Farmacocinètica en el tractament dels microorganismes multiresistents

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Hospital del Mar
Barcelona.

- Múltiples mecanismos de resistencia a los antimicrobianos.

Tabla 1
Ejemplos de resistencia codificada por mutaciones bacterianas

Antimicrobiano	Genes	Mecanismo
Rifampicina	*rpoB*	Alteración de la subunidad beta de la ARN polimerasa
Estreptomicina	*rpsL*	Alteración en proteína del ribosoma
Quinolonas	*gyrA*, *gyrB*, *parC*, *parE*	Alteraciones en las topoisomerasas de tipo II
Quinolonas, β-lactámicos y otros	*acrR*, *mexR*	Hiperexpresión de bombas de expulsión (AcrAB-Tolc, MexAB-OprM)
Penicilinas, cefalosporinas	*ampC*	Hiperproducción de la β-lactamasa AmpC
Carbapenémicos	*oprD*	Pérdida de la porina OprD
Oxazolidinonas	*rrn*	Alteración del 23SARN

Martínez-Martínez L, et al. Enf Infecc Microbiol Clin 2010;28(Supl 4):4-9.

Tabla 2
Principales mecanismos de resistencia codificados por plásmidos

Antimicrobiano	Mecanismo	Especies
β-lactámicos	β-lactamasas	Gramnegativos, grampositivos
Aminoglucósidos	Acetilación, adenilación, fosforilación	Gramnegativos, grampositivos
Aminoglucósidos	Metilación	Gramnegativos
Quinolonas	Protección de la diana	Enterobacterias, grampositivos
Quinolonas	Acetilación	Gramnegativos
Glucopéptidos	Cambio en la diana	*Enterococcus* spp., otros grampositivos
Macrólidos	Metilación del ARN ribosómico	Grampositivos
Tetraciclinas	Expulsión activa	Gramnegativos, grampositivos
Trimetoprim	Alteración de la dihidrofolatoreductasa	Grampositivos, gramnegativos

Martínez-Martínez L. Enf Infecc Microbiol Clin 2010; 28(Supl 4);4-9.

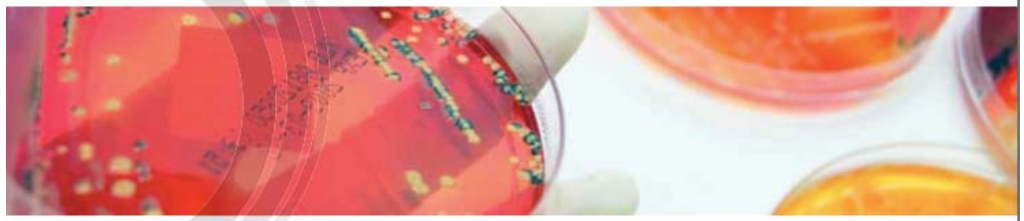
Tabla 3
Mecanismos bioquímicos de resistencia a los antimicrobianos

Tipo de mecanismo	Ejemplos
Disminución de la permeabilidad	Pérdida de porinas
	Alteración estructural de porinas
	Alteración del lipopolisacárido
Modificación del antimicrobiano	β-lactamasas
	Enzimas modificadoras de aminoglucósidos
	Acetiltransferasa de cloranfenicol
	Acetilasa de quinolonas
Expulsión activa	Bombas de expulsión activa de corto espectro
	Bombas de expulsión activa multidroga
Alteración de la diana	Expresión de PBP2a en *S. aureus*
	PBPs en mosaico de *S. pneumoniae*
	Alteraciones de las topoisomerasas
	Alteración del peptidoglucano en *Enterococcus* resistente a glucopéptidos
	Metilasas ribosómicas
Nuevas vías metabólicas	Auxotrofismo de timina
Protección de la diana	Proteínas de las familias Qnr
Hiperproducción de la diana	Hiperproducción de dihidrofolato sintetasa

Martínez-Martínez L. Enf Infecc Microbiol Clin 2010; 28(Supl 4);4-9.

- **ECDC TECHNICAL REPORT Risk assessment on the spread of carbapenemase-producing Enterobacteriaceae (CPE) through patient transfer between healthcare facilities**

SURVEILLANCE REPORT



Antimicrobial resistance surveillance in Europe

2009

www.ecdc.europa.eu

Figure 5.8: *Staphylococcus aureus*: proportion of invasive isolates resistant to meticillin (MRSA) in 2009

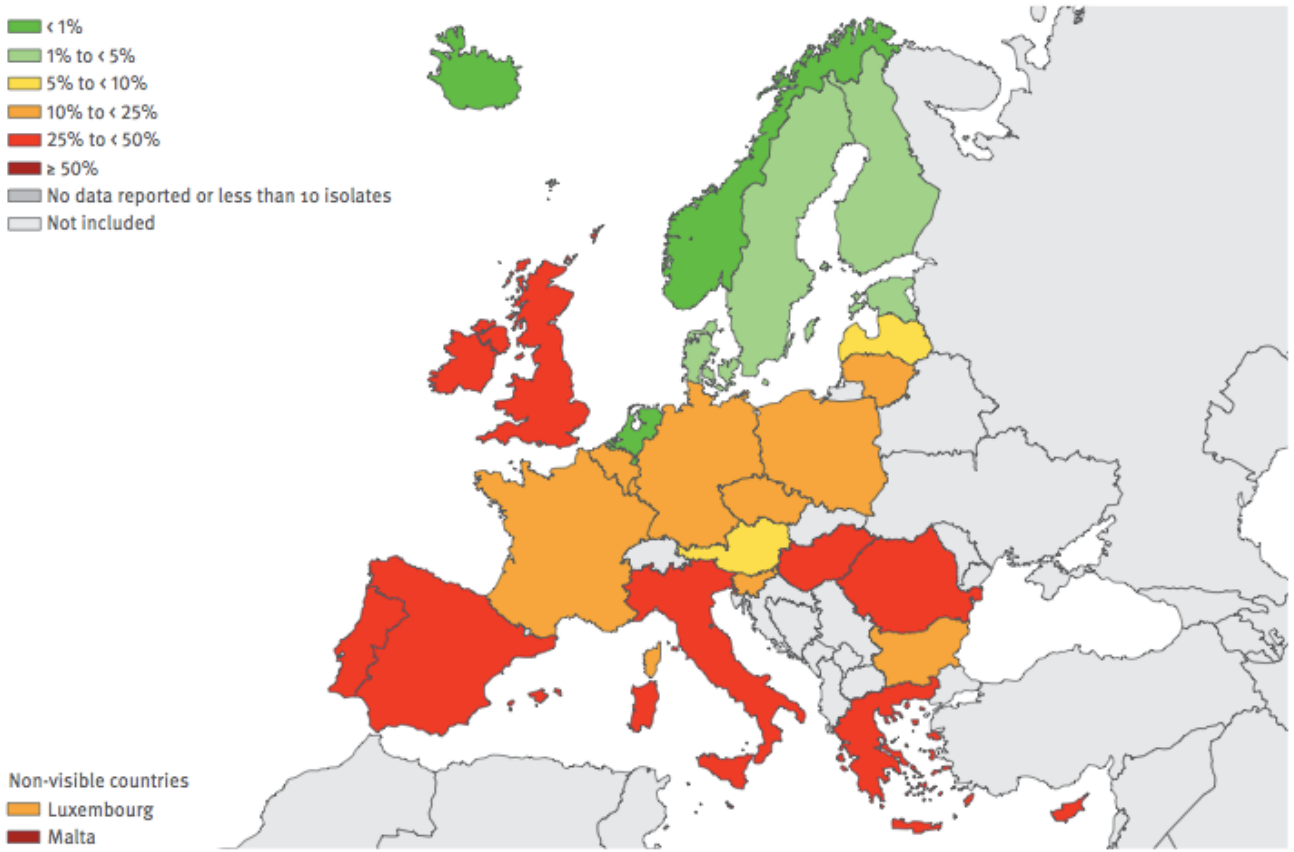


Figure 5.10: *Enterococcus faecalis*: proportion of invasive isolates with high-level resistance to aminoglycosides in 2009

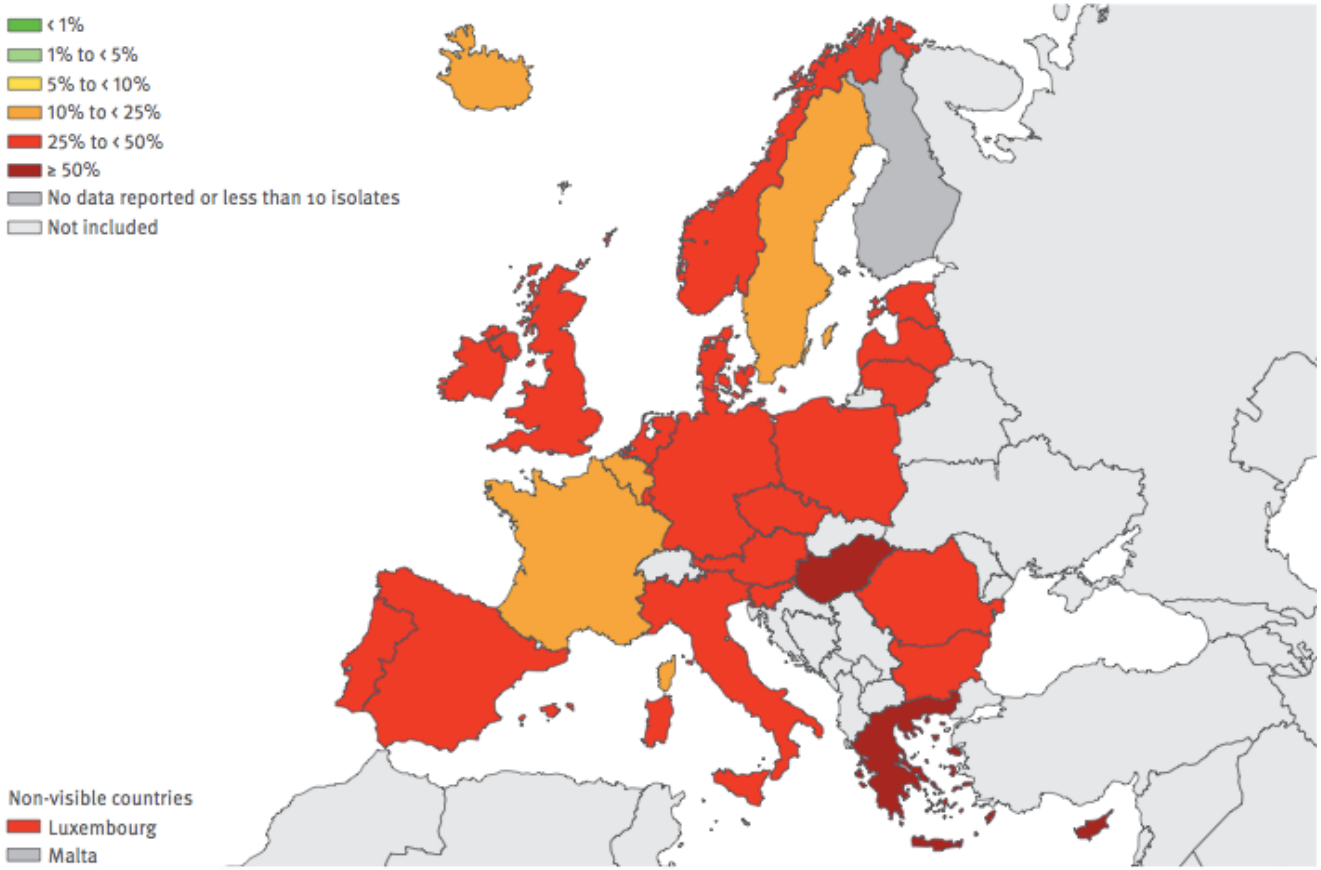


Figure 5.12: ***Enterococcus faecium*****: proportion of invasive isolates resistant to vancomycin in 2009**

