Antimicrobial activity of ceftazidime-avibactam and comparators against levofloxacin-resistant *Escherichia coli* collected from four geographic regions, 2012–2018

Gregory G. Stone1* and Meredith A. Hackel2

**Abstract**

**Background:** Increases in resistance to fluoroquinolones have been correlated with the use of levofloxacin in the treatment of infections caused by *Escherichia coli*. The analysis presents the in vitro activity of ceftazidime-avibactam and comparator agents against 10,840 levofloxacin-resistant *E. coli* isolates collected from four geographic regions (Africa/Middle East, Europe, Asia/South Pacific, Latin America) between 2012 and 2018.

**Methods:** Non-duplicate clinical isolates of *E. coli* were collected from participating centres and shipped to IHMA, Inc., (Schaumburg, IL, USA). Susceptibility testing was performed with frozen broth microdilution panels manufactured by IHMA, according to CLSI guidelines. Levofloxacin-resistance was defined at a minimum inhibitory concentration of ≥ 2 mg/L. Isolates collected between 2012 and 2015 were tested for extended-spectrum β-lactamase (ESBL) activity by determining susceptibility to cefotaxime, cefotaxime-clavulanate, ceftazidime, and ceftazidime-clavulanate as recommended by CLSI guidelines. Isolates collected between 2016 and 2018 were identified as ESBL-positive by genotype using multiplex polymerase chain reaction assays.

**Results:** A total of 74.8% of levofloxacin-resistant *E. coli* isolates in the analysis were from three culture sources: urinary tract infections (N = 3229; 29.8%), skin and skin structure infections (N = 2564; 23.7%) and intra-abdominal infections (N = 2313; 21.3%). Susceptibility rates to ceftazidime-avibactam were consistently high in all regions against both ESBL-positive (97.0% in Asia/South Pacific to 99.7% in Africa/Middle East and Latin America) and ESBL-negative isolates (99.4% in Asia/South Pacific to 100% in Latin America). Susceptibility was also high in each region among ESBL-positive and ESBL-negative isolates to colistin (≥ 98.5%), imipenem (≥ 96.5%), meropenem (≥ 96.5%) and tigecycline (≥ 94.1%).

**Conclusions:** Antimicrobial susceptibility to ceftazidime-avibactam among levofloxacin-resistant *E. coli* isolates, including ESBL-positive isolates, collected from four geographical regions between 2012 and 2018 was consistently high. Susceptibility to the comparator agents colistin, tigecycline, imipenem and meropenem was also high.

**Keywords:** Ceftazidime-avibactam, Levofloxacin-resistant *Escherichia coli*, Extended-spectrum β-lactamase

*Correspondence: GregoryG.Stone@pfizer.com
1 Hospital Business Unit, Global Products Development, Groton Laboratories, 558 Eastern Point Road, Groton, CT 06340, USA
Full list of author information is available at the end of the article

© The Author(s) 2022. Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article’s Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article’s Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/. The Creative Commons Public Domain Dedication waiver (http://creativecommons.org/publicdomain/zero/1.0/) applies to the data made available in this article, unless otherwise stated in a credit line to the data.
Background
The frequency of antimicrobial resistance has increased worldwide and has been associated with the inappropriate use of antimicrobials [1]. Fluoroquinolones, which have high bioavailability, oral administration and good tissue distribution [2], are commonly used agents; however, increases in resistance to fluoroquinolones have been correlated with the use of levofloxacin in the treatment of infections caused by *E. coli* [3]. Resistance to fluoroquinolones often arises by mutations in the drug targets, DNA gyrase and DNA topoisomerase IV [4, 5], and a frequency of >20% resistance to fluoroquinolones among uropathogens, including *E. coli* has been reported [6, 7]. The availability of treatment options is further complicated in infections caused by members of the Enterobacterales as resistance to fluoroquinolones has been associated with extended-spectrum β-lactamase (ESBL) positive isolates, and ESBL production is associated with the hydrolysis of penicillins and β-lactams, including third-generation cephalosporins [8–10]. ESBL-producing bacteria are now pervasive worldwide, and according to one estimate, over 1.5 billion people are colonised with ESBL-producing Enterobacterales [11].

Avibactam is a diazabicyclooctane, non-β-lactam, β-lactamase-inhibitor, and the combination of ceftazidime with avibactam possesses in vitro activity against Enterobacterales carrying β-lactamases of Ambler class A (ESBLs and *Klebsiella pneumoniae* carbapenemases), class C (AmpC cephalosporinases) and some class D (e.g. OXA-48-type, many of which co-carry ESBLs) [12–16]. The in vitro activity of ceftazidime-avibactam and a panel of comparator agents has been tracked via the International Network for Optimal Resistance Monitoring (INFORM) surveillance program, which was established in 2012, and the Antimicrobial Testing Leadership and Surveillance (ATLAS) study [17], which succeeded INFORM.

The data presented here describe the in vitro activity of ceftazidime-avibactam and comparator agents against ESBL-positive and ESBL-negative levofloxacin-resistant *E. coli* isolates collected from four geographic regions (Africa/Middle East, Europe, Asia/South Pacific, Latin America) between 2012 and 2018.

Materials and methods
Bacterial isolates
Non-duplicate clinical isolates of *E. coli* were collected from participating centres in Africa/Middle East, Asia/South Pacific, Europe and Latin America between 2012 and 2018. All isolates were obtained from specimens collected from patients with community-associated or hospital-associated infections from intra-abdominal, skin, wounds, blood, respiratory tract, urine (limited to no more than 25% of all isolates), fluids, and other defined sources. Each site was requested to collect 25 *E. coli* isolates, and only one isolate per patient were accepted according to the protocol. All isolates were determined to be clinically significant by participating laboratory algorithms and were collected irrespective of antimicrobial susceptibility profile. Following their shipment to the central reference laboratory (IHMA, Schaumburg, IL, USA), samples were identified using matrix-assisted laser desorption ionization-time of flight (MALDI-TOF) mass spectrometry (Bruker Biotyper, Bruker Daltonics, Billerica, MA, USA).

