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Letter to the Editor

Distributions of plasmidic genes encoding extended-spectrum and AmpC β-lactamases, and susceptibilities of global non-carbapenemase-producing meropenem-resistant Enterobacterales to ceftazidime-avibactam, meropenem-vaborbactam, and aztreonam-avibactam, 2017–2022

Dear Editor,

We read with great interest the article by Lee et al., which addressed the emergence of index infections caused by 18 clonally unrelated carbapenem-resistant Enterobacterales (CRE) isolates exhibiting reduced susceptibilities to ceftazidime-avibactam (CZA) due to their carriage of genes encoding various metallo-β-lactamases among 48 patients hospitalized in a tertiary hospital in Taiwan in 2021.[1] The majority of them had received CZA therapy within three months of their index infection episodes. Interestingly, reduced CZA susceptibility was also detected in two CRE isolates (one *Escherichia coli* and one *Klebsiella pneumoniae*) that did not harbor carbapenemase-encoding genes.[1]

Due to the significant global burden of CRE, CZA was extensively prescribed following its launch in February 2015. In Taiwan, CZA was introduced in 2019 and has been used for managing CRE infections since then. Additionally, the clinical efficacy of aztreonam-avibactam (ATM-AVI), which is in vitro active against all Ambler classes of carbapenemases in CRE isolates, was evaluated in a phase 3 comparative clinical trial conducted between 2018 and 2023. Despite available data on the susceptibility profiles of non-carbapenemase-producing (non-CP) CRE isolates to CZA[2] and the minimum inhibitory concentration (MIC) distributions of ATM-AVI against non-CP CRE and CPE isolates,[3] there remains a lack of information in the PubMed database. Specifically, geographic and species-specific differences in the susceptibility rates of global non-CP CRE isolates to CZA and the novel antibiotic meropenem-vaborbactam (MVB), as well as MIC distributions for ATM-AVI, are underreported.

The Antimicrobial Testing Leadership and Surveillance (ATLAS) program, initiated in 2006, investigates the global in vitro susceptibility of target microorganisms to key antibiotics. Only the first isolate from a specific source was collected from a single patient per year. To compare difference in resistance rates to CZA among the studied Enterobacterales isolates after CZA was launched, the study period was divided into two stages: 2017–2019 (first stage) and 2020–2022 (second stage).

Isolates of Enterobacterales species were initially identified using conventional biochemical methods in local laboratories and then accurately identified to the species level using matrix-assisted laser desorption ionization time-of-flight mass spectrometry (Bruker Biotyper, Bruker Daltonics, Billerica, MA, USA) at International Health Management Associates (IHMA, Schaumburg, IL, USA). The broth microdilution method was used to determine the MICs of CZA, MVB, and ATM-AVI against the tested Enterobacterales isolates.

In this study, we analyzed data from the 2017–2022 ATLAS program, focusing on isolates of meropenem-resistant Enterobacterales classified as CRE that were confirmed to lack carbapenemase-encoding genes. Susceptibility data for Enterobacterales to MVB have been available since 2020 in the ATLAS database. The susceptibility rates of Enterobacterales isolates to CZA and MVB were determined using the breakpoints established by the Clinical and Laboratory Standards Institute (CLSI) 2024 guidelines.[4] However, the CLSI 2024 guidelines do not include susceptibility MIC breakpoints for ATM-AVI against Enterobacterales. Therefore, this study adopted the tentative susceptibility breakpoint of $\leq$8 mg/L for ATM-AVI, as proposed by Cornely et al., based on pharmacokinetic and pharmacodynamic indices.[5] Differences in susceptibility rates of non-CP CRE isolates to CZA, MVB, and ATM-AVI across various regions and stages were analyzed using the chi-square test, as appropriate. Genes encoding plasmid-mediated non-carbapenemase β-lactamases [including important extended-spectrum β-lactamases (ESBLs) and plasmidic AmpC β-lactamases] in non-CP CRE isolates were detected using multiplex PCR.

