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In Vitro Activity of Ceftaroline against Gram-Positive and Gram-Negative Pathogens Isolated from Patients in Canadian Hospitals in 2009▽

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The *in vitro* activities of ceftaroline and comparative agents were determined for a collection of the most frequently isolated bacterial pathogens from hospital-associated patients across Canada in 2009 as part of the ongoing CANWARD surveillance study. In total, 4,546 isolates from 15 sentinel Canadian hospital laboratories were tested using the Clinical and Laboratory Standards Institute (CLSI) broth microdilution method. Compared with other cephalosporins, including ceftobiprole, cefepime, and ceftriaxone, ceftaroline exhibited the greatest potency against methicillin-susceptible *Staphylococcus aureus* (MSSA), with a MIC_{90} of 0.25 μg/ml. Ceftaroline also demonstrated greater potency than ceftobiprole against community-associated methicillin-resistant *S. aureus* (MRSA) (MIC_{90}, 0.5 μg/ml) and health care-associated MRSA (MIC_{90}, 1 μg/ml) and was at least 4-fold more active than other cephalosporins against *Staphylococcus epidermidis*; all isolates of MSSA and MRSA tested were susceptible to ceftaroline (MIC, ≤1 μg/ml). Against streptococci, including *Streptococcus pneumoniae*, ceftaroline MICs (MIC_{90}, ≤0.03 μg/ml) were comparable to those of ceftobiprole; however, against penicillin-nonsusceptible, macrolide-nonsusceptible, and multidrug-nonsusceptible isolates of *S. pneumoniae*, ceftaroline demonstrated 2- to 4-fold and 4- to 16-fold more potent activities than those of ceftobiprole and ceftriaxone, respectively. All isolates of *S. pneumoniae* tested were susceptible to ceftaroline (MIC, ≤0.25 μg/ml). Among Gram-negative isolates, ceftaroline demonstrated potent activity (MIC_{90}, ≤0.5 μg/ml) against *Escherichia coli* (92.2% of isolates were susceptible), *Klebsiella pneumoniae* (94.1% of isolates were susceptible), *Proteus mirabilis* (97.7% of isolates were susceptible), and *Haemophilus influenzae* (100% of isolates were susceptible). Ceftaroline demonstrated less potent activity (MIC_{90}, ≥4 μg/ml) against *Enterobacter* spp., *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *Klebsiella oxytoca*, *Serratia marcescens*, and *Stenotrophomonas maltophilia*. Overall, ceftaroline demonstrated potent *in vitro* activity against a recent collection of the most frequently encountered Gram-positive and Gram-negative isolates from patients attending hospitals across Canada in 2009.

Antimicrobial-resistant bacteria are well recognized as causes of substantial patient morbidity and mortality and are frequently reported to contribute significantly to rising health care costs. Important antimicrobial-resistant bacterial human pathogens currently include but are not limited to methicillin-resistant *Staphylococcus aureus* (MRSA; community associated and health care associated), vancomycin-resistant *Enterococcus faecium* and *Enterococcus faecalis* (VRE), penicillin-resistant *Streptococcus pneumoniae* (PRSP), extended-spectrum-β-lactamase (ESBL)-producing *Escherichia coli* and *Klebsiella* species, and fluoroquinolone-resistant and carbapenem-resistant *Enterobacteriaceae* and *Pseudomonas aeruginosa*. The prevalence of each of the aforementioned antimicrobial-resistant bacteria appears to be increasing worldwide, and treatment options are often limited because many isolates are multidrug resistant (MDR) (3). Among the solutions to this burgeoning problem is the development of new agents, ideally with unique, bactericidal mechanisms of action, to treat patients with infections arising from these MDR pathogens.

Ceftaroline fosamil, the prodrug of ceftaroline (formerly known as PPI-0903, T-91825, and TAK-599), is a novel, bactericidal, broad-spectrum oxyimino cephalosporin that was approved by the U.S. Food and Drug Administration (U.S. FDA) in 2010 for the treatment of acute bacterial skin and skin structure infections caused by susceptible Gram-positive and Gram-negative bacteria, including MRSA, and for community-acquired bacterial pneumonia caused by *S. pneumoniae*, methicillin-susceptible *S. aureus* (MSSA), and commonly encountered facultative Gram-negative bacilli (5, 8, 11, 27, 30). Ceftaroline fosamil is rapidly converted *in vivo* by plasma phosphatases to its microbiologically active form, ceftaroline, by hydrolysis of its phosphonate group (30). Ceftaroline demonstrates low protein binding (<20%), a serum half-life of 2.6 h, and a volume of distribution of 0.37 liter/kg of body weight (28.3 liters) (30).

In the current study, the *in vitro* activities of ceftaroline and

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relevant comparator agents were evaluated against a 2009 Canadian collection of common Gram-positive and Gram-negative hospital pathogens associated with skin and skin structure, respiratory, urinary tract, and bacteremic infections. The isolates tested in this study were collected and tested as part of the ongoing CANWARD surveillance study. The CANWARD surveillance study, initiated in 2007, is a national, annual, ongoing population-based surveillance system intended to assess changing patterns of antimicrobial-resistant pathogens in hospital-associated patients in medical/surgical wards, emergency rooms, and intensive care units in Canada (www.can-r.ca).

MATERIALS AND METHODS

Bacterial isolates. From January 2009 to December 2009, 15 sentinel Canadian hospital laboratories were asked to submit consecutive bacterial pathogens (1 per patient) from blood ($n = 165$), respiratory ($n = 100$), urine ($n = 50$), and wound/intravenous ($n = 50$) infections. All isolates collected were deemed clinically significant by the participating site, and isolate inclusion was independent of patient age. Primary isolate identification was performed by the submitting site. Isolates were reidentified by the coordinating laboratory, using morphological characteristics and spot tests. If an isolate identification made by the coordinating laboratory was not consistent with that provided by the submitting site, the isolate was removed from the study. In total, 5,375 isolates were submitted and 4,546 isolates were tested for antimicrobial susceptibility. Yeasts, coagulase-negative staphylococci not identified to the species level, *Streptococcus agalactiae*, viridans group streptococci, *Moraxella catarrhalis*, and species with fewer than 10 isolates were not tested for antimicrobial susceptibility. Of the 4,546 isolates tested, 1,894 (41.7%) were from blood, 1,303 (28.7%) were from respiratory sources, 696 (15.3%) were from urine, and 653 (14.4%) were from wounds. Bacterial isolates tested included 1,871 Gram-positive (41.2%) and 2,675 Gram-negative (58.8%) isolates. The 15 sentinel hospital laboratory sites were geographically distributed in a population-based fashion across Canada, as follows: 1 site in British Columbia, 1 site in Alberta, 1 site in Saskatchewan, 1 site in Manitoba, 5 sites in Ontario, 4 sites in Quebec, 1 site in New Brunswick, and 1 site in Nova Scotia.