Susceptibility testing
Susceptibility testing was performed according to CLSI and ISO guidelines, [18, 19] with frozen broth microdilution panels manufactured by IHMA. Panel preparation and quality control followed guidelines from the CLSI [18, 20]. Avibactam was tested at a fixed concentration of 4 mg/L in combination with doubling dilutions of ceftazidime (testing range, ≤0.015–128 mg/L). MICs were interpreted using EUCAST 2020 breakpoints, version 10.0 [21] Resistance to levofloxacin was based on EUCAST guidelines and was defined as a minimum inhibitory concentration (MIC) of ≥2 mg/L. Isolates collected between 2012 and 2015, with MICs of ≥2 mg/L to ceftazidime or aztreonam, were tested for ESBL activity by determining susceptibility to cefotaxime, cefotaxime-clavulanate, ceftazidime, and ceftazidime-clavulanate as recommended by CLSI guidelines [20]. Isolates collected between 2016 and 2018 with MICs ≥2 mg/L to meropenem, ceftazidime or aztreonam were screened for β-lactamase genes, using multiplex polymerase chain reaction assays, and ESBL-positive isolates were identified by genotype [22]. All detected β-lactamase genes, excluding original spectrum β-lactamases were amplified using flanking primers and sequenced. Sequences were compared against publicly available databases.

Statistical analyses
The Cochran-Armitage Trend Test was used to assess changes over the study years in the proportion of levofloxacin-resistant *E. coli* isolates that were identified as ESBL-positive. A p-value of <0.01 was interpreted as statistically significant as the n values in the analysis were high and therefore the test was likely to be over-powered. Analyses were performed with SAS® version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results
Distribution of levofloxacin-resistant *E. coli* isolates
A total of 10,840 isolates collected from four geographic regions and identified as resistant to levofloxacin were
included in the analysis. Isolates were most commonly collected from UTIs (N = 3229; 29.8%), followed by 2564 (23.7%) from skin and skin structure infections, 1482 (13.7%) from lower respiratory tract infections, and 1204 (11.1%) from bloodstream infections, whilst 48 (0.4%) were from an unknown or other source. A similar distribution was observed among ESBL-positive and ESBL-negative isolates (data not shown).

The highest proportion of isolates were collected from Europe (N = 4663; 43.0%). The proportion of isolates collected from Latin America (N = 2699; 24.9%) and Asia/South Pacific (N = 2337; 21.6%) were similar, and a minority were from Africa/Middle East (N = 1141; 10.5%).

### Analysis of regions combined against levofloxacin-resistant E. coli

Table 1 shows the in vitro activity of ceftazidime-avibactam and comparators against levofloxacin-resistant ESBL-positive and ESBL-negative E. coli when data from all regions of collection were combined. Rates of susceptibility to ceftazidime-avibactam and colistin were similar (≥ 99.0%) in both sets of isolates. Other comparator agents with high susceptibility rates against both sets of isolates were meropenem and imipenem (≥ 98.5%), and tigecycline (≥ 94.6%). A high susceptibility rate was observed to amikacin among ESBL-negative isolates (95.1%); however, a lower rate of 83.4% was observed among ESBL-positive isolates. For cefepime, ceftazidime and aztreonam relatively high rates of susceptibility were

| Antimicrobial                   | MIC<sub>50</sub> (mg/L) | MIC<sub>90</sub> (mg/L) | Range (mg/L) | %S  | %I  | %R  |
|--------------------------------|-------------------------|-------------------------|--------------|-----|-----|-----|
| **ESBL-positive (N = 5749)**   |                         |                         |              |     |     |     |
| Ceftazidime-avibactam          | 0.12                    | 0.5                     | ≤ 0.015–≥ 256| 99.0| –   | 1.0 |
| Ceftazidime<sup>a</sup>         | 32                      | 128                     | 0.12–≥ 256   | 5.3 | 148 | 79.9|
| Cefepime<sup>a</sup>            | 32                      | 32                      | ≤ 0.12–≥ 64  | 3.0 | 10.0| 86.9|
| Ampicillin                      | ≥ 64                    | ≥ 64                    | 1–≥ 64       | 0.2 | –   | 99.8|
| Amoxicillin-clavulanate<sup>a</sup> | 16                      | 32                      | ≤ 0.12–≥ 64  | 29.3| –   | 70.7|
| Piperacillin-tazobactam         | 8                       | 64                      | ≤ 0.25–≥ 256 | 64.8| 15.2| 20.0|
| Aztreonam<sup>a</sup>           | 32                      | 128                     | 0.06–≥ 256   | 0.2 | 8.2 | 91.6|
| Imipenem                       | 0.25                    | 0.25                    | ≤ 0.03–≥ 16  | 98.5| 0.4 | 1.1 |
| Meropenem                       | 0.03                    | 0.06                    | ≤ 0.004–≥ 32 | 98.5| 0.6 | 1.0 |
| Colistin<sup>b</sup> (N = 4470) | 0.25                    | 1                       | ≤ 0.06–≥ 16  | 99.1| –   | 0.9 |
| Amikacin                        | 4                       | 16                      | 0.5–≥ 128    | 83.4| –   | 16.6|
| Tigecycline                     | 0.25                    | 0.5                     | ≤ 0.015–≥ 16 | 95.7| –   | 4.3 |
| **ESBL-negative (N = 5091)**   |                         |                         |              |     |     |     |
| Ceftazidime-avibactam          | 0.12                    | 0.25                    | ≤ 0.015–≥ 256| 99.6| –   | 0.4 |
| Ceftazidime                     | 0.25                    | 4                       | ≤ 0.015–≥ 256| 88.5| 2.3 | 9.2 |
| Cefepime                        | ≤ 0.12                  | 1                       | ≤ 0.12–≥ 64  | 91.8| 3.8 | 4.4 |
| Ampicillin                      | ≥ 64                    | ≥ 64                    | 0.5–≥ 64     | 17.4| –   | 82.6|
| Amoxicillin-clavulanate         | 8                       | 32                      | ≤ 0.12–≥ 64  | 51.4| –   | 48.6|
| Piperacillin-tazobactam         | 2                       | 64                      | ≤ 0.12–≥ 256 | 81.9| 5.0 | 13.1|
| Aztreonam                       | 0.12                    | 4                       | ≤ 0.015–≥ 256| 88.9| 2.7 | 8.3 |
| Imipenem                        | 0.12                    | 0.25                    | ≤ 0.03–≥ 16  | 99.1| 0.3 | 0.6 |
| Meropenem                       | 0.03                    | 0.06                    | ≤ 0.004–≥ 32 | 99.3| 0.3 | 0.4 |
| Colistin<sup>b</sup> (N = 3864) | 0.25                    | 1                       | ≤ 0.06–≥ 16  | 99.0| –   | 1.0 |
| Amikacin                        | 2                       | 8                       | ≤ 0.25–≥ 128 | 95.1| –   | 4.9 |
| Tigecycline                     | 0.25                    | 0.5                     | ≤ 0.015–4   | 94.6| –   | 5.4 |

