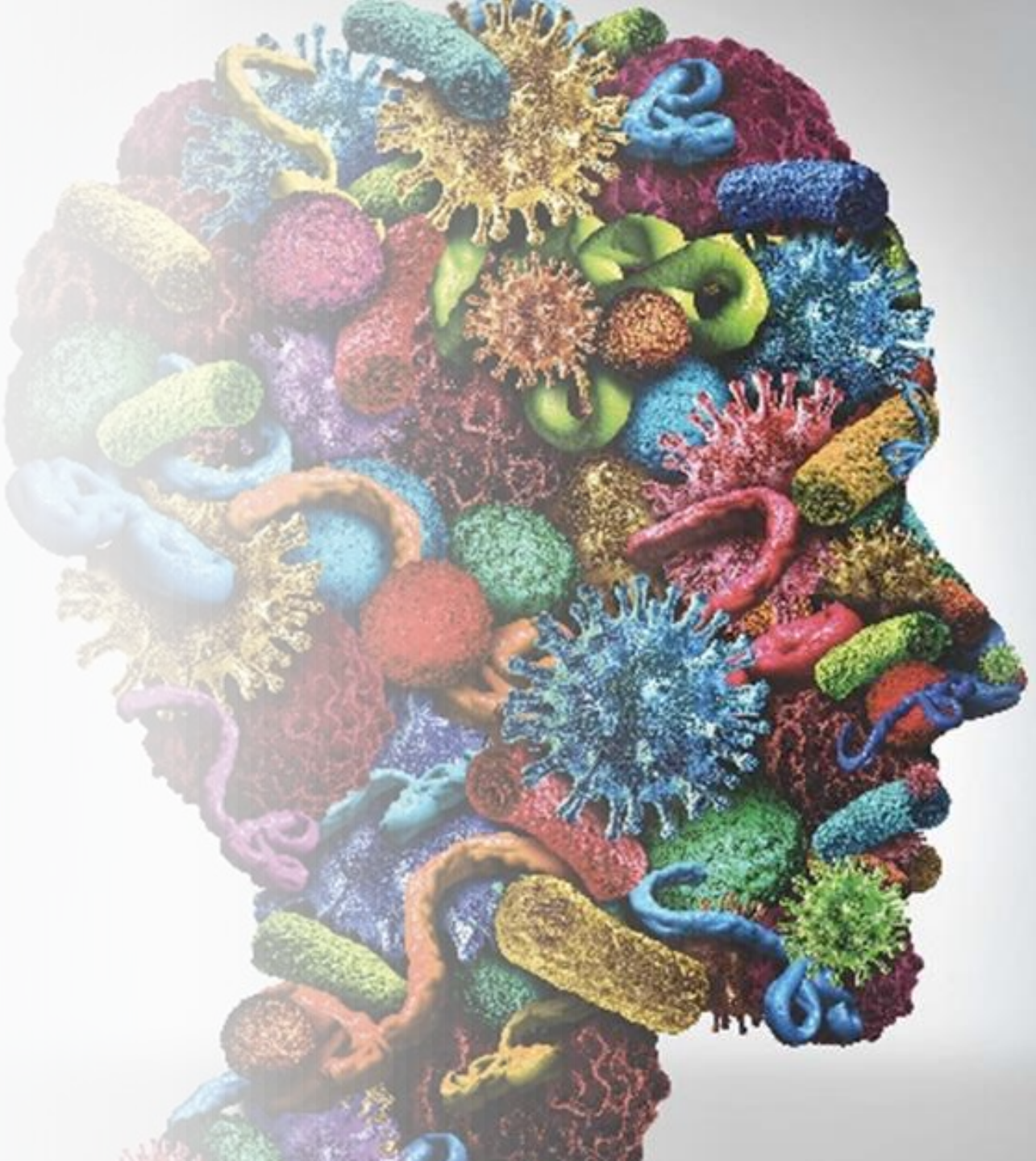
AGIDEI
ASOCIACION GALLEGA PARA LA INVESTIGACION Y DOCENCIA EN ENFERMEDADES INFECCIOSAS

Dimension actual y manejo de las infecciones por microorganismos multirresistentes



Dr. Jose Luis del Pozo León

Servicio de Enfermedades Infecciosas

Servicio de Microbiología

Clínica Universidad de Navarra (Pamplona)

Octubre de 2023

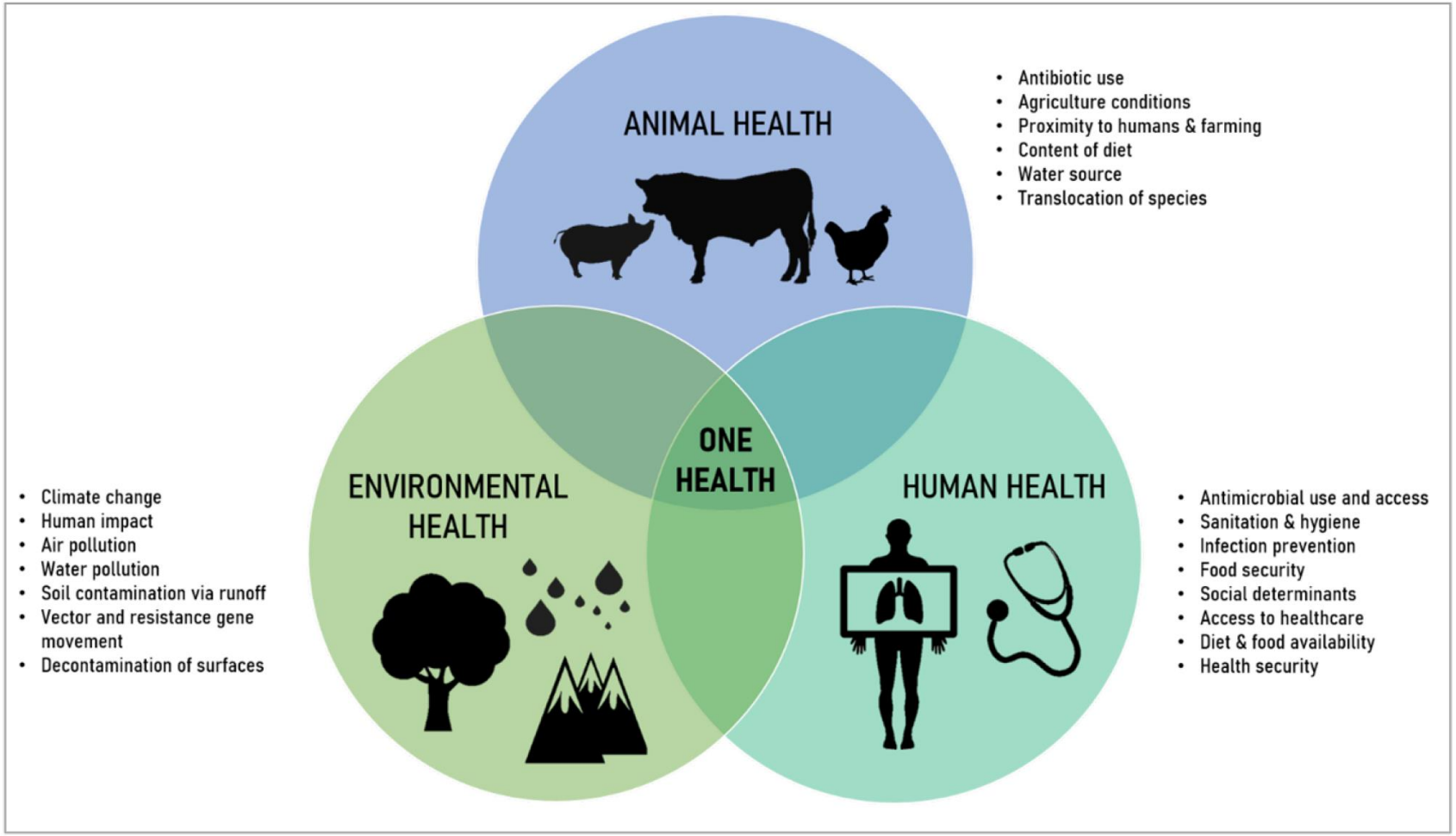
AGENDA

1. *El fenómeno de la resistencia antibiótica*
2. *Retos actuales en infecciones por microorganismos gramnegativos*
3. *Retos actuales en infecciones por microorganismos grampositivos*
4. *Retos actuales en infecciones fúngicas*
5. *Discusión*

El fenómeno de la resistencia antibiótica

Antimicrobial Resistance: A Review of a Broad-Spectrum Problem and Future Needs

Andrea Prinzi, Infection Control tips 2022



Understanding the mechanisms and drivers of antimicrobial resistance

Alison H Holmes, Lancet 2016

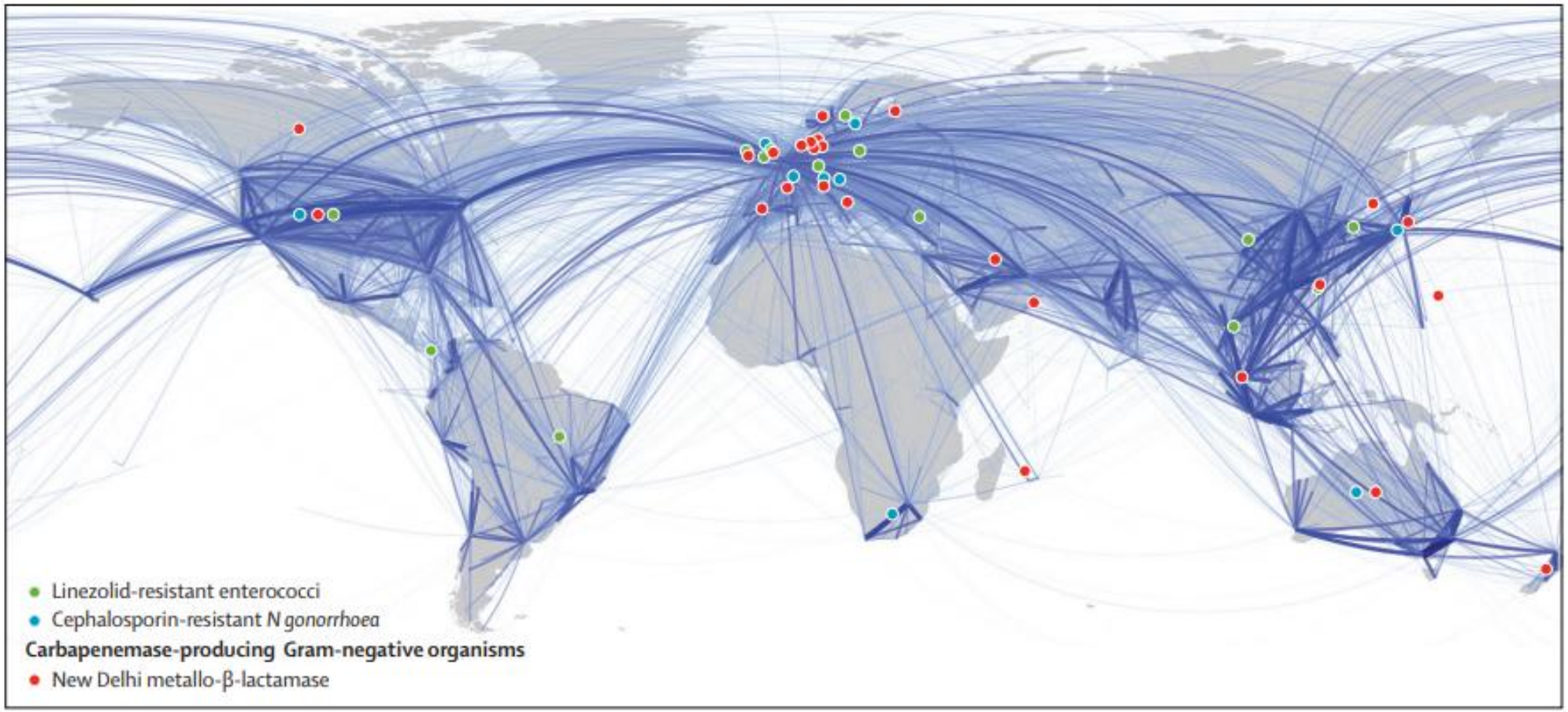


Figure 2: **Worldwide travel routes and emergence of antimicrobial resistance**

Genomic analysis of sewage from 101 countries reveals global antimicrobial resistance

Munk et al., Nature 2022

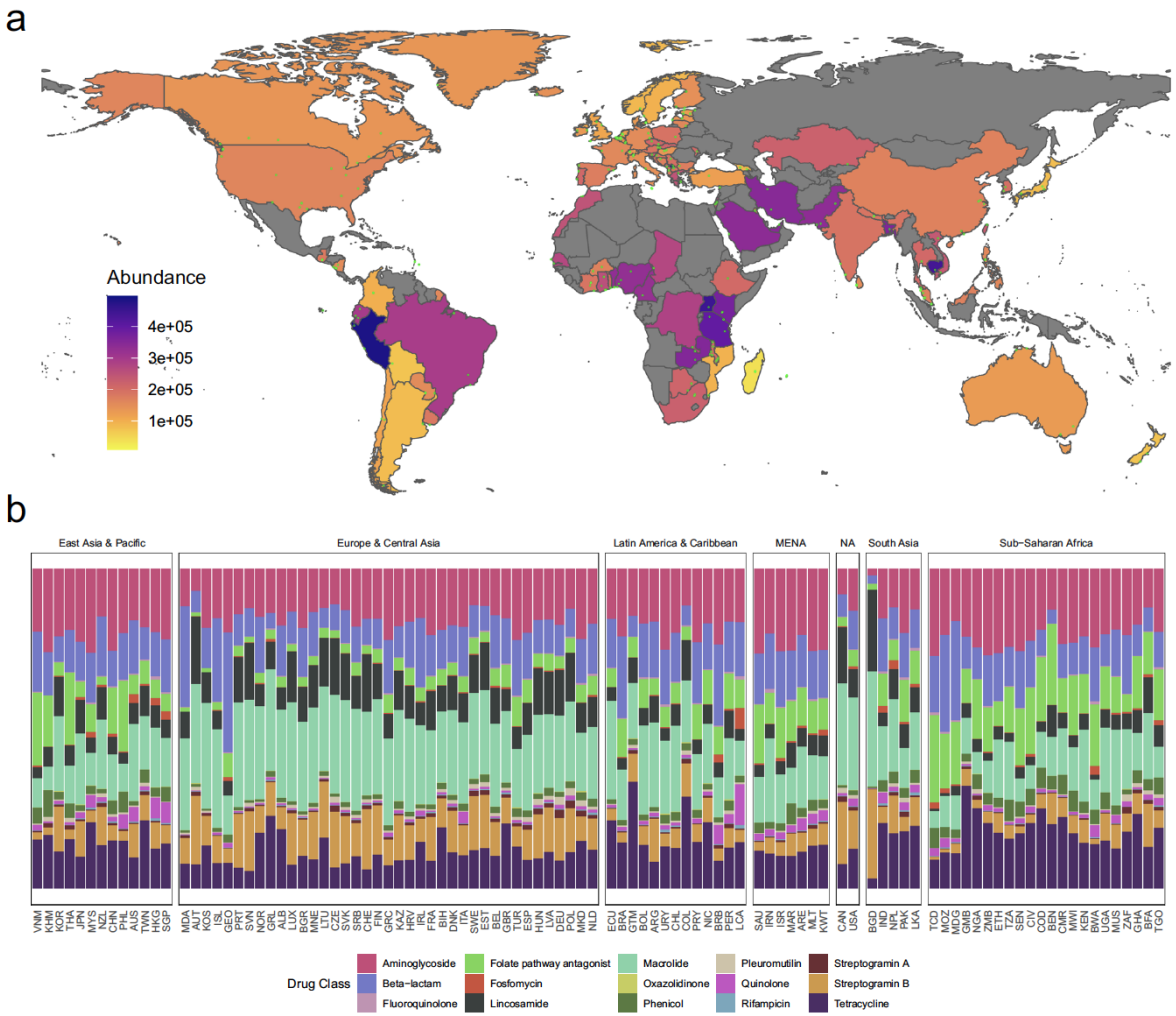
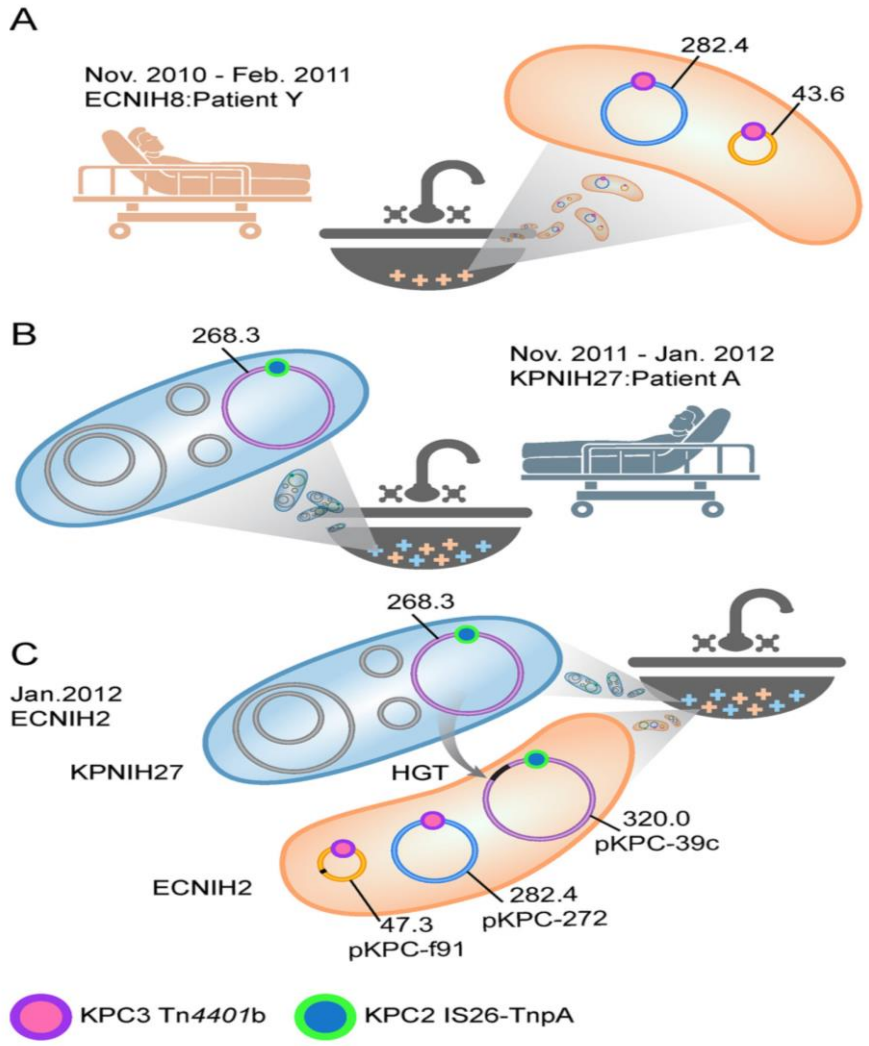
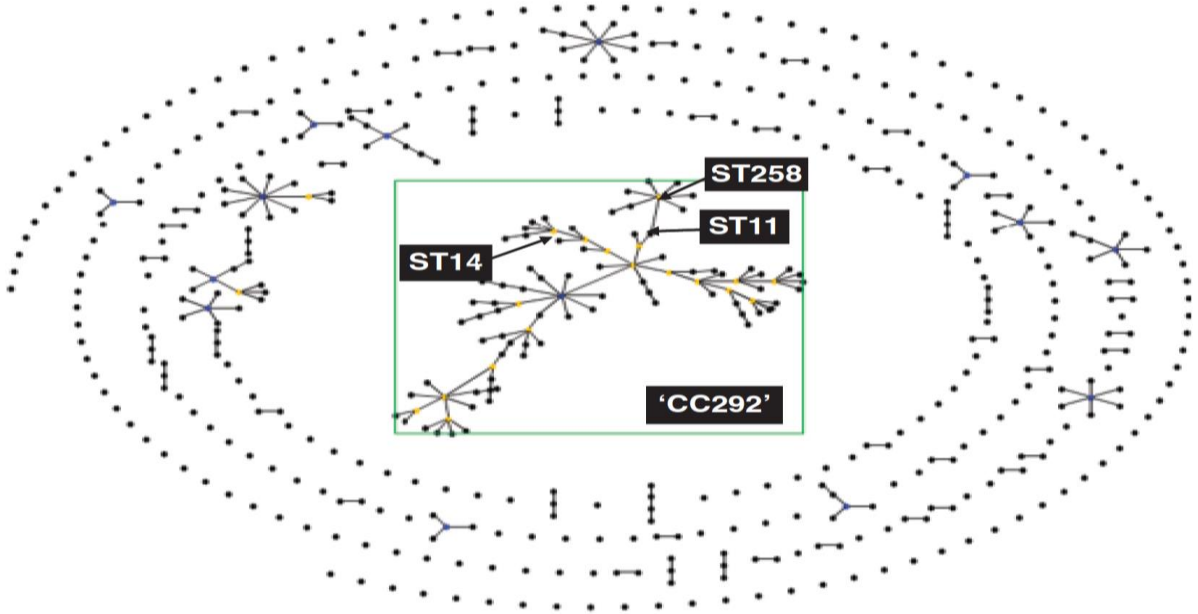


Fig. 1 | The global resistome based on sewage-based monitoring. a Choropleth of the world coloured by the country-wise average total AMR load (see methods). Small green dots show unique sampling sites contributing to the average. Some areas are disputed, and we realize that exact border placement is difficult due to geopolitical issues. **b** Stacked bar chart of relative abundances per drug class per country. Each panel represent countries in a World Bank region and is ordered by the Shannon diversity of class-level AMR.