The studied non-CP CRE isolates represented 4.4% (1840/42,121) and 6.9% (3384/49,102) of the tested global Enterobacterales isolates collected during the first and second periods, respectively, of the ATLAS program. Additionally, the non-CP CRE isolates collected from patients hospitalized in intensive care units, patients older than 60 years, and *K. pneumoniae* isolates accounted for 45.3% and 48.7%, 51.1% and 50.8%, and 80.4% and 78.7% among overall non-CP CRE isolates collected in the first and second stages, respectively. The most common infection sources were the bloodstream (26% and 30%) and the respiratory tract (27.7% and 29.8%) in the first and second stages, respectively.

Isolates of non-CP CRE collected in North America and Oceania were excluded from this study due to small sample sizes (n=115 and 12, respectively). The numbers of *K. pneumoniae* collected in the first and second stage were 316 and 864 in Asia, 107 and 296 in Africa/the Middle East, 783 and 884 in Europe, and 273 and 568 in Latin America, respectively. Additionally, 109 and 327 isolates of *E. coli* were collected, along with 232 and 324 isolates of potentially chromosomal AmpC-hyperproducing Enterobacterales species (including *Citrobacter* spp., *Cronobacter* spp., *Enterobacter* spp., *Morganella* spp., *Providencia* spp., *Serratia* spp., and *Klebsiella aerogenes*) across four regions during the two stages.

Table 1 presents the distributions of dominant plasmidic genes encoding non-carbapenemase β-lactamases (including important ESBLs and plasmidic AmpC β-lactamases) among isolates of predominant non-CP CRE species, as well as associated CZA resistance rates across different regions, globally, and in different periods. Among all ESBLs observed in non-CP CR-*K. pneumoniae* isolates (n=1479 and 2662), CTX-M-15 was the most frequently identified

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Table 1
Distributions of the dominant plasmidic genes encoding non-carbapenemase β-lactamases (including three leading CTX-M types, other important extended-spectrum β-lactamases, and plasmidic AmpC β-lactamases) among isolates of predominant non-carbapenemase-producing meropenem-resistant Enterobacterales species and associated rates of resistance to ceftazidime-avibactam in different regions or globally in two different periods.

