

# ***Escherichia coli* clinical isolates harbouring mcr-1 and mcr-1.5 genes recovered from an University Hospital in Buenos Aires, Argentina.**

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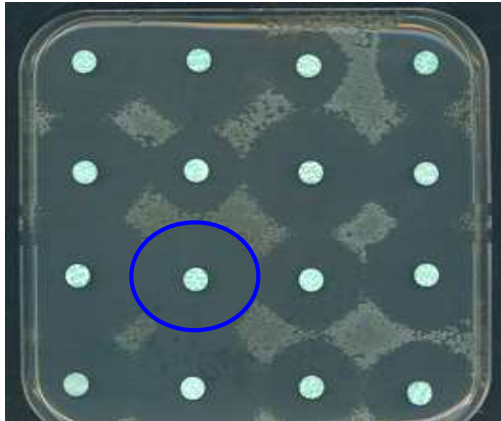


# Transparency Declaration

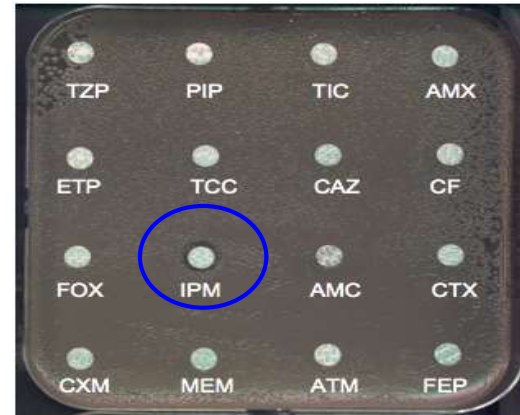
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- None to declare.

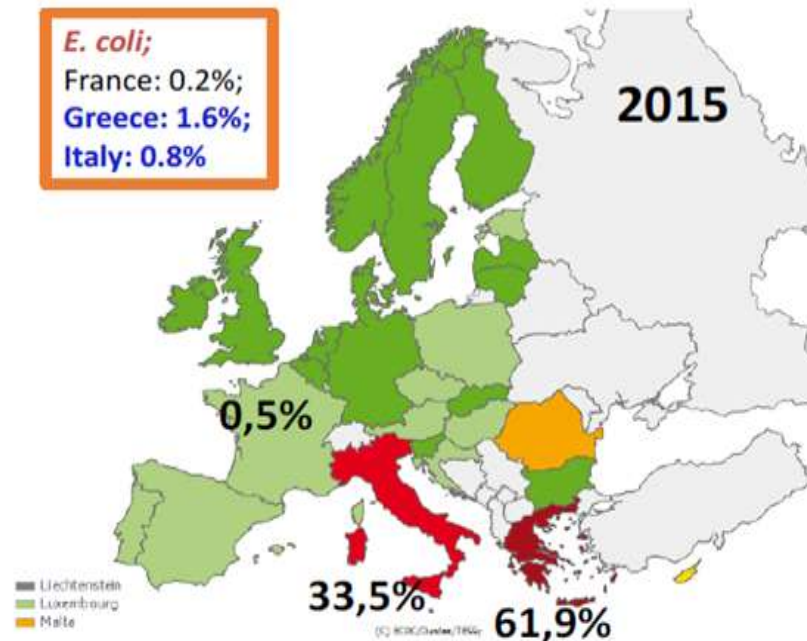
## *E. coli* of our childhood



## *E. coli* of modern times



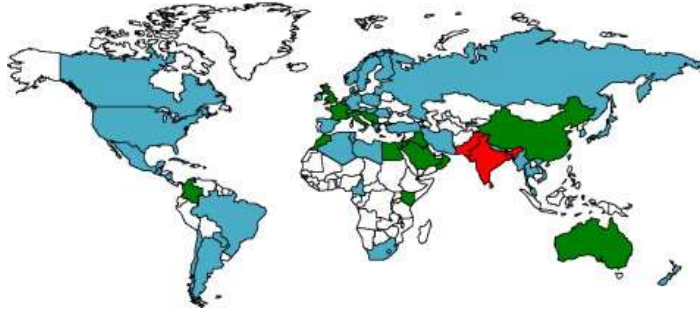
# Prevalence of Carbapenem-Resistant Enterobacteria (bacteriemia)



# Where are these CPEs?

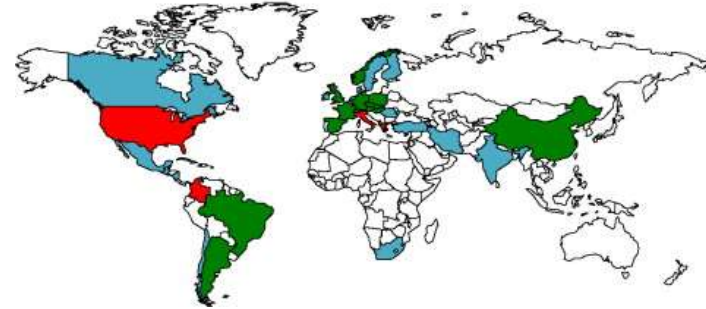
## NDM producers.

