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ReFORMÚLaTE

En busca del tesoro

"La evolución de las resistencias"

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La evolución de las resistencias

Disclosures

- **Participation in educational programs**
  - FastInov
  - MSD
  - Pfizer
  - Roche
  - Shionogi
- **Participation in research studies**
  - BioMerieux
  - Cepheid
  - FastInov
  - Quantamatrix
  - MSD
  - Resistell
  - Shionogi
- **Evaluation of clinical trials**
  - MSD
  - Pfizer

EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING
European Society of Clinical Microbiology and Infectious Diseases

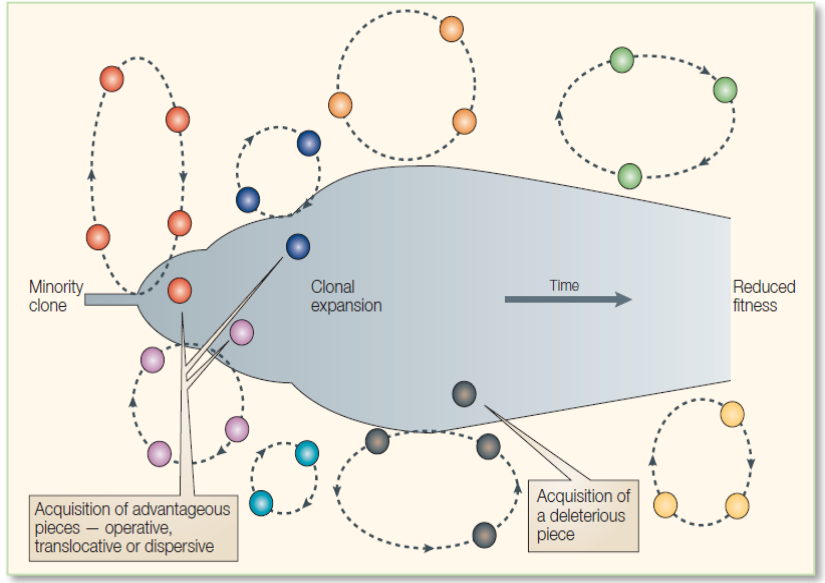
Acknowledgements

ciberinfec isciii

Antimicrobial resistance: *a microbiological view*

- Consequence of **"genetic capitalisms"**

Baquero et al. ASM News 2003; 69: 547-51; Cantón et al. Curr Opin Infect Dis 2003; 16:315-25; Canton, Ruiz-Garbajosa Curr Opin Pharmacol 2011; 11:477-85



- Association with ***high-risk*** **clones**

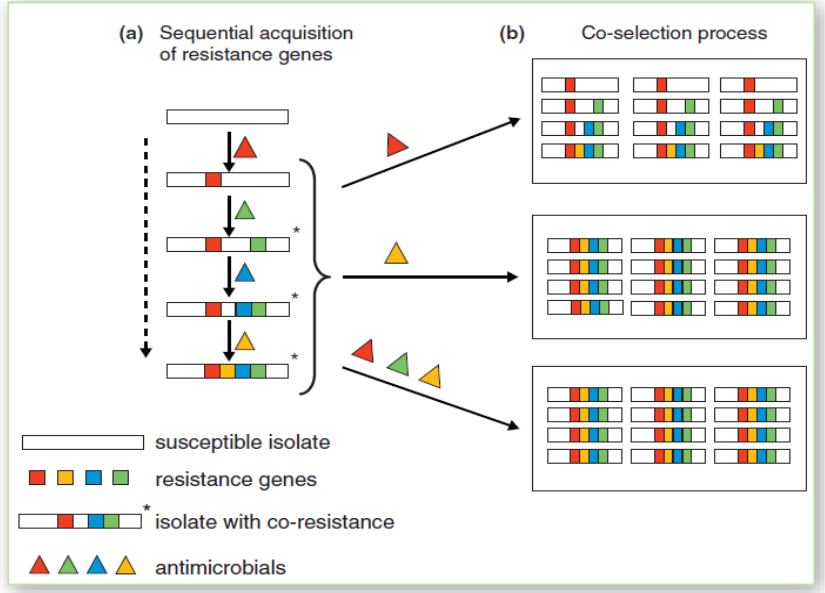
  - Efficiently colonize human hosts during long periods of time
  - Ability to be transmitted with high efficiency among patients
  - Ability to produce severe or invasive infections
  - Major role to spread resistance mechanisms of critical importance

TROCAR FP7 Health EU project (Baquero F); Woodford et al. FEMS Microbiol Rev 2011; 35:736-55; Cantón R, Ruiz-Garbajosa P. Curr Opin Pharmacol 2011; 11:477-85; Cantón R, et al. Curr Opin Crit Care. 2020;26(5):433-441

- Consequence of **selection and co-selection processes**

  - Different antimicrobials might select the same resistant bacteria
  - A single antimicrobial might select different resistant bacteria

Baquero F & Cantón R. Evolutionary Biology of Drug Resistance. In: Antimicrobial Drug Resistance. Lerner SA (ed). 2nd ed. 2017



High risk clones and antimicrobial resistance

Specie	Clon	Mechanism of antimicrobial resistance	Coresistance
Escherichia coli	ST131	ESBL (CTX-M-15, -14, -27)	Fluoroquinolones [topoisomerase mutations, *qnr*, *aac(6′)-Ib-cr*...]; plasmidic AmpC beta-lactamases, carbapenemases; colistin resistance (*mcr-1*)
Klebsiella pneumoniae	ST11 ST15 ST101 ST147	ESBL (CTX-M-15, ...) Carbapenemases (KPC, VIM, NDM, OXA-48)	Fluoroquinolones [topoisomerases mutations, *qnr*, *aac(6′)-Ib-cr*...]; plasmidic AmpC beta-lactamases (DHA-1), aminoglycoside resistance (ArmA, RmtB methylases)
	ST258	Carbapenemases (KPC)	Colistin resistance (mutations in *pmrB*), ceftazidime-avibactam resistance
	ST307	Carbapenemases (KPC-like, NDM)	Ceftazidime-avibactam resistance
	ST405	Carbapenemases (OXA-48)	ESBL (CTX-M-15)
Pseudomonas aeruginosa	ST101 ST175 ST235 ST244	Multiresistance	Carbapenemases (VIM-2, GES-7, VEB-1, IMP-1, KPC-2, PER-1)
Acinetobacter baumannii	ST2	Carbapenemases (OXA-23)	Carbapenemases (OXA-24, OXA-58, NDM-1); aminoglycosides [AAC(3)-Ia, AADA, ANT(2″)-I, APH(3′)-VI, ... and methylases (ArmA)]

CTX-M, Active on cefotaxime, first isolated at Munich; ESBL, extended-spectrum beta-lactamases; GES, Guiana-extended spectrum; IMP, active on imipenem; KPC, *Klebsiella pneumoniae* carbapenemase; NDM, New Dehli metallo-beta-lactamase; OXA, Active on oxacillin; PER, *Pseudomonas* extended resistant; VEB, Vietnamese extended-spectrum β-lactamase; VIM, Verona integron encoded metallo-beta-lactamases.

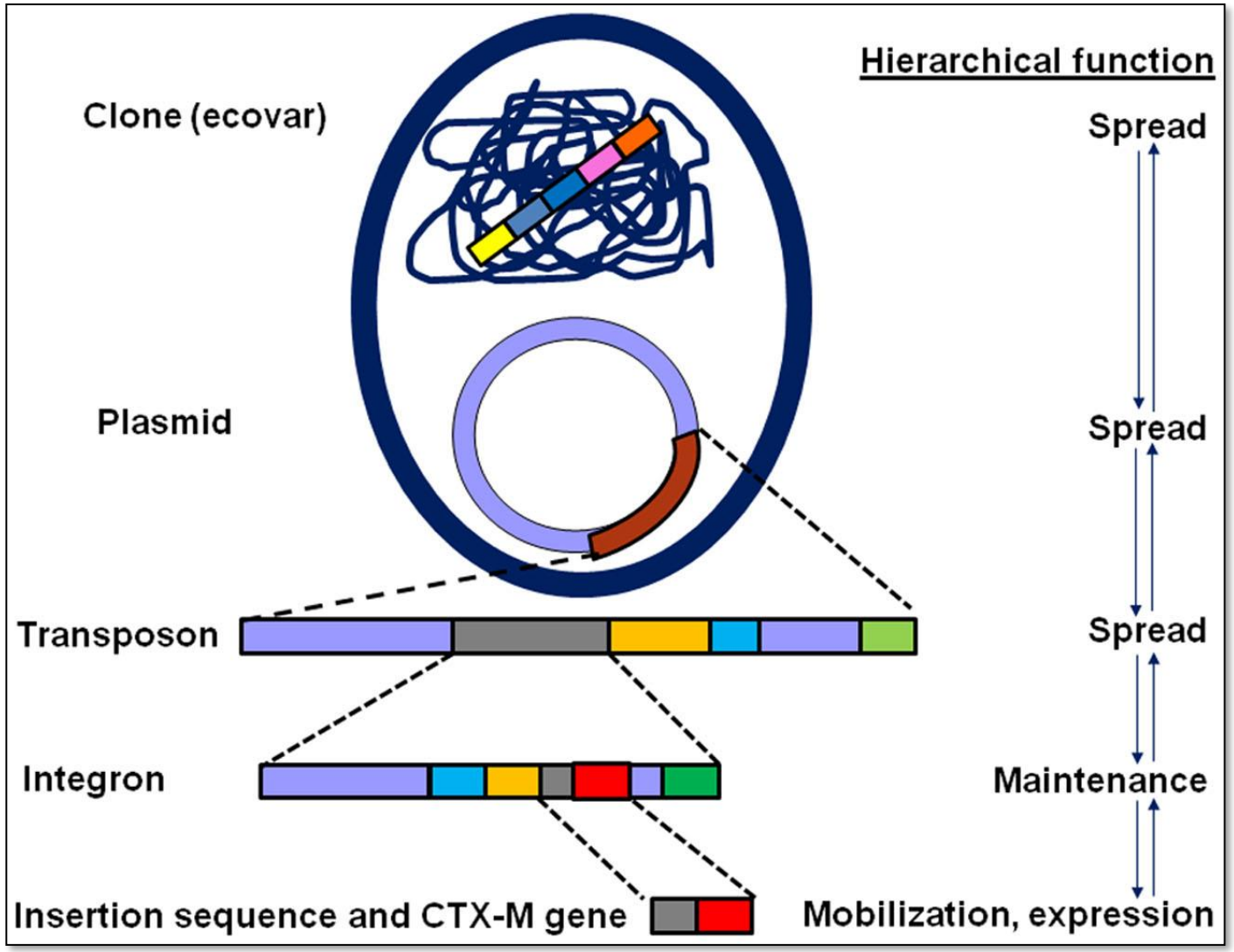
High-risk clones:

Highly specialized genetic populations or subpopulations with enhanced ability to **colonize**, **spread and persist** in particular niches after having **acquired a diversity of adaptative traits** that increase their **epidemicity** and/or **pathogenic potential,** including **antibiotic resistance**

Baquero F, Coque TM. Multilevel population genetics in antibiotic resistance. FEMS Microbiol Rev. 2011;35:705-6

Cantón R, Gijón D, Ruiz-Garbajosa P. Antimicrobial resistance in ICUs: an update in the light of the COVID-19 pandemic. Curr Opin Crit Care. 2020; 26:433-41

Antibiotic resistance: genetic capitalisms and *high-risk clones*

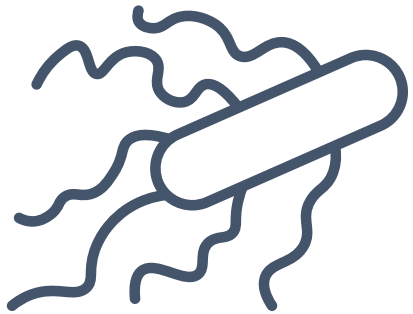


Associated with
high-risk clones

Cantón et al. Front Microbiol 2012;3:110; Baquero F et al. Clin Microbiol Rev. 2021; 34(4):e0005019

ST131 *Escherichia coli* high-risk clone

- Classified as an **extra-intestinal pathogenic *E. coli*** (ExPEC)
- Belongs to **phylogroup B**2 and are **serotype O16:H5 or O25b:H4**
- **World wide distributed**, most frequently isolated in **patients with urinary tract infections (UTI)** and **bacteremia emanating from the urinary tract**



- Initially describe late 80', most commonly associated with community-onset healthcare
- Involved in the spread of **multi-drug resistance**

1980s - emergence of ciprofloxacin resistance
- 70% of total ESBL-producing isolates (IncF plasmids)
- 80% of total fluoroquinolone resistant isolates
- high co-existence (>50%) of ESBL and fluoroquinolone resistance

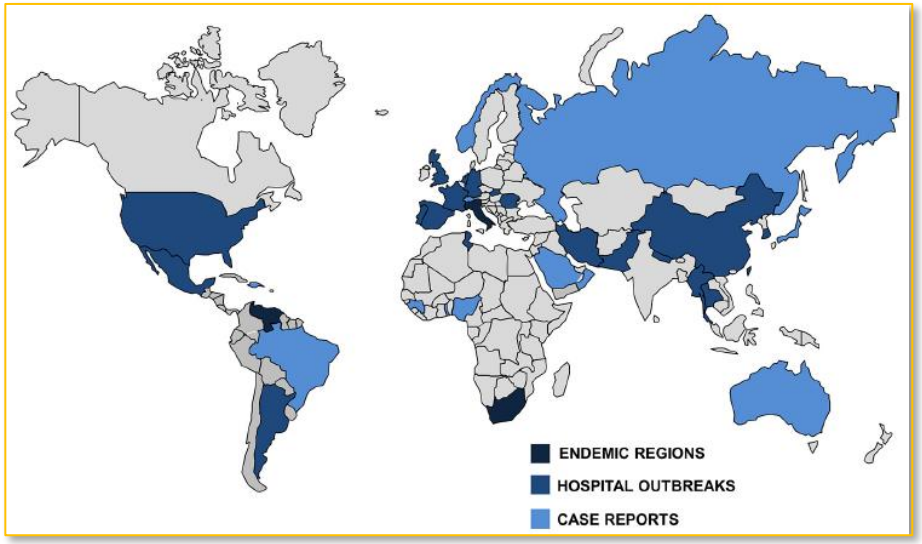
2020s - emergence and spread of carbapenemase producers

- Described causing **community acquired uncomplicated urinary tract** and **nosocomial infections**

Phillips I et al. Lancet 1988; 8593:1038-41; Coque TM et al. Emerg Infect Dis. 2008;14:195-200;Nicolas-Chanoine MH, et al. Clin Microbiol Rev 2014; 27:543-74; Mathers AJ, et al. Adv Appl Microbiol 2015;90:109-54; Pitout JDD, Finn TJ. Infect Genet Evol. 2020; 81:104265.

ST307 *Klebsiella pneumoniae* high-risk clone

- 1990s Emerged in Europe during the early to mid-1990s
  - linked with *gyrA* S831 and *parC* S810 mutations (QRDR region) devoting **quinolone resistance**
- 2000s **3rd gen. cephalosporin resistance** (FIB-like plasmids with $bla_{CTX\text{-}M\text{-}15}$)
  - associated with aminoglycoside [*strA, strB, aac(3)-IIa, aac(6')-Ib-cr*], quinolone [*qnrB1, oqxAB*] and other resistances genes [*sul2, dfrA14, catB, fosA*]
- 2010s **Carbapenem resistance** due to OXA-48, OXA-181, KPC-2, KPC-3, VIM-1, NDM-1 carbapenemases
  Colistin resistance associated with *mcr-1*
  Ceftazidime-avibactam resistance due to KPC mutations
- Widely distributed and currently endemic in Italy, Colombia, Argentina, United States, Spain, China, …
- High ability to colonized
- Enhanced pathogenicity



Peirano G, Chen L, Kreiswirth BN, Pitout JDD. Emerging antimicrobial-resistant high-risk *Klebsiella pneumoniae* clones ST307 and ST147. Antimicrob Agents Chemother 2020 Sep 21;64(10):e01148-20

Antimicrobial resistance: *the clinical view*

Term	Definition	Comment
Multi-drug resistant (MDR)	**Non-susceptibility** to at least one agent in three or more antimicrobial categories*	• R to multiple antimicrobial agents (≥3), classes or subclasses • Includes XDR and PDR • Definition based on in-vitro susceptibility data with the aim to alert clinicians when treating patients and infection control
Extremely drug resistant (XDR)	**Non-susceptibility** to at least one agent in all but two or fewer antimicrobial categories*	• R to all, or almost all, approved antimicrobial agents
Pan-drug resistant (PDR)	**Non-susceptibility** to all agents in all antimicrobial categories *	• Organisms **resistant to**: - almost **all** commercially available antimicrobials - **all** antimicrobials routinely tested - **all** antimicrobial available for empirical treatment

*therapeutic categories (i.e., aminoglycosides, fluoroquinolones, cephalosporins, carbapenems, …)

ecdc EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL & TATFAR & CDC CENTERS FOR DISEASE CONTROL AND PREVENTION

Magiorakos et al. Clin Microbiol Infect 2012; 18:268-81

Multi-drug resistant (MDR) *versus* difficult to treat resistant (DTR) pathogens

Multi-drug resistant (MDR)

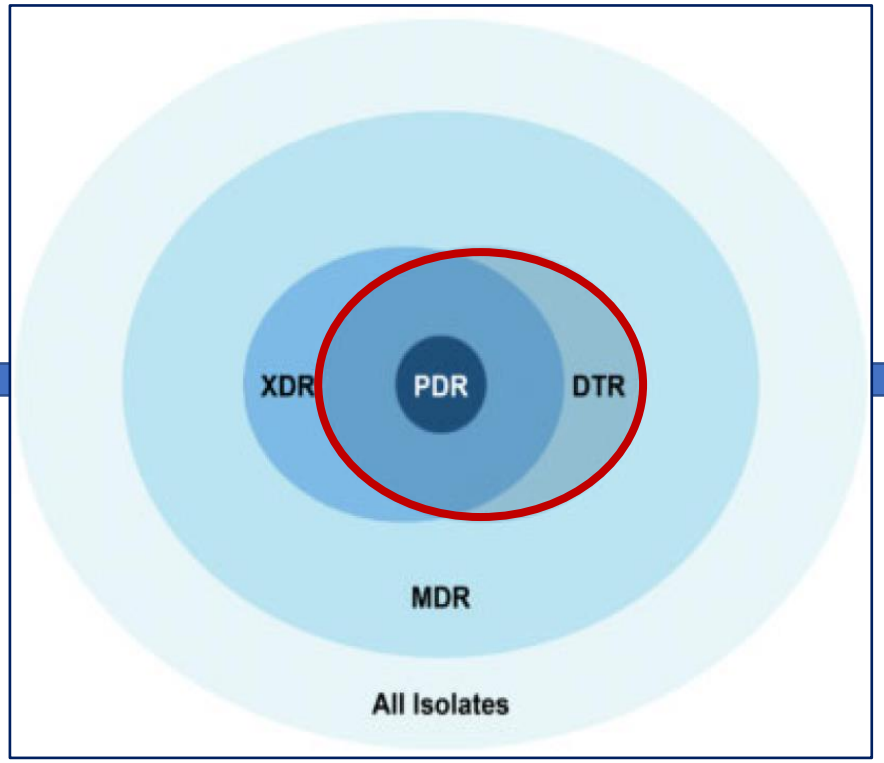
Non-susceptible to at least one antimicrobial in three or more antimicrobial categories

Extensive-drug resistant (XDR)

Non-susceptible to at least one antimicrobial in all but two or fewer antimicrobial categories

Pan-drug resistant (PDR)

