ΕΛΛΗΝΙΚΗ ΔΗΜΟΚΡΑΤΙΑ
Εθνικόν και Καποδιστριακόν Πανεπιστήμιον Αθηνών
ΙΔΡΥΘΕΝ ΤΟ 1837

PREVENTING ANTIMICROBIAL RESISTANCE TOGETHER

Η επιδημιολογία της αντιμικροβιακής αντοχής στην Ελλάδα

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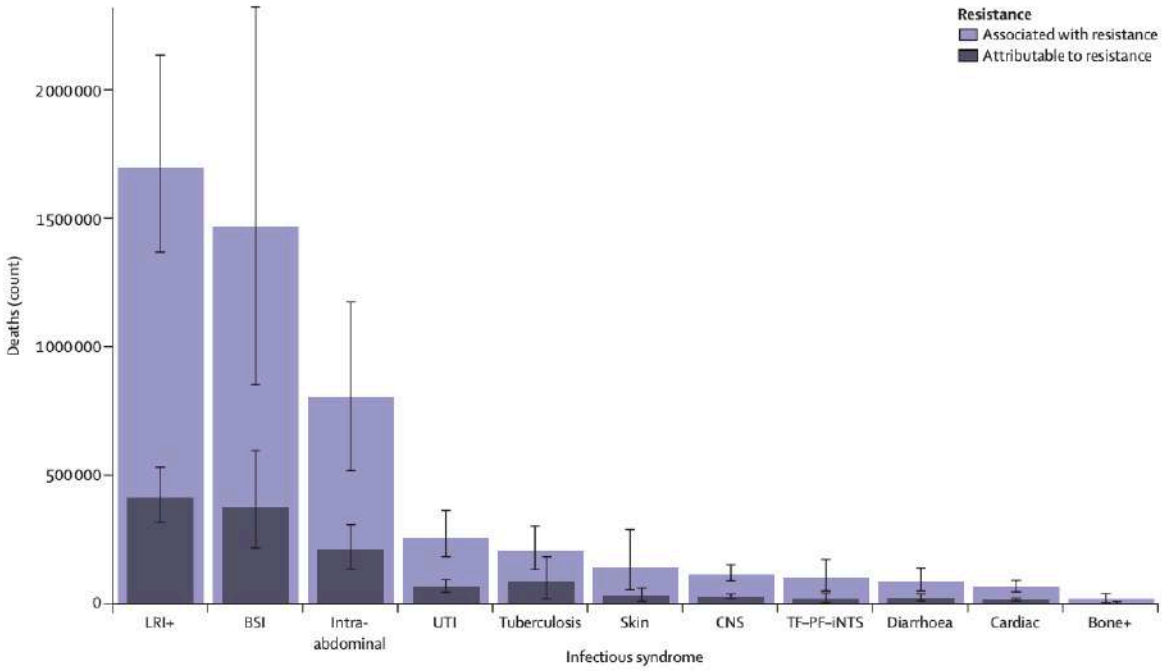
Β΄Κλινική Εντατικής Θεραπείας, ΕΚΠΑ

ΠΜΣ
"ΛΟΙΜΩΞΙΟΛΟΓΙΑ"
ΤΗΣ ΙΑΤΡΙΚΗΣ ΣΧΟΛΗΣ
ΑΘΗΝΩΝ

THE LANCET
Public Health

The burden of bacterial antimicrobial resistance



Antimicrobial Resistance Collaborators. Lancet. 2022; 399 (10325): 629-655.

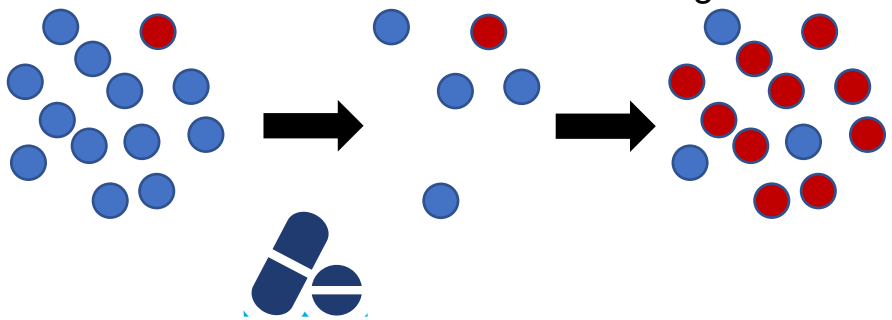
	Associated with AMR				Attributable to AMR			
	Deaths		DALYs		Deaths		DALYs	
	Counts	Rate, per 100 000 population	Counts	Rate, per 100 000 population	Counts	Rate, per 100 000 population	Counts	Rate, per 100 000 population
BSI	195 000 (104 000–333 000)	20·9 (11·1–35·8)	4 180 000 (2 270 000–6 870 000)	448·3 (243·5–737·3)	47 200 (24 700–79 300)	5·1 (2·7–8·5)	1 020 000 (566 000–1 670 000)	109·4 (60·7–178·9)
Bacterial skin infections	14 300 (5700–30 000)	1·5 (0·6–3·2)	258 000 (106 000–557 000)	27·7 (11·3–59·8)	3080 (1180–6700)	0·3 (0·1–0·7)	56 000 (22 100–124 000)	6·0 (2·4–13·3)
Bone and joint infections	1530 (477–3500)	0·2 (0·1–0·4)	31 100 (9210–72 100)	3·3 (1·0–7·7)	342 (104–817)	0 (0–0·1)	7020 (2050–16 700)	0·8 (0·2–1·8)
CNS infections*	2130 (1380–3640)	0·2 (0·1–0·4)	90 500 (59 400–148 000)	9·7 (6·4–15·8)	504 (322–902)	0·1 (0–0·1)	21 100 (13 600–34 900)	2·3 (1·5–3·7)
Cardiac infections	20 000 (13 200–29 400)	2·1 (1·4–3·2)	354 000 (242 000–525 000)	38·0 (25·9–56·3)	4670 (3030–7000)	0·5 (0·3–0·8)	83 600 (55 000–127 000)	9·0 (5·9–13·6)
Diarrhoea	649 (361–1090)	0·1 (0–0·1)	42 200 (24 400–69 200)	4·5 (2·6–7·4)	145 (78–252)	0 (0–0)	7780 (4290–13 000)	0·8 (0·5–1·4)
Gonorrhoea and chlamydia	..	..	2420 (1380–3870)	0·3 (0·1–0·4)	..	..	243 (70–492)	0 (0–0·1)
Intra-abdominal infections	127 000 (81 900–185 000)	13·7 (8·8–19·8)	2 860 000 (1 800 000–4 200 000)	307·2 (193·3–451·0)	31 200 (19 900–45 600)	3·3 (2·1–4·9)	708 000 (438 000–1 050 000)	76·0 (47·0–113·1)
LRI and thorax infections	120 000 (94 500–154 000)	12·9 (10·1–16·6)	2 760 000 (2 240 000–3 460 000)	296·0 (240·8–370·9)	28 500 (21 200–38 500)	3·1 (2·3–4·1)	656 000 (502 000–855 000)	70·4 (53·8–91·8)
Tuberculosis	11 800 (9150–15 000)	1·3 (1·0–1·6)	501 000 (390 000–626 000)	53·7 (41·8–67·2)	5670 (2190–9510)	0·6 (0·2–1·0)	219 000 (86 500–365 000)	23·5 (9·3–39·2)
Typhoid, paratyphoid, and iNTS	67 (37–121)	0 (0–0)	3130 (1340–6470)	0·3 (0·1–0·7)	13 (4–31)	0 (0–0)	629 (144–1670)	0·1 (0–0·2)
UTI	48 700 (35 600–68 000)	5·2 (3·8–7·3)	833 000 (600 000–1 190 000)	89·4 (64·4–127·2)	11 500 (8310–16 800)	1·2 (0·9–1·8)	201 000 (143 000–297 000)	21·6 (15·3–31·9)
All infectious syndromes	541 000 (370 000–763 000)	58·1 (39·7–81·9)	11 900 000 (8 190 000–16 700 000)	1278·5 (879·0–1794·0)	133 000 (90 100–188 000)	14·3 (9·7–20·2)	2 980 000 (2 020 000–4 210 000)	319·8 (216·5–451·8)

Data are estimates (95% uncertainty interval). Estimates were aggregated across drugs, accounting for the co-occurrence of resistance to multiple drugs. For gonorrhoea and chlamydia, we did not estimate the fatal burden, thus only the DALY burden is presented. AMR=antimicrobial resistance. BSI=bloodstream infections. DALYs=disability-adjusted life-years. LRI=lower respiratory infections. iNTS=invasive non-typhoidal salmonellae. UTI=urinary tract infections. *Includes meningitis.

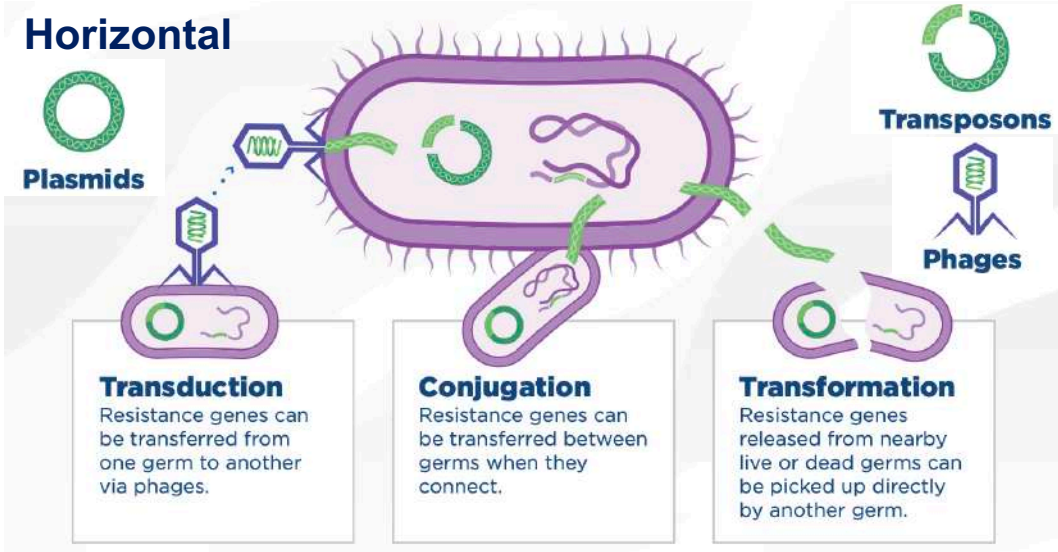
European Antimicrobial Resistance Collaborators. Lancet Public Health. 2022;7(11):e897-e913.

How resistance happens

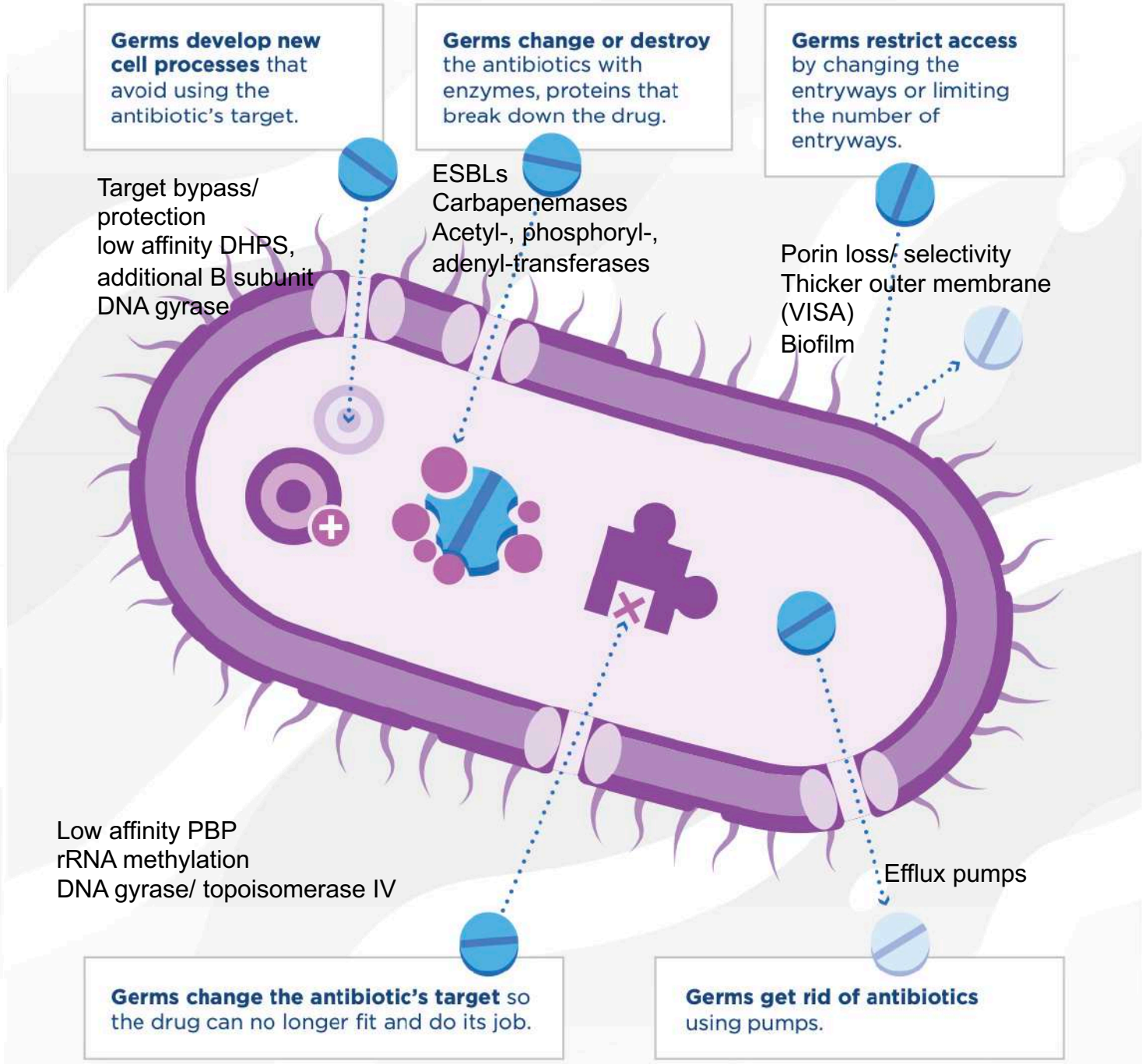
Vertical



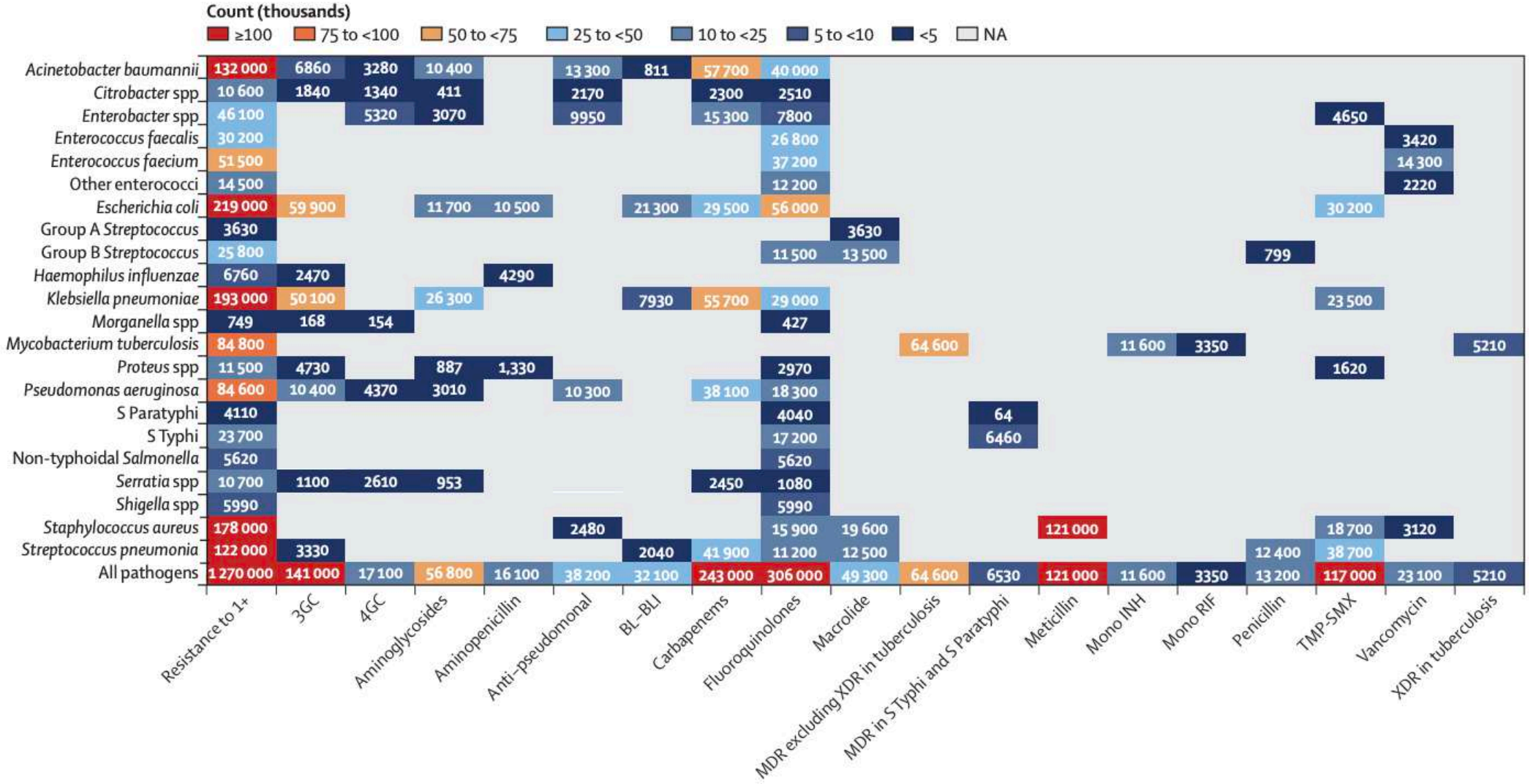
Horizontal



https://www.cdc.gov/drugresistance/

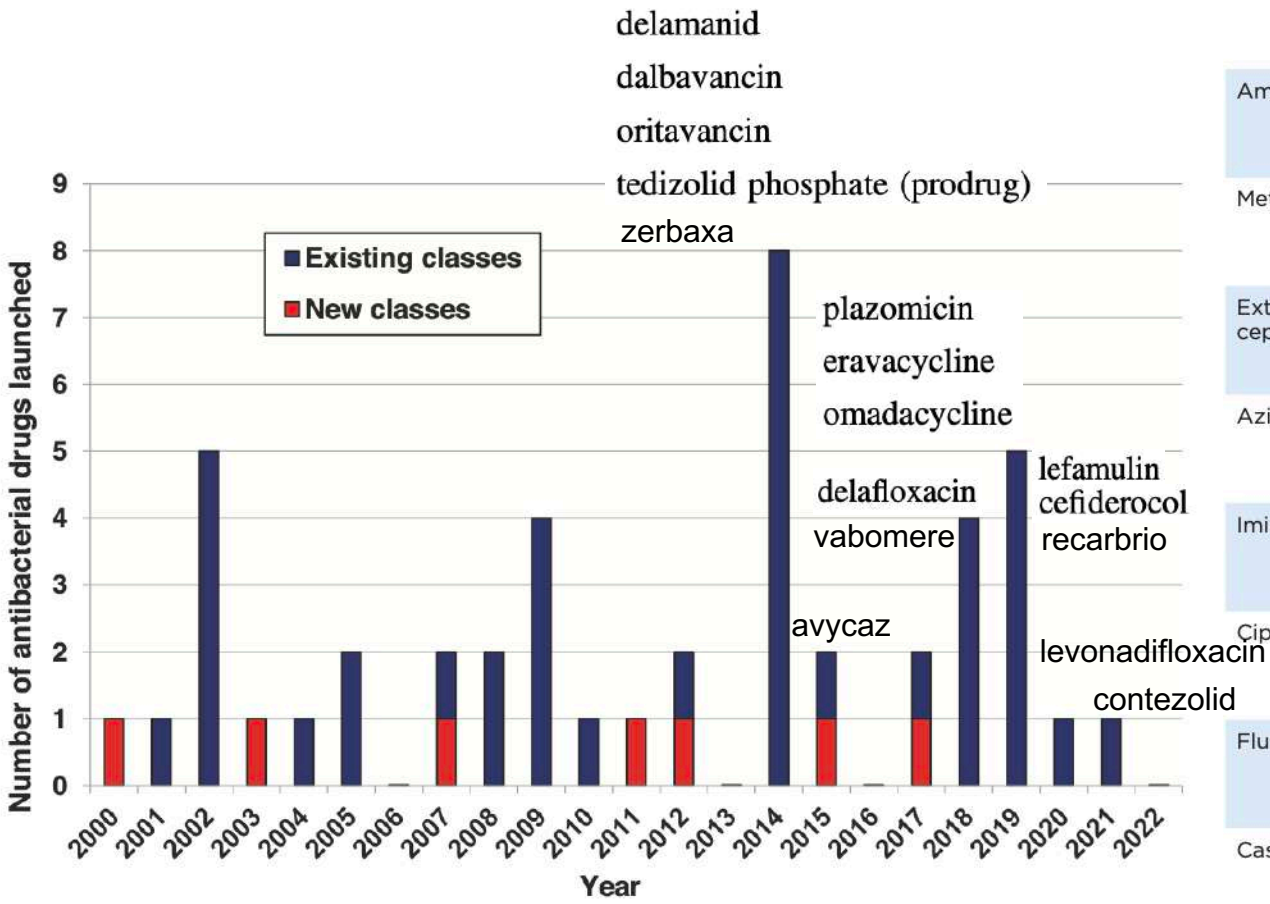


Attributable mortality: which pathogens?



