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KOÇ UNIVERSITY - İŞBANK
CENTER FOR INFECTIOUS DISEASES

SEMINAR ON PET-RELATED AND EMERGING ZOONOTIC INFECTIONS

DATE: 23 & 24 OCTOBER 2025

Emerging Antimicrobial Resistance and its Relation with Animal Sources

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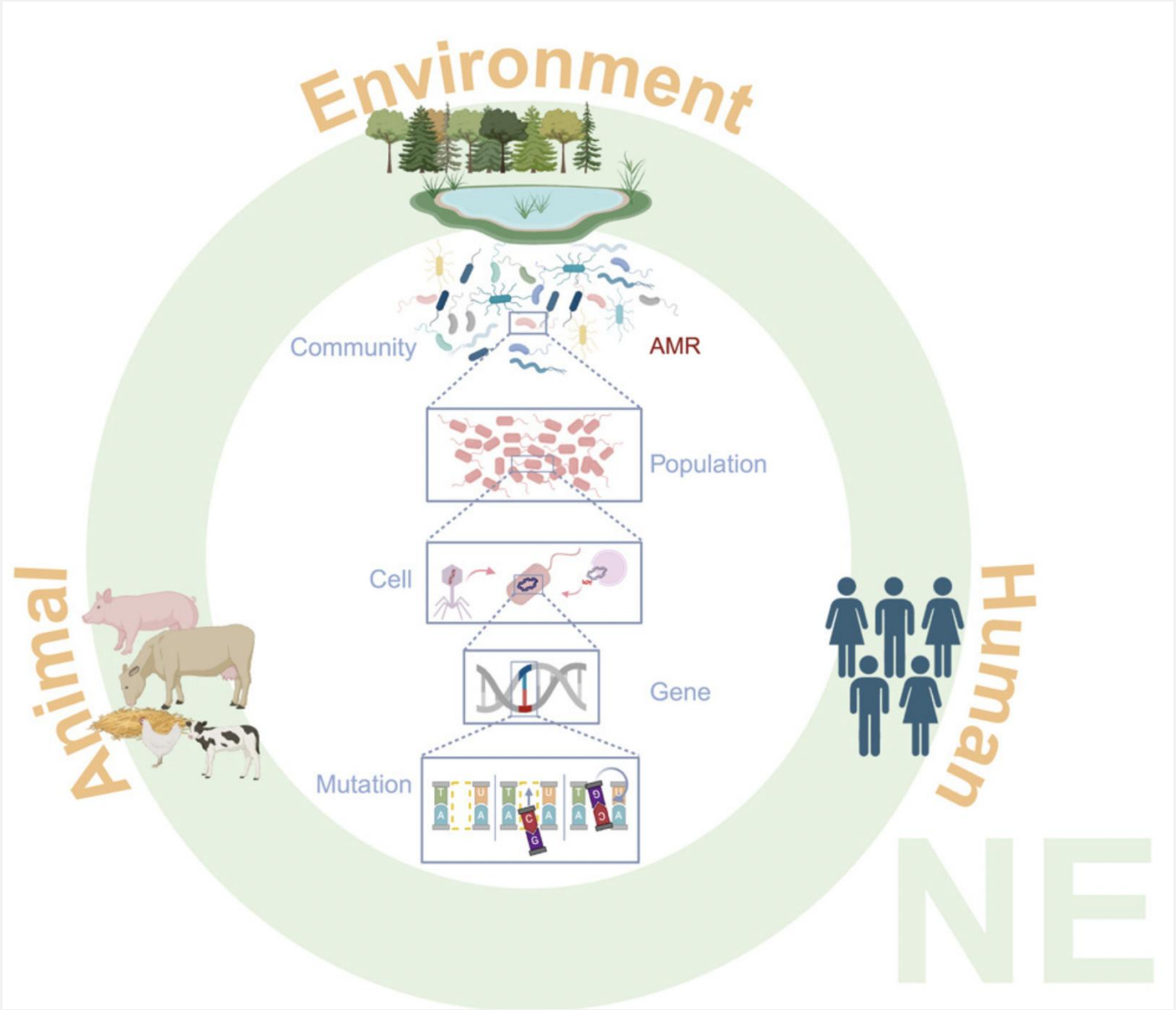
24 October 2025
Hong Kong

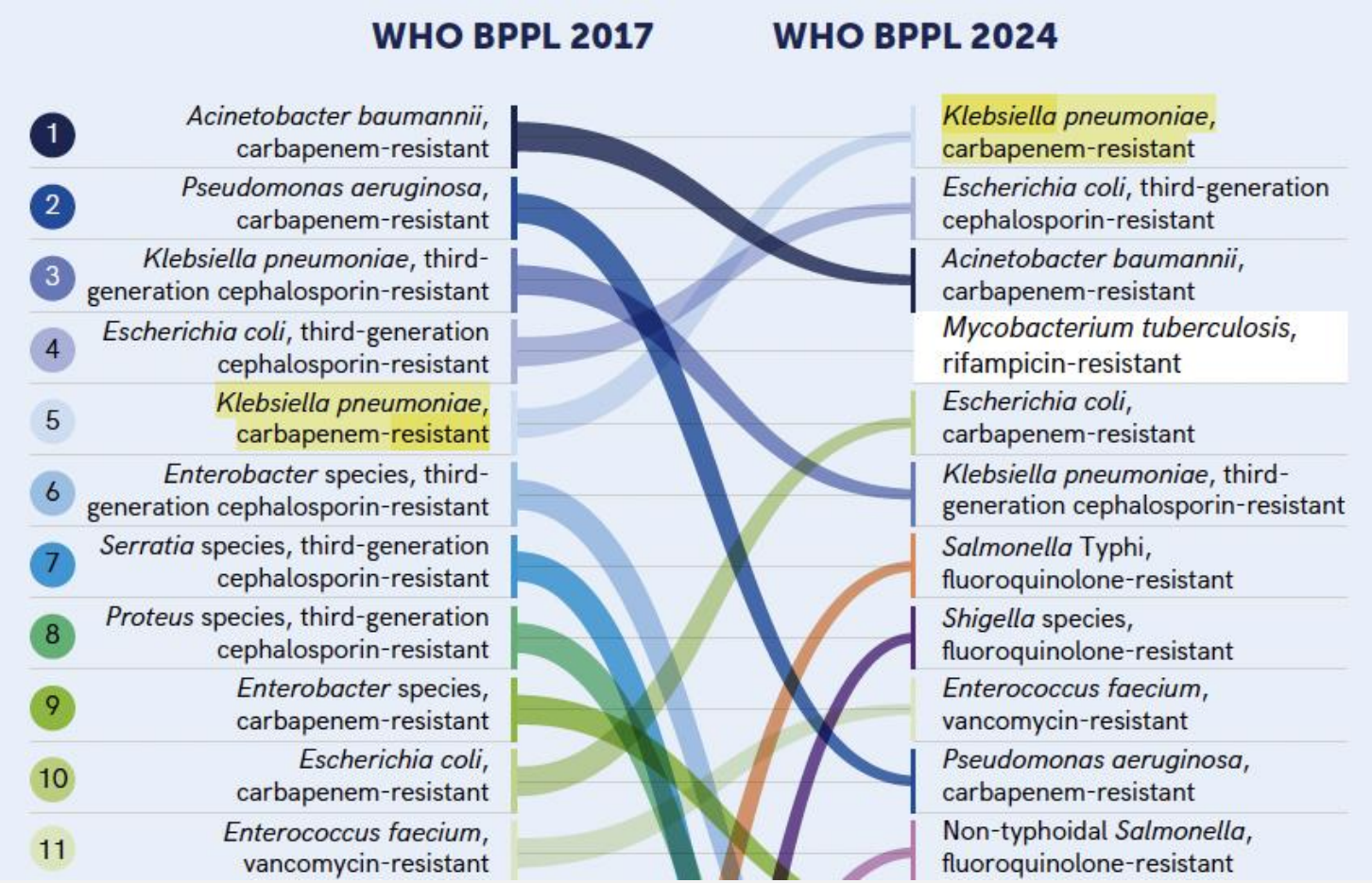
Content

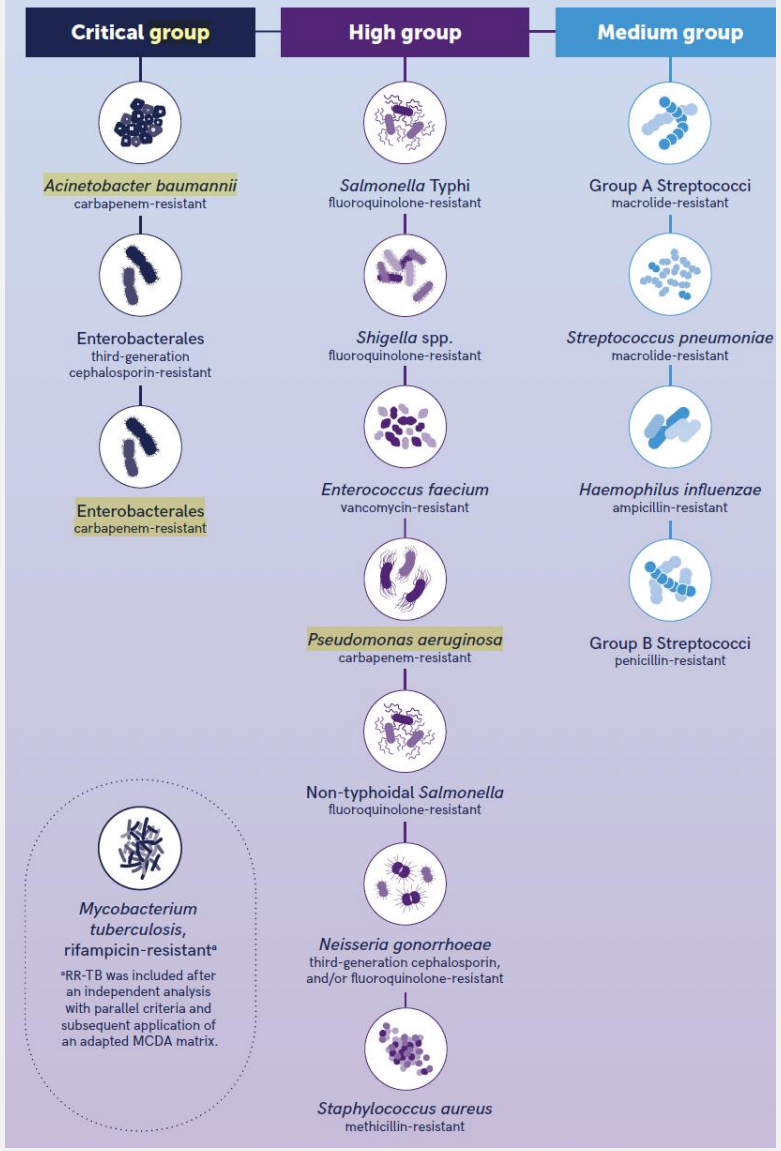
1. AMR: Clinical Impact, limited treatment options
2. Antibiotic Consumption
3. Environmental sources (ONE HEALTH)



Bustamante M, et al. An eco-evolutionary perspective on antimicrobial resistance in the context of One Health. iScience. 2024

WHO Global Priority Pathogen List 2024





WHO global priority pathogens list of antibiotic-resistant bacteria (2024)

Priority 1: CRITICAL

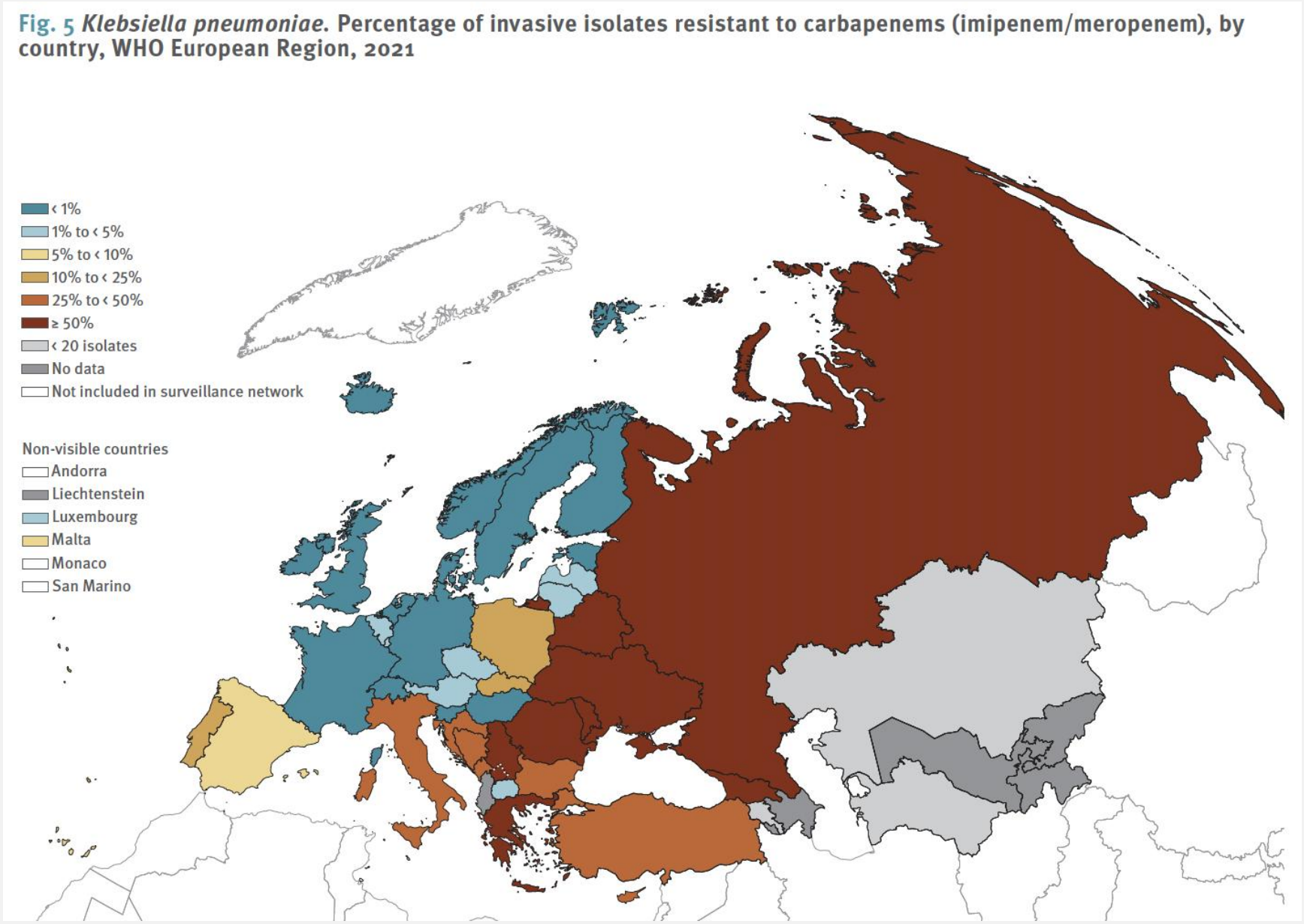
1. Enterobacterales, carbapenem-resistant
2. Enterobacterales, third generation cephalosporin-resistant
3. *Acinetobacter baumannii*, carbapenem-resistant
4. *Mycobacterium tuberculosis*, rifampicin-resistant

Priority 2: HIGH

1. *Salmonella* Typhi, fluoroquinolone-resistant
2. *Shigella* spp., fluoroquinolone-resistant
3. *Enterococcus faecium*, vancomycin-resistant
4. *Pseudomonas aeruginosa*, carbapenem-resistant
5. Non-typhoidal *Salmonella*, fluoroquinolone-resistant
6. *Neisseria gonorrhoeae*, third-generation cephalosporin, and/or fluoroquinolone-resistant
7. *Staphylococcus aureus*, methicillin-resistant

Priority 3: MEDIUM

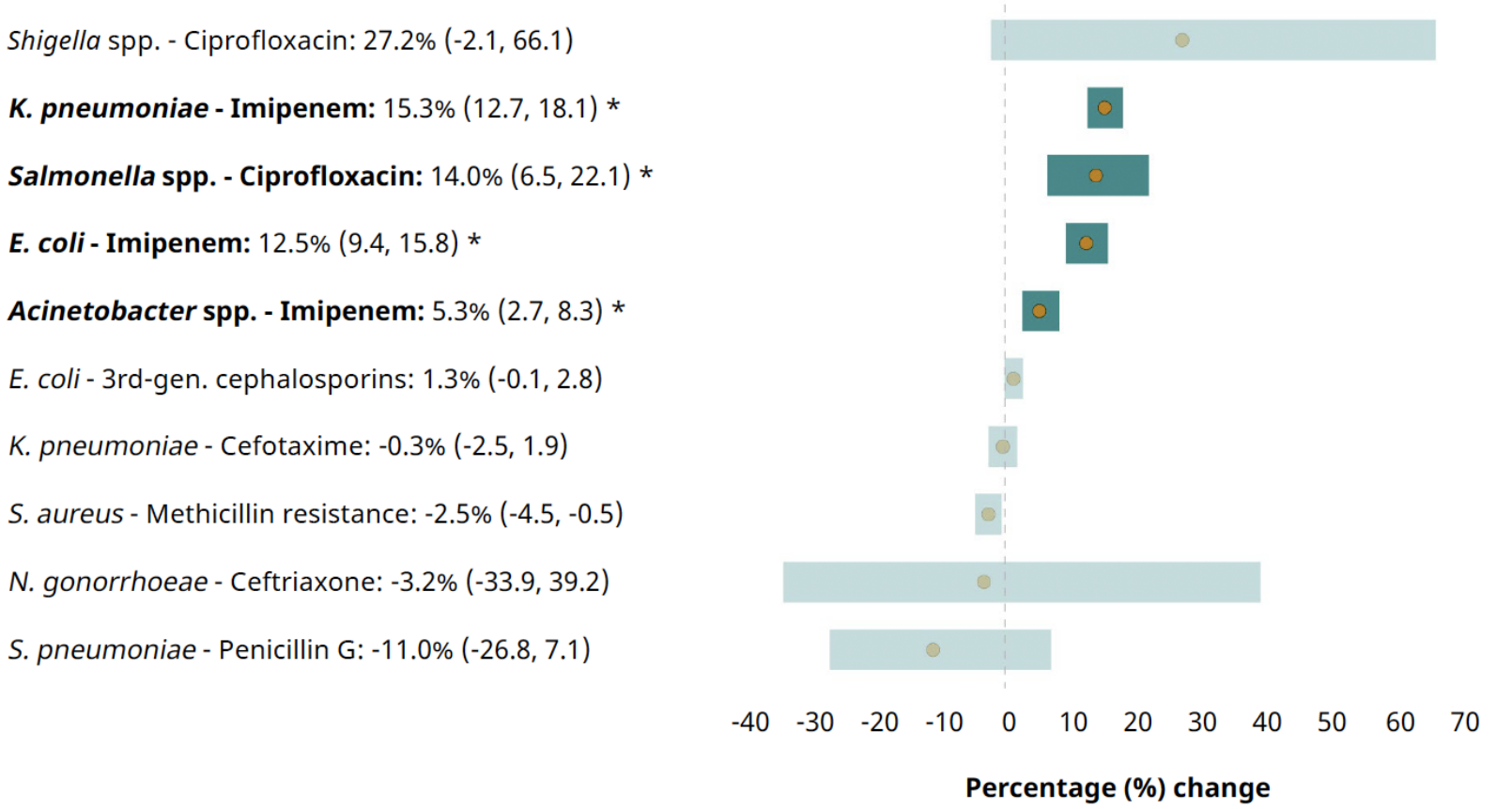
1. Group A Streptococci, macrolide-resistant
2. *Streptococcus pneumoniae*, macrolide-resistant
3. *Haemophilus influenzae*, ampicillin-resistant
4. Group B Streptococci, penicillin-resistant



