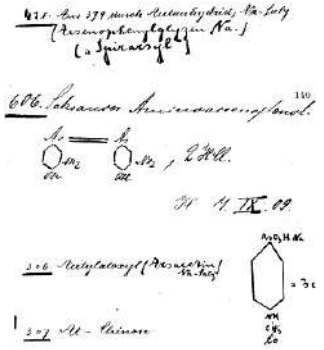
Dirençli Gram-Negatif Çomak (GNÇ) İnfeksiyonları: Yerel Sorunlar ve Çözüm Önerileri

Direncin Epidemiyolojisi, Ülkemizde ve Dünyada Son Durum

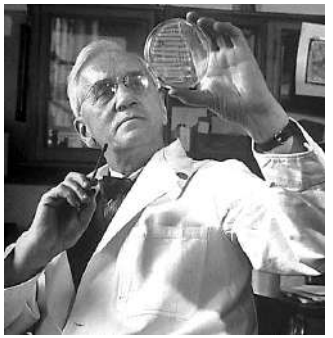
Dr. Emel YILMAZ
BUÜTF Enf Hast ve Kl. Mik AD
Görükle-BURSA

18.11.2022 -İzmir

- 1910, Paul Ehrlich'in geliştirdiği "sihirli mermi"

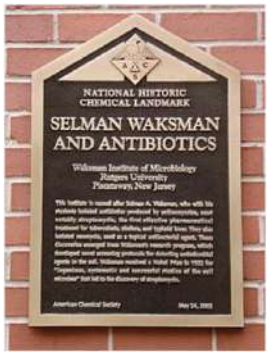


- 1928'de penisilin keşfi



- 1940'da penisilinin klinik kullanımı

- 1952 (Nobel Ödülü) vereme karşı ilk antibiyotik streptomisinin keşfi



- Aktinomisin
- Klavasin
- Grisein
- Neomisin
- Frasidin
- …….

". . .Uzmanlar 2000 yılına kadar viral ve bakteriyel hastalıkların ortadan kaldırılacağı konusunda hemfikir" (Time, Şubat 1966);

Singh SB, Barrett JF. Biochem Pharmacol 2006;71:1006-15
Neu HC. Science 1992;257:1064–73.
Travis J. Science 1994;264:360–2.

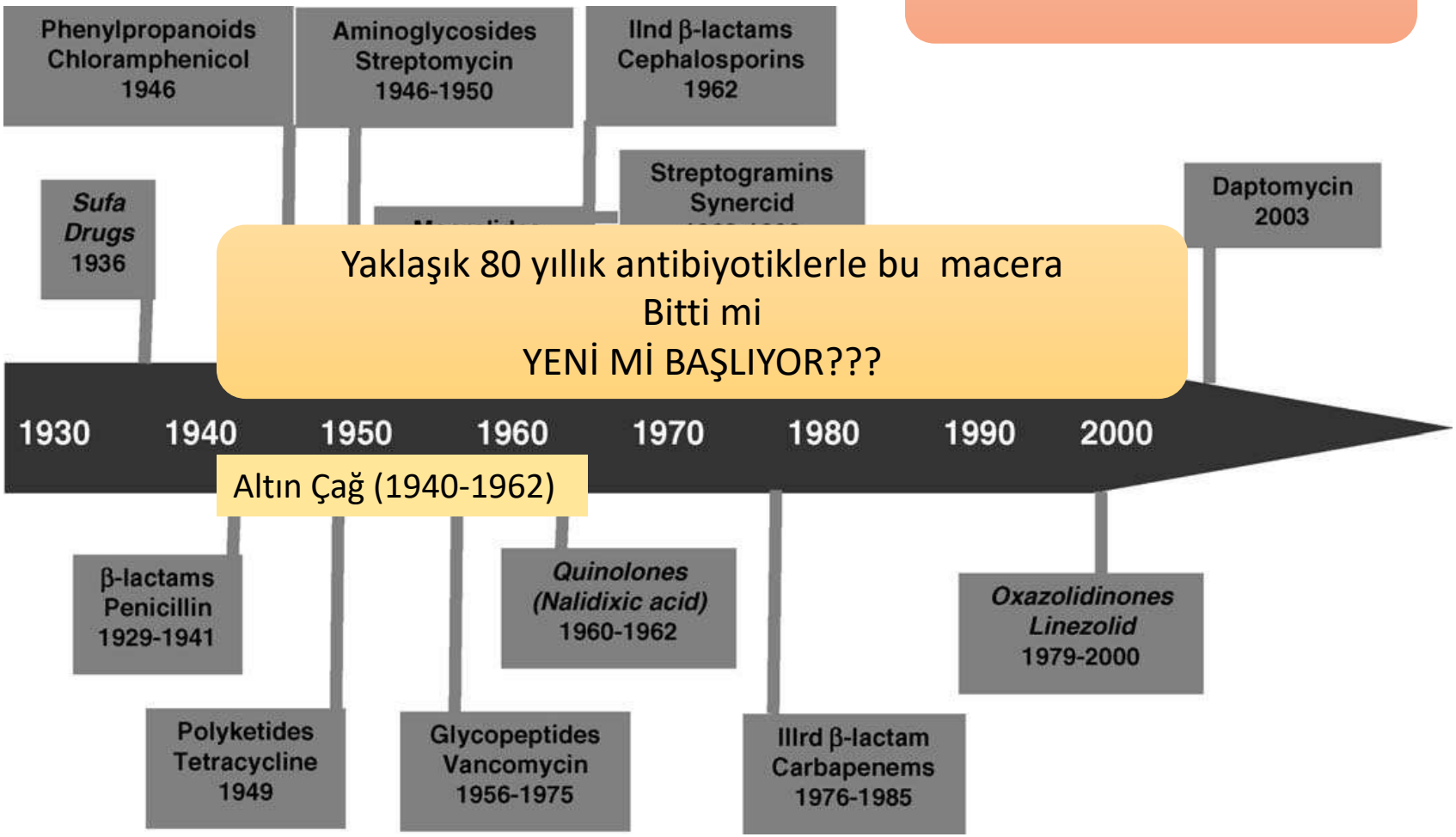
“Enfeksiyon hastalıklarını mağlup ettik ve enfeksiyon hastalıkları kitabını kapatabiliriz”

William H. Stewart
ABD Kongresi 1969

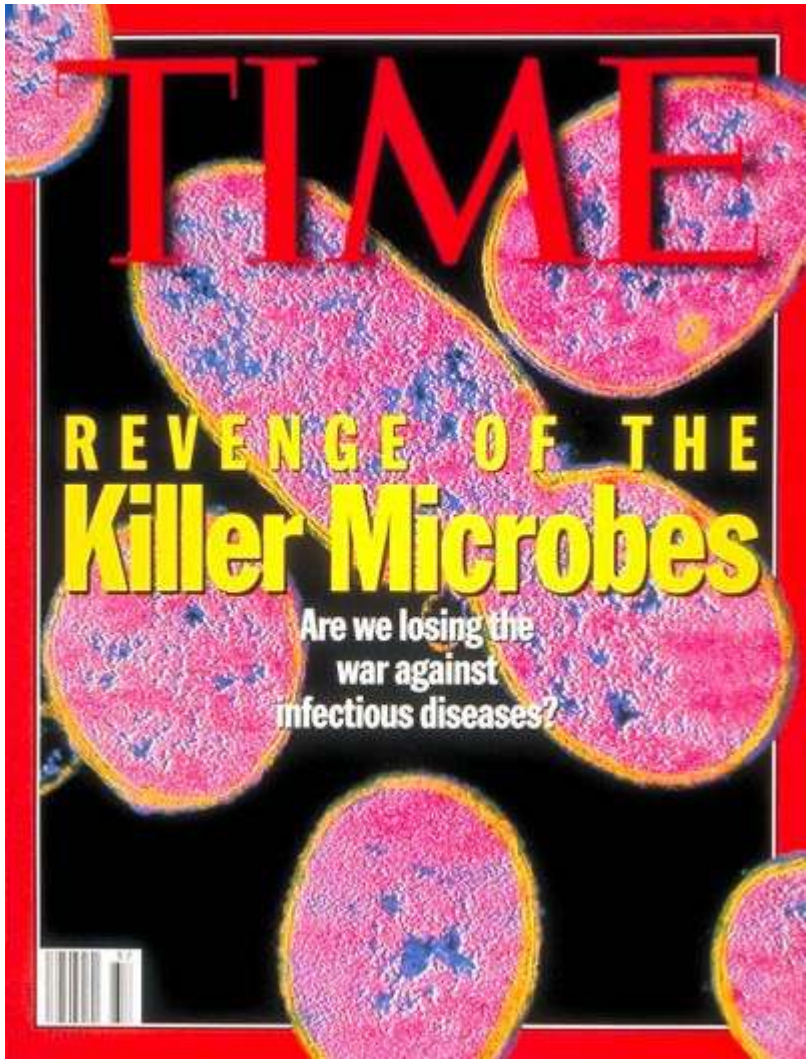
Singh SB, Barrett JF. Biochem Pharmacol 2006;71:1006-15
Neu HC. Science 1992;257:1064–73.
Travis J. Science 1994;264:360–2.

Antibiyotiklerin Keşfi

1980'lerde yavaşladı



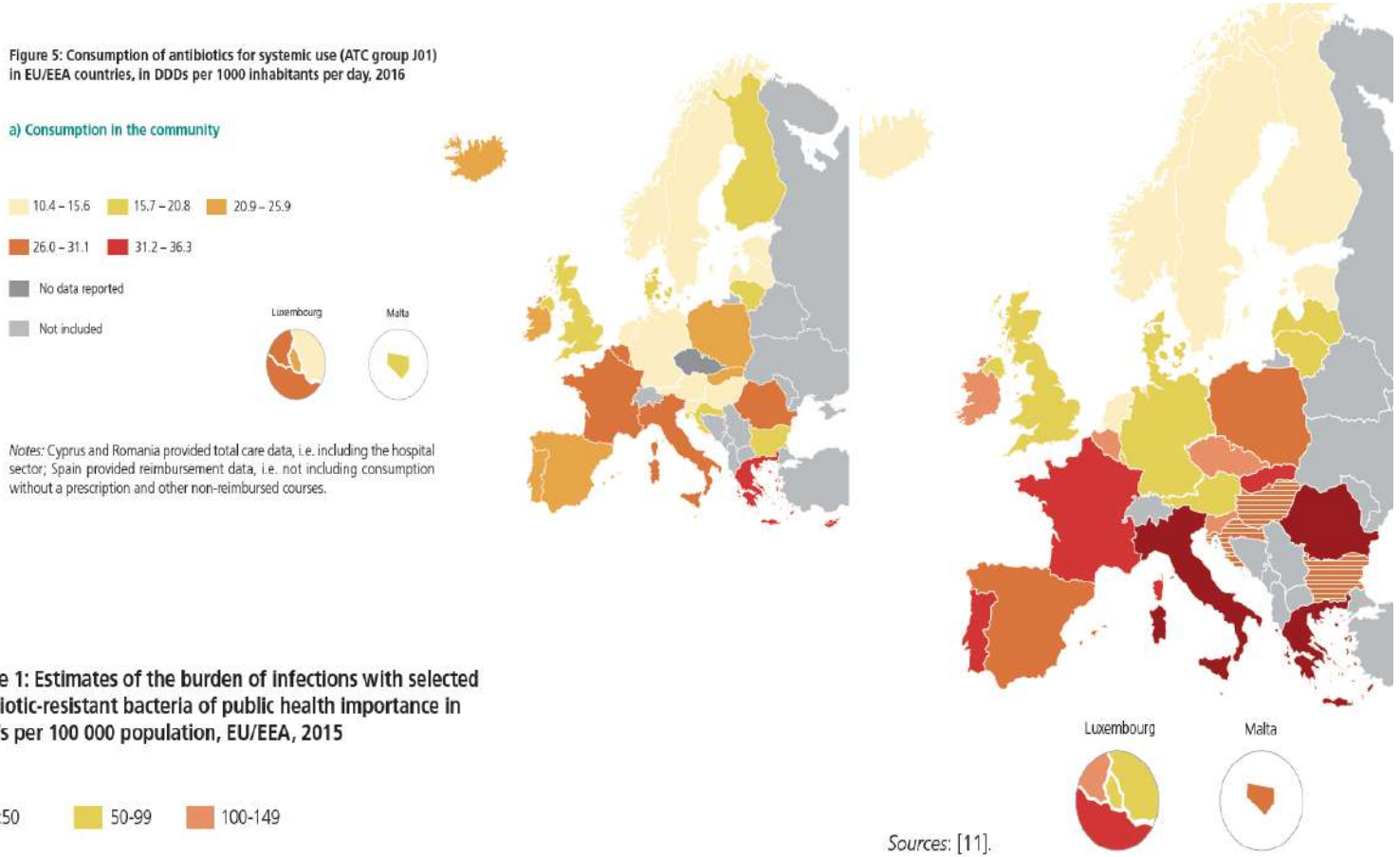
Singh SB, Barrett JF. Biochem Pharmacol 2006;71:1006-15


TIME
REVENGE OF THE
Killer Microbes
Are we losing the
war against
infectious diseases?

Antibiyotik direnci yoğun kullanılan ülkelerde daha fazla

Figure 5: Consumption of antibiotics for systemic use (ATC group J01) in EU/EEA countries, in DDDs per 1000 inhabitants per day, 2016

a) Consumption in the community



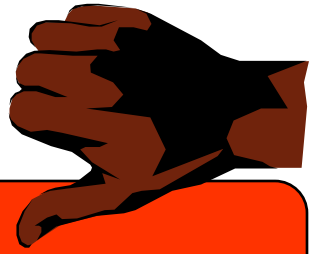
Notes: Cyprus and Romania provided total care data, i.e. including the hospital sector; Spain provided reimbursement data, i.e. not including consumption without a prescription and other non-reimbursed courses.

Figure 1: Estimates of the burden of infections with selected antibiotic-resistant bacteria of public health importance in DALYs per 100 000 population, EU/EEA, 2015

Sources: [11].

Global Antimicrobial Resistance and Use Surveillance System (GLASS) Report

2021



Antibiyotiksiz dönem

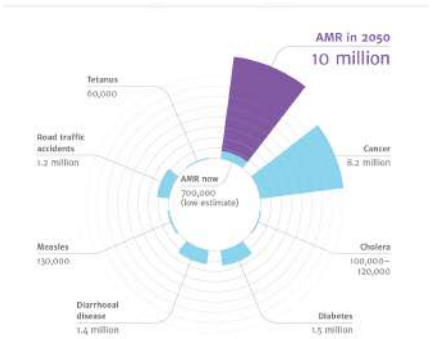
Karbapenem direnci

1. ve 2. kuşak sefalosporinler

Kolistin kullanımı

?????.....

Kolistin dirençli
Acinetobacter spp, E coli

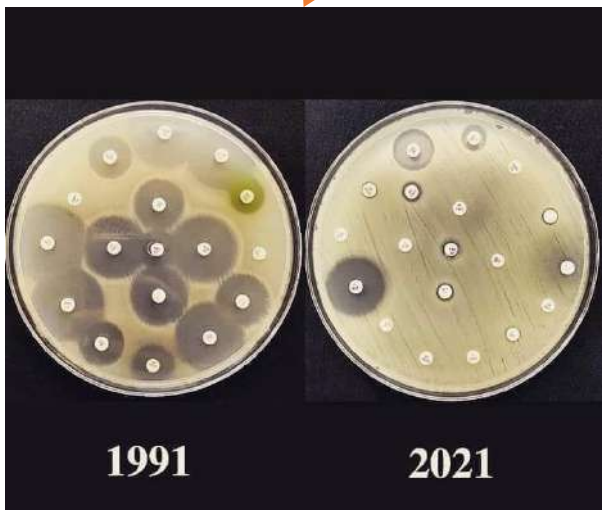


ESBL: ‘’Sonun Başlangıcı’’

ORGANİZMA

(1) ESCHERİCHİA COLİ 100.000 CFU/ml

ANTİBİYOGRAM	SONUÇ 1	SONUÇ 2
AMIKASIN	Duyarlı (<=8)	
AMOKSİSİSLİN/KLAVULANİK ASİT	Duyarlı (8/2)	
AMPİSİLİN	Duyarlı (<=4)	
ERTAPENEM	Duyarlı (<=0.25)	
GENTAMISIN	Duyarlı (<=2)	
IMIPENEM	Duyarlı (<=0.25)	
LEVOFLOKSASİN	Duyarlı (<=0.5)	
MEROPENEM	Duyarlı (<=0.125)	
NİTROFURANTOİN	Duyarlı (<=32)	
PİPERASİLİN/TAZOBAKTAM	Duyarlı (<=4/4)	
SEFAZOLIN	Orta Duyarlı (<=4)	
SEFIKSIM	Duyarlı (<=0.5)	
SEFTRIAKSON	Duyarlı (<=1)	
SİPROFLOKSASİN	Duyarlı (<=0.25)	
TOBRAMISIN	Duyarlı (<=2)	
TRİMETOPRİM SÜLFAMETOKSAZOL	Duyarlı (<=2/38)	



ORGANİZMA

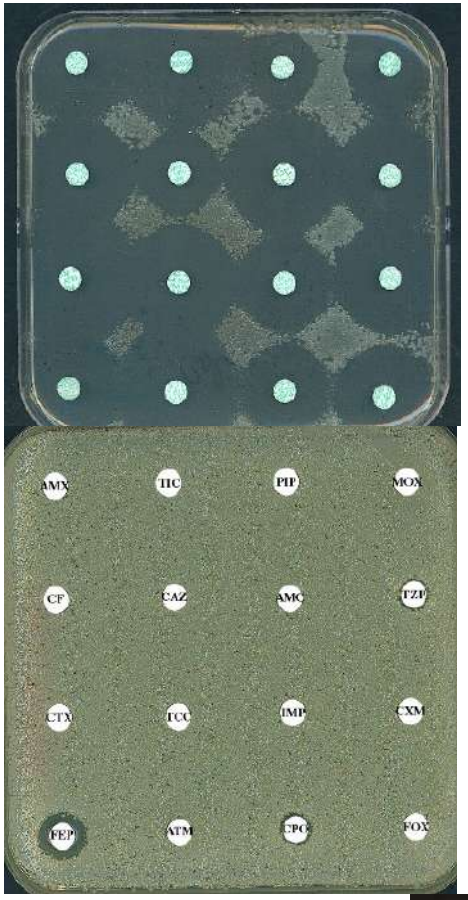
(1) KLEBSİELLA PNEUMONİAE RMK[Extended Spectrum Beta-lactamase] RMK[Isolate tested resistant to one or more carbapenems] 100.000 CFU/ml

ANTİBİYOGRAM	SONUÇ 1	SONUÇ 2	S
AMIKASIN	Duyarlı (<=8)		
AMOKSİSİSLİN/KLAVULANİK ASİT	Dirençli (>32/2)		
AMPİSİLİN	Dirençli (>16)		
ERTAPENEM	Dirençli (>2)		
FOSFOMİSİN W/G6P	Duyarlı (<=16)		
GENTAMISIN	Dirençli (>8)		
IMIPENEM	Dirençli (>8)		
LEVOFLOKSASİN	Dirençli (1)		
MEROPENEM	Dirençli (>8)		
PİPERASİLİN/TAZOBAKTAM	Dirençli (>32/4)		
SEFAZOLIN	Dirençli (>32)		
SEFIKSIM	Dirençli (>4)		
SEFTAZIDIM	Dirençli (>16)		
SEFTRIAKSON	Dirençli (>4)		
SİPROFLOKSASİN	Dirençli (>1)		
TOBRAMISIN	Dirençli (>8)		
TRİMETOPRİM SÜLFAMETOKSAZOL	Dirençli (>8/152)		

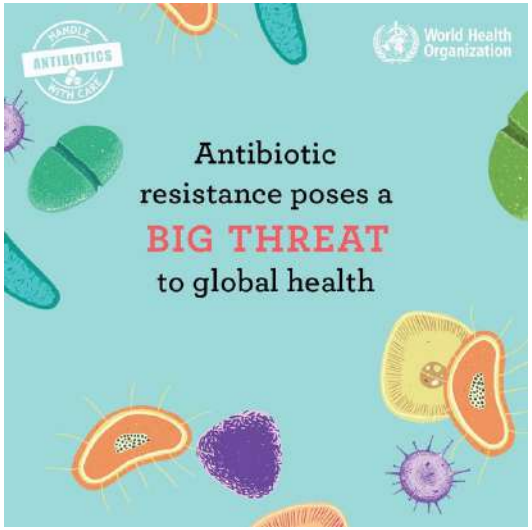
ORGANİZMA

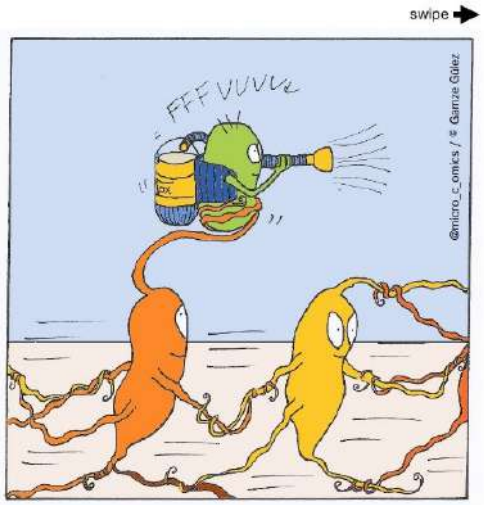
(1) ACİNETOBACTER BAUMANNİİ RMK[Class D Carbapenemase Producer] 100.000 CFU/ml

ANTİBİYOGRAM	SONUÇ 1	SONUÇ 2	SONUÇ
AMIKASIN	Dirençli (>32)		
GENTAMISIN	Dirençli (>4)		
IMIPENEM	Dirençli (>8)		
KOLİSTİN	Dirençli (>4)		
LEVOFLOKSASİN	Dirençli (>8)		
MEROPENEM	Dirençli (>8)		
SİPROFLOKSASİN	Dirençli (>1)		
TOBRAMISIN	Dirençli (>8)		
TRİMETOPRİM SÜLFAMETOKSAZOL	Dirençli (>8/152)		


AMX
TIC
PIP
MOX
CF
CAZ
AMC
TZP
CTX
TCC
IMP
CXM
FEP
ATM
CPO
FOX


En Kötü
Ne Olabilir ki?


