



Kolistin Direnci Nereye Gidiyor

Dr.Fusun CAN

Koç Üniversitesi Tıp Fakültesi

Tıbbi Mikrobiyoloji AD



Antibiyotik Direnci Küresel Problem



- Mortality 25.000 /yıl
- Maliyet 1.500.000.000 €



- Mortality 23.000/yıl
- Maliyet 35 .000.000.000 USD

Küresel Antibiyotik Direnci



2050 Yılı

10m

ölüm



Maliyet

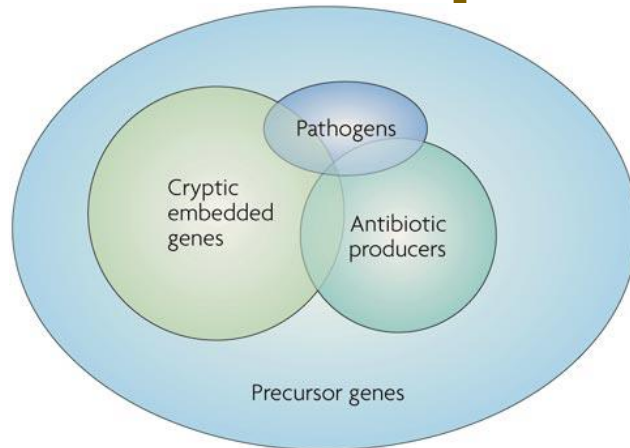
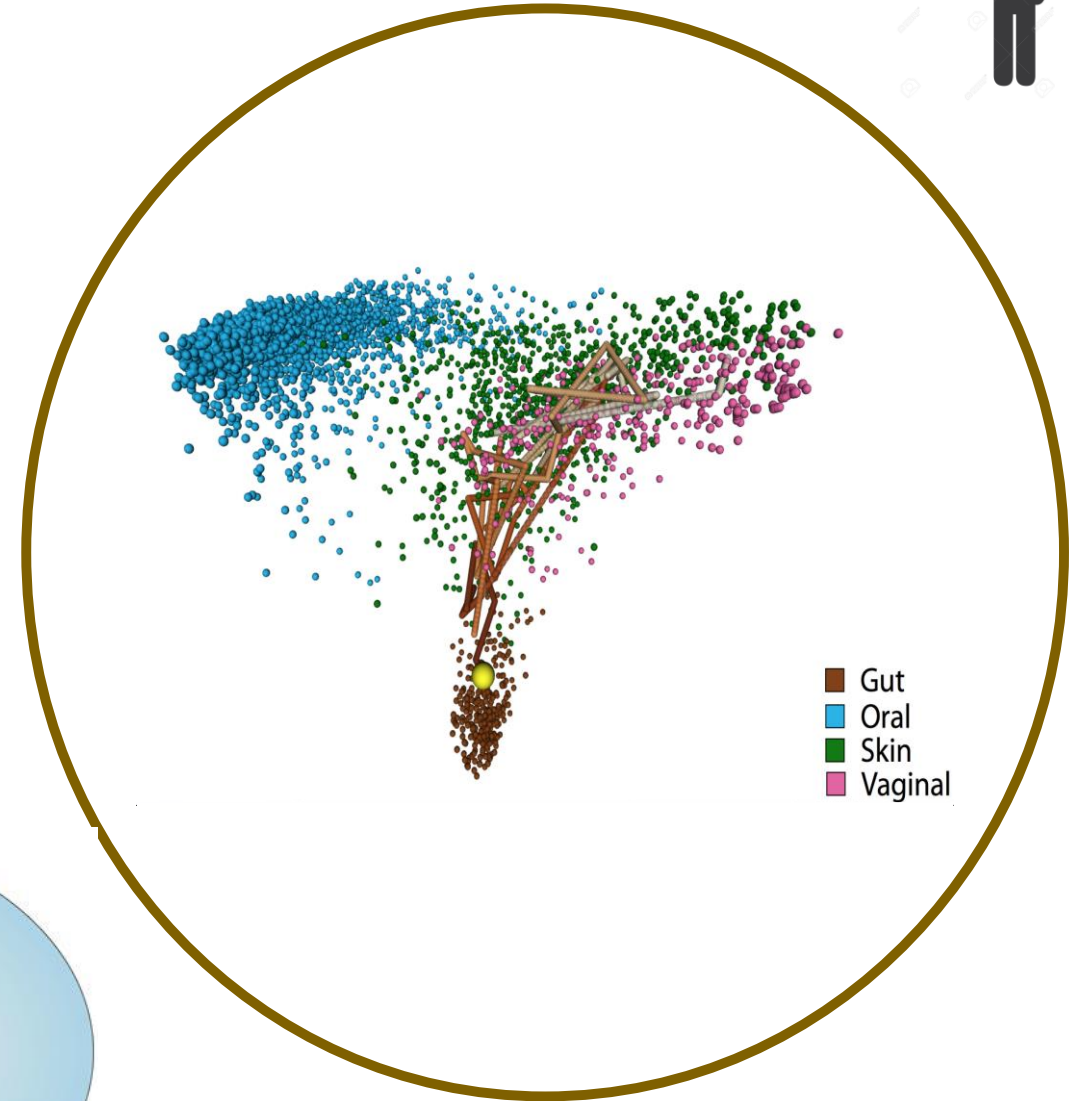
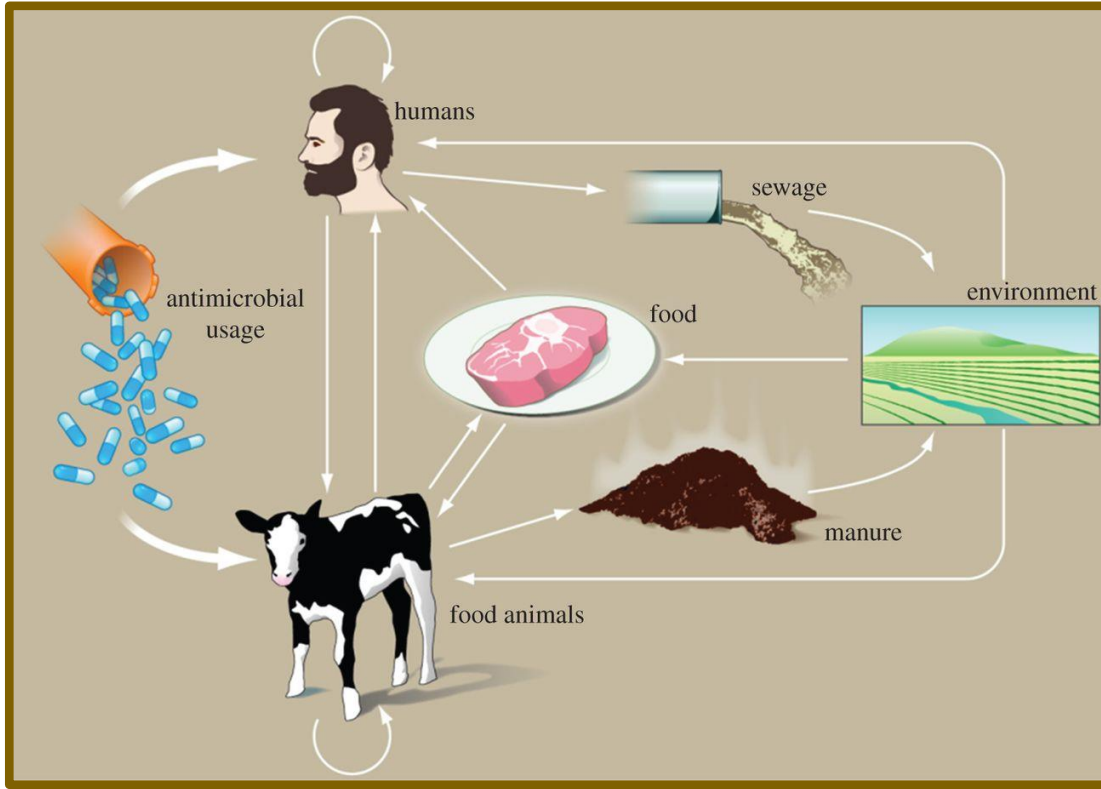
66 trilyon

Euro

Pre-antibiyotik Era nedir???



Antibiyotik Direnci Tüketimin Artmasına Bağlı Artıyor



**A defined daily dose (DDD) of antibiotics
per 1000 people**



İngiltere



Türkiye

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*, Yang Wang*, Timothy R Walsh, Ling-Xian Yi, Rong Zhang, James Spencer, Yohei Doi, Guobao Tian, Baolei Dong, Xianhui Huang, Lin-Feng Yu, Danxia Gu, Hongwei Ren, Xiaojie Chen, Luchao Lv, Dandan He, Hongwei Zhou, Zisen Liang, Jian-Hua Liu, Jianzhong Shen

Summary

Background Until now, polymyxin resistance has involved chromosomal mutations but has never been reported via horizontal gene transfer. During a routine surveillance project on antimicrobial resistance in commensal *Escherichia coli* from food animals in China, a major increase of colistin resistance was observed. When an *E coli* strain, SHP45, possessing colistin resistance that could be transferred to another strain, was isolated from a pig, we conducted further analysis of possible plasmid-mediated polymyxin resistance. Herein, we report the emergence of the first plasmid-mediated polymyxin resistance mechanism, MCR-1, in Enterobacteriaceae.

