Global Trends of Antimicrobial Susceptibility of Ceftaroline and Ceftazidime-Avibactam: A Surveillance Study from the ATLAS Program (2012-2016)

Hui Zhang
Peking Union Medical College Hospital
Yingchun Xu
Peking Union Medical College Hospital
Peiyao Jia
Peking Union Medical College Hospital
Ying Zhu
Peking Union Medical College Hospital
Ge Zhang
Peking Union Medical College Hospital
Jingjia Zhang
Peking Union Medical College Hospital
Simeng Duan
Peking Union Medical College Hospital
Wei Kang
Peking Union Medical College Hospital
Tong Wang
Peking Union Medical College Hospital
Ran Jing
Peking Union Medical College Hospital
Jingwei Cheng
Peking Union Medical College Hospital
Yali Liu
Peking Union Medical College Hospital
Qiwen Yang (yangqiwen81@vip.163.com)

Research

Keywords: ceftaroline, ceftazidime-avibactam, antibiotics, surveillance, antimicrobial resistance

Posted Date: June 4th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-31962/v1

Version of Record: A version of this preprint was published on October 27th, 2020. See the published version at https://doi.org/10.1186/s13756-020-00829-z.

Abstract

Background: Antibiotic resistance is a global health threat.This study reported the global trends of antimicrobial susceptibility ofceftaroline and ceftazidime-avibactam using data from the Antimicrobial Testing Leadership And Surveillance (ATLAS)programbetween2012and2016.

Methods: Theminimum inhibitory concentrations (MICs) and*in vitro* susceptibilities of ceftarolineandceftazidime-avibactam were assessed using the Clinical andLaboratory Standards Institute (CLSI) guidelines.

Results: Between 2012 and 2016, a total of 176,345 isolates were collected globally and included for analysis.Regarding Gram-negative bacteria, ceftazidime-avibactam demonstrated high susceptibility (>90%) against *Enterobacteriaceae*and*Pseudomonas aeruginosa,* with increasedantimicrobial 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 susceptibility of ceftaroline and ceftazidime-avibactam were mostly stable from 2012 to 2016. Nevertheless, the susceptibility ofceftazidime-avibactam to carbapenem-resistant *Klebsiella pneumoniae*(CRKPN, 88.4% to 81.6%) and to CR-*Pseudomonas aeruginosa*(CRPAE, 89.6% to 72.7%) decreased. In terms of regional difference, susceptibilities of MRSA to ceftaroline in Asia and of CRKPN to ceftazidime-avibactam in Asia/Africa-Middle East were loweras compared with other regions whereas the susceptibility of CRPAE to ceftazidime-avibactam in North America was higher.

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

Introduction

The rapidly increasing and wide spreading resistance of bacteriato antibiotics in recent years is a serious challenge for clinicians and a global health crisis.[1]Multidrug 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]Especiallyproblematic has been the increase in the third-generation cephalosporin- and carbapenem-resistant (CR)*Enterobacteriaceae*(CRE), CR-*Pseudomonasaeruginosa*(CRPAE) and CR-*Acinetobacterbaumannii*(CRABA), which has tremendously increased the mortality and morbidityrates.[3,4]Recently, the World Health Organization has rated the CRE, CRPAE and CRABA as top critical-priority resistant bacteria, outweighing methicillin-resistant*Staphylococcus aureus* (MRSA).[5]Consequently, the availability of updated epidemiological data on antibiotic resistance is needed to adapt the treatment strategies to the actual reality, which changes at an alarming rate.[4,6-8]

Ceftaroline is a fifth-generation broad-spectrum cephalosporin.It isactive mainly against MRSA and Gram-positive bacteria,but also shows some efficacy against Gram-negative bacteria.[9]Ceftarolineis indicated for community-acquired pneumonia and complicated skin infections.[10-13]Avibactam is a diazabicyclooctane derivative antibiotic that can reversibly inhibiting 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)enzymesby covalentacylation of the active-site serine residue.[14] Ceftazidime-avibactam is a novel β-lactam/ β-lactamase inhibitor combination that has shown potency against a wide variety of CRE and 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.[15]

