Kolistin Direnci Nereye Gidiyor

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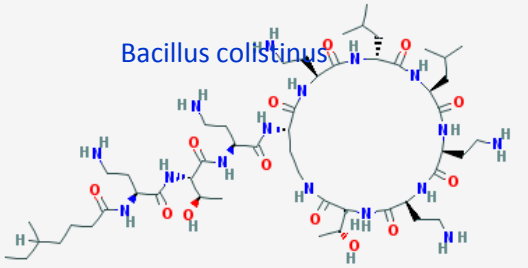
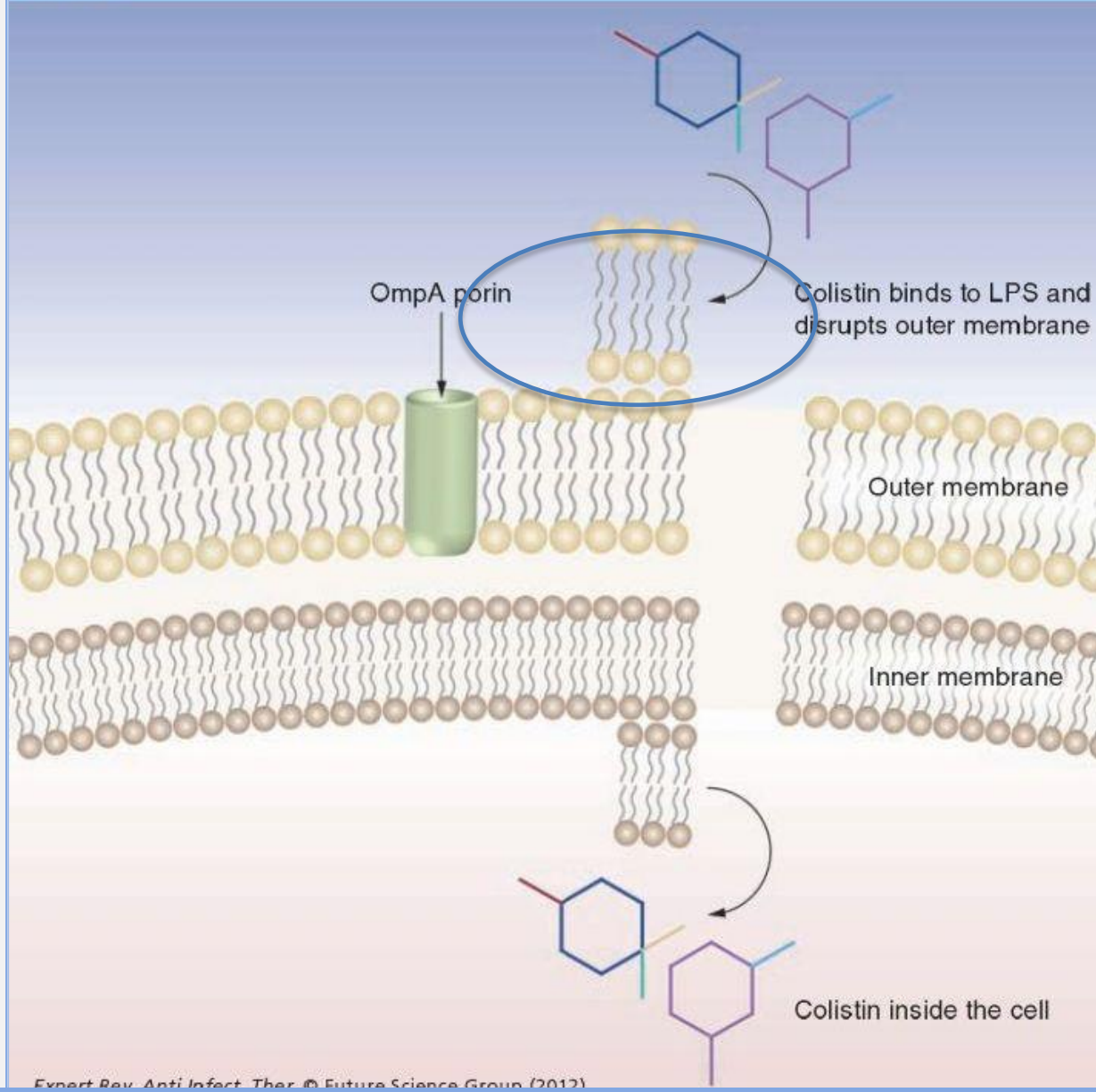
Mikrobiyoloji A.D

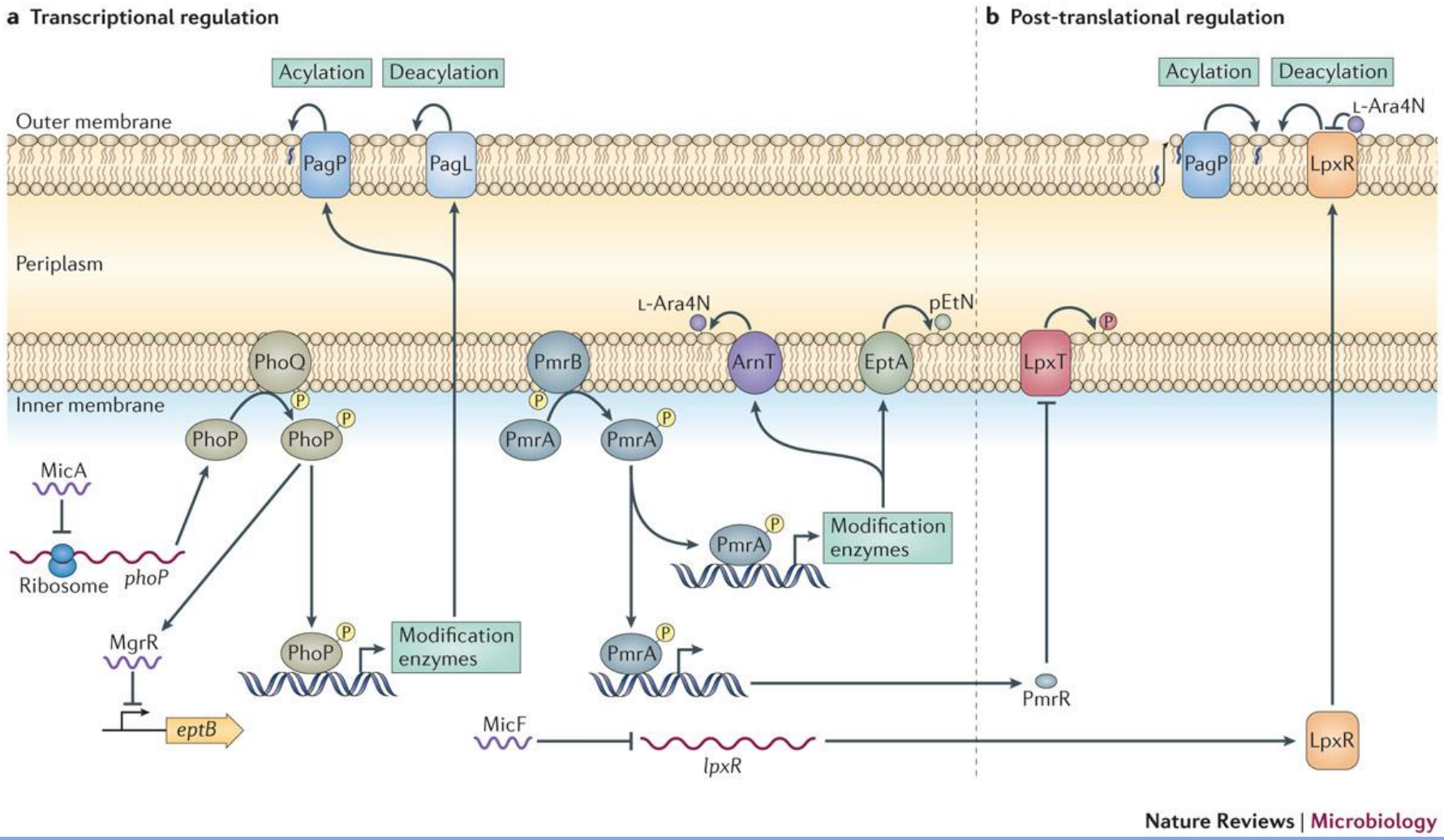
Kolistin yapısı ve Etki Mekanizması





- Membran fosfolipid gruplarda Ca ve Mg ile yer değiştirir
- Permiabilite artar, hücre ölümü

Kolistin Direnci



- Hücre membranında negatif yükün azalması
- Lipid A fosfat grupları 4-amino- 4-deoxy-l-arabinose ve/veya phosphoethanolamine değişimi

