

# Emerging Antibiotic Resistances and Perspectives



**NARA**  
Nationales Referenzlaboratorium zur Früherkennung  
neuer Antibiotikaresistenzen und Resistenzmechanismen



Institut national  
de la santé et de la recherche médicale

**French INSERM European Unit,  
University of Fribourg, Switzerland**



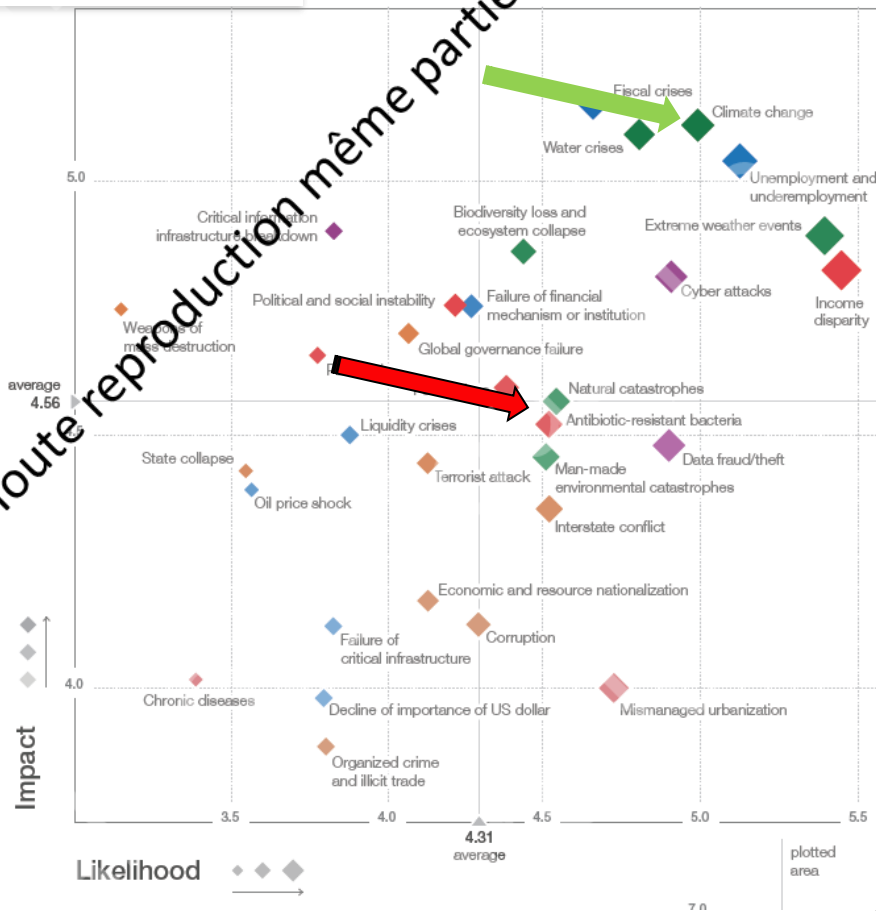
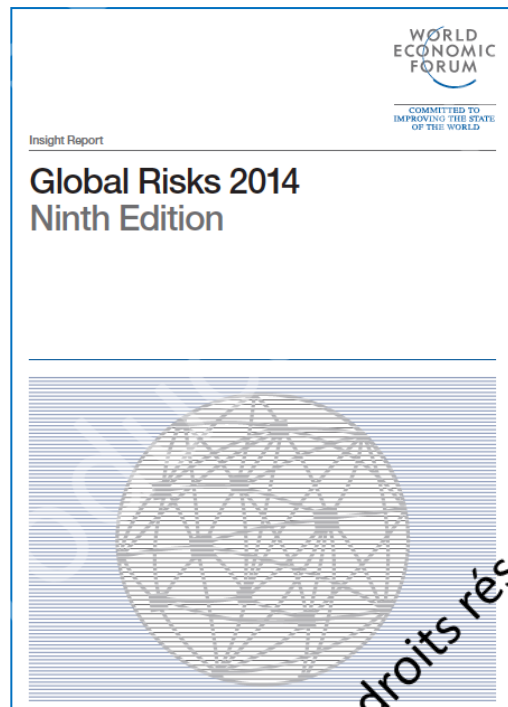
**Prof. Patrice Nordmann**

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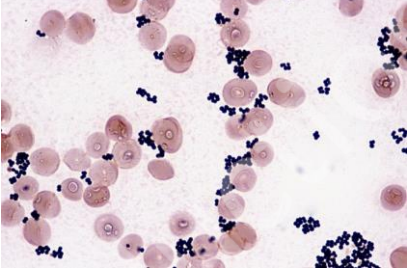
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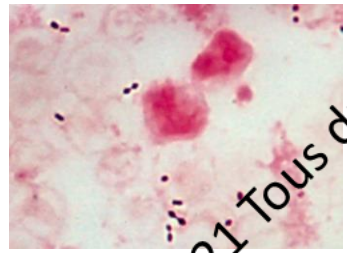
## Gram positives

*Staphylococcus*



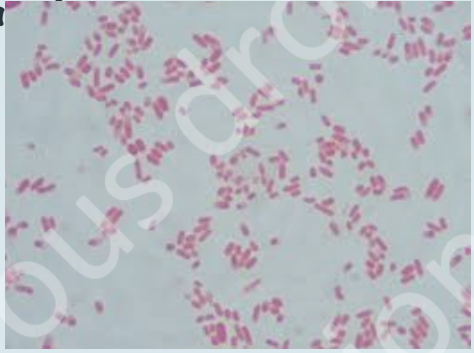
*Enterococcus*

*Streptococcus*

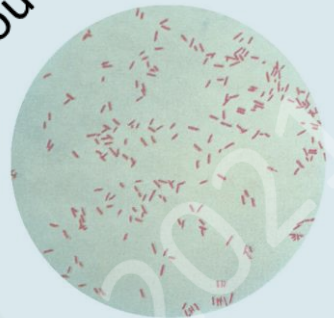


## Gram negatives

Enterobacteriaceae (*E. coli*,  
*K. pneumoniae*)



*Pseudomonas aeruginosa*



*Acinetobacter baumannii*



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# Extended-spectrum $\beta$ -lactamases in Gram negatives