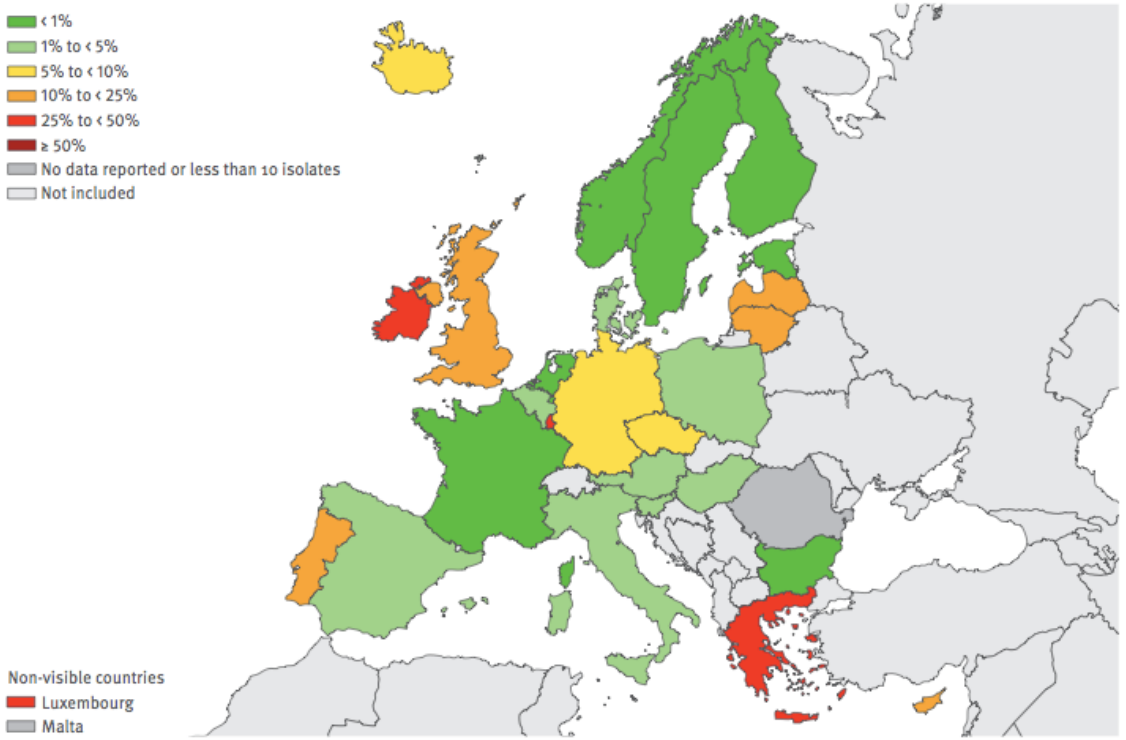


Figure 5.14: *Escherichia coli*: proportion of third-generation cephalosporin resistance in 2009

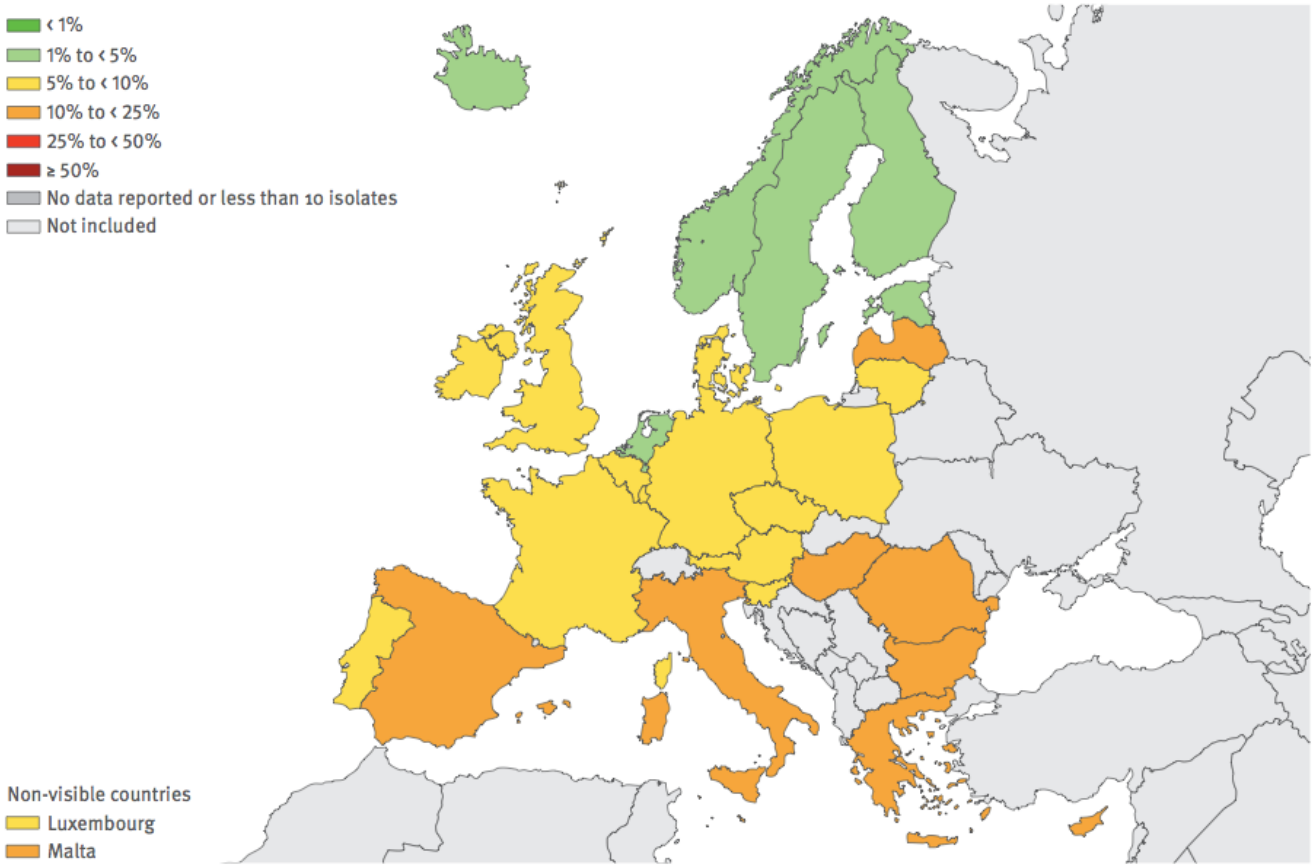


Figure 5.15: *Escherichia coli*: proportion of invasive isolates with resistance to fluoroquinolones in 2009

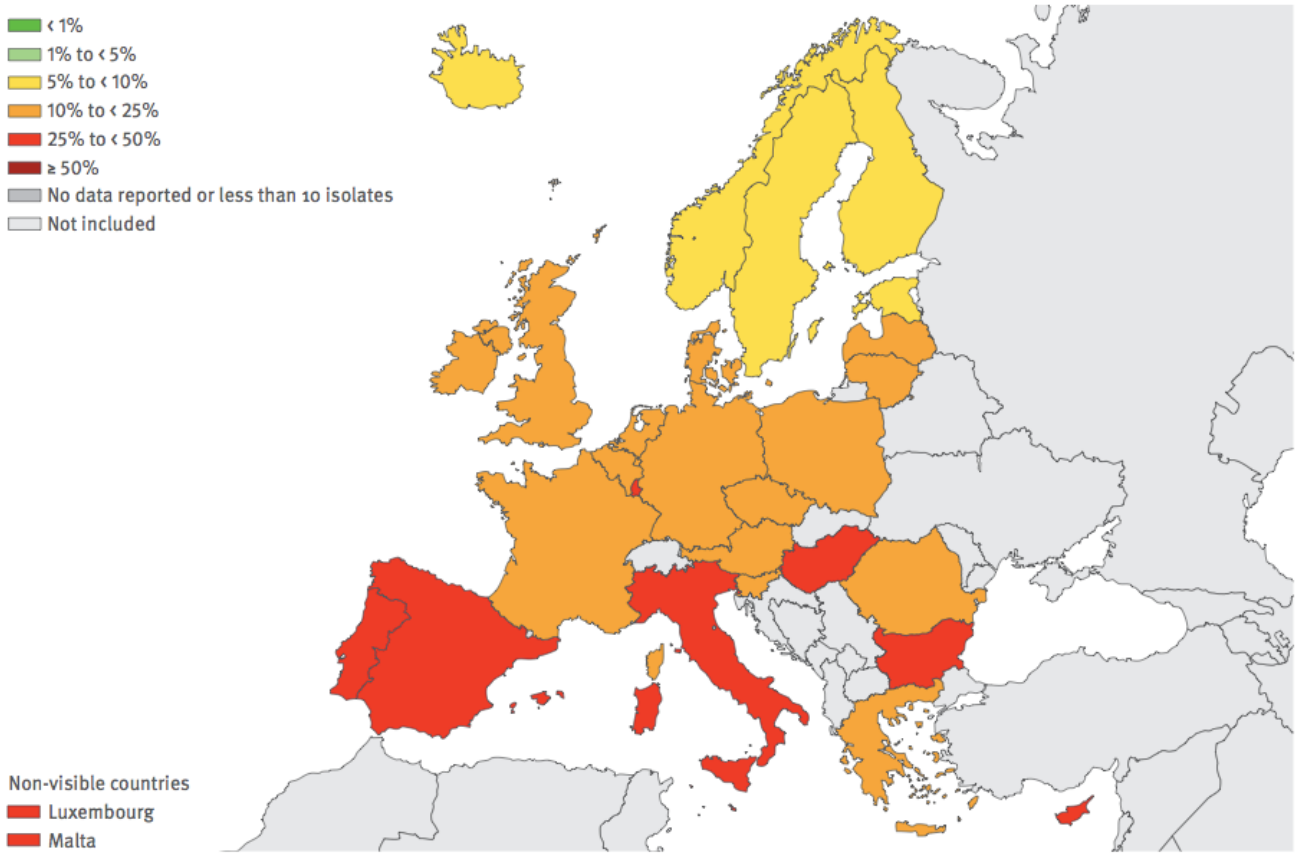
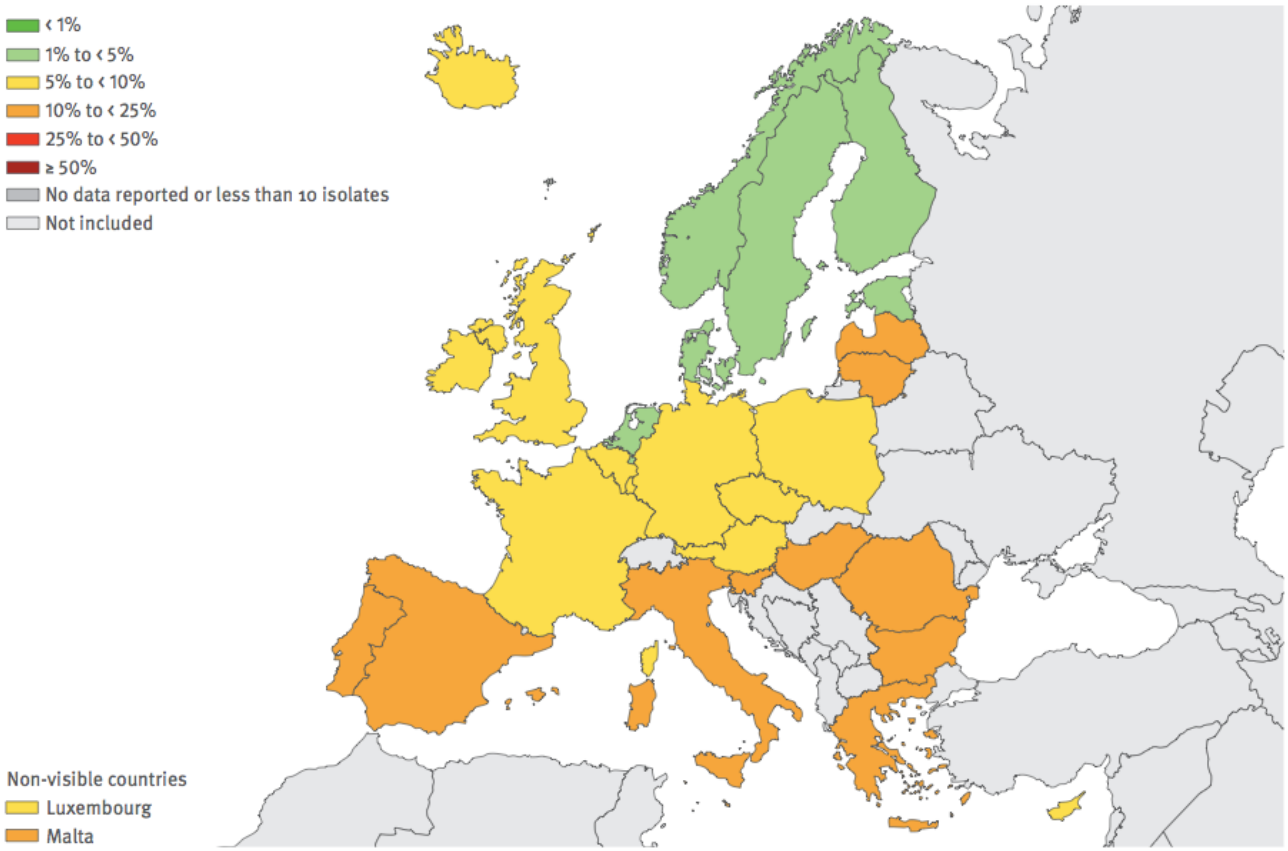