Methods The *mcr-1* gene in *E coli* strain SHP45 was identified by whole plasmid sequencing and subcloning. MCR-1 mechanistic studies were done with sequence comparisons, homology modelling, and electrospray ionisation mass spectrometry. The prevalence of *mcr-1* was investigated in *E coli* and *Klebsiella pneumoniae* strains collected from five provinces between April, 2011, and November, 2014. The ability of MCR-1 to confer polymyxin resistance in vivo was examined in a murine thigh model.

Findings Polymyxin resistance was shown to be singularly due to the plasmid-mediated *mcr-1* gene. The plasmid carrying *mcr-1* was mobilised to an *E coli* recipient at a frequency of 10^{-1} to 10^{-3} cells per recipient cell by conjugation, and maintained in *K pneumoniae* and *Pseudomonas aeruginosa*. In an in-vivo model, production of MCR-1 negated the efficacy of colistin. MCR-1 is a member of the phosphoethanolamine transferase enzyme family, with expression in *E coli* resulting in the addition of phosphoethanolamine to lipid A. We observed *mcr-1* carriage in *E coli* isolates collected from 78 (15%) of 523 samples of raw meat and 166 (21%) of 804 animals during 2011–14, and 16 (1%) of 1322 samples from inpatients with infection.

Interpretation The emergence of MCR-1 heralds the breach of the last group of antibiotics, polymyxins, by plasmid-mediated resistance. Although currently confined to China, MCR-1 is likely to emulate other global resistance mechanisms such as NDM-1. Our findings emphasise the urgent need for coordinated global action in the fight against pan-drug-resistant Gram-negative bacteria.

Lancet Infect Dis 2015

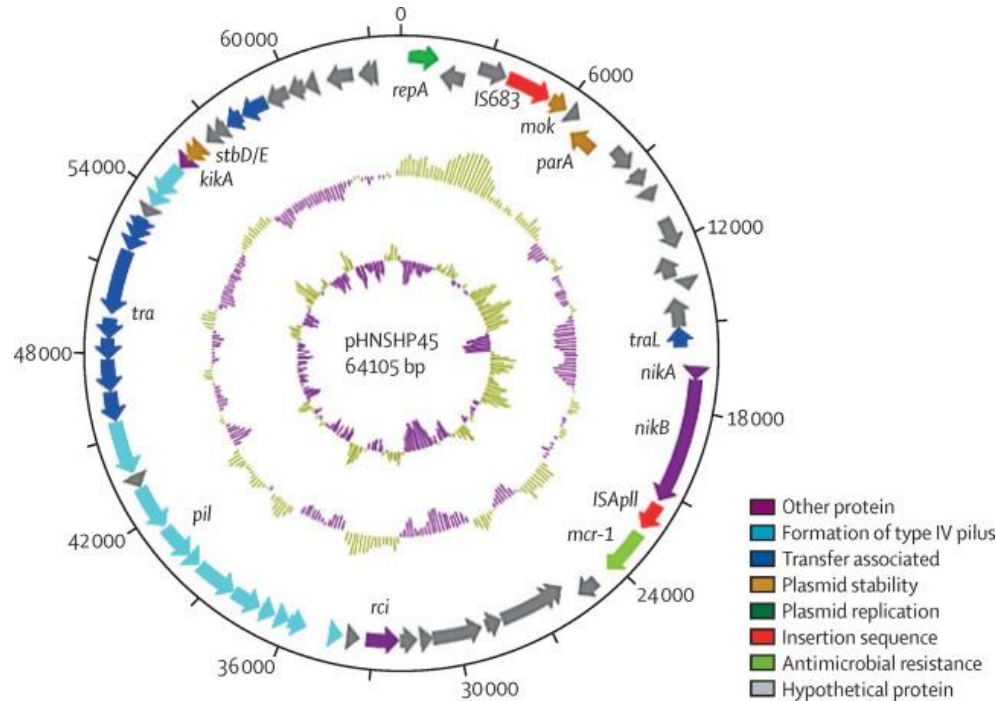
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See Online/Articles
[http://dx.doi.org/10.1016/S1473-3099\(15\)00463-6](http://dx.doi.org/10.1016/S1473-3099(15)00463-6)

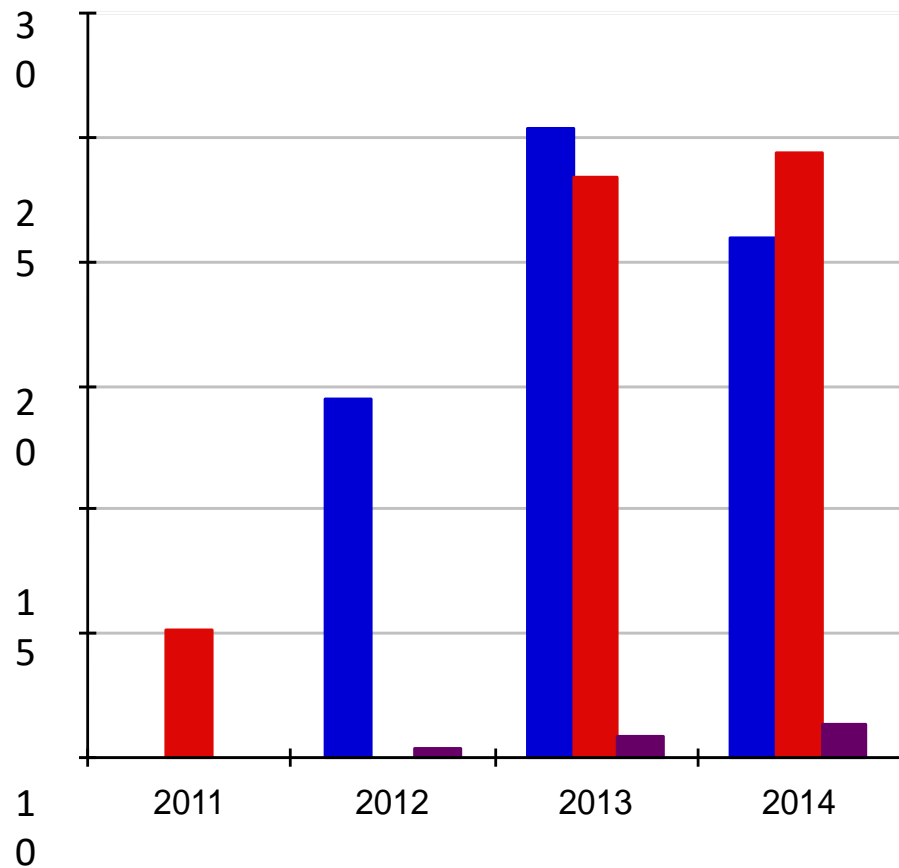
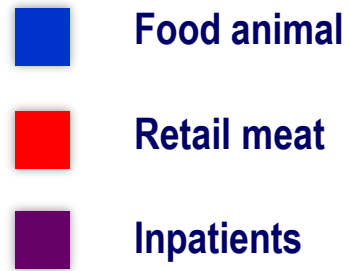
*Contributed equally

College of Veterinary Medicine, National Risk Assessment Laboratory for Antimicrobial Resistance of Microorganisms in Animals, South China Agricultural University, Guangzhou, China (Y-Y Liu BS, L-X Yi BS, X Huang PhD, L-F Yu BS, X Chen MS, L Lv MS, D He MS, Prof Z Liang MS, Prof J-H Liu PhD); Beijing Advanced Innovation Center for Food Nutrition and Human Health, College of Veterinary Medicine, China Agricultural University, Beijing, China (Y Wang PhD, B Dong BS, H Ren BS, Prof J Shen PhD); Department of Medical Microbiology and Infectious Disease, Institute of Infection

