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In vitro activity of aztreonam-avibactam (ATM-AVI) against a global collection of *Klebsiella pneumoniae*, collected from defined culture sources, in 2016 and 2017

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Running head [limit 54 characters and spaces]: Activity of aztreonam-avibactam against *K. pneumoniae*

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Highlights

- Treatment options are limited against carbapenem-resistant *K. pneumoniae*
- Aztreonam is a monobactam and avibactam is a non-β-lactam β-lactamase inhibitor
- Aztreonam-avibactam is active against *K. pneumoniae* from a range of culture sources
- Aztreonam-avibactam MIC_{90} against meropenem-resistant *K. pneumoniae* is 0.5 mg/L
- Aztreonam-avibactam MICs against metallo-β-lactamase positive isolates ≤0.5 mg/L

Abstract (max 250 words, current count 250)

Objectives: This study reports on the activity of aztreonam-avibactam against a collection of *Klebsiella pneumoniae* collected in 2016 and 2017.

Methods: Non-duplicate isolates of *K. pneumoniae* were collected from four regions (Africa/Middle East, n=785; Asia-Pacific, n=1433; Europe, n=4236; Latin America, n=1499) and five culture sources (blood, n=902; intra-abdominal, n=992; urinary tract, n=2148; skin and skin structure, n=1409; lower respiratory tract, n=2502). Minimum inhibitory concentrations (MICs) were determined at the central laboratory using Clinical Laboratory Standards Institute broth microdilution methodology. Susceptibility was determined using European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints.

Results: For all culture sources, against all *K. pneumoniae*, the highest rates of susceptibility were seen for amikacin (>84%), ceftazidime-avibactam (>94%), colistin (>92%), and meropenem (>83%) and >99.9% of isolates were inhibited by an aztreonam-avibactam MIC of ≤4 mg/L. Among meropenem-resistant (MEM-R, n=583) and meropenem-resistant metallo-β-lactamase negative (MEM-R-MBLN, n=469) isolates susceptibility was highest to ceftazidime-avibactam (79.9%, 99.4%, respectively) and colistin (67.2%, 62.7%, respectively). All MEM-R-MBLN isolates from blood, intra-abdominal, urinary tract and skin and skin structure sources, and all but one isolate from respiratory sources, were inhibited by an aztreonam-avibactam MIC of ≤2 mg/L. Against the meropenem-resistant metallo-β-lactamase positive (MEM-R-MBLP, n=114) isolates susceptibility to colistin was between 75.0% (urinary tract isolates) and 93.3% (lower respiratory tract isolates). All MEM-R-MBLP isolates were inhibited by an aztreonam-avibactam MIC of ≤0.5mg/L.

Conclusions: Aztreonam-avibactam is active against *K. pneumoniae* isolates from a range of culture sources across Africa/Middle East, Asia-Pacific, Europe, and Latin America. Aztreonam-avibactam also has activity against MEM-R-MBLN and MEM-R-MBLP isolates.

Keywords: aztreonam-avibactam, antimicrobial, surveillance, meropenem, *Klebsiella*, metallo-β-lactamase.

1. Introduction

Infections caused by members of the Enterobacterales, such as *Klebsiella pneumoniae*, have become increasingly problematic to treat due to antimicrobial resistance. In particular, carbapenem resistance among the Enterobacterales has left physicians with few options in the treatment of infections caused by these drug-resistant organisms. Carbapenem-resistant Enterobacterales have been listed by the World Health Organization (WHO) as critical, priority one pathogens for which there is an urgent need for new antimicrobials [**1**]. Carbapenem resistance has spread globally and can be mediated through a number of different carbapenemases which can be classified as either serine β-lactamases (Ambler Class A and Class D) or metallo β-lactamases (Ambler Class B) [**2, 3**]. Infections involving organisms producing metallo-β-lactamases are difficult to treat because serine β-lactamase inhibitors (for example, clavulanic acid and tazobactam) are not effective against them. Metallo-β-lactamases hydrolyze the majority of β-lactams; one exception to this is the monobactam aztreonam [**3**].

Aztreonam-avibactam is a combination of aztreonam and the bridged diazabicyclooctane non-β-lactam β-lactamase inhibitor, avibactam. Although aztreonam maintains activity against bacteria that produce metallo-β-lactamases, it is vulnerable to hydrolysis by a range of other β-lactamases. Avibactam is able to protect aztreonam from β-lactamases including Class A (for example TEM, CTX-M and KPC carbapenemases), Class C (for example CMY and ACT) and some Class D enzymes (for example OXA-48-type) [**4**–**8**]. Aztreonam-avibactam is being developed for the treatment of serious infections for which there are limited or no treatment options. This study reports on in vitro activity data for aztreonam-avibactam and comparators against *K. pneumoniae* isolates collected in 2016 and 2017 from Africa/Middle East, Asia-Pacific, Europe, and Latin America. Data from the USA are not

included. Information on the culture source of each isolate was collected as part of the study and data are analyzed according to culture source.

2. Methods

Each center was required to submit a predefined number of *K. pneumoniae* isolates from patients (adult or pediatric) with a documented infection. Isolates were accepted regardless of antimicrobial susceptibility. Only one isolate was accepted per patient and isolates were only accepted into the study if they were considered to be the probable causative pathogen of the documented infection.

Isolate identification was confirmed at the central laboratory (International Health Management Associates [IHMA], Inc., Schaumburg, IL, USA) using matrix-assisted laser desorption ionization-time of flight spectrometry (Bruker Biotyper MALDI-TOF, Bruker Daltonics, Billerica, MA, USA). Minimum inhibitory concentration (MIC) determination was carried out at the central laboratory using the broth microdilution methodology of the Clinical Laboratory Standards Institute (CLSI) [**9**]. The antimicrobials tested included amikacin, aztreonam, aztreonam-avibactam, cefepime, ceftazidime, ceftazidime-avibactam, colistin, levofloxacin, meropenem, piperacillin-tazobactam and tigecycline. For ceftazidime-avibactam and aztreonam-avibactam, avibactam was tested at a fixed concentration of 4 mg/L as described by Bradford et al. for ceftazidime-avibactam [**11**]. Susceptibility was determined according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints (Version 10) [**10**]. Aztreonam-avibactam does not currently have approved breakpoints.

K. pneumoniae isolates with a meropenem, ceftazidime or aztreonam MIC of ≥2 mg/L were screened for the presence of β-lactamase genes as previously described [**12**]. Genes were amplified for sequencing using primers designed for flanking regions. Sequences were compared with publicly available databases. Isolates were included in the metallo-β-lactamase positive group if they possessed a NDM, IMP, VIM, GIM and/or SPM gene.

Isolates categorized as metallo-β-lactamase negative may have possessed other β-lactamases, but the IMP, VIM, NDM, GIM or SPM genes were not detected.

3. Results

3.1. Klebsiella pneumoniae

A total of 7,953 isolates of *K. pneumoniae* with information on culture source were collected from centers in Africa/Middle East, Asia-Pacific, Europe, and Latin America in 2016 and 2017. The culture source information was used to split the isolates into five categories: blood (11.3% [n=902]), intra-abdominal (12.5% [n=992] included intra-abdominal abscess, appendix, colon, diverticulum, gall bladder, liver, pancreas, peritoneal fluid, small intestine, stomach), urinary tract (27.0% [n=2,148] included kidneys, prostate, ureter, urethra, urinary bladder, urine), skin and skin structure (17.7% [n=1,409] included soft tissue abscess, burn, carbuncle, cellulitis or erysipelas, decubitus, furuncle, impetiginous lesions, skin ulcer, wound) and lower respiratory tract (31.5% [n=2,502] included lung biopsy, sputum, thoracentesis, bronchial brushing, endotracheal aspirate, bronchoalveolar lavage).