Penicillins

Cephalosporins

Carbapenems

Extended-spectrum  $\beta$ -lactamases (ESBL); CTX-M



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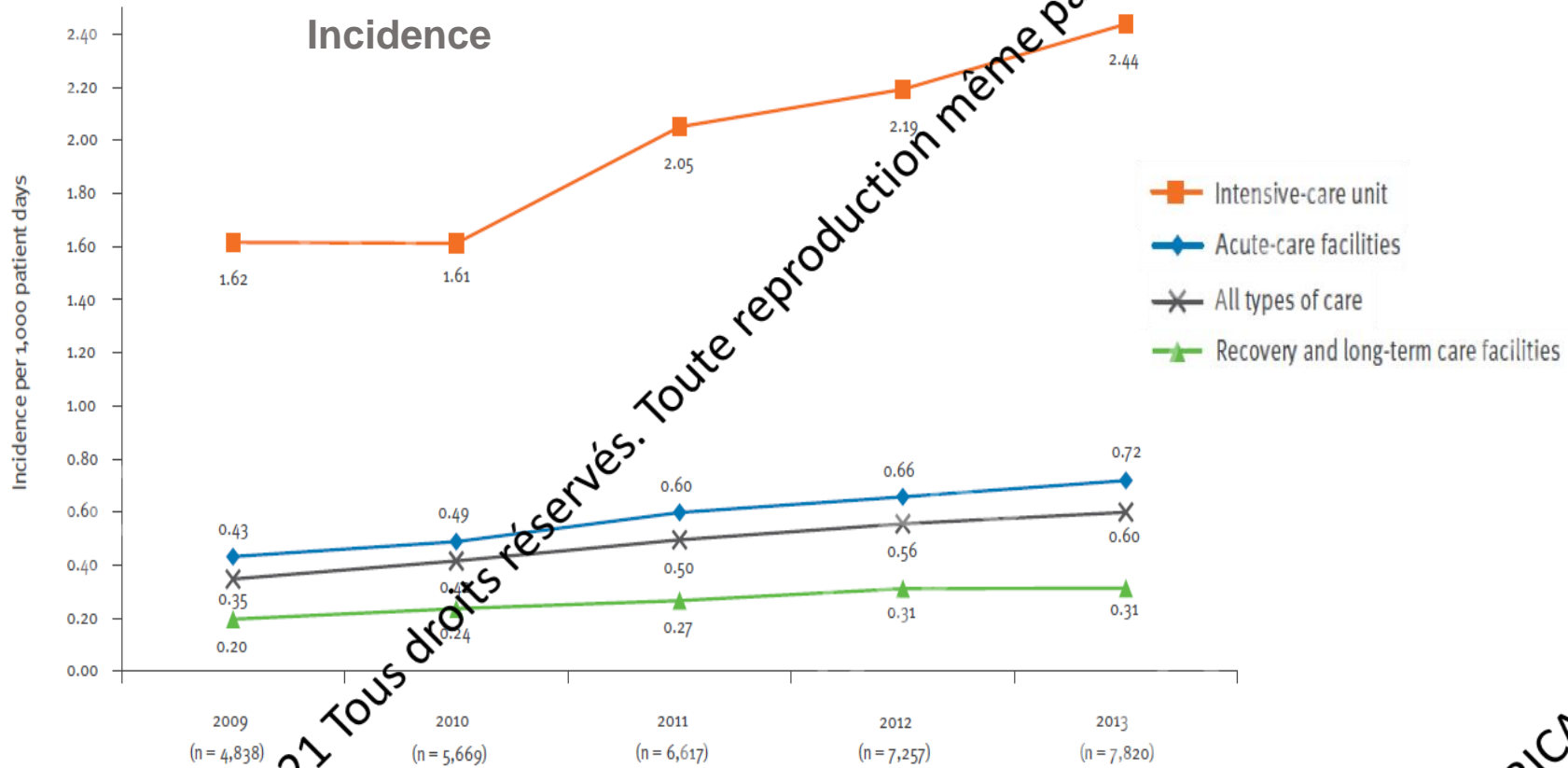
# Multidrug resistance of ESBL-producing *Escherichia coli*



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# Incidence Enterobacteriaceae (ESBL)- France - 2009 -2013



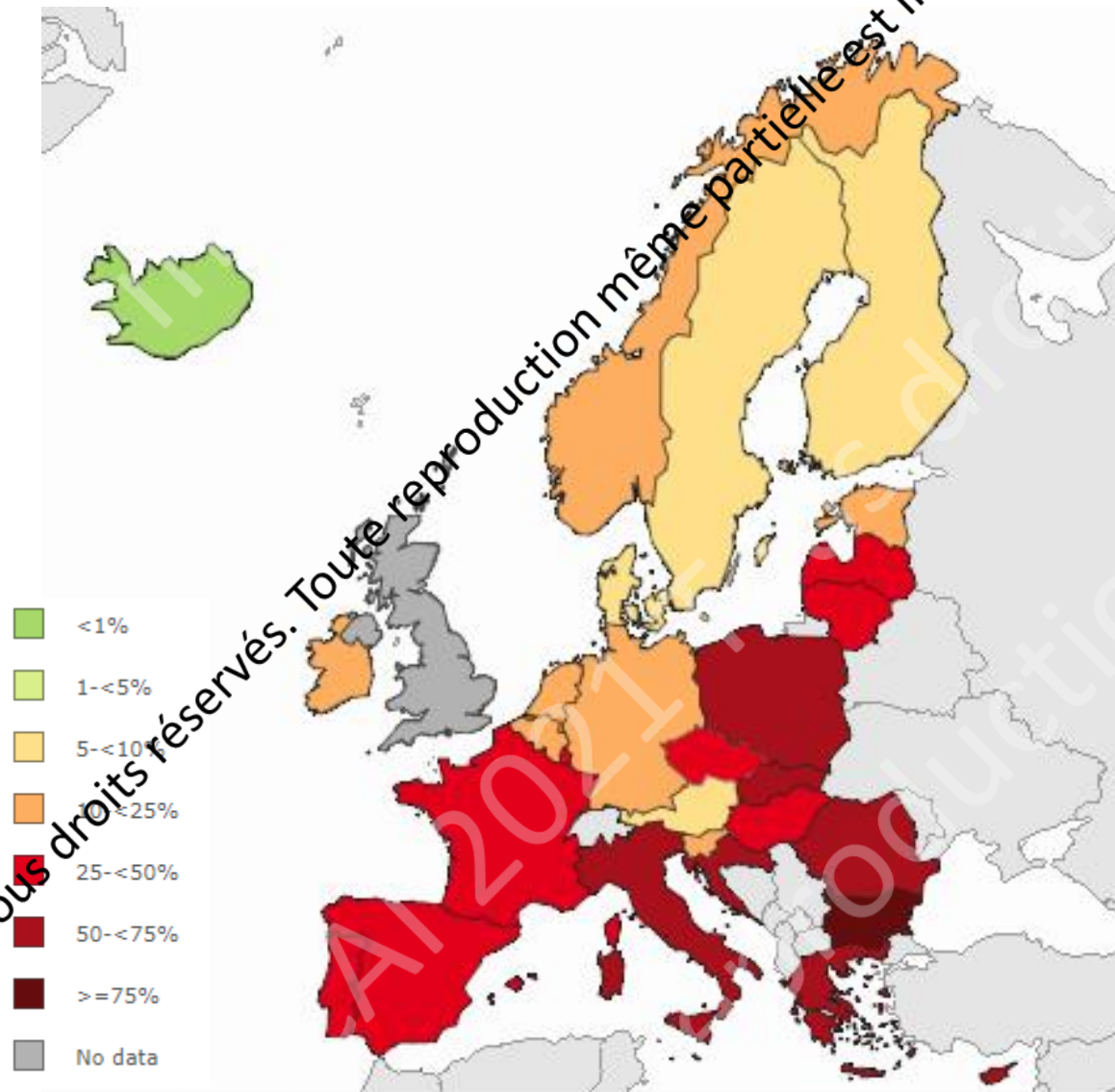
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# Invasive *K. pneumoniae* producers of ESBLs