Antimicrobial Resistance Collaborators. Lancet. 2022;399(10325):629-655.

AMR: An ongoing process



Butler MS, et al. J Antibiot (Tokyo). 2023;76(8):431-473.

Antibiotic Approved or Released	Year Released	Resistant Germ Identified	Year Identified
Penicillin	1941	Penicillin-resistant *Staphylococcus aureus*[20, 21]	1942
		Penicillin-resistant *Streptococcus pneumoniae*[9,10]	1967
		Penicillinase-producing *Neisseria gonorrhoeae*[11]	1976
Vancomycin	1958	Plasmid-mediated vancomycin-resistant *Enterococcus faecium*[12,13]	1988
		Vancomycin-resistant *Staphylococcus aureus*[14]	2002
Amphotericin B	1959	Amphotericin B-resistant *Candida auris*[15]	2016
Methicillin	1960	Methicillin-resistant *Staphylococcus aureus*[16]	1960
Extended-spectrum cephalosporins	1980 (Cefotaxime)	Extended-spectrum beta-lactamase- producing *Escherichia coli*[17]	1983
Azithromycin	1980	Azithromycin-resistant *Neisseria gonorrhoeae*[18]	2011
Imipenem	1985	*Klebsiella pneumoniae* carbapenemase (KPC)-producing *Klebsiella pneumoniae*[19]	1996
Ciprofloxacin	1987	Ciprofloxacin-resistant *Neisseria gonorrhoeae*[20]	2007
Fluconazole	1990 (FDA approved)	Fluconazole-resistant *Candida*[21]	1988
Caspofungin	2001	Caspofungin-resistant *Candida*[22]	2004
Daptomycin	2003	Daptomycin-resistant methicillin-resistant *Staphylococcus aureus*[23]	2004
Ceftazidime-avibactam	2015	Ceftazidime-avibactam-resistant KPC-producing *Klebsiella pneumoniae*[24]	2015

https://www.cdc.gov/drugresistance/about/how-resistance-happens.html

IDSA

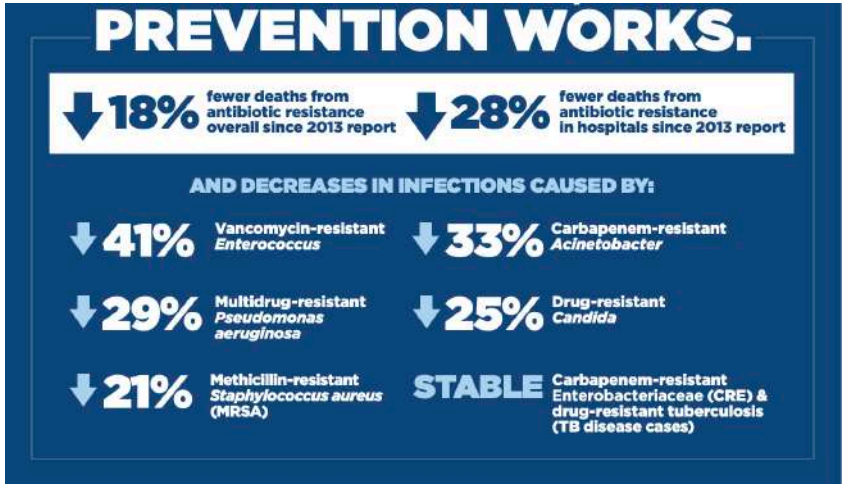
BAD BUGS, NO DRUGS

As Antibiotic Discovery Stagnates ...
A Public Health Crisis Advances

ANTIBIOTIC RESISTANCE THREATS IN THE UNITED STATES

CDC

2019



E *Enterococcus faecium*
S *Staphylococcus aureus*
K *Klebsiella pneumoniae*
A *Acinetobacter baumannii*
P *Pseudomonas aeruginosa*
E *Enterobacter Species*

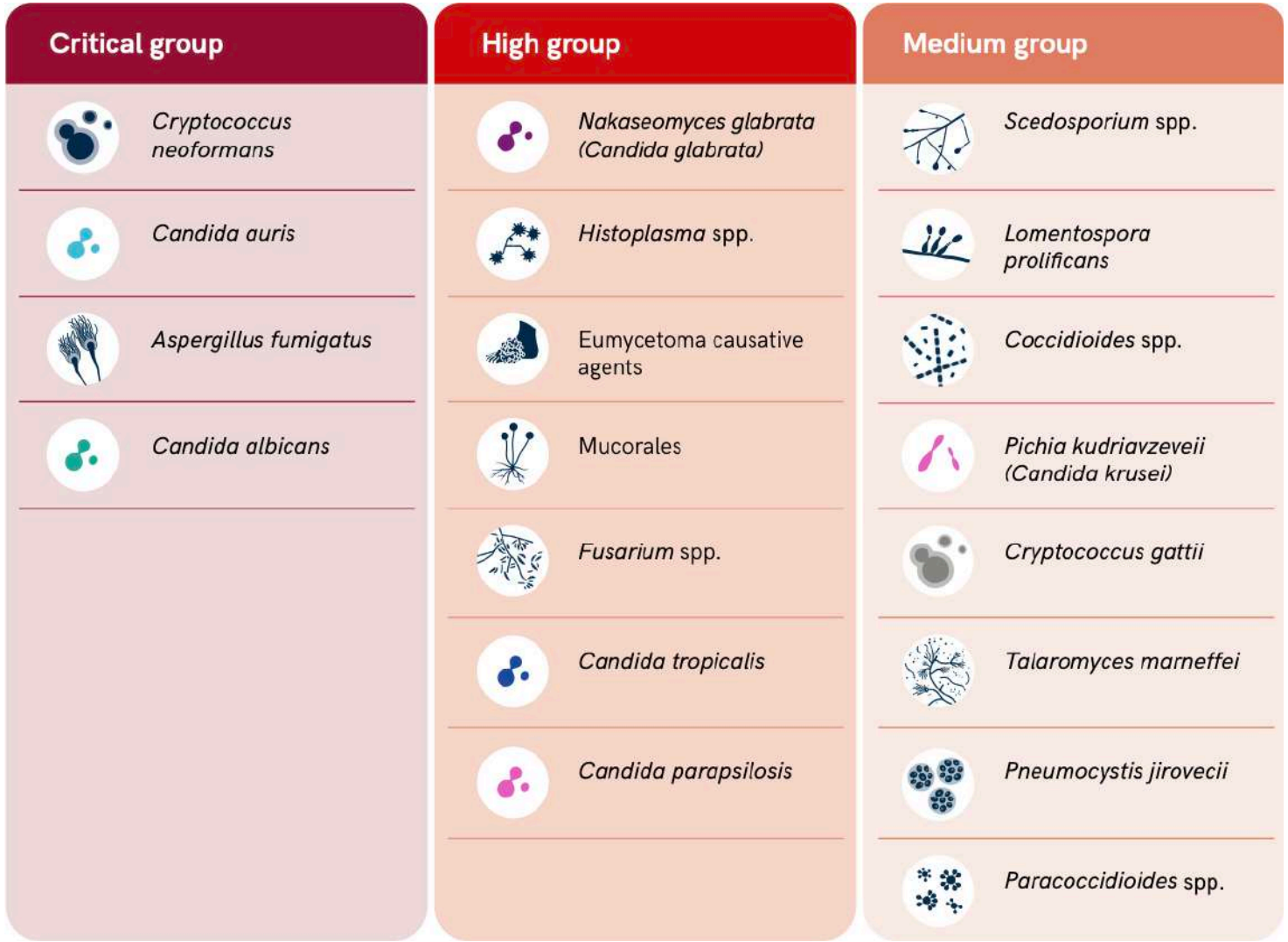
Urgent Threats

- Carbapenem-resistant *Acinetobacter*
- *Candida auris (C. auris)*
- *Clostridioides difficile (C. difficile)*
- Carbapenem-resistant Enterobacteriaceae (CRE)
- Drug-resistant *Neisseria gonorrhoeae (N. gonorrhoeae)*

Cases over time from 2012–2017	⬇ Decrease
Cases over time from 2015–2018	⬆ Increase
Cases over time from 2012–2017	Stable
Resistance over time from 2000–2017	⬆ Increase

Boucher HW, et al. Clin Infect Dis. 2009;48(1):1-12. https://www.cdc.gov/drugresistance/pdf/threats-report/2019-ar-threats-report-508.pdf

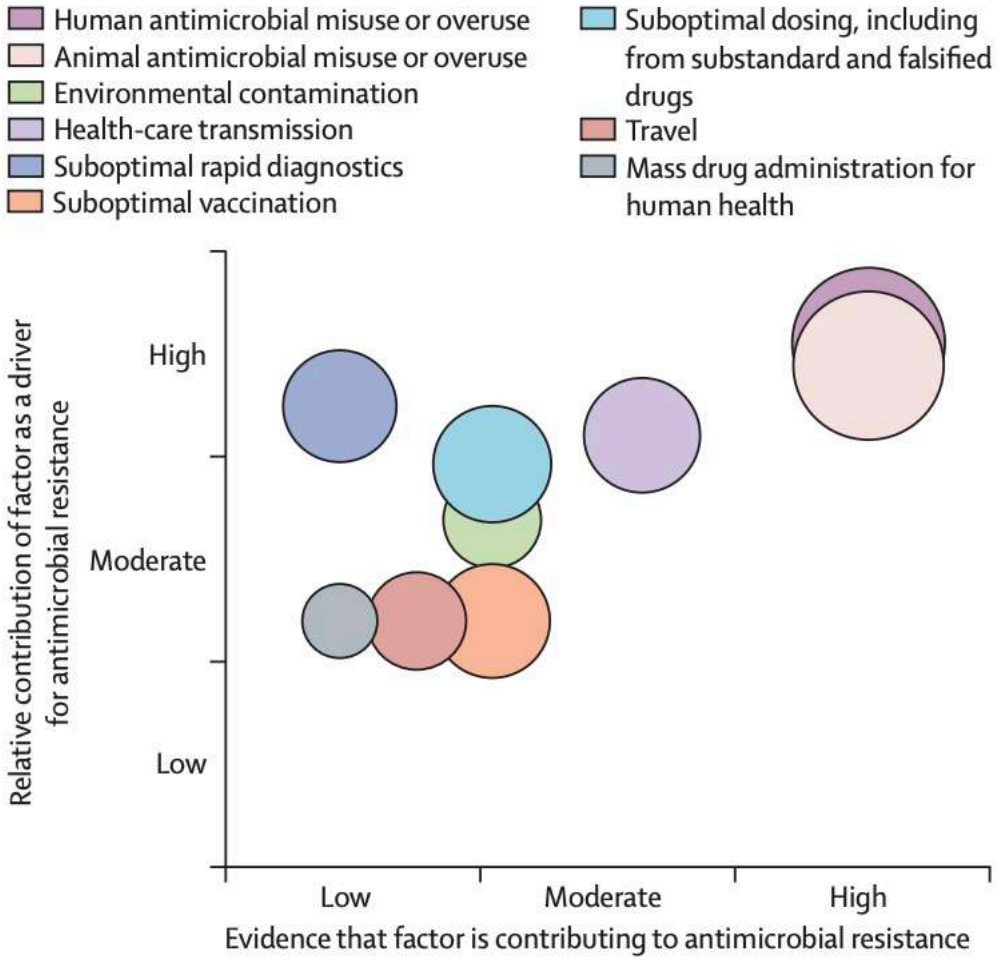
Fungal Priority Pathogens List (FPPL)- 2022 update



World Health Organization. (2022, October 25). *WHO fungal priority pathogens list to guide research, development and public health action*. Retrieved from https://www.who.int/publications/i/item/9789240060241

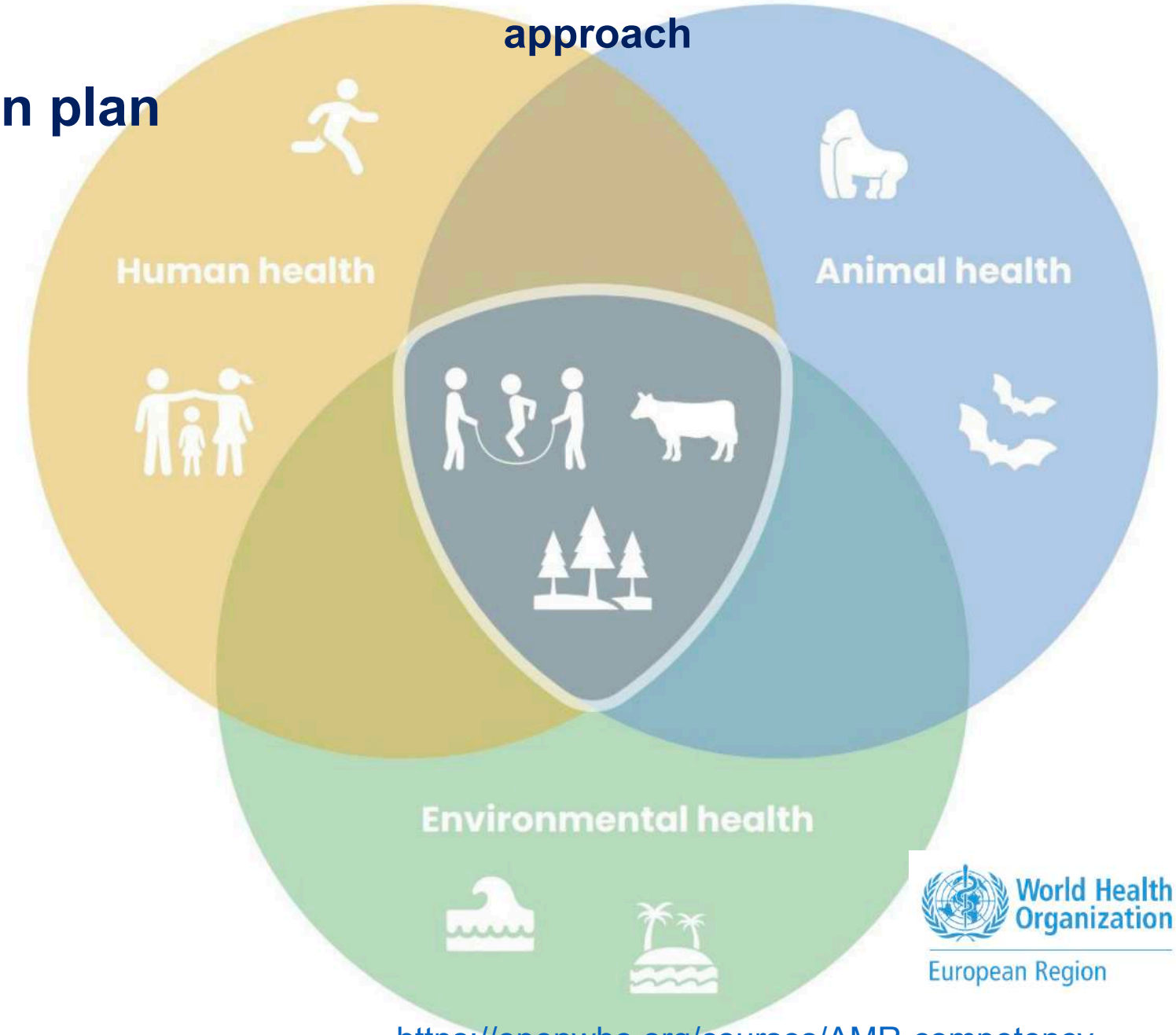
Multiple causes, one action plan

Main determinants of AMR



Holmes AH, et al. Lancet. 2016;387(10014):176-87.