Non-susceptible to all antimicrobial agents



Difficult to treat resistant (DTR) pathogens

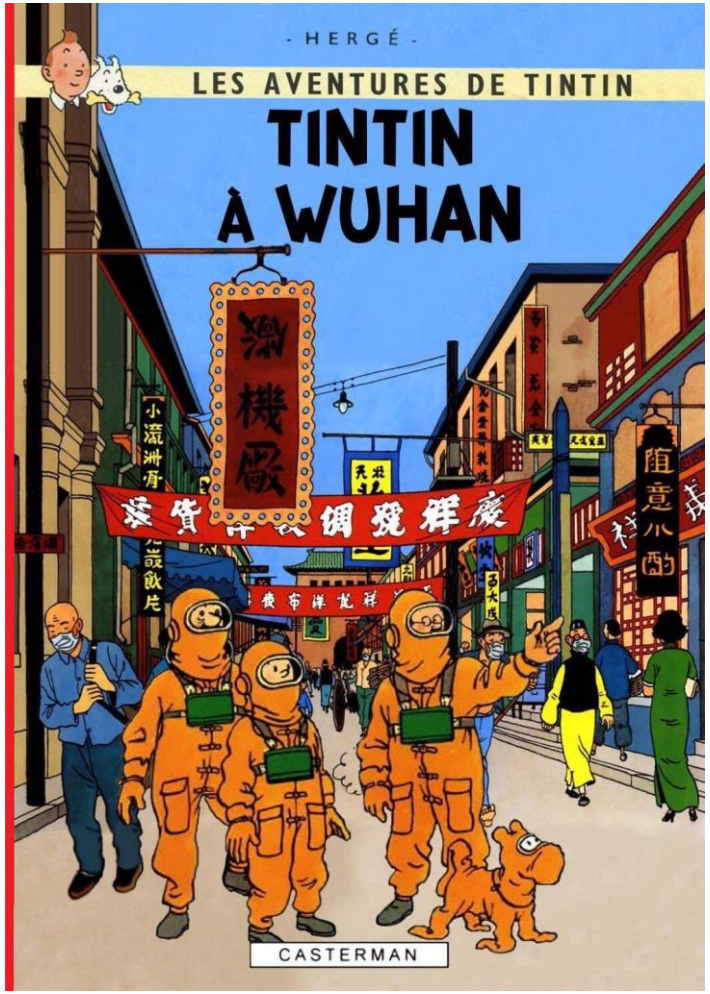
Resistant to all first-line high efficacy, low-toxicity agents, but susceptible to 'reserve agents', including colistin, aminoglycosides and tigecycline

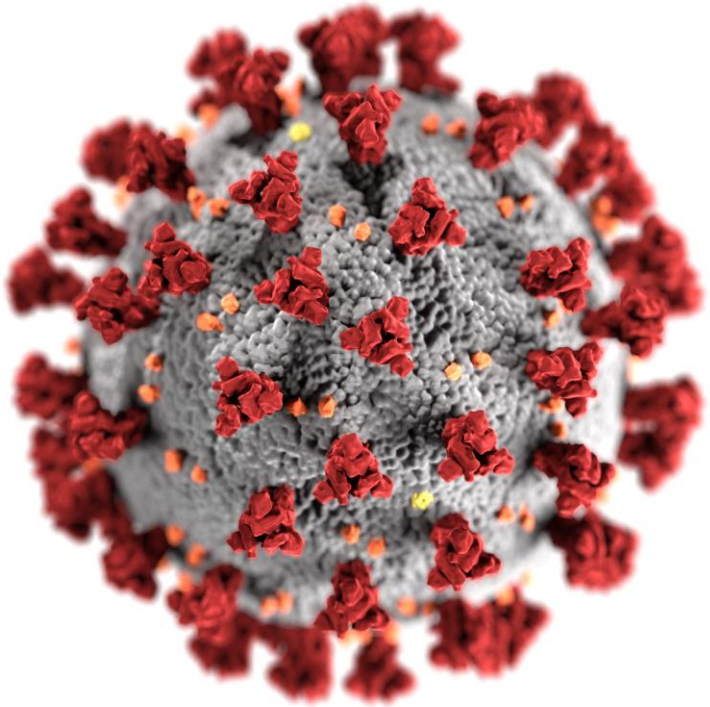
ESKAPE microorganisms

Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, Enterobacter spp

Magiorakos AP et al. Clin Microbiol Infect. 2012; 18:268-81. Strich JR et. Respir Crit Care Med. 2019; 40:419-34. Kadri SS et al. Clin Infect Dis. 2018; 67(12):1803-14. Cantón R et al. Curr Opin Crit Care. 2020; 26:433-441.

SARS-CoV-2 – COVID-19





SARS-CoV-2

Total cases*

641.069.082

Total deaths*

6.629.849

*Disponible en: https://coronavirus.jhu.edu/map.html. Último acceso 26/ 11/2022

COVID-19 – coinfections/superinfections and excess of antimicrobial use

Bacterial co-infection and secondary infection in patients with COVID-19: a living rapid review and meta-analysis

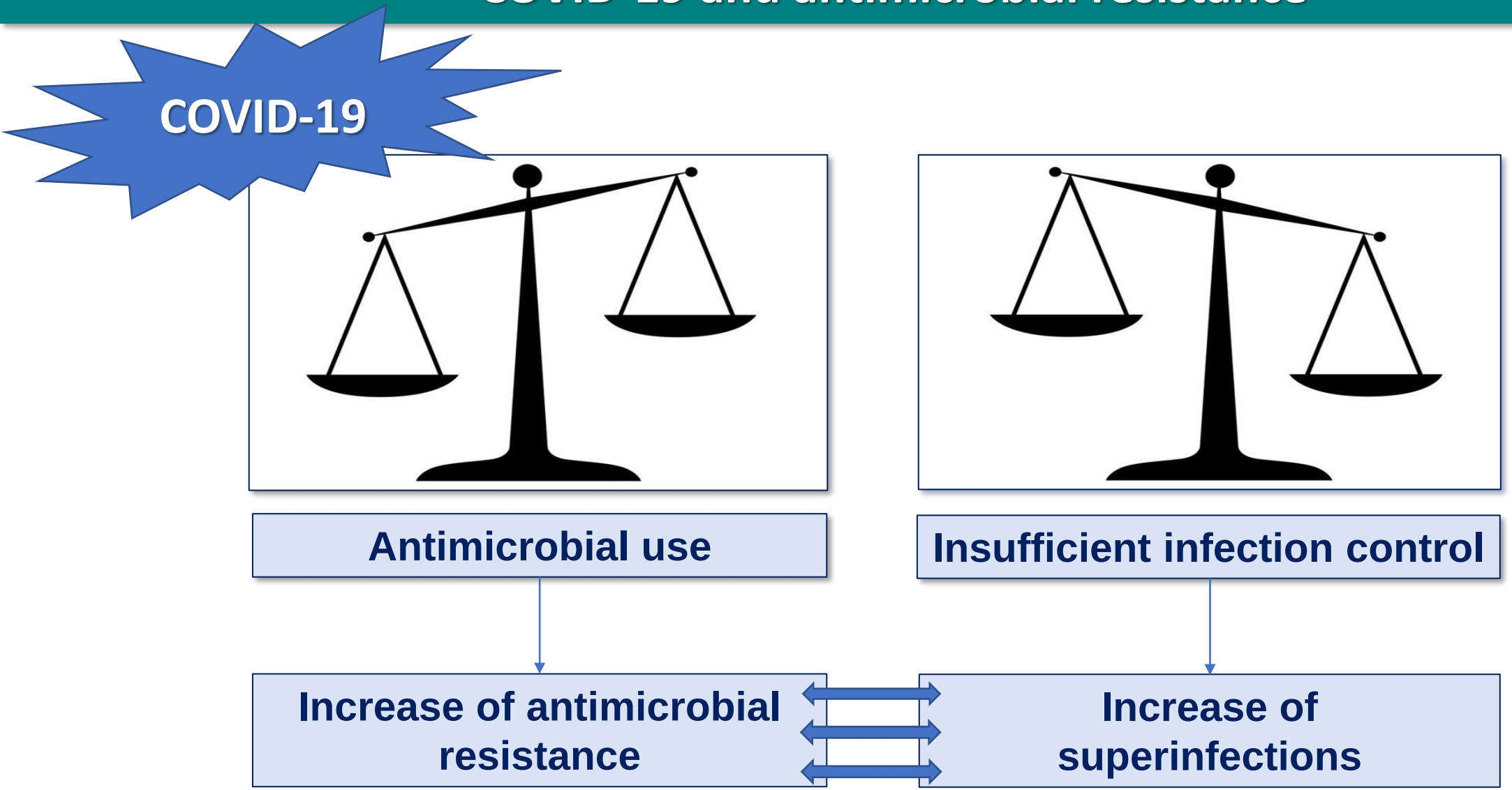
Bradley J. Langford [1,2,*], Miranda So [3,4,5], Sumit Raybardhan [6], Valerie Leung [1,7], Duncan Westwood [8], Derek R. MacFadden [9], Jean-Paul R. Soucy [10], Nick Daneman [1,4,8,11]

Clinical Microbiology and Infection 26 (2020) 1622–1629

Indicator	Proportion of patients (95% CI)
Bacterial coinfection (at admission)	3.5 (0.4-6.7)
Secondary infection (during admission)	14.3 (9.6-18.9)
Overall infections	**6.9 (4.3-9.5)**
Antibiotic use	**71.9 (56.1-87.7)**

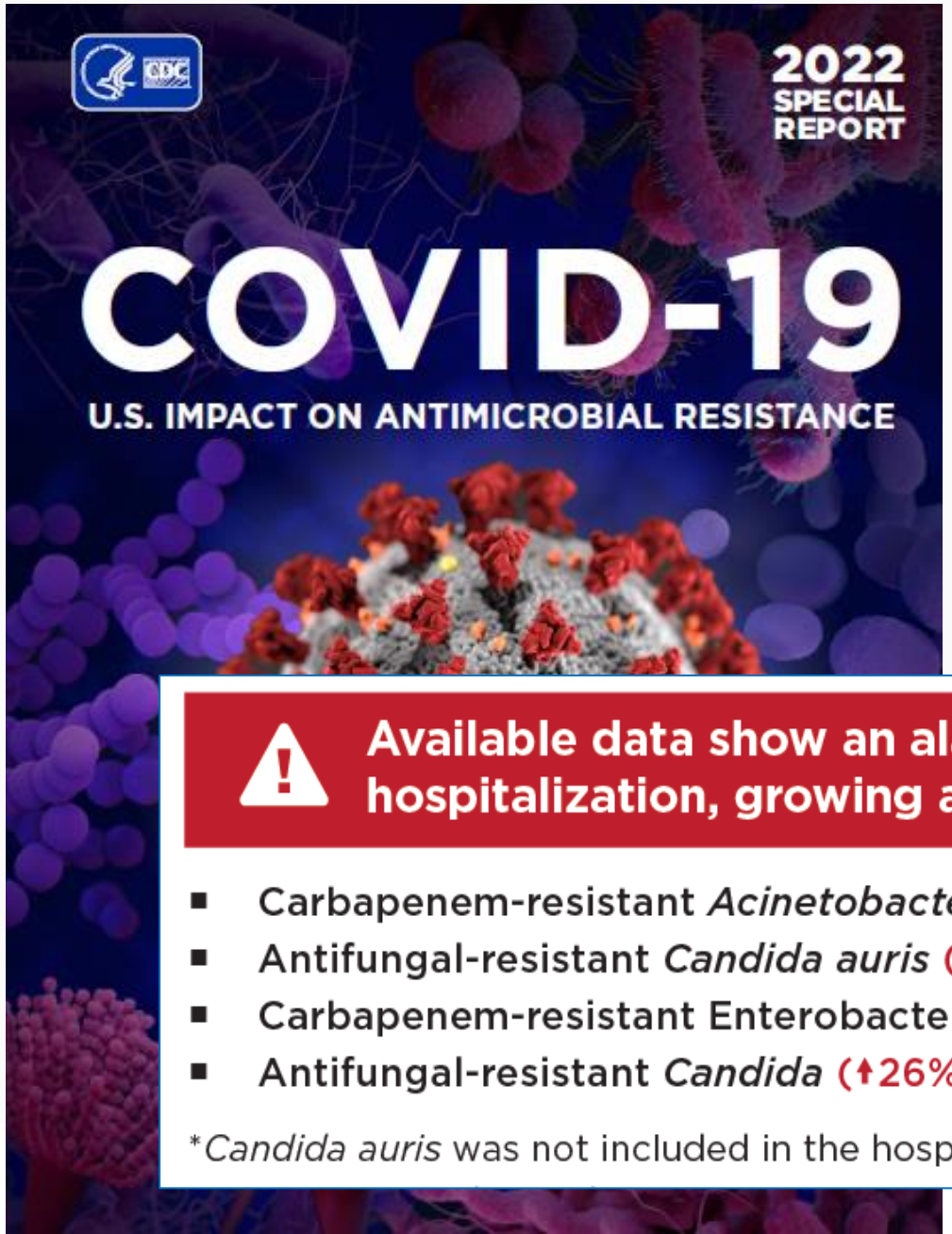
Excess of antimicrobial use!

COVID-19 and antimicrobial resistance



Cantón R, et al. Curr Opin Crit Care. 2020; 26:433-41; Ruiz-Garbajosa P, Cantón R. Rev Esp Quimioter. 2021; 34 (Suppl 1):63-8

Antibiotic resistance and COVID-19



https://www.cdc.gov/drugresistance/pdf/covid19-impact-report-508.pdf

Available data show an alarming increase in resistant infections starting during hospitalization, growing at least 15% from 2019 to 2020.

- Carbapenem-resistant *Acinetobacter* (↑78%)
- Antifungal-resistant *Candida auris* (↑60%)*
- Carbapenem-resistant Enterobacterales (↑35%)
- Antifungal-resistant *Candida* (↑26%)
- ESBL-producing Enterobacterales (↑32%)
- Vancomycin-resistant Enterococcus (↑14%)
- Multidrug-resistant *P. aeruginosa* (↑32%)
- Methicillin-resistant *Staphylococcus aureus* (↑13%)

**Candida auris* was not included in the hospital-onset rate calculation of 15%.

Multi-drug resistant microorganisms

WHO priority list of pathogens to guide research and development of new antibiotics

Priority 1: CRITICAL#

Acinetobacter baumannii, carbapenem-resistant

Pseudomonas aeruginosa, carbapenem-resistant

Enterobacteriaceae*, carbapenem-resistant, 3rd generation cephalosporin-resistant

Priority 2: HIGH

Enterococcus faecium, vancomycin-resistant

Staphylococcus aureus, methicillin-resistant, vancomycin intermediate and resistant

Helicobacter pylori, clarithromycin-resistant

Campylobacter, fluoroquinolone-resistant

Salmonella spp., fluoroquinolone-resistant

Neisseria gonorrhoeae, 3rd generation cephalosporin-resistant, fluoroquinolone-resistant

Priority 3: MEDIUM

Streptococcus pneumoniae, penicillin-non-susceptible

Haemophilus influenzae, ampicillin-resistant

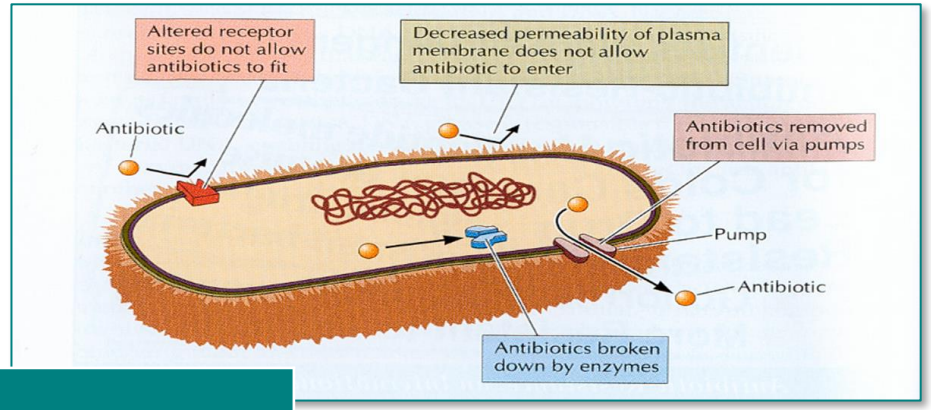
Shigella spp., fluoroquinolone-resistant

Tacconelli and Magrini, 25 Feb 2017

World Health Organization

Antibacterial agents in clinical development: an analysis of the antibacterial clinical development pipeline, including tuberculosis. Geneva: World Health Organization; 2017 (WHO/EMP/IAU/2017.11). https://www.who.int/medicines/publications/WHO-PPL-Short_Summary_25Feb-ET_NM_WHO.pdf

Carbapenem resistant microorganisms



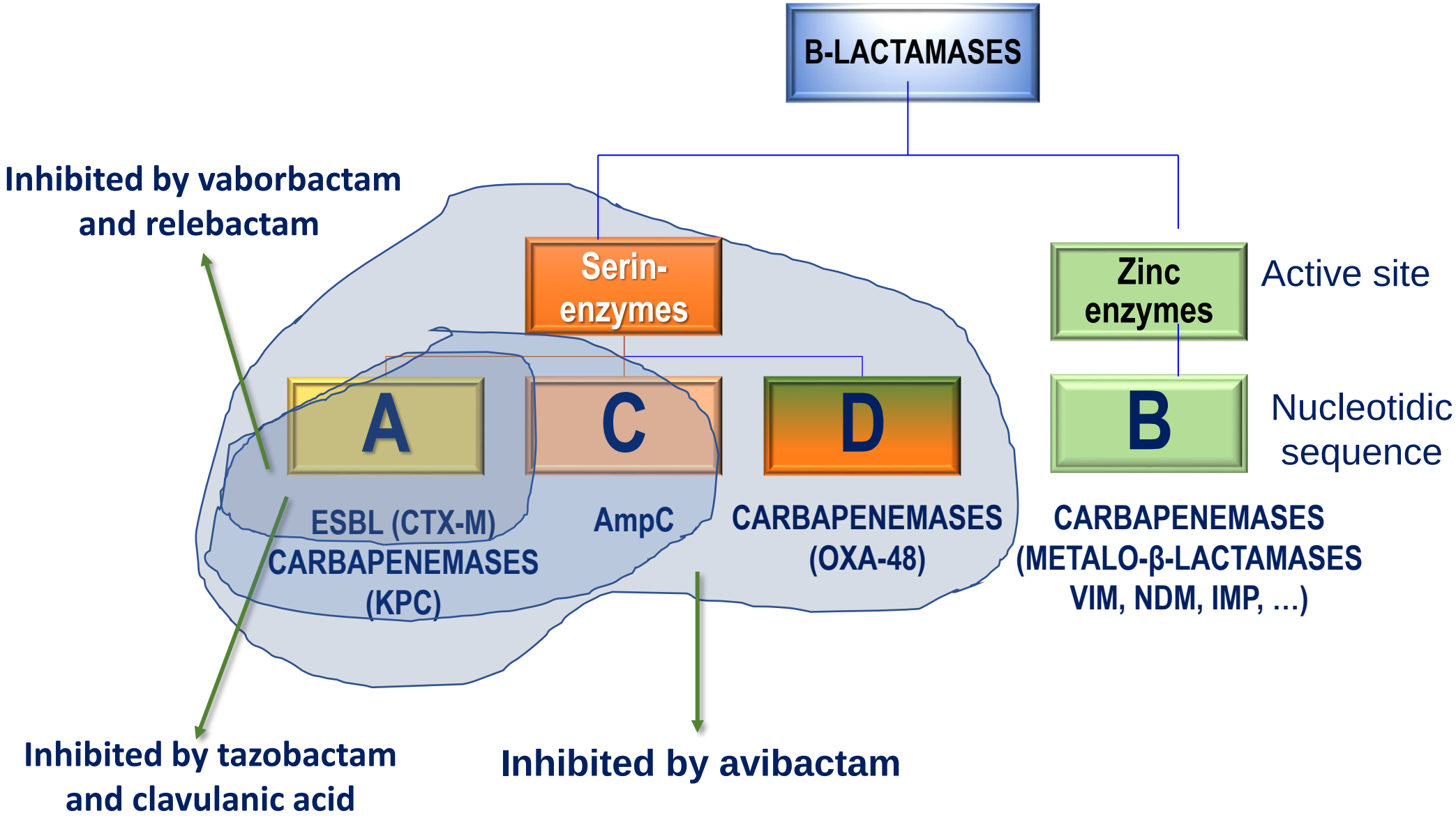
Relative contribution of different resistance mechanism in carbapenem resistance in different pathogens