Figure 5.16: *Escherichia coli*: proportion of invasive isolates with resistance to aminoglycosides in 2009



E coli: Tendencias R quinolonas, cefalosporinas 3G y aminoglucósidos 2006-2009

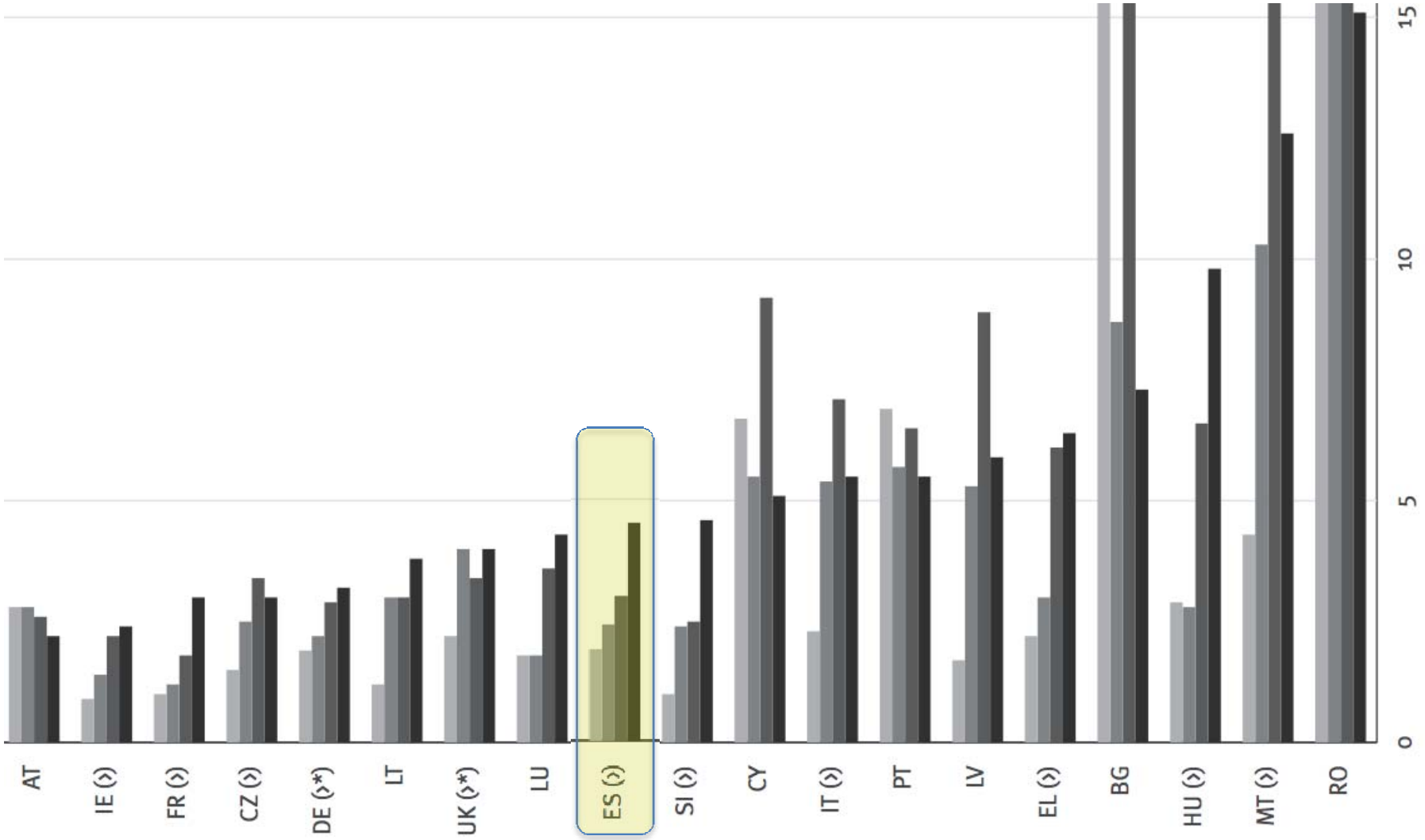


Figure 5.22: *Klebsiella pneumoniae*: proportion of invasive isolates resistant to third-generation cephalosporins in 2009

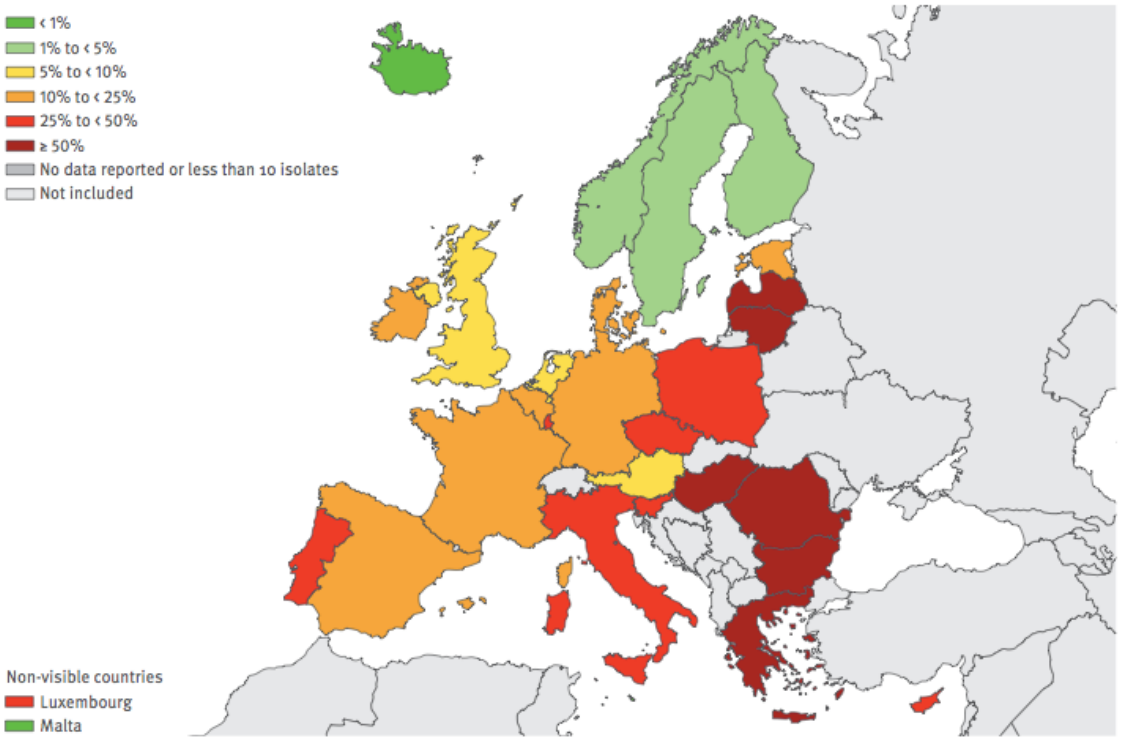


Figure 5.23: *Klebsiella pneumoniae*: proportion of invasive isolates resistant to fluoroquinolones in 2009

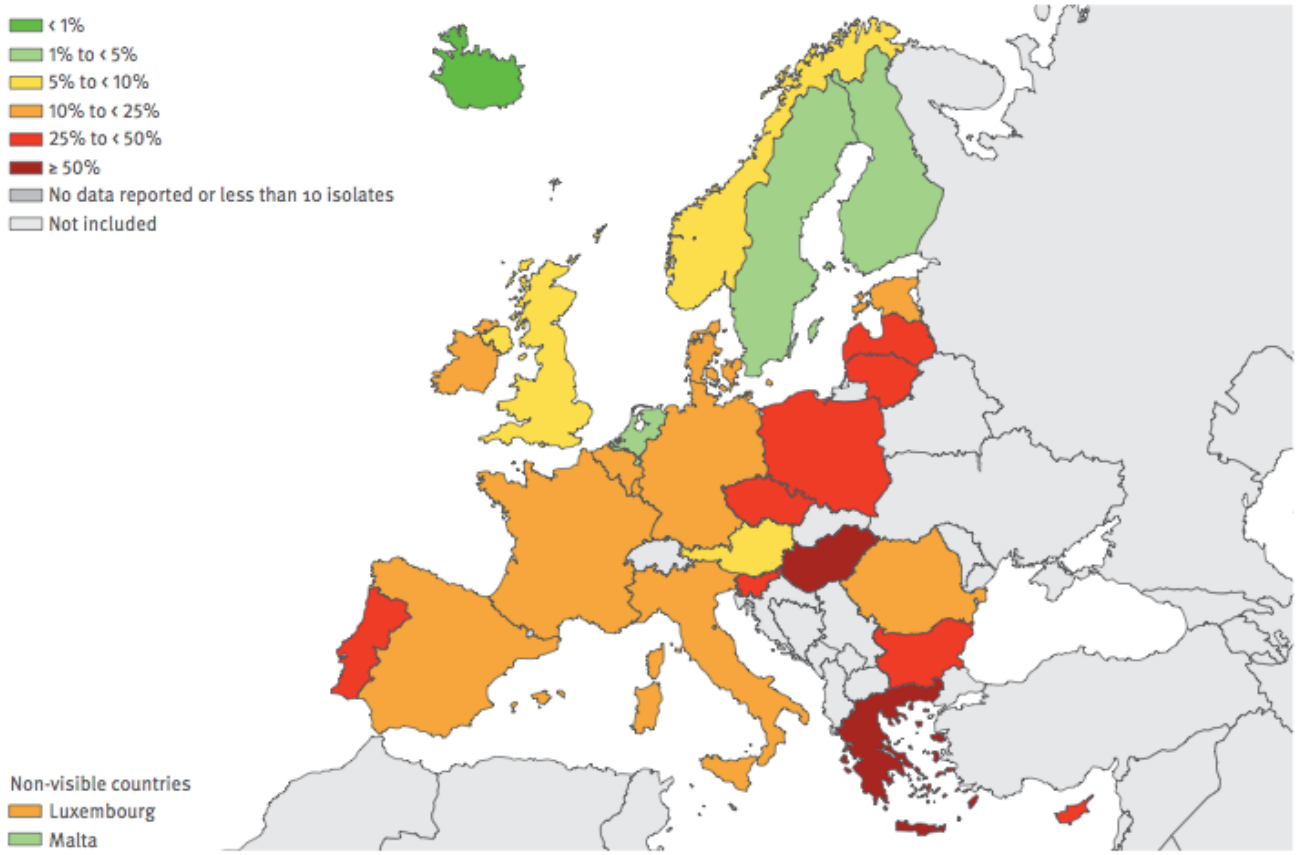


Figure 5.24: *Klebsiella pneumoniae*: proportion of invasive isolates resistant to aminoglycosides in 2009