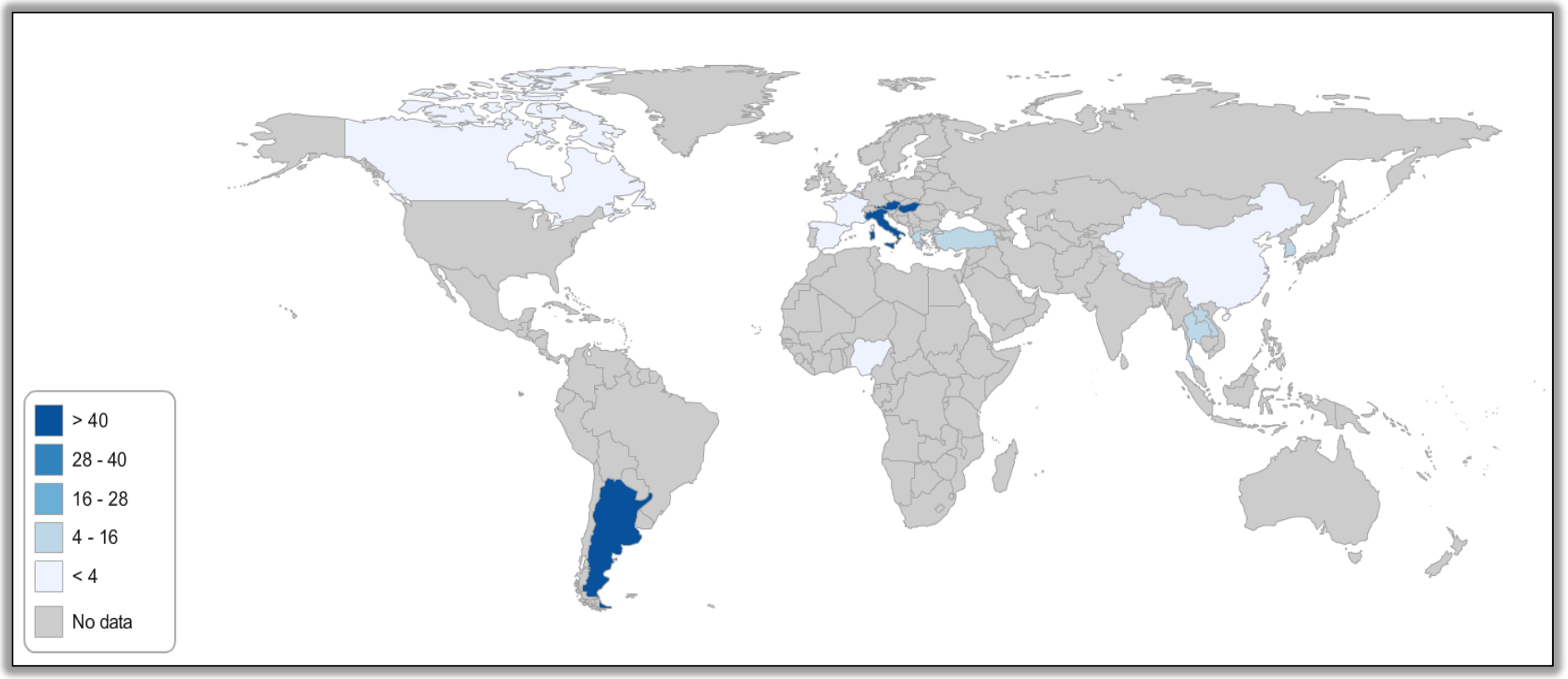
Kolistin Direnci Evrimi

2010 öncesi

2010-2015

2015-

K.pneumoniae Kolistin Direnci Bildiren Ulkeler

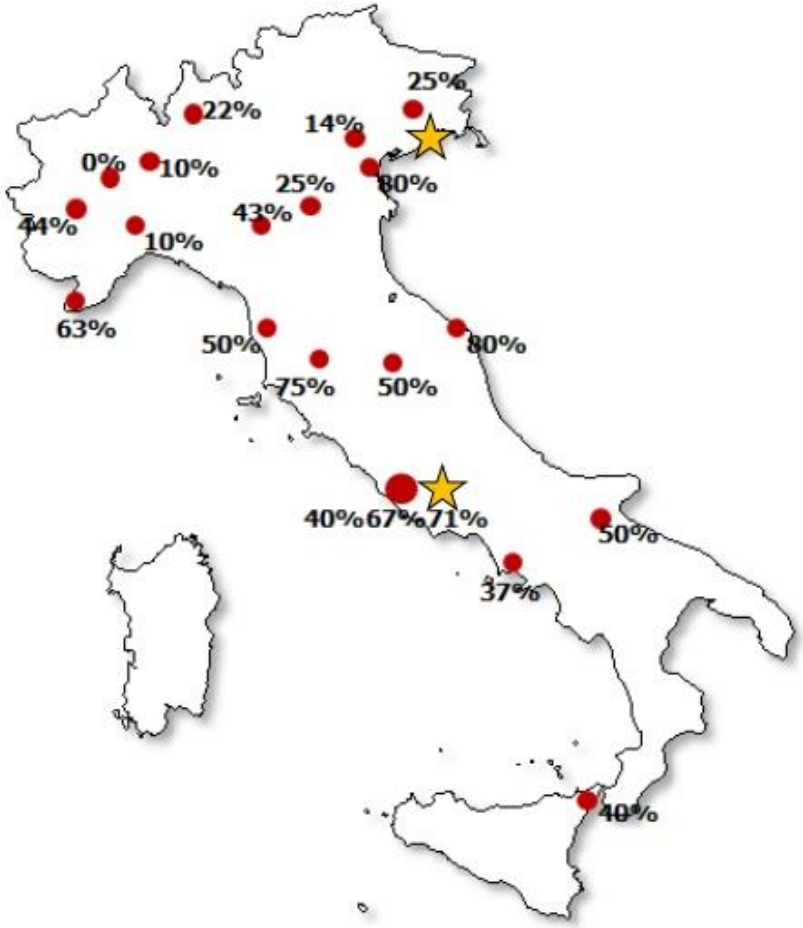


Gucer LS.ve ark, PS-155. KLIMIK 2016

Antibiotic susceptibility of 179 *K. pneumoniae*-KPC isolates (EuSCAPE-Italy)

ANTIBIOTIC	S		I		R	
	n°	%	n°	%	n°	%
Ciprofloxacin	1	0.6	0	0	178	99.4
Amikacin	19	11.3	14	8.3	135	80.3
Ertapenem	0	0	0	0	179	100
Imipenem	0	0	6	3.4	173	96.6
Meropenem	0	0	1	0.6	178	99.4
Trimetho/Sulfa	32	17.8	0	0	147	82.2
Gentamicin	149	83.2	6	3.4	24	16.7
Colistin	103	57.0	0	0	76	43.0
Tigecycline	168	94.0	10	5.5	1	0.5

EuSCAPE-Italy



Colistin resistance in *K. pneumoniae*-KPC
(% of Col/Res in each hospital laboratory)

Türkiye’de Kolistin Direnci

- Acinetobacter baumannii izolatlarında % 0-6

  Ergönül ve ark., 2014; Gundeslioglu ve ark., 2014; Guven ve ark., 2014; Ece ve ark., 2014

  Sari ve ark., 2015

- Karbapenem dirençli Acinetobacter suşlarında % 0-2.5

  Cakirlar ve ark., 2015; Cikman ve ark., 2015

- Klebsiella suşlarında %5

  Ergönül ve ark., 2014

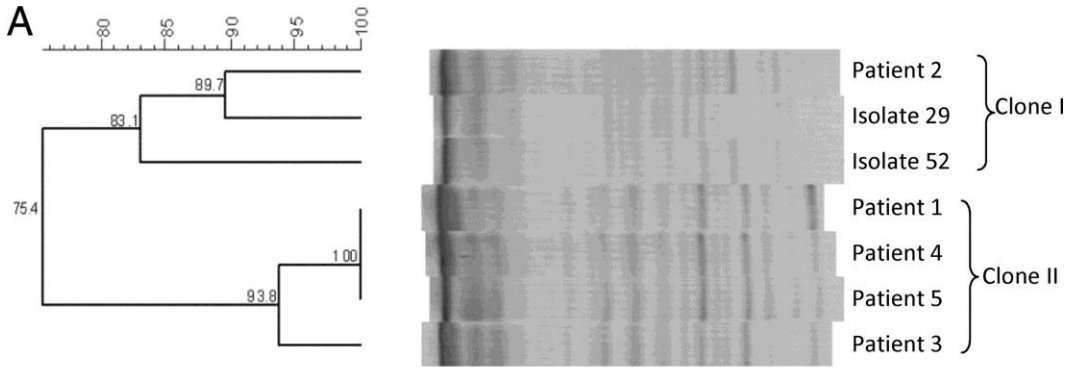
- Karbapenem dirençli Klebsiella suşlarında %0-2,7

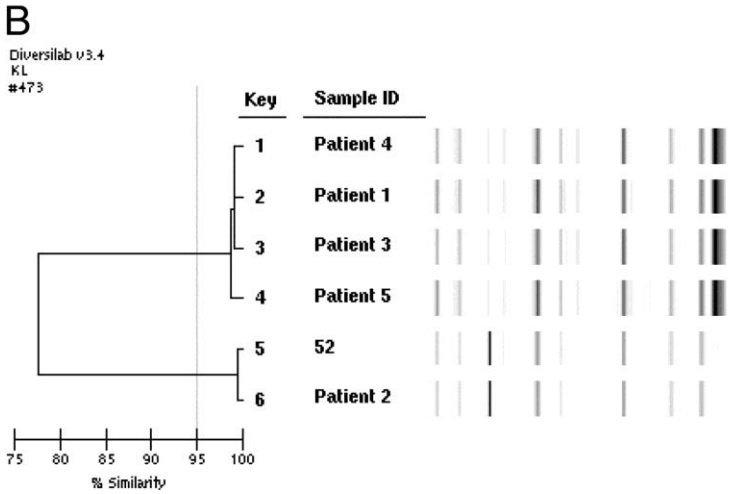
  Dizbay ve ark., 2014; Iraz ve ark., 2015)

- Çok ilaca dirençli Pseudomonas suşlarında % 0-1.7

  Ergönül ve ark.,2014; Ece ve ark., 2014)

Outbreak of Colistin-Resistant, Carbapenem-Resistant Klebsiella pneumoniae in Metropolitan Detroit, Michigan





- Patient 1 indeks vaka
- 20 gün sonra 4 hastadan klonal izolatlar

Dendrograms of carbapenem-resistant Klebsiella species strains, DMC, 2009.