Microorganisms	Porin deficiency	Porin deficiency + ESBL	PBP modifications	Eflux pumps overexpresion	Carbapenemases
Enterobacterales		√			√√√
Pseudomonas aeruginosa	√√		√	√√	√√
Acinetobacter baumannii	√		√	√	√√√
Stenotrophomonas maltophilia	√			√√	√√√

ESBL: extended spectrum β-lactamase; CP: carbapenemase

Information obtained from Eichenberger EM, Thaden JT. Antibiotics 2019 Apr 6;8(2):37; Gil-Gil T, et al. Anti Infect Ther 2020; 18:335-47; Glen KA, Lamont IL. Pathogens 2021 Dec 18;10(12):1638; Mancuso G, et al. Pathogens 2021 Oct 12;10(10):1310; Kyriakidis I et al. Pathogens. 2021 Mar 19;10(3):373; Lepe JA, Martínez-Martínez L. Med Intensiva 2022; 46:392-402; Canton R et al. Expert Rev Anti Infect Ther 2022; 20:1077-94

Carbapenemases and β-lactamase inhibitors



Information obtained from Bush & Bradford. Cold Spring Harb Perspect Med. 2016; 6(8). pii: a025247; Bush & Bradford Nat Rev Micobiol 2019; 17:295-306

Carbapenemases and β-lactamase inhibitors

- Inhibit the enzymatic action of β-lactamases
- Marketed in association with β-lactam antibiotics depending on the type of enzyme to be inhibited and their pharmacokinetics
- In general, they act as suicide inhibitors:
  - β-lactamases hydrolyse the inhibitors leaving the β-lactam to act
- There is no universal β-lactamase inhibitor
- Used in the laboratory to recognize the different enzymes

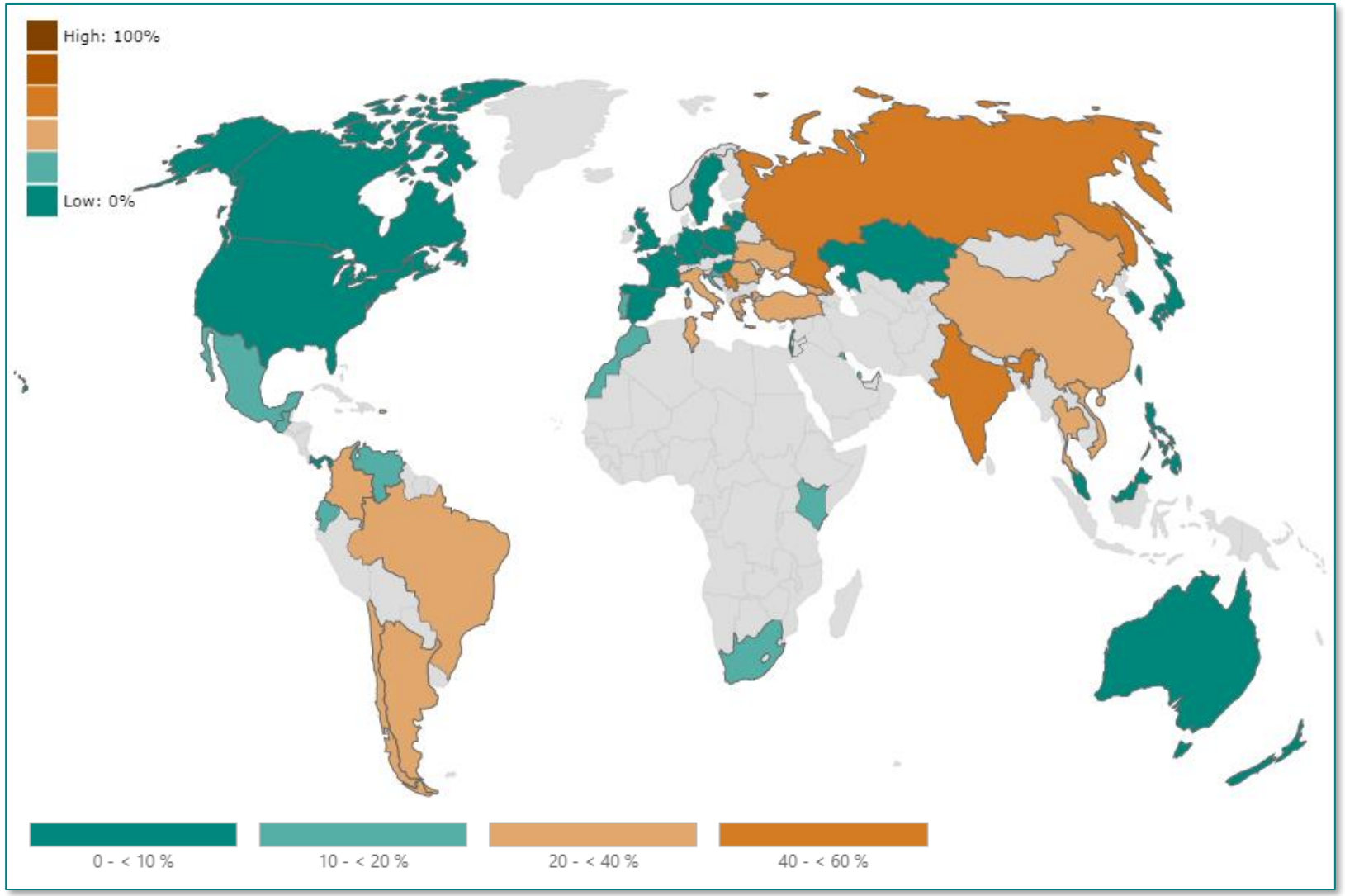
β-lactamase inhibitor	A		C	D		B
	ESBL	CP (KPC)	AmpC	ESBL	CP (OXA-48)	CP (VIM, NDM)
Clavulanic ac.	+++	-	-	-	-	-
Sulbactam	++	-	-	-	-	-
Tazobactam	+++	-	+ / -	-	-	-
Avibactam	+++	+++	++	++ / -	++	-
Vaborbactam	+++	+++	++	-	-	-
Relebactam	+++	+++	++	-	-	-
ANT431	-	-	-	-	-	++
Taniborbactam	+++	+++	++	+++	+++	++/+

ESBL: extended spectrum β-lactamase; CP: carbapenemase

Information obtained from Bush & Bradford Nat Rev Micobiol 2019; 17:295-306

Carbapenem (meropenem) resistant *K. pneumoniae* – SMART database

Non-susceptible heatmap for meropenem resistance in *K. pneumoniae* (n = 10015) in 2019. CLSI criteria

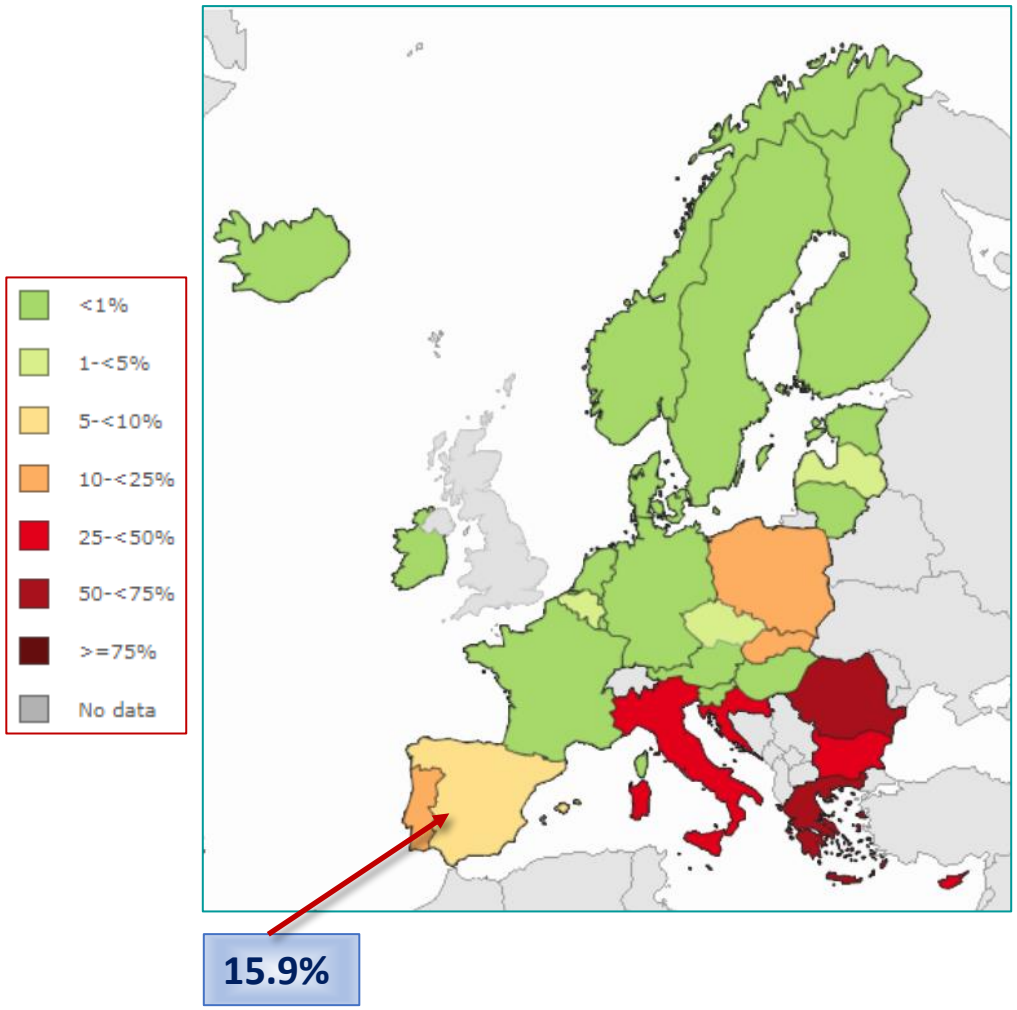


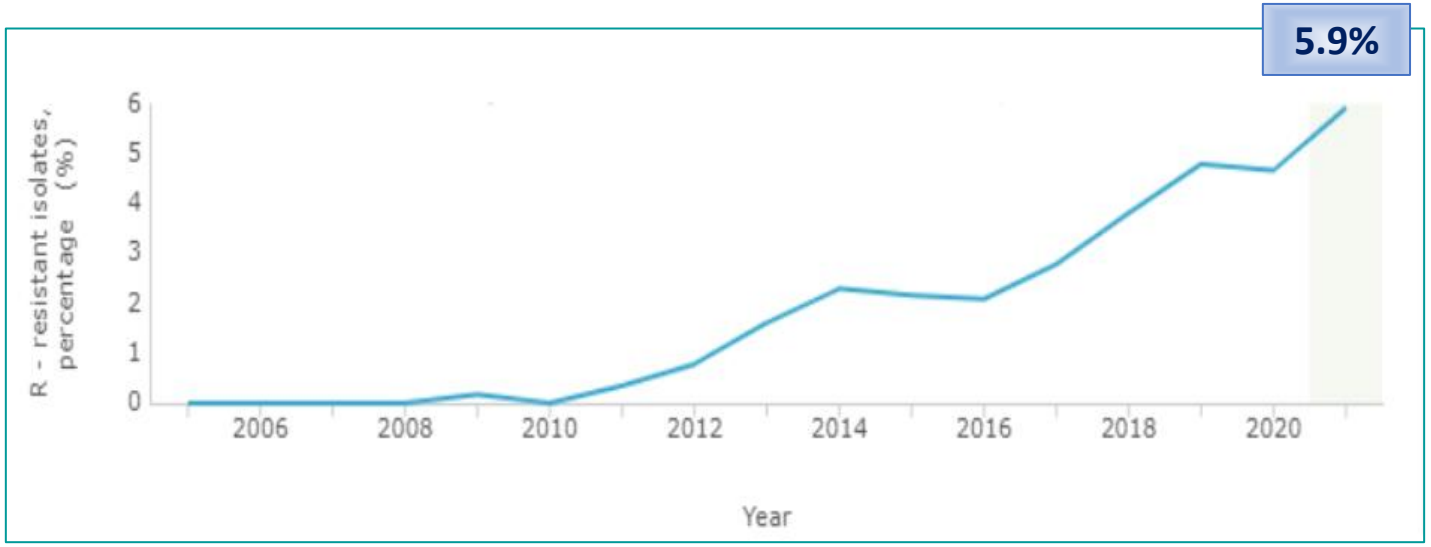
SMART
Study for Monitoring Antimicrobial Resistance Trends

https://globalsmartsite.com/#/heatmaps

Klebsiella pneumoniae (invasive isolates, EARS-net, 2005-2021)

% of carbapenem resistant isolates



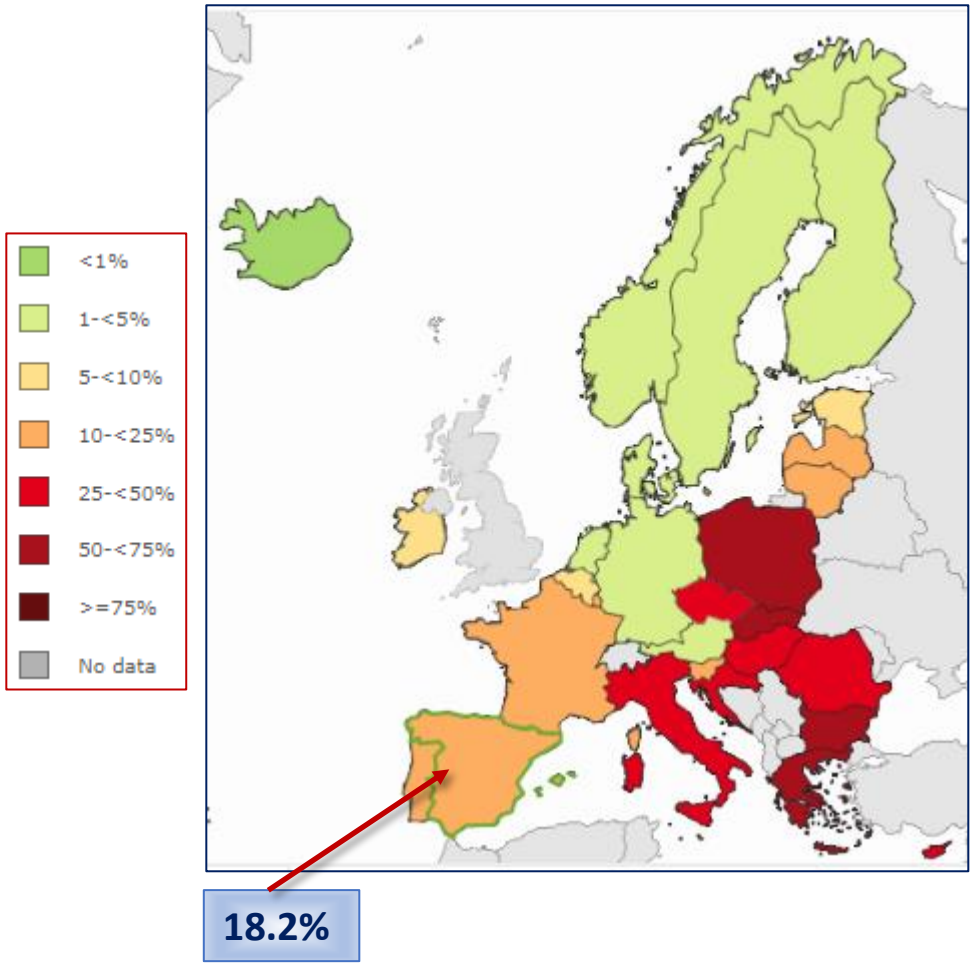


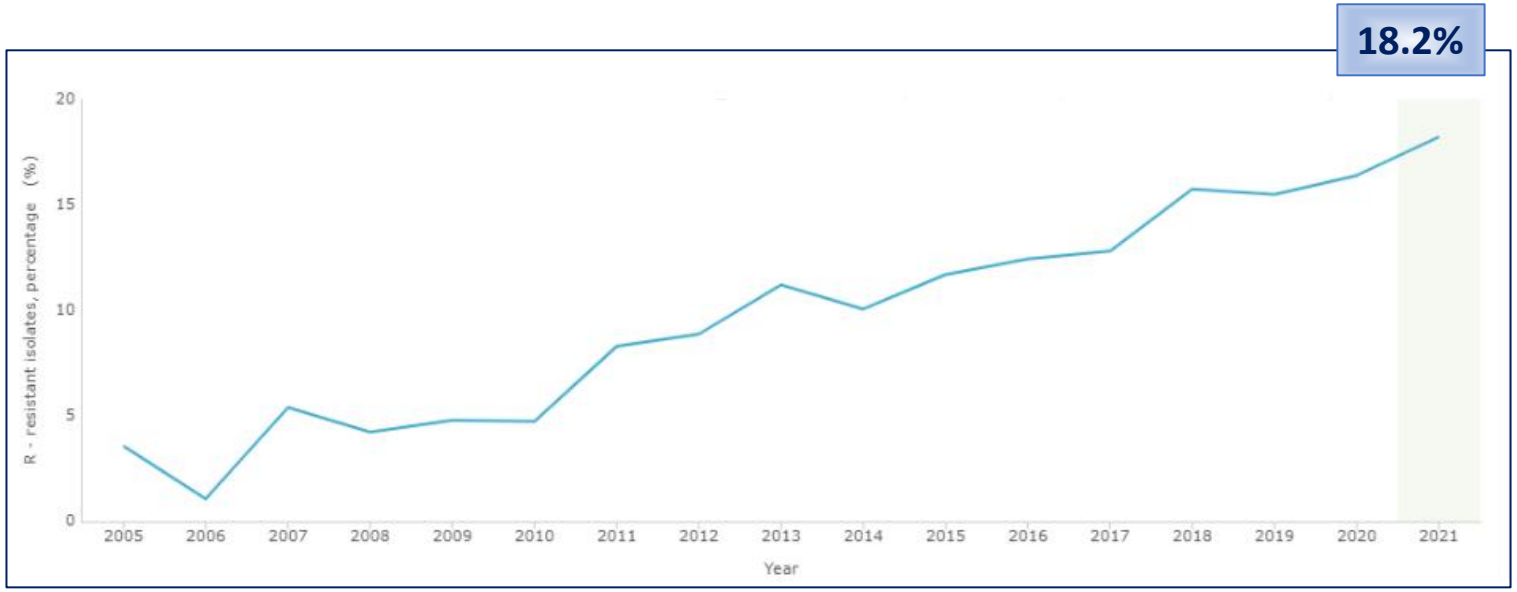
Data obtained from https://www.ecdc.europa.eu/en/antimicrobial-resistance/surveillance-and-disease-data/data-ecdc [Accessed 20/11/2022]

Klebsiella pneumoniae (invasive isolates, EARS-net, 2005-2021)