Non-carbapenemase β-lactamases-encoding genes (%), CRE species (isolate no.), in different regions or globally, in different periods	Regions			
	Non-CP CR-*Klebsiella pneumoniae*			
Periods	Asia (7 countries)	Africa/the Middle East (8 countries)	Europe (18 Countries)	Latin America (8 Countries)
2017–2019	(n=316) Class A CTX-M-15: 276 (87.3%; CZA-R: 54%) CTX-M-3: 2 CTX-M-1: 1 CTX-M-27: 1 CTX-M-65: 1 SHV-ESBL: 18 (CZA-R: 33.3%) VEB-1: 1 (CZA-R: 100%) Class C AMPC: 6 CMY: 4 DHA: 10 Combinations of the above enzymes CTX-M-15 + SHV-ESBL: 14 CTX-M-15 + AMPC: 2 CTX-M-15 + CMY: 3 CTX-M-15 + DHA: 3 SHV-ESBL + AMPC: 1 SHV-ESBL + CMY: 1 SHV-ESBL + DHA: 1	(n=107) Class A CTX-M-15: 80 (74.8%; CZA-R: 53.8%) CTX-M-9: 5 CTX-M-1: 2 SHV-ESBL: 9 (CZA-R: 100%) Class C AMPC: 4 CMY: 7 Combinations of the above enzymes CTX-M-1) + SHV-ESBL: 6 CTX-M-15 + AMPC: 1 CTX-M-15 + CMY: 4 SHV-ESBL + AMPC: 4 SHV-ESBL + CMY: 5	(n=783) Class A CTX-M-15: 466 (59.5%; CZA-R: 32.8%) CTX-M-9: 12 CTX-M-3: 7 SHV-ESBL: 12 (CZA-R: 25%) VEB-1: 8 (CZA-R: 0%) Class C AMPC: 15 (CZA-R: 80%) CMY: 30 (CZA-R: 66.7%) DHA: 13 (CZA-R: 76.9%) Combinations of the above enzymes CTX-M-15 + SHV-ESBL: 4 CTX-M-15 + AMPC: 8 CTX-M-15 + CMY: 15 CTX-M-15 + DHA: 11 SHV-ESBL + AMPC: 1 SHV-ESBL + CMY: 1	(n=273) Class A CTX-M-15: 121 (44.3%; CZA-R: 30.6%) CTX-M-2: 21 (CZA-R: 0%) CTX-M-14: 16 (CZA-R: 6.3%) SHV-ESBL: 23 (CZA-R: 21.7% TEM-ESBL: 1 GES-2: 5 (CZA-R: 100%) Class C AMPC: 14 (CZA-R:92.9%) CMY: 14 (CZA-R: 92.9%) Combinations of the above enzymes CTX-M-15 + SHV-ESBL: 6 CTX-M-15 + AMPC: 11 CTX-M-15 + CMY: 11 SHV-ESBL + AMPC: 4 SHV-ESBL + CMY: 4
2020–2022	(n=864) Class A CTX-M-15: 766 (88.7%; CZA-R: 58.4%) CTX-M-1: 9 CTX-M-14: 9 SHV-ESBL: 60 (CZA-R: 35%) VEB-1: 1 (CZA-R: 0%) Class C CMY: 9 DHA: 15 (CZA-R: 60%) Combinations of the above enzymes CTX-M-15 + SHV-ESBL: 42 CTX-M-15 + CMY: 8 CTX-M-15 + DHA: 9 SHV-ESBL + DHA: 3	(n=296) Class A CTX-M-15: 255 (86.1%; CZA-R: 74.9%) CTX-M-9: 28 (CZA-R: 75%) CTX-M-1: 3 SHV-ESBL: 3 PER-1: 1 (CZA-R: 100%) Class C CMY: 4 DHA: 6 Combinations of the above enzymes CTX-M-15 + CMY: 3 CTX-M-15 + DHA: 6	(n=884) Class A CTX-M-15: 518 (58.6%; CZA-R: 33%) CTX-M-55: 17 CTX-M-9: 15 SHV-ESBL: 31 (CZA-R: 41.9%) VEB-1: 4 (CZA-R: 25%) Class C CMY: 27 (CZA-R:96.3%) DHA: 9 Combinations of the above enzymes CTX-M-15 + SHV-ESBL: 11 CTX-M-15 + CTX-M-9: 3 CTX-M-15 + CMY: 14 CTX-M-15 + DHA: 4 SHV-ESBL + CMY: 1 SHV-ESBL + DHA: 1	(n=568) Class A CTX-M-15: 286 (50.4%; CZA-R: 49.7%) CTX-M-14: 49 (CZA-R: 6.1%) CTX-M-2: 33 (CZA-R: 3%) SHV-ESBL: 75 (CZA-R: 53.3%) TEM-ESBL: 1 GES-2: 8 (CZA-R: 100%) Class C CMY: 33 (CZA-R: 100%) DHA: 1 FOX: 1 Combinations of the above enzymes CTX-M-15 + SHV-ESBL: 29 CTX-M-15 + CMY: 30 SHV-ESBL + CMY: 2
Global non-CP CR-*Escherichia coli* isolates				
2017–2019	(n=109) Class A CTX-M-15: 62 (56.9%; CZA-R: 83.9%) CTX-M-55: 4 CTX-M-27: 3 SHV-ESBL: 4 (CZA-R: 100%)	GES-2: 1 (CZA-R: 100%) PER-1: 1 (CZA-R: 100%) Class C AMPC: 20 CMY: 37 (33.9%; CZA-R: 94.6%) DHA: 4	Combination of the above enzymes CTX-M-15 + SHV-ESBL: 1 CTX-M-15 +AMPC: 6 CTX-M-15 + CMY: 17 CTX-M-15 + DHA: 1	CTX-M-55 + AMPC: 1 CTX-M-55 + CMY: 1 SHV-ESBL + AMPC: 1 SHV-ESBL + CMY: 1 SHV-ESBL + DHA: 1
2020–2022	(n=327) Class A CTX-M-15: 187 (57.2%; CZA-R: 90.9%) CTX-M-27: 4 CTX-M-65: 3	SHV-ESBL: 8 (CZA-R: 62.5%) GES-2: 3 (CZA-R: 100%) Class C CMY: 148 (45.3%; CZA-R: 93.2%) DHA: 11 (CZA-R: 100%)	Combinations of the above enzymes CTX-M-15 + SHV-ESBL: 4 CTX-M-15 + CMY: 45 CTX-M-15 + DHA: 10	CTX-M-27 + CMY: 1 SHV-ESBL + CMY: 2
Global isolates of non-CP CR-potentially chromosomal AmpC-hyperproducing species				
2017–2019	(n=232) Class A CTX-M-15: 86 (37.1%; CZA-R: 70.9%) CTX-M-9: 6 CTX-M-3: 5	PER-7: 1 VEB-1: 7 (CZA-R: 85.7%) VEB-6: 1 VEB-9: 6 (CZA-R: 100%) Class C ACC: 2	Combinations of the above enzymes CTX-M-15 + SHV-ESBL: 1 CTX-M-15 + VEB-9: 1 CTX-M-15 + AMPC: 3	SHV-ESBL + AMPC: 1 SHV-ESBL + CMY: 1 VEB-9 + AMPC: 3 VEB-9 + CMY: 2 VEB-9 + DHA: 1