Genomic Analysis of Hospital Plumbing Reveals Diverse Reservoir of Bacterial Plasmids Conferring Carbapenem Resistance

Weingarten et al., mBio 2018

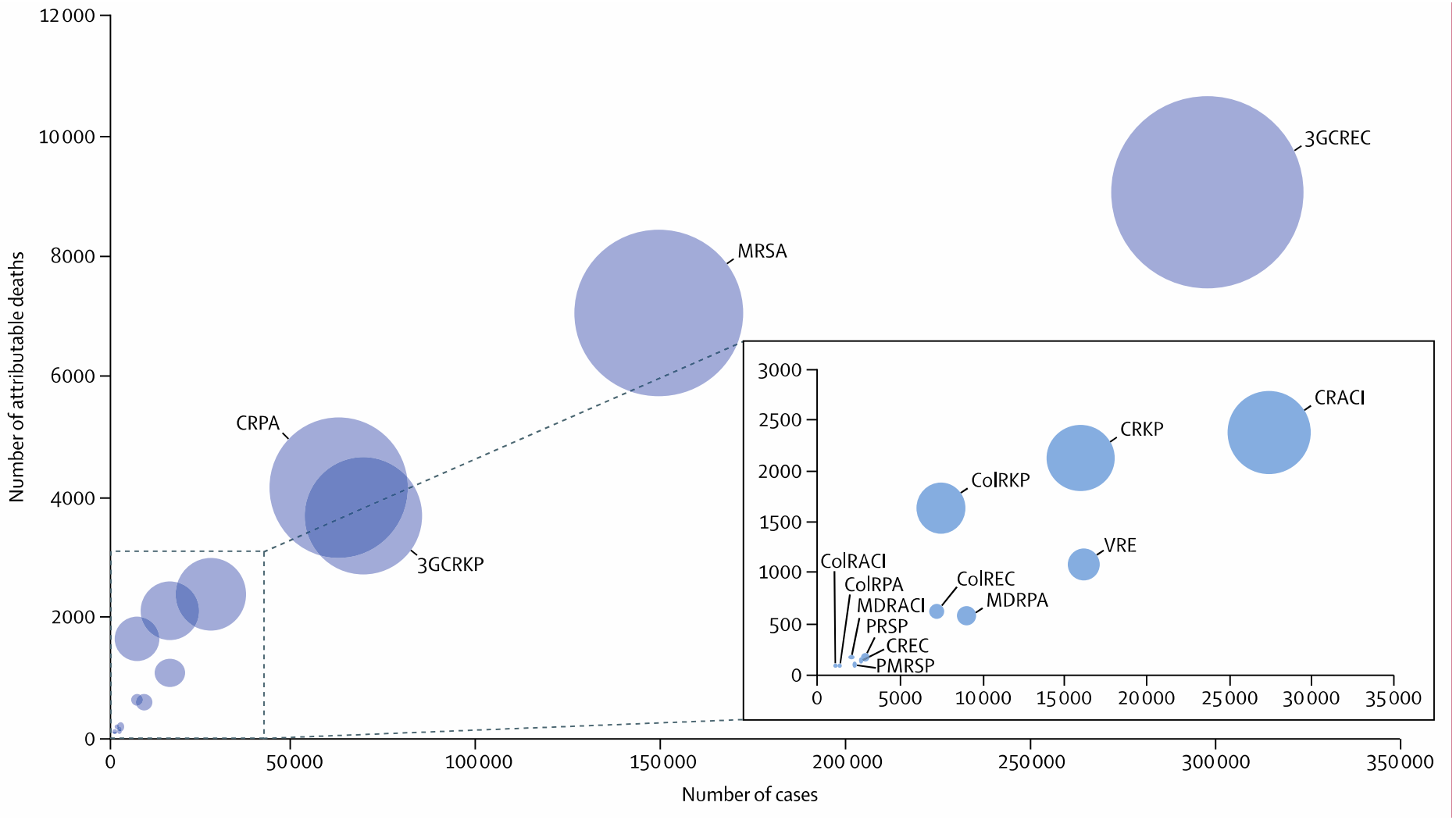




ST131 en *Escherichia coli* (CTXM15)
ST258 en *Klebsiella* spp (KPC)

Attributable deaths and disability-adjusted life-years by infections with antibiotic-resistant bacteria in the European Economic Area in 2015: a population-level modelling analysis

Cassini et al., Lancet Infect Dis 2018



Retos en infecciones por microorganismos gramnegativos

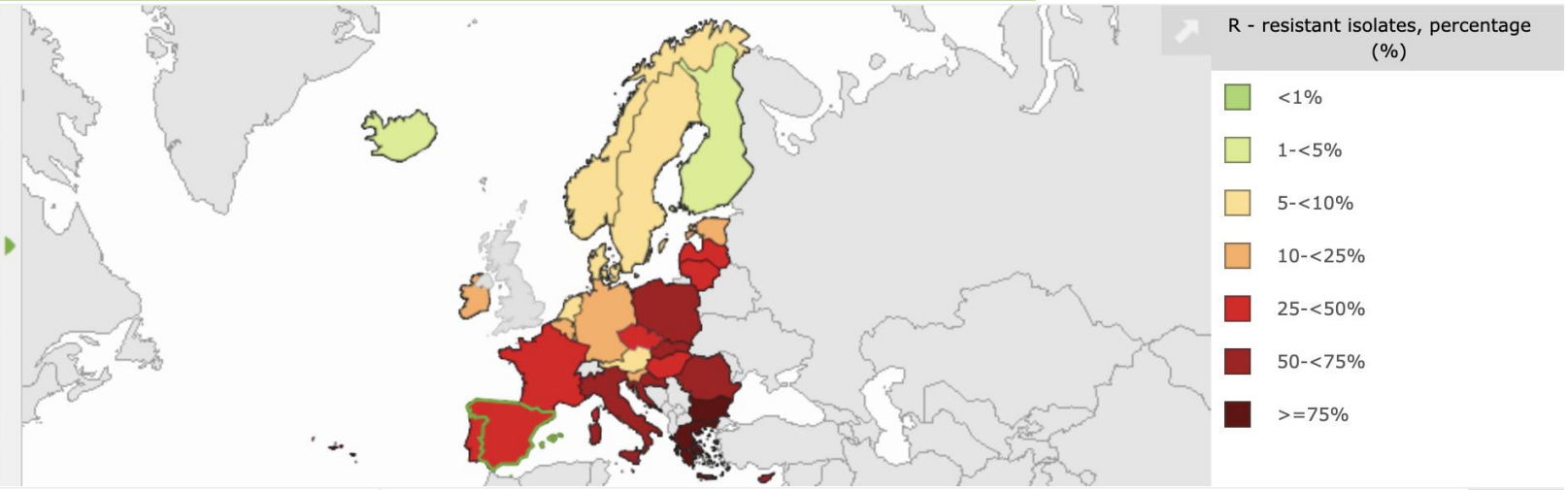
Klebsiella pneumoniae ESBL
http://atlas.ecdc.europa.eu/public/index.aspx

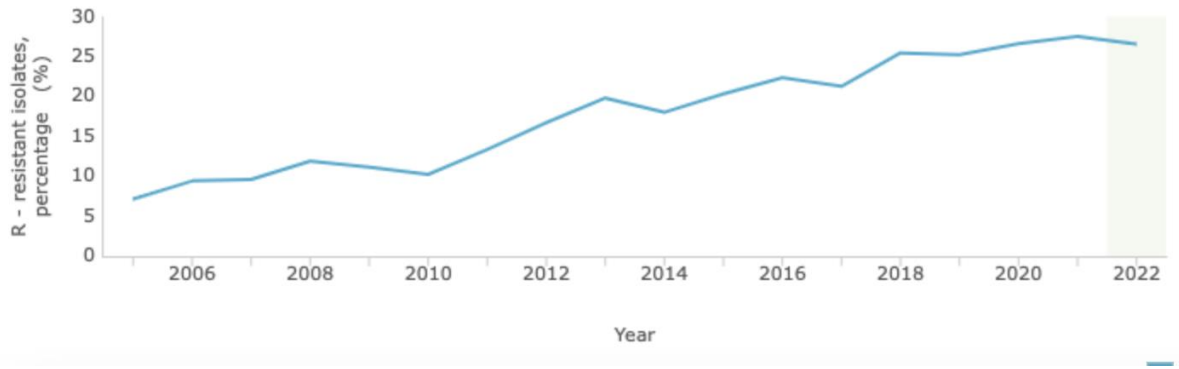
Surveillance Atlas of Infectious Diseases

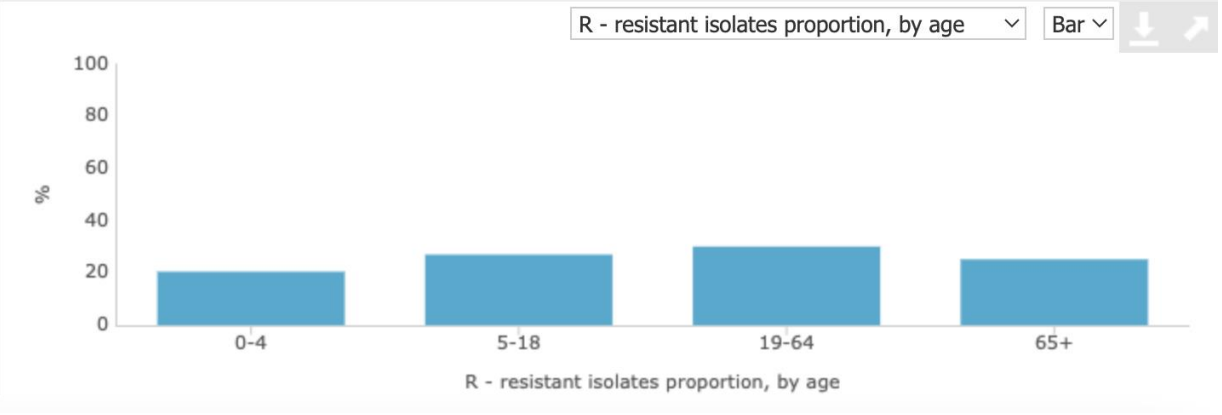
Antimicrobial resistance | Klebsiella pneumoniae | Third-generation cephalosporins | R - resistant isolates, percentage

2022

Region	R - resistant isolates, percentage (%)
Luxembourg	18.8
Malta	27.5
Netherlands	9.8
Norway	6.6
Poland	61.9
Portugal	45.2
Romania	63.5
Slovakia	56.1
Slovenia	20.7
Spain	26.6
Sweden	7.8







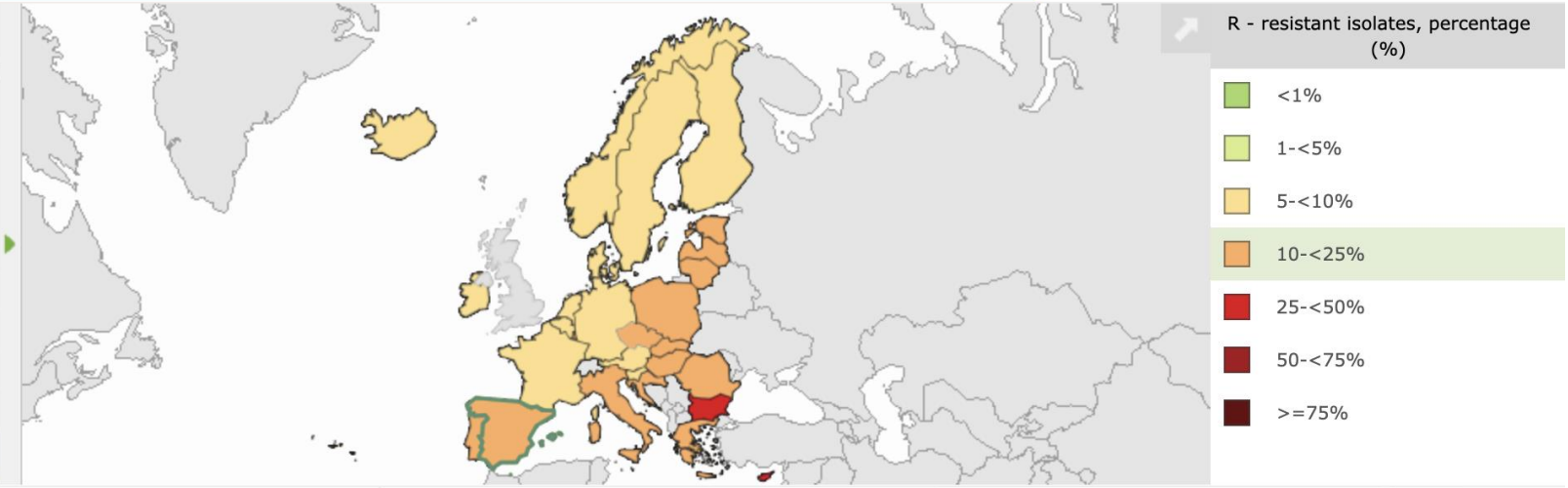
Escherichia coli ESBL
http://atlas.ecdc.europa.eu/public/index.aspx

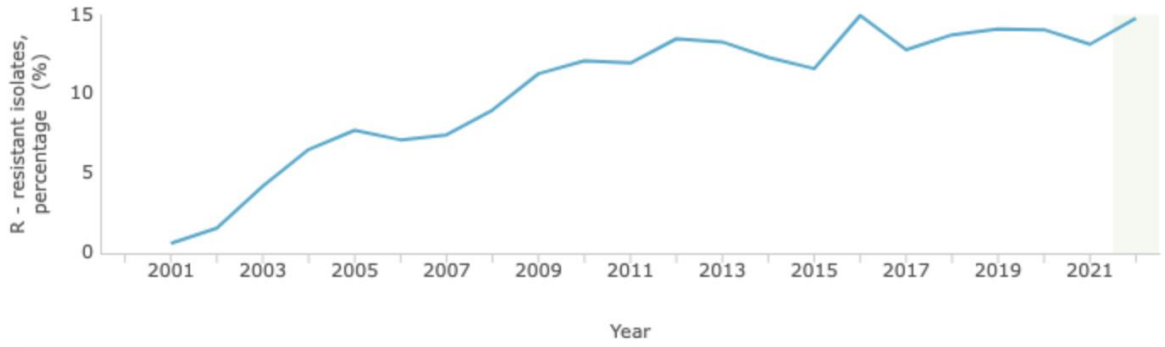
Surveillance Atlas of Infectious Diseases

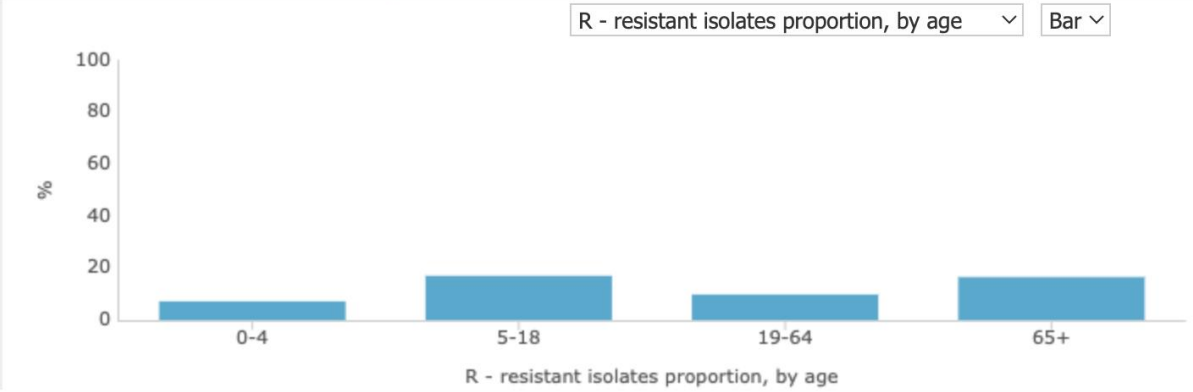
Antimicrobial resistance | Escherichia coli | Third-generation cephalosporins | R - resistant isolates, percentage

2022

Region	R - resistant isolates, percentage (%)
Luxembourg	10.4
Malta	11.3
Netherlands	7.7
Norway	5.8
Poland	18.7
Portugal	14.1
Romania	17.8
Slovakia	23.7
Slovenia	9.3
Spain	14.8







Global Dissemination of Carbapenemase-Producing Klebsiella pneumoniae: Epidemiology, Genetic Context, Treatment Options, and Detection Methods

Chang-Ro Lee et al., Frontiers in Microbiology 2016

OXA-48

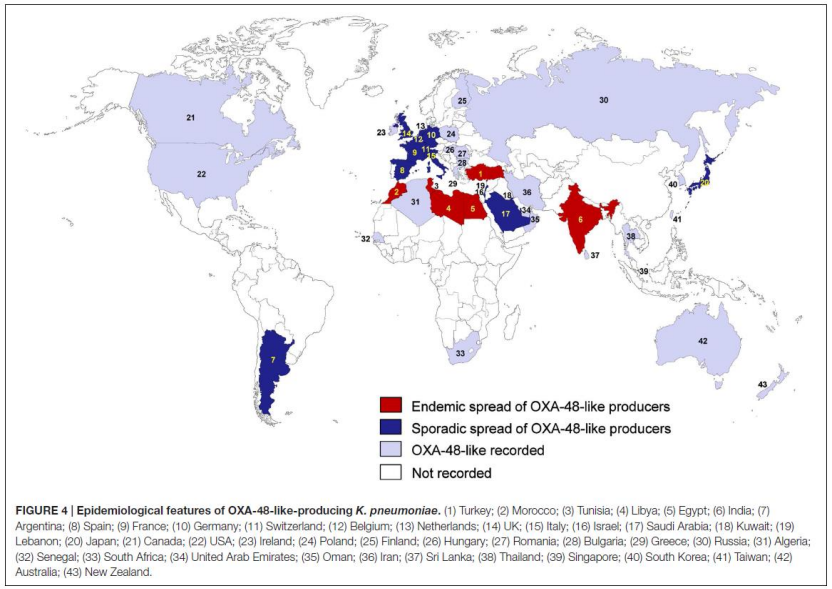


FIGURE 4 | Epidemiological features of OXA-48-like-producing *K. pneumoniae*. (1) Turkey; (2) Morocco; (3) Tunisia; (4) Libya; (5) Egypt; (6) India; (7) Argentina; (8) Spain; (9) France; (10) Germany; (11) Switzerland; (12) Belgium; (13) Netherlands; (14) UK; (15) Italy; (16) Israel; (17) Saudi Arabia; (18) Kuwait; (19) Lebanon; (20) Japan; (21) Canada; (22) USA; (23) Ireland; (24) Poland; (25) Finland; (26) Hungary; (27) Romania; (28) Bulgaria; (29) Greece; (30) Russia; (31) Algeria; (32) Senegal; (33) South Africa; (34) United Arab Emirates; (35) Oman; (36) Iran; (37) Sri Lanka; (38) Thailand; (39) Singapore; (40) South Korea; (41) Taiwan; (42) Australia; (43) New Zealand.