ECDC 2023 (data of 2021)

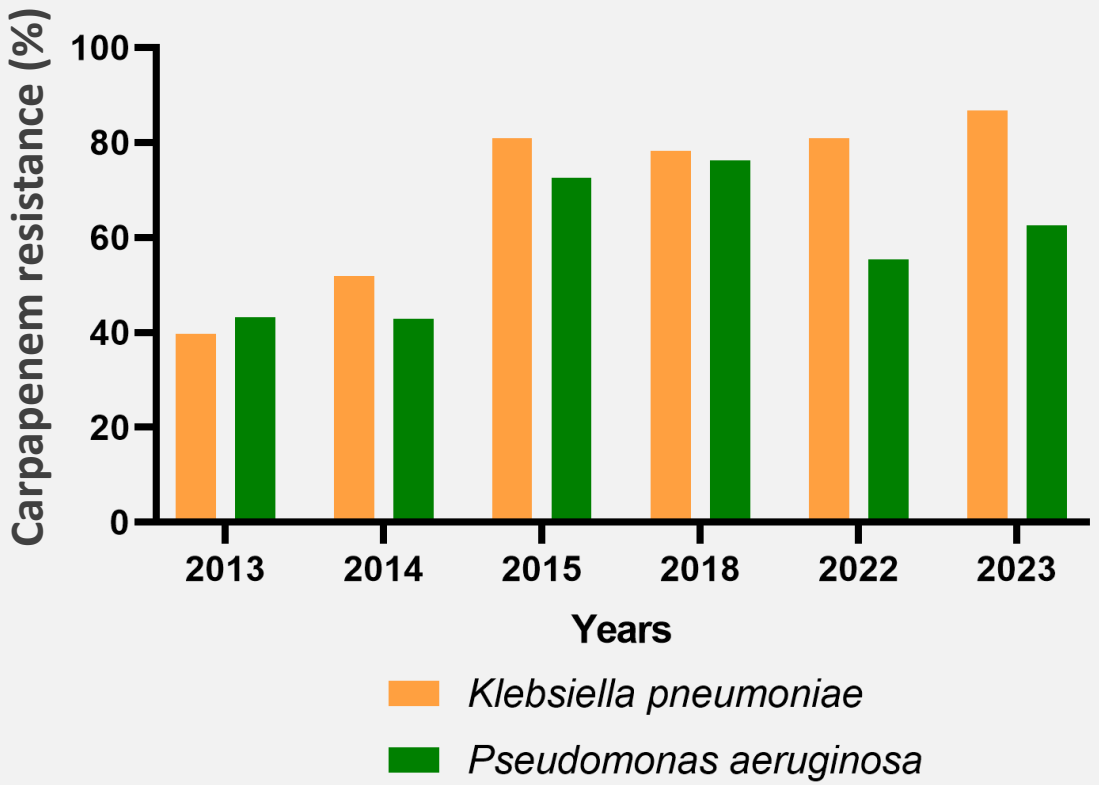
Global antibiotic resistance surveillance report 2025

Figure 3. Trends of AMR: median annual change in percentage, 2018–2023



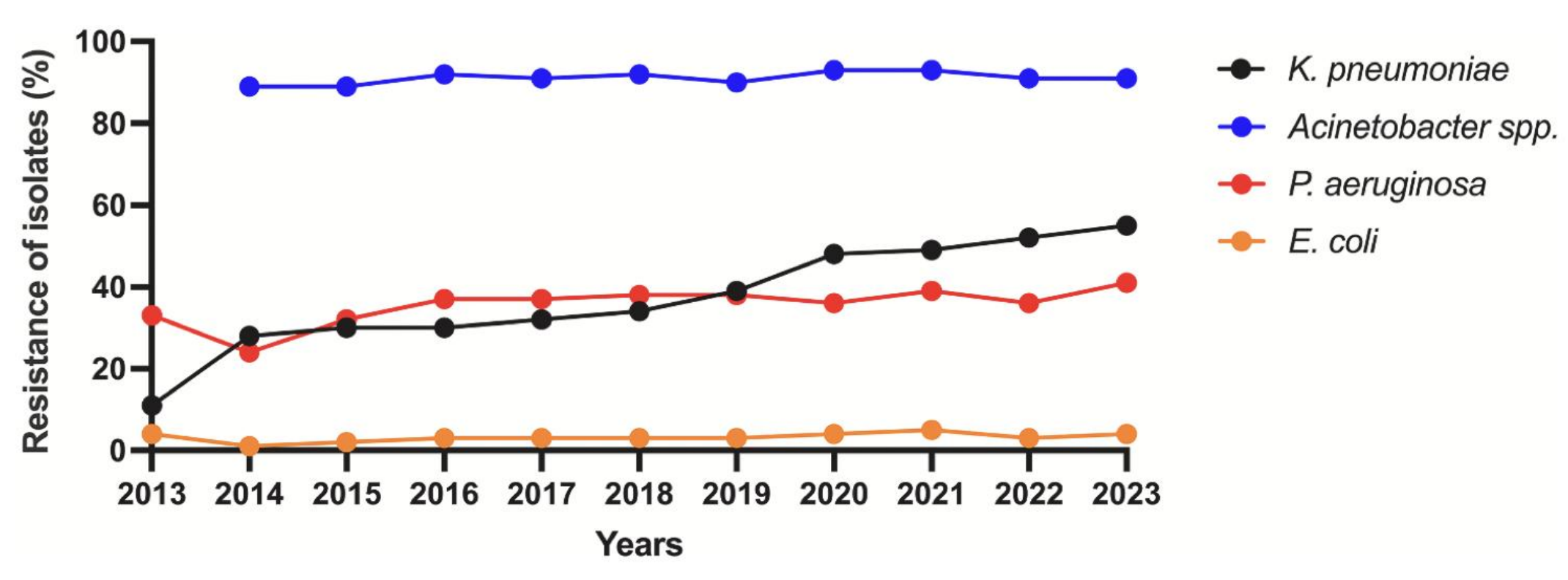
Population-weighted median annual percentage change in AMR between 2018 and 2023, represented by a dot, with 95% CrI. An asterisk (*) indicates a statistically meaningful trend. When trends were available for several infection types, only that with the highest annual percentage change is shown in the figure.

Carbapenem Resistance in Türkiye

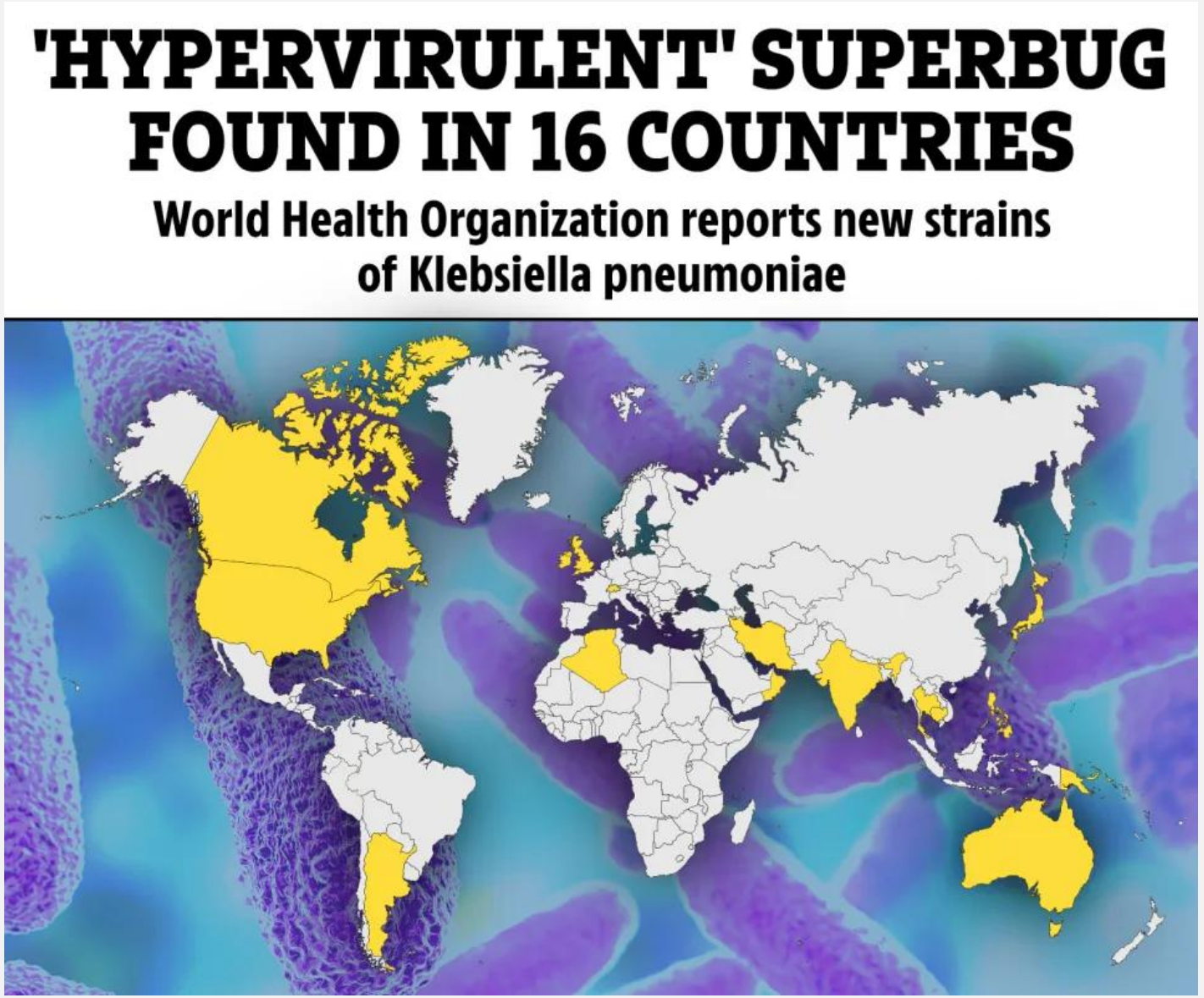


Multicentric studies:
Ergonul O, 2016
Aydin M, 2018
Aydin M, 2019

Carbapenem resistance in Türkiye



Alhan Ö, Özger HS, Karatuna O, Azap ÖK, Madran B, Keske Ş, Çınar G, Akdemir İ, Ergönül Ö. Antibiotic resistance in Türkiye: what has been done and what needs to be done urgently? Clin Microbiol Infect. 2025



Global Health Concern

- The **WHO** has warned of hv-CRKP spreading in **at least 16 countries**.

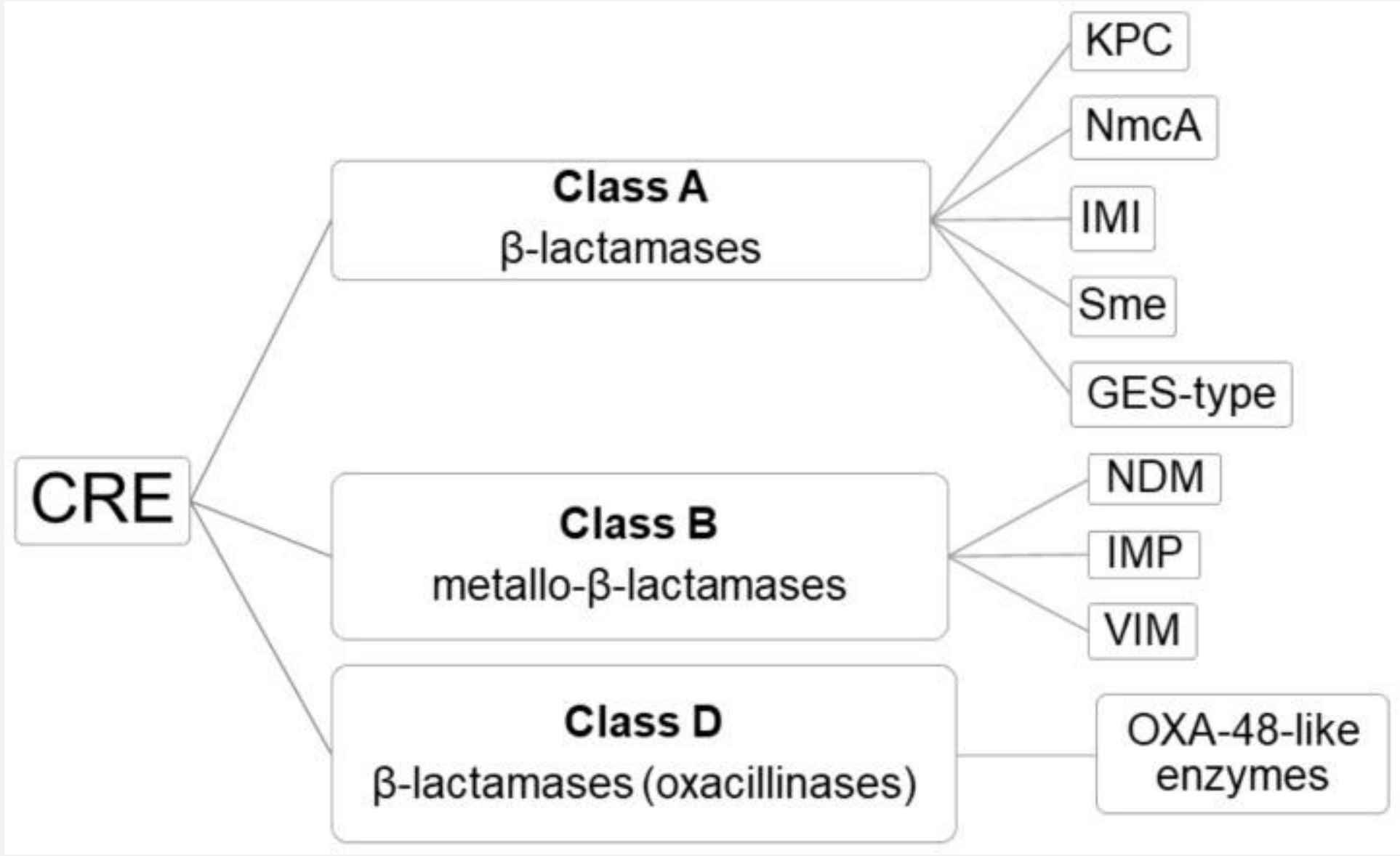
- Even **previously healthy individuals** are at risk, with reports of sudden deaths from community-acquired infections.

The Nightmare Scenario
Dual Threat of Resistance + Virulence

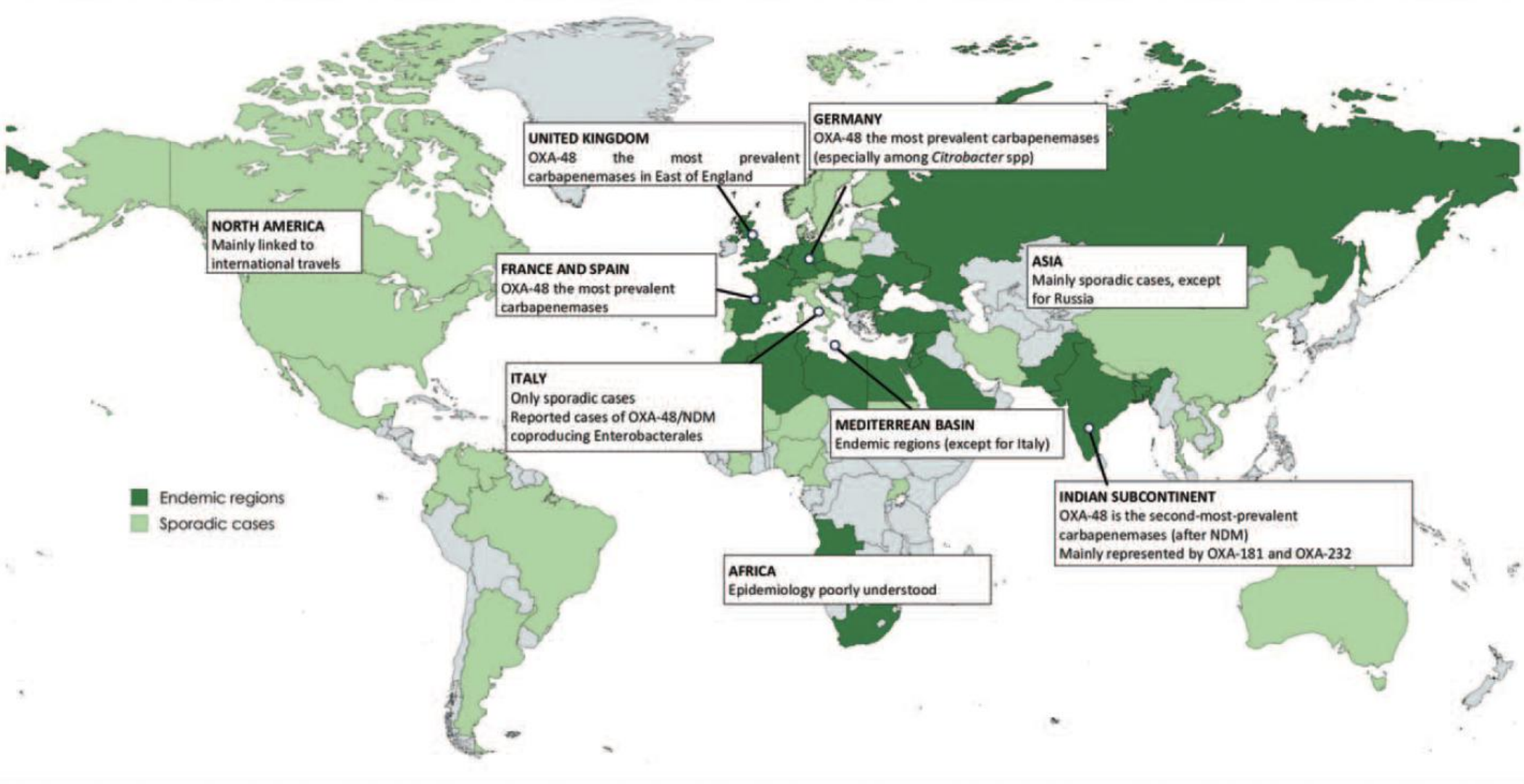
These strains combine:

- **Carbapenem resistance** (e.g., *blaKPC*, *blaNDM*, *blaOXA-48*)
- **Hypervirulence genes** (e.g., *rmpA*, *iucA*, *ybtA*)

This makes them both harder to treat and more capable of causing severe, rapidly progressing infections.

