUncomplicated UTI only.^gUsing nonmeningitis breakpoints.^hUsing meningitis breakpoints.ⁱUsing oral breakpoints.^jUsing parenteral, meningitis breakpoints.^kUsing parenteral, nonmeningitis breakpoints.^lOrganisms included *Streptococcus anginosus* (n = 27), *S. anginosus* group (n = 9), *Streptococcus australis* (n = 1), *Streptococcus bovis* group (n = 2), *Streptococcus constellatus* (n = 5), *Streptococcus cristatus* (n = 1), *Streptococcus equinus* (n = 1), *Streptococcus gallolyticus* (n = 7), *Streptococcus gordonii* (n = 7), *Streptococcus intermedius* (n = 5), *Streptococcus lutetiensis* (n = 2), *Streptococcus massiliensis* (n = 1), *Streptococcus mitis* group (n = 37), *S. mitis*/*Streptococcus oralis* (n = 1), *Streptococcus parasanguinis* (n = 9), *Streptococcus salivarius* (n = 3), *S. salivarius* group (n = 1), *S. salivarius*/*Streptococcus vestibularis* (n = 3), *Streptococcus sanguinis* (n = 4), and *S. vestibularis* (n = 1).^mOrganisms included *Streptococcus agalactiae* (n = 240), *Streptococcus canis* (n = 2), *Streptococcus dysgalactiae* (n = 67), and *Streptococcus pyogenes* (n = 276).

regardless of the vancomycin susceptibility patterns. Daptomycin, linezolid, and tigecycline (98.9%, 98.9%, and 99.4% susceptible, respectively) provided the best coverage against *E. faecium* (Table S2).

Susceptibility testing results for *Streptococcus pneumoniae* isolates ($n = 698$; 3.0% penicillin nonsusceptible [MIC of ≥ 4 mg/liter]) are shown in Table 1. Ceftobiprole (MIC₅₀, 0.015 mg/liter; MIC₉₀, 0.5 mg/liter) and ceftaroline (MIC₅₀, ≤ 0.008 mg/liter; MIC₉₀, 0.12 mg/liter) were the most active β -lactam agents tested against the *S. pneumoniae* isolate set, which was 99.7% susceptible to both antimicrobials by EUCAST criteria. All isolates were susceptible to linezolid. Levofloxacin resistance was noted for 0.9% of the isolates, whereas the rates of resistance were much higher for erythromycin (45.8%), tetracycline (20.1%), and trimethoprim-sulfamethoxazole (17.2%) (Table 1). Ceftobiprole was active against 86.7% of ceftriaxone-nonsusceptible *S. pneumoniae* isolates (Table S2).

According to MIC₉₀ values, ceftaroline (MIC₅₀, 0.015 mg/liter; MIC₉₀, 0.06 mg/liter) and ceftobiprole (MIC₅₀, 0.06 mg/liter; MIC₉₀, 0.25 mg/liter) were the most active β -lactams tested against the viridans group streptococcal (VGS) isolates ($n = 127$), and 96.1% of VGS isolates were susceptible to ceftobiprole at the *S. pneumoniae* susceptible breakpoint of ≤ 0.5 mg/liter (Table 1 and Table S1). The rate of penicillin resistance was 3.1%, and that of levofloxacin resistance was 7.1%. Rates of resistance to clindamycin and erythromycin were 15.7% and 44.9%, respectively. The VGS isolates were 100% susceptible to daptomycin and linezolid, both of which exhibited the broadest coverage of the antimicrobials tested in this study against this pathogen group (Table 1).

Ceftobiprole was very potent (MIC₉₀, 0.03 mg/liter) against β -hemolytic streptococcal (BHS) isolates ($n = 585$), and no MIC value exceeded 0.12 mg/liter (Table 1). All isolates were susceptible to ceftaroline, ceftriaxone, daptomycin, linezolid, meropenem, penicillin, and vancomycin. The levofloxacin resistance rate was 0.2%. Rates of resistance to clindamycin and erythromycin were 16.2% and 32.0%, respectively (Table 1).

Activities of ceftobiprole and comparator antimicrobials against *Enterobacteriaceae* isolates. The activities of ceftobiprole and comparison agents tested against *Enterobacteriaceae* isolates ($n = 4,469$) are summarized in Table 2 and Table S3. Among all *Enterobacteriaceae* isolates, 82.5% and 75.5% of isolates were susceptible to ceftobiprole and ceftaroline, respectively (Table 2). Susceptibility rates were 98.7% for meropenem, 97.7% for tigecycline, 88.8% for cefepime, 91.6% for piperacillin-tazobactam, 85.9% for ceftazidime, and 81.9% for ceftriaxone.