The patterns of resistance to ceftaroline and ceftazidime-avibactam around the globe still 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 between 2012 and 2016 using data from a global antibiotic surveillance program, the Antimicrobial Testing Leadership And Surveillance (ATLAS) program; 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, 205medical centers located in Africa-Middle East (AM, n=12), Asia-Pacific (n=32), Europe (EU, n=94), Latin America (LA, n=26), North America (NA, n=31), and Oceania(n=10) contributed to consecutive collection of clinical isolates. The specimens were obtained from patients with various specific types of infections, including skin and skin structure infection (SSSI), intra-abdominal infection (IAI), urinary tract infection (UTI), lower respiratory tract infection (LRTI) and blood infection. Pathogens were isolated and identified by each participating center, storedin tryptic soy broth with glycerol at -70°C, and shippedtothe International Health Management Associates, Inc. (IHMA; Schaumburg, IL, USA) forsusceptibilitytesting.The present study only included the isolates considered to be the potential pathogen of the patient's infection. Only the first isolate per patient per infectious episode was included.

Antimicrobial susceptibility testing

IHMA (Schaumburg, IL, USA) carried out all antimicrobial susceptibility testing using the broth microdilution method. Minimum inhibitory concentrations (MICs) were interpreted using theClinical and Laboratory Standards Institute (CLSI) and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints[16,17].Tigecycline was interpreted using the Food and Drug Administration and EUCAST 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, quinupristindalfopristinandoxacillin.In the present study, data were analyzed for *Escherichia coli, Klebsiella pneumoniae, Enterobactercloacae, Citrobacter freundii, Proteus mirabilis, Pseudomonas aeruginosa, Acinetobacter baumannii, Staphylococcus aureus, Streptococcus pneumoniae,*α- and β-hemolytic *Streptococcus*, coagulase-negative *Staphylococcus* (CoNS), *Enterococcus faecalis*, and *Enterococcus faecium*as well as resistant species includingCR-*Escherichia coli* (CRECO)*,* CR-*Klebsiella pneumoniae* (CRKPN)*, CR-Enterobacter cloacae* (CRECL), CRPAE, CRABA, MRSA and Penicillin-resistant *Streptococcus pneumoniae* (PRSP). 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, *Staphylococcusaureus* ATCC 29213, and *Streptococcus pneumoniae* ATCC 49619 were used for quality control (QC) according to CLSI guidelines,and all QC results were within published ranges.

Results

Sample retrieval

A total of 176,345isolates were collected between 2012 and 2016. The numbers of isolates of each species group tested are listed in Table 1 and 2. The largest number of isolates were collected from patients of over 60 years (82,518, 46.8%) and of 31-60 years (59,428, 33.7%), followed by patients of under 18 years (19,446, 11.0%) and of 19-30 years (13,350, 7.6%). Regarding infection type, 64,032 (36.3%) isolates were collected from SSSI, 52,077 (29.5%) from LRTI, 26,868 (15.2%) from UTI, 12,847 (7.3%) from IAI and 11,930 (6.8%) from 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 received from patients in the general medical wards, general surgical wards, emergency rooms, medical intensive care unit (ICUs), surgical ICUs and general pediatric wards,respectively.

In vitro activities of ceftaroline and ceftazidime-avibactamagainstGram-negativebacteria from 2012 to 2016

Tables 1 (Gram-negative) and 2 (Gram-positive) show the *in vitro* activities of ceftaroline, ceftazidime-avibactam and comparator antibiotics against key bacterial species.

Ceftazidime-avibactam demonstrated high activities against all tested Gram-negative species (CLSI/EUCAST susceptibility, 91.9%-99.8%), exceptfor *Acinetobacter baumannii*(MIC_{50}/$MIC_{90,}$ 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 susceptibilities of 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_{90}(ceftazidime, MIC_{50}/$MIC_{90,}$ 64/256 mg/L).Regarding comparator agents, the susceptibility of *Enterobacteriaceae* was in general high to carbapenems and tigecycline (>90%). For *Acinetobacter baumannii,*the most potent antibiotics were colistin and tigecycline (MIC_{50}/MIC_{90}, 1/2 mg/L), with a MIC_{50} of ≥8 and a MIC_{90} of ≥16 mg/L observed for all other tested agents.

