Antimicrobial activity of ceftazidime-avibactam and comparators against *Pseudomonas aeruginosa* and *Enterobacterales* collected in Croatia, Czech Republic, Hungary, Poland, Latvia and Lithuania: ATLAS Surveillance Program, 2019

V Adámková¹ · I Mareković² · J Szabó³ · L Pojnar⁴ · S Billová⁵ · S Horvat Herceg⁶ · A Kuraieva⁷ · B Moţejko-Pastewka⁸

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Abstract
Antimicrobial susceptibility of clinical isolates collected from sites in central Europe in 2019 was tested by CLSI broth microdilution method and EUCAST breakpoints. Most active were amikacin, ceftazidime-avibactam and colistin; respectively, susceptibility rates among *P. aeruginosa* (*n* = 701) were 89.2%, 92.2% and 99.9%; difficult-to-treat (DTR) isolates, 62.5%, 37.5% and 100%; multidrug-resistant (MDR) isolates, 68.3%, 72.9% and 99.5%; meropenem-resistant (MEM-R), metallo-β-lactamase-negative (MBL-negative) isolates, 72.8%, 78.6% and 100%. Among *Enterobacterales* (*n* = 1639), susceptibility to ceftazidime-avibactam, colistin and tigecycline was ≥ 97.9%; MDR *Enterobacterales*, 96.8%, 94.4% and 100%, respectively; DTR isolates, ≥ 76.2% to ceftazidime-avibactam and colistin; MEM-R, MBL-negative isolates, ≥ 90.0% to ceftazidime-avibactam and colistin.

Keywords Ceftazidime-avibactam · *Pseudomonas aeruginosa* · *Enterobacterales* · Antimicrobial surveillance · ATLAS · Difficult-to-treat

Introduction

*Pseudomonas aeruginosa* and members of the *Enterobacterales* are important pathogens that cause a range of infections. Their treatment can be problematic due to acquired and/or intrinsic antimicrobial resistance [1, 2]. Ceftazidime (a third-generation cephalosporin) in combination with avibactam (a diazabicyclooctane, non-β-lactam, β-lactamase inhibitor) has activity against Gram-negative organisms with Ambler class A, class C and some class D (e.g. OXA-48 type) β-lactamases, although the combination is not active against class B metallo-β-lactamases (MBLs) [3–5].

ATLAS (Antimicrobial Testing Leadership And Surveillance) is a freely accessible antimicrobial surveillance program with a searchable online database ([www.atlas-surveillance.com](http://www.atlas-surveillance.com)) designed to chart the in vitro activity of antimicrobial agents against Gram-positive and Gram-negative organisms collected globally. In this analysis, we evaluate the in vitro activity of ceftazidime-avibactam and comparator agents against *Pseudomonas aeruginosa* and *Enterobacterales* isolates collected in 2019 from patients in Croatia, Czech Republic, Hungary, Poland, Latvia and Lithuania.
Materials and methods

Isolates of *P. aeruginosa* and *Enterobacterales* (*N* = 2340) were submitted by study centres in Croatia (*n* = 4), Czech Republic (*n* = 4), Hungary (*n* = 3), Poland (*n* = 4), Latvia (*n* = 1) and Lithuania (*n* = 2) in 2019 from patients of all ages. Acceptable sources were intra-abdominal, urinary tract, skin and skin structure, lower respiratory tract and bloodstream; only non-duplicate isolates of causative pathogens were accepted. Demographic information (specimen source, patient age and sex, and type of hospital setting) was recorded for each isolate.

Bacterial identification was confirmed at the central laboratory, International Health Management Associates, Inc. (IHMA; Schaumburg, IL, USA), using matrix-assisted laser desorption ionization-time of flight spectrometry (MALDI-TOF; Bruker Daltonics, Billerica, MA, USA). Susceptibility testing was according to the Clinical Laboratory Standards Institute (CLSI) broth microdilution methodology [6]. Cef-tazidime-avibactam was tested with fixed concentration of avibactam at 4 mg/L. All minimum inhibitory concentration (MIC) values were interpreted using EUCAST breakpoints [7].

Difficult-to-treat (DTR) isolates were resistant to aztreonam, cefepime, ceftazidime, imipenem, meropenem, ciprofloxacin, levofloxacin and piperacillin-tazobactam. Multidrug-resistant (MDR) isolates were resistant to ≥1 agent from ≥3 classes: cephalosporins (cefazidime, cefepime), monobactams (aztreonam), β-lactam/β-lactamase-inhibitor combinations (piperacillin-tazobactam), carbapenems (meropenem, imipenem), fluoroquinolones (levofloxacin, ciprofloxacin), aminoglycosides (amikacin) and polymyxins (colistin). Meropenem-resistant (MEM-R) isolates were isolates with an MIC to meropenem of ≥16 mg/L. Carbapenemase and metallo-β-lactamase (MBL) genes were determined using polymerase chain reaction (PCR) assays [8, 9]. Detected genes were amplified using flanking primers and sequenced, and sequences were compared against publicly available databases. Carbapenemase-positive isolates were identified as those with genes encoding a KPC, OXA-48-like, IMP, VIM, NDM, GES, GIM and/or SPM enzyme, and MBL-positive isolates were identified as those with genes encoding an NDM, IMP, VIM, GIM and/or SPM enzyme. MBL-negative isolates were defined as those that underwent testing but did not possess NDM, IMP, VIM, GIM and SPM genes.