Against all 1,747 *Escherichia coli* isolates, colistin (99.6% susceptible [EUCAST criteria]), meropenem (99.9% susceptible), imipenem (99.9% susceptible), and tigecycline (99.9% susceptible) were the most active agents tested (Table 2). Like other extended-spectrum cephalosporins, ceftobiprole activity against *E. coli* was bimodal (Table 2 and Table S1), with MIC₅₀ and MIC₉₀ values of 0.03 mg/liter and >16 mg/liter, respectively (82.5% of isolates were susceptible at the EUCAST breakpoint of ≤ 0.25 mg/liter). Rates of *E. coli* resistance to gentamicin, levofloxacin, and trimethoprim-sulfamethoxazole were 12.9%, 30.3%, and 35.1%, respectively (Table 2).

Among 330 *E. coli* isolates (18.9%) that exhibited an extended-spectrum β -lactamase (ESBL) phenotype, the potencies for all selected agents except for the carbapenems, colistin, and tigecycline were markedly decreased (Table S3). In contrast to the excellent antimicrobial activity exhibited against non-ESBL *E. coli* isolates (99.8% susceptible), ceftobiprole exhibited little activity against the majority of ESBL producers (8.2% susceptible) (Table 2 and Table S3).

Similar to findings observed for *E. coli*, ceftobiprole displayed bimodal activity against *Klebsiella pneumoniae* ($n = 959$), with MIC₅₀ and MIC₉₀ values of 0.03 mg/liter and >16 mg/liter, respectively (Table 2 and Table S1). *K. pneumoniae* susceptibility (83.4%) to ceftobiprole was comparable to that of *E. coli* (82.5%). The best overall coverage against *K. pneumoniae* was provided by tigecycline (98.6% susceptible), colistin (98.4% susceptible [EUCAST criteria]), and the carbapenems (97.0%).

For most tested antimicrobial agents (Table S3), higher resistance rates were observed for ESBL-phenotype *K. pneumoniae* isolates (17.5% [168 isolates]). Ampicillin-

TABLE 2 Activities of ceftobiprole and comparator antimicrobial agents against Gram-negative species and groups collected in 2016