As to resistantGram-negative strains, theactivities of ceftazidime-avibactam were moderatefor CRECO (MIC_{50}/MIC_{90}, 0.5/256 mg/L), CRKPN (MIC_{50}/MIC_{90}, 1/256 mg/L) and CRPAE (MIC_{50}/MIC_{90}, 4/64 mg/L) and low for CRECL and CRABA (MIC_{50}/$MIC_{90,}$ 64-128/256 mg/L) (Table 3).Regarding comparator agents, the susceptibilities to CRECO, CRKPN, CRECL, CRPAE and CRABA were low for the vast majority of tested antibiotics. Good potency was observed for tigecycline against all tested *Enterobacteriaceae* (MIC_{50}/$MIC_{90,}$ 0.25-1/1-4 mg/L), and for colistin against CRECO, CRECL, CRPAE and CRABA (MIC_{50}/$MIC_{90,}$ 0.5-1/1-2 mg/L).

The susceptibilities of various antibiotic agents against Gram-negative bacteria (total, regardless of drug resistance) were in general comparable using CLSI and EUCAST breakpoints, with the exception of imipenem and tigecycline against*Proteus mirabilis* (Table 1). Nevertheless, the susceptibilities of a number of resistant species was lower using the EUCAST breakpoints as compared with the CLSI breakpoints. For example, the susceptibilities of CRECO (72.3% vs. 40.5%) and CRECL (42.3% vs. 21.9%) to ceftazidime-avibactam, and the susceptibilities ofCRECO, CRKPN, CRECL and CRPAE to levofloxacin, tigecycline, amikacin (all with a >10% difference) were noticeably lower when EUCAST breakpoints were applied (Table 3).

In vitro activities of ceftaroline and ceftazidime-avibactam againstGram-positivebacteria from 2012 to 2016

In the Gram-positivestrains, ceftaroline showed more than 90% susceptibility rates for *Staphylococcus aureus*,*Streptococcus pneumoniae*, α-hemolytic *Streptococcus*, and β-hemolytic *Streptococcus* (CLSI). TheMIC_{50}/MIC_{90} of ceftarolinefor CoNS 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 CoNS*, 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 (with the exception of*Enterococcus faecium* to vancomycin). High activities (susceptibility, >90%) of levofloxacin and moxifloxacin were also observed for *Streptococcus.*

Regarding resistant Gram-positive strains, ceftaroline demonstrated high activities against MRSA (CLSIsusceptibility, 89.0%) and PRSP (CLSI 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 susceptibility, >95%) against MRSA was observed for linezolid, tigecycline, vancomycin, teicoplanin, daptomycin and trimethoprim sulfa whereas the susceptibility of PRSP (CLSI susceptibility, >95%) was high to linezolid, tigecycline, vancomycin, levofloxacin and moxifloxacin (Table 3).

Thesusceptibilities ofGram-positive bacteria (regardless of drug resistance) were similar for CLSI and EUCAST breakpoints, expect for the susceptibility of CoNS toteicoplaninand gentamicin. In terms of resistant strains, noticeably lower susceptibility of PRSP to ceftaroline (98.2% vs. 86.8%) and meropenem (3.4% vs. 100%) was observed using ECUAST breakpoints as compared with CLSI breakpoints.

Global trend of susceptibility of pathogens against ceftaroline and ceftazidime-avibactam from 2012 to 2016

Figure 1 presents the trends of susceptibility to ceftaroline against key bacterial species over time in different regions using the CLSI 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. For *Escherichia coli*,the susceptibility was consistently higher in NA (77.1%-82.0%) and lower in Asian (45.1%-53.0%). Higher susceptibilities in NA were also observed for *Klebsiella pneumoniae* and *Proteus mirabilis* and lower susceptibility in Asia was observed for *Staphylococcus aureus*.For *Enterobacter clocae,* 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 breakpoint. The susceptibility of *Escherichia coli*, *Klebsiella pneumoniae*, and *Proteus mirabilis* to ceftazidime-avibactam remained high (>95%) and relatively stable over time in all regions. The susceptibility of *Enterobacter cloacae*and *Citrobacter freundii*to ceftazidime-avibactam remained relatively stable over time in all regions, but the susceptibility in Asia (2013/2016: 94.6%/94.6% and 94.9%/94.7%) decreased in 2013 and was consistently lower than the global ratesthereafter (2013/2016: 98.3%/97.4% and 99.7%/97.6%). The global susceptibility of *Pseudomonas aeruginosa* to ceftazidime-avibactam globally decreased from 2012 to 2016 (2012/2016: 97.1%/92.0%), with lower rates observed in LA (2012/2016: 92.7%/86.6%), and higher rates observed in NA (2012/2016: 97.9%/96.6%).

