Global trends of antimicrobial susceptibility of ceftaroline and ceftazidime-avibactam: a surveillance study from the ATLAS program (2012-2016)

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Research

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Abstract

Background: This study reports the global trends of antimicrobial susceptibility to ceftaroline and ceftazidime-avibactam using data from the Antimicrobial Testing Leadership And Surveillance (ATLAS) program between 2012 and 2016.

Methods: For the 2012-2016 ATLAS program, 205 medical centers located in Africa-Middle East (n=12), Asia-Pacific (n=32), Europe (n=94), Latin America (n=26), North America (n=31), and Oceania (n=10) consecutively collected the clinical isolates. The minimum inhibitory concentrations (MICs) and in vitro susceptibilities to ceftaroline and ceftazidime-avibactam were assessed using the Clinical and Laboratory Standards Institute (CLSI) 2019 and European Committee on Antimicrobial Susceptibility Testing (EUCAST) 2019 guidelines.

Results: Between 2012 and 2016, 176,345 isolates were collected from around the globe and included in the analysis. Regarding Gram-negative bacteria, ceftazidime-avibactam demonstrated high susceptibility (>90%) against Enterobacteriaceae and Pseudomonas aeruginosa, with increased antimicrobial activity observed from the addition of avibactam (4 mg/L) to ceftazidime. Regarding Gram-positive bacteria, ceftaroline showed >90% susceptibility against Staphylococcus aureus, Streptococcus pneumoniae, α- and β-hemolytic Streptococcus. The antimicrobial susceptibilities to ceftaroline and ceftazidime-avibactam were mostly stable from 2012 to 2016, but the susceptibilities to ceftazidime-avibactam to carbapenem-resistant (CR) Klebsiella pneumoniae (88.4% to 81.6%) and to CR-Pseudomonas aeruginosa (89.6% to 72.7%) decreased over time. In terms of regional difference, the susceptibilities of methicillin-resistant Staphylococcus aureus to ceftaroline in Asia and of CR-Klebsiella pneumoniae to ceftazidime-avibactam in Asia/Africa-Middle East were lower compared with other regions, while the susceptibility of CR-Pseudomonas aeruginosa to ceftazidime-avibactam in North America was higher.

Conclusion: The addition of avibactam improves the activity of ceftazidime against Enterobacteriaceae and Pseudomonas aeruginosa. The global antimicrobial susceptibilities to ceftaroline and ceftazidime-avibactam were, in general, stable from 2012 to 2016, but a marked reduction in the susceptibilities of specific species and CR-Pseudomonas aeruginosa to ceftazidime-avibactam was observed.

Introduction

The rapidly increasing and global spreading of the resistance of bacteria to antibiotics in recent years is a serious challenge for clinicians and a global health crisis.\(^1\) Multi-drug resistance in both Gram-negative and -positive bacteria often leads to untreatable infections using conventional antibiotics, and even last-resort antibiotics are losing their power.\(^2\) The increases in the occurrence of infections caused by third-generation cephalosporin- and carbapenem-resistant (CR)-Enterobacteriaceae, CR-Pseudomonasaeruginosa, and CR-Acinetobacterbaumannii are of particular concern since they are associated with tremendously increased mortality and morbidity rates.\(^3,4\) Recently, the World Health Organization has rated CR-Enterobacteriaceae, CR-Pseudomonas aeruginosa, and CR-Acinetobacter baumannii as top critical-priority resistant bacteria, outweighing methicillin-resistant Staphylococcus aureus.\(^5\) Consequently, updated epidemiological data on antibiotic resistance is needed to adapt the treatment strategies to the reality, which changes at an alarming rate.\(^4,6-8\)
Ceftaroline is a fifth-generation broad-spectrum cephalosporin. It is mainly active against methicillin-resistant *Staphylococcus aureus* and Gram-positive bacteria, but also against Gram-negative bacteria. Ceftaroline is indicated for community-acquired pneumonia and complicated skin infections. Avibactam is a diazabicyclooctane derivative antibiotic that can reversibly inhibit β-lactamase enzymes, including Ambler class A (ESBL and KPC), class C, and partial class D (including OXA-1, OXA-10, and OXA-48-like) enzymes by covalent acylation of the active-site serine residue. Ceftazidime-avibactam is a novel β-lactam/β-lactamase inhibitor combination that has shown potency against a wide variety of CR-Enterobacteriaceae. Ceftazidime-avibactam has been approved for the management of complicated urinary tract infections, complicated intra-abdominal infections, hospital-acquired pneumonia, and infections from aerobic Gram-negative bacteria with limited treatment options.

Ceftaroline and ceftazidime-avibactam are relatively novel antibiotics that show promises in the control of antibiotic-resistant pathogens. They are readily available around the globe. The patterns of resistance to ceftaroline and ceftazidime-avibactam around the globe remain to be defined exactly and represent crucial data for monitoring global health threats. Therefore, this study aimed to: 1) examine the *in vitro* activities of ceftaroline, ceftazidime-avibactam, and various comparative agents from 2012 to 2016 using the data from a global antibiotic surveillance program, the Antimicrobial Testing Leadership And Surveillance (ATLAS) program; and 2) compare the susceptibility profile of various pathogen species over time and across different regions of the world, with an emphasis on antibiotic-resistant pathogens.

**Materials And Methods**

**Bacterial isolates**

For the 2012-2016 ATLAS program, 205 medical centers located in Africa-Middle East (n=12), Asia-Pacific (n=32), Europe (n=94), Latin America (n=26), North America (n=31), and Oceania (n=10) contributed to the consecutive collection of clinical isolates. The specimens were obtained from inpatients with specific types of infections (skin and skin structure infection, intra-abdominal infection, urinary tract infection, lower respiratory tract infection, and blood infection). The pathogens were isolated and identified by each participating center, stored in tryptic soy broth with glycerol at -70°C, and shipped to International Health Management Associates, Inc. (IHMA; Schaumburg, IL, USA) for susceptibility testing. The present study only included the isolates considered to be the potential pathogen of the patient’s infection. If multiple samples were taken from the same patient during an infectious event, only the first positive sample for this infectious event was included in the ATLAS program. The pathogen identification was confirmed by MALDI-TOF at IHMA (Schaumburg, IL, USA) prior to susceptibility testing. Methicillin-resistant *Staphylococcus aureus* is defined in this study as *Staphylococcus aureus* resistant to oxacillin.

**Antimicrobial susceptibility testing**

IHMA (Schaumburg, IL, USA) carried out all antimicrobial susceptibility tests using the broth microdilution method. The minimum inhibitory concentrations (MICs) were interpreted using the Clinical and Laboratory Standards Institute (CLSI) 2019 and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) 2019 breakpoints. Tigecycline was interpreted using the Food and Drug Administration and
EUCAST 2019 interpretative breakpoints. Ceftaroline, ceftazidime-avibactam (avibactam at a fixed concentration of 4 mg/L), and the following comparator agents were tested: ceftazidime, cefepime, penicillin, ampicillin, piperacillin-tazobactam, doripenem, imipenem, meropenem, levofloxacin, moxifloxacin, clindamycin, erythromycin, vancomycin, teicoplanin, linezolid, daptomycin, gentamicin, tigecycline, minocycline, trimethoprim-sulfamethoxazole, amikacin, colistin, aztreonam, quinupristin-dalfopristin, and oxacillin. In the present study, the data were analyzed for *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Citrobacter freundii*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Staphylococcus aureus*, *Streptococcus pneumoniae*, *α- and β-hemolytic Streptococcus*, coagulase-negative *Staphylococcus*, *Enterococcus faecalis*, and *Enterococcus faecium*, as well as resistant species including CR-*Escherichia coli*, CR-*Klebsiella pneumoniae*, CR-*Enterobacter cloacae*, CR-*Pseudomonas aeruginosa*, CR-*Acinetobacter baumannii*, methicillin-resistant *Staphylococcus aureus*, and penicillin-resistant *Streptococcus pneumoniae*. All tests included quality control strains from the American Type Culture Collection (ATCC; Manassas, VA, USA). *Escherichia coli* ATCC 25922, *Klebsiella pneumoniae* ATCC 700603, *Pseudomonas aeruginosa* ATCC 27853, *Staphylococcus aureus* ATCC 29213, and *Streptococcus pneumoniae* ATCC 49619 were used for quality control according to the CLSI 2019 guidelines. All quality control results were within the published ranges.

**Results**

**Sample retrieval**

A total of 176,345 isolates were collected between 2012 and 2016. The numbers of isolates of each species group tested are listed in Tables 1 and 2. The largest number of isolates were collected from patients >60 years (82,518, 46.8%) and 31-60 years (59,428, 33.7%), followed by patients <18 years (19,446, 11.0%) and 19-30 years (13,350, 7.6%). Regarding the infection types, 64,032 (36.3%) isolates were collected from skin and skin structure infections, 52,077 (29.5%) from lower respiratory tract infections, 26,868 (15.2%) from urinary tract infections, 12,847 (7.3%) from intra-abdominal infections, and 11,930 (6.8%) from the blood. In regard to hospital location, 74,554 (42.3%), 32,430 (18.4%), 17,024 (9.7%), 16,339 (9.3%), 10,130 (5.7%), and 8,200 (4.6%) isolates were from patients in the general medical wards, general surgical wards, emergency rooms, medical intensive care unit (ICUs), surgical ICUs, and general pediatric wards, respectively.