ONE HEALTH approach

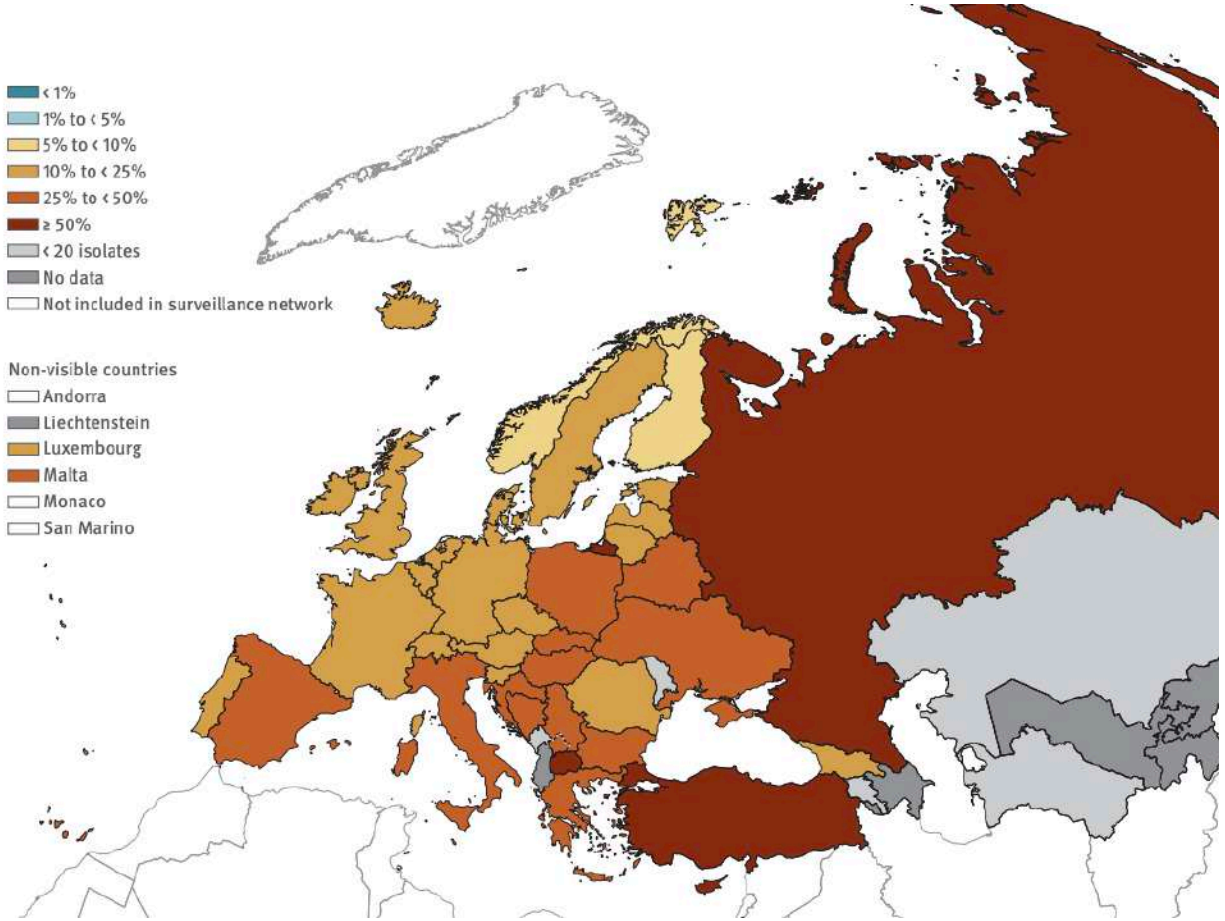


World Health Organization
European Region

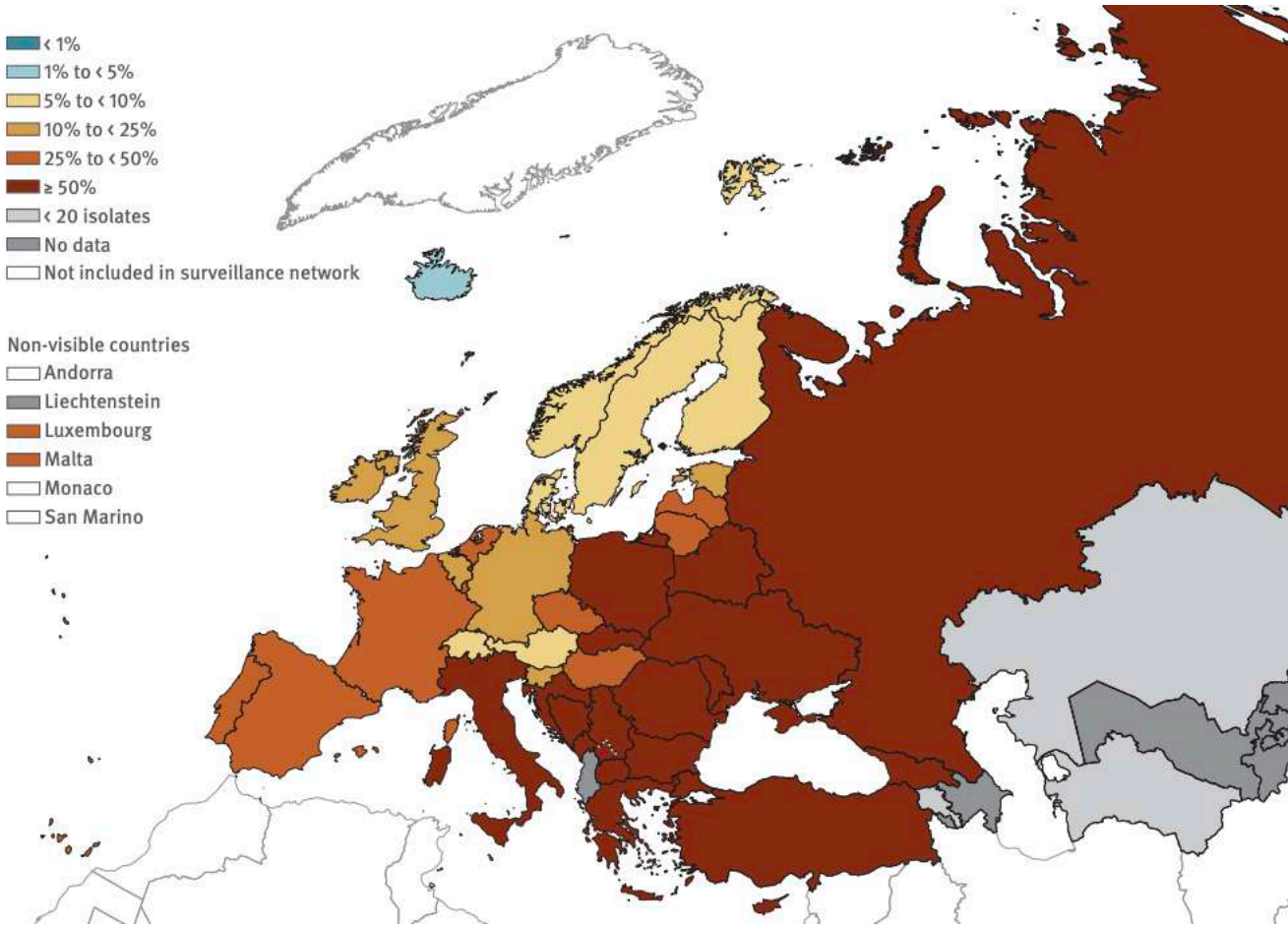
https://openwho.org/courses/AMR-competency

Where are we now?

FQN-R *E. coli*



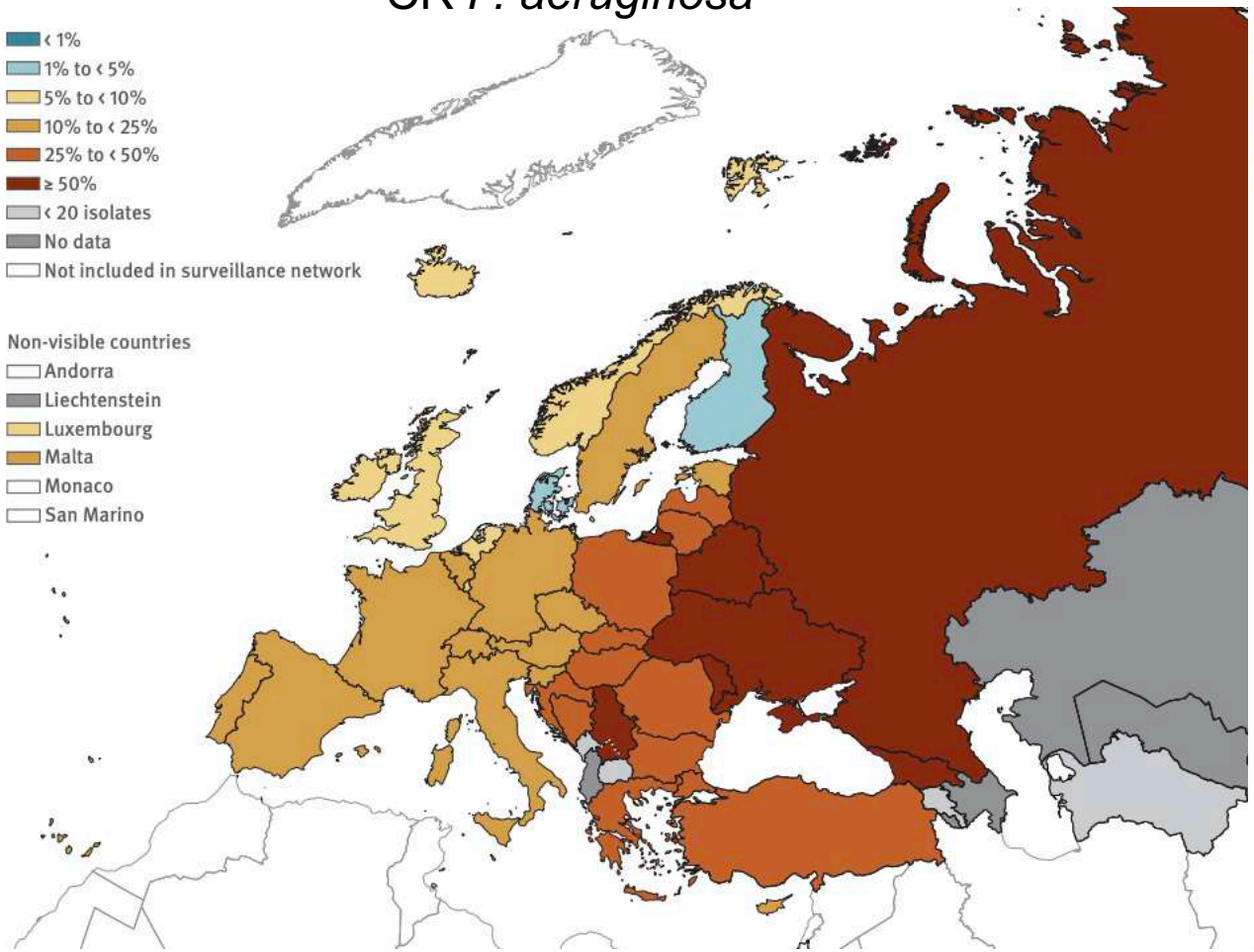
3GC-R *K. pneumoniae*



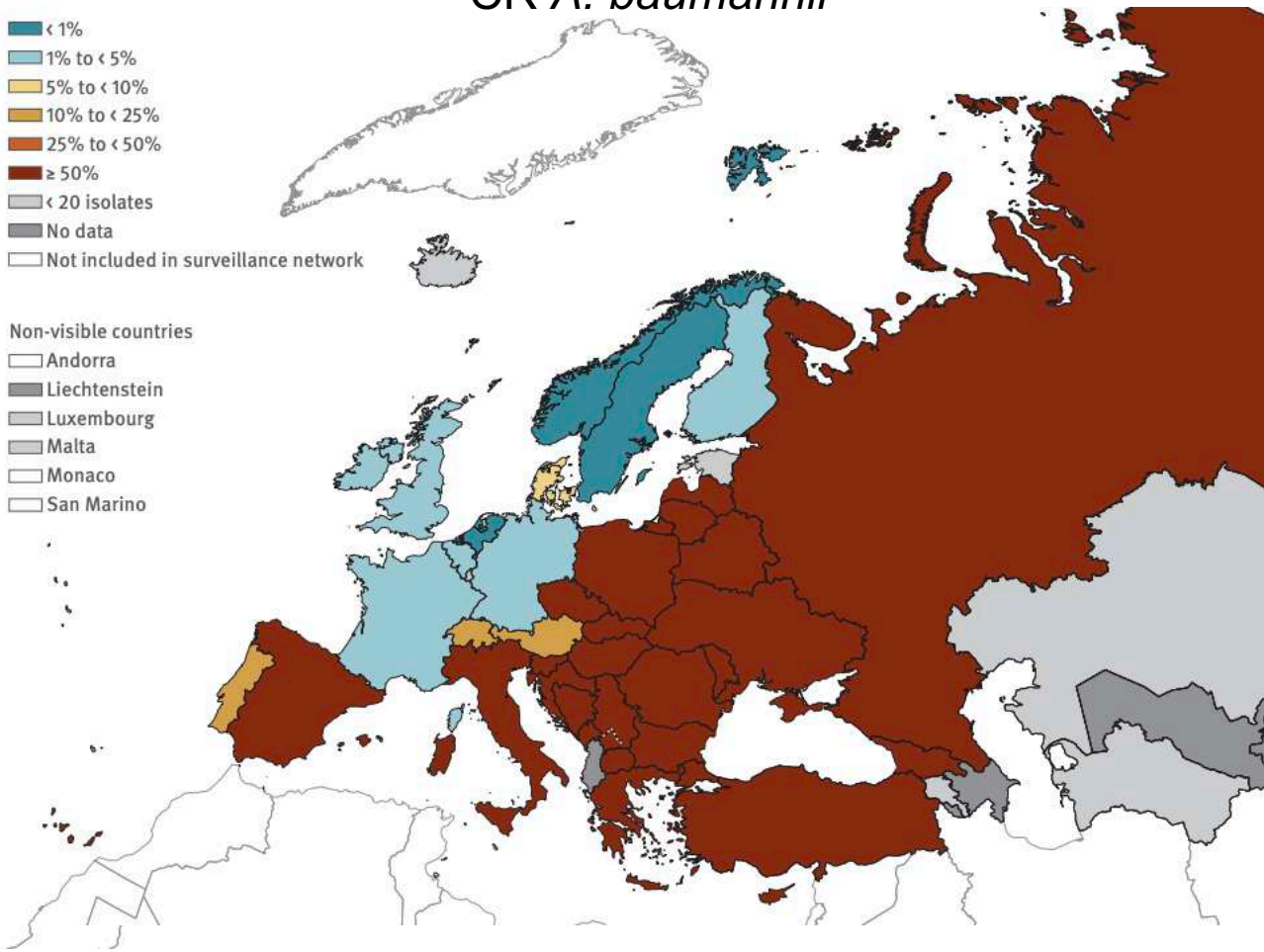
Antimicrobial resistance surveillance in Europe 2023 - 2021 data. Stockholm: ECDC and WHO; 2023.

Where are we now?

CR *P. aeruginosa*



CR *A. baumannii*



Antimicrobial resistance surveillance in Europe 2023 - 2021 data. Stockholm: ECDC and WHO; 2023.

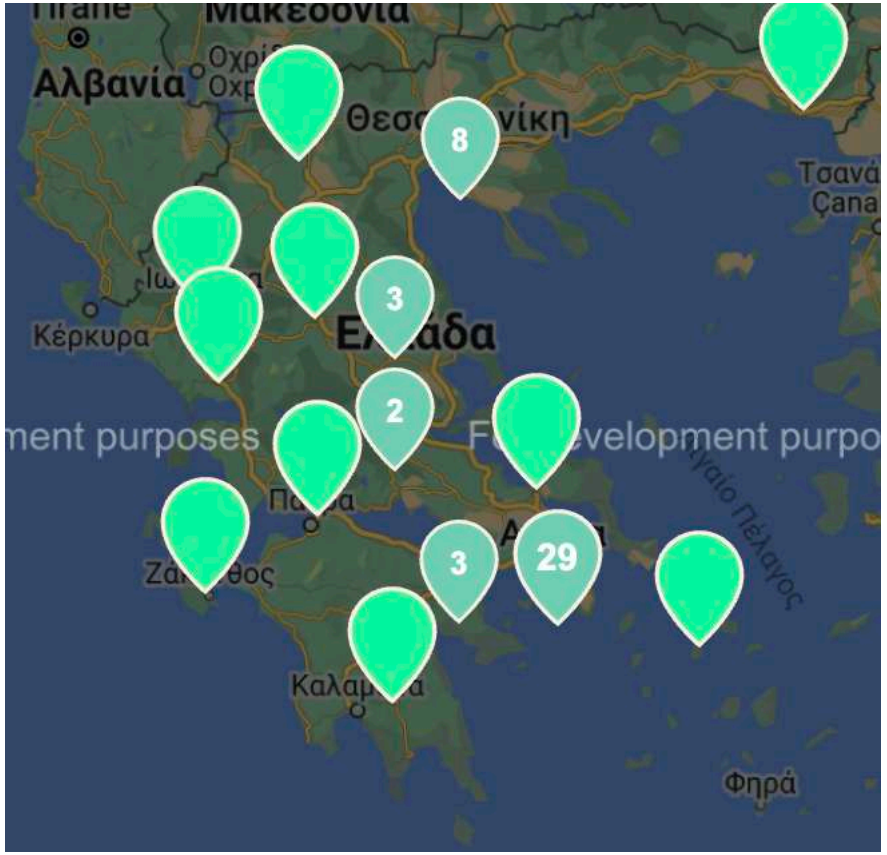
Registry data

HS SG

Hellenic Sepsis Study Group

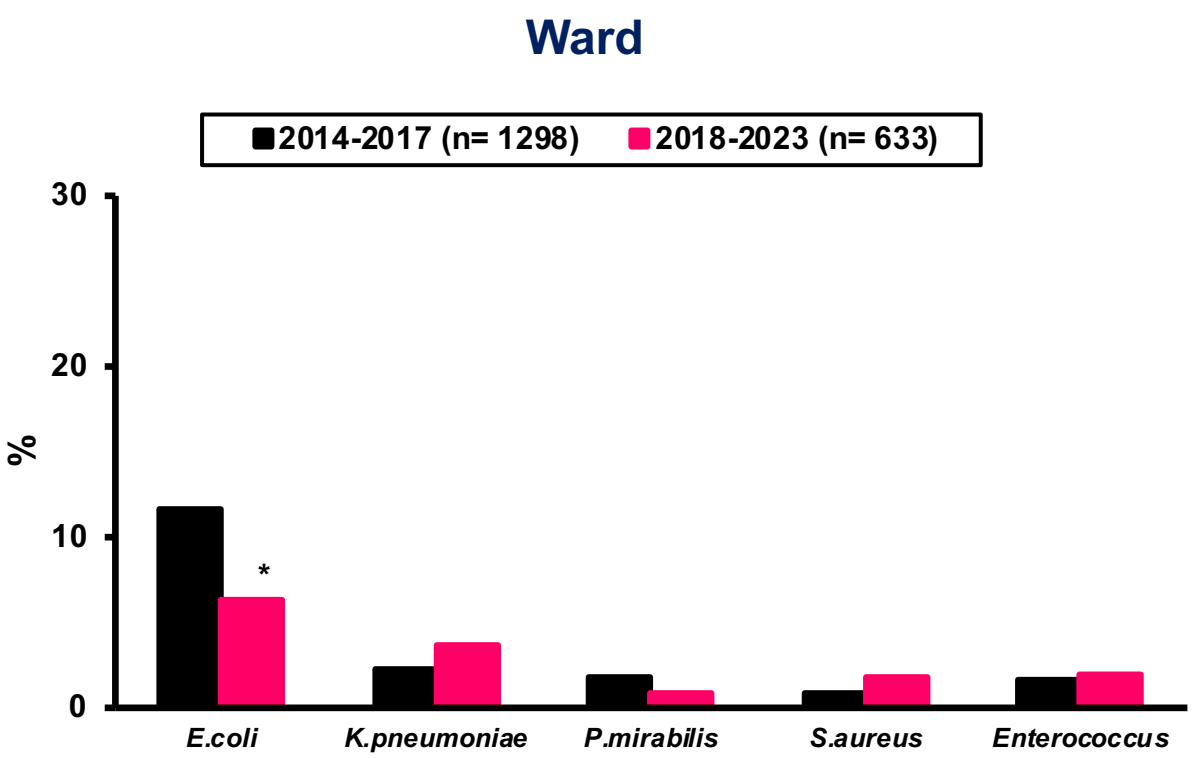
HELLENIC INSTITUTE FOR THE STUDY OF SEPSIS

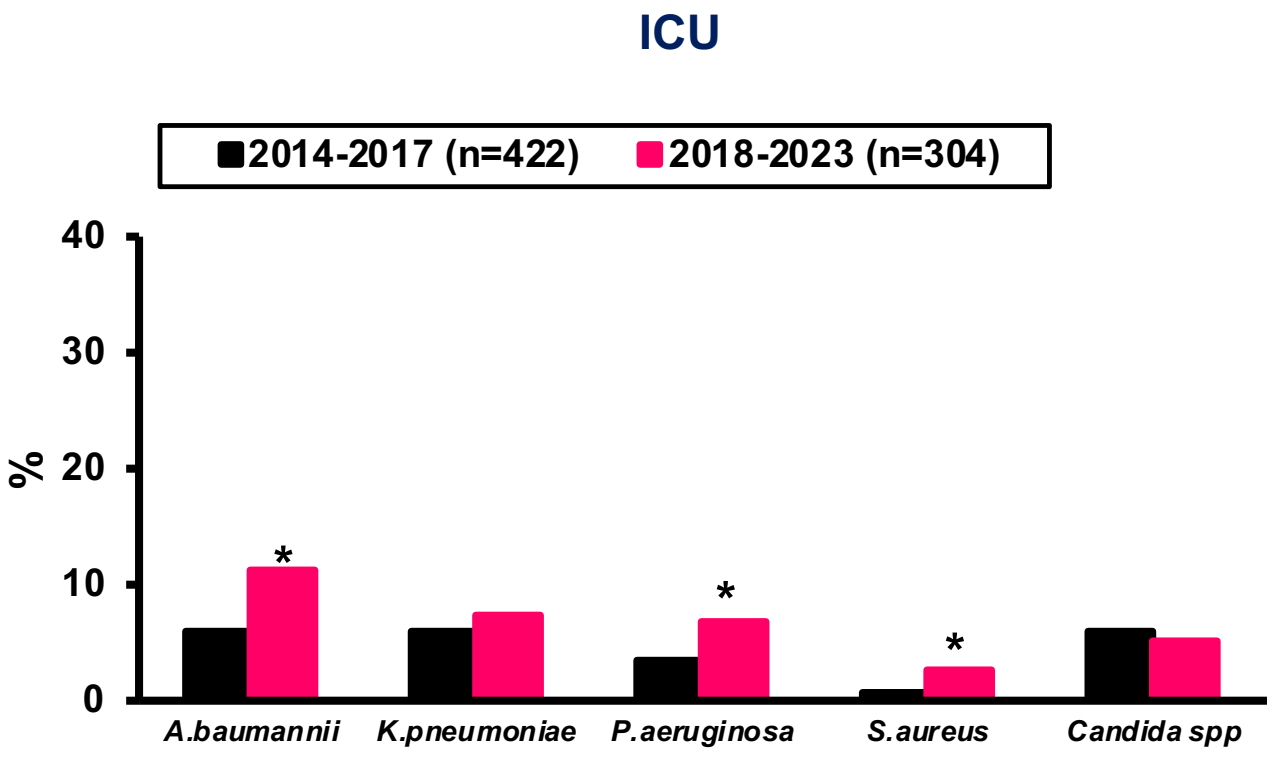
- Multi-center prospective observational study
- Since 2006
- >9000 patients with sepsis
- Ward and ICU



https://sepsis.gr

Most common pathogens in sepsis (blood cultures)



