



Resistance to novel beta-lactams

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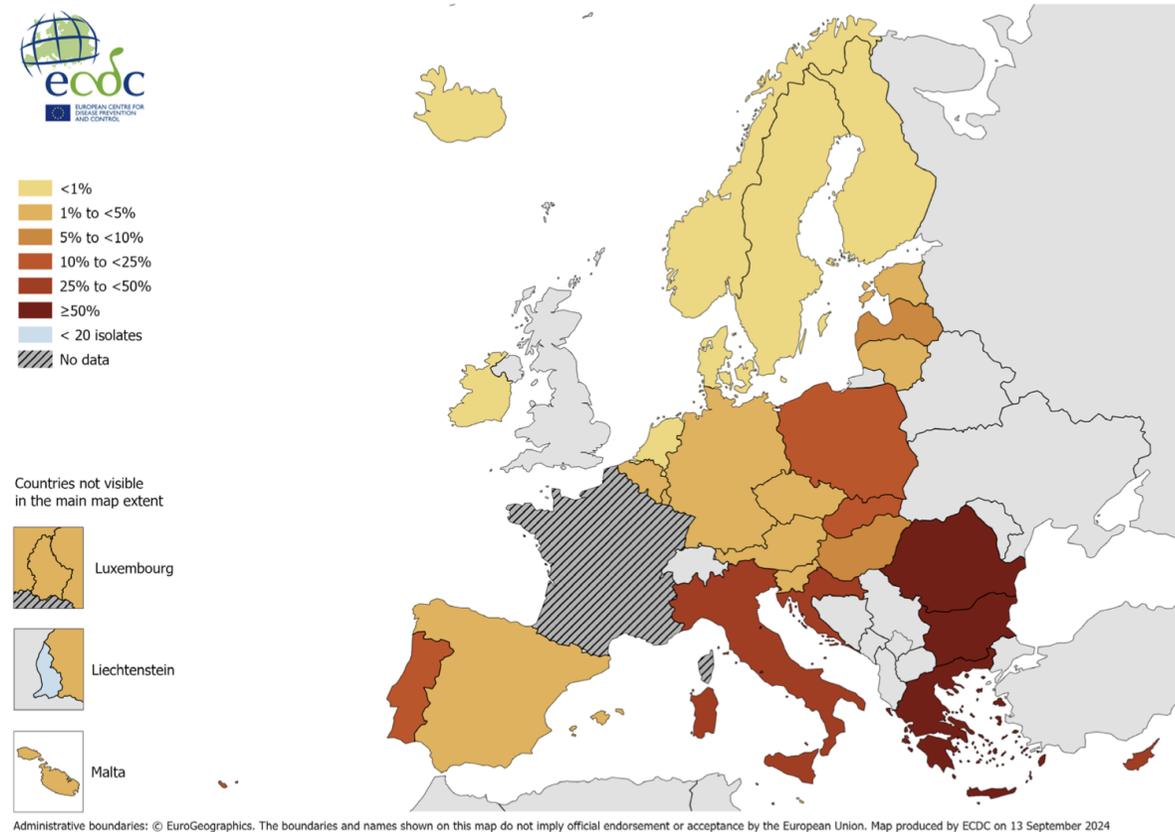
Karolinska Institutet and Karolinska University Hospital

NordicAST workshop 27-28 May 2025

Background epidemiology

Most recent European data (2023)

Figure 5. *Klebsiella pneumoniae*. Percentage of invasive isolates resistant to carbapenems (imipenem/meropenem), by country, EU/EEA, 2023



Data published in Global Antibiotic Awareness Week 2024

Increasing incidence 2019-2023

Bacterial species	Antimicrobial group/agent	Estimated incidence ^b of isolates from bloodstream infections with resistance phenotype (n per 100 000 population)						
		2019 (baseline year)	2020	2021	2022	2023	Trend 2019-2023 ^c	Change 2019-2023 (%) ^d
<i>Escherichia coli</i>	Aminopenicillin (amoxicillin/ampicillin) resistance	28.46	24.80	23.89	26.25	28.42	-	-0.1
	Third-generation cephalosporin (cefotaxime/ceftriaxone/ceftazidime) resistance	10.74	8.88	7.87	9.12	10.35	-	-3.6
	Carbapenem (imipenem/meropenem) resistance	0.20	0.10	0.08	0.12	0.14	-	-30.0
	Fluoroquinolone (ciprofloxacin/levofloxacin/ofloxacin) resistance	16.82	14.34	12.64	14.00	15.70	-	-6.7
	Aminoglycoside (gentamicin/netilmicin/tobramycin) resistance ^e	7.17	6.16	5.17	5.76	6.59	-	-8.1
	Combined resistance to third-generation cephalosporins, fluoroquinolones, and aminoglycosides ^e	3.81	3.01	2.54	2.89	3.36	-	-11.8
<i>Klebsiella pneumoniae</i>	Third-generation cephalosporin (cefotaxime/ceftriaxone/ceftazidime) resistance	7.59	7.26	7.67	7.93	9.25	↑	+21.9
	Carbapenem (imipenem/meropenem) resistance	2.52	2.77	3.19	3.11	3.97	↑	+57.5
	Fluoroquinolone (ciprofloxacin/levofloxacin/ofloxacin) resistance	7.48	7.24	7.46	7.65	8.83	↑	+18.0
	Aminoglycoside (gentamicin/netilmicin/tobramycin) resistance ^e	5.07	4.69	5.01	5.11	5.96	↑	+17.6
	Combined resistance to third-generation cephalosporins, fluoroquinolones, and aminoglycosides ^e	4.46	4.14	4.47	4.52	5.26	↑	+17.9