- Unknown distribution of NDM producers
- Sporadic spread of NDM producers
- Outbreaks caused by NDM producers
- Endemicity of NDM producers



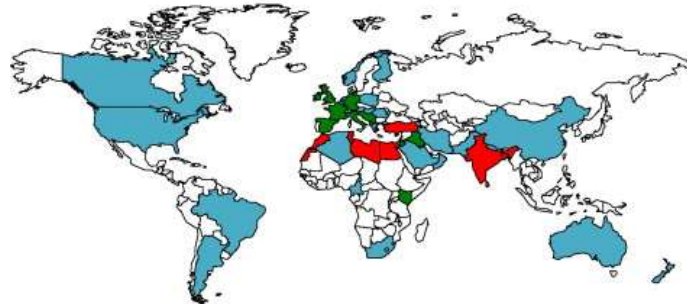
## KPC producers.

- Unknown distribution of KPC producers
- Sporadic spread of KPC producers
- Outbreaks caused by KPC producers
- Endemicity of KPC producers



## OXA-48 producers.

- Unknown distribution of OXA-48 producers
- Sporadic spread of OXA-48 producers
- Outbreaks caused by OXA-48 producers
- Endemicity of OXA-48 producers





Scientists discover a new superbug,

- $\beta$ -lactamase inhibitors
- New targets
- Fast diagnostic tools



[Clin Infect Dis](#). 2005 May 1;40(9):1333-41. Epub 2005 Mar 22.

**Colistin: the revival of polymyxins for the management of multidrug-resistant gram-negative bacterial infections.**

[Ther Drug Monit](#). 2015 Aug;37(4):419-27. doi: 10.1097/FTD.000000000000172.

**Colistin: Revival of an Old Polymyxin Antibiotic.**

[Dijkmans AC](#)<sup>1</sup>, [Wilms EB](#), [Kamerling IM](#), [Birkhoff W](#), [Ortiz-Zacarias NV](#), [van Nieuwkoop C](#),

EXPERT OPINION ON DRUG METABOLISM & TOXICOLOGY, 2017  
<http://dx.doi.org/10.1080/17425255.2017.1230200>