KPC

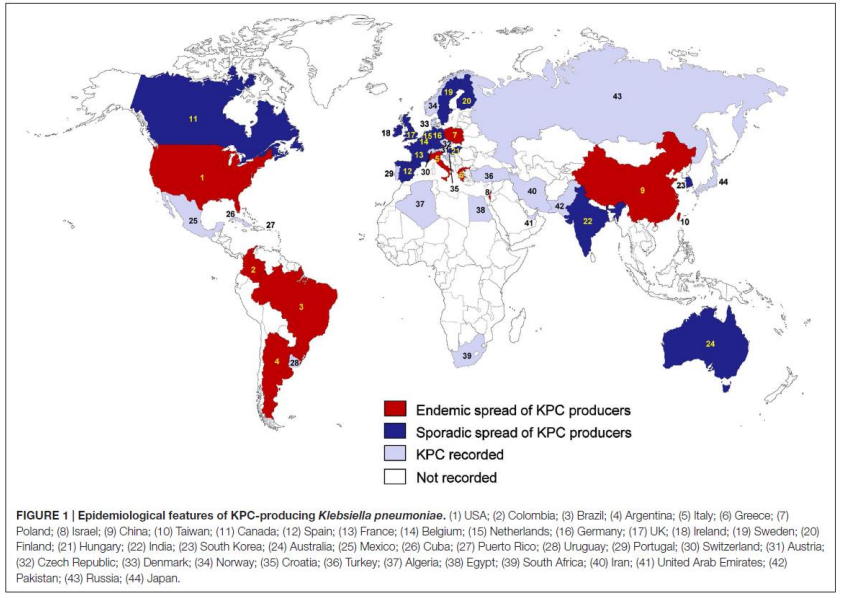


FIGURE 1 | Epidemiological features of KPC-producing *Klebsiella pneumoniae*. (1) USA; (2) Colombia; (3) Brazil; (4) Argentina; (5) Italy; (6) Greece; (7) Poland; (8) Israel; (9) China; (10) Taiwan; (11) Canada; (12) Spain; (13) France; (14) Belgium; (15) Netherlands; (16) Germany; (17) UK; (18) Ireland; (19) Sweden; (20) Finland; (21) Hungary; (22) India; (23) South Korea; (24) Australia; (25) Mexico; (26) Cuba; (27) Puerto Rico; (28) Uruguay; (29) Portugal; (30) Switzerland; (31) Austria; (32) Czech Republic; (33) Denmark; (34) Norway; (35) Croatia; (36) Turkey; (37) Algeria; (38) Egypt; (39) South Africa; (40) Iran; (41) United Arab Emirates; (42) Pakistan; (43) Russia; (44) Japan.

NDM

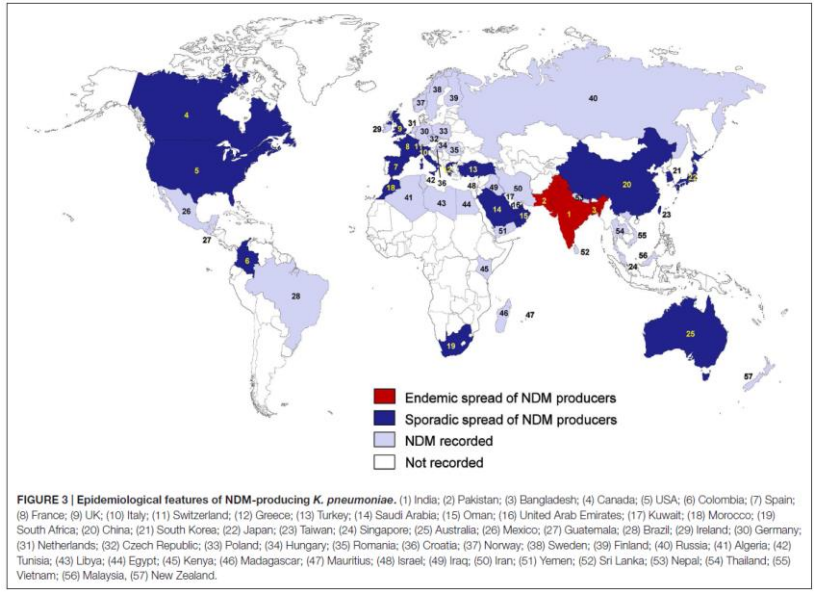


FIGURE 3 | Epidemiological features of NDM-producing *K. pneumoniae*. (1) India; (2) Pakistan; (3) Bangladesh; (4) Canada; (5) USA; (6) Colombia; (7) Spain; (8) France; (9) UK; (10) Italy; (11) Switzerland; (12) Greece; (13) Turkey; (14) Saudi Arabia; (15) Oman; (16) United Arab Emirates; (17) Kuwait; (18) Morocco; (19) South Africa; (20) China; (21) South Korea; (22) Japan; (23) Taiwan; (24) Singapore; (25) Australia; (26) Mexico; (27) Guatemala; (28) Brazil; (29) Ireland; (30) Germany; (31) Netherlands; (32) Czech Republic; (33) Poland; (34) Hungary; (35) Romania; (36) Croatia; (37) Norway; (38) Sweden; (39) Finland; (40) Russia; (41) Algeria; (42) Tunisia; (43) Libya; (44) Egypt; (45) Kenya; (46) Madagascar; (47) Mauritius; (48) Israel; (49) Iraq; (50) Iran; (51) Yemen; (52) Sri Lanka; (53) Nepal; (54) Thailand; (55) Vietnam; (56) Malaysia, (57) New Zealand.

European Centre for Disease Prevention and Control. Carbapenem-resistant Enterobacteriaceae, second update – 26 September 2019. ECDC: Stockholm; 2019

Figure 1. Percentage of invasive *K. pneumoniae* isolates with resistance to carbapenems, EU/EEA, 2017 [1]

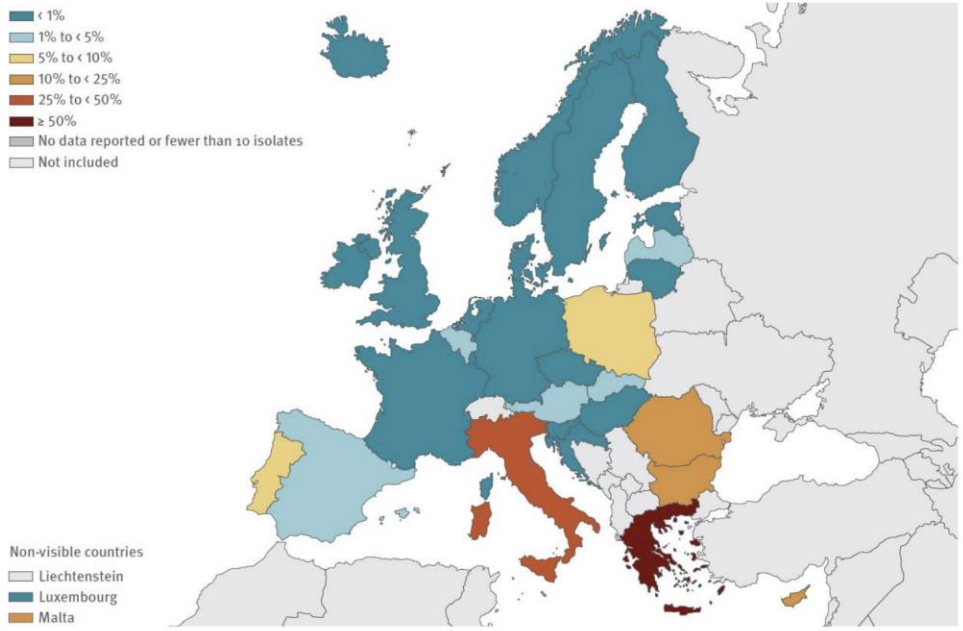
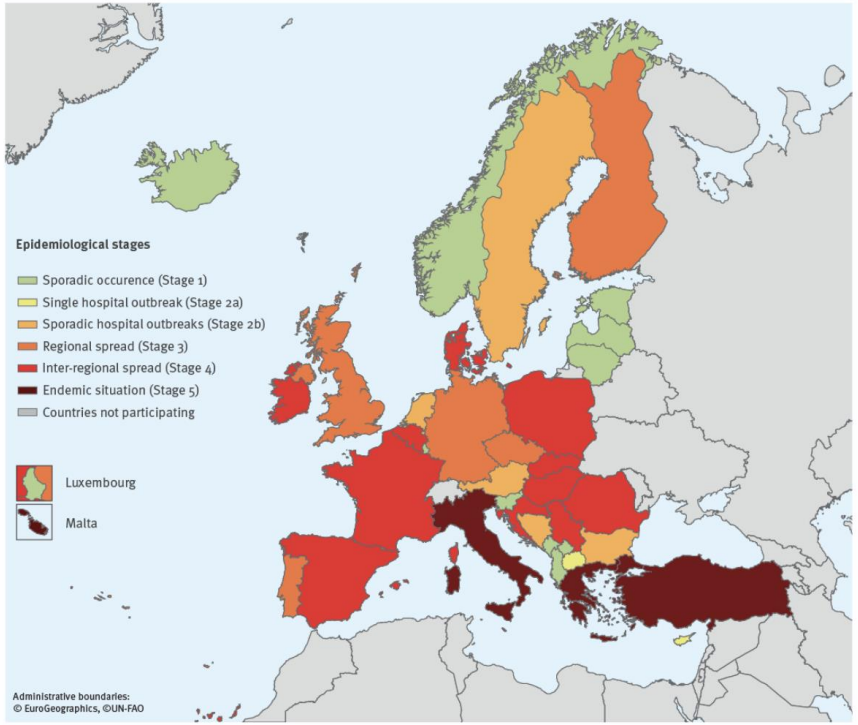
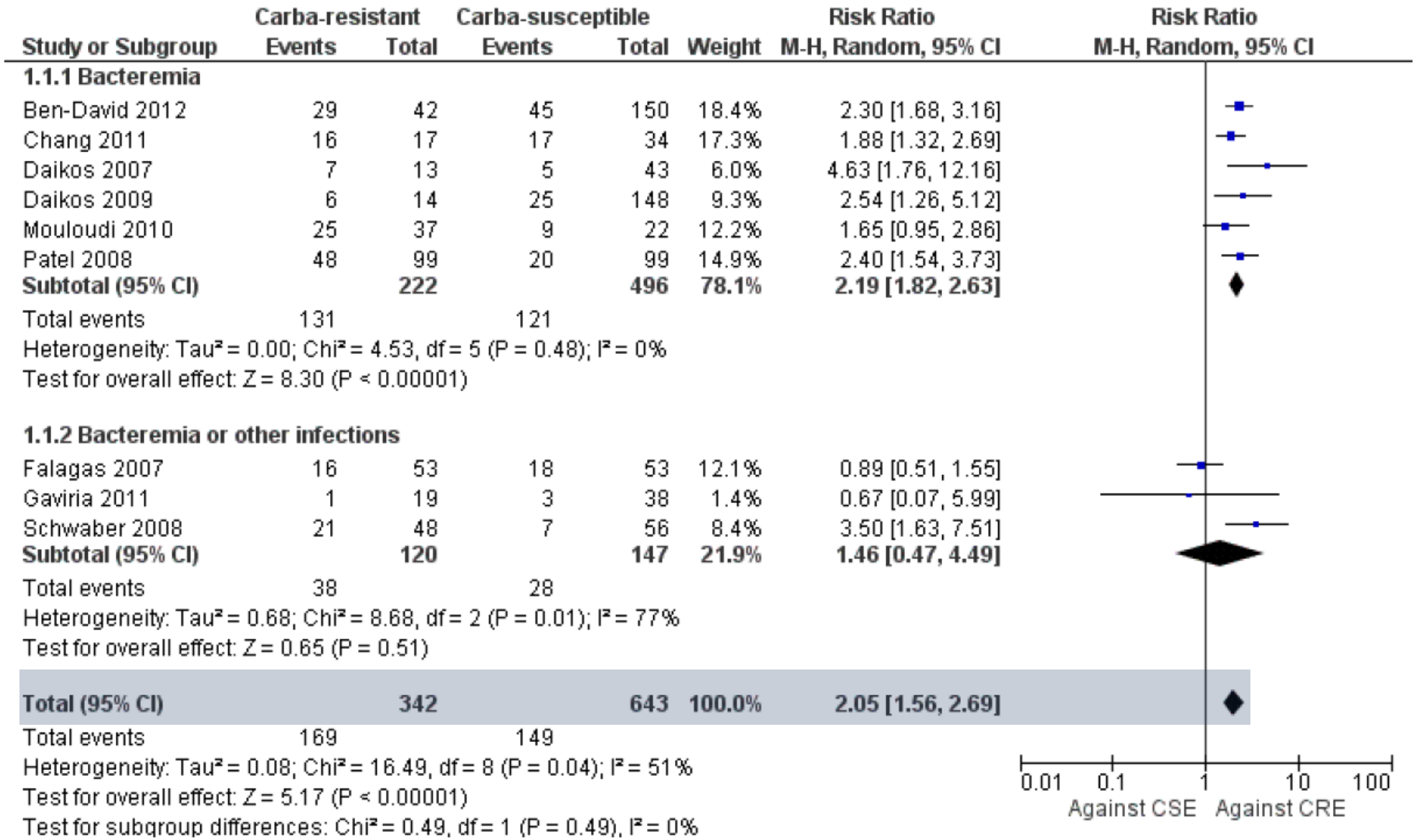


Figure 2. Epidemiological situation of carbapenemase-producing Enterobacteriaceae, assessment by national experts in European countries, July 2018 (n=37) [2]



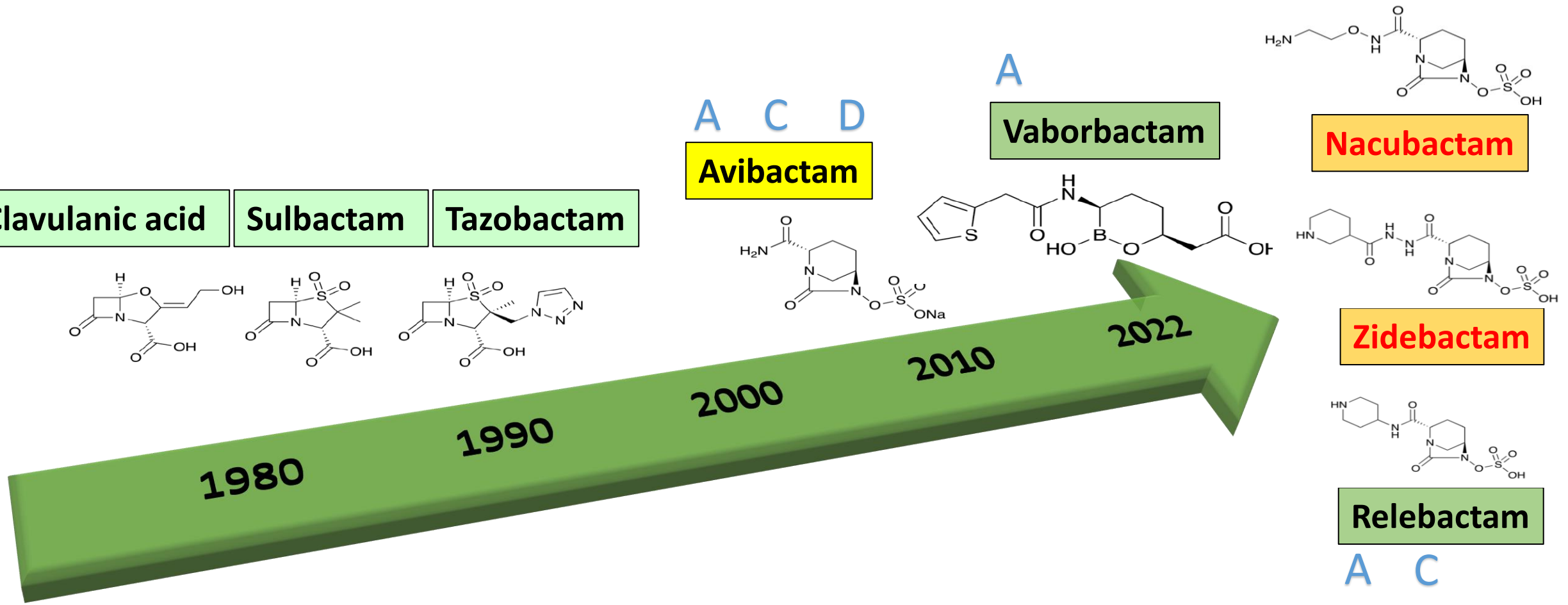
Deaths Attributable to Carbapenem-Resistant Enterobacteriaceae Infections

Falagas et al., Emerg Infect Dis 2014



β-lactam/β-lactamase inhibitor combinations: an update

Tehrani et al., Medchemcomm 2018



Infectious Diseases Society of America 2022 Guidance on the Treatment of Extended-Spectrum β-lactamase Producing Enterobacterales (ESBL-E), Carbapenem-Resistant Enterobacterales (CRE), and Pseudomonas aeruginosa with Difficult-to-Treat Resistance (DTR-P. aeruginosa)

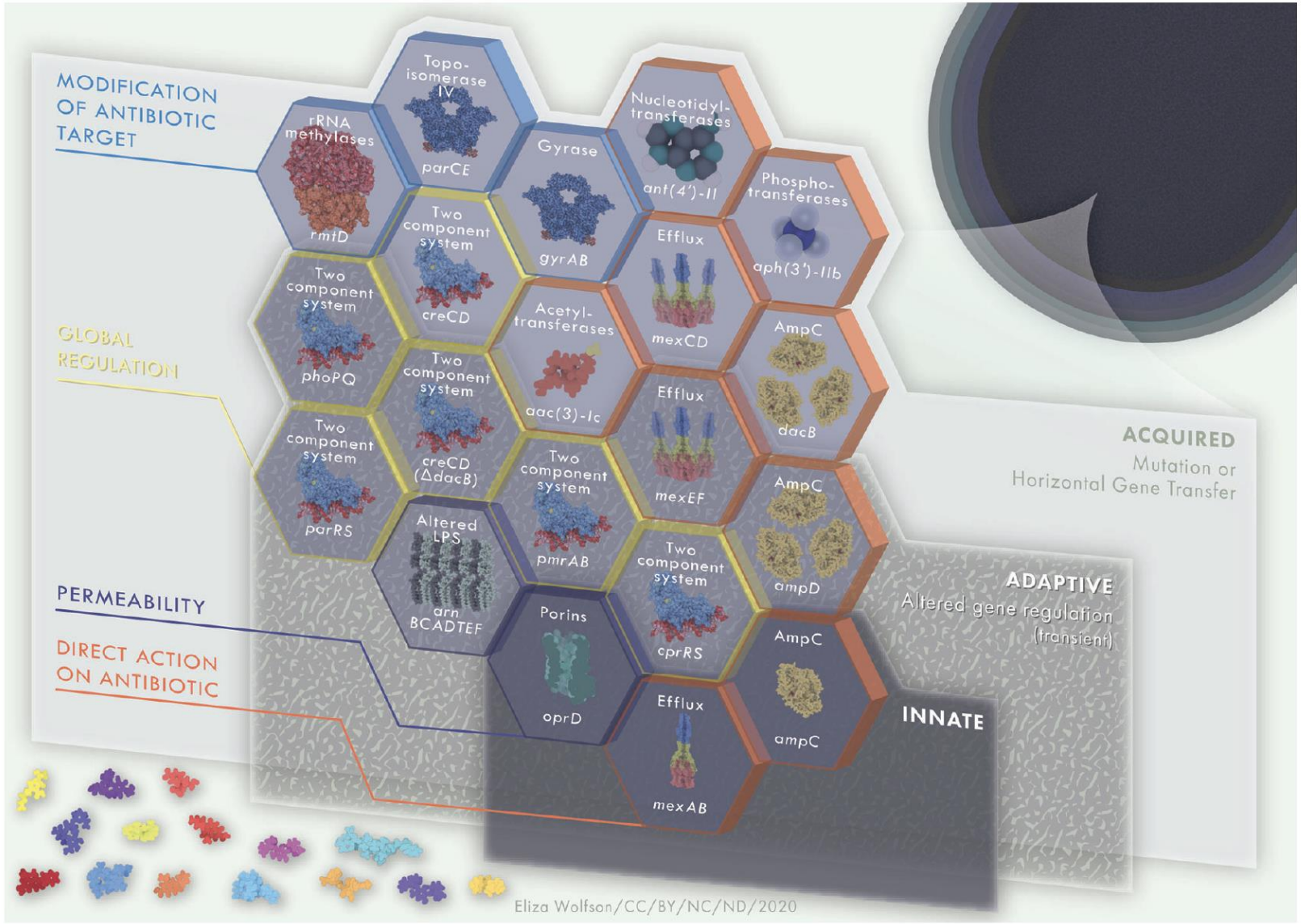
Tamma et al., Last updated March 7, 2022, and posted online at https://www.idsociety.org/practice-guideline/amrguidance/

Question 5: What are the preferred antibiotics for the treatment of infections outside of the urinary tract caused by CRE if carbapenemase production is present?

