

## Introduction

Ceftaroline fosamil, the prodrug of ceftaroline, is a parenteral cephem approved for the treatment of patients with acute bacterial skin and skin structure infections (ABSSSI) caused by *Staphylococcus aureus* (both methicillin-susceptible [MSSA] and methicillin-resistant [MRSA] isolates), *Streptococcus pyogenes*, and select species of Enterobacteriales (*Escherichia coli*, *Klebsiella pneumoniae*, *Klebsiella oxytoca*). The current study is part of the ATLAS (Antimicrobial Testing Leadership and Surveillance) program and evaluated the current activities of ceftaroline and comparator agents against commonly encountered bacterial isolates associated with ABSSSIs.

## Methods

From 2012 to 2018 the ATLAS program received 90,119 bacterial isolates that had been cultured by 370 clinical laboratories in 56 countries from samples of patients diagnosed with SSSIs. All isolates were transported to IHMA, (Schaumburg, IL, USA) where their identities were confirmed using MALDI-TOF mass spectrometry, and antimicrobial susceptibility testing was performed following standardized CLSI broth microdilution methodology [1]. CLSI interpretive guidelines were applied to define susceptibility [2]. ESBL-negative Enterobacteriales consist of *Escherichia coli*, *Klebsiella pneumoniae*, *K. oxytoca* and *Proteus mirabilis* screened and confirmed for ESBL activity according to CLSI guidelines [2].