% of MDR* isolates

(R ≥3 antimicrobials: piper/tazob, ceftazidime, fluoroquinolones, aminoglycosides and/or carbapenems)





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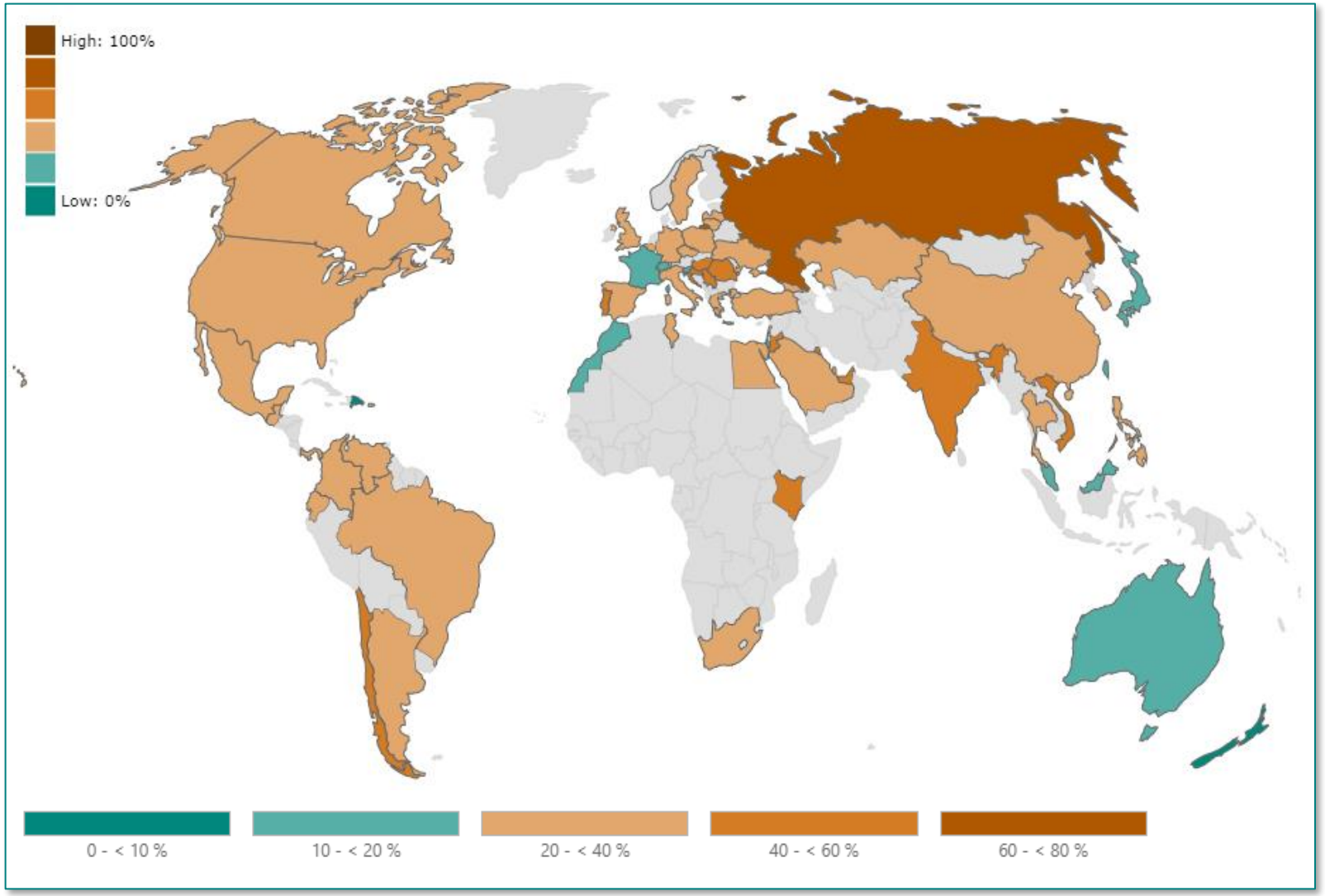
Carbapenem (meropenem) resistant *P. aeruginosa* – SMART database

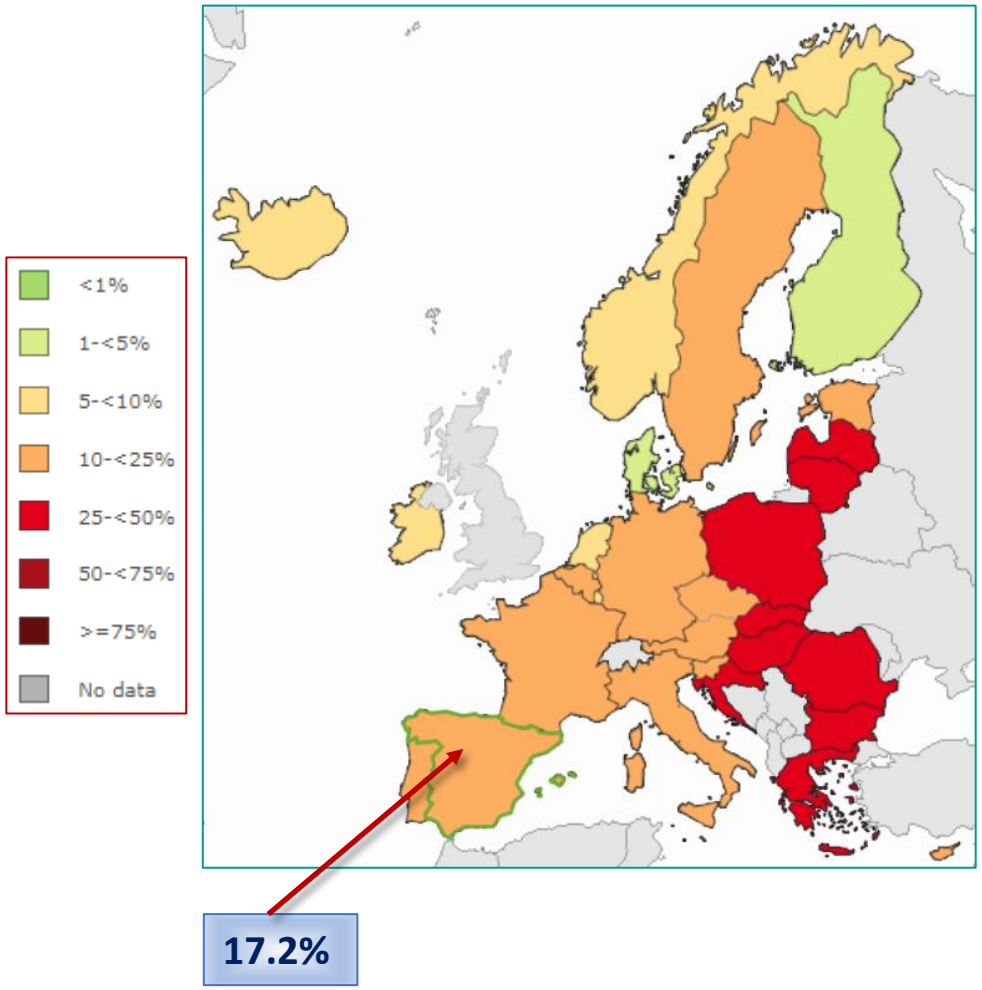
Non-susceptible heatmap for meropenem resistance in *P. aeruginosa* (n = 10015) in 2019. CLSI criteria

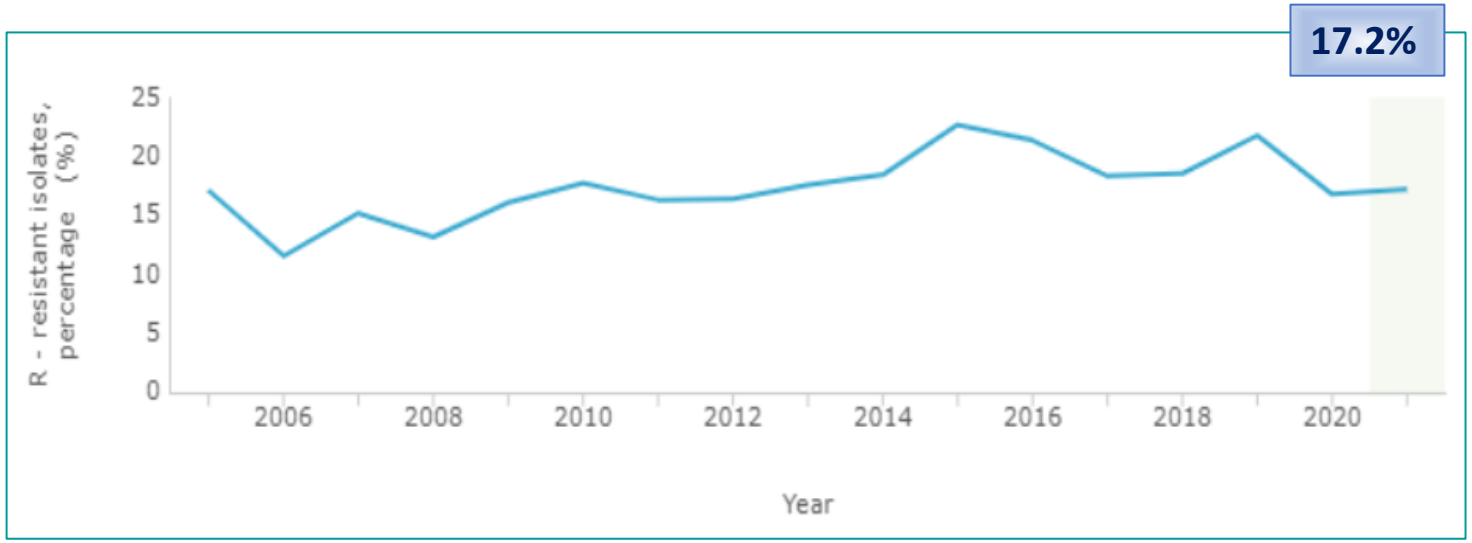


https://globalsmartsite.com/#/heatmaps

Pseudomonas aeruginosa (invasive isolates, EARS-net, 2005-2021)

% of carbapenem resistant isolates





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Pseudomonas aeruginosa (invasive isolates, EARS-net, 2005-2021)

% of MDR* isolates

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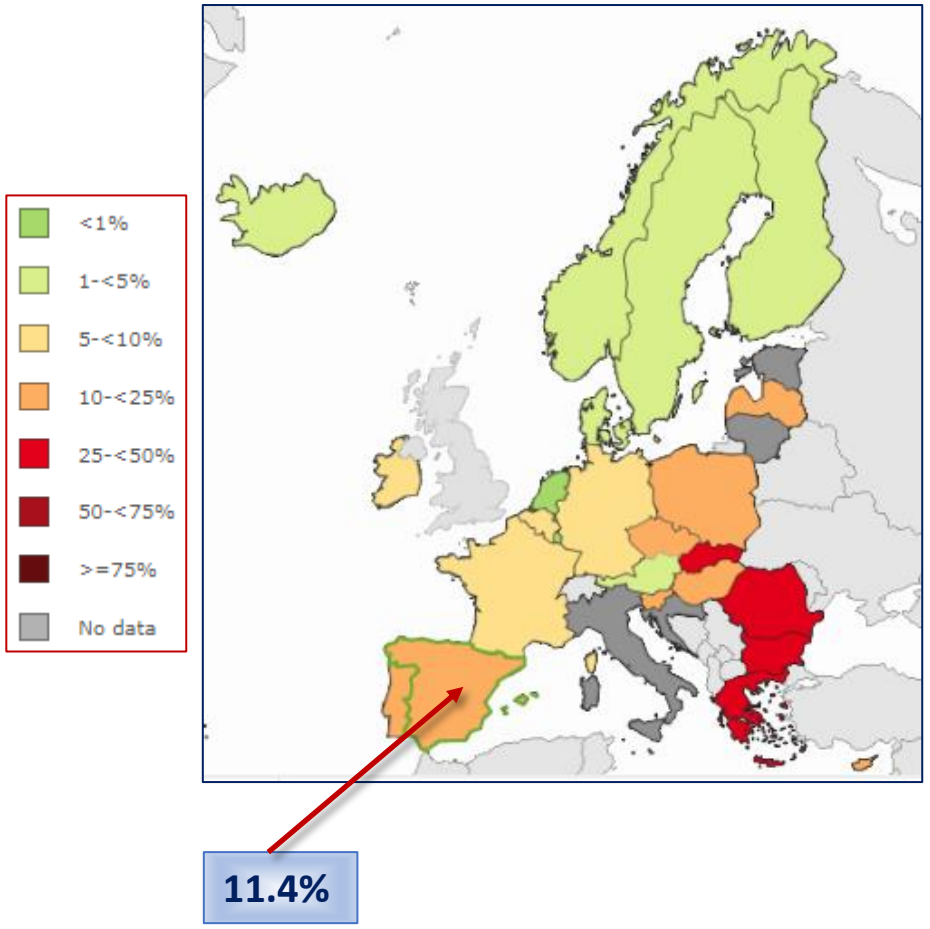
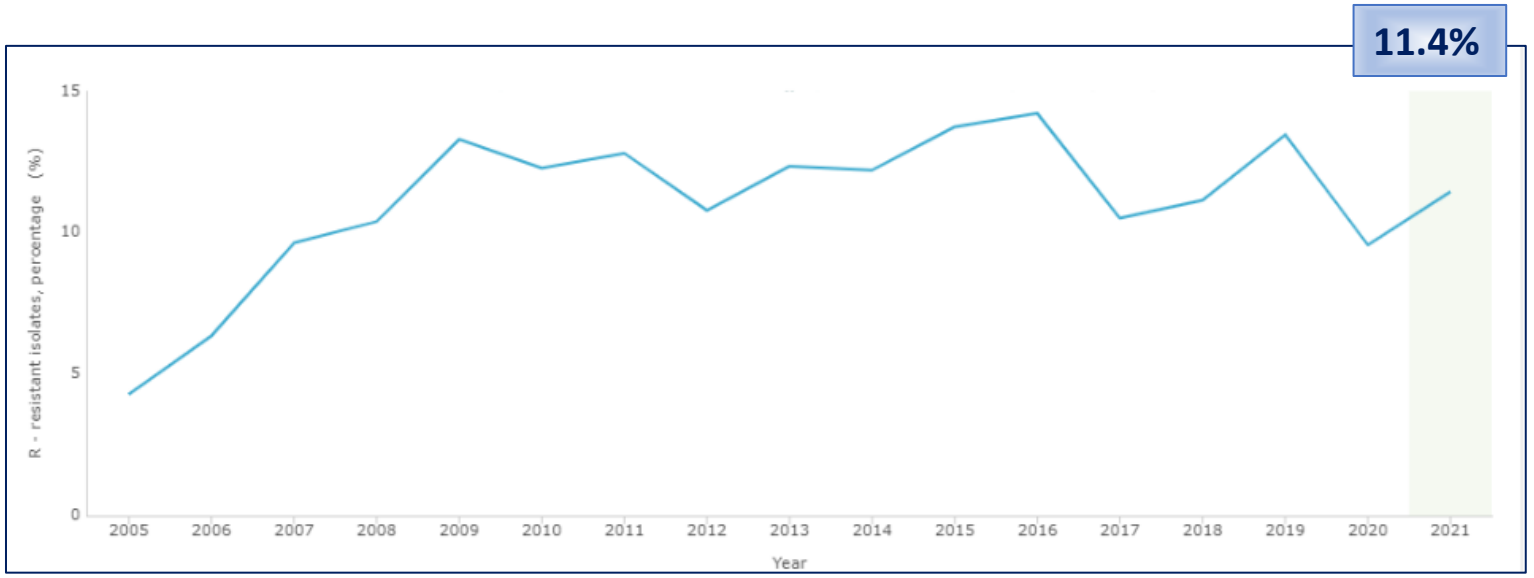
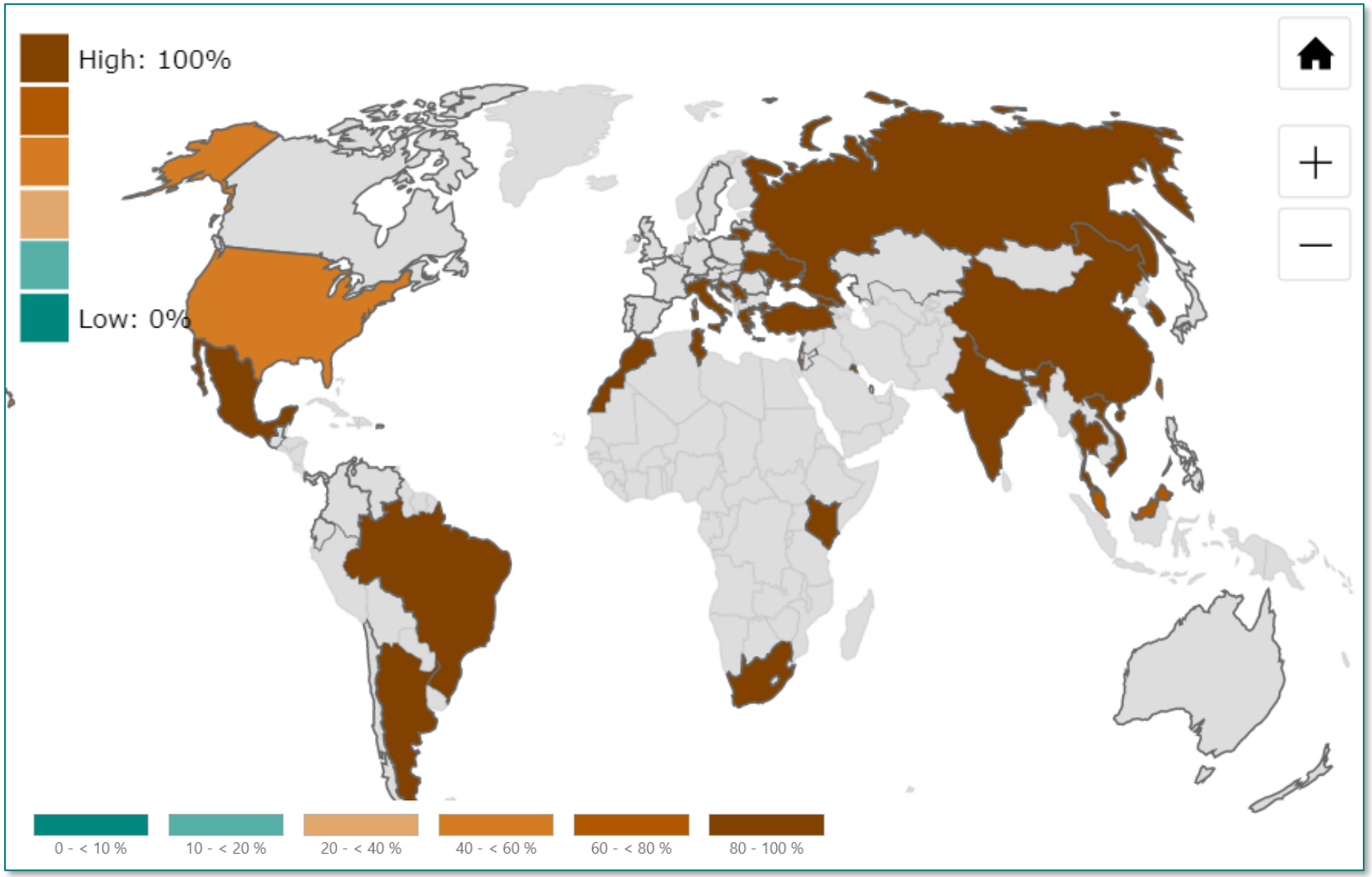