– Indicates no breakpoint for the agent

ESBL extended-spectrum β-lactamase, % percentage of isolates susceptible, increased exposure, MIC minimum inhibitory concentration, MIC<sub>50</sub> MIC required to inhibit growth of 50% of isolates (mg/L), MIC<sub>90</sub> MIC required to inhibit growth of 90% of isolates (mg/L), %R percentage of isolates resistant, %S percentage of isolates susceptible, standard dosing

<sup>a</sup> Not suitable for use in the treatment of infections caused by ESBL-positive isolates

<sup>b</sup> Colistin was included on the comparator panel from 2014 onwards
observed among ESBL-negative isolates (≥ 88.5%); however, a susceptibility rate of <10% was seen among ESBL-positive isolates.

Analysis by region against levofloxacin-resistant *E. coli*

For the regional analysis of all years pooled (2012–2018), presented in Table 2, susceptibility rates to ceftazidime-avibactam were consistently high in all regions for both ESBL-positive (97.0% in Asia/South Pacific to 99.7% in Africa/Middle East and Latin America) and ESBL-negative (99.4% in Asia/South Pacific to 100% in Latin America) levofloxacin-resistant *E. coli*. High susceptibility rates were also observed in each region among ESBL-positive and ESBL-negative isolates for colistin (≥ 98.5%), imipenem (≥ 96.5%), meropenem (≥ 96.5%) and tigecycline (≥ 94.1%).

Susceptibility rates to amikacin among ESBL-negative isolates were similar in all regions, from 94.4% in Africa/Middle East and Latin America to 96.5% in Europe. Among ESBL-positive isolates, susceptibility to amikacin was lower (79.9% in Asia/South Pacific to 89.8% in Asia/South Pacific). The susceptibility rates observed among ESBL-negative isolates to piperacillin-tazobactam were lowest in Europe (79.6%) and highest in Latin America (84.9%). In comparison, rates of susceptibility to piperacillin-tazobactam among ESBL-positive isolates were lower in each region, ranging from 61.1 to 74.0%.

High rates of susceptibility were observed among ESBL-negative levofloxacin-resistant *E. coli* for cefepime in all regions (between 91.1 and 93.3%) and for ceftazidime in three of the four regions (91.0 to 93.0%). A lower susceptibility rate to ceftazidime of 77.9% was observed among ESBL-negative isolates in Asia/South Pacific. Few ESBL-positive isolates from any region were susceptible to cefepime or ceftazidime (≤ 6.3%). Susceptibility rates to ampicillin and amoxicillin-clavulanate were lower compared with all other agents in each region for ESBL-negative isolates. Among each regional set of ESBL-positive isolates, susceptibility rates to ampicillin and amoxicillin-clavulanate were ≤ 41.6%.

In vitro activity data, by year, for ceftazidime-avibactam, colistin, meropenem, imipenem, and tigecycline against ESBL-positive and ESBL-negative isolates are presented in Additional file 1: Tables S1–S5. Over time, ceftazidime-avibactam, colistin, meropenem and imipenem showed consistently high and stable rates of susceptibility (≥ 96.7%) in Africa/Middle East, Europe and Latin America (Additional file 1: Tables S1–S4). For ESBL-positive isolates collected in the Asia/South Pacific region, reduced susceptibility rates were observed in 2018 to ceftazidime-avibactam (91.8%, Additional file 1: Table S1), and to imipenem (90.4%) and meropenem (91.1%) (Additional file 1: Tables S3 and S4) when compared with each of the preceding years. Susceptibility to tigecycline was > 92.6% between 2013 and 2018; rates of susceptibility were lower in 2012.

Regional trend tests against levofloxacin-resistant *E. coli* over time

Figure 1 shows the proportion of levofloxacin-resistant *E. coli* isolates identified as ESBL-positive from each region and by year. Any changes in the rates of ESBL-positive, levofloxacin-resistant *E. coli* over time were not statistically significant in Africa/Middle East and Latin America. For isolates from Europe and Asia/Pacific there was a statistically significant increase in the rates of ESBL-positive isolates over time (p = 0.0029 and p = 0.0001, respectively) with rates in 2018 of 54.4% in Europe and 61.3% in Asia–Pacific.

