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Introduction

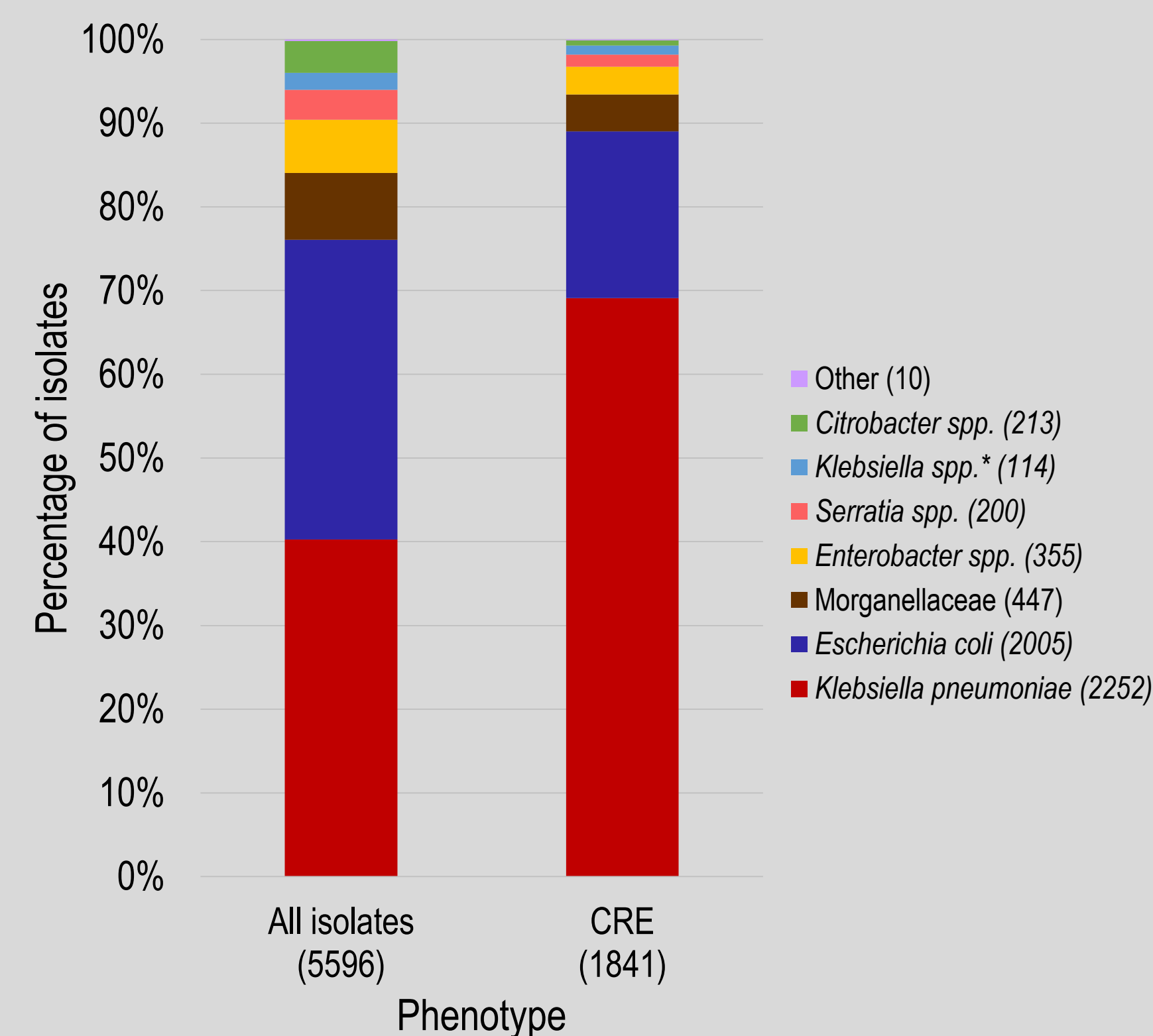
Aztreonam-avibactam is an approved therapeutic in the United States, Europe, and India. Aztreonam is stable to hydrolysis by metallo-β-lactamases (MBLs), while avibactam inhibits class A, C, and some class D β-lactamases, often co-carried by MBL-positive isolates, that inactivate aztreonam. This study demonstrates the *in vitro* activity of aztreonam-avibactam (ATM-AVI) against carbapenem-resistant Enterobacterales (CRE) isolates collected from 2019-2023 in India as a part of the ATLAS global surveillance program [1].