Species or group and antimicrobial agent	MIC (mg/liter)			CLSI criteria ^a			EUCAST criteria ^a		
	MIC ₅₀	MIC ₉₀	MIC range	% S	% I	% R	% S	% I	% R
<i>Enterobacteriaceae</i> (n = 4,469) ^b									
Ceftobiprole	0.03	>16	≤0.008 to >16				82.5		17.5
Ampicillin-sulbactam	16	>32	≤0.25 to >32	47.8	16.7	35.5	47.8		52.2
Aztreonam	0.12	>16	≤0.03 to >16	85.3	1.4	13.3	83.2	2.1	14.7
Cefepime	≤0.12	4	≤0.12 to >16	88.8	2.3	8.9 ^c	87.1	3.0	9.9
Ceftaroline	0.12	>32	≤0.015 to >32	75.5	4.1	20.4	75.5		24.5
Ceftazidime	0.25	16	0.03 to >32	85.9	1.8	12.3	82.9	3.1	14.1
Ceftriaxone	≤0.06	>8	≤0.06 to >8	81.9	1.0	17.1	81.9	1.0	17.1
Colistin	0.25	>8	≤0.06 to >8				82.6		17.4
Gentamicin	0.5	2	≤0.06 to >8	90.8	0.9	8.3	90.3	0.5	9.2
Imipenem	≤0.12	1	≤0.12 to >8	92.8	5.1	2.1	97.9	1.5	0.6
Levofloxacin	0.06	>4	≤0.03 to >4	82.2	1.9	15.9	78.3	2.7	19.0
Meropenem	0.03	0.06	≤0.015 to >32	98.7	0.2	1.1	98.9	0.5	0.6
Piperacillin-tazobactam	2	16	≤0.5 to >64	91.6	3.7	4.7	87.9	3.7	8.4
Tigecycline	0.25	1	≤0.06 to 8	97.7	2.2	0.1 ^d	92.9	4.8	2.3
Trimethoprim-sulfamethoxazole	≤0.5	>4	≤0.5 to >4	78.1		21.9	78.1	0.6	21.3
<i>Escherichia coli</i> (n = 1,747)									
Ceftobiprole	0.03	>16	0.015 to >16				82.5		17.5
Ampicillin-sulbactam	16	>32	0.5 to >32	48.5	20.2	31.3	48.5		51.5
Aztreonam	0.12	>16	≤0.03 to >16	84.3	2.1	13.6	81.7	2.6	15.7
Cefepime	≤0.12	>16	≤0.12 to >16	84.1	2.5	13.4 ^c	83.2	1.9	14.9
Ceftaroline	0.12	>32	≤0.015 to >32	78.5	2.2	19.4	78.5		21.5
Ceftazidime	0.25	16	0.03 to >32	85.9	2.5	11.7	82.4	3.5	14.1
Ceftriaxone	≤0.06	>8	≤0.06 to >8	82.0	0.2	17.7	82.0	0.2	17.7
Colistin	0.12	0.25	≤0.06 to 8				99.6		0.4
Gentamicin	0.5	>8	0.12 to >8	86.9	0.2	12.9	86.7	0.2	13.1
Imipenem	≤0.12	≤0.12	≤0.12 to 4	99.9	0.0	0.1	99.9	0.1	0.0
Levofloxacin	≤0.03	>4	≤0.03 to >4	67.6	2.1	30.3	66.3	1.0	32.7
Meropenem	≤0.015	0.03	≤0.015 to 8	99.9	0.0	0.1	99.9	0.1	0.0
Piperacillin-tazobactam	2	8	≤0.5 to >64	95.1	2.2	2.7	91.8	3.3	4.9
Tigecycline	0.12	0.25	≤0.06 to 4	99.9	0.1	0.0 ^d	99.9	0.0	0.1
Trimethoprim-sulfamethoxazole	≤0.5	>4	≤0.5 to >4	64.9		35.1	64.9	0.7	34.3
Non-ESBL <i>E. coli</i> (n = 1,417)									
Ceftobiprole	0.03	0.06	0.015 to 1				99.8		0.2
Ampicillin-sulbactam	4	>32	0.5 to >32	55.9	22.0	22.1	55.9		44.1
Aztreonam	0.06	0.25	≤0.03 to 1	100.0	0.0	0.0	100.0	0.0	0.0
Cefepime	≤0.12	≤0.12	≤0.12 to 8	99.9	0.1	0.0 ^c	99.6	0.3	0.1
Ceftaroline	0.06	0.25	≤0.015 to >32	96.0	2.3	1.6	96.0		4.0
Ceftazidime	0.12	0.25	0.03 to 1	100.0	0.0	0.0	100.0	0.0	0.0
Ceftriaxone	≤0.06	0.12	≤0.06 to 0.5	100.0	0.0	0.0	100.0	0.0	0.0
Colistin	0.12	0.25	≤0.06 to 8				99.7		0.3
Gentamicin	0.5	2	0.12 to >8	92.1	0.2	7.7	91.9	0.2	7.9
Imipenem	≤0.12	≤0.12	≤0.12 to 1	100.0	0.0	0.0	100.0	0.0	0.0
Levofloxacin	≤0.03	>4	≤0.03 to >4	79.9	2.1	18.0	78.7	1.0	20.4
Meropenem	≤0.015	0.03	≤0.015 to 0.12	100.0	0.0	0.0	100.0	0.0	0.0
Piperacillin-tazobactam	2	4	≤0.5 to >64	97.8	0.9	1.3	97.0	0.8	2.2
Tigecycline	0.12	0.25	≤0.06 to 1	100.0	0.0	0.0 ^d	100.0	0.0	0.0
Trimethoprim-sulfamethoxazole	≤0.5	>4	≤0.5 to >4	71.2		28.8	71.2	0.5	28.3
<i>Klebsiella pneumoniae</i> (n = 959)									
Ceftobiprole	0.03	>16	0.015 to >16				83.4		16.6
Ampicillin-sulbactam	8	>32	1 to >32	71.7	8.6	19.7	71.7		28.3
Aztreonam	0.06	>16	≤0.03 to >16	85.6	0.5	13.9	84.3	1.4	14.4
Cefepime	≤0.12	>16	≤0.12 to >16	86.7	1.6	11.7 ^c	85.7	1.8	12.5
Ceftaroline	0.12	>32	≤0.015 to >32	80.4	2.1	17.5	80.4		19.6
Ceftazidime	0.25	32	0.03 to >32	85.6	1.3	13.1	83.1	2.5	14.4
Ceftriaxone	≤0.06	>8	≤0.06 to >8	84.5	0.3	15.2	84.5	0.3	15.2
Colistin	0.12	0.25	≤0.06 to >8				98.4		1.6
Gentamicin	0.25	1	≤0.06 to >8	91.0	1.6	7.4	90.8	0.2	9.0
Imipenem	≤0.12	0.25	≤0.12 to >8	97.0	0.2	2.8	97.2	0.8	2.0
Levofloxacin	0.06	2	≤0.03 to >4	91.0	1.8	7.2	86.1	3.8	10.1
Meropenem	0.03	0.03	≤0.015 to >32	97.0	0.4	2.6	97.4	0.2	2.4
Piperacillin-tazobactam	2	16	≤0.5 to >64	90.6	3.1	6.3	84.9	5.7	9.4
Tigecycline	0.25	1	≤0.06 to 4	98.6	1.4	0.0 ^d	95.2	3.4	1.4
Trimethoprim-sulfamethoxazole	≤0.5	>4	≤0.5 to >4	82.2		17.8	82.2	0.5	17.3
Non-ESBL <i>K. pneumoniae</i> (n = 791)									
Ceftobiprole	0.03	0.06	0.015 to 0.5				99.6		0.4
Ampicillin-sulbactam	8	16	1 to >32	85.8	8.2	5.9	85.8		14.2