Antimicrobial susceptibility testing. Isolates were tested for antimicrobial susceptibility by use of in-house-prepared 96-well broth microdilution panels according to Clinical and Laboratory Standards Institute (CLSI) guidelines (9, 10). The antimicrobial agents tested were obtained as laboratory-grade powders from their respective manufacturers. Ceftaroline was supplied by Forest Laboratories, Inc. (New York, NY). Stock solutions and dilutions were prepared as described by CLSI document M07-A8, using cation-adjusted Mueller-Hinton broth (MHB), MHB with 5% laked horse blood (LHB), and *Haemophilus* test medium (HTM) (9). Quality control was performed following CLSI recommendations, and MICs were interpreted using CLSI M100-S20 (2010) breakpoints (10) or U.S. FDA-approved MIC breakpoints where available. Health Canada MIC interpretative breakpoints were used for ceftobiprole.

ESBL and AmpC confirmation. The production of ESBLs by isolates of *E. coli* and *Klebsiella* spp. was confirmed using the disk diffusion method as described by CLSI (9), using disks containing ceftazidime (30 μg), ceftazidime-clavulanic acid (30 μg-10 μg), cefotaxime (30 μg), and cefotaxime-clavulanic acid (30 μg-10 μg) supplied by Mast Diagnostics (United Kingdom). PCR and sequence analysis were used to identify bla_{SHV}, bla_{TEM}, and $bla_{CTX\text{-}M}$ among isolates (20, 24, 29). Putative AmpC producers were screened for acquired *ampC* genes and for mutations within the chromosomal *ampC* promoter and/or attenuator region by PCR and sequencing as previously described (1, 6).

MRSA confirmation. Potential methicillin resistance in *S. aureus* isolates was confirmed using the cefoxitin disk test described by the CLSI (10) and by PCR amplification of the *mecA* gene (19). Other molecular methods, including Panton-Valentine leukocidin (PVL) analysis (19) and staphylococcal protein A (*spa*) typing (16), were used to assess whether the isolates were community associated or health care associated.

VRE confirmation. Potential vancomycin resistance in *E. faecium* and *E. faecalis* isolates was confirmed with the vancomycin agar dilution test as described by the CLSI (10). All confirmed VRE isolates underwent further analysis to determine the type of vancomycin resistance present. A multiplex PCR method was used to detect the presence of *vanA*, *vanB*, *vanC*, *vanD*, or *vanE* (4).

Pneumococcal serotyping. A modified version of a previously described multiplex PCR algorithm (25) with updated multiplex primers and conditions described by the CDC *Streptococcus* Laboratory protocol website (7) was used to assess the serotypes of the *S. pneumoniae* isolates. As an internal control, primers targeting the *cpsA* locus, found in all pneumococci, were included in all multiplex reaction mixtures.

RESULTS

Compared with the other cephalosporins tested, including ceftobiprole, ceftaroline exhibited the greatest potency against MSSA, with a MIC_{90} of 0.25 μg/ml (Table 1). Ceftaroline also demonstrated greater potency than ceftobiprole against community-associated MRSA (MIC_{90}, 0.5 μg/ml) and health care-associated MRSA (MIC_{90}, 1 μg/ml) (Table 2) and was at least 4-fold more active than other cephalosporins against *Staphylococcus epidermidis* (Table 1). All isolates of *S. aureus* tested, including both MSSA and MRSA, were susceptible to ceftaroline (MIC_{90}, ≤1 μg/ml). Ceftaroline demonstrated a 2-fold greater potency against methicillin-resistant *S. epidermidis* (MIC_{90}, 0.5 μg/ml) than against MRSA.

Against streptococci, including *S. pneumoniae*, ceftaroline MICs (MIC_{90}, ≤0.03 μg/ml) were comparable to those of ceftobiprole but lower than those of ceftriaxone, cefuroxime, meropenem, and piperacillin-tazobactam (Table 1). Ceftaroline demonstrated 2- to 4-fold more potent activities than ceftobiprole and ceftriaxone against penicillin-nonsusceptible and macrolide-nonsusceptible respiratory and blood isolates of *S. pneumoniae* (Table 3). Ceftaroline demonstrated 4- to 16-fold more activity than ceftobiprole and ceftriaxone against multidrug-nonsusceptible respiratory and blood isolates of *S. pneumoniae*. All isolates of *S. pneumoniae* tested were susceptible to ceftaroline (MIC, ≤0.25 μg/ml). Of the 25 isolates of *S. pneumoniae* with penicillin MICs of ≥0.12 μg/ml, 9 were serotype 19A isolates, 7 were nontypeable, 2 were serotype 23F isolates, 2 were serotype 6A isolates, and 1 each was a serotype 19C, 19F, 14, 15A, or 15C isolate.

Like other cephalosporins, ceftaroline demonstrated reduced activity against *E. faecalis* (MIC_{90}, 8 μg/ml) and was inactive against all *E. faecium* isolates, including vancomycin-resistant *E. faecium* (Table 1).

Against the Gram-negative isolates tested, ceftaroline demonstrated potent activity (MIC_{90}, ≤0.5 μg/ml) against the large majority of *E. coli* (92.2% of isolates were susceptible), *Klebsiella pneumoniae* (94.1% of isolates were susceptible), *Proteus mirabilis* (97.7% of isolates were susceptible), and *Haemophilus influenzae* (100% of isolates were susceptible) isolates (Table 4). Ceftaroline, ceftobiprole, and ceftriaxone were less active against ESBL-positive ($n = 47$ [4.3% of isolates]) (MIC_{90}s of >64, >64, and >64 μg/ml, respectively) and AmpC-positive ($n = 31$ [2.8% of isolates]) (MIC_{90}s of 16, 0.5, and 16 μg/ml, respectively) isolates of *E. coli* than against non-ESBL/non-AmpC isolates ($n = 1,019$ [92.9% of isolates]) (MIC_{90}s of 0.25, ≤0.06, and ≤0.25 μg/ml, respectively) (data not shown). Twelve isolates of *K. pneumoniae* were ESBL producers (3.4%); none of the isolates of *Klebsiella oxytoca* or *P. mirabilis* were ESBL positive. Ceftaroline, ceftobiprole, and ceftriaxone were less active against ESBL-positive (MIC_{90}s of >64, 64, and >64 μg/ml, respectively) isolates of *K. pneumoniae* than against non-ESBL/non-AmpC isolates ($n = 345$ [96.6% of isolates]) (MIC_{90}s of 0.25, ≤0.06, and ≤0.25 μg/ml, respectively) (data not shown). Ceftaroline demonstrated less potent ac-

TABLE 1. *In vitro* activities of ceftaroline and comparators against Gram-positive pathogens