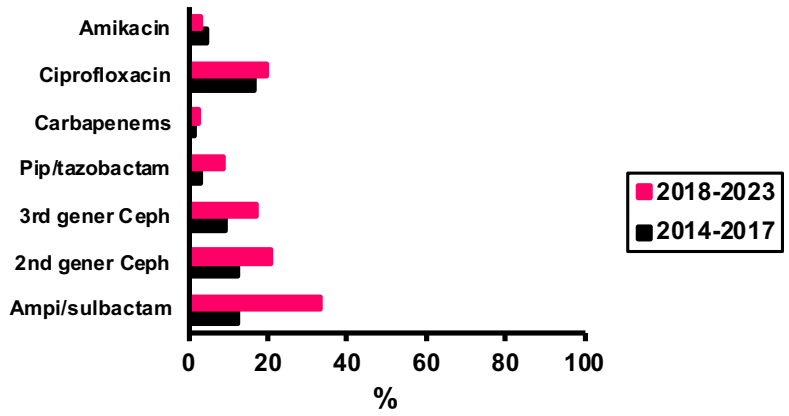


https://sepsis.gr/wp-content/uploads/2023/10/HISS_Booklet_on_Sepsis_2023.pdf

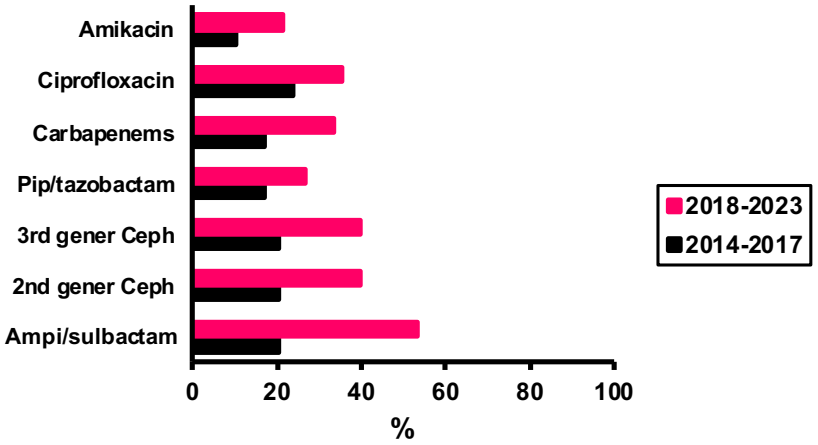
Resistance (%) profiles in the ward

Blood

Escherichia coli

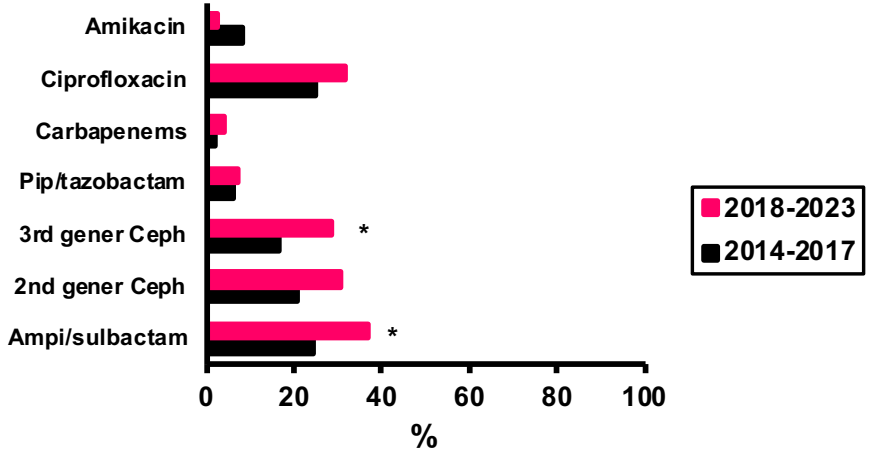


Klebsiella pneumoniae

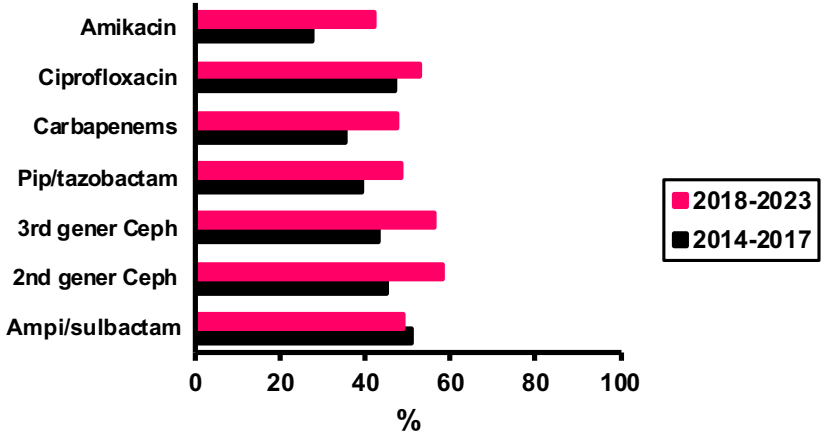


Urine

Escherichia coli

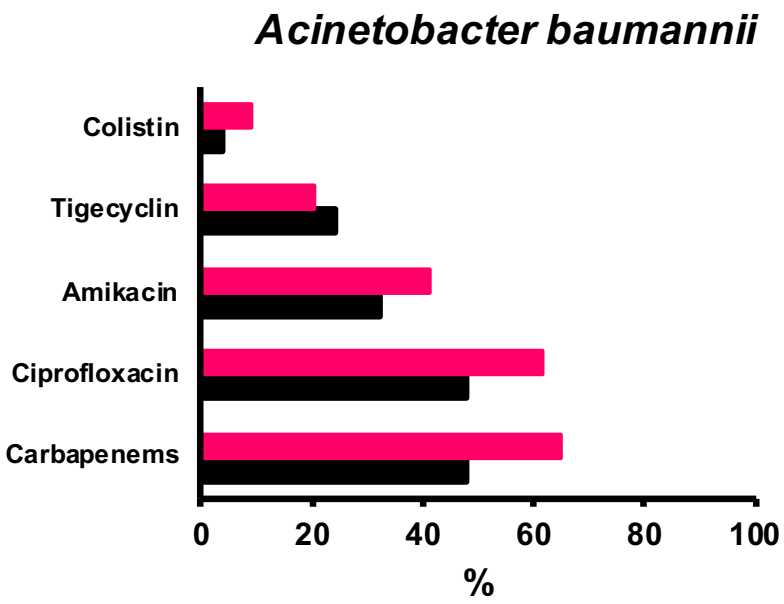


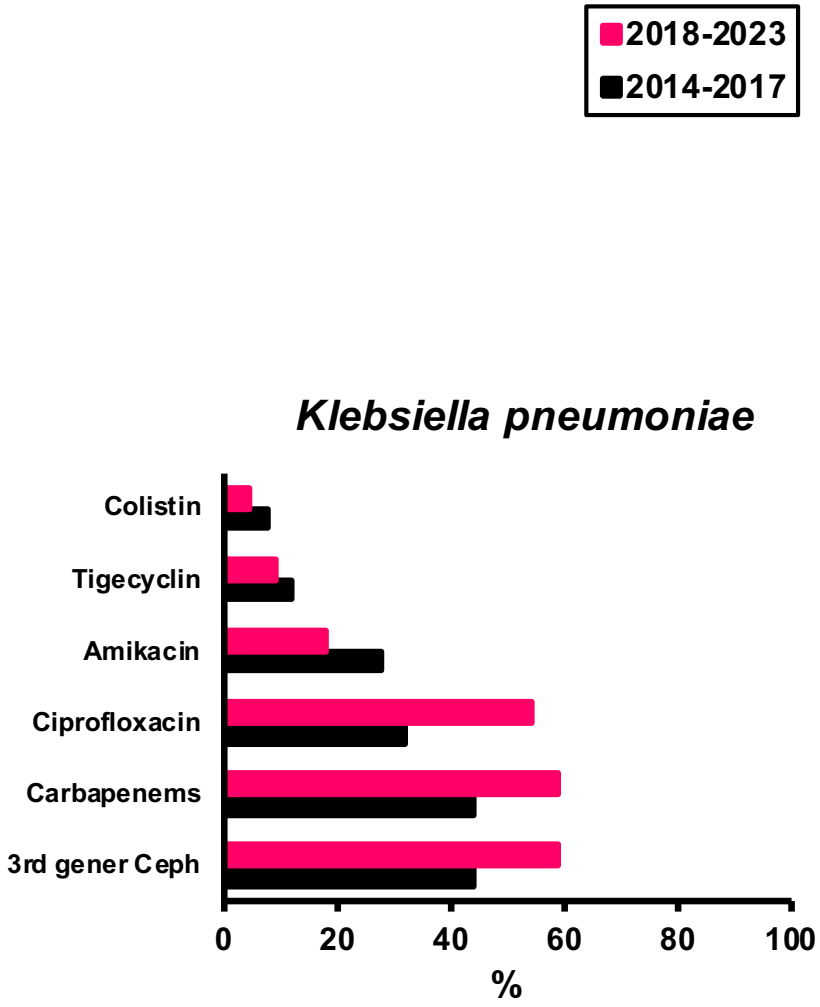
Klebsiella pneumoniae

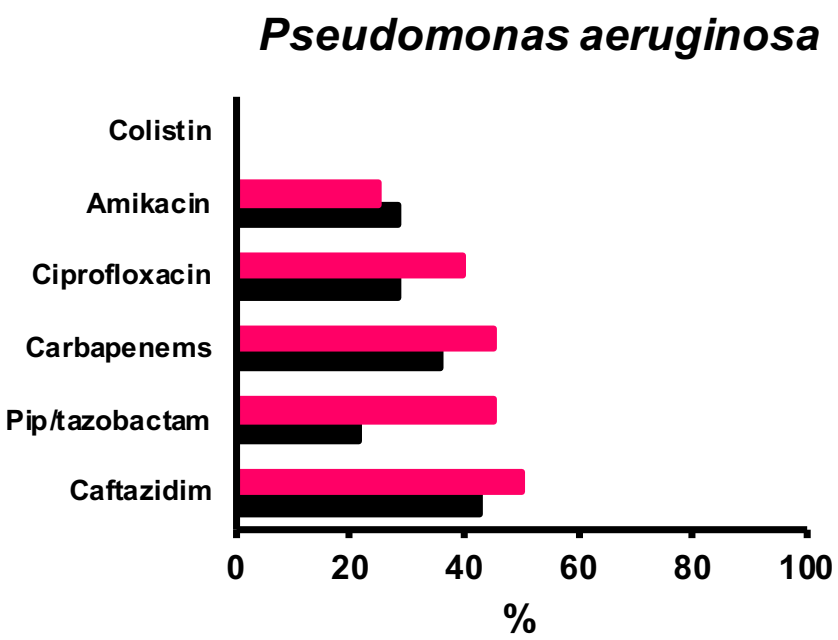


https://sepsis.gr/wp-content/uploads/2023/10/HISS_Booklet_on_Sepsis_2023.pdf

Resistance (%) profiles in the ICU (blood cultures)







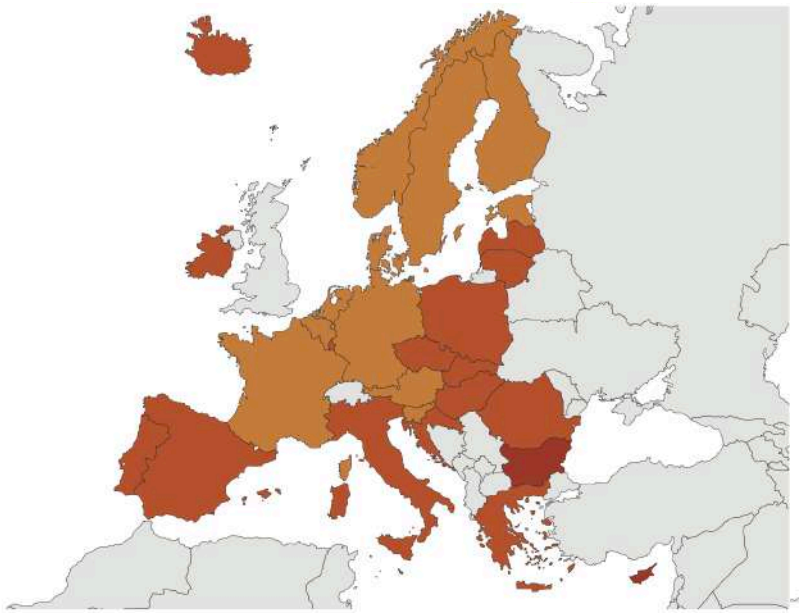
https://sepsis.gr/wp-content/uploads/2023/10/HISS_Booklet_on_Sepsis_2023.pdf

E. coli (%) resistance 2022

FQN-R

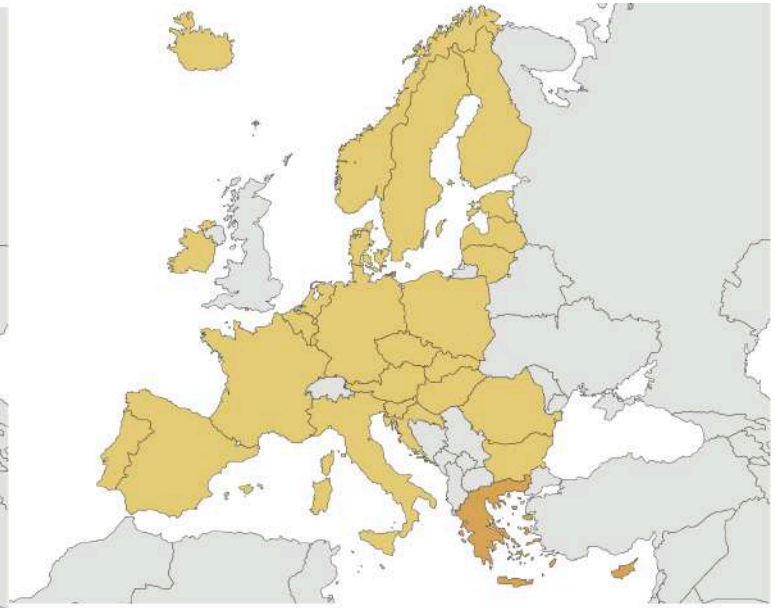
Greece: 37.8%

3GC-R



23.3%

CR

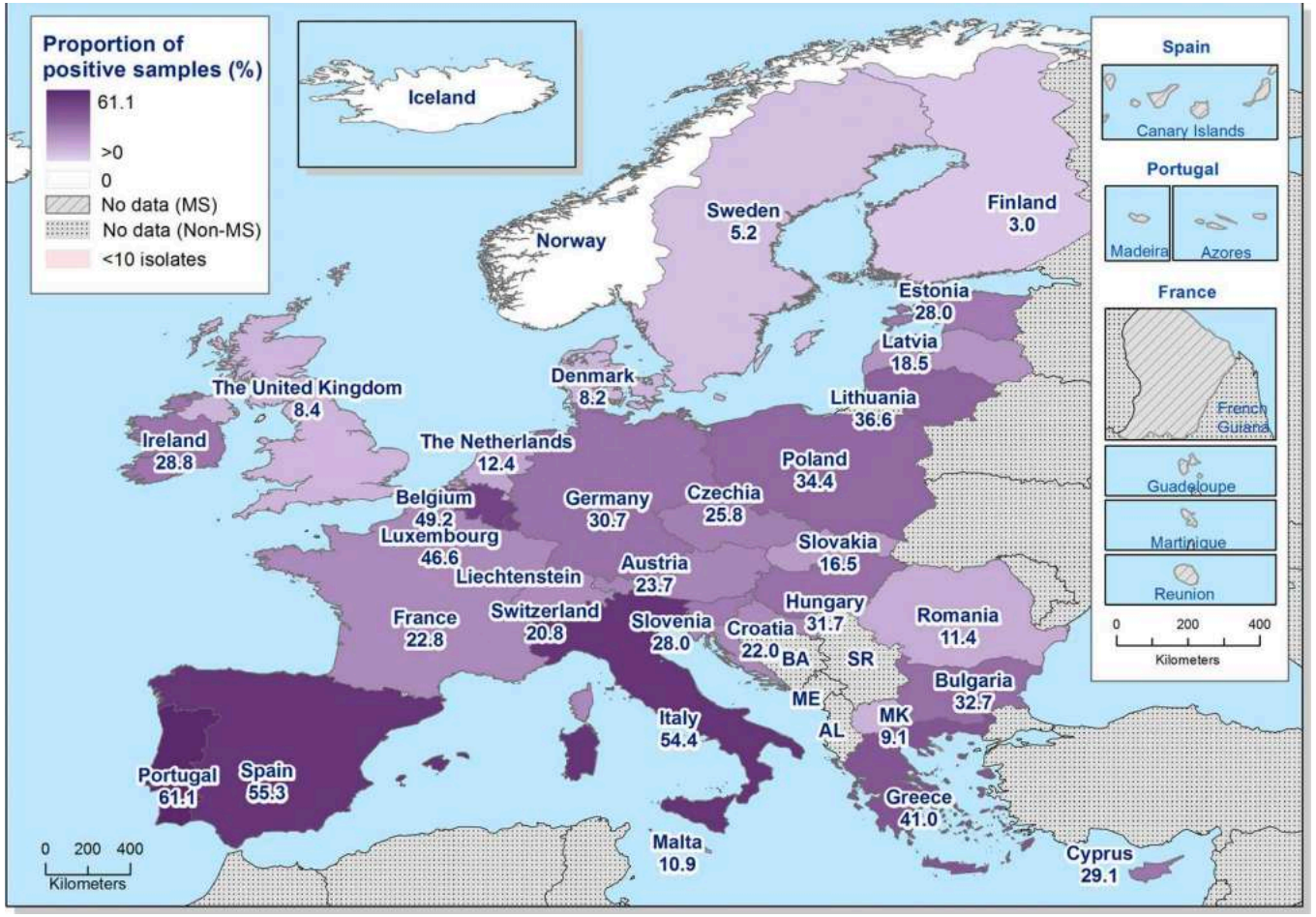


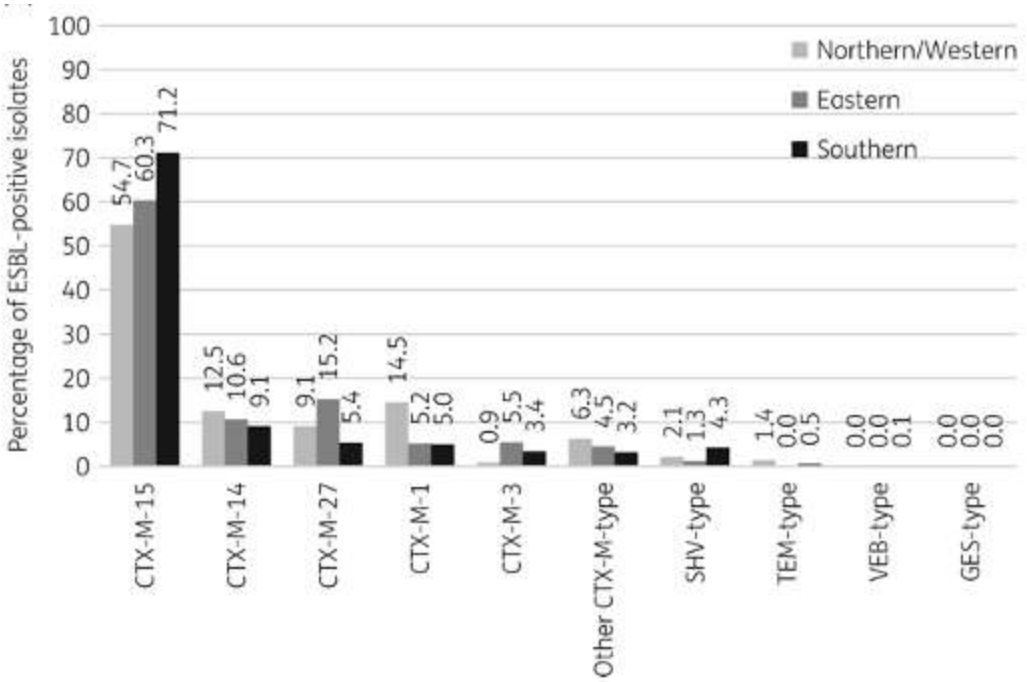
1.5%

ESBL suspicion

Antimicrobial resistance surveillance in Europe 2023 - 2021 data. Stockholm: ECDC and WHO; 2023.