(Continued on next page)

TABLE 2 (Continued)

Species or group and antimicrobial agent	MIC (mg/liter)			CLSI criteria ^a			EUCAST criteria ^a		
	MIC ₅₀	MIC ₉₀	MIC range	% S	% I	% R	% S	% I	% R
Aztreonam	0.06	0.12	≤0.03 to 1	100.0	0.0	0.0	100.0	0.0	0.0
Cefepime	≤0.12	≤0.12	≤0.12 to 1	100.0	0.0	0.0 ^c	100.0	0.0	0.0
Ceftaroline	0.12	0.25	≤0.015 to 2	97.3	2.0	0.6	97.3		2.7
Ceftazidime	0.12	0.5	0.03 to 1	100.0	0.0	0.0	100.0	0.0	0.0
Ceftriaxone	≤0.06	0.12	≤0.06 to 1	100.0	0.0	0.0	100.0	0.0	0.0
Colistin	0.12	0.25	≤0.06 to >8				99.2		0.8
Gentamicin	0.25	0.5	≤0.06 to >8	99.2	0.0	0.8	99.1	0.1	0.8
Imipenem	≤0.12	0.25	≤0.12 to 2	99.9	0.1	0.0	100.0	0.0	0.0
Levofloxacin	0.06	0.25	≤0.03 to >4	98.6	0.4	1.0	95.2	2.7	2.2
Meropenem	0.03	0.03	≤0.015 to 0.25	100.0	0.0	0.0	100.0	0.0	0.0
Piperacillin-tazobactam	2	8	≤0.5 to >64	98.0	1.3	0.8	93.4	4.6	2.0
Tigecycline	0.25	0.5	≤0.06 to 4	99.2	0.8	0.0 ^d	96.5	2.8	0.8
Trimethoprim-sulfamethoxazole	≤0.5	1	≤0.5 to >4	93.8		6.2	93.8	0.3	5.9
<i>Pseudomonas aeruginosa</i> (n = 1,017)									
Ceftobiprole	2	16	0.12 to >16				72.7 ^e		27.3
Amikacin	4	8	≤0.25 to >32	96.7	1.4	2.0	91.5	5.1	3.3
Aztreonam	8	>16	0.06 to >16	72.3	10.7	17.0	5.9	77.1	17.0
Cefepime	2	16	≤0.12 to >16	85.5	11.5	2.9	85.5		14.5
Ceftaroline	16	>32	0.25 to >32						
Ceftazidime	2	16	0.12 to >32	86.0	4.3	9.6	86.0		14.0
Colistin	1	1	≤0.06 to >8	99.6		0.4	99.6		0.4
Gentamicin	2	8	≤0.06 to >8	86.5	6.5	7.0	86.5		13.5
Imipenem	1	8	≤0.12 to >8	78.1	3.6	18.3	81.7	9.3	8.9
Levofloxacin	0.5	>4	≤0.03 to >4	76.3	7.5	16.2	66.7		33.3
Piperacillin-tazobactam	4	64	≤0.5 to >64	80.8	10.4	8.8	80.8		19.2
<i>Haemophilus influenzae</i> (n = 450)									
Ceftobiprole	0.06	0.12	0.015 to >1						
Amoxicillin-clavulanic acid	1	2	0.12 to >8	99.1		0.9	92.0		8.0
Ampicillin	1	>8	0.12 to >8	59.6	8.4	32.0	59.6		40.4 ^f
Azithromycin	0.5	1	0.12 to >32	98.9			0.7	98.2	1.1
Cefepime	0.06	0.25	≤0.015 to 2	100.0			97.6		2.4
Ceftaroline	0.015	0.03	0.002 to 2	99.6			92.0		8.0
Ceftriaxone	0.004	0.015	≤0.001 to 0.5	100.0			99.1		0.9
Imipenem	0.5	2	≤0.03 to >4	98.9			98.0		2.0
Levofloxacin	0.015	0.03	0.008 to 1	100.0			98.0		2.0
Piperacillin-tazobactam	0.015	0.06	≤0.008 to 0.5	100.0		0.0	92.0		8.0
Tetracycline	0.5	1	≤0.06 to >8	99.8	0.0	0.2	99.6	0.2	0.2
Tigecycline	0.12	0.25	0.06 to 1	96.7 ^d					
Trimethoprim-sulfamethoxazole	0.12	>4	≤0.06 to >4	66.4	2.2	31.3	66.4	0.9	32.7
<i>Moraxella catarrhalis</i> (n = 237)									
Ceftobiprole	0.12	0.25	≤0.008 to >1						
Amoxicillin-clavulanic acid	0.12	0.25	≤0.06 to 0.5	100.0		0.0	100.0		0.0
Azithromycin	0.015	0.03	0.008 to 1	99.6			99.6	0.0	0.4
Cefepime	0.5	2	0.06 to >2				100.0		0.0
Ceftaroline	0.12	0.25	0.002 to 2						
Ceftazidime	0.06	0.25	≤0.015 to 0.25	100.0					
Ceftriaxone	0.25	0.5	0.004 to 2	100.0			99.6	0.4	0.0
Imipenem	≤0.03	0.06	≤0.03 to 0.12				100.0		0.0
Levofloxacin	0.03	0.06	0.015 to 0.12	100.0			100.0		0.0
Tetracycline	0.25	0.5	0.12 to 0.5	100.0	0.0	0.0	100.0	0.0	0.0
Tigecycline	0.06	0.06	≤0.015 to 0.12						
Trimethoprim-sulfamethoxazole	0.12	0.25	≤0.06 to 2	97.0	3.0	0.0	97.0	1.7	1.3

