Antimicrobial Resistance in Turkey and Emerging Colistin Resistance

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Outlines

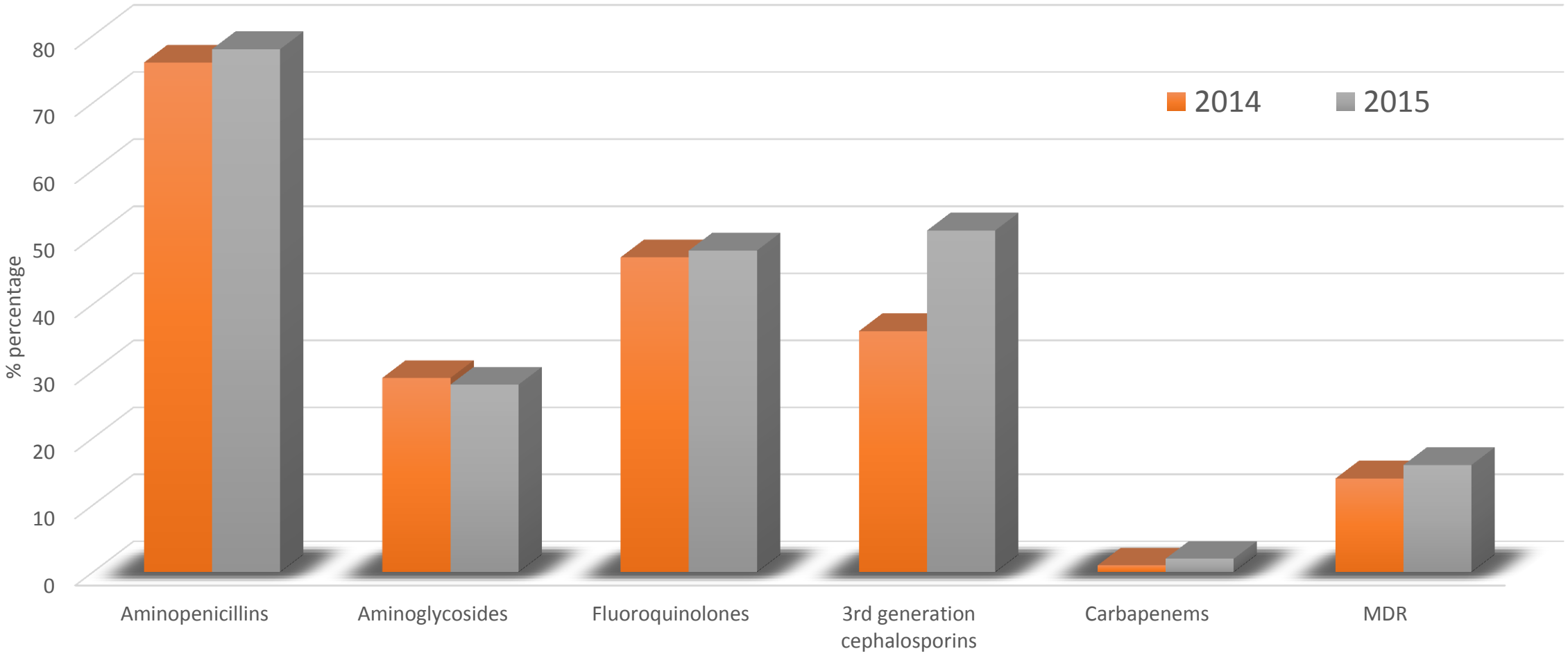
- Resistance Data of Turkey
- Prevalence of colistin resistance
- Colistin resistance mechanisms
- Outcomes of colistin resistance

Antibiotic resistance in Turkey

- Turkey ranks high among countries where antibiotic resistance is rising
- Antibiotic consumption is 42 DDD/1000
- In 2003, Nationwide antibiotic restriction program
  - Approval of infectious disease specialists
  - Short term
    - decline in DDD and cost savings
  - Long term
    - Gram negative resistance problem became more significant

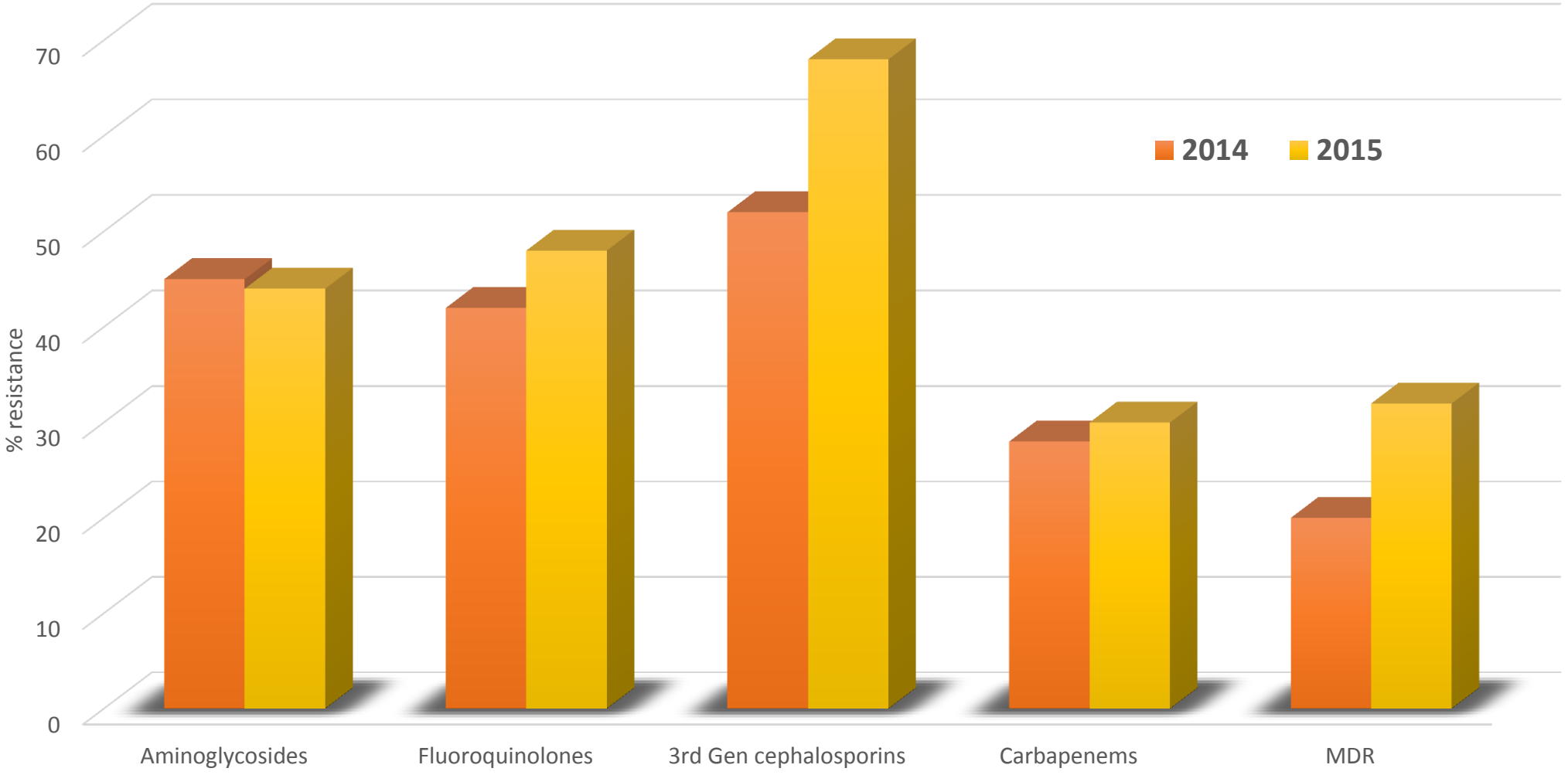
Akıcı A, et al. National Drug Consumption Surveillance-2011, Ministry of Health-2015