**Results**

The majority of *P. aeruginosa* (*n* = 701) and *Enterobacterales* isolates (*n* = 1639) were collected from male patients, patients ≥18 years of age and non-ICU wards (Table 1). The highest proportion of *P. aeruginosa* isolates were from respiratory sources. Similar percentages of *Enterobacterales* isolates were from blood, respiratory or skin/musculoskeletal sources (Table 1).

**Pseudomonas aeruginosa**

The agents against which *P. aeruginosa* had the highest rates of susceptibility (using standard dosing susceptibility breakpoints) were amikacin (89.2%), ceftazidime-avibactam (92.2%) and colistin (99.9%) (Table 2). For ceftazidime alone, 74.3% of isolates were susceptible (increased exposure). A total of 5.7% (40/701) of isolates were classified as DTR and 28.4% (199/701) were MDR. Among these isolates, susceptibility to colistin was unchanged (100% and 99.5%, respectively) relative to the whole *P. aeruginosa* set. Susceptibility rates to amikacin and ceftazidime-avibactam were 62.5% and 37.5%, respectively, against DTR isolates and 68.3% and 72.9%, respectively, against MDR isolates (Table 2). Results against MEM-R isolates were similar to those seen against MDR isolates for the majority of agents (Table 2). Against all three resistant subsets, rates of susceptibility (increased exposure) to ceftazidime (DTR, 0.0%; MDR, 16.1%; MEM-R, 24.0%) were lower

| Table 1 Demographic data for *Pseudomonas aeruginosa* and *Enterobacterales* isolates, collected from Croatia, Czech Republic, Hungary, Poland, Latvia and Lithuania, 2019 |
|---|---|---|---|---|
| **Pseudomonas aeruginosa** | **Enterobacterales** |
| *N* = 701 | *N* = 1639 |
| **Age groups (years)*** | | | |
| 0 to 17 | 85 | 12.1 | 151 | 9.2 |
| 18 to 64 | 261 | 37.2 | 525 | 32.0 |
| ≥ 65 | 353 | 50.4 | 958 | 58.5 |
| Unknown | 2 | 0.3 | 5 | 0.3 |
| **Sex** | | | |
| Female | 246 | 35.1 | 678 | 41.4 |
| Male | 453 | 64.6 | 955 | 58.3 |
| Unknown | 2 | 0.3 | 6 | 0.4 |
| **Patient location** | | | |
| ICU | 271 | 38.7 | 511 | 31.2 |
| General wards, Emergency | 395 | 56.3 | 1043 | 63.6 |
| Unknown/Other | 35 | 5.0 | 85 | 5.2 |
| **Isolates sources** | | | |
| Circulatory (blood) | 114 | 16.3 | 403 | 24.6 |
| Genitourinary | 82 | 11.7 | 253 | 15.4 |
| Intestinal | 34 | 4.9 | 213 | 13.0 |
| Respiratory | 296 | 42.2 | 415 | 25.3 |
| Skin/musculoskeletal | 174 | 24.8 | 355 | 21.7 |
| Unknown | 1 | 0.1 | 0 | 0.0 |
Table 2  Antimicrobial activity of ceftazidime-avibactam and comparators against *Pseudomonas aeruginosa* isolates collected from Croatia, Czech Republic, Hungary, Poland, Latvia and Lithuania in 2019