(*continued on next page*)

Table 1 (*continued*)

Non-carbapenemase β-lactamases-encoding genes (%), CRE species (isolate no.), in different regions or globally, in different periods Periods	Regions Non-CP CR-*Klebsiella pneumoniae*			
	Asia (7 countries)	Africa/the Middle East (8 countries)	Europe (18 Countries)	Latin America (8 Countries)
	SHV-ESBL: 12 (CZA-R: 91.7%) PER-1: 3 (CZA-R: 33.3%)	ACT-MIR: 2 AMPC: 21 (CZA-R: 85.7%) CMY: 34 (14.7%; CZA-R: 97.1%) DHA: 11 (CZA-R: 81.8%)	CTX-M-15 + CMY: 5 CTX-M-15 + DHA: 4	
2020–2022	(n=324) Class A CTX-M-15: 113 (34.9%; CZA-R: 77.9%) CTX-M-9: 14 (CZA-R: 85.7%) CTX-M-12: 4 SHV-ESBL: 29 (9%; CZA-R: 100%) TEM-ESBL: 3 GES-1: 1 (CZA-R: 0%) GES-2: 2 (CZA-R: 50%)	PER-1: 1 (CZA-R: 100%) PER-4: 1 (CZA-R: 100%) VEB-1: 3 (CZA-R: 100%) VEB-6: 2 (CZA-R: 100%) VEB-9: 21 (CZA-R: 100%) VEB-14: 1 (CZA-R: 100%) VEB-24: 1 (CZA-R: 100%)	Class C ACC: 1 CMY: 60 (18.5%; CZA-R: 91.7%) DHA: 27 (CZA-R: 92.6%) FOX-1 Combinations of the above enzymes CTX-M-15 + SHV-ESBL: 4 CTX-M-15 + CMY: 6 CTX-M-15 + DHA: 4	SHV-ESBL + CMY: 3 SHV-ESBL + (DHA: 2 all VEB + CMY: 5 all VEB + DHA: 6

Abbreviations: CRE, carbapenem-resistant Enterobacterales. non-CP, non-carbapenemase-producing. no., number. CZA, ceftazidime-avibactam. R, resistant. ESBL, extended-spectrum β-lactamase.

CTX-M genotype (63.8% and 68.6%), with the highest incidence observed in Asia (87.3% [276/316] and 88.7% [766/864], respectively) and the lowest incidence in Latin America (44.3% [121/273] and 50.4% [286/568], respectively) during the two stages (Table 1). The CTX-M-15 variant was also the predominant ESBL enzyme among global isolates of non-CP CR-*E. coli* (56.9–57.2%) and CR-potentially chromosomal AmpC-hyperproducing Enterobacterales species (34.9–37.1%) during the study period.

Notably, after excluding isolates that harbored dual bla_{ESBL}s or a single bla_{ESBL} plus a single bla_{AmpC} variant collected between 2017 and 2022, the remaining isolates harboring $bla_{\text{CTX-M-15}}$ alone accounted for the majority of non-CP CR-*K. pneumoniae* isolates in each region (92.2% [961/1042] in Asia, 94% [315/335] in Africa/the Middle East, 90.9% [894/984] in Europe, and 78.6% [320/407] in Latin America, respectively; Table 1). Meanwhile, a significantly lower percentage of $bla_{\text{CTX-M-15}}$ alone is observed among non-CP CR-*E. coli* isolates across the four regions (66.3% [165/249]) compared to those for non-CP CR-*K. pneumoniae* isolates in each region (Table 1).