^aCriteria were published by CLSI (22) and EUCAST (14). S, susceptible; I, intermediate; R, resistant.

^bOrganisms included *Citrobacter amalonaticus* (n = 6), *Citrobacter amalonaticus/Citrobacter farmeri* (n = 2), *Citrobacter braakii* (n = 3), *Citrobacter farmeri* (n = 2), *Citrobacter freundii* (n = 56), *C. freundii* species complex (n = 59), *Citrobacter koseri* (n = 87), *Citrobacter sedlakii* (n = 2), *Citrobacter youngae* (n = 2), *Edwardsiella tarda* (n = 1), *Enterobacter aerogenes* (n = 157), *Enterobacter cloacae* (n = 181), *E. cloacae* species complex (n = 258), *Escherichia coli* (n = 1,747), Gram-negative rods in the family *Enterobacteriaceae* (n = 1), *Hafnia alvei* (n = 4), *Klebsiella oxytoca* (n = 232), *K. pneumoniae* (n = 959), *Kluyvera ascorbata* (n = 1), *Kosakonia cowanii* (n = 1), *Leclercia adecarboxylata* (n = 2), *Morganella morganii* (n = 101), *Pantoea agglomerans* (n = 7), *Pantoea calida* (n = 2), *Pluralibacter gergoviae* (n = 3), *Proteus mirabilis* (n = 244), *Proteus penneri* (n = 2), *Proteus vulgaris* (n = 2), *P. vulgaris* group (n = 31), *Providencia alcalifaciens* (n = 1), *Providencia rettgeri* (n = 29), *Providencia stuartii* (n = 26), *Rahnella aquatilis* (n = 1), *Raoultella ornithinolytica* (n = 6), *Raoultella planticola* (n = 1), *Serratia fonticola* (n = 1), *Serratia liquefaciens* (n = 14), *Serratia marcescens* (n = 224), *Cedecea* not identified to the species level (n = 1), *Pantoea* not identified to the species level (n = 5), *Providencia* not identified to the species level (n = 2), and *Raoultella* not identified to the species level (n = 3).

^cIntermediate interpreted as susceptible-dose dependent.

^dBreakpoints from FDA website, revised December 2017 (23).

^eUsing the pharmacokinetic/pharmacodynamic (non-species-related) breakpoint based on the standard dose (EUCAST [14]).

^fβ-Lactamase test-positive reported as resistant for penicillins without inhibitors.

sulbactam and piperacillin-tazobactam had substantially lower activity against the *K. pneumoniae* ESBL isolate subset (5.4% and 56.0% susceptible, respectively, by CLSI criteria). Ceftobiprole (7.1% susceptible) also had limited activity against most *K. pneumoniae* ESBL isolates, as did meropenem and imipenem (resistance rates of 14.9% and 16.1%, respectively) (Table S3). Conversely, ceftobiprole was very active against non-ESBL *K. pneumoniae* isolates ($n = 791$; 99.6% susceptible) (Table 2).

