Ceftaroline fosamil (Teflaro), the prodrug of ceftaroline, was approved in 2010 by the U.S. Food and Drug Administration (FDA) for the treatment of acute bacterial skin and skin structure infections (ABSSSI) due to susceptible isolates of *Staphylococcus aureus* (including methicillin-susceptible [MSSA] and -resistant [MRSA] isolates), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Klebsiella oxytoca*. Ceftaroline fosamil was also approved for community-acquired bacterial pneumonia (CAPB) due to *Streptococcus pneumoniae* (including cases with concurrent bacteremia), *S. aureus* (MSSA only), *Haemophilus influenzae*, *K. pneumoniae*, *K. oxytoca*, and *E. coli* (1–3).

An antimicrobial resistance surveillance program, known as the Assessing Worldwide Antimicrobial Resistance and Evaluation (AWARE) Program, was designed to monitor the activity of ceftaroline and comparator agents (4). This program provides contemporary and longitudinal information on the activity of this agent against relevant pathogens. Previous reports from the AWARE program have provided analyses of ceftaroline activity against bacterial isolates recovered from indicated sites of infections (ABSSSI and CAPB) during the initial years of the program (5, 6) as well as resistant subsets of organisms from indicated species (4, 7, 8). In this report, we summarized the results of 5 years (2009 to 2013) of the AWARE Program in the United States.

A total of 84,704 bacterial isolates were collected from clinical infections, as defined by local clinical criteria. The isolates were collected from January 2009 to December 2013 from 191 medical centers distributed across all nine U.S. census regions, and target numbers of strains for each of the requested bacterial species/genus were predetermined by study protocol. Only isolates deemed clinically relevant by the submitting laboratory were included in the investigation. If multiple isolates of the same organism (species) were collected multiple times during the same infection episode, the investigator was instructed to provide only the first isolate. The isolates were from skin and skin structure infections (27,395; 32.3%), respiratory tract infections (23,931; 28.3%), bloodstream infections (17,685; 20.9%), urinary tract infections (7,814; 9.2%), intra-abdominal infections (1,521; 1.8%), and infections at other sites (6,358; 7.5%). Isolates were sent to the coordinator laboratory (JMI Laboratories, North Liberty, IA, USA) for reference susceptibility testing. Only one strain per patient infection episode was included in the surveillance.

Isolates were tested for susceptibility to ceftaroline and multiple comparator agents by reference broth microdilution methods as described by Clinical and Laboratory Standards Institute (CLSI) standard M07-A9 (9), and CLSI interpretations were based on M100-S24 and M45-A2 breakpoints (9, 10). Ceftaroline and comparator agents were tested simultaneously using the same bacterial inoculum and testing reagents. Isolates with positive extended-spectrum β-lactamase (ESBL) screening test results, i.e., MICs of >1 μg/ml for ceftazidime and/or ceftriaxone and/or aztreonam, were categorized as “ESBL phenotype” for the purpose of susceptibility testing result analysis. Although other β-lactamases, such as AmpC and KPC, may also produce an ESBL phenotype, these strains were grouped together because they usually demonstrate resistance to various broad-spectrum β-lactam compounds (10). *K. pneumoniae* isolates with MICs of >1 μg/ml for meropenem or imipenem isolated in 2009, 2010, 2012, and 2013 (all years except 2011) were screened for *bla*KPC by PCR as previously described (11, 12). Streptococcal isolates were tested in Mueller-Hinton broth supplemented with 2.5 to 5% lysed horse blood, and *Haemophilus* species isolates were tested in *Haemophilus* test medium (HTM), whereas all other organisms were tested in cation-adjusted Mueller-Hinton broth. Concurrent testing of quality control (QC) strains ensured proper test conditions.
Staphylococcus aureus and coagulase-negative staphylococci (CoNS) were particularly susceptible to ceftaroline, with MICs at which 90% of the isolates tested were inhibited (MIC90) of 1 and 0.5 μg/ml, respectively. Ceftaroline inhibited 98.8% of S. aureus strains at the susceptible breakpoint of ≤ 1 μg/ml (Table 1). Rates of susceptibility to levofloxacin and clindamycin were 60.2 and 71.1%, respectively, according to CLSI breakpoints. Rates of susceptibility to daptomycin, linezolid, tigecycline, and vancomycin were >99.9% (data not shown).