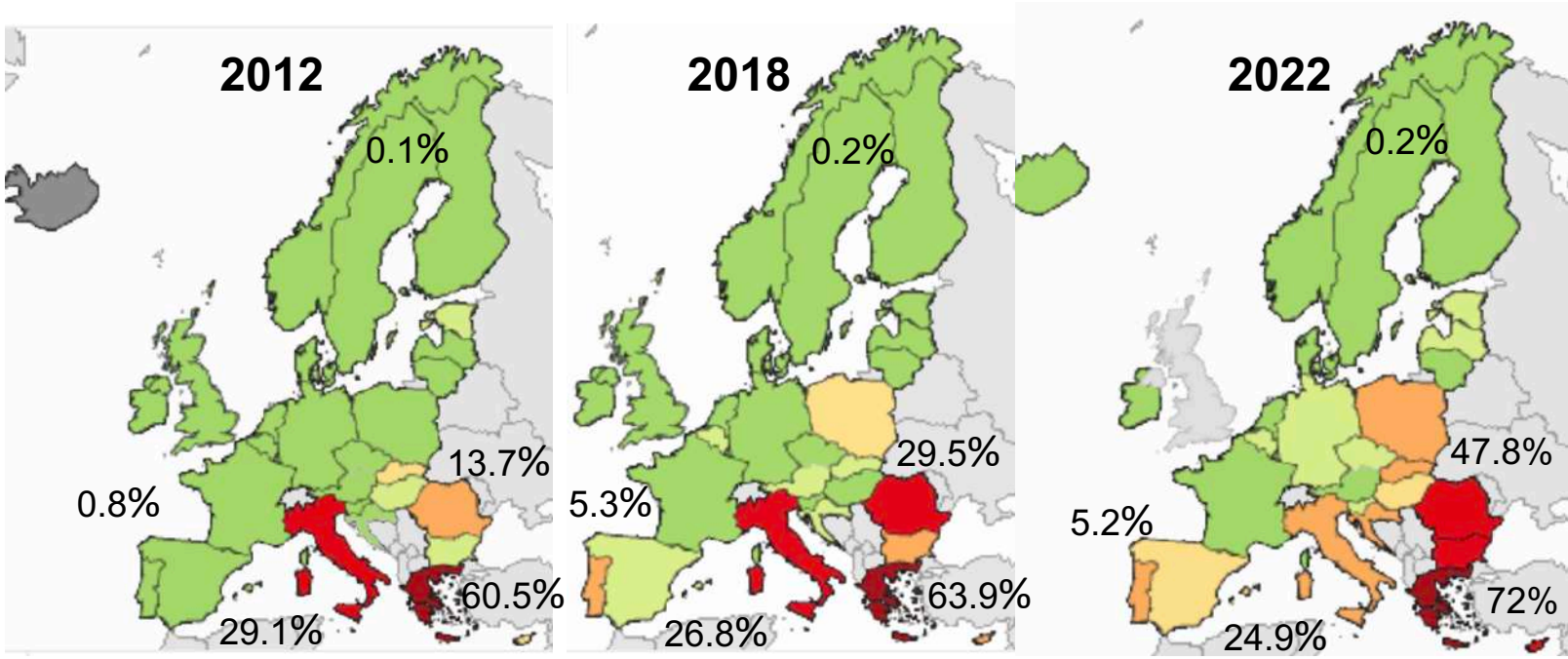
Extended-Spectrum Beta-Lactamase (ESBL)- producing *E. coli*

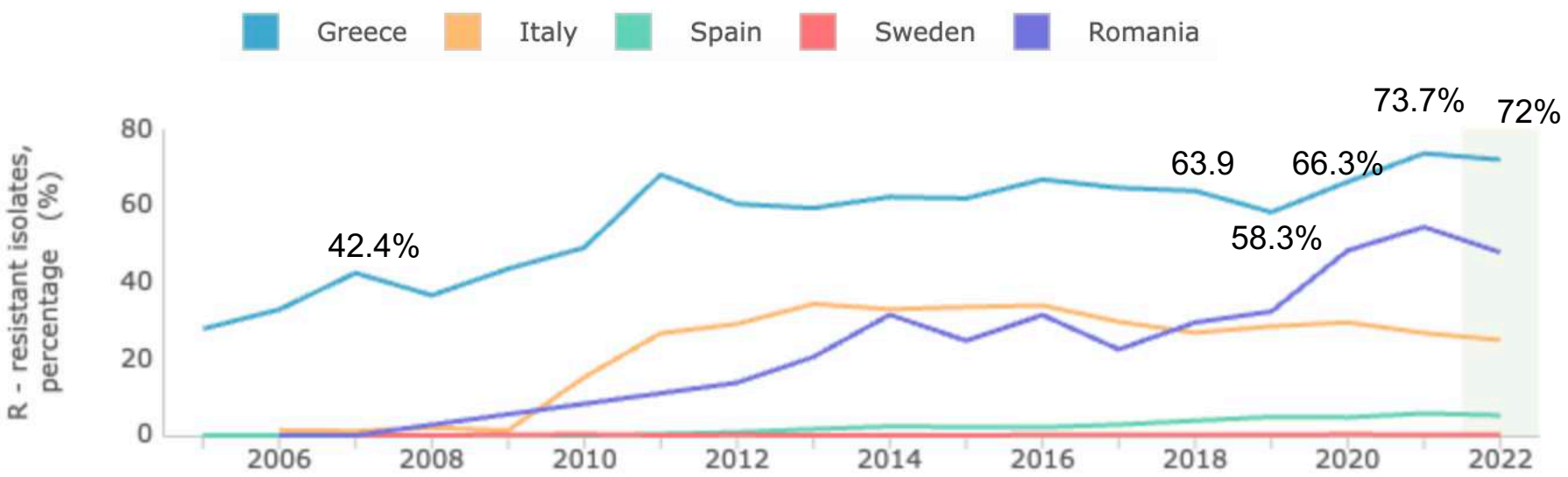




EFSA and ECDC. EFSA Journal 2021;19(4):6490, doi:10.2903/j.efsa.2021.6490
Kazmierczak KM, et al. J Antimicrob Chemother. 2020;75(5):1165-1173

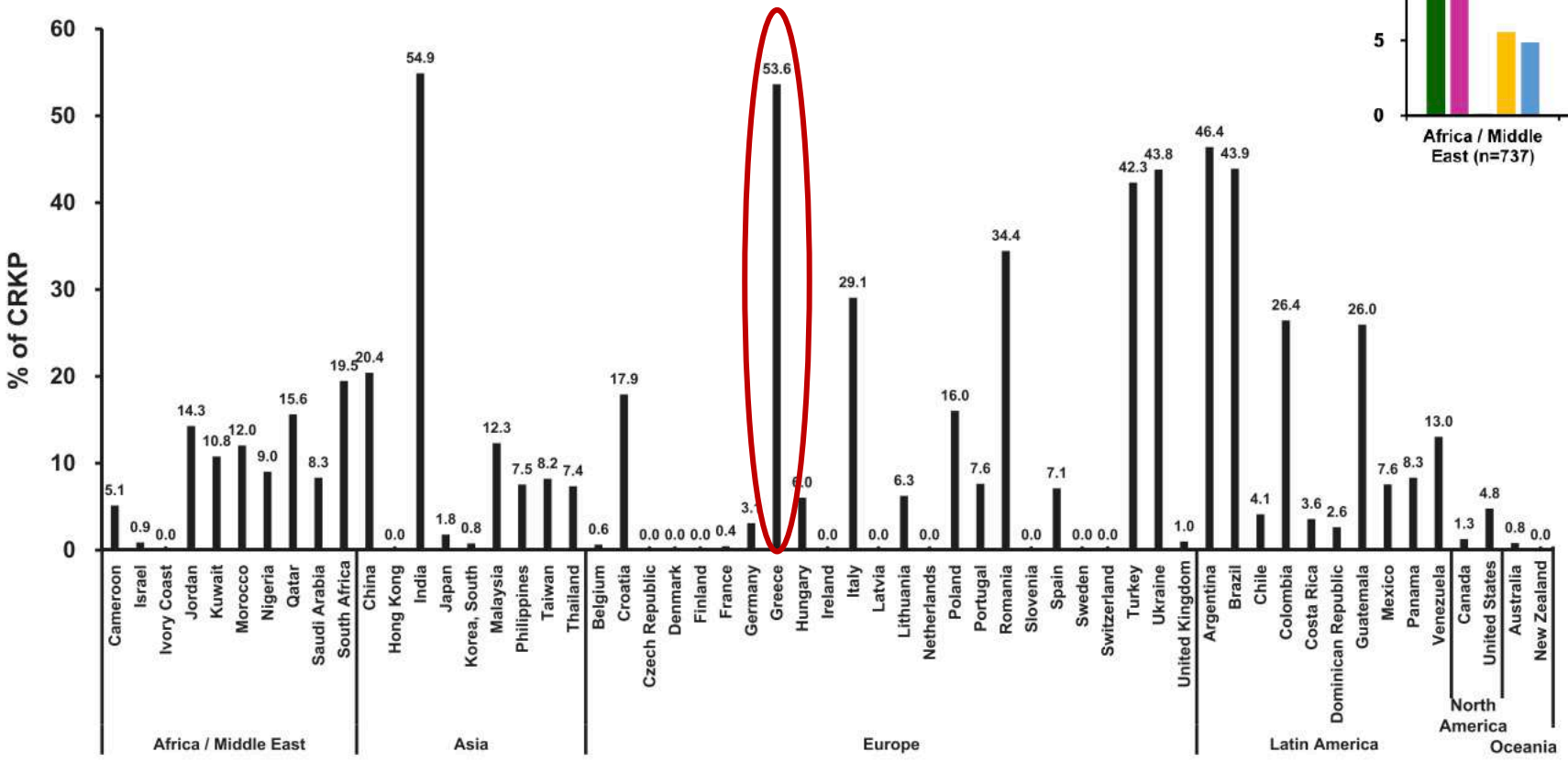
CR *K. pneumoniae* (%) resistance 2022

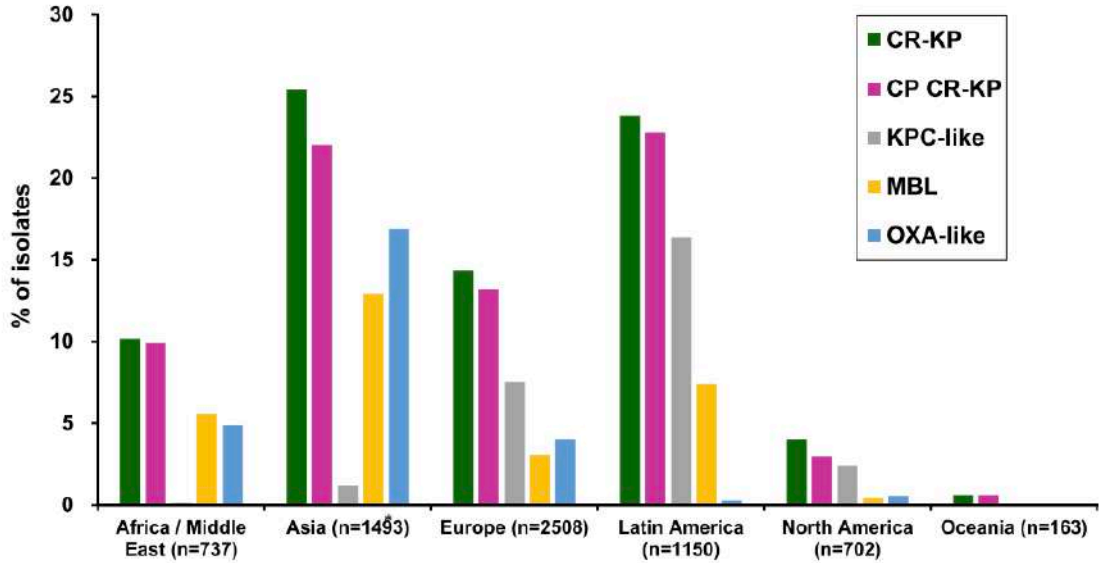




Antimicrobial resistance surveillance in Europe 2023 - 2021 data. Stockholm: ECDC and WHO; 2023.

Global distribution of CR-KP isolates

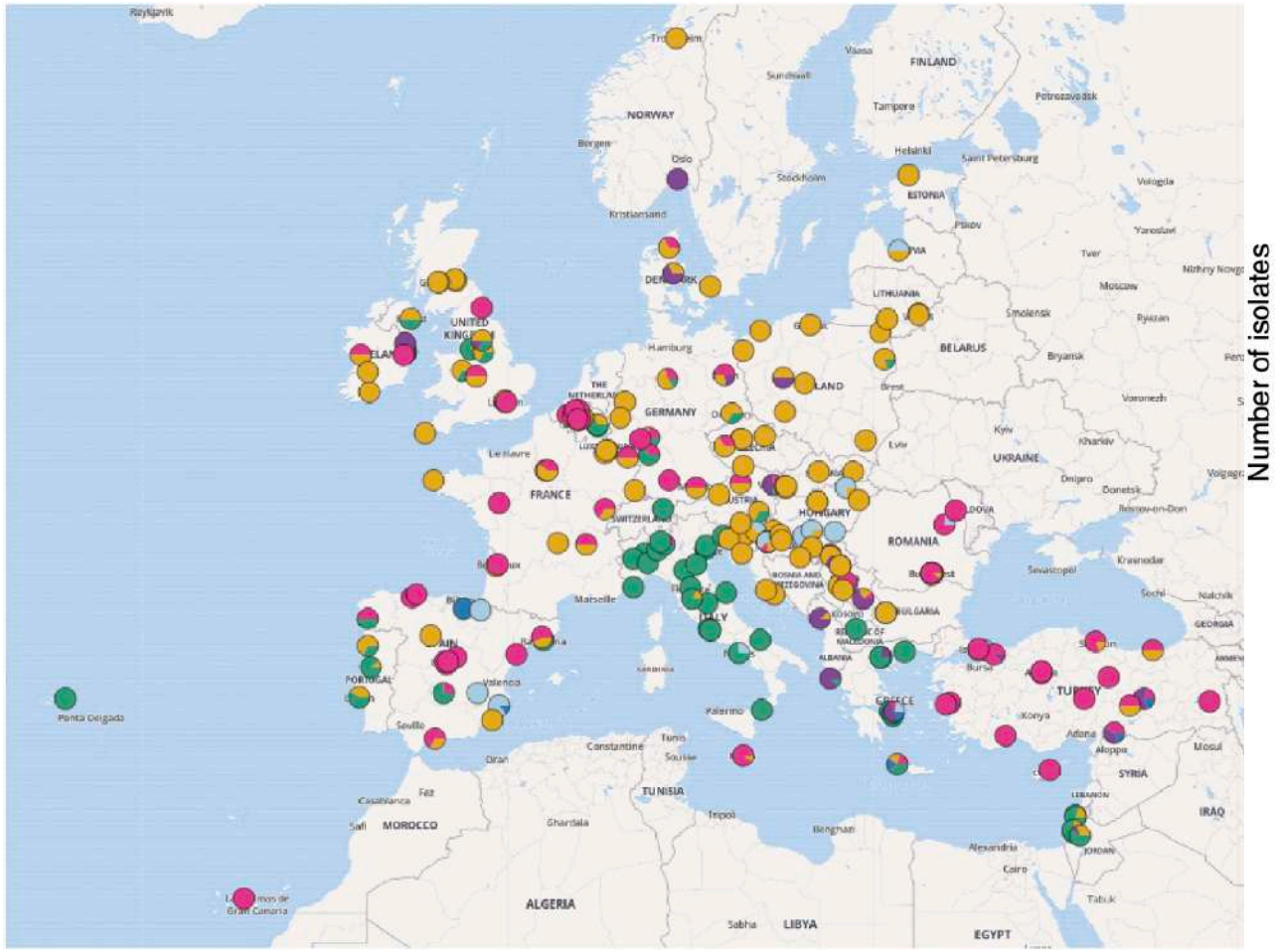


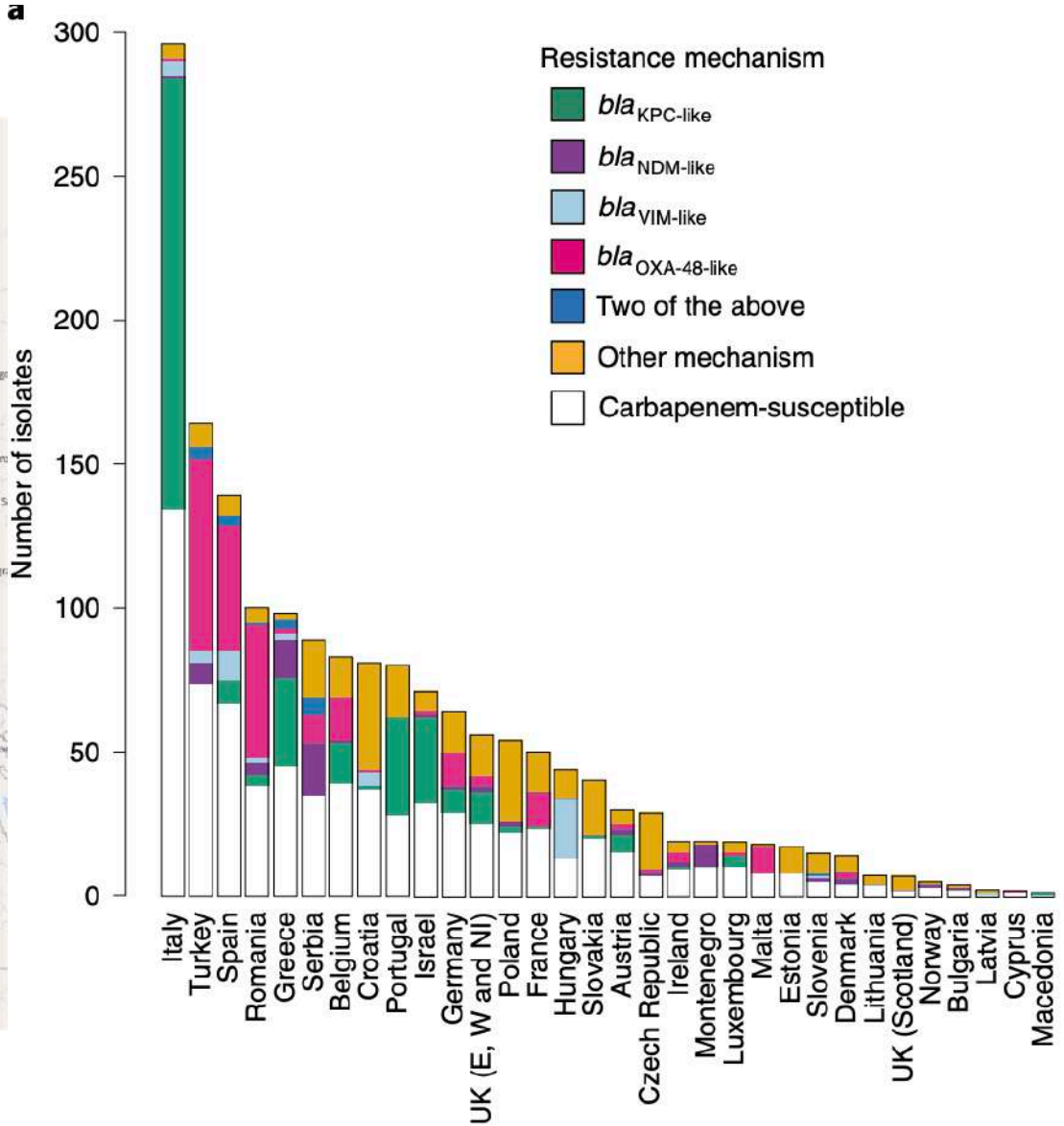


Carb-R K. Pneum. N, (%)	Greece (n=59)	Croatia (n=19)
KPC-like	39 (66)	2 (12)
MBL (NDM-1)	7 (11)	6 (33)
VIM-like	13 (21)	0 (0)
OXA-like	1 (2)	12 (65)

Lee YL, et al. Int J Antimicrob Agents. 2022;60(5-6):106679.