| Antimicrobial                  | MIC<sub>90</sub> (mg/L) | Range (mg/L) | Susceptible, standard dosing | Susceptible, increased exposure | Resistant |
|--------------------------------|-------------------------|--------------|------------------------------|--------------------------------|-----------|
| **P. aeruginosa (n = 701)**    |                         | n            | %                            | n                | %         |
| Amikacin                       | 32                      | 0.5 – ≥ 128  | 625                          | 89.2              | 76        | 10.8     |
| Aztreonam                      | 32                      | 0.25 – ≥ 256 | –                            | 586               | 83.6      | 115      | 16.4     |
| Cefepime                       | 32                      | 0.5 – ≥ 64   | –                            | 539               | 76.9      | 162      | 23.1     |
| Ceftazidime                    | 64                      | 0.25 – ≥ 256 | –                            | 521               | 74.3      | 180      | 25.7     |
| Ceftazidime-avibactam          | 8                       | 0.12 – ≥ 256 | 646                          | 92.2              | –         | 55       | 7.8      |
| Ciprofloxacin                  | ≥ 8                     | 0.12 – ≥ 8   | –                            | 477               | 68.0      | 224      | 32.0     |
| Colistin                       | 2                       | 0.25 – ≥ 16  | 700                          | 99.9              | –         | 1        | 0.1      |
| Gentamicin                     | ≥ 32                    | 0.12 – ≥ 32  | –                            | –                 | –         | –        | –        |
| Imipenem                       | ≥ 16                    | 0.06 – ≥ 16  | –                            | 473               | 67.5      | 228      | 32.5     |
| Levofloxacin                   | ≥ 16                    | 0.25 – ≥ 16  | –                            | 437               | 62.3      | 264      | 37.7     |
| Meropenem                      | 16                      | 0.06 – ≥ 32  | 471                          | 67.2              | 10.5      | 125      | 17.8     |
| Piperacillin-tazobactam        | ≥ 128                   | 0.12 – ≥ 128 | –                            | 501               | 71.5      | 200      | 28.5     |
| Tigecycline                    | ≥ 16                    | 1 – ≥ 16     | –                            | –                 | –         | –        | –        |
| **DTR P. aeruginosa (n = 40)** |                         |              |                              |                   |           |          |          |
| Amikacin                       | 64                      | 2 – ≥ 128    | 25                           | 62.5              | –         | 15       | 37.5     |
| Aztreonam                      | 64                      | 32 – ≥ 256   | –                            | 0                 | 0.0       | 40       | 100      |
| Cefepime                       | ≥ 64                    | 16 – ≥ 64    | –                            | 0                 | 0.0       | 40       | 100      |
| Ceftazidime                    | ≥ 256                   | 16 – ≥ 256   | –                            | 0                 | 0.0       | 40       | 100      |
| Ceftazidime-avibactam          | ≥ 256                   | 4 – ≥ 256    | 15                           | 37.5              | –         | 25       | 62.5     |
| Ciprofloxacin                  | ≥ 8                     | 1 – ≥ 8      | –                            | 0                 | 0.0       | 40       | 100      |
| Colistin                       | 2                       | 0.5 – 2      | 40                           | 100               | –         | 0        | 0.0      |
| Gentamicin                     | ≥ 32                    | 0.25 – ≥ 32  | –                            | –                 | –         | –        | –        |
| Imipenem                       | ≥ 16                    | 8 – ≥ 16     | –                            | 0                 | 0.0       | 40       | 100      |
| Levofloxacin                   | ≥ 16                    | 4 – ≥ 16     | –                            | 0                 | 0.0       | 40       | 100      |
| Meropenem                      | ≥ 32                    | 16 – ≥ 32    | 0                            | 0                 | 0.0       | 40       | 100      |
| Piperacillin-tazobactam        | ≥ 128                   | 32 – ≥ 128   | –                            | 0                 | 0.0       | 40       | 100      |
| Tigecycline                    | ≥ 16                    | 1 – ≥ 16     | –                            | –                 | –         | –        | –        |
| **MDR P. aeruginosa (n = 199)**|                         |              |                              |                   |           |          |          |
| Amikacin                       | ≥ 128                   | 0.5 – ≥ 128  | 136                          | 68.3              | –         | 63       | 31.7     |
| Aztreonam                      | 64                      | 4 – ≥ 256    | –                            | 88                | 44.2      | 111      | 55.8     |
| Cefepime                       | ≥ 64                    | 2 – ≥ 64     | –                            | 45                | 22.6      | 154      | 77.4     |
| Ceftazidime                    | ≥ 256                   | 2 – ≥ 256    | –                            | 32                | 16.1      | 167      | 83.9     |
| Ceftazidime-avibactam          | 64                      | 1 – ≥ 256    | 145                          | 72.9              | –         | 54       | 27.1     |
| Ciprofloxacin                  | ≥ 8                     | 0.12 – ≥ 8   | –                            | 51                | 25.6      | 148      | 74.4     |
| Colistin                       | 2                       | 0.25 – ≥ 16  | 198                          | 99.5              | –         | 1        | 0.5      |
| Gentamicin                     | ≥ 32                    | 0.12 – ≥ 32  | –                            | –                 | –         | –        | –        |
| Imipenem                       | ≥ 16                    | 0.5 – ≥ 16   | –                            | 54                | 27.1      | 145      | 72.9     |
| Levofloxacin                   | ≥ 16                    | 0.25 – ≥ 16  | –                            | 38                | 19.1      | 161      | 80.9     |
| Meropenem                      | ≥ 32                    | 0.06 – ≥ 32  | 40                           | 20.1              | 46        | 23.1     | 113      | 56.8     |
| Piperacillin-tazobactam        | ≥ 128                   | 8 – ≥ 128    | –                            | 20                | 10.1      | 179      | 89.9     |
| Tigecycline                    | ≥ 16                    | 1 – ≥ 16     | –                            | –                 | –         | –        | –        |
| **MEM-R P. aeruginosa (n = 125)**|                      |               |                              |                   |           |          |          |
| Amikacin                       | ≥ 128                   | 1 – ≥ 128    | 82                           | 65.6              | –         | 43       | 34.4     |
| Aztreonam                      | 64                      | 4 – ≥ 256    | –                            | 68                | 54.4      | 57       | 45.6     |
| Cefepime                       | ≥ 64                    | 2 – ≥ 64     | –                            | 39                | 31.2      | 86       | 68.8     |
| Ceftazidime                    | ≥ 256                   | 2 – ≥ 256    | –                            | 30                | 24.0      | 95.0     | 76.0     |
| Ceftazidime-avibactam          | 64                      | 2 – ≥ 256    | 82                           | 65.6              | –         | 43       | 34.4     |
than susceptibility rates (standard dosing) reported for ceftazidime-avibactam.