2020



European Antimicrobial  
Resistance Surveillance System  
(EARSnet), Atlas

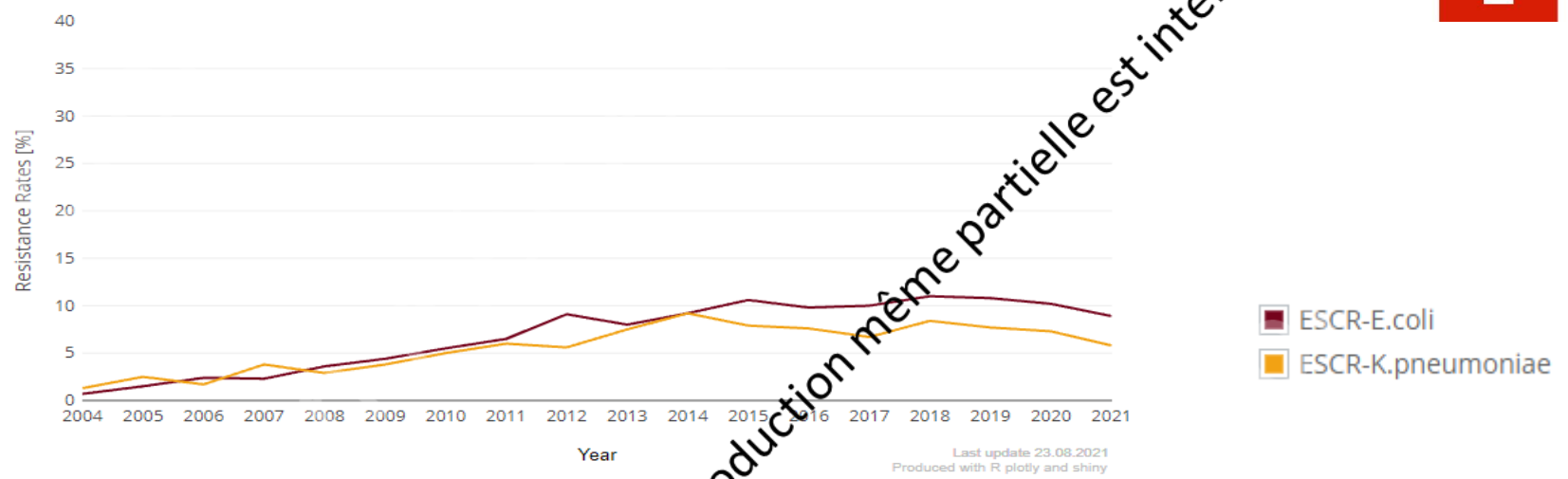
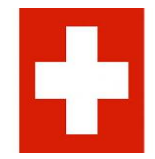


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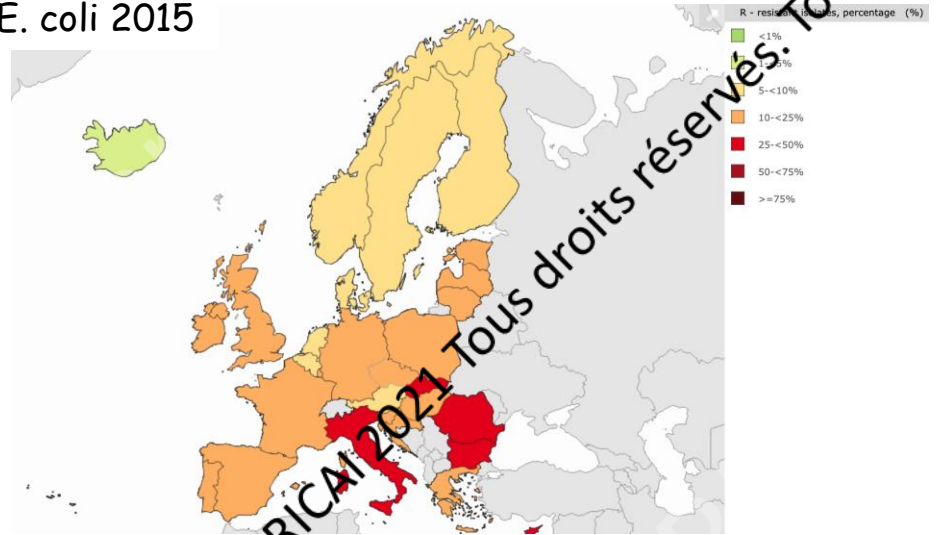
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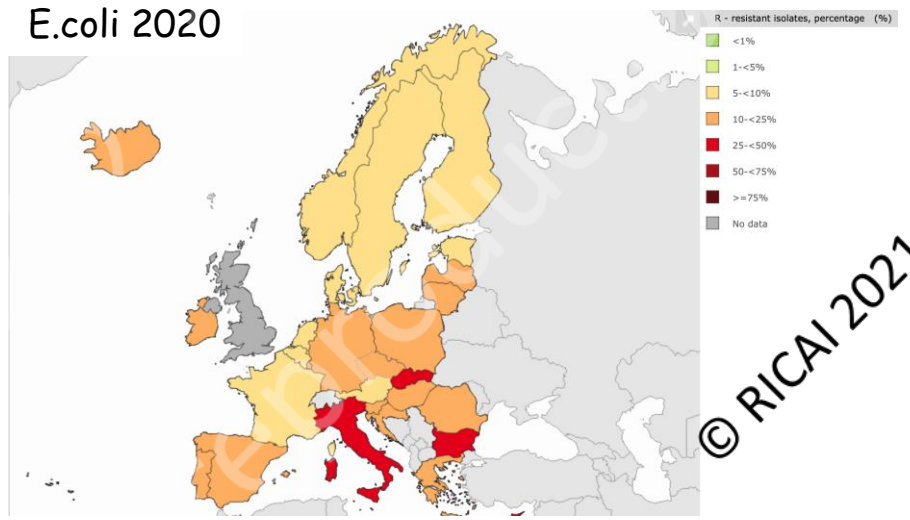
# Invasive ESBL producers in *E. coli* and *K. pneumoniae*