The overall methicillin-resistant S. aureus (MRSA) rate was 49.2%, varying from a low of 46.0% in 2009 to a high of 50.5% in 2010, with no trend toward increase or decrease during the study period (Table 2). Overall, 97.6% of MRSA isolates (12,514 strains tested) were susceptible to ceftaroline (MIC50/90 = 0.5/1 μg/ml; highest MIC, 2 μg/ml [Table 1]). When tested against MSSA, ceftaroline (MIC50 and MIC90 0.25 μg/ml [Table 1]) was 16-fold more potent than ceftriaxone (MIC50 and MIC90, 4 μg/ml [data not shown]).

Ceftaroline (MIC50/90 ≤0.015/0.12 μg/ml) inhibited all (100.0%) 10,096 S. pneumoniae strains at the MIC of ≤0.5 μg/ml, which is the susceptible breakpoint established by the CLSI and U.S. FDA (3, 10), and showed potent activity against ceftriaxone-nonsusceptible (MIC, ≥2 μg/ml) strains (n = 952; ceftaroline MIC50 and MIC90, 0.25 μg/ml). When tested against penicillin-resistant (MIC, ≥8 μg/ml) strains (n = 117), ceftaroline (MIC50/90, 0.25/0.5 μg/ml [Table 1]) was 8- to 16-fold more potent than ceftriaxone (MIC50/90, 2/8 μg/ml [data not shown]). The overall rate of ceftaroline-nonsusceptible S. pneumoniae was 9.4% and decreased gradually during the study period from 12.7% in 2009 to 6.5% in 2013 (Table 2). Penicillin-nonsusceptible S. pneumoniae rates showed a similar trend toward lower rates, varying from 16.0% in 2009 to 7.2% in 2013 (Table 2).

Ceftaroline demonstrated potent activity against beta-hemolytic streptococci (MIC50 and MIC90 ≤0.015 μg/ml; highest MIC, 0.12 μg/ml; 100.0% susceptible) and viridans group streptococci (MIC50/90, 0.03/0.06 μg/ml; highest MIC, 1 μg/ml) but exhibited limited activity against Enterococcus faecalis (MIC50/90, 2/8 μg/ml [Table 1]).

Ceftaroline activity against Enterobacteriaceae strains (n = 25,192) at MICs of 0.5 g/ml) inhibited all (100.0%) 9,522 S. pneumoniae, including multi-drug-resistant strains, such as S. aureus with decreased susceptibility to linezolid, daptomycin, or vancomycin and emerging S. pneumoniae serotypes 19A, 35B, and 6C (7, 8, 15). The data presented here provide further documentation of the excellent activity of ceftaroline when tested against significant collections of contemporary U.S. isolates. We evaluated ceftaroline activity against 25,192 S. aureus and 10,096 S. pneumoniae contemporary clinical isolates collected from 191 U.S. medical centers distributed throughout all nine census regions, and ceftaroline was active against 98.8% of S. aureus and all (100.0%) of the S. pneumoniae isolates at the respective susceptible breakpoints. It is important to note that all ceftaroline-nonsusceptible S. aureus (all MRSA) isolates exhibited ceftaroline MIC values only 1 doubling dilution higher than the susceptible breakpoint (i.e., 2 μg/ml, intermediate), and no ceftaroline-resistant S. aureus isolate was detected during these 5 years of surveillance in the United States. Furthermore, Monte Carlo simulations using ceftaroline pharmokinetic and pharmacodynamic properties have indicated that target attainment rates (stasis or 1 log10 CFU/g bacterial cell kill) remained >95% up to an MIC of 2 μg/ml, suggesting clinical efficacy in treating ABSSSI against strains up to this MIC (16).

Ceftaroline also demonstrated potent and consistent (2009 to 2013) in vitro activity against large collections of beta-hemolytic streptococci (n = 5,679; MIC90 ≤0.015 μg/ml), viridans group streptococci (n = 2,332; MIC90 0.06 μg/ml), coagulase-negative staphylococci (CoNS) (n = 3,379; MIC90 0.5 μg/ml), H. influenzae (n = 3,906; MIC90 0.015/0.03 μg/ml), Moraxella catarrhalis (MIC50/90, 0.06/0.12 μg/ml) strains, independent of β-lactamase production (Table 1).