Recommendation: Meropenem-vaborbactam, ceftazidime-avibactam, and imipenem-cilastatin-relebactam are preferred treatment options for KPC-producing infections outside of the urinary tract. Ceftazidime-avibactam in combination with aztreonam, or cefiderocol as monotherapy, are preferred treatment options for NDM and other metallo-β-lactamase-producing infections. Ceftazidime-avibactam is the preferred treatment option for OXA-48-like-producing infections.

The Building Blocks of Antimicrobial Resistance in Pseudomonas aeruginosa: Implications for Current Resistance-Breaking Therapies

R. Frèdi Langendonk et al., Front. Cell. Infect. Microbiol. 2021



Epidemiología molecular, sensibilidad antibiótica y mecanismos de resistencia en P. aeruginosa en España: segundo Estudio GEMARA-SEIMC/CIBERINFEC 2022

Miquel Àngel Sastre Femenia et al., SEIMC 2022

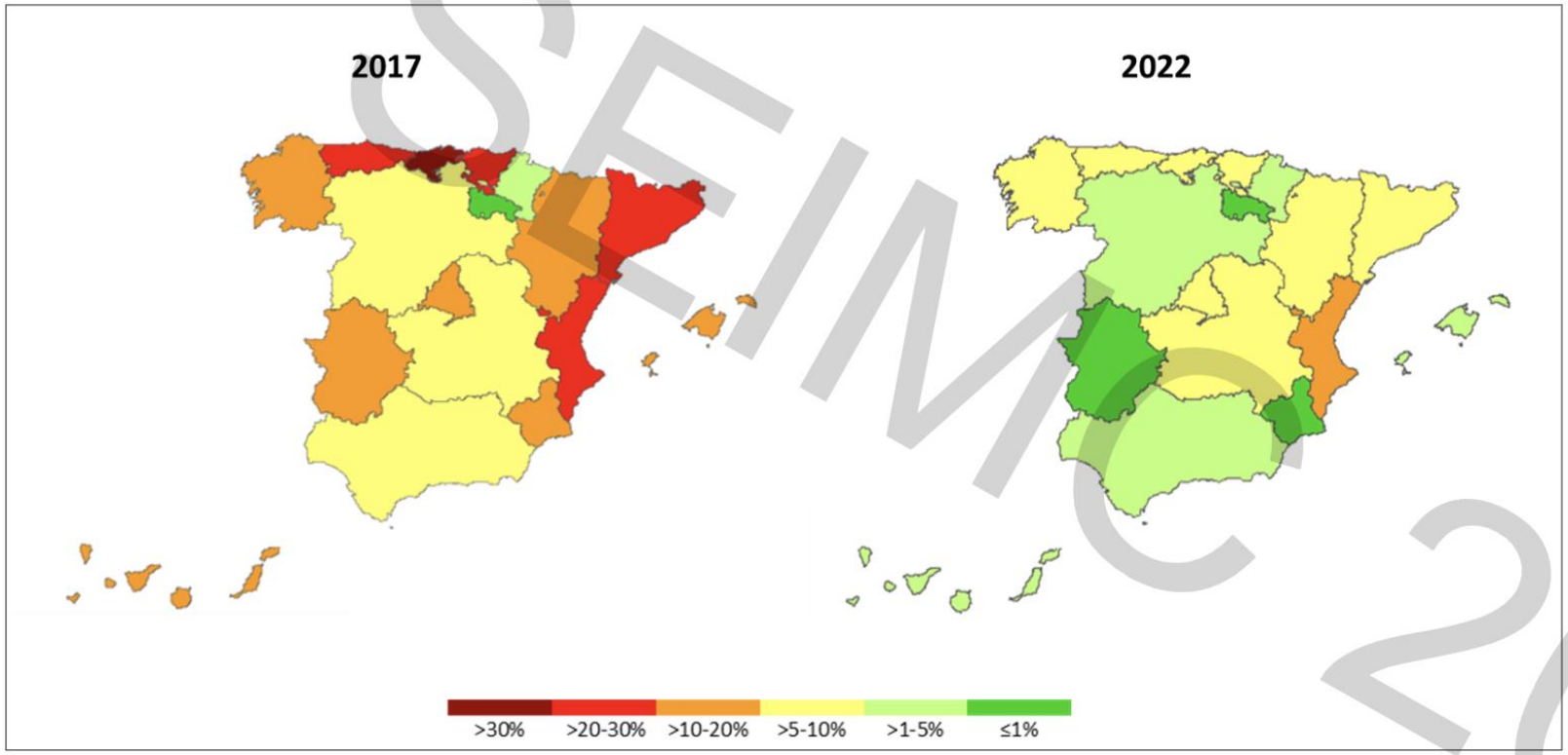


Figura 5. Diferencias en la distribución de los fenotipos XDR en España en 2017 y 2022.

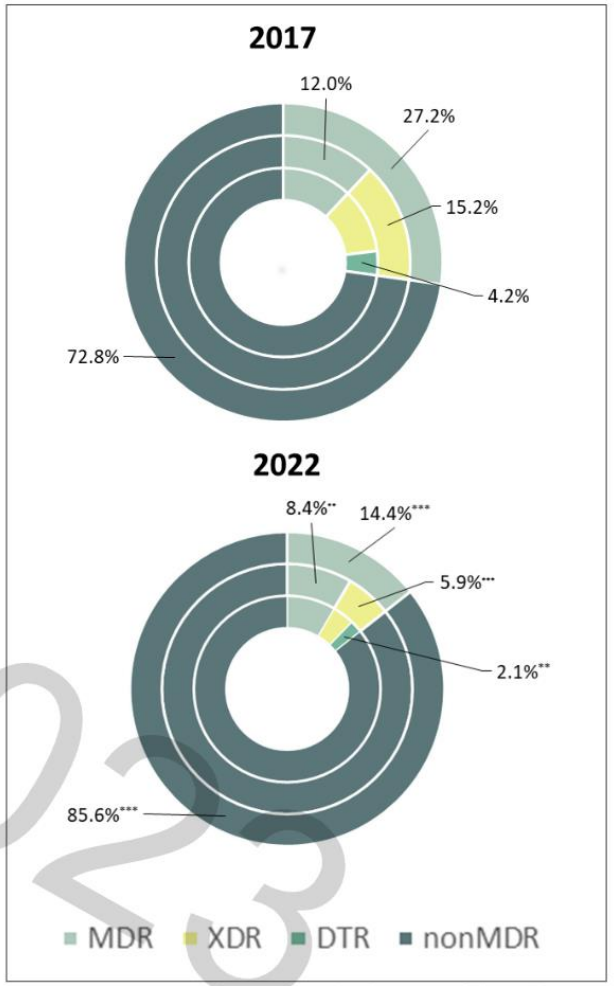


Figura 6. Comparativa de los perfiles de resistencia 2017vs2022.
***p<0.0001; ** p<0.01; *p<0.05

Epidemiología molecular, sensibilidad antibiótica y mecanismos de resistencia en P. aeruginosa en España: segundo Estudio GEMARA-SEIMC/CIBERINFEC 2022

Miquel Àngel Sastre Femenia et al., SEIMC 2022

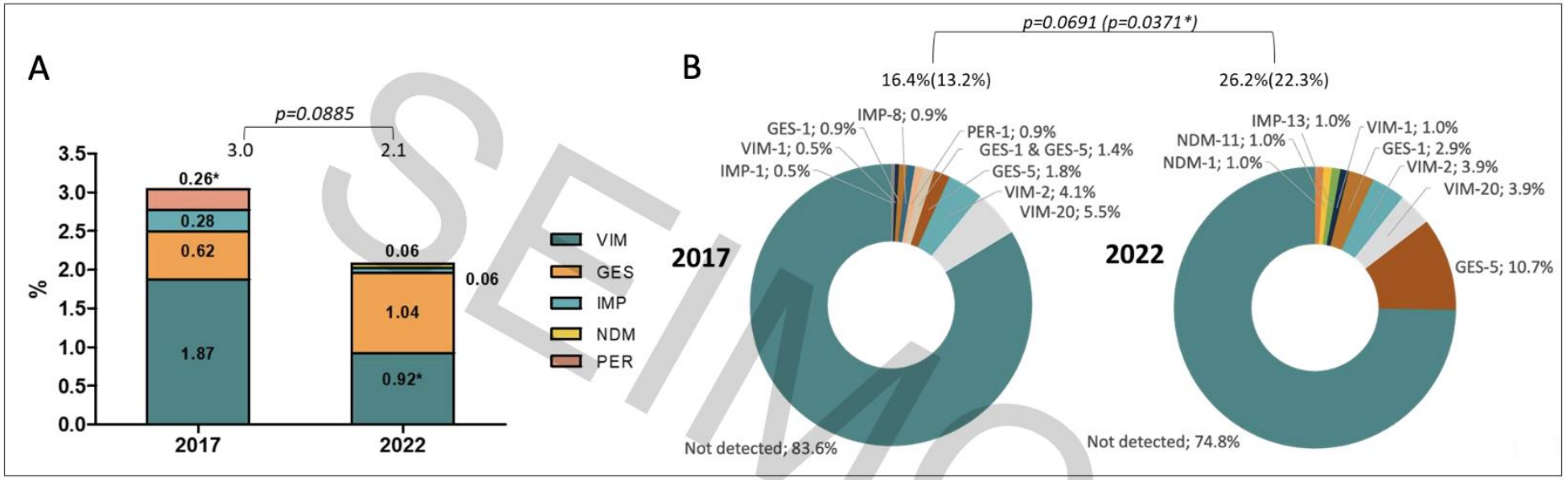


Figura 9. Prevalencia de carbapenemasas y BLEE en el total de aislados (A) y en aquellos XDR (B). *p<0.05

Influence of Multidrug Resistance and Appropriate Empirical Therapy on the 30-Day Mortality Rate of Pseudomonas aeruginosa Bacteremia

Morata L et al. Antimicrob Agents Chemother. 2012;56(9):4833-4837

TABLE 4 Multivariate analysis of risk factors associated with 30-day mortality in *P. aeruginosa* bacteremia

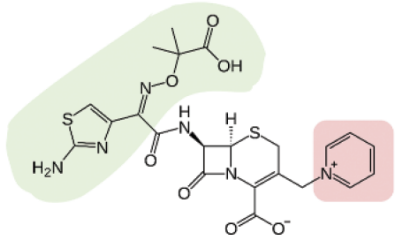
Factor	OR (95% CI)	*P* value
Age	1.02 (1.002–1.033)	0.022
Septic shock	6.58 (4.022–10.767)	<0.0001
Liver cirrhosis	3.30 (1.423–7.649)	0.005
Risk level of infection source		
Low (<15%)	(Used as reference)	
Intermediate (15–30%)	2.47 (1.410–4.326)	0.002
High (>30%)	7.27 (4.092–12.928)	<0.0001
Empirical antibiotic therapy		
Non-MDR with appropriate agent	(Used as reference)	
Non-MDR with inappropriate agent	2.18 (1.215–3.899)	0.009
MDR and inappropriate agent	4.09 (2.156–7.778)	<0.0001
MDR and appropriate agent	2.25 (0.930–5.436)	0.072

Treatment of carbapenem-resistant P. aeruginosa infections: a case for cefiderocol

R Cantón et al., Expert Review of Anti-infective Therapy 2022 20(8):1077-1094

Ceftazidime
Approved: 1984

Ceftazidime + avibactam
Approved: 2015



- Improved spectrum of activity
- Stability against broad-spectrum beta-lactamases
- Good activity against *P. aeruginosa*

- Avibactam: inhibitory activity against Class C beta-lactamases, Class A and some Class D carbapenemases

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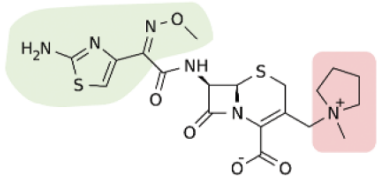
Cefepime
Approved: 1994



- Broader spectrum of activity
- Higher stability against beta-lactamases
- Good activity against *P. aeruginosa*
- Less affected by porin defects and by AmpC hyperproduction
- Reduced potential of resistance development versus ceftazidime

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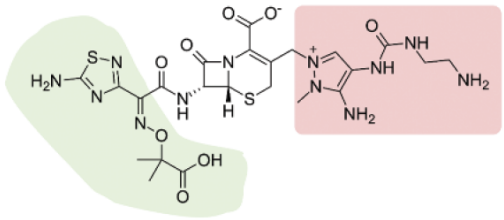
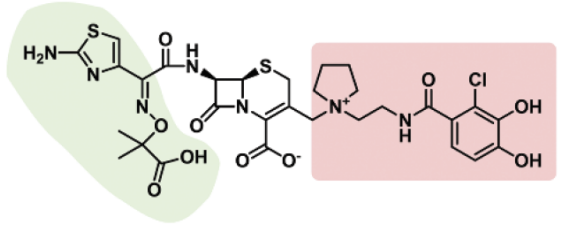
Ceftolozane + tazobactam
Approved: 2014–2015



- Increased stability against AmpC-hyperproducing *P. aeruginosa*
- Reduced potential of resistance development versus ceftazidime
- Limited Gram-positive activity

- Tazobactam: inhibitory effect of ESBLs

Cefiderocol
Approved: 2019–2020



- Iron chelation and active transport
- Improved antibacterial activity
- No activity against Gram-positives or anaerobes
- Increased stability against serine-beta-lactamases, including ESBLs, and metallo-beta-lactamases
- Activity extends to *Acinetobacter* spp. and other non-fermenters (*S. maltophilia*, *A. xylosoxidans*, *Burkholderia* spp.)

Clinical Microbiology and Infection 28 (2022) 521–547

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journal homepage: www.clinicalmicrobiologyandinfection.com

Guidelines

European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines for the treatment of infections caused by multidrug-resistant Gram-negative bacilli (endorsed by European society of intensive care medicine)

Mical Paul [1, 2, §], Elena Carrara [3, §], Pilar Retamar [4, 5], Thomas Tängdén [6], Roni Bitterman [1, 2], Robert A. Bonomo [7, 8, 9], Jan de Waele [10], George L. Daikos [11], Murat Akova [12], Stephan Harbarth [13], Celine Pulcini [14, 15], José Garnacho-Montero [16], Katja Seme [17], Mario Tumbarello [18], Paul Christoffer Lindemann [19], Sumanth Gandra [20], Yunsong Yu [21, 22, 23], Matteo Bassetti [24, 25], Johan W. Mouton [26, †], Evelina Tacconelli [3, 27, 28, *, §], Jesús Rodríguez-Baño [4, 5, §]

Enfermedades Infecciosas y Microbiología Clínica

Available online 27 July 2022

In Press, Corrected Proof What's this?

Consensus Document

Executive summary of the consensus document of the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC) on the diagnosis and antimicrobial treatment of infections due to carbapenem-resistant Gram-negative bacteria

Resumen ejecutivo del documento de consenso de la Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica (SEIMC) sobre el diagnóstico y tratamiento antimicrobiano de las infecciones por bacterias gramnegativas resistentes a carbapenémicos ☆

Vicente Pintado [a b], Patricia Ruiz-Garbajosa [c], David Aguilera-Alonso [d e], Fernando Baquero-Artigao [f], Germán Bou [g], Rafael Cantón [c], Santiago Grau [h i j],

Defining the Role of Novel β-Lactam Agents That Target Carbapenem-Resistant Gram-Negative Organisms

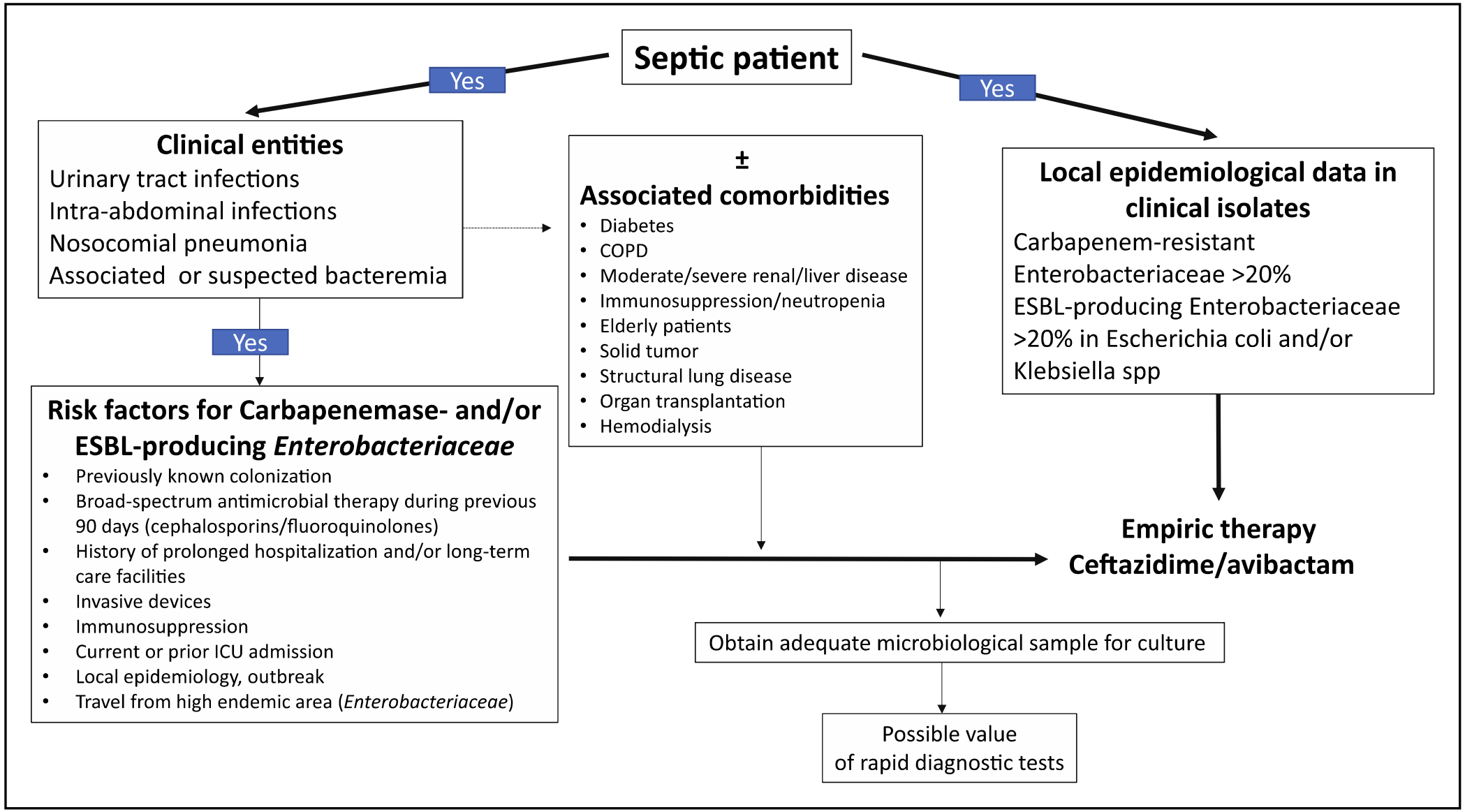
Tamma et al., J Pediat Infect Dis 2019 8(3):251-260

Agent	KPC-producer	NDM-producer	OXA-48-like-producer	Carbapenem-resistant *Pseudomonas aeruginosa*	Carbapenem-resistant *Acinetobacter baumannii*	*Stenotrophomonas maltophilia*
Aztreonam-avibactam						
Cefiderocol						
Ceftazidime-avibactam[1]						
Ceftolozane-tazobactam[1]						
Eravacycline[1,2]						
Fosfomycin (intravenous)						
Imipenem-relebactam[3]						
Meropenem-vaborbactam[1]						
Plazomicin[1,4]						
Polymyxin B[1,5] or Colistin[1,5]						
Tigecycline[1,2]						

Figure 1. Select antibiotics with activity against carbapenem-resistant organisms. Green, susceptibility anticipated to be >80%; yellow, susceptibility anticipated to be 30% to 80%; red, intrinsic resistance or susceptibility anticipated to be <30%. [1], US Food and Drug Administration–approved agent; [2], synthetic tetracycline derivative; [3], imipenem-cilastatin–relebactam; [4], synthetic aminoglycoside; [5], polymyxin class. Abbreviations: KPC, *Klebsiella pneumoniae* carbapenemase; NDM, New Delhi metallo-β-lactamase.