Number of global deaths attributable to AMR

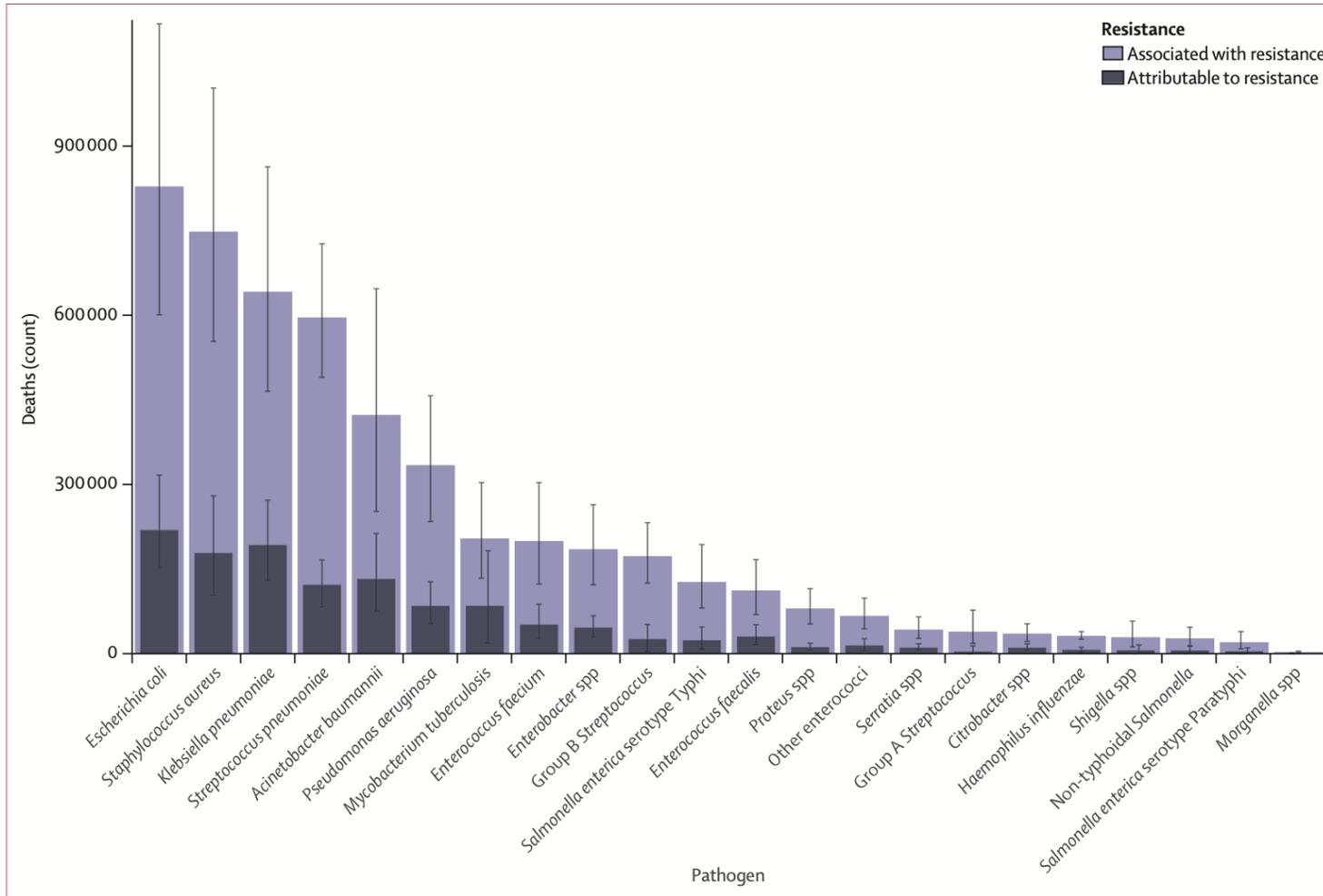
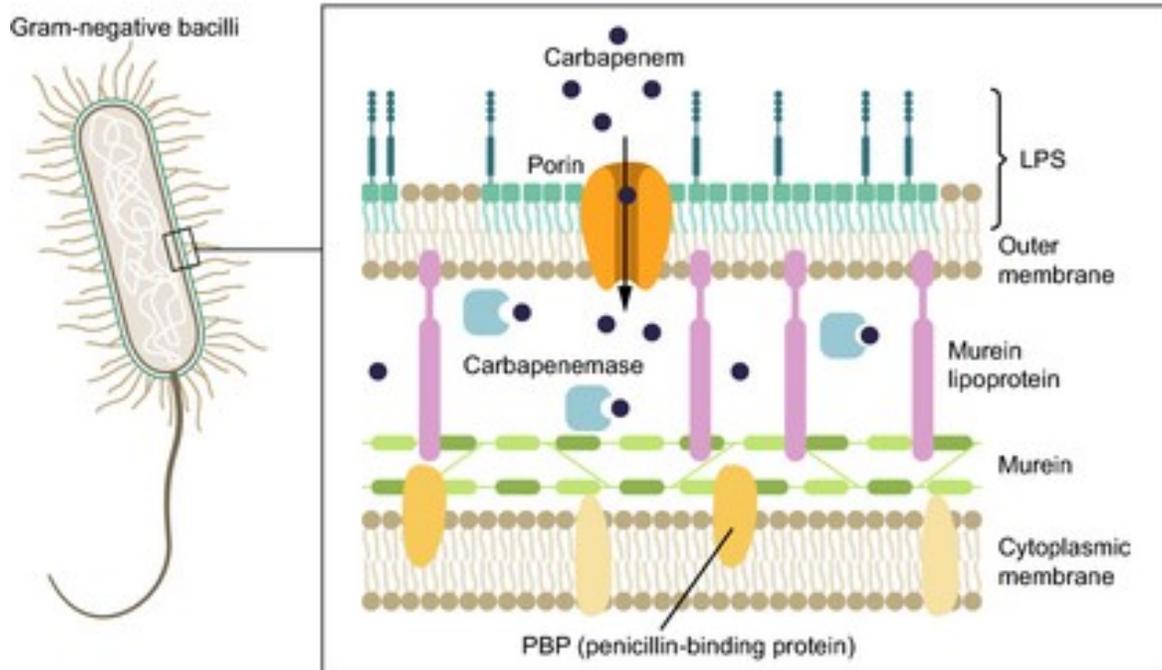