**Table 1:** *In vitro* susceptibilities of Gram-negative strains obtained from the ATLAS program, 2012-2016.
| Organism/Antibiotic | No. of isolates | MIC<sub>50</sub> | MIC<sub>90</sub> | MIC Range | CLSI† | EUCAST† |
|---------------------|-----------------|-----------------|-----------------|-----------|-------|---------|
|                      |                 |                 |                 |           | S%    | I%      | R%     | S%    | I%    | R%     |
| *Escherichia coli*   |                 |                 |                 |           |       |         |        |       |       |        |
| Ceftaroline         | 21903           | 0.12            | 256             | 0.015-256 | 66.5  | 2.6     | 30.9   | 66.5  | 0     | 33.5   |
| Ceftazidime-avibactam | 21903       | 0.12            | 0.25            | 0.015-256 | 99.8  | 0       | 0.2    | 99.8  | 0     | 0.2    |
| Ceftazidime         | 21903           | 0.25            | 32              | 0.015-256 | 79.2  | 3.0     | 17.8   | 74.0  | 5.1   | 20.8   |
| Cefepime            | 21903           | 0.12            | 32              | 0.12-32   | 76.2  | 4.7     | 19.1   | 74.6  | 3.6   | 21.8   |
| Pip-taz             | 21903           | 2               | 16              | 0.25-256  | 90.3  | 4.6     | 5.1    | 84.8  | 5.4   | 9.8    |
| Doripenem           | 21903           | 0.03            | 0.06            | 0.008-16  | 99.6  | 0.1     | 0.3    | 99.6  | 0.1   | 0.3    |
| Imipenem            | 21903           | 0.25            | 0.25            | 0.03-16   | 99.1  | 0.4     | 0.5    | 99.5  | 0.4   | 0.2    |
| Meropenem           | 21903           | 0.03            | 0.06            | 0.004-16  | 99.5  | 0.1     | 0.4    | 99.6  | 0.2   | 0.2    |
| Levofoxacin         | 21903           | 0.25            | 16              | 0.004-16  | 62.3  | 1.7     | 36.0   | 58.8  | 2.8   | 38.4   |
| Tigecycline         | 21903           | 0.25            | 0.5             | 0.015-16  | 99.8  | 0.2     | 0      | 99.0  | 0.8   | 0.2    |
| Amikacin            | 21903           | 2               | 8               | 0.25-64   | 98.2  | 0.9     | 0.9    | 94.5  | 3.7   | 1.8    |
| Colistin            | 13964           | 0.5             | 1               | 0.06-16   | NA    | NA      | NA     | 99.5  | 0     | 0.5    |
| Aztreonam           | 21903           | 0.12            | 64              | 0.015-256 | 76.0  | 3.1     | 20.9   | 72.3  | 3.7   | 24.0   |
| *Klebsiella pneumoniae* |             |                 |                 |           |       |         |        |       |       |        |
| Ceftaroline         | 18114           | 0.25            | 256             | 0.015-256 | 57.5  | 2.0     | 40.5   | 57.5  | 0     | 42.5   |
| Ceftazidime-avibactam | 18114       | 0.12            | 1               | 0.015-256 | 98.8  | 0       | 1.2    | 98.8  | 0     | 1.2    |
| Ceftazidime         | 18114           | 0.25            | 128             | 0.015-256 | 64.3  | 1.9     | 33.8   | 61.6  | 2.7   | 35.7   |
| Cefepime            | 18114           | 0.12            | 32              | 0.12-32   | 65.1  | 6.0     | 28.9   | 63.7  | 3.2   | 33.1   |
| Pip/taz             | 18114           | 4               | 256             | 0.25-256  | 73.0  | 7.8     | 19.2   | 64.4  | 8.6   | 27.0   |
| Doripenem           | 18114           | 0.06            | 0.5             | 0.008-16  | 91.6  | 1.0     | 7.4    | 91.6  | 1.0   | 7.4    |
| Imipenem            | 18114           | 0.25            | 1               | 0.03-16   | 90.3  | 1.9     | 7.8    | 92.2  | 2.4   | 5.5    |
| Meropenem           | 18114           | 0.06            | 0.5             | 0.004-16  | 91.1  | 1.1     | 7.9    | 92.1  | 2.0   | 5.9    |
| Levofoxacin         | 18114           | 0.12            | 8               | 0.004-16  | 73.2  | 3.1     | 23.7   | 61.8  | 9.1   | 29.1   |
| Tigecycline         | 18114           | 0.5             | 2               | 0.015-16  | 96.4  | 3.1     | 0.5    | 88.2  | 8.2   | 3.6    |
| Amikacin            | 18114           | 1               | 8               | 0.25-64   | 93.6  | 3.0     | 3.4    | 91.0  | 2.6   | 6.4    |
| Colistin            | 12884           | 0.5             | 1               | 0.06-16   | NA    | NA      | NA     | 96.3  | 0     | 3.7    |
| Aztreonam           | 18114           | 0.12            | 256             | 0.015-256 | 64.2  | 1.0     | 34.8   | 62.4  | 1.8   | 35.8   |
| *Enterobacter cloacae* |               |                 |                 |           |       |         |        |       |       |        |
| Ceftaroline         | 4330            | 0.5             | 256             | 0.015-256 | 60.0  | 3.1     | 37.0   | 60.0  | 0.0   | 40.1   |
| Antibiotic                  | MIC (μg/mL) | 256 | 0.015-0.06 | 0.03-0.12 | 0.12-3.8 | 3.8-8 | 8-12.7 | 12.7-30.8 | 30.8-99.7 | 99.7-167 | 167-2.4 | 2.4-1 | 1-0.3 | 0.3-0.015 | 0.015-0.008 | 0.008-0.004 | 0.004-0.015 |
|-----------------------------|-------------|-----|-------------|------------|----------|-------|--------|----------|----------|----------|--------|------|-----|----------|--------------|-------------|-------------|
| **Citrobacter freundii**    |             |     |             |            |          |       |        |          |          |          |       |     |    |          |               |             |             |
| Ceftaroline                 | 2327        | 0.25| 128         | 0.015-0.256| 61.9     | 2.1   | 36.0   | 61.9     | 0.0      | 38.1     |       |     |    |          |               |             |             |
| Ceftazidime-avibactam       | 2327        | 0.12| 0.5         | 0.015-0.256| 98.5     | 0.0   | 1.5    | 98.5     | 0.12     | 1.5      |       |     |    |          |               |             |             |
| Ceftazidime                 | 2327        | 0.5 | 128         | 0.015-0.256| 68.0     | 1.9   | 30.1   | 64.3     | 0.03-0.12| 32.0     |       |     |    |          |               |             |             |
| Cefepime                    | 2327        | 0.12| 4           | 0.015-0.256| 89.8     | 3.6   | 6.7    | 84.4     | 0.03-0.12| 7.3      | 8.4   |     |    |          |               |             |             |
| Pip-taz                     | 2327        | 4   | 128         | 0.008-0.64  | 77.1     | 12.0  | 11.0   | 70.5     | 0.008-0.16| 6.6      | 23.0  |     |    |          |               |             |             |
| Doripenem                   | 2327        | 0.06| 0.12        | 0.008-0.16  | 97.9     | 0.3   | 1.8    | 97.9     | 0.03-0.16| 0.3      | 1.8   |     |    |          |               |             |             |
| Imipenem                    | 2327        | 0.5 | 2           | 0.004-0.16  | 88.9     | 8.5   | 2.6    | 97.4     | 0.004-0.16| 2.1      | 0.5   |     |    |          |               |             |             |
| Meropenem                   | 2327        | 0.03| 0.06        | 0.004-0.16  | 97.7     | 0.5   | 1.8    | 98.2     | 0.004-0.16| 1.2      | 0.6   |     |    |          |               |             |             |
| Levofoxacin                 | 2327        | 0.12| 4           | 0.008-0.16  | 87.0     | 4.0   | 9.0    | 76.5     | 0.008-0.16| 6.2      | 17.3  |     |    |          |               |             |             |
| Tigecycline                 | 2327        | 0.5 | 1           | 0.015-0.016 | 98.9     | 1.1   | 0      | 94.9     | 0.015-0.016| 4.0      | 1.1   |     |    |          |               |             |             |
| Amikacin                    | 2327        | 2   | 4           | 0.004-0.64  | 98.4     | 0.4   | 1.2    | 97.1     | 0.004-0.64| 1.3      | 1.6   |     |    |          |               |             |             |
| Colistin                    | 1593        | 0.5 | 1           | 0.004-0.16  | NA       | NA    | NA     | 99.6     | 0.004-0.16| 0.4      |       |     |    |          |               |             |             |
| Aztreonam                   | 2327        | 0.25| 64          | 0.015-0.256 | 69.2     | 2.4   | 28.4   | 66.2     | 0.015-0.256| 3.1      | 30.8  |     |    |          |               |             |             |

**Proteus mirabilis**

| Antibiotic                  | MIC (μg/mL) | 256 | 0.015-0.256 | 0.03-0.12 | 0.12-3.8 | 3.8-8 | 8-12.7 | 12.7-30.8 | 30.8-99.7 | 99.7-167 | 167-2.4 | 2.4-1 | 1-0.3 | 0.3-0.015 | 0.015-0.008 | 0.008-0.004 |
|-----------------------------|-------------|-----|-------------|------------|----------|-------|--------|----------|----------|----------|--------|------|-----|----------|--------------|-------------|-------------|
| Ceftaroline                 | 3950        | 0.12| 128         | 0.015-0.256| 79.4     | 2.0   | 18.6   | 79.4     | 0.0      | 20.6     |       |     |    |          |               |             |             |
| Ceftazidime-avibactam       | 3950        | 0.03| 0.06        | 0.015-0.256| 99.7     | 0.0   | 0.3    | 99.7     | 0.0      | 0.3      |       |     |    |          |               |             |             |
| Ceftazidime                 | 3950        | 0.06| 1           | 0.015-0.256| 95.2     | 1.7   | 3.1    | 91.1     | 0.05     | 4.1      | 4.8   |     |    |          |               |             |             |
| Cefepime                    | 3950        | 0.12| 8           | 0.12-256   | 88.2     | 3.4   | 8.5    | 86.9     | 0.12-256| 2.9      | 10.3  |     |    |          |               |             |             |
| Antibiotic        | MIC Range | Sensitivity | Resistance |
|-------------------|-----------|-------------|------------|
| Pip-taz           | 0.25-256  | 98.5        | 0.9        |
| Doripenem        | 0.008-16  | 98.4        | 1.0        |
| Imipenem         | 0.03-16   | 25.8        | 45.9       |
| Meropenem        | 0.004-16  | 99.6        | 0.2        |
| Levofloxacin     | 0.015-16  | 76.6        | 5.5        |
| Tigecycline      | 0.03-16   | 52.2        | 37.3       |
| Amikacin         | 0.25-64   | 95.6        | 1.1        |
| Colistin         | 0.25-16   | NA          | NA         |
| Aztreonam        | 0.015-256 | 95.9        | 0.8        |