The ideal patient for new beta-lactam/betalactamase inhibitors

Montravers et al., Curr Opin Infect Dis 2018



Shorter Is Better

Diagnosis	Short (d)	Long (d)	Result	#RCT
CAP	3-5	5-14	Equal	13
Atypical CAP	1	3	Equal	1
VAP	8	15	Equal	2
cUTI/Pyelonephritis	5 or 7	10 or 14	Equal	9*
Intra-abdominal Infection	4	10	Equal	2
GNB Bacteremia	7	14	Equal	3**
Cellulitis/Wound/Abscess	5-6	10	Equal	4†
Debrided non-osteo DFI	10	20	Equal	1
Osteomyelitis	42	84	Equal	2
Osteo with Removed Implant	28	42	Equal	1
Debrided Diabetic Osteo	10-21	42-90	Equal	2‡
Septic Arthritis	14	28	Equal	1
AECB & Sinusitis	≤5	≥7	Equal	>25
Neutropenic Fever	AFx72 h	+ANC>500	Equal	1
Post Op Prophylaxis	0-1	1-5	Equal	54Ψ
P. vivax Malaria	7	14	Equal	1

Total: 16 Conditions — 122 RCTs

*2 RCT included males, the smaller one found lower 10-18 d f/up cure in males with 7 days of therapy but no difference at longer follow-up, larger exclusive male study found no diff in cure; **GNB bacteremia also in UTI/cIAI RCTs; †3 RCTs equal, 1 (low dose oral flucox) ↑relapses 2° endpoint; ‡all patients debrided, in 1 study total bone resection (clean margins); ΨIncludes meta-analysis of 52 RCTs; refs at https://www.bradspellberg.com/shorter-is-better

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Retos actuales en infecciones por microorganismos grampositivos

The Microbiology of Bloodstream Infection: 20-Year Trends from the SENTRY Antimicrobial Surveillance Program

Daniel J. Diekema et al., Antimicrob Agents and Chem 2019

TABLE 4 Rank order of pathogens causing BSI worldwide submitted to the SENTRY Program, 1997–2016, by community or hospital onset

	Pathogen (%)	
Rank	Community onset (*n* = 102,638)	Hospital onset (*n* = 103,945)
1	*E. coli* (26.6)	*S. aureus* (21.3)
2	*S. aureus* (22.4)	*E. coli* (15.6)
3	*K. pneumoniae* (7.2)	*K. pneumoniae* (8.8)
4	*S. pneumoniae* (5.2)	*P. aeruginosa* (7.4)
5	*E. faecalis* (4.7)	*E. faecalis* (6.4)
6	*P. aeruginosa* (3.7)	*S. epidermidis* (4.8)
7	*E. cloacae* (2.4)	*E. faecium* (4.3)
8	*S. agalactiae* (2.3)	*E. cloacae* (4.0)
9	*S. epidermidis* (2.2)	*A. baumannii*[a] (3.2)
10	*P. mirabilis* (2.0)	*S. marcescens* (2.1)

[a]*Acinetobacter baumannii-Acinetobacter calcoaceticus* species complex.

The Microbiology of Bloodstream Infection: 20-Year Trends from the SENTRY Antimicrobial Surveillance Program

Daniel J. Diekema et al., Antimicrob Agents and Chem 2019

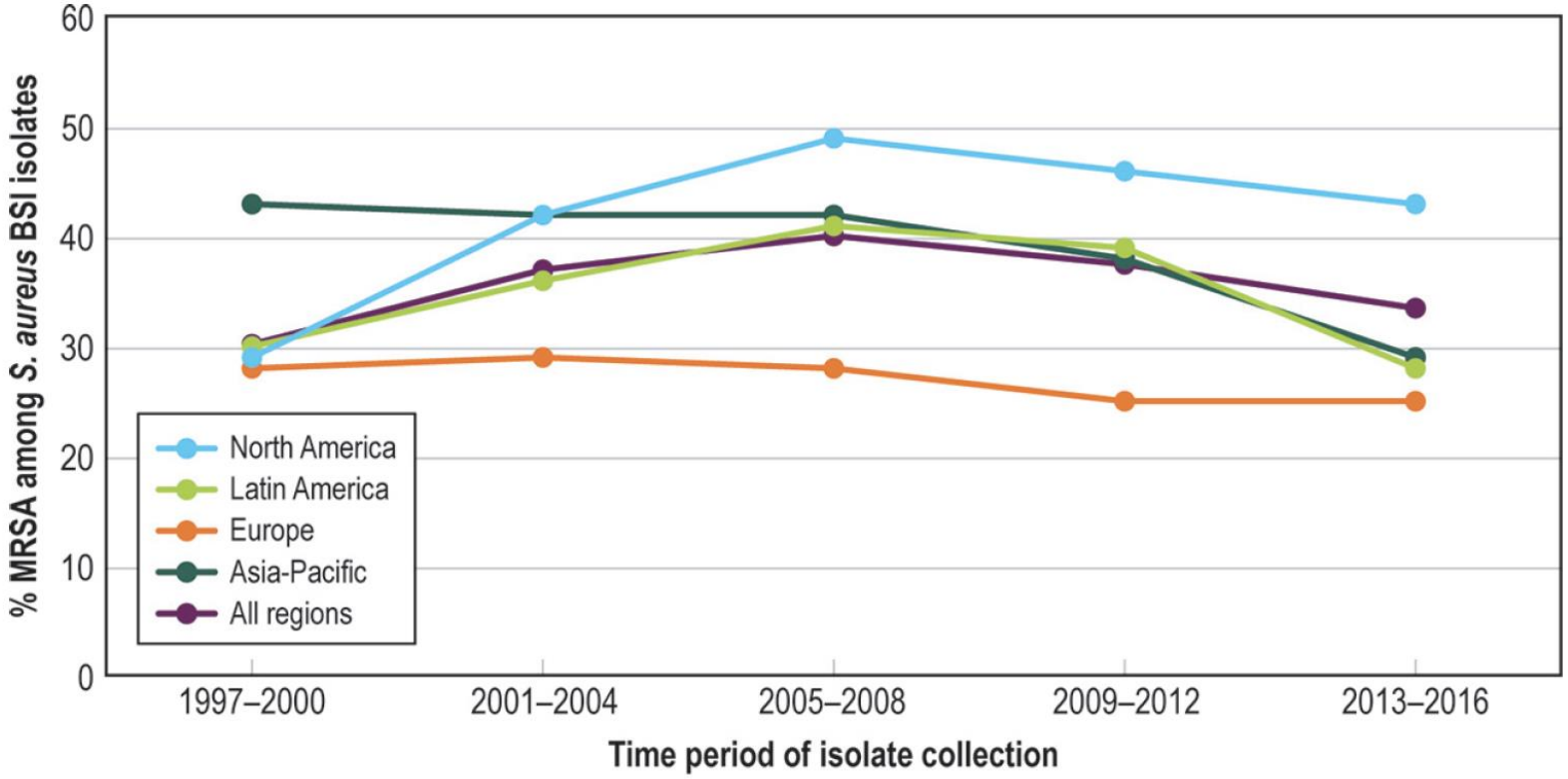


FIG 1 Twenty-year trend in percent methicillin-resistant *S. aureus* (MRSA) among all *S. aureus* bloodstream infections, SENTRY, 1997 to 2016.

Antimicrobial Treatment of Staphylococcus aureus Biofilms

Felipe Francisco Tuon et al., Antibiotics 2023

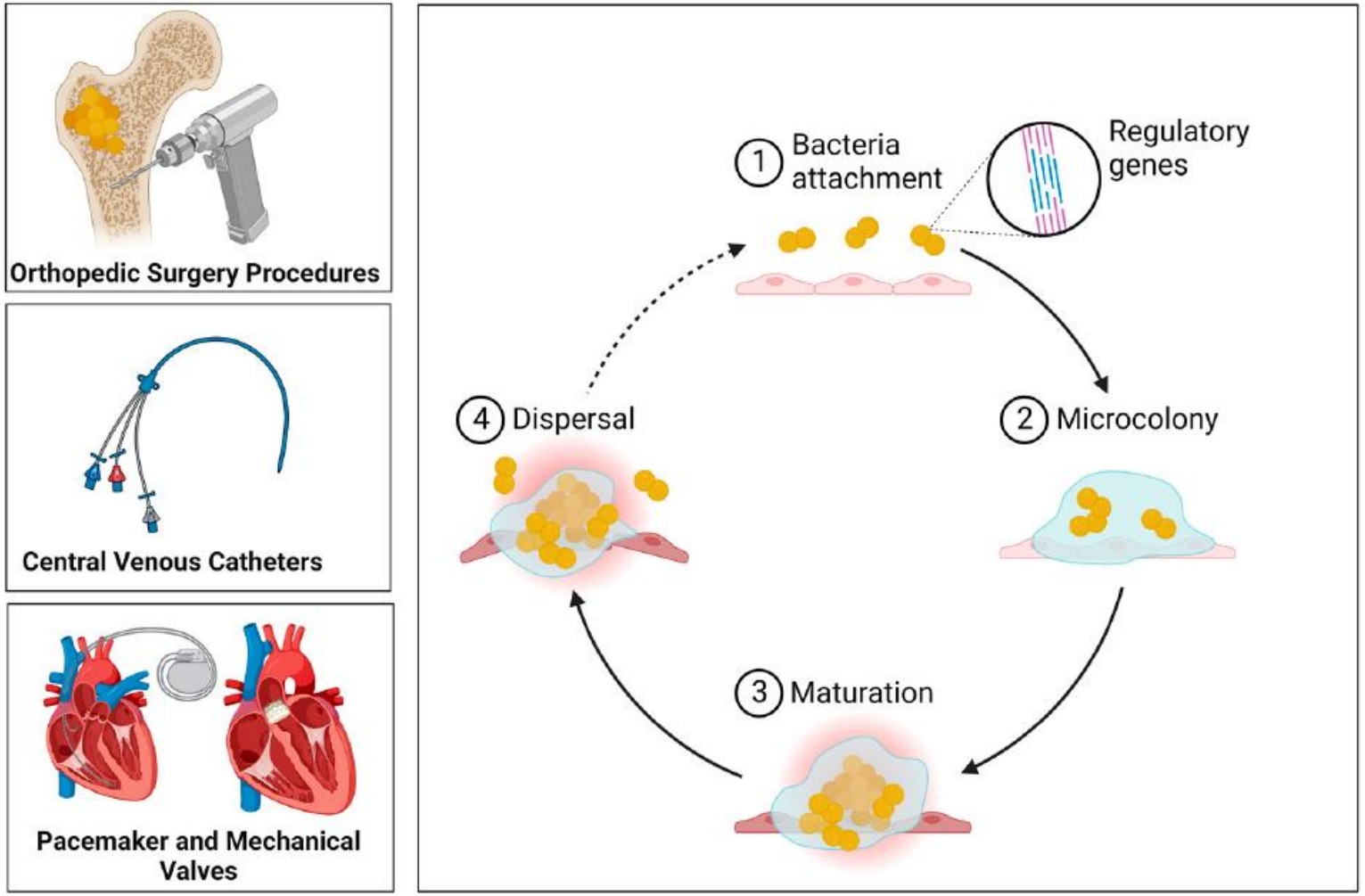
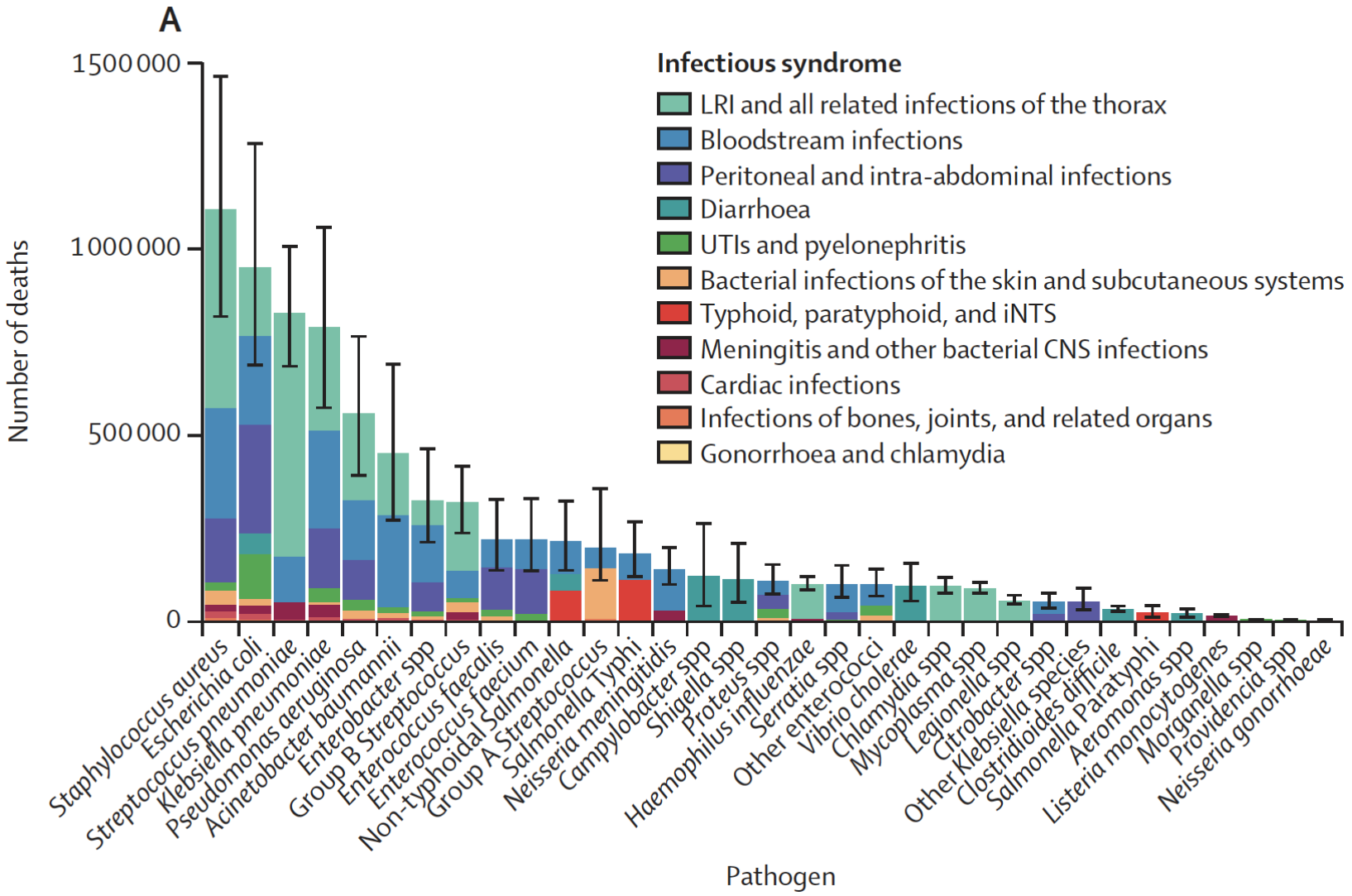


Figure 2. Development of staphylococcal biofilm.

