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Antimicrobial Susceptibility Studies

Activity of ceftaroline against pathogens associated with community-acquired pneumonia collected as part of the AWARE surveillance program, 2015–2016

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ABSTRACT

We report Assessing Worldwide Antimicrobial Resistance Evaluation (AWARE) program data for ceftaroline and comparators against isolates collected from identified lower respiratory tract sources in 2015 and 2016. MICs and susceptibility were determined using CLSI broth microdilution methodology and EUCAST breakpoints. Ceftaroline susceptibility among penicillin-resistant *Streptococcus pneumoniae* (MIC≥4 mg/L [nonmeningitis breakpoint]) ranged from 77.4% (Asia, 72/93) to 100% (Oceania, 16/16; Latin America, 15/15). Among MRSA, ceftaroline susceptibility ranged from 72.3% (Asia, 553/765) to 100% (Oceania, 39/39). Among β-lactamase–positive *Haemophilus influenzae*, ceftaroline susceptibility ranged from 69.2% (Asia, 36/52) to 100% (Oceania, 19/19). Susceptibility to ceftaroline against non–ESBL-producing *Klebsiella pneumoniae* was between 91.4% (Europe, 659/721) and 100% (Oceania, 55/55) and for *Escherichia coli* between 85.7% (Africa/Middle East, 42/49) and 92.1% (Oceania, 35/38). Ceftaroline is not active against ESBL producers. In this study, susceptibility to ceftaroline was high among the *S. pneumoniae*, *Staphylococcus aureus*, β-lactamase–negative *H. influenzae*, and ESBL-negative *K. pneumoniae* and *E. coli* collected.

1. Introduction

According to World Health Organization (WHO) figures, lower respiratory infections caused approximately 3.0 million deaths worldwide in 2016 (WHO, 2018). Furthermore, community-acquired pneumonia (CAP) is one of the most common infectious diseases and a major cause of mortality and morbidity worldwide (Baer et al., 2018; Blasi et al., 2012; Isturiz et al., 2010; Welte et al., 2012).

A number of the resistant phenotypes of pathogens commonly associated with CAP are listed on the WHO priority pathogens list for research and development of new antimicrobials (WHO, 2017). Included on the list are: carbapenem-resistant and third-generation cephalosporin-resistant Enterobacteriaceae (critical 'priority 1'); methicillin-resistant *Staphylococcus aureus* (MRSA; high 'priority 2'); and penicillin nonsusceptible *Streptococcus pneumoniae* and ampicillin-resistant *Haemophilus influenzae* (medium 'priority 3').

Ceftaroline, the active metabolite of the prodrug ceftaroline fosamil, is a broad-spectrum cephalosporin with activity against many of the pathogens associated with CAP (Farrell et al., 2013; Flamm et al., 2013, 2014; Jones et al., 2011; Karlowsky et al., 2016; Sader et al., 2018). Phase 3 clinical trials, FOCUS 1 (NCT00621504) and FOCUS 2 (NCT00509106), showed that ceftaroline fosamil was noninferior to ceftriaxone for the treatment of hospitalized adult patients with CAP (File et al., 2011; Low et al., 2011). Ceftaroline fosamil was approved by the United States Food and Drug Administration (US-FDA) for the treatment of community acquired bacterial pneumonia in 2010 (TEFLARO®, 2018) and by the European Medicines Agency (EMA) for the treatment of CAP in 2012 (European Medicines Agency (EMA), 2018). Ceftaroline is bactericidal by irreversibly binding penicillin-binding proteins (PBPs) in vitro to inhibit the biosynthesis of the bacterial cell wall (Moisan et al., 2010), and in rare cases the activity of ceftaroline against MRSA can be affected by mutations in PBP2a (Alm et al., 2014).

The Assessing Worldwide Antimicrobial Resistance Evaluation (AWARE) surveillance program is an ongoing global surveillance study that has monitored the in vitro activity of ceftaroline against clinically important pathogens. In 2018, AWARE became part of the Antimicrobial Testing Leadership and Surveillance program. This report presents the antimicrobial susceptibility data for ceftaroline and comparators against pathogens frequently associated with CAP (*S. pneumoniae*, *S. aureus*, *H. influenzae*, *Klebsiella pneumoniae*, *Klebsiella oxytoca*, and *Escherichia coli*). Isolates were collected from identified

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lower respiratory tract sources in 2015 and 2016 from centers in Africa/Middle East, Asia, Europe, Oceania, and Latin America as part of the AWARE program.

2. Materials and methods

Nonduplicate isolates of organisms frequently associated with CAP (*S. pneumoniae*, *S. aureus*, *H. influenzae*, *K pneumoniae*, *K. oxytoca*, and *E.coli*) were collected between 2015 and 2016 as part of the AWARE surveillance program. All isolates were collected from identified lower respiratory tract sources at 132 study centers across 5 regions: Africa/Middle East ($n = 11$); Asia ($n = 18$); Europe ($n = 72$); Oceania ($n = 7$), and Latin America ($n = 24$). One isolate per species per patient was collected, and demographic data recorded included specimen source, primary site of infection, sex and age of the patient, and the ward location of hospitalized patients.

Isolates were identified locally and shipped to a central laboratory where their identities were confirmed and susceptibility testing was performed (International Health Management Associates, Inc., Schaumburg, IL, USA). Isolates were identified using matrix-assisted laser desorption ionization-time of flight (MALDI-TOF) mass spectrometry (Bruker Biotyper MALDI-TOF, Bruker Daltonics, Billerica, MA, USA). Susceptibility testing was performed using frozen CLSI reference broth microdilution panels (CLSI, 2015). MIC values were interpreted using EUCAST 2018 breakpoints where available (European Committee on Antimicrobial Susceptibility Testing, 2018). Ceftriaxone was tested against *K pneumoniae*, *K. oxytoca*, and *E.coli* in 2016 only. The methicillin resistance status of each *S. aureus* isolate was determined using the oxacillin MIC method, in accordance with CLSI guidelines (CLSI, 2017). β-Lactamase production among *H. influenzae* isolates was detected using the nitrocefin disk method (Isenberg, 1998), and extended-spectrum β-lactamase (ESBL) production among the Enterobacteriaceae was detected according to CLSI guidelines.

3. Results

A total of 12,321 isolates were collected from identified lower respiratory tract specimens globally in 2015 and 2016 as part of the AWARE program. Isolates included were of organisms frequently associated with CAP: *S. pneumoniae* ($n = 2696$; 21.9%), *S. aureus* ($n = 4615$; 37.5%), *H. influenzae* ($n = 1177$; 9.6%), *K. pneumoniae* ($n = 2335$; 19.0%), *K. oxytoca* ($n = 356$; 2.9%), and *E. coli* ($n = 1142$; 9.3%). The majority (57.5%) were collected in Europe (Table 1). Approximately one third of isolates (34.4%) were collected from patients in the intensive care unit (ICU), and the large majority were from in-patients (89.2%). The most common culture sources were sputum (55.1%) and endotracheal aspirate (25.4%).

Table 1
Patient demographics and culture sources for organisms from identified lower respiratory tract sources collected as part of the AWARE program, 2015–2016.

Demographic parameter	*n* (%) of patients ($N = 12,321$)
Region	
Africa/Middle East	988 (8.0)
Asia	2545 (20.7)
Europe	7089 (57.5)
Oceania	420 (3.4)
Latin America	1279 (10.4)
Gender	
Male	7662 (62.2)
Female	4615 (37.5)
Unknown	44 (0.4)
Patient location	
ICU	4243 (34.4)
Non-ICU	7576 (61.5)
Unknown	502 (4.1)
Inpatient	10,993 (89.2)
Outpatient	826 (6.7)
Unknown	502 (4.1)
Culture source	
Bronchials	899 (7.3)
Bronchoalveolar lavage	1449 (11.8)
Endotracheal aspirate	3125 (25.4)
Lungs	55 (0.4)
Sputum	6793 (55.1)
Patient age (years)	
0–18	1661 (13.5)
18–64	5170 (42.0)
65 and over	5431 (44.1)
Unknown	59 (0.5)

ICU = intensive care unit.