Figure 4: Global deaths (counts) attributable to and associated with bacterial antimicrobial resistance by pathogen, 2019
Estimates were aggregated across drugs, accounting for the co-occurrence of resistance to multiple drugs. Error bars show 95% uncertainty intervals.

Emerging resistance to novel agents

How do you kill a Gram-negative?

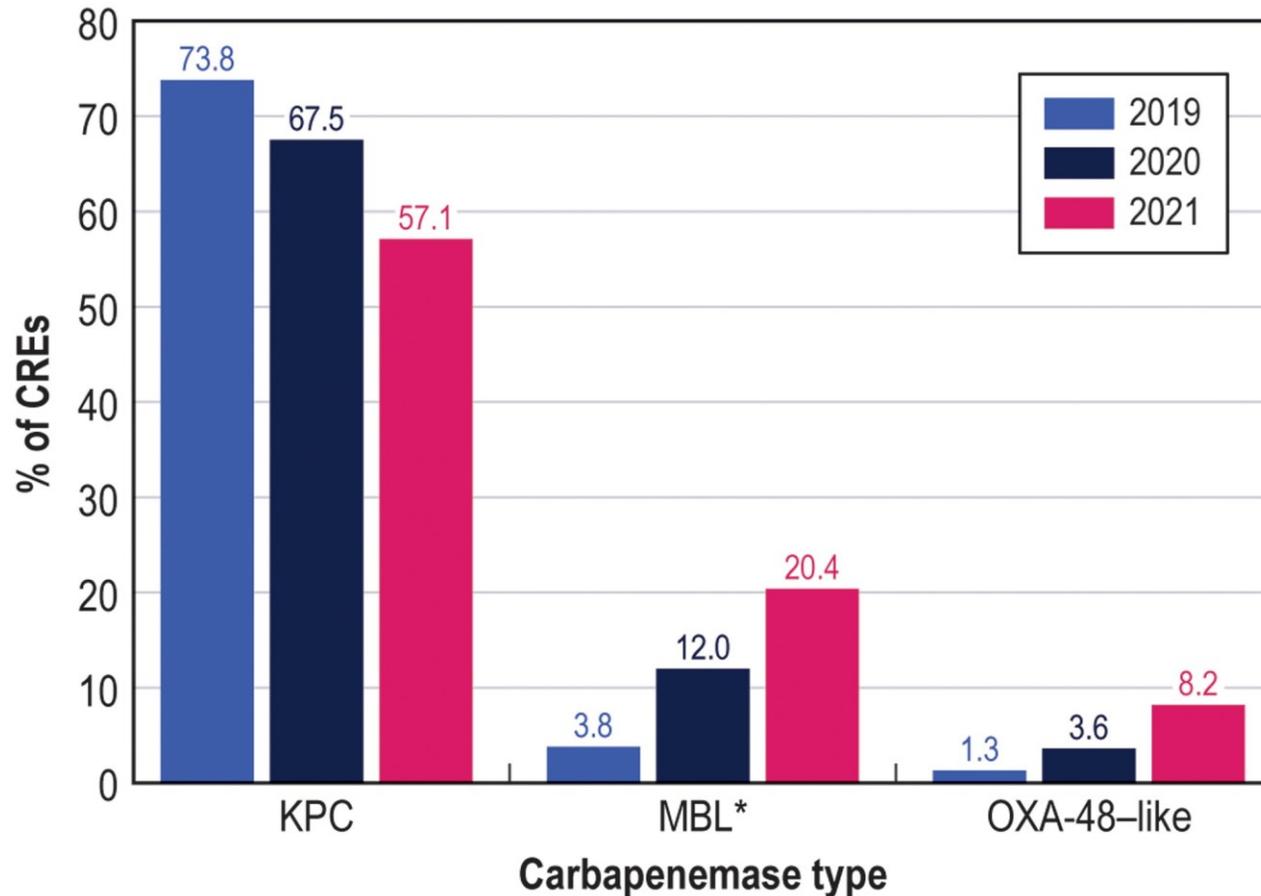