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

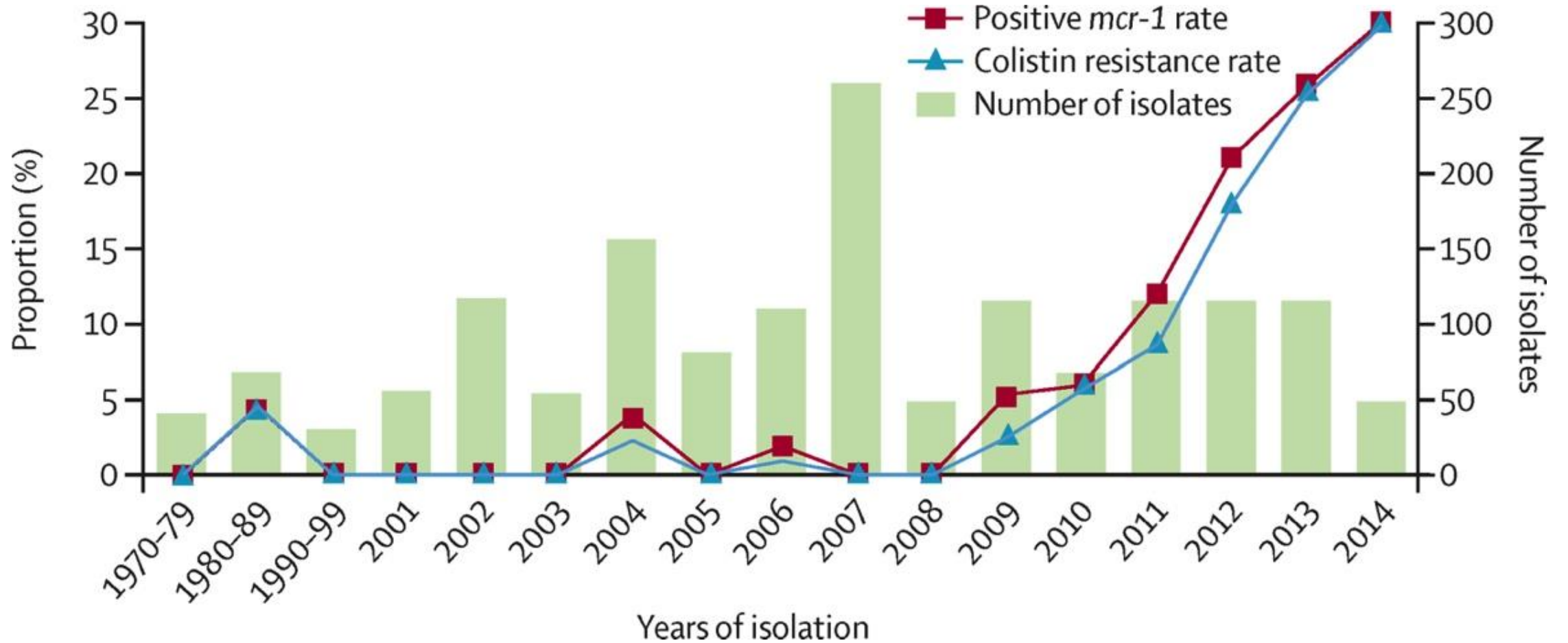


- MCR-1 liposhoethanolamine transferase ailesinden
- Lipid A'ya phosphoethanolamine eklenmesi
- Plazmidin E.coli'ye geçişi 10^{-1} to 10^{-3}



	Year	Positive isolates (%) / number of isolates
<i>Escherichia coli</i>		
Pigs at slaughter	All	166 (20.6%) / 804
Pigs at slaughter	2012	31 (14.4%) / 216
Pigs at slaughter	2013	68 (25.4%) / 268
Pigs at slaughter	2014	67 (20.9%) / 320
Retail meat	All	78 (14.9%) / 523
Chicken	2011	10 (4.9%) / 206
Pork	2011	3 (6.3%) / 48
Chicken	2013	4 (25.0%) / 16
Pork	2013	11 (22.9%) / 48
Chicken	2014	21 (28.0%) / 75
Pork	2014	29 (22.3%) / 130
Inpatient	2014	13 (1.4%) / 902
<i>Klebsiella pneumoniae</i>		
Inpatient	2014	3 (0.7%) / 420

Table 2: Prevalence of colistin resistance gene *mcr-1* by origin

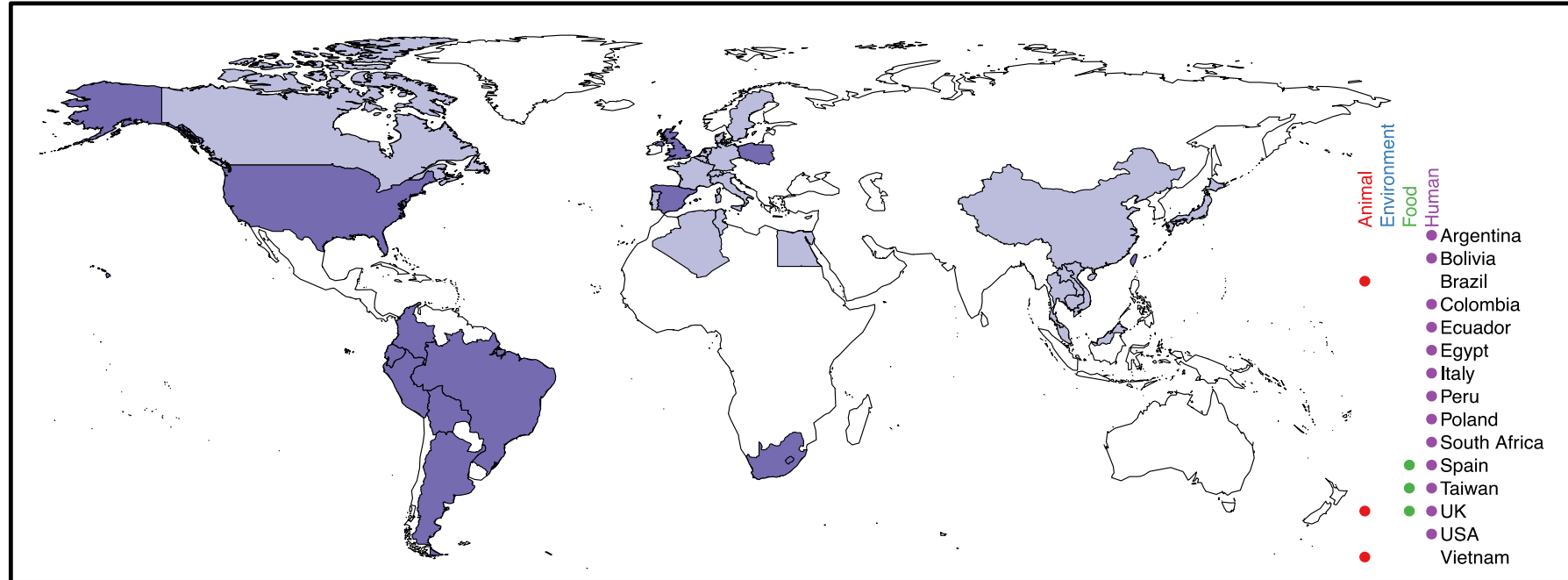


- Çin 1970-2014 yıllarında izole 1611 E.coli (Tavuk)
- 104 *mcr-1*pozitif
- %2 (2009)-%30 (2014)
- Kolistin direnci ve *mcr-1* paralel artıyor