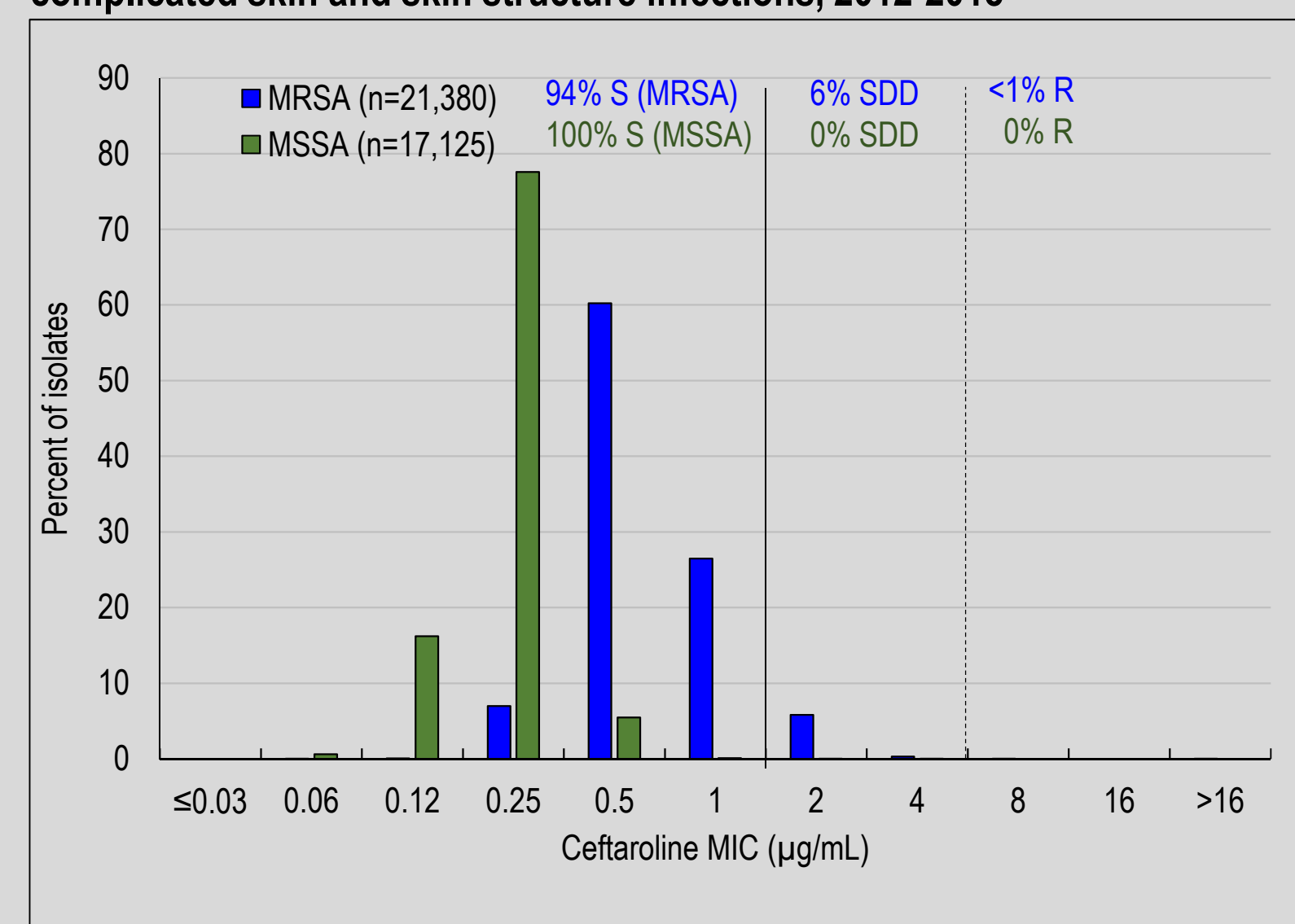
## Results

**Table 1. In vitro activity of ceftaroline and comparator agents against isolates from complicated skin and skin structure infections, 2012-2018**