Organism (no. of isolates tested) and antimicrobial	MIC (μg/ml)			% Susceptible isolates[a]	% Intermediate isolates[a]	% Resistant isolates[a]
	50%	90%	Range			
Methicillin-susceptible *Staphylococcus aureus* (871)[b]						
Ceftaroline	0.25	0.25	≤0.12–0.5	100	NA	NA
Ceftobiprole	0.25	0.5	≤0.06–2	100	NA	NA
Ceftriaxone	4	4	≤0.25–16	99.7	0.3	0
Cefepime	2	4	≤0.25–16	99.9	0.1	0
Cefazolin	≤0.5	1	≤0.5–4	100	0	0
Ceftazidime	16	16	≤0.25–>32	16.9	82.3	0.8
Meropenem	0.12	0.25	≤0.03–4	100	0	0
Piperacillin-tazobactam	≤1	≤1	≤1–32	99.8	NA	0.2
Vancomycin	1	1	0.5–2	100	0	0
Daptomycin	0.12	0.25	≤0.03–0.5	100	NA	NA
Linezolid	2	2	≤0.12–4	100	NA	0
Tigecycline	0.25	0.25	≤0.03–0.5	100	NA	NA
Trimethoprim-sulfamethoxazole	≤0.12	≤0.12	≤0.12–>8	99.7	NA	0.3
Methicillin-resistant *Staphylococcus aureus* (232)[b,c]						
Ceftaroline	0.5	1	0.25–1	100	NA	NA
Ceftobiprole	1	2	0.5–2	100	NA	NA
Ceftriaxone	>64	>64	8–>64	0	0	100
Cefepime	>64	>64	4–>64	0	0	100
Cefazolin	64	>128	1–>128	0	0	100
Ceftazidime	>32	>32	16–>32	0	0	100
Meropenem	8	32	0.12–>32	0	0	100
Piperacillin-tazobactam	64	128	2–256	0	0	100
Vancomycin	1	1	0.5–2	100	0	0
Daptomycin	0.12	0.25	0.12–0.5	100	NA	NA
Linezolid	2	2	0.5–4	100	NA	0
Tigecycline	0.25	0.5	0.12–1	98.3	NA	1.7
Trimethoprim-sulfamethoxazole	≤0.12	≤0.12	≤0.12–>8	95.3	NA	4.7
Methicillin-susceptible *Staphylococcus epidermidis* (83)						
Ceftaroline	0.25	0.25	≤0.12–0.5	NA	NA	NA
Ceftobiprole	0.5	1	≤0.06–2	NA	NA	NA
Ceftriaxone	8	32	≤0.25–>64	74.7	21.7	3.6
Cefepime	4	16	≤0.25–>64	86.8	7.2	6.0
Cefazolin	1	4	≤0.5–8	100	0	0
Ceftazidime	16	32	≤0.25–>32	42.2	24.1	33.7
Meropenem	2	8	0.06–16	79.5	16.9	3.6
Piperacillin-tazobactam	≤1	4	≤1–16	98.8	NA	1.2
Vancomycin	1	2	≤0.12–2	100	0	0
Daptomycin	0.12	0.25	≤0.03–0.25	100	NA	NA
Linezolid	0.5	1	≤0.12–2	100	NA	NA
Tigecycline	0.12	0.5	≤0.03–0.5	NA	NA	NA
Trimethoprim-sulfamethoxazole	≤0.12	8	≤0.12–8	71.1	NA	28.9
Methicillin-resistant *Staphylococcus epidermidis* (19)						
Ceftaroline	0.5	0.5	0.25–1	NA	NA	NA
Ceftobiprole	1	2	1–4	NA	NA	NA
Ceftriaxone	>64	>64	4–>64	5.3	15.8	78.9
Cefepime	>64	>64	1–>64	5.3	10.5	84.2
Cefazolin	128	>128	16–>128	0	10.5	89.5
Ceftazidime	>32	>32	32–>32	0	0	100
Meropenem	32	32	8–>32	0	10.5	89.5
Piperacillin-tazobactam	32	64	16–128	0	NA	100
Vancomycin	2	2	1–2	100	0	0
Daptomycin	0.12	0.25	0.12–0.25	100	NA	NA
Linezolid	1	1	0.5–1	100	NA	NA
Tigecycline	0.12	0.25	0.06–0.25	NA	NA	NA
Trimethoprim-sulfamethoxazole	4	8	≤0.12–>8	26.3	NA	73.7
Streptococcus pneumoniae (208)[b]						
Ceftaroline	≤0.03	≤0.03	≤0.03–0.25	100	NA	NA
Ceftobiprole	≤0.03	≤0.03	≤0.03–0.5	NA	NA	NA
Ceftriaxone	≤0.12	≤0.12	≤0.12–4	99.0	0.5	0.5
Cefuroxime	≤0.25	≤0.25	≤0.12–>16	96.2	0.5	3.4
Penicillin	≤0.03	0.12	≤0.03–2	88.0[d]	9.6[d]	2.4[d]

Continued on following page

TABLE 1—*Continued*

Organism (no. of isolates tested) and antimicrobial	MIC (μg/ml)			% Susceptible isolates[a]	% Intermediate isolates[a]	% Resistant isolates[a]
	$50\%_0$	90%	Range			
Meropenem	≤0.06	≤0.06	≤0.06–1	97.1	1.0	1.9
Piperacillin-tazobactam	≤1	≤1	≤1–4	NA	NA	NA
Vancomycin	0.25	0.25	≤0.12–0.5	100	0	0
Daptomycin	0.06	0.06	≤0.03–0.12	NA	NA	NA
Linezolid	0.5	1	≤0.12–1	100	NA	NA
Tigecycline	0.03	0.03	≤0.015–0.06	100	NA	NA
Trimethoprim-sulfamethoxazole	≤0.12	0.5	≤0.12–>8	90.9	2.4	6.7
Streptococcus pyogenes (103)[b]						
Ceftaroline	≤0.03	≤0.03	≤0.03–0.06	NA[c]	NA	NA
Ceftobiprole	≤0.03	≤0.03	≤0.03–0.12	100	NA	NA
Ceftriaxone	≤0.12	≤0.12	≤0.12	100	NA	NA
Cefuroxime	≤0.25	≤0.25	≤0.25	NA	NA	NA
Meropenem	≤0.06	≤0.06	≤0.06	100	NA	NA
Piperacillin-tazobactam	≤1	≤1	≤1	NA	NA	NA
Vancomycin	0.25	0.5	≤0.12–0.5	100	NA	NA
Daptomycin	≤0.03	0.06	≤0.03–0.06	100	NA	NA
Linezolid	0.5	1	0.25–1	100	NA	NA
Tigecycline	0.03	0.03	≤0.015–0.06	100	NA	NA
Trimethoprim-sulfamethoxazole	≤0.12	≤0.12	≤0.12–8	NA	NA	NA
Enterococcus faecalis (127)[b]						
Ceftaroline	2	8	0.25–16	NA	NA	NA
Ceftobiprole	0.5	1	≤0.06–2	NA	NA	NA
Ceftriaxone	>64	>64	4–>64	NA	NA	NA
Cefepime	32	>64	8–>64	NA	NA	NA
Cefazolin	32	64	8–>128	NA	NA	NA
Ceftazidime	>32	>32	0.5–>32	NA	NA	NA
Meropenem	4	8	0.5–16	NA	NA	NA
Piperacillin-tazobactam	4	8	≤1–8	NA	NA	NA
Vancomycin	1	2	0.5–4	100	0	0
Daptomycin	0.5	1	0.25–2	100	NA	NA
Linezolid	2	2	1–2	100	0	0
Tigecycline	0.12	0.25	0.06–0.5	96.9	NA	3.1
Trimethoprim-sulfamethoxazole	≤0.12	1	≤0.12–8	NA	NA	NA
Enterococcus faecium (43)[f]						
Ceftaroline	>64	>64	1–>64	NA	NA	NA
Ceftobiprole	>64	>64	2–>64	NA	NA	NA
Ceftriaxone	>64	>64	>64	NA	NA	NA
Cefepime	>64	>64	>64	NA	NA	NA
Cefazolin	>128	>128	>128	NA	NA	NA
Ceftazidime	>32	>32	>32	NA	NA	NA
Meropenem	>32	>32	>32	NA	NA	NA
Piperacillin-tazobactam	>512	>512	16–>512	NA	NA	NA
Vancomycin	1	>32	0.25–>32	79.1	0	20.9
Daptomycin	1	1	0.12–2	100	NA	NA
Linezolid	2	2	0.5–4	97.9	2.3	0
Tigecycline	0.12	0.12	0.06–0.25	NA	NA	NA
Trimethoprim-sulfamethoxazole	2	>8	≤0.12–>8	NA	NA	NA