Dünyada *mcr-1* yayılımı



Aralık 2015-Mart 2016

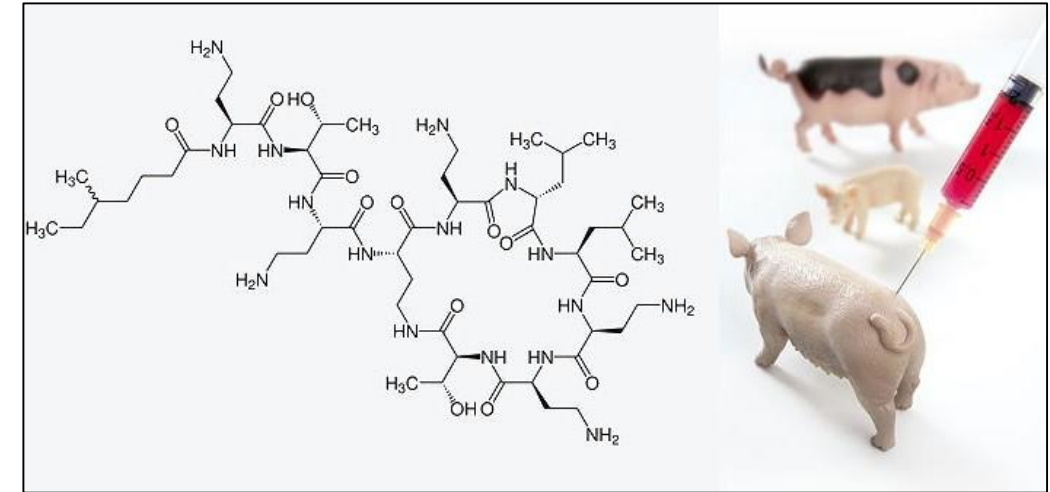


Mart 2016-Temmuz 2016

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

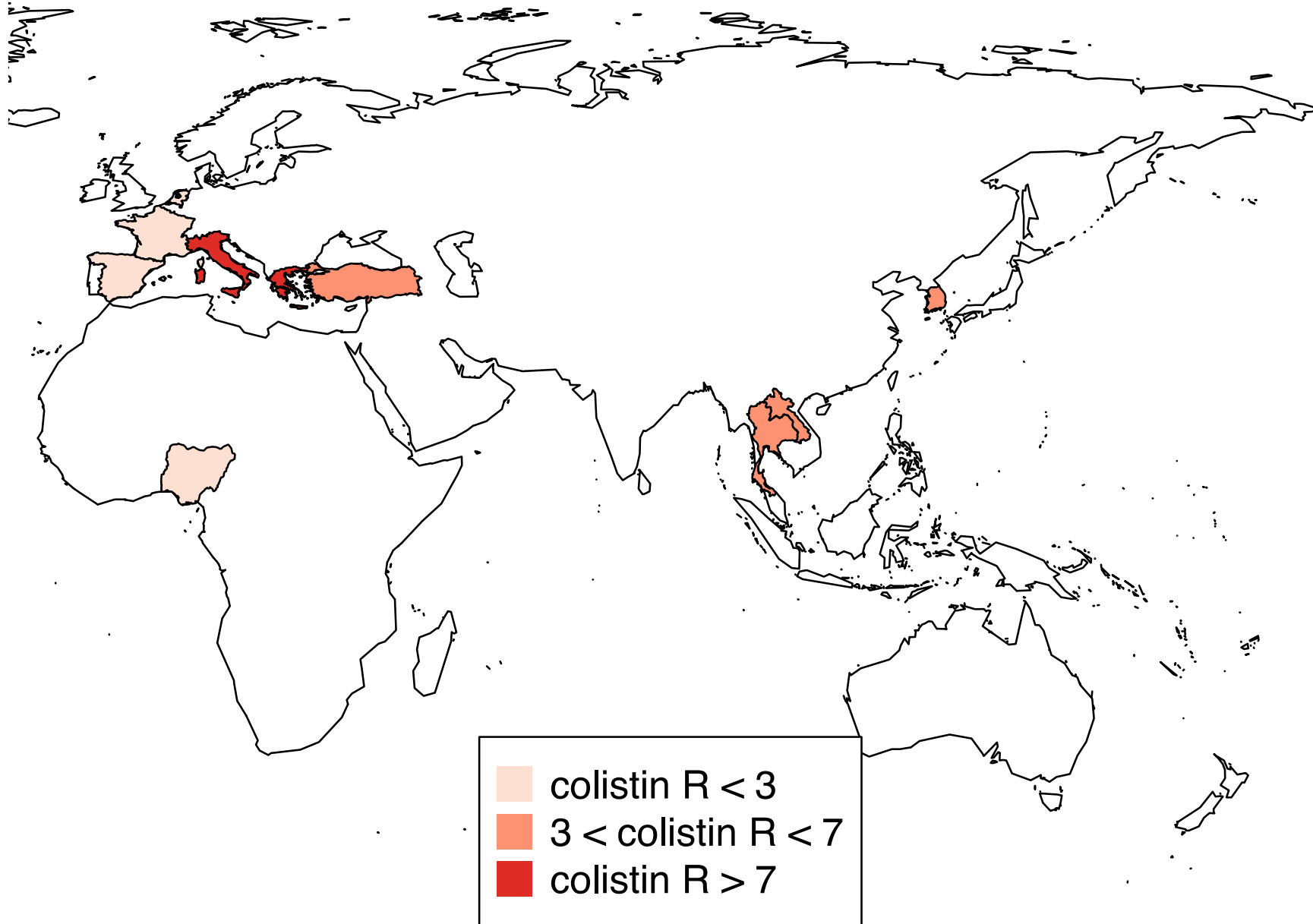
İsviçre

- 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

Emerging Colistin Resistance: What is the Clinical Impact of Increased Awareness?



Ergonul O., Can F ve ark

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

- Karbapenem dirençli Klebsiella suşlarında %0-2,7

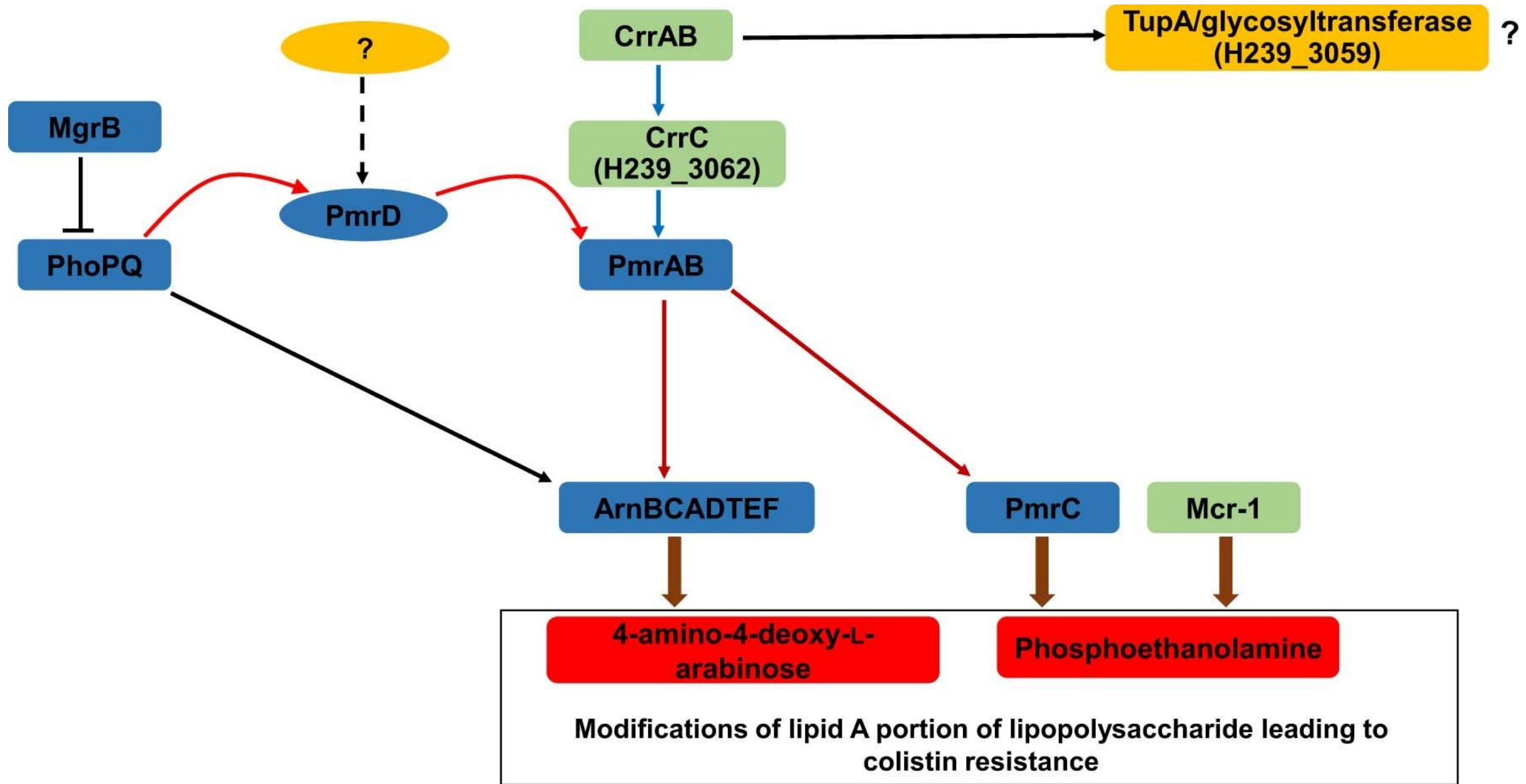
Dizbay ve ark., 2014; Iraz ve ark., 2015)

- Klebsiella suşlarında %7

Ergönül ve ark., 2016

- Çok ilaca dirençli Pseudomonas suşlarında % 0-1.7

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



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

[Tommaso Giania](#), [Fabio Arena](#), [Guendalina Vaggelli](#), [Viola Contea](#), [Adriana Chiarellia](#), [Lucia Henrici De Angelis](#), [Rossella Fornaini](#), [Maddalena Grazzini](#), [Fabrizio Niccolini](#), [Patrizia Pecile](#) and [Gian Maria Rossolini](#) ^{b, e, f}