Global trend of susceptibility of ceftaroline and ceftazidime-avibactam against multidrug-resistant species

The proportion of MRSA among all *Staphylococcus aureus* remained stable from 2012 to 2016 (59.8% at both 2012 and 2016), with higher prevalence observed for NA (2012/2016: 66.5%/68.1%) and lower prevalence observed for LA (2012/2016: 55.9%/53.3%). The overall global susceptibility of MRSA to ceftarolineincreased slightly from 87.5% in 2012 to 91.7% in 2016, with marked increase observed in AM (2012/2016: 88.7%/97.8%), Europe (2012/2016: 89.8%/96.2%) and LA (2012/2016: 78.2%/88.2%) (Figure 3A). The susceptibility of MRSA to ceftaroline in Asia was consistently lower than all other regions (2012/2016: 75.2%/75.5%).

The proportion of CRKPN among all *Klebsiella pneumoniae* slightly increased from 6.7% in 2012 to8.2% in 2016, with higher prevalence observed for LA (2012/2016: 9.2%/11.2%) and Europe (2012/2016: 9.3%/10.4%). Conversely, the overall global susceptibility of CRKPN to ceftazidime-avibactam decreased from 88.4% in 2012 to 81.6% in 2016, with marked decrease observed in AM (2012/2016: 100%/63.6%), Asia (2012/2016: 76.9%/68.2%), and LA (2012/2016: 100%/90%) (Figure 3B). The susceptibility rates in Asia and AM were in general lower than other regions during the study period.

The proportion of CRPAE among all *Pseudomonas aeruginosa* remained relatively stable over time (2012/2016: 26.5%/26.7%), with higher prevalence observed for LA (2012/2016: 36.3%/34.4%). The overall global susceptibility of CRPAE to ceftazidime-avibactam decreased from 89.6% in 2012 to 72.7% in 2016, with marked decrease observed for all regions (Figure 3). The susceptibility rate in NA (2012/2016: 93.2%/86.0%) was in general higher than 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.[10-13,15] 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 susceptibility 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 ofCRPAE 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 stains 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 from the addition of avibactam to ceftazidime.Further analysis of data in China showed that similar to the global pattern, the susceptibilities of *Escherichia coli, Klebsiella pneumoniae* and *Pseudomonas aeruginosa* to ceftazidime-avibactam were high (92.9%-99.0%)in China. Those results are generally similar with those of

surveillance studies in China,[18] Asia[19]the United States,[20-22] and Europe,[23]and from the AWARE surveillance program,[24-26] but with some minute differences that could be due to the specimens' area of origin, since the present study includedspecimens 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 vary 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 in *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.[20]A study across different United States regions also reported good susceptibility profiles of ceftaroline against respiratory pathogens.[27]A recent report from the World Health Organization revealed high rates of antibiotic resistance all over the world.[28,29]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.[30-32]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.[33]In addition, specific resistance mechanisms (e.g. the New Delhi metallo-β-lactamase-1) are also encountered in Asia.[34] 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.[35]

There is a plea for worldwide, automated, and comprehensive surveillance of antimicrobial resistance patterns.[8,36,37] Such surveillance can help optimize the worldwide use of antibiotics to improve infection control and minimize the apparition of resistant strains.[38] In fact, surveillance and proper actions are necessary to avoid medical, social, and economic setbacks that could threatens the very fabric of the global community.[38]Even if the present study focused on ceftaroline and ceftazidime-avibactam, the ATLAS program provides the comprehensive global susceptibility profiles of a large number of antibiotics in a large number of bacterial species. ATLAS receives datafrom all regions of the world and covers many years. Therefore, it helps provide certain help for global surveillanceof bacterial resistance.

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

susceptibility of ceftaroline and ceftazidime-avibactam was in general stablefrom 2012 to 2016, but a marked reduction in the susceptibility of CRPAE for ceftazidime-avibactam was observed.