HANDLE ANTIBIOTICS WITH CARE
World Health Organization
Antibiotic resistance poses a
BIG THREAT
to global health


swipe
FFFVUVVV
@micro_c_omics / © Gamze Gülez


Hiçbir şey çok kötü değildir, ancak daha kötü olabilir.
İngiliz Atasözü

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

Antibiotic Resistance Threats in the United States, 2019

Sir Samuel Luke Fildes (1843-1927) The Doctor

World Health Organization
REGIONAL OFFICE FOR Europe

WHO PRIORITY PATHOGENS LIST FOR R&D 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

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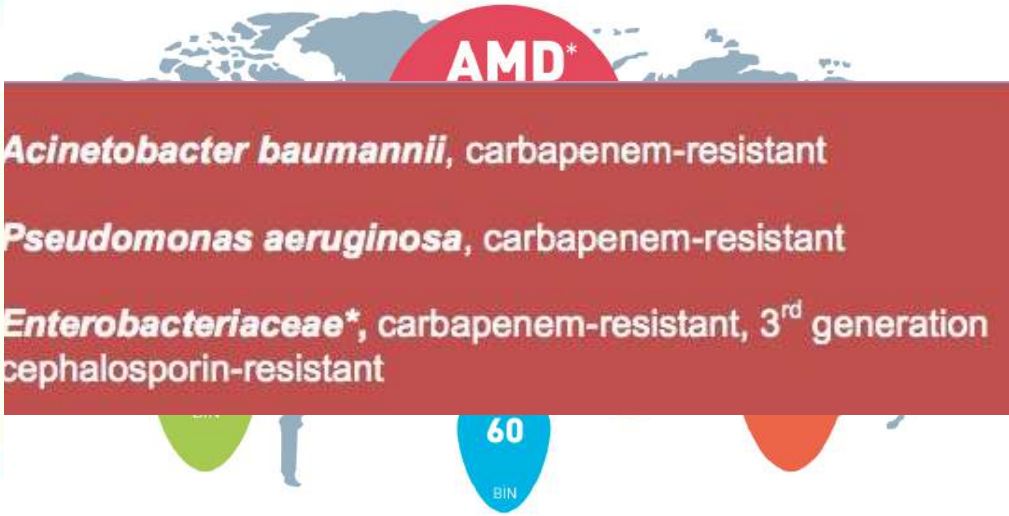
REVIEW

Check for updates

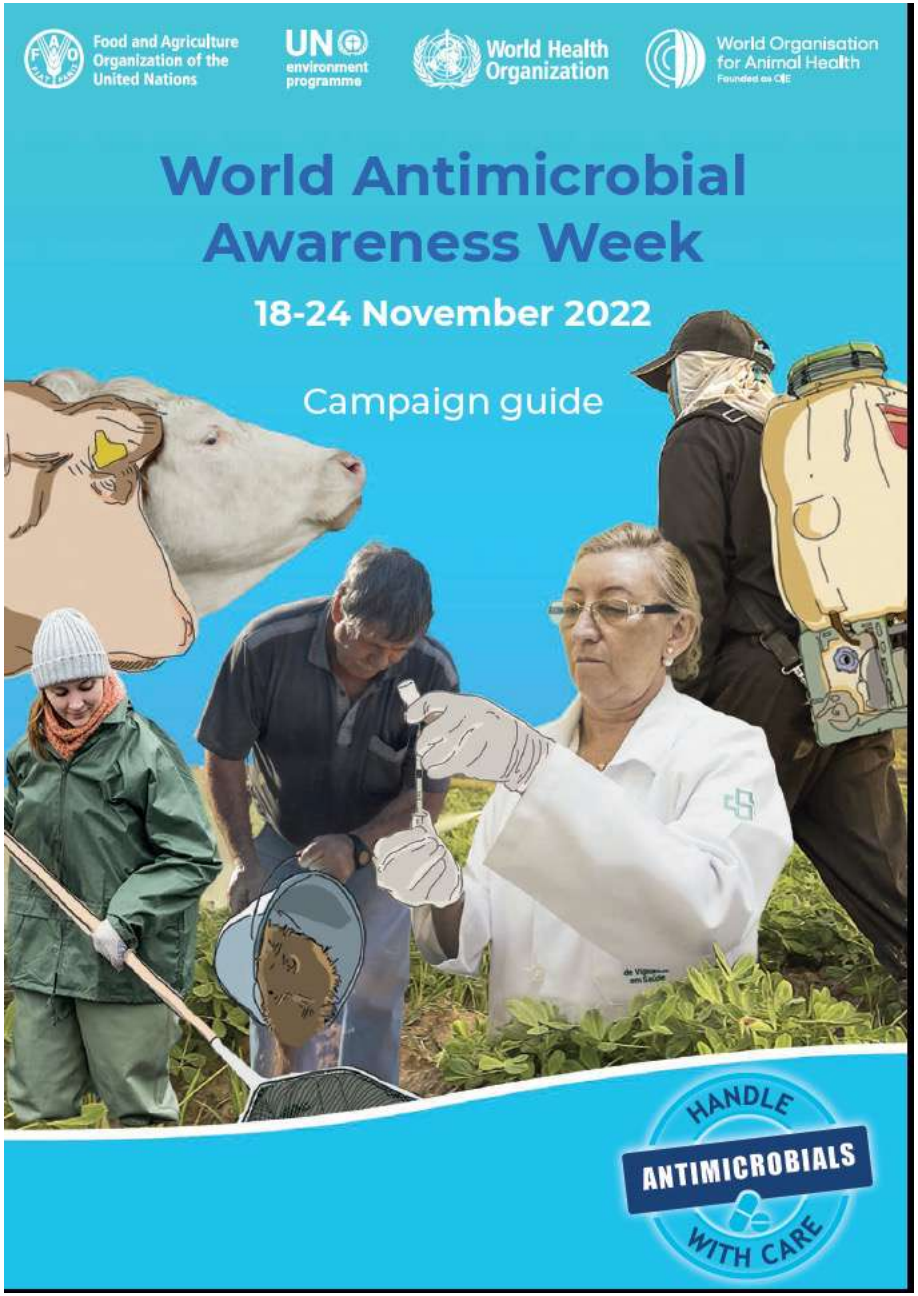
Antimicrobial Resistance in ESKAPE Pathogens

David M. P. De Oliveira,[a,b] Brian M. Forde,[a,b] Timothy J. Kidd,[a,b] Patrick N. A. Harris,[b,c] Mark A. Schembri,[a,b] Scott A. Beatson,[a,b] David L. Paterson,[b,c] Mark J. Walker[a,b]

2017'de yeni antibiyotik geliştirilmesi aciliyetine göre bakterileri önem sınıfına ayırmıştır



WHO publishes list of bacteria for which new antibiotics are urgently needed News Release http://www.who.int/mediacentre/news/releases/2017/bacteria-antibiotics-needed/en/



WAAW 2022 Theme
Preventing antimicrobial resistance together

HANDLE ANTIMICROBIALS WITH CARE

The theme of WAAW 2022 is "Preventing antimicrobial resistance together". AMR is a threat to humans, animals, plants and the environment. It affects us all. That is why this year's theme calls for cross-sectoral collaboration to preserve the efficacy of these important products.

To curb AMR effectively, all sectors must use antimicrobials prudently and adopt other preventive measures. The following actions can help reduce the need for antimicrobials and minimize the emergence of AMR:

- strengthen infection prevention and control in health facilities, farms and food industry premises;
- ensure access to clean water, sanitation and hygiene, and vaccines;
- implement best practices in food and agricultural production; and
- minimize pollution and ensure proper waste and sanitation management.

- Bir bakterinin üreme fonksiyonlarını bozan veya ölümüne neden olan bir ilaca karşı koyma yeteneğidir

- Antibiyotik direnci bakterilerin hayatta kalma mücadelesidir
- Her canlı yaşamlarını idame ettirmek ve soylarını devam ettirmeye programlı
- Fiziksel, doğal, dış tehditlere karşı daha güçlü bir şekilde dirençli olanlar seleksiyona uğrarlar

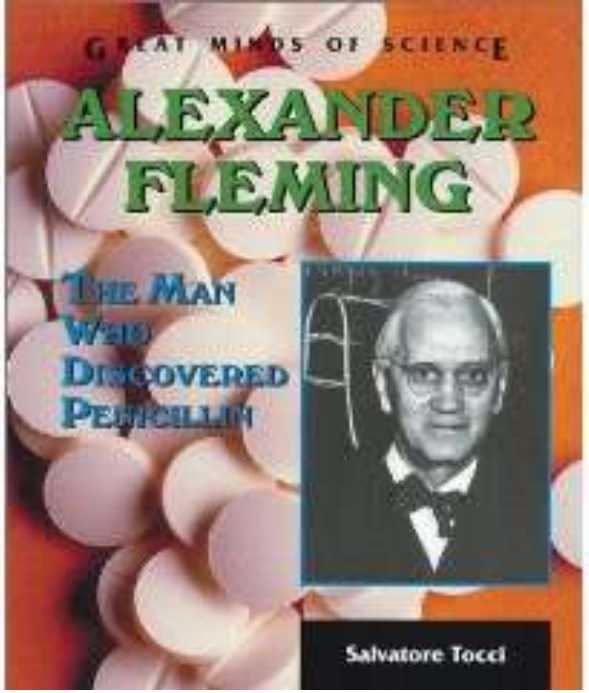
Tek Derdi Hayatta Kalabilmek

Doğal Direnç

- Bakteri tür özelliğinden dolayı hedefi taşımaması ya da kendisinin ürettiği antibiyotiğe dirençli olması

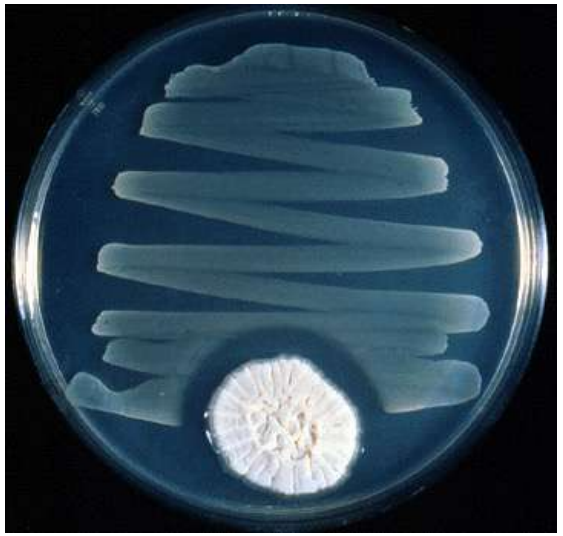
Kazanılmış Direnç

- Genetik özelliğinde ortaya çıkan değişiklikler ile daha önce duyarlı iken antibiyotiğe dirençli hale gelmesi



Penicillum spp
1940

Penisilin



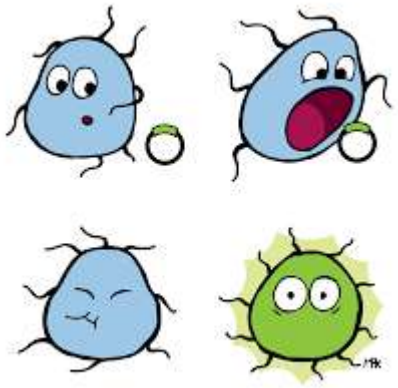
Giuseppe Brotzu

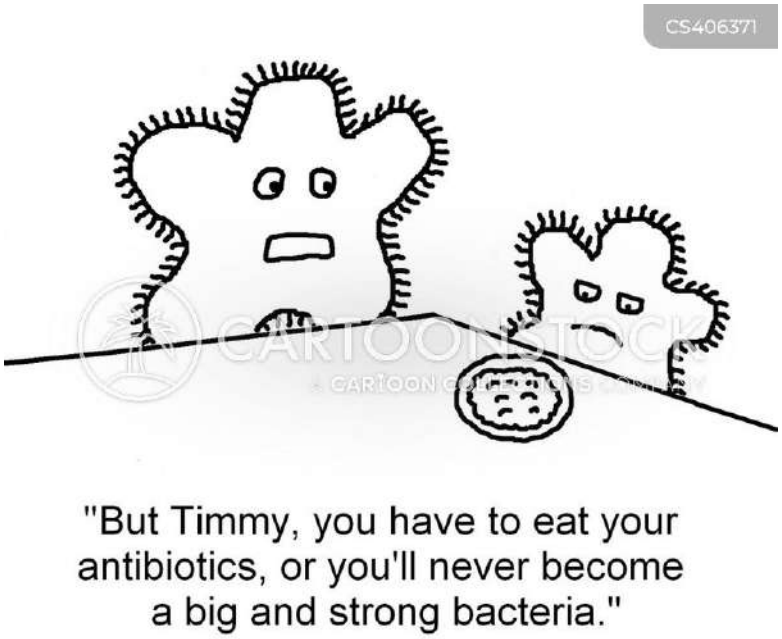
Cephalosporium acremonium
1945

Sefalosporinler

Su Siccu, near the harbor of Cagliari, the site where cephalosporin was discovered

- Milyarlarca yıldır bakteriler antibiyotik üretiyor
- Direnç genleri zaten var
- Antibiyotik baskısı ile direnç mekanizmaları zenginleşiyor
- Ölü bakteri bile direnç genlerini diğer bakterilere aktarabiliyor





Antibiyotikler sadece dirençli suşları seçmez, direnç genini de ortaya çıkarır

frontiers in Microbiology

REVIEW
published: 19 February 2016
doi: 10.3389/fmicb.2016.00173

Dissemination of Antimicrobial Resistance in Microbial Ecosystems through Horizontal Gene Transfer

Christian J. H. von Wintersdorff[1], John Penders[1,2], Julius M. van Niekerk[2], Nathan D. Mills[1], Snehali Majumder[2], Lieke B. van Alphen[2], Paul H. M. Savelkoul[1,2,3] and Petra F. G. Wolffs[1,2]

- Kromozomal: Nokta mutasyonu
- Plazmid
- Transpozon
- İntegron

Hareketli genetik elamanlar

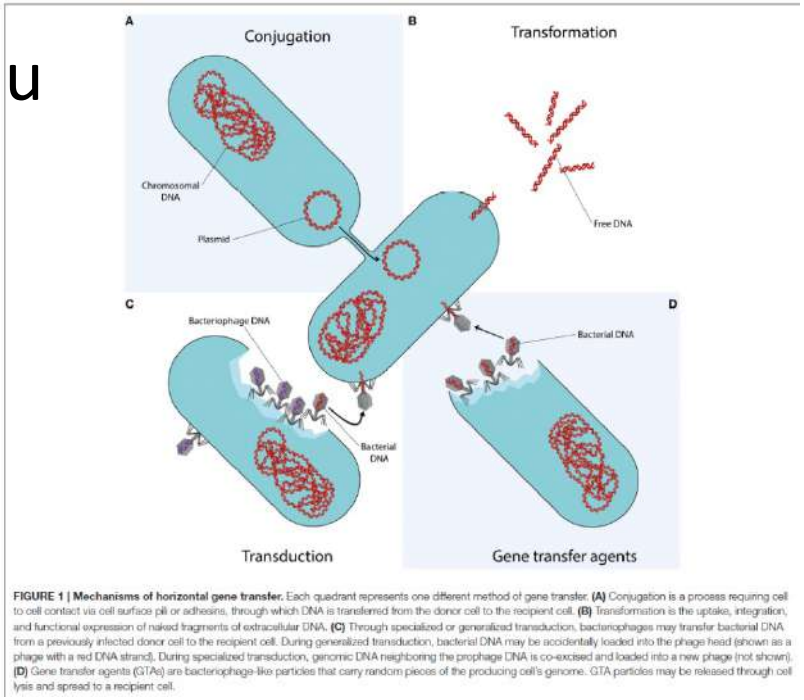
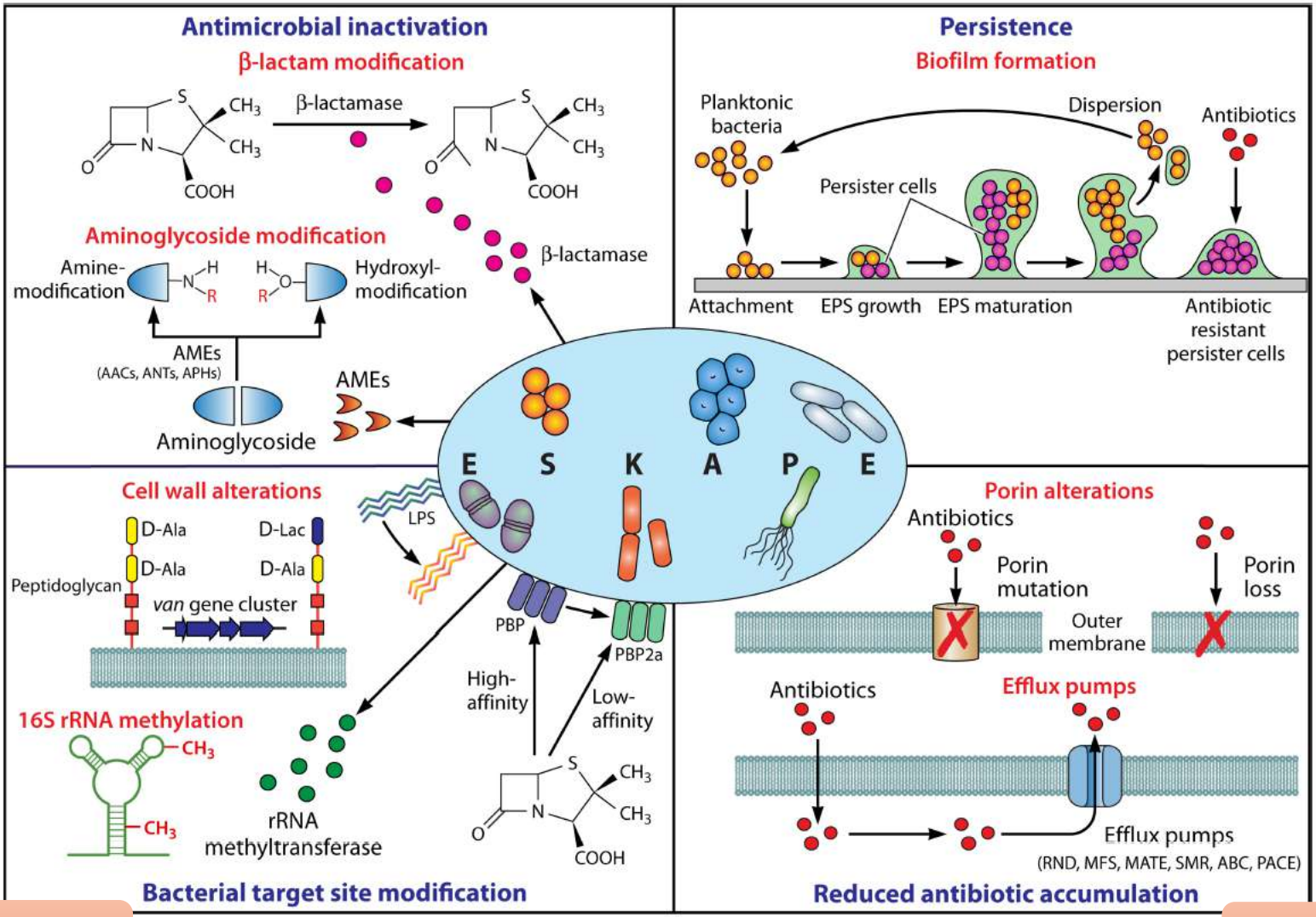


FIGURE 1 | Mechanisms of horizontal gene transfer. Each quadrant represents one different method of gene transfer. **(A)** Conjugation is a process requiring cell to cell contact via cell surface pili or adhesins, through which DNA is transferred from the donor cell to the recipient cell. **(B)** Transformation is the uptake, integration, and functional expression of naked fragments of extracellular DNA. **(C)** Through specialized or generalized transduction, bacteriophages may transfer bacterial DNA from a previously infected donor cell to the recipient cell. During generalized transduction, bacterial DNA may be accidentally loaded into the phage head (shown as a phage with a red DNA strand). During specialized transduction, genomic DNA neighboring the prophage DNA is co-excised and loaded into a new phage (not shown). **(D)** Gene transfer agents (GTAs) are bacteriophage-like particles that carry random pieces of the producing cell's genome. GTA particles may be released through cell lysis and spread to a recipient cell.

http://www.sciam.com/1998/0398issue/0398levybox3.html

Gene Transfer in the Environment. Levy & Miller, 1989
Wintersdorff CJH et. al. Front Microbiol 2016; 7: 173



Kinolonlar

P aeruginosa
A baumanniii

De Oliveria DM et al. Clin Mic Rev 2020; 33

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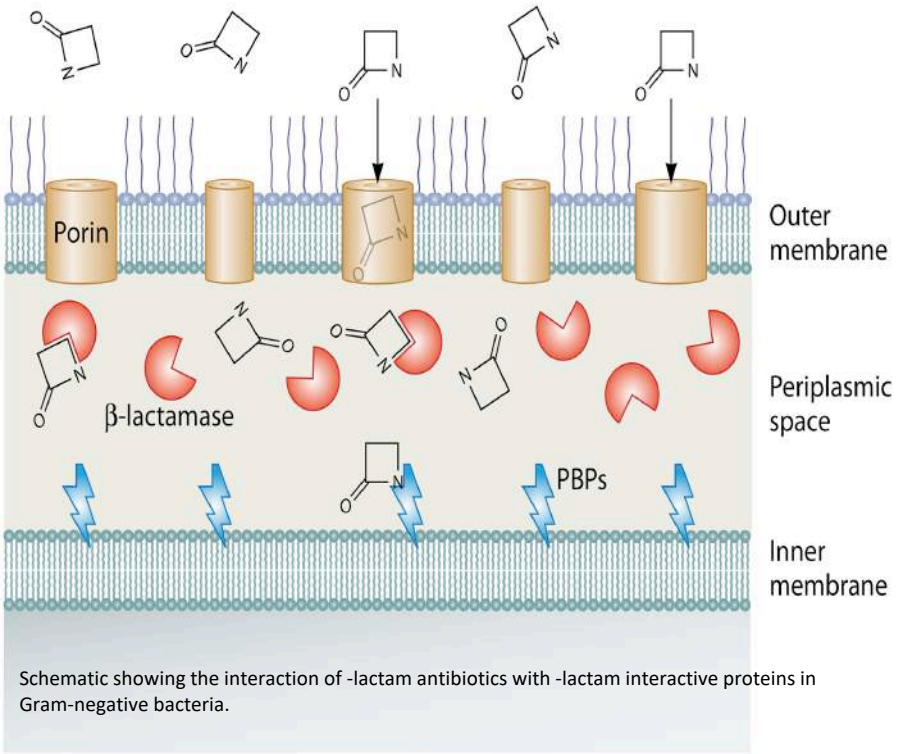
Epidemiology of β-Lactamase-Producing Pathogens

Karen Bush,[a] Patricia A. Bradford[b]



Schematic showing the interaction of -lactam antibiotics with -lactam interactive proteins in Gram-negative bacteria.

Evolution of β-Lactamases

- Wild-Type
  - Penicillins
- β-lactamase (TEM-1, TEM-2, SHV-1)
  - β-lactam/β-lactamase inhibitors; Cephalosporins
- AmpC; ESBL (TEM, SHV, CTX-M)
  - Carbapenems
- Carbapenemase (KPC, MBL,NDM-1)

Bush K et al.. Clin Mic Rev 2020; 33

TABLE 1 Table of Firsts: the dates, organisms, and locations of the first of a series of β-lactamase-producing isolates with long-term clinical significance

Original β-lactamase name (currently recognized name)	Yr of first verified isolation	Organism	Location	First description in literature	Reference(s)
Penicillinase (chromosomal AmpC)	1940	*Bacillus coli* (*Escherichia coli*)	England	1940	1
Penicillinase	1942	*Staphylococcus aureus*	England	1942	65
OXA	1962	*Salmonella enterica* serovar Typhimurium, *Escherichia coli*[a]	England	1965 1967	87, 215
TEM-1	1963	*Escherichia coli*	Greece	1965	85
SHV-1	1972	*Klebsiella pneumoniae*	Unknown	1972	216
Transferable ESBL (SHV-2)	Pre-1983	*K. pneumoniae*	Germany	1983	217
Serine (class A, group 2f) carbapenemase (SME-1)	1982 1985	*Serratia marcescens*	England (London) USA (Minnesota)	1990 1986	148, 150
Plasmid-encoded AmpC (MIR-1)	1988	*K. pneumoniae*	USA (Massachusetts)	1990	141
Plasmid-encoded MBL (IMP-1)	1988	*Pseudomonas aeruginosa*	Japan	1991	151
Inhibitor-resistant TEM (TEM-30)	1991	*E. coli*	France (Paris)	1994	118
KPC-type (KPC-2)	1996	*K. pneumoniae*	USA (North Carolina)	2000	158
NDM-1	2006	*K. pneumoniae*	India (New Delhi)	2009	175, 176

[a]Anderson and Datta described a *Salmonella* Typhimurium isolate from 1962 that later was confirmed to produce the OXA-2 enzyme (215). Egawa et al. described an *E. coli* isolate in 1967 that produced the OXA-1 enzyme (87).

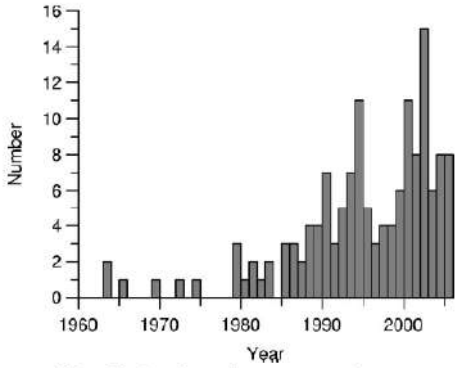


FIG. 1. Number of new β-lactamases reported per year.