Methods

- 5,596 Enterobacterales isolates were collected from 12 sites in India in 2019-2023. Two of these sites did not participate in the entire five-year period.
- Broth microdilution was performed according to CLSI guidelines and aztreonam-avibactam susceptibility was interpreted according to EUCAST 2025 breakpoints [2,3].
- Isolates with meropenem MICs >1 µg/mL were screened for β-lactamases by PCR as previously described [4]. 1881/5596 of isolates were meropenem-nonsusceptible and 1841 of these were available to characterize by PCR.

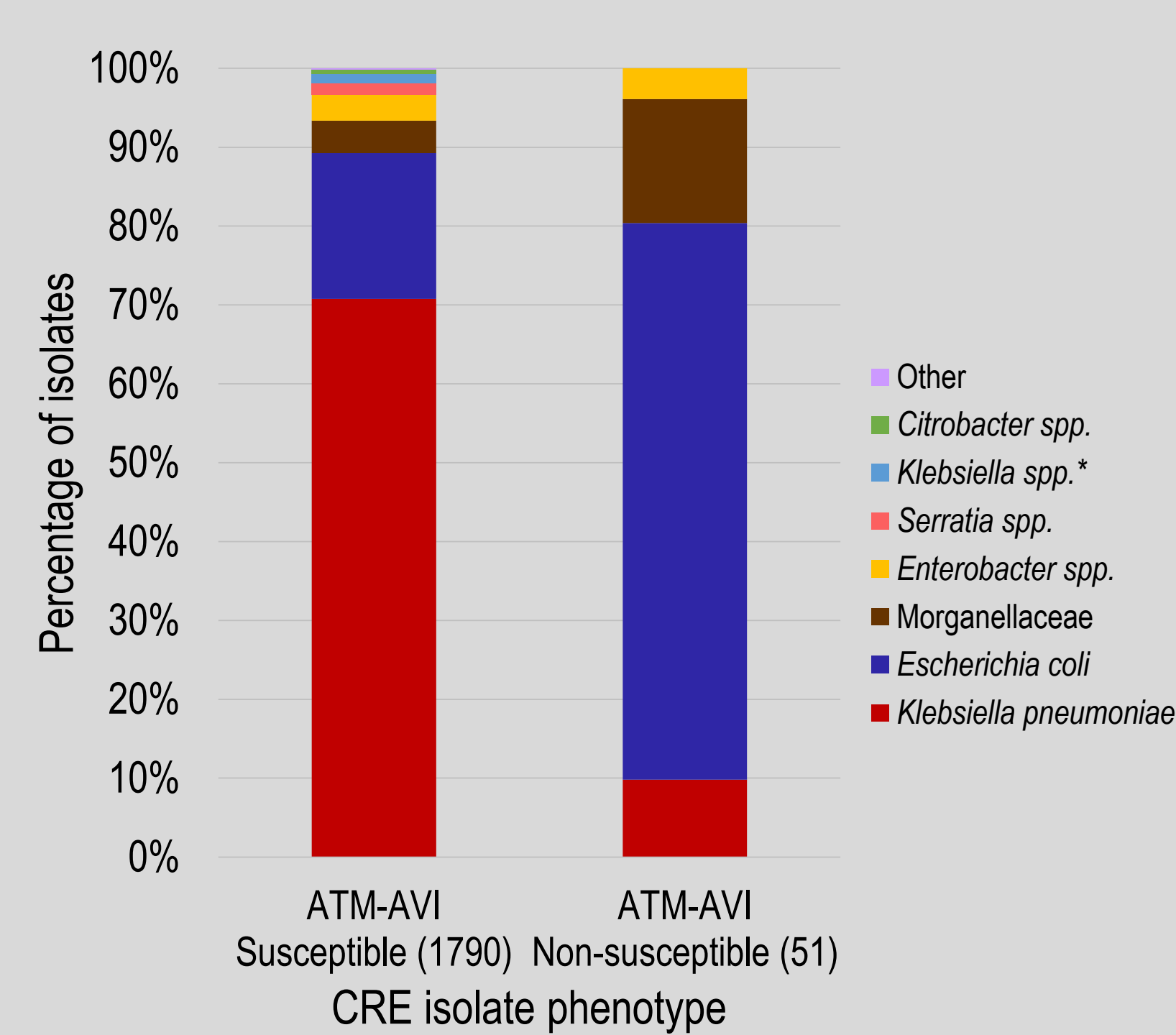
Results

Figure 1A. Isolates in this study, by taxonomy



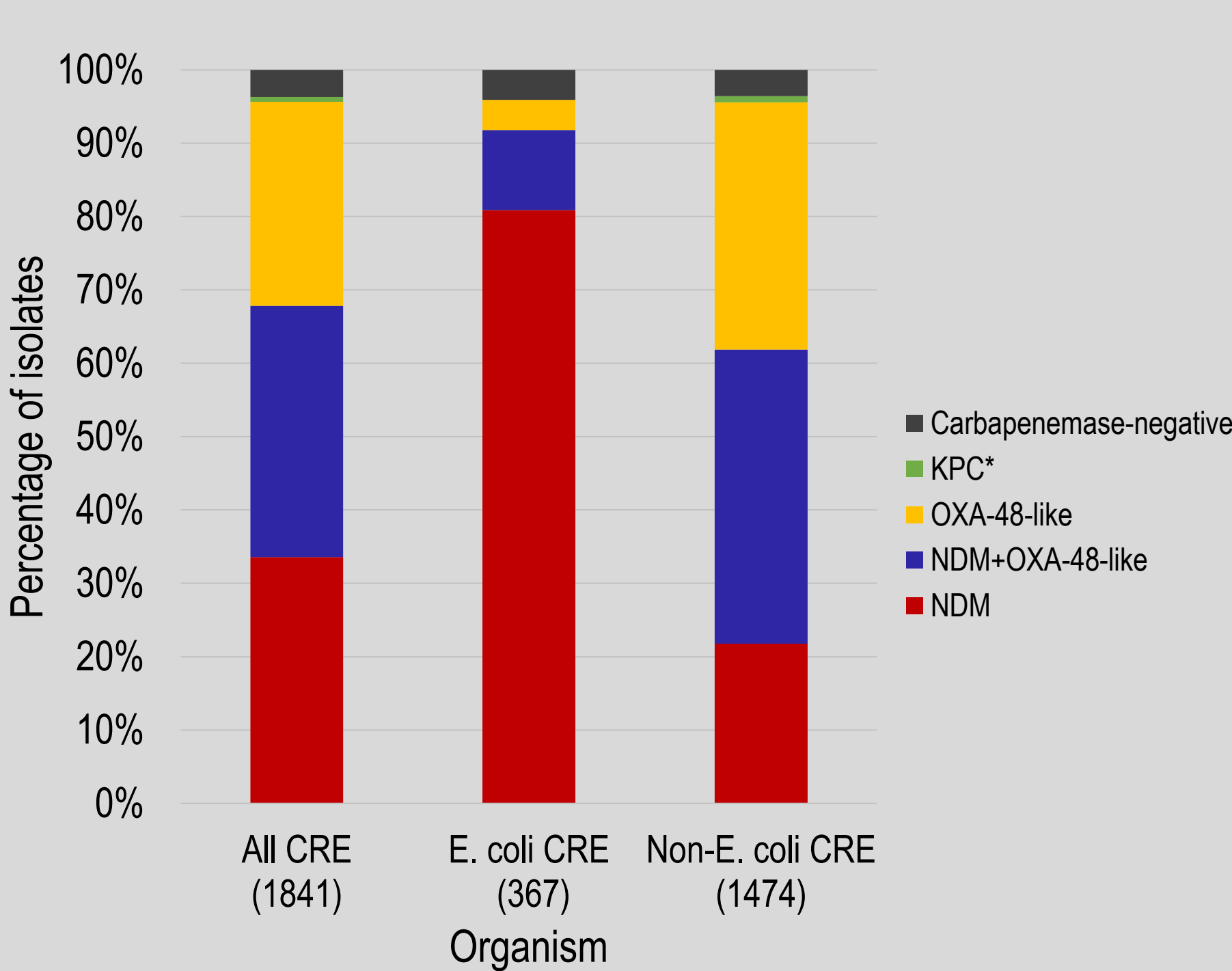
* Species other than *Klebsiella pneumoniae*