Antimicrobial activity, susceptibility and resistance data against isolates of *K. pneumoniae* according to region of collection and culture source are shown in **Table 1** and **Table 2**. Among isolates from blood, the highest rates of susceptibility were seen for amikacin (84.2%–97.7%), ceftazidime-avibactam (97.6%–99.2%), colistin (92.7%–100%), and meropenem (83.0%–97.7%) (**Table 1**). For aztreonam, susceptibility ranged from 32.3% for isolates from Africa/Middle East to 71.8% for isolates from the Asia-Pacific region. MIC_{90} values for aztreonam were ≥256 mg/L in all regions (**Table 2**). In contrast, all isolates from blood from all regions were inhibited by ≤2 mg/L of aztreonam-avibactam.

High rates of susceptibility were seen for amikacin (88.7%–98.7%), ceftazidime-avibactam (94.3%–99.3%), colistin (94.5%–98.6%) and meropenem (84.7%–98.0%) against *K. pneumoniae* from intra-abdominal sources (**Table 1**). Rates of susceptibility to aztreonam, cefepime and ceftazidime were lower among isolates from Africa/Middle East and Latin

America than from Asia-Pacific or Europe and rates of susceptibility to levofloxacin and piperacillin-tazobactam were lower among isolates from Latin America when compared with the other regions. Susceptibility to aztreonam varied between 50.4% (Latin America) and 71.8% (Asia-Pacific) and the MIC_{90} value was ≥128 mg/L in all regions (**Table 1**, **Table 2**). For aztreonam-avibactam, all isolates were inhibited at a concentration of ≤4 mg/L.

For isolates from urinary tract sources, susceptibility was high to amikacin (89.6%–97.3%), ceftazidime-avibactam (96.5%–99.6%), colistin (93.4%–99.1%) and meropenem (86.7%–99.6%) (**Table 1**). By region, rates of susceptibility to amikacin, aztreonam, cefepime, ceftazidime, meropenem and piperacillin-tazobactam were lower among isolates from Latin America when compared with the other regions. Similarly, susceptibility to levofloxacin was also lower in Latin America (52.4% susceptible) when compared with rates in Africa/Middle East and Asia-Pacific (approximately 66%) but the rate was similar to that seen for isolates from Europe (55.9%). MIC_{90} values for aztreonam-avibactam were similar across the regions (0.12–0.25 mg/L) and all isolates were inhibited at a concentration of ≤4 mg/L (**Table 2**).

Among isolates from skin and skin structure sources, susceptibility was highest to amikacin (91.5%–95.1%), ceftazidime-avibactam (94.7%–98.4%), colistin (94.2%–98.9%) and meropenem (87.7%–96.2%) (**Table 1**). There were only small variations in susceptibility among the regions, with the exception of isolates collected from Latin America, for which lower rates of susceptibility to aztreonam, cefepime, and ceftazidime were reported. All isolates from skin and skin structure sources were inhibited at an aztreonam-avibactam concentration of ≤4 mg/L (**Table 2**).

Among isolates from the lower respiratory tract, as seen for other culture sources, susceptibility to amikacin (90.3%–97.6%), ceftazidime-avibactam (97.5%–99.4%), colistin

(93.7%–99.5%) and meropenem (88.1%–95.7%) was high (**Table 1**). Susceptibility to aztreonam varied from 51.9% (Africa/Middle East) to 64.6% (Asia-Pacific) with MIC_{90} values of ≥256 mg/L in three of the four regions (**Table 1**, **Table 2**). All isolates from Africa/Middle East, Asia-Pacific and Latin America were inhibited by ≤4 mg/L of aztreonam-avibactam (**Table 2**). However, for isolates from Europe the MIC range was ≤0.015–32 mg/L with 99.9% inhibited at a concentration of ≤2 mg/L (MIC of 32 mg/L for one isolate).

3.2. Meropenem-resistant *Klebsiella pneumoniae*

A total of 583 (7.3%) *K. pneumoniae* isolates were meropenem-resistant (MEM-R). Rates of meropenem resistance according to culture source and region of collection are shown in **Figure 1**.

The majority of MEM-R isolates were metallo-β-lactamase negative (80.4%, 469/583); 19.6% (114/583) were identified as metallo-β-lactamase positive. Antimicrobial activity and susceptibility data for the collection of MEM-R *K. pneumoniae* as well as the meropenem-resistant metallo-β-lactamase negative (MEM-R-MBLN) and meropenem-resistant metallo-β-lactamase positive (MEM-R-MBLP) isolates are presented in **Table 3**. Data are not shown by region because of the relatively low n values.

From the panel of agents, ceftazidime-avibactam and colistin displayed the highest rates of susceptibility against MEM-R isolates and the subset of MEM-R-MBLN isolates (**Table 3**). For ceftazidime-avibactam, all MEM-R-MBLN isolates from blood, intra-abdominal and urinary tract sources were susceptible, along with 98.7% from skin and skin structure and 98.6% from lower respiratory tract sources. Between 60% and 70% of MEM-R-MBLN isolates from blood, intra-abdominal, urinary tract and lower respiratory tract sources and 55.8% of isolates from skin and skin structure sources were susceptible to colistin. Against

the MEM-R-MBLP isolates, ceftazidime-avibactam was not active; however, susceptibility to colistin was between 75.0% (urinary tract isolates) and 93.3% (lower respiratory tract isolates).

Only small numbers of MEM-R isolates were susceptible to aztreonam (≤5%) (**Table 3**). All MEM-R-MBLN isolates from blood, intra-abdominal, urinary tract and skin and skin structure sources were inhibited by an aztreonam-avibactam MIC of ≤2 mg/L (**Table 3**). All but one isolate from respiratory sources (99.3%), were inhibited by an aztreonam-avibactam MIC of ≤2 mg/L; a single lower respiratory tract isolate from Europe was identified with an aztreonam-avibactam MIC of 32 mg/L. The cumulative MIC distributions of aztreonam and aztreonam-avibactam against all isolates of MEM-R-MBLN *K. pneumoniae* are shown in **Figure 2**. All MEM-R-MBLP isolates were inhibited by an aztreonam-avibactam concentration of ≤0.5 mg/L (**Table 3, Figure 3**).

4. Discussion

This report presents data on the activity of a panel of antimicrobial agents, including aztreonam-avibactam, against a collection of *K. pneumoniae*, reported according to the culture source of the isolates and their geographical region of collection.

Aztreonam-avibactam demonstrated potent activity against isolates of *K. pneumoniae*, irrespective of culture source or region of collection, with 7,952 of the 7,953 (>99.9%) isolates inhibited at a concentration of ≤4 mg/L. This is in agreement with other studies that have reported on the activity of aztreonam-avibactam [**13–15**]. A study from the US of 10,451 Enterobacterales isolates collected in 2016 reported that 99.9% of isolates were inhibited by an aztreonam-avibactam MIC of ≤1 mg/L and that 100% of 2,200 *K. pneumoniae* isolates, including meropenem-non-susceptible isolates, were inhibited by aztreonam-avibactam at a concentration of ≤2 mg/L [**13**]. The present study also shows that aztreonam-avibactam is active against *K. pneumoniae* that are metallo-β-lactamase producers (MICs ≤0.5 mg/L). Karlowsky et al have previously reported on the activity of aztreonam-avibactam against metallo-β-lactamase producing Enterobacterales, with 100% of 267 isolates inhibited by an MIC of ≤8 mg/L [**16**]. In the current study, the only other agent in the panel to show activity against the metallo-β-lactamase positive isolates was colistin, with >91% of isolates from blood, skin and skin structure or lower respiratory tract sources being susceptible. These percentages are similar to the 92.6% susceptibility to colistin reported by Bradford et al for metallo-β-lactamase positive Enterobacterales collected between 2012 and 2013 [**15**], but percentages from the other culture sources reported in our study were lower (75.0%, urinary tract isolates; 78.9%, intra-abdominal isolates). Karlowsky et al reported that 87.8% of metallo-β-lactamase positive Enterobacterales were susceptible to colistin [**16**], similar to the overall rate of 86.0% reported in our study. The variability in percentages by

culture source may be a result of the relatively low number of MEM-R-MBLP *K. pneumoniae* collected (≤30 isolates per culture source). However, there are reports of increasing resistance to colistin among *K. pneumoniae* [**17**], demonstrating that all antimicrobials should be used with caution.