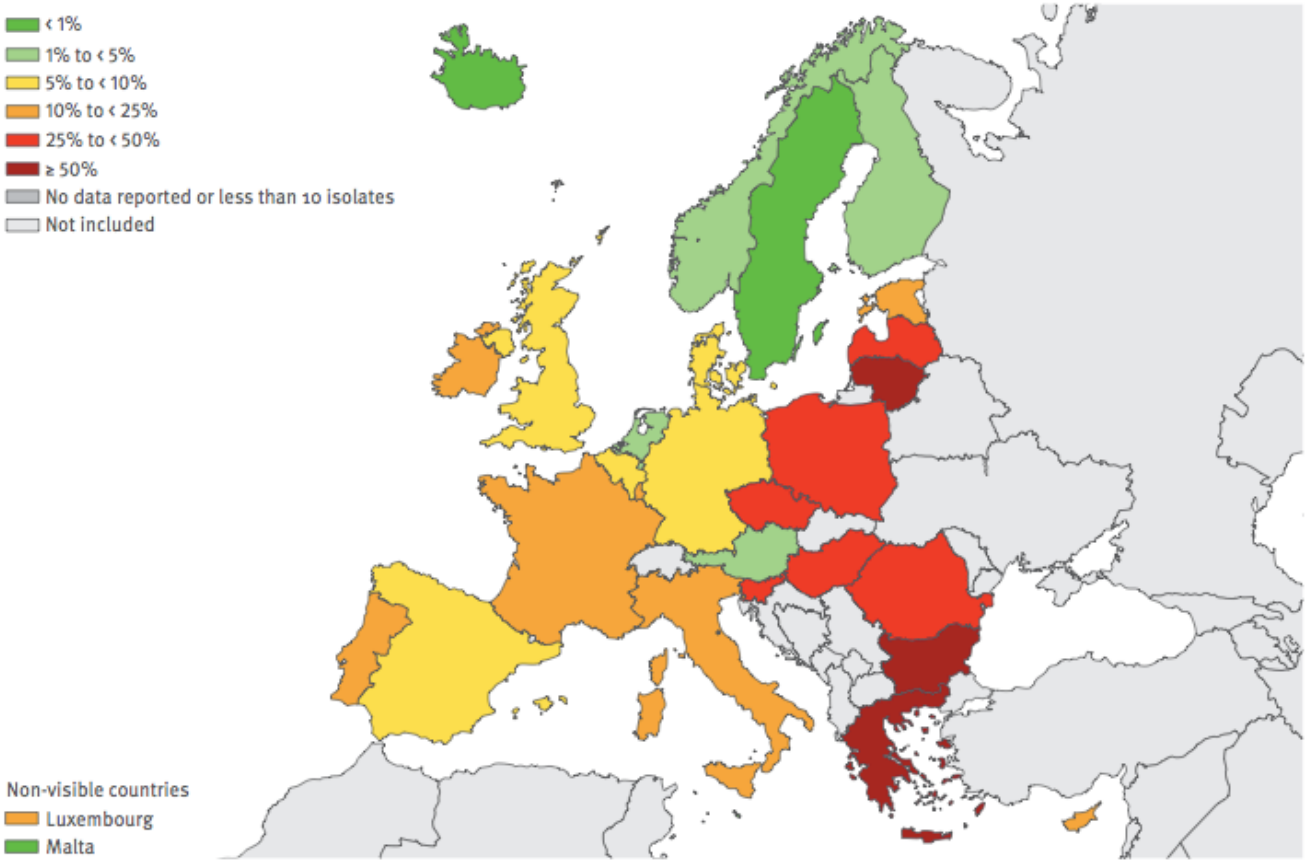
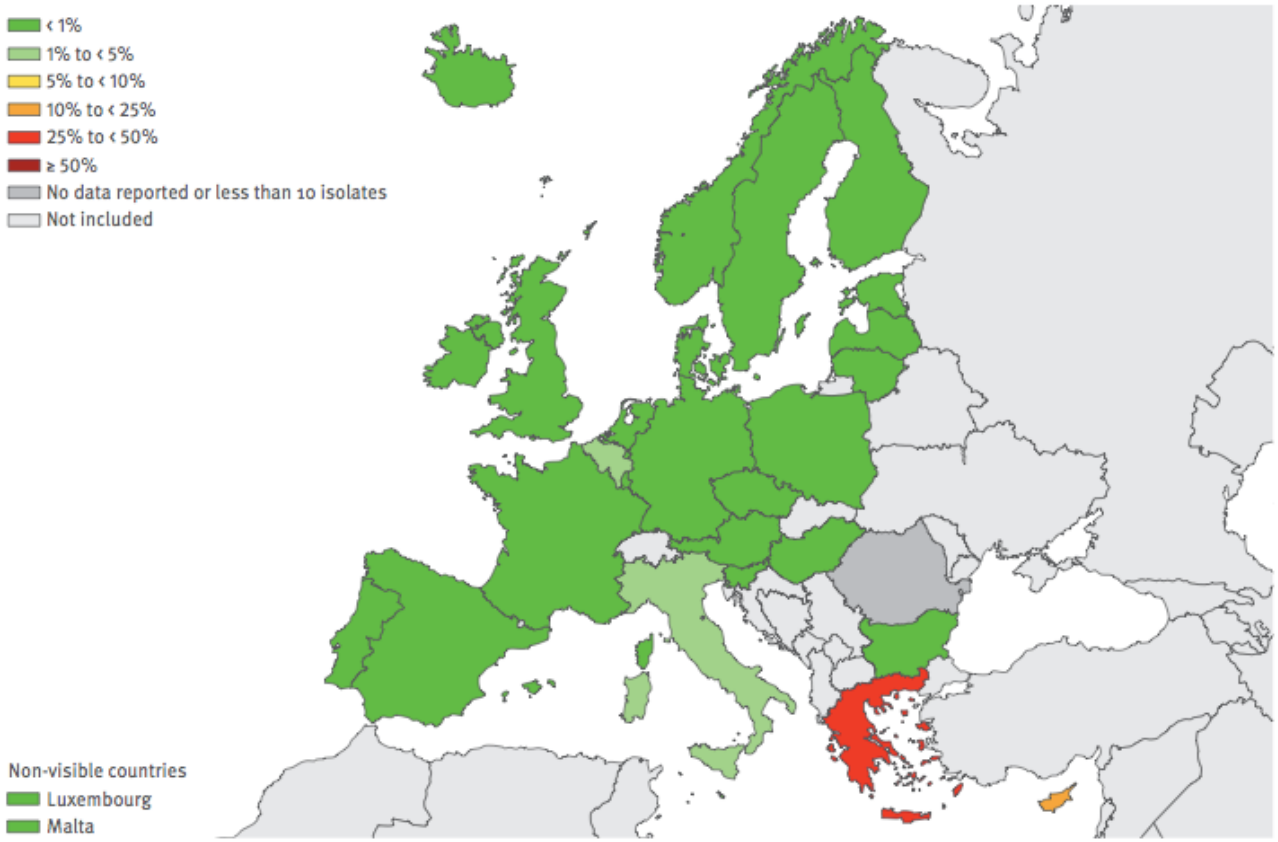


Figure 5.25: *Klebsiella pneumoniae*: proportion of invasive isolates resistant to carbapenems in 2009



K pneumoniae: Tendencias R cefalosporinas 3G, fluoroquinolonas y aminoglucósidos 2006-2009

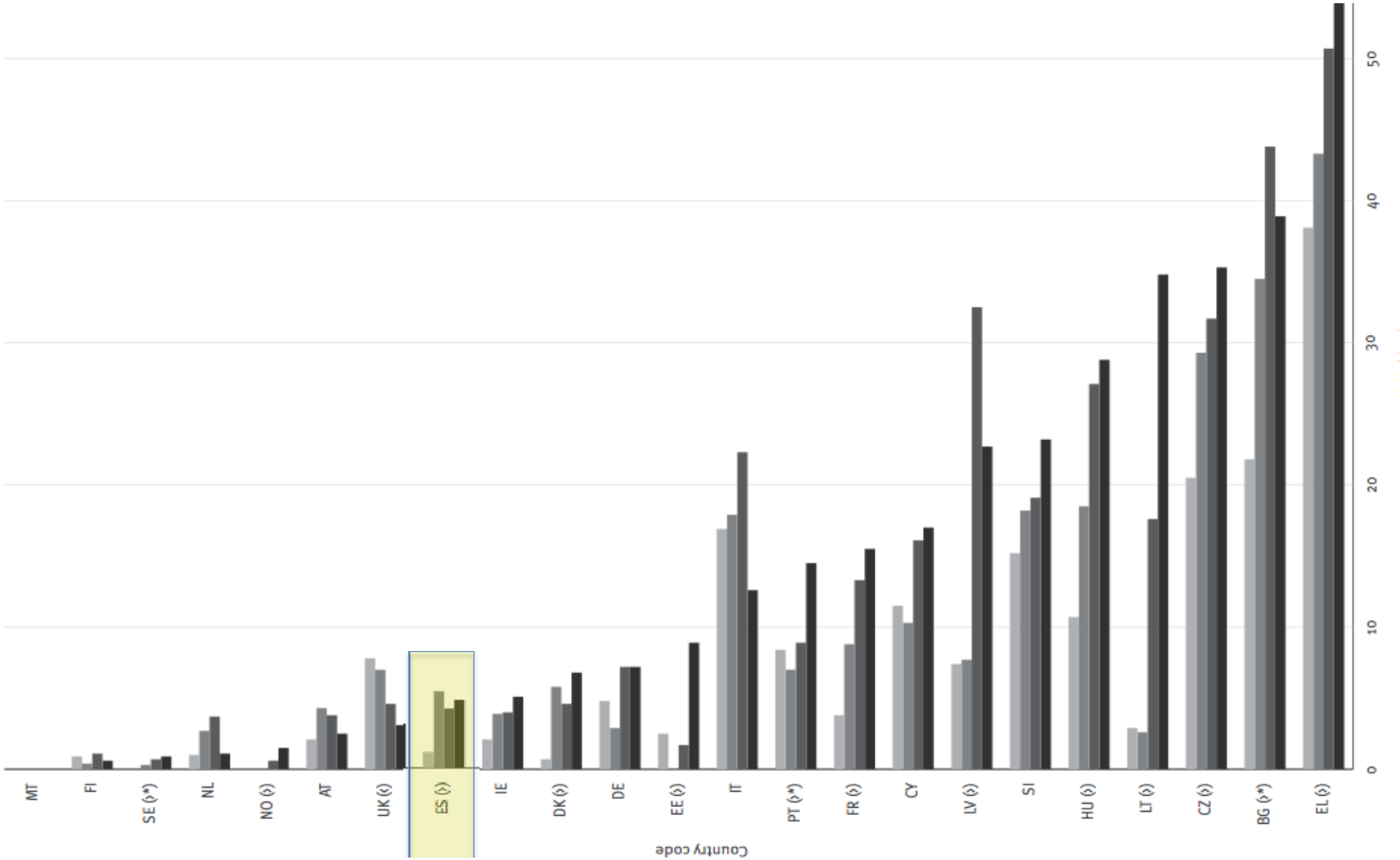


Figure 5.30: *Pseudomonas aeruginosa*: proportion of invasive isolates resistant to piperacillin±tazobactam in 2009