Figure 1B. Taxonomy of CRE isolates by ATM-AVI susceptibility



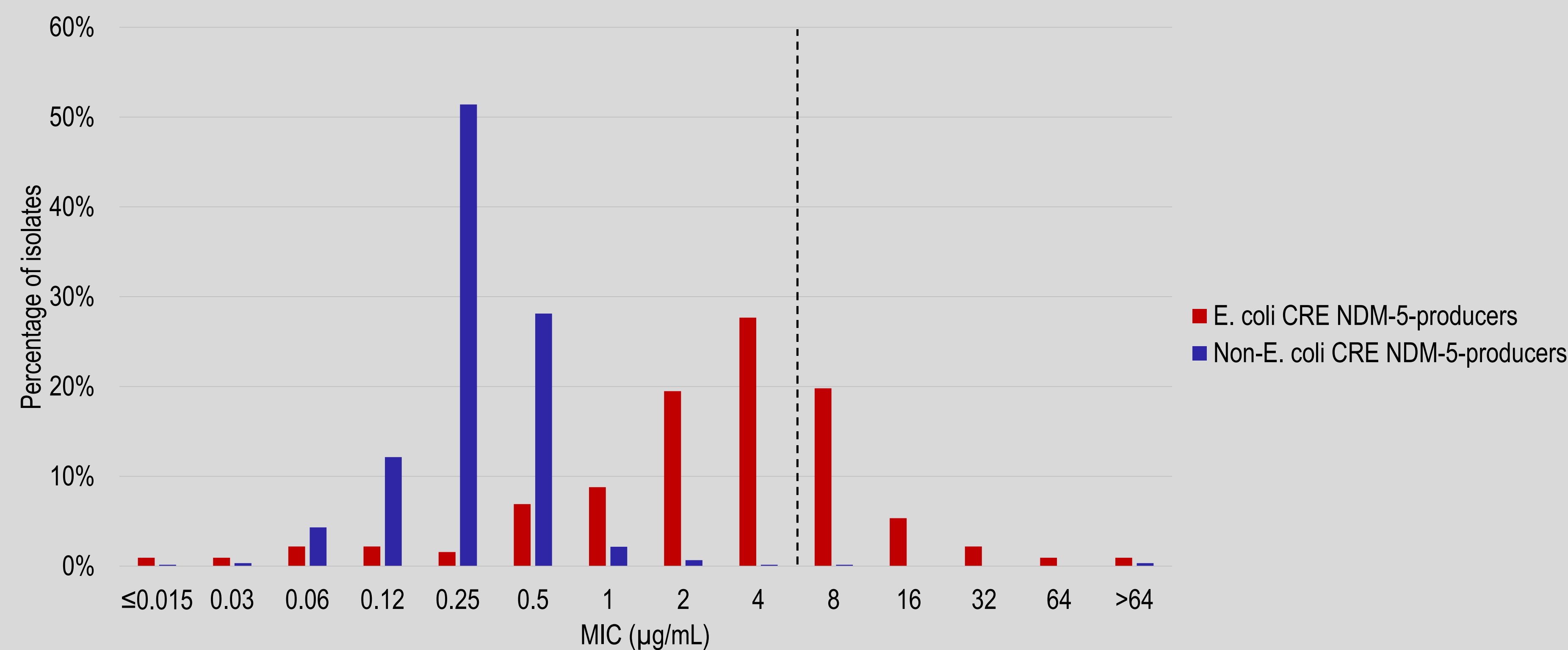
*Species other than *Klebsiella pneumoniae*.

Figure 2. Carbapenemases identified among all CRE, *E. coli* CRE, and non-*E. coli* CRE



*Includes two isolates that also co-carry OXA-48-like carbapenemases.

Figure 3. Frequency distribution of aztreonam-avibactam MIC of *E. coli* and non-*E. coli* NDM-5-producers



The dotted line indicates EUCAST 2025 breakpoint of 4 µg/mL aztreonam with 4 µg/mL avibactam.

Table 1. *In vitro* activity of aztreonam-avibactam against characterized CRE, *E. coli* and non-*E. coli*, by carbapenemase