Organism	Antimicrobial	Global				Asia/South Pacific				Europe				Latin America				MidEast/Africa				North America				
		N	%S	MIC <sub>50</sub>	Range	N	%S	MIC <sub>50</sub>	Range	N	%S	MIC <sub>50</sub>	Range	N	%S	MIC <sub>50</sub>	Range	N	%S	MIC <sub>50</sub>	Range	N	%S	MIC <sub>50</sub>	Range	
<i>Staphylococcus aureus</i> , MRSA	Ceftaroline	21380	93.8 (>99.9*)	1	0.03 - > 32	4001	89.5 (99.8*)	2	0.03 - > 32	9591	95.1 (100*)	1	0.03 - 4	3082	90.0 (100*)	1	0.12 - 4	1822	93.8 (100*)	1	0.25 - 2	2884	99.6 (100*)	1	0.25 - 2	
	Clindamycin	21380	67.9	> 4	≤0.03 - > 4	4001	62.4	> 4	≤0.03 - > 4	9591	68.7	> 4	≤0.03 - > 4	3082	65.8	> 4	≤0.03 - > 4	1822	67.5	> 4	≤0.03 - > 4	2884	75.5	> 2	≤0.03 - > 4	
	Daptomycin	21380	99.7	1	≤0.06 - > 2	4001	99.9	1	≤0.06 - > 2	9591	99.4	1	≤0.06 - > 2	3082	99.9	1	≤0.06 - > 2	1822	99.9	1	0.12 - 2	2884	99.9	1	0.12 - > 2	
	Erythromycin	21380	36.0	> 8	≤0.12 - > 8	4001	43.7	> 8	≤0.12 - > 8	9591	36.5	> 8	≤0.12 - > 8	3082	43.8	> 8	≤0.12 - > 8	1822	42.4	> 8	≤0.12 - > 8	2884	11.4	> 8	≤0.12 - > 8	
	Gentamicin	14093	82.8	> 32	≤0.06 - > 32	2694	73.7	> 32	≤0.06 - > 32	6262	86.6	32	≤0.06 - > 32	2168	79.4	> 32	≤0.06 - > 32	1250	70.0	> 32	≤0.06 - > 32	1719	97.1	> 2	≤0.06 - > 32	
	Levofloxacin	23771	40.3	> 4	≤0.015 - > 32	4089	61.1	> 4	≤0.015 - > 32	10649	28.2	> 4	0.03 - > 32	3229	59.4	> 4	0.03 - > 32	1929	36.8	> 4	≤0.06 - > 32	3875	37.8	> 4	0.03 - > 32	
	Linezolid	23771	100	2	≤0.5 - > 8	4089	100	2	≤0.5 - 4	10649	100	2	≤0.5 - > 8	3229	100	2	≤0.5 - 4	1929	100	2	≤0.5 - > 8	3875	>99.9	2	≤0.5 - 8	
	Trimethoprim Sulfa	14093	95.7	≤1	≤0.03 - > 4	4089	100	2	≤0.25 - 4	10649	100	1	≤0.12 - 4	3229	100	2	≤0.25 - 2	1929	100	2	≤0.25 - 2	3875	>99.9	2	≤0.12 - 4	
	Vancomycin	23771	>99.9	1	≤0.12 - 4	2694	91.2	2	≤0.03 - > 4	6262	97.4	≤1	≤0.03 - > 4	2168	99.0	≤1	0.06 - > 4	1250	90.0	2	0.06 - > 4	1719	96.6	≤1	0.06 - > 4	
	<i>Staphylococcus aureus</i> , MSSA	Ceftaroline	17125	100	0.25	≤0.015 - 4	3056	100	0.25	≤0.015 - 2	8454	100	0.25	≤0.015 - 4	2477	100	0.25	0.03 - 1	1571	100	0.25	≤0.015 - 0.5	1567	100	0.25	≤0.015 - 0.5
Clindamycin		17125	95.5	0.12	≤0.03 - > 4	3056	90.6	0.25	≤0.03 - > 4	8454	96.6	0.12	≤0.03 - > 4	2477	97.0	0.12	≤0.03 - > 4	1571	98.5	0.12	≤0.03 - > 4	1567	94.1	0.12	≤0.03 - > 4	
Daptomycin		17125	99.8	1	≤0.06 - > 2	3056	99.9	1	0.12 - 2	8454	100	1	≤0.06 - > 2	2477	100	1	≤0.06 - 1	1571	100	1	≤0.06 - 1	1567	99.7	1	≤0.06 - > 2	
Erythromycin		17125	76.3	> 4	≤0.12 - > 8	3056	75.6	8	≤0.12 - > 8	8454	80.0	> 4	≤0.12 - > 8	2477	75.0	8	≤0.12 - > 8	1571	79.2	> 4	≤0.12 - > 8	1567	57.6	8	≤0.12 - > 8	
Gentamicin		11395	95.5	≤2	≤0.06 - > 32	1994	91.4	≤2	≤0.06 - > 32	5560	97.4	≤2	≤0.06 - > 32	1786	93.1	≤2	≤0.06 - > 32	1065	93.6	≤2	≤0.06 - > 32	990	98.9	≤2	≤0.06 - > 32	
Levofloxacin		21368	92.6	0.5	≤0.015 - > 32	3163	94.2	0.5	≤0.06 - 32	11124	93.0	0.5	≤0.015 - > 32	2695	96.3	0.5	≤0.015 - 8	1804	88.6	> 2	0.03 - 32	2582	87.5	> 2	≤0.015 - > 32	