[a] NA, not available.
[b] Interpretative breakpoints were defined by Health Canada (ceftobiprole) or the U.S. FDA (ceftaroline and tigecycline) where applicable. Isolates of *S. aureus* and *E. faecalis* testing as nonsusceptible to tigecycline were reported as resistant.
[c] The 232 MRSA (*mecA*-positive) isolates included 74 community-associated isolates (CMRSA7 [USA400] and CMRSA10 [USA300]), 151 genotypically defined health care-associated isolates (various genotypes), and 7 *mecA*-positive isolates with unique staphylococcal protein A (*spa*) types.
[d] Penicillin MICs were interpreted using oral penicillin V breakpoints according to CLSI document M100-S20 (10).
[e] Unable to determine % susceptible isolates because the susceptible breakpoint (≤0.015 μg/ml) is lower than the lowest dilution tested.
[f] Includes nine vancomycin-resistant isolates (all *vanA* positive).

tivity (MIC_{90}, ≥4 μg/ml) against *Enterobacter* spp., *Acinetobacter baumannii*, *P. aeruginosa*, *K. oxytoca*, *Serratia marcescens*, and *Stenotrophomonas maltophilia* than against the other Gram-negative bacilli tested and was less potent *in vitro* than ceftobiprole against isolates of *Enterobacteriaceae* (Table 4).

DISCUSSION

Ceftaroline is a broad-spectrum cephalosporin with *in vitro* and *in vivo* activity against community- and health care-associated MRSA, methicillin-resistant *S. epidermidis*, and penicillin-resistant, cefotaxime-resistant, and multidrug-resistant *S.*

TABLE 2. *In vitro* activities of ceftaroline and comparators against community-associated and health care-associated MRSA

Organism (no. of isolates tested) and antimicrobial	MIC (μg/ml)			% Susceptible isolates[a]	% Intermediate isolates[a]	% Resistant isolates[a]
	50%	90%	Range			
Community-associated MRSA (74)[b]						
Ceftaroline[c]	0.5	0.5	0.25–1	100	NA	NA
Ceftobiprole[c]	1	1	0.5–1	100	NA	NA
Ceftriaxone	64	>64	8–>64	0	0	100
Vancomycin	1	1	0.5–2	100	0	0
Ciprofloxacin	16	>16	0.25–>16	45.9	1.4	52.7
Gentamicin	≤0.5	≤0.5	≤0.5–32	98.6	0	1.4
Clindamycin	≤0.12	>8	≤0.12–>8	89.2	0	10.8
Daptomycin	0.25	0.25	0.12–0.25	100	NA	NA
Linezolid	2	2	1–2	100	NA	0
Tigecycline[c]	0.25	0.5	0.12–0.5	100	NA	NA
Trimethoprim-sulfamethoxazole	≤0.12	≤0.12	≤0.12–0.25	100	NA	0
Healthcare-associated MRSA (151)						
Ceftaroline	1	1	0.5–1	100	NA	NA
Ceftobiprole	1	2	0.5–2	100	NA	NA
Ceftriaxone	>64	>64	16–>64	0	0	100
Vancomycin	1	1	0.5–2	100	0	0
Ciprofloxacin	>16	>16	0.5–>16	3.3	0	96.7
Gentamicin	≤0.5	1	≤0.5–32	91.4	0	8.6
Clindamycin	>8	>8	≤0.12–>8	34.4	0	65.6
Daptomycin	0.12	0.25	0.12–0.5	100	NA	NA
Linezolid	2	2	0.5–4	100	NA	0
Tigecycline	0.25	0.5	0.12–1	100	NA	NA
Trimethoprim-sulfamethoxazole	≤0.12	≤0.12	≤0.12–>8	92.7	NA	7.3

[a] NA, not available.
[b] Community-associated isolates of MRSA were defined as isolates with the CMRSA7 (USA400) and CMRSA10 (USA300) staphylococcal protein A (*spa*) types; health care-associated isolates of MRSA were defined as isolates with one of the other 10 Canadian MRSA epidemic staphylococcal protein A (*spa*) types.
[c] Interpretative breakpoints were defined by Health Canada (ceftobiprole) or the U.S. FDA (ceftaroline and tigecycline) where applicable.

pneumoniae (11, 15, 26, 27, 28, 30; this study) (Tables 1, 2, and 3). The enhanced potency demonstrated by ceftaroline compared with other broad-spectrum cephalosporins and penicillins is the result of its greater affinity for target penicillin-binding proteins (PBPs), namely, PBP2a in MRSA and PBP2X in penicillin-nonsusceptible *S. pneumoniae* (18).

MRSA continues to increase in prevalence in Canada, the United States, and throughout the world and is well recognized

TABLE 3. *In vitro* activities of ceftaroline, ceftobiprole, and ceftriaxone against combined blood and respiratory isolates of *S. pneumoniae* with various antibiotic resistance phenotypes

S. pneumoniae group[a] (*n*) and antimicrobial	MIC (μg/ml)			% Susceptible isolates[c]	% Intermediate isolates[c]	% Resistant isolates[c]
	50%	90%	Range			
Penicillin-nonsusceptible isolates (25)[b]						
Ceftaroline	≤0.03	0.12	≤0.03–0.25	100	NA	NA
Ceftobiprole	0.06	0.25	≤0.03–0.5	NA	NA	NA
Ceftriaxone[d]	≤0.12	1	≤0.12–4	92.0	4.0	4.0
Clarithromycin-nonsusceptible isolates (33)						
Ceftaroline	≤0.03	0.12	≤0.03–0.25	100	NA	NA
Ceftobiprole	≤0.03	0.25	≤0.03–0.5	NA	NA	NA
Ceftriaxone	≤0.12	1	≤0.12–4	94.0	3.0	3.0
Multidrug-nonsusceptible isolates (17)						
Ceftaroline	≤0.03	0.12	≤0.03–0.25	100	NA	NA
Ceftobiprole	0.12	0.5	≤0.03–0.5	NA	NA	NA
Ceftriaxone	≤0.12	1	≤0.12–4	88.2	5.9	5.9

[a] Penicillin-nonsusceptible isolates had MICs of ≥0.12 μg/ml (penicillin MICs were interpreted using oral penicillin V breakpoints from CLSI document M100-S20 [10]). Clarithromycin-nonsusceptible isolates had MICs of ≥0.5 μg/ml. Multidrug-nonsusceptible isolates were penicillin nonsusceptible and clarithromycin nonsusceptible.
[b] For the 25 penicillin-nonsusceptible isolates, the penicillin MIC for 11 isolates was 0.12 μg/ml, that for 3 isolates was 0.25 μg/ml, that for 3 isolates was 0.5 μg/ml, that for 3 isolates was 1 μg/ml, and that for 5 isolates was 2 μg/ml.
[c] NA, not available.
[d] Using ceftriaxone breakpoints (susceptible, ≤1 μg/ml; intermediate, 2 μg/ml; and resistant, ≥4 μg/ml), the percentages of isolates that were susceptible, intermediate, and resistant were 99.0, 0.5, and 0.5% for all isolates, 100, 0, and 0% for blood isolates, and 98.0, 1.0, and 1.0% for respiratory isolates.

