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### **Amended Abstract**

Objective: The activity of ceftaroline, an investigational cephalosporin, was studied against prevailing US adult and pediatric serotypes of Streptococcus pneumoniae. Ceftaroline has broad spectrum activity against gram-positive organisms including methicillin-resistant Staphylococcus aureus (MRSA) and multidrug-resistant S. pneumoniae (MDRSP), and common gramnegative pathogens.

Methods: S. pneumoniae isolates were received in 2008 from 22 cities in 19 states throughout the US. Serotyping was performed by capsular swelling with commercial antisera. Serotype 6C was identified by PCR. MICs of ceftaroline, penicillin, amoxicillin, and ceftriaxone were determined by CLSI broth microdilution method.

Results: A total of 891 isolates were tested. Isolates came from all body sites, with distribution as follows: lower respiratory tract 58.9%, blood 15.6%, upper respiratory tract 8.4%, middle ear 7.4%, and other sites 9.7%. Serotype distribution by age for 859 strains with age data available is shown in the Table:

Serotype (%)	Adult isolates (%) (N=574)	Pediatric isolates (%) (N=285)	All isolates (%) (N=859)
Vaccine*	5.9	7.0	6.3
19A	15.0	32.6	20.8
3	10.5	6.3	9.1
35B	7.5	5.6	6.9
7F	7.0	3.9	5.9
11A	5.7	4.6	5.4
6C	4.5	4.9	4.7
15A	4.9	3.2	4.3
22F	4.9	2.5	4.1
23A	3.8	3.9	3.8
23B	3.8	3.5	3.7
Other	26.5	22.1	25.0

7-valent conjugate vaccine serotypes

Ceftaroline was the most active of the tested agents against S. pneumoniae, with MICs ranging from ≤0.008 to 0.5 mg/L and MIC<sub>oo</sub>s of 0.12 mg/L for adult isolates and 0.25 mg/L for pediatric isolates. MIC<sub>oo</sub>s were 2 and 4 mg/L for penicillin, 4 and 8 mg/L for amoxicillin, and 1 and 2 mg/L for ceftriaxone, with pediatric isolates less susceptible than adult isolates.

Conclusions: Pediatric and adult pneumococcal isolates differed widely in serotype distribution, with serotype 19A providing one third of isolates among children. Vaccine serotypes were uncommon in both age groups. Pediatric isolates were less susceptible to penicillin, amoxicillin, and ceftriaxone than were adult isolates. Ceftaroline was more active against S. pneumoniae than any other tested agent.

### Introduction

Streptococcus pneumoniae is a major cause of morbidity and mortality, with its management being further complicated by the recent unexpected spread of resistant serotypes in the United States, such as serotype 19A. Ceftaroline fosamil is a novel investigational cephalosporin for parenteral use. Ceftaroline, the active form of ceftaroline fosamil, has shown good in vitro activity against both methicillin-susceptible and -resistant Staphylococcus aureus, as well as low MICs against S. pneumoniae and viridans group streptococci, including penicillinand levofloxacin-nonsusceptible strains. It is also active against many common Gram-negative respiratory pathogens. Ceftaroline fosamil demonstrated efficacy in phase III studies for the treatment of community-acquired pneumonia (CAP) and complicated skin and skin structure infections (cSSSIs), and is currently under review in the US for approval of these indications.

In this *in vitro* study, ceftaroline was investigated against recent clinical strains of S. pneumoniae isolated from various institutions across the US. Isolates were also characterized as to serotype and analyzed in relation to those included in the 7-valent pneumococcal conjugate vaccine (PCV7) in both adult and pediatric patients.