Distribution of CR-KP isolates within Europe

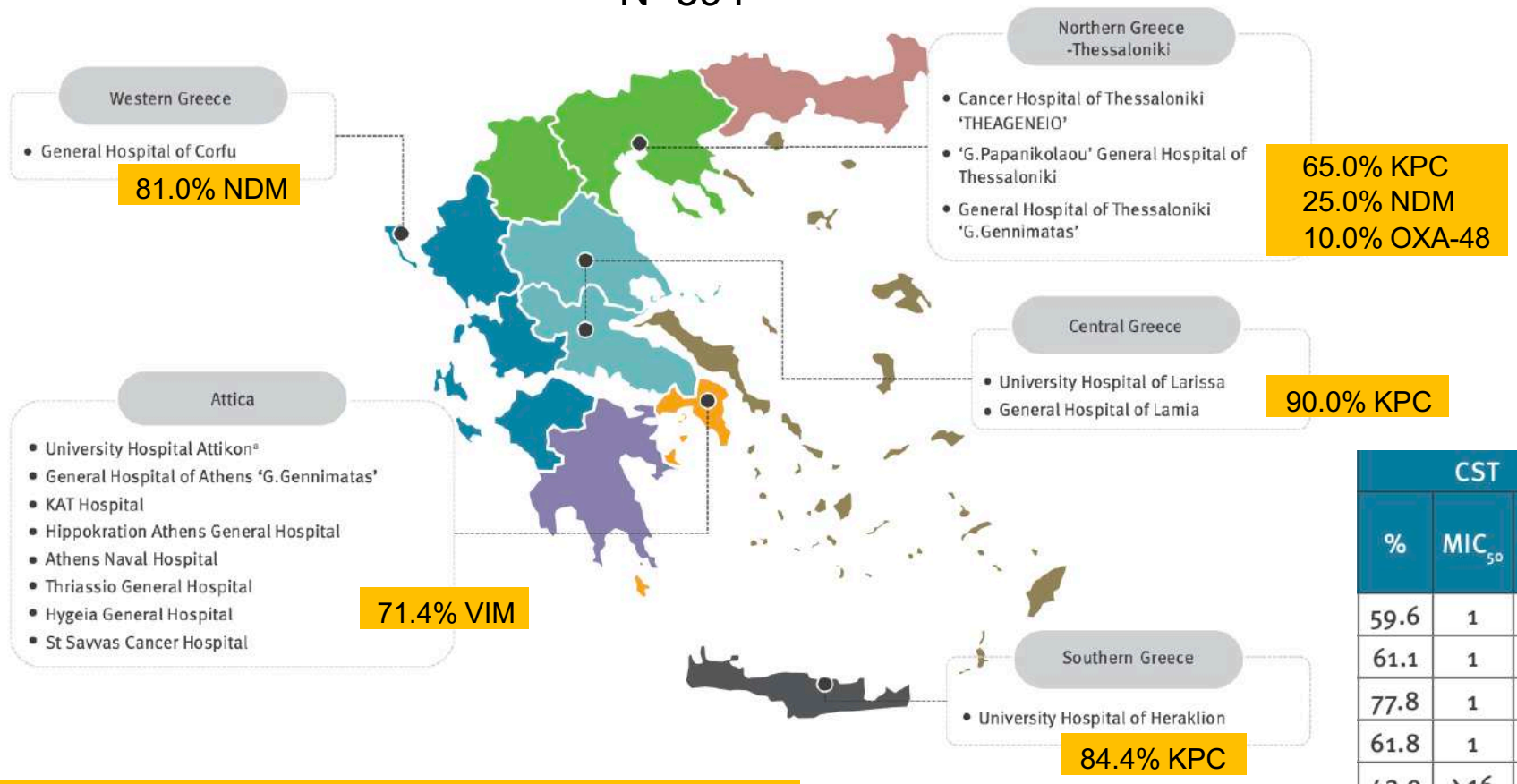




David S, et al. Nat Microbiol. 2019;4(11):1919-1929.

Distribution of CR-KP isolates within Greece (2014-2016)

N=394



Total: 66.5% KPC, 13.7% NDM, 8.6% VIM, 3.6% OXA-48

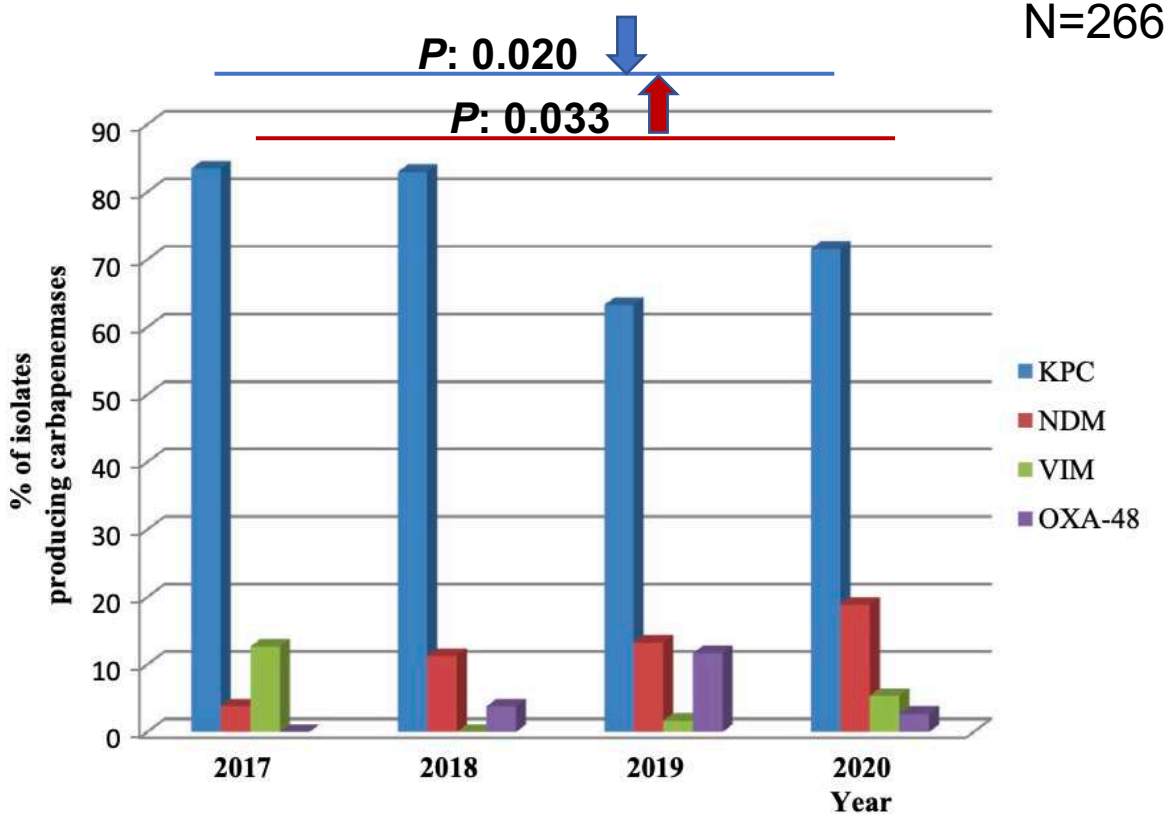
susceptible

Isolates (number)	CZA			CST			TG			FOS		
	%	MIC_{50}	MIC_{90}	%	MIC_{50}	MIC_{90}	%	MIC_{50}	MIC_{90}	%	MIC_{50}	MIC_{90}
All (n = 394)	ND	ND	ND	59.6	1	> 16	51.5	1	4	58.4	32	256
KPC (n = 262)	99.6	1	2	61.1	1	> 16	51.9	1	4	57.3	32	512
NDM (n = 54)	ND	ND	ND	77.8	1	> 16	66.7	1	2	81.5	16	256
VIM (n = 34)	ND	ND	ND	61.8	1	> 16	38.2	2	8	47.1	64	128
OXA-48 (n = 14)	100.0	1	1	42.9	> 16	> 16	71.4	1	8	78.6	16	128
KPC + VIM (n = 22)	ND	ND	ND	9.0	> 16	> 16	27.0	2	2	27.3	64	128

Galani I,et al. Euro Surveill. 2018;23(31). doi: 10.2807/1560-7917.ES.2018.23.30.1700775.

Distribution of Carb-R isolates within Greece (2017-2020)

N=266



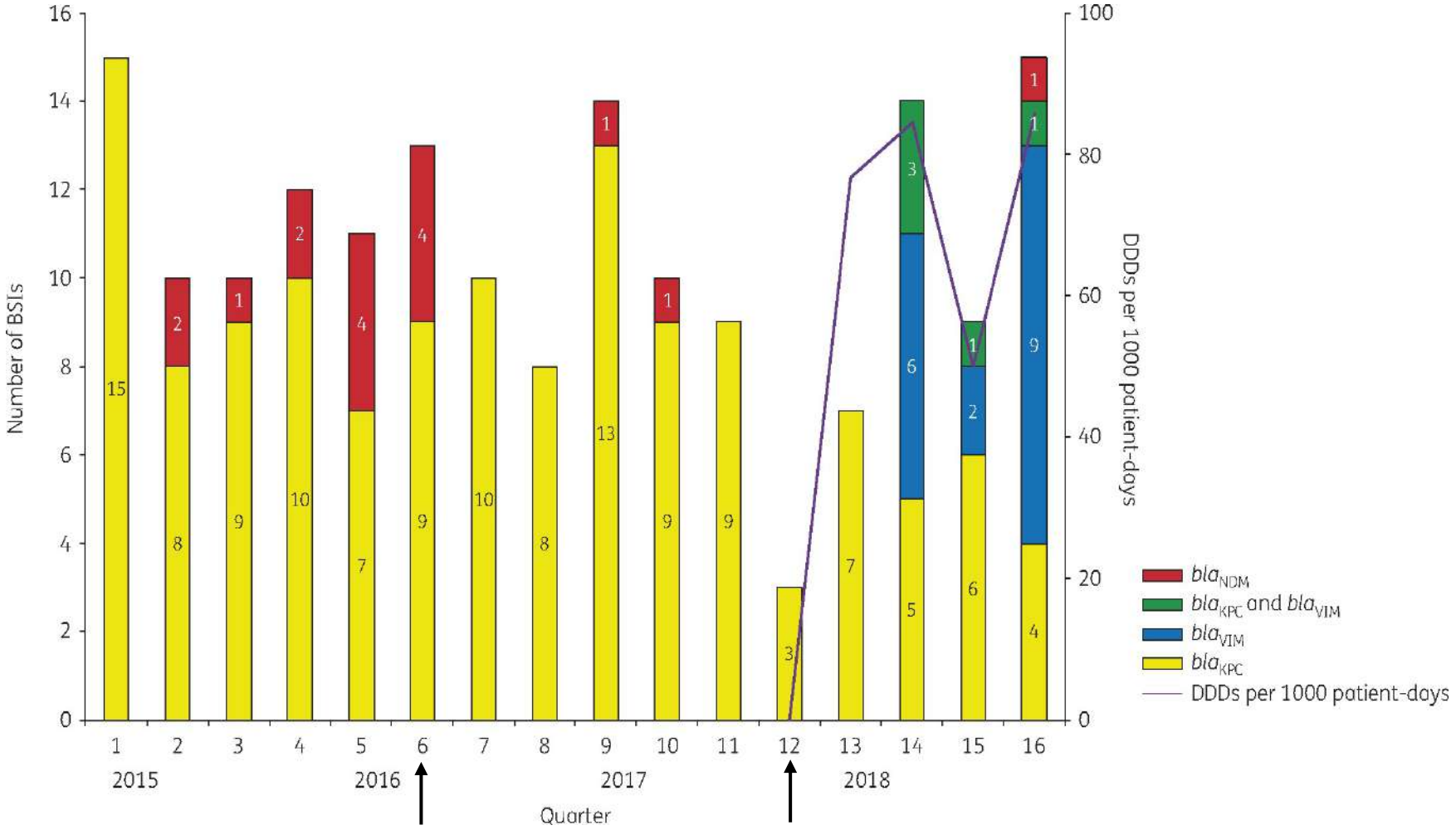
Isolates (number)	CAZ/AVI			M/V			I/R		
	MIC_{50}	MIC_{90}	S%	MIC_{50}	MIC_{90}	S%	MIC_{50}	MIC_{90}	S%
All ($n=266$)	0.5	>256	79.7	0.25	32	76.3	0.75	>32	75.2
KPC ($n=201$)	0.38	1	100	0.25	0.5	100	0.75	1	98.5
NDM ($n=31$)	>256	>256	0	32	>256	0	>32	>32	0
VIM ($n=15$)	>256	>256	0	48	>256	0	>32	>32	0
OXA-48 ($n=11$)	0.75	1.5	100	32	>256	0	12	16	0

Tigecycline			Fosfomycin			Colistin		
MIC_{50}	MIC_{90}	S%	MIC_{50}	MIC_{90}	S%	MIC_{50}	MIC_{90}	S%
1.5	3	80.5	12	64	83.8	<=0.25	>16	65.8
1.5	3	81.1	8	32	91.5	<=0.25	>16	62.7
1.5	4	80.6	48	>1024	48.4	<=0.25	16	83.9
1	12	80	12	64	86.7	<=0.25	8	80
2	3	81.8	64	>1024	36.4	<=0.25	>16	54.5

Total: 75.6% KPC, 11.7% NDM, 5.6% VIM, and 4.1% OXA-48

Maraki S, et al. Infection. 2022;50(2):467-474.

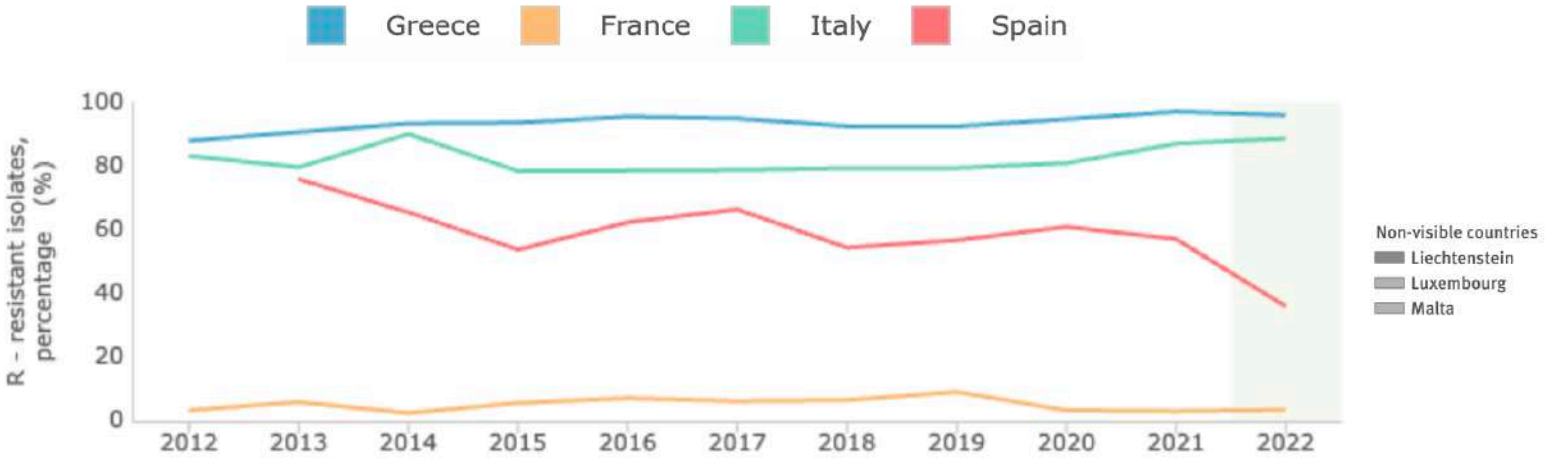
Impact of CAZ-AVI on bloodstream infections due to CR-KP (ICU)



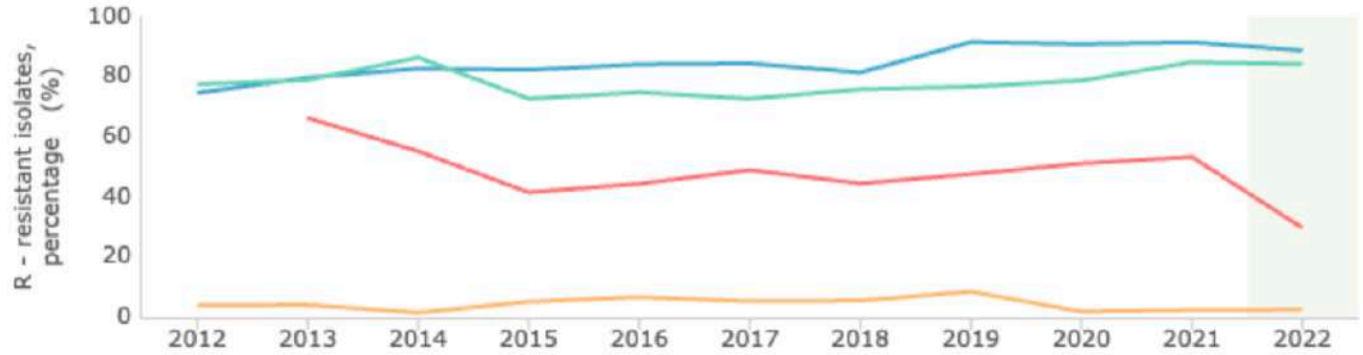
Papadimitriou-Olivgeris M, et al. J Antimicrob Chemother. 2019;74(7):2051-2054.

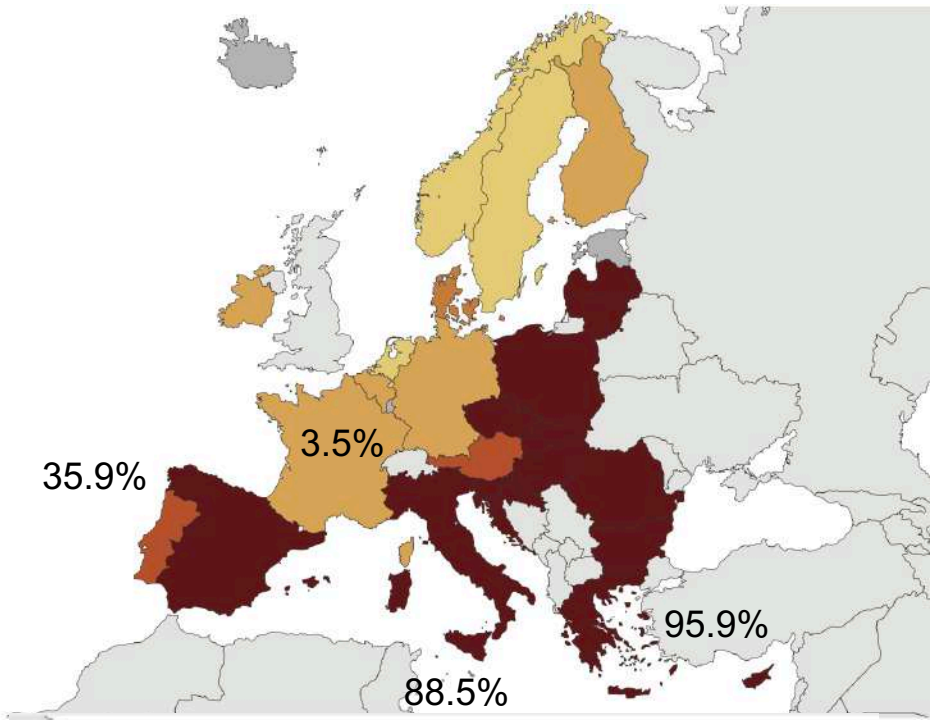
CR- *A. Baumannii* (CRAB) (%) resistance 2022

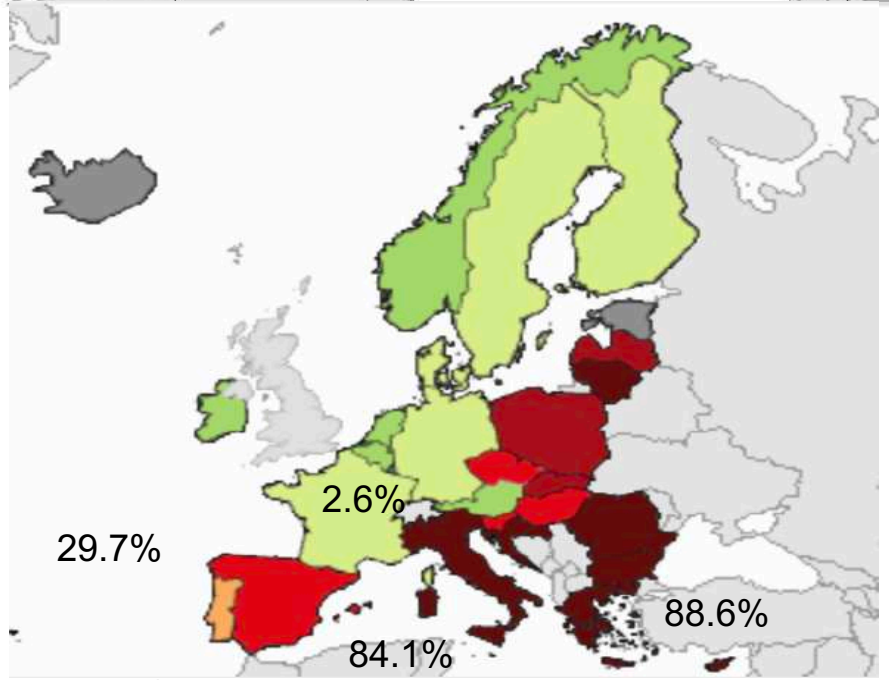
Carbapenem resistance



Combined resistance (carbapenems, aminoglycosides, fluoroquinolones)