Ceftobiprole susceptibility was lower among *Klebsiella oxytoca* isolates (68.1% susceptible) (Table S3). Notably, both the ESBL-phenotype (14.2%) and non-ESBL-phenotype (85.8%) isolates of *K. oxytoca* were less susceptible to ceftobiprole (0.0% and 79.4% susceptible, respectively) than were isolates of *K. pneumoniae* (7.1% and 99.6% susceptible, respectively) (Table 2 and Table S3). Rates of susceptibility to carbapenems (97.4% and 97.8% for imipenem and meropenem, respectively) and tigecycline (100.0%) were slightly higher for *K. oxytoca* than for *K. pneumoniae* (Table 2 and Table S3).

Ceftobiprole activity against isolates of other *Enterobacteriaceae* species, including *Enterobacter* spp. (80.0% susceptible), *Citrobacter* spp. (82.2% susceptible), *Proteus mirabilis* (95.9% susceptible), indole-positive Proteaeae (79.2% susceptible), and *Serratia* spp. (89.5% susceptible), was comparable to the activity of other extended-spectrum cephalosporins (applying CLSI criteria) (Table S3). Overall, meropenem was the most active β -lactam compound tested against *Enterobacter* spp. (97.7% susceptible), *Citrobacter* spp. (98.2% susceptible), indole-positive Proteaeae (100.0% susceptible), and *Serratia* spp. (98.7% susceptible) (Table S3).

Activities of ceftobiprole and comparators against nonfermentative Gram-negative bacilli. Colistin (MIC₉₀, 1 mg/liter; 99.6% susceptible) was the most potent agent tested against *P. aeruginosa* isolates ($n = 1,017$) (Table 2). Ceftobiprole inhibited 72.7% of *P. aeruginosa* isolates at ≤ 4 mg/liter (MIC₅₀, 2 mg/liter; MIC₉₀, 16 mg/liter) (Table 2), while cefepime and ceftazidime inhibited 85.5% and 86.0% of the isolates at their respective breakpoints (Table 2). For most isolates, ceftobiprole (MIC₅₀, 2 mg/liter) was 8-fold more potent than ceftaroline (MIC₅₀, 16 mg/liter). Among the comparator agents, the greatest rates of resistance were observed for levofloxacin (16.2%), aztreonam (17.0%), and imipenem (18.3%) (Table 2).

Ceftobiprole displayed limited activity against *Acinetobacter* spp. (MIC₉₀, >16 mg/liter) and inhibited 61.5% of the isolates at ≤ 4 mg/liter (Table S3); this activity was comparable to that of cefepime and ceftazidime (57.2% and 61.0% susceptible, respectively) (Table S3). Among other agents tested, colistin (MIC₉₀, 4 mg/liter; 86.6% susceptible) and tigecycline (MIC₉₀, 4 mg/liter) were the most active, with gentamicin, imipenem, ampicillin-sulbactam, and amikacin exhibiting susceptibility rates of 62.6% to 77.0% (Table S3).

As for all β -lactam agents, ceftobiprole was inactive against almost all *Stenotrophomonas maltophilia* isolates (MIC₅₀, >16 mg/liter). Among the non- β -lactam agents tested, trimethoprim-sulfamethoxazole was the most active (MIC₉₀, 2 mg/liter; 93.2% susceptible) (Table S3).

Activities of ceftobiprole and comparators against *Haemophilus* spp. and *Moraxella catarrhalis* isolates. Ceftobiprole inhibited 99.6% of *Haemophilus influenzae* isolates at ≤ 1 mg/liter (MIC₅₀, 0.06 mg/liter; MIC₉₀, 0.12 mg/liter) (Table 2 and Table S1). The activity of imipenem and the cephalosporins (including ceftobiprole) was unaffected by the presence of a β -lactamase enzyme in 31.3% of the isolates (Table S3). Ceftobiprole also demonstrated potent activity against 11 *Haemophilus parainfluenzae* isolates, inhibiting all isolates at ≤ 0.25 mg/liter (Table S3). All other agents tested exhibited potent activity against *Haemophilus* spp. except for trimethoprim-sulfamethoxazole (*H. influenzae* and *H. parainfluenzae* isolates were 31.3% and 18.2% resistant, respectively) (Table 2 and Table S3).

Ceftobiprole inhibited 99.6% of *M. catarrhalis* isolates at ≤ 0.5 mg/liter (Table S1). All tested agents exhibited excellent activity against *M. catarrhalis* (Table 2).