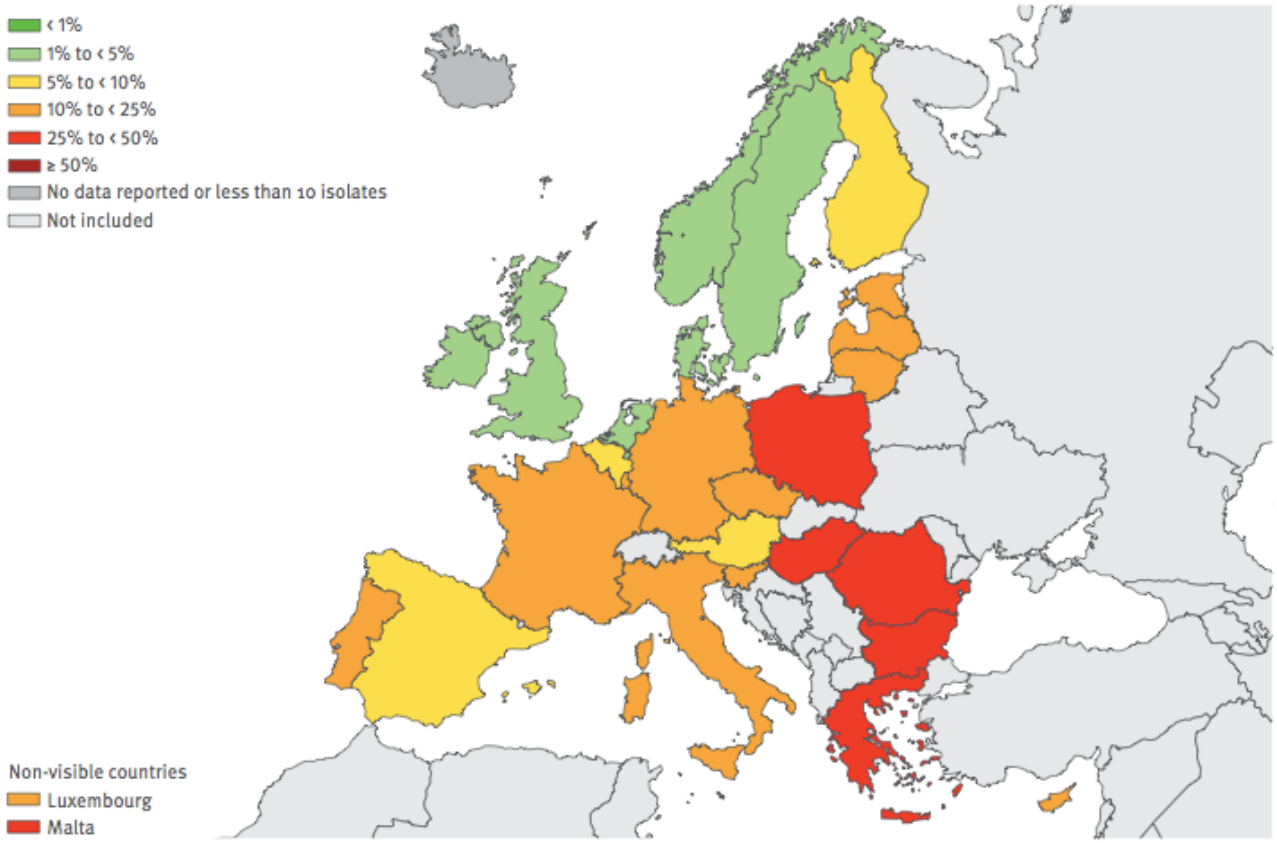


Figure 5.31: *Pseudomonas aeruginosa*: proportion of invasive isolates resistant to ceftazidime in 2009

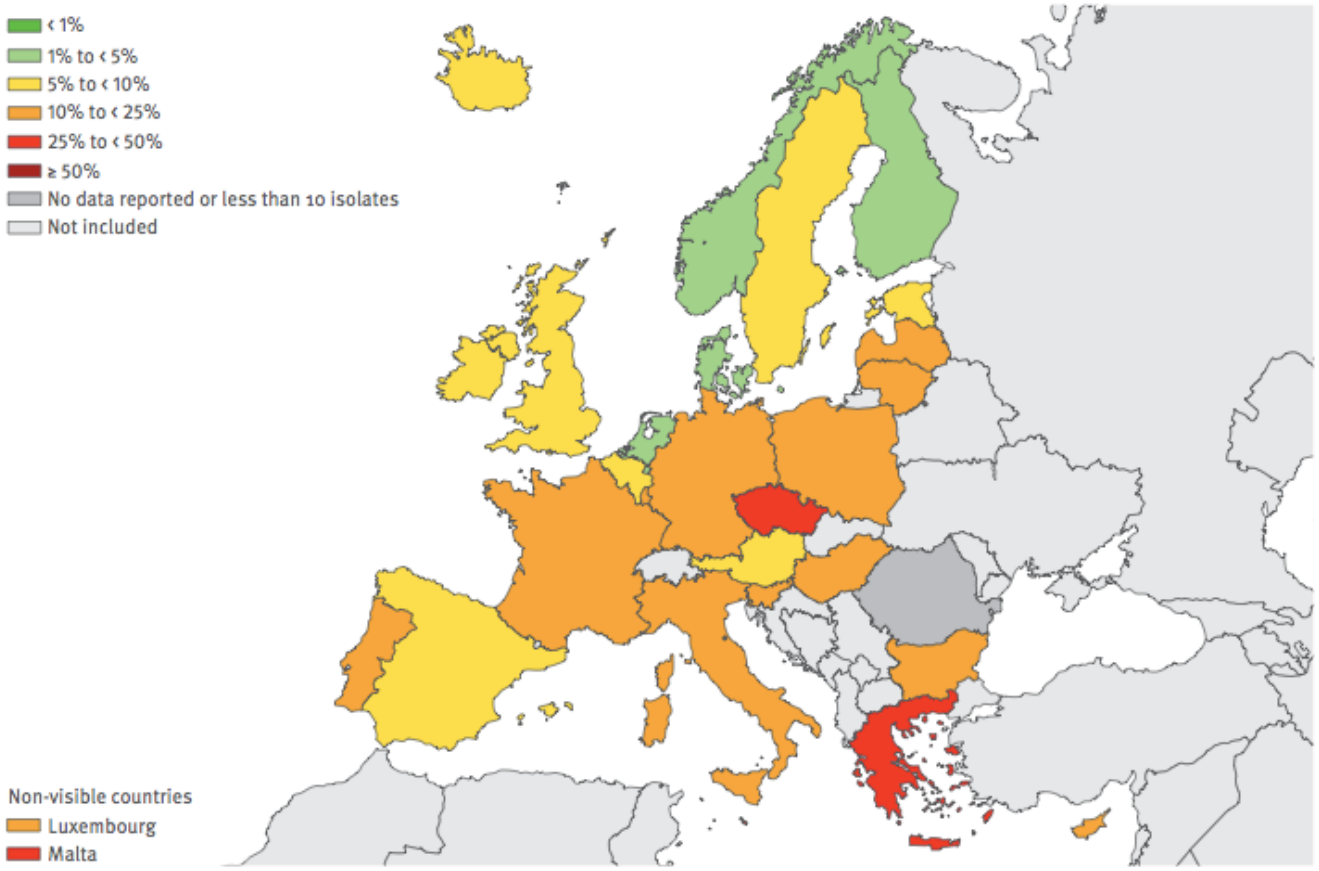


Figure 5.32: *Pseudomonas aeruginosa*: proportion of invasive isolates resistant to fluoroquinolones in 2009

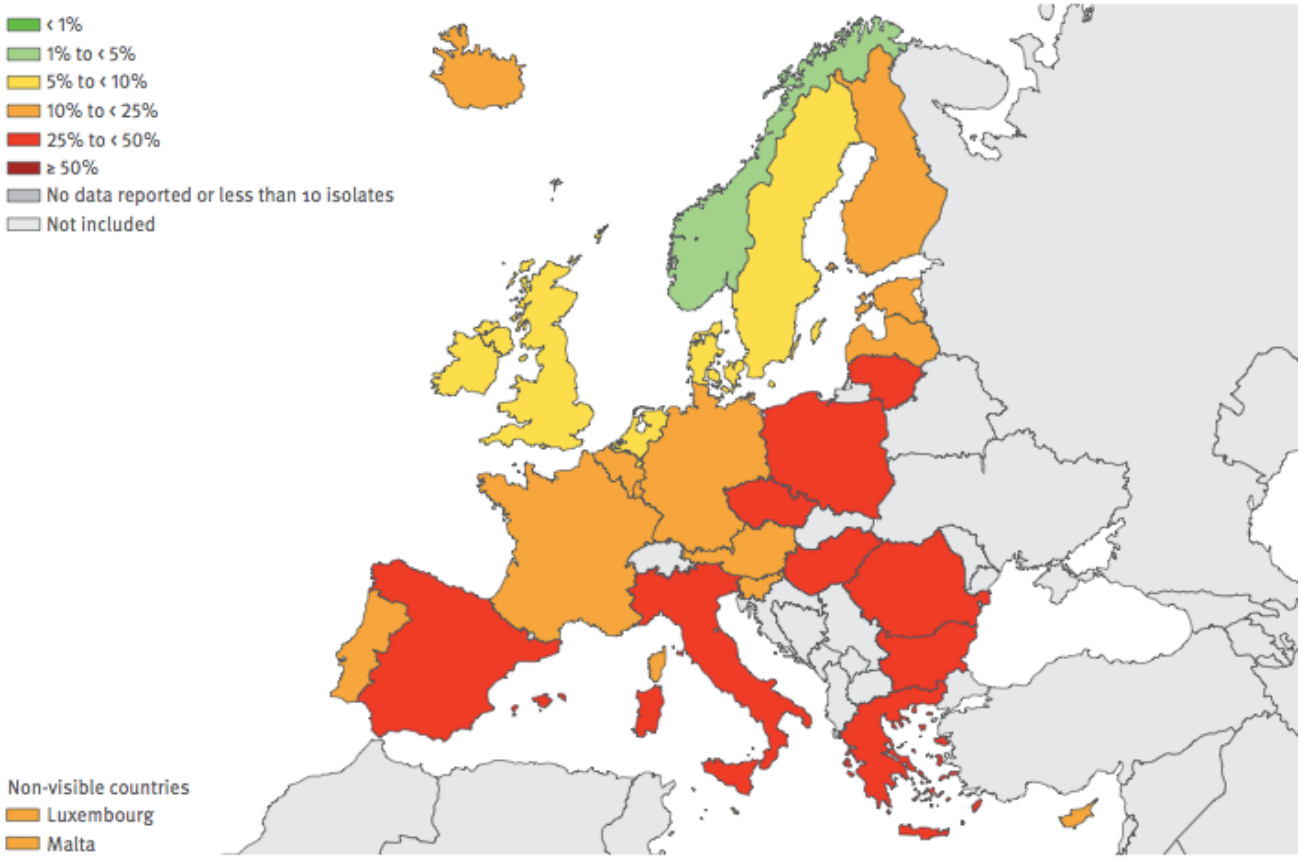


Figure 5.33: *Pseudomonas aeruginosa*: proportion of invasive isolates resistant to aminoglycosides in 2009