TABLE 4. *In vitro* activities of ceftaroline and comparators against Gram-negative pathogens

Organism (no. of isolates tested) and antimicrobial	MIC (μg/ml)			% Susceptible isolates[a]	% Intermediate isolates[a]	% Resistant isolates[a]
	50%	90%	Range			
Escherichia coli (1,097)						
Ceftaroline[b]	≤0.12	0.5	≤0.12–>64	92.2	1.6	6.3
Ceftobiprole[b]	≤0.06	≤0.06	≤0.06–>64	95.5	0.4	4.1
Ceftriaxone	≤0.25	≤0.25	≤0.25–>64	94.0	0.3	5.7
Cefepime	≤0.25	≤0.25	≤0.25–>64	98.1	1.3	0.6
Cefazolin	2	16	≤0.5–>128	37.6	35.0	27.3
Ceftazidime	≤0.25	0.5	≤0.25–>32	96.2	0	3.8
Meropenem	≤0.03	≤0.03	≤0.03–1	100	0	0
Ertapenem	≤0.03	≤0.03	≤0.03–4	99.9	0.1	0
Piperacillin-tazobactam	2	4	≤1–512	98.5	1.0	0.5
Amoxicillin-clavulanate	4	8	≤0.06–>32	92.6	5.9	1.5
Ciprofloxacin	≤0.06	>16	≤0.06–>16	77.9	0.5	21.6
Tigecycline[b]	0.5	1	0.12–2	100	0	0
Trimethoprim-sulfamethoxazole	≤0.12	>8	≤0.12–>8	72.6	NA	27.4
Klebsiella pneumoniae (357)						
Ceftaroline	≤0.12	0.5	≤0.12–>64	94.1	1.4	4.5
Ceftobiprole	≤0.06	0.12	≤0.06–>64	96.6	0.6	2.8
Ceftriaxone	≤0.25	≤0.25	≤0.25–>64	96.4	0.3	3.4
Cefepime	≤0.25	≤0.25	≤0.25–>64	97.8	0.8	1.4
Cefazolin	2	4	≤0.5–>128	47.6	38.1	14.3
Ceftazidime	≤0.25	1	≤0.25–>32	97.8	0	2.2
Meropenem	≤0.03	≤0.03	≤0.03–4	100	0	0
Ertapenem	≤0.03	≤0.03	≤0.03–16	99.4	0	0.6
Piperacillin-tazobactam	2	8	≤1–512	97.2	0.8	2.0
Amoxicillin-clavulanate	2	8	1–>32	96.6	2.8	0.6
Ciprofloxacin	≤0.06	0.5	≤0.06–>16	91.9	0.8	7.3
Tigecycline	1	2	0.25–4	96.9	3.1	0
Trimethoprim-sulfamethoxazole	≤0.12	1	≤0.12–>8	91.9	NA	8.1
Enterobacter cloacae (144)						
Ceftaroline	≤0.12	32	≤0.12–>64	75.7	3.5	20.8
Ceftobiprole	≤0.06	0.25	≤0.06–>64	92.4	2.8	4.9
Ceftriaxone	≤0.25	32	≤0.25–>64	77.8	2.8	19.4
Cefepime	≤0.25	0.5	≤0.25–8	100	0	0
Cefazolin	>128	>128	2–>128	0	3.5	96.5
Ceftazidime	0.5	16	≤0.25–>32	86.8	2.1	11.1
Meropenem	≤0.03	0.06	≤0.03–2	100	0	0
Ertapenem	≤0.03	0.25	≤0.03–16	99.3	0	0.7
Piperacillin-tazobactam	2	16	≤1–128	93.1	5.6	1.4
Amoxicillin-clavulanate	32	>32	2–>32	8.3	19.4	72.2
Ciprofloxacin	≤0.06	≤0.06	≤0.06–8	96.5	1.4	2.1
Tigecycline	1	1	0.25–16	97.2	0.7	2.1
Trimethoprim-sulfamethoxazole	≤0.12	1	≤0.12–>8	93.1	NA	6.9
Klebsiella oxytoca (96)						
Ceftaroline	0.25	4	≤0.12–>64	86.5	3.1	10.4
Ceftobiprole	0.25	8	≤0.06–64	92.4	2.8	4.9
Ceftriaxone	≤0.25	0.5	≤0.25–8	92.7	1.0	6.3
Cefepime	≤0.25	≤0.25	≤0.25–1	100	0	0
Cefazolin	8	>128	≤0.5–>128	6.3	14.6	79.2
Ceftazidime	≤0.25	0.5	≤0.25–1	100	0	0
Meropenem	≤0.03	≤0.03	≤0.03–0.06	100	0	0
Ertapenem	≤0.03	≤0.03	≤0.03–0.12	100	0	0
Piperacillin-tazobactam	2	128	≤1–>512	89.6	0	10.4
Amoxicillin-clavulanate	2	8	1–>32	92.7	4.2	3.1
Ciprofloxacin	≤0.06	0.12	≤0.06–1	100	0	0
Tigecycline	0.5	1	0.12–4	97.9	2.1	0
Trimethoprim-sulfamethoxazole	≤0.12	0.25	≤0.12–>8	94.8	NA	5.2
Proteus mirabilis (85)						
Ceftaroline	≤0.12	0.25	≤0.12–8	97.7	0	2.4
Ceftobiprole	≤0.06	≤0.06	≤0.06–0.12	100	0	0
Ceftriaxone	≤0.25	≤0.25	≤0.25–1	100	0	0
Cefepime	≤0.25	≤0.25	≤0.25–0.5	100	0	0
Cefazolin	4	8	2–>128	0	3.5	96.5