One European MEM-R-MBLN isolate from a respiratory source was identified with an aztreonam-avibactam MIC of 32 mg/L. This isolate was resistant to aztreonam (MIC ≥256 mg/L), cefepime (≥32 mg/L), ceftazidime (≥256 mg/L), ceftazidime-avibactam (128 mg/L), colistin (≥16 mg/L), levofloxacin (8 mg/L) and piperacillin-tazobactam (≥256 mg/L) but was susceptible to amikacin (MIC 2 mg/L) and the MIC to tigecycline was 2 mg/L. Karlowsky et al reported on 25 metallo-β-lactamase negative Enterobacterales isolates, including four *K. pneumoniae*, with aztreonam-avibactam MICs of between 16 and >128 mg/L [**16**]; the mechanism(s) responsible for these elevated aztreonam-avibactam MICs remain undefined and warrant further investigation.

In this study the agents with the highest rates of susceptibility, irrespective of culture source, were amikacin, ceftazidime-avibactam, colistin, and meropenem. These findings are in agreement with other reports. Zhang et al also reported high regional rates of susceptibility to amikacin and meropenem among *K. pneumoniae* from blood cultures collected between 2012 and 2016 as part of the TEST program [**18**]. High rates of susceptibility to colistin and ceftazidime-avibactam among isolates of Enterobacterales, including *K. pneumoniae*, have also been previously reported [e.g. **8, 15, 16, 19**] although in the current study susceptibility to colistin was marginally lower among isolates from Europe and Latin America when compared with isolates from Africa/Middle East and Asia-Pacific across the culture sources. For a number of agents there was variability in rates of susceptibility among the regions; however, the magnitude of the variation differed depending on the culture source. Among

isolates from blood, rates of susceptibility were lower to levofloxacin, meropenem and piperacillin-tazobactam among *K. pneumoniae* collected from Latin America when compared with the other regions. In contrast, recent data from the TEST study reported similar or higher rates of susceptibility to levofloxacin, meropenem and piperacillin-tazobactam among blood isolates from Latin America, when compared with other regions (excluding North America) [**18**]. Susceptibility results against Latin American intra-abdominal source isolates in this study were similar or lower than those reported by Karlowsky et al for *K. pneumoniae* from intra-abdominal infections collected between 2013 and 2015 [**20**]. In particular, susceptibility to levofloxacin was 18% lower in the current study (49.2%) when compared with Karlowsky et al (66.9%) [**20**]. It should be noted that both the Zhang et al [**18**] and Karlowsky et al [**20**] studies applied the 2015 CLSI susceptibility breakpoints which, in the case of meropenem, was one doubling dilution lower, and for levofloxacin and piperacillin-tazobactam, at least one doubling dilution higher, than the 2019 EUCAST breakpoints applied in this study [**10, 21**].

Variations in susceptibility both among the culture sources and the region of collection highlight the importance of having detailed epidemiological information when choosing appropriate antimicrobial treatment. Looking at the rates of meropenem resistance in this study, with the exception of lower respiratory tract isolates, meropenem resistance was highest among isolates from Latin America across the culture sources. A SENTRY study presenting data on carbapenem-resistant Enterobacterales collected between 1997 and 2016 showed that prior to 2009, carbapenem-resistance was relatively low in Latin America (<5%) but in 2015 was higher than that reported in Europe, Asia-Pacific or North America [**16**]. They then reported a decrease in 2016 with the rate in Latin America similar to that reported for Europe (approximately 15% resistant). The study by Castanheira et al also noted that the increase was mainly driven by resistance among *K. pneumoniae* isolates [**17**].

Limitations of this study include the fact that individual centers did not necessarily contribute in both 2016 and 2017, and that the majority of isolates came from European centers, with only relatively low numbers coming from centers in the Africa/Middle East region. In addition, rates of susceptibility or resistance can not be regarded as giving a prevalence of susceptible/resistant isolates within the population, as each center was requested to submit a defined number of *K. pneumoniae* isolates in each year.

In conclusion, this study demonstrates that aztreonam-avibactam is active against *K. pneumoniae* isolates from a range of culture sources across Africa/Middle East, Asia-Pacific, Europe, and Latin America and, importantly, aztreonam-avibactam also has activity against MEM-R-MBLN and MEM-R-MBLP isolates. Treatment options are limited against carbapenem-resistant *K. pneumoniae*, and in particular metallo-β-lactamase positive isolates and aztreonam-avibactam may make an important addition to the armamentarium. Clinical data are awaited with interest.

Contributors

SE and JP participated in data interpretation, as well as drafting and reviewing the manuscript.

GGS was involved in the study design and data interpretation, as well as drafting and reviewing the manuscript.

All authors read and approved the final manuscript.

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Ethical approval

Not required.

Competing interests

SE has no conflicts of interest.

GGS is an employee of Pfizer Inc. and a Pfizer Inc. and AstraZeneca shareholder.

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Data availability

The datasets generated and/or analyzed 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

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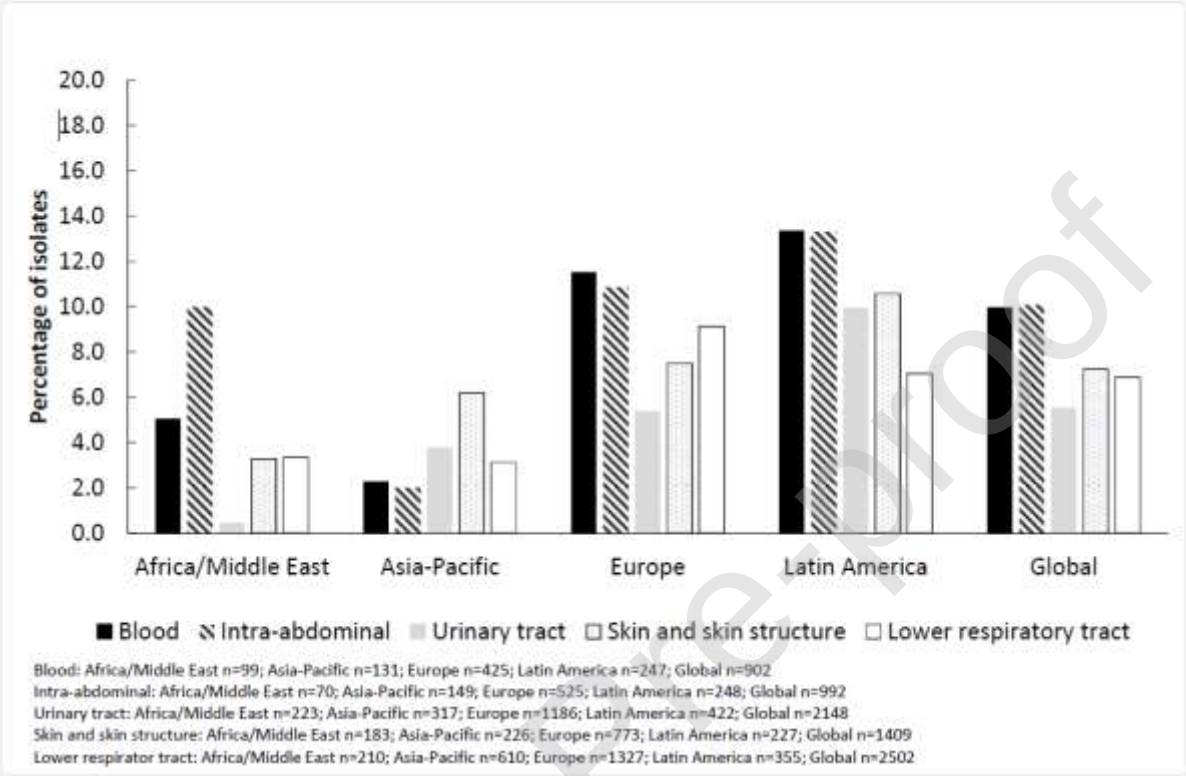
Figure legends

Figure 1. Rates of meropenem resistance among isolates of *Klebsiella pneumoniae* according to region of collection and culture source of the isolates.