REVIEW

**Colistin: still a lifesaver for the 21st century?**

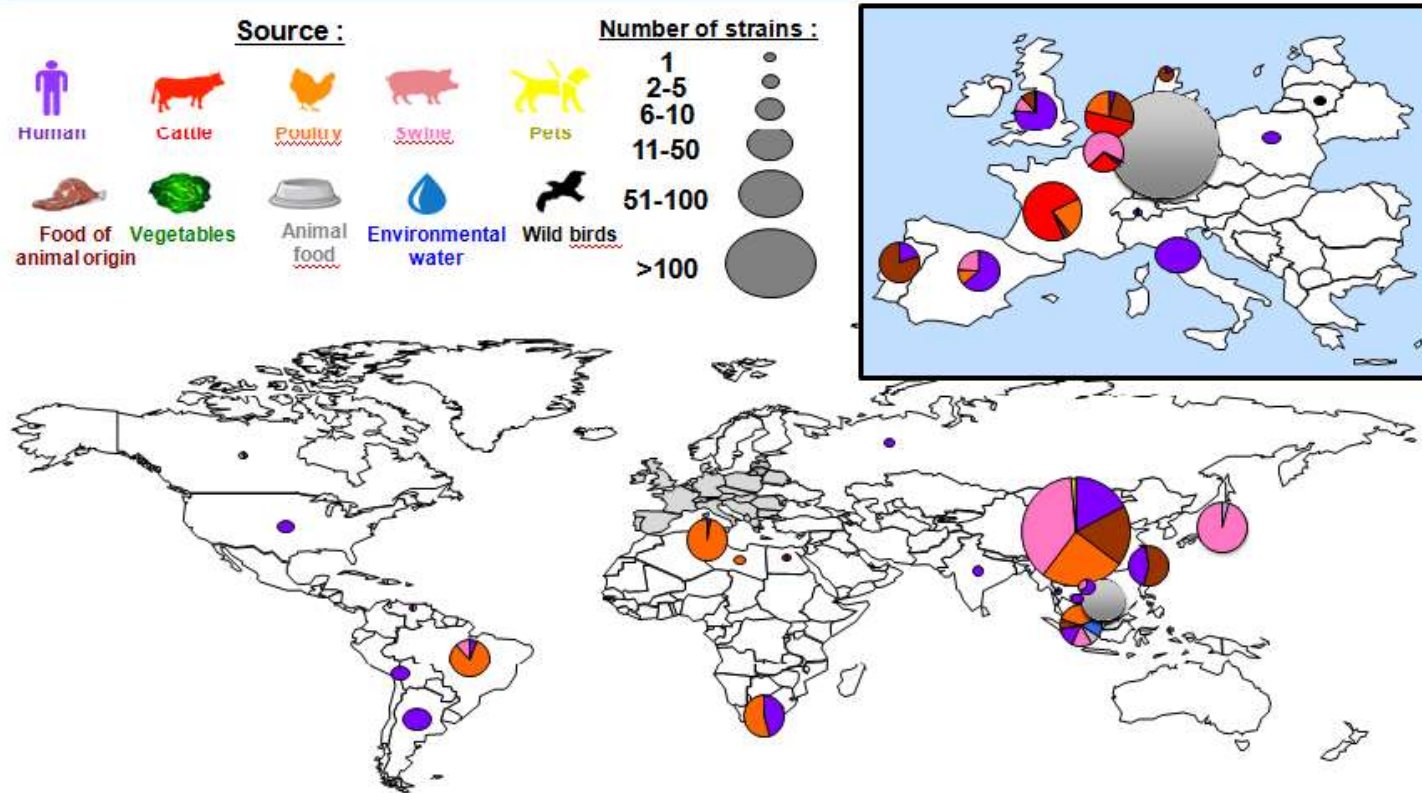
[Ilias Karaikos](#) , [Maria Souli](#) <sup>b,c</sup>, [Irene Galani](#) <sup>b,c</sup> and [Helen Giamarellou](#) <sup>a</sup>

## Colistin resistance ? Is the very last defence line about to fall?

- SENTRY study of the years 2014-2015, have shown a prevalence of **0,4%** among ***E. coli*** isolates (n=13526) and **4,4%** among ***K. pneumoniae*** (n=7480) collected in **183 hospitals worldwide** (Castaheira et al. AAC, 2016)
- **This prevalence is however increasing** as compared to the previous study performed in **Latin America** between 2008 and 2010 (0,2% for *E. coli* and 3,0% for *K. pneumoniae*) (Gales et al. DMID 2012)
- In **Europe** 15% to 25% colistine resistance are reported in countries were carbapenem-resistance is already very high (Greece –Italy)
- In **Greece colistin consumption has increased 6 times** between **2009 -2013**, while colistin resistant *K. pneumoniae* isolates from ICU patients rose from 0% over 2007-2010 to 21,8% over 2010-2013 period (Meletis et al, New Microbiol, 2015)
- Emergence of plasmid encoded colistine resistance *mcr-1*, *mcr-1.2*, and *mcr-2* (Nov 2015)



# Geographical distribution of MCR producing enterobacteria up until 1st august 2016







**Hospital de Clinical  
Jose de San Martin**  
of Buenos Aires,  
Argentina

The carbapenem- resistance in Argentina is mainly due to KPC-2 dissemination.

In this Hospital:

10% of the *Enterobacteriaceae* isolates recovered in 2016 were carbapenemase producing *Enterobacteriaceae*.  
38% KPC producing *K. pneumoniae*.

Rodriguez H. et al unpublished

The colistin resistance in *E. coli* in Argentina was:

0.4 % in 2012

0.8 % in 2014 .

Rapoport M. *et al.* AAC, 2016

The colistin resistance in *E. coli* in this hospital was:

0.2 % in 2014

1.3 % in 2016 .

Nastro M. et al. unpublished

**The aim of the work was to investigate the presence of *mcr-Like* gene among colistine resistant *E. coli* isolates from this University Hospital.**

- Analyze **colistin resistant *Escherichia coli*** clinical isolates, recovered between **2014 and 2016** in a University Hospital of Buenos Aires, **Argentina**.