Percentage of resistance for E.coli among blood and CSF isolates in Turkey in 2014 and 2015



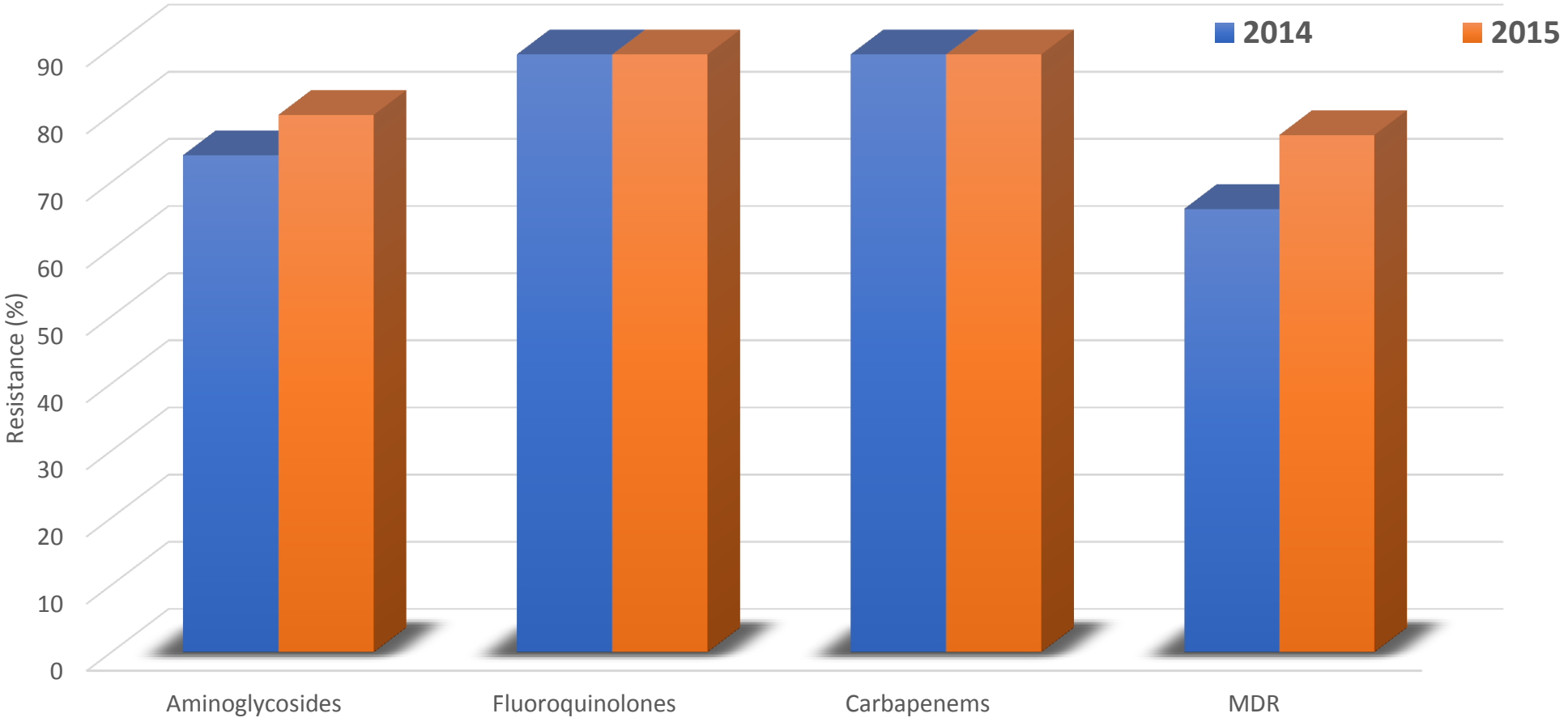
UAMDSS Data in CAESAR 2016 report

Percentage of resistance for K. pneumoniae among blood and CSF isolates in Turkey in 2014- 2015



UAMDSS Data in CAESAR 2016 report

Percentage of resistance for A.baumannii among blood and CSF isolates Turkey between 2014 and 2015