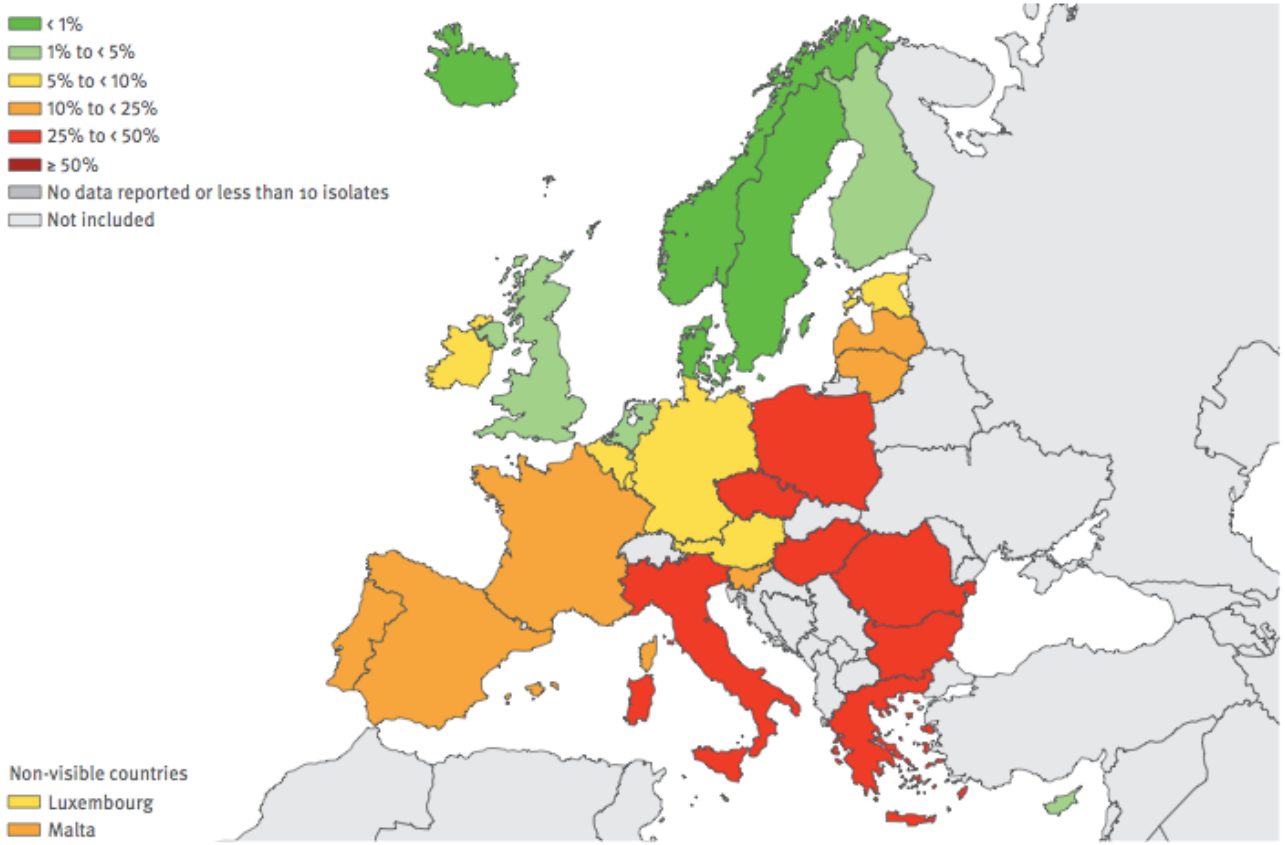
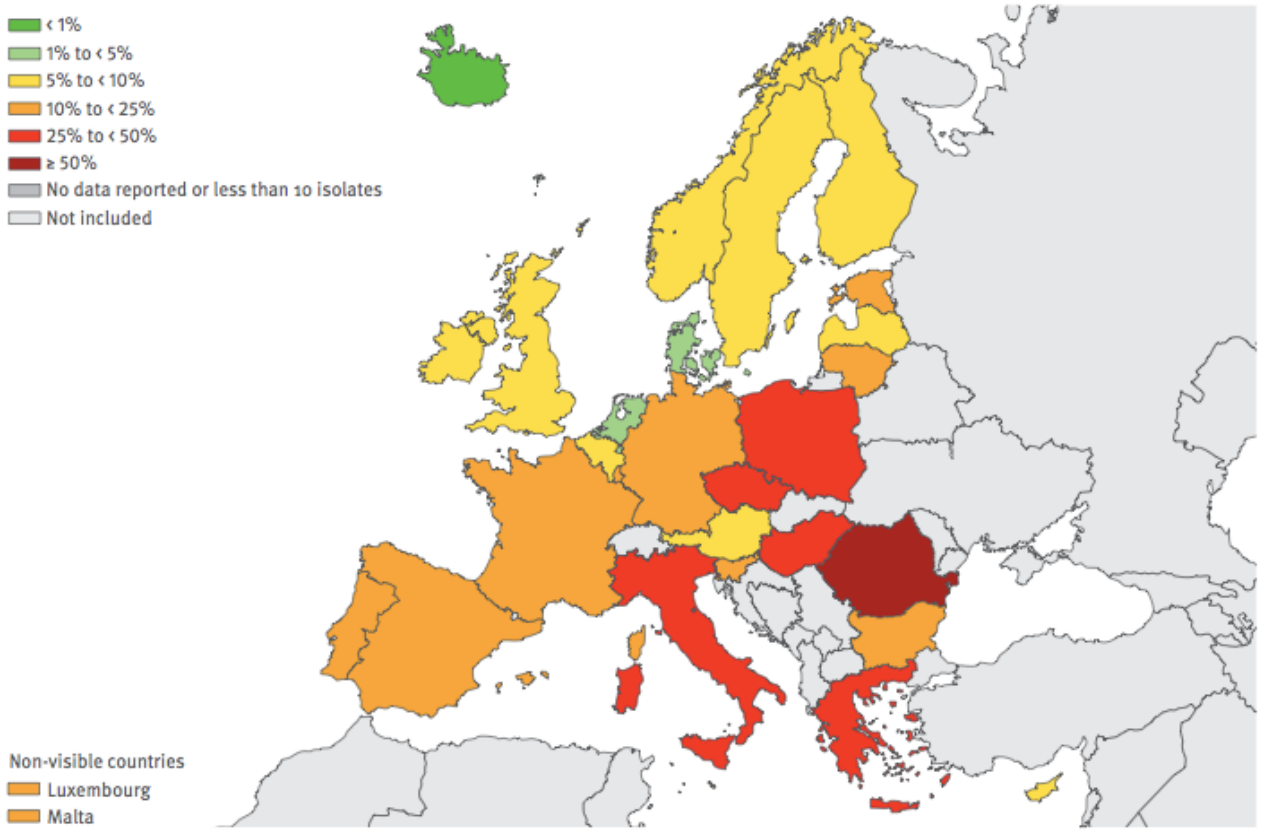
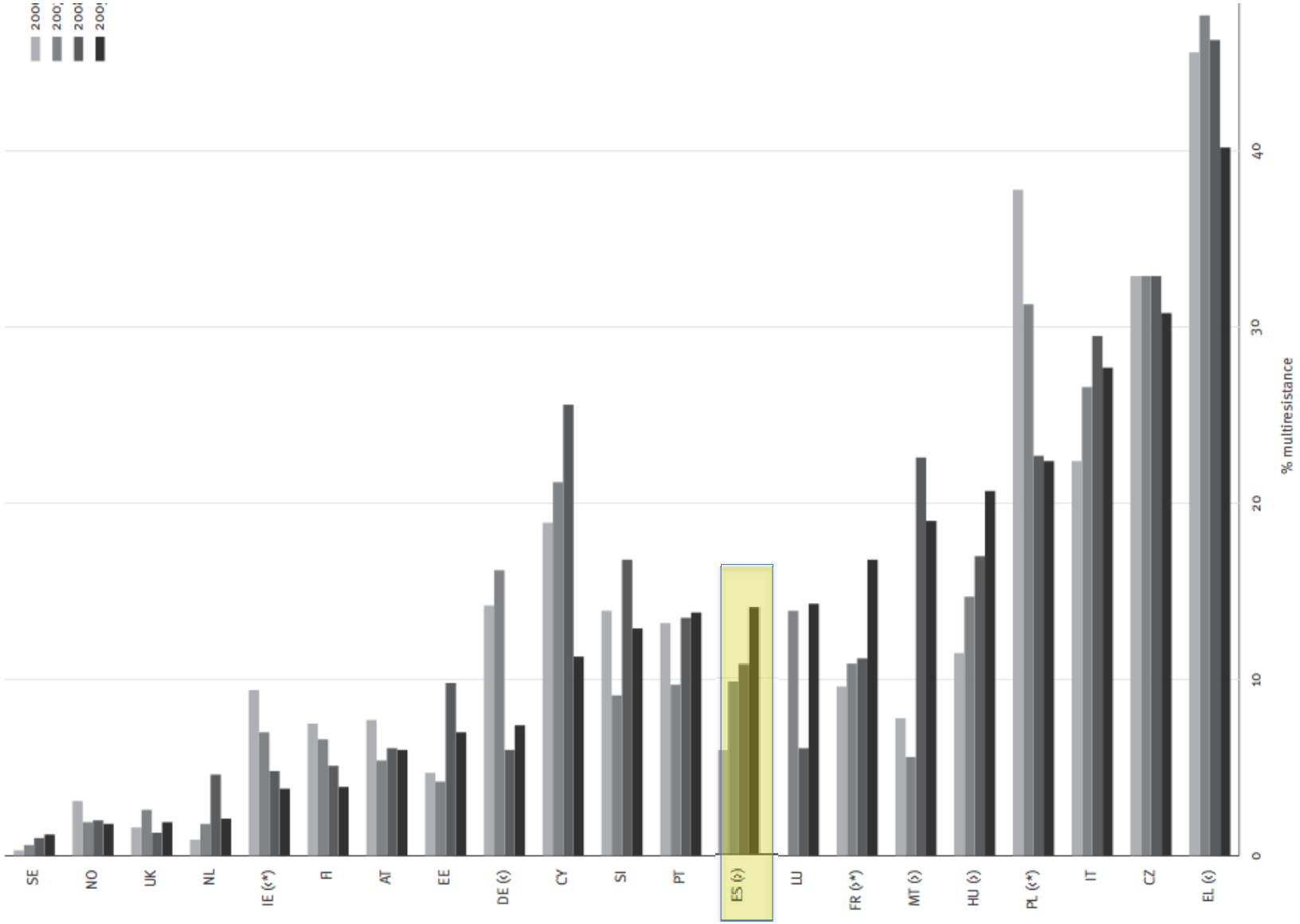


Figure 5.34: *Pseudomonas aeruginosa*: proportion of invasive isolates resistant to carbapenems in 2009



Tendencia a multirresistencia (3 ó + atb) de *P aeruginosa* 2006-2009



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PLoS MEDICINE

Mortality and Hospital Stay Associated with Resistant *Staphylococcus aureus* and *Escherichia coli* Bacteremia: Estimating the Burden of Antibiotic Resistance in Europe

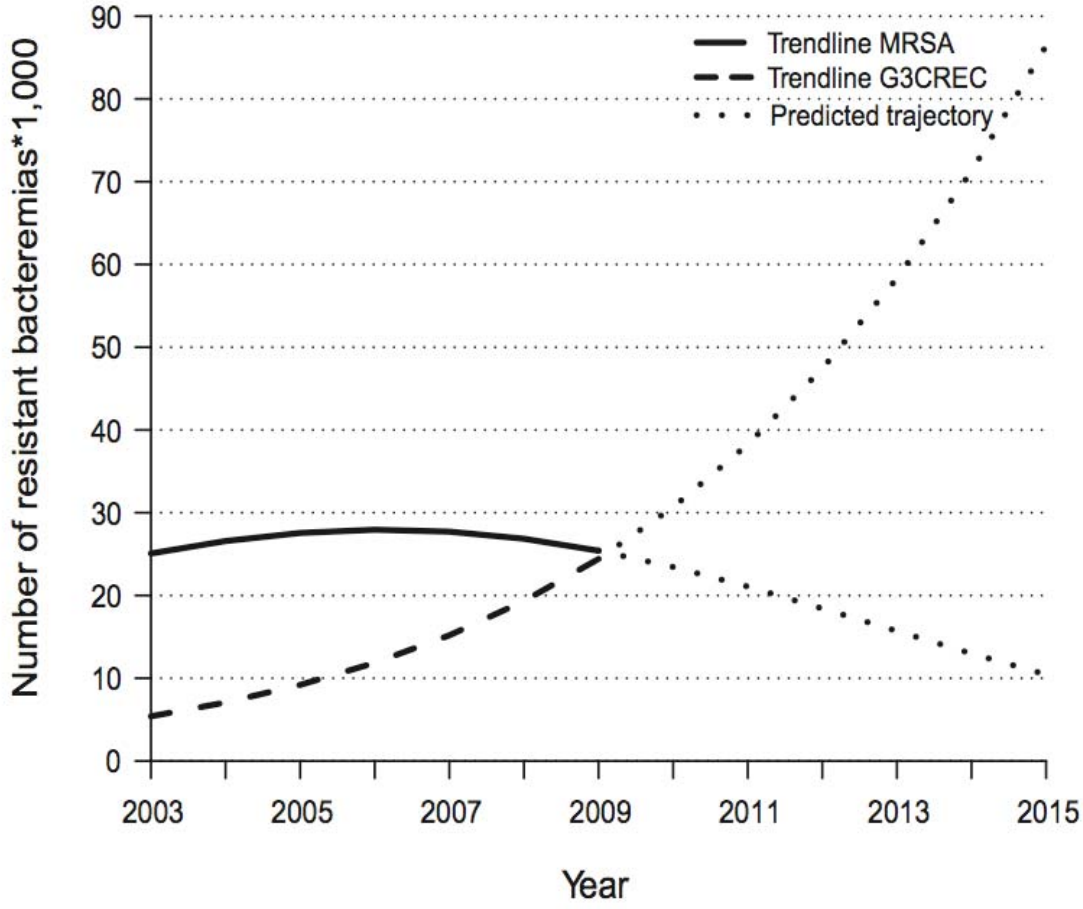
Marlieke E. A. de Kraker[1,2]*, Peter G. Davey[3], Hajo Grundmann[1,2], on behalf of the BURDEN study group