Among the MEM-R *P. aeruginosa*, 82.4% (103/125) were identified as MBL-negative. All MBL-negative isolates were susceptible to colistin (Table 2), 78.6% to ceftazidime-avibactam and 72.8% to amikacin. A total of 29.1% of MBL-negative isolates were susceptible (increased exposure) to ceftazidime alone.

Among the 125 MEM-R isolates, 22 (17.6%) were MBL-positive and 29 (23.2%) were carbapenemase-positive. Colistin was the only agent active against the MBL-positive isolates (100% susceptible, data not shown).

**Enterobacterales**

Susceptibility to amikacin, ceftazidime-avibactam, colistin and meropenem against *Enterobacterales* was ≥ 96.1%, and to ceftazidime alone, 69.5% (Table 3). Susceptibility to tigecycline was 99.8% (*E. coli* and *C. koseri* only).

Of the *Enterobacterales*, 1.3% (21/1639) were DTR and 25.0% (410/1639) were MDR. Among MDR isolates, susceptibility rates were highest to ceftazidime-avibactam (96.8%), colistin (94.4%) and tigecycline (100%, *E. coli* and *C. koseri* only), and among DTR isolates, ≥ 57.1% were susceptible to amikacin, ceftazidime-avibactam and colistin (Table 3). Few isolates were susceptible to ceftazidime alone (MDR, 1.2%; DTR, 0.0%).

Of the 30/1639 isolates that were MEM-R, 66.7% were susceptible to amikacin, 70% to ceftazidime-avibactam and 93.3% to colistin; however, only 3.3% were susceptible to ceftazidime alone. Of the 20 MEM-R, MBL-negative isolates, 95.0% were susceptible to ceftazidime-avibactam, 90.0% were susceptible to colistin and only one isolate was susceptible to ceftazidime alone. Ten MEM-R isolates were MBL-positive, of which 9 were amikacin-susceptible and all 10 were colistin-susceptible (data not shown). Among the 26/30 carbapenemase-positive isolates, 65.4% were susceptible to amikacin, 69.2% to ceftazidime-avibactam and 92.3% to colistin.

### Table 2 (continued)

| Antimicrobial | MIC<sub>90</sub> (mg/L) | Range (mg/L) | Susceptible, standard dosing | Susceptible, increased exposure | Resistant |
|---------------|-------------------------|--------------|------------------------------|--------------------------------|-----------|
| Ciprofloxacin | ≥8                      | ≤0.12 – ≥8   | –                            | 18.4                           | 102       | 81.6     |
| Colistin      | 2                       | 0.25 – 2     | 125 100                      | –                              | 0         | 0.0      |
| Gentamicin    | ≥32                     | 0.25 – ≥32   | –                            | –                              | –         | –        |
| Imipenem      | ≥16                     | 1 – ≥16      | –                            | 2                              | 132       | 98.4     |
| Levofloxacin  | ≥16                     | 0.5 – ≥16    | –                            | 11                             | 8.8       | 91.2     |
| Piperacillin-tazobactam | ≥128 | 4 – ≥128 | –                            | 23                             | 18.4 102 | 81.6 |
| Tigecycline   | ≥16                     | 1 – ≥16      | –                            | –                              | –         | –        |

**MEM-R, MBL-negative *P. aeruginosa* (n = 103)**

| Antimicrobial | MIC<sub>90</sub> (mg/L) | Range (mg/L) | Susceptible, standard dosing | Susceptible, increased exposure | Resistant |
|---------------|-------------------------|--------------|------------------------------|--------------------------------|-----------|
| Amikacin      | 64                      | 1 – ≥128     | 75                            | 28                             | 27.2      |
| Aztreonam     | 64                      | 4 – ≥256     | –                            | 55                             | 48        | 46.6     |
| Cefepime      | 32                      | 2 – ≥64      | –                            | 37                             | 35.9 66   | 64.1     |
| Ceftazidime   | 128                     | 2 – ≥256     | –                            | 30                             | 29.1 73   | 70.9     |
| Ceftazidime-avibactam | 16 | 2 – ≥256 81 | 78.6                           | –                              | 22        | 21.4     |
| Ciprofloxacin | ≥8                      | ≤0.12 – ≥8   | –                            | 18                             | 17.5 85   | 82.5     |
| Colistin      | 2                       | 0.25 – 2     | 103 100                      | –                              | 0         | 0.0      |
| Gentamicin    | ≥32                     | 0.25 – ≥32   | –                            | –                              | –         | –        |
| Imipenem      | ≥16                     | 1 – ≥16      | –                            | 2                              | 1.9 101   | 98.1     |
| Levofloxacin  | ≥16                     | 0.5 – ≥16    | –                            | 8                              | 7.8 95    | 92.2     |
| Piperacillin-tazobactam | ≥128 | 4 – ≥128     | –                            | 22                             | 21.4 81   | 78.6     |
| Tigecycline   | ≥16                     | 1 – ≥16      | –                            | –                              | –         | –        |