### Methods

Twenty-two sites from representative regions around

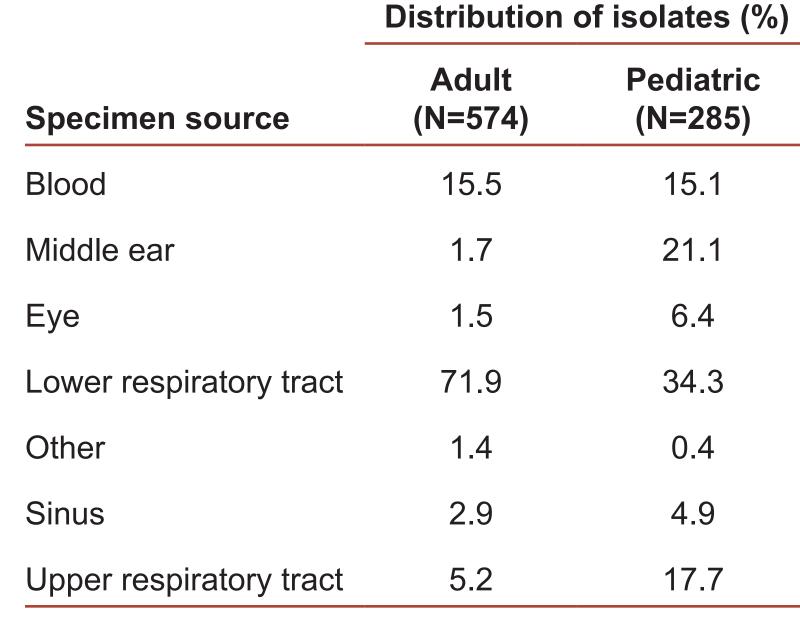
the US participated in the collection of

S. pneumoniae strains for this study. Isolates (N=891, limited to 1 per patient) were collected from all specimen sources, with identification confirmed following standard procedures. Susceptibility testing was performed using broth microdilution testing in commercially prepared trays (TREK Diagnostics; Cleveland, Ohio) according to Clinical and Laboratory Standards Institute (CLSI) methods (M7-A8, 2009) and interpreted according to CLSI breakpoints (M100-S19, 2009). Comparators included penicillins, cephalosporins, imipenem, erythromycin, clindamycin, quinolones, linezolid, vancomycin, and trimethoprim/sulfamethoxazole. Isolates were serotyped by the capsular swelling reaction using commercial group- and type-specific antisera (Statenserum Institute; Copenhagen, Denmark). Serotype 6C was identified by PCR. Multidrug-resistant (MDR) isolates were defined as resistant to 2 or more of the following antibiotics: penicillin, cefuroxime, macrolides, tetracyclines, and trimethoprim/sulfamethoxazole. Demographic data, particularly patient age, were available for 859 of the isolates.

 Of the 859 isolates, 285 (33.2%) were isolated from pediatric patients. Specimen sources for isolates from adult and pediatric patients are shown in Table 1. The lower respiratory tract was the most frequent source in both adults and children, followed by blood in adults and middle ear in children

- Serotyping revealed that 11 serotypes accounted for 72.1% of the total, with 42 serotypes identified overall (Figure 1)
- One serotype, 19A, accounted for 21.2% of all strains. Serotype 19A accounted for nearly one third (32.6%) of isolates collected from pediatric patients and 15.0% of isolates collected from adults. In both age groups it was the most frequently isolated serotype
- Serotypes associated with PCV7 accounted for 7.0% of pediatric isolates and 5.9% of adult
- Susceptibilities for all isolates, overall and for each of the 11 most common types, are shown in Table 2
- Histograms of MIC distributions of ceftaroline are shown in Figures 2 and 3
- Cumulative penicillin, ceftaroline, and ceftriaxone MICs are shown in Figure 4. Ceftaroline MIC<sub>oo</sub>s were lower than those of penicillin and ceftriaxone for all strains and for each of the 11 major serotypes (MIC<sub>oo</sub>s for all strains  $0.12 \mu g/mL vs 4 \mu g/mL and 1 \mu g/mL$ respectively) in both adult and pediatric patients
- Among pediatric patient isolates, susceptibilities were penicillin G, 75.8% susceptible; penicillin V, 45.6%; amoxicillin/clavulanate, 73.3%; ceftriaxone, 84.2%; and cefuroxime, 57.9%; ceftaroline MIC<sub>oo</sub> was 0.25 µg/mL
- Among adult patient isolates, susceptibilities were penicillin G, 91.1% susceptible; penicillin V, 64.3%; amoxicillin/clavulanate, 87.5%; ceftriaxone, 93.9%; and cefuroxime, 76.3%; ceftaroline MIC<sub>on</sub> was 0.12 µg/mL
- The most resistant serotype, serotype19A, had  $MIC_{50/90}$  values of 0.12/0.25 µg/mL for ceftaroline, compared with 4/4 µg/mL, 8/8 µg/mL, 1/2 μg/mL, and 8/>8 μg/mL for penicillin, amoxicillin/clavulanic acid, ceftriaxone, and cefuroxime, respectively. Susceptibilities for this serotype were: penicillin G, 46.6% susceptible; penicillin V, 13.8%; amoxicillin/clavulanate, 45.0%; ceftriaxone, 65.6%; and cefuroxime, 36.1%
- Among 125 MDR isolates, 101 (80.8%) were serotype 19A and 19 (15.2%) were serotype 19F. The highest MIC for ceftaroline against MDR isolates was 0.5 µg/mL
- Serotype 19A strains showed lower susceptibility to erythromycin, clindamycin, imipenem, and trimethoprim/sulfamethoxazole compared with other serotypes. Other serotypes with decreased susceptibility included 19F, 35B, and the newly identified serotype, 6C.