Before CZA was launched, the CZA resistance rate among global non-CP CRE isolates collected between 2012 and 2014 was 17% (74/436; not shown in Table 1). Furthermore, most of the non-CP CRE isolates harboring either dual class A genes or a single class A gene plus a class C gene exhibited resistance to CZA (> 96%). However, substantial fractions of non-CP CR-*K. pneumoniae* isolates collected in Asia and Africa/the Middle East, as well as global isolates of non-CP CR-*E. coli* and CR-potentially chromosomal AmpC-hyperproducing Enterobacterales species, exhibited resistance to CZA [all were > 49%, Fig. 1**(A)** and 1**(C)**]. Additionally, rates of CZA susceptibility among non-CP CR-*K. pneumoniae* isolates collected in Europe and Latin America were higher (> 68%) compared to those in Asia and Africa/the Middle East [< 51%; Fig. 1**(A)**], with statistical differences (all *P* values < 0.001). Similar geographic variations were also observed in MVB susceptibilities among non-CP CR-*K. pneumoniae* (MVB susceptibility rates, 5.3% in Asia, 4.7% in Africa/the Middle East, 45.8% in Europe, and 66.7% in Latin America, respectively; *P* values < 0.001). Susceptibility rates of non-CP CR-*K. pneumoniae* isolates to MVB were significantly lower than those to CZA (*P* < 0.001; Fig. 1**(B)**), except in Latin America (*P*=0.66). Moreover, the MIC_{50} values of MVB being 16–32 mg/L were noted among global non-CP CR-*K. pneumoniae*, *E. coli*, and potentially chromosomal AmpC-hyperproducing Enterobacterales isolates, except for non-CP CR-*K. pneumoniae* isolates in Latin America (1 mg/L; Supplementary Table).

Between the two periods, significant differences were observed in rates of CZA susceptibility among non-CP CR-*K. pneumoniae* isolates in Africa/the Middle East and Latin America [both *P* values were < 0.001, Fig. 1**(A)**], and among global non-CP CR-*E. coli* isolates [*P*=0.0043, Fig. 1**(D)**]. Rates of MVB susceptibility to non-CP CR-*K. pneumoniae*, *E. coli* and potentially chromosomal AmpC-hyperproducing Enterobacterales isolates collected across four regions between 2020 and 2022 were 33.2%, 15%, and 18.8%, respectively [Fig. 1**(B)** and 1**(D)**]. In striking contrast, susceptibility rates of isolates of these three predominant Enterobacterales classes to ATM-AVI were all > 94% [Fig. 1**(C)** and 1**(D)**].

Supplementary Table presents the MIC_{50} and MIC_{90} data for the three novel antibiotics against isolates of the aforementioned Enterobacterales classes collected both regionally and globally at two different stages.

This 2017–2022 ATLAS study shows that the CTX-M-15 variant has become the overwhelmingly predominant ESBL enzyme in global isolates of non-CP CRE, irrespective of species (Table 1). CTX-M-15 enzyme alone in Enterobacterales species mostly exhibits low hydrolytic activity in vitro against carbapenems. A study by Bonnin et al., which investigated the MIC distributions of CZA to 123 non-CP CRE isolates that were validated to have ESBL production coupled with membrane impermeability, revealed that the CZA susceptibility rate was approximately 90%, significantly higher than susceptibility to MVB (54.5%).[2] The finding of CZA susceptibility (90%)[2] is also significantly higher than those of our study. Similarly, relatively low MVB susceptibility rates to global non-CP CRE isolates (< 33%) in this ATLAS study also significantly contrast with the MVB susceptibility rate among European non-CP CRE isolates in the study of Shortridge et al. (96%).[6]