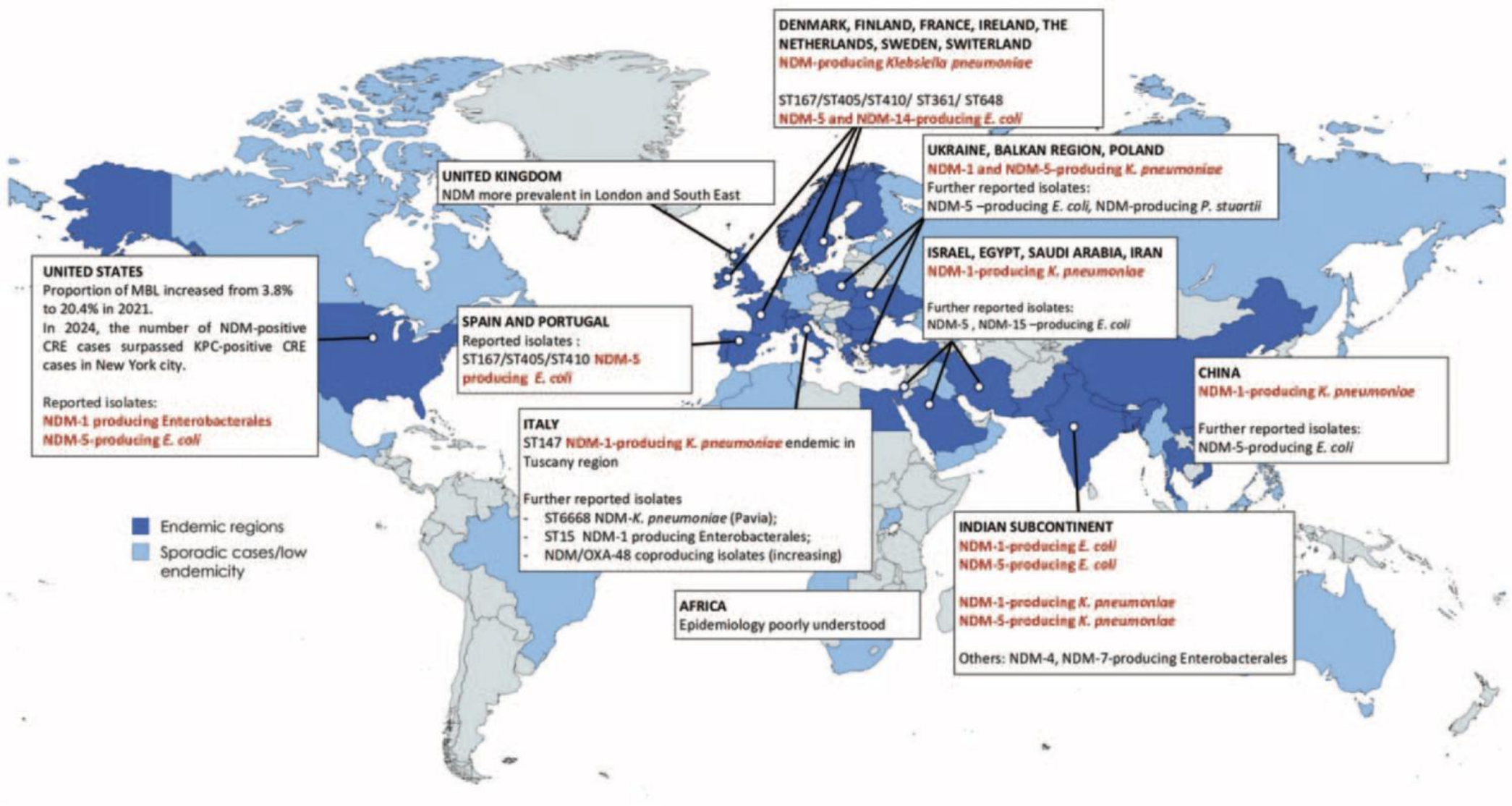

CRE
Class A
β-lactamases
KPC
NmcA
IMI
Sme
GES-type
Class B
metallo-β-lactamases
NDM
IMP
VIM
Class D
β-lactamases (oxacillinases)
OXA-48-like enzymes

Global epidemiology of OXA-48 producing CRE

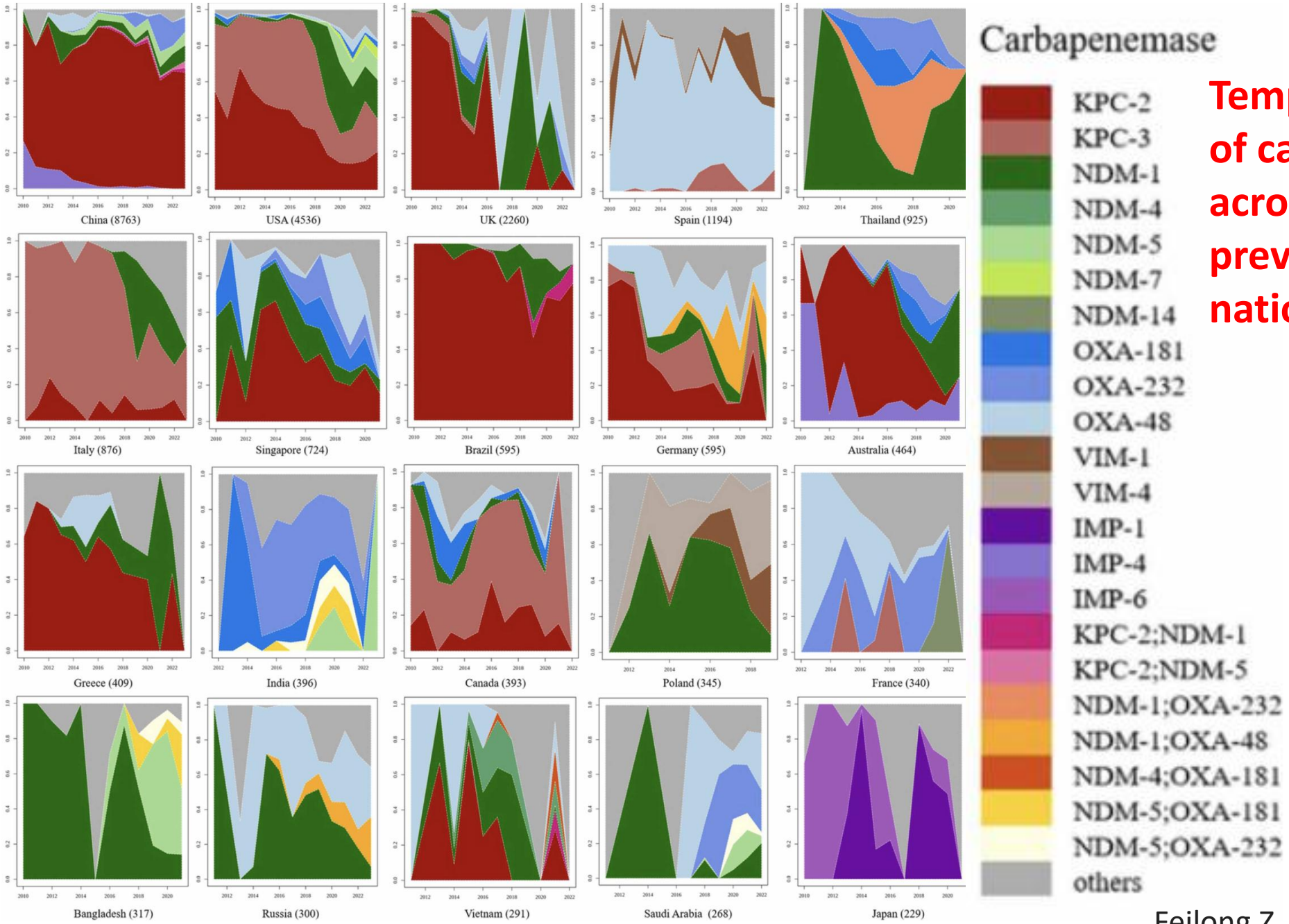


Tiseo G, Galfo V, Falcone M. How I manage patients with New Delhi metallo-beta-lactamase and OXA-48-producing Enterobacterales infections: a practical approach. Curr Opin Infect Dis. 2025

Global epidemiology of NDM-producing CRE



Tiseo G, Galfo V, Falcone M. How I manage patients with New Delhi metallo-beta-lactamase and OXA-48-producing Enterobacterales infections: a practical approach. Curr Opin Infect Dis. 2025



Temporal variation of carbapenemases across twenty high prevalence nations

Feilong Z, et al.. J Infect. 2025

Characteristics and outcomes of carbapenemase harbouring carbapenem-resistant *Klebsiella* spp. bloodstream infections: a multicentre prospective cohort study in an OXA-48 endemic setting

Burcu Isler[1] · Berna Özer[2] · Güle Çınar[3] · Abdullah Tarık Aslan[4] · Cansel Vatansever[2] · Caitlin Falconer[1] · İştar Dolapçı[5] · Funda Şimşek[6] · Necla Tülek[7] · Hamiyet Demirkaya[8] · Şirin Menekşe[9] · Halis Akalin[10] · İlker İnanç Balkan[11] · Mehtap Aydın[12] · Elif Tükenmez Tigen[13] · Safiye Koçulu Demir[14] · Mahir Kapmaz[15] · Şiran Keske[21,22] · Özlem Doğan[2] · Çiğdem Arabacı[16] · Serap Yağcı[17] · Gülşen Hazırolan[18] · Veli Oğuzalp Bakır[19] · Mehmet Gönen[20,21] · Mark D. Chatfield[1] · Brian Forde[1] · Neşe Saltoğlu[11] · Alpay Azap[3] · Özlem Azap[8] · Murat Akova[4] · David L. Paterson[1] · Füsun Can[2,22] · Önder Ergönül[21,22]

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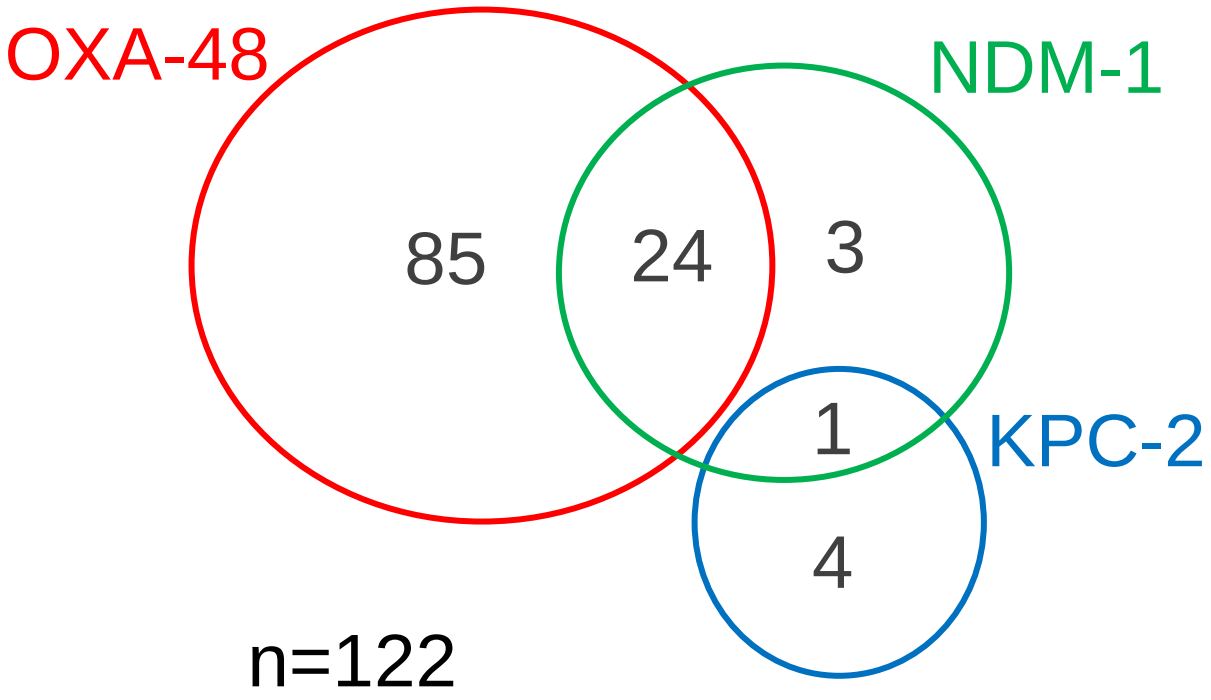
İsler B, et al. Eur J Clin Microbiol Infect 2022

Carbapenemases (Threat Study)
Before Ceftazidim-Avibactam Use in Türkiye



- Prospective observational
- June 2018 – June 2019
- 13 center, 187 patients
  - (R veya I: (EUCAST 2018)

İsler B, et al. Eur J Clin Microbiol Infect 2022

	Univariable analysis			Multivariable analysis[b]		
	HR	CI	*p*	HR	CI	*p*
Demographics						
Age	0.98	0.86–1.13	0.82	…	…	…
Male sex	1.34	0.82–2.20	0.24	…	…	…
Source						
Non-UT source	2.25	0.90–5.60	**0.08**	1.34	0.52–3.46	0.54
Source control	0.60	0.34–1.04	**0.07**	0.69	0.39–1.23	0.21
Comorbidities						
Metastatic/hematologic malignancy	1.27	0.73–2.20	0.40	…	…	…
Immunosuppression	1.43	0.83–2.46	**0.20**	2.14	1.15–4.00	**0.02**
CCI score	0.97	0.88–1.07	0.56	…	…	…
Disease severity						
ICU at presentation	1.82	1.05–3.16	**0.03**	0.88	0.41–1.93	0.76
Invasive mechanical ventilation	1.99	1.22–3.25	**0.01**	1.18	0.58–2.40	0.65
SOFA score (per unit)	1.25	1.17–1.33	**0.00**	1.24	1.15–1.34	**0.000**
Microorganism						
Carbapenemase other than single OXA-48-like [a]	1.33	0.78–2.26	0.30	…	…	…
MLST type (reference other)						
ST2096	2.47	1.25–4.86	**0.01**	1.94	0.95–3.96	**0.07**
ST101	1.92	0.88–4.22	**0.10**	1.92	0.84–4.38	**0.12**
ST14	2.91	1.33–6.36	**0.01**	1.96	0.88–4.44	**0.10**
Treatment						
Active treatment	0.75	0.46–1.22	0.25	0.71	0.42–1.21	0.21

[a]OXA-48/MBL ($n=29$), MBL ($n=11$), KPC ($n=4$), KPC/MBL ($n=2$), [b]excludes those who died within 48 h. p value <0.2 in bold

13 centers, 187 patients.

OXA-48 like 75%
OXA-48 like/NDM 16%.

30-day mortalite: %44

All OXA-48-like CZA susceptible

İsler B, et al. Eur J Clin Microbiol Infect 2022

Susceptibility (susceptible/total tested)	Total, *n* (%)	ST2096, *n* (%)	ST101, *n* (%)	ST14, *n* (%)
Colistin	43/187 (23)	11/61 (18)	5/37 (14)	10/28 (36)
Tigecycline	67/157 (43)	12/51 (24)	24/33 (73)	8/26 (31)
Amikacin	45/177 (25)	7/59 (12)	7/32 (22)	5/27 (19)
Gentamicin	42/164 (26)	7/59 (12)	11/26 (42)	3/26 (12)
Trimethoprim-sulfamethoxazole	20/165 (12)	1/60 (2)	6/26 (23)	1/25 (4)
Ceftazidime-avibactam	152/187 (81)	61/61 (100)	37/37 (100)	9/28 (32)

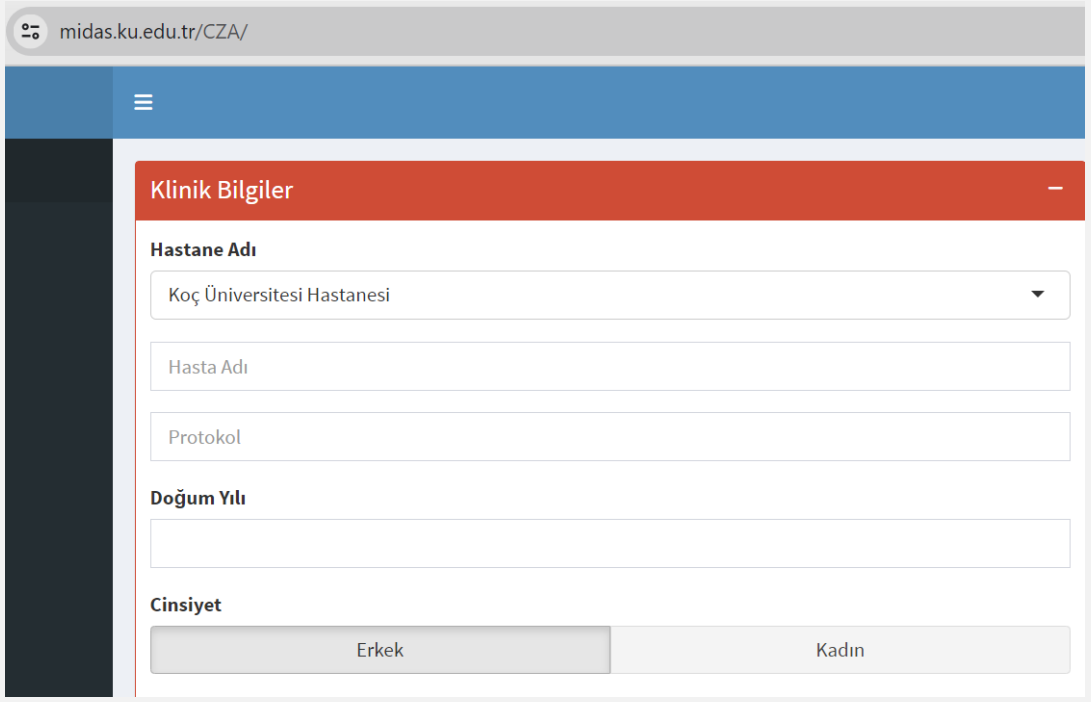
Isler B, Özer B, Çınar G, Aslan AT, Vatansever C, Falconer C, Dolapçı İ, Şimşek F, Tülek N, Demirkaya H, Menekşe Ş, Akalin H, Balkan İİ, Aydın M, Tigen ET, Demir SK, Kapmaz M, Keske Ş, Doğan Ö, Arabacı Ç, Yağcı S, Hazırolan G, Bakır VO, Gönen M, Chatfield MD, Forde B, Saltoğlu N, Azap A, Azap Ö, Akova M, Paterson DL, Can F, Ergönül Ö.