Discussion

This analysis of levofloxacin-resistant *E. coli* isolates collected between 2012 and 2018 in four geographical regions as part of the ATLAS study, showed high susceptibility rates to ceftazidime-avibactam among ESBL-positive and ESBL-negative isolates. Data also showed high susceptibility rates to colistin, meropenem, imipenem, and tigecycline, rates that were common to all regions and both ESBL-positive and ESBL-negative isolates. Susceptibility to cefepime, ceftazidime and aztreonam was also high against ESBL-negative isolates; however, susceptibility was reduced against ESBL-positive isolates with < 10% of isolates susceptible to cefepime, ceftazidime or aztreonam.

The year-by-year analysis for the Asia/Pacific region revealed lower rates of susceptibility to meropenem, imipenem and ceftazidime-avibactam in 2018 when compared with the 2012–2017 period. There have been reports of *E. coli* strains that are resistant to fluoroquinolones becoming more widespread during recent years [23]. Of particular concern has been the global spread of *E. coli* strain ST131, which is characterised by co-resistance to fluoroquinolones and other agents [8–10, 24, 25]. It is unlikely that this strain could be the cause of the lowered susceptibility we observed to ceftazidime-avibactam and the two carbapenems in the Asia/South Pacific region in 2018. Among *E. coli* ST131 the rate of resistance to carbapenems is considered to be low, and a recent study of the in vitro activity of ceftazidime-avibactam and comparators against *E. coli* ST131 isolates in the USA reported no resistance to ceftazidime-avibactam or meropenem [26]. A possible explanation may be the appearance of metallo-β-lactamases (MBLs) in isolates collected in the Asia/South Pacific region during 2018. Whilst MBL-positive isolates are frequently reported among *Klebsiella pneumoniae*, they are also disseminated
### Table 2
Activity of ceftazidime-avibactam and comparator agents against levofloxacin-resistant *E. coli*; ATLAS, by region, 2012–2018

| Antimicrobial                  | MIC$_{50}$ (mg/L) | MIC$_{90}$ (mg/L) | Range (mg/L) | %S | %I | %R |
|--------------------------------|-------------------|-------------------|--------------|----|----|----|
| **Africa/Middle East, ESBL-positive (N = 609)** |                   |                   |              |    |    |    |
| Ceftazidime-avibactam         | 0.25              | 0.5               | ≤ 0.015–256  | 99.7 | –  | 0.3 |
| Ceftazidime*                  | 32                | 128               | 0.12–256     | 2.8  | 13.3 | 83.9 |
| Cefepime*                     | 32                | ≥ 64              | 0.25–256     | 2.5  | 7.2  | 90.3 |
| Ampicillin                    | ≥ 64              | ≥ 64              | 16–256       | 0.0  | –  | 100 |
| Amoxicillin-clavulanate*      | 16                | 32                | 1–256        | 26.9 | –  | 73.1 |
| Piperacillin-tazobactam       | 8                 | 128               | ≤ 0.25–256   | 61.1 | 18.2 | 20.7 |
| Aztreonam*                    | 64                | 128               | 2–256        | 0.0  | 5.3  | 94.7 |
| Imipenem                      | 0.25              | 0.25              | 0.06–16      | 99.3 | 0.3  | 0.3 |
| Meropenem*                    | 0.03              | 0.06              | 0.015–32     | 99.5 | 0.3  | 0.2 |
| Colistin*b (N = 472)          | 0.5               | 1                 | ≤ 0.06–8     | 99.2 | –  | 0.8 |
| Amikacin                      | 4                 | 16                | 0.5–1.28     | 85.2 | –  | 14.8 |
| Tigecycline                   | 0.25              | 0.5               | 0.06–4       | 96.2 | –  | 3.8 |
| **Africa/Middle East, ESBL-negative (N = 532)** |                   |                   |              |    |    |    |
| Ceftazidime-avibactam         | 0.12              | 0.25              | ≤ 0.015–256  | 99.6 | –  | 0.4 |
| Ceftazidime                   | 0.25              | 0.5               | ≤ 0.015–256  | 93.0 | 0.9  | 5.6 |
| Cefepime                      | ≤ 0.12            | 1                 | ≤ 0.12–256   | 92.7 | 3.2  | 4.1 |
| Ampicillin                    | ≥ 64              | ≥ 64              | 1–256        | 15.0 | –  | 85.0 |
| Amoxicillin-clavulanate       | 8                 | 32                | ≤ 0.12–256   | 56.0 | –  | 44.0 |
| Piperacillin-tazobactam       | 2                 | 32                | 0.12–256     | 82.3 | 5.6  | 12.0 |
| Aztreonam                     | 0.12              | 0.5               | ≤ 0.015–256  | 93.0 | 1.5  | 5.5 |
| Imipenem                      | 0.12              | 0.25              | 0.06–16      | 99.1 | 0.4  | 0.6 |
| Meropenem                     | 0.03              | 0.06              | 0.008–16     | 99.2 | 0.2  | 0.6 |
| Colistin*b (N = 413)          | 0.25              | 1                 | ≤ 0.06–16    | 98.5 | –  | 1.5 |
| Amikacin                      | 2                 | 8                 | 0.5–128      | 94.4 | –  | 5.6 |
| Tigecycline                   | 0.25              | 0.5               | 0.06–4       | 94.9 | –  | 5.1 |
| **Asia/South Pacific, ESBL-positive (N = 1283)** |                   |                   |              |    |    |    |
| Ceftazidime-avibactam         | 0.12              | 0.5               | ≤ 0.015–256  | 97.0 | –  | 3.0 |
| Ceftazidime                   | 16                | 128               | 0.25–256     | 6.3  | 16.4 | 77.3 |
| Cefepime                      | 32                | ≥ 64              | 0.12–256     | 1.5  | 11.0 | 87.5 |
| Ampicillin                    | ≥ 64              | ≥ 64              | 4–256        | 0.2  | –  | 99.8 |
| Amoxicillin-clavulanate       | 16                | 32                | 2–256        | 41.6 | –  | 58.4 |
| Piperacillin-tazobactam       | 4                 | 128               | 0.5–256      | 74.0 | 9.8  | 16.1 |
| Aztreonam*                    | 32                | 128               | 0.06–256     | 0.5  | 7.9  | 91.7 |
| Imipenem                      | 0.25              | 0.5               | ≤ 0.03–16    | 96.5 | 0.3  | 3.2 |
| Meropenem                     | 0.03              | 0.12              | 0.008–32     | 96.5 | 0.5  | 3.0 |
| Colistin*b (N = 1012)         | 0.25              | 1                 | ≤ 0.06–16    | 98.8 | –  | 1.2 |
| Amikacin                      | 4                 | 16                | 0.5–128      | 89.8 | –  | 10.2 |
| Tigecycline                   | 0.25              | 0.5               | 0.03–16      | 94.3 | –  | 5.7 |
| **Asia/South Pacific, ESBL-negative (N = 1054)** |                   |                   |              |    |    |    |
| Ceftazidime-avibactam         | 0.12              | 0.25              | ≤ 0.015–256  | 99.4 | –  | 0.6 |
| Ceftazidime                   | 0.25              | 32                | ≤ 0.015–256  | 77.9 | 3.1  | 19.0 |
| Cefepime                      | ≤ 0.12            | 1                 | ≤ 0.12–256   | 91.4 | 3.9  | 4.7 |
| Ampicillin                    | ≥ 64              | ≥ 64              | 0.5–256      | 17.0 | –  | 83.0 |
| Amoxicillin-clavulanate       | 8                 | 52                | ≤ 0.12–64    | 52.4 | –  | 47.6 |
| Piperacillin-tazobactam       | 2                 | 32                | 0.25–256     | 83.5 | 4.9  | 11.6 |
| Aztreonam                     | 0.12              | 16                | ≤ 0.015–256  | 79.7 | 4.6  | 15.7 |
| Imipenem                      | 0.25              | 0.5               | ≤ 0.03–16    | 99.3 | 0.2  | 0.5 |
| Meropenem                     | 0.03              | 0.06              | ≤ 0.004–32   | 99.4 | 0.1  | 0.5 |
Table 2 (continued)