In this study, only a few non-CP CR-*K. pneumoniae* isolates harbored various plasmidic bla_{AmpC} genes during the study period (≤ 5.4%, Table 1). Vaborbactam shares identical entry porins (primarily OmpK36, followed by OmpK35) with meropenem in *K. pneumoniae*. However, Nicolas-Chanoine et al. observed that the production of CTX-M-15, combined with overproduction of the AcrAB/OqxAB efflux pumps and/or OmpK35/36 porin dysfunction, did not confer significantly reduced CZA susceptibilities in *K. pneumoniae* strains.[7] In contrast, Pagès et al. demonstrated that outer membrane impermeability, unrelated to dysfunction of major porins (OmpK35/36 in *K. pneumoniae*, and OmpF/C in *E. coli*), likely results in reduced CZA susceptibility among some multidrug-resistant

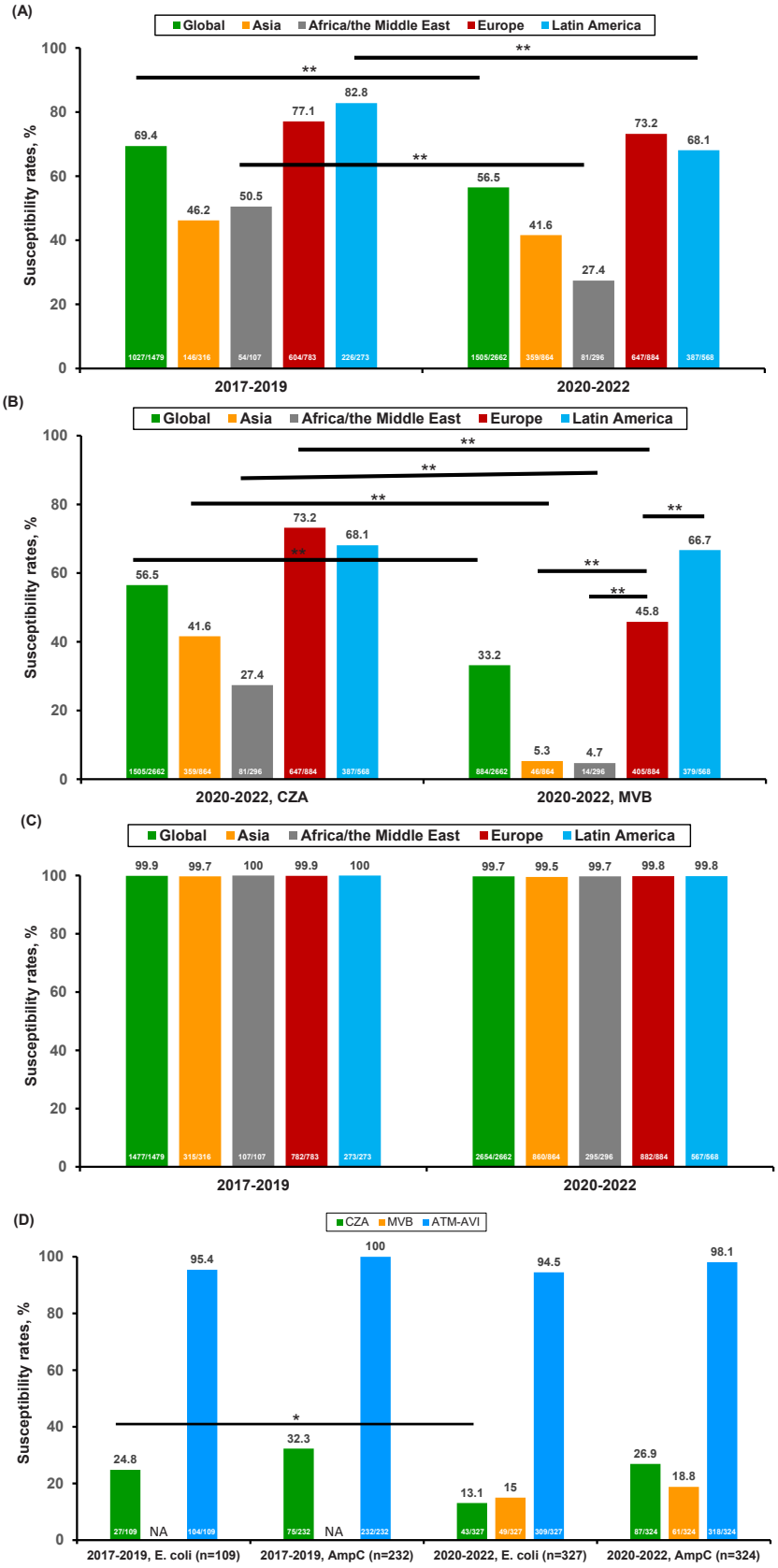

Fig. 1. Geographic differences in susceptibility rates of isolates of non-carbapenemase-producing, meropenem-resistant *Klebsiella pneumoniae*, *Escherichia coli*, and potentially chromosomal AmpC-hyperproducing Enterobacterales to ceftazidime-avibactam [**1(A)**, **1(B)**, and **1(D)**], aztreonam-avibactam (using the susceptibility breakpoint of ≤8 mg/L)[5] [**1(C)**, and **1(D)**], and meropenem-vaborbactam [**1(B)**, and **1(D)**]. Data were obtained from the 2017–2022 Antimicrobial Testing Leadership and Surveillance database. The numerals at the bottom of each bar represent the number of isolates susceptible to the indicated antibiotic and the total number of isolates studied in each region or globally during two different stages. **Abbreviations:** AmpC, isolates of potentially chromosomal AmpC-hyperproducing Enterobacterales species; CZA, ceftazidime-avibactam; MVB, meropenem-vaborbactam; ATM-AVI, aztreonam-avibactam; NA, not applicable. $^{**}P < 0.001$; $^{*}P < 0.01$.

Enterobacterales isolates.[8] Complex combinations of ESBL hyperproduction, outer membrane impermeability, and OmpK35/36 porin dysfunction likely work together to confer resistance to CZA and MVB in non-CP CR-*K. pneumoniae* isolates, which may be prevalent in Asia and Africa/the Middle East to a significant extent [Table 1, Fig. 1**(A)** and 1**(B)**].