Blood: Africa/Middle East n=99; Asia-Pacific n=131; Europe n=425; Latin America n=247; Global n=902
Intra-abdominal: Africa/Middle East n=70; Asia-Pacific n=149; Europe n=525; Latin America n=248; Global n=992
Urinary tract: Africa/Middle East n=223; Asia-Pacific n=317; Europe n=1186; Latin America n=422; Global n=2148
Skin and skin structure: Africa/Middle East n=183; Asia-Pacific n=226; Europe n=773; Latin America n=227; Global n=1409
Lower respirator tract: Africa/Middle East n=210; Asia-Pacific n=610; Europe n=1327; Latin America n=355; Global n=2502

Figure 2. Cumulative minimum inhibitory concentration (MIC) distribution of aztreonam (ATM) and aztreonam-avibactam (ATM-AVI) against meropenem-resistant metallo-β-lactamase negative *Klebsiella pneumoniae* isolates from all culture sources (n=469).

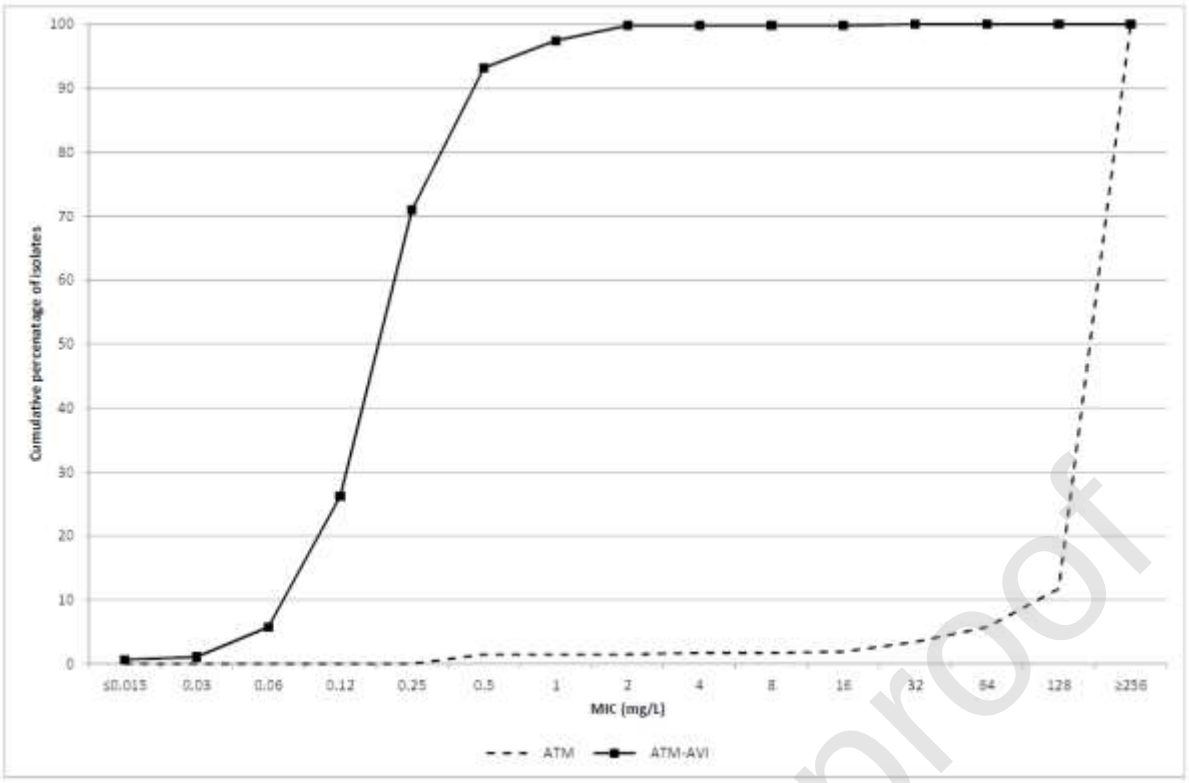


Figure 3. Cumulative minimum inhibitory concentration (MIC) distribution of aztreonam (ATM) and aztreonam-avibactam (ATM-AVI) against meropenem-resistant metallo-β-lactamase positive *Klebsiella pneumoniae* isolates from all culture sources (n=114).

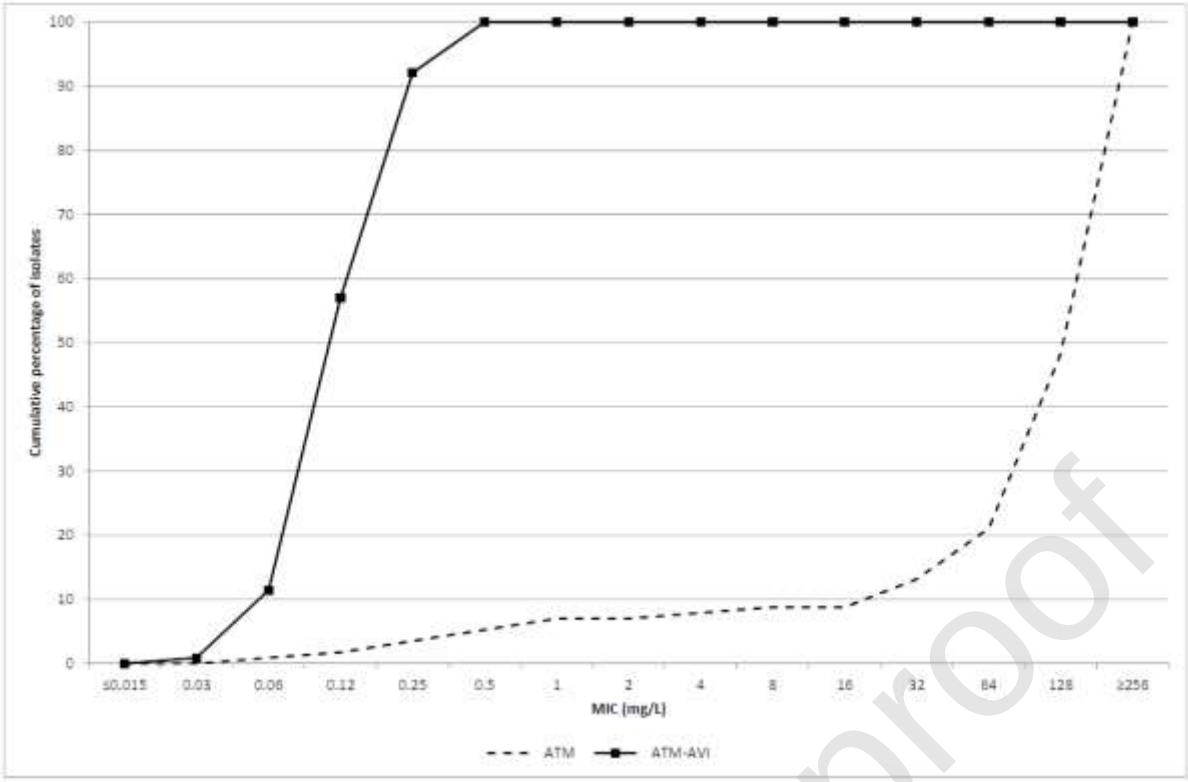


Table 1. Antimicrobial susceptibility (standard dosing [%S], increased exposure [%I]) and resistance (%R) of *Klebsiella pneumoniae* isolates collected in 2016 and 2017 to the panel of antimicrobial agents, according to the region of collection and culture source of isolates.