Dror Marchaim et al. Antimicrob. Agents Chemother. 2011;55:593-599

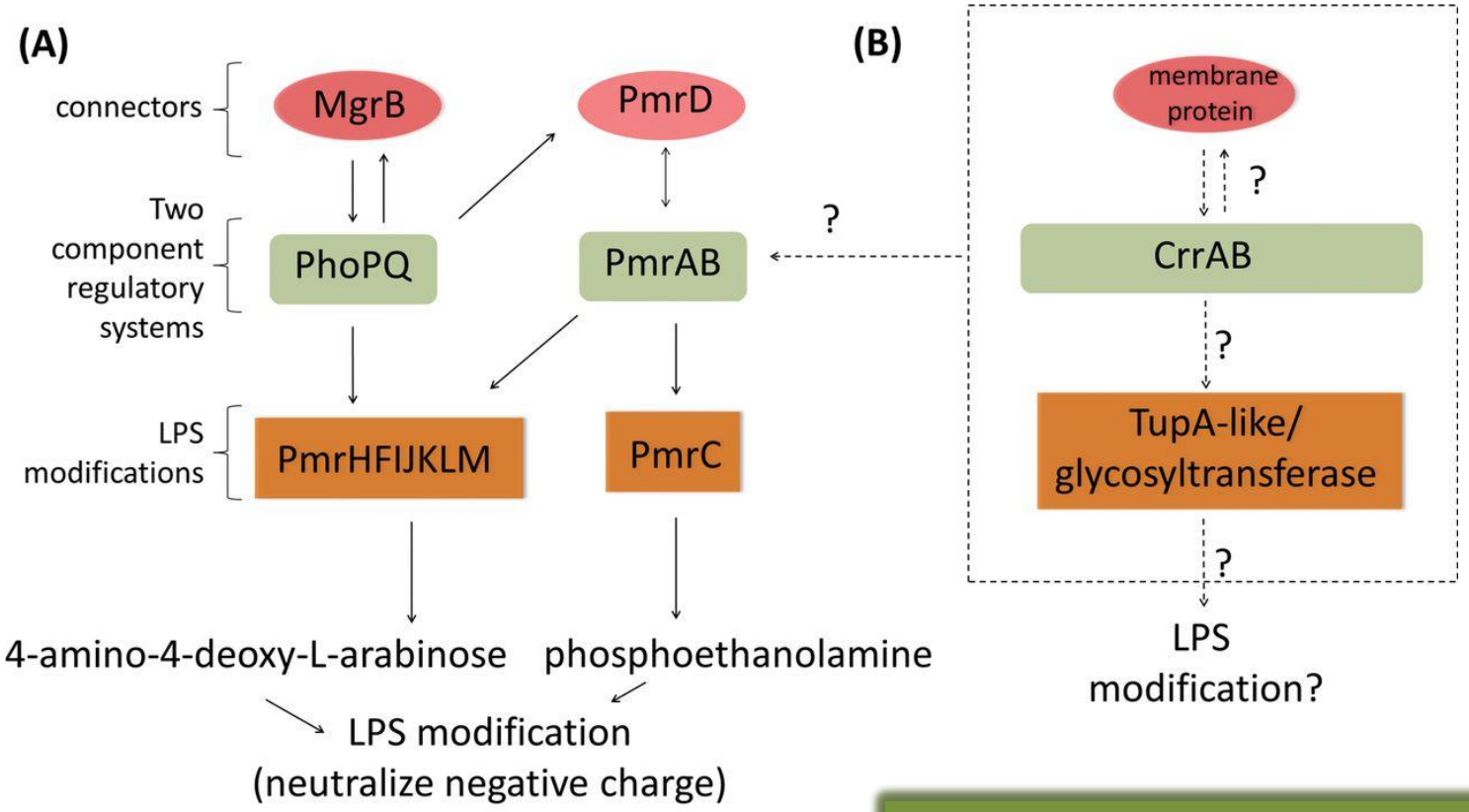
Large Nosocomial Outbreak of Colistin-Resistant, Carbapenemase-Producing *Klebsiella pneumoniae* Traced to Clonal Expansion of an *mgrB* Deletion Mutant

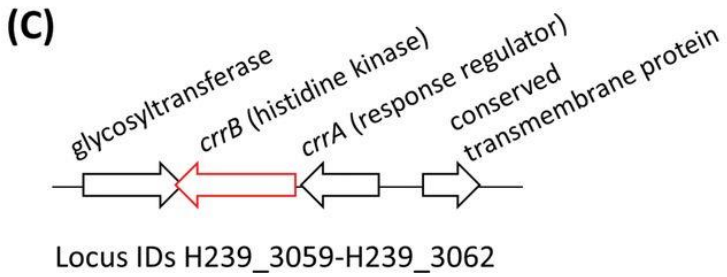
Tommaso Giania, Fabio Arenaa, Guendalina Vaggellib, Viola Contea, Adriana Chiarellia, Lucia Henrici De Angelisa, Rossella Fornainic, Maddalena Grazzinid, Fabrizio Niccolinid, Patrizia Pecileb and Gian Maria Rossolinia,b,e,f

- Kolistin dirençli KPC *Klebsiella pneumoniae*
- 93 Kan enfeksiyonu
- Karbapenamaz: KPC-3
- Sekans Tip: ST512
- Direnç Mekanizması: mgrB delesyonu

Gianni T., JCM 2015

Kolistin Direnci Moleküler Mekanizmaları

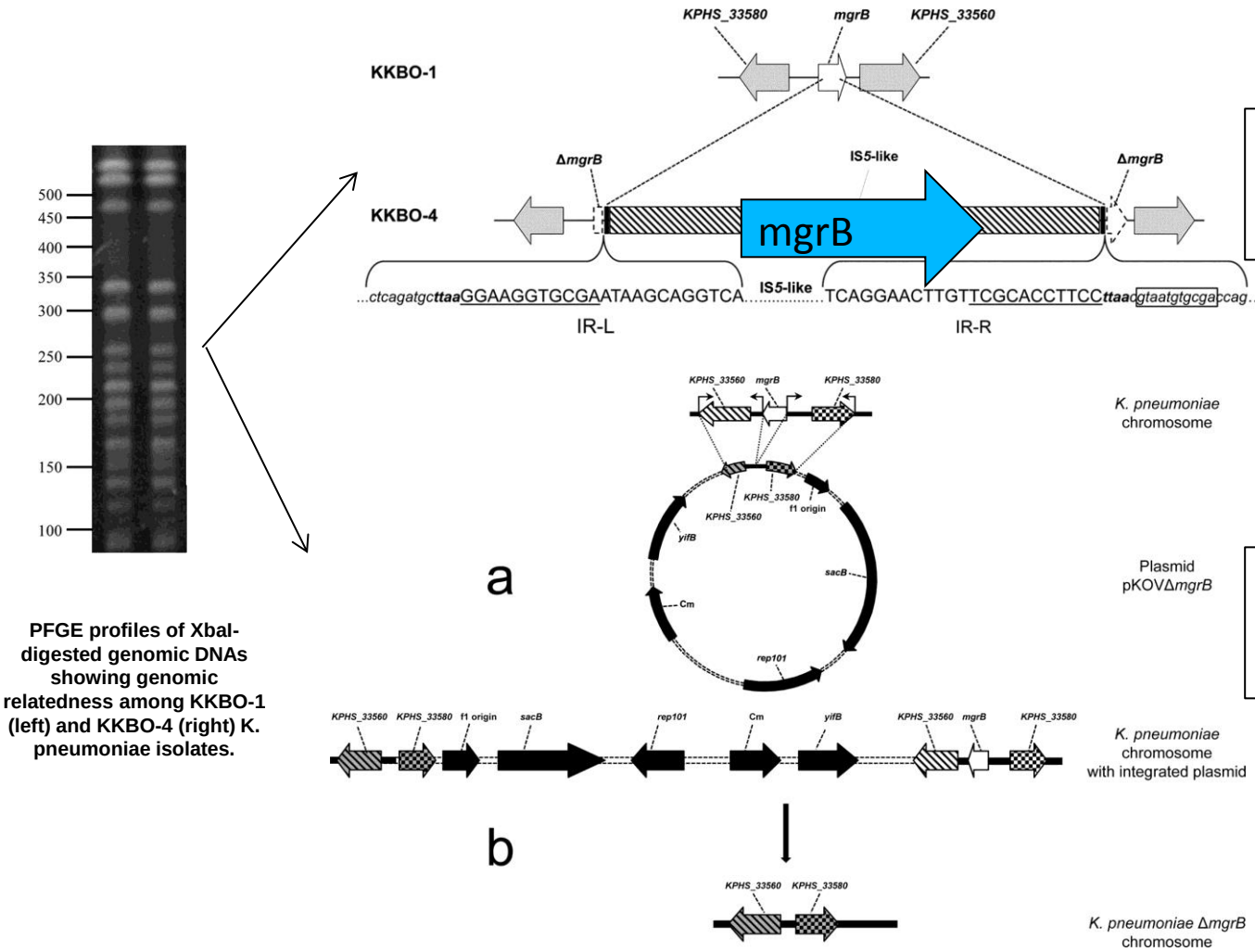




Kolistin ve LPS afinitesini azaltan modifikasyonlar

Meredith S. Wright et al. Antimicrob. Agents Chemother. 2015;59:536-543

In Vivo Emergence of Colistin Resistance in *Klebsiella pneumoniae* Producing KPC-Type Carbapenemases Mediated by Insertional Inactivation of the PhoQ/PhoP *mgrB* Regulator



PhoQ/PhoP ekspresyon artişı *pmrHFIJKLM* operon aktivasyonu

PhoQ/PhoP ekspresyon artişı *pmrHFIJKLM* operon aktivasyonu

PFGE profiles of XbaI-digested genomic DNAs showing genomic relatedness among KKBO-1 (left) and KKBO-4 (right) K. pneumoniae isolates.