E. coli 2015



E.coli 2020

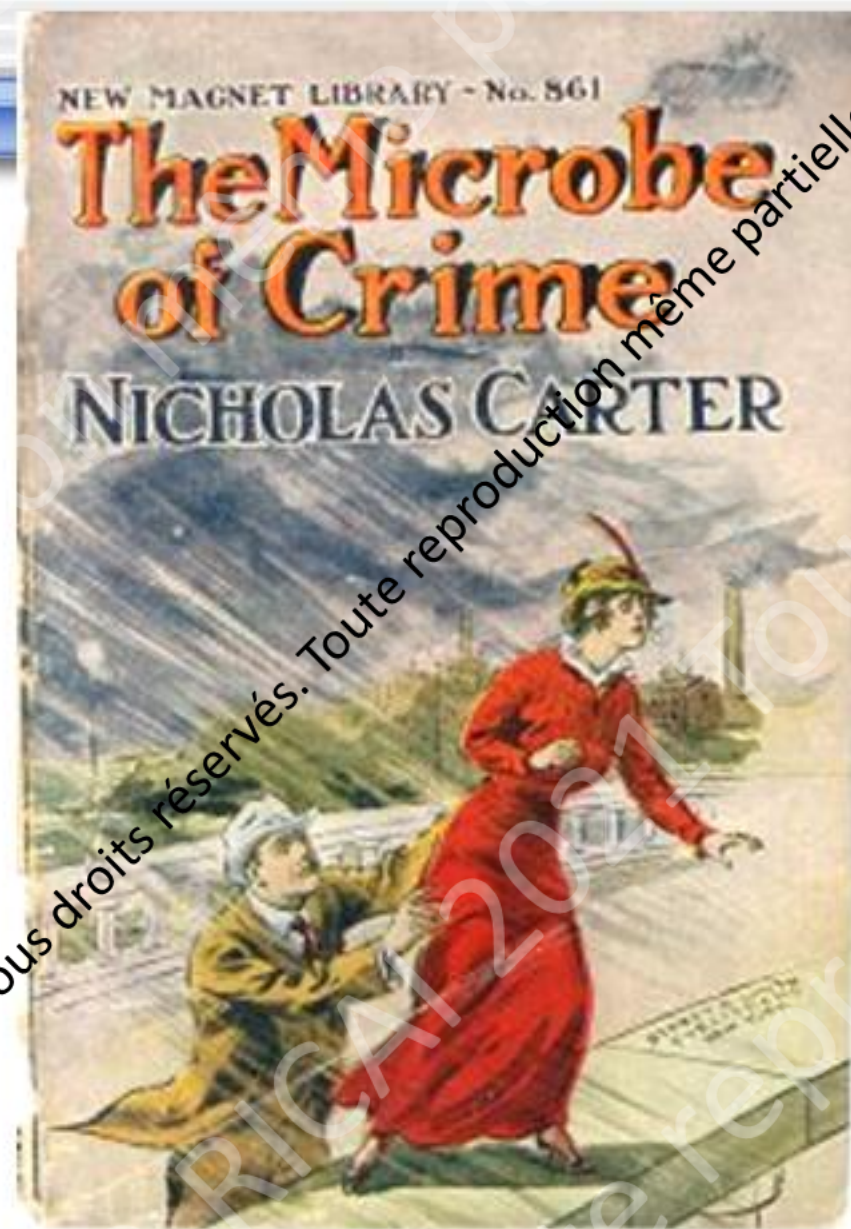


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# Broad-spectrum $\beta$ -lactamases in Gram Negatives

Penicillins

Cephalosporins

Carbapenems

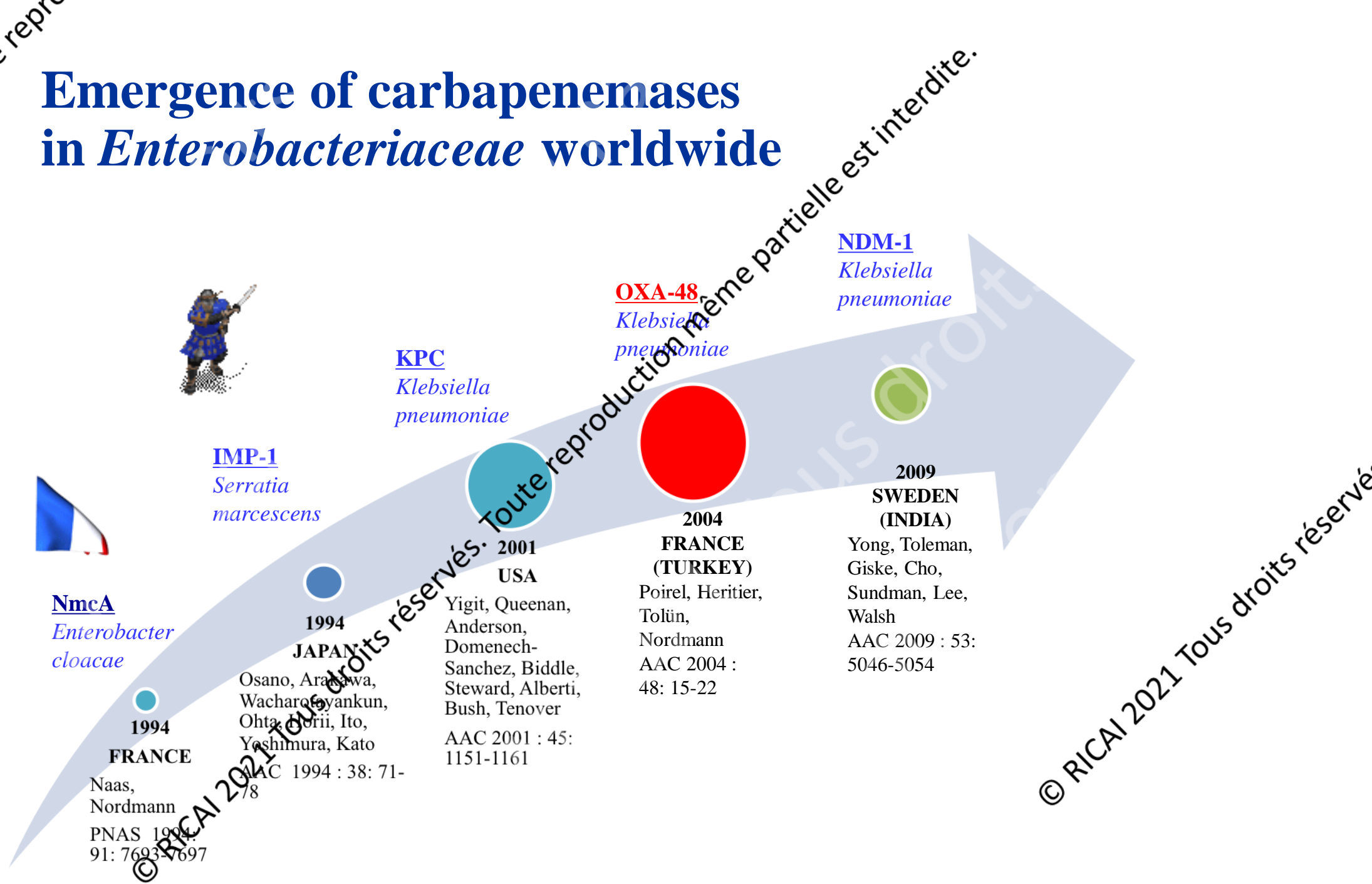
Extended-spectrum  $\beta$ -lactamases (ESBL); CTX-M