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TABLE 4—*Continued*

Organism (no. of isolates tested) and antimicrobial	MIC (μg/ml)			% Susceptible isolates[a]	% Intermediate isolates[a]	% Resistant isolates[a]
	50%	90%	Range			
Ceftazidime	≤0.25	≤0.25	≤0.25–2	100	0	0
Meropenem	0.06	0.12	≤0.03–0.12	100	0	0
Ertapenem	≤0.03	≤0.03	≤0.03–0.06	100	0	0
Piperacillin-tazobactam	≤1	≤1	≤1–2	100	0	0
Amoxicillin-clavulanate	1	2	0.5–16	97.6	2.4	0
Ciprofloxacin	≤0.06	2	≤0.06–>16	89.6	4.7	5.9
Tigecycline	8	16	4–>16	0	14.1	85.9
Trimethoprim-sulfamethoxazole	≤0.12	>8	≤0.12–>8	84.7	NA	15.3
Serratia marcescens (75)						
Ceftaroline	0.5	8	0.25–>64	50.7	25.3	24.0
Ceftobiprole	≤0.06	0.25	≤0.06–>64	96.0	1.3	2.7
Ceftriaxone	≤0.25	1	≤0.25–>64	96.0	0	4.0
Cefepime	≤0.25	0.5	≤0.25–64	98.7	0	1.3
Cefazolin	>128	>128	128–>128	0	0	100
Ceftazidime	0.5	1	≤0.25–>32	97.3	0	2.7
Meropenem	0.06	0.06	≤0.03–>32	98.7	0	1.3
Ertapenem	≤0.03	0.25	≤0.03–>32	97.3	1.3	1.3
Piperacillin-tazobactam	≤1	4	≤1–128	96.0	1.3	2.7
Amoxicillin-clavulanate	32	>32	16–>32	0	22.7	77.3
Ciprofloxacin	≤0.06	1	≤0.06–16	92.0	2.7	5.3
Tigecycline	4	4	1–8	46.7	49.3	4.0
Trimethoprim-sulfamethoxazole	0.5	2	≤0.12–>8	93.3	NA	6.7
Enterobacter aerogenes (33)[b]						
Ceftaroline	≤0.12	16	≤0.12–32	72.7	3.0	24.2
Ceftobiprole	≤0.06	≤0.06	≤0.06–8	97.0	0	3.0
Ceftriaxone	≤0.25	16	≤0.25–>64	72.7	0	27.3
Cefepime	≤0.25	≤0.25	≤0.25–16	97.0	3.0	0
Cefazolin	64	>128	2–>128	0	3.0	97.0
Ceftazidime	≤0.25	>32	≤0.25–>32	75.8	0	24.2
Meropenem	≤0.03	0.06	≤0.03–0.12	100	0	0
Ertapenem	0.06	0.25	≤0.03–1	100	0	0
Piperacillin-tazobactam	2	32	≤1–128	87.9	9.1	3.0
Amoxicillin-clavulanate	32	>32	8–>32	3.0	18.2	78.8
Ciprofloxacin	≤0.06	0.25	≤0.06–>16	90.9	0	9.1
Tigecycline	1	2	0.5–8	93.9	3.0	3.0
Trimethoprim-sulfamethoxazole	≤0.12	0.5	≤0.12–1	100	NA	0
Pseudomonas aeruginosa (470)						
Ceftaroline	16	>64	0.25–>64	NA	NA	NA
Ceftobiprole	4	16	0.25–>64	NA	NA	NA
Ceftriaxone	16	>64	≤0.25–>64	20.6	48.9	30.4
Cefepime	4	16	≤0.25–>64	81.3	12.6	6.2
Ceftazidime	4	32	≤0.25–>32	82.1	5.3	12.6
Meropenem	0.5	8	≤0.03–>32	88.1	5.1	6.8
Ertapenem	8	>32	0.06–>32	NA	NA	NA
Piperacillin-tazobactam	4	64	≤1–>512	90.9	0	9.1
Ciprofloxacin	0.25	8	≤0.06–>16	71.3	8.3	20.4
Tigecycline	>16	>16	0.5–>16	NA	NA	NA
Trimethoprim-sulfamethoxazole	8	>8	≤0.12–>8	NA	NA	NA
Stenotrophomonas maltophilia (79)						
Ceftaroline	>64	>64	32–>64	NA	NA	NA
Ceftobiprole	>64	>64	32–>64	NA	NA	NA
Ceftriaxone	>64	>64	64–>64	NA	NA	NA
Cefepime	32	64	8–>64	NA	NA	NA
Ceftazidime	>32	>32	2–>32	28.8	15.0	56.3
Meropenem	>32	>32	4–>32	NA	NA	NA
Ertapenem	>32	>32	8–>32	NA	NA	NA
Piperacillin-tazobactam	128	>512	16–>512	NA	NA	NA
Ciprofloxacin	2	>16	0.25–>16	NA	NA	NA
Tigecycline	2	8	0.5–16	NA	NA	NA
Trimethoprim-sulfamethoxazole	0.5	2	≤0.12–>8	93.7	NA	6.3

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TABLE 4—*Continued*

Organism (no. of isolates tested) and antimicrobial	MIC (μg/ml)			% Susceptible isolates[a]	% Intermediate isolates[a]	% Resistant isolates[a]
	50%	90%	Range			
Acinetobacter baumannii (23)						
Ceftaroline	2	64	0.5–>64	NA	NA	NA
Ceftobiprole	0.5	16	0.12–64	NA	NA	NA
Ceftriaxone	8	64	2–>64	60.9	17.4	21.7
Cefepime	2	64	0.5–>64	78.3	4.3	17.4
Ceftazidime	4	>32	2–>32	73.9	0	26.1
Meropenem	0.5	2	0.25–>32	91.3	0	8.7
Ertapenem	4	16	0.12–>32	NA	NA	NA
Piperacillin-tazobactam	≤1	64	≤1–>512	78.3	13.0	8.7
Ciprofloxacin	0.25	2	≤0.06–>16	87.0	4.3	8.7
Tigecycline	0.5	8	0.25–>16	NA	NA	NA
Trimethoprim-sulfamethoxazole	0.25	8	≤0.12–>8	82.6	NA	17.4
Haemophilus influenzae (159)						
Ceftaroline	≤0.06	≤0.06	≤0.06–0.12	100	NA	NA
Ceftobiprole	≤0.06	≤0.06	≤0.06–0.25	NA	NA	NA
Ceftriaxone	≤0.06	≤0.06	≤0.06–0.12	100	NA	NA
Cefepime	≤0.25	≤0.25	≤0.25–0.5	100	NA	NA
Cefuroxime	2	4	≤0.25–8	94.3	5.7	0
Meropenem	≤0.06	0.12	≤0.06–0.5	100	NA	NA
Ertapenem	≤0.03	0.12	≤0.03–0.25	100	NA	NA
Piperacillin-tazobactam	≤1	≤1	≤1	100	NA	0
Amoxicillin-clavulanate	0.5	2	≤0.06–4	100	NA	0
Ampicillin	≤0.25	16	≤0.25–>128	83.0	1.3	15.1
Ciprofloxacin	≤0.015	≤0.015	≤0.015–0.03	100	NA	NA
Clarithromycin	8	16	0.25–32	74.8	22.0	3.1
Trimethoprim-sulfamethoxazole	≤0.12	4	≤0.12–>8	80.4	4.4	15.2

[a] NA, not available.
[b] Interpretative breakpoints were defined by Health Canada (ceftobiprole) or the U.S. FDA (ceftaroline and tigecycline) where applicable.