Antonio Cannatelli et al. Antimicrob. Agents Chemother. 2013;57:5521-5526

MgrB Gene Analysis

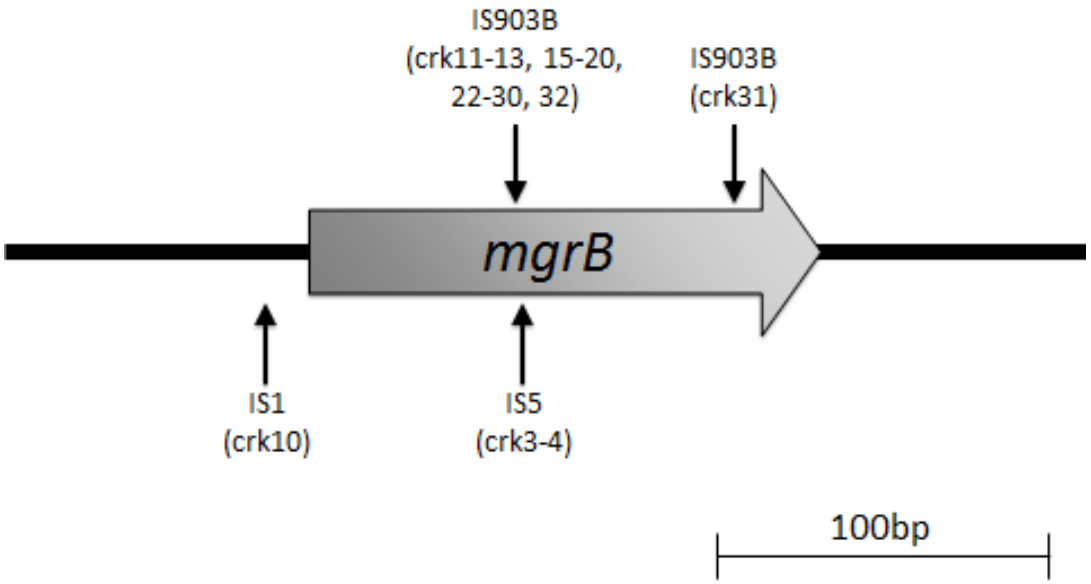
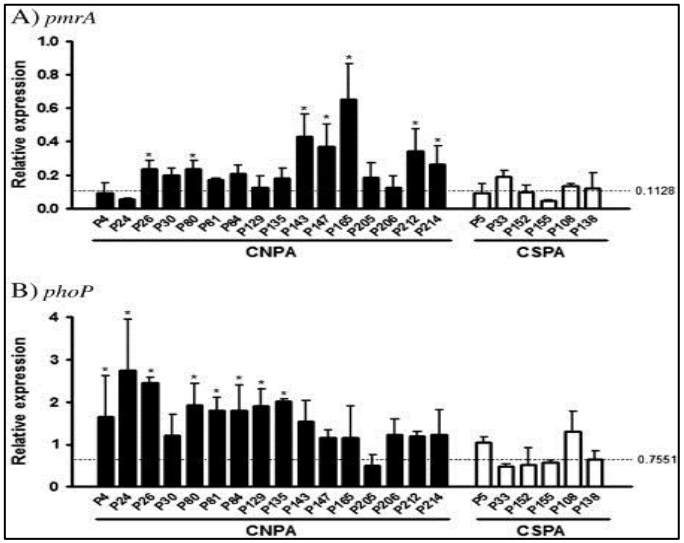


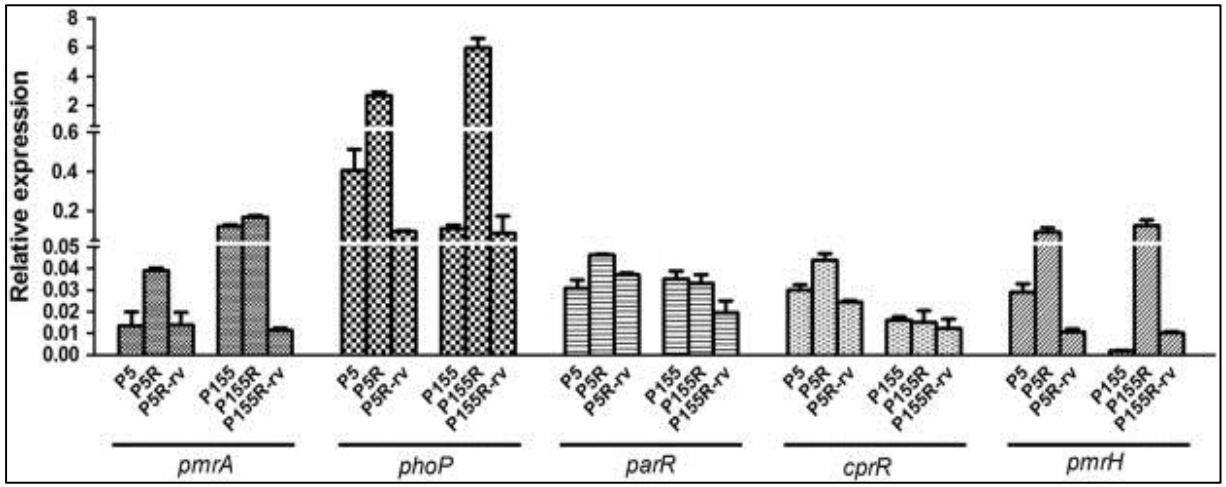
Figure 9. Insertion positions of different ISs. IS1 was found at upstream region of the *mgrB* gene, however other ISs, located into the gene

Ispir P, 2015

Mutations and expression of PmrAB and PhoPQ related with colistin resistance in Pseudomonas aeruginosa clinical isolates



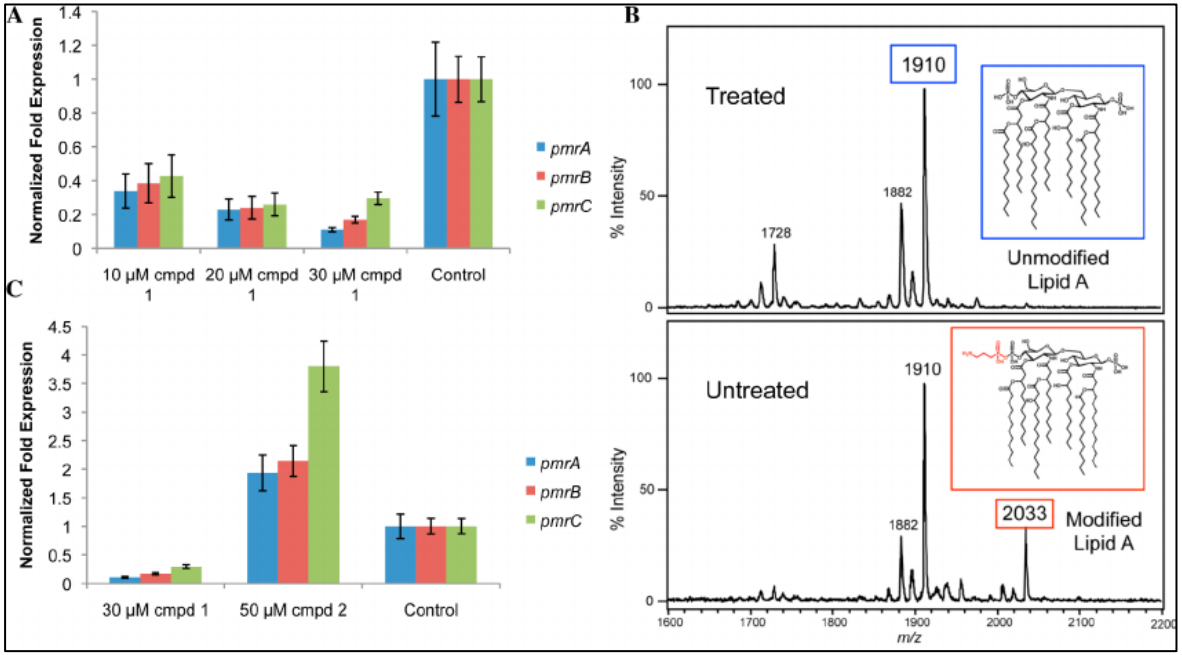
- 16 ColR ve 6 ColS izolat
- İzolatların cogunda pmrA ve pmrB relatif ekspresyon oranları yüksek