MIC, minimum inhibitory concentration; DTR, difficult to treat; MDR, multidrug resistant; MEM-R, meropenem resistant; MBL, metallo-β-lactamase.
| Antimicrobial | MIC<sub>90</sub> (mg/L) | MIC range (mg/L) | Susceptible, standard dosing | Susceptible, increased exposure | Resistant |
|---------------|----------------------|-------------------|-----------------------------|--------------------------------|-----------|
| **Enterobacterales (n = 1639)** | | | n | % | n | % | n | % |
| Amikacin | 8 | $\leq 0.25 \leq 128$ | 1575 | 96.1 | – | – | 64 | 3.9 |
| Amoxicillin-clavulanate | $\geq 32$ | $\leq 0.12 \leq 32$ | 923 | 56.3 | – | – | 716 | 43.7 |
| Aztreonam | 64 | $\leq 0.015 \leq 256$ | 1157 | 70.6 | 39 | 2.4 | 443 | 27.0 |
| Cefepime | $\geq 64$ | $\leq 0.12 \leq 64$ | 1198 | 73.1 | 70 | 4.3 | 371 | 22.6 |
| Ceftazidime | 64 | $\leq 0.015 \leq 256$ | 1139 | 69.5 | 52 | 3.2 | 448 | 27.3 |
| Ceftazidime-avibactam | 0.5 | $\leq 0.015 \leq 256$ | 1626 | 99.2 | – | – | 13 | 0.8 |
| Ciprofloxacin | $\geq 8$ | $\leq 0.12 \leq 8$ | 1092 | 66.6 | 45 | 2.7 | 502 | 30.6 |
| Colistin<sup>a</sup> | 1 | $\leq 0.06 \leq 16$ | 1304 | 97.9 | – | – | 28 | 2.1 |
| Gentamicin | $\geq 32$ | $\leq 0.12 \leq 32$ | 1314 | 80.2 | – | – | 325 | 19.8 |
| Imipenem | 2 | $\leq 0.06 \leq 16$ | 1362 | 83.1 | 231 | 14.1 | 46 | 2.8 |
| Levofloxacin | $\geq 16$ | $\leq 0.25 \leq 16$ | 1170 | 71.4 | 87 | 5.3 | 382 | 23.3 |
| Meropenem | 0.12 | $\leq 0.06 \leq 32$ | 1587 | 96.8 | 22 | 1.3 | 30 | 1.8 |
| Piperacillin-tazobactam | $\geq 128$ | $\leq 0.12 \leq 128$ | 1240 | 75.7 | – | – | 399 | 24.3 |
| Tigecycline<sup>b</sup> | 2 | 0.06 – 8 | 472 | 99.8 | 0 | 0.0 | 1 | 0.2 |
| **DTR Enterobacterales (n = 21)** | | | | | | | | |
| Amikacin | $\geq 128$ | 2 – $\geq 128$ | 12 | 57.1 | – | – | 9 | 42.9 |
| Amoxicillin-clavulanate | $\geq 32$ | $\geq 32$ | 0 | 0.0 | – | – | 21 | 100 |
| Aztreonam | $\geq 256$ | 16 – $\geq 256$ | 0 | 0.0 | 0 | 0.0 | 21 | 100 |
| Cefepime | $\geq 64$ | 32 – $\geq 64$ | 0 | 0.0 | 0 | 0.0 | 21 | 100 |
| Ceftazidime | $\geq 256$ | 32 – $\geq 256$ | 0 | 0.0 | 0 | 0.0 | 21 | 100 |
| Ceftazidime-avibactam | $\geq 256$ | 0.5 – $\geq 256$ | 16 | 76.2 | – | – | 5 | 23.8 |
| Ciprofloxacin | $\geq 8$ | 4 – $\geq 8$ | 0 | 0.0 | 0 | 0.0 | 21 | 100 |
| Colistin<sup>a</sup> | 2 | 0.25 – 16 | 20 | 95.2 | – | – | 1 | 4.8 |
| Gentamicin | $\geq 32$ | 0.5 – $\geq 32$ | 8 | 38.1 | – | – | 13 | 61.9 |
| Imipenem | $\geq 16$ | $\geq 16$ | 0 | 0.0 | 0 | 0.0 | 21 | 100 |
| Levofloxacin | $\geq 16$ | 2 – $\geq 16$ | 0 | 0.0 | 0 | 0.0 | 21 | 100 |
| Meropenem | $\geq 32$ | $\geq 32$ | 0 | 0.0 | 0 | 0.0 | 21 | 100 |
| Piperacillin-tazobactam | $\geq 128$ | $\geq 128$ | 0 | 0.0 | – | – | 21 | 100 |
| Tigecycline<sup>b</sup> | 2 | 0.25 – 4 | – | – | – | – | – | – |
| **MDR Enterobacterales (n = 410)** | | | n | % | n | % | n | % |
| Amikacin | 16 | 0.5 – $\geq 128$ | 366 | 89.3 | – | – | 44 | 10.7 |
| Amoxicillin-clavulanate | $\geq 32$ | 2 – $\geq 32$ | 108 | 26.3 | – | – | 302 | 73.7 |
| Aztreonam | $\geq 256$ | $0.03 \leq 256$ | 5 | 1.2 | 6 | 1.5 | 399 | 97.3 |
| Cefepime | $\geq 64$ | $\leq 0.12 \leq 64$ | 35 | 8.5 | 39 | 9.5 | 336 | 82.0 |
| Ceftazidime | $\geq 256$ | 0.25 – $\geq 256$ | 5 | 1.2 | 12 | 2.9 | 393 | 95.9 |
| Ceftazidime-avibactam | 2 | 0.06 – $\geq 256$ | 397 | 96.8 | – | – | 13 | 3.2 |
| Ciprofloxacin | $\geq 8$ | $\leq 0.12 \leq 8$ | 69 | 16.8 | 9 | 2.2 | 332 | 81.0 |
| Colistin<sup>a</sup> | 1 | 0.12 – $\geq 16$ | 371 | 94.4 | – | – | 22 | 5.6 |
| Gentamicin | $\geq 32$ | $\leq 0.12 \leq 32$ | 180 | 43.9 | – | – | 230 | 56.1 |
| Imipenem | 4 | 0.12 – $\geq 16$ | 347 | 84.6 | 26 | 6.3 | 37 | 9.0 |
| Levofloxacin | $\geq 16$ | $\leq 0.25 \leq 16$ | 120 | 29.3 | 45 | 11.0 | 245 | 59.8 |
| Meropenem | 4 | $\leq 0.06 \leq 32$ | 358 | 87.3 | 22 | 5.4 | 30 | 7.3 |
| Piperacillin-tazobactam | $\geq 128$ | 0.5 – $\geq 128$ | 81 | 19.8 | – | – | 329 | 80.2 |
| Tigecycline<sup>b</sup> | 2 | 0.06 – 8 | 53 | 100 | 0 | 0.0 | 0 | 0.0 |
| **MEM-R Enterobacterales (n = 30)** | | | | | | | | |
| Amikacin | $\geq 128$ | 0.5 – $\geq 128$ | 20 | 66.7 | – | – | 10 | 33.3 |
| Amoxicillin-clavulanate | $\geq 32$ | 16 – $\geq 32$ | 0 | 0.0 | – | – | 30 | 100 |
Discussion