- 1) Get in the cell
- 2) Evade inactivating enzymes
- 3) Bind to the receptor

Drug development in recent years has considered 2), but not 1) and 3)...

Tängdén T and Giske CG. J Intern Med. 2015;277(5):501-12.

Gradual shift of carbapenemase types (US)



* Includes NDM type (87.9%) and IMP type (12.1%).

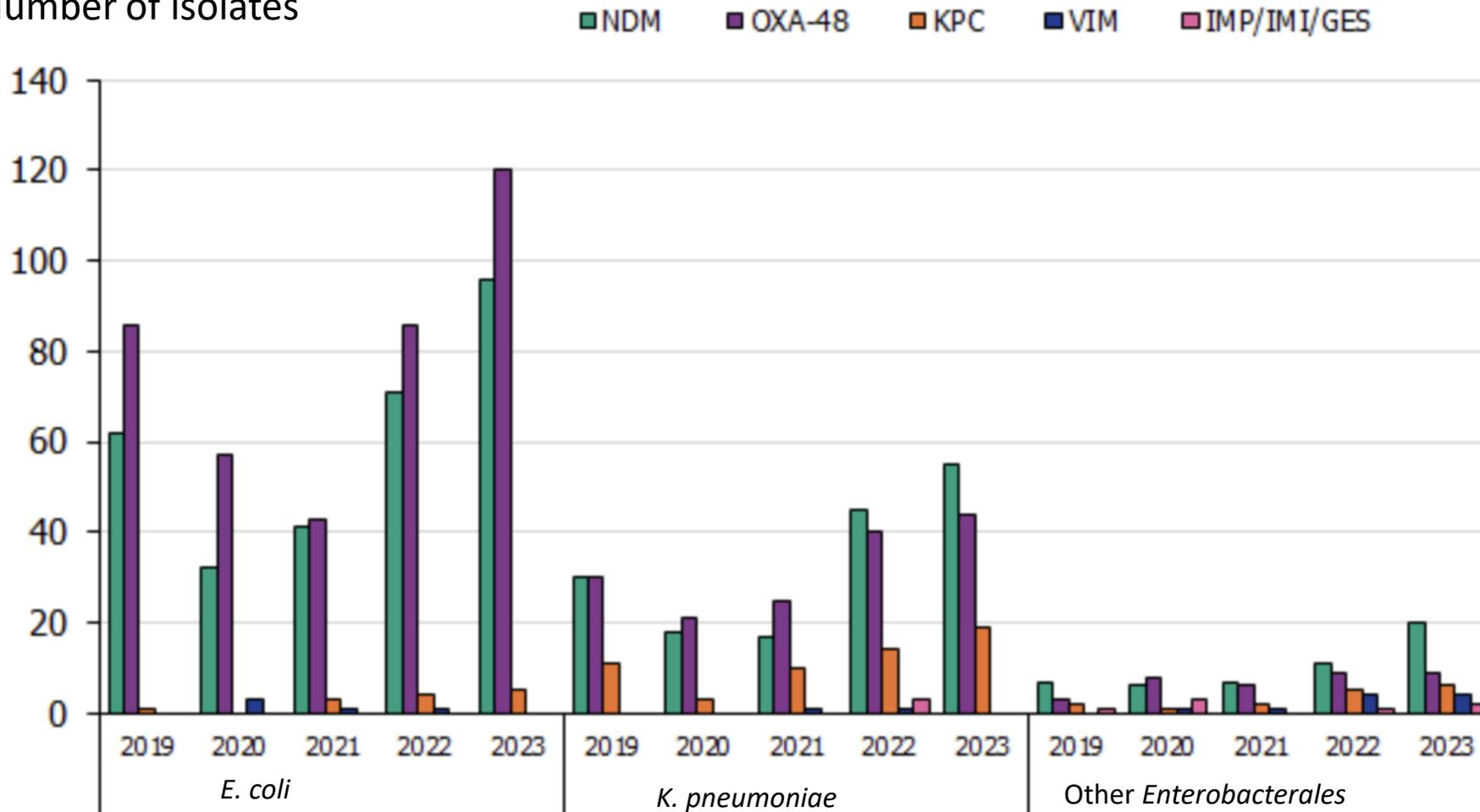
261 CRE cases from 44 medical centers in the US