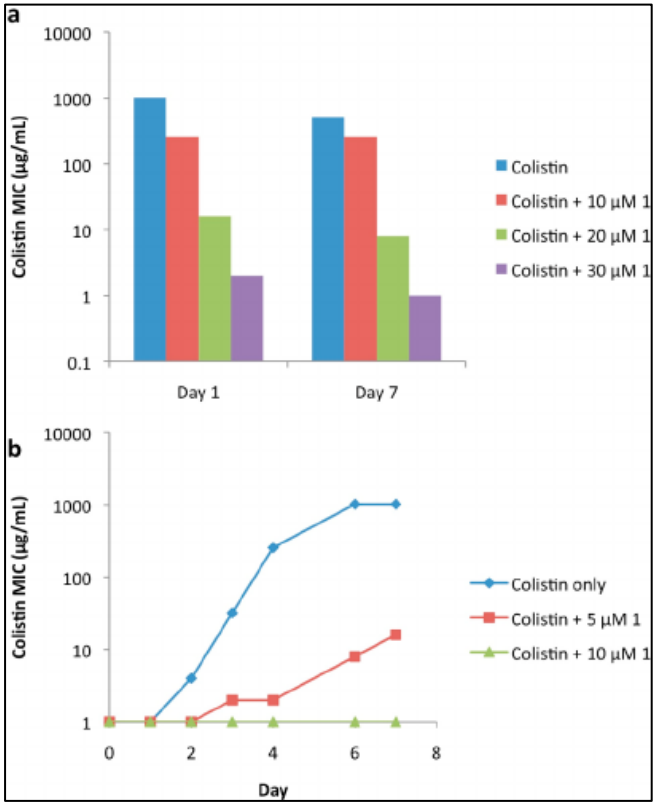
- 2 Duyarlı izolat (155 ve 5)
- Dirençli mutantları(P5R and P155R)
- Geri döndürülmüş mutantlar (155-rv, 5-rv)

Ji-Young Lee, Kwan Soo Ko, Diagn Microbiol and Infect Dis, 2014

Small Molecule Downregulation of PmrAB Reverses Lipid A Modification and Breaks Colistin Resistance



Lipid A yapısında değişim



Azalmış MİK

Harris T.L, ACS chemical biology, 2013

Risk Faktörleri

- Kolistin kullanımı
  - Kolistin dirençli bakteri ile kolonizasyon veya infeksiyon

Kontopidou F. ve ark.,Clin Microbiol İnfec 2009
Matthaiou DK ve ark. ,Crit Care Med 2000

- Sub-optimal doz veya uzamış monoterapi tedavi

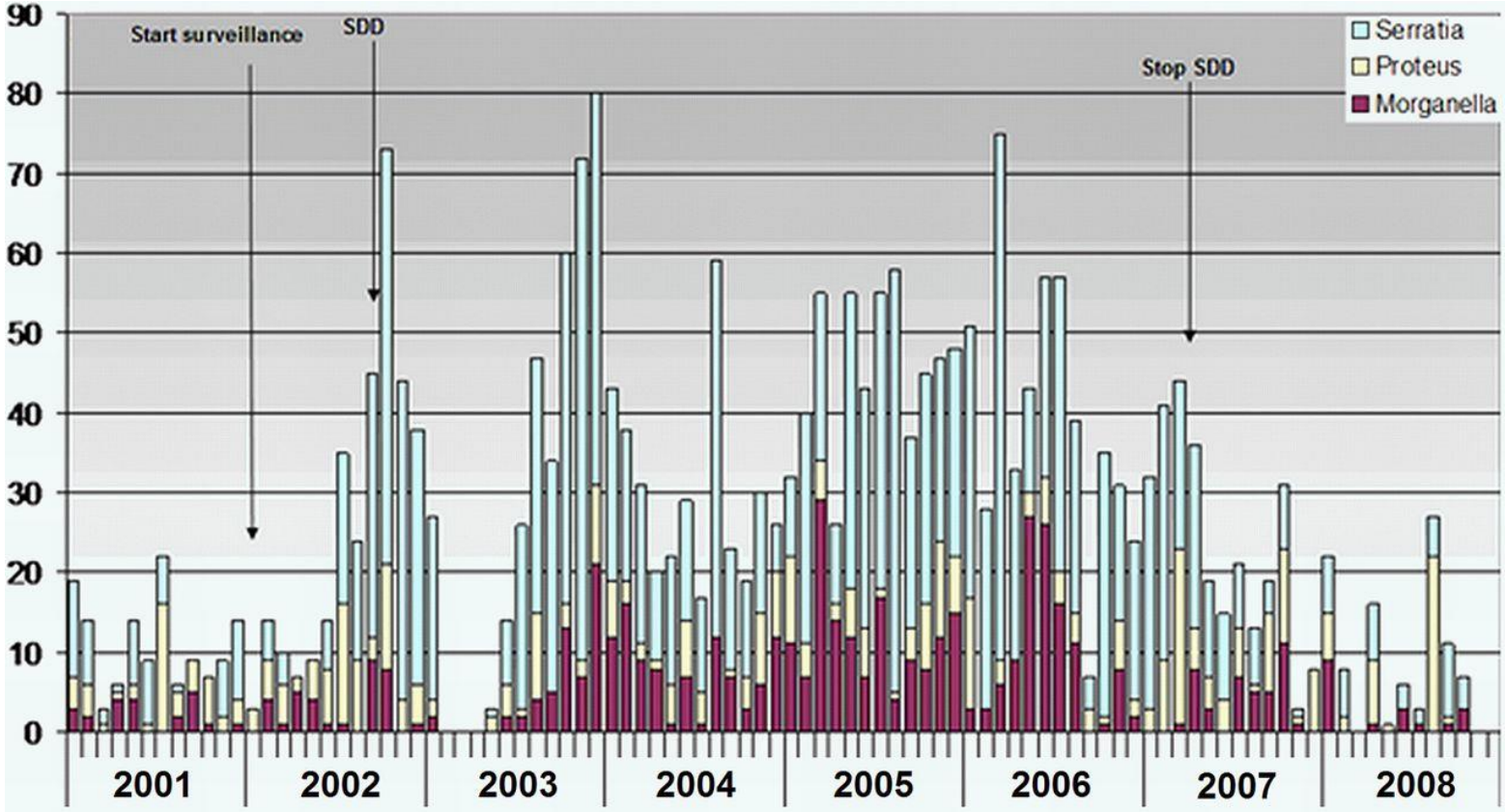
Poudyal A ve ark., JAC 2008

- Digestive sistem selektif dekontaminasyonu

Teysir Halaby et al., Antimicrob. Agents Chemother 2013

Ah YM, Int J Antimicrobial Agents, 2014

Emergence of Colistin Resistance in *Enterobacteriaceae* after the Introduction of Selective Digestive Tract Decontamination in an Intensive Care Unit



Monthly occurrence of CIR isolates (n = 2,572) between 2001 and 2008.

Direnç oranları %0-6 dan %55-69a çıkmış

Teysir Halaby et al. Antimicrob. Agents Chemother. 2013;57:3224-3229

Kolistin direnci ölümü belirleyen bağımsız risk faktörü

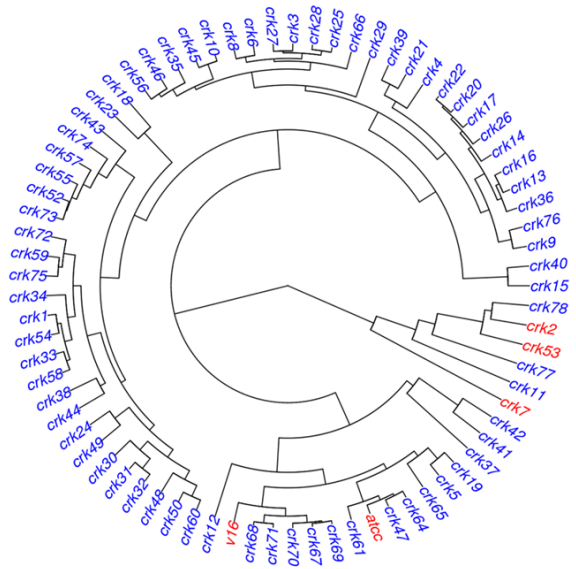
Multivariate analysis of risk factors for in-hospital mortality in patients with infection due carbapenem-resistant *Klebsiella pneumoniae* (CR-KP), adjusted for appropriate antibiotic treatment, combination therapy and removal of the infectious source

	OR (95% CI)	**p**
Charlson comorbidity score	1.42 (1.15–1.76)	0.001
Hospitalization in intensive-care unit	18.05 (3.90–83.51)	0.001
Bloodstream infection	4.92 (1.35–17.28)	0.01
Infection due to a colistin-resistant strain	**4.15 (1.17–14.74)**	**0.02**

- Kolistin dirençli K.pneumoniae %20-%100 mortalite
- İnfeksiyona bağlı ölüm oranı: %25-%71