Susceptibility among *P. aeruginosa* was highest to amikacin, ceftazidime-avibactam and colistin and among the *Enterobacterales*, to ceftazidime-avibactam, colistin and tigecycline (*E. coli* and *C. koseri* only), followed by meropenem and amikacin. Similar results have been reported for isolates collected in 2012–2015 across Europe [10, 11], although for colistin and tigecycline, susceptibility rates among *Enterobacterales* were lower than in our study [11]. This is likely due to inclusion of a broader range of species of *Enterobacterales* by Kazmierczak et al. [11]. Similar ATLAS data were also reported for Central Europe/Israel (2014–2018) [12], indicating that susceptibility rates to ceftazidime-avibactam, colistin and amikacin remain stable in the region. As previously reported [10, 11], susceptibility rates to ceftazidime alone were low compared with ceftazidime and avibactam combined, particularly among resistant subsets.
Among *P. aeruginosa* and *Enterobacterales* 5.7% and 1.3% were DTR, respectively. DTR is a valuable category, comprising isolates that are not susceptible to first-line, high-efficacy, low-toxicity agents [13]. The majority of DTR isolates in our study were susceptible to colistin (*P. aeruginosa*, 100%; *Enterobacterales*, 95.2%) and most DTR *Enterobacterales* were susceptible to ceftazidime-avibactam (76.2%); however, the rate was reduced against DTR were susceptible to ceftazidime-avibactam (76.2%); however, the rate was reduced against DTR *P. aeruginosa* (37.5% susceptible). Amikacin susceptibility rates against DTR isolates were 62.5% (*P. aeruginosa*) and 57.1% (*Enterobacterales*).