Data obtained from https://www.ecdc.europa.eu/en/antimicrobial-resistance/surveillance-and-disease-data/data-ecdc [Accessed 20/11/2022]

Carbapenem (meropenem) resistant *A. baumannii* – SMART database

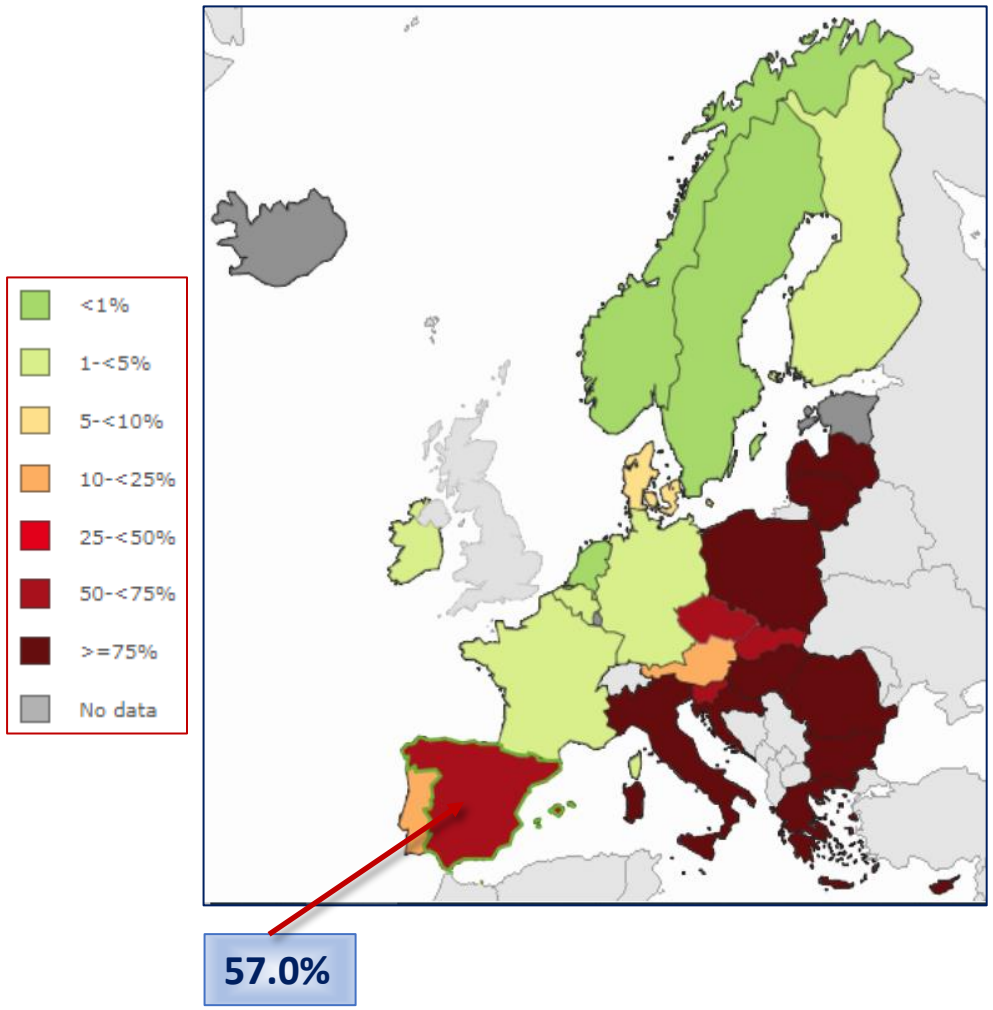
Non-susceptible heatmap for meropenem resistance in *A. baumannii* (n = 2553) in 2019. CLSI criteria

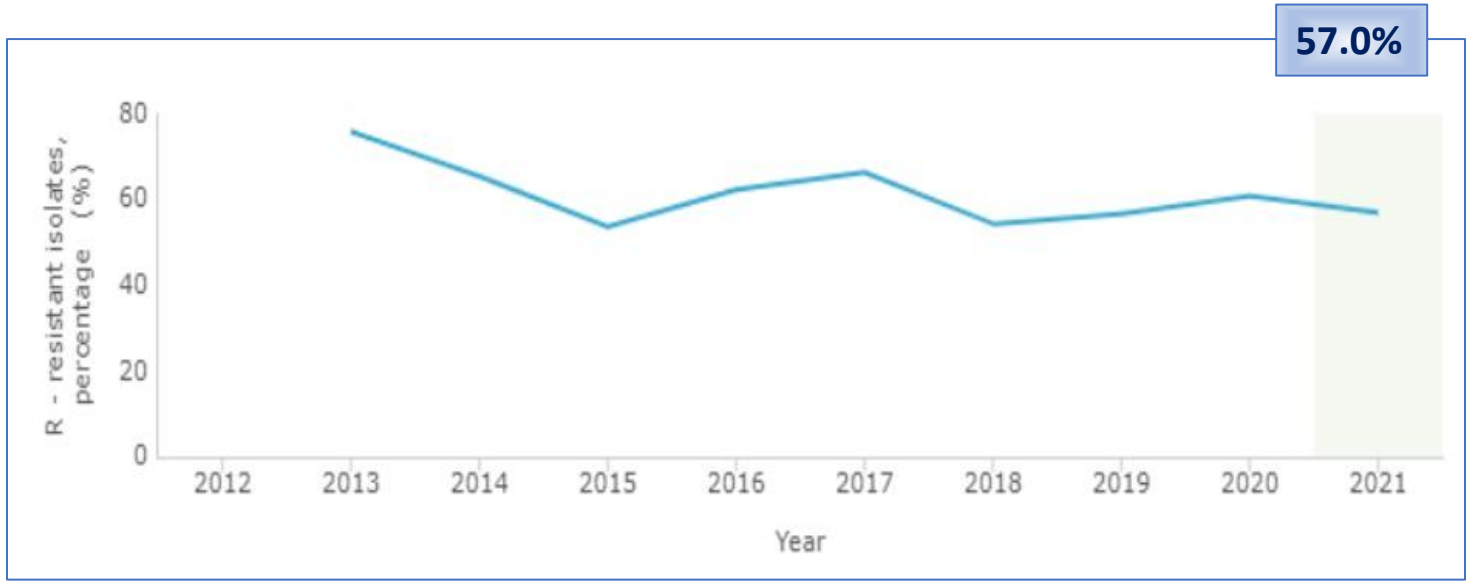


https://globalsmartsite.com/#/heatmaps

Acinetobacter baumannii (invasive isolates, EARS-net, 2013-2021)

% of carbapenem resistant isolates



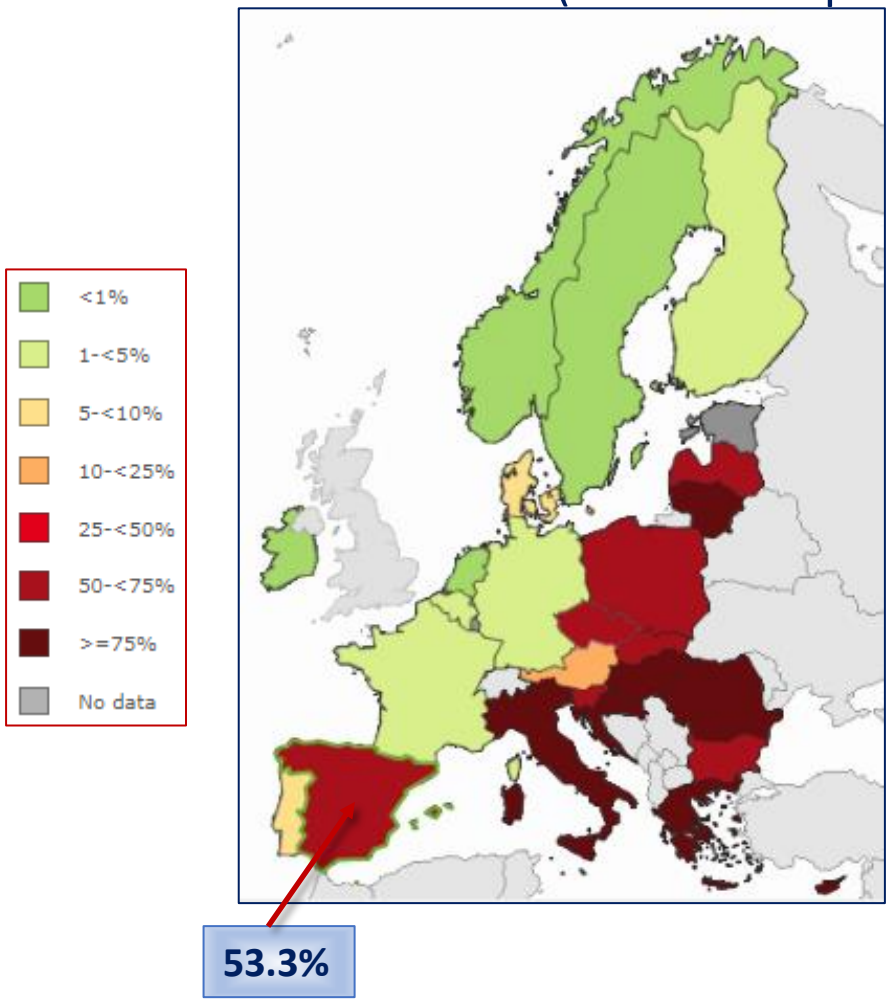


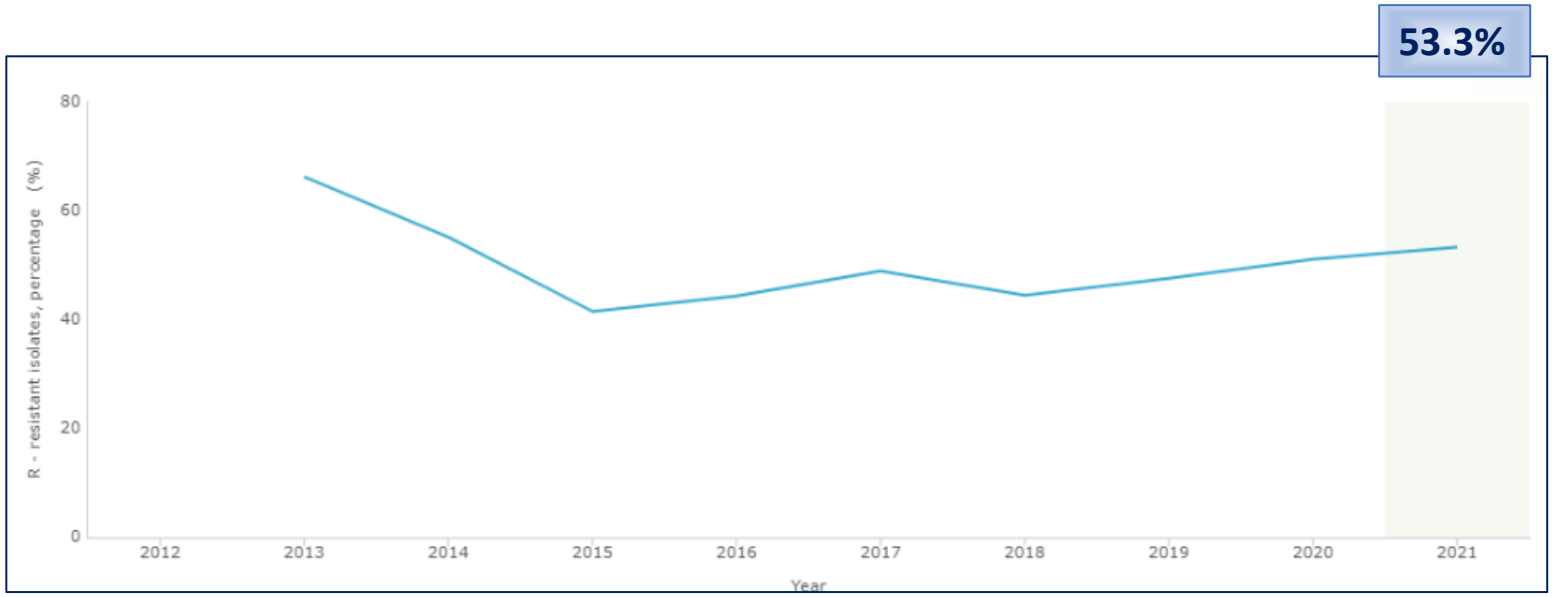
Data obtained from https://www.ecdc.europa.eu/en/antimicrobial-resistance/surveillance-and-disease-data/data-ecdc [Accessed 20/11/2022]

Acinetobacter baumannii (invasive isolates, EARS-net, 2013-2021)

% of MDR* isolates

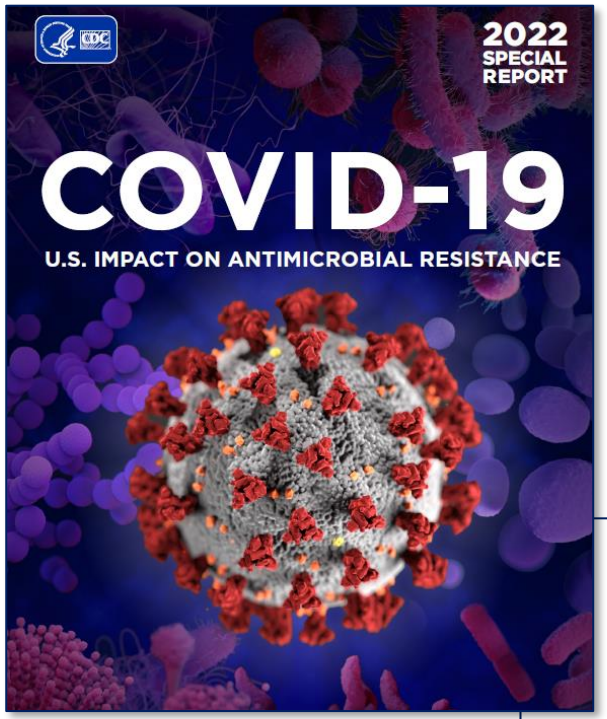
(R ≥3 fluoroquinolones, aminoglycosides and/or carbapenems)



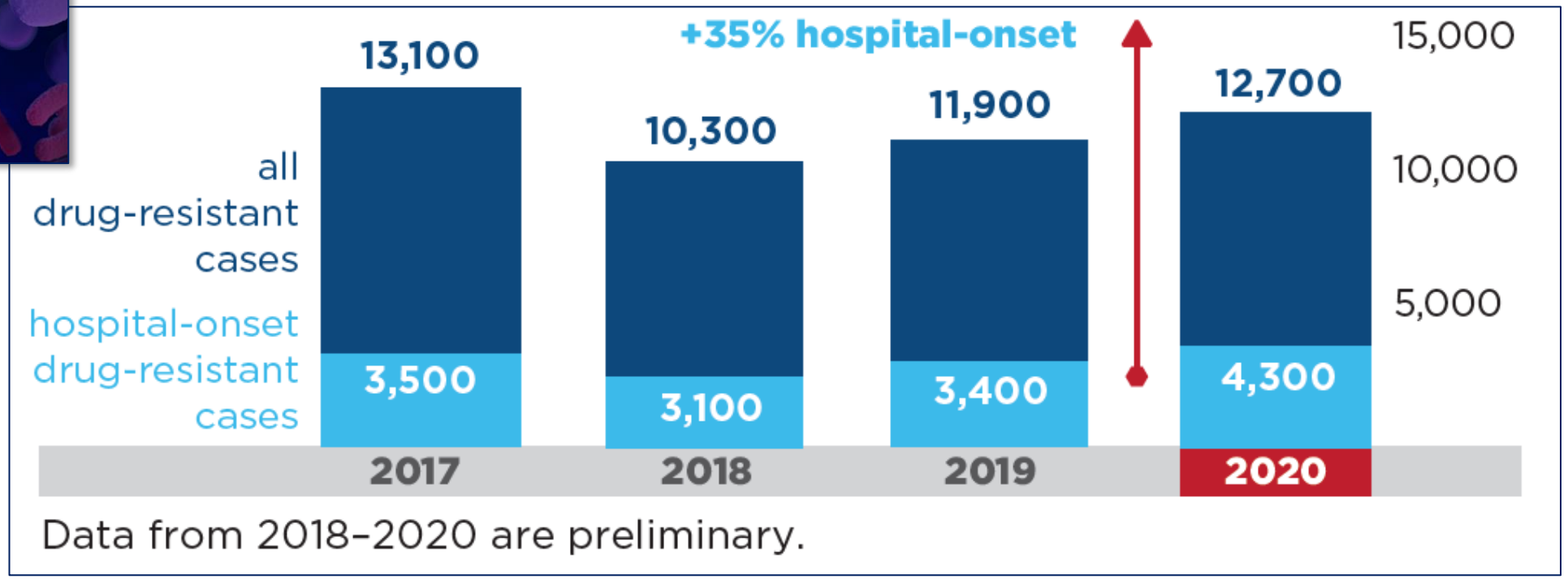


Data obtained from https://www.ecdc.europa.eu/en/antimicrobial-resistance/surveillance-and-disease-data/data-ecdc [Accessed 20/11/2022]

Carbapenem resistant Enterobacterales (CRE)



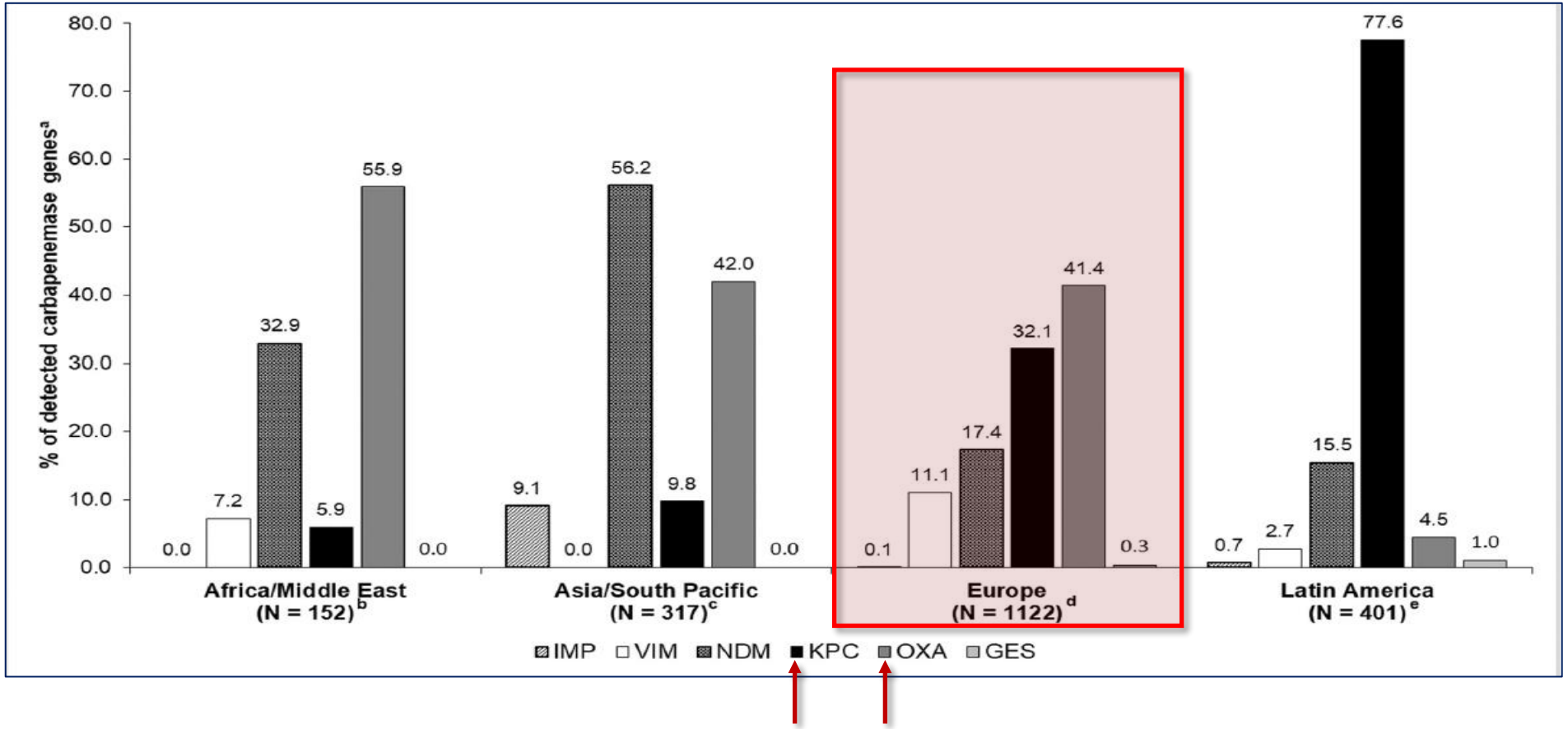
- The **rate of CRE cases** declined significantly from 2017 to 2018, but began to rise again in 2019 and continued into 2020 (↑ 35% hospital-onset) due to **challenges created by the pandemic**