	Africa/Middle East			Asia-Pacific			Europe			Latin America		
	%S	%I	%R	%S	%I	%R	%S	%I	%R	%S	%I	%R
Blood	**n=99**			**n=131**			**n=425**			**n=247**		
AMK	94.9	--	5.1	97.7	--	2.3	92.0	--	8.0	84.2	--	15.8
ATM	32.3	1.0	66.7	71.8	1.5	26.7	55.1	0.9	44.0	43.3	2.8	53.8
FEP	35.4	1.0	63.6	72.5	2.3	25.2	56.2	2.4	41.4	42.1	6.1	51.8
CAZ	32.3	0.0	67.7	71.8	2.3	26.0	54.4	2.8	42.8	42.5	2.8	54.7
CZA	98.0	--	2.0	99.2	--	0.8	98.8	--	1.2	97.6	--	2.4
CST	100	--	0.0	99.2	--	0.8	92.7	--	7.3	94.3	--	5.7
LVX	61.6	20.2	18.2	73.3	4.6	22.1	58.1	8.9	32.9	51.0	5.3	43.7
MEM	93.9	1.0	5.1	97.7	0.0	2.3	87.1	1.4	11.5	83.0	3.6	13.4
TZP	53.5	13.1	33.3	78.6	6.9	14.5	60.0	8.9	31.1	49.8	4.9	45.3
Intra-abdominal	**n=70**			**n=149**			**n=525**			**n=248**		
AMK	91.4	--	8.6	98.7	--	1.3	90.1	--	9.9	88.7	--	11.3
ATM	54.3	0.0	45.7	71.8	4.7	23.5	65.1	1.3	33.5	50.4	0.4	49.2
FEP	54.3	2.9	42.9	77.9	5.4	16.8	65.9	1.3	32.8	51.2	2.4	46.4
CAZ	52.9	0.0	47.1	72.5	2.0	25.5	63.0	2.3	34.7	47.6	4.8	47.6
CZA	94.3	--	5.7	99.3	--	0.7	97.1	--	2.9	99.2	--	0.8

	Africa/Middle East			Asia-Pacific			Europe			Latin America		
	%S	%I	%R	%S	%I	%R	%S	%I	%R	%S	%I	%R
CST	98.6	--	1.4	96.6	--	3.4	94.5	--	5.5	94.8	--	5.2
LVX	60.0	14.3	25.7	66.4	12.8	20.8	65.7	6.7	27.6	49.2	13.7	37.1
MEM	88.6	1.4	10.0	98.0	0.0	2.0	86.9	2.3	10.9	84.7	2.0	13.3
TZP	62.9	4.3	32.9	75.8	5.4	18.8	67.0	3.8	29.1	56.9	4.4	38.7
Urinary tract	**n=223**			**n=317**			**n=1186**			**n=422**		
AMK	97.3	--	2.7	95.3	--	4.7	94.1	--	5.9	89.6	--	10.4
ATM	59.6	2.2	38.1	69.4	3.5	27.1	57.5	1.9	40.6	53.1	2.1	44.8
FEP	61.4	2.2	36.3	72.2	4.7	23.0	57.5	3.4	39.1	53.1	4.0	42.9
CAZ	60.1	1.8	38.1	65.6	5.0	29.3	56.4	2.3	41.3	50.9	6.4	42.7
CZA	99.6	--	0.4	96.5	--	3.5	98.6	--	1.4	98.8	--	1.2
CST	99.1	--	0.9	99.1	--	0.9	95.6	--	4.4	93.4	--	6.6
LVX	66.4	7.6	26.0	65.9	6.9	27.1	55.9	9.8	34.3	52.4	4.7	42.9
MEM	99.6	0.0	0.4	94.6	1.6	3.8	92.7	1.9	5.4	86.7	3.3	10.0
TZP	70.4	11.2	18.4	72.6	7.6	19.9	64.3	7.6	28.1	59.7	4.7	35.5
Skin and skin structure	**n=183**			**n=226**			**n=773**			**n=227**		
AMK	95.1	--	4.9	95.1	--	4.9	91.5	--	8.5	92.1	--	7.9
ATM	55.7	2.2	42.1	54.9	6.2	38.9	55.2	1.4	43.3	45.4	1.8	52.9
FEP	57.4	4.4	38.3	61.5	1.8	36.7	55.4	2.6	42.0	46.3	4.4	49.3
CAZ	54.6	4.4	41.0	56.2	3.5	40.3	52.3	3.9	43.9	44.9	3.1	52.0
CZA	98.4	--	1.6	94.7	--	5.3	98.1	--	1.9	98.2	--	1.8
CST	98.9	--	1.1	98.2	--	1.8	94.2	--	5.8	95.2	--	4.8

	Africa/Middle East			Asia-Pacific			Europe			Latin America		
	%S	%I	%R	%S	%I	%R	%S	%I	%R	%S	%I	%R
LVX	60.7	16.4	23.0	58.8	10.2	31.0	56.9	9.4	33.6	55.9	7.9	36.1
MEM	96.2	0.5	3.3	92.5	1.3	6.2	88.0	4.5	7.5	87.7	1.8	10.6
TZP	69.9	9.3	20.8	68.6	5.8	25.7	58.9	7.2	33.9	55.9	5.7	38.3
Lower respiratory tract	**n=210**			**n=610**			**n=1327**			**n=355**		
AMK	97.6	--	2.4	94.8	--	5.2	90.3	--	9.7	91.5	--	8.5
ATM	51.9	2.9	45.2	64.6	2.6	32.8	57.2	1.4	41.4	59.2	2.0	38.9
FEP	52.4	4.3	43.3	68.4	3.8	27.9	57.0	3.1	39.9	60.0	4.5	35.5
CAZ	52.4	3.3	44.3	63.6	1.8	34.6	56.3	2.3	41.4	58.0	3.9	38.0
CZA	99.0	--	1.0	97.5	--	2.5	98.6	--	1.4	99.4	--	0.6
CST	99.5	--	0.5	98.2	--	1.8	93.7	--	6.3	96.1	--	3.9
LVX	66.7	15.2	18.1	64.8	8.9	26.4	56.5	8.7	34.8	63.7	8.2	28.2
MEM	95.7	1.0	3.3	95.1	1.8	3.1	88.1	2.8	9.1	91.0	2.0	7.0
TZP	66.2	6.2	27.6	71.6	6.6	21.8	58.5	6.3	35.2	69.6	6.2	24.2

%S, percentage of isolates susceptible, standard dosing; %I, percentage of isolates susceptible, increased exposure; %R, percentage of isolates resistant
AMK, Amikacin; ATM, Aztreonam; FEP, Cefepime; CAZ, Ceftazidime; CZA, Ceftazidime-avibactam; CST, Colistin; LVX, Levofloxacin MEM, Meropenem; TZP, Piperacillin-tazobactam
Aztreonam-avibactam and tigecycline not included in the table as no EUCAST breakpoints available
-- No EUCAST susceptible, increased exposure breakpoints (%I) available for amikacin, ceftazidime-avibactam or colistin

Table 2. Antimicrobial activity (MIC_{50}, MIC_{90}, MIC range) of the panel of antimicrobial agents against *Klebsiella pneumoniae* collected in 2016 and 2017, according to the region of collection and culture source of isolates.