1 Centre for Infectious Disease Control, National Institute for Public Health and the Environment (RIVM), Bilthoven, The Netherlands, **2** Department of Medical Microbiology, Academic Medical Centre Groningen, Groningen, The Netherlands, **3** Quality, Safety and Informatics Research Group, Dundee, United Kingdom

- Exceso de 5.503 muertes en bacteriemias por SARM y 255.683 días de hospitalización.

- Exceso de 2.712 muertes en bacteriemias por *E coli* R a cefalosporinas de 3G y 120.065 días de hospitalización.

Tendencias bacteriemias por SARM y *E coli* R cefalosporinas 3G en Europa



De Kraker, et al. PLoS Medicine 2011;8:e1001104.

Journal of Antimicrobial Chemotherapy Advance Access published June 23, 2011

J Antimicrob Chemother
doi:10.1093/jac/dkr261

Journal of Antimicrobial Chemotherapy

The urgent need for new antibacterial agents

Richard Wise* on behalf of the BSAC Working Party on The Urgent Need: Regenerating Antibacterial Drug Discovery and Development†

British Society for Antimicrobial Chemotherapy, Griffin House, 53 Regent Place, Birmingham B1 3NJ, UK

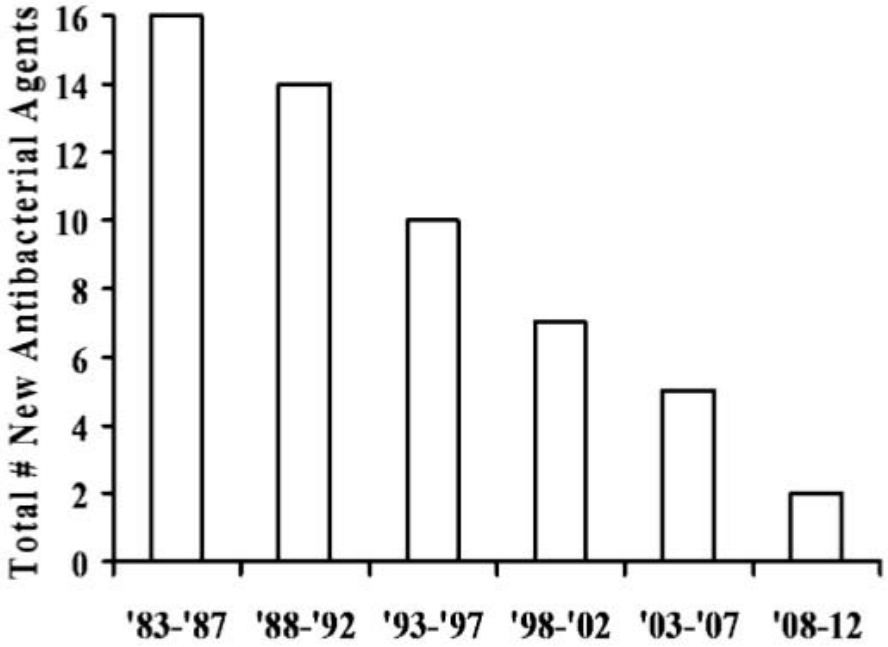


Figure 1. Number of New Molecular Entity (NME) Systemic Antibiotics Approved by the US FDA Per Five-year Period, Through 3/11.

IDSA. Clin Infect Dis 2011;52:S397-S428

Reducción mortalidad era antibiótica

Infección	Mortalidad Pre-atb (%)	Mortalidad (%)	Reducción mortalidad (%)
CAP	23	7	16
HAP	60	30	30
Endocarditis	100	25	75
Meningitis	80	< 20	60
SSTI	11	< 5	10

IDSA. Clin Infect Dis 2011;52:S397-S428

Journal of Antimicrobial Chemotherapy Advance Access published September 15, 2011

J Antimicrob Chemother
doi:10.1093/jac/dkr370

Journal of Antimicrobial Chemotherapy

Using antibiotics responsibly: right drug, right time, right dose, right duration

Matthew Dryden[1]*, Alan P. Johnson[2], Diane Ashiru-Oredope[2] and Mike Sharland[3]

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Nov. 2011, p. 5412 Vol. 55, No. 11
0066-4804/11/$12.00 doi:10.1128/AAC.05564-11

New Antimicrobial Agents Approved by the U.S. Food and Drug Administration in 2010 and 2011 and New Indications for Previously Approved Agents[a]

Nuevos antibióticos aprobados por la FDA 2010 - 2011

Fecha aprobación	Principio activo	Indicación
23 feb 2010	Aztreonam	Fibrosis quística
24 marzo 2010	Rifaximina	Encefalopatía hepática
27 abril 2010	Lopinavir, ritonavir	VIH
18 mayo 2010	Gatifloxacino	Conjuntivitis
16 julio 2010	Clindamicina, tretinoina	Acné
18 octubre 2010	Entecavir	Hepatitis B
29 octubre 2010	Ceftarolina	SSTI, CAP
19 nov 2010	Moxifloxacino	Conjuntivitis
29 marzo 2011	Nevirapina	VIH
13 mayo 2011	Boceprevir	Hepatitis C
20 mayo 2011	Rilpivirina	VIH
23 mayo 2011	Telapravir	Hepatitis C
27 mayo 2011	Fidaxomicina	Diarrea *C difficile*

Bassetti M, et al. Expert Rev Anti Infect Ther 2011;9:909-22

Table 2. MIC_{90} of some new agents and comparators against Gram-negative rods in different studies.

Bacteria (number of isolates)	MIC_{90} (range), mg/l		Ref.
Novel β-lactam & β-lactamase inhibitors			
BLI-489	**Piperacillin + tazobactam**	**Piperacillin + BLI-489**	[65]
E. coli (52)	2 (0.5–128)	2 (0.25–64)	
E. coli ESBL-A† (31)	>128 (1 to >128)	16 (1–32)	
E. coli AmpC (17)	32 (2–64)	16 (1–16)	
E. cloacae (52)	>128 (0.5 to >128)	16 (0.5–16)	
K. pneumoniae (54)	16 (1 to >128)	8 (1–16)	
K. pneumoniae ESBL-A (36)	>128 (2 to >128)	2–128 (32)	
K. pneumoniae AmpC (30)	>128 (8 to >128)	>128 (4 to >128)	
Acinetobacter spp. (30)	32 (≤0.12 to >128)	16 (0.5–32)	
P. aeruginosa (55)	>128 (4 to >128)	64 (4 to >128)	
ME1071	**Meropenem**	**Meropenem + ME1071**	[80]
MBL-producing *P. aeruginosa* (174)	>64 (0.5 to >64)	>64 (0.25 to >64)	
Non MBL-producing *P. aeruginosa* (16)	64 (0.12–64)	64 (0.5–64)	
Tomopenem	**Meropenem**	**Tomopenem**	[55]
E. coli (25)	≤0.03 (≤0.03–0.25)	≤0.03 (≤0.03–0.12)	
K. pneumoniae (25)	≤0.03 (≤0.03–0.06)	0.06 (≤0.03–0.12)	
P. aeruginosa (100)	16 (0.06 to >32)	4 (0.06–32)	
Novel polymyxins			
CB-182,804	**Colistin**	**CB-182,804**	[86]
E. coli (80)	0.5	2	
K. pneumoniae (81)	2	4	
P. aeruginosa (100)	2	2	
Acinetobacter spp. (81)	4	4	
Protein synthesis inhibitors			
AN3365	**Imipenem**	**AN3365**	[90]
P. aeruginosa (101)	>64 (0.25 to >64)	8 (1–16)	
Acinetobacter spp. (25)	>64 (8 to >64)	16 (4–32)	

†Class A ESBL.
ESBL: Extended-spectrum β-lactamase; MBL: Metallo-β-lactamase.

Bassetti M, et al. Expert Rev Anti Infect Ther 2011;9:909-22

Table 5. Old and new β-lactamase inhibitors and specific activity against different classes of β-lactamases.

Inhibitor	Class				US FDA status
	A	*B*	*C*	*D*	
Inhibitors with β-lactam structure					
Clavulanic acid	+	-	+	+	Approved
Tazobactam	+	-	+	+	Approved
Sulbactam	+	-	+	+	Approved
BLI-489	+	?	+	+	Phase I†
BAL30376	?	+	+	?	Phase I†
LK-157	+	?	+	?	Preclinical
Oxapenems	+	?	+	+	Preclinical
Inhibitors without β-lactam structure					
NXL104	+	+	+	+	Phase I and II†‡
ME1071	?	+	?	?	Phase I (Japan)†
MK7655	+	?	+	?	Phase I‡

†Complete results not published.
‡In combination with ceftaroline and ceftazidime, respectively.
+: Active; -: Nonactive; ?: Unknown.

Bassetti M, et al. Expert Rev Anti Infect Ther 2011;9:909-22

Table 6. US FDA status and antimicrobial activity of novel antimicrobials against multidrug-resistant Gram-negative strains.

Drug	US FDA status	Antimicrobial class	*In vitro* activity against MDR Gram-negative bacteria			
			Escherichia coli	*Klebsiella pneumoniae*	*Pseudomonas aeruginosa*	*Acinetobacter baumannii*
KB001	Phase II	Antibody fragment	-	-	+	-
CB-182,804	Phase I	Polymyxins	+	+	+	+
AN3665	Phase I	Protein synthesis inhibitors	+	+	+	+
TP-434	Phase I	Tetracyclines	+	+	+	+
MBX agents	Preclinical	Bis-indoles	?	+	?	?
CHIR-090	Preclinical	LpxC inhibitors	+	?	+	?

+: Active; -: Nonactive; ?: Unknown; MDR: Multidrug resistant.
Data from [101].