Declaration

ETHICS APPROVAL

The protocol has been reviewed by the human research ethics committee of the Institutional Review Board (IRB) of the Peking Union Medical College Hospital and since the project falls under the category observational study and all bacterial strains were from residual samples used in clinical diagnosis or were strains from their subcultures, it has been determined to meet the criteria for exemption,. This project does not involve any patient information nor does it affect the normal diagnosis and treatment of patients, and after consultation with the IRB, formal ethical approval was reviewed and waived and written patient consent was not required (Ethics Approval Number: S-K238).

Acknowledgments

We are grateful to IHMA laboratory staff for their work on the antimicrobial susceptibility tests.

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 tothe content of the manuscript have been disclosed.

FUNDING

This study was supported byPfizer Inc.Further support was provided by the National Key Research and Development Program of China (2018YFC1200100, 2018YFC1200105), CAMSInitiative for Innovative Medicine (grant no. 2016-I2M-3–014). The funders had no role in the study design, collection and analysis of data,interpretation of results, or preparation of the manuscript.

AUTHOR CONTRIBUTION

H.Z., Y.C.X.,P.Y.Jand 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. The European Committee on Antimicrobial Susceptibility Testing (EUCAST).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.Breakpoint tables for interpretation of MICs and zone diameters. Version 9.0.
17. Available at: 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 Journal of antimicrobial chemotherapy* 2011; **66 Suppl 3**: iii69-80.
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. 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.