as a leading cause of nosocomial infections (2, 30). In the past decade, MRSA has also emerged as a significant community-associated pathogen capable of causing disease in young, otherwise healthy individuals lacking traditional risk factors for MRSA acquisition and infection (2, 30). Community-associated MRSA strains, in addition to skin and soft tissue infections, have been associated with severe invasive disease, including necrotizing pneumonia, bacteremia, and septic shock (12). Community-associated MRSA genotypes have also begun to replace traditional health care-associated MRSA in hospitals (12). Previous studies have shown that ceftaroline has potent activity against health care-associated and community-associated MRSA genotypes as well as bactericidal activity against vancomycin-intermediate *S. aureus* (VISA), heteroresistant VISA (hVISA), vancomycin-resistant *S. aureus* (VRSA), and daptomycin-nonsusceptible *S. aureus* (MIC_{90}s, 0.5 to 1 μg/ml; MIC ranges, 0.12 to 1 μg/ml) (28). The current study found a MIC_{90} of 1 μg/ml for ceftaroline for all isolates of MRSA; health care-associated and community-associated isolates of MRSA were susceptible to ceftaroline at concentrations of 1 and 0.5 μg/ml, respectively, similar to results reported by other investigators (5, 15, 27, 28). Mushtaq and colleagues reported that they were unable to select higher-level resistance to ceftaroline in MSSA, MRSA, and VISA by use of an *in vitro* multistep procedure at four times the MIC (22).

S. pneumoniae has acquired resistance to several classes of antimicrobial agents, including penicillins, macrolides, trimethoprim-sulfamethoxazole, and fluoroquinolones. Although recent introduction of a pneumococcal conjugate vaccine led to a decrease in invasive and noninvasive pneumococcal disease in all age groups, strains of antimicrobial-resistant and MDR *S. pneumoniae* not covered by the vaccine have emerged and are filling the niche vacated by the vaccine serotypes (14). During the 1980s, infections due to penicillin-nonsusceptible pneumococci emerged and became widespread. β-Lactam resistance in *S. pneumoniae* arises due to alterations in one or more of its six PBPs; point mutations and mosaic genes following recombination arise most frequently in the case of PBP1A, PBP2X, and PBP2B. Both ceftaroline and ceftobiprole inhibit these three PBPs in penicillin-susceptible isolates (while ceftriaxone inhibits only PBP1A and PBP2) (13, 18) and retain potent activity *in vitro* against penicillin-resistant isolates of pneumococci. A recent publication by Patel et al. (26) reported that ceftaroline was a more potent agent *in vitro* than ceftobiprole against MDR *S. pneumoniae*. That paper was the first direct comparison of the activities of these two cephalosporins against pneumococci. The current study confirms the relative activities of ceftaroline, ceftobiprole, and ceftriaxone against penicillin-resistant, macrolide-resistant, and MDR *S. pneumoniae* (Table 3), that is, it shows that against isolates of *S. pneumoniae* with elevated penicillin MICs, ceftaroline is a more potent agent *in vitro* than ceftobiprole. Ceftaroline has potential to be a useful agent in the treatment of pneumococcal infections, including penicillin-nonsusceptible and multidrug-nonsusceptible pneumococcal infections (17). Jacobs and colleagues also found that a few replacement serotypes, predominantly 19A and 6C, are now among the most commonly isolated penicillin-resistant serotypes (17). The introduction of

new higher-valency conjugate vaccines among adults, especially those with underlying illnesses, will likely further decrease the incidence of pneumococcal disease (17).

In the current study, the *in vitro* activity of ceftaroline against Gram-negative pathogens was similar to the activities of cefotaxime and ceftriaxone. Ceftaroline demonstrated lower potency *in vitro* than ceftobiprole against *Enterobacteriaceae*, likely due to its lower stability against hydrolysis by constitutively expressed AmpC β-lactamases. Ceftaroline has been reported to be hydrolyzed by AmpC, ESBL, KPC β-lactamases, and metallo-β-lactamases; its *in vitro* activity is reflected by the prevalence of these β-lactamases in a collection of isolates (22). Other papers also reported that ceftaroline possessed no activity against ESBL producers (5, 27) or ceftazidime-nonsusceptible isolates of *Enterobacteriaceae* (15). Mushtaq and Livermore demonstrated that ceftaroline is a weak inducer of AmpC β-lactamases at or below the MIC, similar to other oxyimino cephalosporins (21). They speculated that *in vivo* induction of AmpC by ceftaroline should not occur frequently because AmpC-inducible *Enterobacteriaceae* are infrequent pathogens in community-acquired pneumonia and complicated skin and skin structure infections (ceftaroline-approved indications), and for indications where AmpC-inducible *Enterobacteriaceae* are likely, such as nosocomial pneumonia, ceftaroline is being developed in combination with NXL104, a non-β-lactam β-lactamase inhibitor which inhibits AmpC and many other β-lactamases (21, 23). In one study, NXL104 used at a concentration of ≤4 μg/ml protected ceftaroline from hydrolysis by all structural types of β-lactamases except metallo-β-lactamases (23).

Ceftaroline was approved by the U.S. FDA in 2010 for the treatment of acute bacterial skin and skin structure infections, including those caused by MRSA, and for treatment of community-acquired bacterial pneumonia (5, 8, 11, 27, 30). Generally, ceftaroline fosamil has been reported to be well tolerated by patients; in clinical trials, adverse events occurred at low rates and were generally mild in nature (11, 30). In the current study, ceftaroline demonstrated potent *in vitro* activity against a diverse collection of recent, frequently encountered Gram-positive and Gram-negative isolates from hospitals across Canada. This paper is the first publication that provides a direct *in vitro* comparison of ceftaroline and ceftobiprole for isolates of staphylococci and Gram-negative bacilli and confirms previously published data showing greater *in vitro* potency of ceftaroline than that of ceftobiprole or any other available cephalosporin against penicillin-resistant and MDR pneumococci (26). Ceftaroline is a promising new broad-spectrum cephalosporin with demonstrated activity against staphylococci, including methicillin-resistant and MDR isolates. Ceftaroline demonstrates potent activity against many *Enterobacteriaceae* but does possess significant lability in the presence of ESBLs and AmpC β-lactamases and also some vulnerability to enterobacterial penicillinases, such as TEM-1 (22). Ceftaroline's inactivation by β-lactamases can largely be overcome by using it in combination with NXL104 (23).