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

MgrB Gene Analysis

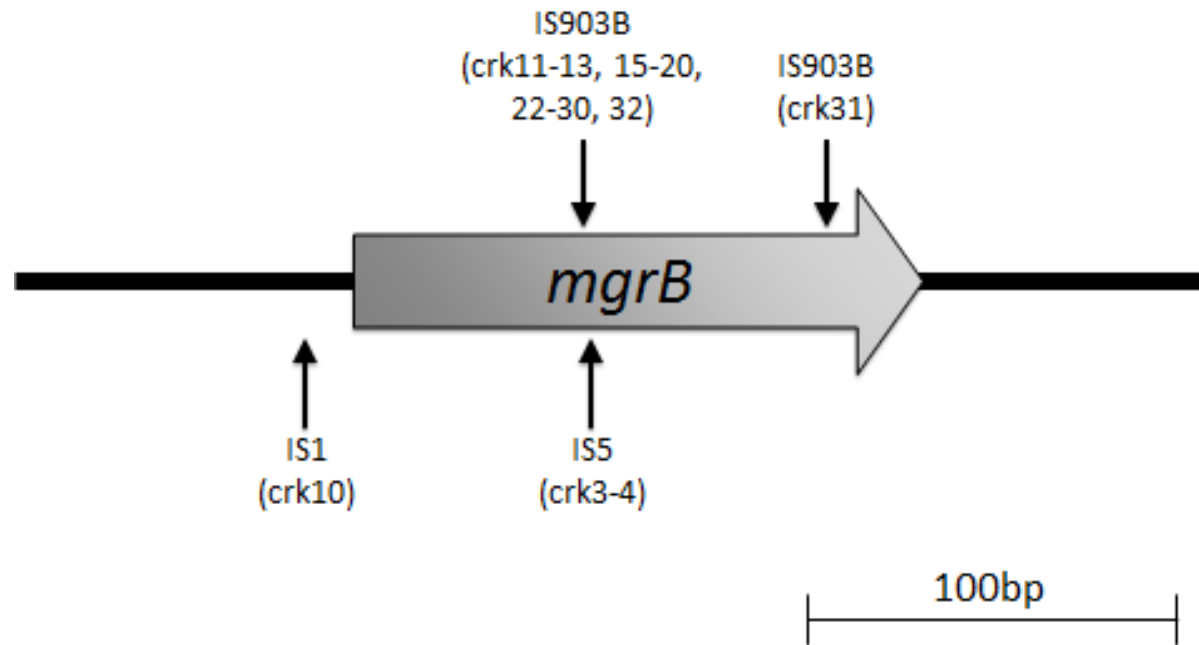
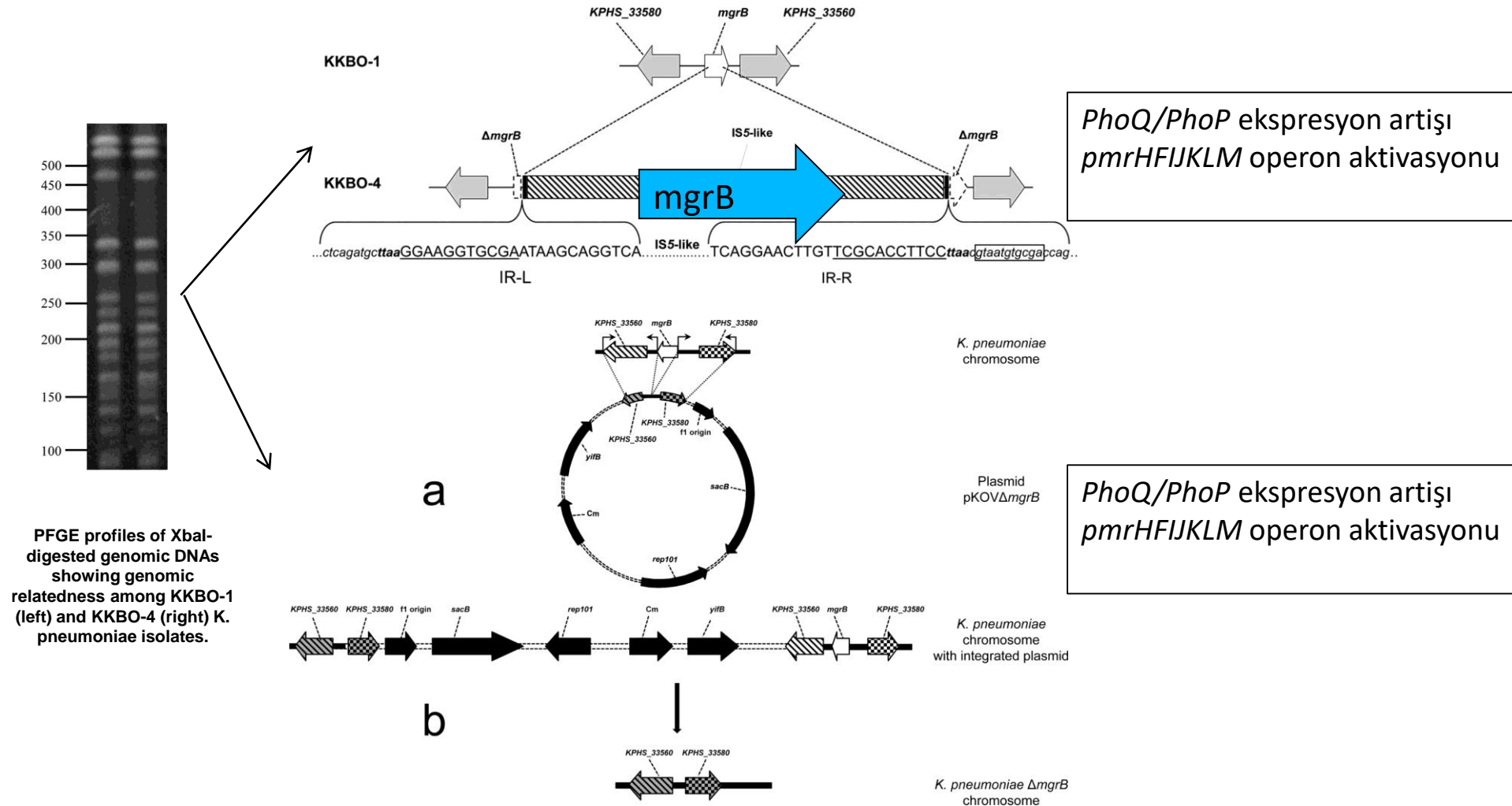
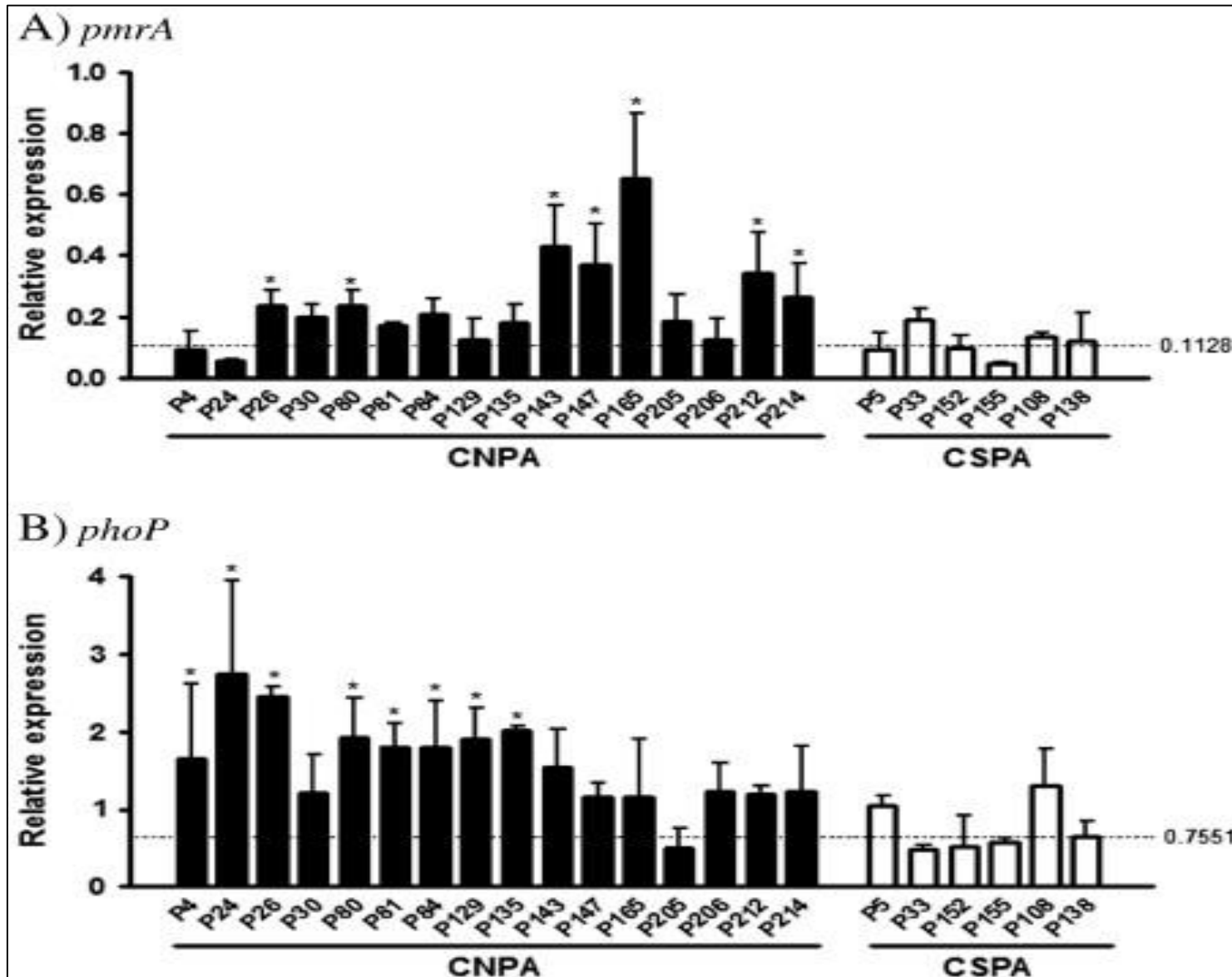


Figure 9. Insertion positions of different ISs. IS1 was found at upstream region of the *mgrB* gene, however other ISs, located into the gene

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



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



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

Colistin Direnci Risk Faktörleri

- Kolistin kullanımı
 - Kolistin dirençli bakteri ile kolonizasyon veya infeksiyon