Global mortality associated with 33 bacterial pathogens in 2019: a systematic analysis for the Global Burden of Disease Study 2019

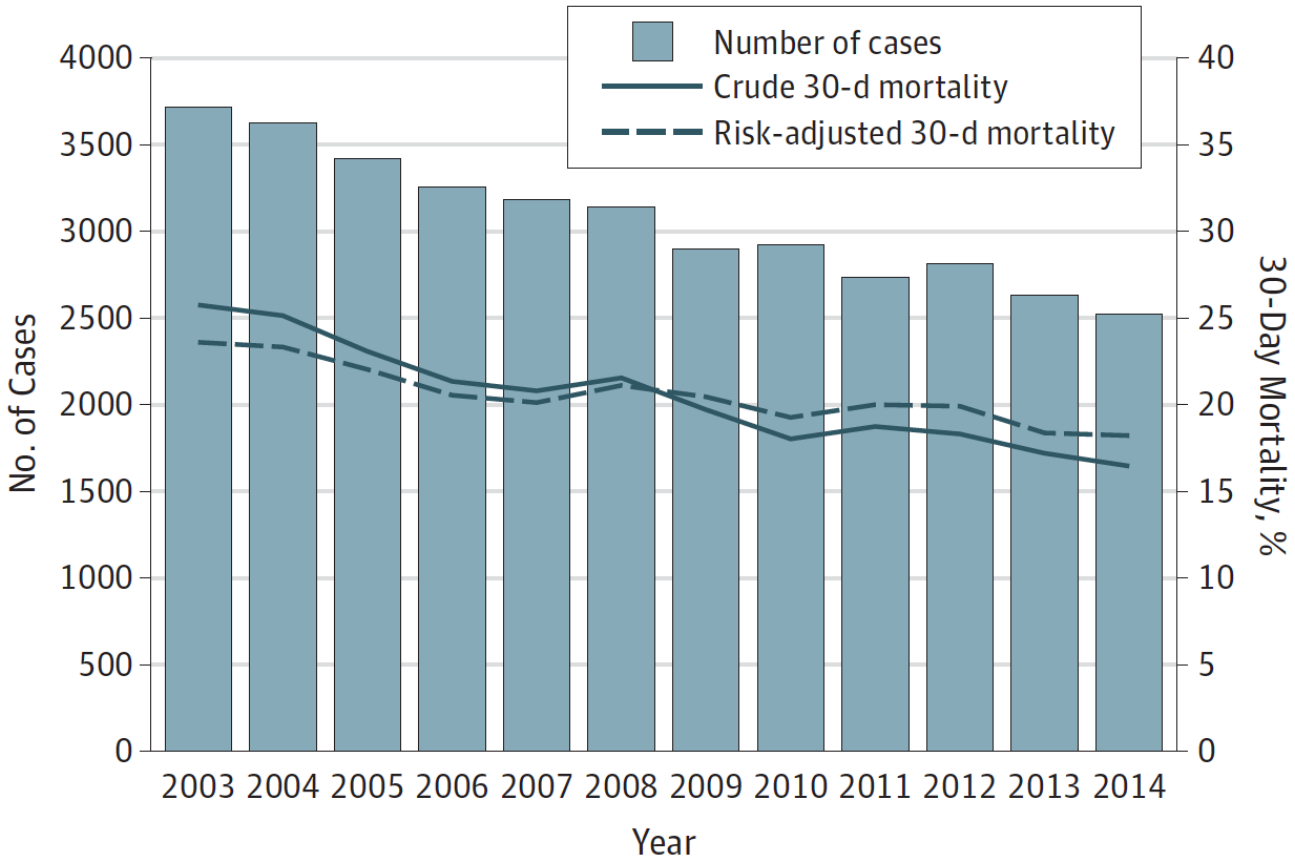
GBD 2019 Antimicrobial Resistance Collaborators. Lancet 2022



Association of Evidence-Based Care Processes With Mortality in S. aureus BSI at Veterans Hospitals, 2003-2014

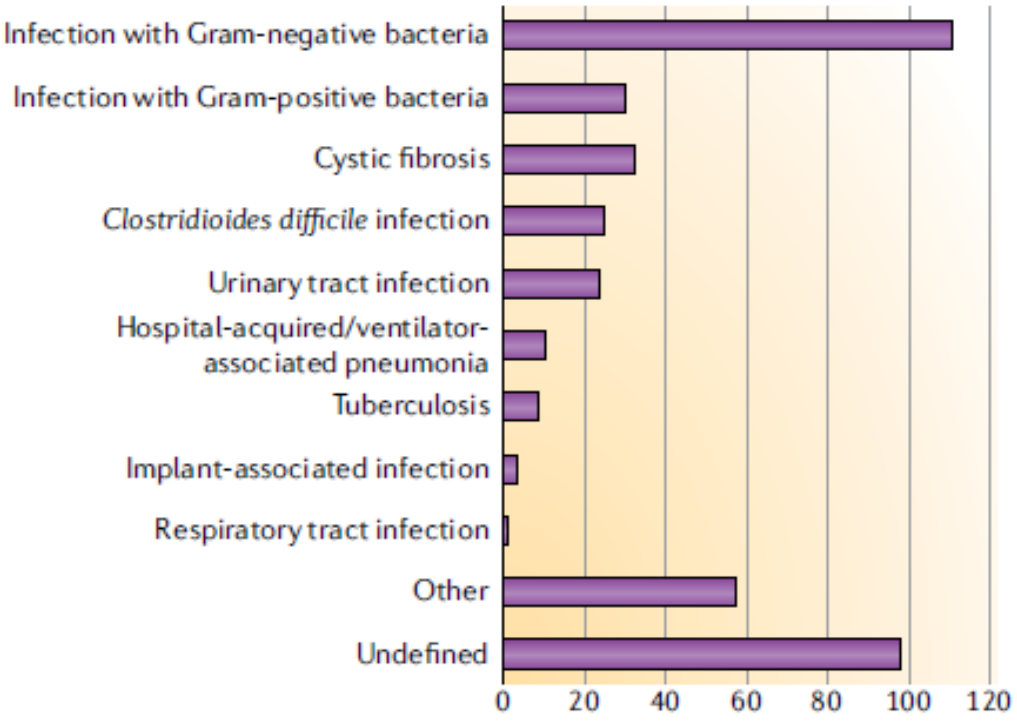
Goto et al., JAMA Intern Med 2017

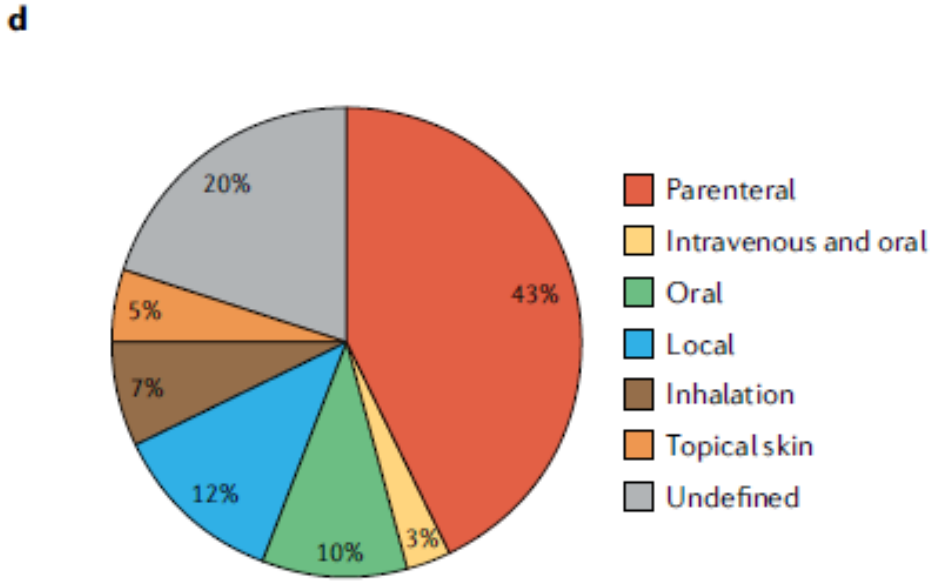
Figure 1. Trends in the Incidence of *Staphylococcus aureus* Bacteremia and All-Cause 30-Day Mortality, 2003-2014



The global preclinical antibacterial pipeline

Ursula Theuretzbacher et al., Microbiology Spectrum 2017





Clindamicina
Cotrimoxazol
Rifampicina
Doxiciclina
Minociclina
Ácido fusídico
Levofloxacino

Vancomicina
Teicoplanina

Vancomicina
Teicoplanina
Linezolid
Daptomicina

Vancomicina
Teicoplanina
Linezolid
Daptomicina
Tigeciclina
Ceftarolina
Ceftobiprole

Vancomicina
Teicoplanina
Linezolid
Daptomicina
Tigeciclina
Ceftarolina
Ceftobiprole
Dalbavancina
Tedizolid

Vancomicina
Teicoplanina
Linezolid
Daptomicina
Tigeciclina
Ceftarolina
Ceftobiprole
Dalbavancina
Tedizolid
Oritavancina
Telavancina*
Delafloxacino

Vancomicina
Teicoplanina
Clindamicina
Cotrimoxazol
Rifampicina
Doxiciclina
Minociclina
Ácido fusídico
Levofloxacino
Linezolid
Daptomicina
Tigeciclina
Ceftarolina
Ceftobiprole
Dalbavancina
Tedizolid
Oritavancina
Telavancina*
Delafloxacino
Omadaciclina*
Iclaprim*
Lefamulina*
Nemonoxacina*
…

*Fármacos no comercializados en España

Treatment of osteoarticular, cardiovascular, intravascular-catheter-related and other complicated infections with dalbavancin and oritavancin: A systematic review

Geren Thomas et al., Int J Antimicrob Agents 2020

isms [7,8]. To date, ABSSSIs remain the only approved indication for both laLGPs, but this may be an inefficient use of their properties. Factors weighing against the use of these agents as empiric therapy are their cost relative to other glycopeptide antibiotics, and the risk of prolonged – even unnecessary – exposure to the drug if the causative pathogen is non-susceptible or susceptible to more narrow intravenous (IV) or oral therapies. This unnecessary administration may lead to development of antimicrobial resistance and adverse drug reactions (ADRs).

Management of Staphylococcus aureus Bloodstream Infections

Aurelia Kimmig et al., Frontiers in Microbiol 2021

- Ceftarolina
- Combinaciones con Cefazolina
- Combinaciones con Ceftarolina
- Lipoglicopéptidos

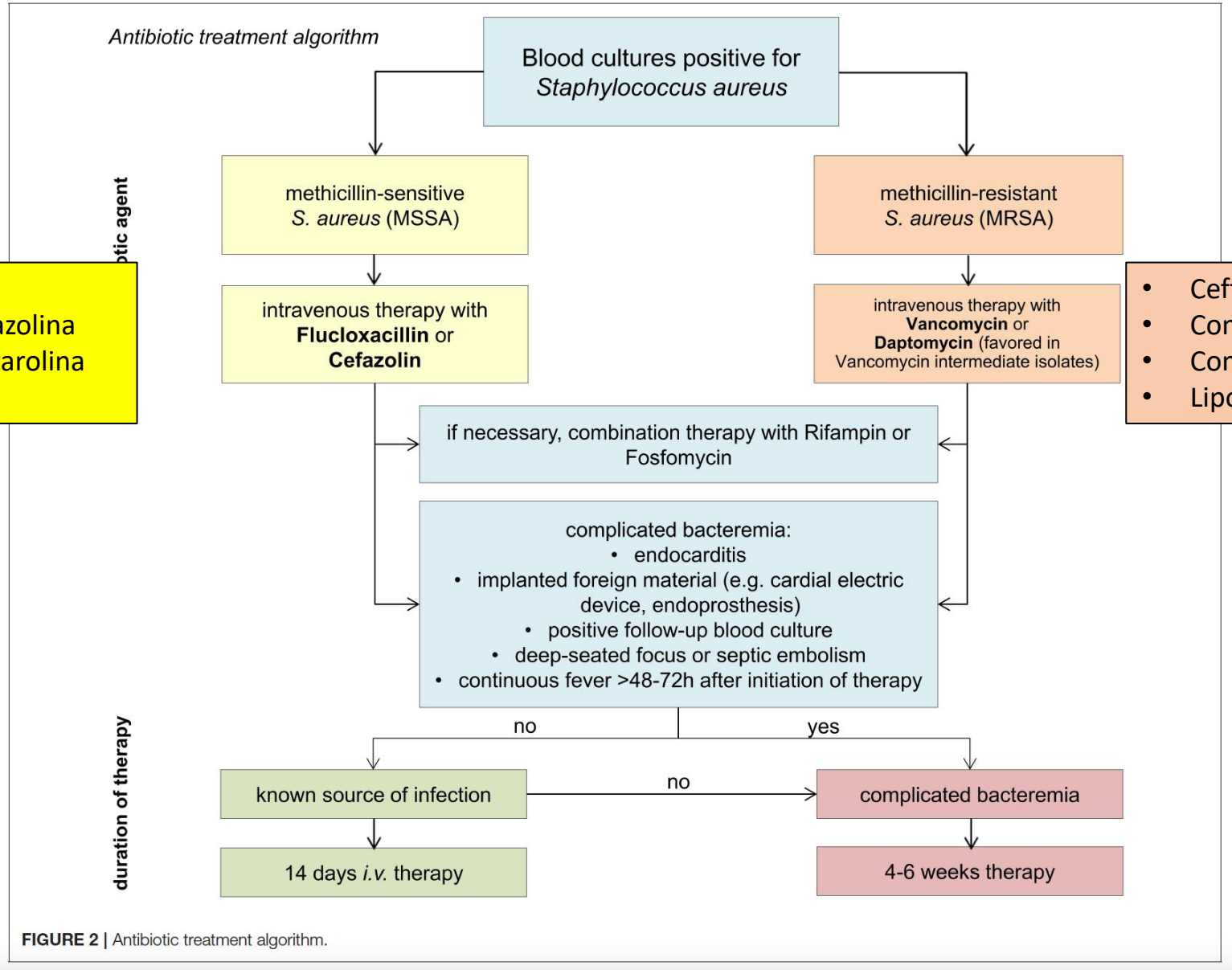


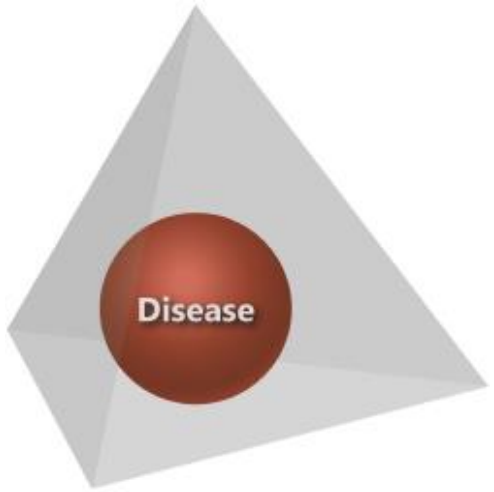
FIGURE 2 | Antibiotic treatment algorithm.

- Ceftarolina
- Combinaciones con Ceftarolina
- Combinaciones con Daptomicina
- Lipoglicopéptidos

Retos actuales en infecciones fúngicas

Recent Advances in Fungal Infections: From Lung Ecology to Therapeutic Strategies With a Focus on Aspergillus spp

Palmieri et al., Frontiers in Medicine 2022



Recent Advances in Fungal Infections: From Lung Ecology to Therapeutic Strategies With a Focus on Aspergillus spp

Palmieri et al., Frontiers in Medicine 2022

El RETO de una IFI distinta

-Paciente emergente
-Patogenia diferente
-Presentación diferente
-Diagnóstico diferente
-Profilaxis y tratamiento diferente
-Mortalidad diferente

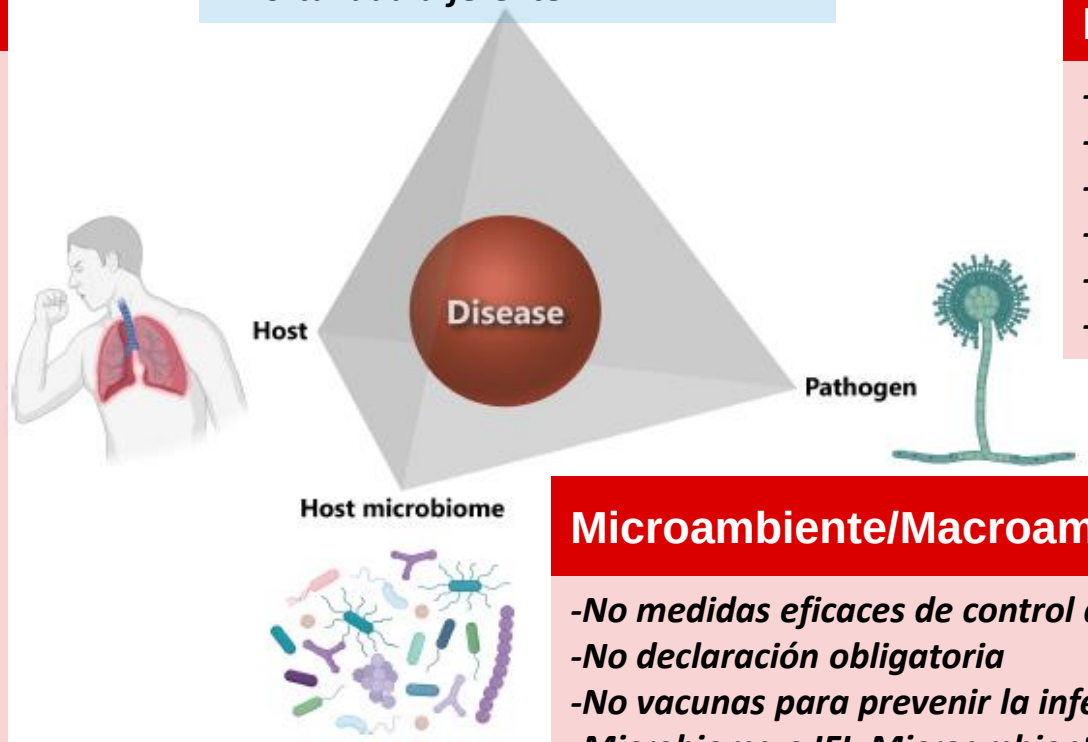
Pacientes emergentes Poblaciones especiales

-Neutropenia

-Aumento de la población de riesgo = Aumento de las tasas de infección fúngica: UCI, corticosteroides, EPOC, TOS, neoplasia sólida, VIH, cirrosis descompensada, gripe, nuevos IS, malnutrición, diabetes, sepsis, SARSCoV2,…

-Infección fúngica relacionada con la asistencia sanitaria

+++ La dificultad inherente del paciente crítico/hematológico



Hongos emergentes Resistencias emergentes

-Candida auris
-Especies de Candida resistentes
-Especies crípticas de Aspergillus
-Resistencia a azoles
-Nuevos fármacos
-Nuevas posibilidades diagnósticas

Microambiente/Macroambiente

-No medidas eficaces de control ambiental
-No declaración obligatoria
-No vacunas para prevenir la infección
-Microbioma e IFI. Microambiente pulmonar (Fe, Ca, pH,…)

WHO fungal priority pathogens list to guide research, development and public health action. Nov 2022

Critical group	High group	Medium group
 *Cryptococcus neoformans*	 *Nakaseomyces glabrata (Candida glabrata)*	 *Scedosporium* spp.
 *Candida auris*	 *Histoplasma* spp.	 *Lomentospora prolificans*
 *Aspergillus fumigatus*	 Eumycetoma causative agents	 *Coccidioides* spp.
 *Candida albicans*	 Mucorales	 *Pichia kudriavzeveii (Candida krusei)*
	 *Fusarium* spp.	 *Cryptococcus gattii*
	 *Candida tropicalis*	 *Talaromyces marneffei*
	 *Candida parapsilosis*	 *Pneumocystis jirovecii*
		 *Paracoccidioides* spp.

The global problem of antifungal resistance: prevalence, mechanisms, and management

David S Perlin et al., Lancet 2017

	Azole	Echinocandin	Polyene
Target site modification	Yes	Yes	..
Target abundance	Yes	..	Yes
Target site overexpression	Yes	..	..
Drug pump upregulation	Yes	..	..
Biofilm formation	Yes	Yes	Yes
Non-target effects	Yes	Yes	Yes
Most *Candida* spp and *Aspergillus* spp covered			

Table: **Major categories of mechanisms of resistance by drug class**

The importance of antimicrobial resistance in medical mycology

Gow et al., Nature Com 2022

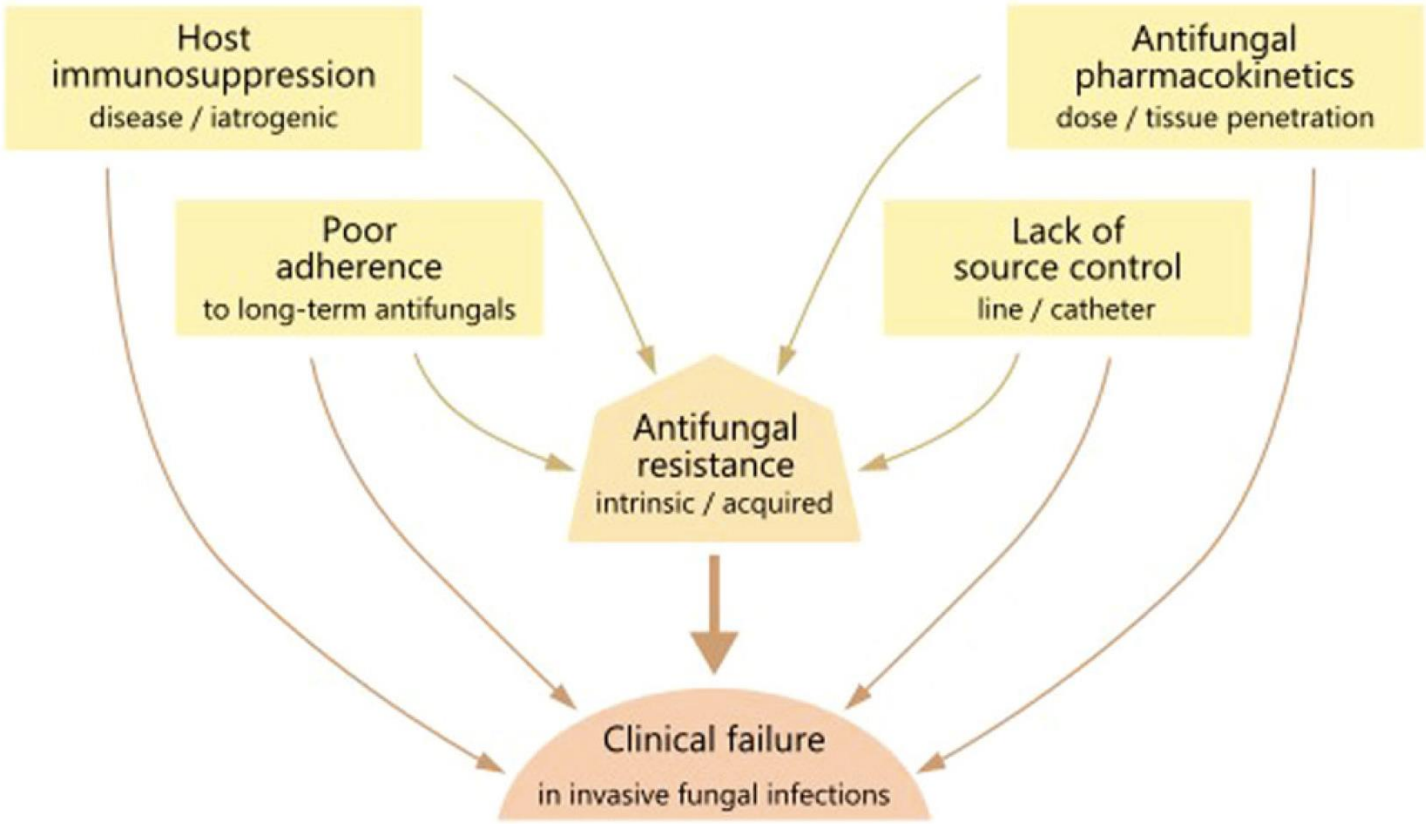


Fig. 2 | Factors mediating the contribution of antifungal resistance to clinical failure. All of the factors contributing to clinical failure in invasive fungal infection are also drivers of antifungal resistance.