This study shows high susceptibility rates of the main non-CP CRE species to ATM-AVI [> 94%; Fig. 1**(C)** and 1**(D)**]. The resistance mechanism of CMY-16 production, coupled with dysfunctional porins (OmpK35/36), has been reported to confer non-CP CR-*K. pneumoniae* isolates exhibiting high MICs (≥ 16 mg/L) to ATM-AVI.[9] Nevertheless, the 2017–2022 ATLAS database indicates that all 126 non-CP CR-*K. pneumoniae* isolates harboring various bla_{CMY} genes exhibited MICs of ≤ 2 mg/L (MIC_{90} value: 1 mg/L) to ATM-AVI (not shown in Table 1**)**. Additionally, Mendes et al. demonstrated that the resistance mechanisms involving the production of either DHA-1 or PER-2, coupled with overexpression of *acrA*, and/or dysfunction of OmpK35 or OmpK36 porins, confer MICs of ATM-AVI ≥ 4 mg/L in *K. pneumoniae*.[10] The prevalence rates of *K. pneumoniae* isolates harboring either bla_{DHA} or bla_{PER} were low in this 2017–2022 ATLAS study (Table 1).

The limitations of this study are as follows. First, the ATLAS project did not contain data on CZA consumption for the countries participating in the ATLAS study. Thus, we could not analyze the relationship between yearly CZA consumption and non-susceptibility rates of non-CP CRE to CZA. Second, this study did not include clonal relatedness or phylogenetic analyses of the tested non-CP CRE isolates.

In conclusion, although the actual mechanisms of CZA/MVB resistance are not thoroughly elucidated among non-CP CRE isolates in this ATLAS study, the in vitro susceptibility findings of this investigation underscore the need to understand regional susceptibility profiles of non-CP CRE isolates to novel antibiotics, ensuring appropriate prescription choices for treating these highly resistant isolates.

Ethics approval

The ATLAS program was approved by the institutional review board of each participating center, including National Taiwan University Hospital (NTUH; Taipei, Taiwan) [NTUH 201211047RSC].

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Declaration of Generative AI and AI-assisted technologies in the writing process

Generative AI and AI-assisted technologies were not used in the writing process of this manuscript.

Declaration of Competing Interest

All authors declare that they have no competing interests.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jinf.2024.106380.

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