| Antimicrobial                        | MIC$_{50}$ (mg/L) | MIC$_{90}$ (mg/L) | Range (mg/L) | %S | %I | %R |
|--------------------------------------|------------------|------------------|--------------|----|----|----|
| Colistinb (N = 780)                  | 0.25             | 1                | ≤ 0.06– ≥ 16 | 99.4 | –  | 0.6 |
| Amikacin                             | 2                | 8                | ≤ 0.25– ≥ 128 | 96.5 | –  | 3.5 |
| Tigecycline                          | 0.25             | 0.5              | 0.03–4       | 94.7 | –  | 5.3 |
| Europe, ESBL-positive (N = 2290)     |                  |                  |              |     |    |    |
| Ceftazidime-avibactam                | 0.12             | 0.5              | ≤ 0.015– ≥ 256 | 99.6 | –  | 0.4 |
| Ceftazidimea                         | 16               | 128              | 0.12– ≥ 256  | 60  | 17.2 | 76.9 |
| Cefepimea                            | 32               | ≥ 64             | ≤ 0.12– ≥ 64 | 4.6 | 12.6 | 82.8 |
| Ampicillin                           | ≥ 64             | ≥ 64             | 1– ≥ 64      | 0.3 | –   | 99.7 |
| Amoxicillin-clavulanatea             | 16               | 32               | ≤ 0.12– ≥ 64 | 25.9 | –  | 74.1 |
| Piperacillin-tazobactam              | 8                | 128              | ≤ 0.25– ≥ 256 | 61.3 | 15.8 | 22.9 |
| Aztreonam                            | 32               | 128              | 0.5– ≥ 256   | 0.3 | 10.3 | 89.4 |
| Imipenem                             | 0.25             | 0.25             | ≤ 0.03– ≥ 16 | 99.0 | 0.4 | 0.6 |
| Meropenem                            | 0.03             | 0.06             | ≤ 0.004– ≥ 32 | 98.9 | 0.6 | 0.5 |
| Colistinb (N = 1754)                 | 0.5              | 1                | ≤ 0.06– ≥ 16 | 99.1 | –  | 0.9 |
| Amikacin                             | 4                | 16               | 0.5– ≥ 128   | 79.9 | –  | 20.1 |
| Tigecycline                          | 0.25             | 0.5              | ≤ 0.015–4    | 96.3 | –  | 3.7 |
| Europe, ESBL-negative (N = 2373)     |                  |                  |              |     |    |    |
| Ceftazidime-avibactam                | 0.12             | 0.25             | ≤ 0.015– ≥ 256 | 99.5 | –  | 0.5 |
| Ceftazidime                          | 0.25             | 1                | 0.03– ≥ 256  | 91.0 | 2.4 | 6.7 |
| Cefepime                             | ≤ 0.12           | 1                | ≤ 0.12– ≥ 64 | 91.1 | 4.3 | 4.6 |
| Ampicillin                           | ≥ 64             | ≥ 64             | ≤ 0.5– ≥ 64  | 160 | –  | 84.0 |
| Amoxicillin-clavulanatea             | 16               | 32               | ≤ 0.12– ≥ 64 | 47.8 | –  | 52.2 |
| Piperacillin-tazobactam              | 2                | 64               | ≤ 0.12– ≥ 256 | 79.6 | 5.1 | 15.3 |
| Aztreonam                            | 0.12             | 1                | ≤ 0.015– ≥ 256 | 91.4 | 2.6 | 6.0 |
| Imipenem                             | 0.12             | 0.25             | ≤ 0.03– ≥ 16 | 98.7 | 0.5 | 0.8 |
| Meropenem                            | 0.03             | 0.06             | ≤ 0.004– ≥ 32 | 99.2 | 0.4 | 0.4 |
| Colistinb (N = 1786)                 | 0.25             | 1                | ≤ 0.06– ≥ 16 | 98.9 | –  | 1.1 |
| Amikacin                             | 2                | 8                | 0.5– ≥ 128   | 95.0 | –  | 5.0 |
| Tigecycline                          | 0.25             | 0.5              | ≤ 0.015–4    | 94.1 | –  | 5.9 |
| Latin America, ESBL-positive (N = 1567) |            |                  |              |     |    |    |
| Ceftazidime-avibactam                | 0.12             | 0.5              | ≤ 0.015– ≥ 256 | 99.7 | –  | 0.3 |
| Ceftazidimea                         | 32               | 128              | 0.5– ≥ 256   | 4.3 | 10.7 | 84.9 |
| Cefepimea                            | 32               | 32               | ≤ 0.12– ≥ 64 | 23.3 | –  | 76.7 |
| Ampicillin                           | ≥ 64             | ≥ 64             | 8– ≥ 64      | 0.1 | –  | 99.9 |
| Amoxicillin-clavulanatea             | 16               | 32               | ≤ 0.12– ≥ 64 | 25.3 | –  | 74.7 |
| Piperacillin-tazobactam              | 8                | 64               | ≤ 0.25– ≥ 256 | 63.8 | 17.7 | 18.5 |
| Aztreonam                            | 64               | 128              | 0.5– ≥ 256   | 0.1 | 6.4 | 93.5 |
| Imipenem                             | 0.12             | 0.25             | 0.06– ≥ 16   | 99.2 | 0.4 | 0.4 |
| Meropenem                            | 0.03             | 0.06             | 0.015– ≥ 32  | 99.0 | 0.6 | 0.4 |
| Colistinb (N = 1232)                 | 0.25             | 1                | ≤ 0.06–8     | 99.1 | –  | 0.9 |
| Amikacin                             | 4                | 16               | 0.5– ≥ 128   | 82.6 | –  | 17.4 |
| Tigecycline                          | 0.25             | 0.5              | ≤ 0.015–4    | 95.8 | –  | 4.2 |
| Latin America, ESBL-negative (N = 1132) |          |                  |              |     |    |    |
| Ceftazidime-avibactam                | 0.12             | 0.25             | ≤ 0.015–4    | 100 | –  | 0.0 |
| Ceftazidime                          | 0.25             | 1                | 0.03– ≥ 256  | 91.1 | 1.7 | 7.2 |
| Cefepime                             | ≤ 0.12           | 1                | ≤ 0.12– ≥ 64 | 93.3 | 3.1 | 3.6 |
| Ampicillin                           | ≥ 64             | ≥ 64             | 1– ≥ 64      | 22.0 | –  | 78.0 |
| Amoxicillin-clavulanatea             | 8                | 32               | ≤ 0.12– ≥ 64 | 56.0 | –  | 44.0 |
| Piperacillin-tazobactam              | 2                | 32               | 0.25– ≥ 256  | 84.9 | 4.4 | 10.7 |
to a lesser extent among *E. coli*, and so their inclusion among a population of levofloxacin-resistant isolates would be plausible [27].