Kontopidou F. ve ark., Clin Microbiol Infec 2009

[Matthaiou](#) DK ve ark. , Crit Care Med 2000

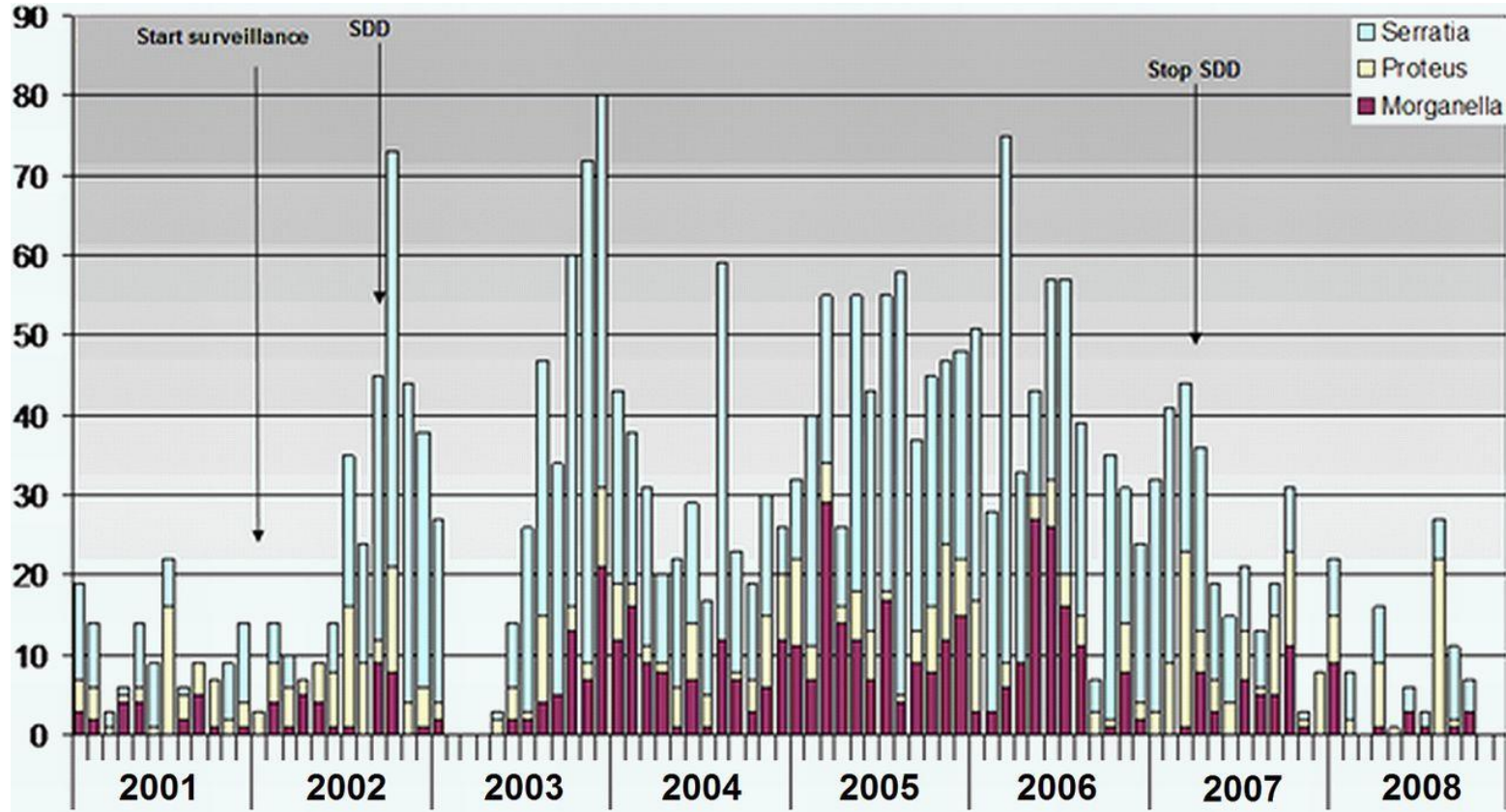
- Sub-optimal doz veya uzamış monoterapi tedavisi

Poudyal A ve ark., JAC 2008

- Digestive sistem selektif dekontaminasyonu

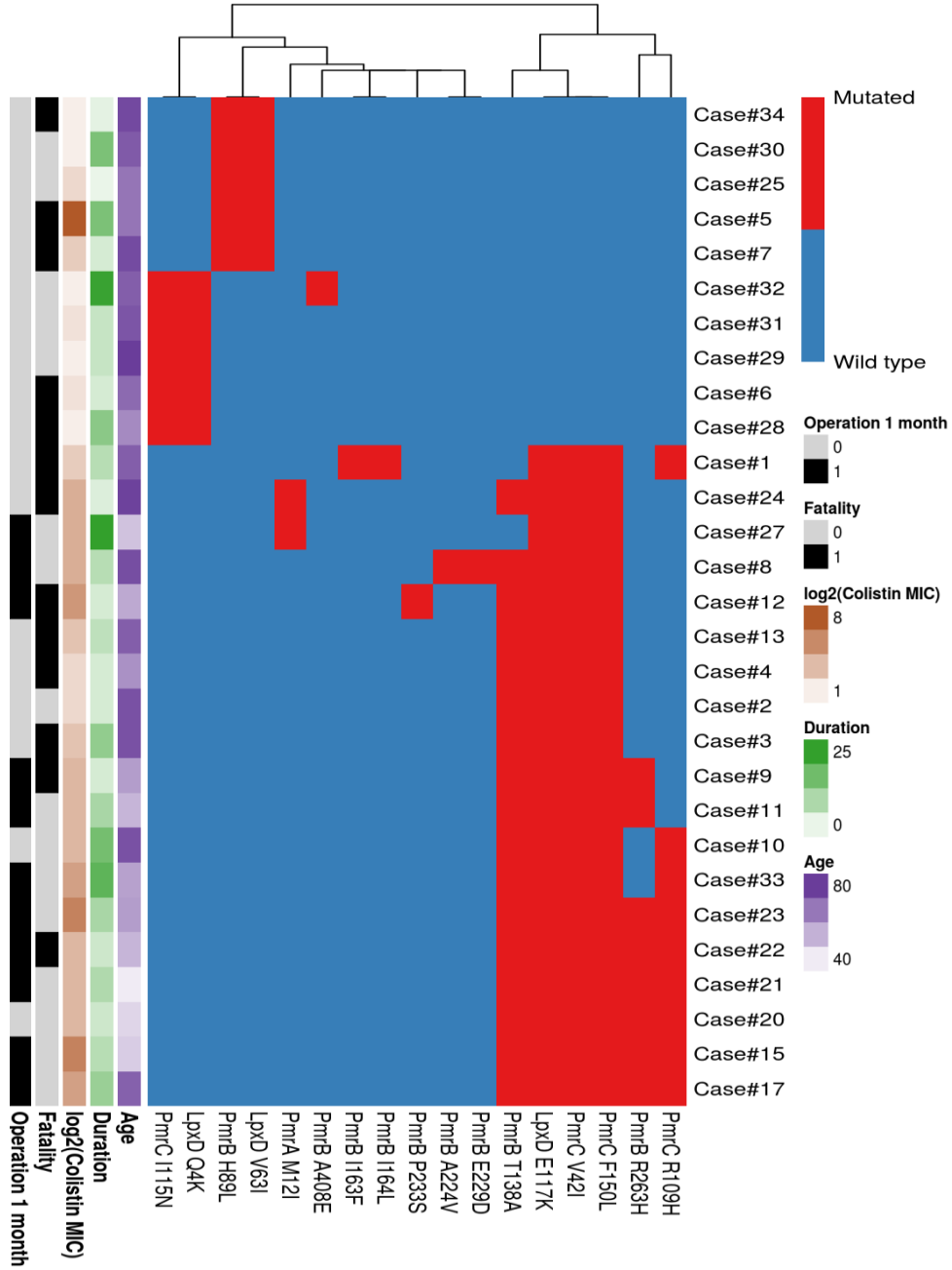
Teysir Halaby et al., Antimicrob. Agents Chemother 2013

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



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

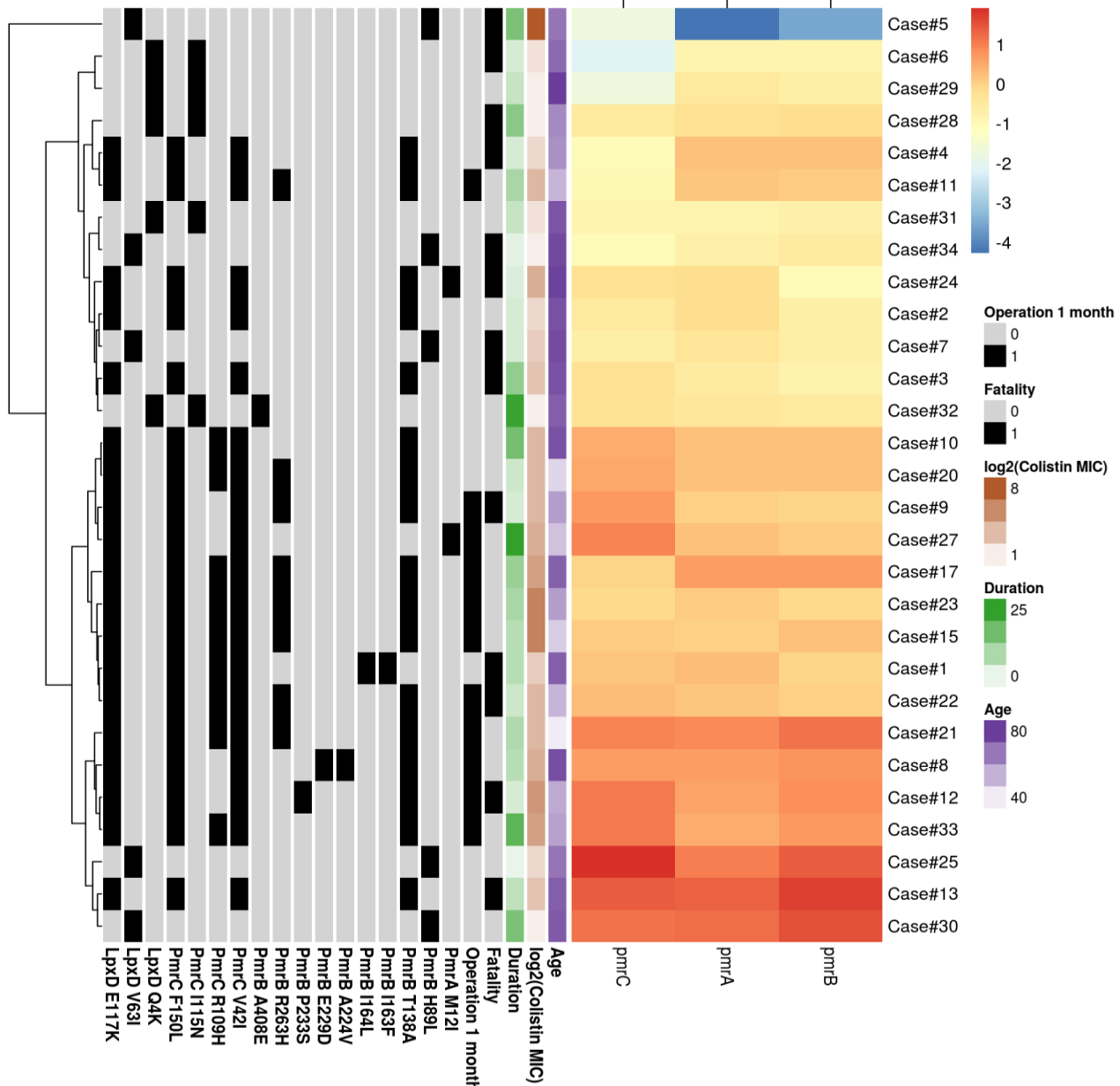
Acinetobacter baumannii Kolistin Direncine Neden Olan Mutasyonlar