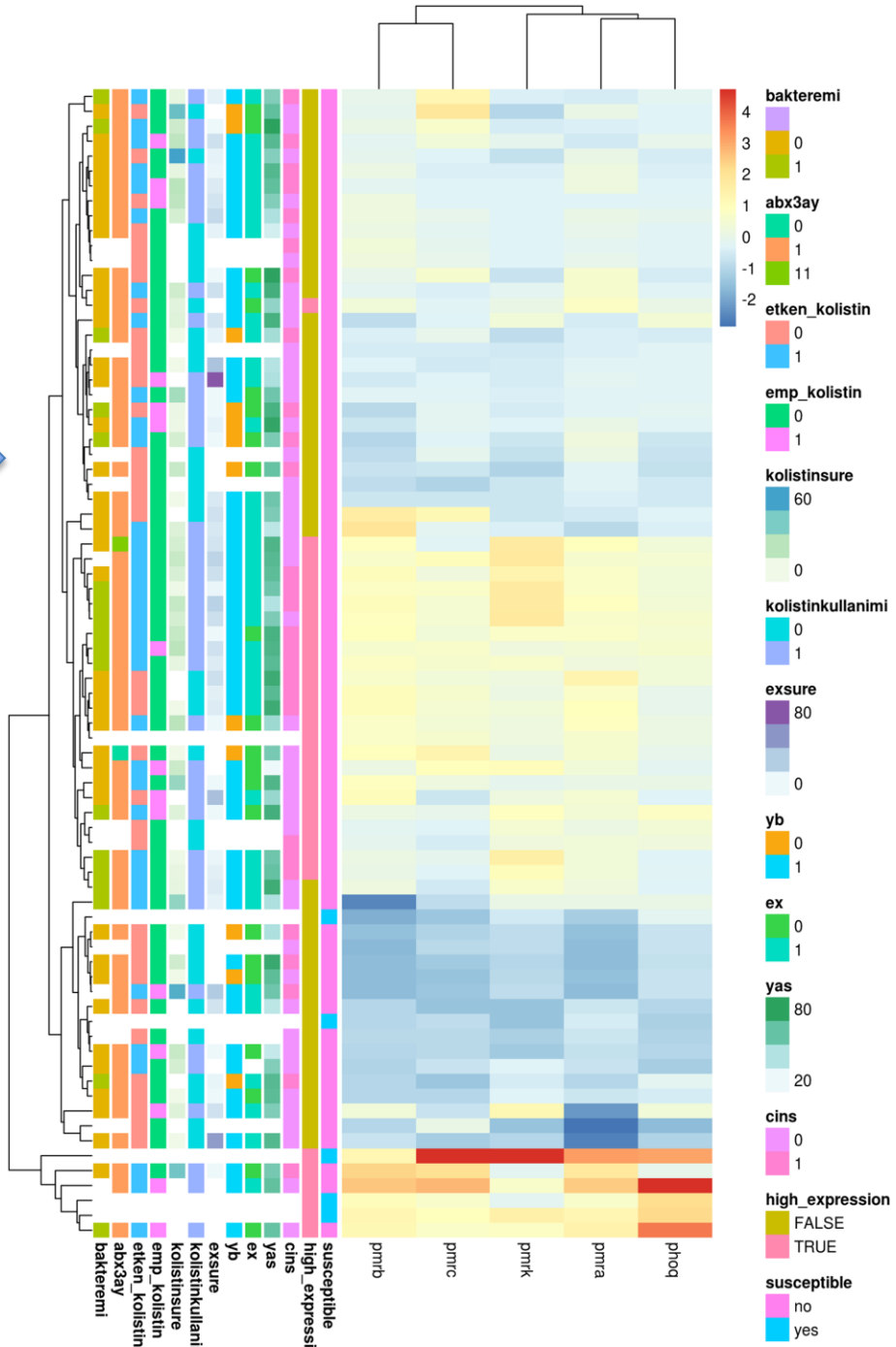
Capone A ve ark. CMI 2013

pmrABC ve PhoQ eskpresyonlarını etkileyen klinik faktörler



Ekspresyon Dendrogram

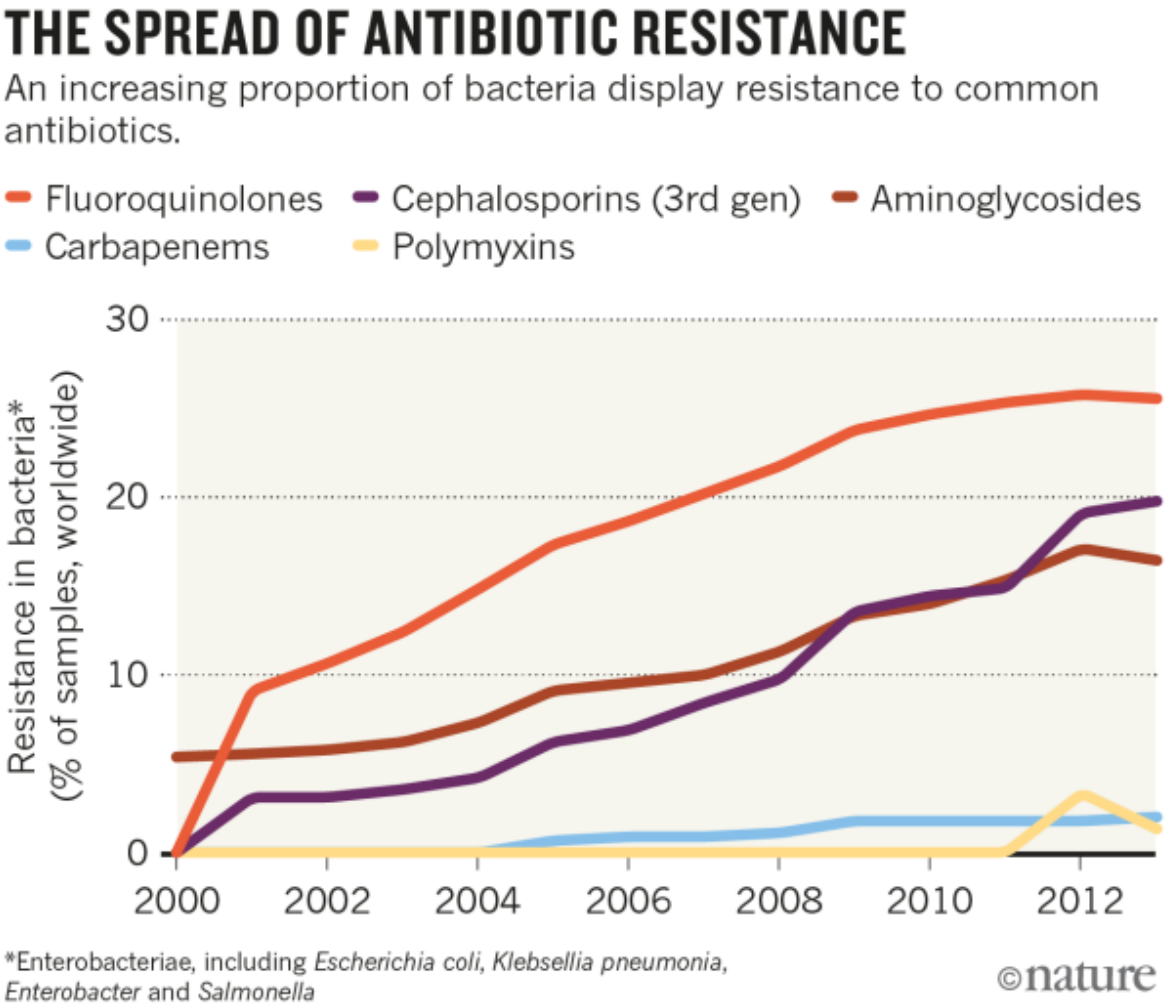
Kolistin Dirençli K.pneumoniae izolatlarında da kolistin kullanımı ile ekspresyon artıyor



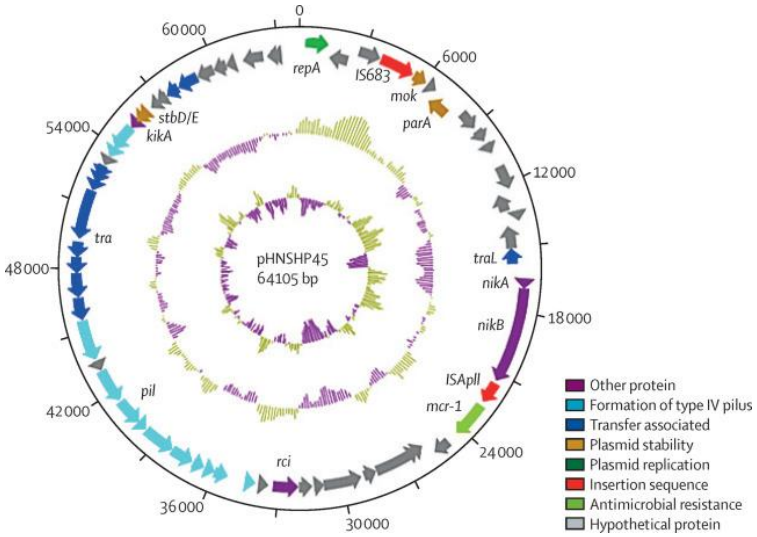
Karaarslan D.C ve ark., KLİMİK 2016

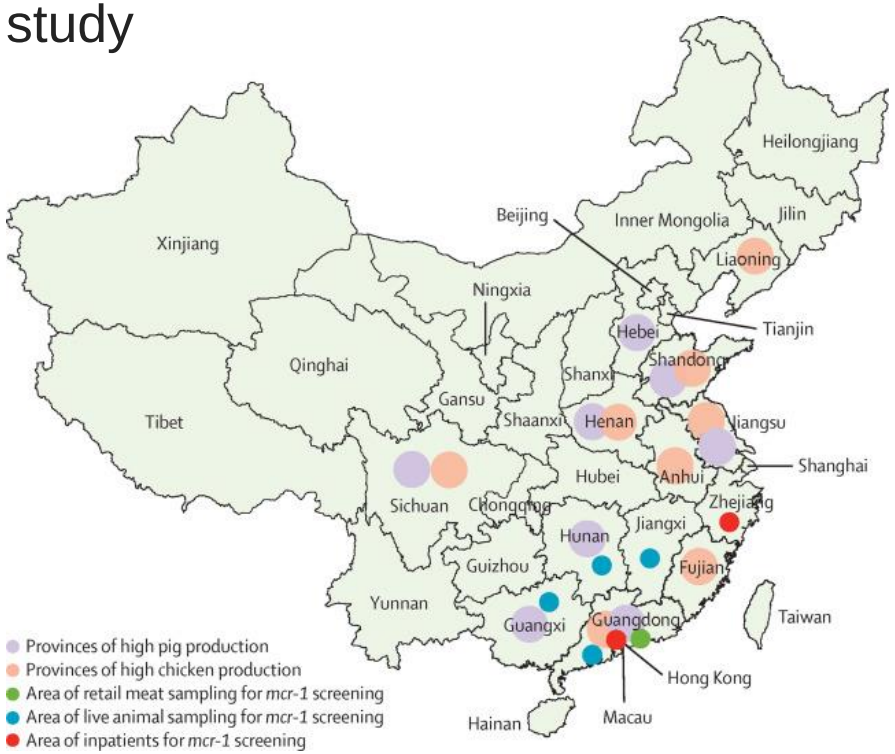
Spread of antibiotic-resistance gene does not spell bacterial apocalypse — yet

A ‘last resort’ drug to which bacteria are rapidly developing resistance is not quite the end of the antibiotic line.