Figures

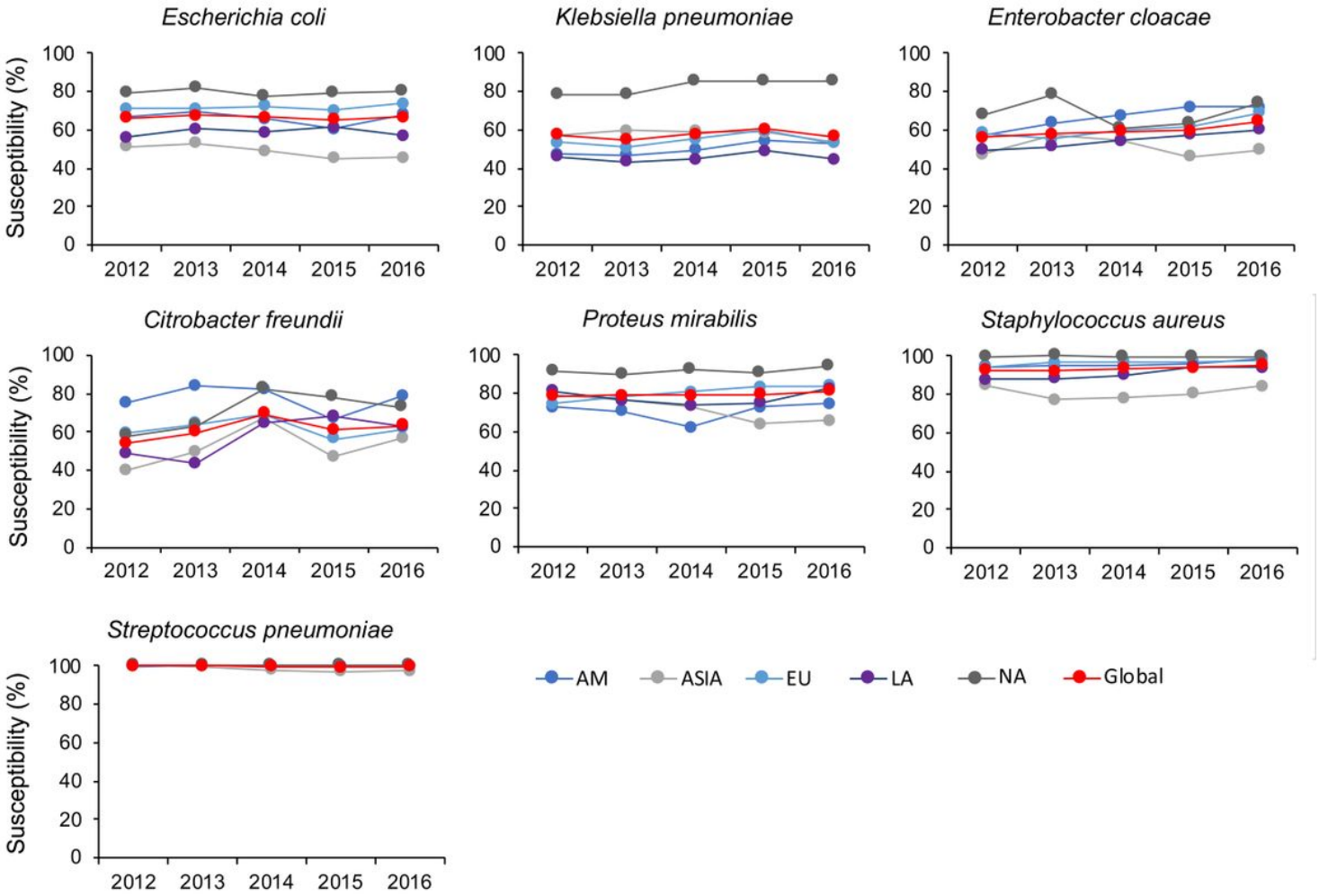

Figure 1

Trend of in vitro susceptibility to ceftaroline against various bacterial species over time in different regions using the CLSI breakpoint. AM: Africa/Middle-East; EU: Europe; LA: Latin America; NA: North America. Data are not presented for Oceania due to limited number of isolates.