3.1. Streptococcus pneumoniae

A total of 2696 *S. pneumoniae* isolates were collected during the study; 1597 (59.2%) were penicillin-susceptible (MIC ≤0.06 mg/L [nonmeningitis EUCAST breakpoint]), 255 (9.5%) were penicillin-resistant (MIC ≥4 mg/L [nonmeningitis EUCAST breakpoint]), and 844 (31.3%) exhibited penicillin-intermediate susceptibility (Fig. 1a). The rate of penicillin resistance among *S. pneumoniae* isolates varied between regions and ranged from 5.6% in Europe to 18.9% in Asia. All penicillin-susceptible *S. pneumoniae* (PSSP) were susceptible to ceftaroline (Table 2), and susceptibility rates to ceftaroline among penicillin-intermediate *S. pneumoniae* (PISP) were 100% in all regions except Asia (1 PISP isolate collected in Asia in 2015 was resistant [MIC 0.5 mg/L]). Rates of susceptibility to ceftaroline remained above 90% among penicillin-resistant *S. pneumoniae* (PRSP) isolates collected in Europe (94.6%), Oceania (100%), and Latin America (100%) but were 86.8% and 77.4% in Africa/Middle East and Asia, respectively.

All *S. pneumoniae* isolates collected during the study were susceptible to vancomycin, and the susceptibility rates among isolates of PSSP, PISP, and PRSP to linezolid were 100% except for PISP isolates collected in Africa/Middle East (99.2%) (Table 2). Rates of susceptibility to levofloxacin and moxifloxacin were high among PSSP, PISP, and PRSP isolates (≥93.8% in each region with the exception of PRSP isolates collected in Asia [81.7% for both antimicrobials]). As with the agents listed above, susceptibility to ceftriaxone was high against PSSP isolates (100% in all regions except Asia [99.5%]); however, rates were lower among PISP isolates (range from 52.8% in Asia to 80.6% in Oceania) and PRSP isolates (≤6.7% in all regions).

3.2. Staphylococcus aureus

Of the 4615 *S. aureus* isolates that were collected during this study; 1909 (41.4%) were methicillin-susceptible *S. aureus* (MSSA). Across all regions, all isolates of MSSA were susceptible to ceftaroline, daptomycin, vancomycin, and linezolid (Table 2). Rates of susceptibility to the fluoroquinolones levofloxacin and moxifloxacin were ≥92.5% in each region. For the remaining antimicrobials with EUCAST susceptibility breakpoints (gentamicin, minocycline, teicoplanin, tigecycline, and trimethoprim-sulfamethoxazole), susceptibility rates among MSSA isolates were ≥90.3%.

A total of 2706 (58.6%) *S. aureus* isolates collected globally were MRSA (Fig. 1b). Rates of MRSA ranged from 49.9% in Latin America and 50.6% in Oceania to 69.2% in Asia. Susceptibility to daptomycin, vancomycin, linezolid, and tigecycline was high among MRSA isolates (≥98.0% in each region) (Table 2). The percentage of isolates that were susceptible to ceftaroline varied between regions, from 72.3% in Asia to 100% in Oceania. There was some variability in MRSA susceptibility to gentamicin, minocycline, teicoplanin, and trimethoprim-sulfamethoxazole between regions; however, with the exception of trimethoprim-sulfamethoxazole, rates are generally lower in Asia

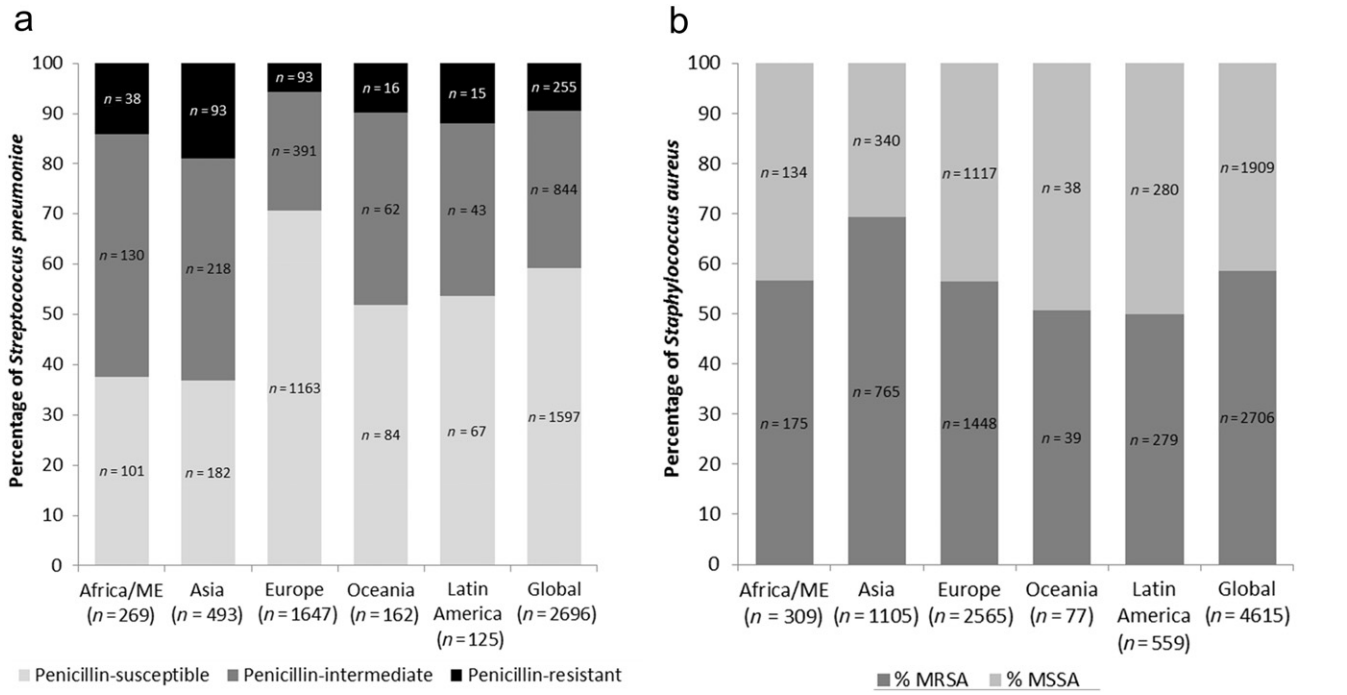

Fig. 1. Regional and global rates of (a) penicillin-susceptible (MIC ≤0.06 mg/L [nonmeningitis EUCAST breakpoint]), -intermediate, and -resistant (MIC ≥4 mg/L [nonmeningitis EUCAST breakpoint]) *S. pneumoniae* isolates and (b) MRSA and MSSA isolates from identified respiratory tract sources collected as part of the AWARE program, 2015–2016. Africa/ME, Africa/Middle East.

compared with the other regions. Susceptibility to levofloxacin and moxifloxacin was lower than seen for other antimicrobials in the panel (≤46.2% in each region).

3.3. Haemophilus influenzae

A total of 1177 *H. influenzae* isolates were collected during the study; 937 (79.6%) were β-lactamase negative (βL-negative), and 240 (20.4%) were β-lactamase positive (βL-positive). Rates of βL-positive *H. influenzae* varied between regions; the lowest rate was in Europe (17.8%), and the highest in Oceania (29.7%) (Fig. 2). Rates of susceptibility to ceftaroline among βL-negative isolates were ≥91.1% in each of the regions except Asia (82.2%) (Table 3). Among βL-positive *H. influenzae* isolates, ceftaroline susceptibility was ≥86.4% in each region except Asia (69.2%).

Susceptibility of βL-negative *H. influenzae* to ceftriaxone was relatively lower in Asia (89.1%) when compared to the other regions (100% in Africa/Middle East, Oceania and Latin America, and 99.5% in Europe) (Table 3). All βL-positive *H. influenzae* isolates collected in Europe, Oceania, and Latin America were susceptible to ceftriaxone, and susceptibility rates in Africa/Middle East and Asia were 95.5% and 86.5%, respectively. Isolates of both βL-negative and βL-positive *H. influenzae* collected in Asia, Europe, Oceania, and Latin America were susceptible to levofloxacin (≥ 91.5%), and rates among isolates collected in Africa/Middle East were 87.2% and 77.3% for βL-negative and βL-positive isolates, respectively. All *H. influenzae* isolates were susceptible to meropenem, and susceptibility to doripenem and imipenem was high in each region (≥95.6% among βL-negative and ≥96.2% among βL-positive *H. influenzae*).