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





- MCR-1 liphosphoethanolamine transferase ailesinden
- Lipid A'ya phosphoethanolamine eklenmesi
- Plazmidin E.coli'ye geçişi 10^{-1} to 10^{-3}
- *K pneumoniae* and *Pseudomonas aeruginosa*'da stabilite

- 523 et 78 (%15)
- 804 hayvan 166 (%21)
- 1322 hasta 16 (%1)

Liu YY ve ark. Lancet Infec Dis 2016

Possible genetic events producing colistin resistance gene *mcr-1*

	Biosample information				Species information, strain	Sequence information				
	Collection date	Sample origin	Isolation source	Biosample ID		RefSeq ID: *mcr-1* cds position	Length (bps)	pHNSHP45 14Kb block present?	ISA*pl1* upstream *mcr-1* gene?	ISA*pl1* in other contigs?
University of Malaya (Malaysia, Dec 09, 2014)	September, 2013	Selangor, Malaysia	Chicken liver	SAMN03256216	*Escherichia coli*, EC5	NZ_JWKF01000084.1: 4213-5838 (–)	16 531	Yes	No, but *nikB* gene	No
University of Malaya (Malaysia, Dec 9, 2014)	September, 2013	Selangor, Malaysia	Chicken spleen	SAMN03256224	*E coli*, EC7	NZ_JWKG01000081.1 10696-12321 (+)	16 534	Yes	No, but *nikB* gene	No
University of Malaya (Malaysia, Dec 9, 2014)	September, 2013	Selangor, Malaysia	Water	SAMN03256245	*E coli*, EC13	NZ_JUJZ01000081.1: 8977-10602 (–)	21 926	Yes	No, but *nikB* gene	No
University of Malaya (Malaysia, Dec 9, 2014)	September, 2013	Selangor, Malaysia	Chicken heart and liver	SAMN03256247	*E coli*, EC2_1	NZ_JWKJ01000115.1: 213-1838 (+)	8052	No	Yes, last 45 bp	Yes
University of Malaya (Malaysia, Dec 9, 2014)	September, 2013	Johor, Malaysia	Pig faecal swab	SAMN03256164	*E coli*, EC2	NZ_JWKC01000186.1: 817-2442 (–)	2648	Downstream *mcr-1* only	Yes, last 29 bp	Yes
University of Coimbra (Portugal, Dec 9, 2014)	June, 2011	Not reported	Food sample	SAMN03774870	*Salmonella enterica*, Sa 125	NZ_LFCC01000022.1: 285-1910 (+)	50 981	No	Yes, last 98 bp	Yes

bp=base pairs.

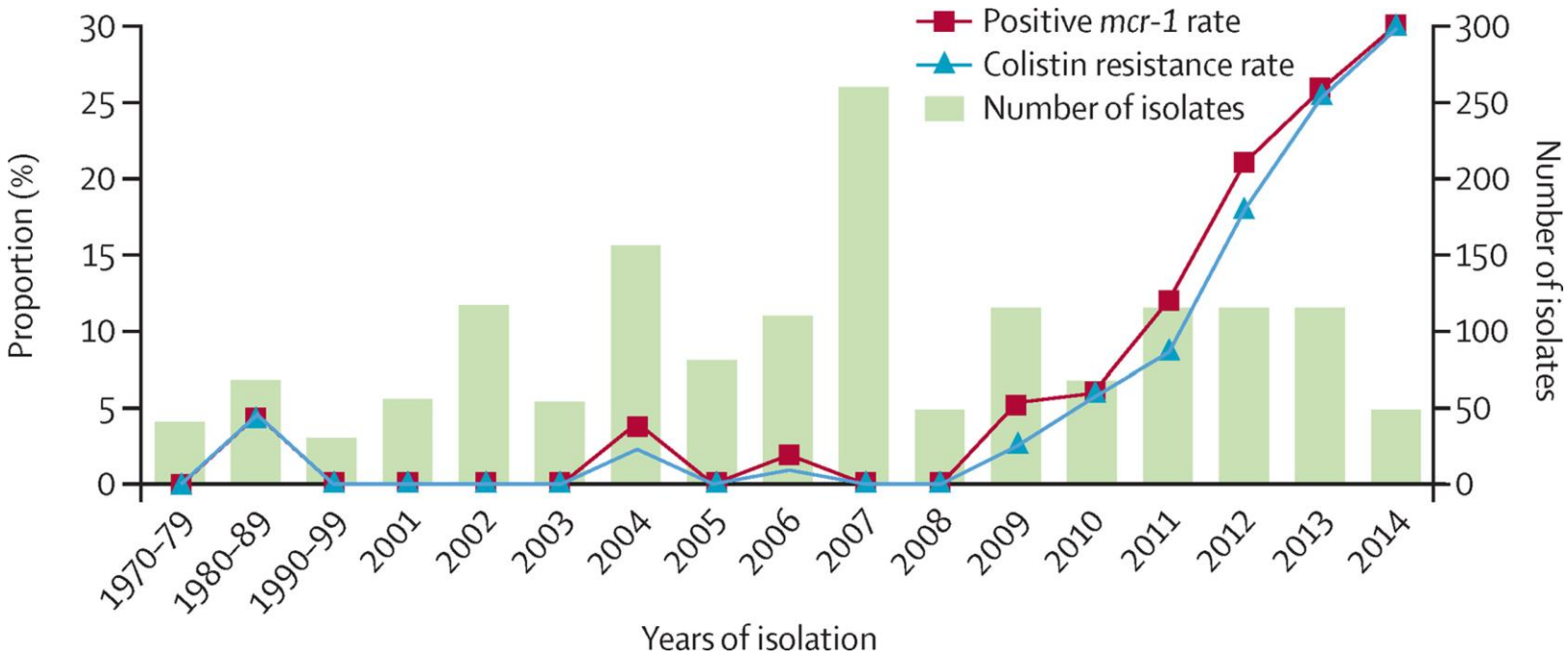
Table: **Summary information on the origin and features of identified sequences found in the NCBI RefSeq database as described in the text, by submitter (country, date)**