**Pseudomonas aeruginosa**

| Antibiotic        | MIC Range | Sensitivity | Resistance |
|-------------------|-----------|-------------|------------|
| Ceftaroline       | 0.015-256 | NA          | NA         |
| Ceftazidime-avibactam | 0.015-256 | 91.9       | 0          |
| Ceftazidime      | 0.06-256  | 76.7        | 4.6        |
| Cefepime         | 0.12-32   | 78.4        | 11.2       |
| Pip-taz          | 0.25-32   | 68.9        | 13.8       |
| Doripenem        | 0.008-16  | 74.3        | 7.6        |
| Imipenem         | 0.03-16   | 63.4        | 8.2        |
| Meropenem        | 0.008-16  | 72.5        | 6.0        |
| Levofloxacin     | 0.004-16  | 70.4        | 6.8        |
| Amikacin         | 0.25-64   | 90.4        | 2.7        |
| Colistin         | 0.06-16   | 96.6        | 0          |
| Aztreonam        | 0.015-256 | NA          | NA         |

**Acinetobacter baumannii**

| Antibiotic        | MIC Range | Sensitivity | Resistance |
|-------------------|-----------|-------------|------------|
| Ceftaroline       | 0.015-256 | NA          | NA         |
| Ceftazidime-avibactam | 0.03-256  | NA          | NA         |
| Ceftazidime      | 0.015-256 | 30.1        | 2.4        |
| Cefepime         | 0.12-32   | 29.9        | 10.4       |
| Pip-taz          | 0.25-32   | 25.4        | 3.7        |
| Doripenem        | 0.015-16  | 33.2        | 1.4        |
| Imipenem         | 0.03-16   | 33.8        | 1.2        |
| Meropenem        | 0.015-16  | 32.8        | 1.6        |

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| Antibiotic   | ATCC | MIC (μg/mL) | Viable (%) | 0.03-16 | 9.6  | 61.4 | 26.1 | 1.0  | 73  |
|--------------|------|-------------|------------|---------|------|------|------|------|-----|
| Levofloxacin | 3567 | 8           | 16         | 0.03-16 | 29   | 9.6  | 61.4 | 26.1 | 1.0 |
| Tigecycline  | 3567 | 1           | 2          | 0.015-16| NA   | NA   | NA   | NA   | NA  |
| Amikacin     | 3567 | 64          | 64         | 0.25-64 | 42.5 | 5.8  | 51.7 | 40.2 | 2.3 |
| Colistin     | 2404 | 1           | 2          | 0.06-16 | 94.3 | 0    | 5.7  | 94.3 | 0   |
| Aztreonam    | 3567 | 64          | 256        | 0.015-256| NA  | NA  | NA  | NA  | NA  |

†Cefepime CLSI susceptibility for *Enterobacteriaceae* adopted the susceptible, susceptible-dose-dependent, and resistant categories.

CLSI=Clinical Laboratory and Standards Institute; EUCAST= European Committee on Antimicrobial Susceptibility Testing; NA=not applicable.

**Table 2:** *In vitro* susceptibilities of Gram-positive strains obtained from the ATLAS program, 2012-2016.
| Organism/Antibiotic | No. of isolates | MIC<sub>50</sub> | MIC<sub>90</sub> | MIC Range | CLSI S% | CLSI I% | CLSI R% | EUCAST S% | EUCAST I% | EUCAST R% |
|---------------------|-----------------|-----------------|-----------------|------------|----------|----------|----------|-----------|-----------|-----------|
| **Staphylococcus aureus** | | | | | | | | | | | |
| Ceftaroline | 50525 | 0.5 | 1 | 0.015-64 | 93.4 | 6.2 | 0.4 | 93.4 | 6.2 | 0.4 |
| Ceftazidime-avibactam | 50525 | 32 | 64 | 0.015-64 | NA | NA | NA | NA | NA | NA |
| Ceftazidime | 50525 | 32 | 64 | 0.015-64 | NA | NA | NA | NA | NA | NA |
| Pip-taz | 50525 | 8 | 32 | 0.12-32 | NA | NA | NA | NA | NA | NA |
| Levofloxacin | 50525 | 0.5 | 8 | 0.015-8 | 56.9 | 0.4 | 42.7 | 56.9 | 0 | 43.1 |
| Moxifloxacin | 50525 | 0.12 | 4 | 0.008-8 | 57.1 | 2.7 | 40.1 | 56.8 | 0 | 43.2 |
| Tigecycline | 50525 | 0.12 | 0.25 | 0.015-4 | 98.9 | 1.1 | 0 | 98.9 | 0 | 1.1 |
| Minocycline | 50525 | 0.12 | 1 | 0.12-16 | 93.2 | 3.4 | 3.4 | 89.4 | 1.4 | 9.2 |
| Gentamicin | 31019 | 0.5 | 64 | 0.06-64 | 85 | 0.7 | 14.3 | 56.1 | 0 | 43.9 |
| Daptomycin | 50525 | 0.5 | 1 | 0.06-4 | 99.8 | 0.2 | 0 | 99.8 | 0 | 0.2 |
| Trimethoprim sulfa | 31019 | 0.25 | 1 | 0.25-8 | 96.8 | 0 | 3.3 | 96.8 | 0.7 | 2.6 |
| Teicoplanin | 50525 | 0.5 | 1 | 0.12-32 | 100 | 0 | 0 | 98.1 | 0 | 1.9 |
| Vancomycin | 50525 | 1 | 2 | 0.25-4 | 100 | 0 | 0 | 100 | 0 | 0 |
| Clindamycin | 50525 | 0.12 | 4 | 0.03-8 | 74.8 | 0.3 | 24.9 | 74.2 | 0.6 | 25.2 |
| Erythromycin | 50525 | 1 | 16 | 0.12-16 | 48 | 3.4 | 48.6 | 50.6 | 0.3 | 49.1 |
| Linezolid | 50525 | 2 | 2 | 0.5-16 | 100 | 0 | 0 | 100 | 0 | 0 |
| Oxacillin | 50525 | 4 | 8 | 0.06-8 | 40.4 | 0 | 59.6 | NA | NA | NA |
| **Streptococcus pneumoniae** | | | | | | | | | | | |
| Ceftaroline | 11005 | 0.008 | 0.12 | 0.004-32 | 99.7 | 0.3 | 0 | 98.7 | 0 | 1.3 |
| Ceftazidime-avibactam | 11005 | 0.25 | 16 | 0.015-128 | NA | NA | NA | NA | NA | NA |
| Ceftazidime | 11005 | 0.25 | 16 | 0.015-128 | NA | NA | NA | NA | NA | NA |
| Doripenem | 11005 | 0.015 | 1 | 0.015-8 | 98 | 2 | 0 | 98 | 0 | 2 |
| Meropenem | 11005 | 0.015 | 1 | 0.008-2 | 78 | 9.2 | 12.8 | 100 | 0 | 0 |
| Levofloxacin | 11005 | 1 | 1 | 0.12-16 | 98.5 | 0.2 | 1.3 | 98.5 | 0 | 1.5 |
| Moxifloxacin | 11005 | 0.12 | 0.25 | 0.03-8 | 98.5 | 0.5 | 1.1 | 98.4 | 0 | 1.6 |
| Tigecycline | 11005 | 0.03 | 0.03 | 0.008-2 | 99.9 | 0.1 | 0 | NA | NA | NA |
| Minocycline | 11005 | 0.12 | 4 | 0.015-4 | 71.3 | 5.1 | 23.6 | 69.6 | 1.7 | 28.7 |
| Daptomycin | 11005 | 0.25 | 0.5 | 0.03-8 | NA | NA | NA | NA | NA | NA |
| Vancomycin | 11005 | 0.25 | 0.5 | 0.008-2 | 100 | 0 | 0 | 100 | 0 | 0 |
| Clindamycin | 11005 | 0.06 | 2 | 0.008-2 | 74.8 | 0.4 | 24.8 | 75.2 | 0 | 24.8 |
| Erythromycin | 11005 | 0.06 | 2 | 0.008-2 | 64.3 | 0.3 | 35.4 | 64.3 | 0.3 | 35.4 |
| Linezolid | 11005 | 1 | 2 | 0.06-4 | 100 | 0 | 0 | 100 | 0 | 0 |
|                |          |      |        |       |       |       |       |       |
|----------------|----------|------|--------|-------|-------|-------|-------|-------|
| Penicillin     | 11005    | 0.03 | 2      | 0.015-16 | 61.8 | 20.7 | 17.5  | 61.8  | 28.9 | 9.3  |