Characteristics and outcomes of carbapenemase harbouring carbapenem-resistant Klebsiella spp. bloodstream infections: a multicentre prospective cohort study in an OXA-48 endemic setting.

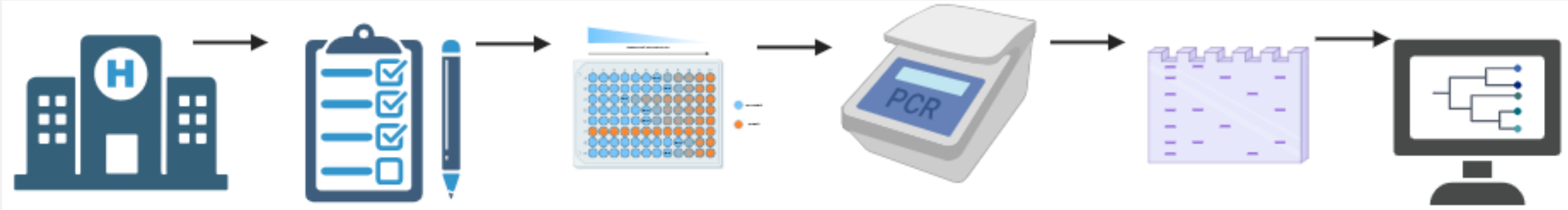
Eur J Clin Microbiol Infect Dis. 2022

Carbapenem Resistant Klebsiella pneumonia (BSI and/or Pneumonia)
KAPSAR Study

- Prospective cohort, 16 centers
- Hospitalized adults (≥18 years old)
- 1 Jan 2022 – 1 Nov 2023
- Digital database (midas)



Method


9 cities;
16 hospitals
Demographic and clinical data collection
Susceptibility testing by microbroth dilution
PCR
Carbapenemase positivity testing by PCR
Clonality assessment by PFGE
Analysis of PFGE Results

Klebsiella pneumoniae to 30-day mortality (n=655, CFR=47%)

KAPSAR Study

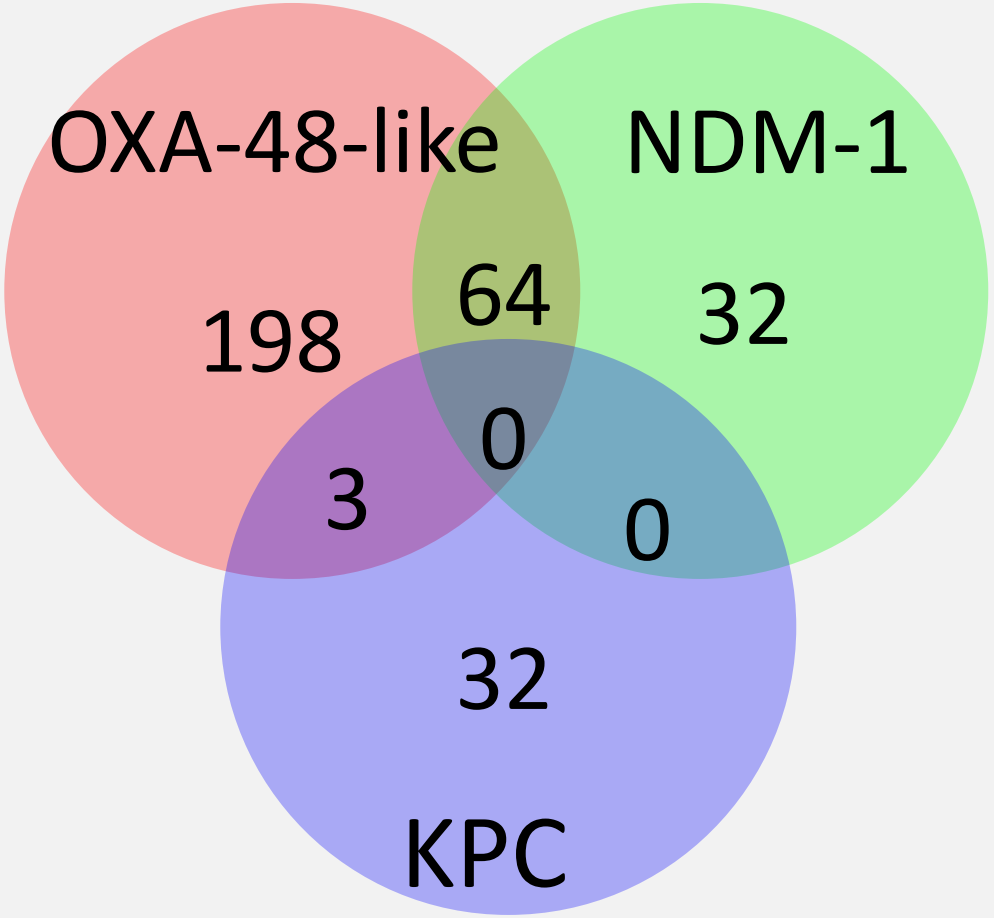
	Fatal (%) n=310	Survived (%) n=345	p-value
Demographics			
Male Gender	194 (62.6)	225 (65.2)	0.483
Median Age [IQR]	70 [60-79]	66 [56-74]	<0.001
Age>60	273 (58)		
Comorbidities			
Solid Organ Malignancy	96 (31.0)	107 (31.0)	0.990
Hematologic Malignancy	26 (8.4)	35 (10.1)	0.440
Diabetes Mellitus Type II	85 (27.4)	86 (24.9)	0.468
Chronic Kidney Disease	45 (14.5)	52 (15.1)	0.841
Congestive Heart Failure	37 (11.9)	29 (8.4)	0.134
Chronic Liver Disease	27 (8.7)	17 (4.9)	0.054
COPD	28 (9.0)	33 (9.6)	0.815
COVID-19	20 (6.5)	19 (5.5)	0.610

Distribution of Betalactamases

	CR-Kp n=427 (%)
OXA-48	275 (65)
NDM	110 (25)
KPC	35 (8)
OXA-48 and NDM	64 (15)
OXA-48 and KPC	3 (<1)
NDM and KPC	0

Kapsar study, ECCMID 2024

Molecular Features of Carbapenem Resistant *Klebsiella pneumoniae*, n=427



Antibiotic resistance rates in carbapenem-resistant *Klebsiella pneumoniae* infections, KAPSAR study

Antibiotic	Carbapenem Resistant Samples (%) n=427	Carbapenem Resistant NDM Negative Samples (%) n=317
Piperacillin-tazobactam	418 (97.89)	-
Ceftolozane-tazobactam	409 (95.78)	-
Ceftazidime-avibactam	181 (42.39)	95 (29.96)
Colistin	152 (35.60)	-

Resistance and the Impact on 30 day Fatality among Kp

Multivariate analysis	n=635 (%)	OR (confidence interval)
Carbapenem resistance	476 (75)	4 (2.7-6)
Age>70	297 (45)	2.3 (1.7-3.3)

Resistance and the Impact on 30 day Fatality among CR-Kp

Multivariate analysis	n=427	
CZA resistance	181 (42)	1.7 (1.09-2.6)
Age>70	221 (46)	2.4 (1.59-3.61)
Hypervirulent Kp	121 (29)	0.86 (0.54-1.39)

Hypervirulence is based on hypermucoviscosity(rmpA/rmpA2) and aerobactin (iutA/iucA)

WHO Report; July 2024

🌍 Global Risk Assessment: CR-hvKp

⚠ Risk Level: Moderate

The global risk from CR-hvKp is considered **moderate**, based on current data, trends, and system capacities.

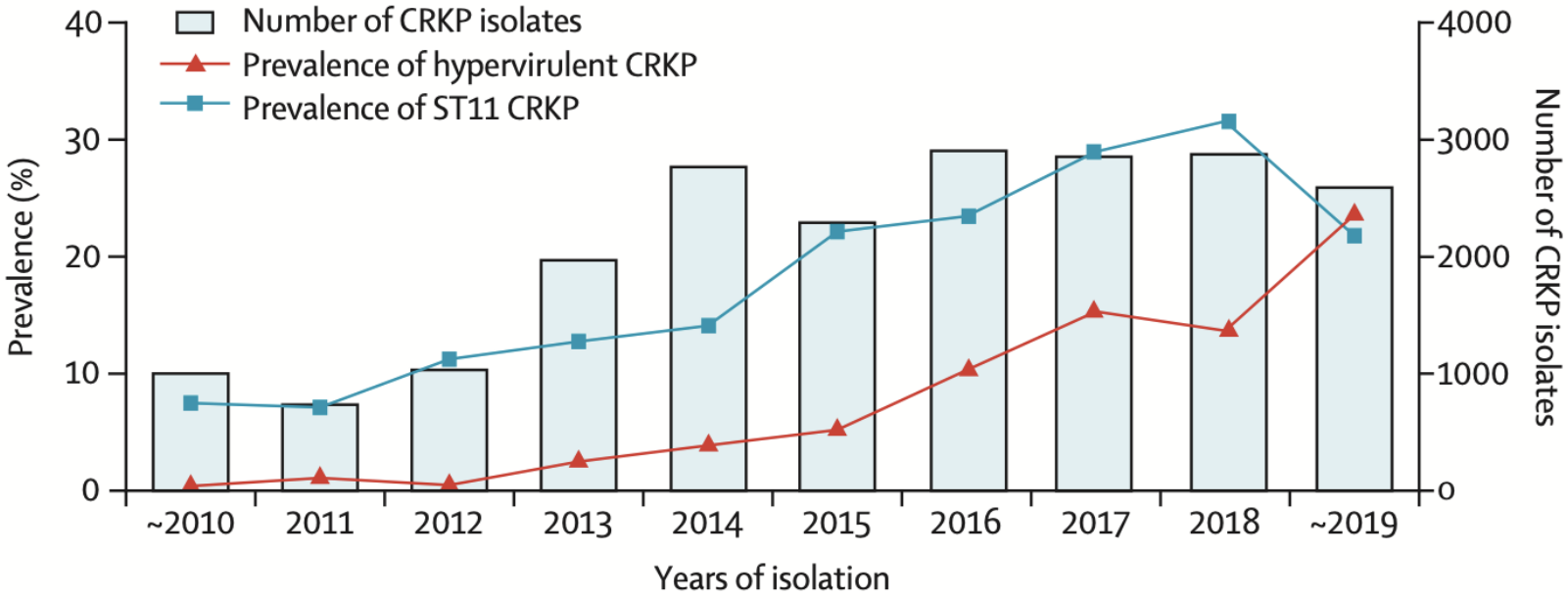
🧬 Clinical and Epidemiological Concerns

•Traditionally community-acquired in **Asia**, hvKp causes **high morbidity and mortality**.

•Recently detected in **health-care settings** across Europe and Asia (e.g., China), raising concern about nosocomial transmission.

•The **concurrence of hypervirulence + antimicrobial resistance** increases potential for both **community and hospital outbreaks**.

Global evolution and geographic diversity of hypervirulent carbapenem-resistant *Klebsiella pneumoniae*

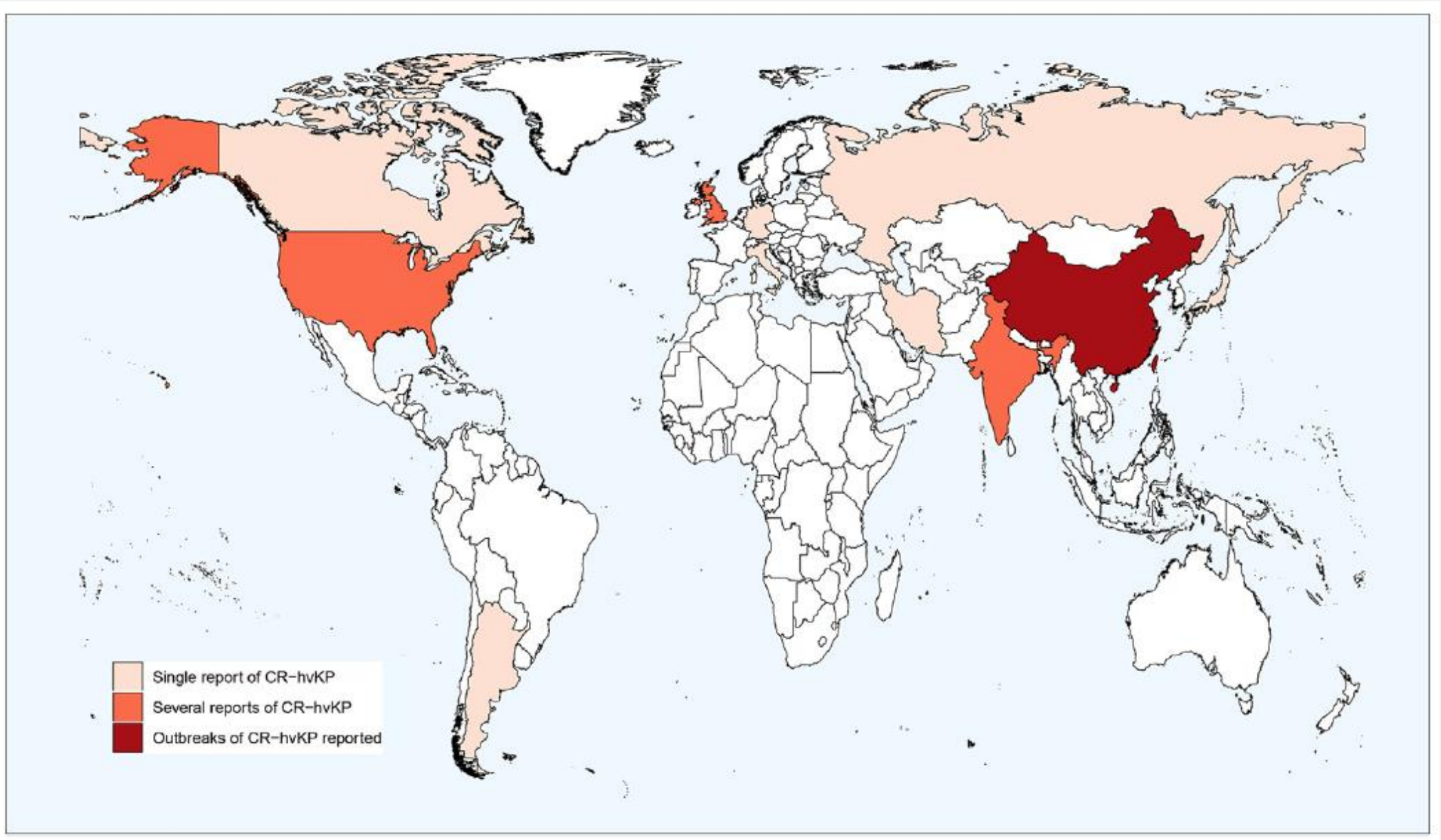


21 016 strains of CRKP from the National Center for Biotechnology Information GenBank database, including 697 complete genome sequences and 20 319 draft genome sequences, from 1980 to 2022 in 105 countries.

We found that carriage of genes specific to hypervirulent K pneumoniae was prevalent among CRKP strains (0·40–27·03%). Worldwide, 51·68% of CRKP strains have yersiniabactin genes, which are the virulence genes with the highest frequency. The proportion of CRKP harbouring yersiniabactin and aerobactin genes has increased significantly over the past two decades, with yersiniabactin genes increasing from 24·58% to 49·89% and aerobactin genes from 0·50% to 31·43%.

Wu Y, et al Lancet ID 2022

Global distribution of hypervirulent and carbapenem-resistant Klebsiella pneumoniae (CR-hvKP)



Lan P, et al. J Glob Antimicrob Resist. 2021 Jun;25:26-34.

Higher Mortality Rates

Meta-analysis (2025): hv-CRKP infections show a **pooled mortality rate of ~28%**

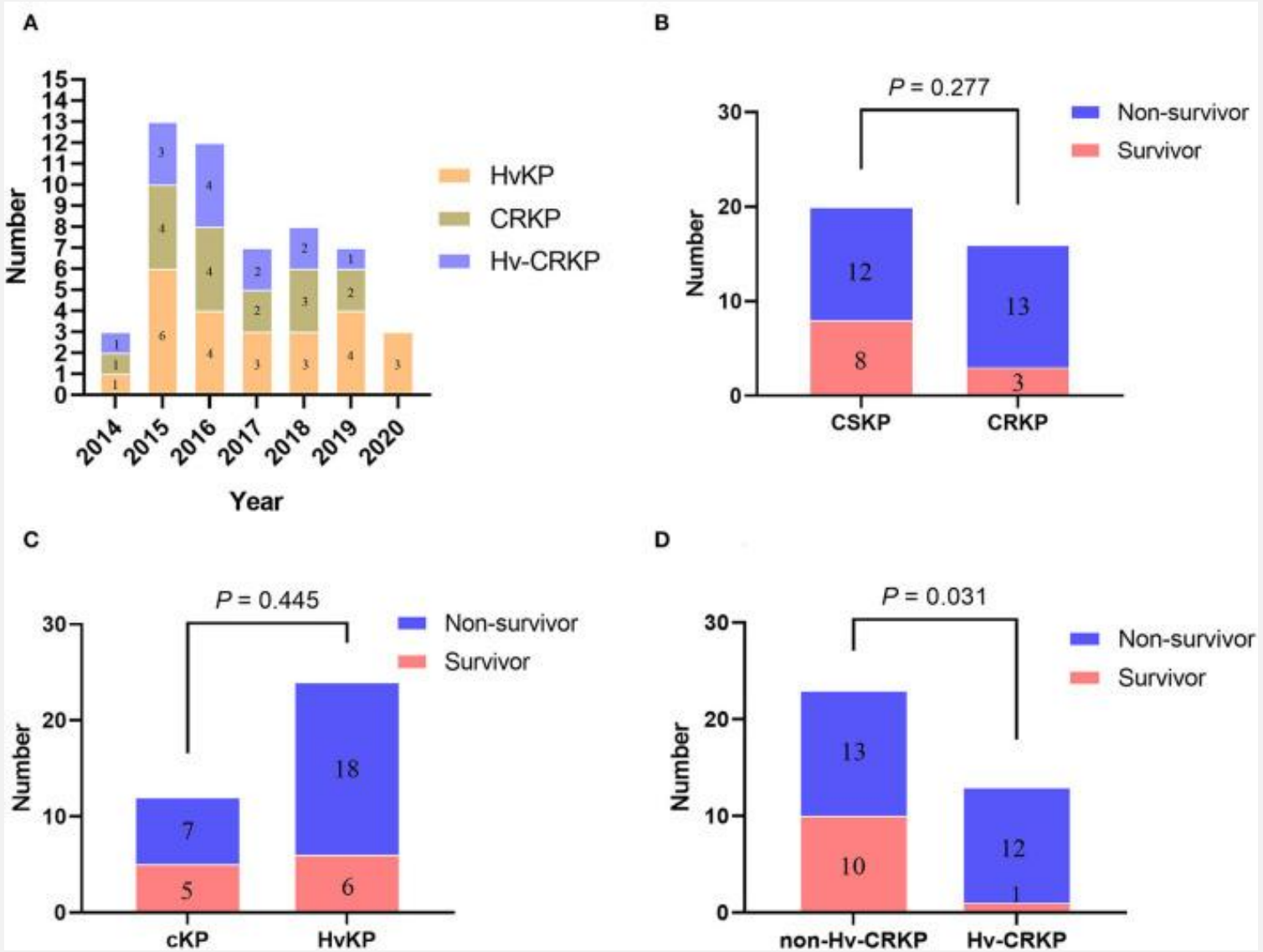
Qala Nou, *et al.* Systematic review and meta-analysis on the carbapenem-resistant hypervirulent *Klebsiella pneumoniae* isolates. *BMC Pharmacol Toxicol* 2025.