Linezolid		21368	100	2	≤0.5 - > 8	3163	>99.9	2	≤0.5 - > 8	11124	100	2	≤0.5 - 4	2695	100	2	≤0.5 - 4	1804	100	2	≤0.5 - 4	2582	100	2	≤0.5 - 4	
Trimethoprim Sulfa		11395	98.3	≤1	≤0.03 - > 4	1994	99.9	1	≤0.25 - 2	5560	100	1	≤0.12 - 2	2695	100	1	≤0.25 - 2	1804	100	1	≤0.25 - 2	2582	100	1	≤0.12 - 2	
Vancomycin		21368	100	1	≤0.12 - 2	1994	96.6	≤1	≤0.03 - > 4	5560	99.1	≤1	≤0.03 - > 4	1786	99.2	≤1	≤0.03 - > 4	1065	95.7	1	≤0.03 - > 4	990	98.8	≤1	≤0.03 - > 4	
<i>Streptococcus pyogenes</i>		Ceftaroline	5451	100	0.008	≤0.004 - 0.5	987	100	0.008	≤0.004 - 0.5	2990	100	0.008	≤0.004 - 0.25	468	100	0.008	≤0.004 - 0.12	385	100	0.008	≤0.004 - 0.06	621	100	0.008	≤0.004 - 0.015
	Ceftriaxone	5881	100	0.03	≤0.015 - 2	988	100	0.03	≤0.015 - 0.5	3414	99.9	0.03	≤0.015 - 2	468	100	0.03	≤0.015 - 0.5	385	100	0.03	≤0.015 - 0.5	626	100	0.03	≤0.015 - 0.25	
	Clindamycin	5451	95.6	0.06	≤0.008 - > 1	987	91.1	0.12	≤0.008 - > 1	2990	96.7	0.06	≤0.008 - > 1	468	97.4	0.06	≤0.008 - > 1	385	99.0	0.06	≤0.008 - > 1	621	94.2	0.06	≤0.008 - > 1	
	Daptomycin	5451	90.0	0.25	≤0.008 - > 1	987	86.6	> 1	≤0.008 - > 1	2990	91.1	0.06	≤0.008 - > 1	468	94.0	0.06	≤0.008 - > 1	385	95.3	0.06	≤0.008 - > 1	621	83.9	> 1	≤0.008 - > 1	
	Erythromycin	5881	99.7	1	≤0.06 - > 8	988	99.1	1	≤0.12 - > 8	3414	99.7	1	≤0.06 - 8	468	100	1	≤0.12 - 2	385	100	1	≤0.12 - 2	626	100	1	≤0.06 - 2	
	Linezolid	5881	100	2	≤0.06 - 2	988	100	1	≤0.06 - 2	3414	100	2	≤0.06 - 2	468	100	1	0.12 - 2	385	100	2	0.25 - 2	626	100	2	≤0.06 - 2	
	Penicillin	5881	100	≤0.06	≤0.015 - 0.12	988	100	0.03	≤0.015 - 0.12	3414	100	≤0.06	≤0.015 - 0.12	468	100	0.03	≤0.015 - 0.12	385	100	0.03	≤0.015 - 0.12	626	100	≤0.06	≤0.015 - 0.12	
	Vancomycin	5881	100	0.5	≤0.008 - 1	988	100	0.5	≤0.008 - 1	3414	100	0.5	≤0.008 - 1	468	100	0.5	0.12 - 1	385	100	0.5	0.015 - 0.5	626	100	0.5	≤0.008 - 1	
	ESBL-negative Enterobacteriales	Ceftaroline	10567	92.3	0.5	≤0.015 - > 128	1453	92.5	0.5	≤0.015 - > 128	5406	92.0	0.5	≤0.015 - > 128	1300	91.0	0.5	≤0.015 - > 128	1195	91.7	0.5	≤0.015 - > 128	1213	95.6	0.5	≤0.015 - > 128
		Ceftazidime	10567	99.98	0.25	≤0.015 - > 128	1453	100	0.25	≤0.015 - 1	5406	99.98	0.25	≤0.015 - > 128	1300	100	0.25	≤0.015 - 1	1195	100	0.25	≤0.015 - 1	1213	99.92	0.5	≤0.015 - 64
Colistin		7583	0	> 8	≤0.06 - > 8	1043	0	> 8	≤0.12 - > 8	3867	0	> 8	≤0.06 - > 8	990	0	> 8	≤0.06 - > 8	881	0	> 8	≤0.06 - > 8	802	0	> 8	0.12 - > 8	
Levofloxacin		10567	79.0	> 4	≤0.004 - > 8	1453	76.0	> 4	≤0.03 - > 8	5406	81.5	> 4	≤0.004 - > 8	1300	71.1	8	0.008 - > 8	1195	74.8	> 4	0.015 - > 8	1213	83.6	> 4	0.015 - > 8	
Meropenem		10567	99.8	0.06	≤0.004 - 16	1453	99.8	0.06	0.008 - 4	5406	99.8	0.06	≤0.004 - 16	1300	99.9	0.06	0.008 - > 8	1195	99.8	0.06	0.008 - > 8	1213	99.9	0.06	≤0.004 - 4	
Piperacillin-tazobactam		10567	96.1	4	≤0.12 - > 128	1453	97.7	4	≤0.12 - > 128	5406	95.4	8	≤0.12 - > 128	1300	95.7	8	≤0.12 - > 128	1195	96.0	8	≤0.12 - > 128	1213	98.1	4	≤0.12 - > 128	