The ATLAS program is intended for antimicrobial surveillance and is not designed as an epidemiological study. Therefore, the observations regarding the frequency of ESBLs need to be considered with caution. Furthermore, it must be remembered that the isolates included in this analysis are all levofloxacin-resistant, predisposing the collection to higher rates of ESBL-positive isolates than might be identified in other clinical collections of *E. coli*. Additionally, centres that have participated in ATLAS

**Table 2** (continued)

| Antimicrobial | MIC<sub>50</sub> (mg/L) | MIC<sub>90</sub> (mg/L) | Range (mg/L) | %S | %I | %R |
|---------------|---------------------------|--------------------------|--------------|----|----|----|
| Aztreonam     | 0.12                      | 1                        | ≤0.015–≥256  | 90.5 | 1.9 | 7.6 |
| Imipenem      | 0.12                      | 0.25                     | ≤0.03–≥16    | 99.5 | 0.1 | 0.4 |
| Meropenem     | 0.03                      | 0.06                     | 0.008–≥32    | 99.4 | 0.4 | 0.3 |
| Colistin<sup>b</sup> (N = 885) | 0.25 | 1 | ≤0.06–≥16 | 99.1 | – | 0.9 |
| Amikacin      | 2                         | 8                        | ≤0.25–≥128   | 94.4 | – | 5.6 |
| Tigecycline   | 0.25                      | 0.5                      | ≤0.015–4     | 95.5 | – | 4.5 |

<sup>–</sup> Indicates no breakpoint for the agent

ESBL, extended-spectrum β-lactamase; %I, percentage of isolates susceptible, increased exposure; MIC, minimum inhibitory concentration; MIC<sub>50</sub>, MIC required to inhibit growth of 50% of isolates (mg/L); MIC<sub>90</sub>, MIC required to inhibit growth of 90% of isolates (mg/L); %R, percentage of isolates resistant; %S, percentage of isolates susceptible, standard dosing

<sup>a</sup> Not suitable for use in the treatment of infections caused by ESBL-positive isolates