Bush K Antimicrob Agent Chemother 2018; 62

Sawa et al. Journal of Intensive Care (2020) 8:13
https://doi.org/10.1186/s40560-020-0429-6

Journal of Intensive Care

REVIEW Open Access

Molecular diversity of extended-spectrum β-lactamases and carbapenemases, and antimicrobial resistance

Teiji Sawa[1*], Kunihiko Kooguchi[2] and Kiyoshi Moriyama[3]

Karbapenem Direnci

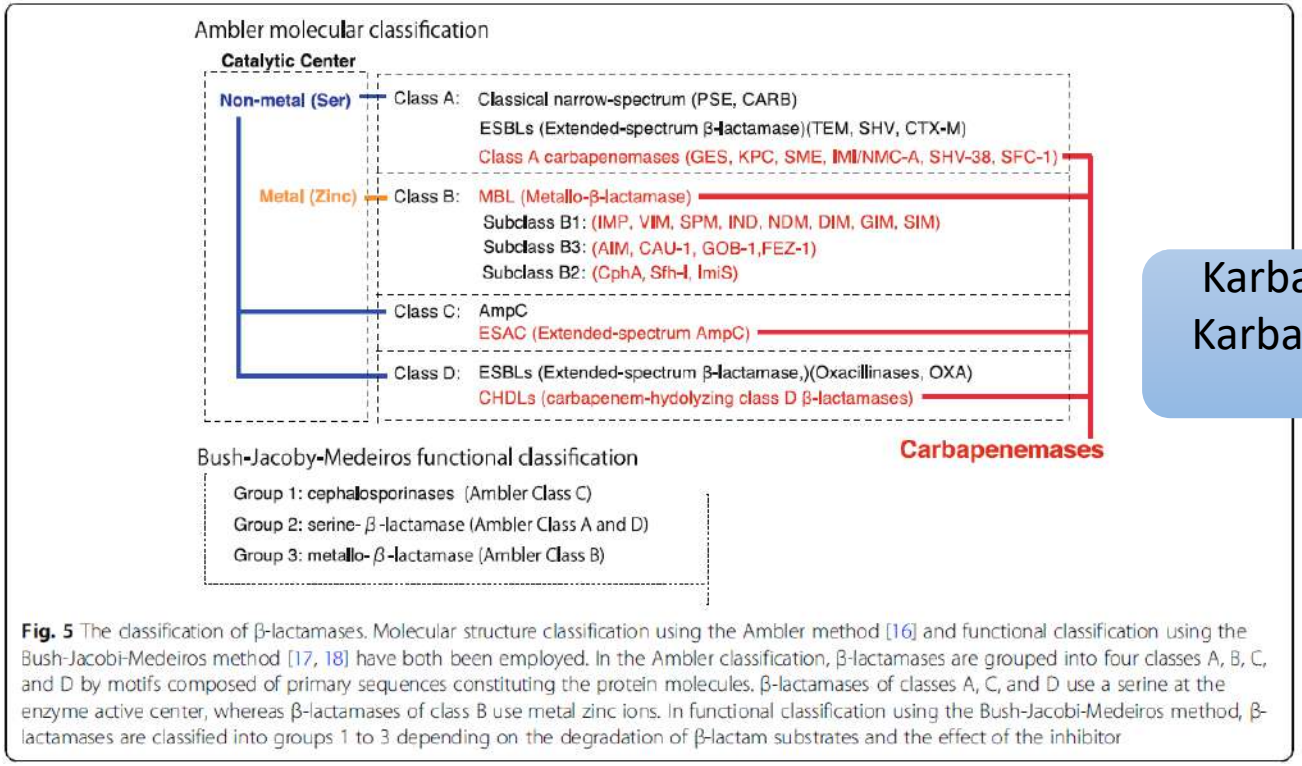


Fig. 5 The classification of β-lactamases. Molecular structure classification using the Ambler method [16] and functional classification using the Bush-Jacobi-Medeiros method [17, 18] have both been employed. In the Ambler classification, β-lactamases are grouped into four classes A, B, C, and D by motifs composed of primary sequences constituting the protein molecules. β-lactamases of classes A, C, and D use a serine at the enzyme active center, whereas β-lactamases of class B use metal zinc ions. In functional classification using the Bush-Jacobi-Medeiros method, β-lactamases are classified into groups 1 to 3 depending on the degradation of β-lactam substrates and the effect of the inhibitor

Karbapenem Direnci
Karbapenemaz±Porin kaybı

Sawa T et al. J Inten Care 2020; 8

TABLE 3 Increasing numbers of β-lactamases in well-characterized families[a]

Enzyme type	Class	Functional group	No. in class by yr						
			1961	1995	2000	2005	2010	2015	2018
CMY	C	1	0	1	6	22	64	136	139
PDC[b]	C	1	0	(1)	(1)	(1)	10	30	226
ADC[c]	C	1	0	0	(1)	7	7	7	81
All TEMs	A	2b, 2be, 2br	0	36	86	153	178	219	224
All SHVs	A	2b, 2be, 2br	0	6	26	89	134	182	193
CTX-M	A	2be	0	2	9	51	103	172	182
KPC	A	2f	0	0	0	3	11	22	24
All OXAs	D	2d	0	18	28	88	202	498	520
IMP	B	3	0	1	3	23	29	48	53
VIM	B	3	0	0	2	12	27	41	46
NDM	B	3	0	0	0	0	1	12	14
Estimated total of all unique β-lactamases			(<13)[d]	217	309	584	1,003	1,855	2,771

[a]Some data are from reference 224, as well as from http://www.lahey.org/Studies/ and https://www.ncbi.nlm.nih.gov/bioproject/PRJNA313047.
[b]PDC, *Pseudomonas*-derived cephalosporinase family, first named in 2009 (136). AmpC pseudomonal cephalosporinases were described as early as 1965 (137). This family was not included in the Lahey database http://www.lahey.org/Studies/.
[c]ADC, *Acinetobacter*-derived cephalosporinase, family first named in 2005 (190). The name ADC-1 was assigned to an enzyme first described in 2000 (135). This family was not included in the Lahey database http://www.lahey.org/Studies/.
[d]Estimated, based on data from references 18 and 92 that most likely included some of the same enzymes.

β-Lactamases and β-Lactamase Inhibitors in the 21st Century

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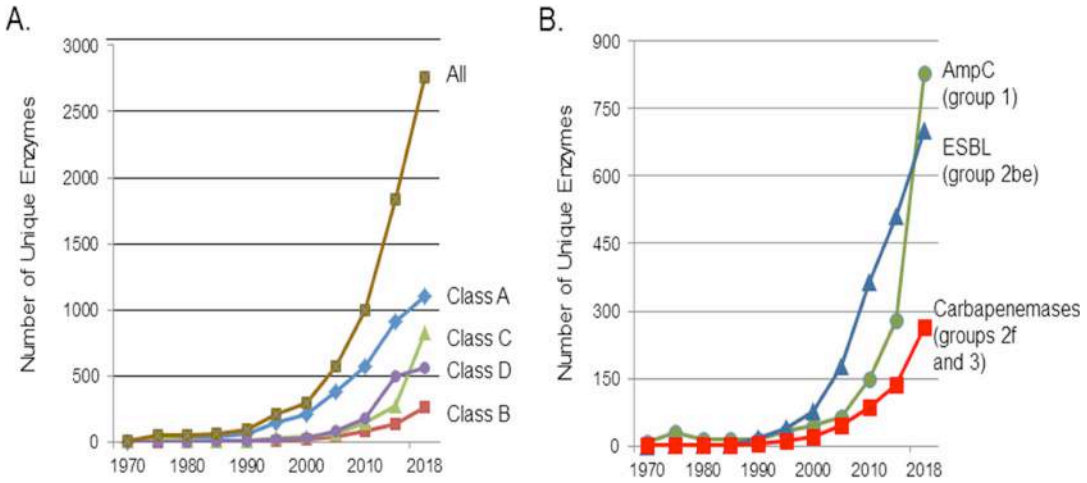
https://doi.org/10.1016/j.jmb.2019.04.002
Edited by C.G. Dowson

Abstract

>4300 beta laktamaz çeşidi var



http://www.lahey.org/studies

www.lahey.org/Studies/ and https://www.ncbi.nlm.nih.gov/bioproject/PRJNA313047

Table 2. Major mechanisms of carbapenem resistance in *Acinetobacter baumannii*

Mechanism	Acquisition	Determinant
B-lactamase:		
Class A. Serine carbapenemases	MGE	KPC[a]
Class B. Metallo-β-lactamases	MGE	VIM (-1, -2, -3, -4, and -11) SIM-1 IMP (-1, -2, -4, -5, -6, -8, -10, -11, and -19) NDM (-1, -2)
Class D. Oxacillinase-type	MGE	OXA-23 cluster: (OXA-23, -27 and -49) OXA-24/40 cluster (OXA-25, -26, -40 and -72) OXA-58 OXA-51 cluster ($n = 14$ variants) OXA-48[a] OXA-235
	CM	High-level OXA-51
Impermeability	CM	Functional loss of porins CarO, Omp 33–36 and OprD homolo
Efflux pumps	CM	AdeABC
Altered penicillin-binding proteins	CM	Variable binding

CM, chromosomal mutation; KPC, *Klebsiella pneumoniae* carbapenemase; MGE, mobile genetic element; NDM, New Delhi metallo-β-lactamase; OXA, oxacillinase; VIM, Verona-integrated metalloprotease.
[a]Rare.

Table 3. Major mechanisms of carbapenem resistance in *Enterobacterales*

Mechanism	Acquisition	Determinant
β-lactamases:		
Class A. Serine carbapenemases	MGE	KPC[a] ($n = 22$ variants) IMI (-1,-2) SME[b] GES[b,c] NMC-A[b] FRI-1[b] IMI-1[b] SFC[b] SHV-38[b]
Class B. Metallo-beta-lactamases	MGE	VIM[a] ($n = 46$ variants) NDM[a] ($n = 16$ variants) IMP ($n = 52$ variants) GIM-1[b] SIM[b] SPM[b]
Class C. Cephalosporinase	MGE	CMY-10[b]
Class D. Oxacillinase-type	MGE	OXA-48-like[a] ($n = 13$ variants)
Impermeability (porin lesions)	CM	ompK35 ompK36 ompC ompF ompK37

CM, chromosomal mutation; KPC, *Klebsiella pneumoniae* carbapenemase; MGE, mobile genetic element; NDM, New Delhi metallo-β-lactamase; OXA, oxacillinase; VIM, Verona-integrated metalloprotease.
[a]Most common.
[b]Geographically variable but less common or rare and sporadic.
[c]Low-level carbapenem hydrolysis.

Table 1. Major mechanisms of carbapenem resistance in *Pseudomonas aeruginosa*

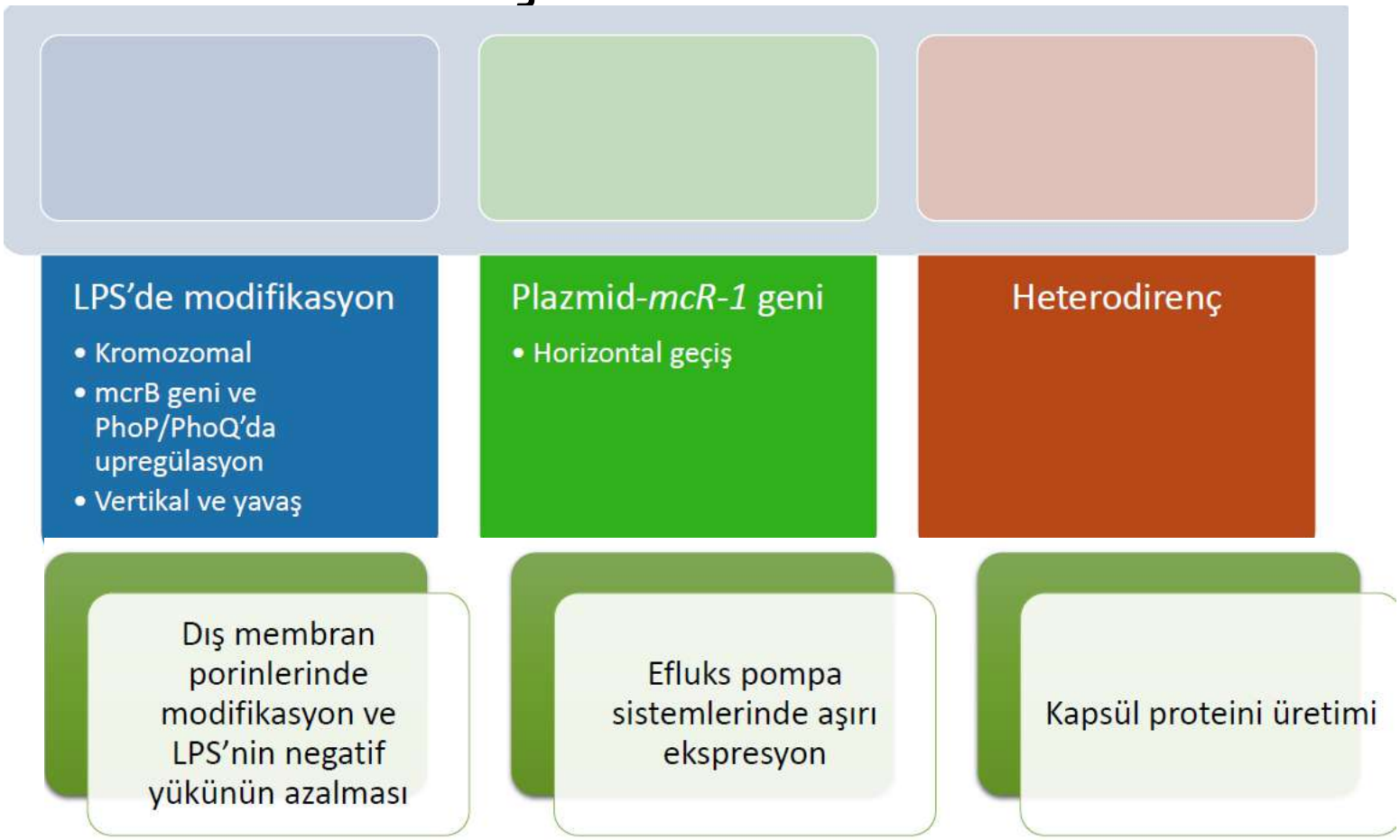
Mechanism	Genetic event	Determinant
β-lactamases:		
Class A. Serine carbapenemases	MGE	KPC[a]
Class B. Metallo-β-lactamase	MGE	VIM[b] ($n = 24$ variants) IMP[b] ($n = 33$ variants) SIM[a] GIM[a] KHM[a] SPM[a] AIM[a] SMB[a] TMB[a] FIM[a] SIM[a] DIM[a] NDM[a]
Class D. Oxacillinase-type	MGE	OXA-40[a] OXA-198[a]
Impermeability	CM	Loss of OprD
Efflux pumps	CM	MexAB-OprM MexEF-OprN MexCD-OprJ

CM, chromosomal mutation; KPC, *Klebsiella pneumoniae* carbapenemase; MGE, mobile genetic element; NDM, New Delhi metallo-β-lactamase; OXA, oxacillinase; VIM, Verona-integrated metalloprotease.
[a]Geographically variable but less common or rare and sporadic.
[b]Most common.

Nordmann P et al. Clin Infect Dis 2019; 69: S521-8.

Brink AJ. Curr Opin Infect Dis 2019; 32: 609-16

Kolistin Direnç Mekanizmaları



Current Medical Research and Opinion 2015;31:707-721
J of Global Antimicrob Resistance 2018;12:124-36

Plazmid geçişli mcr geni

Emergence of plasmid-mediated colistin resistance mechanism MCR-1 in animals and human beings in China: a microbiological and molecular biological study

Yi-Yun Liu, BS[†], Yang Wang, PhD[†], Prof Timothy R Walsh, DSc, Ling-Xian Yi, BS, Rong Zhang, PhD, James Spencer, PhD, Yohei Doi, MD, Guobao Tian, PhD, Baolei Dong, BS, Xianhui Huang, PhD, Lin-Feng Yu, BS, Danxia Gu, PhD, Hongwei Ren,

- Çiğ et örnekleri %15
- Hayvanlar %21
- İnsanlar %1

Aktarılabilir ve hızlı yayılım riski var
Türler arası transfer

E. coli
Salmonella
Shigella
Klebsiella
Enterobacter

The Lancet Infectious Diseases 2016;16:161-8

J of Global Antimicrob Resistance 2018;12:124-36
Lancet Infect Dis. 2016;16(3):292–3.

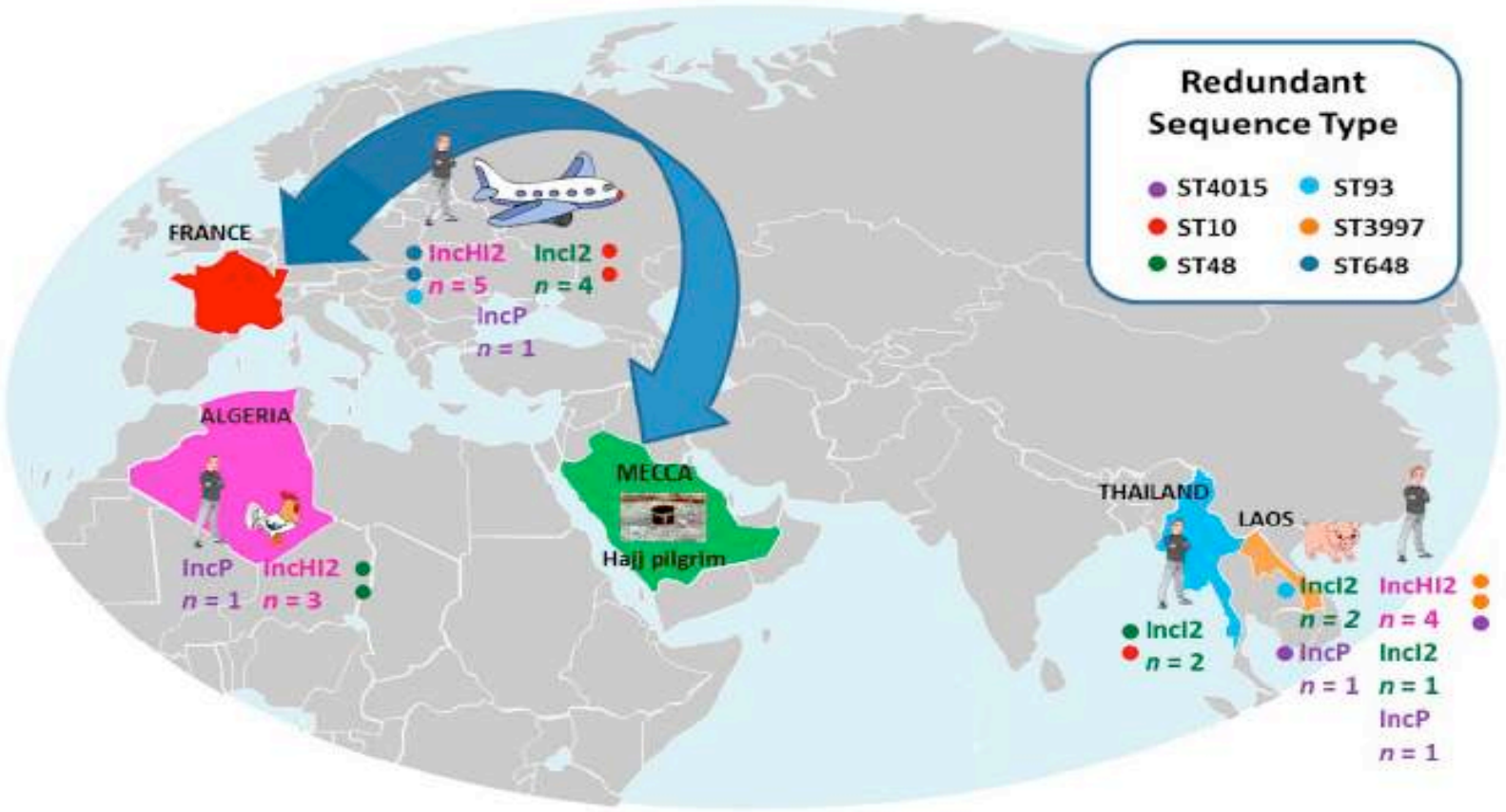


Figure 1. Origins and plasmid type of *mcr-1* strains collected in our study.

Hadjadj L et al. Genes 2017; 8: 394

PHILOSOPHICAL TRANSACTIONS B

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Review

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Surveillance of antibiotic resistance

Alan P. Johnson

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Surveillance involves the collection and analysis of data for the detection and monitoring of threats to public health. Surveillance should also inform as to the epidemiology of the threat and its burden in the population. A further key component of surveillance is the timely feedback of data to stakeholders with a view to generating action aimed at reducing or preventing the public health threat being monitored. Surveillance of antibiotic resistance involves

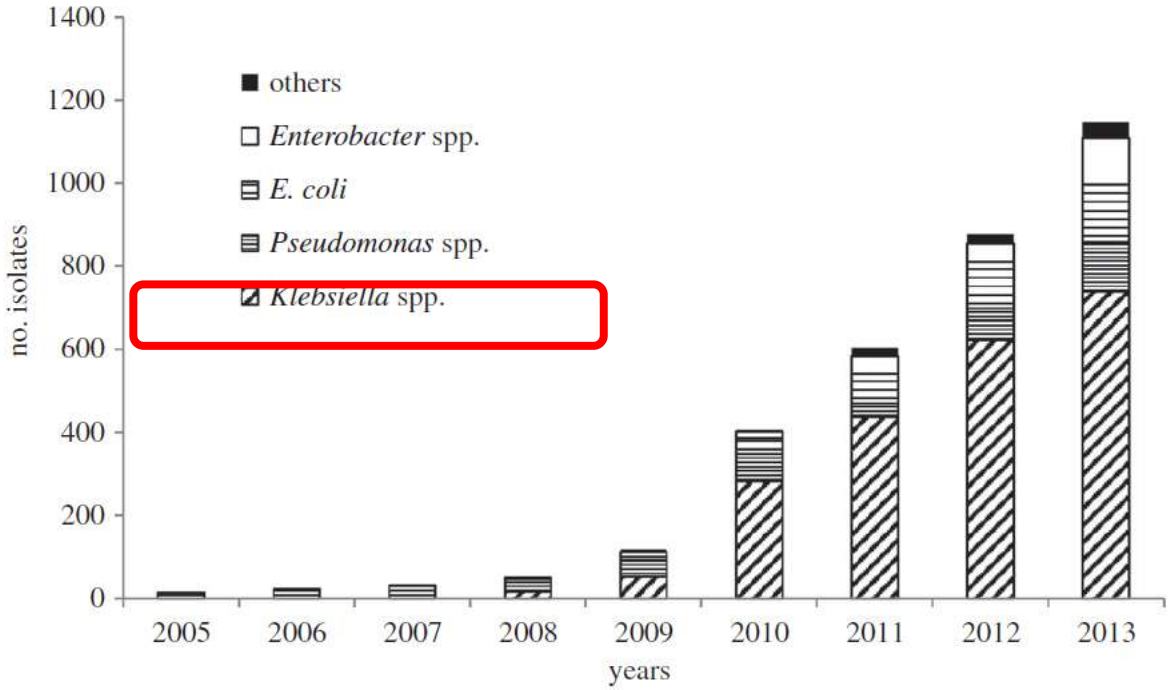

Figure 5. Isolates of Gram-negative bacteria confirmed as carbapenemase producers by the Antimicrobial Resistance and Healthcare Associated Infections Reference Unit of PHE, between 2005 and 2013.

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Hypervirulent *Klebsiella pneumoniae* – clinical and molecular perspectives

J. E. Choby[1,2,3], J. Howard-Anderson[4], D. S. Weiss[1,2,3,4,5]

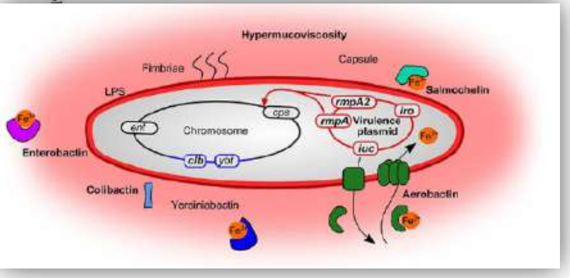
ST11-ST23 Karbapenem R yaygın olan

A non-exhaustive listing of recent clinical isolates demonstrating multidrug resistance and hypervirulence

Location	Sequence Type (ST)	Capsule (K)	Clinical context	Notes[a]	Ref
Classical strains that acquired virulence genes					
China	ST11	K47	Ventilator-associated pneumonia	5 isolates; widespread resistance; HMV+, 170 kb pLVPK-like plasmid of ST43. Retrospective analysis suggested ST11 isolates acquired virulence multiple times	[55]
	ST11	K47	Retrospective study	pLVPK-like plasmid and two AR plasmids; unique feature of five tandem copies of bla_{KPC-2}	[174]
India	ST147	K54	Sepsis and kidney injury	HMV+, limited acquisition of virulence genes, colistin resistant	[175]
United States	ST258	K107	Retrospective study	HMV+/*rmpA*–, a few virulence genes on hybrid AR plasmid; chromosomal siderophore receptor genes	[152]
Norway	ST15		Two bacteremia isolates	300 or 346 kb mosaic plasmids of pK2044-like virulence plasmid and conjugative AR plasmid	[176]
China	ST15		Elderly patients with pneumonia and other lung trauma	Clonal expansion of $bla_{OXA-232}$ encoding isolate; virulence genes detected but not hypervirulent in laboratory models	[177]
hvKp isolates acquiring resistance					
China	ST23	K1	Two bloodstream isolates	bla_{SHV-36} with colistin resistance in addition to pLVPK-like plasmid and canonical virulence genes	[178]
China	ST23	K1	Bloodstream, kidney abscess	Hybrid of pLVPK-like virulence plasmid with transposon-mediated integration of $bla_{CTX-M-24}$	[160]
United States	ST23	K1	Urine sample	bla_{SHV-36}, *fosA*, *oqxAB* on chromosome; AR plasmid with bla_{KPC-2}, bla_{TEM-1A} and truncated bla_{OXA-9}	[153]
China	ST23	K1	Sepsis	pLVPK-like virulence plasmid with insertion of bla_{KPC-2} and *dfrA14* genes	[158] [12]
China	ST36	K62	Bloodstream; burn wounds	pLVPK-like plasmid and AR plasmid encoding bla_{KPC-2}, *fosA*, *oqxAB*, along with resistance to aminoglycosides, macrolides, sulfonamides and others	[179]
China	ST65	K2	Meningitis	Most canonical virulence genes on chromosome and pLVPK-like plasmid; encodes bla_{SHV-11}, bla_{TEM-1}, $bla_{CTX-M-3}$, $bla_{CTX-M-4}$	[180]
China	ST65	K2	Infant bloodstream	Encodes *ent* and *iuc* but not *ybt* or *kfu*; hypervirulent in mouse model; bla_{SHV-11}, bla_{TEM-53}, decreased expression of *ompK35/36*	[155]
France	ST86	K2	Carriage	Encodes $bla_{CTX-M-3}$	[150]
China	ST86	K2	Burn wound	bla_{KPC-2} and bla_{NDM-1}; 215 kb virulence plasmid	[181]
Canada	ST86	KL2	UTI	pLVPK-like plasmid; plasmid with bla_{KPC-2} as well as bla_{SHV-1} and *fosA*	[182]

AR, antimicrobial resistance; *bla*, beta-lactamase provides resistance to penicillins, first- and second-generation cephalosporins; *blaCTX-M-24*, *blaCTX-M-3* and *blaCTX-M-4* ESBLs with particular activit … nd bla O… extend… outer … 35/36

[a] Abbr…



K1-K2 serotip en sık görülen

Antibiyogramda duyarlı bile olsa klinik yanıt başarısız

Virülans faktörü dikkate alınmayan önemli bir belirleyici

2016'da ilk Çin'de sonra Orta Asya, Avrupa, ABD'ye yayıldı

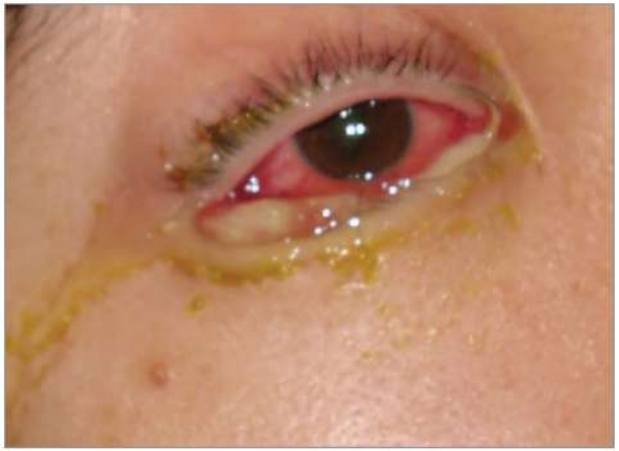


Figure 2. Endophthalmitis as the presenting symptom for hypervirulent *K. pneumoniae* infection in a previously healthy 33-year-old male.