Comparison of ceftobiprole activities against target pathogens collected a decade apart (2006 and 2016). Figure 1 and Table S1 display comparisons of ceftobiprole activity against key species of Gram-positive and Gram-negative patho-

FIG. 1 Comparative activities of ceftobiprole against U.S. clinical isolates collected in 2006 and 2016. The MIC test ranges differed between 2006 and 2016 for many of the species and groups. In those cases, the data were truncated here such that the MIC test ranges were identical for both years. The full data set is presented as a cumulative distribution table in Table S1 in the supplemental material.

gens collected in 2006 versus 2016. All isolates were obtained from patients hospitalized in U.S. medical centers. Results from both years were generated using CLSI reference broth microdilution methods as part of the SENTRY Antimicrobial Surveillance Program (JMI Laboratories, North Liberty, IA, USA), although the dilution range tested in 2016 was generally broader than that used in 2006.

Among the Gram-positive species that are target pathogens for ceftobiprole, ceftobiprole activity was largely unchanged between 2006 and 2016, including *S. aureus* (>99.9% and 99.7% susceptible, respectively, at ≤ 2 mg/liter) (Fig. 1A), CoNS (98.8% and 97.7% susceptible, respectively, at ≤ 2 mg/liter) (Fig. 1B), *E. faecalis* (99.8% and 100.0% inhibited, respectively, at ≤ 4 mg/liter) (Fig. 1B), *S. pneumoniae* (98.9% and 99.7% susceptible, respectively, at ≤ 0.5 mg/liter) (Fig. 1C), VGS (96.7% and 96.1% inhibited, respectively, at ≤ 0.5 mg/liter) (Fig. 1C), and BHS (100.0% and 100.0% inhibited, respectively, at ≤ 0.5 mg/liter) (Fig. 1C). Ceftobiprole also had similar activities against *Enterobacteriaceae* isolates in both years (Fig. 1D). As expected, however, the ceftobiprole *Enterobacteriaceae* MIC₉₀ values were higher for more recent isolates, which was likely due to a greater proportion of ESBL-phenotype isolates observed in 2016 (17.1%), compared to 2006 (9.6%; data not shown). Ceftobiprole was highly active (MIC₉₀ ≤ 0.06 mg/liter) against non-ESBL-phenotype *E. coli* and *K. pneumoniae* isolates from both 2006 and 2016 (Fig. 1E and F). Similarly, the ceftobiprole MIC₅₀ and MIC₉₀ values for *P. aeruginosa* and *H. influenzae* agreed within a 2-fold range when results from 2006 and 2016 were compared (Fig. 1D). These data are shown in tabular form in Table S1.

DISCUSSION

Previous MIC results (2, 3), including those presented here from the 2006 U.S. SENTRY Program (Fig. 1 and Table S1), demonstrated that ceftobiprole exhibits broad-spectrum activity against Gram-positive and Gram-negative species of clinical importance. The data reported here for 2016 isolates do not reveal any unexpected shifts in the MIC distributions for ceftobiprole, compared to analogous data from the 2006 study. Although the MIC₉₀ value for the full *Enterobacteriaceae* isolate set increased from 0.5 mg/liter in 2006 to >16 mg/liter in 2016 (Fig. 1 and Table S1), this can be ascribed to the increased frequency of ESBL-producing isolates within the *E. coli*, *K. pneumoniae*, and *P. mirabilis* subsets tested in this study (also see reference 15). Thus, by comparing MIC data from 2006 and 2016, we conclude that ceftobiprole continues to exhibit potent antimicrobial activity against target pathogens in the United States.

The unique characteristics of ceftobiprole, including its potency, bactericidal nature, and broad-spectrum activity that includes MRSA, *E. faecalis*, penicillin-resistant *S. pneumoniae*, and non-ESBL *Enterobacteriaceae*, helped lead to its current indications for use in Europe and several non-European countries to treat community-acquired pneumonia and hospital-acquired pneumonia (excluding ventilator-associated pneumonia). With the aim of expanding potential indications and supporting registration in the United States, ceftobiprole is currently being evaluated in two phase 3 clinical trials. The first study is exploring the use of ceftobiprole in treating adult patients with *S. aureus* bacteremia (including infective endocarditis), and the second study is investigating ceftobiprole in treating adult patients with acute bacterial skin and skin structure infections. Previous reports (16–18) and this work demonstrate the promising *in vitro* activity of ceftobiprole against recent isolates from bacteremia/endocarditis and skin and skin structure infections (including diabetic foot infections). Thus, ceftobiprole may be an attractive therapeutic option for the treatment of infections in which *S. aureus* (and particularly MRSA) is a concern, infections for which monotherapy is recommended, and/or infections in which Gram-positive and Gram-negative pathogens may both be present (5, 19).