<sup>b</sup> Colistin was included on the comparator panel from 2014 onwards

![Fig. 1](image-url)  
Fig. 1 Proportion of levofloxacin-resistant *Escherichia coli* isolates identified as ESBL-positive, 2012–2018. **All regions:** 2012, n = 487/1012; 2013, n = 792/1494; 2014, n = 844/1615; 2015, n = 718/1365; 2016, n = 901/1739; 2017, n = 887/1625; 2018, n = 1111/1990. **Africa/Middle East:** 2012, n = 39/86; 2013, n = 98/170; 2014, n = 109/204; 2015, n = 68/118; 2016, n = 77/157; 2017, n = 82/160; 2018, n = 136/246. **Asia/South Pacific:** 2012, n = 123/254; 2013, n = 148/291; 2014, n = 159/309; 2015, n = 152/271; 2016, n = 206/379; 2017, n = 204/358; 2018, n = 291/475. **Europe:** 2012, n = 175/422; 2013, n = 361/701; 2014, n = 347/727; 2015, n = 305/620; 2016, n = 316/709; 2017, n = 343/669; 2018, n = 443/815. **Latin America:** 2012, n = 150/250; 2013, 185/332; 2014, n = 229/375; 2015, n = 193/356; 2016, n = 311/494; 2017, n = 258/438; 2018, n = 241/454
have not been required to do so in each year, so the analysis of longitudinal data could be influenced by changes in the distribution of isolates over time. In our analyses, data were not available for India or China, and so our findings cannot reasonably be applied to these individual countries. Whilst centres from many countries have participated in this analysis, their geographical distribution has focused around the four main regions included in this analysis and so the observations that we present may not be fully representative of global susceptibility trends.

Conclusions

In conclusion, we report that the in vitro susceptibility to ceftazidime-avibactam among levofloxacin-resistant *E. coli* isolates, including ESBL-positive isolates, collected from four geographical regions between 2012 and 2018 was consistently high (≥ 97.0%). Susceptibility to the comparator agents colistin, tigecycline, imipenem and meropenem was also high (≥ 94.1%), whilst susceptibility to other agents on the panel was lower, particularly among ESBL-positive isolates. A modest reduction in susceptibility to imipenem, meropenem, and ceftazidime-avibactam in the Asia/South Pacific region in 2018 warrants continued antimicrobial surveillance. The identification of global and regional trends of antimicrobial resistance can help to guide appropriate treatment of infectious disease where *E. coli* is the suspected or confirmed causative organism.

Abbreviations

ATLAS: Antimicrobial Testing Leadership and Surveillance; ESBL: Extended-spectrum β-lactamase; INFQRN: International Network for Optimal Resistance Monitoring; MALDI-TOF: Matrix-assisted laser desorption ionization-time of flight mass spectrometry; MBL: Metallo-β-lactamase; MIC: Minimum inhibitory concentration; UTI: Urinary tract infection.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12941-022-00504-8.

Additional file 1: Table S1. Activity of ceftazidime-avibactam against levofloxacin-resistant *E. coli*, ATLAS, by region and year, 2012–2018.

Table S2. Activity of colistin against levofloxacin-resistant *E. coli*, ATLAS, by region and year, 2014*–2018.

Table S3. Activity of imipenem against levofloxacin-resistant *E. coli* isolates, ATLAS, by region and year, 2012–2018.

Table S4. Activity of meropenem against levofloxacin-resistant *E. coli* isolates, ATLAS, by region and year, 2012–2018.

Table S5. Activity of tigecycline against levofloxacin-resistant *E. coli*, ATLAS, by region and year, 2012–2018.

Acknowledgements

The ATLAS program is a large surveillance study which collects isolates from institutions globally. The authors of this work would like to extend their thanks to the individuals at each centre who were involved in collecting and submitting isolates to the ATLAS program, as well as the staff at IHMA for their work on the coordination of the study and analysis of the isolates. Medical writing support was provided by Mike Leedham at Micron Research Ltd., Ely, UK, which was funded by Pfizer. Micron Research Ltd. also provided data management services, which were funded by Pfizer.

Authors’ contributions

GGS was involved in the study design and data interpretation, as well as drafting and reviewing the manuscript. MAH was involved in data production and interpretation and reviewing and redrafting the manuscript. Both authors read and approved the final manuscript.

Funding

This study is funded by Pfizer Inc. Pfizer Inc. was involved in the study design and the decision to submit the work for publication.

Availability of data and materials

The datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request. Data from the global ATLAS study can be accessed at https://atlas-surveillance.com.

Declarations

Ethics approval and consent to participate

As the ATLAS program does not require any additional tests, expenses, or procedures on behalf of the patient outside of normal patient care and no patient identifiers are collected ethical approval was not required.

Consent for publication

Each participating Investigator/Institution was required to sign a participation agreement that gave explicit rights allowing the submitted organisms to be included in ATLAS and confirming acceptance that the data may be used for publication.

Competing interests

GGS is an employee of Pfizer Inc. and a Pfizer Inc. shareholder. MAH is an employee of IHMA and has no personal financial interests in the sponsor of the study (Pfizer, Inc.).

Author details

1 Hospital Business Unit, Global Products Development, Groton Laboratories, 558 Eastern Point Road, Groton, CT 06340, USA.

2 IHMA, Schaumburg, IL, USA.

Received: 26 May 2021 Accepted: 11 March 2022

Published online: 21 March 2022

References

1. World Health Organization (WHO). Antimicrobial resistance. Global action plan on antimicrobial resistance. Geneva: WHO; 2015. http://apps.who.int/iris/bitstream/handle/10665/193736/9789241509763_eng.pdf. Accessed 15 Sept 2020.

2. Drusano G, Labro M-T, Cars O, Mendes P, Shah P, Sörgel F, et al. Pharmacokinetics and pharmacodynamics of fluoroquinolones. Clin Microbiol Infect. 1998;4(Suppl 2):S27–41.

3. Wu H-H, Liu H-Y, Lin Y-C, Hsueh P-R, Lee Y-J. Correlation between levofloxacin consumption and the incidence of nosocomial infections due to fluoroquinolone-resistant *Escherichia coli*. J Microbiol Immunol Infect. 2016;49:424–9.

4. Hooper DC. Bacterial topoisomerases, anti-topoisomerases, and anti-topoisomerase resistance. Clin Infect Dis. 1998;27(Suppl 1):S54-63.