REVIEW

Virulence 4:2, 107–118; February 15, 2013; © 2013 Landes Bioscience

Hypervirulent (hypermucoviscous) *Klebsiella pneumoniae*

A new and dangerous breed

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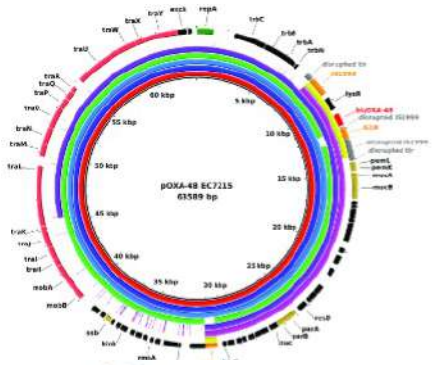
[1]Department of Medicine; University at Buffalo-State University of New York; Buffalo, NY USA; [2]Department of Microbiology and Immunology; University at Buffalo-State University of New York; Buffalo, NY USA; [3]The Witebsky Center for Microbial Pathogenesis; University at Buffalo-State University of New York; Buffalo, NY USA; [4]Veterans Administration Western New York Healthcare System; Buffalo, NY USA

Keywords: *Klebsiella pneumoniae*, hypervirulent, hypermucoviscous, pathogenesis, epidemiology, treatment, diagnosis, infection

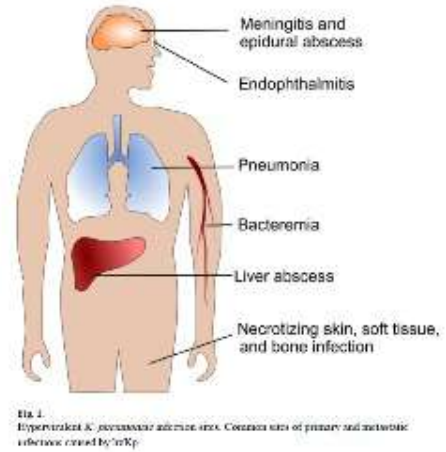
Figure 1. Positive "string test" on a hypervirulent strain of *K. pneumoniae*.

Bakteriyel Virülans Faktörleri

- Ocak 2015'te sekiz karaciğer Tx hastasında tekrarlayan sepsis atakları (2 hastada bir kez, geri kalan altı hastada 2 ve daha fazla sepsis atağı) gelişmiş
- 5 erkek, 3 kadın; yaş: 25-55 arasında
- Yoğun bakımda ortalama yatış süresi: 47.13+44.36 gün, min=1, max=145



No	PFGE Type	Gene	Unit	Meropenem MIC
14	1	OXA-48	Transplantation ICU	2
15	1	OXA-48	Transplantation ICU	8
17	1	OXA-48	Transplantation ICU	2
20	1	OXA-48	Transplantation ICU	8
21	1	OXA-48	Transplantation ICU	2
23	1a	OXA-48	Internal Medicine I.	2
22	1b	OXA-48	Anesthesia ICU	8



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15	1	OXA-48	Transplantation ICU	8
17	1	OXA-48	Transplantation ICU	2
20	1	OXA-48	Transplantation ICU	8
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23	1a	OXA-48	Internal Medicine I.	2
22	1b	OXA-48	Anesthesia ICU	8

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Commentary

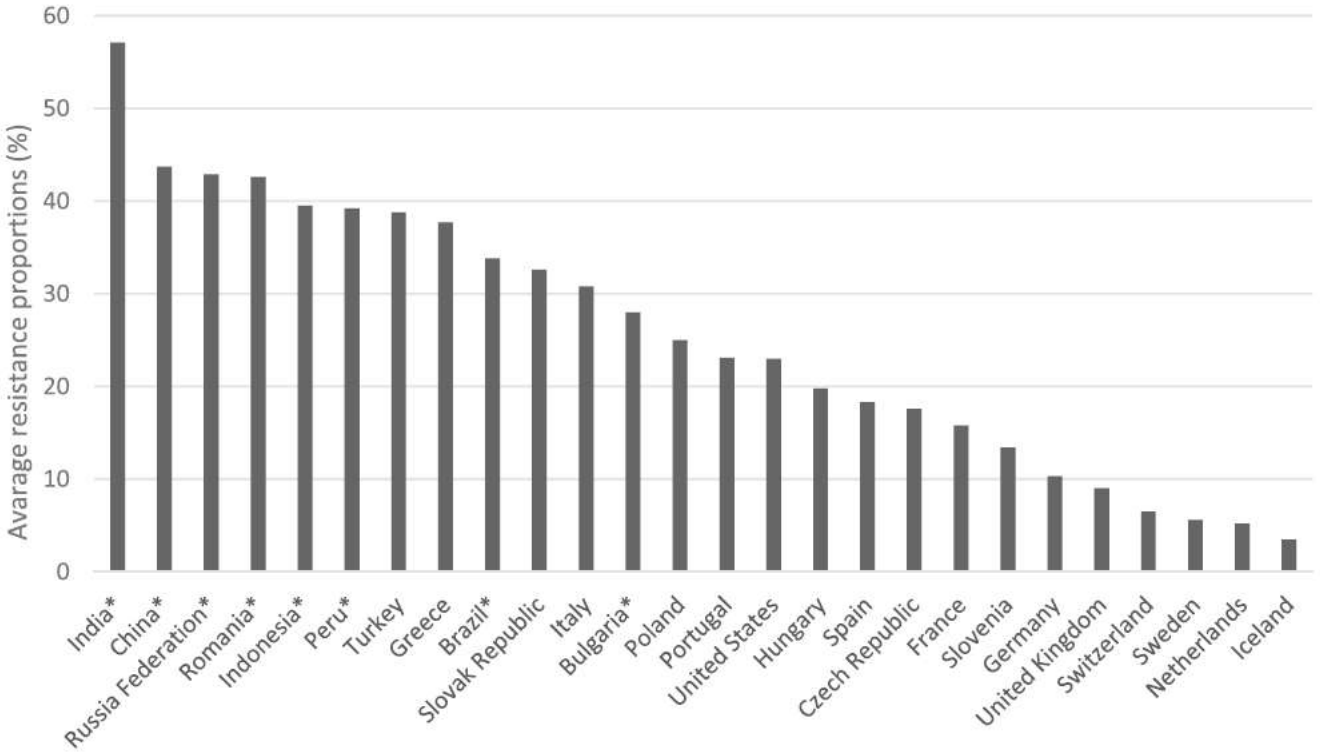
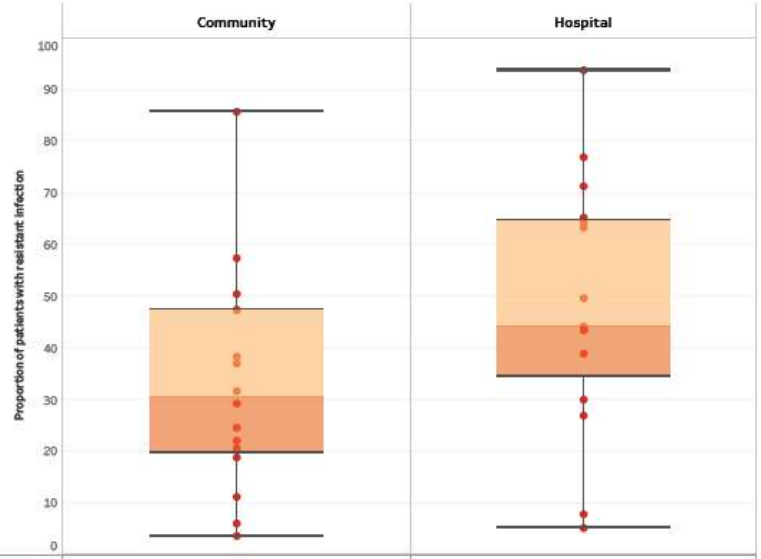


Fig. 1. Average antibiotic resistance proportions in 2015 for eight high-priority antibiotic–bacterium combinations for selected OECD and non-OECD (*) countries [3]. FREC, fluoroquinolone-resistant *Escherichia coli*; VRE, vancomycin-resistant *Enterococcus faecium and E. faecalis*; 3GCREC, third-generation cephalosporin-resistant *E. coli*; CRKP, carbapenem-resistant *Klebsiella pneumoniae*; 3GCRKP, third-generation cephalosporin-resistant *K. pneumoniae*; CRPA, carbapenem-resistant *Pseudomonas aeruginosa*; MRSA, methicillin-resistant *Staphylococcus aureus*; PRSP, penicillin-resistant *Streptococcus pneumoniae*; CRAB, carbapenem-resistant *Acinetobacter baumannii*.

Fig. 2.16. Proportion of patients with UTIs caused by *E. coli* resistant to ciprofloxacin by infection origin

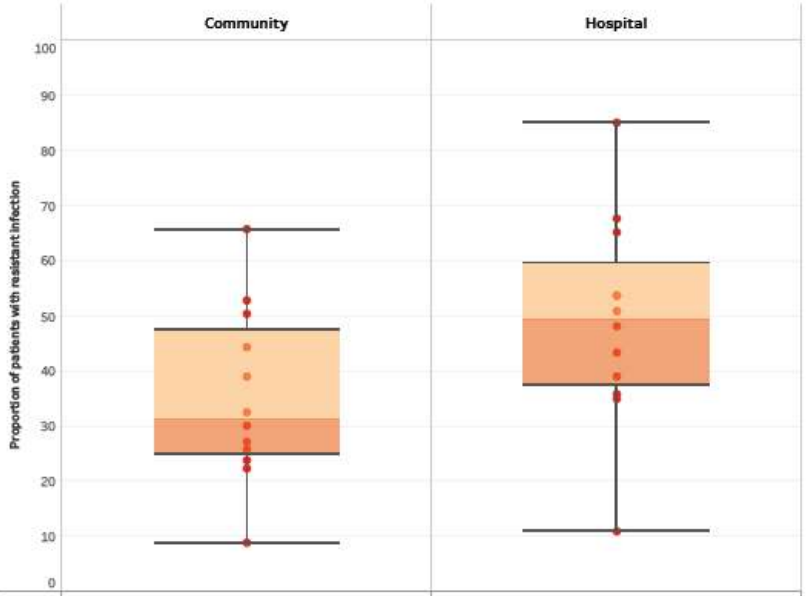


	Community	Hospital
Reporting countries *(n)*	16	28
Patients with AST results *(n)*	267 553	102 829

Global Antimicrobial Resistance and Use Surveillance System (GLASS) Report

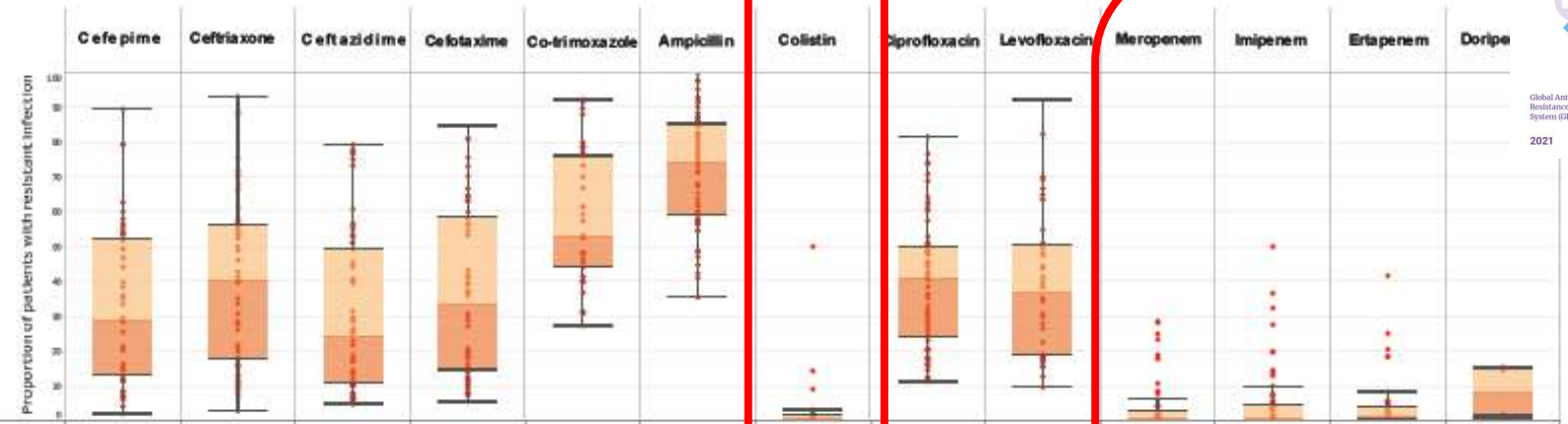
2021

Fig. 2.18. Proportion of patients with UTIs caused by *E. coli* resistant to co-trimoxazole by infection origin



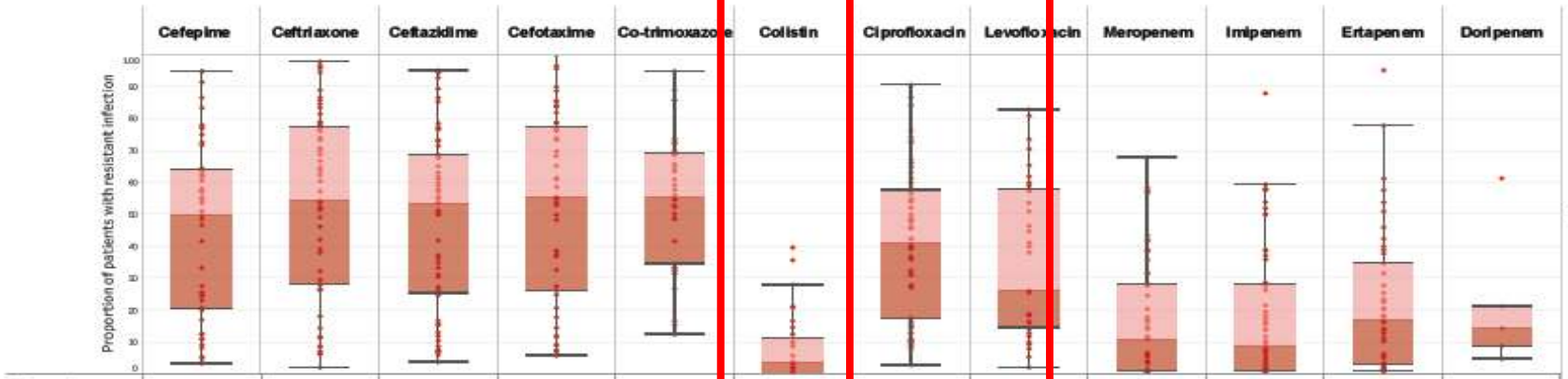
	Community	Hospital
Reporting countries *(n)*	12	12
Patients with AST results *(n)*	141 212	18 499

Fig. 2.12. Proportion of patients with BSIs caused by resistant *E. coli*



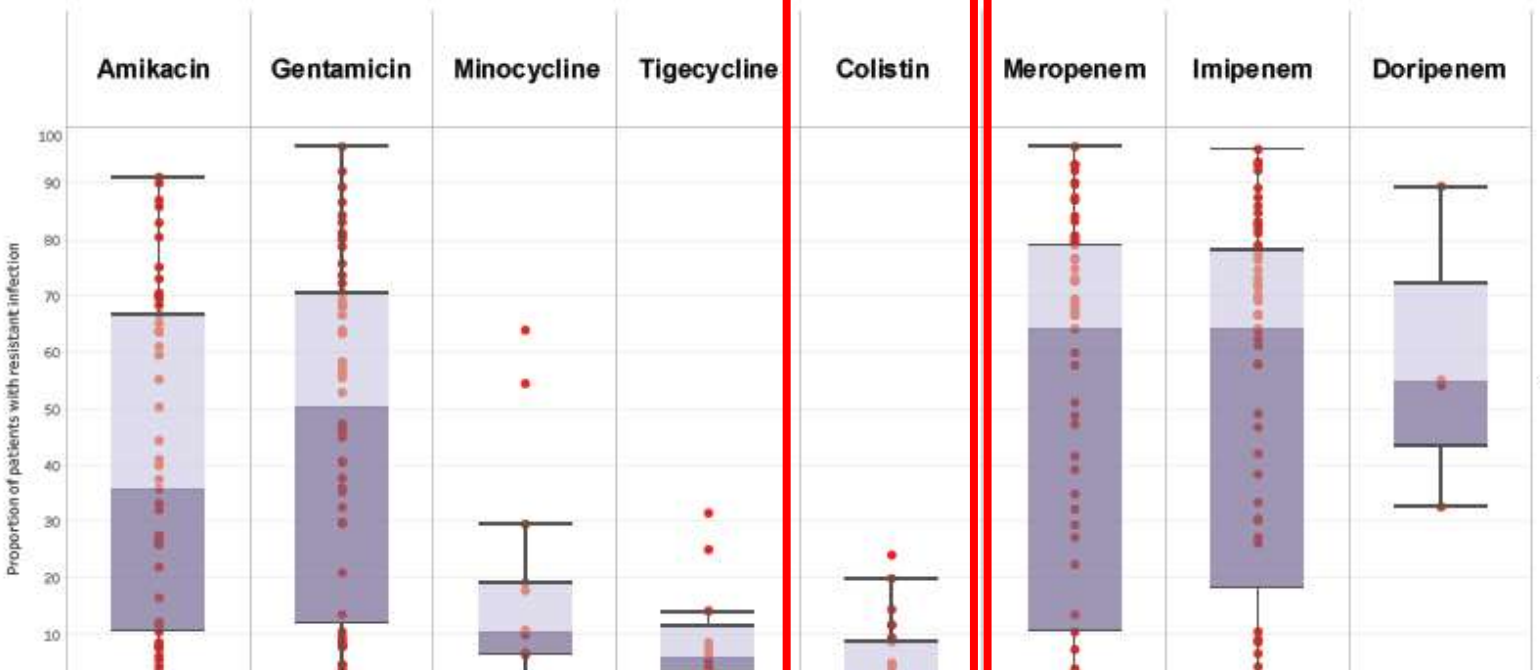
	Cefepime	Ceftriaxone	Ceftazidime	Cefotaxime	Co-trimoxazole	Ampicillin	Colistin	Ciprofloxacin	Levofloxacin	Meropenem	Imipenem	Ertapenem	Doripe
Reporting countries *(n)*	46	55	58	52	37	57	27	63	36	58	60	45	4
Patients with AST results *(n)*	146 061	126 630	235 051	189 801	33 737	194 891	17 931	213 010	120 532	232 270	175 833	98 567	1 712

Fig. 2.13. Proportion of patients with BSIs caused by resistant *K. pneumoniae*



	Cefepime	Ceftriaxone	Ceftazidime	Cefotaxime	Co-trimoxazole	Colistin	Ciprofloxacin	Levofloxacin	Meropenem	Imipenem	Ertapenem	Doripenem
Reporting countries *(n)*	47	56	57	50	38	31	62	35	59	58	45	5
Patients with AST results *(n)*	59 726	45 414	81 448	69 088	23 946	11 202	75 627	39 047	82 783	68 190	38 556	947

Fig. 2.11. Proportion of patients with BSIs caused by resistant *Acinetobacter* spp

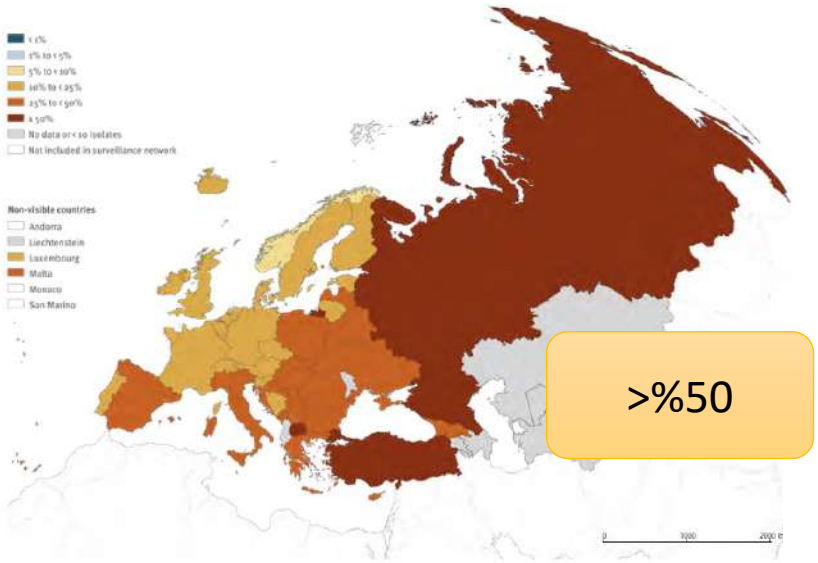


	Amikacin	Gentamicin	Minocycline	Tigecycline	Colistin	Meropenem	Imipenem	Doripenem
Reporting countries *(n)*	53	56	13	12	30	57	55	4
Patients with AST results *(n)*	15 705	15 130	4 756	2 599	4 070	18 340	17 793	312

Antimicrobial resistance surveillance in Europe

2022

Fig. 1 *E. coli*: percentage of invasive isolates resistant to fluoroquinolones (ciprofloxacin/levofloxacin/ofloxacin), by country/area, WHO European Region, 2020

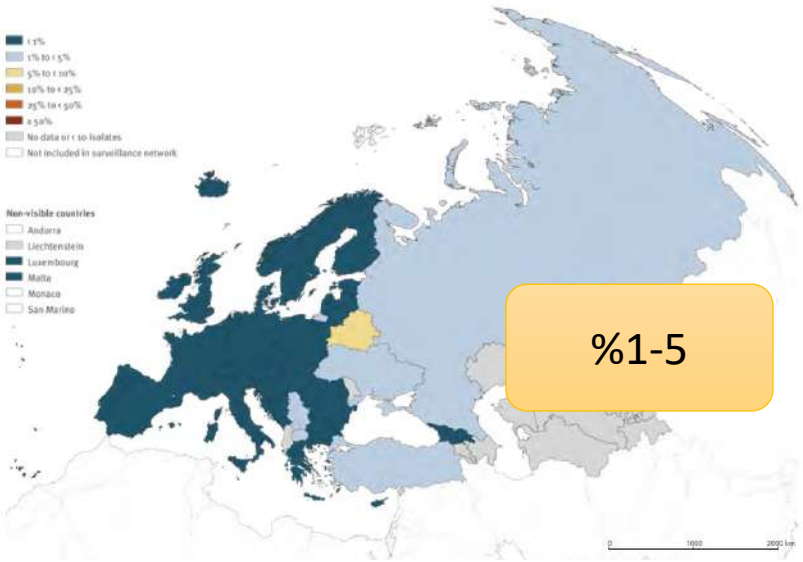


>%50

Fig. 2 *E. coli*: percentage of invasive isolates resistant to third-generation cephalosporins (cefotaxime/ceftriaxone/ceftazidime), by country/area, WHO European Region, 2020

>%50

Fig. 3 *E. coli*: percentage of invasive isolates resistant to carbapenems (imipenem/meropenem), by country/area, WHO European Region, 2020



%1-5

Fig. 5 *K. pneumoniae*: percentage of invasive isolates resistant to carbapenems (imipenem/meropenem), by country/area, WHO European Region, 2020

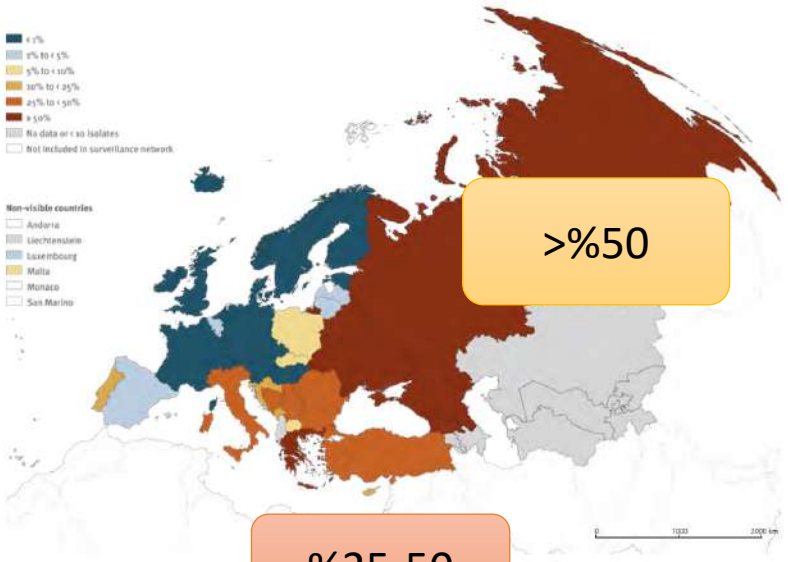


Fig. 4 *K. pneumoniae*: percentage of invasive isolates resistant to third-generation cephalosporins (cefotaxime/ceftriaxone/ceftazidime), by country/area, WHO European Region, 2020