Severe Outcomes in Specific Infections

Meningitis study in China: hv-CRKP meningitis had a **92.3% mortality rate**, much higher than 56.5% for non-hypervirulent cases.

ICU outbreak report: hv-CRKP caused a **100% fatality** rate in 8 ICU patients during a localized outbreak.

Hypervirulent carbapenem-resistant *Klebsiella pneumoniae* causing highly fatal meningitis in southeastern China.



Huang N, et al. Front Public Health. 2022

Is Hypervirulent *Klebsiella pneumoniae* more Fatal?

Hypervirulent *Klebsiella pneumoniae* have better clinical outcomes than classical *Klebsiella pneumoniae* for lower respiratory tract infection patients.
Zhuo, X., Lei, Z., Pu, D. *et al. BMC Microbiol* **25**, 40 (2025)

Statistically no difference

Clinical Characterization, Risk Factors, and Mortality in Patients with Carbapenem-Resistant Hypervirulent Klebsiella pneumoniae Intra-Abdominal Infections.
Qiu M, et al. Infection and Drug Resistance 2025

Genomically defined hypervirulent *Klebsiella pneumoniae*contributed to early-onset increased mortality.
Tang, Y., Du, P., Du, C. *et al.* *Nat Commun* **16**, 2096 (2025)

Hypervirulent *Klebsiella pneumoniae* (hvKp) can cause severe infections

Liver or non-hepatic abscess
Pneumonia
Endophthalmitis
Meningitis
Necrotizing fasciitis

Namikawa H, Oinuma KI, Yamada K, Kaneko Y, Kakeya H, Shuto T. Predictors of hypervirulent Klebsiella pneumoniae infections: a systematic review and meta-analysis. J Hosp Infect. 2023

Characteristics of the studies included in the systematic review and meta-analysis

First author (year)	Country	Design	Period	Population	Infection type	Hypervirulence factor	HvKp
Li (2014) [12]	China	Retrospective observational study	2010–2012	88 patients with *K. pneumoniae* infection	BSIs, pneumonia, UTI, others	HMV phenotype	29 (33.0%)
Zhang (2016) [13]	China	Prospective observational study	2013	230 patients with *K. pneumoniae* infection	BSIs, HAP, others	Aerobactin	87 (37.8%)
Yu (2017) [15]	Taiwan	Retrospective observational study	2009–2010	48 patients with ESBL-Kp infection	BSIs	K1/K2, HMV phenotype *rmpA*, or *rmpA2*,	19 (39.6%)
Li (2018) [9]	China	Retrospective cohort study	2015–2016	143 patients with *K. pneumoniae* infection	BSIs	*rmpA* and *iucA*	35 (24.5%)
Liu (2018) [16]	China	Retrospective observational study	2008–2017	202 patients with *K. pneumoniae* infection	BSIs, pneumonia, UTI, others	Aerobactin	96 (47.5%)
Liu (2018) [14]	China	Retrospective cohort study	2008–2017	73 patients with *K. pneumoniae* infection	VAP	Aerobactin	34 (46.6%)
Liu (2019) [17]	China	Retrospective observational study	2008–2014	175 patients with *K. pneumoniae* infection	BSIs, HAP, UTI, HMV phenotype and others	Aerobactin	80 (45.7%)
Yang (2020) [23]	China	Observational study	2015	113 patients with *K. pneumoniae* infection	Pneumonia, UTI, others	HMV phenotype, *rmpA*, *rmpA2*, *iucA*, *iroB*, *peg-344*, and *peg-589*	59 (52.2%)
Liu (2020) [20]	China	Retrospective cohort study	2008–2018	117 patients with nosocomial *K. pneumoniae* infection	BSIs, pneumonia, UTI, others	*rmpA*, *rmpA2*, *iucA*, *iroB*, and *peg-344*	53 (45.3%)
Ding (2022) [19]	China	Retrospective observational study	2016–2018	123 patients with *K. pneumoniae* infection	BSIs, pneumonia, others	Aerobactin and *Galleria mellonella* infection model	53 (43.1%)
Wei (2022) [24]	China	Retrospective observational study	2020	80 patients with carbapenem-resistant *K. pneumoniae* infection	BSIs, pneumonia, UTI, others	*rmpA*, *rmpA2*, *iucA*, *iroN*, or *peg-344*	51 (63.8%)

Namikawa H, Oinuma KI, Yamada K, Kaneko Y, Kakeya H, Shuto T. Predictors of hypervirulent Klebsiella pneumoniae infections: a systematic review and meta-analysis. J Hosp Infect. 2023

Call for prudent use of the term hypervirulence in carbapenem-resistant Klebsiella pneumoniae

In July, 2024, WHO issued a global alert regarding the increasing incidence of hypervirulent *Klebsiella pneumoniae* (hvKP) sequence type (ST) 23, which carry genes encoding carbapenemases that confer hvKP with resistance to the vast majority of clinically available β-lactams. ST23 *K pneumoniae* is a well known hypervirulent lineage and can acquire carbapenemase genes.

The term hypervirulence should be used more prudently when applied to CRKP strains, until providing easy and reproducible evidence of a hypervirulent phenotype is possible. If hypervirulence is to be used in reporting cases or studies, then attributed clinical evidence or data, or both, of murine or equivalent mammalian infection models should be provided for verification

Yang Y, McNally A, Zong Z. Call for prudent use of the term hypervirulence in carbapenem-resistant Klebsiella pneumoniae. Lancet Microbe. 2025 May;6(5):101090

	Cefiderocol (N=250)	Standard of care (N=254)
Age, years*	62 (15)	61 (16)
Sex		
Female	108 (43%)	102 (40%)
Male	142 (57%)	152 (60%)
BMI, kg/m²†	23 (21–27)	24 (21–27)
Country		
Australia	20 (8%)	20 (8%)
Malaysia	75 (30%)	62 (24%)
Singapore	40 (16%)	30 (12%)
Taiwan	38 (15%)	55 (22%)
Thailand	50 (20%)	59 (23%)
Türkiye	27 (11%)	28 (11%)
Charlson Comorbidity Score†‡	5 (3–7)	5 (3–7)
Comorbidity		
Congestive heart failure	12 (5%)	21 (8%)
Chronic pulmonary disease	14 (6%)	17 (7%)
Diabetes	91 (36%)	112 (44%)
Moderate or severe renal disease	69 (28%)	76 (30%)
Moderate or severe liver disease	19 (8%)	18 (7%)
Solid tumour	71 (28%)	66 (26%)
Haematological malignancy	60 (24%)	48 (19%)
AIDS	3 (1%)	4 (2%)
Immunosuppression§	152 (61%)	147 (58%)
Neutropenia¶	48 (19%)	42 (17%)
Acquisition of bloodstream infection		
Hospital-acquired	156 (62%)	153 (60%)
Health care-associated	94 (38%)	101 (40%)

	Cefiderocol (N=250)	Standard of care (N=254)
(Continued from previous column)		
Organisms in index blood culture		
Escherichia coli	90 (36%)	77 (30%)
Klebsiella pneumoniae	73 (29%)	80 (31%)
Enterobacter spp	19 (8%)	21 (8%)
Other Enterobacterales spp‖	26 (10%)	33 (13%)
Pseudomonas spp**	27 (11%)	24 (9%)
Acinetobacter spp††	18 (7%)	25 (10%)
Stenotrophomonas maltophilia	5 (2%)	3 (1%)
Aeromonas spp	7 (3%)	3 (1%)
Miscellaneous non-fermenter	8 (3%)	7 (3%)
Other species	1 (<1%)	2 (1%)
Antimicrobial-resistant organisms		
Third-generation cephalosporin-resistant Enterobacterales spp	66 (26%)	72 (28%)
Carbapenem-resistant Enterobacterales spp	32 (13%)	32 (13%)
Cefiderocol-resistant Enterobacterales spp	12 (5%)	10 (4%)
KPC-producing Enterobacterales spp	1 (<1%)	3 (1%)
OXA-48-like-producing Enterobacterales spp	11 (4%)	15 (6%)
MBL-producing Enterobacterales spp	16 (6%)	11 (4%)
Carbapenem-resistant *Acinetobacter* spp	11 (4%)	14 (6%)
Cefiderocol-resistant *Acinetobacter* spp	2 (1%)	0 (0)
Carbapenem-resistant *Pseudomonas* spp‡‡	8 (3%)	8 (3%)
Cefiderocol-resistant *Pseudomonas* spp	2 (1%)	0 (0)
Carbapenem-resistant Gram-negative bacilli	64 (26%)	63 (25%)

Cefiderocol versus standard therapy for hospital-acquired and health-care-associated Gram-negative bacterial bloodstream infection **(GAME CHANGER)**: an open-label, parallel-group, randomised trial

Paterson DL, et al. Lancet ID 2025

Cefiderocol versus standard therapy for hospital-acquired and health-care-associated Gram-negative bacterial bloodstream infection (the GAME CHANGER trial): an open-label, parallel-group, randomised trial

*David L Paterson, Helmi Sulaiman, Po-Yu Liu, Mark D Chatfield, Mesut Yilmaz, Zeti Norfidiyati Salmuna, Mohd Zulfakar Mazlan, Siriluck Anunnatsiri, Rujipas Sirijatuphat, Darunee Chotiprasitsakul, David C Lye, Jyoti Somani, Shirin Kalimuddin, Abdullah T Aslan, Visanu Thamlikitkul, Yi-Tzu Lee, Ya-Sung Yang, Yi-Tsung Lin, Wan Nurliyana Wan Ramli, Chien-Hao Tseng, Sophia Archuleta, Yvonne Fu Zi Chan, Brian M Forde, Hugh Wright, Adam G Stewart, Kay A Ramsay, Weiping Ling, Vicki Rossi, Tiffany M Harris-Brown, Patrick N A Harris, on behalf of the GAME CHANGER Trial Investigators**

Among patients with a hospital-acquired or health-care-associated Gram-negative bloodstream infection, cefiderocol resulted in non-inferior 14-day mortality compared with standard of care.

In both the main analysis population and the carbapenem-resistant subset, cefiderocol was not superior to standardof care. This evidence suggests that cefiderocol is efficacious in patients with health-care-associated Gram-negative bloodstream infection who are at high risk of antibiotic resistance, but more evidence is required to define its efficacy when carbapenem-resistant organisms are the cause.

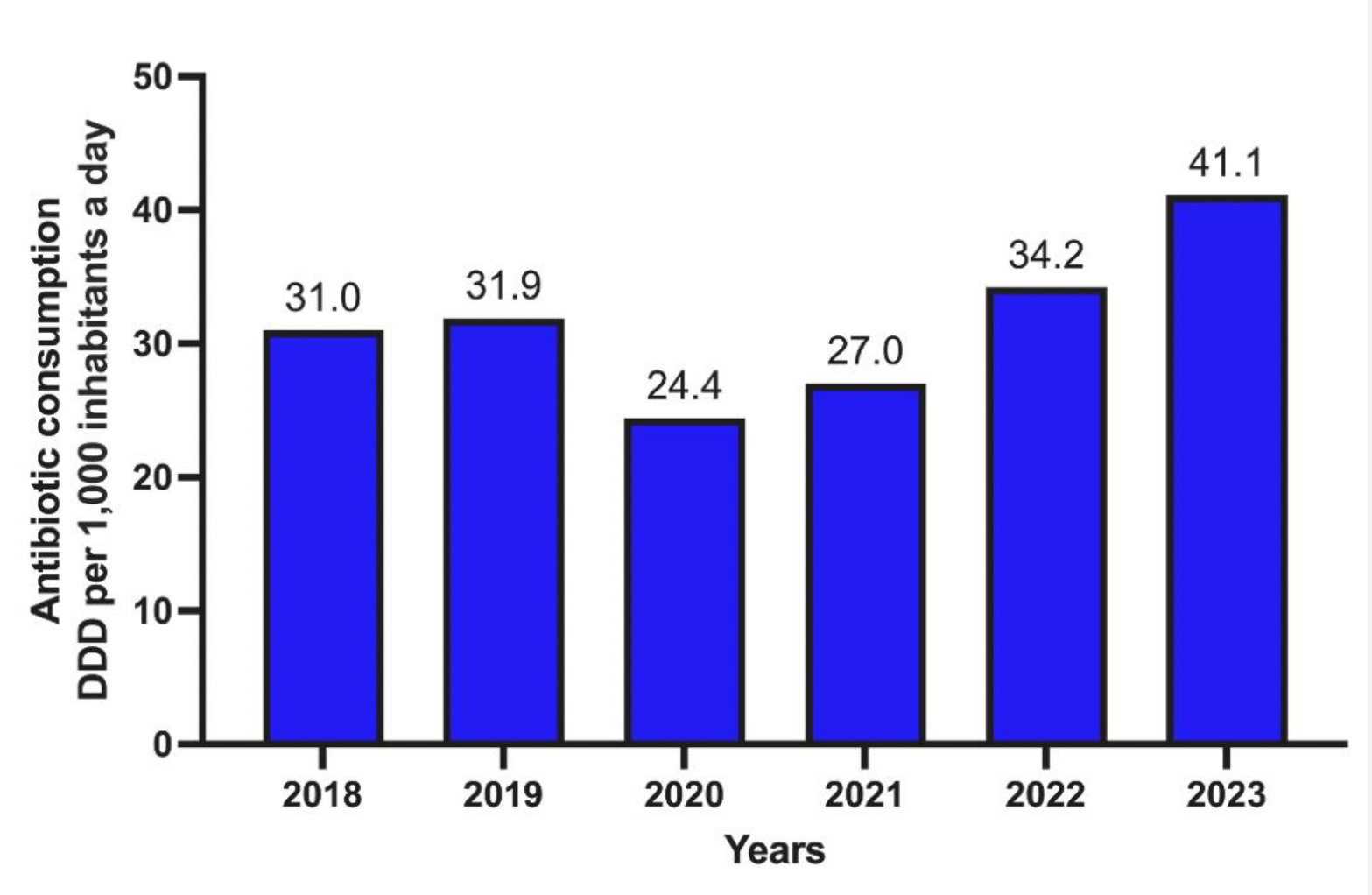
Paterson DL, et al. Lancet ID 2025

Current Treatment Choices for MBL Enterobacterales

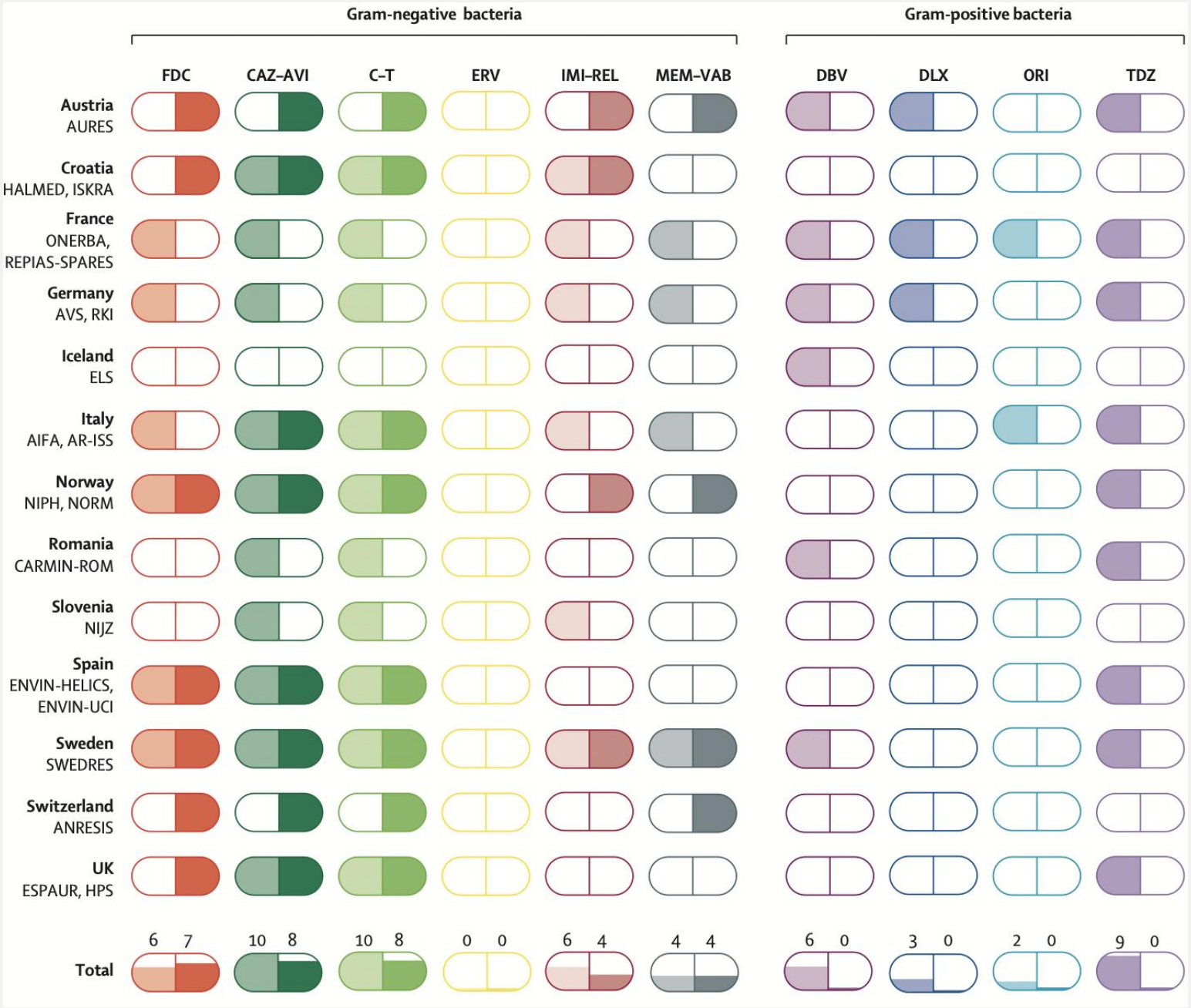
	ESBL	Amp C	Ambler A KPC & IMI	MBL NDM, VIM, IMP	Ambler D OXA-48
CZA					
Aztreonam Avibactam					
Cefiderecol					
Meropenem-vaborbactam					
Imipenem-relebactam					
Ceftolozane-tazobactam					
Sulbactam-durlobactam					