3.4. Klebsiella pneumoniae

During the course of the study, 2335 *K. pneumoniae* isolates were collected, of which 1380 (59.1%) were non-ESBL producers (Table 3). Susceptibility to ceftaroline among non–ESBL-producing *K. pneumoniae* was high in all regions (≥91.4%). Susceptibility rates of the carbapenems against non–ESBL-producing *K. pneumoniae* isolates were ≥99.4% in each region, and rates for amikacin, colistin, and tigecycline rates were ≥94.5%. Rates of susceptibility to ceftriaxone among non–ESBL-producing *K. pneumoniae* were 100% in all regions except Europe (98.9%).

A total of 955 (40.9%) *K. pneumoniae* isolates were ESBL producers (Fig. 2). The rate of ESBL producers was lowest in Oceania (12.7%) compared to the other regions (40.2% in Europe, 41.2% in Asia, 44.8% in Latin America, and 46.6% in Africa/Middle East). Only 8 isolates of ESBL-producing *K. pneumoniae* were collected in Oceania, and susceptibility rates were therefore not calculated for this region. Susceptibility to ceftaroline and ceftriaxone among ESBL-producing *K. pneumoniae* isolates was negligible (≤2.3% and ≤6.6%, respectively, in each region not including Oceania) (Table 3). Susceptibility to carbapenems among ESBL producers was lower among isolates collected in Europe (72.0% for imipenem and meropenem; 70.9% for doripenem) compared with Africa/Middle East, Asia, and Latin America (range 81.9–95.5% for imipenem, 81.3–95.5% for doripenem, and 83.9–95.5% for meropenem). Rates of susceptibility to colistin ranged from 87.6% in Europe to 98.9% in Africa/Middle East.

3.5. Klebsiella oxytoca

A total of 356 *K. oxytoca* isolates were collected during the study. Susceptibility of *K. oxytoca* isolates to ceftaroline was lower in Asia (63.4%) compared with the other regions where susceptibility ranged between 79.2% (Latin America) and 100% (Oceania) (Table 3). There were regional differences in susceptibility to ceftriaxone, and rates ranged from 75.9% and 77.8% in Asia and Latin America, respectively, to 100% in Africa/Middle East and Oceania. Susceptibility of *K. oxytoca* isolates to levofloxacin was high in Africa/Middle East, Europe, and Oceania (96.4%, 93.9%, and 100%, respectively) and lower in Asia (75.6%) and Latin America (81.3%). Susceptibility to the carbapenems was 100% in each region except Europe; however, rates in Europe were also high (≥97.8%). All *K. oxytoca* isolates collected in Africa/Middle East, Oceania, and Latin America were susceptible to colistin (97.6% and 99.6% in Asia and Europe, respectively).

Table 2
Antimicrobial activity against *S. aureus* and *S. pneumoniae* isolates from identified lower respiratory tract sources collected as part of the AWARE program, 2015–2016.