CDC. COVID-19: U.S. Impact on Antimicrobial Resistance, Special Report 2022. Atlanta, GA: US Department of Health and Human Services, CDC; 2022. https://www.cdc.gov/drugresistance/covid19.html

Carbapenemase distribution in Enterobacterales: pre-COVID-19 pandemic

Carbapenemase genes (%) in carbapenemase-producing Enterobacterales isolates
(Atlas program 2016-2018)



Kiratisin P et al. Journal of Global Antimicrobial Resistance. 2021; 27:132-41

Carbapenemase-producing *Enterobacterales* infections in COVID-19 patients

Carbapenemase-producing *Enterobacterales* infections in COVID-19 patients

Infect Dis (Lond) 2022; 54:36-45

Vicente Pintado[a], Patricia Ruiz-Garbajosa[b], Rosa Escudero-Sanchez[a], Francesca Gioia[a], Sabina Herrera[a], Pilar Vizcarra[a], Jesús Fortún[a], Javier Cobo[a], Pilar Martín-Dávila[a], María Isabel Morosini[b], Rafael Cantón[b] and Santiago Moreno[a]

- **More frequent CPE infections** in COVID-19 patients (1.1 vs. 0.5%, p=0.005).
- COVID-19 patients were younger, had lower frequency of underlying diseases (p=0.01), and lower median Charlson score (p=0.002) than controls
- **Predisposing factors**: antimicrobial use, mechanical ventilation, ICU admission (p<0.05).
- More frequent
  - hospital acquired infections (UTI, 47.9%; pneumonia, 23.3%) diagnosed at the ICU (p<.001)
  - severe sepsis or shock (p=0.01) with higher median SOFA score (p<0.04)
  - overall 30-d mortality rate 30% vs 16.7% (p=0.25).
- CPE: *K. pneumoniae* (80.8%), *S. marcescens* (11%) and *E. cloacae* (4.1%)
- **Carbapenemases**: KPC 56.2% OXA-48 26% and VIM 17.8%)

Impact of COVID-19 on antimicrobial resistance

Journal of Clinical Medicine
J. Clin. Med. 2021, 10, 2067. https://doi.org/10.3390/jcm10102067
MDPI

Review

Carbapenem-Resistant *Klebsiella pneumoniae* Infections in ICU COVID-19 Patients—A Scoping Review

Wioletta Mędrzycka-Dąbrowska [1,*], Sandra Lange [2], Katarzyna Zorena [3], Sebastian Dąbrowski [4], Dorota Ozga [5] and Lucyna Tomaszek [6]

antibiotics
Antibiotics 2021, 10, 561. https://doi.org/10.3390/antibiotics10050561
MDPI

Case Report

Carbapenem-Resistant *Klebsiella pneumoniae* Associated with COVID-19

Irina Magdalena Dumitru [1,2,3,*], Mirela Dumitrascu [1], Nicoleta Dorina Vlad [1,3], Roxana Carmen Cernat [1,2], Carmen Ilie-Serban [1], Aurelia Hangan [1,2], Raluca Elena Slujitoru [1], Aura Gherghina [1], Corina Mitroi-Maxim [1], Licdan Curtali [1], Dalia Sorina Carp [1], Anca Dumitrescu [1], Romelia Mitan [1], Rodica Lesanu [1] and Sorin Rugina [1,2,3,4,5]

Journal of Clinical Medicine
J. Clin. Med. 2020, 9, 2744; doi:10.3390/jcm9092744
MDPI

Article

Antimicrobial Stewardship Program, COVID-19, and Infection Control: Spread of Carbapenem-Resistant Klebsiella Pneumoniae Colonization in ICU COVID-19 Patients. What Did Not Work?

Beatrice Tiri [1], Emanuela Sensi [2], Viola Marsiliani [2], Mizar Cantarini [2], Giulia Priante [3], Carlo Vernelli [3], Lucia Assunta Martella [3], Monya Costantini [4], Alessandro Mariottini [5], Paolo Andreani [5], Paolo Bruzzone [6], Fabio Suadoni [7], Marsilio Francucci [8], Roberto Cirocchi [9] and Stefano Cappanera [1,*]

antibiotics
Antibiotics 2021, 10, 1127. https://doi.org/10.3390/antibiotics10091127
MDPI

Article

A Study in a Regional Hospital of a Mid-Sized Spanish City Indicates a Major Increase in Infection/Colonization by Carbapenem-Resistant Bacteria, Coinciding with the COVID-19 Pandemic

Estefanía Cano-Martín [1], Inés Portillo-Calderón [2], Patricia Pérez-Palacios [2], José María Navarro-Marí [3], María Amelia Fernández-Sierra [1] and José Gutiérrez-Fernández [3,4,*]

Infection and Drug Resistance
Dovepress
open access to scientific and medical research
Open Access Full Text Infection and Drug Resistance 2021:14 1855–1863
ORIGINAL RESEARCH

Shift in the Dominant Sequence Type of Carbapenem-Resistant *Klebsiella pneumoniae* Bloodstream Infection from ST11 to ST15 at a Medical Center in Northeast China, 2015–2020

J Antimicrob Chemother
doi:10.1093/jac/dkaa466
Journal of Antimicrobial Chemotherapy

Carbapenemase-producing Enterobacterales causing secondary infections during the COVID-19 crisis at a New York City hospital

Angela Gomez-Simmonds[1], Medini K. Annavajhala[1], Thomas H. McConville[1], Donald E. Dietz[1], Sherif M. Shoucri[1], Justin C. Laracy[1], Felix D. Rozenberg[1], Brian Nelson[1], William G. Greendyke[1], E. Yoko Furuya[1], Susan Whittier[2] and Anne-Catrin Uhlemann[1*]

Journal Pre-proof

Outbreak of ceftazidime-avibactam resistant KPC-producing *Klebsiella pneumoniae* in a COVID-19 Intensive Care Unit, Italy: urgent need for updating diagnostic protocols of surveillance cultures

J Hosp Infect. 2022 Feb 6:S0195-6701(22)00038-X.

Gabriele Bianco[1], Matteo Boattini[1,2], Alessandro Bondi[1,2], Sara Comini[1,2], Teresa Zaccaria[1], Rossana Cavallo[1,2], Cristina Costa[1,2]

- Changing epidemiology during COVID-19

  Increased prevalence of
  - carbapenemase producing *K. pneumoniae* high-risk clones
  - KPC carbapenemases, including KPC-variants