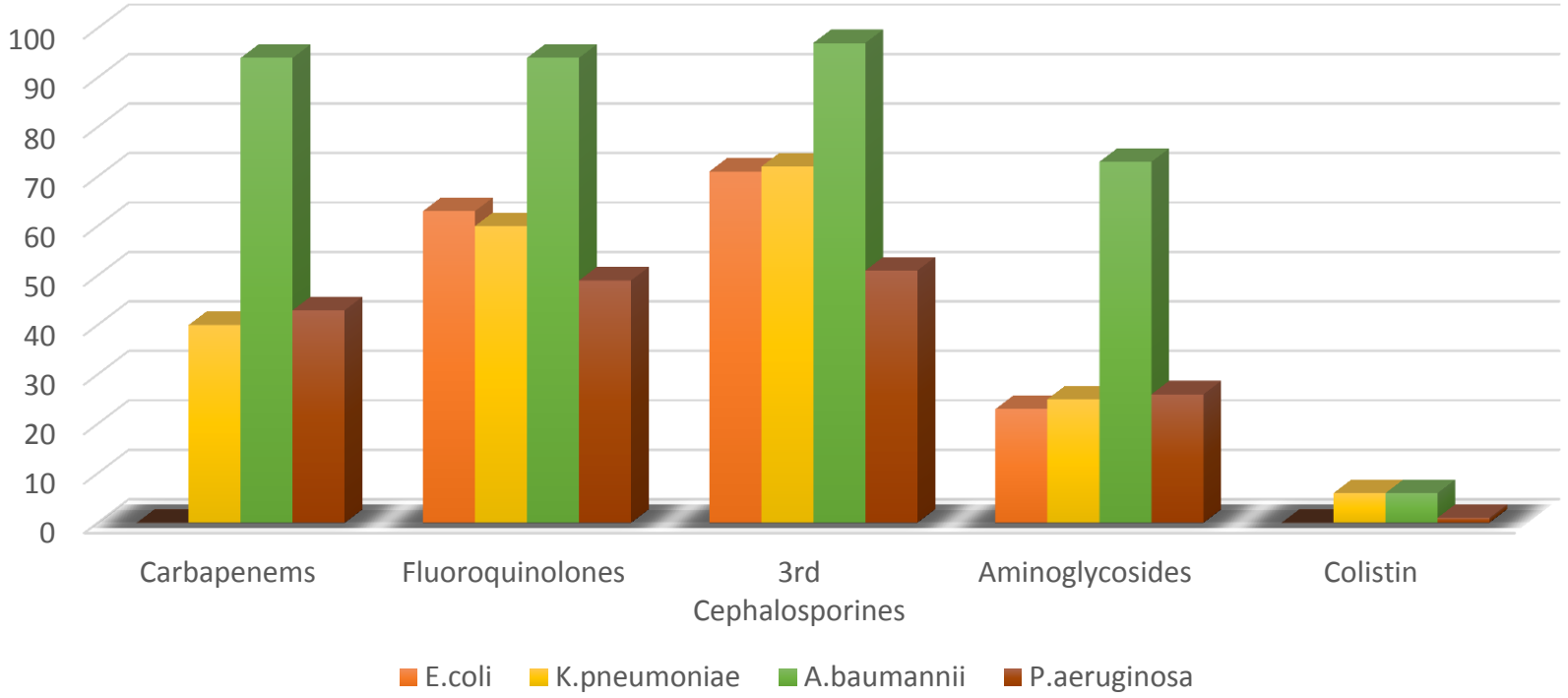


UAMDSS Data in CAESAR 2016 report

Emergence of Colistin Resistance in Health Care Associated Infections

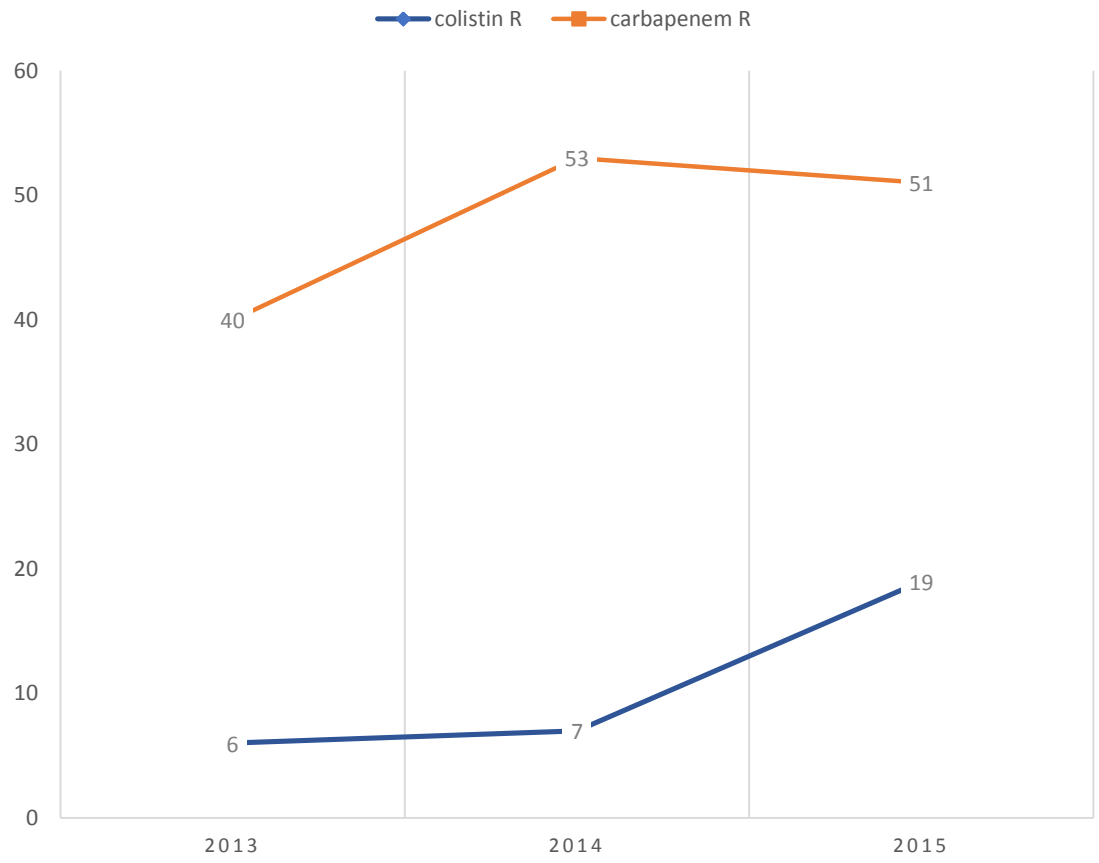
In 2013:

- 17 Centers in Turkey
- 835 Healthcare associated gram negative bloodstream infections



Ergonul et al. J Hosp Infect, 2016

Colistin resistance is increasing in K.pneumoniae



In 2014 and 2015:
1556 cases with healthcare associated Gram negative bloodstream infections