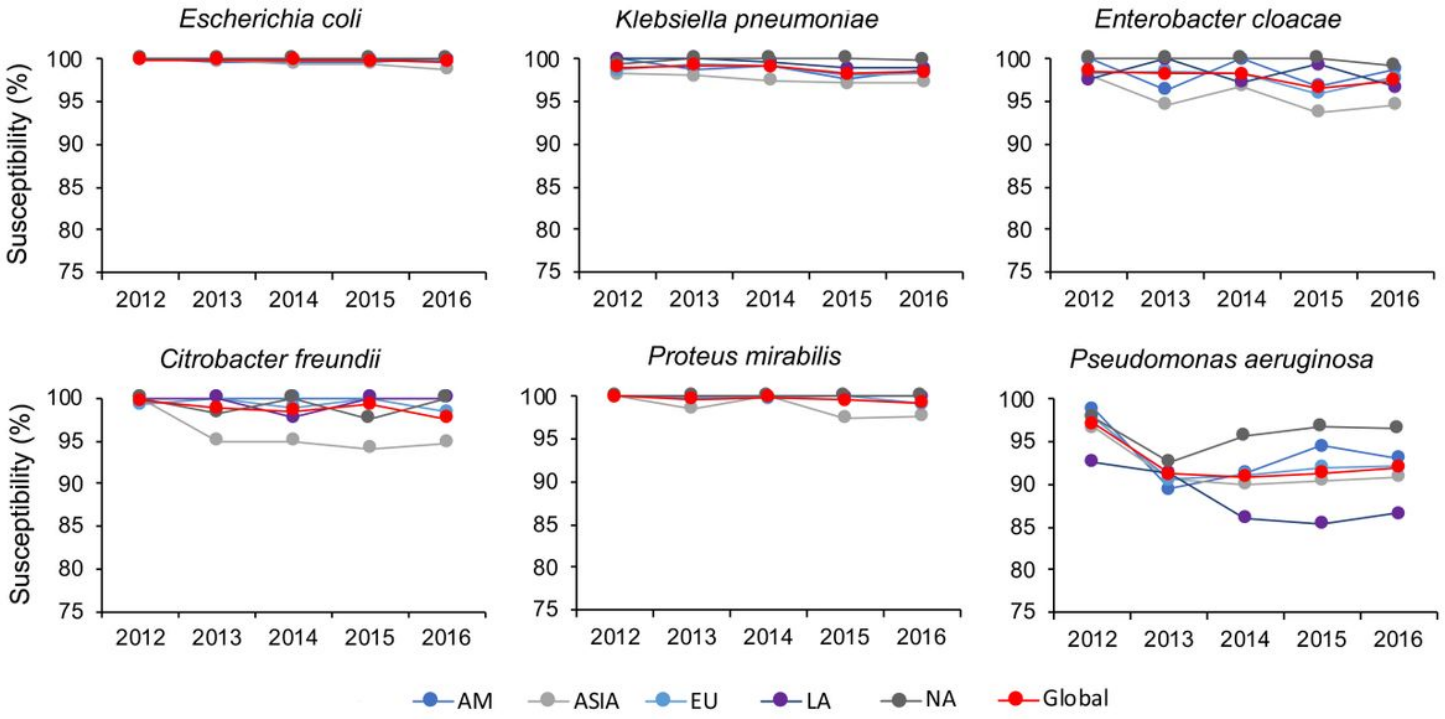

Figure 2

Trend of in vitro susceptibility to ceftazidime-avibactam against various bacterial species over time in different regions using the CLSI breakpoint. AM: Africa/Middle-East; EU: Europe; LA: Latin America; NA: North America; OC: Oceania. Data are not presented for Oceania due to limited number of isolates.

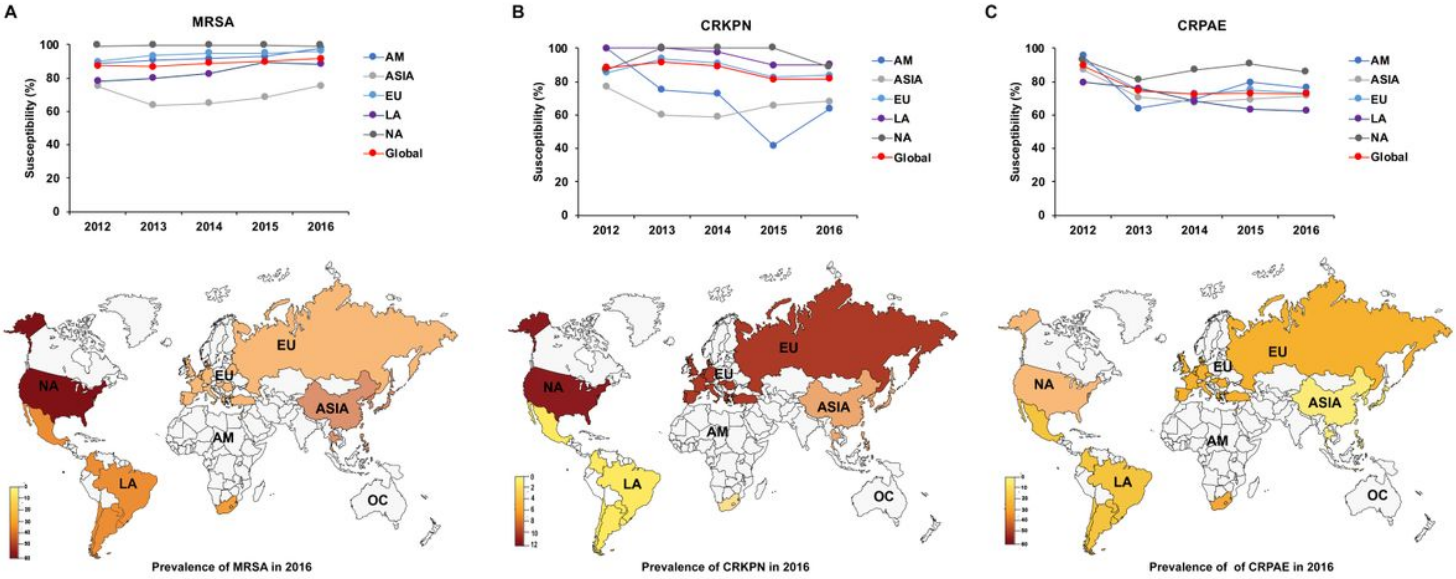

Figure 3

Trend of susceptibility of ceftaroline andceftazidime-avibactam against multi-drug resistant bacteria over time in different regions using the CLSI breakpoint. (A) Susceptibility of ceftaroline against MRSA. (B) Susceptibility of ceftazidime-avibactam against CRKPN. (C) Susceptibility of ceftazidime-avibactam against CRPAE. AM: Africa/Middle-East; EU: Europe; LA: Latin America; NA: North America; MRSA,

methicillin-resistant Staphylococcus aureus; CRKPN: carbapenem-resistant Klebsiella pneumoniae; CRPAE: carbapenem-resistant Pseudomonas aeruginosa. Data are not presented for Oceania due to limited number of isolates.