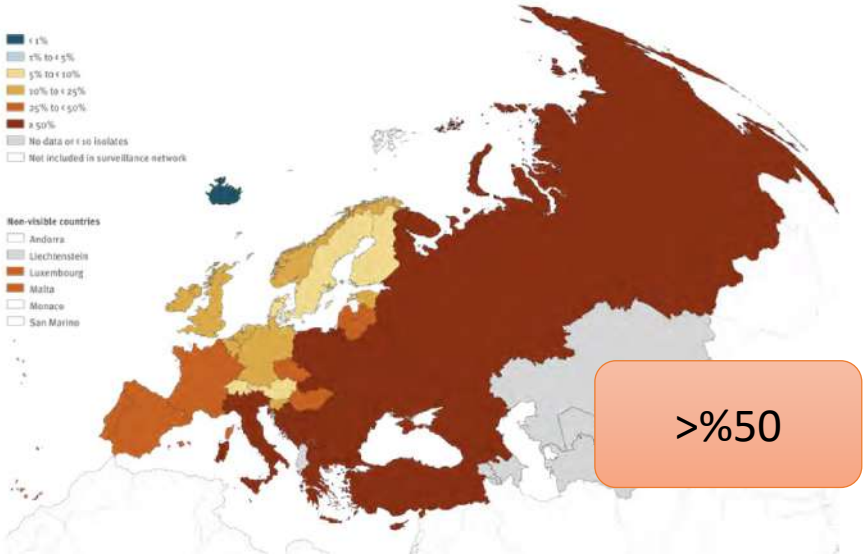
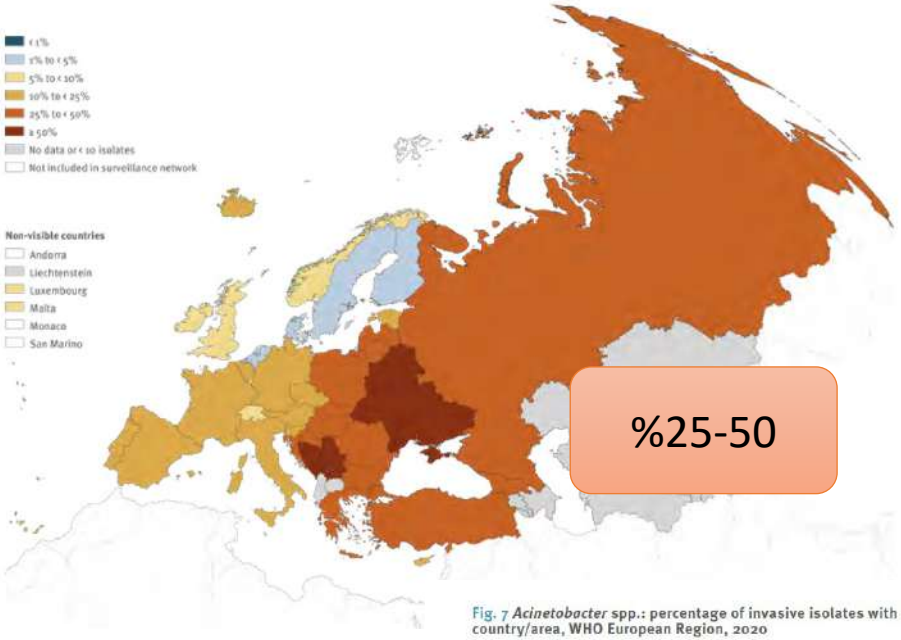


Fig. 6 *P. aeruginosa*: percentage of invasive isolates with resistance to carbapenems (imipenem/meropenem), by country/area, WHO European Region, 2020



%25-50

Fig. 7 *Acinetobacter* spp.: percentage of invasive isolates with resistance to carbapenems (imipenem/meropenem), by country/area, WHO European Region, 2020

>%50

DSÖ 2017 gram negatif basillerde karbapenem direncini önceliklendirdi
Küresel salgın olarak değerlendirdi

- Son zamanlarda önemli problem karbapenemazlar
- KPC ilk kez ABD'de bildirildi (1996)
- NDM (New Delhi metallo-β-lactamaz) ilk kez Hindistan ve Ortadoğu ülkelerinde bildirildi (2006)
- OXA-48 benzeri β-laktamazlar ilk kez Türkiye'de bildirildi

Direnç genlerinin dünyaya yayılımında seyahatlerin rolü büyük

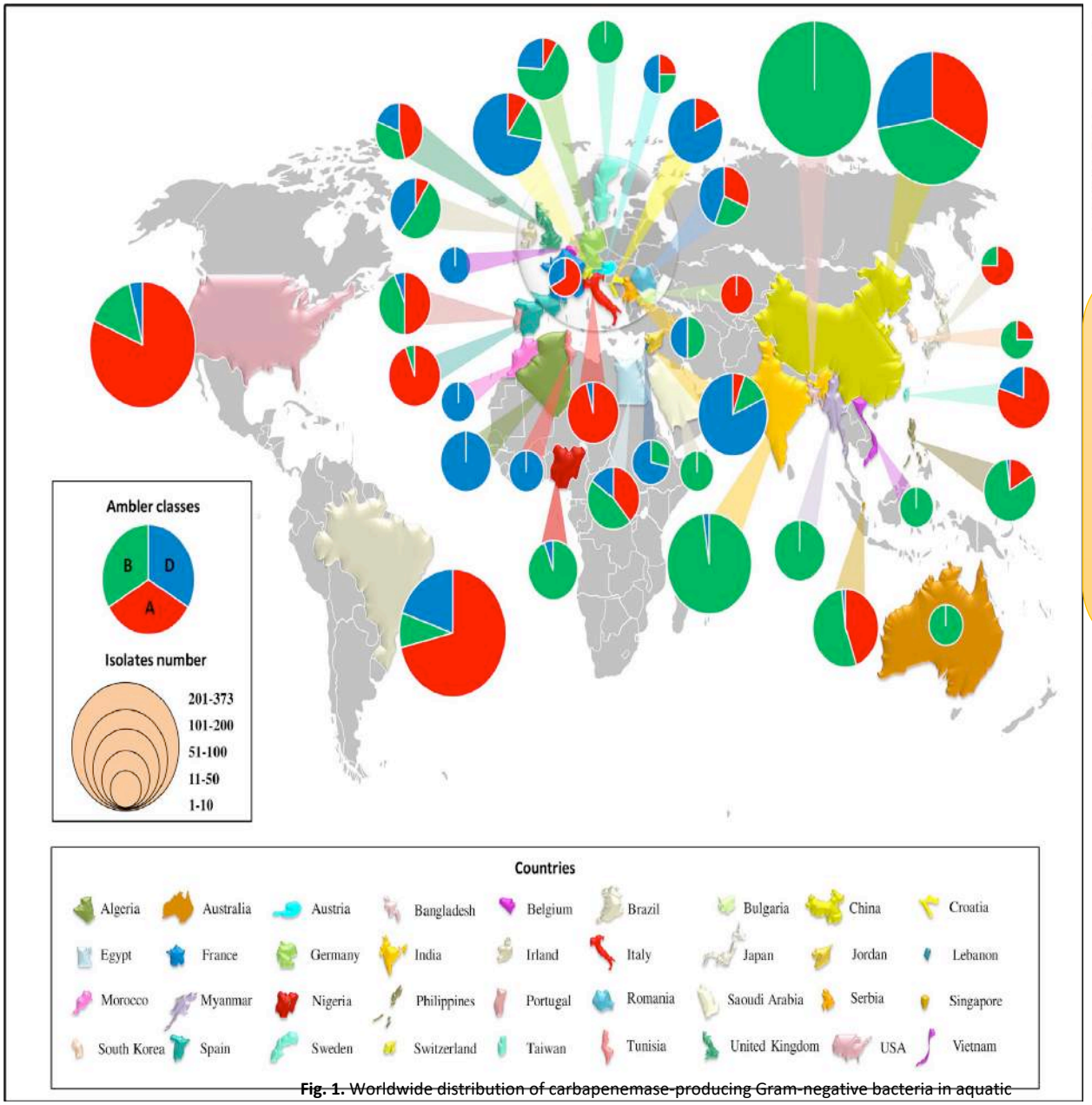


Fig. 1. Worldwide distribution of carbapenemase-producing Gram-negative bacteria in aquatic environments

Journal of Global Antimicrobial Resistance 25 (2021) 287–309

Contents lists available at ScienceDirect

Journal of Global Antimicrobial Resistance

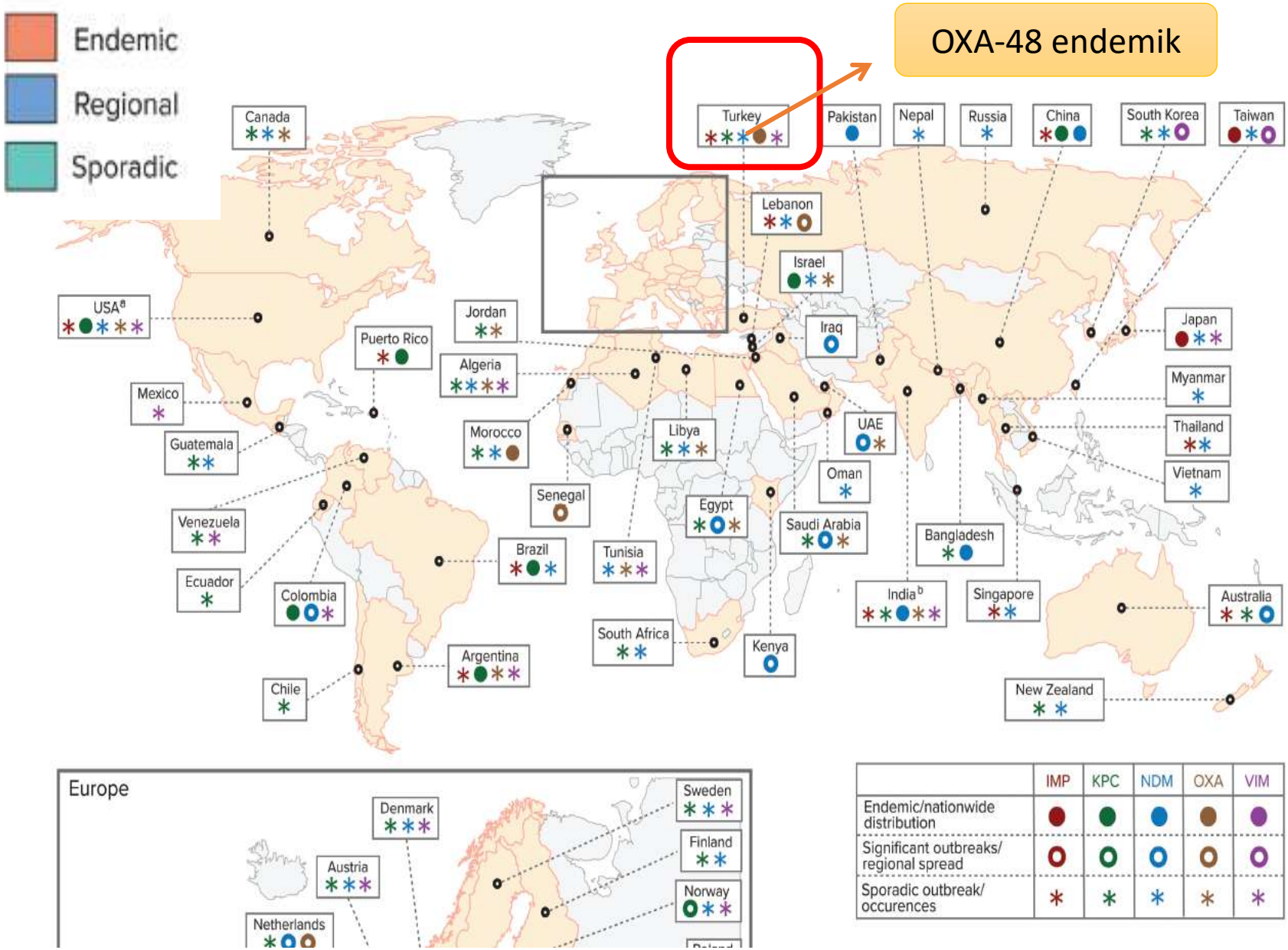
journal homepage: www.elsevier.com/locate/jgar

Carbapenemase-producing Gram-negative bacteria in aquatic environments: a review

Zineb Cherak[a], Lotfi Loucif[b,*], Abdelhamid Moussi[a], Jean-Marc Rolain[c,d]

A CTX-M, KPC
B NDM, VIM, IMP
D OXA-48 …

Cherak Z et al. 2021; 25: 287-309

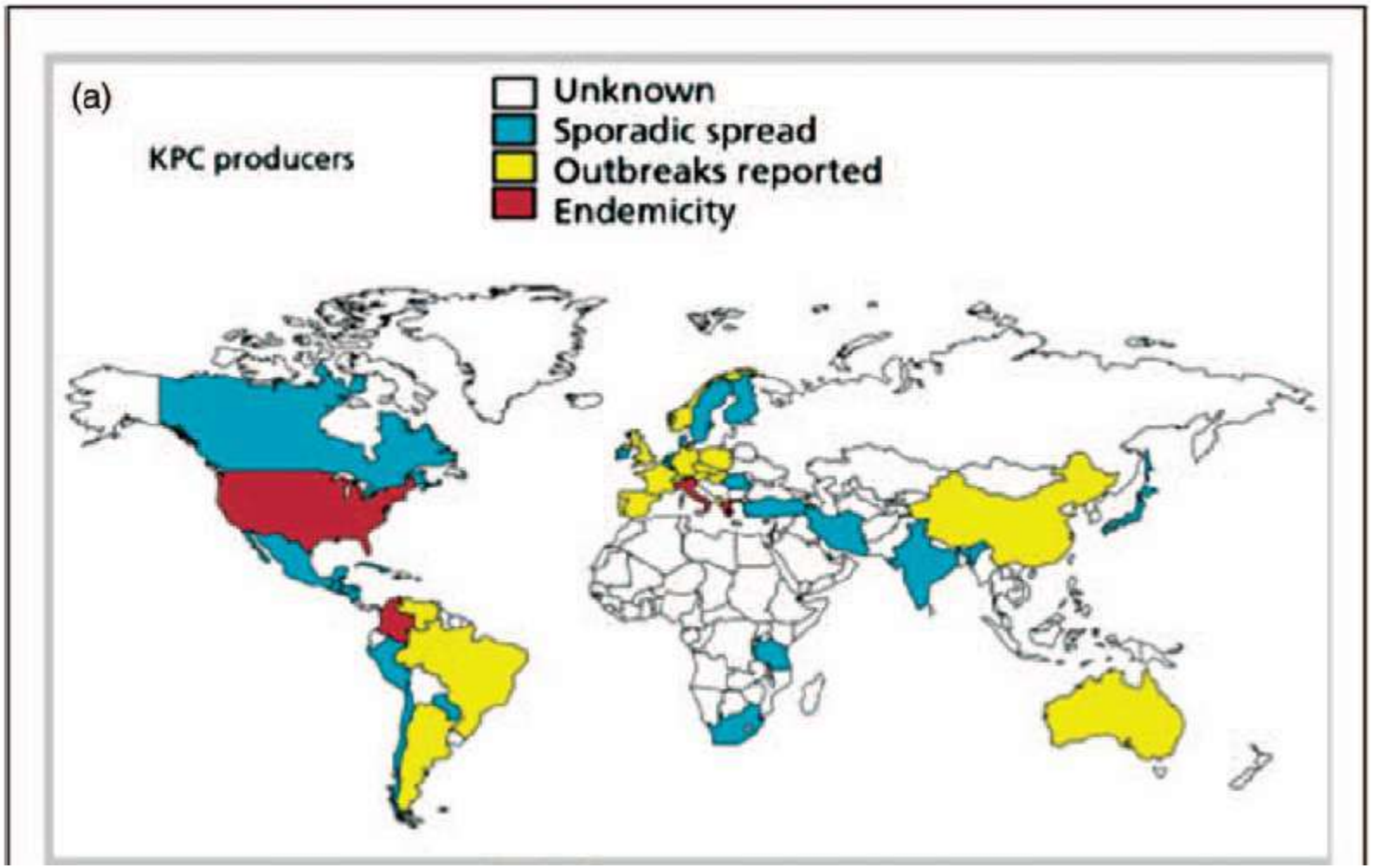


Logan LK et al. JID 2017; 215: suppl 1

REVIEW

Epidemiology of carbapenem-resistant Gram-negative infections globally

Adrian J. Brink



Brink AJ. Curr. Opin Infect Dis 2019; 32: 609-16

REVIEW

Epidemiology of carbapenem-resistant Gram-negative infections globally

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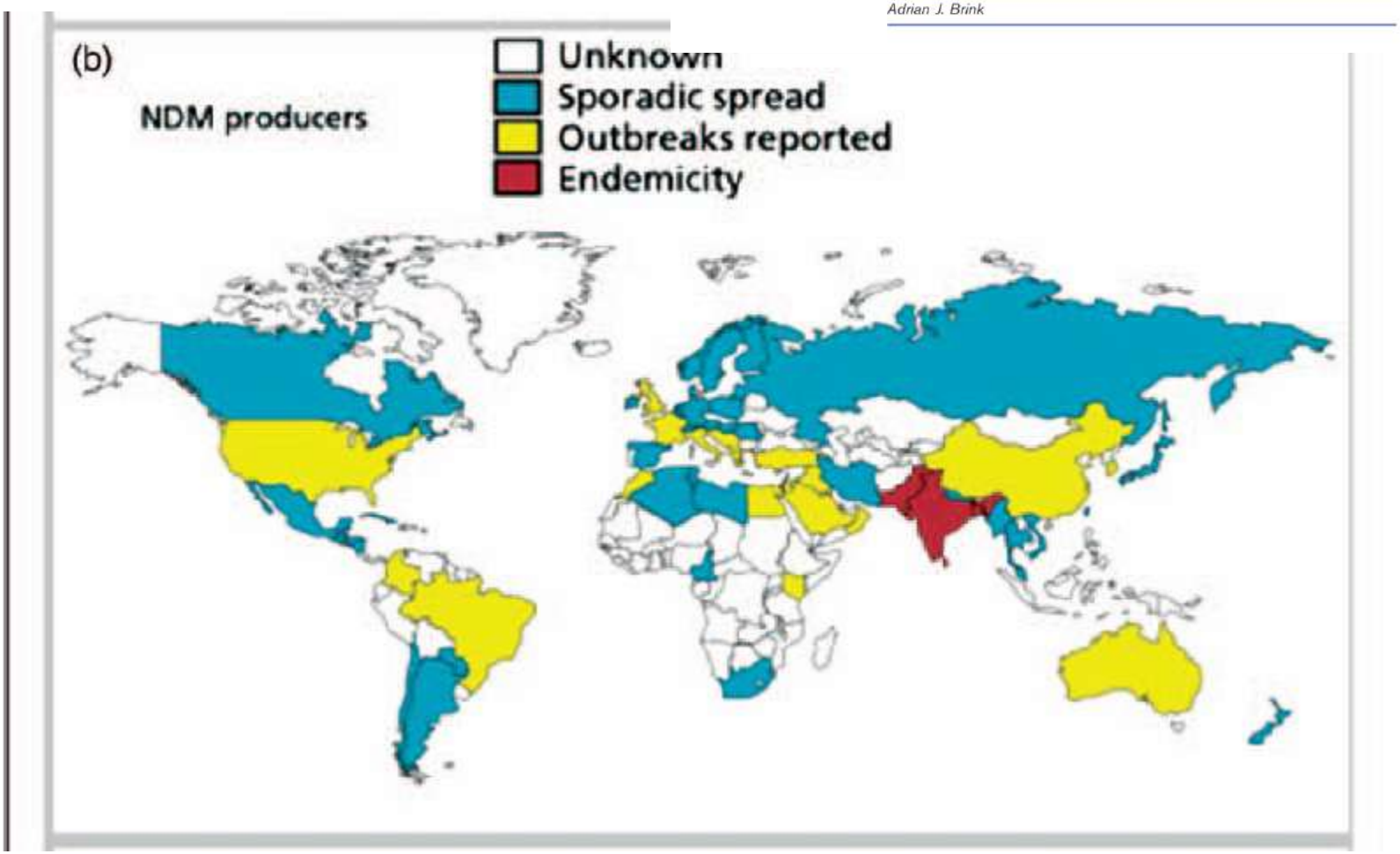

Brink AJ. Curr. Opin Infect Dis 2019; 32: 609-16

Epidemiology of carbapenem-resistant Gram-negative infections globally

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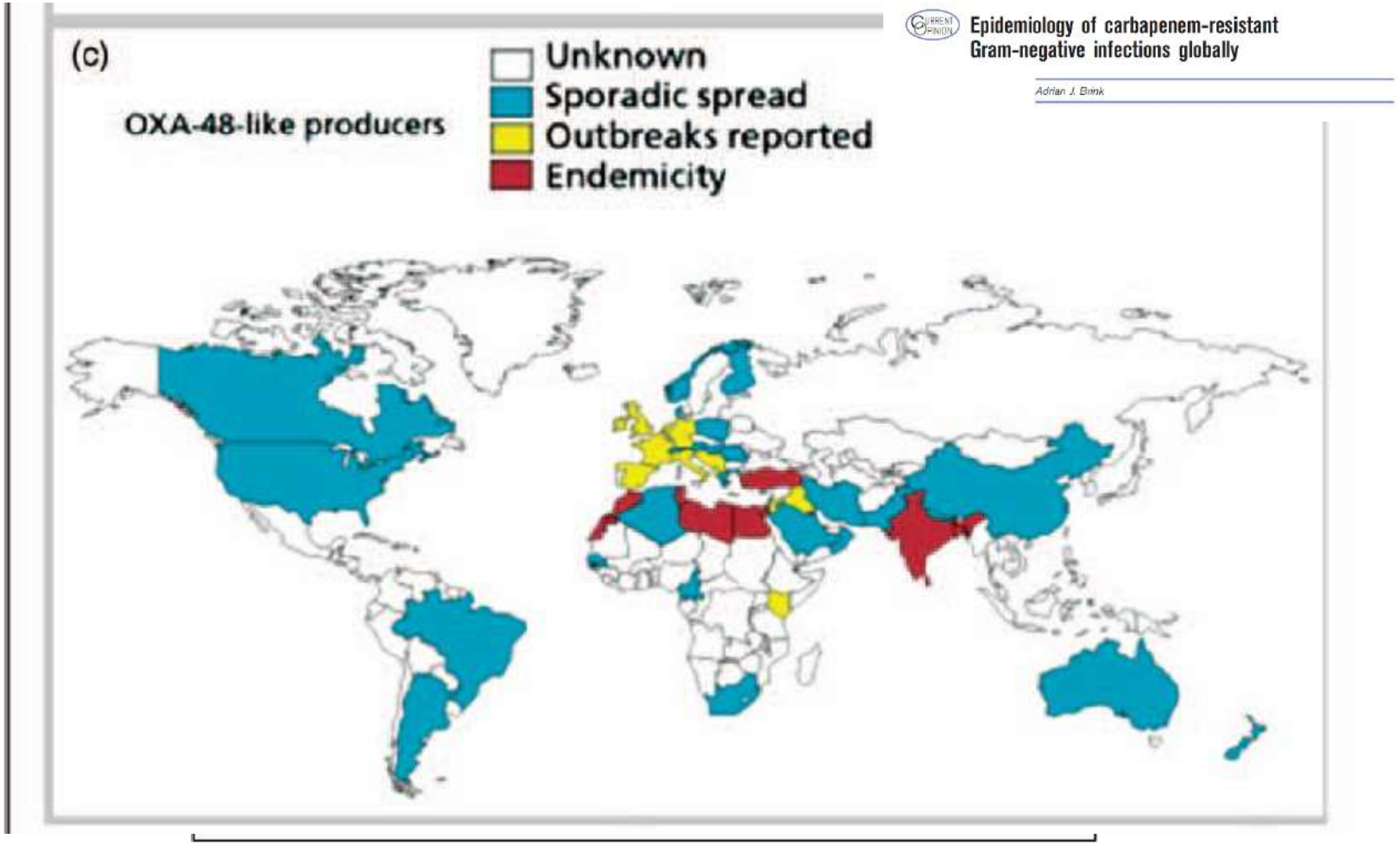


FIGURE 1. Global distribution of carbapenemase-producing Gram-negative bacilli. (a) *Klebsiella pneumoniae* carbapenemase producers in *Enterobacteriaceae* and *Pseudomonas aeruginosa*. (b) New Delhi metallo-β-lactamase producers *in Enterobacteriaceae* and *P. aeruginosa*. (c) Oxacillinase-48-like producers in *Enterobacteriaceae*. KPC, *Klebsiella pneumoniae* carbapenemase; NDM, New Delhi metallo-β-lactamase; OXA-48, oxacillinase-48. Reproduced with permission [49].