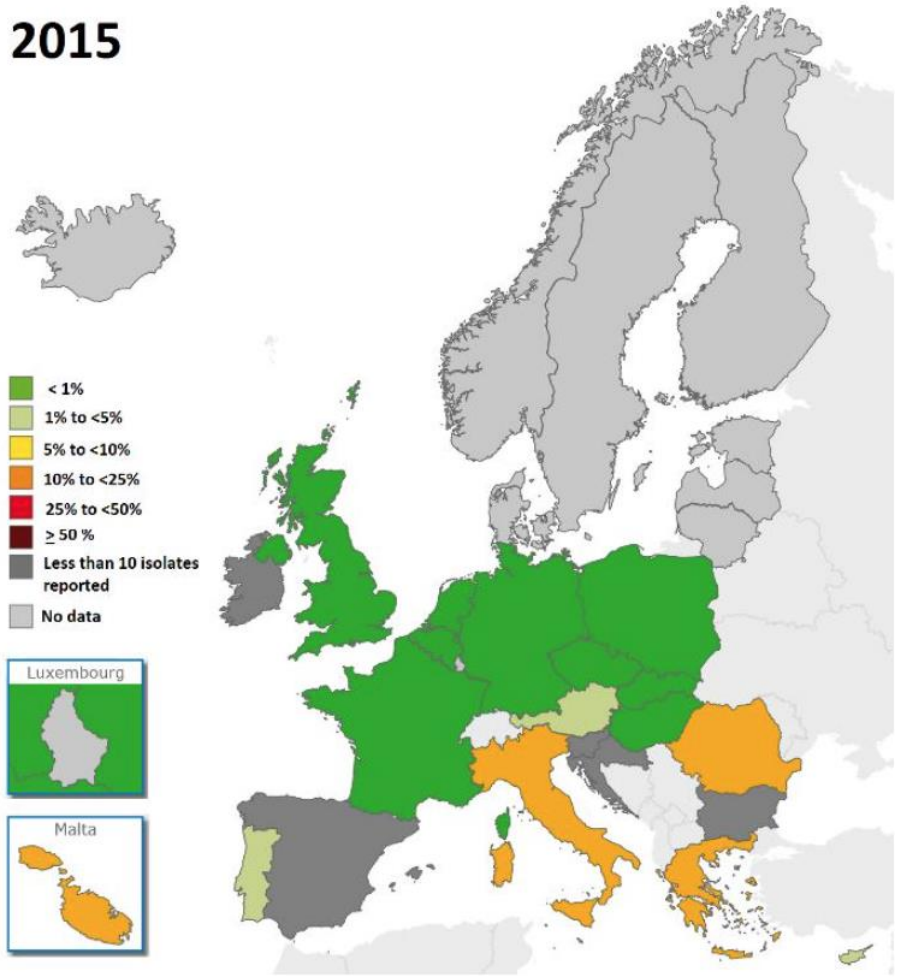
Bacteria	Colistin resistance
- 28% *Acinetobacter baumannii*	2%
- 27% *Klebsiella pneumoniae*	19%
- 22% *Escherichia coli*	
- 13% *Pseudomonas aeruginosa*	
- 10% *Enterobacteriacea* spp	

Colistin resistance in K.pneumoniae is emerging

Colistin MIC is significantly associated with fatality

Aydin M, et al. unpublished Data

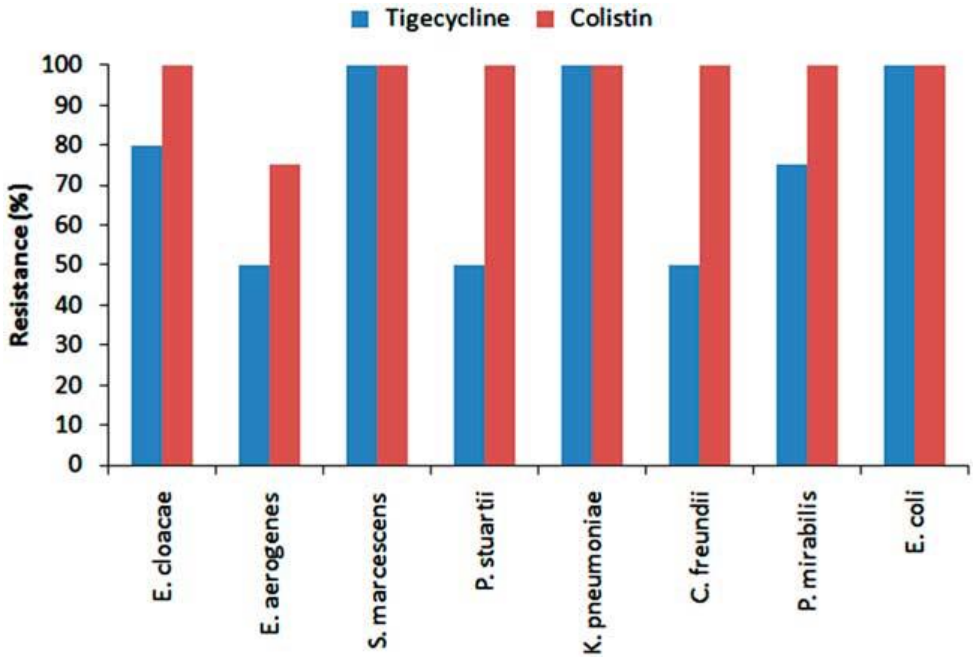
Colistin resistance is high in regions with high carbapenem resistance



ECDC Report 2016

In India:

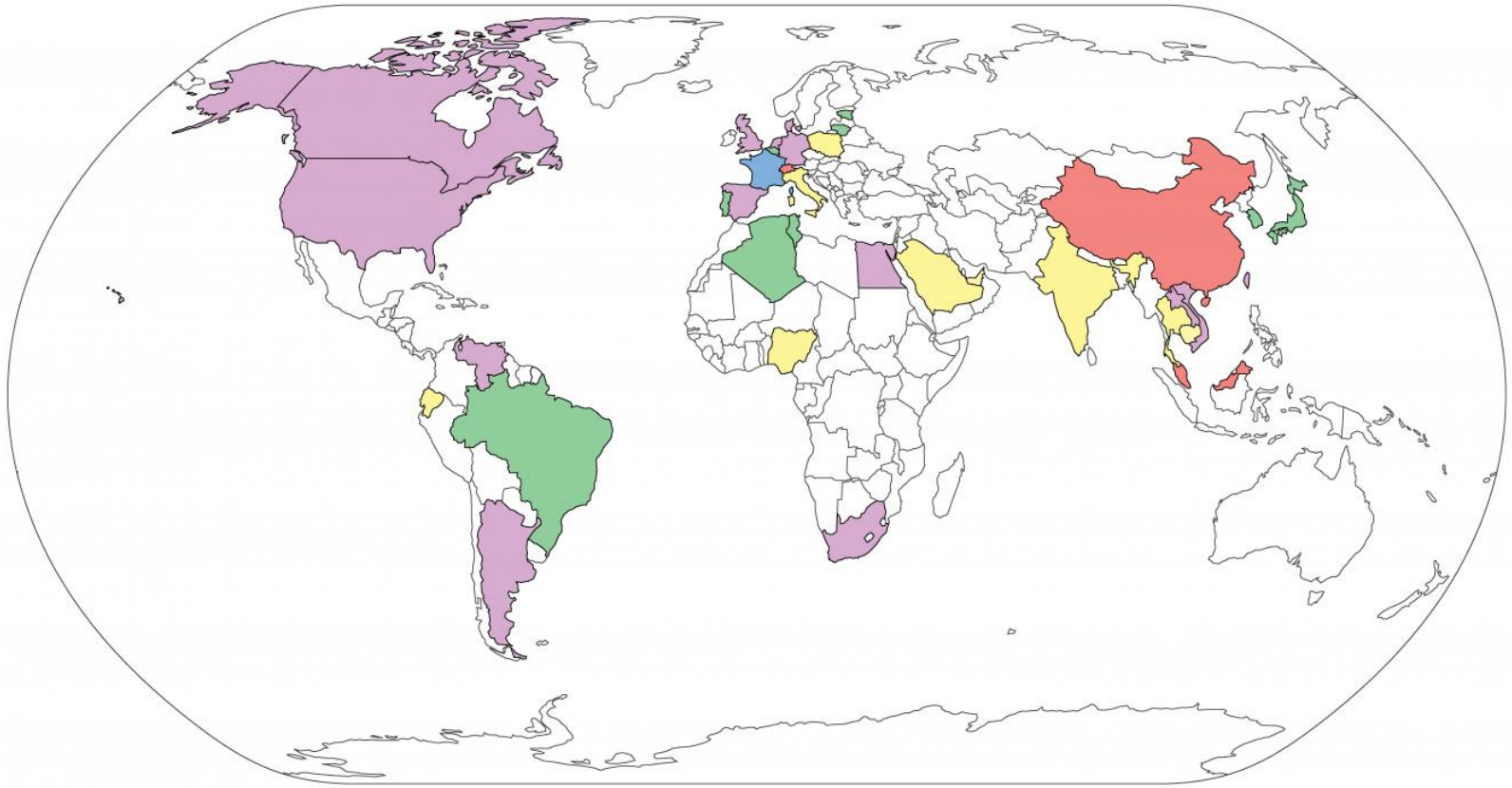
- Between 2013-2015
- 210 Carbapenem resistant Enterobacteriacea



Kumar M. Infection control and hospital epidemiology, 2016

Colistin use is the major risk factor

Countries reporting plasmid-mediated colistin resistance encoded by *mcr-1*



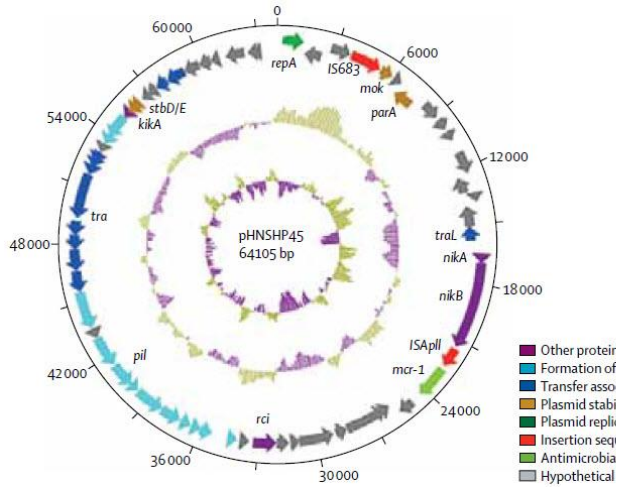
Isolate source(s):

- Animals
- Humans
- Animals and humans
- Animals and environment
- Animals, humans and environment

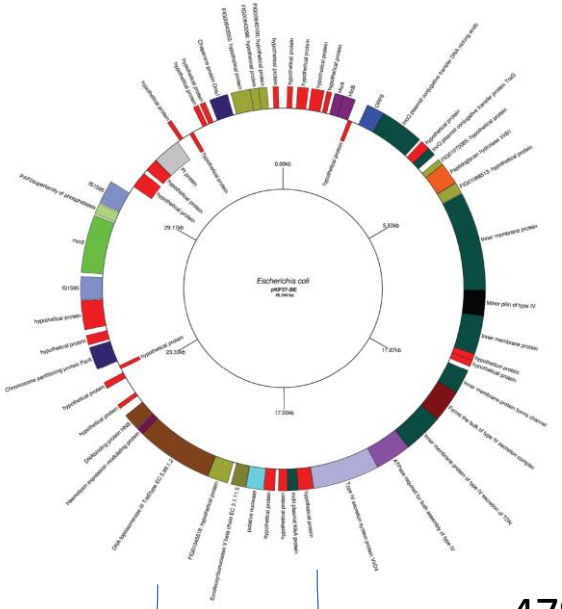
Data source: Al-Tawfiq, J. A., Laxminarayan, R. & Mendelson, M. How should we respond to the emergence of plasmid-mediated colistin resistance in humans and animals? Int. J. Infect. Dis. (2016). doi:10.1016/j.ijid.2016.11.415

Mcr genes were identified in different regions from food, animal and human isolates

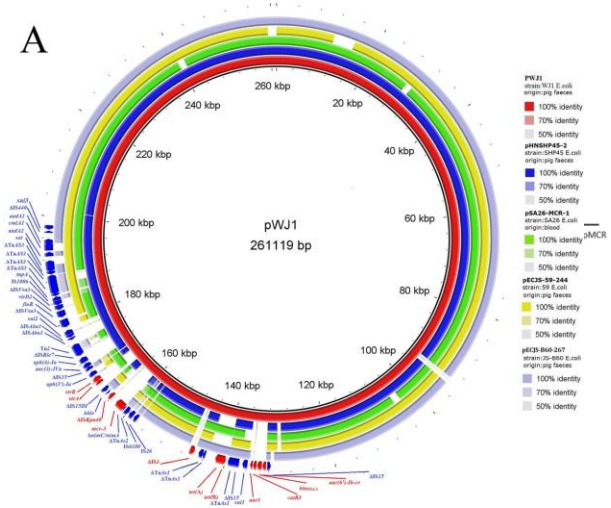
mcr-1



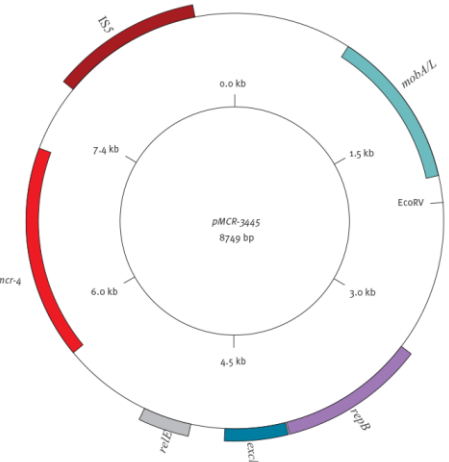
mcr-2



mcr-3



mcr-4



76.7%

47%

49%

45%

35%

34%

- Mcr-1 in China in E.coli
- Mcr-2 in Belgium in porcine and bovine *E.coli*
- Mcr-3 in China in E.coli
- Mcr-4 in Spain, Belgium and Italy