Önder Ergönül

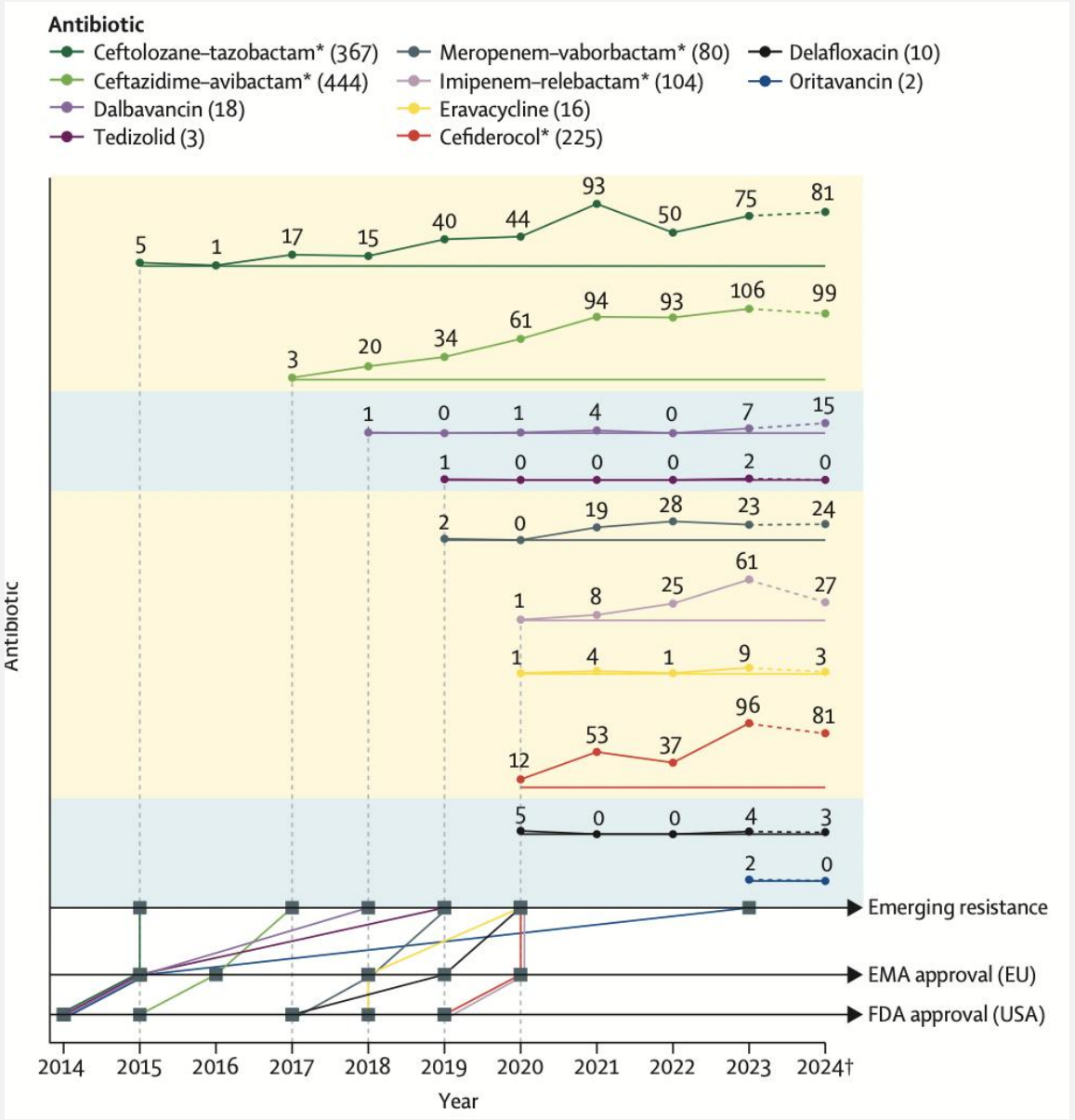
Antibiotic Consumption in Türkiye



Alhan Ö, Özger HS, Karatuna O, Azap ÖK, Madran B, Keske Ş, Çınar G, Akdemir İ, Ergönül Ö. Antibiotic resistance in Türkiye: what has been done and what needs to be done urgently? Clin Microbiol Infect. 2025



Garlasco J, Arieti F, Morra M, Tebon M, Ortiz D, Pezzani MD, Odoj K, Manco F, Cassini A, Harbarth S, Presterl E, Carevic B, Kahlmeter G, Thursky K, Morelli P, Hagel S, Savoldi A, Tacconelli E. The Emerging Resistance Index: tracking early resistance to new antibiotics. Lancet Infect Dis 2025



Garlasco J, Arieti F, Morra M, Tebon M, Ortiz D, Pezzani MD, Odoj K, Manco F, Cassini A, Harbarth S, Presterl E, Carevic B, Kahlmeter G, Thursky K, Morelli P, Hagel S, Savoldi A, Tacconelli E. The Emerging Resistance Index: tracking early resistance to new antibiotics. Lancet Infect Dis 2025

The Emerging Resistance Index: tracking early resistance to new antibiotics

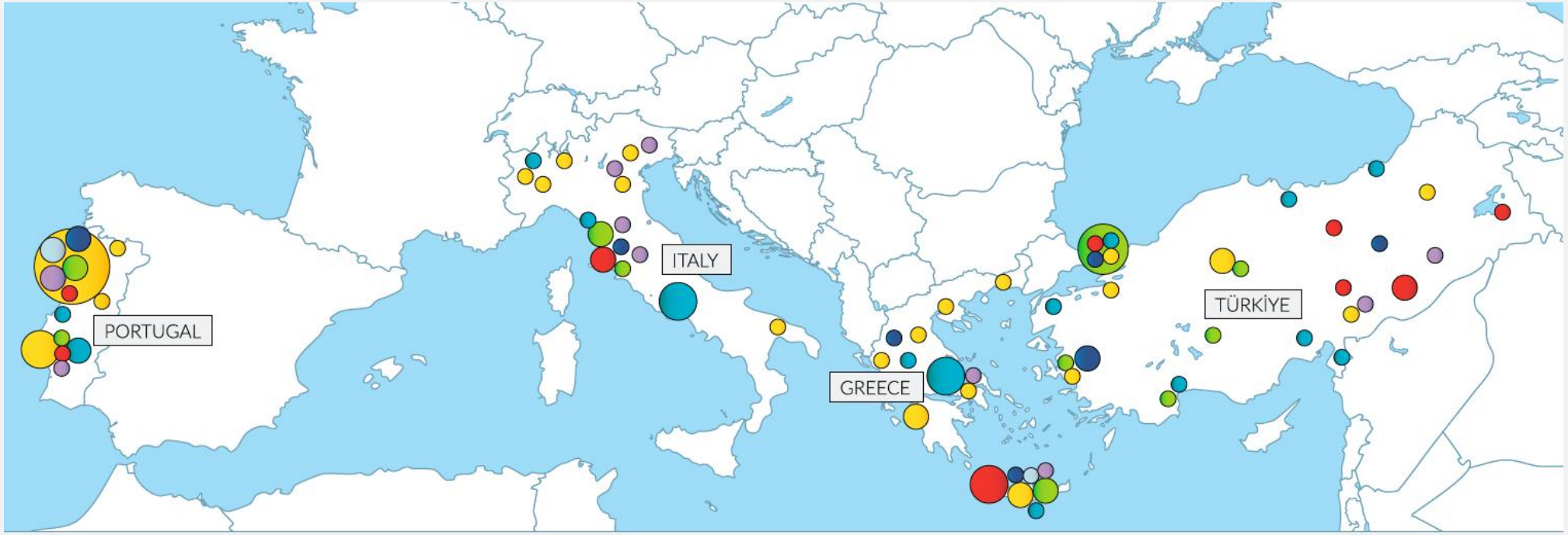
Jacopo Garlasco, Fabiana Arieti*, Matteo Morra, Maela Tebon, Diego Ortiz, Maria Diletta Pezzani, Karin Odoj, Federica Manco, Alessandro Cassini, Stephan Harbarth, Elisabeth Presterl, Biljana Carevic, Gunnar Kahlmeter, Karin Thursky, Paola Morelli, Stefan Hagel, Alessia Savoldi*, Evelina Tacconelli**

	a_i	k_i	A_i	B_i	C_i	ERI numerator	D_i	E_i	ERI denominator	ERI	ERI tier
Imipenem–relebactam	0·239	1·153	3·246	0	1·000	3·469	0·125	0·052	0·444	7·8	Very high
Cefiderocol	0·153	1·076	4·481	0	1·250	3·240	0·115	0·094	0·478	6·8	Very high
Ceftolozane–tazobactam	0·223	0·943	2·384	0	0·444	1·928	0·184	0·086	0·538	3·6	High
Meropenem–vaborbactam	0·187	1·156	1·896	1	0·667	1·098	0·050	0·038	0·328	3·3	High
Ceftazidime–avibactam	0·179	1·044	3·745	1	1·250	1·796	0·196	0·121	0·581	3·1	High
Eravacycline	0·324	1·044	0·590	2	0·000	0·406	0·000	0·000	0·141	2·9	Medium
Delafloxacin	0·359	1·127	0·000	1	0·000	0·577	0·031	0·000	0·226	2·5	Medium
Dalbavancin	0·131	1·163	1·221	3	0·000	0·231	0·105	0·000	0·354	0·7	Low
Tedizolid	0·102	1·000	0·493	4	0·000	0·117	0·156	0·000	0·420	0·3	Low
Oritavancin	0·002	1·000	-2·885	8	0·000	0·001	0·012	0·000	0·178	0·0	Low

Target antibiotics are listed in descending order of ERI score. The parameters were: a_i (pooled prevalence of resistance), k_i (trend of prevalence of resistance), A_i (trend in yearly publication reporting resistance), B_i (time lag between approval and report of resistance), C_i (average number of outbreaks), D_i (availability of surveillance systems monitoring antibiotic consumption), and E_i (availability of surveillance systems assessing resistance rates). The ERI numerator indicates the summary measure of the emerging resistance potential (in the form of exponential of the linear combination of A_i, B_i, and C_i, as described in the Methods section), while the ERI denominator represents the status of surveillance of antimicrobial consumption and resistance (in the form of square root of the linear combination of D_i and E_i). ERI=Emerging Resistance Index.

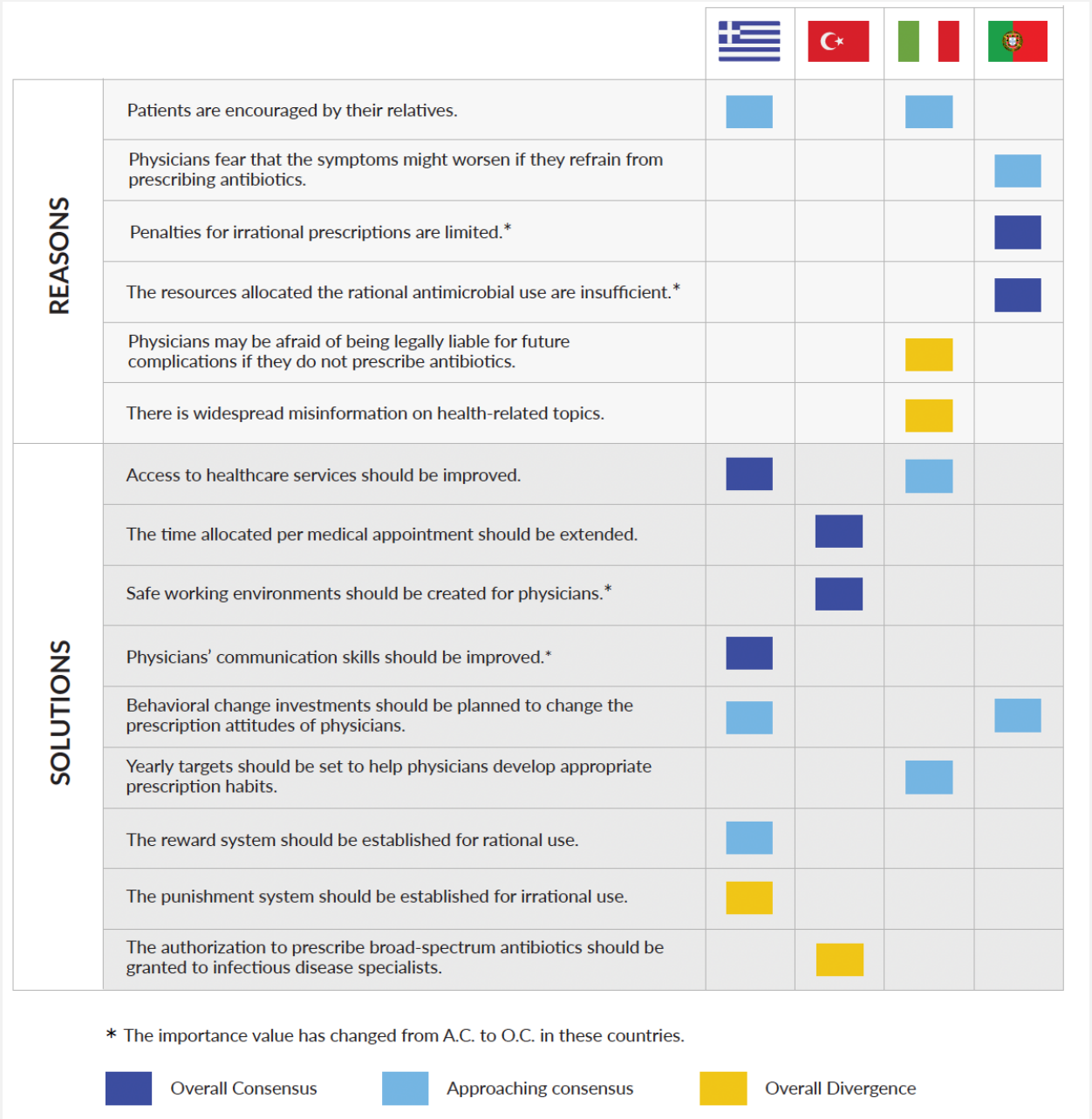
Table: **ERI parameters, value, and tier by antibiotic or antibiotic combination**

Determinants of antibiotics misuse and overuse in High-Risk Countries in the European Region: A Multidisciplinary Delphi Study



Bahar Madran, Önder Ergönül, Sibel Sakarya ve ark. (submitted)

Determinants of antibiotics misuse and overuse in High-Risk Countries in the European Region: A Multidisciplinary Delphi Study



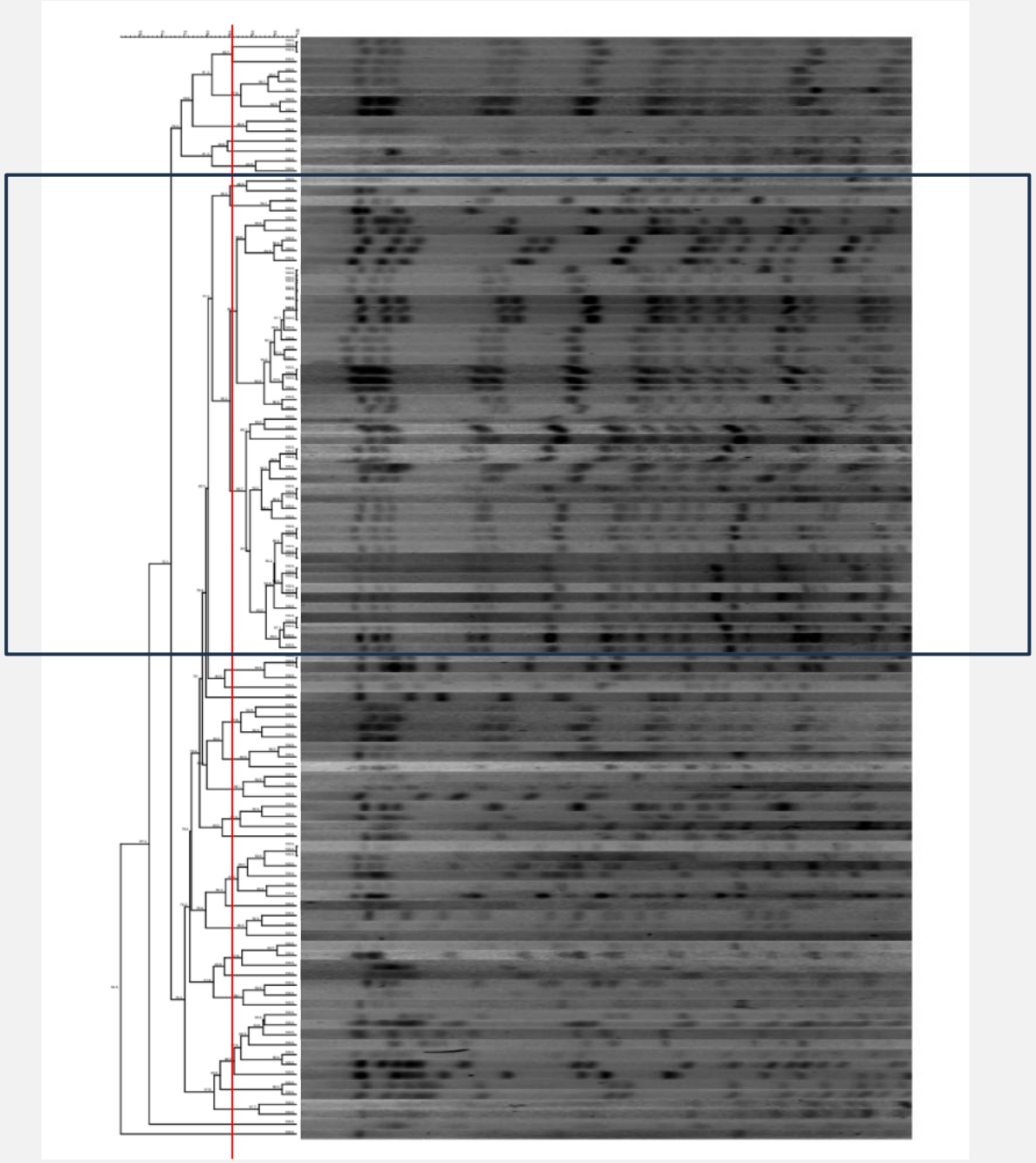
Bahar Madran, Önder Ergönül, Sibel Sakarya ve ark. (submitted)