Part of a global trend of shift towards MBL and OXA-48-like enzymes

Sader HS et al. Open Forum Inf. Dis. 2023; 10.1093

Example from Europe – carbapenemases in Sweden 2023

Number of isolates



Shift towards more NDM and OXA-48

Source: Public Health Sweden

Treatment of KPC-producers (absence of acq. resistance)

Antimicrobials	Activity (<i>in vitro</i>)
Ceftolozane-tazobactam	⊖
Ceftazidime-avibactam	✓
Meropenem-vaborbactam	✓
Imipenem-relebactam	✓
Cefiderocol	✓
Aztreonam-avibactam	✓
Cefepime-enmetazobactam	⊖

Development of resistance can occur to all mentioned agents

Meropenem-vaborbactam has fairly high stability to resistance mechanisms

Treatment of OXA-48-producers (absence of acq. resistance)

Antimicrobials	Activity (<i>in vitro</i>)
Ceftolozane-tazobactam	⊖
Ceftazidime-avibactam	✓
Meropenem-vaborbactam ¹	Variable
Imipenem-relebactam	⊖
Cefiderocol	✓
Aztreonam-avibactam	✓
Cefepime-enmetazobactam ¹	Variable

MER-VAB and FEP-ENM can have activity, but not due to the inhibitor

Treatment of MBL-producers (absence of acq. resistance)

Antimicrobials	Activity (<i>in vitro</i>)
Ceftolozane-tazobactam	⊖
Ceftazidime-avibactam	⊖
Meropenem-vaborbactam	⊖
Imipenem-relebactam	⊖
Cefiderocol	✓
Aztreonam-avibactam ¹	✓
Cefepime-enmetazobactam	⊖

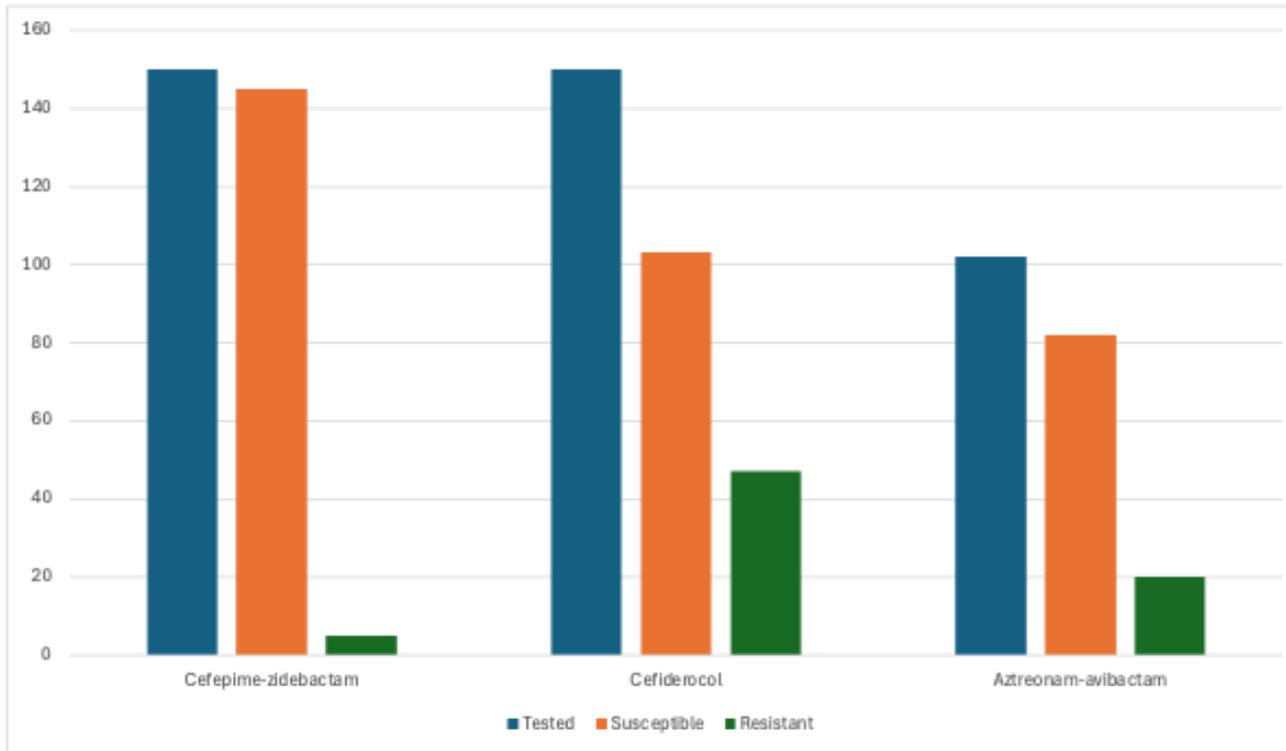
¹So far given as (ceftazidime)-avibactam+aztreonam, but now approved in Europe