Low level colistin resistance

Xavier BB, Eurosurvielance, 2016

Wenjuan Yin et al. mBio 2017

Carottoli A, Eurosurveillance, Aug 2017

Prevalence of *mcr-1* is low in K.pneumoniae

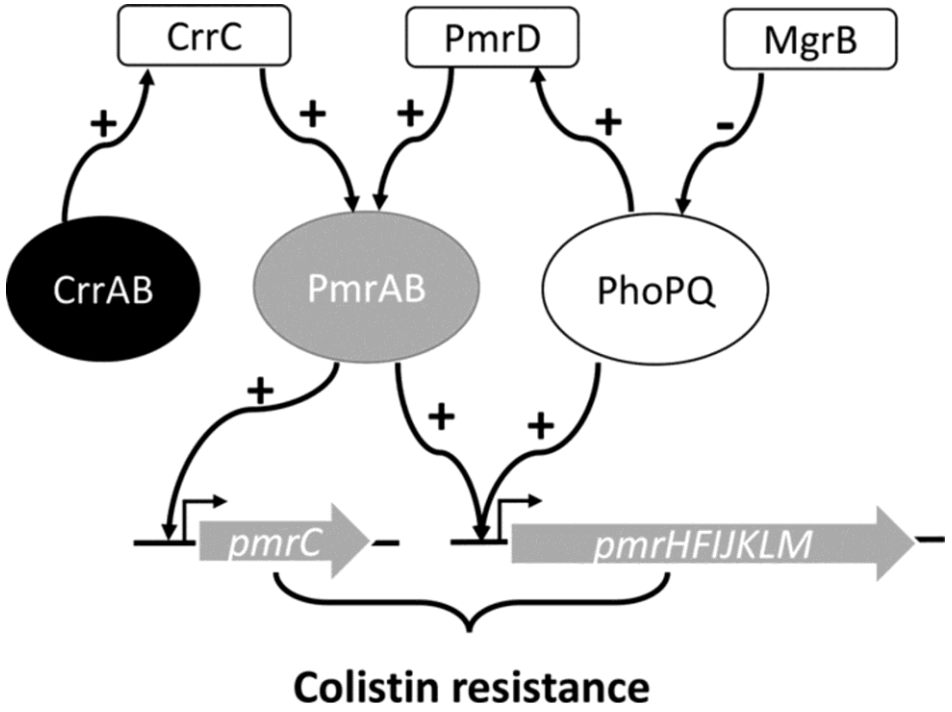
Chromosomal mutations and other intrinsic mechanisms might have important roles in increasing colistin resistance in *K pneumoniae*

a multicentre longitudinal study in China :

Bloodstream infections:
MCR-1 in

- 20 of the 1,495 *E coli* (1.3%)
- 1 of the 571 *K pneumoniae* (0.2%)

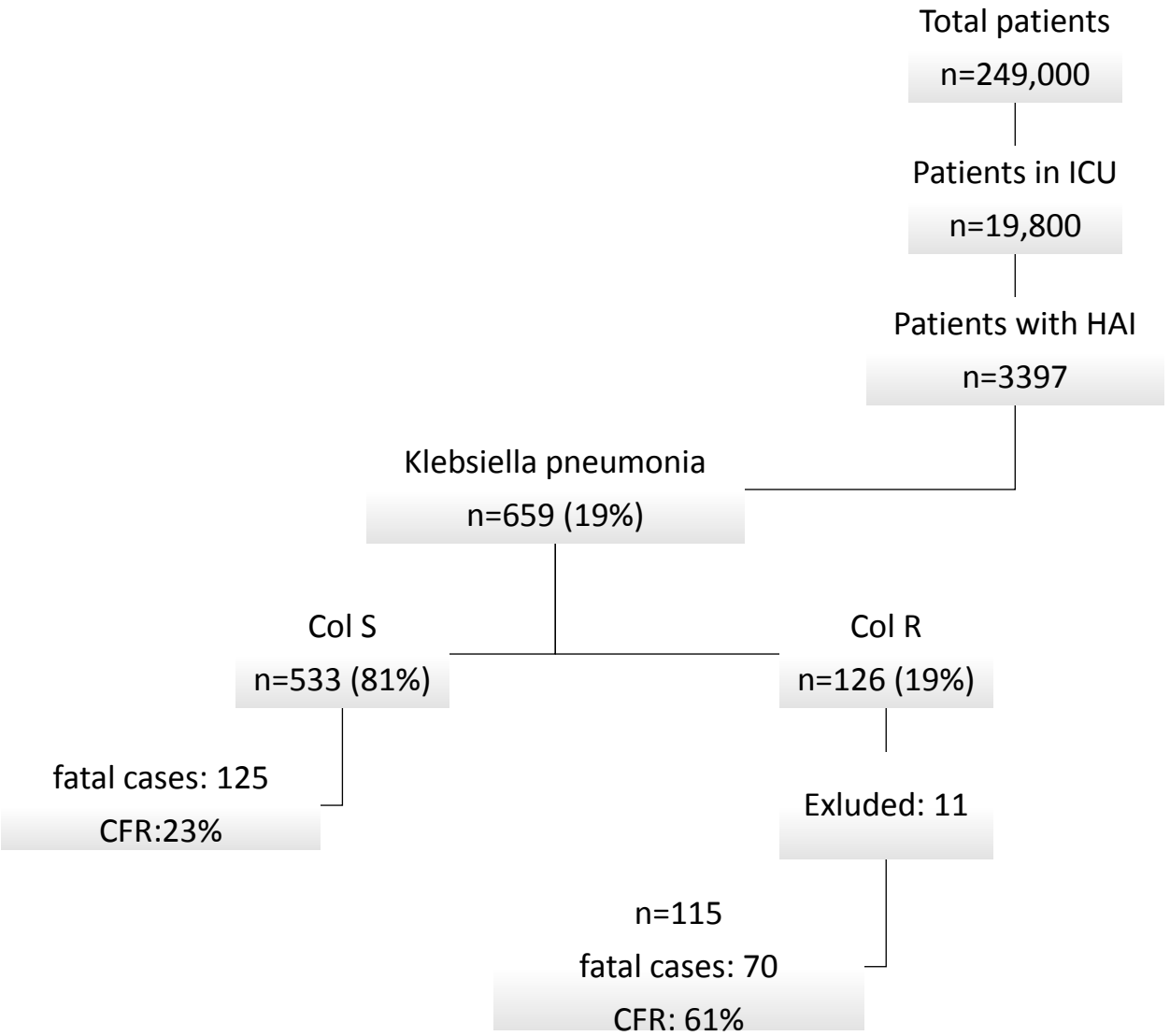
Quan J, *The Lancet Infectious Diseases* , 2017