5. Hooper DC, Jacoby GA. Mechanisms of drug resistance: quinolone resistance. Ann N Y Acad Sci. 2015;1354:12–31.

6. Hsueh P-R, Lau Y-J, Ko W-C, Liu C-Y, Huang C-T, Yen M-Y, et al. Consensus statement on the role of fluoroquinolones in the management of urinary tract infections. J Microbiol Immunol Infect. 2011;44:79–82.

7. European Centre for Disease Prevention and Control. Antimicrobial resistance in the EU/EEA (EARS-Net)—Annual Epidemiological Report 2019. Stockholm: ECDC; 2020.

8. Doi Y, Lovleva A, Bonomo RA. The ecology of extended-spectrum beta-lactamases (ESBLs) in the developed world. J Travel Med. 2017;24(Suppl 1):44–51.
9. Petty NK, Ben Zakour NL, Stanton-Cook M, Skippington E, Totsika M, Forde BM, et al. Global dissemination of a multidrug resistant Escherichia coli clone. Proc Natl Acad Sci USA. 2014;111:5694–9.
10. Johnson JR, Tchesnokova V, Johnston B, Clabots C, Roberts PL, Billig M, et al. Abrupt emergence of a single dominant multidrug-resistant strain of Escherichia coli. J Infect Dis. 2013;207:919–28.
11. Woerther PL, Burdet C, Chachaty E, Andremont A. Trends in human fecal carriage of extended-spectrum β-lactamases in the community: toward the globalization of CTX-M. Clin Microbiol Rev. 2013;26:744–58.
12. Bush K, Bradford PA. Interplay between β-lactamases and new β-lactamase inhibitors. Nat Rev Microbiol. 2019;17:295–306.
13. Ehmann DE, Hajić H, Ross PL, Gu R-F, Hu J, Kern G, et al. Avibactam is a covalent, reversible, non-β-lactam β-lactamase inhibitor. Proc Natl Acad Sci USA. 2012;109:11663–8.
14. Kazmierczak KM, Bradford PA, Stone GG, de Jonge BLM, Sahm DF. In vitro activity of ceftazidime-avibactam and aztreonam-avibactam against OXA-48-carrying Enterobacteriaceae isolated as part of the International Network for Optimal Resistance Monitoring (INFORM) global surveillance program from 2012 to 2015. Antimicrob Agents Chemother. 2018;62:e00592-e618.
15. Levassor P, Girard A-M, Miossec C, Pace J, Coleman K. In vitro antibacterial activity of the ceftazidime-avibactam combination against Enterobacteriaceae, including strains with well-characterized β-lactamases. Antimicrob Agents Chemother. 2015;59:1931–4.
16. Papp-Wallace KM, Bajaksouzian S, Abdelhamed AM, Foster AN, Winkler ML, Gatta JA, et al. Activities of ceftazidime, cefaroline, and aztreonam alone and combined with avibactam against isogenic Escherichia coli strains expressing selected single β-lactamases. Diagn Microbiol Infect Dis. 2015;82:65–9.
17. ATLAS (Antimicrobial Testing Leadership and Surveillance). Pfizer. https://atlas-surveillance.com. Accessed 15 September 2020.
18. Clinical and Laboratory Standards Institute. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically—Tenth Edition: Approved Standard M7-A10. Clinical and Laboratory Standards Institute. 2015. Wayne, PA.
19. International Standards Organization. Clinical laboratory testing and in vitro diagnostic test systems—susceptibility testing of infectious agents and evaluation of performance of antimicrobial susceptibility tests. Part 1: Reference method for testing the in vitro activity of antimicrobial agents against rapidly growing aerobic bacteria involved in infectious diseases. 2006. ISO 20776–1.
20. Clinical and Laboratory Standards Institute. Performance standards for antimicrobial susceptibility testing. Twenty-sixth informational supplement. CLSI document M100-S26. Clinical and Laboratory Standards Institute. 2016. Wayne, PA.
21. The European Committee on Antimicrobial Susceptibility Testing. Breakpoint tables for interpretation of MICs and zone diameters. Version 10.0. 2020. http://www.eucast.org. Accessed 21 May 2020.
22. Lob SH, Kazmierczak KM, Badal RE, Hackel MA, Bouchillon SK, Biedenbach DJ, et al. Trends in susceptibility of Escherichia coli from intra-abdominal infections to ertapenem and comparators in the United States according to data from the SMART Program, 2009 to 2013. Antimicrob Agents Chemother. 2015;59:3606–10.
23. Stapleton AE, Wagenlehner FME, Mulgirigama A, Twynholm M. Escherichia coli resistance to fluoroquinolones in community-acquired uncomplicated urinary tract infection in women: a systematic review. Antimicrob Agents Chemother. 2020;64:e00862-e920.
24. Nicolas-Chanoine M-H, Bertrand X, Madec J-Y. Escherichia coli ST131, an intriguing clonal group. Clin Microbiol Rev. 2014;27(3):543–74.
25. Banerjee R, Johnson JR. A new clone sweeps clean: the enigmatic emergence of Escherichia coli sequence type 131. Antimicrob Agents Chemother. 2014;58:4997–5004.
26. Johnston BD, Thuras PD, Johnson JR. Activity of ceftazidime-avibactam against Escherichia coli isolates from US veterans (2011) in relation to co-resistance and sequence type 131 (ST131) H30 and H30Rx status. Diagn Microbiol Infect Dis. 2020;97:115034.
27. Ko W-C, Stone GG. In vitro activity of ceftazidime–avibactam and comparators against Gram-negative bacterial isolates collected in the Asia-Pacific region as part of the INFORM program (2015–2017). Ann Clin Microbiol Antimicrob. 2020;19:14.

Publisher’s Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.