Brink AJ. Curr. Opin Infect Dis 2019; 32: 609-16

frontiers in Cellular and Infection Microbiology

Antimicrobial Resistance of Hypervirulent *Klebsiella pneumoniae*: Epidemiology, Hypervirulence-Associated Determinants, and Resistance Mechanisms

Chang-Ro Lee[1†], Jung Hun Lee[1†], Kwang Seung Park[1†], Jeong Ho Jeon[1], Young Bae Kim[2], Chang-Jun Cha[3], Byeong Chul Jeong[1*] and Sang Hee Lee[1*]

OPEN ACCESS

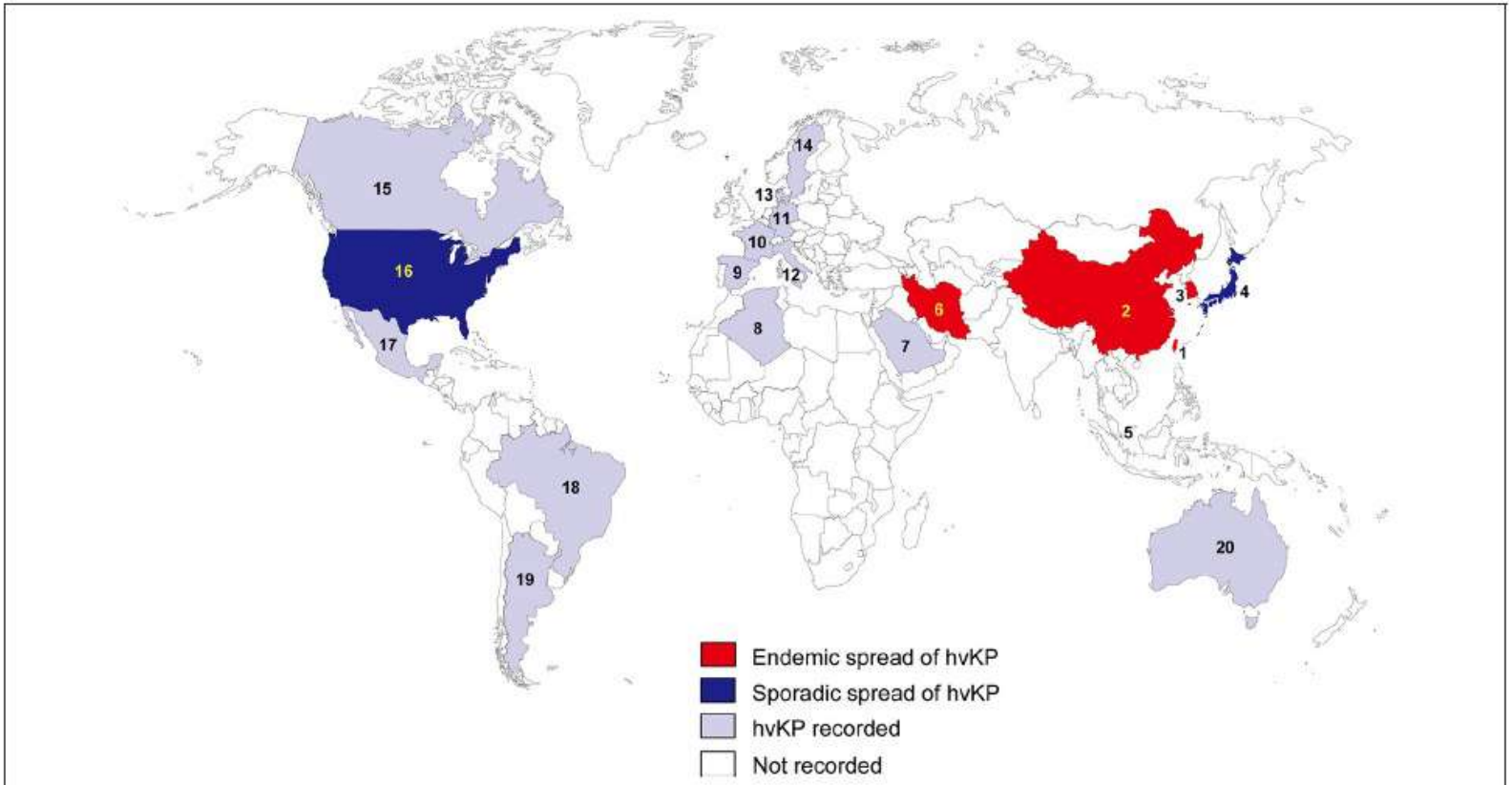


FIGURE 1 | Epidemiological features of hvKP. The endemic spread of hvKP means that multiple outbreaks of hvKP were reported in an indicated region. The sporadic spread of hvKP means that only case studies (no outbreak) were reported in an indicated region. 1, Taiwan; 2, China; 3, South Korea; 4, Japan; 5, Singapore; 6, Iran; 7, Saudi Arabia; 8, Algeria; 9, Spain; 10, France; 11, Germany; 12, Italy; 13, Denmark; 14, Sweden; 15, Canada; 16, United States; 17, Mexico; 18, Brazil; 19, Argentina; 20, Australia.

Lee CR et al. Front Cell Infect Microbiol 2017; 7

International Journal of Antimicrobial Agents 48 (2016) 614–621

Contents lists available at ScienceDirect

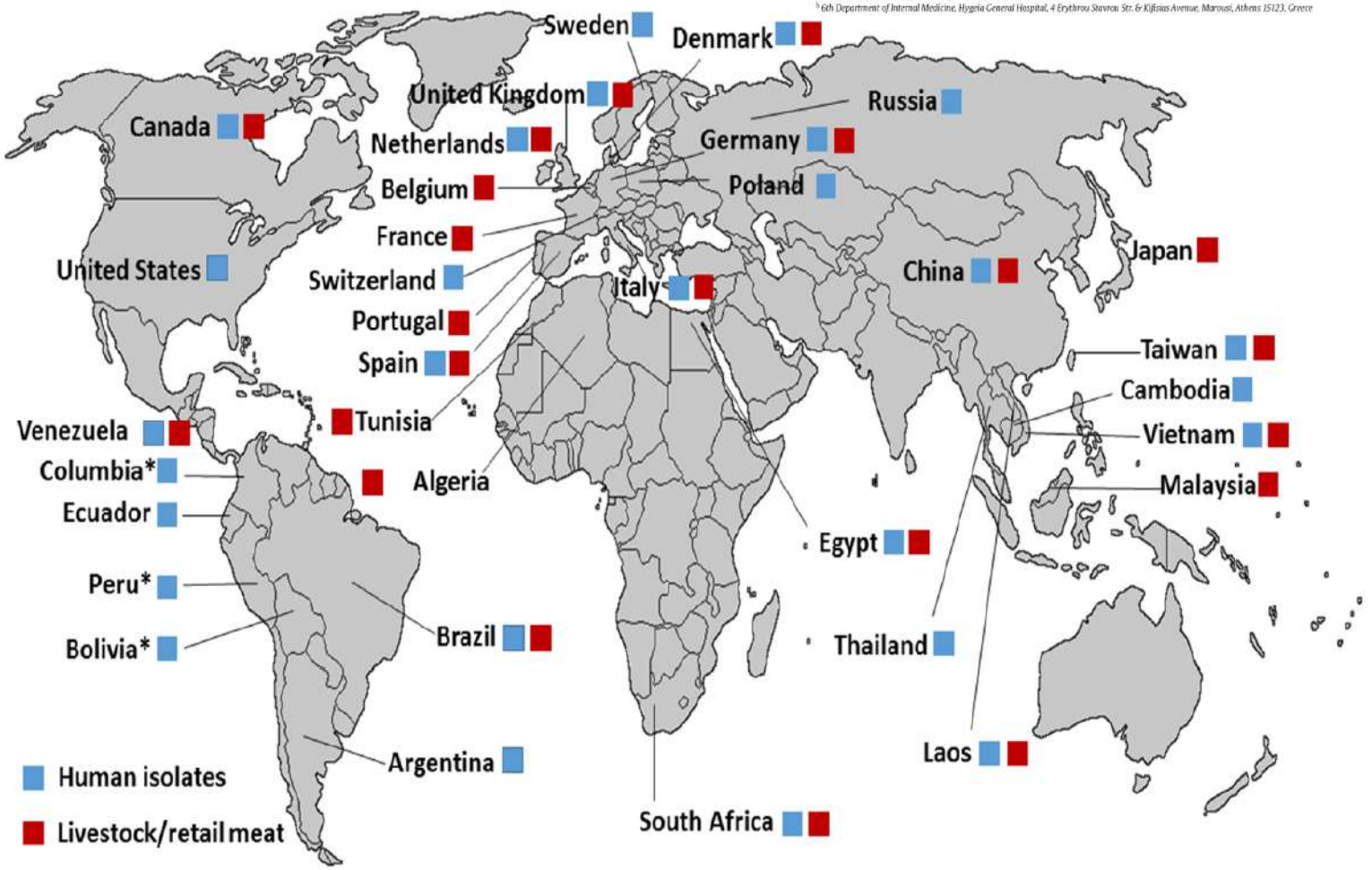
International Journal of Antimicrobial Agents

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

Epidemiology of infections caused by polymyxin-resistant pathogens

Helen Giamarellou [a,b,*]

[a] Internal Medicine, Athens University School of Medicine, Athens, Greece
[b] 6th Department of Internal Medicine, Hygeia General Hospital, 4 Erythrou Stavrou Str. & Kifissias Avenue, Marousi, Athens 15123, Greece



*Visited by Dutch travellers with fecal colonisation of mcr-1 gene and discovered one to two weeks after their return to the Netherlands

Giamarellou H. Int J Antimicrobiol. Agents 2016; 48: 614-21

Fig. 3. Global distribution of the *mcr-1* gene [55,57–68].

frontiers | Frontiers in Cellular and Infection Microbiology
REVIEW
published: 17 June 2022
doi: 10.3389/fcimb.2022.882236

An Update of Mobile Colistin Resistance in Non-Fermentative Gram-Negative Bacilli

Piyatip Khuntayaporn [1,2*], Krit Thirapanmethee [1,2] and Mullika Traidej Chomnawang [1,2]

mcr-3

İlk 2011-2014'de Çin'de mcr-1 plazmid geçiş bildirildi

mcr-1

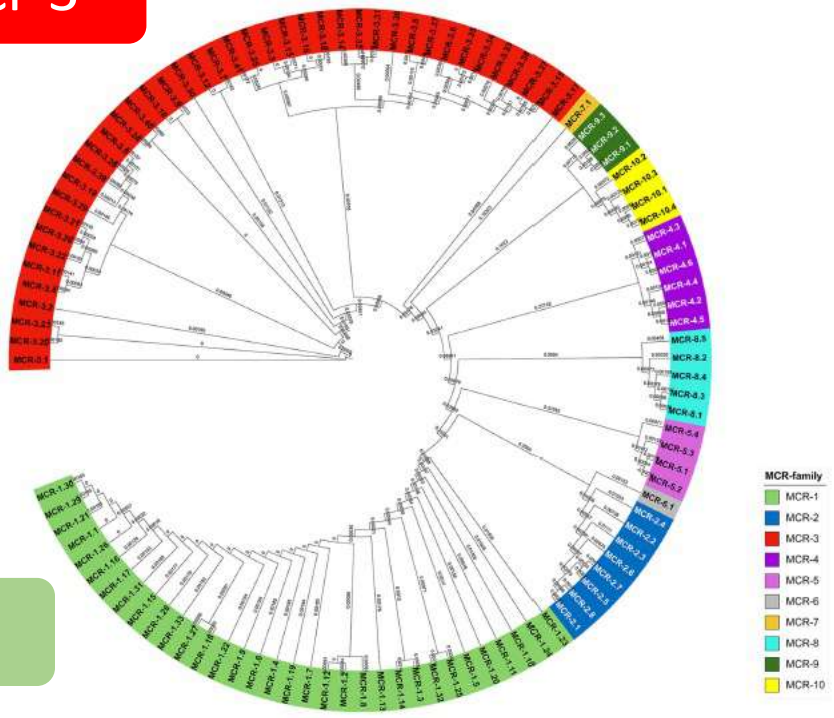


FIGURE 2 | The phylogenetic tree of MCR-gene variants using the Neighbor-Joining method alignment. Multiple sequence alignment was calculated by the clustal omega (Madeira et al., 2019), and the results were illustrated by the Interactive Tree of Life (Letunic and Bork, 2021).

Khuntayaporn P et al. Front Cell Infect Microbiol 2022; 12

Pseudomonas aeruginosa kolistin direnci

Mcr-5 ABD
Mcr-1 Brezilya, İtalya, Hindistan

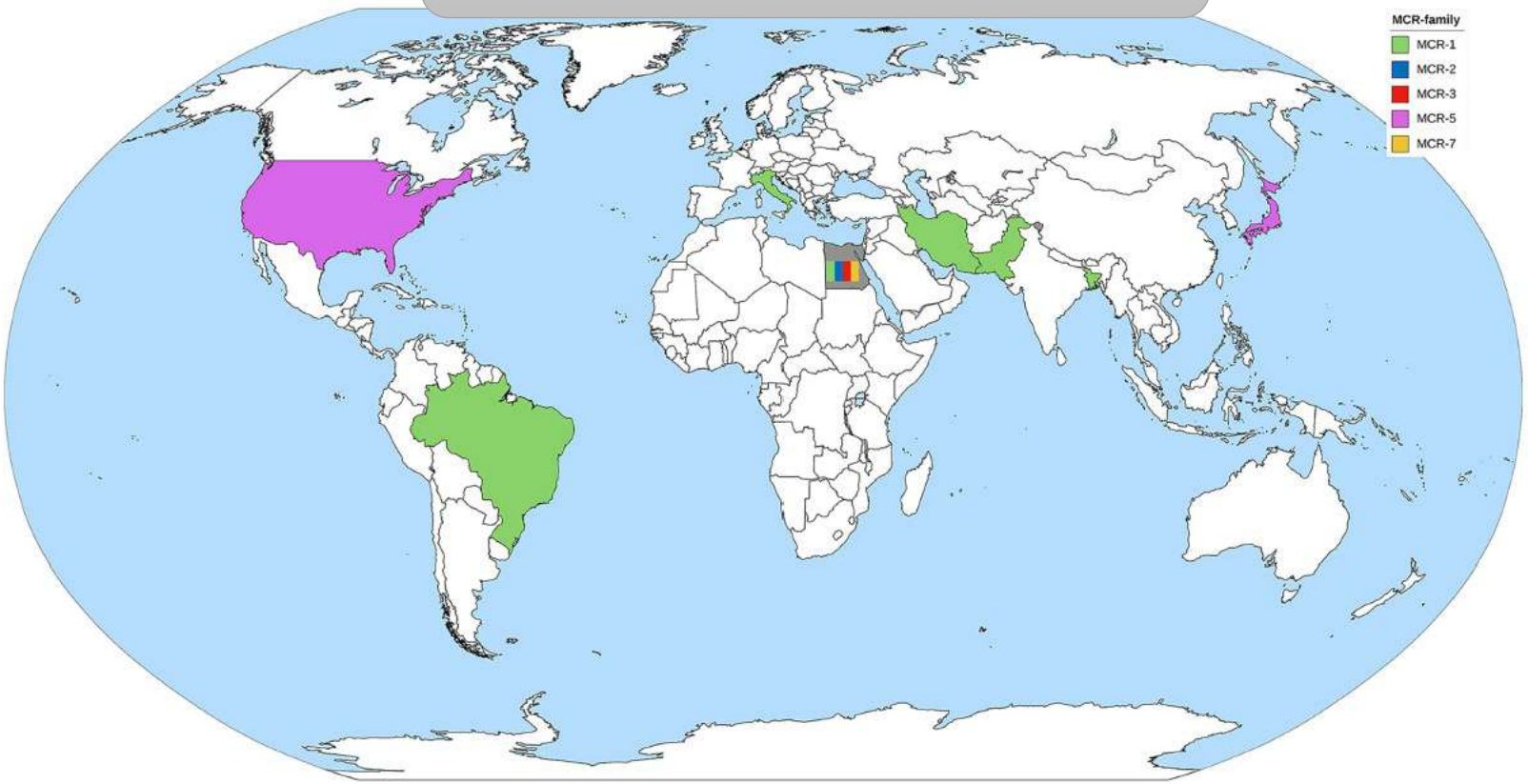


FIGURE 3 | The worldwide dissemination of the *mcr* gene in *Pseudomonas* spp. Countries that reported only one type of *mcr* gene were colored to represent the *mcr* gene. The country that reported more than one type of *mcr* gene was filled with gray background containing color bands of the reported *mcr* gene.

Khuntayaporn P et al. Front Cell Infect Microbiol 2022; 12

Acinetobacter spp kolistin direnci

Mcr-1 İtalya, Pakistan, Suriye, Mısır, Çin
Mcr-4 Tayland, Brezilya, Çin, Finlandiya, Güney Afrika

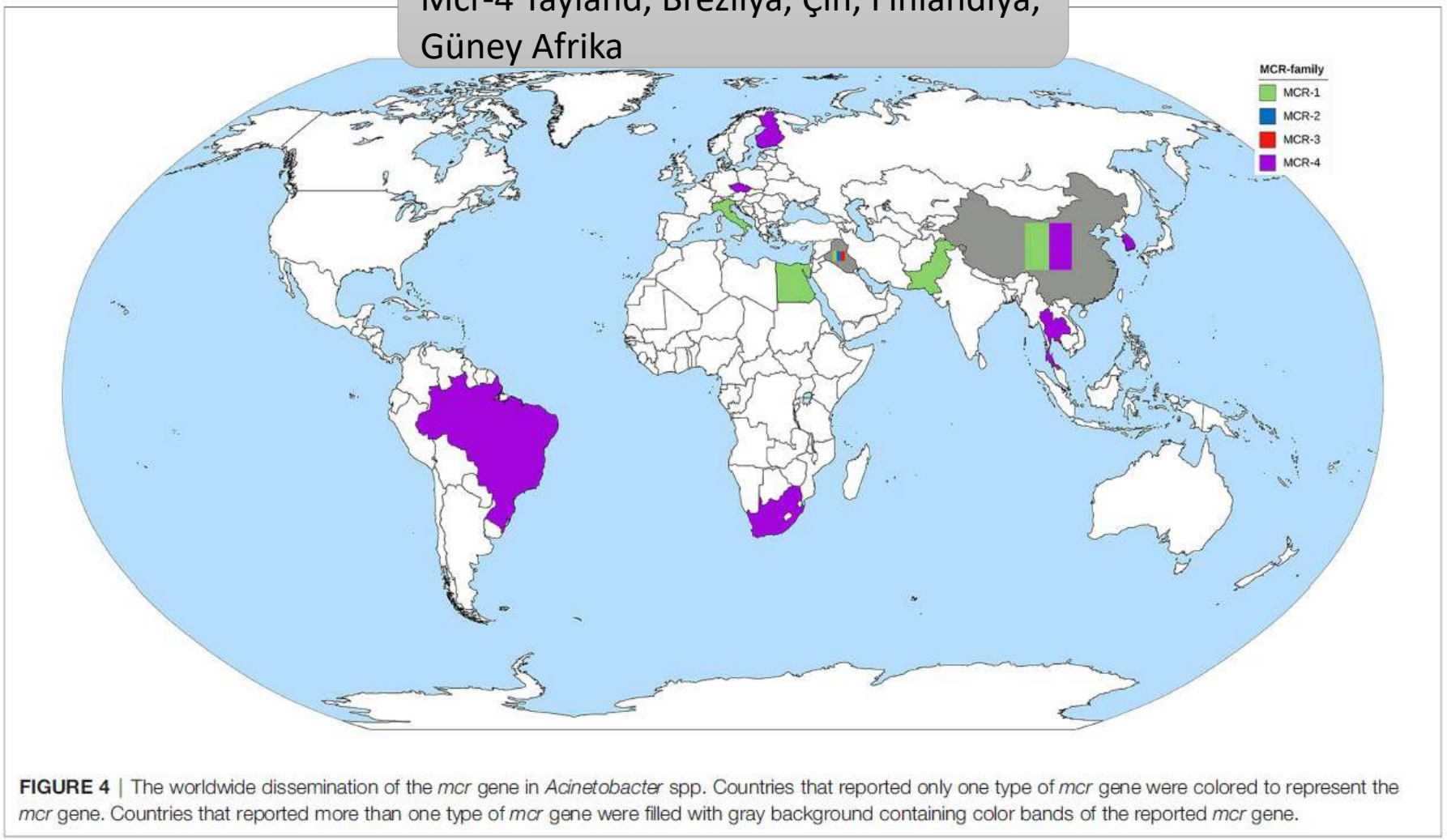


FIGURE 4 | The worldwide dissemination of the *mcr* gene in *Acinetobacter* spp. Countries that reported only one type of *mcr* gene were colored to represent the *mcr* gene. Countries that reported more than one type of *mcr* gene were filled with gray background containing color bands of the reported *mcr* gene.

Khuntayaporn P et al. Front Cell Infect Microbiol 2022; 12

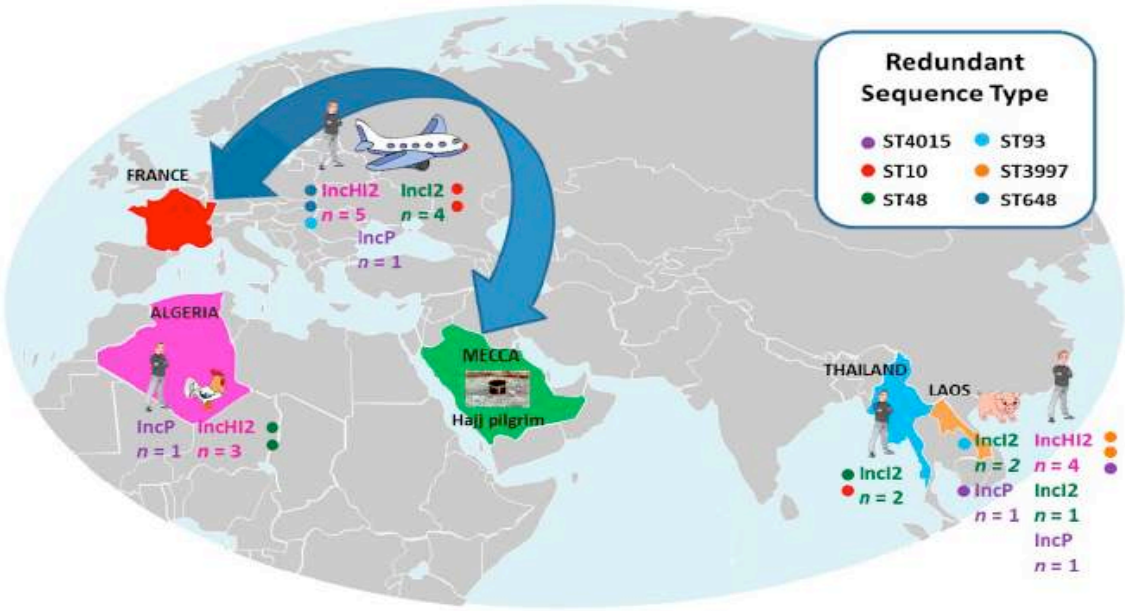


Figure 1. Origins and plasmid type of *mcr-1* strains collected in our study.

Direncini söyle sana hangi ülke olduğunu söyleyeyim
AMA

Karbapenem dirençli 291 *K pneumoniae*

Turk Mikrobiyol Cemiy Derg 2022;52(2):95-102
doi:10.5453/TMCD.2022.05025

Araştırma / *Research Article*

Klebsiella pneumoniae Klinik Suşlarında, 2012-2020 Yılları Arasında Karbapenem Direnç Oranlarındaki Değişimin ve Direnç Genlerinin Araştırılması

Investigetion of Carbapenem Resistance Ratio Changes and Resistange Genes in Clinical Isolates of Klebsiella pneumoniae Between 2012 to 2020

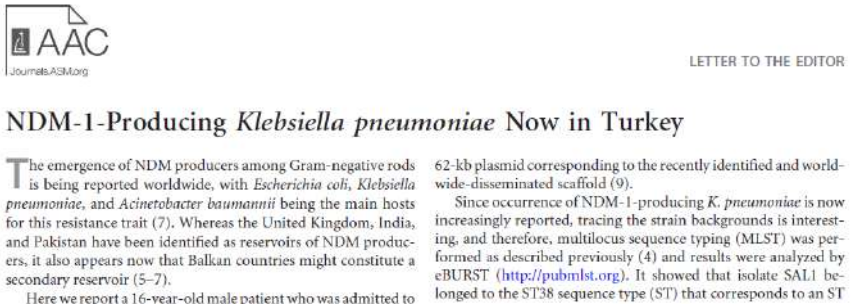
Murat Telli*

* Aydın Adnan Menderes Üniversitesi, Tıp Fakültesi, Tıbbi Mikrobiyoloji Anabilim Dalı, Aydın, Türkiye

Tablo 6. Direnç genleri ve yıllara göre dağılımı

Yıllar	*OXA-48*	*NDM*	*KPC*	*VIM*	*OXA48+NDM*	*OXA-48+KPC*	*OXA-48+VIM*	*NDM+KPC*	*NDM+IMP*	Direnç geni tespit edilemeyen
2012	0	0	0	0	2	0	0	0	0	0
2013	1	0	0	0	1	0	0	0	0	0
2014	2	0	0	0	1	0	0	0	0	0
2015	13	0	0	0	5	0	0	0	0	0
2016	13	5	0	0	17	0	1	0	0	3
2017	7	1	0	1	24	0	0	0	0	0
2018	25	6	1	1	28	0	0	0	1	2
2019	17	4	5	1	27	2	0	1	0	1
2020	35	16	1	2	18	0	0	0	0	0
Toplam (%)	**113 (38.8)**	**32 (11.0)**	**7 (2.4)**	**5 (1.7)**	**123 (42.3)**	**2 (0.7)**	**1 (0.3)**	**1 (0.3)**	**1 (0.3)**	**6 (2.0)**

Telli M Turk Microbiol Cemiy Derg 2022; 52: 95-102



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LETTER TO THE EDITOR

NDM-1-Producing *Klebsiella pneumoniae* Now in Turkey

The emergence of NDM producers among Gram-negative rods is being reported worldwide, with *Escherichia coli*, *Klebsiella pneumoniae*, and *Acinetobacter baumannii* being the main hosts for this resistance trait (7). Whereas the United Kingdom, India, and Pakistan have been identified as reservoirs of NDM producers, it also appears now that Balkan countries might constitute a secondary reservoir (5–7).