Emergence of KPC-variants ceftazidime/avibactam resistant

Multiple evolutionary trajectories conferring resistance to ceftazidime/avibactam due to amino acid substitutions, insertions, and deletions in the Ω-loop of KPC-3 β-lactamase

```
KPC-31  GDTTFRLDRW--ELELNSAIPGDARYTSS--PRAVTESLQKLTLGSALAAPQRQQFVDWLKGNTTGNHRIRAAVPADWAVGDKTGTCGVYGTANDYAVVWPTGRAPIVLAVYTRAPNKDD------KYSEAVIAAAARLALEGLGVNGQ
KPC-70  GDTTFRLDRW--ELELNSAIPGDARYTSS--PRAVTESLQKLTLGSALAAPQRQQFVDWLKGNTTGNHRIRAAVPADWAVGDKTGTCGVYGTANDYAVVWPTGRAPIVLAVYARAPNKDD------KYSEAVIAAAARLALEGLGVNGQ
KPC-49  GDTTFRLDSW--ELELNSAIPGDARDTSS--PRAVTESLQKLTLGSALAAPQRQQFVDWLKGNTTGNHRIRAAVPADWAVGDKTGTCGVYGTANDYAVVWPTGRAPIVLAVYTRAPNKDD------KYSEAVIAAAARLALEGLGVNGQ
KPC-39  GDTTFRLDRW--ELELNSTIPGDARDTSS--PRAVTESLQKLTLGSALAAPQRQQFVDWLKGNTTGNHRIRAAVPADWAVGDKTGTCGVYGTANDYAVVWPTGRAPIVLAVYTRAPNKDD------KYSEAVIAAAARLALEGLGVNGQ
KPC-66  GDTTFRLDRW--EL--NSAIPGDARDTSS--PRAVTESLQKLTLGSALAAPQRQQFVDWLKGNTTGNHRIRAAVPADWAVGDKTGTCGVYGTANDYAVVWPTGRAPIVLAVYTRAPNKDD------KYSEAVIAAAARLALEGLGVNGQ
KPC-69  GDTTFRLDRWGLELELNSAIPGDARDTSS--PRAVTESLQKLTLGSALAAPQRQQFVDWLKGNTTGNHRIRAAVPADWAVGDKTGTCGVYGTANDYAVVWPTGRAPIVLAVYTRAPNKDD------KYSEAVIAAAARLALEGLGVNGQ
KPC-68  GDTTFRLDRW--ELELNSAIPGDARDTSSSSPRAVTESLQKLTLGSALAAPQRQQFVDWLKGNTTGNHRIRAAVPADWAVGDKTGTCGVYGTANDYAVVWPTGRAPIVLAVYTRAPNKDD------KYSEAVIAAAARLALEGLGVNGQ
KPC-67  GDTTFRLDRW--ELELNSAIPGDARDTSS--PRAVTESLQKLTLGSALAAPQRQQFVDWLKGNTTGNHRIRAAVPADWAVGDKTGTCGVYGTANDYAVVWPTGRAPIVLAVYTRAPNKDDKDDKDDKYSEAVIAAAARLALEGLGVNGQ
KPC-29  GDTTFRLDRW--ELELNSAIPGDARDTSS--PRAVTESLQKLTLGSALAAPQRQQFVDWLKGNTTGNHRIRAAVPADWAVGDKTGTCGVYGTANDYAVVWPTGRAPIVLAVYTRAPNKDDKDD---KYSEAVIAAAARLALEGLGVNGQ
KPC-3   GDTTFRLDRW--ELELNSAIPGDARDTSS--PRAVTESLQKLTLGSALAAPQRQQFVDWLKGNTTGNHRIRAAVPADWAVGDKTGTCGVYGTANDYAVVWPTGRAPIVLAVYTRAPNKDD------KYSEAVIAAAARLALEGLGVNGQ
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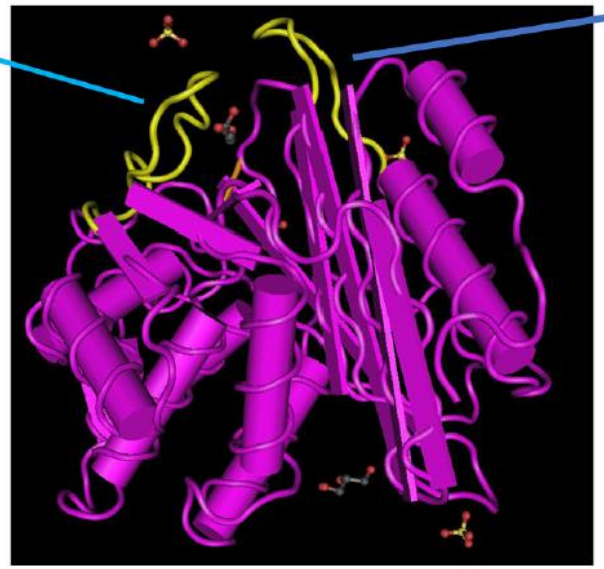


Carattoli A et al. Antimicrob Agents Chemother. 2021; 65(10):e0057421

Emergence of KPC-variants with resistance to new antimicrobials

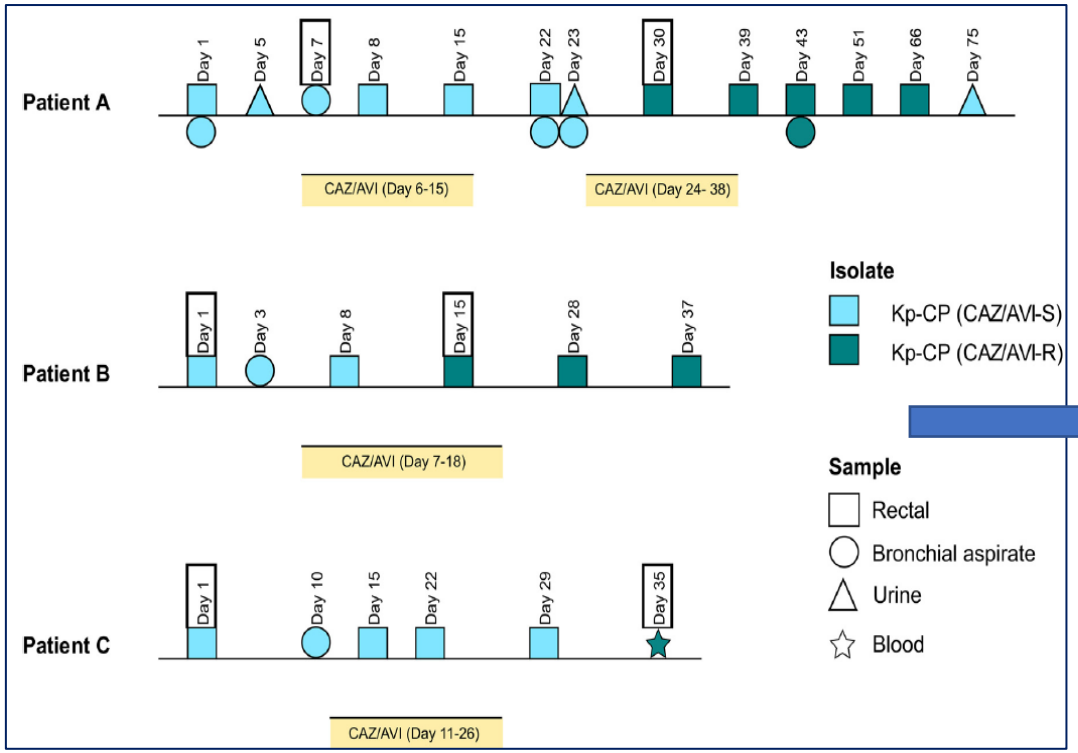
AMERICAN SOCIETY FOR MICROBIOLOGY | Journal of Clinical Microbiology®

EPIDEMIOLOGY

March 2022 Volume 60 Issue 3 e02245-21

Impact of Ceftazidime-Avibactam Treatment in the Emergence of Novel KPC Variants in the ST307-*Klebsiella pneumoniae* High-Risk Clone and Consequences for Their Routine Detection

Marta Hernández-García,[a,b,c] Juan Antonio Castillo-Polo,[a,c] Desirée Gijón Cordero,[a,c] Blanca Pérez-Viso,[a,c] María García-Castillo,[a,c] Javier Saez de la Fuente,[d] María Isabel Morosini,[a,c] Rafael Cantón,[a,b,c] Patricia Ruiz-Garbajosa[a,b,c]



Susceptibility to imipenem/relebactam and meropenem/vaborbactam due to **collateral sensitivity** and/or **relebactam and vaborbactam inhibitory activity**

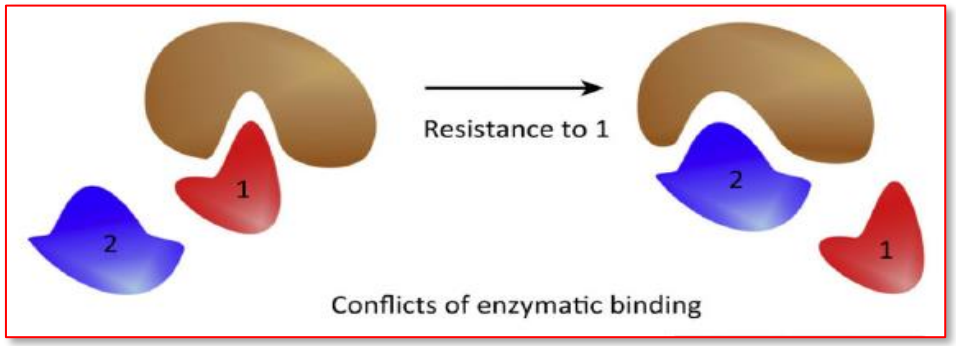
Patient	Sample	KPC	CAZ-AVI	IMP	IMP-REL	MER	MER-VAB	FDC
1	1-1	KPC-3	2/4*	16	0.25/4	8	≤.006/4	0.5
	1-2	**KPC-46**	32/4	≤1	0.25/4	≤.12	≤.006/4	1
2	2-1	KPC-3	2/4	16	0.5/4	>16	≤.006/4	1
	2-2	**KPC-66**	8/4	≤1	0.25/4	≤.12	≤.006/4	2
3	3-1	KPC-3	1/4	16	0.25/4	>16	≤.006/4	1
	3-2	**KPC-92**	8/4	≤1	0.25/4	≤.12	≤.006/4	2

*MIC (mg/L); CAZ-AVI = ceftazidime-avibactam; IMP= imipenem; IMP = imipenem-relebactam
MER = meropenem; MER-VAB = meropenem-vaborbactam: FDC = cefiderocol

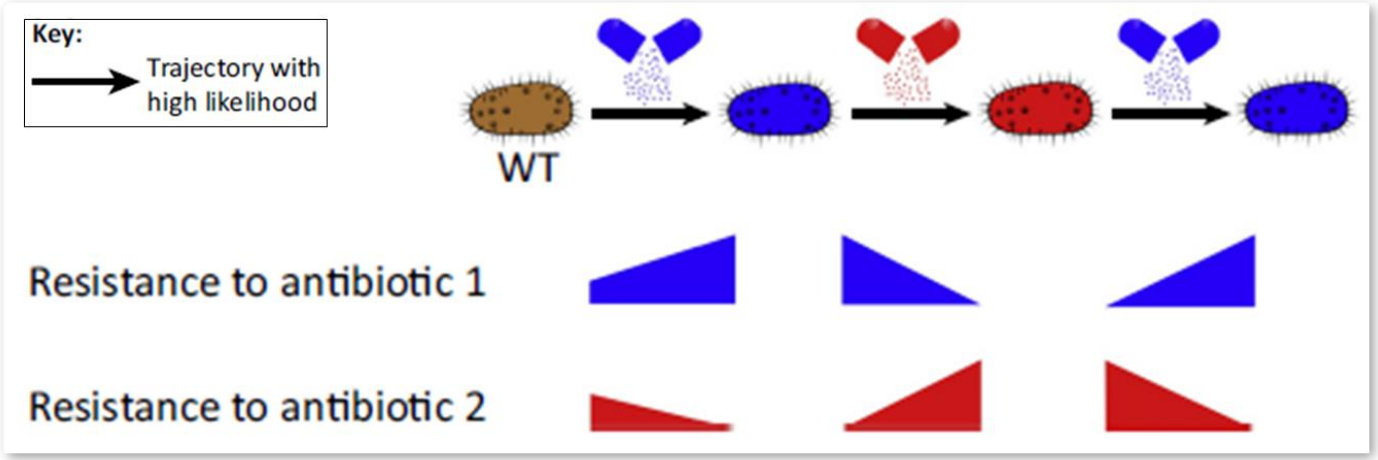
Collateral sensitivity

Collateral sensitivity:

Phenomenon in which an organism that has developed resistance to one drug displays increased sensitivity to a second drug



- Frequently occurs during the **evolution of antibiotic resistance**
- Associated with
  - mutational resistance, including target or enzymatic mutations and those affecting drug uptake and efflux
  - gene expression
- Future clinical applications:
  - drug combinations and cycling strategies



Pál C et al. Trends Microbiol 2015; 23:401
Roemhild R, Andersson DI. PLoS Pathog. 2021; 17(1):e1009172

frontiers in Microbiology

ORIGINAL RESEARCH
published: 10 November 2020
doi: 10.3389/fmicb.2020.589253

First Report of New Delhi Metallo-β-Lactamase-6 (NDM-6) in a Clinical *Acinetobacter baumannii* Isolate From Northern Spain

Kyriaki Xanthopoulou[1,2†], Mikel Urrutikoetxea-Gutiérrez[3†], Matxalen Vidal-Garcia[3], José-Luis Diaz de Tuesta del Arco[3], Sandra Sánchez-Urtaza[4], Julia Wille[1,2], Harald Seifert[1,2], Paul G. Higgins[1,2] and Lucía Gallego[4]*

International Journal of Antimicrobial Agents 59 (2022) 106551

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

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

Molecular characterisation of an outbreak of NDM-7-producing *Klebsiella pneumoniae* reveals ST11 clone expansion combined with interclonal plasmid dissemination

Jesús Machuca[a,*], Lorena Lopez-Cerero[a,b,c,d], Manuel Rodríguez-Maresca[e], Felipe Fernández-Cuenca[a,b,c], Inmaculada López-Hernández[a,b,c], Mercedes Delgado-Valverde[a,b,c], Waldo Sanchez-Yebra[e], Álvaro Pascual[a,b,c,d]

...ew Microbe and New Infect 2020; 34: 100660

Detection of two simultaneous outbreaks of Klebsiella pneumoniae coproducing OXA-48 and NDM-1 carbapenemases in a tertiary-care hospital in Valencia, Spain

B. Fuster[1], N. Tormo[1], C. Salvador[1] and C. Gimeno[1,2]

...ty of Valenci

J Antimicrob Chemother 2019; **74**: 3489–3496
doi:10.1093/jac/dkz366 Advance Access publication 3 September 2019

Journal of Antimicrobial Chemotherapy

Emergence of NDM-producing *Klebsiella pneumoniae* and *Escherichia coli* in Spain: phylogeny, resistome, virulence and plasmids encoding bla_{NDM}-like genes as determined by WGS

María Pérez-Vázquez[1,2]*, Pedr...
Guillermo Ruiz-Carrascoso[2,4], J...
Belén Aracil[1,2], David Sáez[1,2], No...
Robert A. Kingsley[8,9], Gordon Doug...

International Journal of Antimicrobial Agents 59 (2022) 106551

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

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Molecular characterisation of an outbreak of NDM-7-producing *Klebsiella pneumoniae* reveals ST11 clone expansion combined with interclonal plasmid dissemination

Jesús Machuca[a,*], Lorena Lopez-Cerero[a,b,c,d], Manuel Rodríguez-Maresca[e], Felipe Fernández-Cuenca[a,b,c], Inmaculada López-Hernández[a,b,c], Mercedes Delgado-Valverde[a,b,c], Waldo Sanchez-Yebra[e], Álvaro Pascual[a,b,c,d]

J Antimicrob Chemother 2021; **76**: 345–354
doi:10.1093/jac/dkaa459 Advance Access publication 17 November 2020

Journal of Antimicrobial Chemotherapy

Dissemination of NDM-producing *Klebsiella pneumoniae* and *Escherichia coli* high-risk clones in Catalan healthcare institutions

Marta Marí-Almirall[1]†, Clara Cosgaya[1]†, Cristina Pitart[2]†, Joaquim Viñes[3,4], Laura Muñoz[1], Irene Campo[2], Anna Cuscó[4], Laura Rodríguez-Serna[5], Gemina Santana[5], Ana Del P...o[6], Olga Francino[3], Pilar Ciruela[7,8], Isabel Pujol[9,10], Frederic Ballester[11], Francesc Marco[1,2], José Anto...rtínez[6], Álex Soriano[6], Jordi Vila[1,2] and Ignasi Roca[1*] ...half of th... ...T Study Group†

Emergence and dispersion of NDM-producing high-risk clones, including health-care extrahospitalary settings

Enterobacterales with several carbapenemases

frontiers | Frontiers in Microbiology

ORIGINAL RESEARCH
published: 30 June 2022
doi: 10.3389/fmicb.2022.918362

CARB-ES-19 Multicenter Study of Carbapenemase-Producing *Klebsiella pneumoniae* and *Escherichia coli* From All Spanish Provinces Reveals Interregional Spread of High-Risk Clones Such as ST307/OXA-48 and ST512/KPC-3

Javier E. Cañada-García[1†], Zaira Moure[1†], Pedro J. Sola-Campoy[1], Mercedes Delgado-Valverde[2,3], María E. Cano[4], Desirèe Gijón[3,5], Mónica González[3,6], Irene Gracia-Ahufinger[3,7], Nieves Larrosa[3,8], Xavier Mulet[3,9], Cristina Pitart[10], Alba Rivera[11], Germán Bou[3,6], Jorge Calvo[3,4], Rafael Cantón[3,5], Juan José González-López[3,8], Luis Martínez-Martínez[3,7,12], Ferran Navarro[11], Antonio Oliver[3,9], Zaira R. Palacios-Baena[2,3,13], Álvaro Pascual[2,3,13], Guillermo Ruiz-Carrascoso[14], Jordi Vila[3,10], Belén Aracil[1,3], María Pérez-Vázquez[1,3‡], Jesús Oteo-Iglesias[1,3‡] and the GEMARA/GEIRAS-SEIMC/REIPI CARB-ES-19 Study Group[§]*

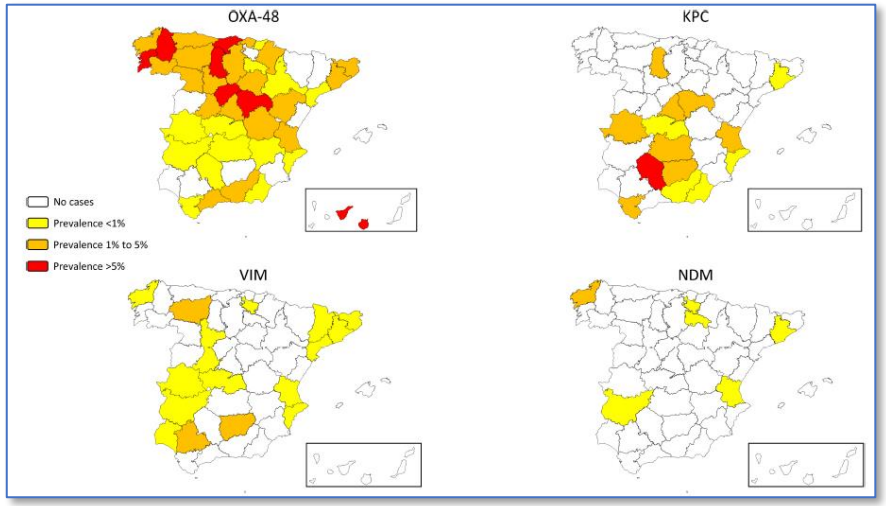
- 377 *K. pneumoniae* isolates (Feb-May 2019)

bla_{OXA-48}	69.8%
bla_{KPC-3}	16.4%
bla_{VIM-1}	7.4%
bla_{NDM-1}	3.2%
Others	5.5%

8 isolates (2.1%) with two carbapenemases →

- 2 OXA-48 + VIM-1
- 2 OXA-48 + KPC
- 1 OXA-48 + NDM-1
- 1 VIM-1 + NDM-1
- 1 NDM-1 + GES-2
- 1 VIM-1 + NDM-3

Prevalence of carbapenemase-producing *K. pneumoniae* according to carbapenemase groups



Antibiotic susceptibility of 377 carbapenemase-producing *K. pneumoniae* isolates

Antibiotic	Susceptibility (%)		
	OXA-48-group-producing isolates (*n* = 262)	KPC-group-producing isolates (*n* = 72)	MBL-group-producing isolates (*n* = 37)
Cefiderocol*	95.8	86.1	94.6
Plazomicin*	93.5	98.6	86.5
Colistin	92.4	81.9	91.9
Meropenem/vaborbactam*	89.3	100	73
Ceftazidime/avibactam	95.4	90.3	0
Imipenem/relebactam*	75.2	100	56.7
Amikacin	86.6	33.3	56.8
Imipenem	68.3	13.9	43.2
Meropenem	64.9	13.9	45.9
Gentamicin	47.3	48.6	32.4
Trimethoprim/sulfamethoxazole	34.7	6.9	13.5
Tobramycin	32.8	9.7	8.1
Aztreonam	17.6	0	27
Cefepime*	16.8	0	0
Ceftazidime	15.3	0	0
Ceftolozane/tazobactam	14.1	0	0
Cefotaxime	8.4	0	0
Ciprofloxacin	7.6	1.4	0
Ertapenem	2.3	0	16.2

Cefiderocol: resistance mechanism

Microorganisms	Cefiderocol MIC (MIC or range) (mg/L)	Resistance mechanism	Country (Year of publication)
K. pneumoniae	16 - >32	Mutation of two-component regulation system (BaeSR and OmpR/EnvZ). Mutation of *exbD* (accessory protein related to iron transport)	Japan (2020)
K. pneumoniae *E. coli* *E. cloacae*	4 - >32	KPC β-lactamase mutants	France (2021)
K. pneumoniae	8	KPC β-lactamase mutant (KPC-31)	Italy (2021)
E. cloacae	>16	AmpC R2 loop deletion	USA (2020)
E. cloacae	≥256	Mutations in *cir*A gene	Germany (2021)
P. aeruginosa	8	Mutations in *pir*A and deletion in piuA	USA (2021)
A. baumannii *B. multivorans* *P. aeruginosa* *S. maltophilia*	>4	PER and NDM β-lactamase Disruption of iron transport genes (*piu*A, *pir*A and *fiu*A)	Russia, Turkey and USA (2020)
A.baumannii	≥32	Loss of *pir*A and *piu*A	USA (2020)

Gijón Cordero D, Polo Castillo JA, Ruiz Garbajosa P, Cantón R. Antibacterial spectum of cefiderocol. Rev Esp Quimioter 2022; 35(Suppl 2)