Significance of Outbreaks

Ceftazidim-Avibaktam Resistant *K. pneumoniae*

PFGE results

- 8 centers: NDM-1 negative 110 samples
- ≥85% similarity index



Gücer L, et al. Unpublished results

Elimination of healthcare-associated Acinetobacter baumannii infection in a highly endemic region

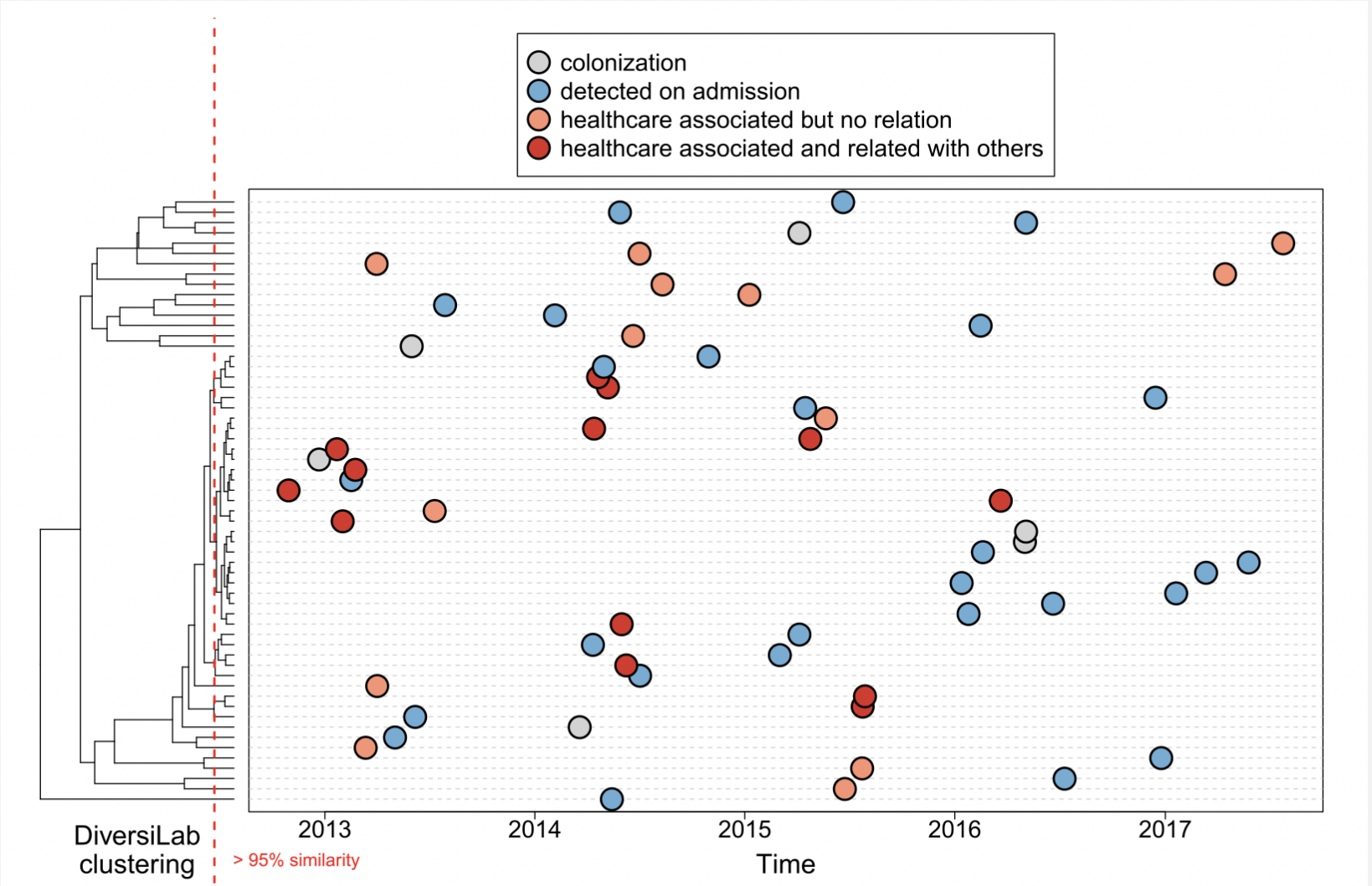


Figure 2. Relatedness of healthcare-associated infections among colonized and infected patients.

Ergonul O, Tokca G, Keske Ş, Donmez E, Madran B, Kömür A, Gönen M, Can F.. Int J Infect Dis. 2022

WHO 2024: Surveillance and Laboratory Limitations

Global gaps in:

- Laboratory capacity for **molecular diagnostics**
- **Routine surveillance** of hvKp?
  - Is it necessary?
- **Systematic reporting** and case documentation

Most affected regions **lack reliable diagnostics**, limiting **sensitivity of detection** and **surveillance coverage**.

WHO 2024 Report: Key Challenges and Recommendations

⚠ Key Challenges

- Lack of data on:
  - Prevalence and transmission scale
  - Hospitalizations and community-level burden
  - Impact on healthcare systems

- **Uncertainty** in surveillance data leads to **moderate confidence** in risk estimates.

◐ Recommendations

- Strengthen **infection prevention and control (IPC)** in hospitals.
- Improve **molecular diagnostic access**.
- Enhance **global surveillance systems** for real-time tracking.
- Promote international cooperation to monitor and contain spread.

The Effect of Environment: Associaton or Causality?

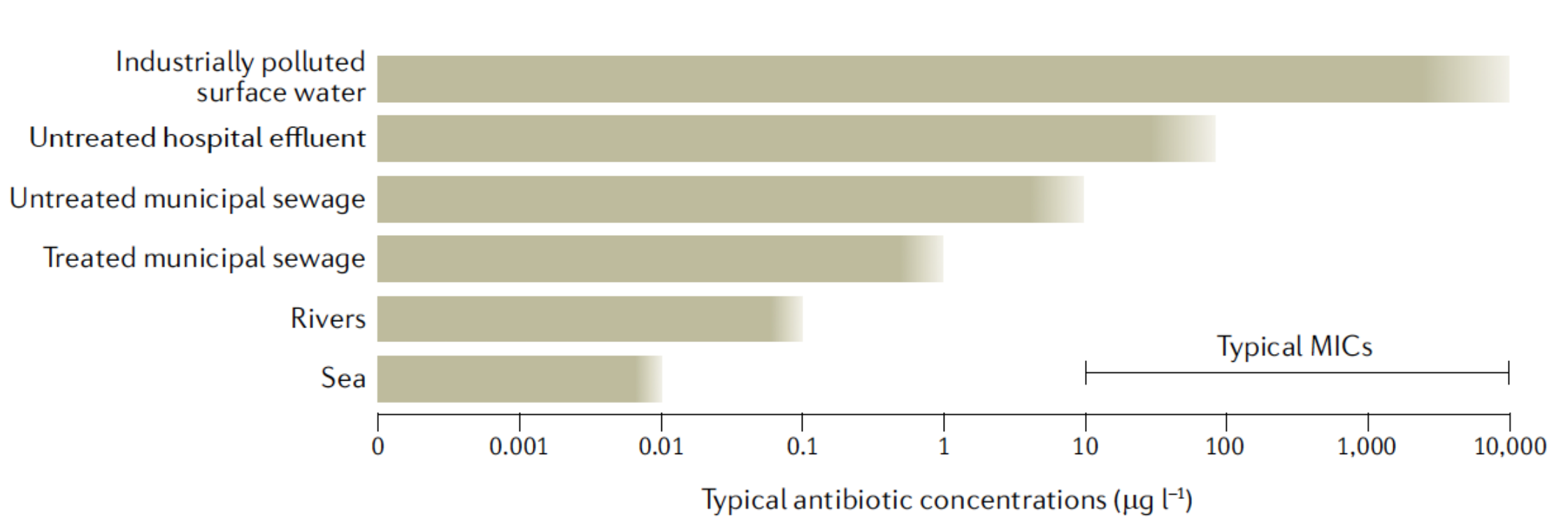
Evidence Type	Example Findings	Strength
Molecular (genomic linkage)	Identical resistance genes and plasmids (e.g., *blaCTX-M-15*, *mcr-1*) found in *E. coli* from poultry meat and humans	Strong (causal linkage plausible)
Ecological (policy natural experiments)	AMR decline in humans after animal antibiotic restrictions (e.g., avoparcin ban in EU reducing *VRE*)	Strong population-level evidence
Epidemiologic (correlation)	Regions with high farm antibiotic use show higher AMR prevalence in human infections (e.g., ESBL in *E. coli*)	Moderate (association, not proof)

Animal sources of antimicrobial-resistant bacterial infections in humans

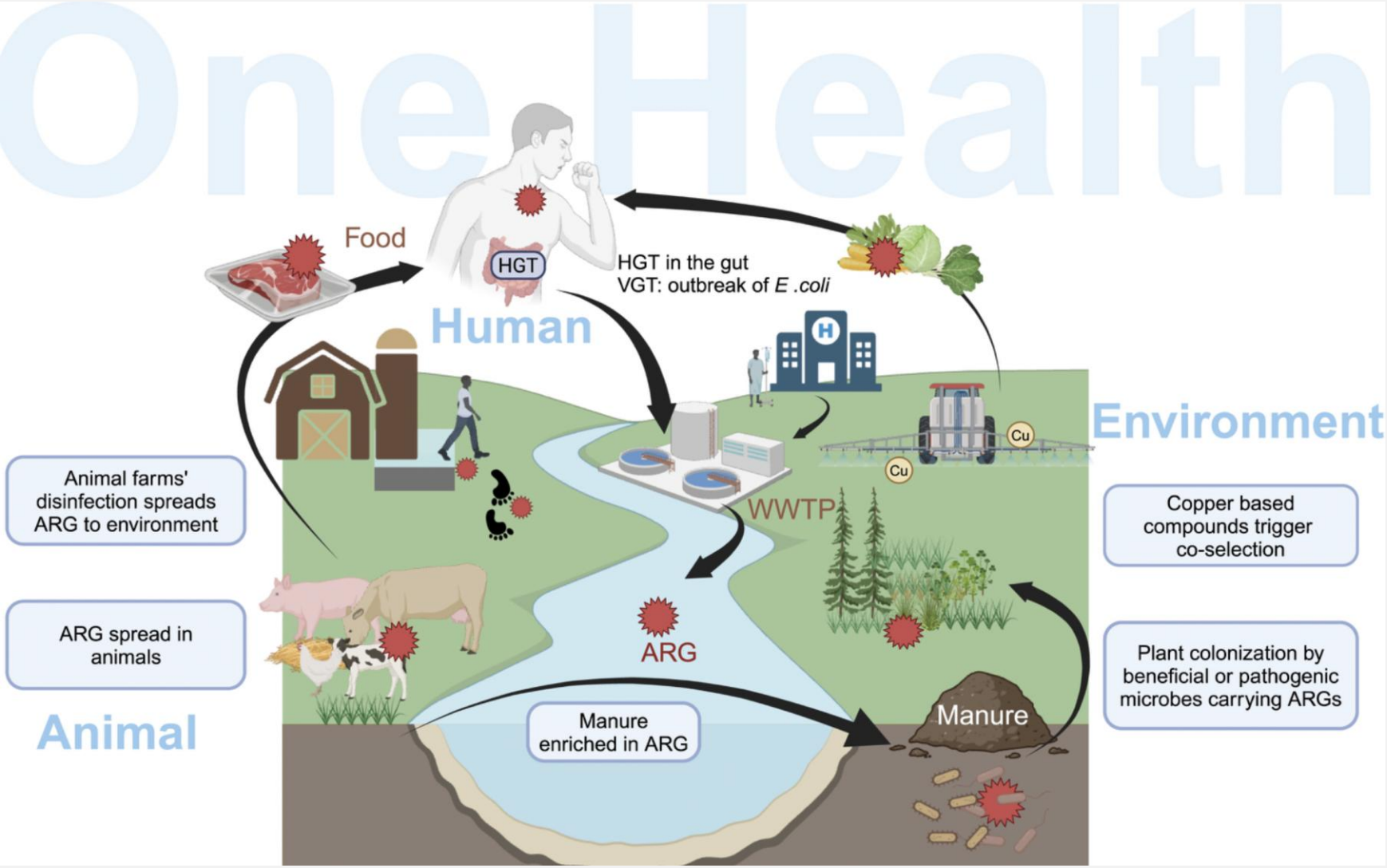
a Hazard definition (number of studies) Overall	Details	Study type	Study	b Outcome*	c Animal-sources: Mode of transmission† — Animal reservoir	Animal contact	Food preparation	Food consumption	c Animal-sources: Animal species¶ — Chicken	Pig	Cattle	Veal calves	Sheep/goat	Turkey/ duck	Fish/ seafood	Dairy/ Eggs	Pets	Other	d Other sources — Humans	Environmental	Other non-animal	Unsampled/unknown	e All sources — most important source overall§ (>50% in bolt)
AMR general (6)	Different bug-drug combinations	RA (S-Q)	Collineau (2018)	HH				■	**1**	3	2	4											NA
		RA (S-Q)	Presi (2018)	HH				■	**1**	2	3	4											NA
	Resistome	MS	Duarte (2021)	C	■				■	■	■		■					■				■	**Human-to-human**
		CEA (QI)	Lechner (2020)	E		B	N	■	2	**1**	3	5			4						■		**Fresh produce**
		RA (QI)	Cheareau (2017)	HH				■	■	■	■	■	■	■	■	■	■				■		AMU, human-to-human
		RA (Q)	Opatowski (2021)	C		O		■	■	■	■	■	■	■	■		■						NA
Escherichia coli (7)	ESBL & (p)AmpC producing	CEA (Q)	Evers (2017)	E				■	3	2	**1**	4	5										NA
		CEA (Q)	Carmo (2014)	E				■	**1**	2	3												NA
		MS	Mughini-Gras (2019)	C		N		■	2	5	4		7	6	3		**1**		■	■	■		**Human-to-human**
	ESBL producing	MS	Perestrelo (2020)	C	■				3	2	**1**						4		■			■	Unknown
		Other	Booton (2021)	I		B		■	■	■	■	■	■	■	■	■	■			■			**Human AMU**
		Other	De Freitas Costa (2022)	C		O		■	■										■				**Open community**
	AMR as subtyping	MS	Mitchell (2021)	C	■				■		■						■	■		■	■		Drinking water
Salmonella (*non-typhoidal*) *(8)*	*Typhimurium* DT104	RA (Q/QI)	Alban (2002)	I				■		T													NA
	Heidelberg (ceftiofur-resistant)	RA (Q)	Collineau (2020)	I				■	T														NA
		RA (Q)	Otto (2014)	I				■	T														NA
	Resistant	RA (Q)	Costard (2020)	I				■			T												NA
		OUT	Brown (2012)	I				■	2	3	**1**			2		3					■	■	Animal-based food
	Invasive (AMR as subtyping)	MS	Parisi (2020)	I	■				**1**	3				2					■			■	**Unobserved**
	Hadar (AMR as subtyping)	MS	Vieira (2016)	I	■				2	3	4			**1**									NA
	ceftriaxone-resistant	OUT	Folster (2017)	I				■	**1**		**1**										■	■	Unknown
Salmonella *spp.(4)*	Resistant	OUT	Holmberg (1984)	I		■	■	■	■	■	■	■	■	■	■	■	■		■		■	■	Food animals & products
		OUT	Waltenburg (2021)	I		N											■						NA
		RA (QI)	Doménech (2015)	HH				■	**1**	2	3												NA
	AMR as subtyping	MS	Hald (2007)	I				■						■		■		■			■	■	Danish & imported food
Campylobacter (2)	*jejuni* clone SA	OUT	Sahin (2012)	I				■	2						**1**						■		Raw milk
	spp. (FQ-resistant)	RA(Q)	Vose (2000)	I				■	T														NA
MRSA (2)	ST398	RA (Q)	Cox Jr. & Popken (2014)	I		O	O	■		T													NA
		RA (Q)	Schoen (2020)	I			N			T													NA

Fastl C, De Carvalho Ferreira HC, Babo Martins S, et al. Animal sources of antimicrobial-resistant bacterial infections in humans: a systematic review. *Epidemiology and Infection*. 2023