**α-hemolytic Streptococcus**

| Medicine       | ID      | MIC  | IC50   | IC50   | IC50   | IC50   | IC50   | IC50   |
|----------------|---------|------|--------|--------|--------|--------|--------|--------|
| Penicillin     | 12138   | 0.008 | 0.12 | 0.004-32 | 99.7 | 0.3 | 0 | 98.7 | 0 | 1.3 |
| Ceftaroline    |         |      |       |        |        |        |        |        |
| Ceftazidime-avibactam | 12138 | 0.25 | 16 | 0.015-128 | NA | NA | NA | NA | NA | NA |
| Ceftazidime    |         |      |       |        |        |        |        |        |
| Penicillin     | 12138   | 0.03 | 2 | 0.015-16 | NA | NA | NA | NA | NA | NA |
| Doripenem      | 12138   | 0.015 | 1 | 0.015-8 | NA | NA | NA | 98 | 0 | 2 |
| Meropenem      | 12138   | 0.015 | 1 | 0.008-2 | NA | NA | NA | 100 | 0 | 0 |
| Levofloxacin   | 12138   | 1 | 2 | 0.12-16 | 98.3 | 0.3 | 1.4 | 98.5 | 0 | 1.5 |
| Moxifloxacin   | 12138   | 0.12 | 0.25 | 0.03-8 | 98.5 | 0.5 | 1.1 | 98.4 | 0 | 1.6 |
| Minocycline    | 12138   | 0.12 | 4 | 0.015-4 | NA | NA | NA | 69.6 | 1.7 | 28.7 |
| Tigecycline    | 12138   | 0.03 | 0.03 | 0.008-2 | NA | NA | NA | 100 | 0 | 0 |
| Clindamycin    | 12138   | 0.06 | 2 | 0.008-2 | 75.6 | 0.4 | 24.1 | 75.9 | 0 | 24.1 |
| Erythromycin   | 12138   | 0.06 | 2 | 0.008-2 | 64.8 | 0.3 | 34.9 | 64.3 | 0.3 | 35.4 |
| Vancomycin     | 12138   | 0.5 | 0.5 | 0.008-2 | 100 | 0 | 0 | 100 | 0 | 0 |
| Linezolid      | 12138   | 1 | 2 | 0.06-8 | 100 | 0 | 0 | 100 | 0 | 0 |
| Daptomycin     | 12138   | 0.25 | 0.5 | 0.03-8 | 99.3 | 0.7 | 0 | 100 | 0 | 0 |

**β-hemolytic Streptococcus**

| Medicine       | ID      | MIC  | IC50   | IC50   | IC50   | IC50   | IC50   | IC50   |
|----------------|---------|------|--------|--------|--------|--------|--------|--------|
| Penicillin     | 9019    | 0.004 | 0.015 | 0.004-1 | 100 | 0 | 0 | NA | NA | NA |
| Ceftaroline    |         |      |       |        |        |        |        |        |
| Ceftazidime-avibactam | 9019 | 0.12 | 0.5 | 0.015-128 | NA | NA | NA | NA | NA | NA |
| Ceftazidime    |         |      |       |        |        |        |        |        |
| Penicillin     | 9019    | 0.015 | 0.06 | 0.015-8 | NA | NA | NA | NA | NA | NA |
| Doripenem      | 9019    | 0.015 | 0.03 | 0.015-8 | NA | NA | NA | 100 | 0 | 0 |
| Meropenem      | 9019    | 0.015 | 0.06 | 0.008-2 | 99.9 | 0.1 | 0 | 100 | 0 | 0 |
| Levofloxacin   | 9019    | 0.5 | 1 | 0.12-16 | 98.3 | 0.2 | 1.5 | 98.2 | 0 | 1.9 |
| Moxifloxacin   | 9019    | 0.12 | 0.25 | 0.03-8 | NA | NA | NA | 98.1 | 0 | 1.9 |
| Minocycline    | 9019    | 0.12 | 4 | 0.015-4 | 69.9 | 30.1 | 0 | 65.6 | 0.9 | 33.4 |
| Tigecycline    | 9019    | 0.03 | 0.06 | 0.008-2 | 100 | 0 | 0 | 100 | 0 | 0 |
| Clindamycin    | 9019    | 0.06 | 0.12 | 0.008-2 | 90.6 | 0.3 | 9 | 91 | 0 | 9 |
| Erythromycin   | 9019    | 0.06 | 2 | 0.008-2 | 83.4 | 0.7 | 15.8 | 84.4 | 0.6 | 15 |
| Vancomycin     | 9019    | 0.5 | 0.5 | 0.008-1 | 100 | 0 | 0 | 100 | 0 | 0 |
| Linezolid      | 9019    | 1 | 2 | 0.06-8 | 100 | 0 | 0 | 100 | 0 | 0 |
| Daptomycin     | 9019    | 0.12 | 0.5 | 0.03-8 | 100 | 0 | 0 | 100 | 0 | 0 |
|                  | CoNS                        | Enterococcus faecalis | Enterococcus faecium |
|------------------|----------------------------|-----------------------|----------------------|
| Ceftaroline      | 8490 0.25 1 0.015-64       | NA NA NA NA NA NA    | NA NA NA NA NA      |
| Ceftazidime-avibactam | 8490 16 64 0.015-64 | NA NA NA NA NA NA    | NA NA NA NA NA      |
| Ceftazidime      | 8490 16 64 0.015-64       | NA NA NA NA NA NA    | NA NA NA NA NA      |
| Pip-taz          | 8490 2 32 0.12-32         | NA NA NA NA NA NA    | NA NA NA NA NA      |
| Levofoxacin      | 8490 4 8 0.015-8          | 46.9 1.8 51.4 46.9 0 53.1 | NA NA NA NA NA      |
| Moxifloxacin     | 8490 1 4 0.008-8          | NA NA NA NA NA NA    | NA NA NA NA NA      |
| Minocycline      | 8490 0.25 0.5 0.12-16     | 48.9 14.6 36.5 46.5 0 53.5 | NA NA NA NA NA      |
| Tigecycline      | 8490 0.25 0.5 0.015-4     | 98.7 1.3 0 98.7 0 1.3  | NA NA NA NA NA      |
| Clindamycin      | 8490 0.12 8 0.03-8        | 65.5 2.1 32.4 63.7 1.9 34.5 | NA NA NA NA NA      |
| Erythromycin     | 8490 8 16 0.12-16         | 33.1 1.1 65.8 33.4 0.3 66.3 | NA NA NA NA NA      |
| Vancomycin       | 8490 1 2 0.25-8           | 99.9 0.1 0 99.9 0 0.1  | NA NA NA NA NA      |
| Teicoplanin      | 8490 2 8 0.12-64          | 98 1.7 0.3 85 0 15    | NA NA NA NA NA      |
| Linezolid        | 8490 1 2 0.5-16           | 99.4 0 0.6 99.4 0 0.6  | NA NA NA NA NA      |
| Daptomycin       | 8490 0.5 1 0.06-4         | 99.6 0.4 0 99.6 0 0.4  | NA NA NA NA NA      |
| Gentamicin       | 5336 2 64 0.06-64         | 54.7 5.5 39.8 33.8 0 66.3 | NA NA NA NA NA      |
| Trimethoprim sulfa | 5336 1 8 0.25-8           | 61 0 39 61 10 28.9   | NA NA NA NA NA      |
| Oxacillin        | 8490 4 8 0.06-8           | 25.7 0 74.3 NA NA NA | NA NA NA NA NA      |
| **Enterococcus faecalis** |                  |                       |                     |
| Ceftaroline      | 3194 1 16 0.015-64       | NA NA NA NA NA NA    | NA NA NA NA NA      |
| Ceftazidime-avibactam | 3194 64 64 1-64 | NA NA NA NA NA NA    | NA NA NA NA NA      |
| Ceftazidime      | 3194 64 64 1-64          | NA NA NA NA NA NA    | NA NA NA NA NA      |
| Levofoxacin      | 3194 1 16 0.06-16        | 68 1.1 30.8 NA NA NA | NA NA NA NA NA      |
| Tigecycline      | 3194 0.12 0.25 0.015-4   | 94.1 5.9 0 94.1 3.9 2 | NA NA NA NA NA      |
| Minocycline      | 3194 16 16 0.06-16       | 25.8 13.7 60.5 NA NA | NA NA NA NA NA      |
| Daptomycin       | 3194 2 4 0.06-8          | 99.8 0.2 0 NA NA NA | NA NA NA NA NA      |
| Teicoplanin      | 3194 0.5 0.5 0.12-64     | 98.3 0.1 1.7 97.8 0 2.2 | NA NA NA NA NA      |
| Vancomycin       | 3194 1 2 0.12-64         | 94.3 3.8 1.9 94.3 0 5.7 | NA NA NA NA NA      |
| Erythromycin     | 3194 16 16 0.06-16       | 14.6 27.4 58 NA NA | NA NA NA NA NA      |
| Linezolid        | 3194 1 2 0.06-8          | 99.3 0.6 0.2 99.8 0 0.2 | NA NA NA NA NA      |
| Quinupristin     | 2014 8 16 0.25-16        | 1 7.7 91.3 NA NA | NA NA NA NA NA      |
| **Enterococcus faecium** |                    |                       |                     |
| Ceftaroline      | 2546 64 64 0.03-64       | NA NA NA NA NA NA    | NA NA NA NA NA      |
| Ceftazidime-avibactam | 2546 64 64 0.12-64 | NA NA NA NA NA NA    | NA NA NA NA NA      |
| Antibiotic          | MIC Range | Percentage Susceptible |
|---------------------|-----------|------------------------|
| Ceftazidime         | 0.12-64   | 91.9%                  |
| Levofloxacin        | 0.06-16   | 91.9%                  |
| Tigecycline         | 0.015-8   | 95.5%                  |
| Minocycline         | 0.06-16   | 95.5%                  |
| Daptomycin          | 0.06-16   | 95.5%                  |
| Teicoplanin         | 0.12-64   | 76%                    |
| Vancomycin          | 0.12-64   | 69.2%                  |
| Erythromycin        | 0.06-16   | 73.2%                  |
| Linezolid           | 0.06-16   | 73.2%                  |
| Quinupristin dalfopristin | 0.06-16 | 73.2% |

**In vitro activities of ceftaroline and ceftazidime-avibactam against Gram-negative bacteria from 2012 to 2016**

Tables 1 (Gram-negative) and 2 (Gram-positive) show the *in vitro* activities of ceftaroline, ceftazidime-avibactam, and comparators against the selected bacteria. Ceftazidime-avibactam demonstrated high activities against all tested Gram-negative bacteria (CLSI/EUCAST 2019 susceptibility, 91.9%-99.8%). The susceptibility of *Acinetobacter baumannii* was not calculated because of the absence of a breakpoint, but the MICs of this antibiotic were higher for *Acinetobacter baumannii* than for the other bacteria (MIC<sub>50</sub>/MIC<sub>90</sub>, 32/128 mg/L). The addition of avibactam drastically increased the activity of ceftazidime against *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Citrobacter freundii*, and *Pseudomonas aeruginosa* (CLSI 2019 susceptibilities to ceftazidime alone, 64.3%-79.2%) whereas a trend of decreased MIC was observed for *Acinetobacter baumannii*, as indicated by a 2-fold reduction in MIC<sub>90</sub> (ceftazidime, MIC<sub>50</sub>/MIC<sub>90</sub>, 64/256 mg/L). Regarding the comparator agents, the susceptibility of *Enterobacteriaceae* was, in general, high for carbapenems and tigecycline (>90%). For *Acinetobacter baumannii*, the most potent antibiotics were colistin and tigecycline (MIC<sub>50</sub>/MIC<sub>90</sub>, 1/2 mg/L), with a MIC<sub>50</sub> of ≥8 and a MIC<sub>90</sub> of ≥16 mg/L observed for all other tested agents.