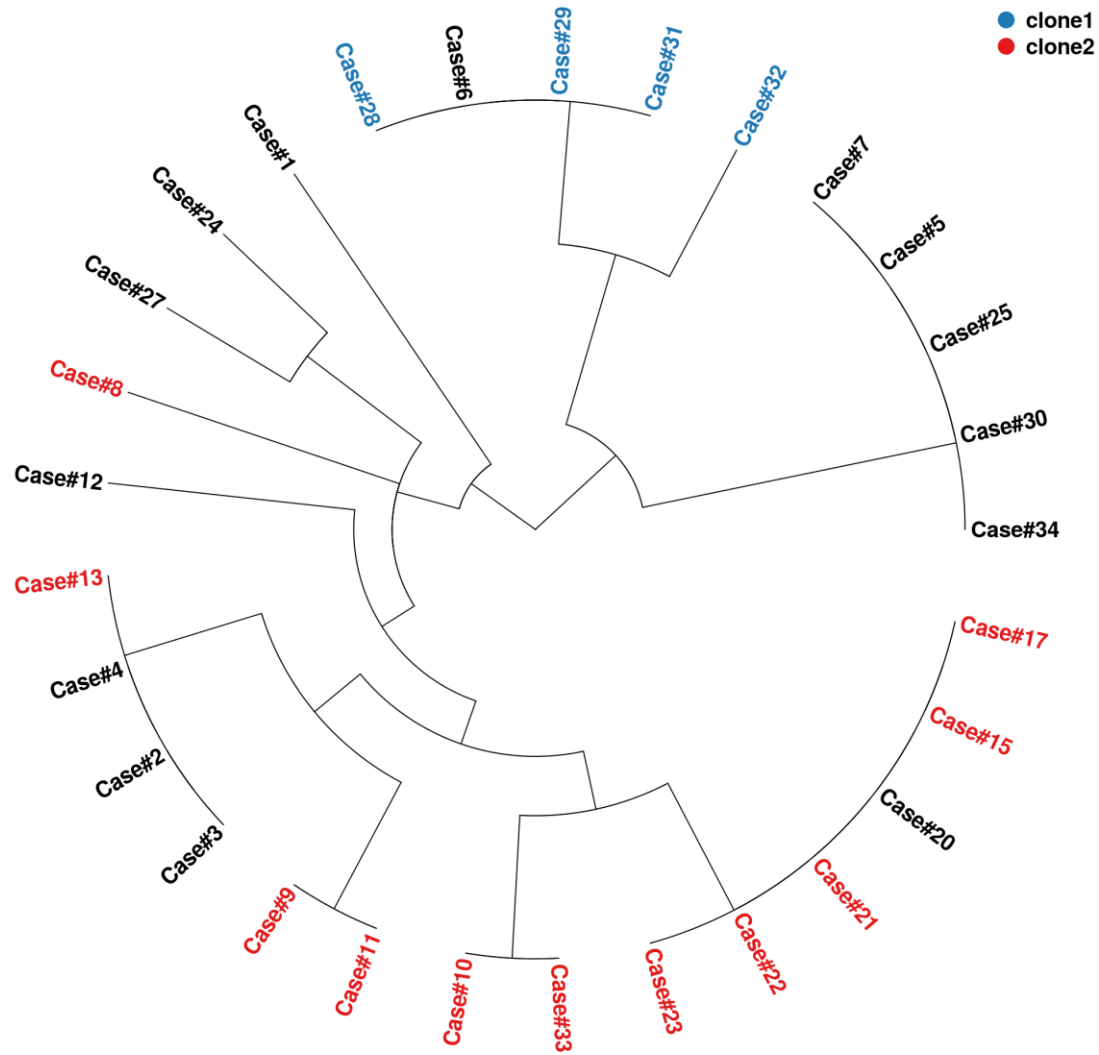
	n=29 (%)
Mean age (min, max)	67 (32-88)
Female gender	17 (58)
Being in ICU	29 (100)
Operation within the last month	11 (38)
Colistin use	28 (96)
Mean duration of colistin therapy	8 days (0-25)
Fatal cases	13 (45)

- PmrC V42I, PmrC F150L, ve LpxD E117K mutasyonları
 - Mutasyonlar ile yüksek MiK
- Operasyon son 1 ay**

pmrA, pmrB ve pmrC gen ekspresyonları

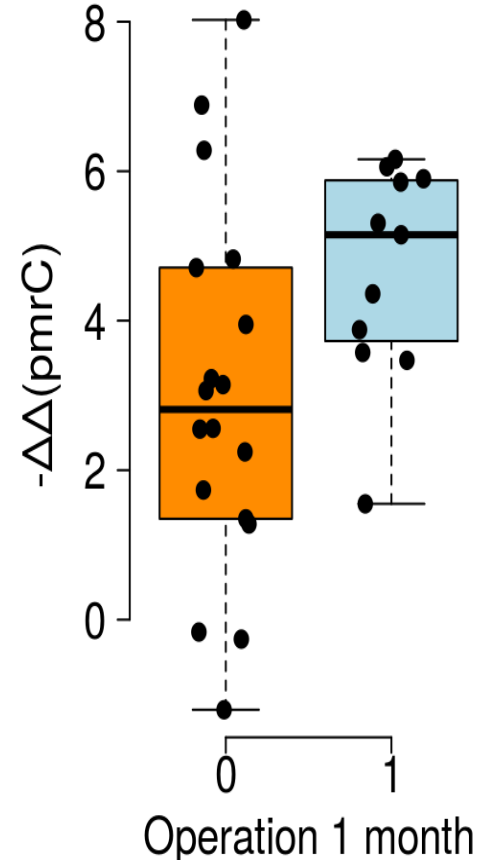
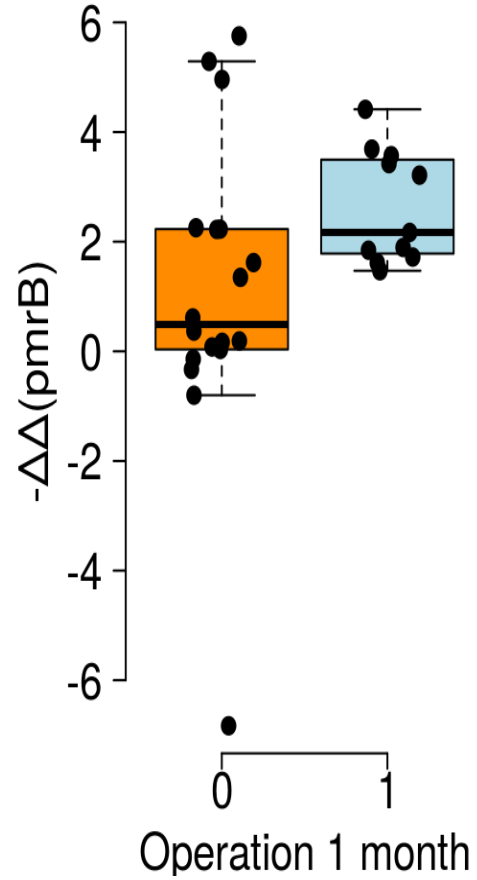
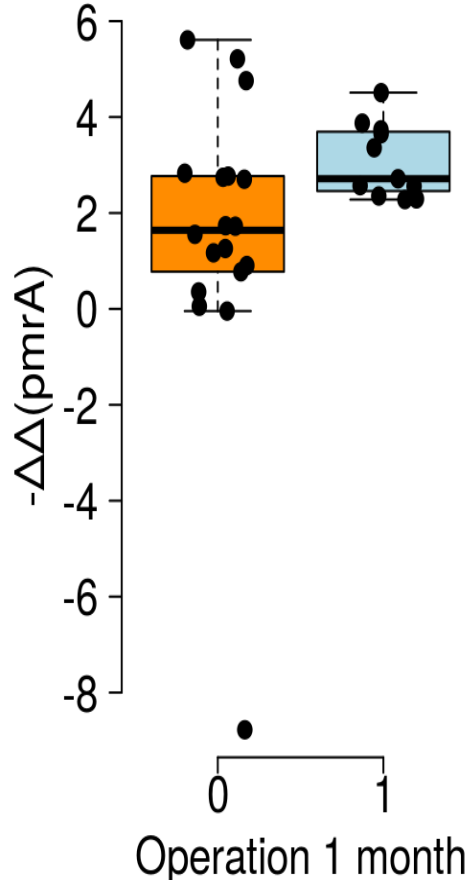