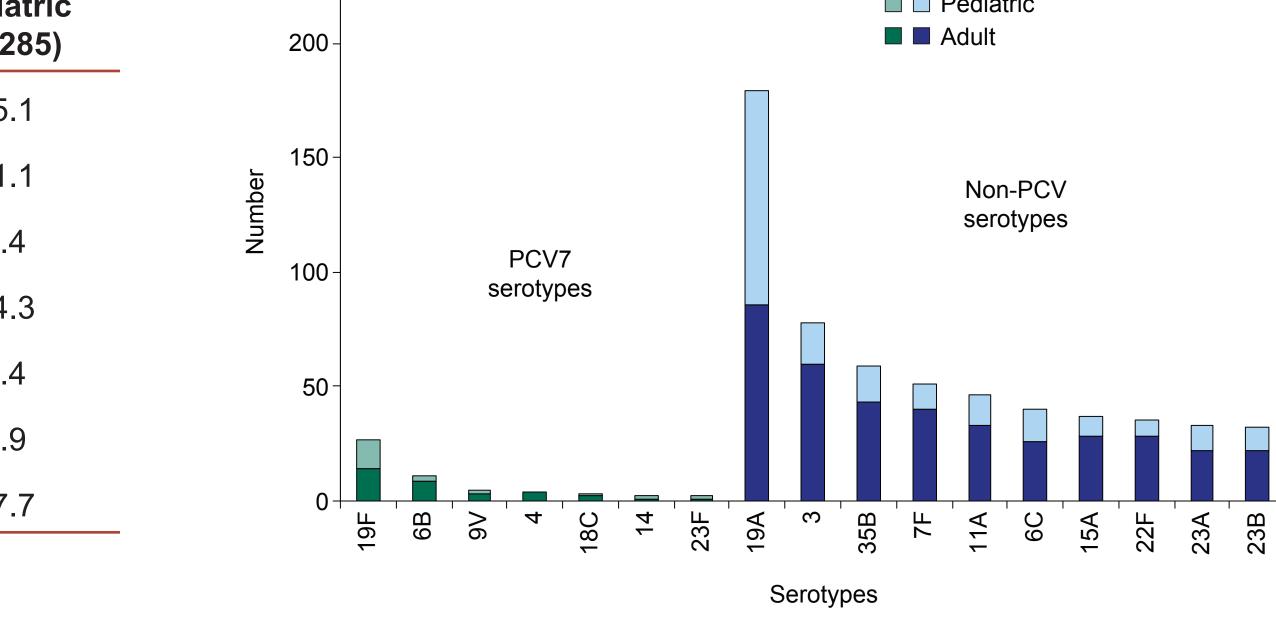
### Table 1. Specimen Sources of Study Isolates for Adult and Pediatric Patients