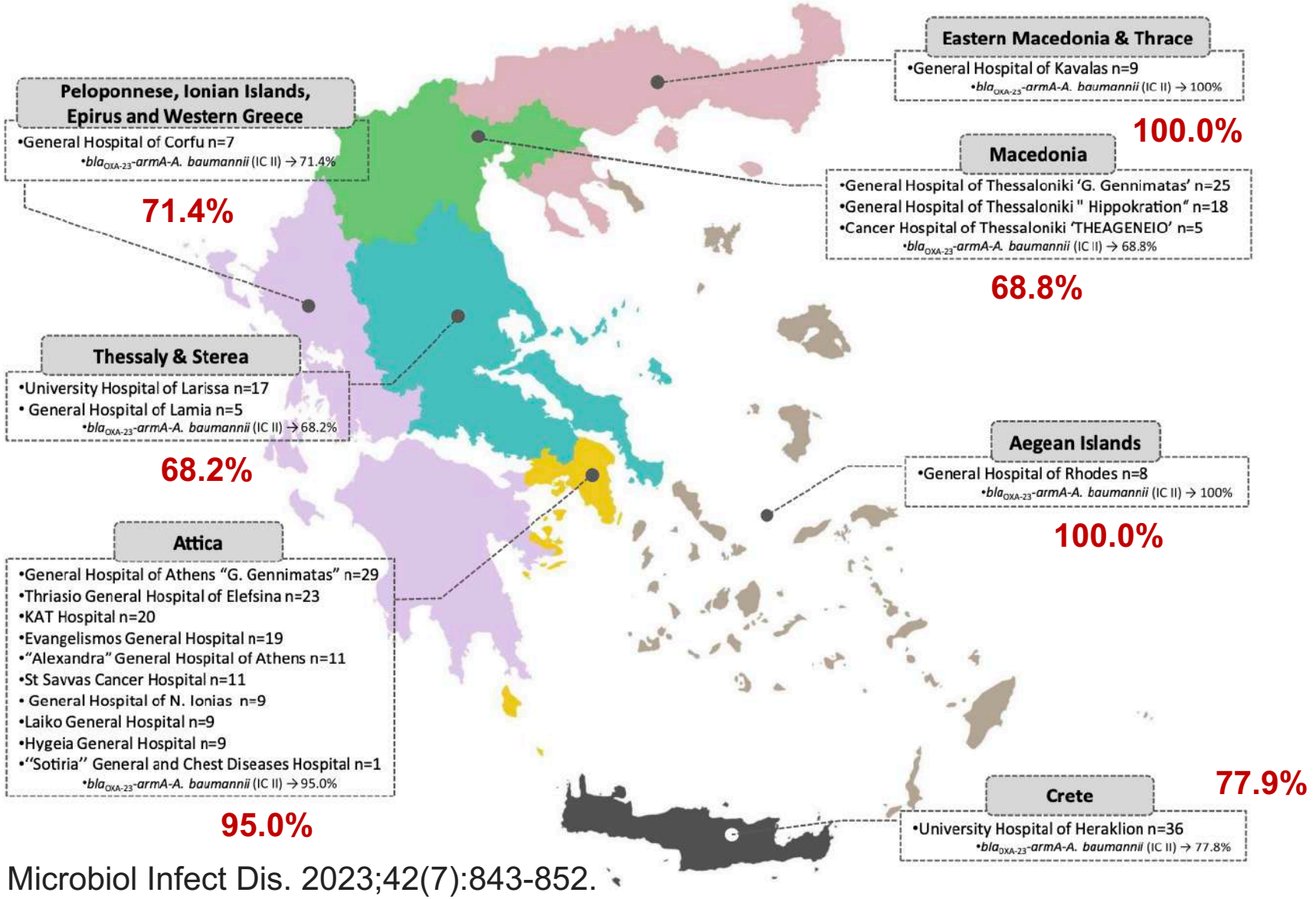




Antimicrobial resistance surveillance in Europe 2023 - 2021 data. Stockholm: ECDC and WHO; 2023.

Cloncal distribution of CRAB in BSIs in Greece (2020-2021)

N=271
Predominance of IC II: blaOXA-51, blaOXA-23, harboring armA



Galani I, et al. Eur J Clin Microbiol Infect Dis. 2023;42(7):843-852.

Therapeutic options?

Changes in antimicrobial resistance of clinical isolates of *A. baumannii* group, 2010-2015

Antibiotic	Resistant % (*n*)						*P* value
Year (*n*)	2010 (1870)	2011 (2154)	2012 (2479)	2013 (1903)	2014 (2070)	2015 (2170)	
Amikacin	74.8 (1398)	70.7 (1524)	70.7 (1753)	72.9 (1387)	73.1 (1513)	73.9 (1603)	0.750
Gentamicin	69.3 (1295)	74.8 (1612)	83.5 (2069)	83.9 (1597)	83.7 (1732)	86.4 (1874)	0.014
Tobramycin	59.8 (1118)	56.7 (1221)	62.7 (1554)	64.8 (1233)	67.6 (1399)	76.8 (1666)	0.011
Amp/sul*	46.2 (864)	70.0 (1508)	80.5 (1996)	80.9 (1540)	83.9 (1737)	88.2 (1914)	0.021
Imipenem	90.3 (1688)	93.1 (2006)	94.6 (2345)	94.0 (1788)	92.5 (1914)	94.5 (2051)	0.198
Meropenem	82.6 (1544)	84.0 (1809)	91.7 (2273)	91.9 (1749)	94.1 (1948)	94.8 (2057)	0.006
Levofloxacin	95.5 (1786)	95.5 (2058)	95.1 (2358)	93.9 (1787)	95.6 (1979)	95.9 (2081)	0.879
Tmp/smx†	90.2 (1686)	84.8 (1827)	70.1 (1738)	64.8 (1234)	61.7 (1277)	69.1 (1499)	0.035
Minocycline	5.2 (97)	23.5 (506)	47.2 (1170)	50.6 (963)	47.4 (981)	58.5 (1270)	0.013
Colistin	7.1 (133)	5.4 (116)	5.8 (144)	10.7 (204)	9.6 (199)	7.5 (163)	0.317

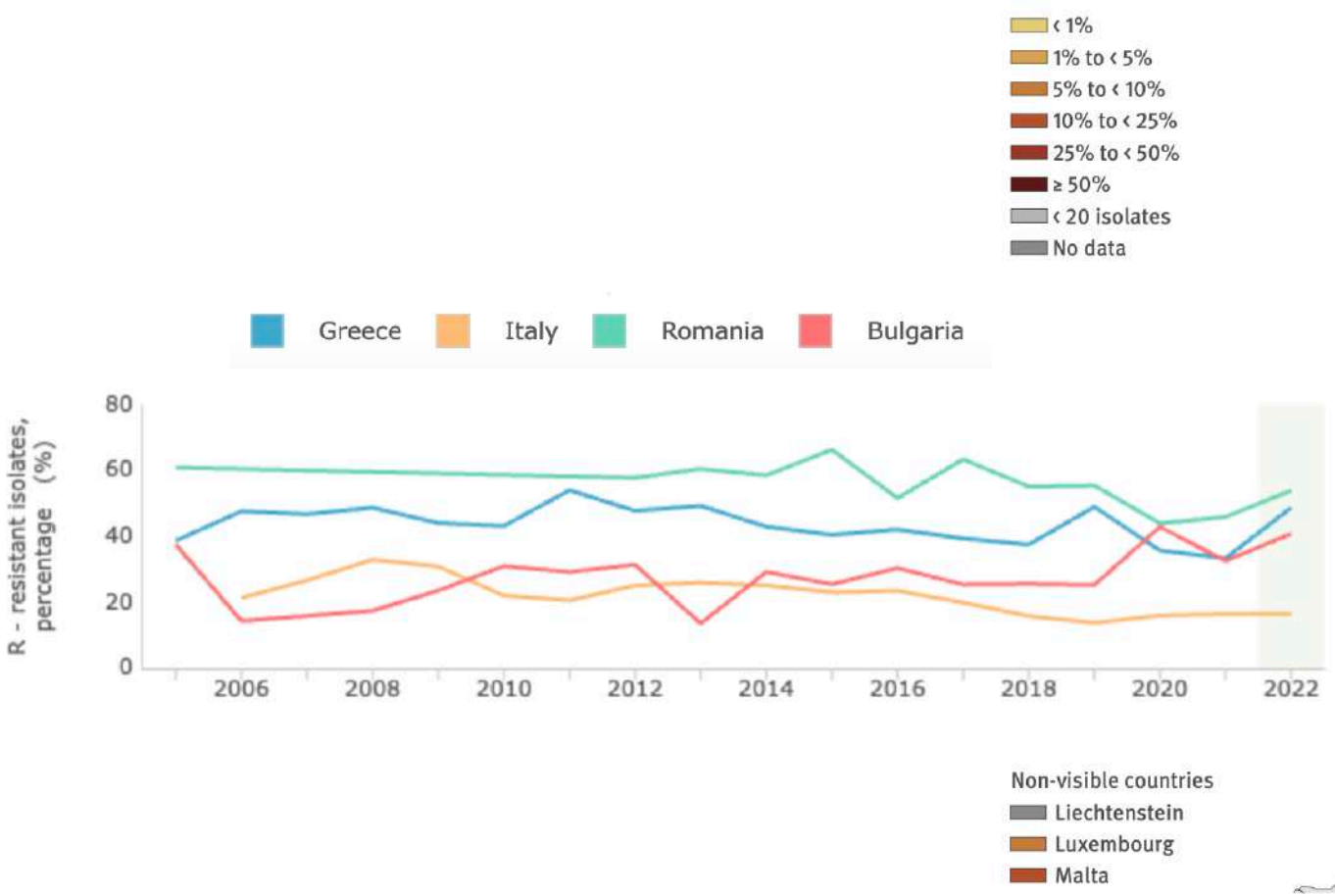
2021 (271)

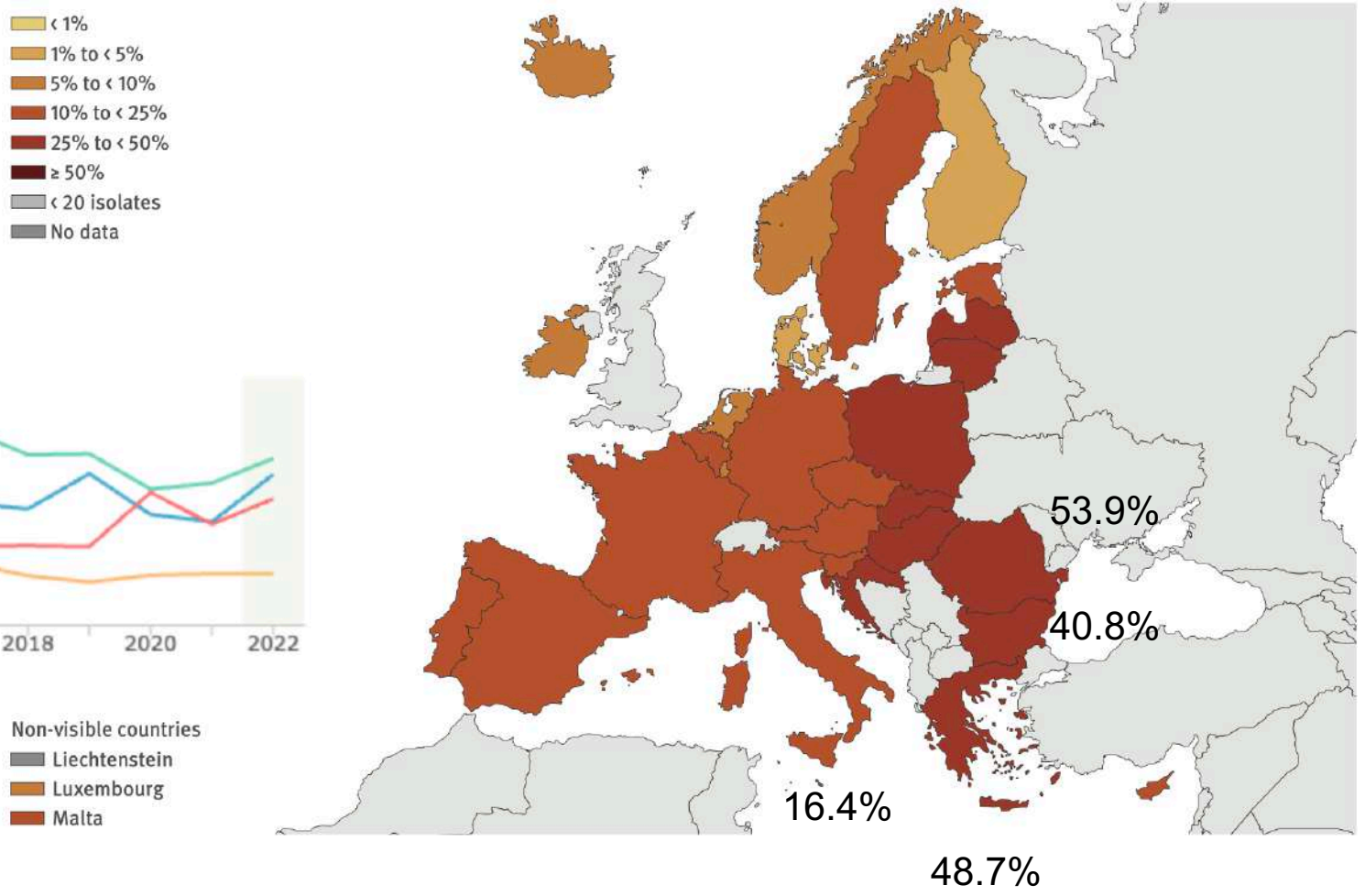
81.2
84.5
14.0
0.0

Cefiderocol
Apramycin (EBL-1003)
Eravacyclin?
Omadacyclin?

Dafopoulou K, Tsakris A, Pournaras S. J Med Microbiol. 2018;67(4):496-498.
Galani I, et al. Eur J Clin Microbiol Infect Dis. 2023;42(7):843-852.

CR *P. aeruginosa* (%) resistance 2022



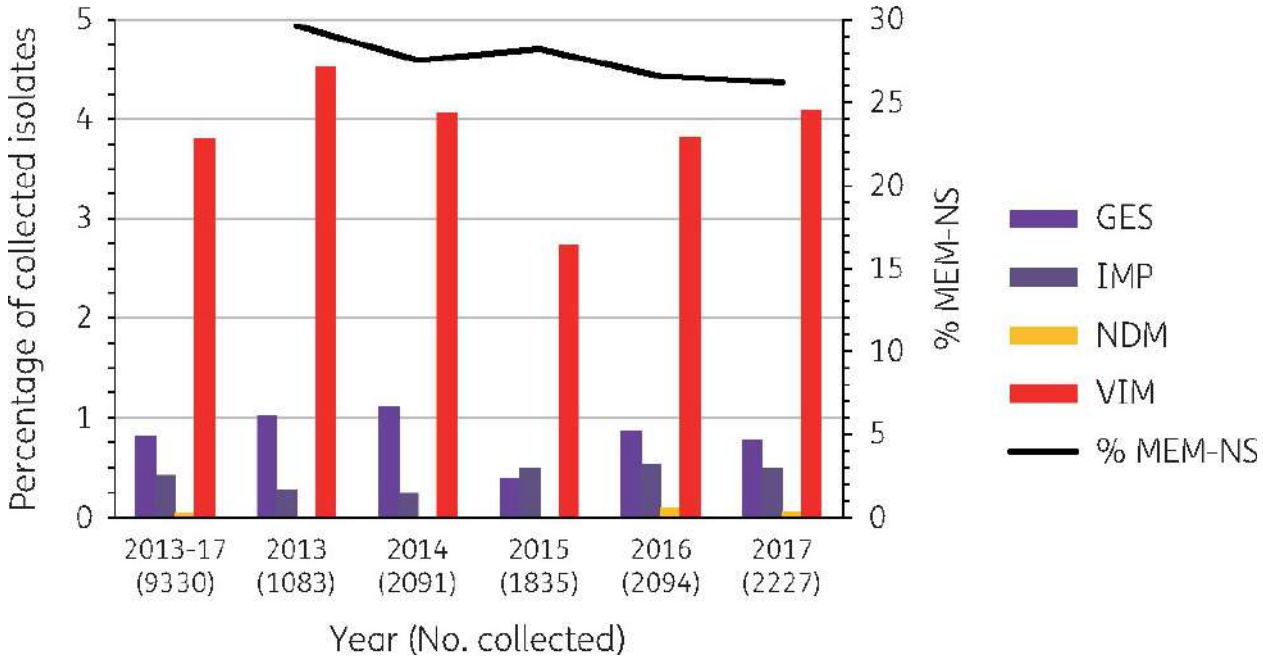


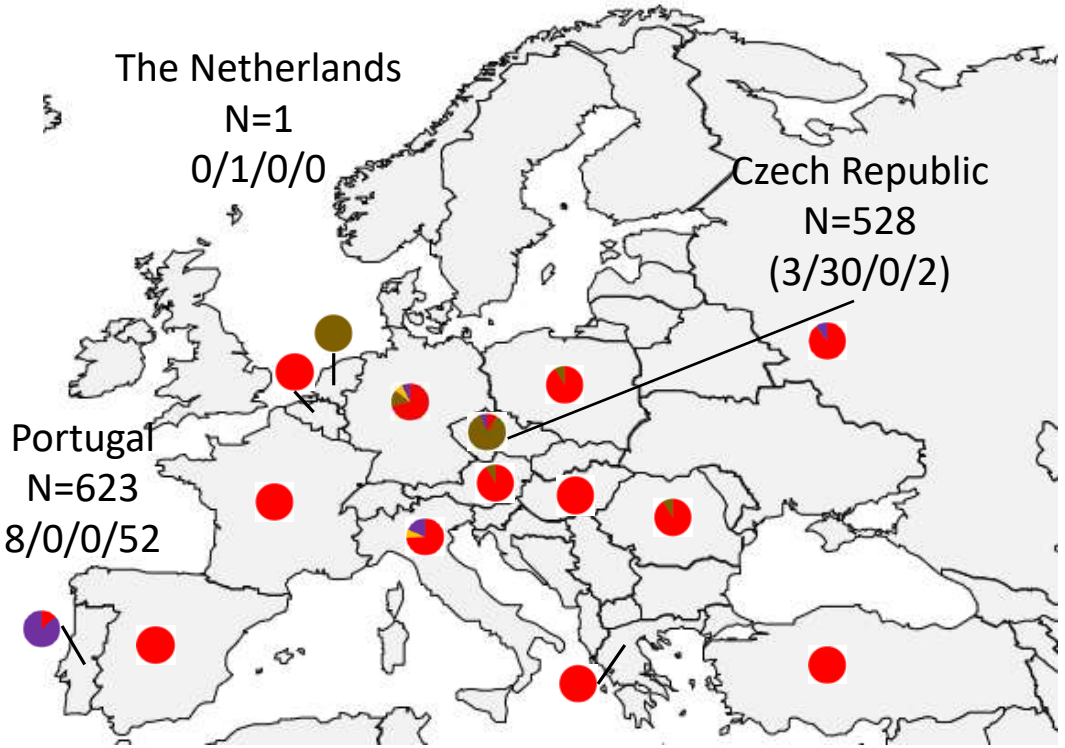
Antimicrobial resistance surveillance in Europe 2023 - 2021 data. Stockholm: ECDC and WHO; 2023.