Regarding resistant Gram-negative strains, the activities of ceftazidime-avibactam were moderate for CR-*Escherichia coli* (MIC<sub>50</sub>/MIC<sub>90</sub>, 0.5/256 mg/L), CR-*Klebsiella pneumoniae* (MIC<sub>50</sub>/MIC<sub>90</sub>, 1/256 mg/L), and CR-*Pseudomonas aeruginosa* (MIC<sub>50</sub>/MIC<sub>90</sub>, 4/64 mg/L) and low for CR-*Enterobacter cloacae* and CR-*Acinetobacter baumannii* (MIC<sub>50</sub>/MIC<sub>90</sub>, 64-128/256 mg/L) (Table 3). Regarding the comparator agents, the susceptibilities of CR-*Escherichia coli*, CR-*Klebsiella pneumoniae*, CR-*Enterobacter cloacae*, CR-*Pseudomonas aeruginosa*, and CR-*Acinetobacter baumannii* were low for the vast majority of the tested antibiotics. Good potency was observed for tigecycline against all tested *Enterobacteriaceae* (MIC<sub>50</sub>/MIC<sub>90</sub>, 0.25-1/1-4 mg/L),
and for colistin against CR-\textit{Escherichia coli}, CR-\textit{Enterobacter cloacae}, CR-\textit{Pseudomonas aeruginosa}, and CR-\textit{Acinetobacter baumannii} (MIC$\text{S}_\text{50}$/MIC$\text{S}_\text{90}$, 0.5-1/1-2 mg/L).

Table 3: \textit{In vitro} susceptibilities of multi-drug resistant strains obtained from the ATLAS program, 2012-2016.
| Organism/Antibiotic | No. of isolates | MIC<sub>50</sub> | MIC<sub>90</sub> | MIC Range | CLSI<sup>†</sup> | EUCAST |
|---------------------|-----------------|-----------------|-----------------|------------|--------------|--------|
|                     |                 |                 |                 |            | S% | I% | R% | S% | I% | R% |
| **CRECO**           |                 |                 |                 |            |    |    |    |    |    |    |
| Ceftaroline         | 119             | 256             | 256             | 0.015-256 | 10.9 | 1.7 | 87.4 | 9.5 | 0 | 90.5 |
| Ceftazidime-avibactam | 119       | 0.5             | 256             | 0.03-256  | 72.3 | 0  | 27.7 | 40.5 | 0 | 59.5 |
| Ceftazidime         | 119             | 64              | 256             | 0.12-256  | 22.7 | 4.2 | 73.1 | 11.9 | 2.4 | 85.7 |
| Cefepime            | 119             | 32              | 32              | 0.12-32   | 8.4  | 16  | 75.6 | 0   | 2.4 | 97.6 |
| Pip-taz             | 119             | 256             | 256             | 0.5-256   | 21.9 | 5.9 | 72.3 | 19.1 | 2.4 | 78.6 |
| Doripenem           | 119             | 4               | 16              | 0.03-16   | 32.8 | 11.8 | 55.5 | 19.1 | 2.4 | 78.6 |
| Imipenem            | 119             | 8               | 16              | 4-16      | 0    | 0   | 100  | 0   | 0   | 100  |
| Meropenem           | 119             | 8               | 16              | 0.015-16  | 26.1 | 6.7 | 67.2 | 19.1 | 7.1 | 73.8 |
| Levofloxacin        | 119             | 8               | 16              | 0.015-16  | 24.4 | 3.4 | 72.3 | 7.1  | 2.4 | 90.5 |
| Tigecycline         | 119             | 0.25            | 1               | 0.03-4    | 98.3 | 1.7 | 0    | 88.1 | 7.1 | 4.8  |
| Amikacin            | 119             | 8               | 64              | 1-64      | 78.2 | 5   | 16.8 | 59.5 | 7.1 | 33.3 |
| Colistin            | 79              | 0.5             | 1               | 0.12-16   | NA   | NA  | NA   | 96.3 | 0  | 3.7  |
| Aztreonam           | 119             | 64              | 256             | 0.015-256 | 23.5 | 0.8 | 75.6 | 16.7 | 2.4 | 81   |
| **CRKPN**           |                 |                 |                 |            |    |    |    |    |    |    |
| Ceftaroline         | 1418            | 256             | 256             | 0.06-256  | 0.6  | 0   | 99.4 | 0   | 0   | 100  |
| Ceftazidime-avibactam | 1418   | 1               | 256             | 0.015-256 | 85.6 | 0   | 14.4 | 83.6 | 0   | 16.4 |
| Ceftazidime         | 1418            | 256             | 256             | 0.12-256  | 4    | 2.5 | 93.5 | 0.6  | 0.7 | 98.7 |
| Cefepime            | 1418            | 32              | 32              | 0.12-32   | 3.5  | 8   | 88.6 | 0.4  | 0.6 | 99   |
| Pip-taz             | 1418            | 256             | 256             | 2-256    | 1.5  | 1.1 | 97.4 | 0.3  | 0.1 | 99.6 |
| Doripenem           | 1418            | 8               | 16              | 0.03-16   | 4.2  | 5.4 | 90.4 | 0.7  | 0.4 | 98.9 |
| Imipenem            | 1418            | 16              | 16              | 4-16      | 0    | 0   | 100  | 0   | 0   | 100  |
| Meropenem           | 1418            | 16              | 16              | 0.015-16  | 2.9  | 4   | 93.1 | 0.8  | 3.9 | 95.3 |
| Levofloxacin        | 1418            | 8               | 16              | 0.03-16   | 12.7 | 3.5 | 83.9 | 3.1  | 1.6 | 95.2 |
| Tigecycline         | 1418            | 1               | 2               | 0.06-16   | 92.6 | 6.3 | 1.1  | 74.7 | 17.1 | 8.2 |
| Amikacin            | 1418            | 16              | 64              | 0.25-64  | 52.1 | 28.1| 19.8 | 30.3 | 13.2 | 56.6 |
| Colistin            | 1046            | 1               | 16              | 0.06-16   | NA   | NA  | NA   | 74.2 | 0   | 25.8 |
| Aztreonam           | 1418            | 256             | 256             | 0.03-256 | 4.4  | 0.4 | 95.1 | 2.7  | 0.2 | 97.1 |
| **CRECL**           |                 |                 |                 |            |    |    |    |    |    |    |
| Ceftaroline         | 149             | 256             | 256             | 0.06-256  | 4.7  | 0.7 | 94.6 | 1.6  | 0   | 98.4 |
| Ceftazidime-avibactam | 149    | 128             | 256             | 0.06-256  | 42.3 | 0   | 57.7 | 21.9 | 0   | 78.1 |
| Ceftazidime         | 149             | 256             | 256             | 0.12-256  | 8.7  | 1.3 | 89.9 | 1.6  | 1.6 | 96.9 |
| Antibiotic          | MIC (µg/mL) | Resistance (%) |
|---------------------|-------------|----------------|
| **Cefepime**        | 149 32 32   | 0.12-32        |
| **Pip-taz**         | 149 256 256 | 2-256          |
| **Doripenem**       | 149 8 16   | 0.06-16        |
| **Imipenem**        | 149 8 16   | 4-16           |
| **Meropenem**       | 149 8 16   | 0.03-16        |
| **Levofloxacin**    | 149 4 16   | 0.03-16        |
| **Tigecycline**     | 149 1 4    | 0.12-8         |
| **Amikacin**        | 149 4 64   | 0.5-64         |
| **Colistin**        | 118 0.5 1  | 0.12-16        |
| **Aztreonam**       | 149 64 256 | 0.06-256       |
| **CRPAE**           |             |                |
| Ceftaroline         | 4546 128 256 | 0.015-256   |
| Ceftazidime-avibactam | 4546 4 64 | 0.015-256    |
| Ceftazidime         | 4546 16 128 | 0.12-256     |
| Cefepime            | 4546 16 32  | 0.25-32       |
| Pip-taz             | 4546 64 256 | 0.25-256     |
| Doripenem           | 4545 8 16   | 0.03-16       |
| Imipenem            | 4546 16 16  | 8-16          |
| Meropenem           | 4546 16 16  | 0.06-16      |
| Levofloxacin        | 4546 8 16   | 0.015-16     |
| Tigecycline         | 4546 16 16  | 0.03-16      |
| Amikacin            | 4546 8 64   | 0.25-64       |
| Colistin            | 3521 1 2    | 0.06-16      |
| Aztreonam           | 4546 16 128 | 0.06-256     |
| **CRABA**           |             |                |
| Ceftaroline         | 2318 256 256 | 2-256        |
| Ceftazidime-avibactam | 2318 64 256 | 0.06-256    |
| Ceftazidime         | 2318 128 256 | 1-256       |
| Cefepime            | 2318 32 32  | 0.25-32      |
| Pip-taz             | 2318 256 256 | 4-256        |
| Doripenem           | 2318 8 16   | 0.5-16       |
| Imipenem            | 2318 16 16  | 8-16         |
| Meropenem           | 2318 16 16  | 1-16         |
| Levofloxacin        | 2318 8 16   | 0.06-16     |
| Tigecycline         | 2318 1 4    | 0.03-16    |
| Amikacin   | 2318 | 64 | 64 | 0.25-64 | 19.3 | 7.8 | 73 | 16.4 | 2.7 | 80.9 |
|------------|------|----|----|---------|------|-----|----|------|-----|------|
| Colistin   | 1552 | 1  | 2  | 0.12-16 | 92.1 | 0   | 7.9 | 92   | 0   | 8    |
| Aztreonam  | 2318 | 64 | 256| 2.256   | NA   | NA  | NA | NA   | NA  | NA   |