- *pmrA* ve *pmrB* gen ekspresyon paternleri benzer
- Mutasyonlar ekspresyonu artırıyor
- Ekspresyon artışı ile Kolistin MIC artıyor
- Son 1 ay operasyon olanlarda ekspresyon yüksek

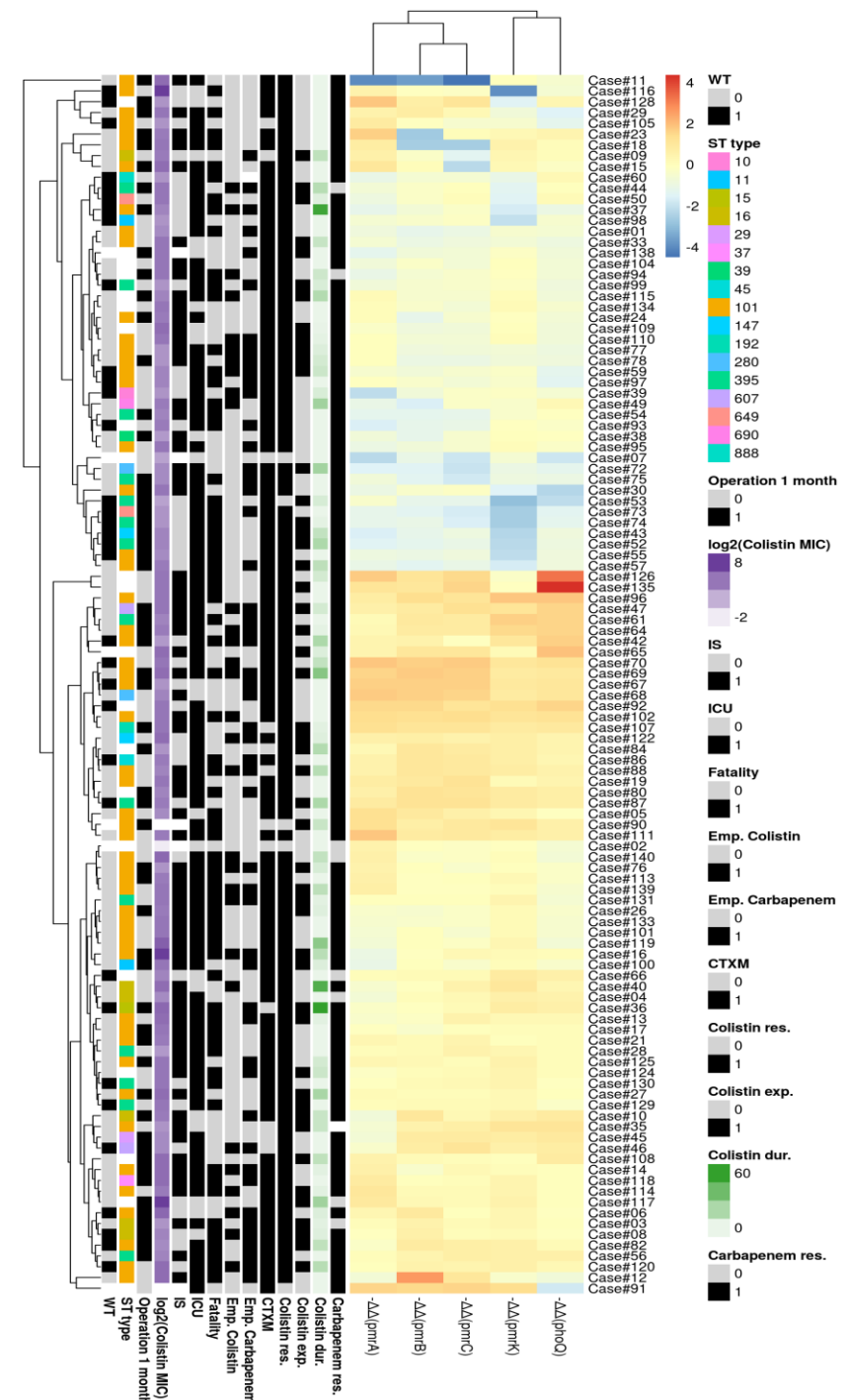
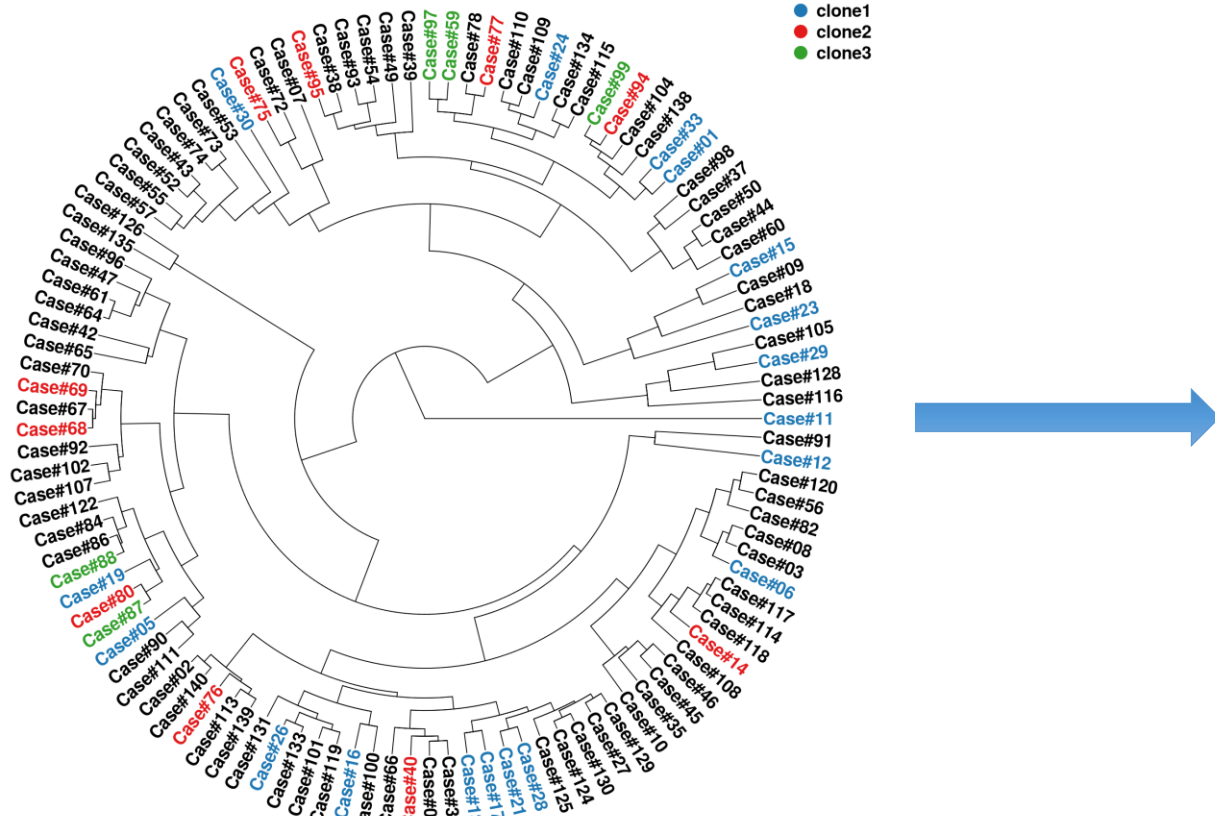


Klonların ekspresyonu farklı

Operasyon ve ekspresyon deęiřimi



Klebsiella pneumoniae pmrABC ve PhoQ espresyonlarını etkileyen klinik faktörler



Kolistin Dirençli *K.pneumoniae* izolatlarında da kolistin kullanım süresi uzadıkça ekspresyon artıyor

Sonuç olarak;

- Dirençli bakteriler sınır tanımıyor, ulusal ve uluslararası tehlike
- Kolistin Direnci artan kullanıma bağlı olarak artıyor
- Gıdalar ile ilişkili olabilir
- Bu tablo antibiyotik kullanımının kontrol altına alınması gerektiğinin göstergesi
- **Antimikrobiyal yönetim uygulamaları zorunlu**
- Her ülke kendi koşullarına göre strateji izlemeli

One World
ONE HEALTH