Phenotype/Genotype	n	Aztreonam-avibactam MIC (µg/mL), cumulative percent inhibited													
		≤0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	>64
Characterized CRE	1841	15	21	79	207	732	386	73	78	115	84	28	8	4	11
		0.8	2	6.2	17.5	57.3	78.2	82.2	86.4	92.7	97.2	98.8	99.2	99.4	100
Characterized <i>E. coli</i> CRE	367	3	3	11	9	15	26	30	65	93	76	20	8	3	5
		0.8	1.6	4.6	7.1	11.2	18.3	26.4	44.1	69.5	90.2	95.6	97.8	98.6	100
NDM	296	3	3	7	7	5	20	24	57	72	66	19	7	3	3
		1.0	2.0	4.4	6.8	8.4	15.2	23.3	42.6	66.9	89.2	95.6	98.0	99.0	100
NDM+OXA-48-like	40						3	5	5	19	6	1			1
							7.5	20.0	32.5	80.0	95.0	97.5			100
OXA-48-like	15			3	1	4	1		1	2	3				
				20.0	26.7	53.3	60.0		66.7	80.0	100				
Characterized Non- <i>E. coli</i> CRE	1474	12	18	68	198	717	360	43	13	22	8	8	1	6	
		0.8	2.0	6.6	20.1	68.7	93.1	96.1	96.9	98.4	99.0	99.5	99.6	100	
NDM+OXA-48-like	590			7	59	287	192	18	5	12	5	3		2	
				1.2	11.2	59.8	92.4	95.4	96.3	98.3	99.2	99.7		100	
OXA-48-like	497	3		2	45	302	124	14	2	3		1		1	
		0.6		1.0	10.1	70.8	95.8	98.6	99.0	99.6		99.8		100	
NDM	321	9	16	57	86	99	30	7	4	4	3	4		2	
		2.8	7.8	25.5	52.3	83.2	92.5	94.7	96.0	97.2	98.1	99.4		100	
KPC	12			1	2	4	2	2					1		
				8.3	25.0	58.3	75.0	91.7					100		

Abbreviations: MIC, minimum inhibitory concentration; n, number of isolates; CRE, carbapenem-resistant Enterobacterales. MIC₉₀ values are in bold. *Includes one isolate that also co-carries OXA-48-like carbapenemase.

Table 2. *In vitro* activity of aztreonam-avibactam against NDM-5-producing *E. coli*, by co-carriage of CMY

Genotype	n	%S	MIC ₅₀	MIC ₉₀
NDM-5-producing <i>E. coli</i>	318	70.8	4	8
CMY-negative	147	87.8	2	8
CMY-positive	171	56.1	4	16

Abbreviations: MIC, minimum inhibitory concentration

Results Summary

- Of Enterobacterales isolates collected, 34% were CRE and 69% of CRE were *Klebsiella pneumoniae* (Figure 1A).
- Among CRE, 135 were ATM-AVI-non-susceptible, with *E. coli* comprising 83% of this subset (Figure 1B).
- Of characterized CRE, 34% carried a variant of NDM, 28% a variant of OXA-48-like, and exclusive of those, a further 34% carried both NDM+OXA-48-like carbapenemases (Figure 2). Among *E. coli* CRE, 91% carried a variant of NDM compared to 61% among non-*E. coli* (including those that co-carried OXA-48-like carbapenemases).
- Of characterized CRE, 92.7% were susceptible to ATM-AVI (MIC₉₀ of 4 µg/mL) (Table 1). Characterized *E. coli* had reduced rates of susceptibility to ATM-AVI compared to non-*E. coli*: 69.5% susceptible and MIC₉₀ of 8 µg/mL compared to 98.4% susceptible and MIC₉₀ of 0.5 µg/mL.
- Of characterized *E. coli* CRE, 87% carried blaNDM-5 ± blaOXA-48-like, a genotype associated with a modal ATM-AVI MIC of 4 µg/mL (Figure 3). NDM-5 was also present in 41% of non-*E. coli* CRE and was associated with a modal ATM-AVI MIC of 0.25 µg/mL.
- Among NDM-producing *E. coli*, those that carried a CMY AmpC enzyme had reduced susceptibility to ATM-AVI compared to those without: 56.1% susceptible and MIC₉₀ of 16 µg/mL vs 87.8% susceptible and MIC₉₀ of 8 µg/mL (Table 2). In *E. coli* select variants of AmpC and mutations in PBP3 have been reported to contribute to elevated ATM-AVI MICs [5].

Conclusions

- Aztreonam-avibactam demonstrated potent *in vitro* activity against isolates of non-*E. coli* CRE carrying carbapenemases.
- Aztreonam-avibactam demonstrated potent *in vitro* activity against non-*E. coli* CRE carrying NDM-5. Acquired AmpC was associated with aztreonam-avibactam-resistance in NDM-5-positive isolates of *E. coli*. Previous reports have shown that PBP3 mutations which were not characterized in this study also contribute to resistance in isolates with both NDM-5 and AmpC. The potent *in vitro* activity of aztreonam-avibactam against NDM-5-positive non-*E. coli* CRE further reinforces that this variant of NDM does not confer resistance to aztreonam-avibactam.

References

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Disclosures

This study was sponsored by Pfizer. GS an KP are employees of Pfizer. ME, JD, HL, and DS are employees of IHMA, which received fees from Pfizer for the conduct of the study and poster preparation.