**MRSA**

| Ceftaroline| 30100 | 0.5 | 2  | 0.03-64 | 89.0 | 10.3 | 0.7 | NA   | NA  | NA   |
|------------|-------|-----|----|---------|------|------|-----|------|-----|------|
| Ceftazidime-avibactam | 30100 | 64 | 64 | 2-64    | NA   | NA  | NA | NA   | NA  | NA   |
| Ceftazidime | 30100 | 64 | 64 | 1-64    | NA   | NA  | NA | NA   | NA  | NA   |
| Pip-taz    | 30100 | 32 | 32 | 0.12-32 | NA   | NA  | NA | NA   | NA  | NA   |
| Doripenem  | 30100 | 2  | 8  | 0.008-8 | NA   | NA  | NA | NA   | NA  | NA   |
| Meropenem  | 30100 | 4  | 16 | 0.015-16| NA   | NA  | NA | NA   | NA  | NA   |
| Levofloxacin | 30100 | 4  | 8  | 0.015-8 | 32.4 | 0.5 | 67.1 | NA  | NA  | NA   |
| Moxifloxacin | 30100 | 2  | 4  | 0.008-8 | 32.6 | 3.9 | 63.5 | NA  | NA  | NA   |
| Minocycline | 30100 | 0.12| 8  | 0.12-16 | 89.4 | 5.3 | 5.4 | NA  | NA  | NA   |
| Tigecycline | 30100 | 0.12| 0.5| 0.015-4 | 98.5 | 1.5 | 0   | NA  | NA  | NA   |
| Clindamycin | 30100 | 0.12| 8  | 0.03-8  | 61   | 0.3 | 38.7 | NA  | NA  | NA   |
| Erythromycin | 30100 | 8  | 16 | 0.12-16 | 29.7 | 2.5 | 67.8 | NA  | NA  | NA   |
| Vancomycin  | 30100 | 1  | 2  | 0.25-4  | 100  | 0   | 0   | NA  | NA  | NA   |
| Teicoplanin | 30100 | 1  | 2  | 0.12-32 | 100  | 0   | 0   | NA  | NA  | NA   |
| Linezolid   | 30100 | 2  | 2  | 0.5-16  | 100  | 0   | 0   | NA  | NA  | NA   |
| Daptomycin  | 30100 | 0.5| 1  | 0.06-4  | 99.7 | 0.3 | 0   | NA  | NA  | NA   |
| Gentamicin  | 18616 | 1  | 64 | 0.06-64 | 78.2 | 0.9 | 21  | NA  | NA  | NA   |
| Trimethoprim sulfa | 18616 | 0.25| 1  | 0.25-8  | 95.6 | 0   | 4.4 | NA  | NA  | NA   |
| Oxacillin   | 30100 | 4  | 8  | 4-8     | 0    | 0   | 100 | NA  | NA  | NA   |

**PRSP**

| Ceftaroline | 1925 | 0.12| 0.25| 0.008-32| 98.2 | 1.8 | 0   | 86.8 | 0  | 13.2 |
|------------|------|-----|-----|---------|------|-----|----|------|----|------|
| Ceftazidime-avibactam | 1925 | 16  | 64  | 1-128   | NA   | NA  | NA | NA   | NA  | NA   |
| Ceftazidime | 1925 | 16  | 64  | 1-128   | NA   | NA  | NA | NA   | NA  | NA   |
| Penicillin  | 1925 | 4   | 8   | 2-16    | 0    | 0   | 100 | 0    | 0  | 100  |
| Doripenem  | 1925 | 1   | 2   | 0.015-8 | 89.4 | 10.6| 0   | 81.1 | 0  | 18.9 |
| Meropenem  | 1925 | 1   | 2   | 0.008-2 | 3.4  | 32.3| 64.3| 100  | 0  | 0    |
| Levofloxacin | 1925 | 1   | 2   | 0.12-16 | 95.3 | 0.5 | 4.2 | 94.1 | 0  | 6    |
| Moxifloxacin | 1925 | 0.12| 0.25| 0.03-8  | 95.7 | 1.5 | 2.8 | 94.6 | 0  | 5.4  |
| Minocycline | 1925 | 4   | 4   | 0.03-4  | 28.5 | 13.2| 58.3| 18.8 | 3  | 78.2 |
| Tigecycline | 1925 | 0.03| 0.03| 0.008-2 | 99.8 | 0.2 | 0   | NA  | NA  | NA   |
| Clindamycin | 1925 | 2   | 2   | 0.008-2 | 32.6 | 0.3 | 67.2| 24.3 | 0  | 75.7 |
| Erythromycin | 1925 | 2   | 2   | 0.008-2 | 13.9 | 0.2 | 86  | 10.9 | 0  | 89   |
Vancomycin

|       | 1925 | 0.5 | 0.5 | 0.015-2 | 99.9 | 0.1 | 0 | 100 | 0 | 0 |

Linezolid

|       | 1925 | 1   | 1   | 0.06-2  | 100  | 0   | 0 | 100 | 0 | 0 |

† Cefepime CLSI susceptibility for Enterobacteriaceae adopted the susceptible, susceptible-dose-dependent, and resistant categories.

CLSI=Clinical Laboratory and Standards Institute; EUCAST= European Committee on Antimicrobial Susceptibility Testing; CRECO=Carbapenem-resistant *Escherichia coli*; CRKPN=Carbapenem-resistant *Klebsiella pneumoniae*; CRECL=Carbapenem-resistant *Enterobacter cloacae*; CRPAE=Carbapenem-resistant *Pseudomonas aeruginosa*; CRABA=Carbapenem-resistant *Acinetobacter baumannii*; MRSA=Methicillin-resistant *Staphylococcus aureus*; PRSP=Penicillin-resistant *Streptococcus pneumoniae*; NA=not applicable.

The susceptibilities to the various antibiotics against Gram-negative bacteria (total, regardless of drug resistance) were in general comparable using CLSI 2019 and EUCAST 2019 breakpoints, except for imipenem and tigecycline against *Proteus mirabilis* (Table 1). Nevertheless, the susceptibilities of many resistant species were lower using the EUCAST 2019 breakpoints compared with the CLSI 2019 breakpoints. For example, the susceptibilities of CR-*Escherichia coli* (72.3% vs. 40.5%) and CR-*Enterobacter cloacae* (42.3% vs. 21.9%) to ceftazidime-avibactam, and the susceptibilities of CR-*Escherichia coli*, CR-*Klebsiella pneumoniae*, CR-*Enterobacter cloacae*, and CR-*Pseudomonas aeruginosa* to levofloxacin, tigecycline, and amikacin (all with a >10% difference) were noticeably lower when the EUCAST 2019 breakpoints were applied (Table 3).

**In vitro activities of ceftaroline and ceftazidime-avibactam against Gram-positive bacteria from 2012 to 2016**

In the Gram-positive strains, ceftaroline showed more than 90% susceptibility rates of *Staphylococcus aureus*, *Streptococcus pneumoniae*, α-hemolytic *Streptococcus*, and β-hemolytic *Streptococcus* (CLSI 2019). The MIC_{50}/MIC_{90} of ceftaroline for coagulase-negative *Staphylococcus* and *Enterococcus faecalis* were 0.25/1 mg/L and 1/16 mg/L, respectively. Ceftaroline demonstrated low activity against *Enterococcus faecium* (MIC_{50}/MIC_{90}=64/64 mg/L) (Table 2). Ceftazidime-avibactam showed low activity against coagulase-negative *Staphylococcus*, *Staphylococcus aureus*, *Enterococcus faecalis*, and *Enterococcus faecium* (MIC_{50}/MIC_{90}: 16-64/64 mg/L), moderate activity against *Streptococcus pneumoniae* and α-hemolytic *Streptococcus*(MIC_{50}/MIC_{90}, 0.25/16 mg/L), and high activity against β-hemolytic *Streptococcus*(MIC_{50}/MIC_{90}, 0.025/0.5 mg/L). The addition of avibactam to ceftazidime was not associated with improved activities against the tested Gram-positive strains. For all tested *Staphylococcus*, *Streptococcus*, and *Enterococcus*, high susceptibility (>90%) to linezolid, tigecycline, daptomycin, and vancomycin were observed (excepted for *Enterococcus faecium* to vancomycin). High activities (susceptibility, >90%) of levofloxacin and moxifloxacin were observed for *Streptococcus*.

Regarding the resistant Gram-positive strains, ceftaroline demonstrated high activities against methicillin-resistant *Staphylococcus aureus* (CLSI 2019 susceptibility, 89.0%) and penicillin-resistant *Streptococcus*.
pneumoniae (CLSI 2019 susceptibility, 98.2%), whereas ceftazidime-avibactam demonstrated limited activities (MIC$_{50}$/MIC$_{90}$: 16-64/64 mg/L) (Table 3). For comparator agents, potent activity (CLSI 2019 susceptibility, >95%) against methicillin-resistant Staphylococcus aureus was observed for linezolid, tigecycline, vancomycin, teicoplanin, daptomycin, and trimethoprim sulfa, whereas the susceptibility of penicillin-resistant Streptococcus pneumoniae (CLSI 2019 susceptibility, >95%) was high to linezolid, tigecycline, vancomycin, levofloxacin, and moxifloxacin (Table 3).