All Strains (N=891) and for the 11 Most Common Serotypes

NA = not applicable; SXT = trimethoprim/sulfamethoxazole

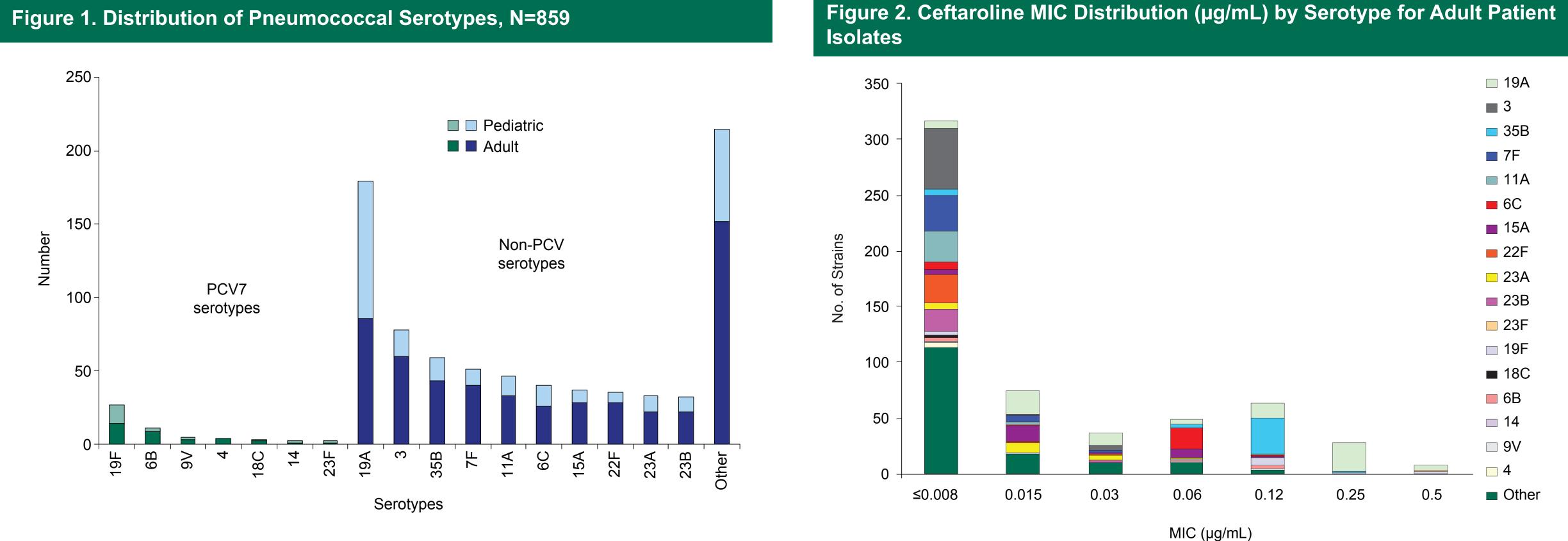
# Pediatric ■ ■ Adult Non-PCV



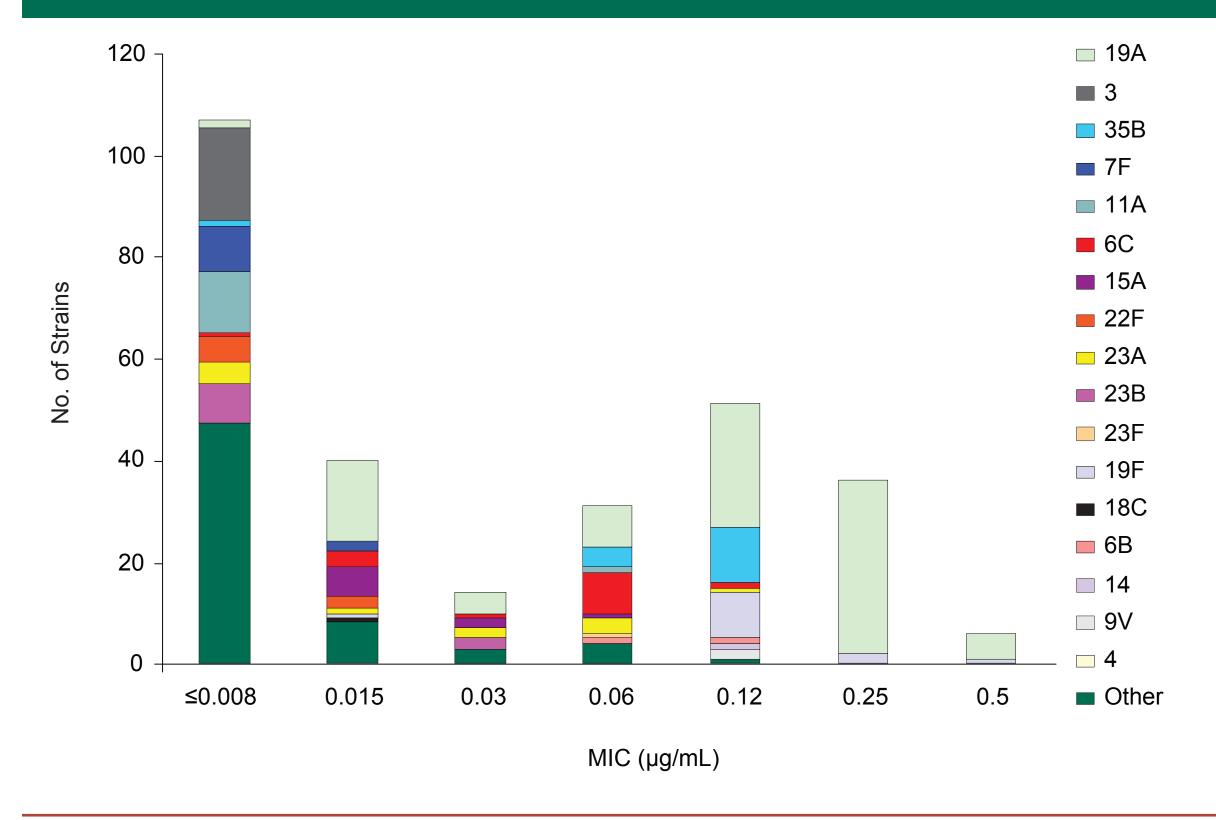
## Table 2. MIC<sub>50</sub> and MIC<sub>90</sub> Values (µg/mL) for Ceftaroline and Percent Susceptibility at CLSI Breakpoints for Tested Antibiotics Against