Resistance mechanism to new compounds: beta-lactamases

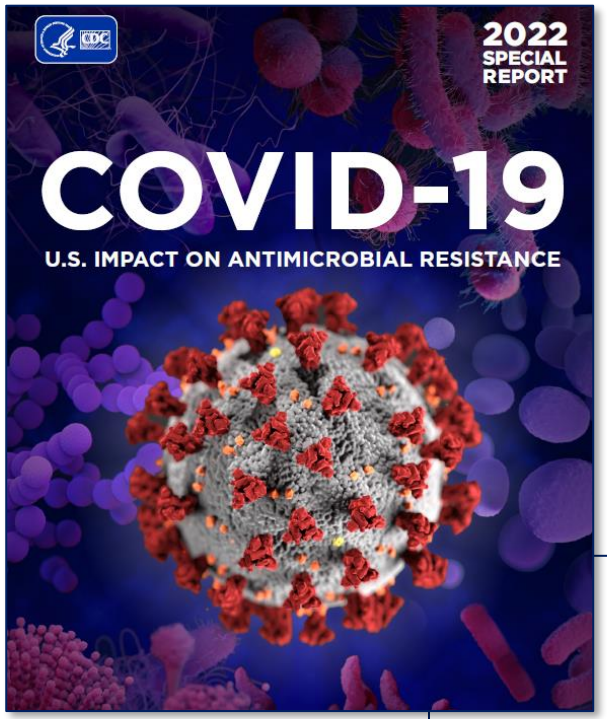
Impact of different beta-lactamases in the susceptibility of new beta-lactams

Microorganisms	Enzyme	C/T	CAZ-AVI	IMP-REL	MER-VAB	FCD
E. coli TOP10	-	0.25*	≤0.125	0.25	0.03	≤0.125
	SHV-12	32	0.5	0.25	0.03	4
	CTX-M-33	4	0.25	0.5	0.03	≤0.125
	GES-1	8	0.25	0.25	0.03	≤0.125
	GES-6	32	2	0.5	0.03	≤0.125
	BEL-2	8	1	0.25	0.03	0.5
	PER-1	64	16	0.5	0.03	4
	GIM-1	16	16	4	0.25	≤0.125
	DIM-1	64	16	2	0.25	≤0.125

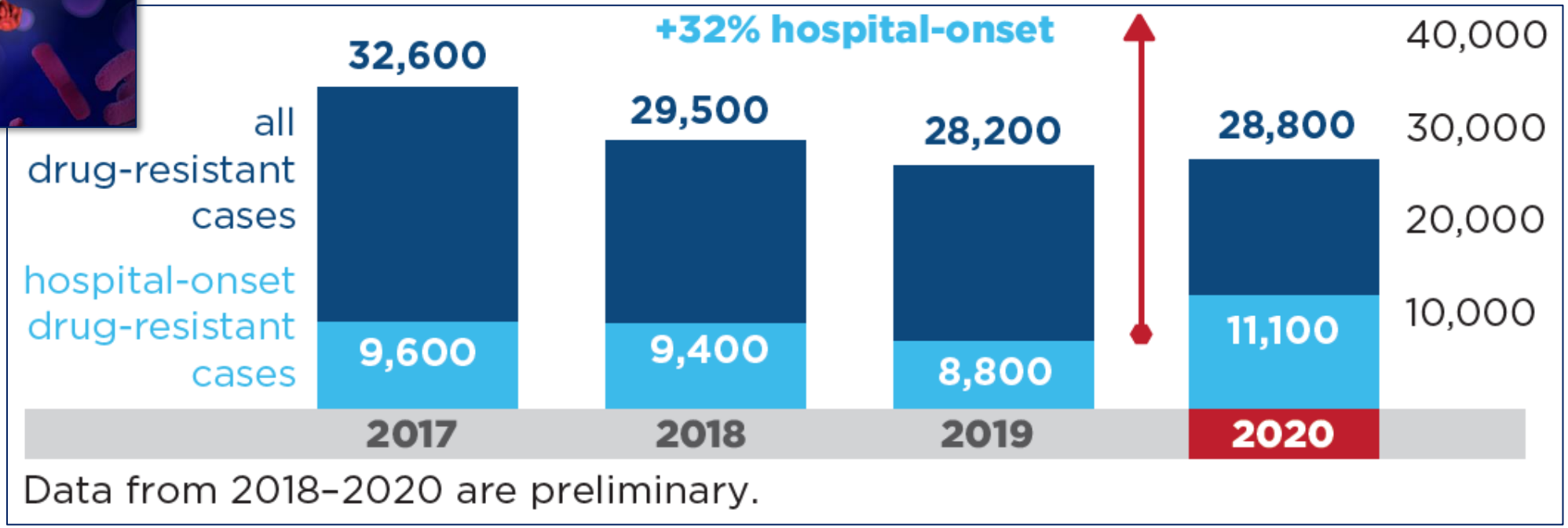
*MIC, mg/L

Poirel L et al. Antimicrob Agents Chemother. 2022 Apr 19;66(4):e0003922

Multi-drug resistant *Pseudomonas aeruginosa*



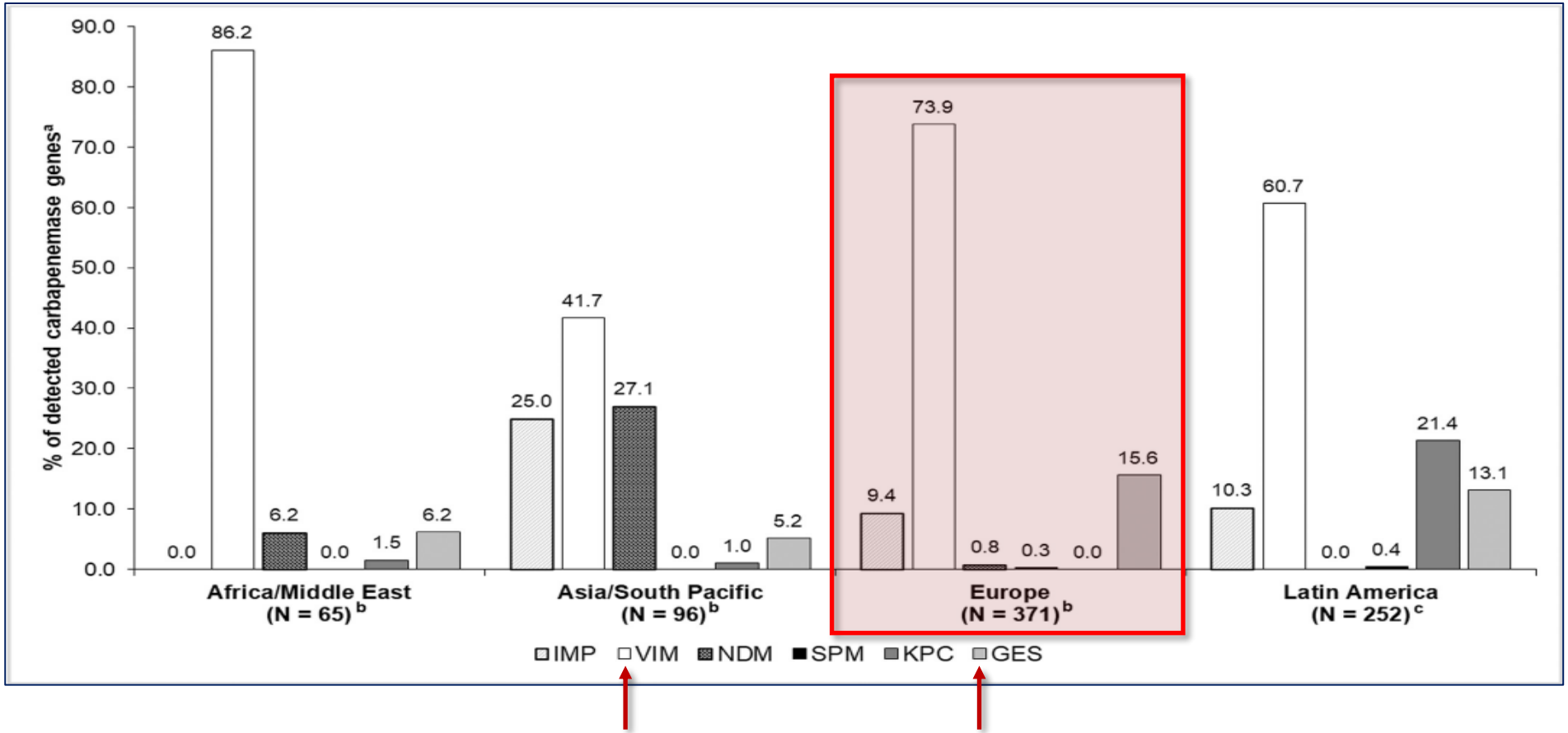
- The **increase of MDR *P. aeruginosa*** in 2020 was driven by hospital-onset cases potentially due to longer hospitalizations and secondary bacterial infections **associated with COVID-19 infections**



CDC. COVID-19: U.S. Impact on Antimicrobial Resistance, Special Report 2022. Atlanta, GA: US Department of Health and Human Services, CDC; 2022. https://www.cdc.gov/drugresistance/covid19.html

Carbapenemase distribution in *P. aeruginosa*: pre-COVID-19 pandemic

Carbapenemase genes (%) in carbapenemase-producing *P. aeruginosa* isolates
(Atlas program 2016-2018)



Kiratisin P et al. Journal of Global Antimicrobial Resistance. 2021; 27:132-41

Multi-drug resistant *Pseudomonas aeruginosa* in Spain and Portugal

2020 Oct 25:dkaa430. doi:10.1093/jac/dkaa430

J Antimicrob Chemother
doi:10.1093/jac/dkaa430

Journal of Antimicrobial Chemotherapy

Distinct epidemiology and resistance mechanisms affecting ceftolozane/tazobactam in *Pseudomonas aeruginosa* isolates recovered from ICU patients in Spain and Portugal depicted by WGS

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Margarida F. Pinto[3], Elsa Gonçalves[4], Valquíria Alves[5], Ana Raquel Vieira[6], Elmano Ramalheira[7], Luísa
José Diogo[9], Rui Ferreira[10], Tânia Silva[11], Catarina Chaves[12], Germán Bou[13], Emilia Cercenado
Mercedes Delgado-Valverde [15], Antonio Oliver[16], Cristina Pitart[17], Jesús Rodríguez-Lozano[18], Nuria
João Romano[20], Leonor Pássaro[20], Laura Paixão[20], Diego López-Mendoza[21], Jazmín Díaz-Regañón
Rafael Cantón [1]* on behalf of the STEP and SUPERIOR study groups†

P. aeruginosa isolates from IAI, UTI and LRTI in ICU patients admitted to 11 Portuguese (STEP) and 8 Spanish (SUPERIOR) hospitals

- ***P. aeruginosa* from ICU patients**:
  - 396 Portugal (**2017-2018**)
  - 80 Spain (**2016-2017**)
- Whole genome sequencing
- Inter-hospital clonal dissemination
  - Portugal CC235, CC244, CC348, C253
  - Spain CC175, CC309
- Different carbapenemase epidemiology

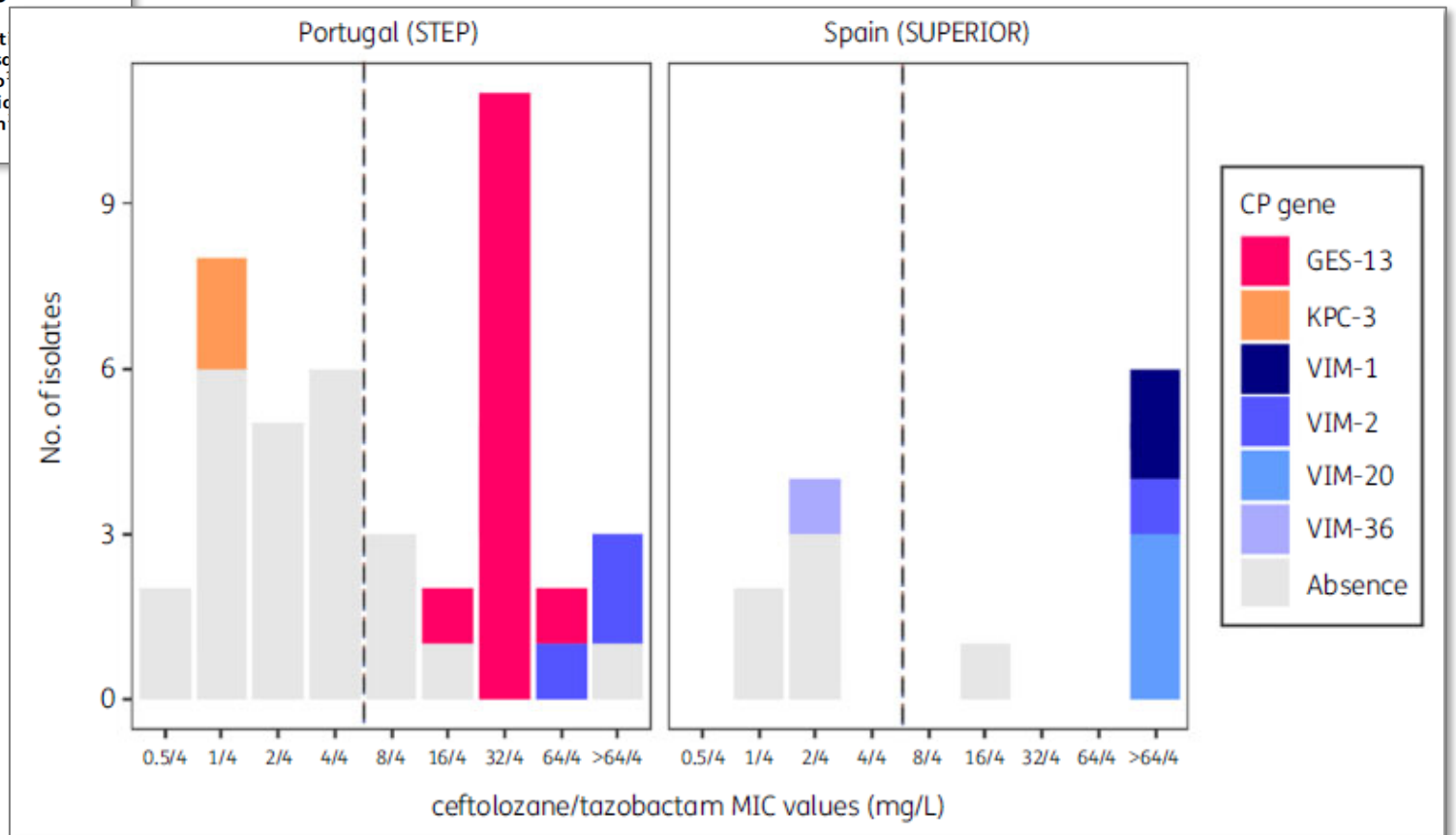

Figure 3. Distribution of *P. aeruginosa* isolates according to different ceftolozane/tazobactam MIC values, the origin country (Portugal, STEP study; Spain, SUPERIOR study) and the detection of carbapenemase-encoding genes by WGS.[14,15] Dotted line represents the ceftolozane/tazobactam EUCAST 2020 breakpoint (S ≤ 4 mg/L; R > 4 mg/L). CP, carbapenemase. This figure appears in colour in the online version of *JAC* and in black and white in the printed version of *JAC*.

Carbapenem resistance and carbapenemases in *P. aeruginosa*

Betalactam agent	MIC breakpoints (mg/L)		Wild type	AmpC derepressed	Porin deficiency (OprD⁻)	Efflux pump (MexAB-OprM)	Metallo-β-lactamase (VIM-2)	Carbapenemase (GES-5)
	S ≤	R >	MIC (category)	MIC (category)	MIC (category)	MIC (category)	MIC (category)	MIC (category)
Piperacillin-tazobactam	0.001[1]	16[1]	4 **(I)**	>64 (R)	8 **(I)**	>64 (R)	>64 (R)	>64 (R)
Ceftazidime	0.001	8	1 **(I)**	>32 (R)	2 **(I)**	2 **(I)**	>32 (R)	>32 (R)
Cefepime	0.001	8	2 **(I)**	>16 (R)	4 **(I)**	4 **(I)**	>16 (R)	>16 (R)
Aztreonam	0.001	16	4 **(I)**	>16 (R)	8 **(I)**	8 **(I)**	4 **(I)**	>16 (R)
Ceftazidime-avibactam	8[1]	8[1]	1 (S)	1 (S)	2 (S)	2 (S)	>32 (R)	4 (S)
Ceftolozane-tazobactam	4[1]	4[1]	0.5 (S)	0.5 (S)	0.5 (S)	0.5 (S)	>16 (R)	>16 (R)
Imipenem	0.001	4	0.5 **(I)**	1 **(I)**	>8 (R)	1 **(I)**	>8 (R)	>8 (R)
Impenem-relebactam	2[1]	2[1]	0.25 (S)	0.5 (S)	8 (R)	0.5 (S)	>8 (R)	>8 (R)
Meropenem	2	8	0.5 (S)	0.5 (S)	2 (S)	8 (R)	>8 (R)	>8 (R)
Meropenem-vaborbactam	8[1]	8[1]	0.5(S)	0.5 (S)	2 (S)	8 (R)	>8 (R)	>8 (R)

For susceptibility testing purposes, the concentration of the inhibitor is fixed at [1]4 mg/L

I = *Susceptible, increased exposure* to the agent provided higher exposure of the microorganism can be achieved (dose, frequency, mode of administration).

Data from Clinical Microbiology Dept. Hosp. Ramón y Cajal. Madrid. Spain

Multi-drug resistant *Pseudomonas aeruginosa* in Spain

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SUSCEPTIBILITY

March 2022 Volume 66 Issue 3 e02161-21

In Vitro Activity of Cefepime-Taniborbactam against Carbapenemase-Producing *Enterobacterales* and *Pseudomonas aeruginosa* Isolates Recovered in Spain

Marta Hernández-García,[a,b] María García-Castillo,[a,b] Patricia Ruiz-Garbajosa,[a,b] Germán Bou,[b,c] María Siller-Ruiz,[d] Cristina Pitart,[e] Irene Gracia-Ahufinger,[f] Xavier Mulet,[b,g] Álvaro Pascual,[b,h,i,j] Nuria Tormo,[k] Rafael Cantón[a,b]

- Carbapenem resistant *Pseudomonas* spp. isolates
  - 163 *P. aeruginosa*; 4 *P. putida*; 3 others
- 8 hospitals in 2020, whole genome sequencing
- 47.1% carbapenamase producers
  - 26.5% VIM, 17.6% GES, 1.8% VIM+GES, 1.2% GES+KPC

Cefepime-taniborbactam MICs and carbapenemases

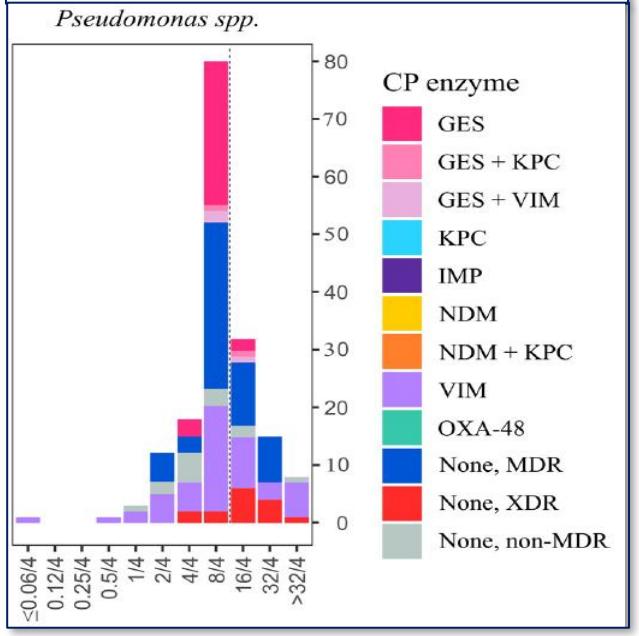

TABLE 2 Activities of cefepime-taniborbactam and comparators in meropenem-resistant isolates according to EUCAST breakpoints by the carbapenemase group detected[a]

	FEP			FTB			CZA			CT			IMR			MEV		
	MIC (mg/L)			MIC (mg/L)			MIC (mg/L)			MIC (mg/L)			MIC (mg/L)			MIC (mg/L)		
Carbapenamase group	MIC_{50}	MIC_{90}	% S	MIC_{50}	MIC_{90}	% S	MIC_{50}	MIC_{90}	% S	MIC_{50}	MIC_{90}	% S	MIC_{50}	MIC_{90}	% S	MIC_{50}	MIC_{90}	% S
Pseudomonas spp. (*n* = 170)	32	>32	20.0	8/4	32/4	67.6	8/4	>32/4	61.2	8/4	>32/4	34.7	16/4	>32/4	37.1	32/8	>32/8	32.9
MER-R (71.8% [122/170])	32	>32	10.7	8/4	32/4	63.9	8/4	>32/4	51.6	8/4	>32/4	17.2	32/4	>32/4	16.4	>32/8	>32/8	8.2
GES (30/122)[b]	>32	>32	0	8/4	8/4	93.3	4/4	8/4	96.7	8/4	8/4	0	32/4	32/4	0	>32/8	>32/8	0
VIM (49/122)[c]	>32	>32	13.0	8/4	>32/4	61.2	>32/4	>32/4	14.3	>32/4	>32/4	0	>32/4	>32/4	0	>32/8	>32/8	4.1
Non-carbapenemase (43/122)	32	>32	16.3	16/4	32/4	46.5	8/4	>32/4	62.8	8/4	>32/4	48.8	4/4	32/4	46.5	16/8	>32/8	18.6

[a]MER, meropenem (S, ≤2 mg/L; R, >8 mg/L); FTB, cefepime-taniborbactam (provisional breakpoint: S, ≤8/4 mg/L; R, >8/4 mg/L); CZA, ceftazidime-avibactam (S, ≤8/4 mg/L; R, >8/4 mg/L); CT, ceftolozane-tazobactam (*Enterobacterales* spp., S, ≤2/4 mg/L, and R, >2/4 mg/L; *Pseudomonas* spp., S, ≤4/4 mg/L, and R, >4/4 mg/L); IMR, imipenem-relebactam (S, ≤2/4 mg/L; R, >2/4 mg/L); and MEV, meropenem-vaborbactam (S, ≤8/8 mg/L; R, >8/8 mg/L).

[b]The GES group includes 29 bla_{GES} isolates and 1 bla_{GES}+bla_{KPC} isolate.

[c]The VIM group includes 46 bla_{VIM} and 3 bla_{VIM}+bla_{GES} isolates.

Resistance mechanism to new compounds: beta-lactamases

Impact of different beta-lactamases in the susceptibility of new beta-lactams

Microorganisms	Enzyme	C/T	CAZ-AVI	IMP-REL	MER-VAB	FCD
P. aeruginosa PAO1	-	0.25	1	0.25	0.25	0.5
	GES-1	16	1	0.25	0.25	0.5
	GES-6	64	2	1	2	2
	BEL-2	32	4	0.25	0.25	4
	KPC-2	32	2	2	8	1
	PER-1	>256	32	0.25	0.5	16
	NDM-1	>256	256	32	>32	4
	SPM-1	>256	128	4	32	8
	OXA-427	>256	128	2	4	4

*MIC, mg/L

Poirel L et al. Antimicrob Agents Chemother. 2022 Apr 19;66(4):e0003922

Resistance mechanism to new compounds: beta-lactamases

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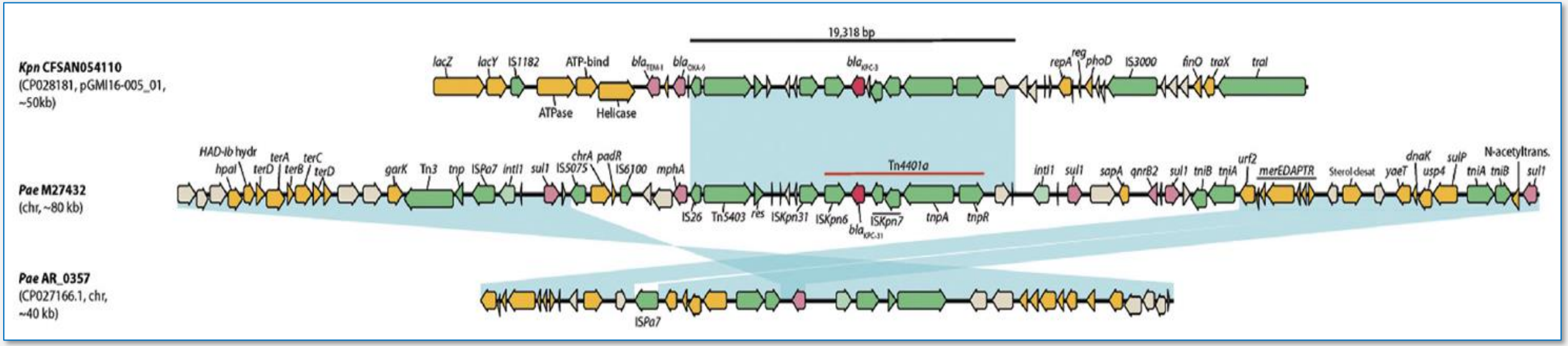
November 2022 Volume 66 Issue 11

Emergence of KPC-31, a KPC-3 Variant Associated with Ceftazidime-Avibactam Resistance, in an Extensively Drug-Resistant ST235 *Pseudomonas aeruginosa* Clinical Isolate

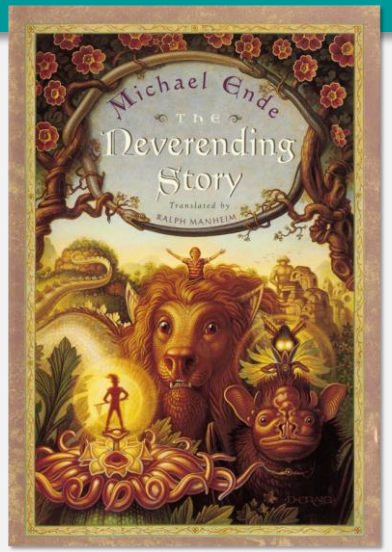
Diego Faccone,[a,b] Juan M. de Mendieta,[a] Ezequiel Albornoz,[a] Magali Chavez,[a] Fabiana Genero,[c] Mariano Echegorry,[a] Paola Ceriana,[a] Andrea Mora,[d] Christine Seah,[e] Alejandra Corso,[a] Roberto G. Melano,[e,f] Fernando Pasteran[a]

Chronic osteomyelitis patient treated with ceftazidime-avibactam in combination with other agents for 130 days (!)



Comparison of sequence with plasmid pGM116-005_01 from *K. pneumoniae* CFSAN054110 and the chromosome of *P. aeruginosa* AR_0357 suggesting a plasmidic origin of an ≈19-kb fragment containing bla_{KPC-31}

Evolución de las resistencias



- **Resistance** is a **growing global problem** that complicates its control
- **High-risk clones** play an important role in the maintenance and spread of resistance
- The **COVID-19 pandemic** has exacerbate the problem of resistance, particularly in **carbapenemase-producing Enterobacterales** and **multidrug-resistant *P. aeruginosa***
- In **Spain,** an **epidemiological change in carbapenemase-producing Enterobacterales,** particularly in ***K. pneumoniae*** has been produced during the **COVID-19 pandemics**
  - increase of KPC carbapenemases and emergence of new KPC variants determining resistance to some of the beta-lactam/beta-lactamase inhibitors combinations
  - maintenance of OXA-48
  - emergence of metallo-betalactamase (NDM), also in socio-sanitary institutions
  - emergence of cefiderocol-resistant isolates
- In **Spain, increased complexity** of resistance mechanisms in **multidrug-resistant *P. aeruginosa***
  - consolidation of **GES carbapenemases** affecting ceftolozane-tazobactam, meropenem-vaborbactam and imipenem-relebactam but not ceftazidime-avibactam
- There is a **need for a continuous follow-up of antimicrobial resistance at local an international level** with **phenotypic and molecular techniques,** including whole genome sequencing

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ReFORMÚLaTE

En busca del tesoro

"La evolución de las resistencias"

RYC MICROBIOLOGÍA HOSPITAL RAMÓN Y CAJAL

SaludMadrid

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Hospital Universitario Ramón y Cajal
SERVICIO DE MICROBIOLOGÍA Y PARASITOLOGÍA

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