Azole resistance in Aspergillus fumigatus: can we retain the clinical use of mold-active antifungal azoles?

Verweij et al., Clin Infect Dis 2016

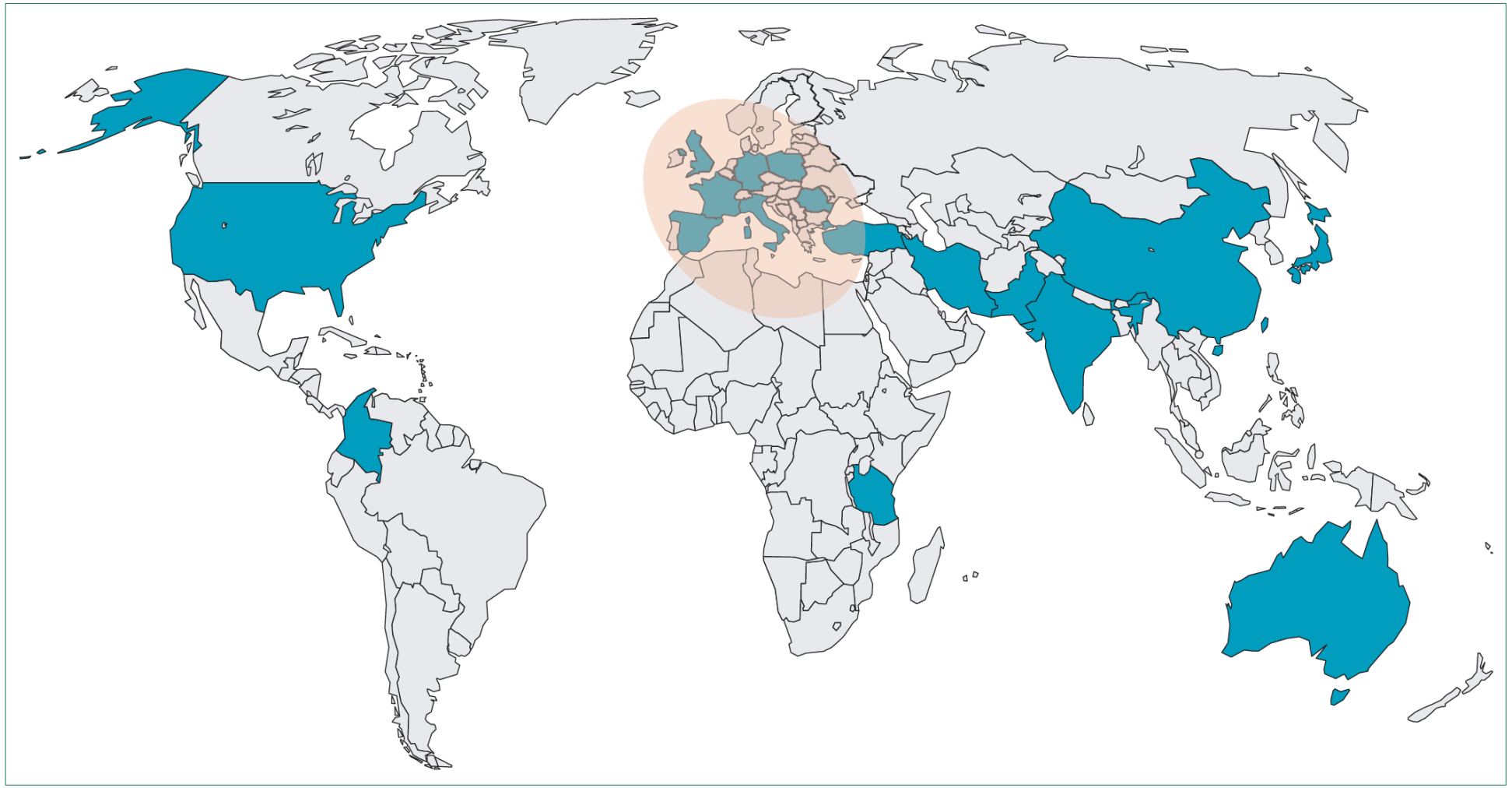


Figure 1: **Countries reporting azole-resistant isolates of *Aspergillus fumigatus* with either TR_{34}/L98H or TR_{46}/Y121F/T289A modifications**
Countries where mechanistic resistance is found are shown in blue. The region of highest burden of resistance is marked by the shaded oval (adapted from Verweij et al[47]).

Azole resistance survey on clinical A fumigatus in Spain

Escribano et al., Clin Microb Infect 2020

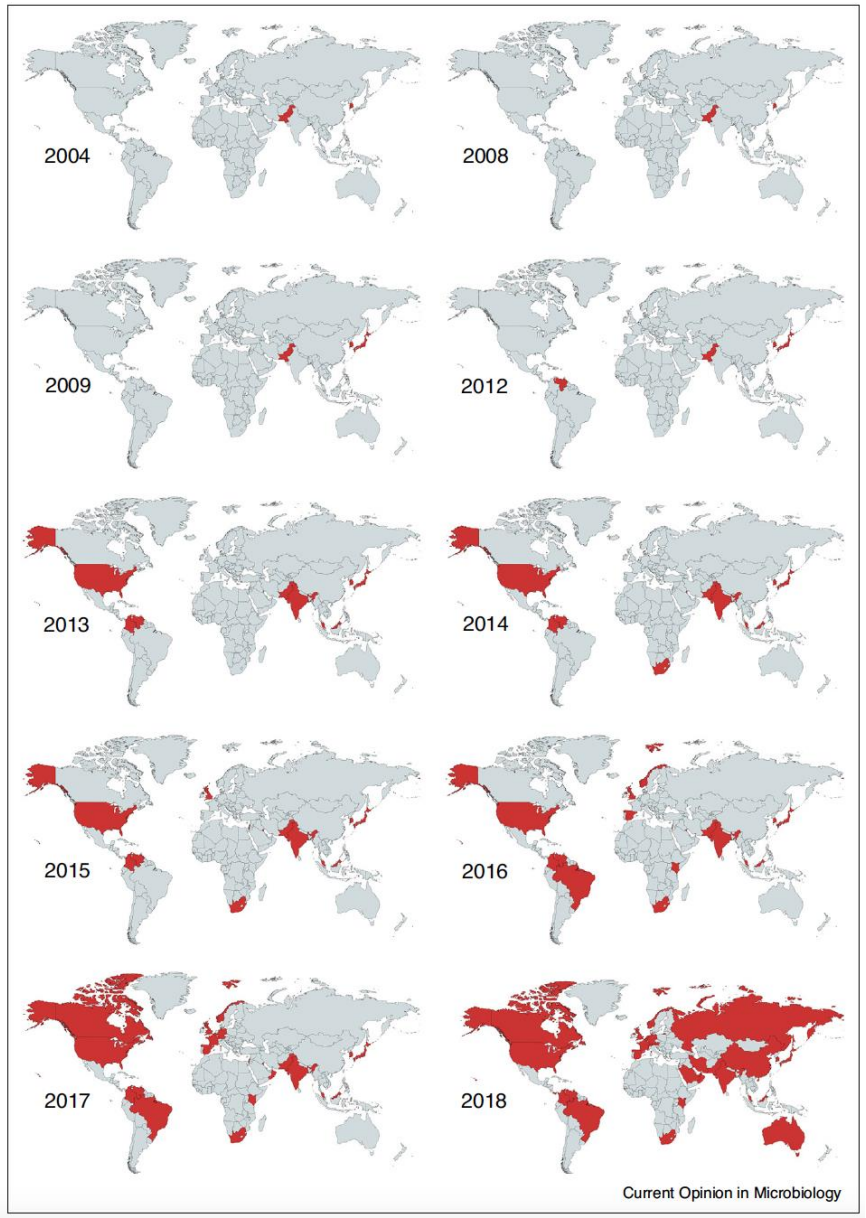
Table 2
Minimum inhibitory concentration distributions for amphotericin B, itraconazole, voriconazole, posaconazole, and isavuconazole against the 847 isolates

	GM	MIC distributions (number of isolates at each MIC, in mg/L)											Non-wild type		Resistance (2018 breakpoints)		Resistance (2020 breakpoints)	
		0.016	0.03	0.06	0.125	0.25	0.5	1	2	4	8	≥16	No. of isolates	%	No. of isolates	%	No. of isolates	%
***A. fumigatus sensu lato* (*n* = 847)**																		
Amphotericin B	0.34	0	1	5	70	407	306	45	**7**	**5**	**1**	**0**	13	1.5	6	0.7	13	1.5
Itraconazole	0.41	0	0	0	26	427	328	21	**2**	**2**	**2**	**39**	45	5.3	43	5.1	45	5.3
Voriconazole	0.62	0	0	0	3	82	529	177	**19**	**27**	**7**	**3**	56	6.6	37	4.4	56	6.6
Posaconazole	0.09	2	46	441	279	42	**27**	**3**	**0**	**1**	**0**	**6**	37	4.4	37	4.4	46	5.4
Isavuconazole	0.75	0	0	0	0	13	440	333	26	**14**	**17**	**4**	35	4.1	61	7.2	48	5.6
***A. fumigatus sensu stricto* (*n* = 828)**																		
Amphotericin B	0.32	0	1	5	68	407	305	42	**0**	**0**	**0**	**0**	0	0	0	0	0	0
Itraconazole	0.39	0	0	0	26	426	326	15	**2**	**1**	**1**	**31**	35	4.2	33	4	35	4.2
Voriconazole	0.59	0	0	0	3	82	529	176	**13**	**19**	**3**	**3**	38	4.6	25	3	38	4.6
Posaconazole	0.09	2	46	440	278	32	**20**	**3**	**0**	**1**	**0**	**6**	30	3.6	30	3.6	34	4.1
Isavuconazole	0.74	0	0	0	0	13	440	327	18	**10**	**16**	**4**	30	3.6	48	5.8	35	4.2
Cryptic species (*n* = 19)																		
Amphotericin B	1.57	0	0	0	2	0	1	3	**7**	**5**	**1**	**0**	13	68.4	6	31.6	13	68.4
Itraconazole	3.61	0	0	0	0	1	2	6	**0**	**1**	**1**	**8**	10	52.6	10	52.5	10	52.6
Voriconazole	3.48	0	0	0	0	0	0	1	**6**	**8**	**4**	**0**	18	94.7	12	63.1	18	94.7
Posaconazole	0.29	0	0	1	1	10	**7**	**0**	**0**	**0**	**0**	**0**	7	36.8	7	36.8	12	63.1
Isavuconazole	2.00	0	0	0	0	0	0	6	8	**4**	**1**	**0**	5	26.3	13	68.4	13	68.4

- *High rate (7.4%) of azole resistance. Higher in cryptic species than in A. fumigatus sensu stricto (95% vs. 5.5%)*
- *No resistance to AMB in A. fumigatus sensu stricto*

Global epidemiology of emerging Candida auris

Rhodes, J. & Fisher, M. C., Curr. Opin. Microbiol 2019



Timeline showing the expanding worldwide detection of *C. auris*.

Invasive Candidiasis

Pappas et al., Nature Revs 2018

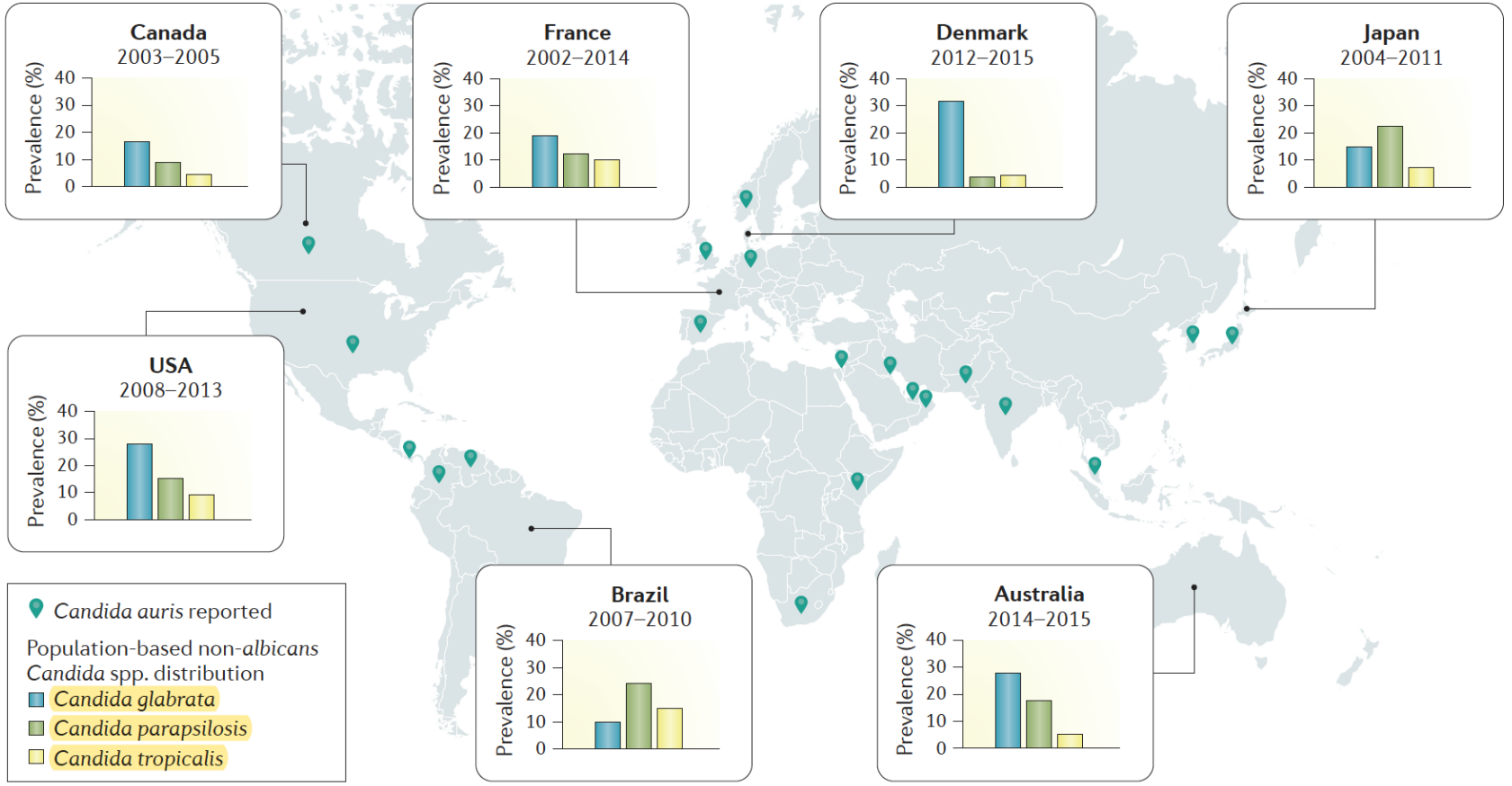


Figure 2 | **Geographical variations in the distribution of *Candida* species.** Globally, *Candida albicans* is the most prevalent species associated with invasive candidiasis; however, the distribution of non-*albicans* *Candida* spp. varies greatly, as exemplified in the representative countries shown. Of note, the species distribution may have changed since the data were collected. An increasing number of countries have reported cases of *Candida auris* infection. Data presented are from Australia, Brazil, Canada, Denmark, France, Japan and the United States[6,200–205]. Data on *C. auris* are from the Centers for Disease Control and Prevention (last accessed 27 March 2018).

The global problem of antifungal resistance: prevalence, mechanisms, and management

David S Perlin et al., Lancet 2017

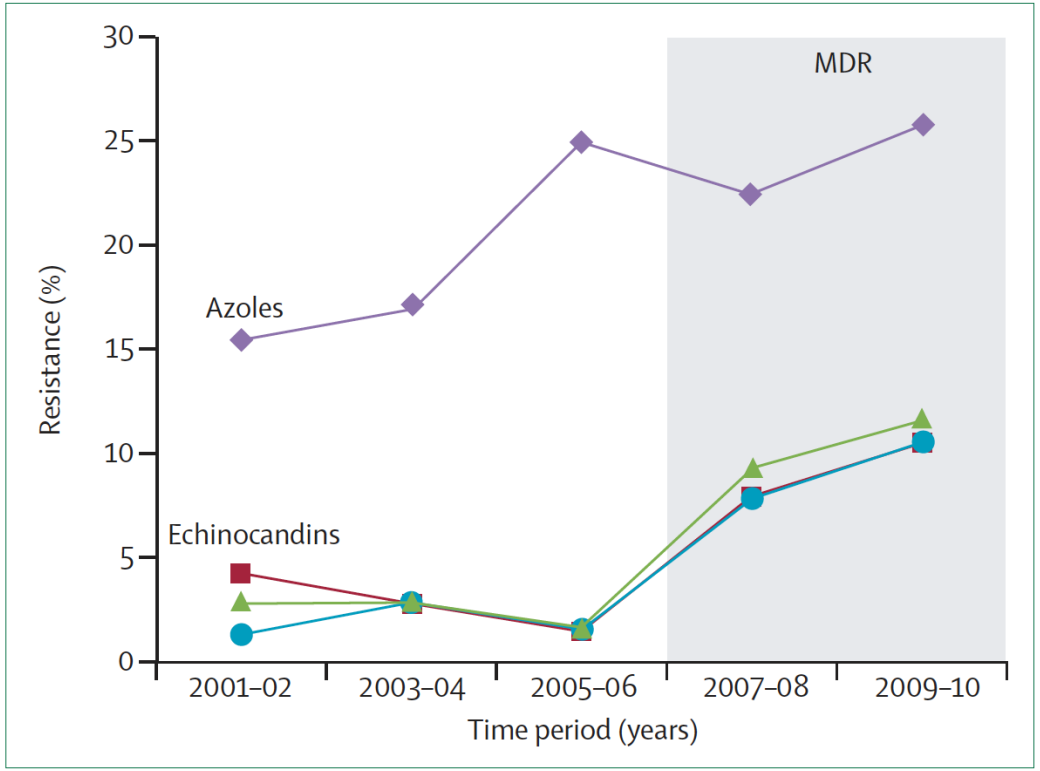


Figure 3: **Parallel rise in azole and echinocandin resistance in *Candida glabrata* bloodstream isolates over a 10-year period, showing emergence of multidrug-resistant strains**

The grey-shaded box shows the time of emergence of substantial multidrug resistance. The three echinocandin-class drugs are shown: red, anidulafungin; green, caspofungin; blue, micafungin (adapted from Alexander et al[73]). MDR=multidrug resistance.