Agent (susceptible CLSI breakpoint [µg/mL])	AII (891)	Serotype										
		19A (189)	3 (82)	35B (59)	7F (52)	11A (49)	6C (43)	15A (38)	22F (35)	23A (33)	23B (33)	19F (29)
Parenteral β-lactams												
Ceftaroline (NA) MIC <sub>50</sub>	≤0.008	0.12	≤0.008	0.12	≤0.008	0.06	0.015	≤0.008	≤0.008	0.12	0.015	0.12
MIC <sub>90</sub>	0.12	0.25	≤0.008	0.12	0.015	0.06	0.06	0.03	0.015	0.25	0.06	0.25
Penicillin G (≤2)	86.2	46.6	98.8	98.3	100	100	100	100	100	100	100	37.9
Ceftriaxone (≤1)	90.7	65.6	98.8	98.3	100	98.0	100	100	100	100	97.0	65.5
Imipenem (≤0.12)	76.2	40.2	98.8	15.3	100	95.9	90.7	100	100	100	100	20.7
Oral β-lactams												
Penicillin V (≤0.06)	58.6	13.8	97.6	10.2	100	95.9	37.2	10.5	100	36.4	84.8	20.7
Amoxicillin/clavulanate (≤2)	83.1	45.0	98.8	62.7	100	98.0	100	100	100	100	100	37.9
Cefuroxime (≤1)	70.1	36.1	98.6	9.6	100	95.2	47.5	91.4	100	96.4	96.8	20.7
Non-β-lactam agents												
Erythromycin (≤0.25)	61.6	26.5	93.9	64.4	100	75.5	41.9	5.3	88.6	78.8	75.8	17.2
Clindamycin (≤0.25)	79.2	43.4	98.7	100	100	95.9	97.7	10.5	100	81.8	100	31.0
Levofloxacin (≤2)	99.4	100	100	98.3	100	100	100	100	100	100	97.0	96.6
Moxifloxacin (≤1)	99.6	100	100	100	100	100	100	100	100	100	97.0	96.6
Vancomycin (≤1)	100	100	100	100	100	100	100	100	100	100	100	NA
SXT (≤0.5)	66.2	16.9	97.6	100	100	87.8	34.9	55.3	97.1	90.9	84.8	17.2
Linezolid (≤2)	100	100	100	100	100	100	100	100	100	100	100	100