Most (82.4%) MEM-R *P. aeruginosa* were MBL-negative and, as with the other subsets in this analysis, their susceptibility was highest to ceftazidime-avibactam, amikacin and colistin. The susceptibility breakpoint for ceftazidime alone only applies at increased exposure, and susceptibility was low compared with ceftazidime-avibactam (29.1% vs. 78.6%), demonstrating the value of combining avibactam with ceftazidime. The other MEM-R isolates (17.6%) were MBL-positive, against which only colistin was active. A lower rate of *Enterobacterales* than *P. aeruginosa* were meropenem-resistant (1.8% vs. 17.8%), similar to the rates reported by Kristof et al. [12]. Two thirds of MEM-R *Enterobacterales* were MBL-negative and, as reported previously [3], most were susceptible to ceftazidime-avibactam and colistin. As with *P. aeruginosa*, few *Enterobacterales* isolates were susceptible to ceftazidime alone, in line with previous reports [3], again demonstrating the value of the combination.

Overall, 55 (7.8%) *P. aeruginosa* isolates were resistant to ceftazidime-avibactam, similar to that reported for European isolates collected in 2012–2015 [10]. Of these, 23/55 were identified as carbapenemase producers (22 MBL-positive [7 IMP, 15 VIM] and 1 carbapenemase-positive [GES] but MBL-negative). No other GES-positive isolates were identified and for the remaining 32 isolates, no carbapenemase or MBL genes were detected. In contrast, 13 (0.8%) *Enterobacterales* isolates were identified as resistant to ceftazidime-avibactam and 12/13 isolates were MBL-positive (4 VIM, 8 NDM-1; *Citrobacter freundii* [n = 1], *Enterobacter cloacae* [n = 8] and *K. pneumoniae* [n = 3]). For the remaining isolate (*E. coli*), no carbapenemase or MBL genes were detected. Ceftazidime-avibactam is known to be inactive against MBL-producing isolates [3].

There are limitations to this analysis; the study collected a predetermined number of isolates from each centre and so cannot be considered epidemiological. With only 1 year of data, some isolate numbers are low, particularly in the resistance subsets, meaning that some of the data should be treated with some caution.

In conclusion, rates of susceptibility to ceftazidime-avibactam were high among isolates of *P. aeruginosa* and *Enterobacterales* collected from Croatia, Czech Republic, Hungary, Poland, Latvia and Lithuania in 2019 and were similar to activity reported in previous years for isolates collected in Europe. Amikacin and colistin also continue to be active against these Gram-negative isolates, as does tigecycline against isolates of *E. coli* and *C. koseri*. Meropenem susceptibility rates were high among *Enterobacterales* isolates but reduced against *P. aeruginosa*. Ceftazidime-avibactam continues to be a good choice for the treatment of MDR Gram-negative infections, it has a safety profile consistent with that previously observed for ceftazidime alone [14–17] and does not require therapeutic drug monitoring.

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**Data availability** 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](https://atlas-surveillance.com).

**Declarations**

**Conflict of interest** IM and JS have no competing interests. VA has received support for conference registration from Pfizer spol. s r.o. LP has received honoraria for poster presentation from Pfizer Polska Sp. z o.o. SB, SHH, AK and BM-P are employees of Pfizer.

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**References**

1. Pang Z, Raudonis R, Glick BR, Lin T-J, Zhenyu Cheng Z (2019) Antibiotic resistance in *Pseudomonas aeruginosa*: mechanisms and alternative therapeutic strategies. Biotechnol Adv 37:177–192. [https://doi.org/10.1016/j.biotechadv.2018.11.013](https://doi.org/10.1016/j.biotechadv.2018.11.013)
2. De Oliveira DMP, Forde BM, Kidd TJ, Harris PNA, Schem-bri MA, Beaton SA, Paterson DL, Walker MJ (2020) Anti-microbial resistance in ESKAPE pathogens. Clin Microbiol Rev 33:e00181-e219. https://doi.org/10.1128/CMR.00181-19

3. de Jonge BLM, Karlowsky JA, Kazmierczak KM, Biedenbach DJ, Sahm DF, Nichols WW (2016) In vitro susceptibility to ceftazidime-avibactam of carbapenem-nonsusceptible Enterobacte-riaceae isolates collected during the INFORM global surveillance study. Antimicrob Agents Chemother 60:3163–3169. https://doi.org/10.1128/AAC.03042-15

4. Levasseur F, Girard AM, Miossec C, Pace J, Coleman K (2015) In vitro antibacterial activity of the ceftazidime-avibactam combination against Enterobacteriaceae, including strains with well-characterized β-lactamases. Antimicrob Agents Chemother 59:1931–1934. https://doi.org/10.1128/AAC.04218-14