Some problems when new drugs arrive

- We don't know the utility of the drug before we have started using it
 - Waiting for randomized controlled trials (e.g. investigator-initiated) takes a long time
 - Real-world evidence is frequently dismissed by expert groups
 - Pragmatic advice based on pre-clinical data is also frequently dismissed
- Frequently labs cannot test the antimicrobials initially
- Managing challenging foci of infection remains difficult
- Sometimes critically ill patients who need high $T > MIC$
- Prevention of emergence of resistance is rarely studied
- Combination therapy is seen as either/or – not as dependent of what/how

Acquired resistance to novel antimicrobials

Carbapenemase-producing *E. coli* from Karolinska University Hospital

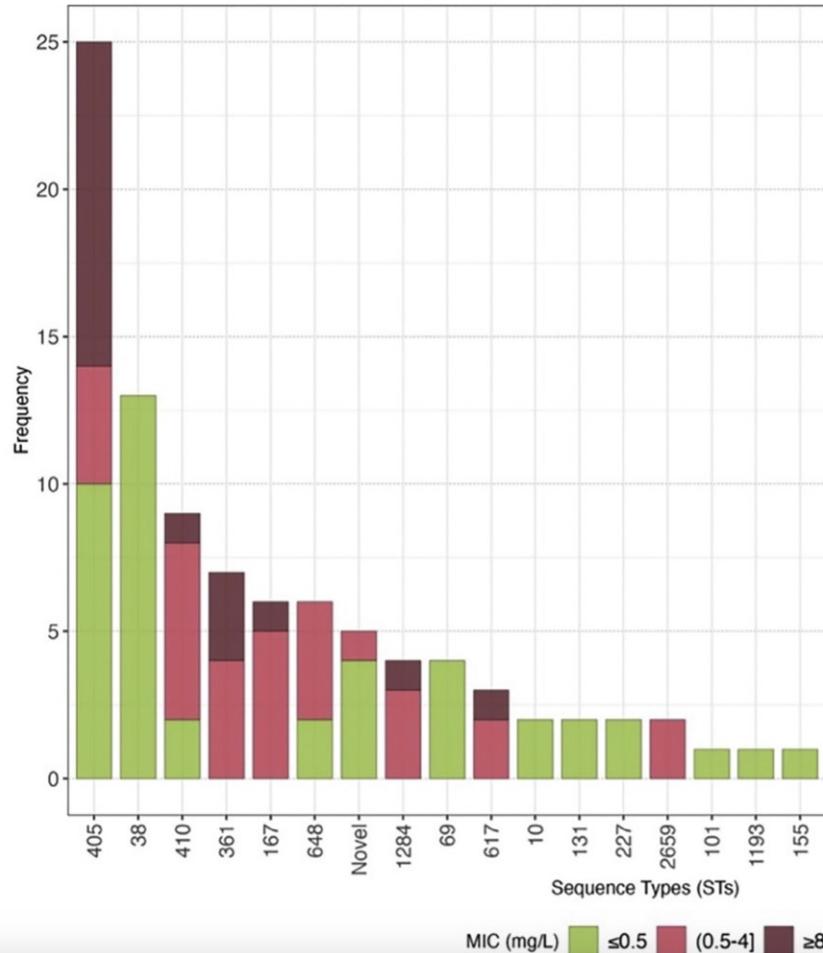


C. Tellapragada

Cefiderocol resistance is overestimated by disk diffusion

Mechanisms of resistance in both: PBP-3 changes (both), iron receptors (cefiderocol), porin deficiency (potentially both)