Two-component systems (CrrAB, PmrAB, and PhoPQ) are regulated by a negative regulator (MgrB) and connectors (CrrC and PmrD).

Cheng Yi-H, Antimicrobial Agents Chemotherapy, 2016

The Impact of Chromosomal Colistin Resistance in Klebsiella pneumoniae infections



Study flowchart

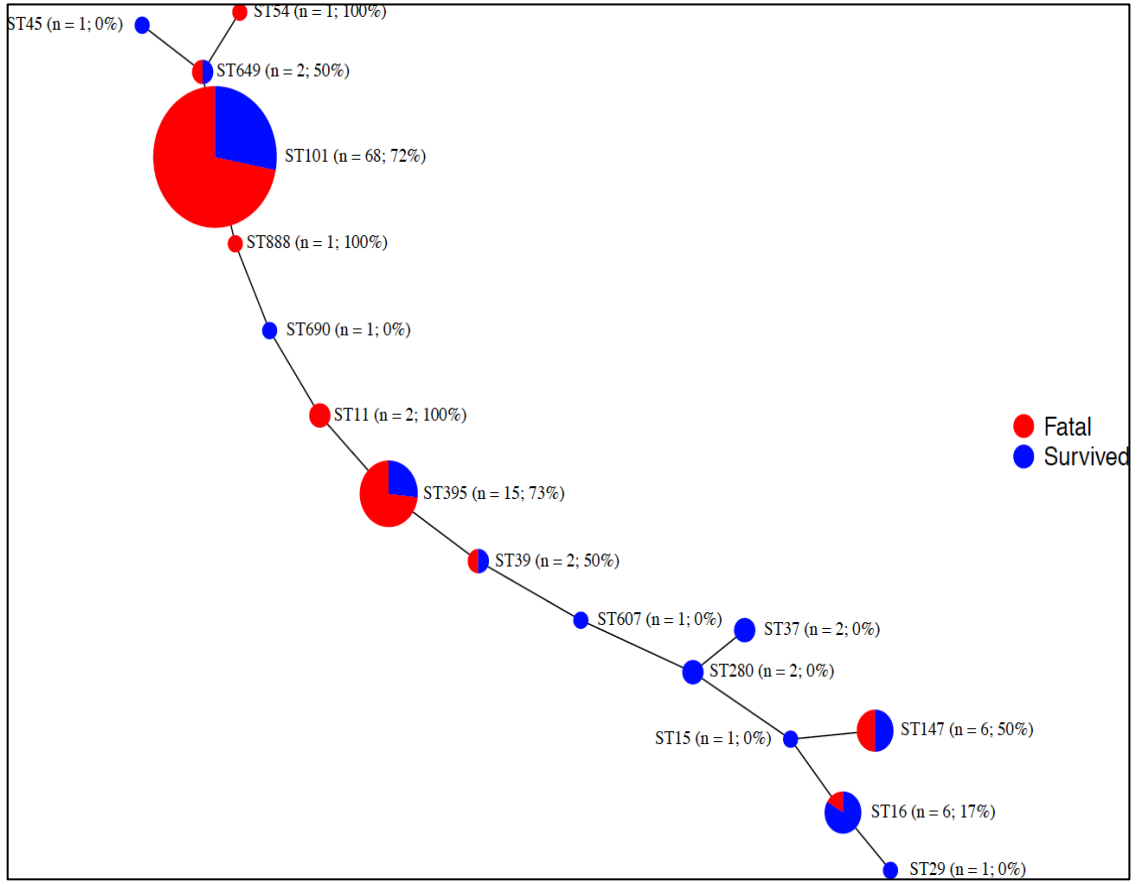
A multicentre study :

- Healthcare-associated infections between 2014-2016
- Patients infected with K.pneumoniae
  - Patients data
  - Therapy of choice
  - 30 days fatality

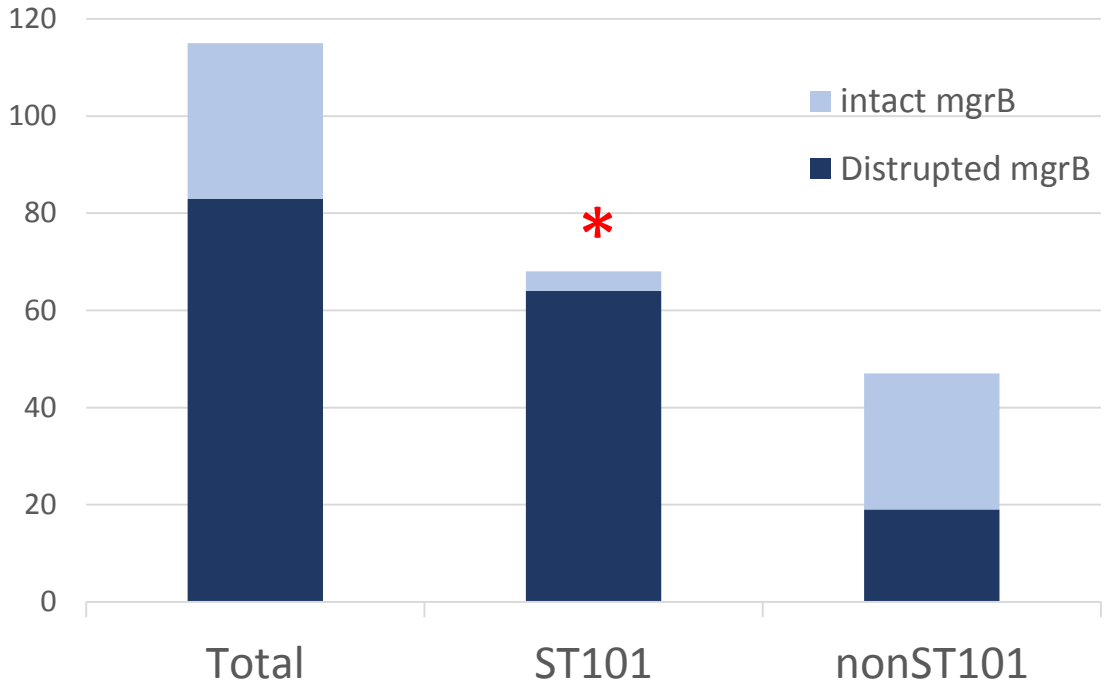
- ColR Klebsiella pneumoniae isolates
  - ST type
  - MgrB alterations
  - PmrCAB expressions
  - Mcr-1