Organism/ agent	Africa/Middle East			Asia			Europe			Oceania			Latin America		
	MIC_{90} (mg/L)	MIC range (mg/L)	%S	MIC_{90} (mg/L)	MIC range (mg/L)	%S	MIC_{90} (mg/L)	MIC range (mg/L)	%S	MIC_{90} (mg/L)	MIC range (mg/L)	%S	MIC_{90} (mg/L)	MIC range (mg/L)	%S
PSSP	***N* = 101**			***N* = 182**			***N* = 1163**			***N* = 84**			***N* = 67**		
CPT	0.015	≤0.004–0.12	100	0.06	≤0.004–0.12	100	0.015	≤0.004–0.06	100	0.015	≤0.004–0.03	100	0.015	≤0.004–0.06	100
AMC	0.06	≤0.015–0.12	-	0.06	≤0.015–0.12	-	0.03	≤0.015–1	-	0.03	≤0.015–0.06	-	0.06	≤0.015–0.12	-
CRO	0.06	≤0.015–0.25	100	0.25	≤0.015–1	99.5	0.06	≤0.015–0.5	100	0.03	≤0.015–0.25	100	0.12	≤0.015–0.25	100
CLI	0.06	≤0.008–≥2	95.0	≥2	≤0.008–≥2	78.0	0.06	≤0.008–≥2	91.7	0.06	0.03–≥2	96.4	0.12	0.03–≥2	92.5
DAP	0.5	0.06–1	-	0.5	0.06–1	-	0.5	≤0.03–2	-	0.5	0.12–1	-	0.5	0.12–0.5	-
DOP	≤0.015	≤0.015–0.03	100	≤0.015	≤0.015–0.06	100	≤0.015	≤0.015–0.12	100	≤0.015	≤0.015–0.015	100	≤0.015	≤0.015–0.06	100
ERY	0.06	0.015–≥2	93.1	≥2	≤0.008–≥2	71.4	0.5	≤0.008–≥2	89.9	0.06	0.015–≥2	90.5	≥2	≤0.008–≥2	88.1
LVX	1	0.25–≥16	98.0	2	≤0.12–2	100	1	≤0.12–≥16	99.3	1	0.25–2	100	1	0.5–≥16	98.5
LZD	2	0.12–2	100	2	0.12–2	100	2	≤0.06–2	100	2	0.12–2	100	2	0.12–2	100
MIN	0.5	≤0.015–≥4	90.1	≥4	≤0.015–≥4	71.4	1	≤0.015–≥4	89.4	0.12	≤0.015–≥4	95.2	≥4	0.03–≥4	83.6
MXK	0.12	0.06–4	98.0	0.25	0.06–0.5	100	0.25	≤0.03–≥8	99.3	0.12	0.06–0.25	100	0.12	0.06–2	98.5
TGC	0.03	≤0.008–0.03	-	0.03	≤0.008–0.06	-	0.03	≤0.008–0.12	-	0.03	≤0.008–0.03	-	0.03	≤0.008–0.03	-
VAN	0.5	0.03–0.5	100	0.5	0.06–0.5	100	0.5	≤0.008–1	100	0.5	0.12–0.5	100	0.5	0.06–0.5	100
PISP	***N* = 130**			***N* = 218**			***N* = 391**			***N* = 62**			***N* = 43**		
CPT	0.12	0.008–0.25	100	0.12	0.015–0.5	99.5	0.12	≤0.004–0.25	100	0.12	0.008–0.25	100	0.12	0.008–0.12	100
AMC	2	≤0.015–8	-	4	≤0.015–≥16	-	2	≤0.015–≥16	-	2	≤0.015–4	-	4	0.06–≥16	-
CRO	1	≤0.015–2	76.9	2	≤0.015–≥8	52.8	1	≤0.015–2	76.7	1	0.06–2	80.6	1	0.03–2	72.1
CLI	≥2	0.015–≥2	67.7	≥2	≤0.008–≥2	39.4	≥2	0.015–≥2	55.0	≥2	0.015–≥2	79.0	≥2	0.03–≥2	55.8
DAP	0.5	0.12–0.5	-	0.5	0.06–1	-	0.5	≤0.03–1	-	0.5	0.12–1	-	0.5	0.12–1	-
DOP	0.5	≤0.015–1	100	1	≤0.015–2	99.1	1	≤0.015–2	99.5	0.5	≤0.015–2	98.4	1	0.03–1	100
ERY	≥2	≤0.008–≥2	41.5	≥2	0.015–≥2	15.6	≥2	0.015–≥2	38.1	≥2	0.015–≥2	53.2	≥2	0.015–≥2	37.2
LVX	1	0.5–2	100	2	0.5–≥16	95.9	1	0.25–≥16	98.5	1	0.5–2	100	1	0.5–8	97.7
LZD	1	≤0.06–4	99.2	2	≤0.06–2	100	2	0.12–2	100	2	0.12–2	100	2	≤0.06–2	100
MIN	≥4	≤0.015–≥4	55.4	≥4	≤0.015–≥4	22.5	≥4	≤0.015–≥4	48.1	≥4	≤0.015–≥4	67.7	≥4	≤0.015–≥4	48.8
MXK	0.12	0.06–0.25	100	0.25	0.06–≥8	96.3	0.12	≤0.03–4	98.2	0.25	0.06–0.5	100	0.25	0.06–2	97.7
TGC	0.03	≤0.008–0.06	-	0.03	≤0.008–0.12	-	0.03	≤0.008–0.06	-	0.03	≤0.008–0.03	-	0.03	≤0.008–0.03	-
VAN	0.5	0.06–0.5	100	0.5	0.06–0.5	100	0.5	0.06–0.5	100	0.5	0.25–0.5	100	0.5	0.12–1	100
PRSP	***N* = 38**			***N* = 93**			***N* = 93**			***N* = 16**			***N* = 15**		
CPT	0.5	0.03–0.5	86.8	1	0.03–8	77.4	0.25	0.03–1	94.6	0.25	0.12–0.25	100	0.25	0.03–0.25	100
AMC	8	2–≥16	-	≥16	0.03–≥16	-	≥16	0.5–≥16	-	8	2–≥16	-	8	4–8	-
CRO	≥8	0.5–≥8	5.3	≥8	0.03–≥8	2.2	4	0.5–≥8	4.3	2	1–2	0.0	2	0.5–2	6.7
CLI	≥2	0.03–≥2	23.7	≥2	0.015–≥2	17.2	≥2	0.03–≥2	35.5	≥2	0.06–≥2	6.3	≥2	0.03–≥2	13.3
DAP	0.5	0.12–0.5	-	0.5	0.12–1	-	0.5	≤0.03–1	-	0.5	0.25–1	-	0.25	0.12–0.25	-
DOP	1	0.5–2	94.7	4	≤0.015–≥8	69.9	2	0.5–2	69.9	2	1–2	62.5	2	0.03–2	80.0
ERY	≥2	0.03–≥2	7.9	≥2	0.03–≥2	6.5	≥2	0.015–≥2	20.4	≥2	2–≥2	0.0	≥2	2–≥2	0.0
LVX	1	0.5–≥16	97.4	≥16	0.5–≥16	81.7	1	0.25–≥16	96.8	2	0.5–4	93.8	1	0.5–1	100
LZD	1	0.25–2	100	1	0.25–2	100	2	0.12–2	100	1	0.25–1	100	0.5	0.25–1	100
MIN	≥4	0.06–≥4	26.3	≥4	0.03–≥4	15.1	≥4	0.03–≥4	31.2	≥4	1–≥4	0.0	≥4	0.06–≥4	13.3
MXK	0.25	0.06–4	97.4	4	0.06–≥8	81.7	0.25	0.06–≥8	97.8	0.12	0.12–0.25	100	0.12	0.12–0.12	100
TGC	0.03	≤0.008–0.03	-	0.03	≤0.008–0.06	-	0.03	0.015–0.06	-	0.03	≤0.008–0.03	-	0.03	0.015–0.03	-
VAN	0.5	0.12–0.5	100	0.5	0.12–0.5	100	0.5	0.06–0.5	100	0.5	0.25–0.5	100	0.5	0.25–0.5	100
MSSA	***N* = 134**			***N* = 340**			***N* = 1117**			***N* = 38**			***N* = 280**		
CPT	0.25	0.12–0.5	100	0.25	0.12–0.5	100	0.25	≤0.015–0.5	100	0.25	0.12–0.25	100	0.25	0.12–0.5	100
DAP	0.5	0.25–1	100	1	0.25–1	100	0.5	≤0.06–1	100	1	0.25–1	100	0.5	0.12–1	100
DOP	0.06	0.015–0.25	-	0.12	0.03–0.5	-	0.12	≤0.008–1	-	0.06	0.03–0.12	-	0.12	≤0.008–0.5	-
GEN	1	0.12–≥64	94.0	1	≤0.06–≥64	90.3	0.5	≤0.06–≥64	96.5	0.5	0.12–≥64	94.7	1	≤0.06–≥64	92.9
LVX	1	0.06–≥8	92.5	0.25	0.06–≥8	95.0	0.5	≤0.015–≥8	94.6	0.25	0.12–0.5	100	0.5	0.06–≥8	96.4
LZD	2	≤0.5–2	100	2	≤0.5–4	100	2	≤0.5–2	100	2	≤0.5–2	100	2	≤0.5–4	100
MEM	0.12	0.06–0.5	-	0.25	0.03–4	-	0.25	≤0.015–2	-	0.25	0.06–0.25	-	0.12	0.03–4	-
MIN	≤0.12	≤0.12–4	99.3	≤0.12	≤0.12–8	98.2	≤0.12	≤0.12–≥16	98.4	≤0.12	≤0.12–0.25	100	≤0.12	≤0.12–≥16	99.3
MXK	0.12	0.015–4	92.5	0.12	0.015–≥8	94.4	0.12	≤0.008–≥8	94.4	0.06	0.03–0.12	100	0.12	0.015–≥8	96.1
TEC	1	0.25–1	100	1	0.25–4	99.7	1	≤0.12–4	99.8	1	0.25–2	100	1	≤0.12–4	98.9
TGC	0.25	≤0.015–0.5	100	0.25	≤0.015–0.5	100	0.25	≤0.015–1	99.9	0.25	0.03–0.25	100	0.25	≤0.015–1	99.6
SXT	0.5	≤0.25–≥8	97.8	≤0.25	≤0.25–≥8	99.1	≤0.25	≤0.25–≥8	99.0	≤0.25	≤0.25–0.25	100	≤0.25	≤0.25–2	100
VAN	2	0.5–2	100	2	≤0.25–2	100	2	≤0.25–2	100	2	0.5–2	100	2	≤0.25–2	100
MRSA	***N* = 175**			***N* = 765**			***N* = 1448**			***N* = 39**			***N* = 279**		
CPT	2	0.25–2	89.7	2	0.12–8	72.3	1	0.06–4	93.0	1	0.25–1	100	2	0.25–4	74.9
DAP	1	0.25–1	100	1	≤0.06–2	99.7	1	0.12–2	99.9	0.5	0.25–1	100	1	0.25–1	100
DOP	≥8	0.06–≥8	-	≥8	0.015–≥8	-	≥8	≤0.008–≥8	-	≥8	0.12–≥8	-	≥8	0.12–≥8	-
GEN	≥64	0.12–≥64	68.0	≥64	≤0.06–≥64	35.3	≥64	≤0.06–≥64	84.6	≥64	0.12–≥64	71.8	≥64	0.12–≥64	67.4
LVX	≥8	0.12–≥8	15.4	≥8	0.06–≥8	23.0	≥8	0.06–≥8	22.4	≥8	0.12–≥8	46.2	≥8	0.12–≥8	30.5
LZD	2	≤0.5–2	100	2	≤0.5–2	100	2	≤0.5–≥16	99.7	2	1–2	100	2	≤0.5–2	100
MIN	4	≤0.12–≥16	88.6	≥16	≤0.12–≥16	49.2	0.25	≤0.12–≥16	91.8	8	≤0.12–≥16	79.5	≤0.12	≤0.12–4	97.1
MXK	≥8	≤0.008–≥8	14.9	≥8	0.015–≥8	22.9	≥8	0.015–≥8	22.0	2	0.03–4	46.2	≥8	0.015–≥8	30.1
TEC	1	0.25–2	100	4	0.25–8	82.9	2	≤0.12–8	97.4	1	0.25–2	100	2	0.25–4	99.6
TGC	0.25	≤0.015–0.5	100	0.5	≤0.015–1	98.0	0.25	≤0.015–0.5	100	0.25	0.06–0.5	100	0.25	0.03–1	99.6
SXT	≥8	≤0.25–≥8	89.1	≥8	≤0.25–≥8	88.4	≤0.25	≤0.25–≥8	98.2	≥8	≤0.25–≥8	74.4	≤0.25	≤0.25–≥8	96.4
VAN	2	≤0.25–2	100	2	0.5–4	99.9	2	≤0.25–2	100	1	0.5–2	100	2	0.5–2	100

MIC = minimum inhibitory concentration; MIC_{90} = MIC required to inhibit growth of 90% of isolates; S = susceptible; MSSA = methicillin-susceptible *S. aureus*; MRSA = methicillin-resistant *S. aureus*; PSSP = penicillin-susceptible *S. pneumoniae*; PISP = penicillin-intermediate *S. pneumoniae*; PRSP = penicillin-resistant *S. pneumoniae*; AMC = amoxicillin-clavulanate; CLI = clindamycin; CPT = ceftaroline; CRO = ceftriaxone; DAP = daptomycin; DOP = doripenem; ERY = erythromycin; GEN = gentamicin; LVX = levofloxacin; LZD = linezolid; MEM = meropenem; MIN = minocycline; MXK = moxifloxacin; TEC = teicoplanin; TGC = tigecycline; SXT = trimethoprim-sulfamethoxazole; VAN = vancomycin.
Data from China were not available.