The susceptibilities of Gram-positive bacteria (regardless of drug resistance) were similar between the CLSI 2019 and EUCAST 2019 breakpoints, except for the susceptibility of coagulase-negative Staphylococcus to teicoplanin and gentamicin. In terms of resistant strains, noticeably lower susceptibility of penicillin-resistant Streptococcus pneumoniae to ceftaroline (98.2% vs. 86.8%) and meropenem (3.4% vs. 100%) was observed using EUCAST breakpoints as compared with CLSI 2019 breakpoints.

**Global trend of the susceptibilities of pathogens against ceftaroline and ceftazidime-avibactam from 2012 to 2016**

Figure 1 presents the trends of susceptibilities to ceftaroline against key bacterial species over time in different regions using the CLSI 2019 breakpoints. For Escherichia coli (2012/2016: 66.2% / 66.5%), Klebsiella pneumoniae (2012/2016: 57.4% / 60.4%), Proteus mirabilis (2012/2016: 78.7% / 81.2%), Staphylococcus aureus (2012/2016: 92.5% / 95.1%) and Streptococcus pneumoniae (2012/2016: 99.9% / 99.7%), the overall global susceptibility to ceftaroline remained relatively stable in all regions from 2012 to 2016, but some decreases were observed in specific areas of the world. For Escherichia coli, the susceptibilities were consistently higher in North America (77.1%-82.0%) and lower in Asia (45.1%-53.0%). Higher susceptibilities in North America were also observed for Klebsiella pneumoniae and Proteus mirabilis, and lower susceptibilities in Asia were observed for Staphylococcus aureus. For Enterobacter cloacae, the global susceptibility gradually increased from 56.2% in 2012 to 64.6% in 2016. For Citrobacter freundii, the global susceptibility peaked at 69.1% in 2014, decreased slightly in 2015, and rebounded to 63.2% in 2016.

Figure 2 presents the trends of susceptibility to ceftazidime-avibactam against key bacterial species over time in different regions using the CLSI 2019 breakpoint. The susceptibility of Escherichia coli, Klebsiella pneumoniae, and Proteus mirabilis to ceftazidime-avibactam remained high (>95%) and relatively stable over time, but with some decreases were observed in specific regions. The susceptibilities of Enterobacter cloacae and Citrobacter freundii to ceftazidime-avibactam remained relatively stable over time in all regions, but the susceptibilities in Asia (2013/2016: 94.6%/94.6% and 94.9%/94.7%) decreased in 2013 and were consistently lower than the global rates thereafter (2013/2016: 98.3%/97.4% and 99.7%/97.6%). The global susceptibilities of Pseudomonas aeruginosa to ceftazidime-avibactam globally decreased from 2012 to 2016 (2012/2016: 97.1%/92.0%), with lower rates observed in Latin America (2012/2016: 92.7%/86.6%), and higher rates observed in North America (2012/2016: 97.9%/96.6%).

**Global trend of the susceptibilities to ceftaroline and ceftazidime-avibactam against multi-drug-resistant species**

The proportion of methicillin-resistant Staphylococcus aureus among all Staphylococcus aureus remained stable from 2012 to 2016 (59.8% in 2012 and 2016), with higher prevalence observed in North America.
(2012/2016: 66.5%/68.1%) and lower prevalence observed in Latin America (2012/2016: 55.9%/53.3%). The overall global susceptibility of methicillin-resistant *Staphylococcus aureus* to ceftaroline increased slightly from 87.5% in 2012 to 91.7% in 2016, with a marked increase observed in Africa-Middle East (2012/2016: 88.7%/97.8%), Europe (2012/2016: 89.8%/96.2%), and Latin America (2012/2016: 78.2%/88.2%) (Figure 3A). The susceptibility of methicillin-resistant *Staphylococcus aureus* to ceftaroline in Asia was consistently lower than in all other regions (2012/2016: 75.2%/75.5%).

The proportion of CR-*Klebsiella pneumoniae* among all *Klebsiella pneumoniae* slightly increased from 6.7% in 2012 to 8.2% in 2016, with higher prevalence observed in Latin America (2012/2016: 9.2%/11.2%) and Europe (2012/2016: 9.3%/10.4%). Conversely, the overall global susceptibility of CR-*Klebsiella pneumoniae* to ceftazidime-avibactam decreased from 88.4% in 2012 to 81.6% in 2016, with a marked decrease observed in Africa-Middle East (2012/2016: 100%/63.6%), Asia (2012/2016: 76.9%/68.2%), and Latin America (2012/2016: 100%/90%) (Figure 3B). The susceptibility rates in Asia and Africa-Middle East were, in general, lower than in the other regions during the study period.

The proportion of CR-*Pseudomonas aeruginosa* among all *Pseudomonas aeruginosa* remained relatively stable over time (2012/2016: 26.5%/26.7%), with higher prevalence observed for Latin America (2012/2016: 36.3%/34.4%). The overall global susceptibility of CR-*Pseudomonas aeruginosa* to ceftazidime-avibactam decreased from 89.6% in 2012 to 72.7% in 2016, with a marked decrease observed for all regions (Figure 3). The susceptibility rate in North America (2012/2016: 93.2%/86.0%) was, in general, higher than in other regions.

**Discussion**

Ceftaroline and ceftazidime-avibactam are relatively recent antibiotics that are active against a variety of bacterial species, including some with innate antibiotic resistance. The exact resistance patterns to those antibiotics still need to be defined exactly, and there is a crucial need for global surveillance of antibiotic resistance. This study reveals the patterns of the susceptibilities of different bacterial species to a variety of antibiotics, with a focus on ceftaroline and ceftazidime-avibactam, around the world, and over 5 years. The results indicate that the global resistance of CR-*Pseudomonas aeruginosa* to ceftazidime-avibactam greatly increased over time, while the susceptibility profile of ceftaroline and ceftazidime-avibactam against other species were relatively stable.

The first objective of this study was to examine the overall *in vitro* activities of ceftaroline and ceftazidime-avibactam using data from the ATLAS program. The results showed that ceftaroline was highly potent (>90% susceptibility) against Gram-positive strains, including *Staphylococcus aureus, Streptococcus pneumoniae,* and *Streptococcus.* On the other hand, ceftazidime-avibactam showed susceptibility >90% against Gram-negative bacteria, including *Enterobacteriaceae, Pseudomonas aeruginosa,* and *Proteus mirabilis,* with overtly increased antimicrobial activity observed with the addition of avibactam to ceftazidime. Further analysis of the data from China showed that similar to the global pattern, the susceptibilities of *Escherichia coli, Klebsiella pneumoniae,* and *Pseudomonas aeruginosato* ceftazidime-avibactam were high (92.9%-99.0%) in China. Those results are generally similar with those of surveillance studies in China, Asia, the United States of America, and Europe, and with the AWARE surveillance program, but with some minute differences.
that could be due to the specimens' area of origin since the present study included specimens from all over the world. Another source of difference could be the tested period since bacterial susceptibility changes over time.

Indeed, as shown by the results to the second objective of the present study, the patterns of resistance varied among species, among world regions, and over time. The main differences were that the susceptibility rates of *Escherichia coli* and *Staphylococcus aureus* to ceftaroline in Asia were lower than the global rates, while those in Europe and North America were generally similar or higher than the global rates. Asia also showed lower susceptibility rates to ceftazidime-avibactam against *Citrobacter freundii*, *Enterobacter cloacae*, and *Proteus mirabilis*. A study examined the resistance patterns to ceftaroline, ceftazidime, and piperacillin-tazobactam and revealed similar patterns between Europe and the United States of America. A study across different areas of the United States of America also reported good susceptibility profiles of ceftaroline against respiratory pathogens. A study across different areas of the United States of America also reported good susceptibility profiles of ceftaroline against respiratory pathogens. A recent report from the World Health Organization revealed high rates of antibiotic resistance all over the world. Antibiotic resistance is a major concern worldwide, and significant differences in the resistance patterns can be observed. The World Health Organization highlighted that even if antibiotic resistance has increased all over the world, the increase was particularly alarming in Asia because of poor health and environment practices such as antibiotic over-prescription, poor infection control, poor waste management, overuse of antibiotics in farming, food security, and restricted access to the newest antibiotics. Furthermore, the Asia-Pacific region is the most populous region in the world. Many of its countries are among the poorest, and poor health infrastructure is often encountered. In addition, specific resistance mechanisms (e.g., the New Delhi metallo-β-lactamase-1) are also encountered in Asia. The TEST study showed that Africa and Asia were the two regions of the world with the highest occurrence of *S. aureus* resistant to multiple antibiotics among blood-borne infections.

There is a plea for worldwide, automated, and comprehensive surveillance of antimicrobial resistance patterns. Such surveillance could help optimize the worldwide use of antibiotics to improve infection control and minimize the occurrence of resistant strains. In fact, surveillance and proper actions are necessary to avoid medical, social, and economic setbacks that could threaten the very fabric of the global community. Even if the present study focused on ceftaroline and ceftazidime-avibactam, the ATLAS program provides the comprehensive global susceptibility profiles of many antibiotics against a large number of bacterial species. ATLAS receives data from all regions of the world and covers many years. Therefore, it helps provide certain help for the global surveillance of bacterial resistance.

This study has limitations. First, this was a retrospective study, with the inevitable confounding biases, such as the nature of the participating hospitals (mostly tertiary university-affiliated centers), the exact patient populations consulting at those hospitals, and the lack of many variables at the patient level. Second, this study is purely descriptive. Because of the large sample size, minute non-clinically significant differences in susceptibility could be statistically significant, which could be misleading; therefore, statistical tests were not performed.

**Conclusion**
In summary, the present study showed that the addition of avibactam improved the activity of ceftazidime against Enterobacteriaceae and Pseudomonas aeruginosa. The global antimicrobial susceptibilities to ceftaroline and ceftazidime-avibactam were, in general, stable from 2012 to 2016, but a marked reduction in the susceptibilities of specific species and CR-Pseudomonas aeruginosa for ceftazidime-avibactam was observed in specific regions of the world.