Carbapenemases: NDM, KPC, OXA-48



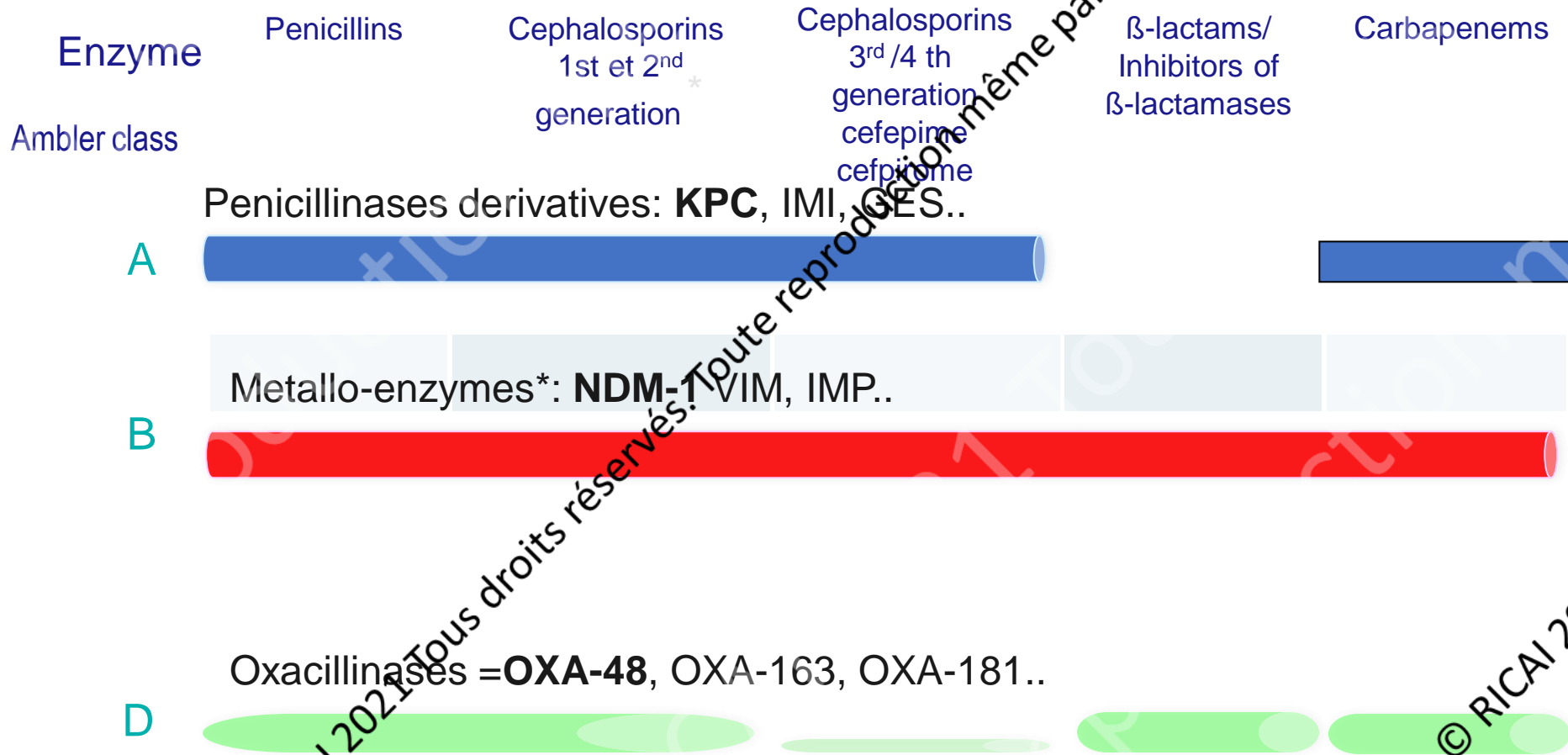
# Emergence of carbapenemases in *Enterobacteriaceae* worldwide



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# The carbapenemases in *Enterobacteriaceae*



\* Aztreonam excluded

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# KPCs; Klebsiella Pneumoniae Carbapenemase



ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Apr. 2001, p. 1151-1155  
0066-4804/01/50040-0 DOI: 10.1128/AAC.45.4.1151-1155.2001  
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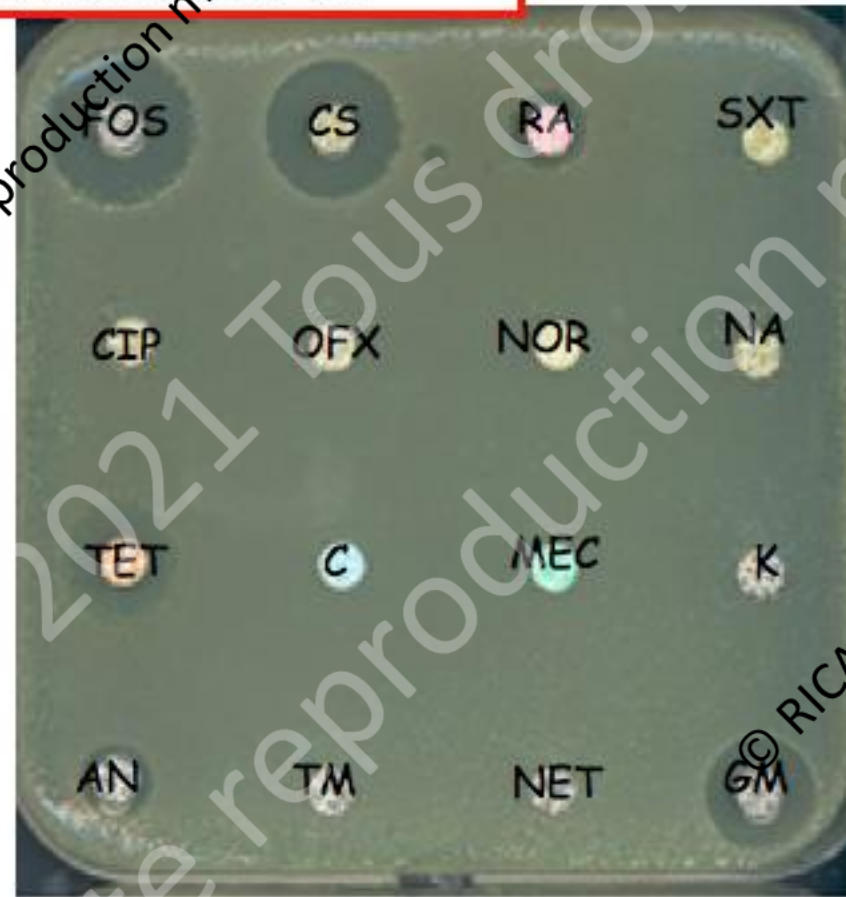
Vol. 45, No. 4