Malezya E.coli örnekleri ve portekizden salmonella

Mcr-1 tarihçesi eski olabilir

IS ile ilişkisi bulaşıcılığını artırdı

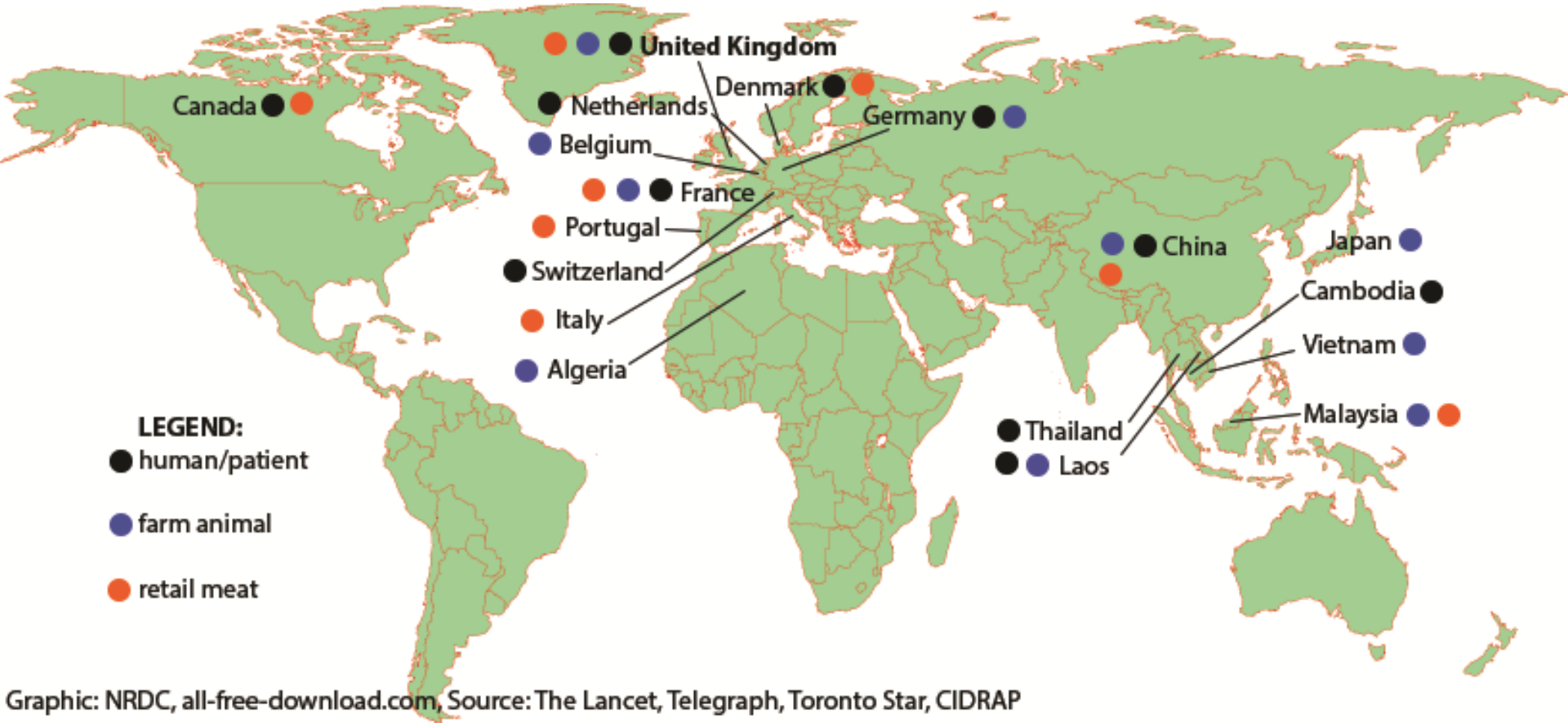
Petrillo M, Lancet Infec Dis, 2016



- Çin 1970-2014 yıllarında izole 1611 E.coli (Tavuk)
- 104 mcr-1pozitif
- %2 (2009)-%30 (2014)
- Kolistin direnci ve mcr-1 paralel artıyor

Shen Z ve ark, Lancet Infec Dis, 2016 march

Mcr-1 pozitif bakteri izole edilen ülkeler

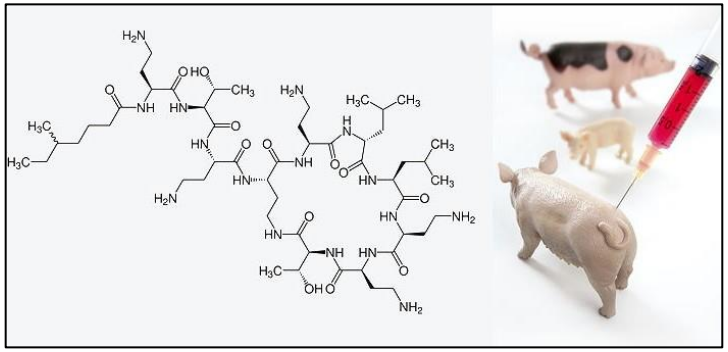


http://switchboard.nrdc.org/blogs/ccordova/were_losing_antibiotics_of_las.html

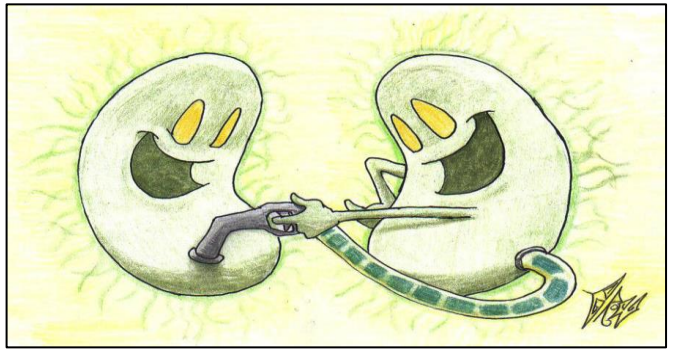
Plasmid-mediated carbapenem and colistin resistance in a clinical isolate of *Escherichia coli*

İsviçre

- 83 yaşında erkek hasta
- İdrar kültüründe kolistin ve karbapenem dirençli E.coli
  - İmipenem-Ertapenem-meropenem MİK=4
  - Kolistin MİK=4
  - Amikasin, tigesiklin ve fosfomisin duyarlı
    - Bla_{vim-1-}
    - mcr-1-
    - floR-florfenikol



Kolistin direnci gıda kaynaklı olabilir



Karbapenem ve kolistin direncinin enterik bakteriler arasında yayılma riski yüksek

Poirel L ve ark .2016 Lancet Infec Dis

Clonal transmission of a colistin-resistant Escherichia coli from a domesticated pig to a human in Laos.

- 190 sağlıklı birey ve 62 çiftlik hayvanı (keçi ve domuz) dışkı kültürü
- Kolistin drençli K.pneumoniae
  - 6 insan
  - 4 domuz

Olaitan AO, et al. *J Antimicrob Chemother* 2015;.

Mcr-1 türler arası geçişi

TABLE 1

Numbers of extended spectrum beta-lactamase and AmpC-producing *E. coli* isolates obtained and analysed by WGS from chicken meat, humans and carbapenemase-producing isolates from humans tested for *mcr-1* using ResFinder, Denmark, November 2015 (n=914)

Isolate origin	No. of isolates analysed by WGS	No. of sequences positive for *mcr-1*
ESBL- and AmpC-producing *E. coli* isolates from Danish chicken meat (2012–2014)	125	0
ESBL- and AmpC-producing *E. coli* isolates from imported chicken meat (2012–2014)	255	5
ESBL- and AmpC-producing *E. coli* isolates from human bloodstream infections (January 2014– beginning of November 2015)	417	1
Carbapenemase-producing isolates from humans (January 2014–beginning of November 2015)	117	0

ESBL: extended spectrum beta-lactamase; No: number; WGS: whole-genome sequence.

4 izolat incI2 replikon
1 izolat incX4 replikon

Türler arası geçiş

Hasman H, Eurosurveilence, Dec 2015

Kolistin direncinin horizontal geçişinde farklı mekanizmalar

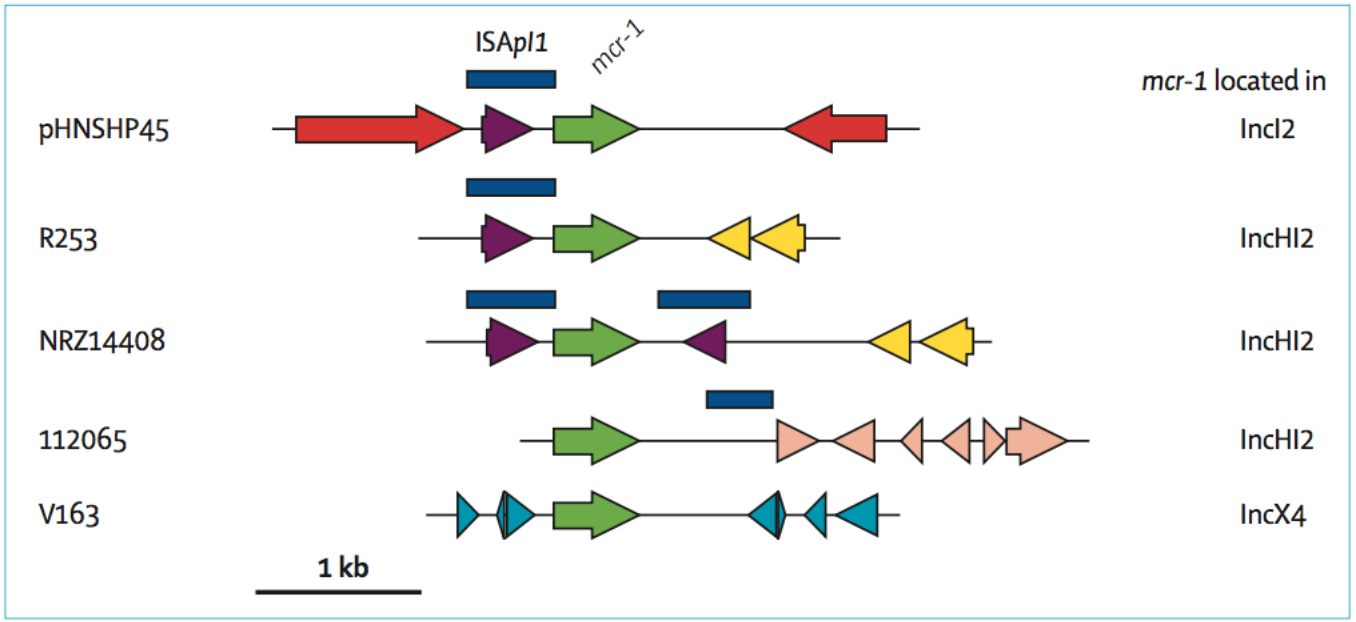


***Figure*: Gene environment surrounding *mcr-1* in 112065, V163, NRZ14408, and R253 compared with plasmid pHNSHP45**
Green arrows depict the *mcr-1* gene, ISA*pl1* is shown by a blue bar with the transposase marked in purple. Other colours refer to unrelated gene segments flanking the *mcr-1* gene.

Almanya,

- Hayvan, gıda ve insan kaynaklı 577 E.coli
- 4 mcr-1 pozitif
- Karbapenemaz pozitif

Antibiyotik seçemediğimiz hasta sayıları artacağa benziyor

Falgenhauer L, Lancet 2016 march

Sonuç olarak;

- Dirençli bakteriler sınırl tanımıyor, ulusal ve uluslararsı tehlike
- İsviçre'den bir çok ilaca dirençli E.coli ile infekte bir hastada veterinerlikte kullanılan florfenikol direnci olması hayvansal orjini gösteriyor
- Bu tablo hayvanlarda antibiyotik kullanımının kontrol altına alınması gerketiğinin göstergesi
- Her ülke kendi koşullarına göre strateji izlemeli


One World
ONE HEALTH