Ceftaroline represents a new class of cephalosporin with anti-MRSA activity. Favorable features of ceftaroline include avid binding to penicillin-binding proteins 2a and 2x of MRSA and penicillin-resistant S. pneumoniae, respectively, and lack of antagonism with other agents used in combination (4, 13, 14). Numerous published studies confirm the potent activity of ceftaroline against S. aureus and S. pneumoniae, including multi-drug-resistant strains, making this agent particularly attractive in the initial treatment of serious infections (1, 2, 18), make this agent particularly attractive in the initial
### TABLE 1

Summary of ceftaroline activity tested against 84,704 bacterial isolates from U.S. medical centers (2009 to 2013)

<table>
<thead>
<tr>
<th>Organism</th>
<th>S, susceptible</th>
<th>I, intermediate</th>
<th>R, resistant</th>
<th>ESBL phenotype</th>
<th>Non-ESBL phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Moraxella catarrhalis</em></td>
<td>86.8%</td>
<td>93.9%</td>
<td>96.3%</td>
<td>98.3%</td>
<td>98.8%</td>
</tr>
<tr>
<td><em>Haemophilus parainfluenzae</em></td>
<td>86.8%</td>
<td>93.9%</td>
<td>96.3%</td>
<td>98.3%</td>
<td>98.8%</td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em></td>
<td>87.1%</td>
<td>97.0%</td>
<td>99.2%</td>
<td>99.8%</td>
<td>100.0%</td>
</tr>
<tr>
<td><em>Acinetobacter baumannii</em></td>
<td>0.5%</td>
<td>3.5%</td>
<td>14.9%</td>
<td>28.5%</td>
<td>4.2%</td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
<td>0.2%</td>
<td>67.1%</td>
<td>14.9%</td>
<td>40.6%</td>
<td>38.4%</td>
</tr>
<tr>
<td><em>Providencia</em></td>
<td>1.0%</td>
<td>3.3%</td>
<td>5.9%</td>
<td>19.3%</td>
<td>35.7%</td>
</tr>
<tr>
<td><em>Serratia marcescens</em></td>
<td>0.2%</td>
<td>11.0%</td>
<td>27.5%</td>
<td>64.3%</td>
<td>74.9%</td>
</tr>
<tr>
<td><em>Citrobacter koseri</em></td>
<td>0.2%</td>
<td>0.6%</td>
<td>1.7%</td>
<td>4.2%</td>
<td>10.5%</td>
</tr>
<tr>
<td><em>Morganella morganii</em></td>
<td>0.3%</td>
<td>2.7%</td>
<td>37.2%</td>
<td>67.2%</td>
<td>73.7%</td>
</tr>
<tr>
<td><em>Enterobacter cloacae</em></td>
<td>0.5%</td>
<td>1.9%</td>
<td>6.5%</td>
<td>31.7%</td>
<td>59.9%</td>
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<tr>
<td><em>Proteus mirabilis</em></td>
<td>0.2%</td>
<td>3.0%</td>
<td>18.9%</td>
<td>46.1%</td>
<td>73.6%</td>
</tr>
<tr>
<td><em>Klebsiella oxytoca</em></td>
<td>0.5%</td>
<td>4.3%</td>
<td>37.8%</td>
<td>66.7%</td>
<td>75.9%</td>
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<tr>
<td><em>Klebsiella pneumoniae</em></td>
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<td><em>Escherichia coli</em></td>
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<td><em>Enterococcus faecalis</em></td>
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<td><em>Streptococcus pyogenes</em></td>
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<td><em>Streptococcus pneumoniae</em></td>
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<tr>
<td><em>Escherichia coli</em></td>
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</table>

**Notes:**
- MIC: Minimum Inhibitory Concentration
- MIC90: The MIC value at which 90% of the isolates are inhibited
- S: Susceptible
- I: Intermediate
- R: Resistant
- ESBL: Extended-Spectrum β-Lactamase
- MSSA: Methicillin-Susceptible Staphylococcus aureus
- MRSA: Methicillin-Resistant Staphylococcus aureus

**References:**
management of CABP and ABSSI patients requiring hospitalization.

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RECORDS

REFERENCES