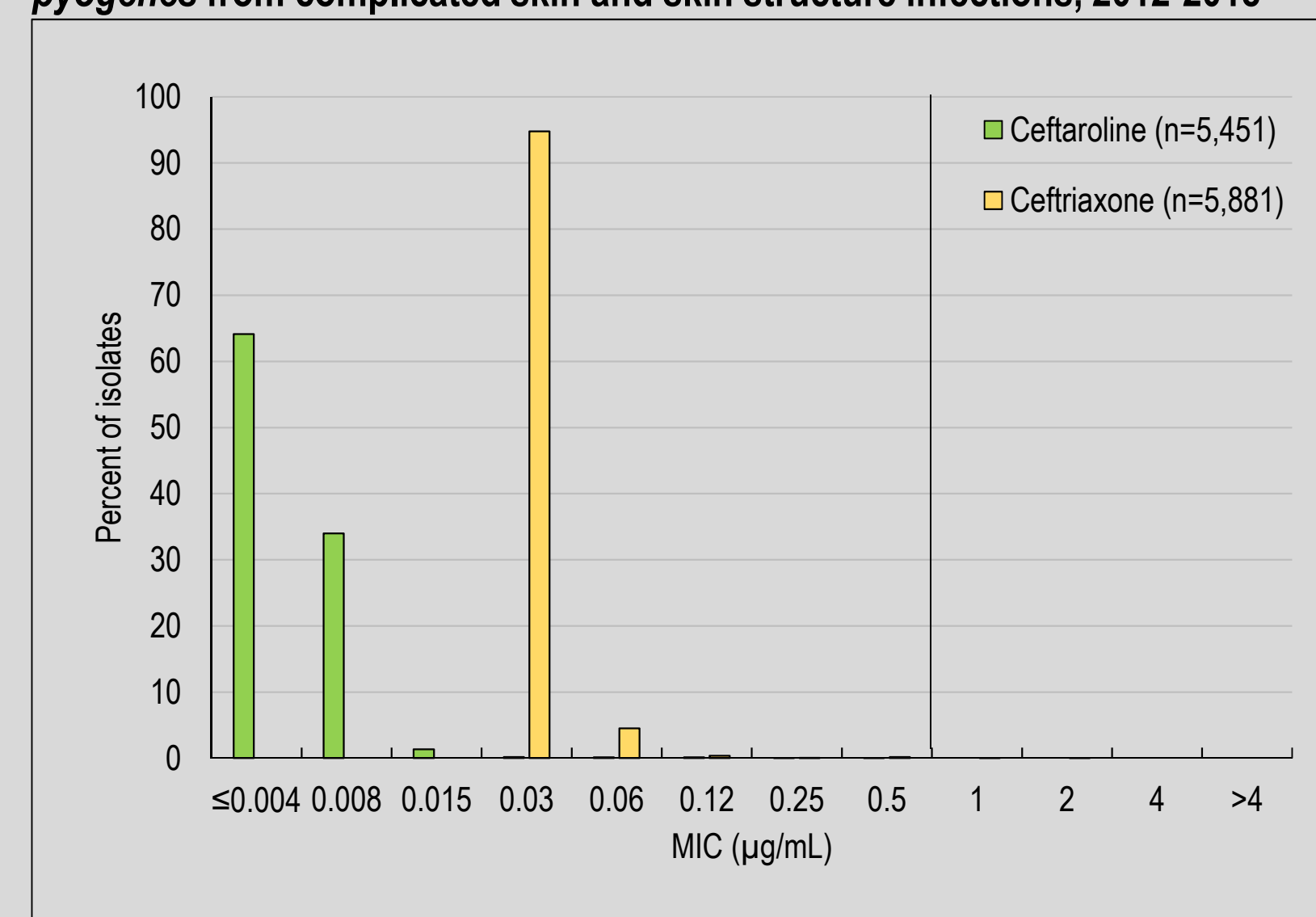
\*%S, percent susceptible; MIC<sub>50</sub>, range in µg/mL; MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-susceptible *S. aureus*; \*Susceptible dose-dependent (SDD) based on a dosage of 600 mg every 8 hours