Can F, et al. unpublished Data

ST101 is a high risk clone for colistin resistance and fatality



Minimum spanning tree of colistin resistant *K.pneumoniae* by MLST type and gene allele profiles.

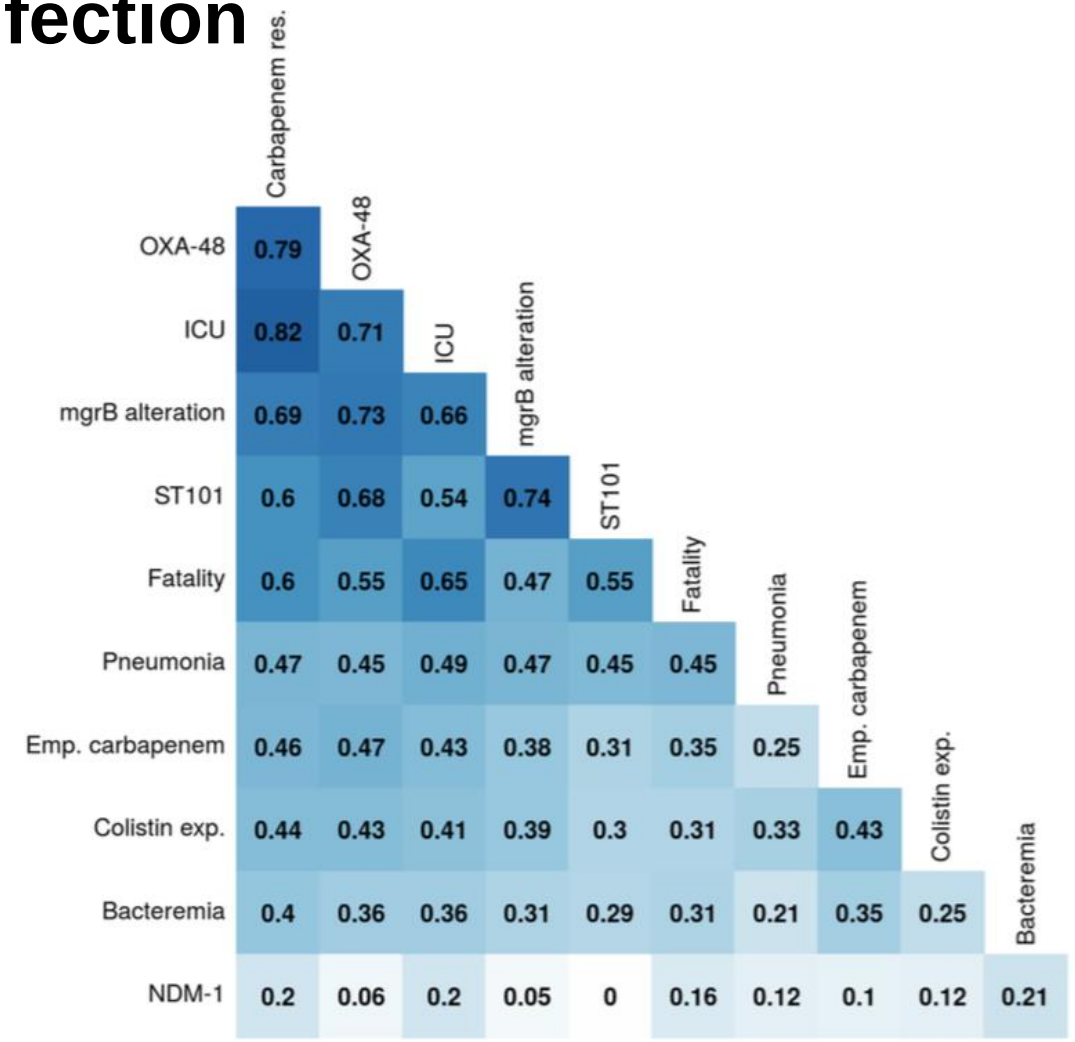


- ST101 clone has significantly higher mgrB alteration by point mutations, deletions or IS insertions
- OXA-48 in 96% of ST101 and 59% of non-ST101

ST101 could be a global threat in dissemination of colistin resistance and increased morbidity and mortality of K.pneumoniae infection

	Univariate analysis			Adjusted analysis*		
	OR	CI	p	OR	CI	p
Female gender	0.7	0.3-1.54	0.341	-	-	-
Being in ICU	6.6	1.85-29.97	**<0.001**	7.4	2.23-29.61	**0.002**
Bacteremia	0.9	0.4-2.1	0.848	-	-	-
Pneumonia	2.3	0.99-5.33	0.038	1.6	0.71-3.86	0.249
Colistin exposure	0.6	0.27-1.41	0.252	-	-	-
Carbapenem resistance	2.2	0.35-15.53	0.43	-	-	-
NDM-1	0.9	0.32-2.69	>0.999	-	-	-
OXA-48	1.4	0.48-3.9	0.628	-	-	-
ST101	3.2	1.36-7.52	**0.004**	3.4	1.46-8.15	**0.005**

Predictors for 30-day fatality among the patients infected with colistin resistant K.pneumoniae



Correlation pilot for selected covariates

What should be done now?

- Detection of colistin-resistant bacteria should be encouraged by promoting the development of reliable techniques for susceptibility testing
- Epidemiological and clinical studies for *mcr* or ST101 and other high risk clones in human or animal isolates should be done
- AMS should be implemented worldwide
- Use of polymyxins as growth promoters in animals should be banned worldwide.