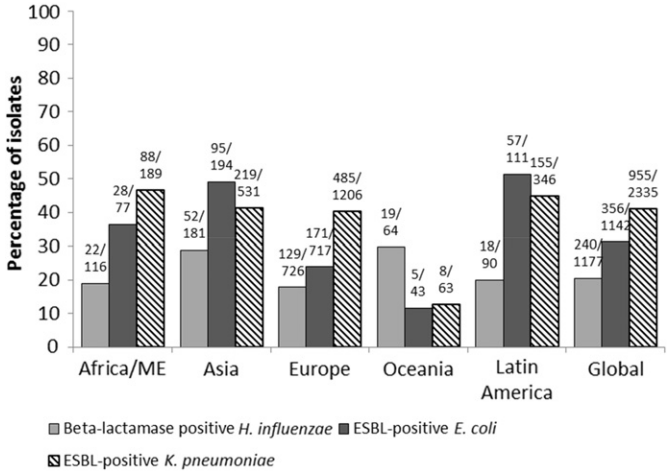

Fig. 2. Regional and global rates of βL-positive *H. influenzae*, ESBL-positive *E. coli*, and ESBL-positive *K. pneumoniae* isolates from identified respiratory tract sources collected as part of the AWARE program, 2015–2016. Africa/ME, Africa/Middle East; ESBL, extended-spectrum β-lactamase.

3.6. Escherichia coli

A total of 1142 *E. coli* isolates were collected, of which 786 (68.8%) were non–ESBL producers (Table 3). Rates of susceptibility to ceftaroline among non–ESBL producers ranged from 85.7% in Asia to 92.1% in Oceania. All non–ESBL-producing *E. coli* isolates collected in Africa/Middle East, Asia, and Latin America were susceptible to ceftriaxone, and rates in Europe and Oceania were high (99.2% and 94.7%, respectively). Rates of susceptibility to levofloxacin varied between regions, ranging from 54.5% in Asia to 86.8% in Oceania. All non–ESBL-producing *E. coli* isolates were susceptible to doripenem, imipenem, and meropenem.

A total of 356 (31.2%) *E. coli* isolates were ESBL producers, and rates of ESBL producers varied between regions (from 11.6% in Oceania to 49.0% in Asia and 51.4% in Latin America) (Fig. 2). Only 5 isolates of ESBL-producing *E. coli* were collected in Oceania, and susceptibility rates were therefore not calculated for this region. Ceftaroline, ceftriaxone, and levofloxacin susceptibility among ESBL-producing *E. coli* was low (≤22.2%) (Table 3). However, susceptibility to carbapenems was high in all regions (≥95.8% in each region not including Oceania). All isolates of ESBL-producing *E. coli* collected in Africa/Middle East, Asia, and Latin America were susceptible to colistin, and the susceptibility rate of isolates collected in Europe was 98.8%.

4. Discussion

CAP is most commonly caused by *S. pneumoniae*, and resistance to penicillin is problematic (Mpenge and MacGowan, 2015; Peto et al., 2014; Torres et al., 2014). In the present study, there were regional differences in rates of PRSP; Europe reported the lowest rate at 5.6%, similar to the rate reported among European isolates (2010) from community-acquired respiratory tract infections (CARTI) as part of the AWARE study (5.9% using EUCAST breakpoints) (Farrell et al., 2013). The highest rate of PRSP in the current study was reported among isolates from Asia (18.9%); countries in Asia have been associated with higher rates of resistance in other studies (Tomic and Dowzicky, 2014).

In the present study, all PSSP and PISP isolates were susceptible to ceftaroline (except 1 PISP isolate collected in Asia). Similarly, an earlier AWARE publication reported that all PSSP and PISP isolates from CARTI collected in Europe in 2010 were susceptible to ceftaroline (Farrell et al., 2013). In our study, ceftaroline susceptibility among PRSP isolates was variable between regions. In Europe, the rate of susceptibility to ceftaroline among PRSP was 94.6%, which is similar to the rate reported among CARTI isolates in a previous AWARE study (99.2%; 2010) (Farrell et al., 2013). Rates were relatively lower in Africa/Middle East (86.8%) and Asia (77.4%). A previous AWARE study reported similar results for PRSP isolates collected in African and Middle Eastern countries (84.6%; 2012–2014) (Karlowsky et al., 2016).

The recommended empirical antimicrobials for the treatment of CAP depend on a number of factors and often include respiratory fluoroquinolones (e.g., levofloxacin and moxifloxacin) and ceftriaxone. As with ceftaroline, susceptibility among PSSP, PISP, and PRSP isolates to levofloxacin and moxifloxacin was high (≥95.9% for PSSP and PISP; ≥81.7% for PRSP). Like ceftaroline, susceptibility among PSSP isolates to ceftriaxone was high (100% in all regions except Asia [99.5%]). A similar rate of susceptibility to ceftriaxone was reported among CARTI PSSP isolates collected in Europe in 2010 (99.8%) (Farrell et al., 2013), but rates were higher in our study than those reported by Karlowsky et al. for isolates collected in Africa and the Middle East (75.5%; 2012–2014) (Karlowsky et al., 2016). However, while susceptibility to ceftaroline among PISP and PRSP isolates remained high, susceptibility to ceftriaxone was reduced among isolates with these phenotypes (range 52.8–80.6% among PISP; ≤6.7% in all regions among PRSP). Farrell et al. (2013) reported a similar pattern of reduced susceptibility to ceftriaxone among the CARTI isolates collected in Europe (87.7% among PISP; 3.1% among PRSP) (Farrell et al., 2013).

S. aureus is another important cause of CAP. The global rate of MRSA in this study was 58.6% and was noticeably higher in Asia compared to the other regions (69.2%). A global T.E.S.T. study (2014–2016) also reported higher MRSA rates in Asia compared with other regions for isolates collected from all body sites (Seifert et al., 2018). Furthermore, a study from the SENTRY program (2015–2017) that included organisms causing community-acquired bacterial pneumonia reported higher MRSA rates in the Asia-Pacific region (31.9%) compared to the other regions included in the study (20.4% and 23.7% in Europe and Latin America, respectively); and rates for each of these regions were noticeably lower than reported in this AWARE study (Sader et al., 2018). Susceptibility to ceftaroline among MRSA isolates in this study varied between regions, demonstrating the need to know regional susceptibility rates. All MSSA isolates collected in each region were susceptible to ceftaroline, and previous AWARE studies have shown that MSSA isolates collected in Africa and the Middle East and Europe were all susceptible to ceftaroline (Jones et al., 2011; Karlowsky et al., 2016). The susceptibility of MSSA isolates to the respiratory fluoroquinolones included in this AWARE study was high (≥ 92.5%); susceptibility was lower than was seen for ceftaroline (100% in each region). A similar result was reported by Karlowsky et al. for MSSA isolates collected in Africa and the Middle East (susceptibility rate 95.0% for both levofloxacin and moxifloxacin, and 100% for ceftaroline) (Karlowsky et al., 2016). The rate of susceptibility among isolates of MRSA was much higher to ceftaroline (range 72.3–100%) than levofloxacin (15.4–46.2%) and moxifloxacin (14.9–46.2%). Karlowsky et al. (2016) also reported that susceptibility was higher to ceftaroline (87.8%) than levofloxacin and moxifloxacin (9.0% for each) against MRSA isolates collected in Africa and the Middle East (Karlowsky et al., 2016).