Emerging resistance to aztreonam-avibactam



Isolate	ST	ARG	CMY	<i>pbp3</i>	<i>acrR</i>	<i>ompF</i>	ATM-AVI MIC (mg/L)	ATM-AVI + PMBN (mg/L)	ATM-AVI+ PAβN (mg/L)
EC27422	361	NDM-5	CMY-145	YRIN	IS		16	2	16*
EC28622	405	NDM-5		YRIK		FS	16	2	4
EC27622	405	NDM-5		YRIK		FS	16	2	4
EC23022	405	NDM-5		YRIK		FS	16	2	4
EC44922	405	NDM-5	CMY-42	YRIK		FS	32	4	16*
EC31122	4450	OXA-244	CMY-42	YRIK			32	4	16*
EC29922	405	NDM-5		YRIK		FS	32	1	4
EC01200	167	NDM-5	CMY-42	YRIN	FS		8	0.5	4*
EC06522	448	OXA-181		YRIN			8	2	8*
EC00700	410	OXA-484	CMY-42	YRIN			8	0.5	2
EC16522	405	OXA-484		YRIK		FS	8	0.5	4*
EC02600	1284	NDM-1		YRIN			8	0.5	8*
EC02121	405	CTX-M-15		YRIK	FS	FS	8	0.5	4*
EC05200	361	NDM-5	CMY-42	YRIN			8	0.5	4*
EC05300	361	NDM-5		YRIN			8	<0.5	0.5
EC11222	405	NDM-5		YRIK		FS	8	0.5	4*
EC45622	405	NDM-5		YRIK		FS	8	0.5	8*
EC45722	405	OXA-48		YRIK		FS	8	0.5	4*
EC33821	405	NDM-5		YRIK		FS	8	2	4*
EC32622	617	NDM-5		YRIK			8	0.5	2

* No or <2-fold reduction in MICs.



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journal homepage: www.elsevier.com/locate/ijantimicag

Short Communication

Resistance to aztreonam-avibactam among clinical isolates of *Escherichia coli* is primarily mediated by altered penicillin-binding protein 3 and impermeability

Chaitanya Tellapragada^{a,*}, Mohammad Razavi^a, Pol Saludes Peris^{a,c}, Patrik Jonsson^b, Martin Vondracek^b, Christian G. Giske^{a,b}

Mentimeter question 1

Which mechanisms are of importance for resistance to aztreonam-avibactam?

- Efflux
- Hyperproduction of beta-lactamases
- Changes in penicillin-binding proteins
- Mutations in beta-lactamases
- Porin alterations

Mentimeter question 1

Which mechanisms are of importance for resistance to aztreonam-avibactam?

- Efflux
- Hyperproduction of beta-lactamases
- **Changes in penicillin-binding proteins**
- Mutations in beta-lactamases
- **Porin alterations**

Emerging resistance to cefepime-zidebactam, *E. coli*

Strain ID	Year of isolation	Carba-penemase	ESBL	AmpC	PBP3 insertions	PBP2 mutations	MLST	ZID MIC	FEP-ZID MIC
28622	2022	NDM-5	CTX-M-15	-	YRIK	V522I	405	8	8
321	2021	NDM-5	CTX-M-15	-	YRIK	V522I	410	>8	>32
420	2020	NDM-5	-	-	YRIK	V522I	648	>8	32
39523	2023	NDM-5	-	-	-	-	648	>8	16
29621	2021	NDM-5	-	CMY-59	-	-	410	>8	8

Combination of PBP-3 insertions and PBP-2 mutations was associated with resistance

J Antimicrob Chemother 2025; **80**: 1137–1140
<https://doi.org/10.1093/jac/dkaf045> Advance Access publication 17 February 2025