Here we report a 16-year-old male patient who was admitted to

62-kb plasmid corresponding to the recently identified and worldwide-disseminated scaffold (9).

Since occurrence of NDM-1-producing *K. pneumoniae* is now increasingly reported, tracing the strain backgrounds is interesting, and therefore, multilocus sequence typing (MLST) was performed as described previously (4) and results were analyzed by eBURST (http://pubmlst.org). It showed that isolate SAL1 belonged to the ST38 sequence type (ST) that corresponds to an ST

- Ülkemiz 2012-2014 NDM ile tanıştı
- 2012 Iraklı bir KİT hastası
- 2013 Kayseri karbapenem dirençli enterobakterlerin %5,3'ü
- 2014 yılı İstanbul Medipol Hastanesi *Enterobacter cloacae* salgını ve 4 *K pneumoniae'da* NDM-1

Poirel Let al. 2012 AAC; 56: 2785-6

Özgün Çalışma/Original Article Mikrobiyol Bul 2021;55(1):1-16/doi: 10.5578/mb.20124
Geliş Tarihi (Received): 25.05.2020 • Kabul Ediliş Tarihi (Accepted): 19.11.2020

Türkiye'de 2019 Yılı İçinde İzole Edilen *Escherichia coli* ve *Klebsiella pneumoniae* İzolatlarında Karbapenemaz Epidemiyolojisi

The Epidemiology of Carbapenemases in *Escherichia coli* and *Klebsiella pneumoniae* Isolated in 2019 in Turkey

Serap SÜZÜK YILDIZ[1](ID), Hüsniye ŞİMŞEK[1](ID), Zekiye BAKKALOĞLU[1](ID), Yasemin NUMANOĞLU ÇEVİK[1](ID), Can Hüseyin HEKİMOĞLU[1](ID), Selçuk KILIÇ[1](ID), Emine ALP MEŞE[2](ID), Ulusal Karbapenemaz Sürveyans Çalışma Grubu*

Tablo I. Çalışmaya Katılan Hastanelerin (n= 28) İstatistiki Bölgelere Göre Dağılımı ve Hastanelerden Gönderilen İzolat Sayıları

Hastane Adı	NUTS-2* Bölgesi	*E.coli*	*K.pneumoniae*	Toplam
Haydarpaşa Eğitim Araştırma Hastanesi	TR10	2	18	20
Şişli Hamidiye Etfal Eğitim ve Araştırma Hastanesi	TR10	4	16	20
Ankara Numune Eğitim ve Araştırma Hastanesi	TR51	10	8	18
Ankara Üniversitesi Tıp Fakültesi, İbn-i Sina Hastanesi	TR51	0	19	19
Selçuk Üniversitesi Tıp Fakültesi Hastanesi	TR52	1	19	20
Bursa Şevket Yılmaz Eğitim ve Araştırma Hastanesi	TR41	3	16	19
Kocaeli Üniversitesi Tıp Fakültesi Hastanesi	TR42	0	19	19
Ege Üniversitesi Tıp Fakültesi Hastanesi	TR31	4	10	14
Adnan Menderes Üniversitesi Tıp Fakültesi Hastanesi	TR32	0	20	20
Manisa Devlet Hastanesi	TR33	10	9	19
Trakya Üniversitesi Tıp Fakültesi Hastanesi	TR21	9	10	19
Onsekiz Mart Üniversitesi Tıp Fakültesi Hastanesi	TR22	10	10	20
Antalya Eğitim ve Araştırma Hastanesi	TR61	8	10	18
Çukurova Üniversitesi Tıp Fakültesi Hastanesi	TR62	0	19	19
Hatay Antakya Devlet Hastanesi	TR63	6	14	20
Karabük Üniversitesi Tıp Fakültesi Hastanesi	TR81	1	19	20
Kastamonu Münif İslamoğlu Devlet Hastanesi	TR82	4	16	20
Tokat Devlet Hastanesi	TR83	10	6	16
Ahi Evran Üniversitesi Tıp Fakültesi Hastanesi	TR71	0	20	20
Cumhuriyet Üniversitesi Tıp Fakültesi Hastanesi	TR72	6	14	20
KTÜ Tıp Fakültesi Hastanesi	TR90	6	13	19
Gaziantep Ersin Arslan Eğitim ve Araştırma Hastanesi	TRC1	10	6	16
Şanlıurfa Mehmet Akif İnan Eğitim ve Araştırma Hastanesi	TRC2			
Mardin Devlet Hastanesi	TRC3	6	13	19
İnönü Üniversitesi Tıp Fakültesi Turgut Özal Hastanesi	TRB1	2	18	20
Van 100. Yıl Üniversitesi Tıp Fakültesi Hastanesi	TRB1	8	12	20
Erzurum Bölge Eğitim ve Araştırma Hastanesi	TRA1	7	12	19
Kars Harakani Devlet Hastanesi	TRA2			
Toplam		127	366	493

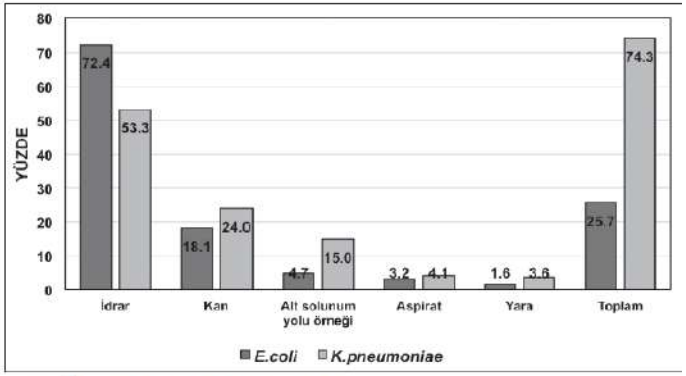
*NUTS-2: İstatistiki Bölge Birimleri Sınıflandırması (Nomenclature of Territorial Units for Statistics).

28 hastanenin (26 sından örnek alınmış) 509 izolat (*E coli* ya da *K pneumoniae* değerlendirilmiş)

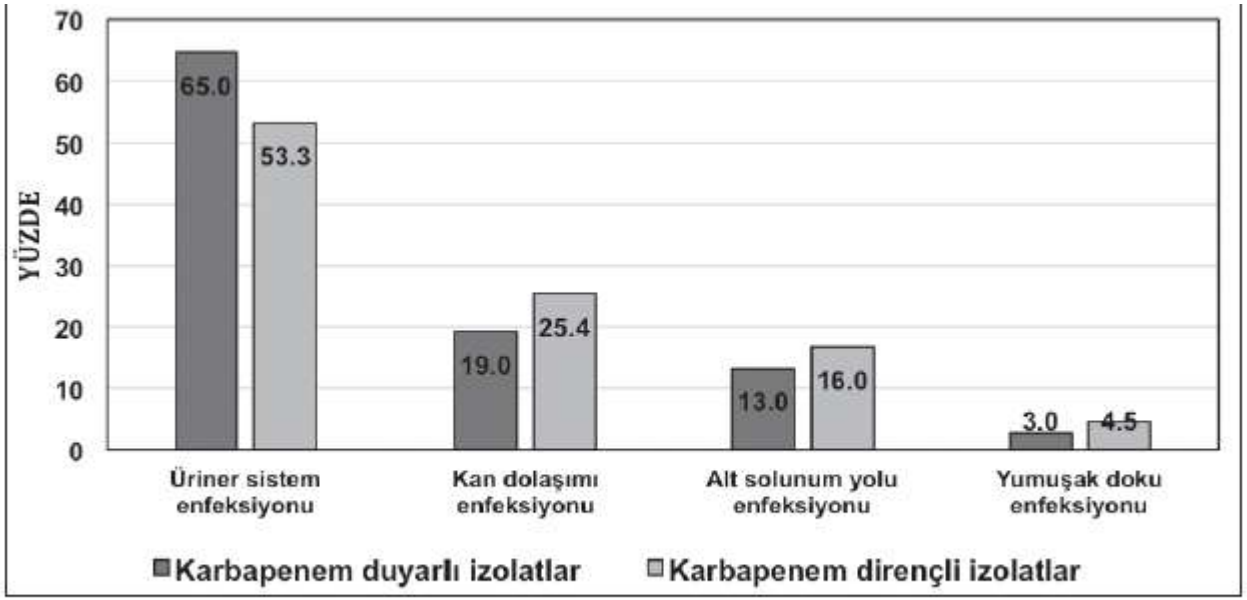
493'ü tür düzeyinde *E.coli* (%25.7, n= 127) ve *K.pneumoniae* (%74.3, n= 366) olarak tanımlanmış

%31'i TKİ, %69'u ise SBİİ etkeni/kolonize imiş

Süzük Yıldız S et al. Mikrobiol Bült 2021; 55

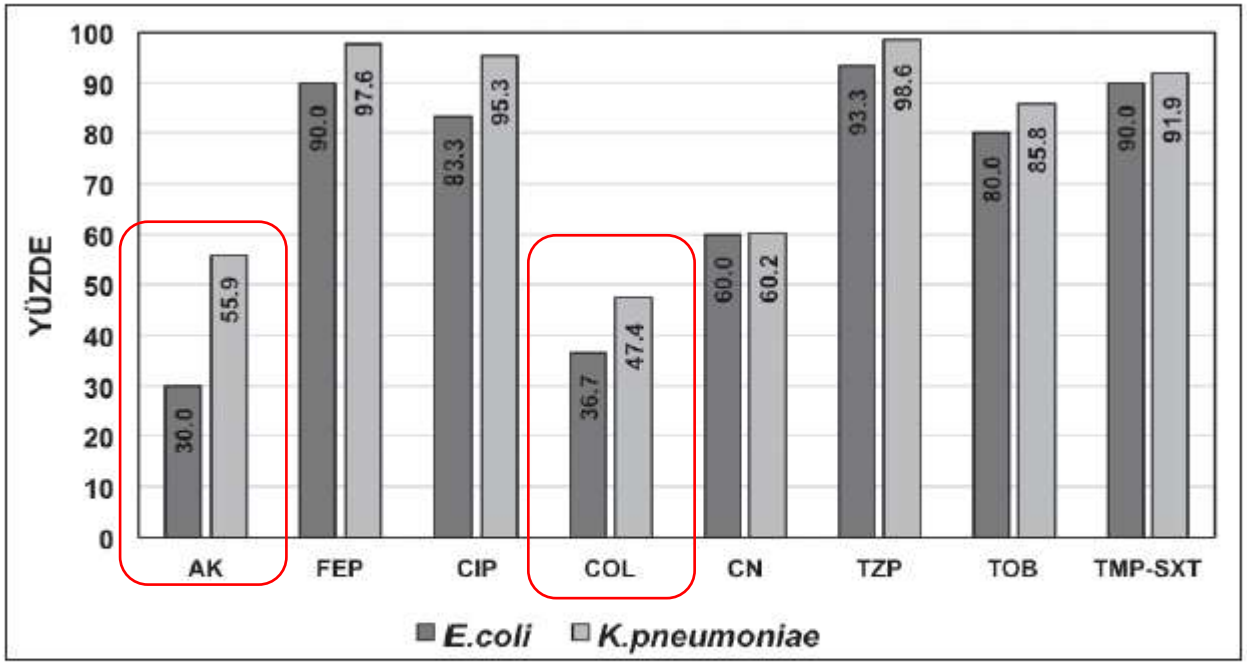


Şekil 1. İzolatların klinik örnek türüne göre dağılımı.



Şekil 2. *Karbapeneme duyarlı ve dirençli izolatların izole edildiği enfeksiyon kaynağına göre dağılımı.*

Süzük Yıldız S et al. Mikrobiol Bült 2021; 55



Şekil 3. Karbapenem dirençli izolatların farklı antibiyotiklere karşı direnç yüzdeleri.

AK: Amikasin, FEP: Sefepim, CIP: Siprofloksasin, COL: Kolistin, CN: Gentamisin, TZP: Piperasilin tazobaktam, TOB: Tobramisin, TMP-SXT: Trimetoprim sülfametoksazol.

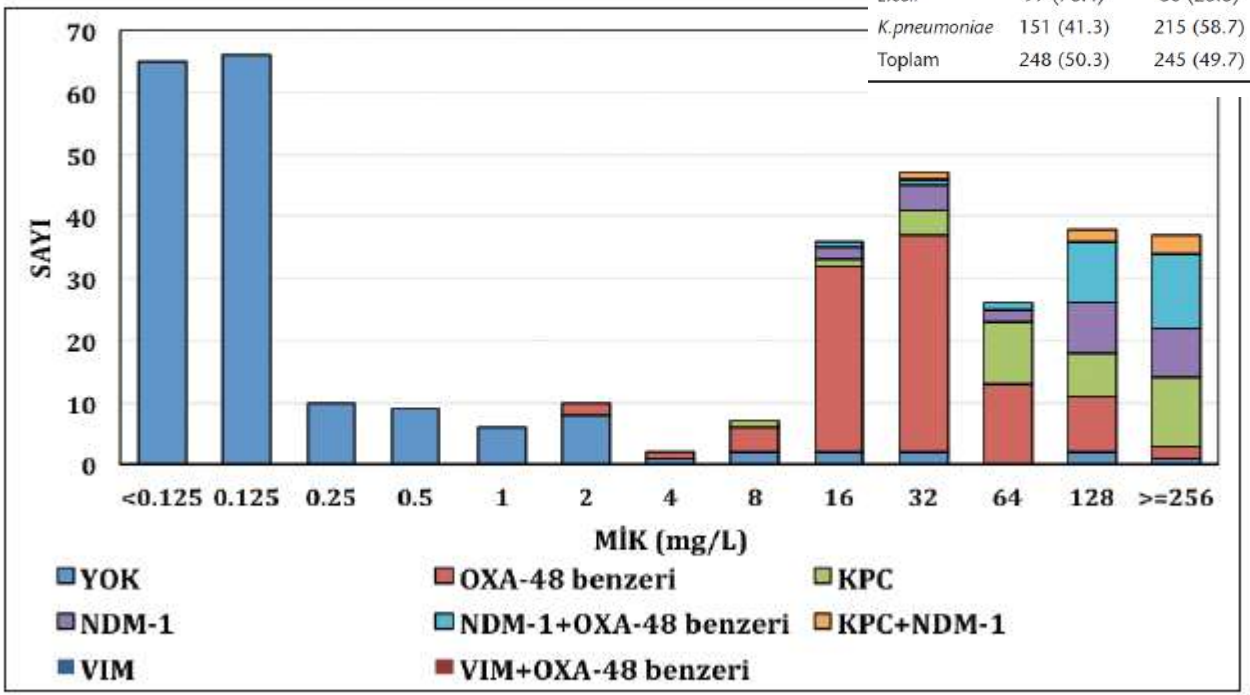
nemaz direnç genine sahip olduğu genotipik olarak belirlenmiştir, ancak fenotipik olarak

Süzük Yıldız S et al. Mikrobiol Bült 2021; 55

Türkiye'de 2019 Yılı İçinde İzole Edilen *Escherichia coli* ve *Klebsiella pneumoniae* İzolatlarında Karbapenemaz Epidemiyolojisi

Tablo IV. Karbapenem ve Kolistine Dirençli İzolatların Dağılımı

	Karbapenem			Kolistin		Toplam
Bakteri	Duyarlı	Herhangi Bir Karbapeneme Dirençli	Üç Karbapeneme Dirençli	Duyarlı	Dirençli	
E.coli	97 (76.4)	30 (23.6)	19 (15.0)	116 (91.3)	11 (8.7)	127
K.pneumoniae	151 (41.3)	215 (58.7)	174 (47.5)	262 (71.6)	104 (28.4)	366
Toplam	248 (50.3)	245 (49.7)	193 (39.1)	378 (76.7)	115 (23.3)	493



Şekil 6. K.pneumoniae izolatlarının meropenem MİK dağılımlarına göre karbapenemaz enzim tipinin dağılımı.

OXA-48 %52,2
KPC %16,4
NDM-1 %15

Süzük Yıldız S et al. Mikrobiol Bült 2021; 55

ST 14 klonlarında OXA-48+NDM-1 mevcut
Sorun CAZ/avibaktam yaygın kullanılırsa baskın suş olabilir

Turk Mikrobiyol Cemiy Derg 2021;51(4):375-81
doi:10.5222/TMCD.2021.94899

Araştırma / *Research Article*

Karbapenem Dirençli *Enterobacterales* İzolatlarında Karbapenemaz Genlerinin Araştırılması: Dokuz Eylül Üniversitesi Hastanesi'nden İlk KPC Bildirimi

Investigation of Carbapenemase Genes in Carbapenem Resistant Enterobacterales Isolates: First KPC Report From Dokuz Eylul University Hospital

Şeyda Şilan Okalin*, Ayşe Nur Sarı Kaygısız*, Mahmut Cem Ergon, İbrahim Mehmet Ali Öktem****

* Dokuz Eylül Üniversitesi, Sağlık Bilimleri Enstitüsü, Klinik Mikrobiyoloji ve Mikrobiyoloji Anabilim Dalı, İzmir, Türkiye
** Dokuz Eylül Üniversitesi, Tıp Fakültesi, Klinik Mikrobiyoloji ve Mikrobiyoloji Anabilim Dalı, İzmir, Türkiye

Tablo 2. Enterobacterales izolatlarının karbapenemaz dağılımı.

Karbapenemaz tipi	*Klebsiella pneumonie* Sayı (%)	*Escherichia coli* Sayı (%)	Toplam Sayı (%)
OXA-48	30 (66.6)	2 (66.6)	32 (66.6)
NDM	2 (4.4)	0	2 (4.16)
OXA-48 + NDM	7 (15.5)	0	7 (14.5)
KPC	6 (13.3)	1 (33.3)	7 (14.5)
IMP	0	0	0
VIM	0	0	0
Toplam	45 (93.75)	3 (6.25)	48 (%100)

Okalın ŞŞ et al. Turk Microbiol Cemiy Derg 2021; 51: 375-81

En yaygın olan ST 2096 OXA 232 kolistin direncini taşıyor

European Journal of Clinical Microbiology & Infectious Diseases (2022) 41:841–847
https://doi.org/10.1007/s10096-022-04425-4

BRIEF REPORT

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

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	Total	OXA-48-like				OXA48-like[b]/ MBL[c]	MBL[c]	KPC-2	KPC-2/MBL[c]
		OXA48	OXA232	OXA244	OXA181				
ST2096	61	2	56	…	…	3[d]	…	…	…
ST101	37	20	…	15	…	2[e]	…	…	…
ST14	28	6	…	1	…	20	1	…	…
ST16	14	8	1	…	3	1	1[g]	…	…
ST307	7	4	…	…	…	…	…	3	…
ST981[a]	6	6	…	…	…	…	…	…	…
ST11	5	3	…	…	…	…	2	…	…
ST15	5	1	…	…	…	1	1	…	2
ST395	5	1	…	…	…	…	4	…	…
Other	19	11	…	1	2	2[f]	2	1	…
Total	187	62	57	17	5	29	11	4	2

MBL, metallo-β-lactamase. [a]All isolates in this MLST are speciated as *Klebsiella variicola*. [b]OXA-48 unless specified otherwise, [c]NDM-1 unless specified otherwise, [d]OXA-48-like type is OXA-232 for all three isolates, [e]OXA-48-like type is OXA-244 for one of the two isolates, [f]NDM type is NDM-5 for one of the two isolates, [g]NDM type is NDM-5

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

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Journal of Antimicrobial Chemotherapy

Impact of the ST101 clone on fatality among patients with colistin-resistant *Klebsiella pneumoniae* infection

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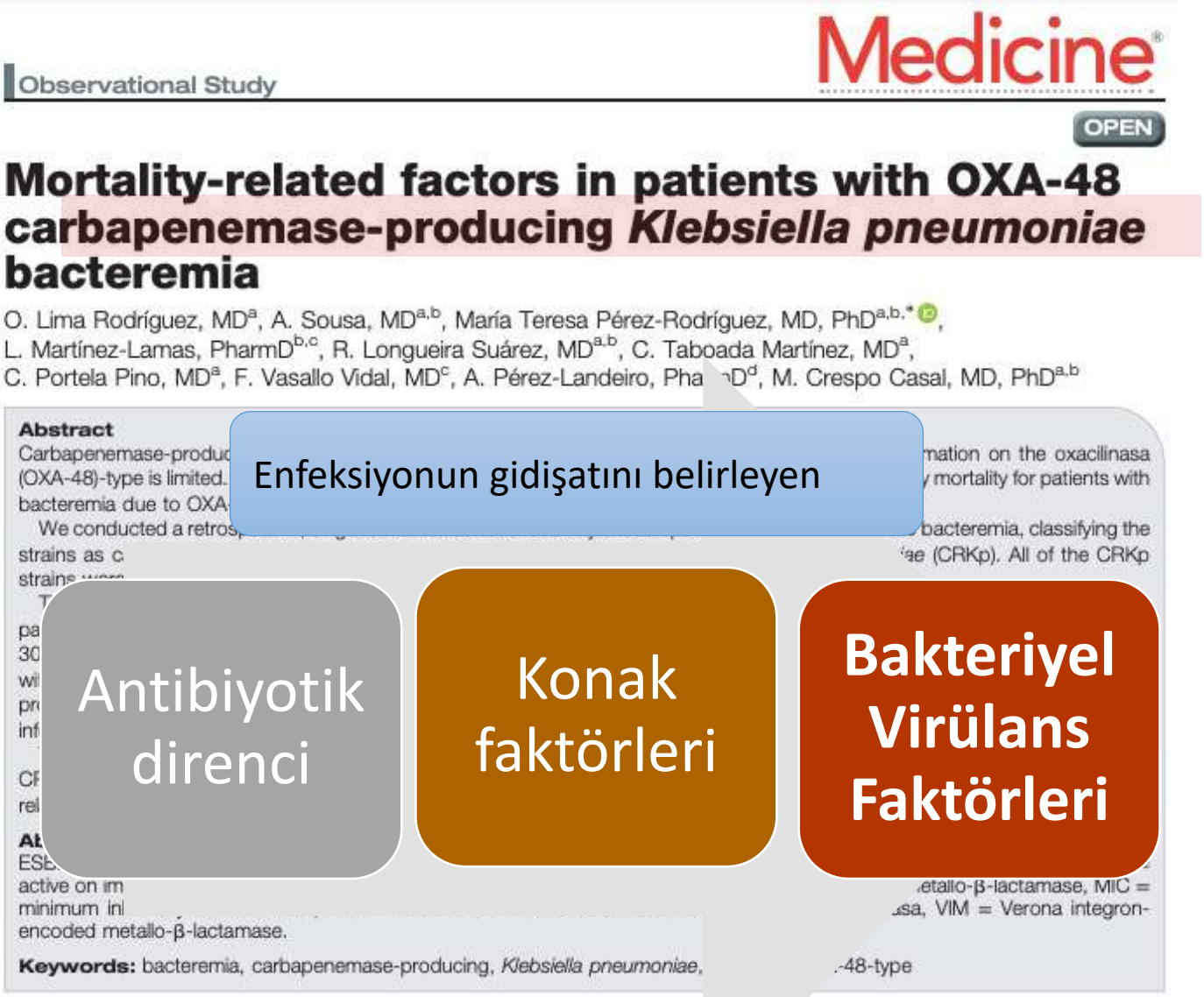
Table 2. Distribution of OXA-48 and NDM-1 among STs

	OXA-48 ($N = 93$)	NDM-1 ($N = 22$)
ST101 ($N = 68$), n (%)	65 (96)	0
ST395 ($N = 15$), n (%)	5 (33)	13 (87)
ST16 ($N = 6$), n (%)	4 (67)	0
ST147 ($N = 5$), n (%)	2 (40)	4 (80)
Other STs ($N = 21$), n (%)	17 (81)	5 (24)

İstanbul, Ankara'dan KDİ 115 hasta
ST101 klonu ve OXA-48 yaygın kolistin R'li suşlarda

Can F et al. J Antimicrob Chemother 2018; 73: 1235-41

Bakteriyel Virülans Faktörleri ?



Observational Study

Medicine

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Mortality-related factors in patients with OXA-48 carbapenemase-producing *Klebsiella pneumoniae* bacteremia

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Abstract

Carbapenemase-produc[illegible]mation on the oxacilinasa (OXA-48)-type is limited. [illegible]y mortality for patients with bacteremia due to OXA-[illegible]

We conducted a retros[illegible] bacteremia, classifying the strains as c[illegible]ae (CRKp). All of the CRKp strains [illegible]

pa[illegible]
30[illegible]
wi[illegible]
pr[illegible]
inf[illegible]

CR[illegible]
rel[illegible]

Ab[illegible]
ESB[illegible]
active on im[illegible]etallo-β-lactamase, MIC = minimum inl[illegible]sa, VIM = Verona integron-encoded metallo-β-lactamase.