5. Papp-Wallace KM, Bajaksouzian S, Abdelhamied AM, Foster AN, Winkler ML, Gatta JA, Nichols WW, Testa R, Bonom RA, Jacobs MR (2015) Activities of ceftazidime, ceftaroline, and aztreonam alone and combined with avibactam against isogenic Escherichia coli strains expressing selected single β-lactamases. Diagn Microbiol Infect Dis 82:65–69. https://doi.org/10.1016/j.diagmicrobio.2015.02.003

6. Clinical and Laboratory Standards Institute (2018) Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; approved standards. 11th ed. CLSI document M07. Wayne, PA: Clinical and Laboratory Standards Institute

7. The European Committee on Antimicrobial Susceptibility Testing (2021) breakpoint tables for interpretation of MICs and zone diameters. Version 11.0. http://www.eucast.org. Accessed 3 Aug 2021

8. Lob SH, Kazmierczak KM, Badal RE, Hackel MA, Bouchillon SK, Biedenbach DJ, Sahm DF (2015) 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, 2009–2013. Antimicrob Agents Chemother 59:3606–3610. https://doi.org/10.1128/AAC.05186-14

9. Nichols WW, de Jonge BLM, Kazmierczak KM, Karlowsky JA, Sahm DF (2016) In vitro susceptibility of global surveillance isolates of Pseudomonas aeruginosa to ceftazidime-avibactam (INFORM 2012 to 2014). Antimicrob Agents Chemother 60:4743–4749. https://doi.org/10.1128/AAC.00220-16

10. Kazmierczak KM, de Jonge BLM, Stone GG, Sahm DF (2018) In vitro activity of ceftazidime/avibactam against isolates of Pseu-domonas aeruginosa isolated in European countries: INFORM global surveillance 2012–15. J Antimicrob Chemother 73:2777–2781. https://doi.org/10.1093/jac/dky267

11. Kazmierczak KM, de Jonge BLM, Stone GG, Sahm DF (2018) In vitro activity of ceftazidime/avibactam against isolates of Enterobacteriaceae collected in European countries: INFORM global surveillance 2012–15. J Antimicrob Chemother 73:2782–2788. https://doi.org/10.1093/jac/dky266

12. Kristof K, Adamkova V, Adler A, Gospodarek-Komkowska E, Rafila A, Billova S, Mozejko-Pastewka B, Kiss F (2021) In vitro activity of ceftazidime-avibactam and comparators against Enterobacteria and Pseudomonas aeruginosa isolates from Central Europe and Israel, 2014–2017 and 2018. Diagn Microbiol Infect Dis 101:115420. https://doi.org/10.1016/j.diagmicrobio.2021.115420

13. Kadri SS, Adjemian J, Lai YL, Spaulding AB, Ricotta E, Prevots DR, Palmore TN, Rhee C, Klompas M, Dekker JP, Powers 3rd JH, Suffredini AF, Hooper DC, Fridkin S, Danner RL, National Institutes of Health Antimicrobial Resistance Outcomes Research Initiative (NIH–ARORI) (2018) Difficult-to-treat resistance in Gram-negative bacteremia at 173 US hospitals: retrospective cohort analysis of prevalence, predictors, and outcome of resistance to all first-line agents. Clin Infect Dis 67:1803–1814. https://doi.org/10.1093/cid/ciy378

14. Carmeli Y, Armstrong J, Lau PJ, Newell P, Stone G, Wardman A, Gasink LB (2016) Ceftazidime-avibactam or best available therapy in patients with ceftazidime-resistant Enterobacteriaceae and Pseudomonas aeruginosa complicated urinary tract infec-tions or complicated intra-abdominal infections (REPRISE): a randomised, pathogen-directed, phase 3 study. Lancet Infect Dis 16:661–673. https://doi.org/10.1016/S1473-3099(16)30004-4

15. Mazuski JE, Gasink LB, Armstrong J, Broadhurst H, Stone GG, Rank D, Llorens L, Newell P, Pachl J (2016) Efficacy and safety of ceftazidime-avibactam plus metronidazole versus meropenem in the treatment of complicated intra-abdominal infection: results from a randomized, controlled, double-blind, phase 3 program. Clin Infect Dis 62:1380–1389. https://doi.org/10.1093/cid/ciw133

16. Torres A, Zhong N, Pachl J, Timsit J-F, Kollef M, Chen Z, Song J, Taylor D, Lau PJ, Stone GG, Chow JW (2018) Ceftazidime-avibactam versus meropenem in nosocomial pneumonia, including ventilator-associated pneumonia (REPROVE): a randomised, double-blind, phase 3 non-inferiority trial. Lancet Infect Dis 18:285–295. https://doi.org/10.1016/S1473-3099(17)30747-8

17. Wagenlehner FM, Sobel JD, Newell P, Armstrong J, Huang X, Stone GG, Yates K, Gasink LB (2016) Ceftazidime-avibactam versus doripenem for the treatment of complicated urinary tract infections, including acute pyelonephritis: RECAPTURE, a phase 3 randomized trial program. Clin Infect Dis 63:754–762. https://doi.org/10.1093/cid/ciw378

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