Antibiotic concentrations in selected aquatic environments

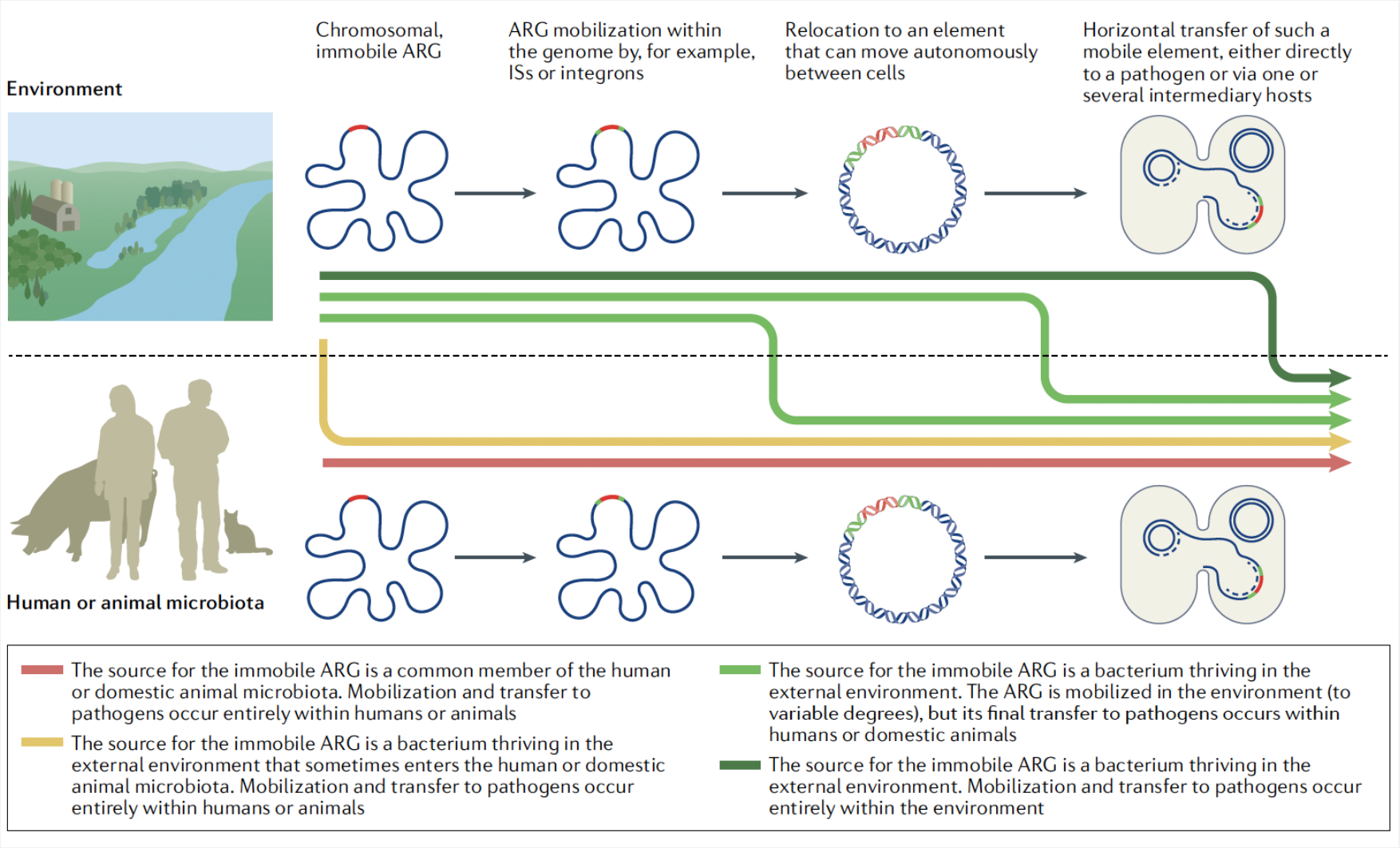


Larsson, D.G.J., Flach, CF. Antibiotic resistance in the environment. *Nat Rev Microbiol* 2022



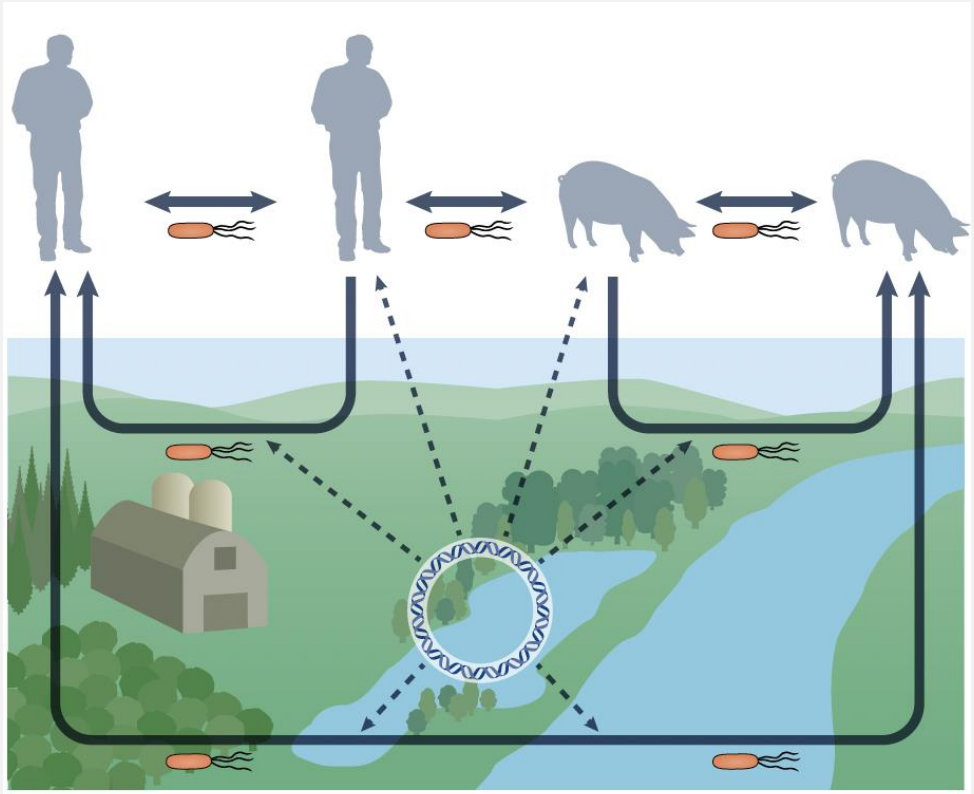
Bustamante M, et al. An eco-evolutionary perspective on antimicrobial resistance in the context of One Health. iScience. 2024

The role of the environment in the emergence of new resistance genes in pathogens



Larsson, D.G.J., Flach, CF. Antibiotic resistance in the environment. *Nat Rev Microbiol* 2022

Pathways for transmission of bacterial pathogens and recruitment of resistance genes from the environmental microbiota.



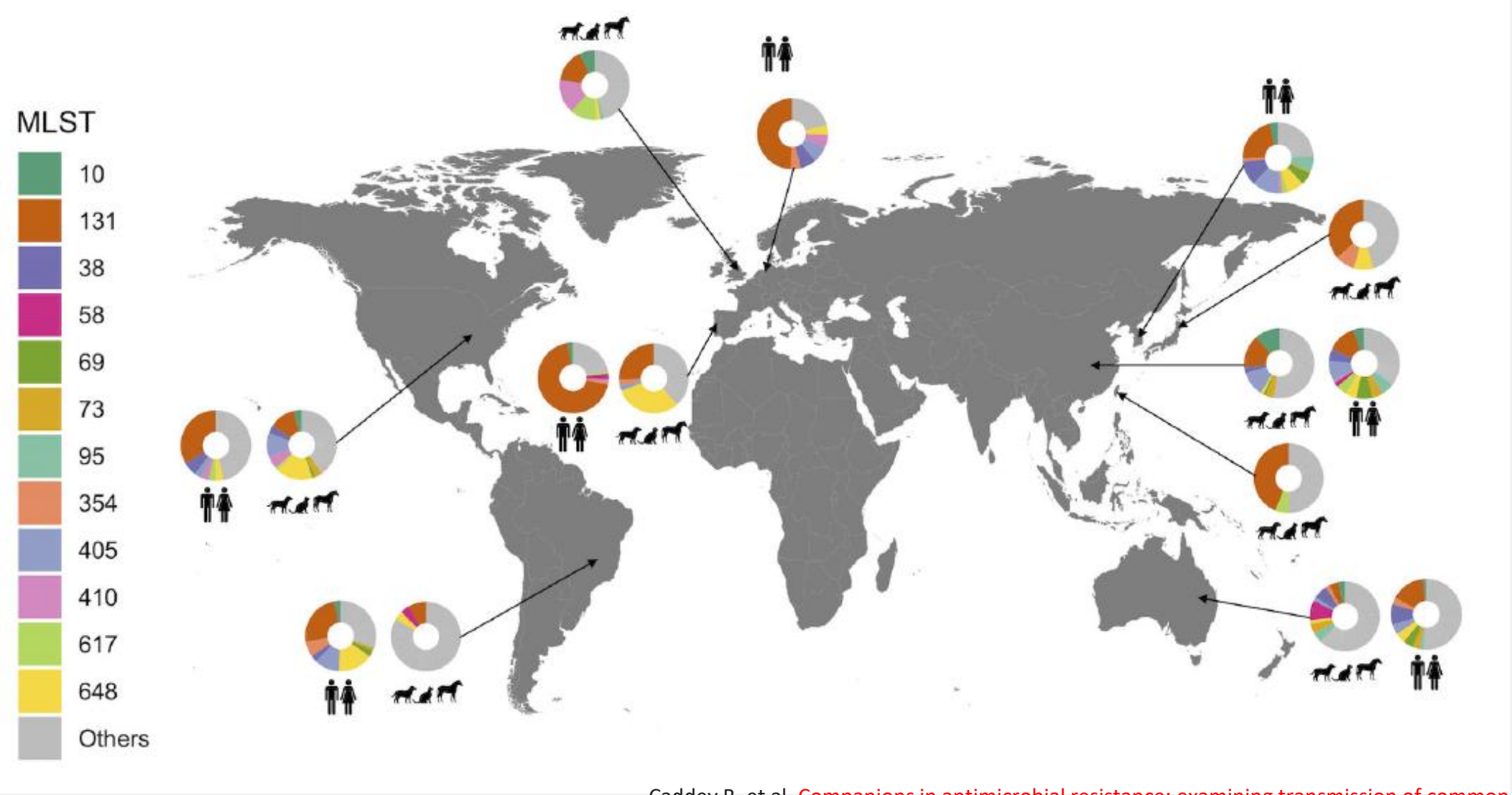
Transmission of pathogenic bacteria between humans, between animals or between humans and animals (either direct or via the environment):	Uptake of new resistance factors from the diverse environmental microbiota:
• Common	• Relatively rare
• Risks are in principle quantifiable and predictable	• More challenging to predict
• Consequences of each transmission event are limited	• Consequences of single transfer events may be vast
• Transmission rates can be reduced	• Irreversible

Larsson, D.G.J., Flach, CF. Antibiotic resistance in the environment. *Nat Rev Microbiol* 2022

Distribution of the most commonly reported MRSA ST types among companion animals

Caddey B, et al.
Companions in antimicrobial resistance: examining transmission of common antimicrobial-resistant organisms between people and their dogs, cats, and horses.
Clin Microbiol Rev. 2025

Global distribution of ESBL producing extraintestinal pathogenic E.coli isolated from human and animals



Caddey B, et al. Companions in antimicrobial resistance: examining transmission of common antimicrobial-resistant organisms between people and their dogs, cats, and horses. Clin Microbiol Rev. 2025

Carbapenemase genes identified in companion animals

Gene	Country (no. of studies identified)[a]	Bacterial species (sequence type)	Animal species
IMP-45	China (1)	*P. aeruginosa* (308)	Dog
KPC-18	USA (1)	*E. coli* (372)	Dog
KPC-2	Brazil (2)	*K. pneumoniae* (11)	Dog
		E. coli (648)	
NDM-4	China (1)	*E. coli* (162, 224, 101, 448, 453, 1421, 167, 226, 410, 457, and 405)	Dog, cat, and turtle
NDM-5	South Korea (3)	*E. coli* (410, 101, 167, 354, 641, 1415, 2115, 3902, 10, 224, and 641)	Dog, cat, and horse
	China (2)	*K. pneumoniae* (378 and 307)	
	Thailand (1)		
	Italy (2)		
	UK (1)		
	Finland (1)		
	USA (3)		
OXA-48	France (3)	*K. pneumoniae* (11, 15, 37, 48, and 307)	Dog and cat
	Germany (1)	*E. coli* (10, 69, 104, 131, 167, 405, 648, 3058, 297, 681, 1196, and 1431)	
	China (1)		
	Switzerland (1)		
OXA-181	Switzerland (1)	*E. coli* (410)	Dog and cat
	Portugal (1)		
OXA-23	Thailand (1)	*A. baumannii* (2, 16, 23, 25, 149, 1093, 1575, 1581, 1, and 7)	Dog and cat
	Pakistan (1)		
	Germany (2)		
	Italy (1)		
	France (2)		
OXA-58	Germany (1)	*A. baumanii* (1)	Dog and cat
VIM-2	South Korea (1)	*P. aeruginosa* (233, 871, 1047, 1203, and 1428)	Dog
	Brazil (1)		

[a]References for studies: (123, 127, 203–234).

Caddey B, et al. Companions in antimicrobial resistance: examining transmission of common antimicrobial-resistant organisms between people and their dogs, cats, and horses. Clin Microbiol Rev. 2025

Fecal carriage prevalence of Carbapenemase producing organism in healthcare- and veterinary-associated settings in China

CPO	Genes	Population	Prevalence (%) (reference)
Enterobacteriaceae	NDM and KPC	ICU patient	16.7 (246)
Escherichia coli	NDM-1/5	General public	1.1 (247)
Enterobacteriaceae	NDM-5	Veterinary workers—small animal practice	7.4 (203)
Enterobacteriaceae	NDM-5	Dogs	17.8 (203)
Enterobacteriaceae	NDM-5	Cats	8.6 (203)

[a]CPO, carbapenemase-producing organism.

Caddey B, et al. Companions in antimicrobial resistance: examining transmission of common antimicrobial-resistant organisms between people and their dogs, cats, and horses. Clin Microbiol Rev. 2025

A Good Example from France

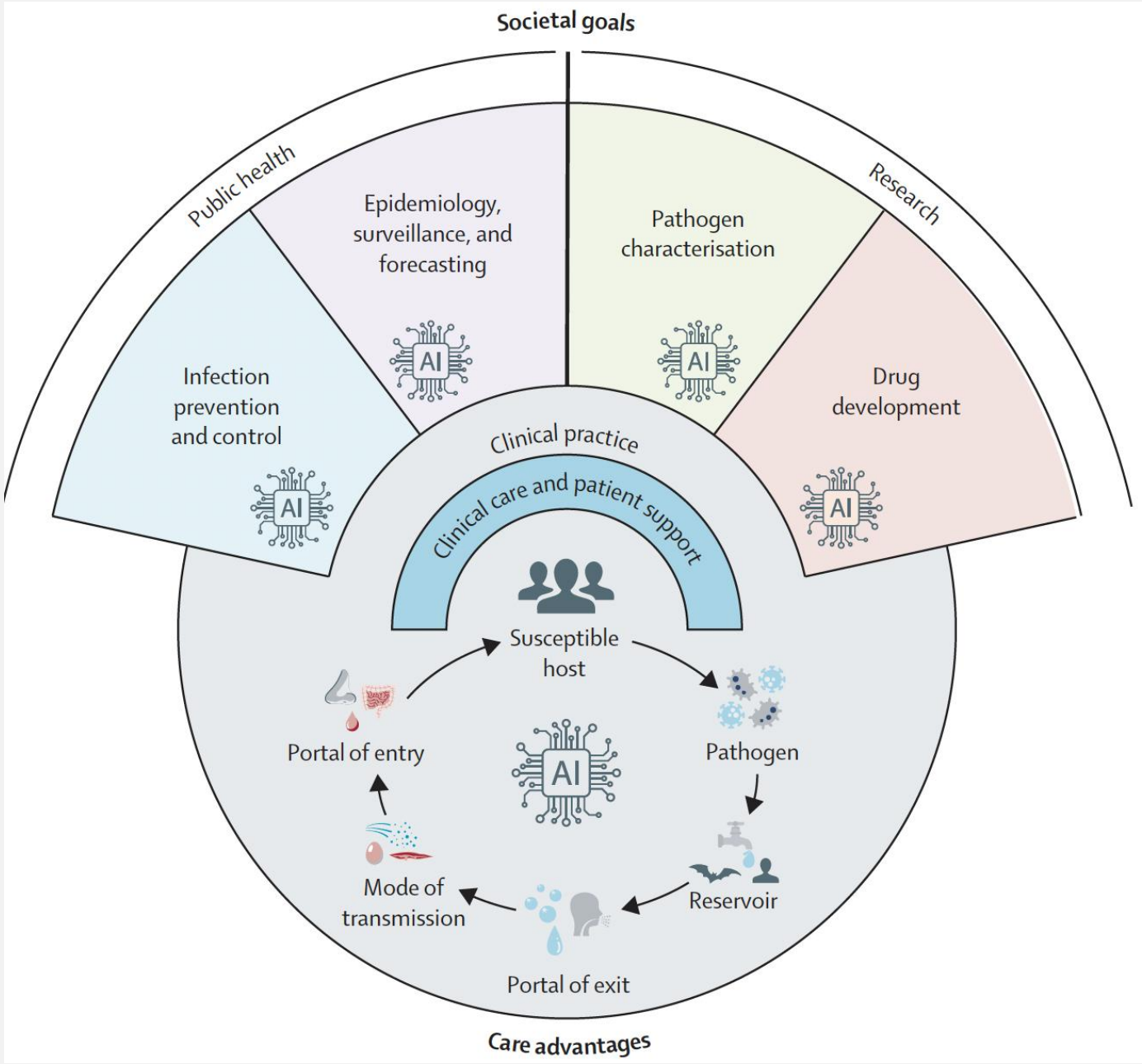
Since 2011, France has implemented three national Ecoantibio plans to reduce antibiotic use in veterinary medicine. These initiatives actively involved farmers, veterinarians, regulators, and researchers.

From 2011 to 2021, the overall antibiotic exposure in livestock decreased by 47%, with substantial reductions, exceeding 90% in some key antimicrobials, such as fluoroquinolones in poultry and colistin in pigs and calves. Of note, colistin, a drug that was once commonly used in livestock, saw a 66% reduction in exposure between 2014 and 2022, surpassing the initial targets.

These policy efforts have produced a measurable biological impact, with data from French national surveillance showing a steady decline in resistance levels over the past decade. The 2023 ANSES scientific report identified 11 priority bacteria–antibiotic combinations to monitor in animals, due to their implications for human health. For most of these, including meticillin-resistant *Staphylococcus aureus*, fluoroquinolone-resistant *Escherichia coli*, and colistin-resistant Enterobacterales, no strong molecular or epidemiological evidence links animal strains to multidrug-resistant infections in humans.

The most crucial, Enterobacterales resistant to carbapenems, remains virtually absent in French livestock and has only been detected sporadically in companion animals.

Khamisse, Elissa et al. Rethinking the role of animals in antimicrobial resistance. The Lancet Microbe 2025



Multilayered conceptual theoretical framework for potential applications AI in infectious disease prevention and management

Odone A, et al. Artificial intelligence and infectious diseases: an evidence-driven conceptual framework for research, public health, and clinical practice. Lancet ID 2025.

Conclusion

The body of evidence on the direct contribution of animal sources to AMR in humans is growing but still relatively small.

Existing studies utilise a broad range of methodologies to address this question.

Recent years have seen promising developments, such as using human resistome data for source attribution, that will aid in tailoring studies to the specific characteristics of the AMR hazard.

Surveillance with molecular methods is necessary

The policymakers should taken an action.

Thank you

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