## Novel Carbapenem-Hydrolyzing $\beta$ -Lactamase, KPC-1, from a Carbapenem-Resistant Strain of *Klebsiella pneumoniae*

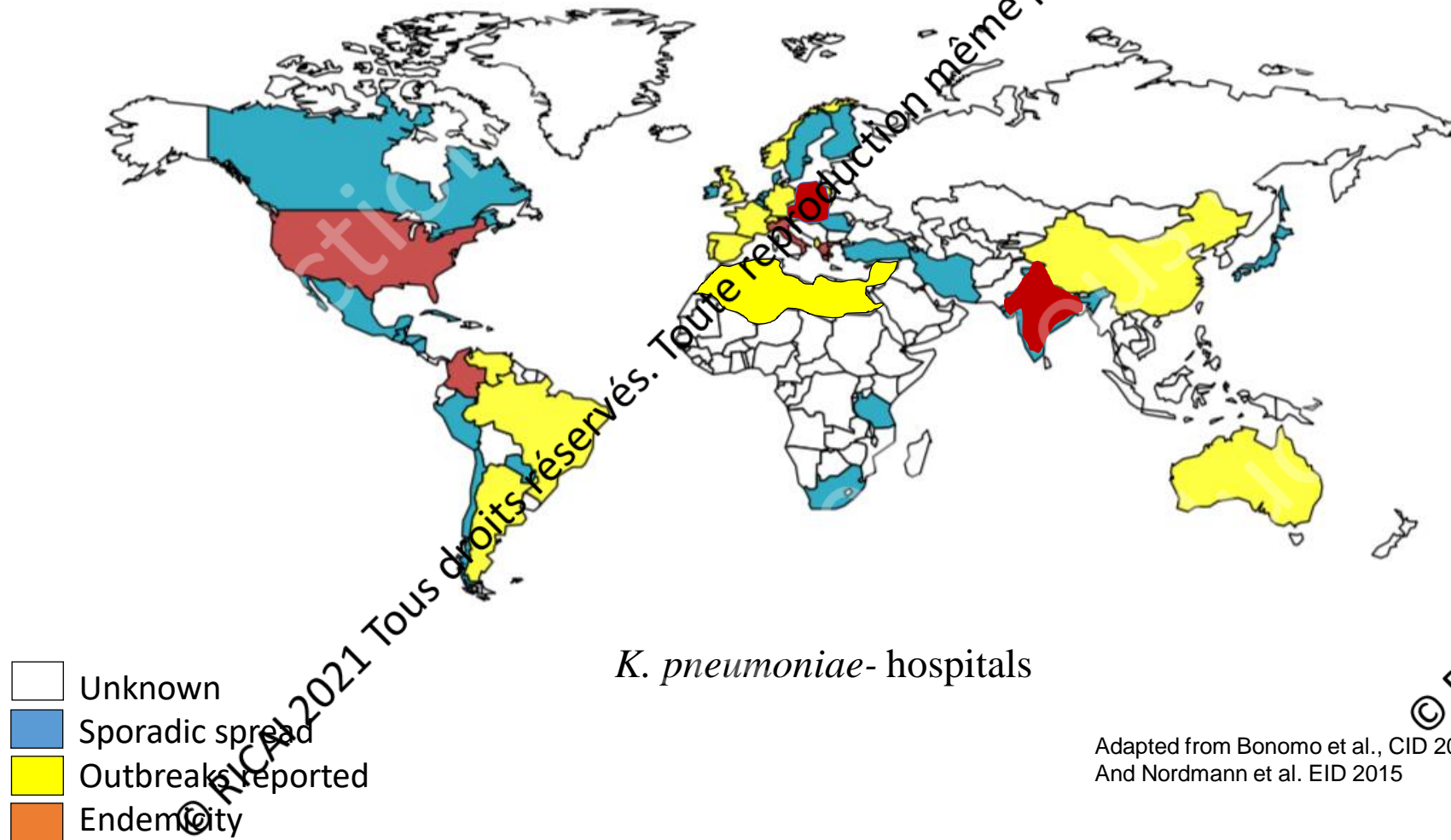
HESNA YIGIT,<sup>1</sup> ANNE MARIE QUEENAN,<sup>2</sup> GREGORY J. ANDERSON,<sup>1</sup>  
ANTONIO DOMENECH-SANCHEZ,<sup>3</sup> JAMES W. BIDDLE,<sup>4</sup> CHRISTINE D. STEWART,<sup>5</sup>  
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Received 19 September 2000/Returned for modification 21 November 2000/Accepted 23 January 2001



# KPC producers Enterobacterales-2021



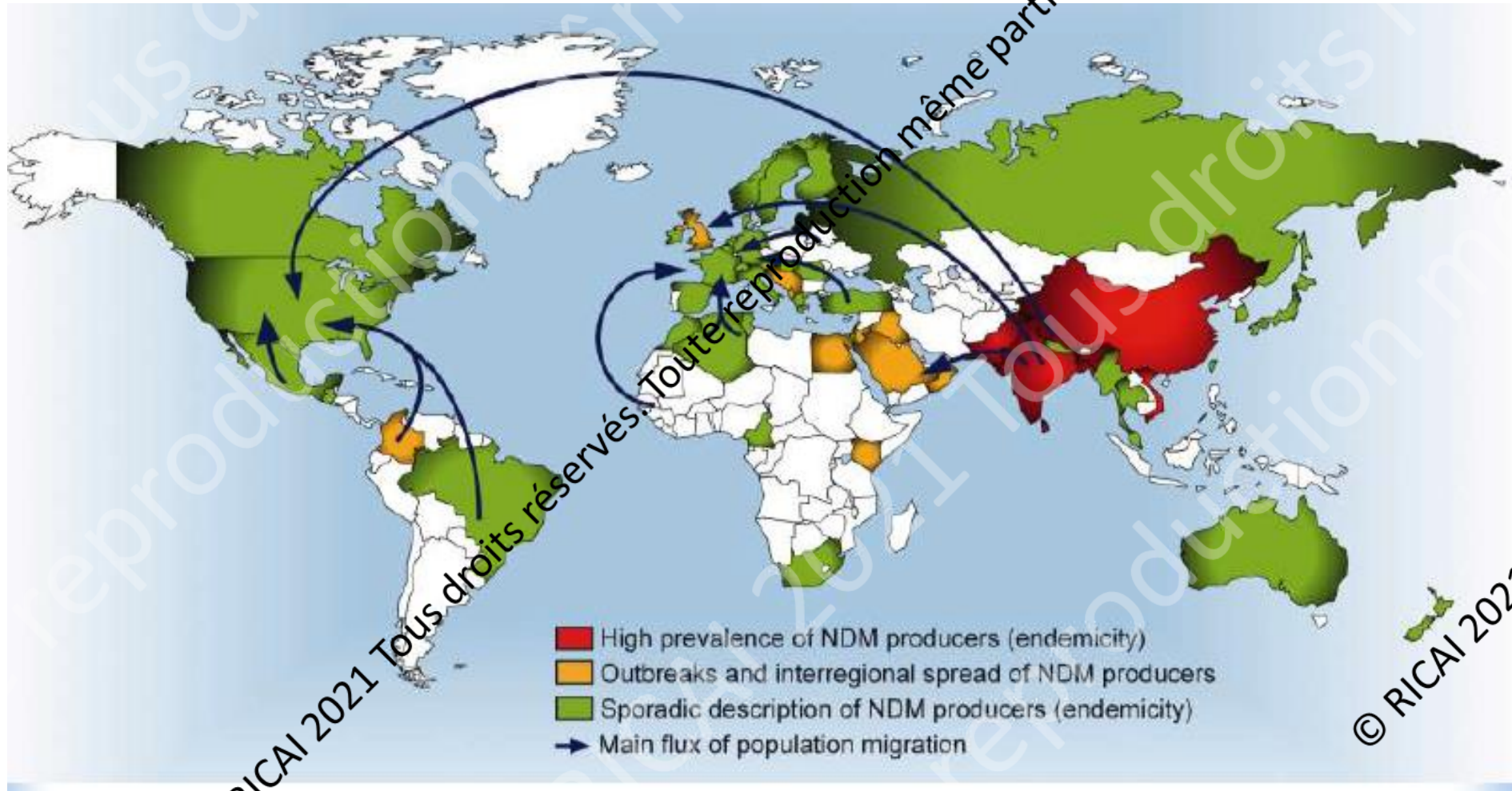
# Characterization of a New Metallo- $\beta$ -Lactamase Gene, *bla*<sub>NDM-1</sub>, and a Novel Erythromycin Esterase Gene Carried on a Unique Genetic Structure in *Klebsiella pneumoniae* Sequence Type 14 from India<sup>∇</sup>