Fluconazole-resistant Candida parapsilosis: A new emerging threat in the fungi arena

Escribano et al., Front. Fungal Bio 2022

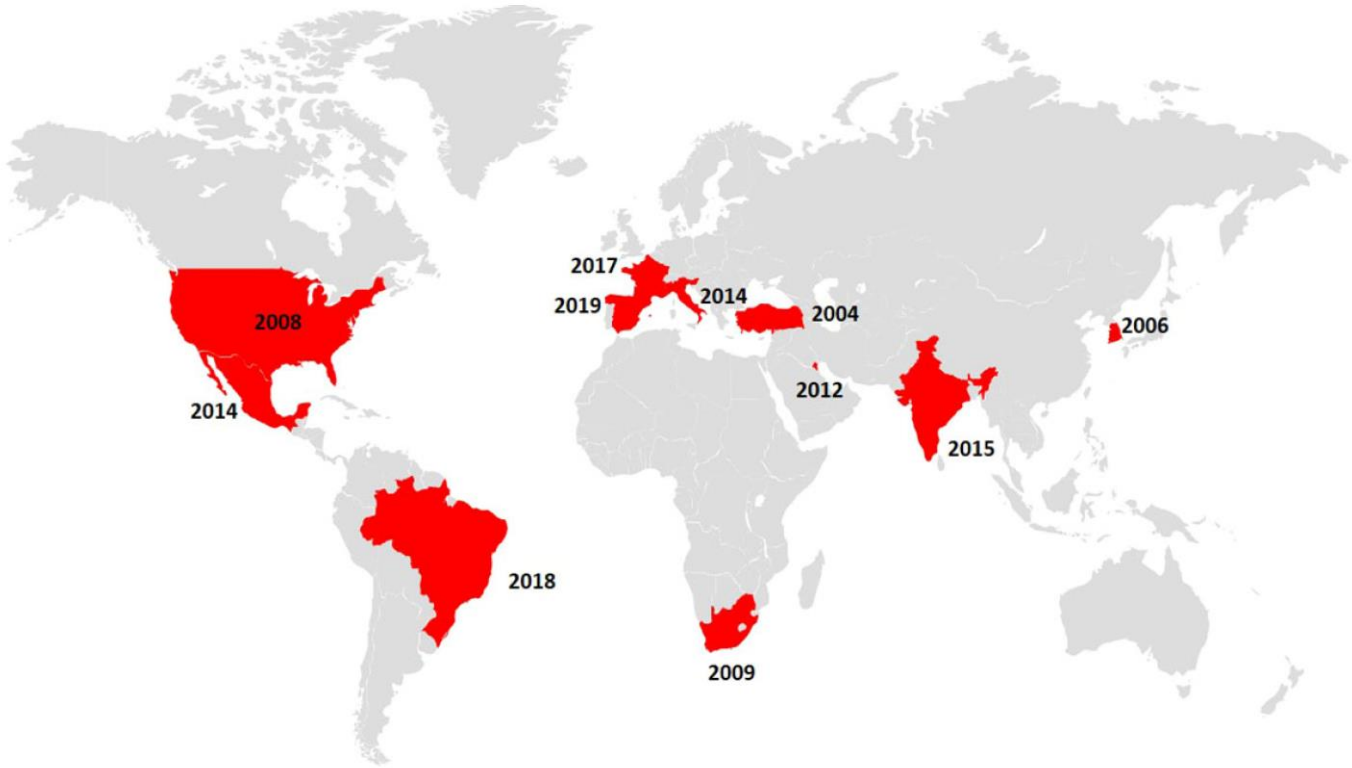
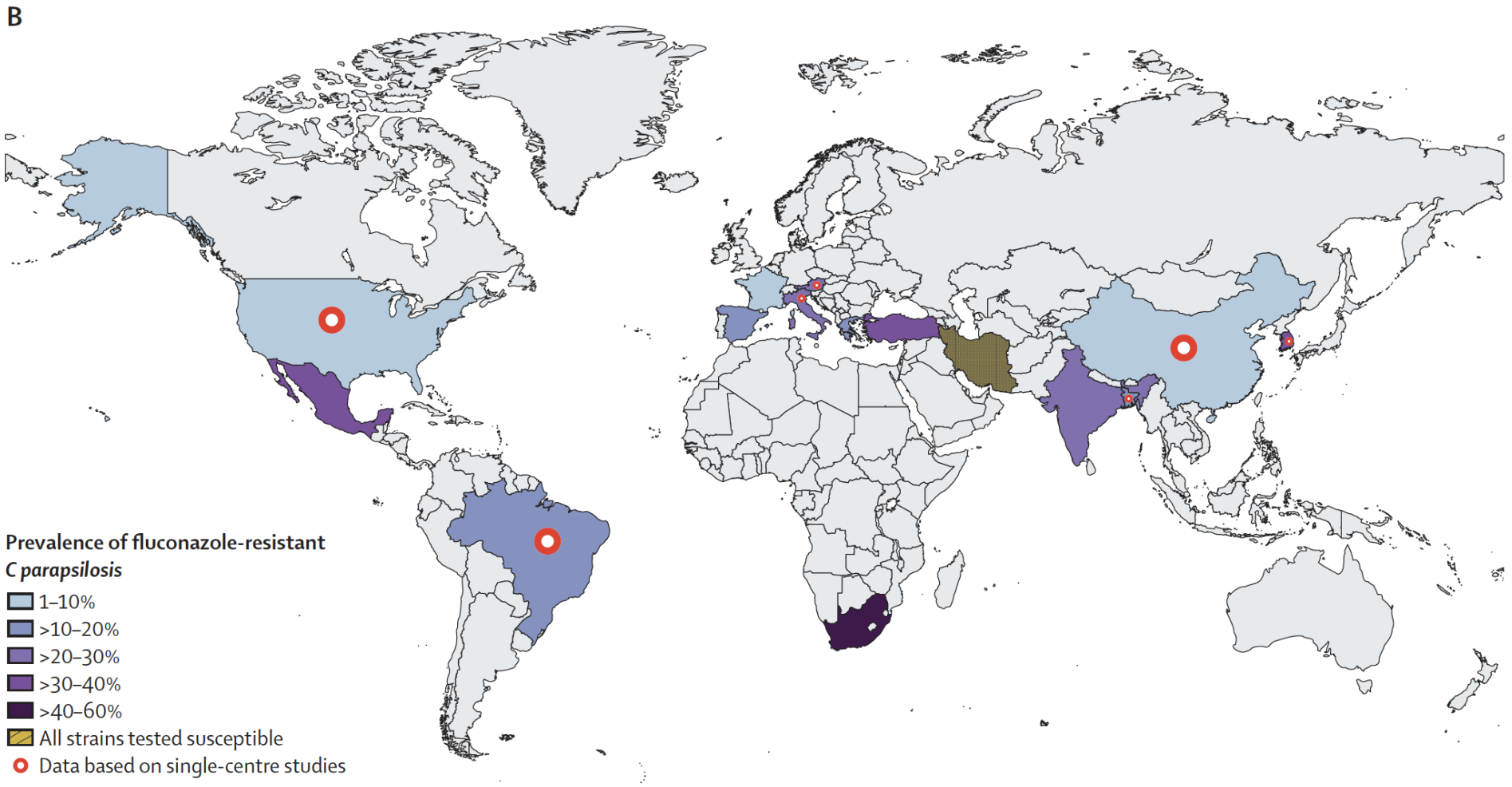


FIGURE 1

Map indicating the countries in which fluconazole-resistant *C. parapsilosis* isolates harbouring the Y132F ERG11p substitution were reported (depicted in red) alongside the year of detection of the first isolate.

Worldwide emergence of fluconazole-resistant Candida parapsilosis: current framework and future research roadmap

Farnaz Daneshnia et al., Lancet Microbe 2023



Environmental Clonal Spread of Azole-Resistant Candida parapsilosis with Erg11 Y132F Mutation Causing a Large Candidemia Outbreak in a Brazilian Cancer Center

Danilo Y Thomaz al., J of Fungi 2021

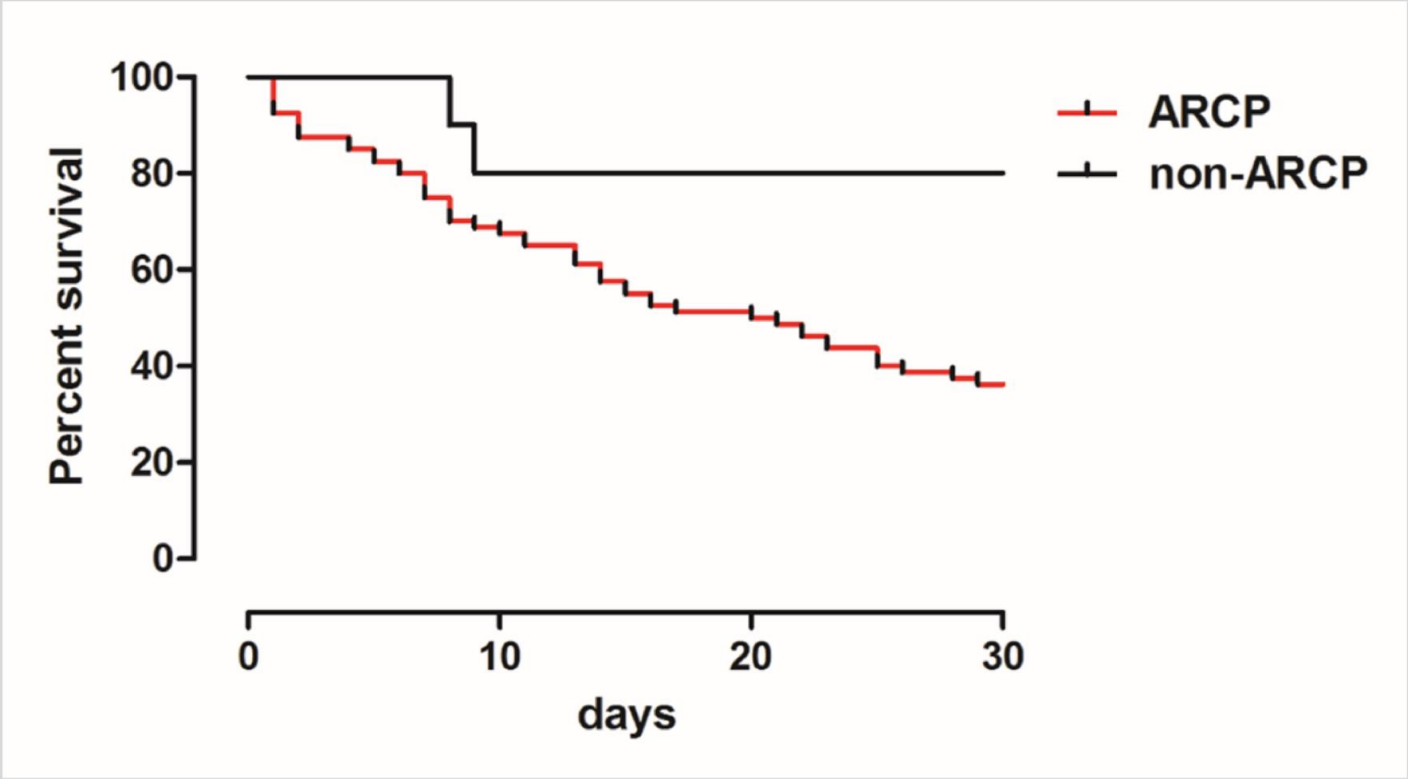


Figure 5. Kaplan–Meier curve for 30-day survival of candidemia patients infected with azole-resistant *C. parapsilosis* (ARCP) vs. non-ARCP ($p = 0.025$). The curve was constructed and compared with the log-rank test.

Invasive candidiasis: current clinical challenges and unmet needs in adult populations

Alex Soriano et al., J Antimicrob and Chem 2023

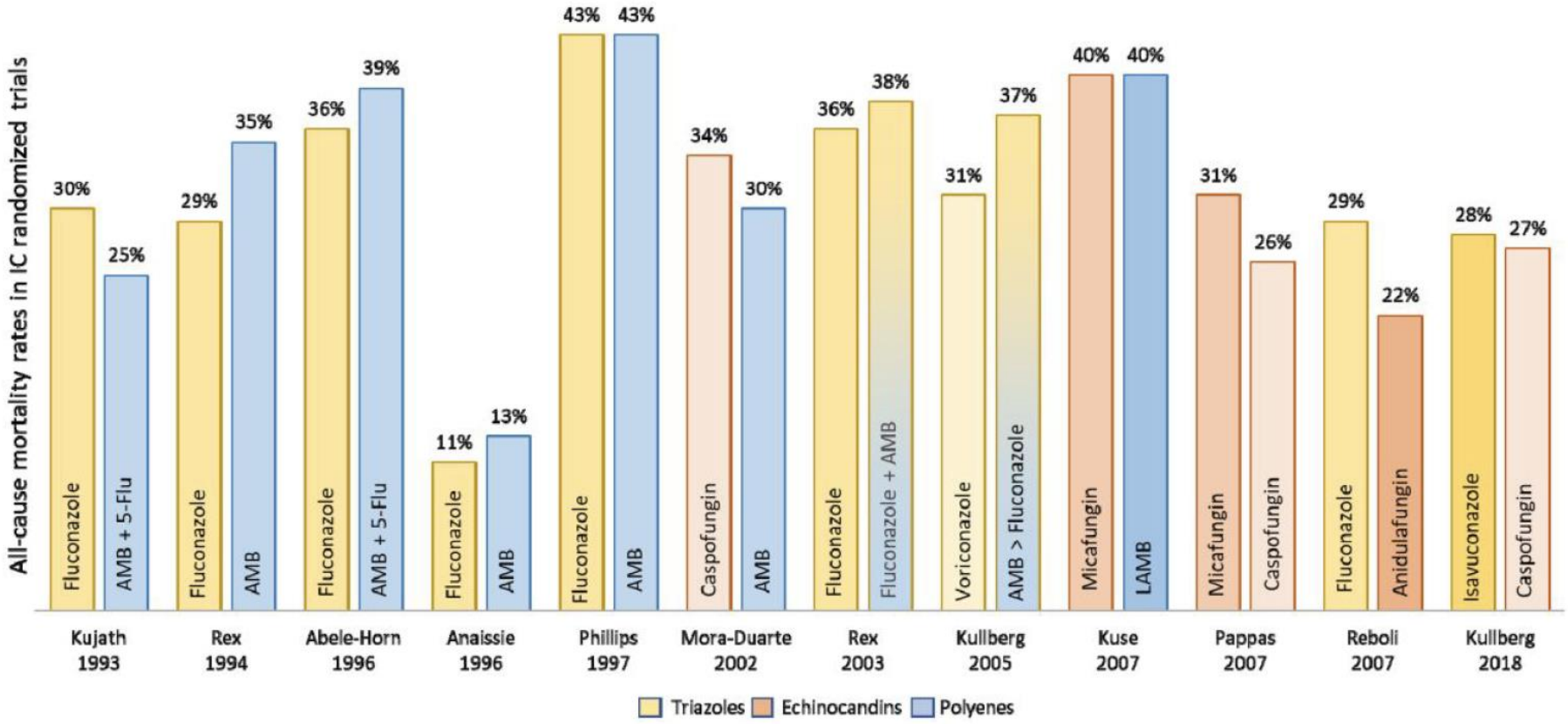


Figure 2. All-cause mortality rates in IC randomized trials (based on data reported by Demir).[18] The figure does not account for differences in study design, namely number of patients randomized, and only includes antifungals currently reimbursed. AMB, amphotericin B; 5-Flu, 5-fluorocytosine; LAMB, lipid formulation of amphotericin B.

The Antifungal Pipeline: Fosmanogepix, Ibrexafungerp, Olorofim, Opelconazole, and Rezafungin

Martin Hoenigl et al., Drugs 2021

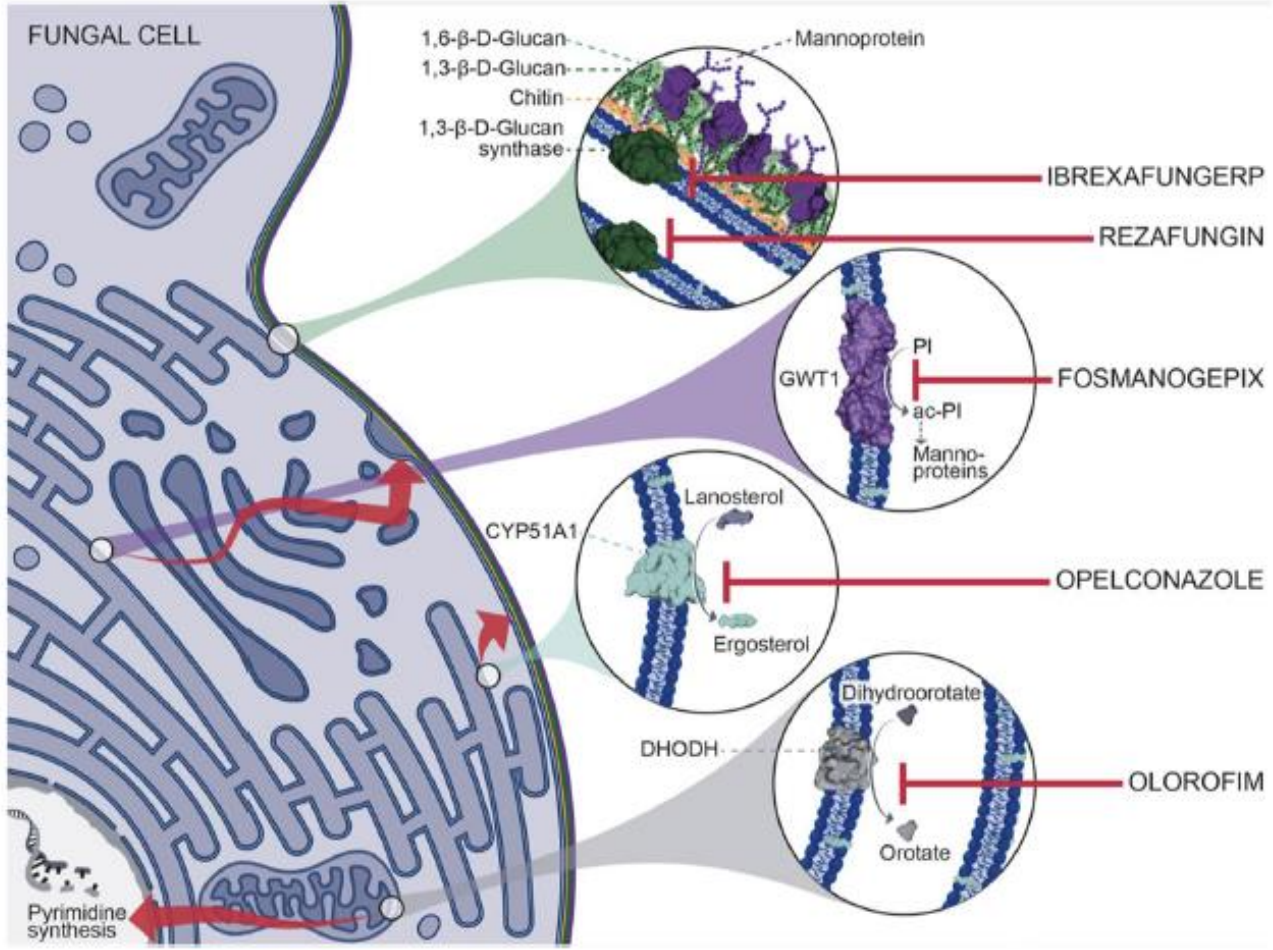


Fig. 1 Mechanism of action of novel antifungal drugs discussed in this review. *DHODH* dihydroorotate dehydrogenase

Gracias!!!

Clínica Universidad de Navarra

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