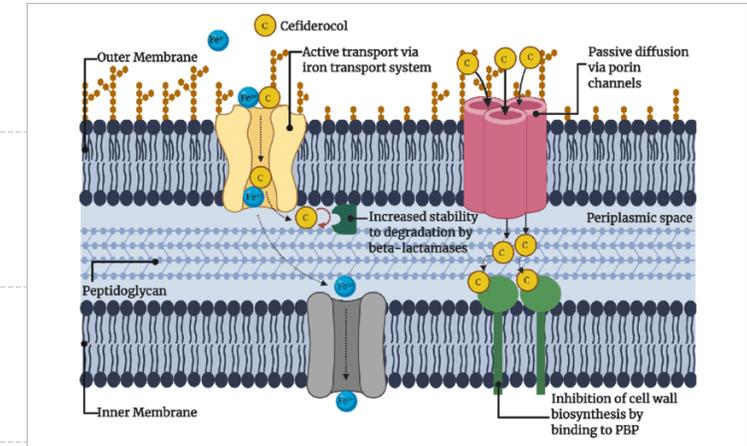
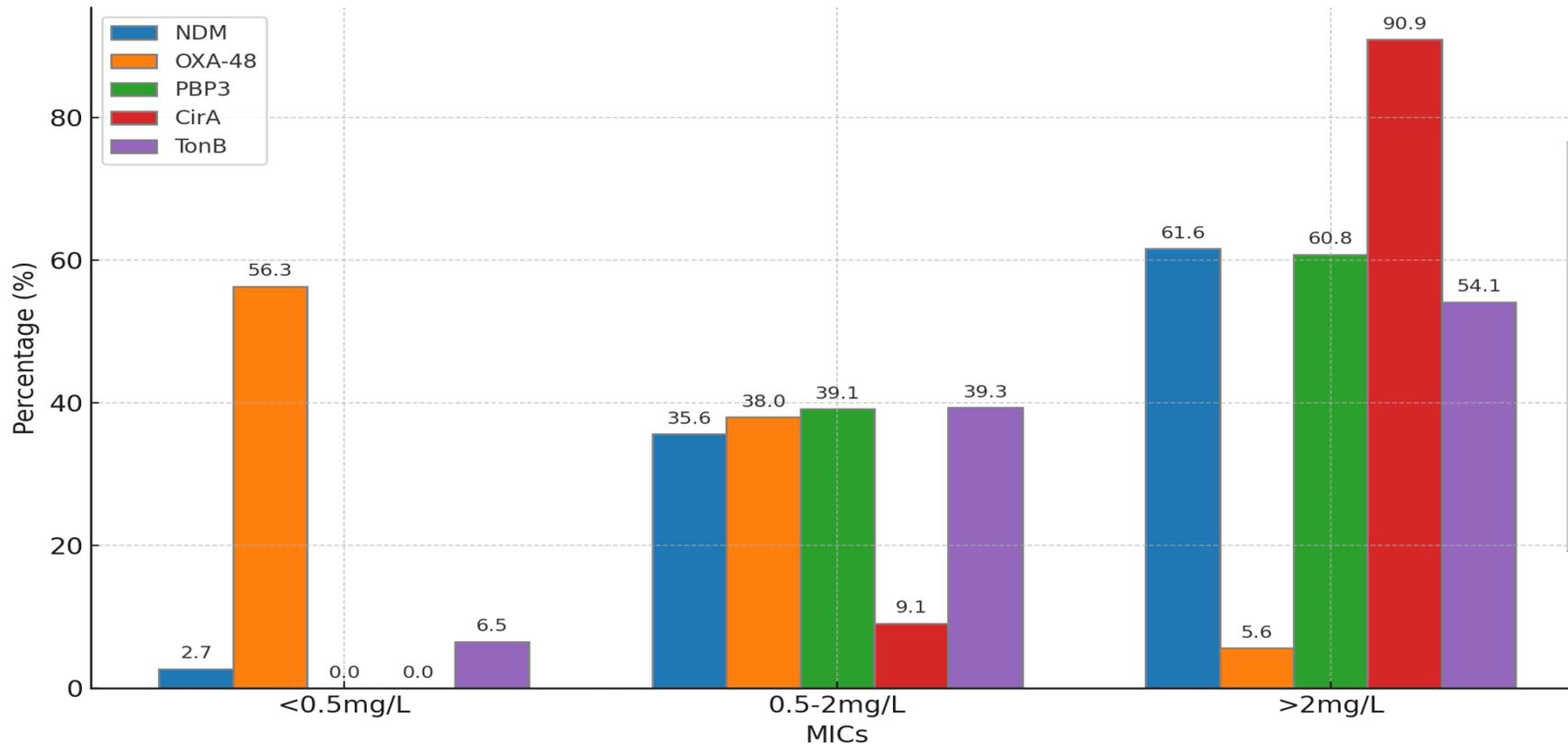


Decreased susceptibility to cefepime/zidebactam among carbapenemase-producing *Escherichia coli* from Stockholm, Sweden with alterations in PBP2

Chaitanya Tellapragada ^{1*}, Chantel Dunleavy ^{1†}, Patrik Jonsson ² and Christian G. Giske ^{1,2}



Emerging resistance to cefiderocol, *E. coli*



Elevated MIC: PBP3-insertions, clinical resistance: PBP-3 insertions plus *cirA* mutations

Mentimeter question 2

In addition to changes in penicillin-binding protein 3 – which mechanism is responsible for cefiderocol resistance?

- Efflux
- Hyperproduction of beta-lactamases
- Mutations in beta-lactamases
- Changes in iron transporters
- Porin alterations

Mentimeter question 2

In addition to changes in penicillin-binding protein 3 – which mechanism is responsible for cefiderocol resistance?

- Efflux
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- Mutations in beta-lactamases
- **Changes in iron transporters**
- Porin alterations

Mechanisms of resistance in NDM-producing *E. coli*

Antimicrobial	Uptake	Receptor	Reference
Aztreonam-avibactam	OmpF mutations	PBP-3 insertions	Tellapragada C. et al. IJAA 2024
Cefiderocol	CirA mutations	PBP-3 insertions	Tellapragada C. et al. Manuscript
Cefepime-zidebactam	None	PBP-3 insertions PBP-2 mutations (zidebactam)	Tellapragada C. et al. Submitted

Conclusions

- NDM and OXA-48 are the most common carbapenemases
- Epidemic hospital clones play a large role in dissemination of resistance
- Emerging resistance to novel agents such as cefiderocol and aztreonam-avibactam is conferred by chromosomal mechanisms such as changes in PBPs and impermeability (e.g. OmpF, CirA)
- Acquired resistance to novel agents is not as rare as expected – testing of strains (easiest with disk diffusion) is of crucial importance