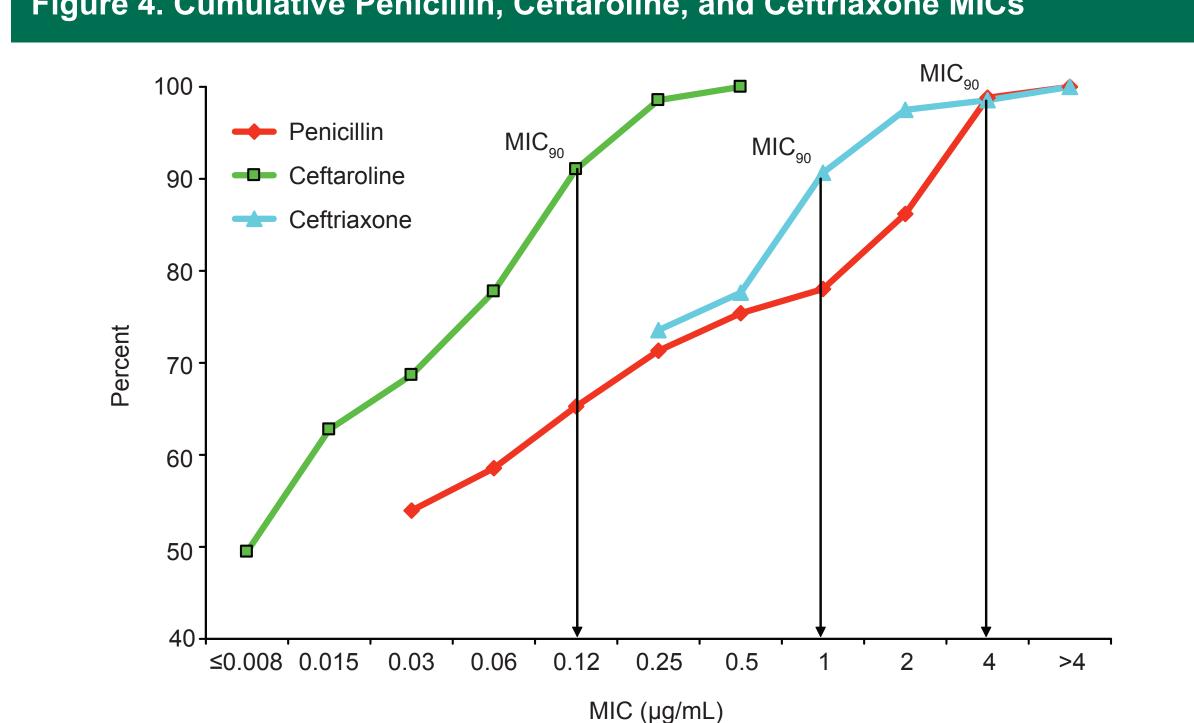
### Results



### Figure 3. Ceftaroline MIC Distribution (µg/mL) by Serotype for Pediatric Patient Isolates







### Conclusions

- Isolates originating in pediatric patients were considerably less susceptible than adult patient isolates to the agents currently available that were tested; ceftaroline was similarly active in pediatric and adult isolates, with MIC<sub>50/90</sub>s of 0.12/0.25 and ≤0.008/0.12 µg/mL, respectively
- A higher proportion of often MDR serotype 19A isolates was found in pediatric patients (32.6% vs 15.0% in adults)
- Significant limitations to the parenteral β-lactam, macrolide, and lincosamide agents currently recommended for treatment of invasive pneumococcal infections were observed. Additionally, several oral agents, including macrolides, lincosamides, cefuroxime, amoxicillin/clavulanate, and trimethoprim/ sulfamethoxazole, had poor activity, particularly against serotype 19A strains
- Inclusion of several common nonvaccine serotypes, particularly serotype 19A, in the new conjugate vaccine formulations will help alleviate these issues. Serotypes 1, 3, 5, 6A, 7F, and 19A have been added to PCV13
- 14% of all pneumococci, representing isolates from all sources collected during 2008 at 22 medical centers located across the US, were
- Ceftaroline had potent in vitro activity against all pneumococcal isolates, with the highest MIC of 0.5 µg/mL, including against the most resistant serotypes such as serotype 19A. These data suggest the potential utility of ceftaroline fosamil in the treatment of infections caused by S. pneumoniae, including those strains resistant to other commonly used antimicrobials.

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Acknowledgment

Supported by Forest Laboratories, Inc.