Dongeun Yong,<sup>1,2</sup> Mark A. Toleman,<sup>2</sup> Christian G. Giske,<sup>3</sup> Hyun S. Cho,<sup>4</sup> Kristina Sundman,<sup>5</sup> Kyungwon Lee,<sup>1</sup> and Timothy R. Walsh<sup>2\*</sup>

Yonsei University College of Medicine, Research Institute of Antimicrobial Resistance, Seoul, Republic of Korea<sup>1</sup>; Department of Medical Microbiology, Cardiff University, Cardiff, United Kingdom<sup>2</sup>; Clinical Microbiology, MTC—Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden<sup>3</sup>; Yonsei University College of Life Science and Biotechnology, Seoul, Republic of Korea<sup>4</sup>; and Department of Clinical Microbiology, Örebro University Hospital, Örebro, Sweden<sup>5</sup>

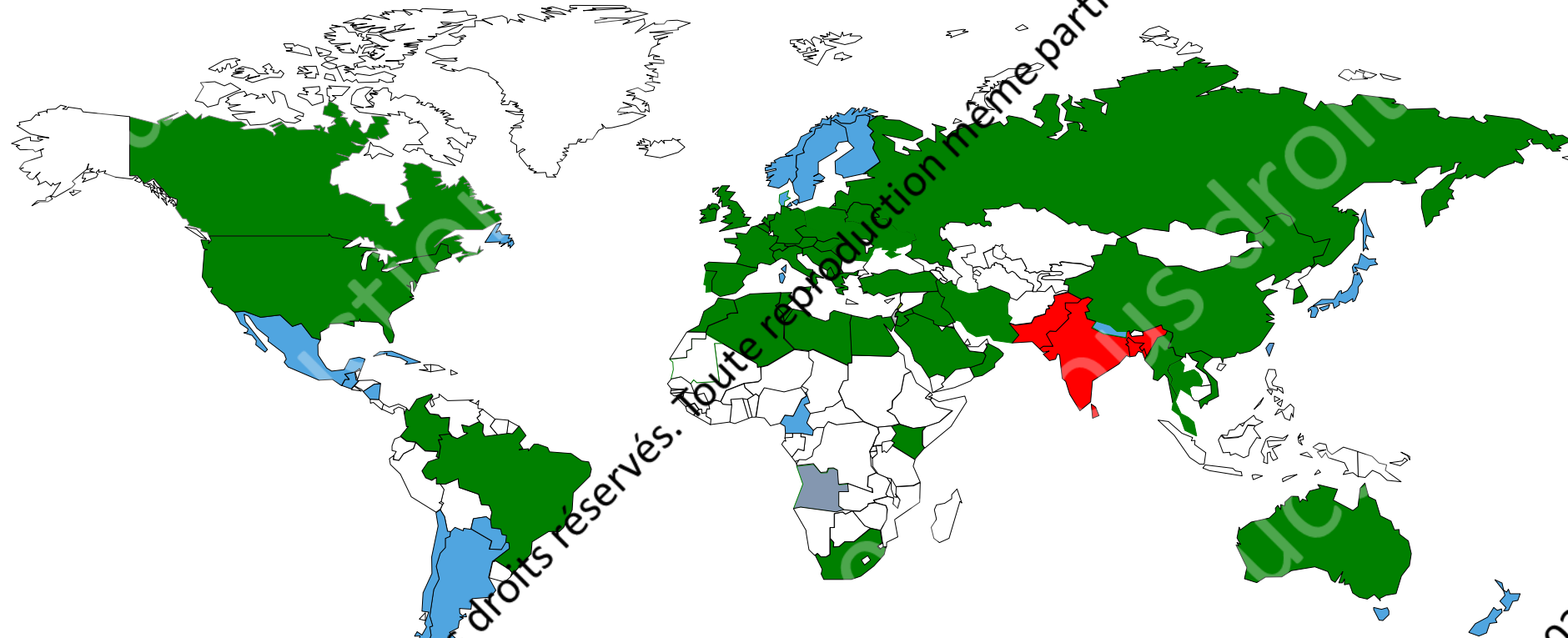


# Worldwide spread of NDM carbapenemases in *Enterobacteriaceae*





# NDM producers- Enterobacterales 2021



Key points:

- Variable resistance levels to carbapenems
- *K. pneumoniae*, *E. coli*, *E. cloacae*...
- Secondary reservoirs; Balkans and the Middle East

- Unknown distribution of NDM producers
- Sporadic spread of NDM producers
- Outbreaks due to NDM producers
- Endemicity of NDM producers

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# OXA-48 + CTX-M-15



ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Jan. 2004, p. 15-22  
0066-4804/04/\$08.00+0 DOI: 10.1128/AAC.48.1.15-22.2004  
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Vol. 48, No. 1