Strains	Bacteria	Sample	Year	Patient	MIC colistin (mg/L)
6383	<i>E. coli</i>	Urine	2014	Hospitalized	4
2336	<i>E. coli</i>	Urine	2014	Hospitalized	16
1724	<i>E. coli</i>	Urine	2016	External	4
1670	<i>E. coli</i>	Urine	2016	Hospitalized	4
979	<i>E. coli</i>	Urine	2016	External	4
789	<i>E. coli</i>	Urine	2016	Hospitalized	16
3258	<i>E. coli</i>	Urine	2016	External	4
4070	<i>E. coli</i>	Urine	2016	External	4
94427	<i>E. coli</i>	Urine	2016	Hospitalized	16
4222	<i>E. coli</i>	Urine	2016	Hospitalized	4

*mcr-1* +

## MLST and resistance genes harbouring *E.coli* MCR-1 producer.

Strain	MLST	Resistance gene for									
		Aminoglycoside	$\beta$ -lactams	Sulphonamide	Tetracycline	Trimethopim	Quinolone	Phenicol	Macrolide	Polymyxin	
979	ST410	<i>aadA1</i>	<i>bla</i> <sub>CTX-M-2</sub>	<i>sul1</i>	<i>tet(A)</i>	-	-	<i>catA1</i>	-	<i>mcr-1</i>	<b>100% identity</b>
1724	ST2722	-	-	-	-	-	<i>qnrB19</i>	-	-	<i>mcr-1</i>	
4070	ST744	<i>aph(3')-Ia, strA, strB, aadA5</i>	<i>bla</i> <sub>TEM-1B</sub>	-	-	-	-	-	<i>mph(A)</i>	<i>mcr-1</i>	
4222	ST101	<i>aadA1, aadB</i>	<i>bla</i> <sub>CTX-M-2</sub>	<i>sul1</i>	<i>tet(A)</i>	<i>drfA1</i>	-	-	-	<i>mcr-1</i>	
6383	ST602	<i>aac(3)-IIId, aadA1, strB, strA</i>	<i>bla</i> <sub>TEM-1B</sub>	<i>sul1, sul2</i>	<i>tet(A)</i>	<i>drfA1</i>	-	-	-	<i>mcr-1</i>	
1670	ST602	<i>aadA1, aadA2, aadB</i>	<i>bla</i> <sub>CTX-M-2</sub>	<i>sul1</i>	<i>tet(A)</i>	<i>drfA12</i>	-	-	<i>mph(A)</i>	<i>mcr-1</i>	

## Sequence alignment of MCR-1 and MCR-1-like proteins

```

MCR-1          MMQHTSVWYRRSVSPFVLVASVAVFLTATANLTFDFKISQTYPIADNLGFVLTIAVVLFG      60
MCR-1.2        --L-----
MCR-1.3        -----V-----
MCR-1.4        -----
6383_MCR-1.N   -----
1670_MCR-1.N   -----
**  *****.*****

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MCR-1          KCEHQSLINAYDNALLATDDFIAQSIQWLQTHSNAYDVSMLYVSDHGESLGENGVYLHGM      480
MCR-1.2        -----
MCR-1.3        -----
MCR-1.4        -----N-----
6383_MCR-1.N   -----Y-----
1670_MCR-1.N   -----Y-----
*****.*****.*****

```

His452Tyr

*Escherichia coli* strain Ec1670 and Ec6383: phosphoethanolamine--lipid A transferase **MCR-1.5** (*mcr-1*) gene, *mcr-1.5* allele, complete cds.