**Figure 1. Ceftaroline MIC distribution against *Staphylococcus aureus* from complicated skin and skin structure infections, 2012-2018**



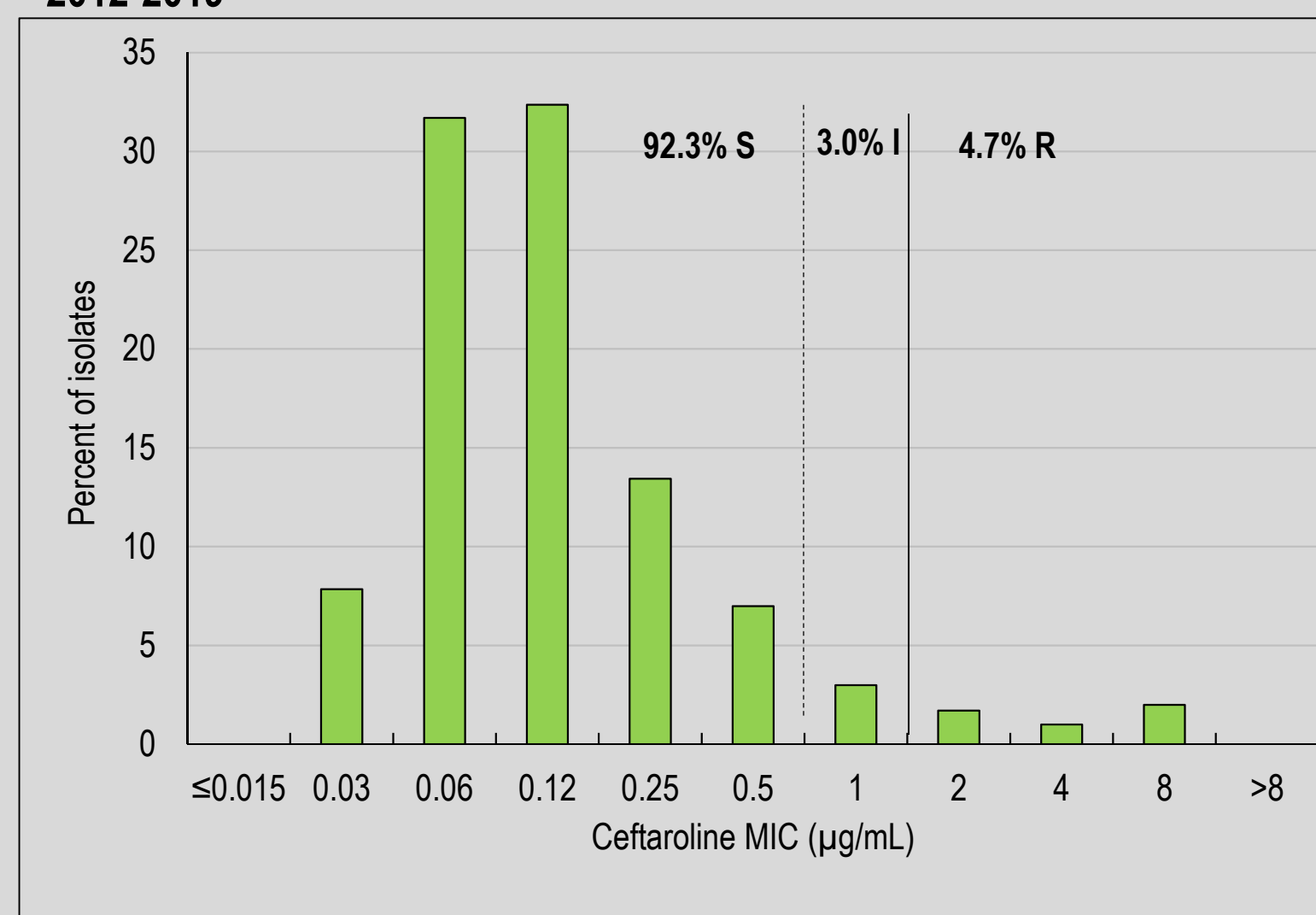
The solid black line represents the CLSI ceftaroline susceptible breakpoint; the dashed line represents the SDD breakpoint based on a dosage of 600 mg every 8 hours administered over 2 hours; MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-susceptible *S. aureus*; % S, SDD, R, percent susceptible, susceptible dose-dependent, resistant, to ceftaroline

**Figure 2. Ceftaroline and ceftriaxone MIC distribution against *Streptococcus pyogenes* from complicated skin and skin structure infections, 2012-2018**



The solid black line represents the CLSI ceftaroline and ceftriaxone susceptible breakpoints

**Figure 3. Ceftaroline MIC distribution against ESBL-negative Enterobacteriales from complicated skin and skin structure infections, 2012-2019**



The solid black line represents the CLSI ceftaroline susceptible breakpoint; the dashed line represents the CLSI resistant breakpoint; S, susceptible to ceftaroline; I, intermediate to ceftaroline; R, resistant to ceftaroline

## Results

- The *in vitro* activity of ceftaroline and comparators against each organism group is provided in Table 1. Ceftaroline MIC distributions are provided in Figures 1 through 3.
- Overall, 100% of MSSA and 93.8% of MRSA from a global population were susceptible to ceftaroline (MIC  $\le 1$  µg/mL), with an additional 6.1% of MRSA susceptible at the dose dependent breakpoint of  $\le 4$  µg/mL (Table 1, Figure 1).
- Nine MRSA isolates from Thailand and one isolate from China were resistant to ceftaroline.
- 100% of *S. pyogenes* from SSSI were susceptible to ceftaroline (Table 1, Figure 2).
- 92.3% of ESBL-negative Enterobacteriales were susceptible to ceftaroline (MIC  $\le 0.5$  µg/mL) (Table 1, Figure 3).

## Conclusions

- Ceftaroline was active against clinically relevant gram-positive SSTI isolates globally.
- Ceftaroline was active against the majority of ESBL-negative gram-negative pathogens with 92.3% of isolates susceptible.
- Overall, ceftaroline demonstrated *in vitro* activity against gram-positive and gram-negative pathogens commonly associated with SSTIs.

## References