A high rate of susceptibility among βL-negative and βL-positive *H. influenzae* to ceftaroline was seen in all regions except Asia, where susceptibility rates were lower and MIC_{90} values were higher (82.2% and 69.2%, respectively; MIC_{90} 0.12 mg/L and 0.25 mg/L, respectively) compared with the other regions, and a similar pattern of susceptibility was observed to ceftriaxone. A previous study from AWARE (2012–2014) also reported higher MIC_{90} values for both ceftaroline and ceftriaxone among βL-negative and βL-positive *H. influenzae* collected from respiratory tract specimens in the Asia-Pacific region in comparison to Europe, Latin America, and Africa/Middle East (Biedenbach et al., 2016). The isolates collected in the present AWARE study are not screened for mechanisms of ceftaroline resistance. However, *H. influenzae* strains with high-level PBP3-mediated resistance

Table 3
Antimicrobial activity against *H. influenzae*, *K. pneumoniae*, *K. oxytoca*, and *E. coli* isolates from identified lower respiratory tract sources collected as part of the AWARE program, 2015–2016.

Organism/ antimicrobial	Africa/Middle East			Asia			Europe			Oceania			Latin America		
	MIC_{90} (mg/L)	MIC range (mg/L)	%S	MIC_{90} (mg/L)	MIC range (mg/L)	%S	MIC_{90} (mg/L)	MIC range (mg/L)	%S	MIC_{90} (mg/L)	MIC range (mg/L)	%S	MIC_{90} (mg/L)	MIC range (mg/L)	%S
βL neg															
H. influenzae	***N* = 94**			***N* = 129**			***N* = 597**			***N* = 45**			***N* = 72**		
CPT	0.03	≤0.015–4	98.9	0.12	≤0.015–0.25	82.2	0.03	≤0.015–0.25	99.2	0.03	≤0.015–0.06	91.1	0.03	≤0.015–0.06	98.6
AMC	2	≤0.06–2	100	4	≤0.06–8	86.0	2	0.12–4	99.2	4	0.12–8	88.9	2	0.12–4	98.6
AMP	1	≤0.06–2	98.9	2	≤0.06–4	81.4	1	≤0.06–2	98.5	1	≤0.06–4	91.1	1	≤0.06–2	98.6
SAM	1	0.06–1	100	2	≤0.03–4	86.0	1	≤0.03–2	99.2	2	0.06–4	88.9	1	0.06–2	98.6
CRO	≤0.03	≤0.03–0.06	100	0.25	≤0.03–0.25	89.1	≤0.03	≤0.03–0.5	99.5	≤0.03	≤0.03–0.12	100	≤0.03	≤0.03–0.06	100
DOP	0.5	≤0.015–1	100	1	0.03–2	97.7	0.5	≤0.015–1	100	1	≤0.015–≥4	95.6	0.5	0.06–1	100
IPM	2	≤0.06–4	98.9	2	≤0.06–8	98.4	1	≤0.06–4	98.7	1	≤0.06–2	100	2	0.25–2	100
LVX	0.5	≤0.004–≥8	87.2	0.03	≤0.004–≥8	91.5	0.03	≤0.004–≥8	97.0	0.03	≤0.004–0.25	95.6	0.03	0.008–0.06	100
MEM	0.12	≤0.015–0.5	100	0.25	≤0.015–0.5	100	0.12	≤0.015–0.5	100	0.25	≤0.015–0.5	100	0.12	0.03–0.25	100
βL pos															
H. influenzae	***N* = 22**			***N* = 52**			***N* = 129**			***N* = 19**			***N* = 18**		
CPT	0.06	≤0.015–0.12	86.4	0.25	≤0.015–1	69.2	0.03	≤0.015–0.25	95.3	0.03	≤0.015–0.03	100	0.06	≤0.015–0.12	88.9
AMC	2	0.25–2	100	4	0.25–8	78.8	2	0.25–16	98.4	2	0.25–2	100	2	0.5–2	100
AMP	≥16	0.12–≥16	4.5	≥16	2–≥16	0.0	≥16	0.25–≥16	1.6	≥16	16–≥16	0.0	≥16	≤0.06–≥16	5.6
SAM	2	0.12–4	50.0	4	0.25–≥16	50.0	2	≤0.03–≥16	52.7	4	0.5–4	31.6	4	1–4	27.8
CRO	≤0.03	≤0.03–0.25	95.5	0.25	≤0.03–0.25	86.5	≤0.03	≤0.03–0.12	100	≤0.03	≤0.03–0.03	100	≤0.03	≤0.03–0.03	100
DOP	0.25	0.03–0.5	100	1	0.03–2	96.2	0.5	≤0.015–1	100	0.5	0.03–0.5	100	0.25	0.03–1	100
IPM	2	≤0.06–2	100	2	0.12–4	98.1	1	0.12–4	96.9	1	0.25–2	100	2	≤0.06–2	100
LVX	1	0.015–≥8	77.3	0.03	≤0.004–≥8	96.2	0.03	≤0.004–0.06	100	0.03	0.015–0.03	100	0.03	≤0.004–0.03	100
MEM	0.06	0.03–0.12	100	0.25	≤0.015–0.25	100	0.12	0.03–0.5	100	0.12	0.03–0.25	100	0.12	≤0.015–0.25	100
Non-ESBL															
K. pneumoniae	***N* = 101**			***N* = 312**			***N* = 721**			***N* = 55**			***N* = 191**		
CPT	0.5	0.06–1	99.0	0.25	≤0.015–4	98.4	0.5	≤0.015–≥256	91.4	0.25	≤0.015–0.5	100	0.25	≤0.015–4	96.9
AMK	2	0.5–4	100	2	≤0.25–4	100	2	≤0.25–≥64	98.9	2	0.5–8	100	2	≤0.25–4	100
AMC	8	1–16	97.0	8	≤0.12–≥64	97.4	16	≤0.12–≥64	87.2	8	1–8	100	8	≤0.12–≥64	93.7
ATM	0.12	≤0.015–0.5	100	0.12	≤0.015–0.5	100	0.25	≤0.015–1	100	0.25	≤0.015–1	100	0.12	≤0.015–1	100
FEP	0.25	≤0.12–1	100	≤0.12	≤0.12–8	99.7	0.25	≤0.12–≥32	98.9	0.25	≤0.12–1	100	≤0.12	≤0.12–4	99.5
CRO	0.12	≤0.06–0.25	100[a]	≤0.06	≤0.06–0.5	100[b]	0.12	≤0.06–16	98.9[c]	0.12	≤0.06–0.25	100[d]	0.12	≤0.06–0.5	100[e]
CST	1	0.12–≥16	98.0	1	0.12–8	99.4	1	0.12–≥16	99.9	1	0.25–4	98.2	1	0.12–≥16	99.0
DOP	0.12	0.03–0.25	100	0.12	≤0.008–0.5	100	0.12	0.015–4	99.4	0.12	0.03–0.5	100	0.12	0.03–0.5	100
IPM	0.5	0.12–2	100	1	0.12–8	99.7	0.5	0.06–4	99.9	0.5	0.12–2	100	0.5	0.12–2	100
LVX	1	0.03–≥16	86.1	1	0.015–≥16	88.1	0.5	0.015–≥16	90.0	0.25	0.03–1	98.2	0.5	0.008–≥16	92.1
MEM	0.06	0.015–0.12	100	0.06	0.015–1	100	0.06	0.03–8	99.7	0.06	0.03–0.12	100	0.06	0.015–0.5	100
TZP	8	1–32	93.1	4	≤0.25–64	97.4	16	≤0.25–≥256	87.1	8	0.5–16	94.5	8	≤0.25–≥256	95.3
TGC	1	0.12–4	95.0	1	0.12–4	95.8	1	0.06–4	95.3	1	0.12–2	94.5	0.5	0.12–8	96.9
ESBL+															
K. pneumoniae	***N* = 88**			***N* = 219**			***N* = 485**			***N* = 8***			***N* = 155**		
CPT	≥256	0.06–≥256	2.3	≥256	0.06–≥256	0.5	≥256	0.25–≥256	0.8				≥256	2–≥256	0.0
AMK	8	0.5–≥64	90.9	16	0.5–≥64	86.3	32	0.5–≥64	73.0				32	1–≥64	76.1
AMC	32	1–≥64	11.4	≥64	2–≥64	10.0	≥64	0.5–≥64	9.3				≥64	4–≥64	8.4
AMP	≥64	16–≥64	0.0	≥64	8–≥64	0.5	≥64	2–≥64	0.2				≥64	64–≥64	0.0
ATM	128	0.03–≥256	3.4	≥256	0.06–≥256	4.1	≥256	0.12–≥256	4.7				≥256	0.25–≥256	3.9
FEP	≥32	≤0.12–≥32	4.5	≥32	≤0.12–≥32	14.6	≥32	≤0.12–≥32	5.8				≥32	≤0.12–≥32	4.5
CRO	≥32	≤0.06–≥32	5.9[f]	≥32	≤0.06–≥32	6.6[g]	≥32	0.12–≥32	4.1[h]				≥32	0.25–≥32	2.7[i]
CST	1	0.12–≥16	98.9	1	0.12–≥16	97.3	8	0.12–≥16	87.6				2	0.25–≥16	92.9
DOP	0.25	0.03–≥16	95.5	4	0.03–≥16	87.2	≥16	0.015–≥16	70.9				≥16	0.03–≥16	81.3
IPM	1	0.12–≥16	95.5	4	0.06–≥16	89.5	≥16	0.06–≥16	72.0				≥16	0.12–≥16	81.9
LVX	≥16	0.06–≥16	33.0	≥16	0.03–≥16	15.1	≥16	0.03–≥16	16.9				≥16	0.03–≥16	24.5
MEM	0.25	0.03–≥16	95.5	8	0.03–≥16	87.7	≥16	0.03–≥16	72.0				≥16	0.03–≥16	83.9
TZP	≥256	2–≥256	43.2	≥256	2–≥256	26.0	≥256	2–≥256	18.8				≥256	2–≥256	31.6
TGC	2	0.25–8	88.6	2	≤0.015–8	82.6	2	0.06–8	86.8				1	0.12–8	90.3
K. oxytoca	***N* = 28**			***N* = 41**			***N* = 228**			***N* = 11**			***N* = 48**		
CPT	4	≤0.015–≥256	89.3	≥256	0.06–≥256	63.4	64	≤0.015–≥256	83.3	0.5	0.06–0.5	100	≥256	≤0.015–≥256	79.2
AMK	4	0.5–32	96.4	2	1–8	100	2	≤0.25–32	99.1	2	1–4	100	4	0.5–16	95.8
AMC	8	≤0.12–16	92.9	16	2–32	82.9	32	≤0.12–≥64	83.8	4	≤0.12–4	100	32	1–≥64	81.3
ATM	4	0.03–128	85.7	128	≤0.015–≥256	65.9	8	≤0.015–≥256	84.2	0.5	0.06–0.5	100	32	≤0.015–≥256	79.2
FEP	0.5	≤0.12–≥32	92.9	8	≤0.12–16	80.5	1	≤0.12–≥32	91.2	≤0.12	≤0.12–0.12	100	4	≤0.12–≥32	87.5
CRO	0.12	≤0.06–0.25	100[j]	≥32	≤0.06–≥32	75.9[k]	8	≤0.06–≥32	84.3[l]	0.12	≤0.06–0.12	100[m]	16	≤0.06–≥32	77.8[n]
CST	1	≤0.12–2	100	0.5	≤0.12–4	97.6	1	≤0.12–≥16	99.6	2	0.25–2	100	0.5	≤0.12–1	100
DOP	0.12	0.06–0.25	100	0.06	0.015–0.12	100	0.12	0.03–≥16	97.8	0.12	0.06–0.12	100	0.12	0.03–0.5	100
IPM	0.5	0.12–1	100	0.5	0.06–0.5	100	0.5	0.12–≥16	98.2	0.5	0.12–1	100	0.5	0.12–2	100
LVX	0.5	0.03–1	96.4	2	0.03–≥16	75.6	0.12	0.008–≥16	93.9	0.12	0.03–0.12	100	1	0.008–≥16	81.3
MEM	0.06	0.03–0.12	100	0.06	0.015–0.06	100	0.06	0.015–≥16	98.2	0.06	0.03–0.06	100	0.12	0.03–0.5	100
TZP	4	1–64	96.4	≥256	1–≥256	78.0	≥256	≤0.25–≥256	87.7	4	2–4	100	≥256	0.5–≥256	87.5
TGC	0.5	0.12–1	100	0.5	0.12–2	97.6	0.5	0.06–2	99.1	0.5	0.25–0.5	100	0.5	0.12–1	100
Non-ESBL															
E. coli	***N* = 49**			***N* = 99**			***N* = 546**			***N* = 38**			***N* = 54**		
CPT	2	≤0.015–16	85.7	1	≤0.015–≥256	89.9	1	≤0.015–≥256	86.4	0.25	0.03–4	92.1	0.5	0.03–1	90.7
AMK	8	1–8	100	4	1–8	100	4	0.5–16	98.4	8	0.5–8	100	4	1–16	98.1
AMC	16	0.25–32	71.4	16	2–≥64	72.7	16	≤0.12–≥64	69.4	16	0.5–32	86.8	16	2–≥64	68.5