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Nov. 2011, p. 4943–4960 Vol. 55, No. 11
0066-4804/11/$12.00 doi:10.1128/AAC.00296-11

MINIREVIEW

Carbapenems: Past, Present, and Future[▽]

Krisztina M. Papp-Wallace,[1,2] Andrea Endimiani,[1,2,3]
Magdalena A. Taracila,[2] and Robert A. Bonomo[1,2,4,5]*

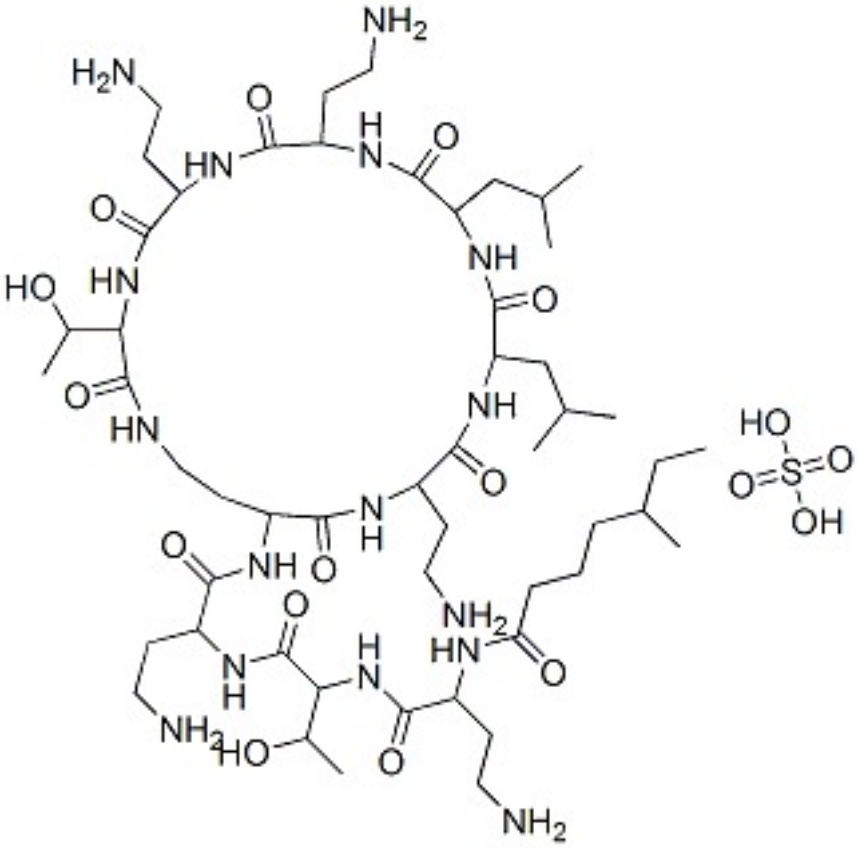
TABLE 1. *In vitro*-tested carbapenem combination therapies[a]

Drug 1	Drug 2	Bacterium (reference[s])[b]	Effect
Doripenem or imipenem	Vancomycin	MRSA (108, 139)	+
Doripenem	Teicoplanin	MRSA (108)	+
Imipenem	Linezolid	MRSA (94)	+
Imipenem	Teicoplanin	VRSA (76)	+
Meropenem	Levofloxacin	*S. pneumoniae* (41)	+
Meropenem	Rifampin	*S. pneumoniae* (60)	−
Imipenem or meropenem	Clavulanic acid	*Nocardia brasiliensis* (238)	−
Meropenem	Clavulanic acid	*Mycobacterium tuberculosis* (90)	+
Meropenem	Ciprofloxacin	*A. baumannii* (54, 169)	+
Imipenem or meropenem	Colistin (and sulbactam)	*A. baumannii* (54, 169, 188, 198)	+
Meropenem	Sulbactam	*A. baumannii* (104)	+
Imipenem	Azithromycin	*A. baumannii* (58)	+
Imipenem	Rifampin	*A. baumannii* (213)	+
Imipenem	Polymyxin B	*A. baumannii* (245)	−
Imipenem	Amikacin	*A. baumannii* (195)	−
Carbapenem	Fluoroquinolone	*P. aeruginosa* (41, 54, 104, 124, 169, 241)	+
Imipenem	Tachyplesin	*P. aeruginosa* (37)	+
Meropenem or imipenem	Colistin	*P. aeruginosa* (37, 54, 169)	+/−
Carbapenem	Aminoglycoside	*P. aeruginosa* (7, 49, 50, 53, 226)	−
Meropenem	Polymyxin B	*P. aeruginosa* (75)	−
Imipenem or meropenem	Tobramycin-rifampin	*B. cepacia* (19)	+
Imipenem or meropenem	Ciprofloxacin	*B. cepacia* (19)	+
Imipenem	Colistin	MBL *K. pneumoniae* (215)	+
Imipenem	Tigecycline	ESBL *K. pneumoniae* and *E. coli* (32)	−
Imipenem	Gentamicin	ESBL *K. pneumoniae* and *E. coli* (32)	−

[a] Some combinations demonstrate positive effects (+), such as extending spectrum or working additively or synergistically. Adverse effects (−) include increased resistance to one of the drugs used in the combination, as well as lack of synergy or additivity and strain dependence.

[b] VRSA, vancomycin-resistant *S. aureus*; ESBL, extended-spectrum β-lactamase producing; MBL, metallo-β-lactamase producing.

colistina


NH2
H2N
O
HN
H
N
O
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HN
NH
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HN
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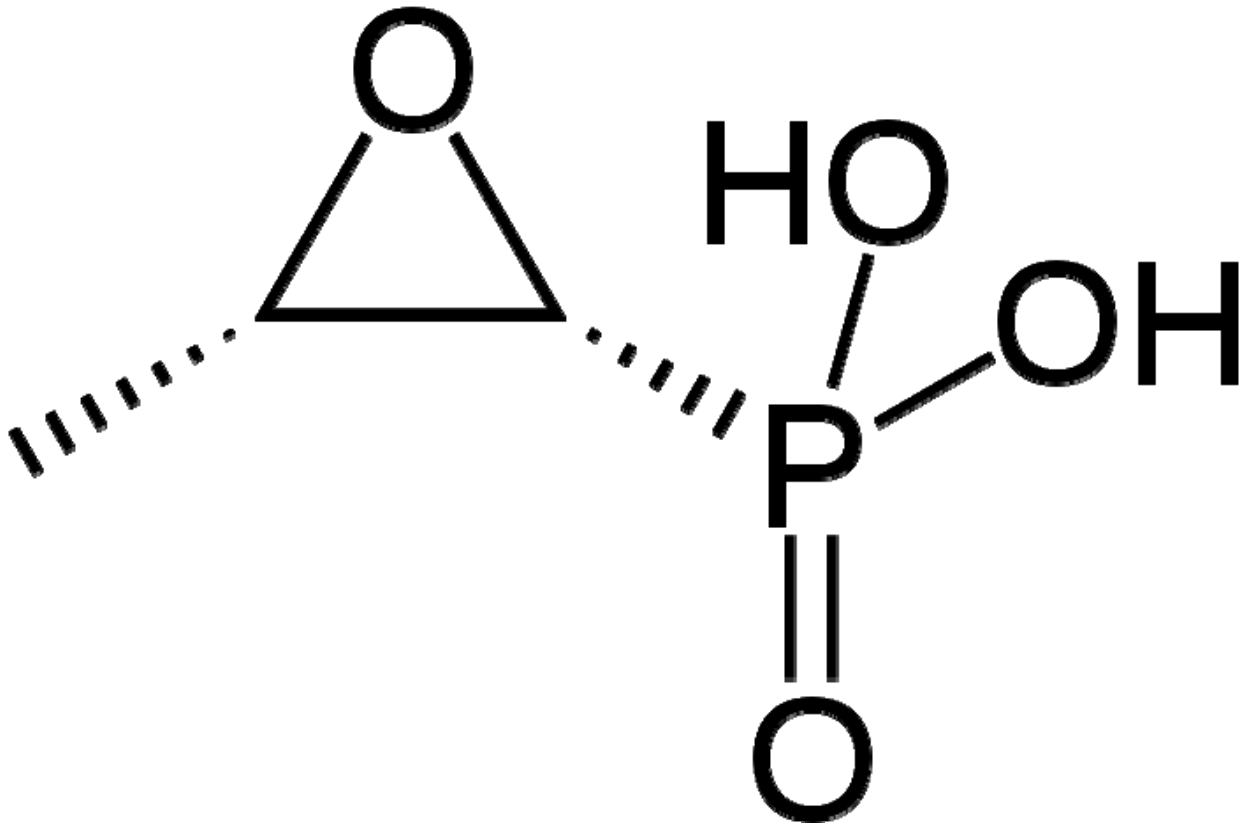
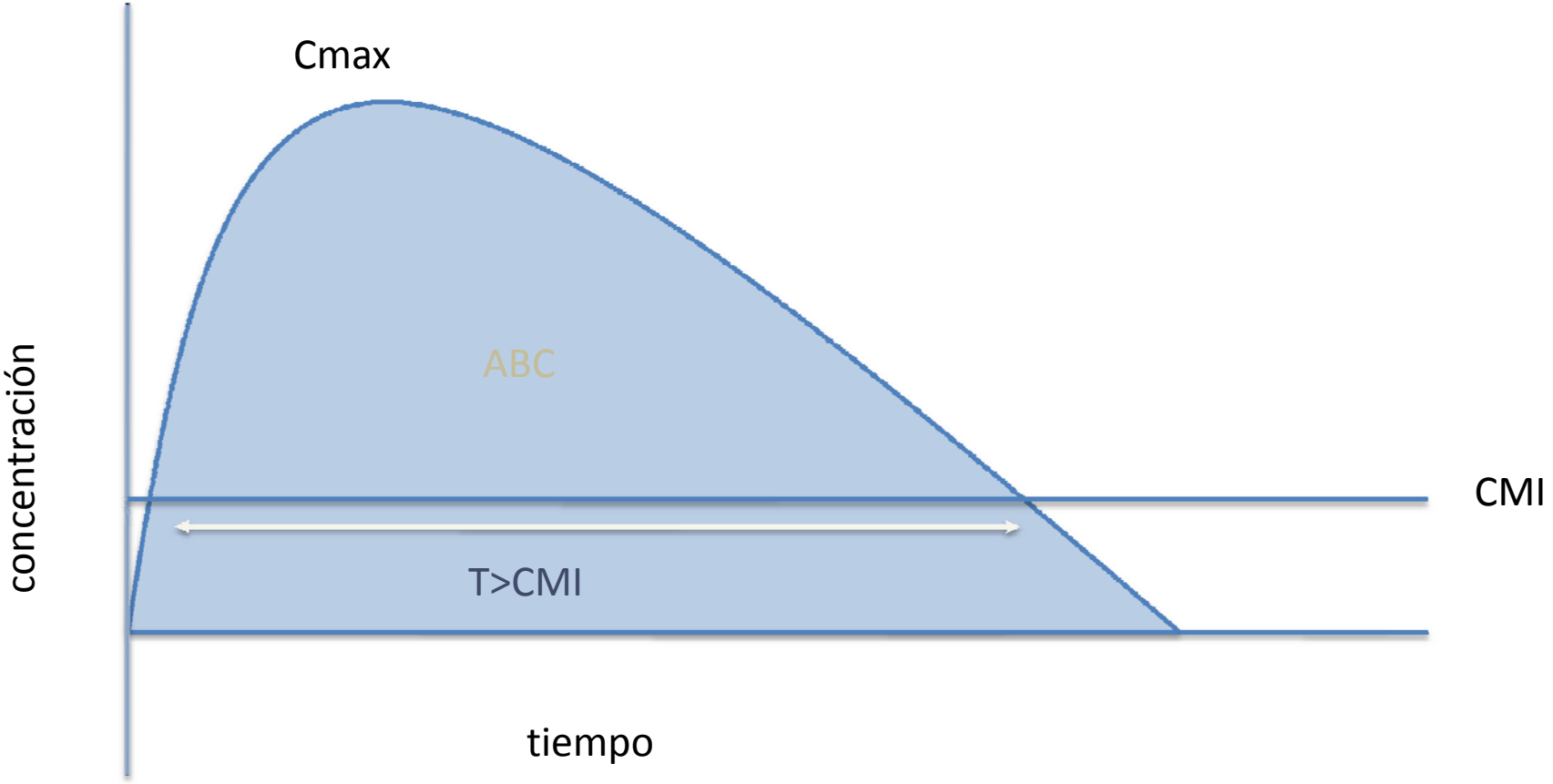
Fosfomicina



pK/pD



Grampositivos

Núria Fernández Hidalgo.
Servei Medicina Infecciosa.

Grampositivos

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