	Africa/Middle East			Asia-Pacific			Europe			Latin America		
	MIC_{50} (mg/L)	MIC_{90} (mg/L)	MIC range (mg/L)	MIC_{50} (mg/L)	MIC_{90} (mg/L)	MIC range (mg/L)	MIC_{50} (mg/L)	MIC_{90} (mg/L)	MIC range (mg/L)	MIC_{50} (mg/L)	MIC_{90} (mg/L)	MIC range (mg/L)
Blood	**n=99**			**n=131**			**n=425**			**n=247**		
AMK	2	8	0.5–≥64	1	4	≤0.25–≥64	1	8	0.5–≥64	2	32	≤0.25–≥64
ATM	32	≥256	≤0.015–≥256	0.06	≥256	≤0.015–≥256	0.25	≥256	≤0.015–≥256	16	≥256	≤0.015–≥256
ATM-AVI	0.06	0.12	≤0.015–2	0.06	0.12	≤0.015–1	0.06	0.25	≤0.015–2	0.06	0.25	≤0.015–2
FEP	16	≥32	≤0.12–≥32	≤0.12	≥32	≤0.12–≥32	0.25	≥32	≤0.12–≥32	8	≥32	≤0.12–≥32
CAZ	32	128	0.03–≥256	0.25	128	≤0.015–≥256	0.5	≥256	≤0.015–≥256	8	≥256	0.03–≥256
CZA	0.25	0.5	≤0.015–≥256	0.12	0.5	≤0.015–≥256	0.12	1	≤0.015–≥256	0.25	1	≤0.015–≥256
CST	0.25	0.5	0.12–2	0.25	0.5	0.12–≥16	0.25	1	0.12–≥16	0.25	1	0.12–≥16
LVX	0.5	8	0.03–≥16	0.12	≥16	0.03–≥16	0.25	≥16	0.03–≥16	0.5	≥16	0.03–≥16
MEM	0.03	1	0.015–≥16	0.03	0.06	0.015–≥16	0.06	≥16	0.015–≥16	0.06	≥16	0.015–≥16
TZP	8	≥256	0.5–≥256	4	32	≤0.25–≥256	4	≥256	≤0.25–≥256	16	≥256	≤0.25–≥256
TGC	0.5	1	0.25–≥16	0.5	1	0.06–4	0.5	1	0.06–8	0.5	2	0.06–≥16
Intra-abdominal	**n=70**			**n=149**			**n=525**			**n=248**		
AMK	1	8	0.5–≥64	1	2	≤0.25 to ≥64	1	8	≤0.25–≥64	1	16	0.5–≥64
ATM	0.12	128	≤0.015–≥256	0.12	≥256	≤0.015–≥256	0.12	≥256	≤0.015–≥256	1	≥256	≤0.015–≥256
ATM-AVI	0.03	0.12	≤0.015–0.5	0.06	0.12	≤0.015–2	0.06	0.25	≤0.015–4	0.06	0.25	≤0.015–1
FEP	1	≥32	≤0.12–≥32	≤0.12	≥32	≤0.12–≥32	≤0.12	≥32	≤0.12–≥32	1	≥32	≤0.12–≥32

	Africa/Middle East			Asia-Pacific			Europe			Latin America		
	MIC_{50} (mg/L)	MIC_{90} (mg/L)	MIC range (mg/L)	MIC_{50} (mg/L)	MIC_{90} (mg/L)	MIC range (mg/L)	MIC_{50} (mg/L)	MIC_{90} (mg/L)	MIC range (mg/L)	MIC_{50} (mg/L)	MIC_{90} (mg/L)	MIC range (mg/L)
CAZ	1	128	≤0.015–≥256	0.25	128	≤0.015 to ≥256	0.25	≥256	≤0.015–≥256	4	128	0.06–≥256
CZA	0.12	1	0.03–≥256	0.12	0.5	≤0.015 to ≥256	0.12	1	≤0.015–≥256	0.25	1	≤0.015–≥256
CST	0.25	1	≤0.06 to ≥16	0.25	0.5	0.12–≥16	0.25	0.5	0.12–≥16	0.25	1	0.12–≥16
LVX	0.12	≥16	0.03–≥16	0.12	≥16	0.03–≥16	0.12	≥16	0.03–≥16	1	≥16	0.03–≥16
MEM	0.03	8	0.015 to ≥16	0.03	0.06	0.015–≥16	0.06	≥16	0.015–≥16	0.06	≥16	0.015–≥16
TZP	4	≥256	1–≥256	4	128	1–≥256	4	≥256	≤0.25–≥256	8	≥256	0.5–≥256
TGC	0.5	1	0.12–≥16	0.5	2	0.03–≥16	0.5	1	0.12–4	0.5	1	0.12–8
Urinary tract	**n=223**			**n=317**			**n=1186**			**n=422**		
AMK	1	4	≤0.25–≥64	1	4	≤0.25–≥64	1	4	≤0.25–≥64	1	16	≤0.25–≥64
ATM	0.12	128	≤0.015–≥256	0.06	≥256	≤0.015–≥256	0.12	≥256	≤0.015–≥256	0.5	≥256	≤0.015–≥256
ATM-AVI	0.06	0.12	≤0.015–0.5	0.06	0.12	≤0.015–4	0.06	0.12	≤0.015–4	0.06	0.25	≤0.015–2
FEP	≤0.12	≥32	≤0.12–≥32	≤0.12	≥32	≤0.12–≥32	0.25	≥32	≤0.12–≥32	0.5	≥32	≤0.12–≥32
CAZ	0.25	64	≤0.015–≥256	0.25	128	0.03–≥256	0.5	128	≤0.015–≥256	1	128	0.03–≥256
CZA	0.12	0.5	≤0.015–≥256	0.12	1	≤0.015–≥256	0.12	0.5	≤0.015–≥256	0.12	1	≤0.015–≥256
CST	0.25	0.5	0.12–≥16	0.25	0.5	0.12–≥16	0.25	0.5	0.12–≥16	0.25	1	0.12–≥16
LVX	0.25	≥16	0.03–≥16	0.12	≥16	0.03–≥16	0.5	≥16	0.008–≥16	0.5	≥16	0.03–≥16
MEM	0.06	0.06	≤0.004–≥16	0.03	0.12	0.008–≥16	0.06	0.25	0.015–≥16	0.06	8	0.015–≥16
TZP	4	64	0.5–≥256	4	≥256	≤0.25–≥256	4	≥256	≤0.25–≥256	4	≥256	0.5–≥256
TGC	0.5	1	0.12–4	0.5	2	0.12–8	0.5	1	0.12–≥16	0.5	1	0.12–≥16
Skin and skin structure	**n=183**			**n=226**			**n=773**			**n=227**		