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REFERENCES

1. **Baudry, P. J., et al.** 2008. Comparison of antimicrobial resistance profiles among extended-spectrum-beta-lactamase-producing and acquired AmpC beta-lactamase-producing *Escherichia coli* isolates from Canadian intensive care units. Antimicrob. Agents Chemother. **52:**1846–1849.
2. **Bordon, J. M., et al.** 2010. Methicillin-resistant *Staphylococcus aureus* resistance to non-β-lactam antimicrobials in the United States from 1996 to 2008. Diagn. Microbiol. Infect. Dis. **67:**395–398.
3. **Boucher, H. W., et al.** 2009. Bad bugs, no drugs: no ESKAPE! An update from the Infectious Diseases Society of America. Clin. Infect. Dis. **48:**1–12.
4. **Boyd, D. A., P. Kibsey, D. Roscoe, and M. R. Mulvey.** 2004. *Enterococcus faecium* N03-0072 carries a new VanD-type vancomycin resistance determinant: characterization of the VanD5 operon. J. Antimicrob. Chemother. **54:**680–683.
5. **Brown, S. D., and M. M. Traczewski.** 2009. In vitro antimicrobial activity of a new cephalosporin, ceftaroline, and determination of quality control ranges for MIC testing. Antimicrob. Agents Chemother. **53:**1271–1274.
6. **Caroff, N., E. Espaze, I. Berard, H. Richet, and A. Reynaud.** 1999. Mutations in the ampC promoter of *Escherichia coli* isolates resistant to oxyimino-cephalosporins without extended spectrum beta-lactamase production. FEMS Microbiol. Lett. **173:**459–465.
7. **Centers for Disease Control and Prevention *Streptococcus* Laboratory.** 2010. PCR deduction of pneumococcal serotypes. CDC, Atlanta, GA. http://www.cdc.gov/ncidod/biotech/strep/pcr.htm.
8. **Citron, D. M., K. L. Tyrrell, C. V. Merriam, and E. J. C. Goldstein.** 2010. In vitro activity of ceftaroline against 623 diverse strains of anaerobic bacteria. Antimicrob. Agents Chemother. **54:**1627–1632.
9. **Clinical and Laboratory Standards Institute.** 2009. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; approved standard—8th edition. M07-A8. CLSI, Wayne, PA.
10. **Clinical and Laboratory Standards Institute.** 2010. Performance standards for antimicrobial susceptibility testing; 19th informational supplement. M100-S20. CLSI, Wayne, PA.
11. **Corey, G. R., et al.** 2010. Integrated analysis of CANVAS 1 and 2: phase 3, multicenter, randomized, double-blind studies to evaluate the safety and efficacy of ceftaroline versus vancomycin plus aztreonam in complicated skin and skin-structure infection. Clin. Infect. Dis. **51:**641–650.
12. **David, M. R., and R. S. Daum.** 2010. Community-associated methicillin-resistant *Staphylococcus aureus*: epidemiology and clinical consequences of an emerging epidemic. Clin. Microbiol. Rev. **23:**616–687.
13. **Davies, T. A., et al.** 2007. Binding of ceftobiprole and comparators to the penicillin-binding proteins of *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Streptococcus pneumoniae*. Antimicrob. Agents Chemother. **51:**2621–2624.
14. **Farrell, D. J., K. P. Klugman, and M. Pichichero.** 2007. Increased antimicrobial resistance among nonvaccine serotypes of *Streptococcus pneumoniae* in the pediatric population after the introduction of 7-valent pneumococcal vaccine in the United States. Pediatr. Infect. Dis. J. **26:**123–128.
15. **Ge, Y., D. Biek, G. H. Talbot, and D. F. Sahm.** 2008. In vitro profiling of ceftaroline against a collection of recent bacterial clinical isolates from across the United States. Antimicrob. Agents Chemother. **52:**3398–3407.
16. **Golding, G. R., et al.** 2008. A preliminary guideline for the assignment of methicillin-resistant *Staphylococcus aureus* to a Canadian pulsed-field gel electrophoresis epidemic type using spa typing. Can. J. Infect. Dis. Med. Microbiol. **19:**273–281.
17. **Jacobs, M. R., et al.** 2010. Activity of ceftaroline against recent emerging serotypes of *Streptococcus pneumoniae* in the United States. Antimicrob. Agents Chemother. **54:**2716–2719.
18. **Kosowska-Shick, K., P. L. McGhee, and P. C. Appelbaum.** 2010. Affinity of ceftaroline and other β-lactams for penicillin-binding proteins from *Staphylococcus aureus* and *Streptococcus pneumoniae*. Antimicrob. Agents Chemother. **54:**1670–1677.

19. **McDonald, R. R., et al.** 2005. Development of a triplex real-time PCR assay for detection of Panton-Valentine leukocidin toxin genes in clinical isolates of methicillin-resistant *Staphylococcus aureus*. J. Clin. Microbiol. **43:**6147–6149.
20. **Mulvey, M. R., et al.** 2004. Ambler Class A extended-spectrum beta-lactamase-producing *Escherichia coli* and *Klebsiella* spp. in Canadian hospitals. Antimicrob. Agents Chemother. **48:**1204–1214.
21. **Mushtaq, S., and D. M. Livermore.** 2010. AmpC induction by ceftaroline. J. Antimicrob. Chemother. **53:**586–588.
22. **Mushtaq, S., M. Warner, Y. Ge, K. Kaniga, and D. M. Livermore.** 2007. In vitro activity of ceftaroline (PPI-0903M, T-91825) against bacteria with defined resistance mechanisms and phenotypes. J. Antimicrob. Chemother. **60:**300–311.
23. **Mushtaq, S., M. Warner, G. Williams, I. Critchley, and D. M. Livermore.** 2010. Activity of chequerboard combinations of ceftaroline and NXL104 versus β-lactamase-producing Enterobacteriaceae. J. Antimicrob. Chemother. **65:**1428–1432.
24. **Nuesch-Inderbinen, M. T., H. Hachler, and F. H. Kayser.** 1996. Detection of genes coding for extended-spectrum SHV beta-lactamases in clinical isolates by a molecular genetic method, and comparison with the Etest. Eur. J. Clin. Microbiol. Infect. Dis. **15:**398–402.
25. **Pai, R., R. E. Gertz, and B. Beall.** 2006. Sequential multiplex PCR approach for determining capsular serotypes of *Streptococcus pneumoniae* isolates. J. Clin. Microbiol. **44:**124–131.
26. **Patel, S. N., et al.** 2009. In vitro activity of ceftaroline, ceftobiprole and cethromycin against clinical isolates of *Streptococcus pneumoniae* collected from across Canada between 2003 and 2008. J. Antimicrob. Chemother. **64:**659–660.
27. **Sader, H. S., T. R. Fritsche, K. Kaniga, Y. Ge, and R. N. Jones.** 2005. Antimicrobial activity and spectrum of PPI-0903M (T-91825), a novel cephalosporin, tested against a worldwide collection of clinical strains. Antimicrob. Agents Chemother. **49:**3501–3512.
28. **Saravolatz, L., J. Pawlak, and L. Johnson.** 2010. In vitro activity of ceftaroline against community-associated methicillin-resistant, vancomycin-intermediate, vancomycin-resistant, and daptomycin-nonsusceptible *Staphylococcus aureus* isolates. Antimicrob. Agents Chemother. **54:**3027–3030.
29. **Speldooren, V., B. Heym, R. Labia, and M.-H. Nicolas-Chanoine.** 1998. Discriminatory detection of inhibitor-resistant β-lactamases in *Escherichia coli* by single-strand conformation polymorphism-PCR. Antimicrob. Agents Chemother. **42:**879–884.
30. **Zhanel, G. G., et al.** 2009. Ceftaroline: a novel broad-spectrum cephalosporin with activity against meticillin-resistant *Staphylococcus aureus*. Drugs **69:**809–831.