Table 3 *(continued)*

Organism/ antimicrobial	Africa/Middle East			Asia			Europe			Oceania			Latin America		
	MIC_{90} (mg/L)	MIC range (mg/L)	%S	MIC_{90} (mg/L)	MIC range (mg/L)	%S	MIC_{90} (mg/L)	MIC range (mg/L)	%S	MIC_{90} (mg/L)	MIC range (mg/L)	%S	MIC_{90} (mg/L)	MIC range (mg/L)	%S
AMP	≥64	2–≥64	32.7	≥64	≤0.5–≥64	37.4	≥64	≤0.5–≥64	42.1	≥64	2–≥64	52.6	≥64	2–≥64	37.0
ATM	0.25	≤0.015–0.5	100	0.25	≤0.015–0.5	100	0.25	≤0.015–1	100	0.12	≤0.015–0.5	100	0.25	≤0.015–1	100
FEP	≤0.12	≤0.12–0.5	100	0.25	≤0.12–0.5	100	0.25	≤0.12–16	99.1	≤0.12	≤0.12–0.25	100	≤0.12	≤0.12–4	98.1
CAZ	0.25	0.06–1	100	0.5	0.06–1	100	0.5	0.03–1	100	0.5	0.06–1	100	0.25	≤0.015–0.5	100
CRO	≤0.06	≤0.06–0.12	100[o]	0.12	≤0.06–0.12	100[p]	≤0.06	≤0.06–≥32	99.2[q]	0.12	≤0.06–2	94.7[r]	≤0.06	≤0.06–0.12	100[s]
CST	1	≤0.06–1	100	0.5	≤0.06–≥16	99.0	1	≤0.06–8	99.5	1	0.12–2	100	1	≤0.06–2	100
DOP	0.06	0.015–0.5	100	0.06	≤0.008–0.5	100	0.06	≤0.008–0.25	100	0.06	0.015–0.12	100	0.06	≤0.008–0.12	100
IPM	0.25	0.12–2	100	0.25	0.12–1	100	0.25	≤0.03–1	100	0.25	0.12–0.5	100	0.25	0.06–0.5	100
LVX	8	0.03–≥16	81.6	≥16	0.015–≥16	54.5	≥16	0.008–≥16	81.1	≥16	0.03–≥16	86.8	≥16	0.03–≥16	59.3
MEM	0.06	0.015–0.12	100	0.03	0.015–0.12	100	0.06	0.008–0.12	100	0.03	0.015–0.06	100	0.06	0.008–0.25	100
TZP	8	1–128	93.9	8	0.5–≥256	93.9	8	≤0.25–≥256	92.9	4	0.5–16	94.7	8	1–64	94.4
TGC	0.25	0.12–0.5	100	0.5	0.06–1	100	0.25	≤0.015–1	100	0.25	0.06–0.5	100	0.5	0.12–0.5	100
ESBL+ *E. coli*	***N* = 28**			***N* = 95**			***N* = 171**			***N* = 5***			***N* = 57**		
CPT	≥256	4–≥256	0.0	≥256	0.12–≥256	3.2	≥256	0.06–≥256	4.1				≥256	32–≥256	0.0
AMK	16	2–32	85.7	8	1–≥64	94.7	16	1–≥64	83.6				16	2–≥64	78.9
AMC	32	4–≥64	21.4	≥64	4–≥64	29.5	32	0.5–≥64	34.5				32	4–≥64	24.6
AMP	≥64	64–≥64	0.0	≥64	64–≥64	0.0	≥64	4–≥64	0.6				≥64	64–≥64	0.0
ATM	128	4–≥256	0.0	128	0.5–≥256	2.1	128	0.25–≥256	5.3				≥256	2–≥256	0.0
FEP	≥32	0.5–≥32	7.1	≥32	≤0.12–≥32	25.3	≥32	≤0.12–≥32	12.3				≥32	0.5–≥32	1.8
CAZ	128	2–≥256	0.0	128	1–≥256	4.2	64	0.25–≥256	7.0				≥256	0.5–≥256	5.3
CRO	≥32	4–≥32	0.0[t]	≥32	0.25–≥32	7.5[u]	≥32	≤0.06–≥32	9.5[v]				≥32	16–≥32	0.0[w]
CST	1	0.12–1	100	0.5	0.12–2	100	0.5	≤0.06–8	98.8				0.5	0.12–1	100
DOP	0.12	0.03–0.25	100	0.12	0.015–≥16	95.8	0.12	≤0.008–4	97.1				0.12	≤0.008–≥16	96.5
IPM	0.5	0.12–1	100	1	0.12–≥16	95.8	0.5	≤0.03–8	95.9				0.5	0.12–8	96.5
LVX	≥16	0.03–≥16	14.3	≥16	0.03–≥16	16.8	≥16	0.03–≥16	22.2				≥16	0.03–≥16	7.0
MEM	0.12	0.03–0.25	100	0.12	0.015–≥16	95.8	0.06	0.015–8	96.5				0.06	0.015–≥16	96.5
TZP	32	1–≥256	64.3	≥256	1–≥256	80.0	≥256	≤0.25–≥256	62.6				128	2–≥256	61.4
TGC	0.5	0.12–4	96.4	0.5	0.12–2	98.9	0.5	0.03–2	99.4				0.5	0.06–1	100