	Africa/Middle East			Asia-Pacific			Europe			Latin America		
	MIC_{50} (mg/L)	MIC_{90} (mg/L)	MIC range (mg/L)	MIC_{50} (mg/L)	MIC_{90} (mg/L)	MIC range (mg/L)	MIC_{50} (mg/L)	MIC_{90} (mg/L)	MIC range (mg/L)	MIC_{50} (mg/L)	MIC_{90} (mg/L)	MIC range (mg/L)
AMK	1	4	0.5–≥64	1	4	0.5–≥64	1	8	≤0.25–≥64	2	8	≤0.25–≥64
ATM	0.12	128	≤0.015–≥256	0.12	≥256	≤0.015–≥256	0.25	≥256	≤0.015–≥256	16	≥256	≤0.015–≥256
ATM-AVI	0.03	0.12	≤0.015–0.5	0.06	0.25	≤0.015–4	0.06	0.25	≤0.015–2	0.06	0.25	≤0.015–1
FEP	0.25	≥32	≤0.12–≥32	≤0.12	≥32	≤0.12–≥32	0.5	≥32	≤0.12–≥32	4	≥32	≤0.12–≥32
CAZ	0.5	64	0.06–≥256	0.5	≥256	0.06–≥256	0.5	128	0.03–≥256	8	128	0.03–≥256
CZA	0.12	0.5	0.03–≥256	0.12	1	≤0.015–≥256	0.12	1	≤0.015–≥256	0.12	1	≤0.015–≥256
CST	0.25	0.5	≤0.06–≥16	0.25	0.5	0.12–≥16	0.25	1	0.12–≥16	0.25	1	0.12–≥16
LVX	0.5	≥16	0.03–≥16	0.25	≥16	0.03–≥16	0.5	≥16	0.008–≥16	0.5	≥16	0.03–≥16
MEM	0.06	0.12	0.015–≥16	0.03	0.5	0.008–≥16	0.06	4	0.015–≥16	0.06	≥16	0.015–≥16
TZP	4	≥256	≤0.25–≥256	4	≥256	≤0.25–≥256	8	≥256	≤0.25–≥256	8	≥256	0.5–≥256
TGC	0.5	2	0.12–4	0.5	1	0.12–≥16	0.5	1	0.12–8	0.5	1	0.12–≥16
Lower respiratory tract	**n=210**			**n=610**			**n=1327**			**n=355**		
AMK	1	4	≤0.25–≥64	1	4	≤0.25–≥64	1	8	≤0.25–≥64	1	4	≤0.25–≥64
ATM	0.25	128	≤0.015–≥256	0.06	≥256	≤0.015–≥256	0.12	≥256	≤0.015–≥256	0.12	≥256	≤0.015–≥256
ATM-AVI	0.06	0.12	≤0.015–0.25	0.06	0.25	≤0.015–4	0.06	0.25	≤0.015–32	0.06	0.12	≤0.015–2
FEP	0.25	≥32	≤0.12–≥32	≤0.12	≥32	≤0.12–≥32	0.25	≥32	≤0.12–≥32	≤0.12	≥32	≤0.12–≥32
CAZ	0.5	64	≤0.015–≥256	0.25	≥256	0.03–≥256	0.5	≥256	0.03–≥256	0.25	128	0.03–≥256
CZA	0.12	0.5	≤0.015–≥256	0.12	0.5	≤0.015–≥256	0.12	1	≤0.015–≥256	0.12	1	≤0.015–≥256
CST	0.25	0.5	≤0.06–≥16	0.25	0.5	≤0.06–≥16	0.25	1	0.12–≥16	0.25	0.5	0.12–≥16
LVX	0.12	≥16	0.03–≥16	0.12	≥16	0.03–≥16	0.5	≥16	0.015–≥16	0.12	≥16	0.03–≥16

	Africa/Middle East			Asia-Pacific			Europe			Latin America		
	MIC_{50} (mg/L)	**MIC_{90} (mg/L)**	**MIC range (mg/L)**	**MIC_{50} (mg/L)**	**MIC_{90} (mg/L)**	**MIC range (mg/L)**	**MIC_{50} (mg/L)**	**MIC_{90} (mg/L)**	**MIC range (mg/L)**	**MIC_{50} (mg/L)**	**MIC_{90} (mg/L)**	**MIC range (mg/L)**
MEM	0.06	0.12	0.015–≥16	0.03	0.12	0.015–≥16	0.06	8	0.015–≥16	0.03	1	0.015–≥16
TZP	4	≥256	≤0.25–≥256	4	≥256	≤0.25–≥256	8	≥256	≤0.25–≥256	4	≥256	≤0.25–≥256
TGC	0.5	1	0.12–8	0.5	1	≤0.015–8	0.5	1	0.06–8	0.5	1	0.12–8

MIC, minimum inhibitory concentration; MIC_{50}, MIC at which 50% of isolates inhibited MIC_{90}, MIC at which 90% of isolates inhibited
AMK, Amikacin; ATM, Aztreonam; ATM-AVI, Aztreonam-avibactam; FEP, Cefepime; CAZ, Ceftazidime; CZA, Ceftazidime-avibactam; CST, Colistin; LVX, Levofloxacin MEM, Meropenem; TZP, Piperacillin-tazobactam; TGC, Tigecycline

Table 3. Antimicrobial activity (MIC_{50}, MIC_{90}, MIC range) and susceptibility (%S, standard dosing) of the panel of antimicrobial agents against meropenem-resistant *Klebsiella pneumoniae* collected in 2016 and 2017, according to the culture source of isolates.

	Meropenem-resistant *K. pneumoniae*				**Meropenem-resistant *K. pneumoniae*, metallo-β-lactamase negative**				**Meropenem-resistant *K. pneumoniae*, metallo-β-lactamase positive**			
	MIC_{50} (mg/L)	**MIC_{90} (mg/L)**	**MIC range (mg/L)**	**%S**	**MIC_{50} (mg/L)**	**MIC_{90} (mg/L)**	**MIC range (mg/L)**	**%S**	**MIC_{50} (mg/L)**	**MIC_{90} (mg/L)**	**MIC range (mg/L)**	**%S**
All isolates	**n=583**				**n=469**				**n=114**			
AMK	16	≥64	≤0.25–≥64	47.7	16	≥64	≤0.25–≥64	48.6	16	≥64	0.5–≥64	43.9
ATM	≥256	≥256	0.06–≥256	2.6	≥256	≥256	0.5–≥256	1.5	≥256	≥256	0.06–≥256	7.0
ATM-AVI	0.25	0.5	≤0.015–32	--	0.25	0.5	≤0.015–32	--	0.12	0.25	0.03–0.5	--
FEP	≥32	≥32	0.25–≥32	0.9	≥32	≥32	0.25–≥32	0.9	≥32	≥32	1–≥32	0.9
CAZ	≥256	≥256	0.5–≥256	0.7	≥256	≥256	0.5–≥256	0.9	≥256	≥256	128–≥256	0.0
CZA	2	≥256	≤0.015–≥256	79.9	1	4	≤0.015–128	99.4	≥256	≥256	64–≥256	0.0
CST	0.5	≥16	0.12–≥16	67.2	0.5	≥16	0.12–≥16	62.7	0.25	≥16	0.12–≥16	86.0
LVX	≥16	≥16	0.06–≥16	2.9	≥16	≥16	0.06–≥16	3.0	≥16	≥16	0.12–≥16	2.6
TZP	≥16	≥16	≥16	0.0	≥16	≥16	≥16	0.0	≥16	≥16	≥16	0.0
TGC	≥256	≥256	64–≥256	--	≥256	≥256	64–≥256	--	≥256	≥256	128–≥256	--
Blood	**n=90**				**n=78**				**n=12**			
AMK	16	≥64	≤0.25–≥64	47.8	16	≥64	≤0.25–≥64	47.4	8	≥64	1–≥64	50.0
ATM	≥256	≥256	0.5–≥256	1.1	≥256	≥256	0.5–≥256	1.3	≥256	≥256	128–≥256	0.0
ATM-AVI	0.25	0.5	0.06–2	--	0.25	1	0.06–2	--	0.12	0.5	0.06–0.5	--