Distribution of CR- *P. aeruginosa* strains 2013-2017

N=2556

N=473 (18.5%) isolates with carbapenemase

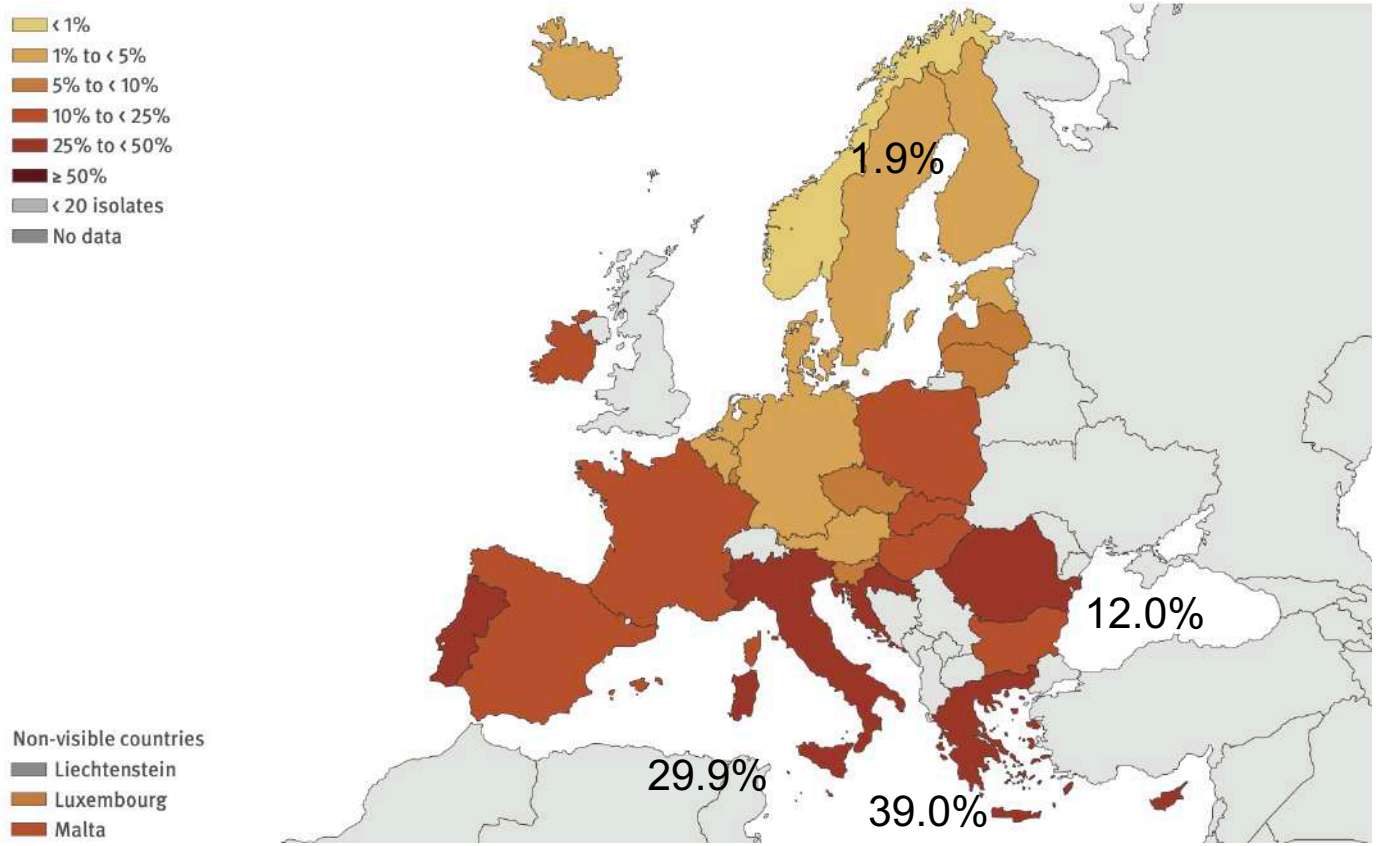




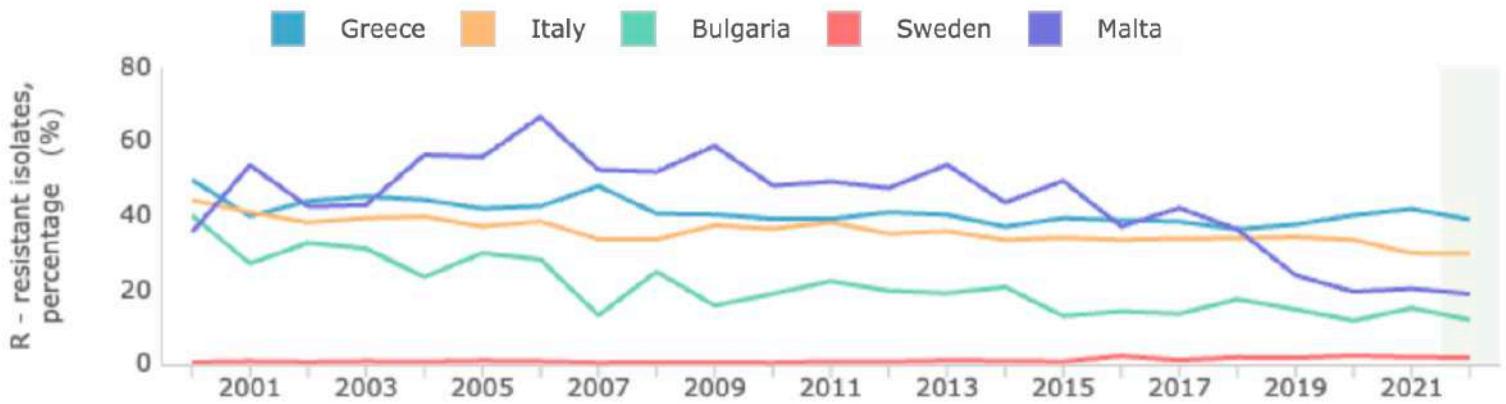
Greece: n=485 isolates. 63 (13.0%) VIM
no other carbapenemases detected (IMP/ NDM/ GES)

Kazmierczak KM, et al. J Antimicrob Chemother. 2020;75(5):1165-1173

Methicilline-Resistant *Staphylococcus Aureus* (MRSA)

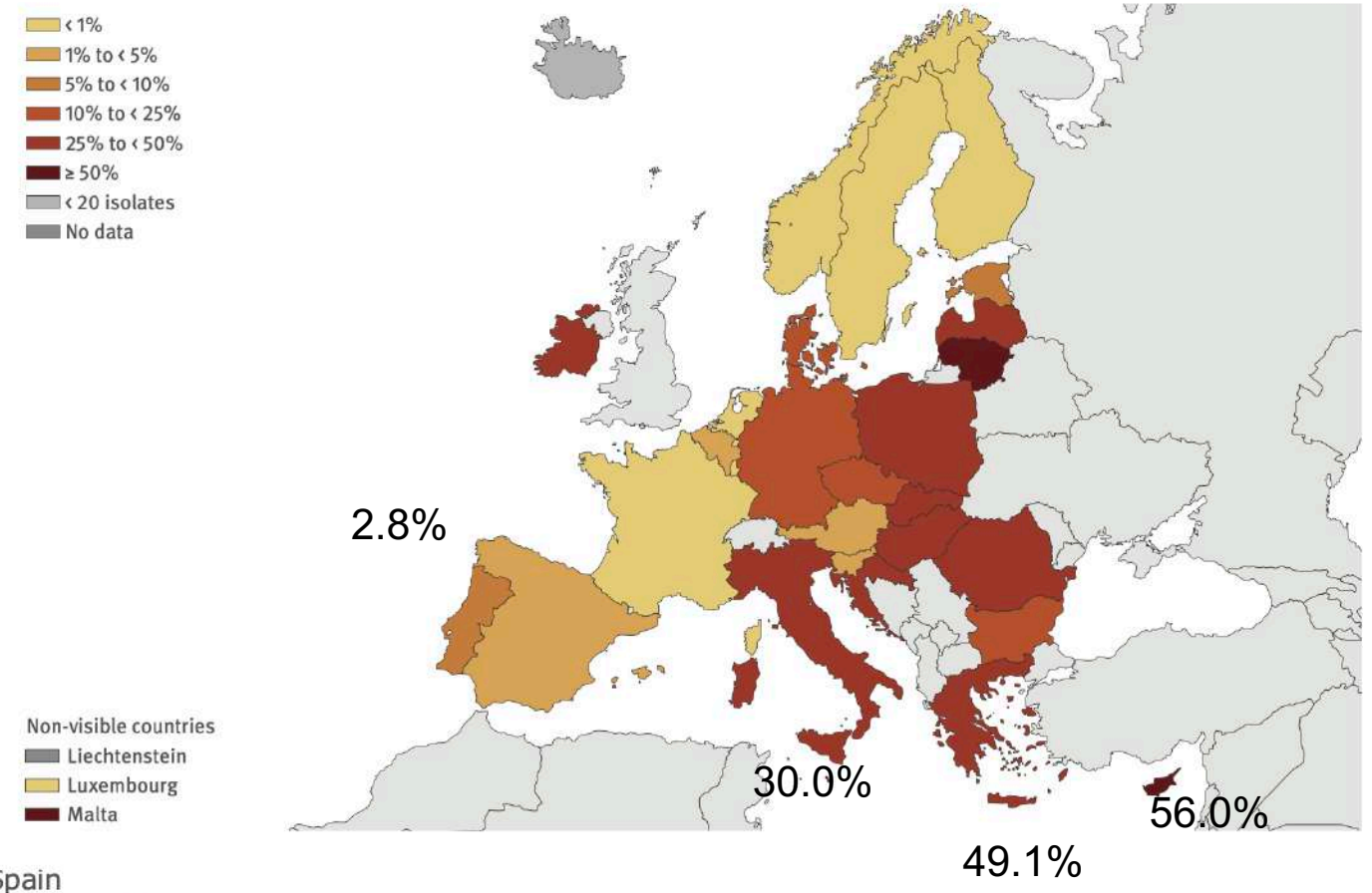


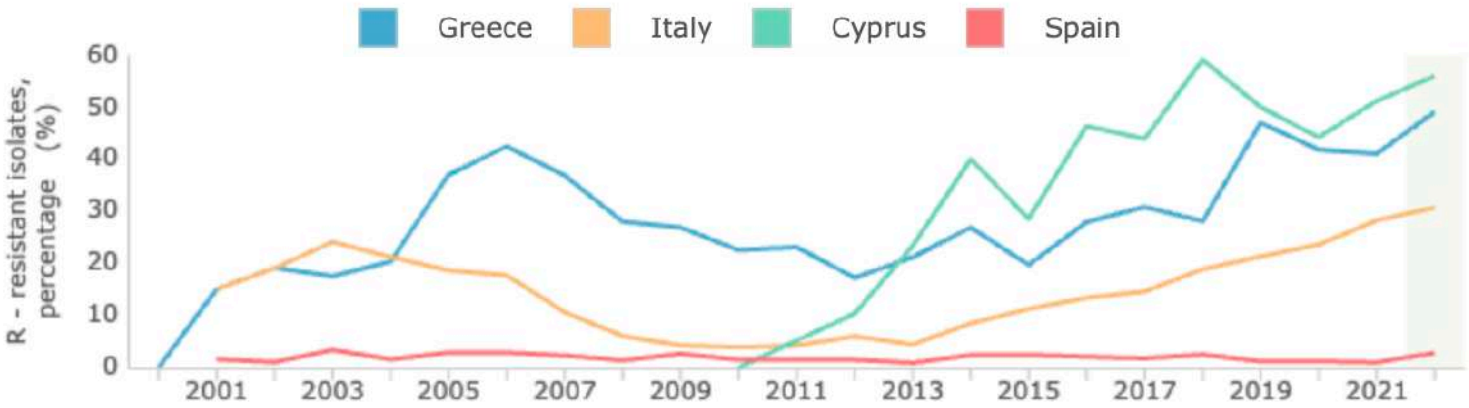
Malta:
19.0%



Antimicrobial resistance surveillance in Europe 2023 - 2021 data. Stockholm: ECDC and WHO; 2023.

Vancomycin-Resistant *Enterococcus faecium* (VRE)

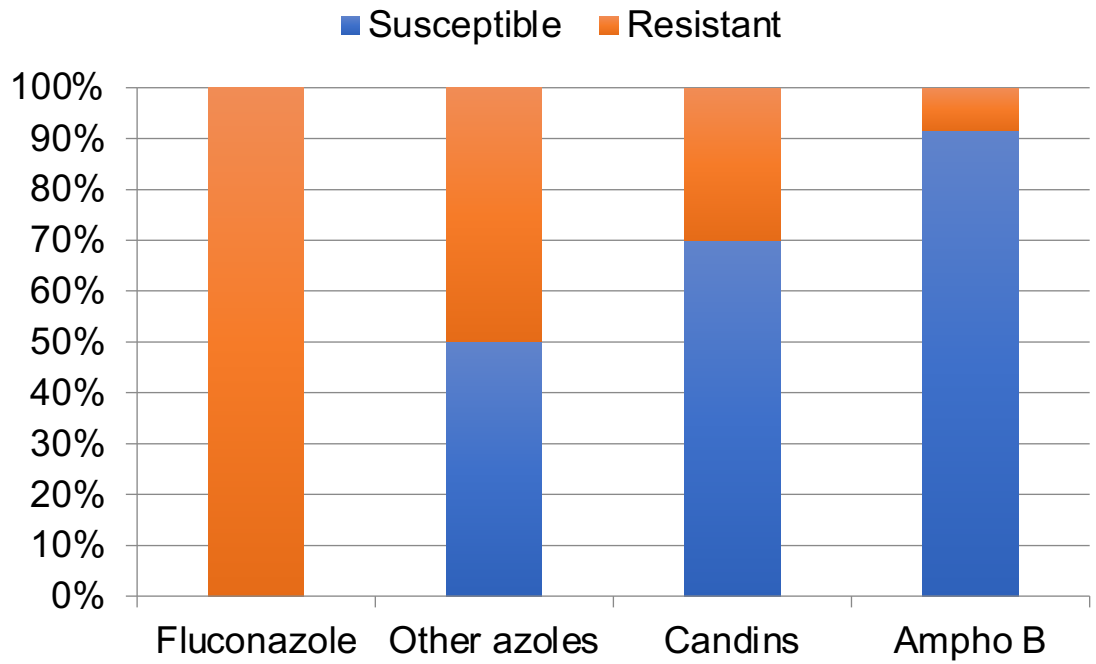




Antimicrobial resistance surveillance in Europe 2023 - 2021 data. Stockholm: ECDC and WHO; 2023.

Candida auris

- Retrospective analysis of all consecutive *C. auris* BSIs in a 55-bed, tertiary, academic ICU
- Index case recorded on June 4th, 2021.
- Among 812 ICU patients (8031 patient-days), a total of 141 were colonized by *C. auris*; of which 12 (8.5%) were diagnosed with BSI
- 28-day mortality in 8 patients (66.7%), treatment failure in 6 (60%)



Patient Characteristics at Diagnosis	Total (N=12)
Age, median (Q1-Q3)	70 (65-77)
Sex (male), n (%)	7 (58.3)
Charlson Comorbidity Index, median (Q1-Q3)	4.5 (3-7)
SOFA score, median (Q1-Q3)	10 (6-14)
COVID-19 diagnosis, n (%)	4 (33.3)
Prior corticosteroid intake, n (%)	7 (58.3)
Prior continuous renal replacement therapy, n (%)	6 (50.0)
Prior total parenteral nutrition, n (%)	1 (8.3)
Prior antibiotic treatment (antibiotic-days), median (Q1-Q3)	69 (47-113)
Presence of a central venous catheter, n (%)	12 (100)
Organ support, n (%)	
Mechanical ventilation	11 (91.7)
Vasopressor use	8 (66.7)
Continuous renal replacement therapy	4 (33.3)

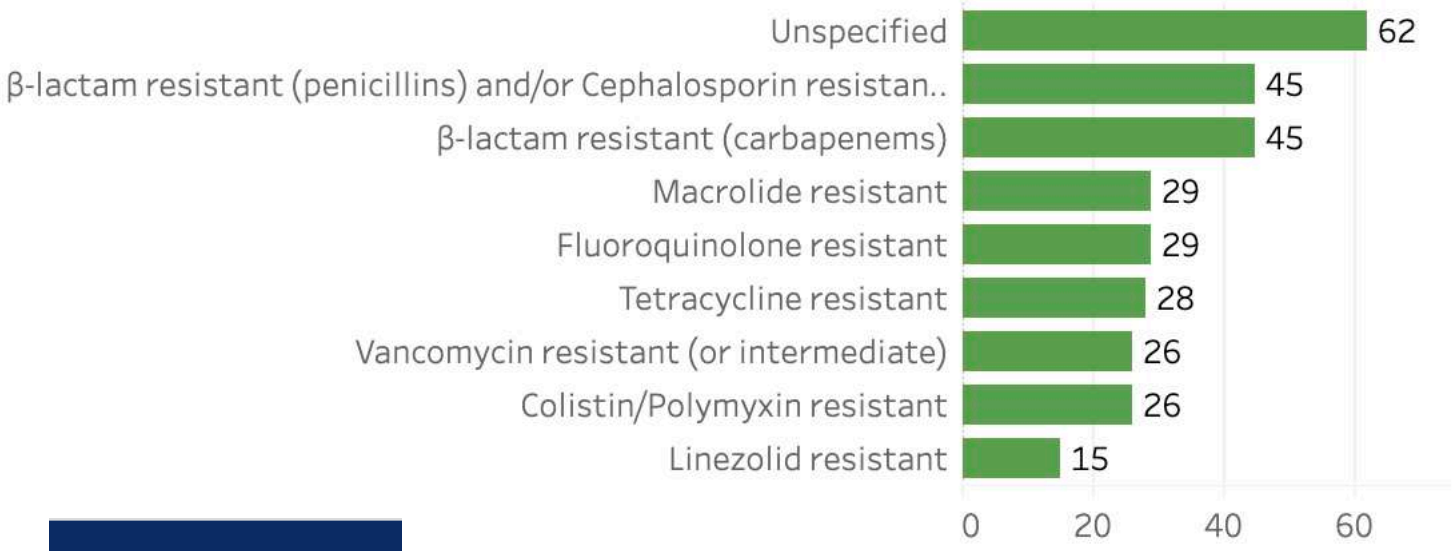
Karakike E, et al, ESICM LIVES 2022: part 2. Intensive Care Med Exp. 2022;10(Suppl 2):40. doi: 10.1186/s40635-022-00469-0.

Are we keeping up with resistance?

WHO antibacterial preclinical pipeline review

Published: June 2022

N=217



World Health Organization

https://www.who.int/observatories/

U.S. FOOD & DRUG ADMINISTRATION

FDA Approves New Treatment for Pneumonia Caused by Certain Difficult-to-Treat Bacteria

For Immediate Release: May 23, 2023

Today, the U.S. Food and Drug Administration approved Xacduro (sulbactam for injection; durlobactam for injection), a new treatment for hospital-acquired bacterial pneumonia (HABP) and ventilator-associated bacterial pneumonia (VABP) caused by susceptible strains of bacteria called Acinetobacter baumannii-calcoaceticus complex.

https://www.fda.gov/news-events/press-announcements/

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HELLENIC INSTITUTE FOR THE STUDY OF SEPSIS

HELLENIC SEPSIS STUDY GROUP
BOOKLET ON SEPSIS

DEFINITIONS-DIAGNOSTIC APPROACH-TREATMENT RECOMMENDATIONS

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ATHENS 2023

PREVENTING ANTIMICROBIAL RESISTANCE TOGETHER

1 in 10 patients get an infection while receiving care.

Health workers can reduce the spread of infections by ensuring their hands, instruments and environment are kept clean.

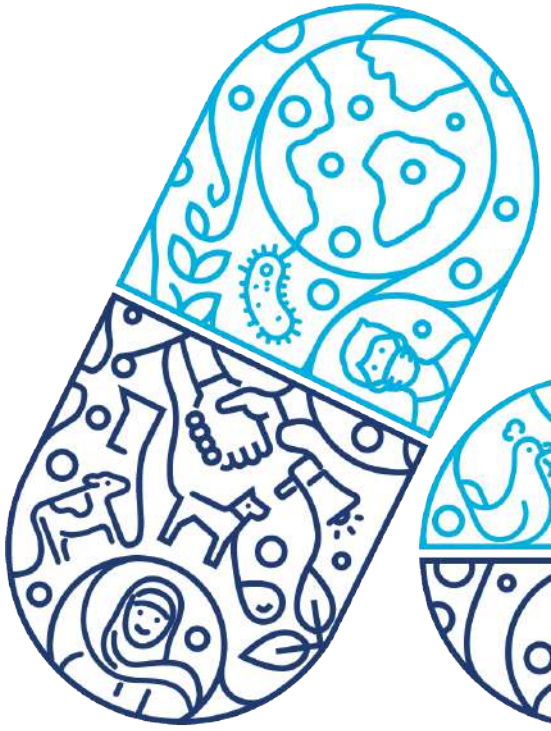
World Health Organization

HANDLE ANTIMICROBIALS WITH CARE

Antibiotics
Antivirals
Antifungals
Antiparasitics

WORLD AMR AWARENESS WEEK

18-24 NOVEMBER



HANDLE ANTIMICROBIALS WITH CARE

Antibiotics
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