MATERIALS AND METHODS

A total of 12,001 nonduplicate, consecutive, clinical isolates from the ceftobiprole SENTRY Antimicrobial Surveillance Program in the United States were submitted from 30 medical centers across all nine U.S. Census Bureau divisions during 2016 (Table S1). All organisms were isolated from documented infections, and only 1 strain per patient infection episode was included in the surveillance collection.

Isolates were derived from hospitalized patients with bloodstream infections (24.7%), skin and skin structure infections (22.6%), pneumonia (33.0%), urinary tract infections (12.9%), intra-abdominal infections (5.6%), and miscellaneous other infections (1.3%), according to a common surveillance design (20). Species identification was performed at the participating medical centers and confirmed at the monitoring laboratory (JMI Laboratories), using the Vitek 2 system (bioMérieux, Hazelwood, MO, USA) and matrix-assisted laser desorption/ionization–time of flight mass spectrometry (Bruker, Billerica, MA, USA) when necessary. The frequencies of key resistant phenotypes among the 2016 isolates were as follows: MRSA isolates, 43.0%; MRCoNS isolates, 60.1%; vancomycin-nonsusceptible *E. faecalis* isolates, 3.7%; penicillin-resistant (meningitis criterion) *S. pneumoniae* isolates, 35.8%; ESBL-phenotype *E. coli* isolates, 18.9%; ESBL-phenotype *K. pneumoniae* isolates, 17.5%; ESBL-phenotype *K. oxytoca* isolates, 14.2% (Table S1). To look for potential temporal changes in ceftobiprole activity, we compared the 2016 MIC data for specific species and groups to MIC data from a previous U.S. SENTRY survey conducted in 2006, which included 10,719 clinical isolates from all U.S. Census Bureau divisions (Table S1).

All isolates were tested by the CLSI broth microdilution method (21), in cation-adjusted Mueller-Hinton broth (with 5% lysed horse blood added for testing fastidious streptococci and *Haemophilus* test medium used for testing *H. influenzae*), with ceftobiprole and comparator antimicrobial agents. MIC values for isolates collected in 2006 were generated using dry-form test panels (Sensititre; TREK Diagnostics, Cleveland, OH, USA), while MIC values for isolates collected in 2016 were generated using frozen-form panels manufactured by JMI Laboratories. All tested agents were provided by the respective manufacturers as reagent-grade formulations of the active compounds. Susceptibility interpretations were based upon the EUCAST breakpoints recently established for ceftobiprole, as follows: *S. aureus*: susceptible, ≤ 2 mg/liter; resistant, > 2 mg/liter; *S. pneumoniae*: susceptible, ≤ 0.5 mg/liter; resistant, > 0.5 mg/liter; *Enterobacteriaceae*: susceptible, ≤ 0.25 mg/liter; resistant, > 0.25 mg/liter; non-species-specific: susceptible, ≤ 4 mg/liter; resistant, > 4 mg/liter (7). MIC results for tested comparator agents obtained for clinical isolates were interpreted using CLSI breakpoint criteria, where published (22). U.S. FDA product package insert criteria (tigecycline) or EUCAST criteria (ceftobiprole, colistin, and tigecycline) were used as alternative breakpoint sources, as necessary (14). *S. aureus* strains were classified as MRSA according to their levels of oxacillin resistance (MIC, ≥ 4 mg/liter). The CLSI MIC screening criterion for potential ESBL production (ceftazidime, ceftriaxone, and/or aztreonam MIC values of ≥ 2 mg/liter) was used to categorize *E. coli*, *K. pneumoniae*, *K. oxytoca*, and *P. mirabilis* isolates as ESBL producers (22). Results are reported as MIC distributions (ceftobiprole only), MIC₅₀ and MIC₉₀ values (MIC values encompassing 50% and 90%, respectively, of the isolates tested), and percent susceptible and resistant according to CLSI interpretive criteria (as well as FDA and EUCAST interpretive criteria, when necessary). Concurrently tested ATCC quality control strains included *S. aureus* ATCC 29213, *E. faecalis* ATCC 29212, *E. coli* ATCC 25922 and ATCC 35218, *P. aeruginosa* ATCC 27853, *S. pneumoniae* ATCC 49619, and *H. influenzae* ATCC 49247. All quality control results were within published limits (22, 24).

SUPPLEMENTAL MATERIAL

Supplemental material for this article may be found at <https://doi.org/10.1128/AAC.01566-18>.

SUPPLEMENTAL FILE 1, PDF file, 0.6 MB.

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