	Meropenem-resistant *K. pneumoniae*				**Meropenem-resistant *K. pneumoniae*, metallo-β-lactamase negative**				**Meropenem-resistant *K. pneumoniae*, metallo-β-lactamase positive**			
	MIC_{50} (mg/L)	**MIC_{90} (mg/L)**	**MIC range (mg/L)**	**%S**	**MIC_{50} (mg/L)**	**MIC_{90} (mg/L)**	**MIC range (mg/L)**	**%S**	**MIC_{50} (mg/L)**	**MIC_{90} (mg/L)**	**MIC range (mg/L)**	**%S**
FEP	≥32	≥32	4–≥32	0.0	≥32	≥32	4–≥32	0.0	≥32	≥32	≥32	0.0
CAZ	≥256	≥256	2–≥256	0.0	≥256	≥256	2–≥256	0.0	≥256	≥256	≥256	0.0
CZA	1	≥256	0.12–≥256	86.7	1	4	0.12–4	100	≥256	≥256	≥256	0.0
CST	0.5	≥16	0.12–≥16	67.8	0.5	≥16	0.25–≥16	64.1	0.25	0.5	0.12–≥16	91.7
LVX	≥16	≥16	0.06–≥16	3.3	≥16	≥16	0.06–≥16	2.6	≥16	≥16	0.12–≥16	8.3
TZP	≥16	≥256	≥256	0.0	≥16	≥256	≥256	0.0	≥16	≥256	≥256	0.0
TGC	≥256	4	0.25–≥16	--	≥256	4	0.25–≥16	--	≥256	4	0.5–4	--
Intra-abdominal	**n=100**				**n=81**				**n=19**			
AMK	16	≥64	0.5–≥64	37.0	16	≥64	0.5–≥64	40.7	≥64	≥64	0.5–≥64	21.1
ATM	≥256	≥256	0.12–≥256	4.0	≥256	≥256	0.5–≥256	1.2	128	≥256	0.12–≥256	15.8
ATM-AVI	0.25	0.5	0.06–2	--	0.25	0.5	0.06–2	--	0.12	0.25	0.06–0.25	--
FEP	≥32	≥32	0.5–≥32	3.0	≥32	≥32	0.5–≥32	2.5	≥32	≥32	1–≥32	5.3
CAZ	≥256	≥256	1–≥256	1.0	128	≥256	1–≥256	1.2	≥256	≥256	128–≥256	0.0
CZA	2	≥256	0.25–≥256	81.0	1	4	0.25–8	100	≥256	≥256	128–≥256	0.0
CST	0.5	≥16	0.12–≥16	72.0	0.5	≥16	0.12–≥16	70.4	0.25	≥16	0.12–≥16	78.9
LVX	≥16	≥16	0.12–≥16	3.0	≥16	≥16	0.12–≥16	3.7	≥16	≥16	2–≥16	0.0
TZP	≥16	≥256	128–≥256	0.0	≥16	≥256	≥256	0.0	≥16	≥256	128–≥256	0.0
TGC	≥256	2	0.12–≥16	--	≥256	2	0.12–≥16	--	≥256	2	0.12–≥16	--
Urinary tract	**n=119**				**n=91**				**n=28**			

	Meropenem-resistant *K. pneumoniae*				**Meropenem-resistant *K. pneumoniae*, metallo-β-lactamase negative**				**Meropenem-resistant *K. pneumoniae*, metallo-β-lactamase positive**			
	MIC_{50} (mg/L)	**MIC_{90} (mg/L)**	**MIC range (mg/L)**	**%S**	**MIC_{50} (mg/L)**	**MIC_{90} (mg/L)**	**MIC range (mg/L)**	**%S**	**MIC_{50} (mg/L)**	**MIC_{90} (mg/L)**	**MIC range (mg/L)**	**%S**
AMK	16	≥64	0.5–≥64	49.6	8	≥64	0.5–≥64	52.7	16	≥64	1–≥64	39.3
ATM	≥256	≥256	0.25–≥256	5.0	≥256	≥256	0.5–≥256	3.3	128	≥256	0.25–≥256	10.7
ATM-AVI	0.25	0.5	≤0.015–2	--	0.25	0.5	≤0.015–2	--	0.12	0.25	0.06–0.5	--
FEP	≥32	≥32	8–≥32	0.0	≥32	≥32	8–≥32	0.0	≥32	≥32	≥32	0.0
CAZ	≥256	≥256	2–≥256	0.0	≥256	≥256	2–≥256	0.0	≥256	≥256	≥256	0.0
CZA	1	≥256	≤0.015–≥256	76.5	1	2	≤0.015–8	100	≥256	≥256	128–≥256	0.0
CST	0.5	≥16	0.12–≥16	66.4	0.5	≥16	0.12–≥16	63.7	0.25	≥16	0.12–≥16	75.0
LVX	≥16	≥16	0.06–≥16	3.4	≥16	≥16	0.06–≥16	3.3	≥16	≥16	0.25–≥16	3.6
TZP	≥16	≥256	64–≥256	0.0	≥16	≥256	64–≥256	0.0	≥16	≥256	≥256	0.0
TGC	≥256	2	0.12–≥16	--	≥256	2	0.12–4	--	≥256	4	0.12–≥16	--
Skin and skin structure	**n=102**				**n=77**				**n=25**			
AMK	8	≥64	0.5–≥64	51.0	16	≥64	0.5–≥64	46.8	8	≥64	1–≥64	64.0
ATM	≥256	≥256	0.06–≥256	1.0	≥256	≥256	4–≥256	0.0	≥256	≥256	0.06–≥256	4.0
ATM-AVI	0.25	0.5	0.03–2	--	0.25	0.5	0.03–2	--	0.12	0.25	0.03–0.5	--
FEP	≥32	≥32	0.25–≥32	1.0	≥32	≥32	0.25–≥32	1.3	≥32	≥32	≥32	0.0
CAZ	≥256	≥256	1–≥256	1.0	128	≥256	1–≥256	1.3	≥256	≥256	≥256	0.0
CZA	2	≥256	0.12–≥256	74.5	1	2	0.12–16	98.7	≥256	≥256	128–≥256	0.0
CST	0.5	≥16	0.25–≥16	64.7	1	≥16	0.25–≥16	55.8	0.25	2	0.25–≥16	92.0

	Meropenem-resistant *K. pneumoniae*				**Meropenem-resistant *K. pneumoniae*, metallo-β-lactamase negative**				**Meropenem-resistant *K. pneumoniae*, metallo-β-lactamase positive**			
	MIC_{50} (mg/L)	**MIC_{90} (mg/L)**	**MIC range (mg/L)**	**%S**	**MIC_{50} (mg/L)**	**MIC_{90} (mg/L)**	**MIC range (mg/L)**	**%S**	**MIC_{50} (mg/L)**	**MIC_{90} (mg/L)**	**MIC range (mg/L)**	**%S**
LVX	≥16	≥16	0.06–≥16	4.9	≥16	≥16	0.06–≥16	5.2	≥16	≥16	0.5–≥16	4.0
TZP	≥16	≥256	128–≥256	0.0	≥16	≥256	128–≥256	0.0	≥16	≥256	128–≥256	0.0
TGC	≥256	2	0.12–≥16	--	≥256	2	0.12–≥16	--	≥256	4	0.12–4	--
Lower respiratory tract	**n=172**				**n=142**				**n=30**			
AMK	8	≥64	0.5–≥64	50.6	8	≥64	0.5–≥64	52.1	16	≥64	1–≥64	43.3
ATM	≥256	≥256	0.5–≥256	1.7	≥256	≥256	0.5–≥256	1.4	≥256	≥256	0.5–≥256	3.3
ATM-AVI	0.25	0.5	≤0.015–32	--	0.25	0.5	≤0.015–32	--	0.12	0.5	0.06–0.5	--
FEP	≥32	≥32	0.5–≥32	0.6	≥32	≥32	0.5–≥32	0.7	≥32	≥32	16–≥32	0.0
CAZ	≥256	≥256	0.5–≥256	1.2	≥256	≥256	0.5–≥256	1.4	≥256	≥256	128–≥256	0.0
CZA	2	≥256	0.12–≥256	81.4	1	4	0.12–128	98.6	≥256	≥256	64–≥256	0.0
CST	0.5	≥16	0.12–≥16	66.3	0.5	≥16	0.12–≥16	60.6	0.5	1	0.12–≥16	93.3
LVX	≥16	≥16	0.06–≥16	1.2	≥16	≥16	0.06–≥16	1.4	≥16	≥16	1–≥16	0.0
TZP	≥16	≥256	128–≥256	0.0	≥16	≥256	≥256	0.0	≥16	≥256	128–≥256	0.0
TGC	≥256	2	0.12–8	--	≥256	2	0.12–8	--	≥256	2	0.12–8	--

MIC, minimum inhibitory concentration; MIC_{50}, MIC at which 50% of isolates inhibited;MIC_{90}, MIC at which 90% of isolates inhibited; %S, percentage of isolates susceptible, standard dosing

AMK, Amikacin; ATM, Aztreonam; ATM-AVI, Aztreonam-avibactam; FEP, Cefepime; CAZ, Ceftazidime; CZA, Ceftazidime-avibactam; CST, Colistin; LVX, Levofloxacin TZP, Piperacillin-tazobactam; TGC, Tigecycline

-- No EUCAST breakpoints available for aztreonam-avibactam or tigecycline