βL neg = β-lactamase negative; βL pos = β-lactamase positive; ESBL+ =extended-spectrum β-lactamase producer; MIC = minimum inhibitory concentration; MIC_{90} = MIC required to inhibit growth of 90% of isolates; S = susceptible; AMK = Amikacin; AMC = Amoxicillin-clavulanate; AMP = Ampicillin; SAM = Ampicillin-sulbactam; ATM = Aztreonam; FEP = Cefepime; CPT = Ceftaroline; CRO = Ceftriaxone; CST = Colistin; DOP = Doripenem; IPM = Imipenem; LVX = Levofloxacin; MEM = Meropenem; TZP = Piperacillin-tazobactam; TGC = Tigecycline.

Data from China were not available.

[a–w]Ceftriaxone tested against *K pneumoniae*, *K. oxytoca*, and *E.coli* in 2016 only. [a], ***N* = 43** ; [b], ***N* = 161**; [c], ***N* = 348**; [d], ***N* = 33**; [e], ***N* = 114**; [f], ***N* = 51**; [g], ***N* = 121**; [h], ***N* = 269**; [i], ***N* = 74**; [j], ***N* = 11**; [k], ***N* = 29**; [l], ***N* = 108**; [m], ***N* = 5**; [n], ***N* = 27**; [o], ***N* = 13**; [p], ***N* = 51**; [q], ***N* = 260**;[r], ***N* = 19**;[s], ***N* = 30**; [t], ***N* = 14**; [u], ***N* = 53**; [v], ***N* = 95**; [w], ***N* = 29**.

* Data not shown as $N \ll 10$.

have been reported in Asia and have emerged elsewhere (Park et al., 2013; Skaare et al., 2014; Ubukata, 2003).

Susceptibility to levofloxacin among βL-negative and βL-positive *H. influenzae* (87.2% and 77.3%, respectively) was lower in Africa/Middle East compared with other regions. This is in contrast to a previous AWARE study which collected RTI pathogens in Africa and the Middle East, where susceptibility to levofloxacin was high among βL-negative and βL-positive *H. influenzae* (97.2% and 100%, respectively; 2012–2014) (Karlowsky et al., 2016). Antimicrobials with high rates of susceptibility against βL-negative *H. influenzae* generally also had high rates against βL-positive isolates (with the exception of ampicillin and ampicillin-sulbactam). However, susceptibility rates to ceftaroline against βL-negative and βL-positive *H. influenzae* isolates collected in Asia were lower than to ceftriaxone, as was the case against βL-positive isolates collected in Africa/Middle East and Latin America, and βL-negative isolates collected in Oceania. Ceftaroline and ceftriaxone have similar β-lactamase stabilities; however, a possible reason could be differences in their affinity for PBP3 of *H. influenzae*.

The in vitro activity of ceftaroline against *H. influenzae* is not affected by β-lactamase production (Ge et al., 2008; Mpenge and MacGowan, 2015; Sader et al., 2005); however, rates of susceptibility to ceftaroline appeared to be lower among βL-positive than βL-negative *H. influenzae* in Africa/Middle East, Asia, and Latin America (differences 12.5%, 13.0% and 9.7%, respectively). Karlowsky et al. (2016) reported a similar finding for RTI pathogens collected in Africa and the Middle East (2012–2014). In the present study, susceptibility rates among βL-positive and βL-negative *H. influenzae* collected in Europe were similar (95.3% [$n = 129$] and 99.2% [$n = 597$], respectively), and in Oceania susceptibility rates were higher among βL-positive isolates (difference 8.9%). Furthermore, Biedenbach et al. (2016) reported ceftaroline MIC_{90} values of ≤ 0.03 mg/L in Africa/Middle East, Europe, and Latin America for both βL-negative and βL-positive *H. influenzae* isolates (MIC_{90} values in Asia-Pacific 0.06 mg/L and 0.12 mg/L, respectively). The numbers of βL-positive isolates were low in a number of the regions in the present study ($n = 22$, $n = 52$, $n = 19$, and $n = 18$ in Africa/Middle East, Asia, Oceania, and Latin America, respectively), limiting the interpretation of the data.

Antimicrobial surveillance programs such as AWARE provide essential information on antimicrobial susceptibility; however, there are limitations to this analysis. Firstly, the present study focused on pathogens associated with CAP collected from identified lower respiratory tract sources rather than isolates that came from patients with a confirmed diagnosis of CAP. AWARE does not collect data on infection type; however, by focusing the analysis on isolates commonly associated with CAP and just selecting isolates from lower respiratory tract sources, it was felt this should give a fair representation of the activity of the antimicrobial panel against such isolates. This study reports on a large collection of isolates ($N = 12{,}321$); however, the study is weighted toward Europe as 57.5% of isolates were collected in Europe compared with only 3.4% in Oceania.

In conclusion, the Gram-positive isolates (*S. pneumoniae* and *S. aureus*) and βL- and ESBL-negative Gram-negative isolates

(*H. influenzae*, *K. pneumoniae* and *E.coli*) collected from identified lower respiratory tract sources demonstrated high rates of susceptibility to ceftaroline. The respiratory fluoroquinolones levofloxacin and moxifloxacin were active against *S. pneumoniae* (PSSP, PISP, and PRSP) and MSSA; however, they were not active against MRSA. Trends in resistant phenotypes among pathogens associated with CAP and susceptibility patterns to frequently used agents need to be monitored by surveillance such as AWARE. Such studies provide crucial information for consideration of selection of appropriate agents on regional, national, and institutional basis.

Declaration of competing interest

I.G.B. has no conflict of interest. G.G.S. is an employee and a shareholder of Pfizer, Inc.

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Contributions

I.G.B. participated in data collection and interpretation, as well as drafting and reviewing the manuscript. G.G.S. was involved in the study design, data interpretation, and the drafting and review of the manuscript. All authors read and approved the final manuscript.

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