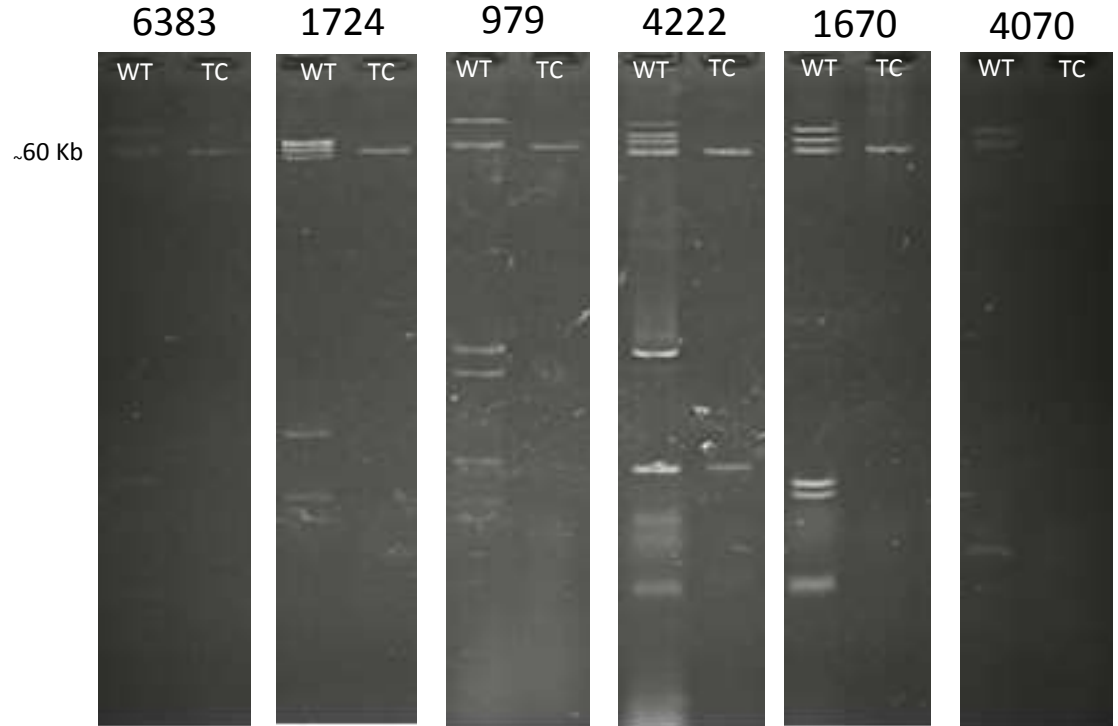
Accession number: KY271416

29/11/2016

Mating-out assay was performed using *E. coli* J53 as receptor strain.

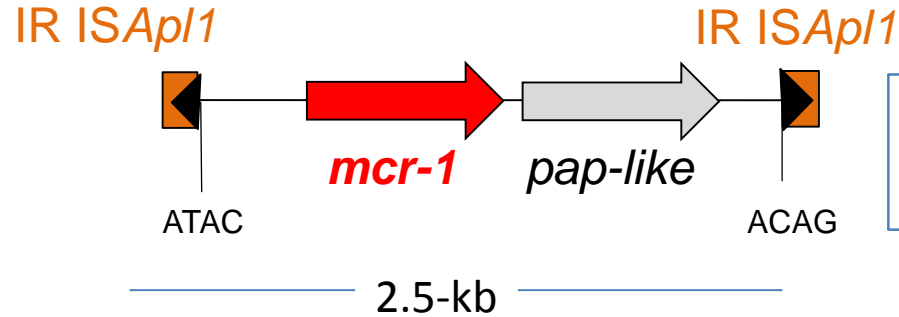
Strains	MIC (mg/L) for colistin	
	WT	Transconjugant (TC)
6383	4	4
1724	4	4
979	4	4
4222	4	4
1670	4	2
4070	4	4

Plasmid	Incompatibility group
p6383	Incl2
p1724	Incl2
p979	Incl2
p4222	Incl2
p1670	Incl2
p4070	Incl2



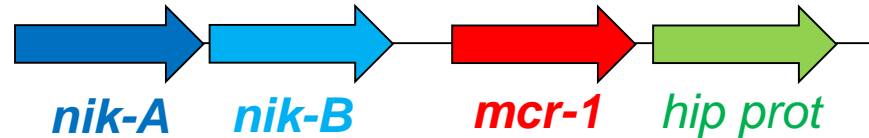
# *mcr-1* gene environment

pS38 (IncHI2)  
247885 pb  
(Genbank KX129782)



p6383  
P1670  
(plasmids of 59-kb)

pECJS-61-63 (IncI2)  
63656 bp pb  
(Genbank KX254342.1)



p1724  
P4070  
p979  
P4222  
(plasmids of 59-kb)

# Conclusions



- In 2016 the % of colistin resistance in *E. coli* was 1.3% .
- 6/10 harboured *mcr-1* gene or *mcr-1-like* gene.
- The differences in the MLST indicates a dissemination of the *mcr-1* gene through highly related plasmids.
- This is the first report of MCR-1.5 .
- Further studies have to be done to complete the characterization of the new variant MCR-1.5.



# Acknowledgements



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- Thierry Naas
- Remy Bonnin
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- Hernan Rodriguez
- Marcela Nastro
- Angela Famiglietti