Keywords: bacteremia, carbapenemase-producing, *Klebsiella pneumoniae*, [illegible]-48-type

Enfeksiyonun gidişatını belirleyen

Antibiyotik direnci

Konak faktörleri

Bakteriyel Virülans Faktörleri

Rodriguez OL et al. Medicine 2021; 100: e-24880

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frontiers in Microbiology

REVIEW

Understanding the Epidemiology of Multi-Drug Resistant Gram-Negative Bacilli in the Middle East Using a One Health Approach

Iman Dandachi[1], Amer Chaddad[1], Jason Hanna[1], Jessika Matta[1] and Ziad Daoud[1,2]*

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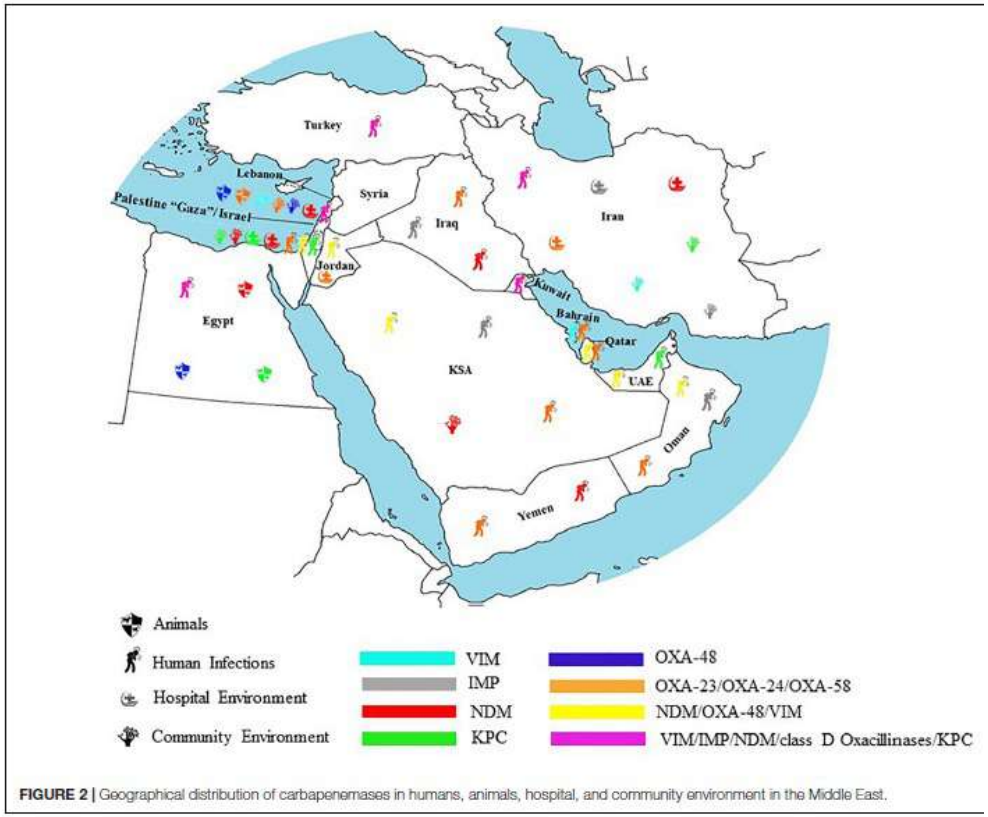

FIGURE 2 | Geographical distribution of carbapenemases in humans, animals, hospital, and community environment in the Middle East.

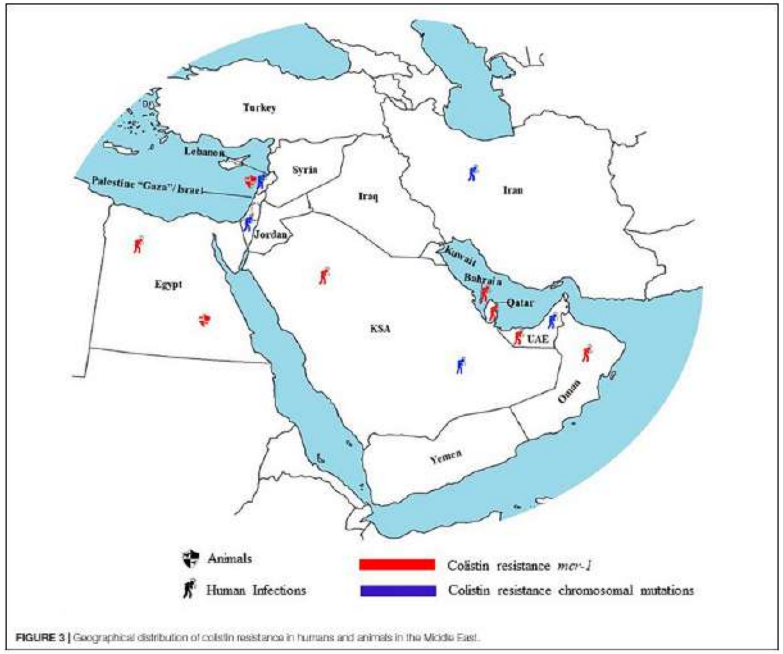

FIGURE 3 | Geographical distribution of colistin resistance in humans and animals in the Middle East.

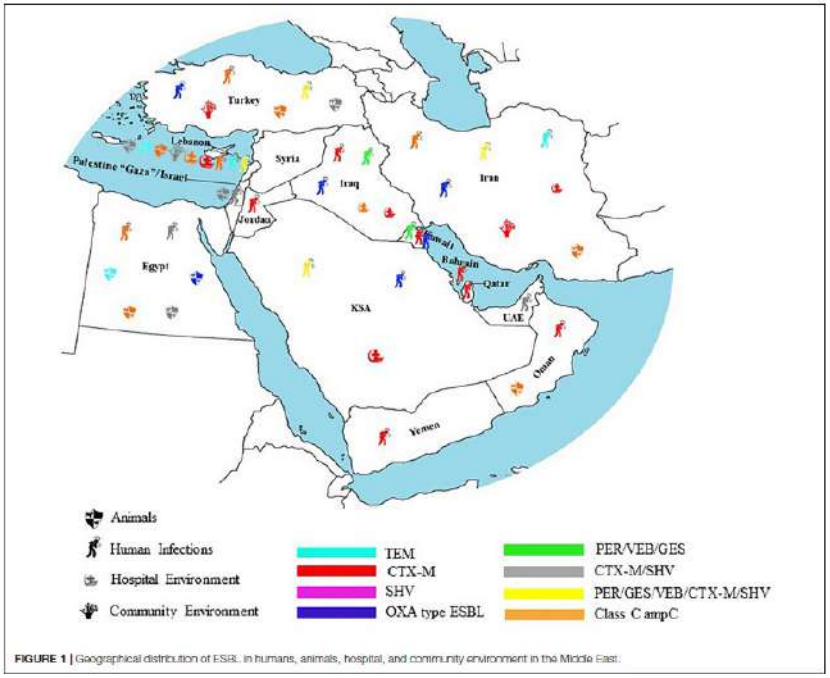

FIGURE 1 | Geographical distribution of ESBL in humans, animals, hospital, and community environment in the Middle East.

Dandachi I et al. Front Microbiol 2019

Direnç gen havuzları en fazla sularda

Journal of Global Antimicrobial Resistance 23 (2020) 430–438

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Antibiotic resistance surveillance systems: A review

Ousmane Oumou Diallo[a,b], Sophie Alexandra Baron[a,b], Cédric Abat[a], Philippe Colson[a,b], Hervé Chaudet[a,c], Jean-Marc Rolain[a,b,*]

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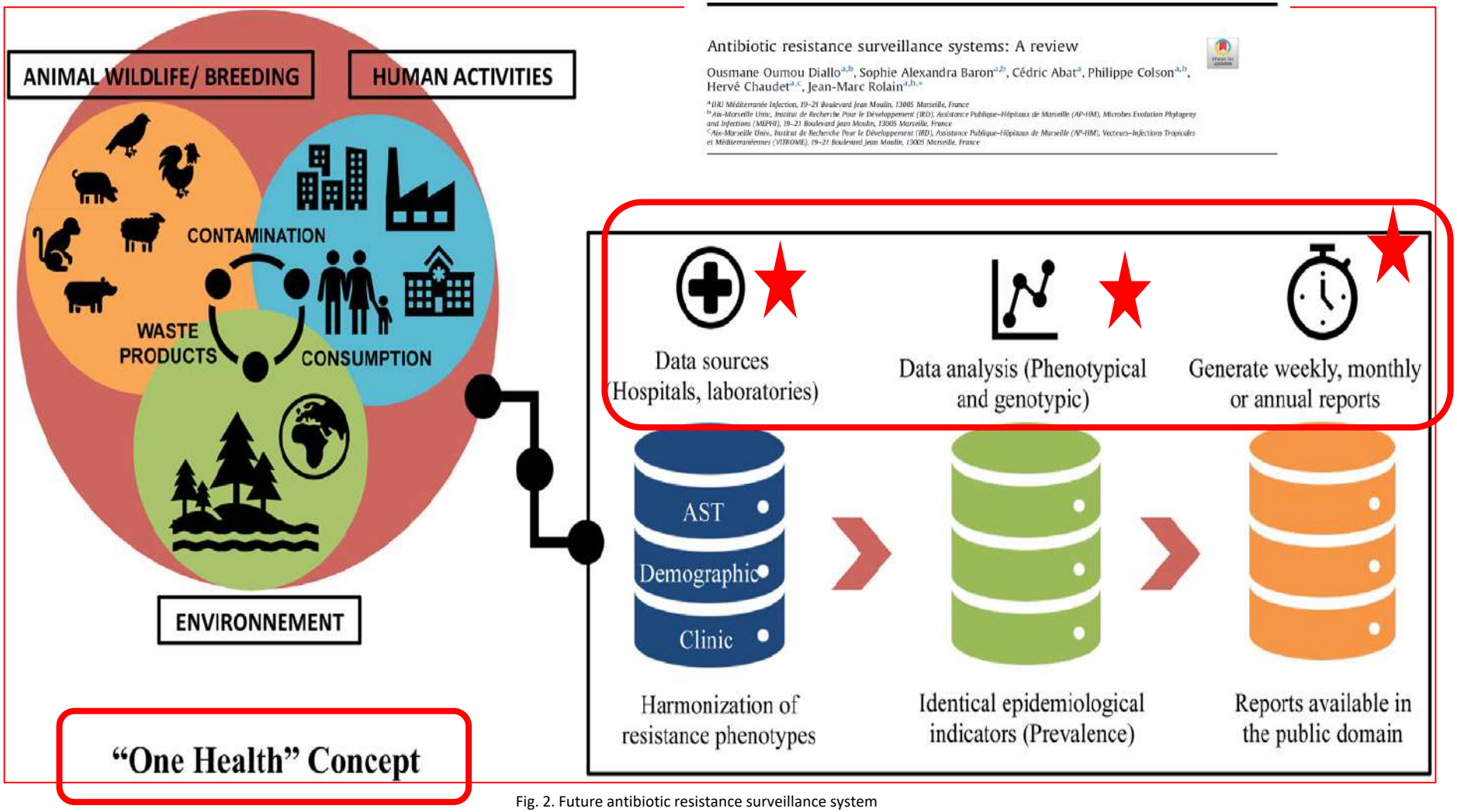


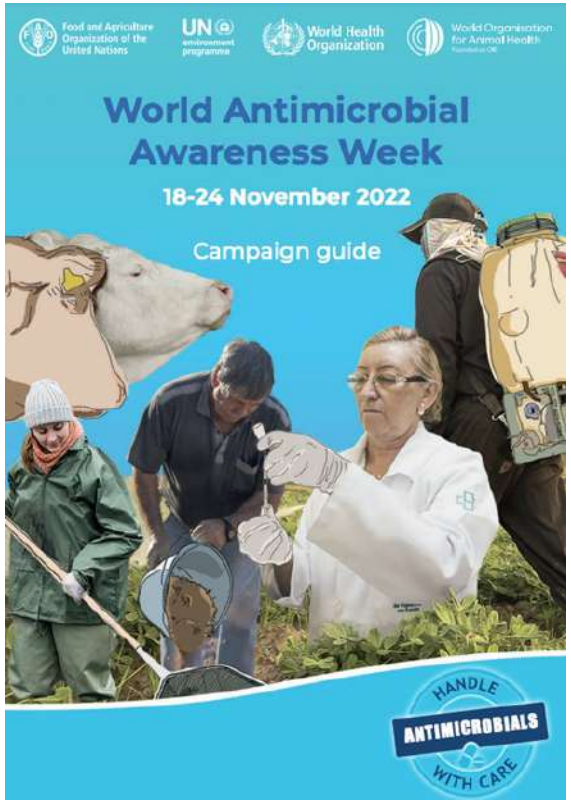
Fig. 2. Future antibiotic resistance surveillance system

Diallo OO et al. J Glob Antimic Resis. 2020; 23: 430-8

- Antibiyotik öncesi döneme dönüş yok aslında
- Antibiyotik direncini önlemek mümkün değil
- Tek sağlık sürveyansı önemli
  - Antibiyotik tüketimi
  - Antibiyotik yönetimi
- Hızlı tanı gerekli (fenotipik ve genotipik)
- Yeni antibiyotikler ve aşı

- Antibiyotiklere direnç dünyanın en önemli halk sağlığı sorunlarından biri
- Direncin önlenmesinde önemli basamaklardan biri direncin izlenmesi
- İzlemin yerel, bölgesel ve küresel olması yayılımın

daha net anlaşılmasına olanak sağlar



Teşekkürler

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Table 2
Antimicrobials commonly tested against carbapenem resistant *Enterobacteriaceae*

Antimicrobial	EUCAST MIC breakpoint indicating resistance	Prevalence[a] of susceptible isolates	Remarks
Ceftazidime	>4	<3%	Resistance usually associated with concurrent expression of ESBL or AmpC β-lactamases
Cefepime	>4	<5%	
Aztreonam		<5%	Susceptibility or low-level resistance may be expected in case of metallo-β-lactamase carbapenemase expression. Resistance is the rule when other carbapenemases (KPC, OXA-48, etc.) or extended spectrum β-lactamases are co-expressed
Piperacillin-tazobactam	>16	<5%	Resistance usually associated with high-level expression of extended spectrum β-lactamases
Ceftazidime-avibactam	>8	>90%	Susceptibility expected in case of KPC or OXA-48 carbapenemase expression. Resistance is the rule when metallo-enzymes (NDM, IMP, VIM, etc.) are expressed
Imipenem	>8	<5%	Variable degrees of resistance may occur according to level of carbapenemase expression and concurrent presence of other mechanisms of carbapenem resistance
Meropenem	>8	<5%	
Doripenem	>2	<5%	
Amikacin	>16	50%	Cross resistance not the rule depending on actual subtype of modifying enzyme expressed
Gentamicin	>4	40%	
Ciprofloxacin	>0.5	<5%	Very low rates of susceptibility expected in endemic settings of carbapenem-resistant *Enterobacteriaceae* prevalence
Trimethoprim-sulphamethoxazole	>4	<5%	Sparse data available
Fosfomycin	>32	50%	Variable results according to the susceptibility method used
Tigecycline	>2	85%	Consistent susceptibility data across multiple studies and settings
Colistin	>2	80%	Broth microdilution recommended to avoid major errors

[a] Conservative estimates based on literature data (average rates) and the author's personal experience.

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LETTER TO THE EDITOR

Ceftazidime-Avibactam and Aztreonam, an Interesting Strategy To Overcome β-Lactam Resistance Conferred by Metallo-β-Lactamases in *Enterobacteriaceae* and *Pseudomonas aeruginosa*

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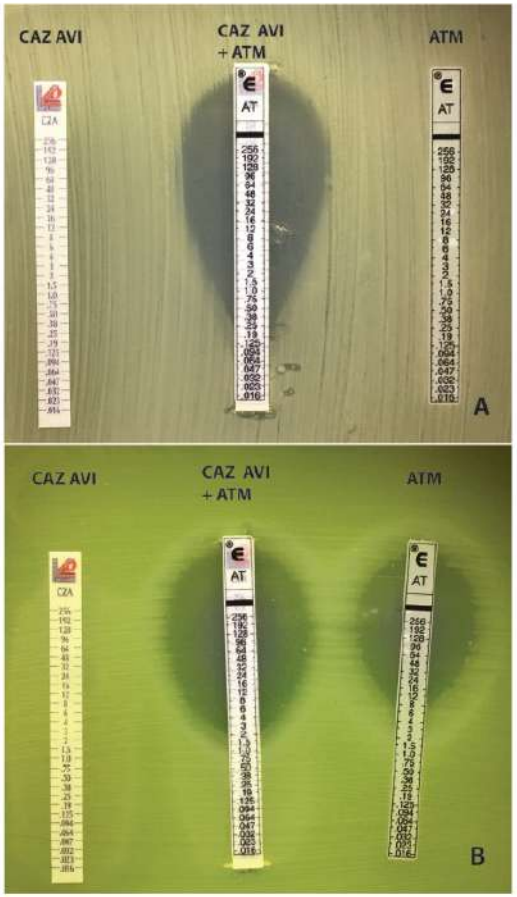

FIG 1 Susceptibility testing showing with ellipsometry the effect of the synergistic combination of CAZ-AVI and ATM. The combination (middle strip) was tested by first applying an ATM strip to the Mueller-Hinton (MH) agar, removing it after 5 min, and then applying a CAZ-AVI strip on the exact same location and placing back the ATM strip to read the susceptibility to ATM in the presence of AVI (and CAZ). (Top panel) *K. pneumoniae* NDM-1/OXA-48 from patient 1. (Bottom panel) *Pseudomonas aeruginosa* NDM-1/AmpC from patient 2.

RAPID COMMUNICATION

Worsening epidemiological situation of carbapenemase-producing Enterobacteriaceae in Europe, assessment by national experts from 37 countries, July 2018

Alma Brolund[1,2], Nina Lagerqvist[1,2,3], Sara Byfors[1], Marc J Struelens[4], Dominique L Monnet[5], Barbara Albiger[4], Anke Kohlenberg[4], European Antimicrobial Resistance Genes Surveillance Network (EURGen-Net) capacity survey group[5]
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5. The members of the capacity survey group are listed at the end of this article

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FIGURE 2

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

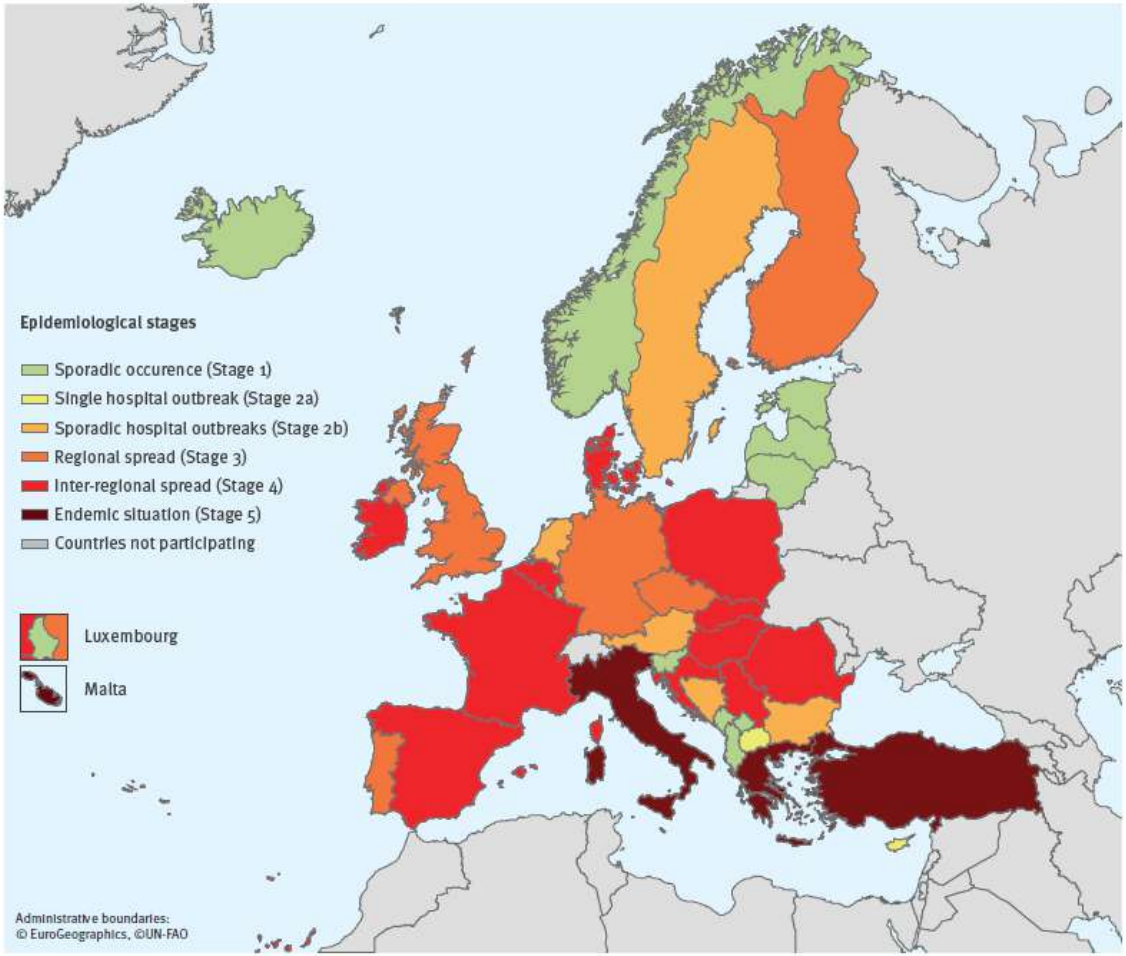

Table 1. Ambler classification of β–lactamases.

Ambler Class	β-Lactamases	Active Site Agent	Examples	Substrates
A	Penicillinases	Serine	PSE TEM, SHV, CTX-M, VEB, PER, GES KPC, SME, IMI/NMC-A	Penicillins Penicillins, 3rd generation cephalosporins All β-lactams
B	Metallo-β-lactamases	Zinc	IMP, VIM, NDM, SPM, GIM	All β-lactams, except monobactams
C	Cephalosporinases	Serine	AmpC	Cephamycins, 3rd generation cephalosporins
D	Oxacillinases	Serine	OXA	All β-lactams, though class D enzymes have highly variable spectra of activity

Abbreviations: CTX-M, active against cefotaxime (CTX) and isolated in Munich (-M); GES, Guiana extended spectrum; GIM, German imipenemase; IMP, active on imipenem; KPC, Klebsiella pneumoniae carbapenemase; NDM, New Delhi metallo-β-lactamase; NMC, not metalloenzyme carbapenemase; OXA, oxacillinase; PER, Pseudomonas aeruginosa RNL-1; PSE, Pseudomonas specific enzyme; SHV, sulfhydrl reagent variable; SME, Serratia marcescens enzyme; SPM, Sao Paulo metallo- β -lactamase; VEB, Vietnamese extended-spectrum β-lactamase; VIM, Verona integron-encoded metallo-β-lactamase.

Eichenberger EM et al. Antibiotics 2019; 37

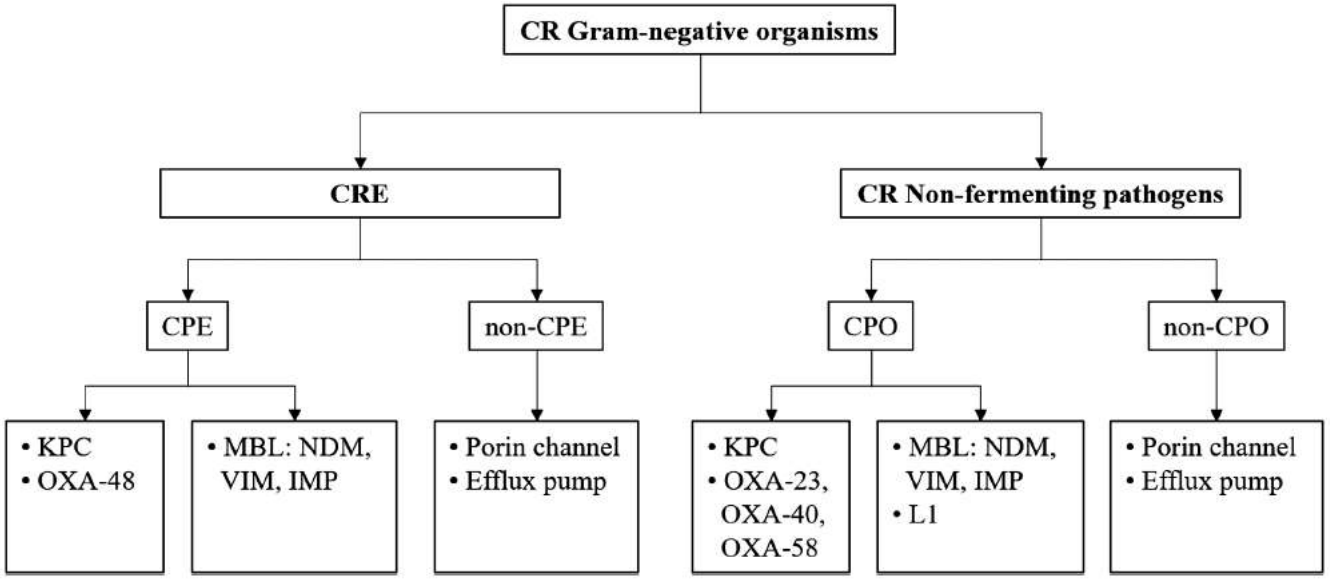

Figure 4. Algorithm to assess potential carbapenem resistance mechanisms in Enterobacteriaceae and nonfermenter species. Abbreviations: CPE, carbapenemase-producing Enterobacteriaceae; CPO, carbapenemase-producing organism; CR, carbapenem resistant; CRE, carbapenem-resistant Enterobacteriaceae; IMP, imipenemase metallo-β-lactamase; KPC, *Klebsiella pneumoniae* carbapenemase; L1, a class B metallo-β-lactamase; MBL, metallo-β-lactamase; NDM, New Delhi metallo-β-lactamase; OXA, oxacillin carbapenemase/oxacillinase; VIM, Verona integron-encoded metallo-β-lactamase.

Nordmann P et al. Clin Infect Dis 2019; 69: S521-8.