Declaration

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Conflict of interest

All authors declare that they have no conflict of interest and have submitted the ICMJE Form for disclosure of potential conflicts of interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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AUTHOR CONTRIBUTION

H.Z., Y.C.X., P.Y.J, and Q.W.Y. conceived and designed the study, performed the experiments, analyzed the data, and wrote the paper. Y.Z., G.Z., J.J.Z., W.K., S.M.D., T.W., R.J., J.W.C., and Y.L.L. helped perform the experiments. All authors read and approved the final version of the manuscript.

References

1. Khameneh B, Diab R, Ghazvini K, Fazly Bazzaz BS. Breakthroughs in bacterial resistance mechanisms and the potential ways to combat them. Microbial pathogenesis 2016; 95: 32-42.
2. Chellat MF, Raguz L, Riedl R. Targeting Antibiotic Resistance. Angewandte Chemie 2016; 55(23): 6600-26.
3. Siddiqui AH, Koirala J. Methicillin Resistant Staphylococcus Aureus (MRSA). StatPearls. Treasure Island (FL); 2019.
4. Akova M. Epidemiology of antimicrobial resistance in bloodstream infections. Virulence 2016; 7(3): 252-66.
5. Tacconelli E, Carrara E, Savoldi A, et al. Discovery, research, and development of new antibiotics: the WHO priority list of antibiotic-resistant bacteria and tuberculosis. The Lancet Infectious diseases 2018; 18(3): 318-27.
6. Chipolombwe J, Torok ME, Mbelle N, Nyasulu P. Methicillin-resistant Staphylococcus aureus multiple sites surveillance: a systemic review of the literature. *Infection and drug resistance* 2016; 9: 35-42.

7. Frieri M, Kumar K, Boutin A. Antibiotic resistance. *Journal of infection and public health* 2017; 10(4): 369-78.

8. Fuhrmeister AS, Jones RN. The Importance of Antimicrobial Resistance Monitoring Worldwide and the Origins of SENTRY Antimicrobial Surveillance Program. *Open forum infectious diseases* 2019; 6(Suppl 1): S1-S4.

9. Duplessis C, Crum-Cianflone NF. Ceftaroline: A New Cephalosporin with Activity against Methicillin-Resistant Staphylococcus aureus (MRSA). *Clinical medicine reviews in therapeutics* 2011; 3.

10. El Hajj MS, Turgeon RD, Wilby KJ. Ceftaroline fosamil for community-acquired pneumonia and skin and skin structure infections: a systematic review. *International journal of clinical pharmacy* 2017; 39(1): 26-32.

11. Pawluk SA, Wilby KJ. Ceftaroline fosamil for community-acquired pneumonia. *The Lancet Infectious diseases* 2015; 15(9): 999.

12. Carreno JJ, Lodise TP. Ceftaroline Fosamil for the Treatment of Community-Acquired Pneumonia: from FOCUS to CAPTURE. *Infectious diseases and therapy* 2014; 3(2): 123-32.

13. Mpenge MA, MacGowan AP. Ceftaroline in the management of complicated skin and soft tissue infections and community acquired pneumonia. *Therapeutics and clinical risk management* 2015; 11: 565-79.

14. Ehmann DE, Jahic H, Ross PL, et al. Avibactam is a covalent, reversible, non-beta-lactam beta-lactamase inhibitor. *Proceedings of the National Academy of Sciences of the United States of America* 2012; 109(29): 11663-8.

15. Shirley M. Ceftazidime-Avibactam: A Review in the Treatment of Serious Gram-Negative Bacterial Infections. *Drugs* 2018; 78(6): 675-92.

16. Clinical and Laboratory Standards Institute (CLSI). Performance standards for antimicrobial susceptibility testing. 29th ed. CLSI supplement M100. Wayne, PA: CLSI; 2019.

17. The European Committee on Antimicrobial Susceptibility Testing (EUCAST). Breakpoint tables for interpretation of MICs and zone diameters. Version 9.0. Available at: [http://www.eucast.org/clinical_breakpoints/](http://www.eucast.org/clinical_breakpoints/) [Accessed 2 January 2019].

18. Zhou M, Chen J, Liu Y, et al. In Vitro Activities of Ceftaroline/Avibactam, Ceftazidime/Avibactam, and Other Comparators Against Pathogens From Various Complicated Infections in China. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2018; 67(suppl_2): S206-S16.

19. Karlowsky JA, Kazmierczak KM, Bouchillon SK, de Jonge BLM, Stone GG, Sahm DF. In Vitro Activity of Ceftazidime-Avibactam against Clinical Isolates of Enterobacteriaceae and Pseudomonas aeruginosa Collected in Asia-Pacific Countries: Results from the INFORM Global Surveillance Program, 2012 to 2015. *Antimicrobial agents and chemotherapy* 2018; 62(7).

20. Jones RN, Farrell DJ, Mendes RE, Sader HS. Comparative ceftaroline activity tested against pathogens associated with community-acquired pneumonia: results from an international surveillance study. *The*
21. Sader HS, Flamm RK, Mendes RE, Farrell DJ, Jones RN. Antimicrobial Activities of Ceftaroline and Comparator Agents against Bacterial Organisms Causing Bacteremia in Patients with Skin and Skin Structure Infections in U.S. Medical Centers, 2008 to 2014. *Antimicrobial agents and chemotherapy* 2016; 60(4): 2558-63.

22. Connor KA. Newer Intravenous Antibiotics in the Intensive Care Unit: Ceftaroline, Ceftolozane-Tazobactam, and Ceftazidime-Avibactam. *AACN advanced critical care* 2016; 27(4): 353-7.

23. Kazmierczak KM, de Jonge BLM, Stone GG, Sahm DF. In vitro activity of ceftazidime/avibactam against isolates of Pseudomonas aeruginosa collected in European countries: INFORM global surveillance 2012-15. *The Journal of antimicrobial chemotherapy* 2018; 73(10): 2777-81.

24. Sader HS, Flamm RK, Streit JM, Farrell DJ, Jones RN. Ceftaroline activity against bacterial pathogens frequently isolated in U.S. medical centers: results from five years of the AWARE surveillance program. *Antimicrobial agents and chemotherapy* 2015; 59(4): 2458-61.

25. Karlowsky JA, Biedenbach DJ, Bouchillon SK, Hackel M, Iaconis JP, Sahm DF. In vitro activity of Ceftaroline against bacterial pathogens isolated from patients with skin and soft tissue and respiratory tract infections in African and Middle Eastern countries: AWARE global surveillance program 2012-2014. *Diagnostic microbiology and infectious disease* 2016; 86(2): 194-9.

26. Bae IG, Stone GG. Activity of ceftaroline against pathogens associated with community-acquired pneumonia collected as part of the AWARE surveillance program, 2015-2016. *Diagnostic microbiology and infectious disease* 2019: 114843.

27. Flamm RK, Sader HS, Farrell DJ, Jones RN. Ceftaroline potency among 9 US Census regions: report from the 2010 AWARE Program. *Clinical infectious diseases: an official publication of the Infectious Diseases Society of America* 2012; 55 Suppl 3: S194-205.

28. Mayor S. First WHO antimicrobial surveillance data reveal high levels of resistance globally. *Bmj* 2018; 360: k462.

29. World Health Organization. Global Antimicrobial Resistance Surveillance System (GLASS) report: early implementation 2016-17. 2017. [http://apps.who.int/iris/bitstream/10665/259744/1/9789241513449-eng.pdf?ua=1](http://apps.who.int/iris/bitstream/10665/259744/1/9789241513449-eng.pdf?ua=1). Retrieved August 21, 2019. Geneva: World Health Organization; 2017.

30. World Health Organization. Antimicrobial resistance in the Asia Pacific region: a development agenda. Geneva: World Health Organization; 2017.

31. Kakkar M, Chatterjee P, Chauhan AS, et al. Antimicrobial resistance in South East Asia: time to ask the right questions. *Global health action* 2018; 11(1): 1483637.

32. Chereau F, Opatowski L, Tourdjman M, Vong S. Risk assessment for antibiotic resistance in South East Asia. *Bmj* 2017; 358: j3393.

33. Jean SS, Hsueh PR. High burden of antimicrobial resistance in Asia. *International journal of antimicrobial agents* 2011; 37(4): 291-5.

34. Kumarasamy KK, Toleman MA, Walsh TR, et al. Emergence of a new antibiotic resistance mechanism in India, Pakistan, and the UK: a molecular, biological, and epidemiological study. *The Lancet Infectious diseases* 2010; 10(9): 597-602.
35. Zhang Z, Chen M, Yu Y, Pan S, Liu Y. Antimicrobial susceptibility among gram-positive and gram-negative blood-borne pathogens collected between 2012-2016 as part of the Tigecycline Evaluation and Surveillance Trial. *Antimicrobial resistance and infection control* 2018; 7: 152.

36. O’Brien TF, Clark A, Peters R, Stelling J. Why surveillance of antimicrobial resistance needs to be automated and comprehensive. *Journal of global antimicrobial resistance* 2019; 17: 8-15.

37. Hendriksen RS, Munk P, Njage P, et al. Global monitoring of antimicrobial resistance based on metagenomics analyses of urban sewage. *Nature communications* 2019; 10(1): 1124.

38. Laxminarayan R, Duse A, Wattal C, et al. Antibiotic resistance-the need for global solutions. *The Lancet Infectious diseases* 2013; 13(12): 1057-98.

39. Ranganathan P, Pramesh CS, Buyse M. Common pitfalls in statistical analysis: Clinical versus statistical significance. *Perspect Clin Res* 2015; 6(3): 169-70.

40. Page P. Beyond statistical significance: clinical interpretation of rehabilitation research literature. *Int J Sports Phys Ther* 2014; 9(5): 726-36.