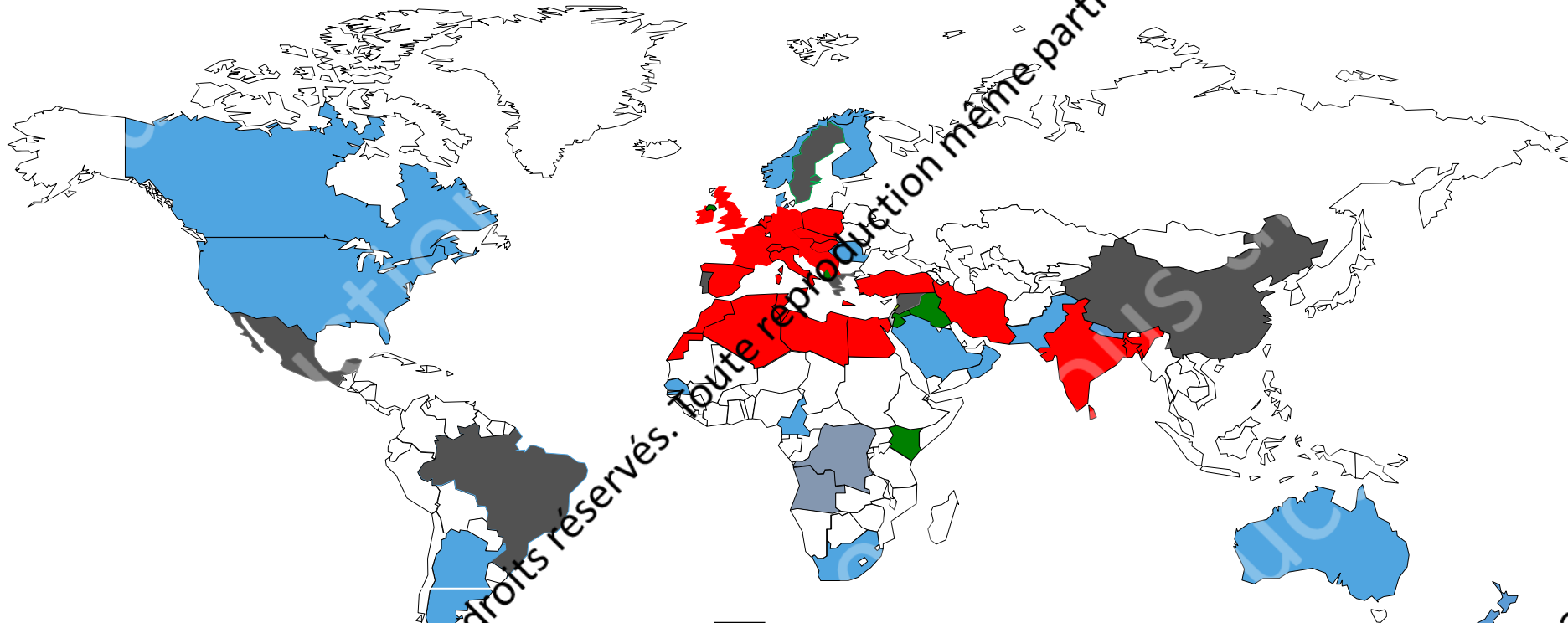
## Emergence of Oxacillinase-Mediated Resistance to Imipenem in *Klebsiella pneumoniae*

Laurent Poirel,<sup>1</sup> Claire Héritier,<sup>1</sup> Venus Tolün,<sup>2</sup> and Patrice Nordmann<sup>1\*</sup>

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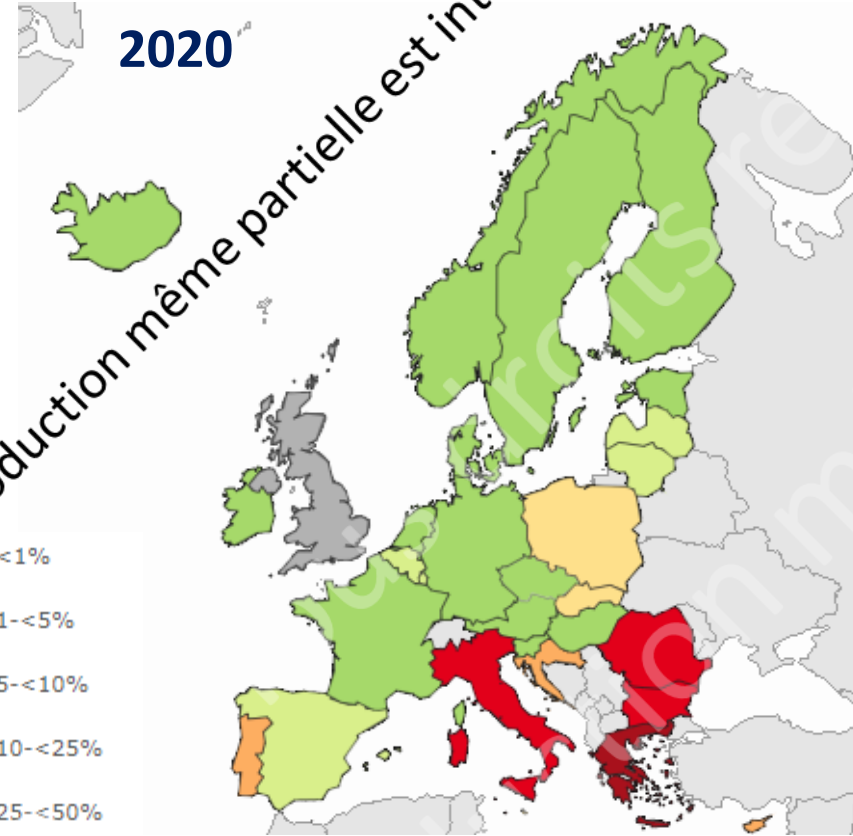
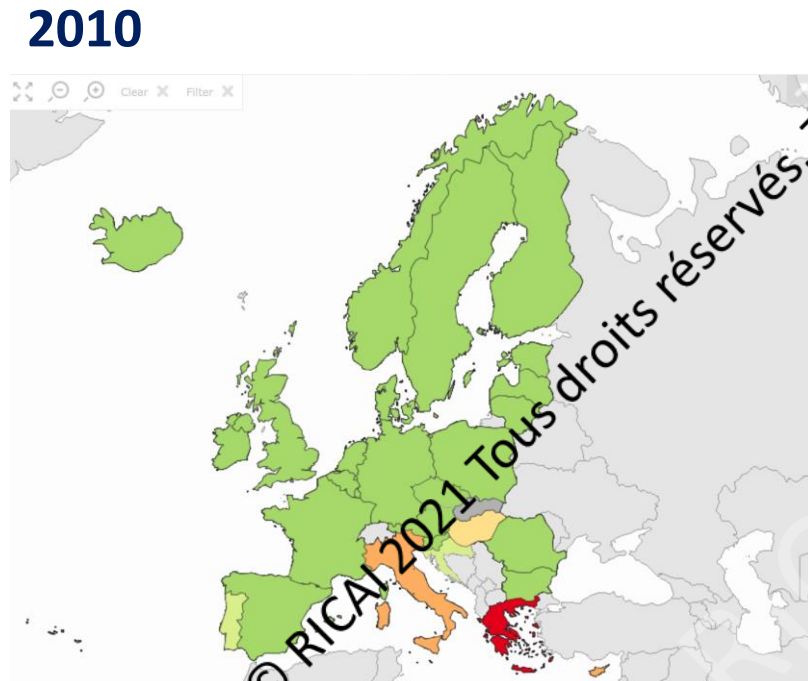
# OXA-48-like producers- *Enterobacteriaceae*, 2021



- Variable resistance levels to carbapenems
- Main known reservoirs; North Africa, Middle East, Turkey and India
- **Community acquisition(+++)** High frequency transfer
- *K.pneumoniae*, *E.cloacae*, *E.coli* (++)

Unknown distribution of OXA-48-like producers  
Sporadic spread of OXA-48-like producers  
Outbreaks due to OXA-48-like producers  
Endemicity of OXA-48-like producers

# Carbapenem-resistant *K. pneumoniae* (invasive isolates)



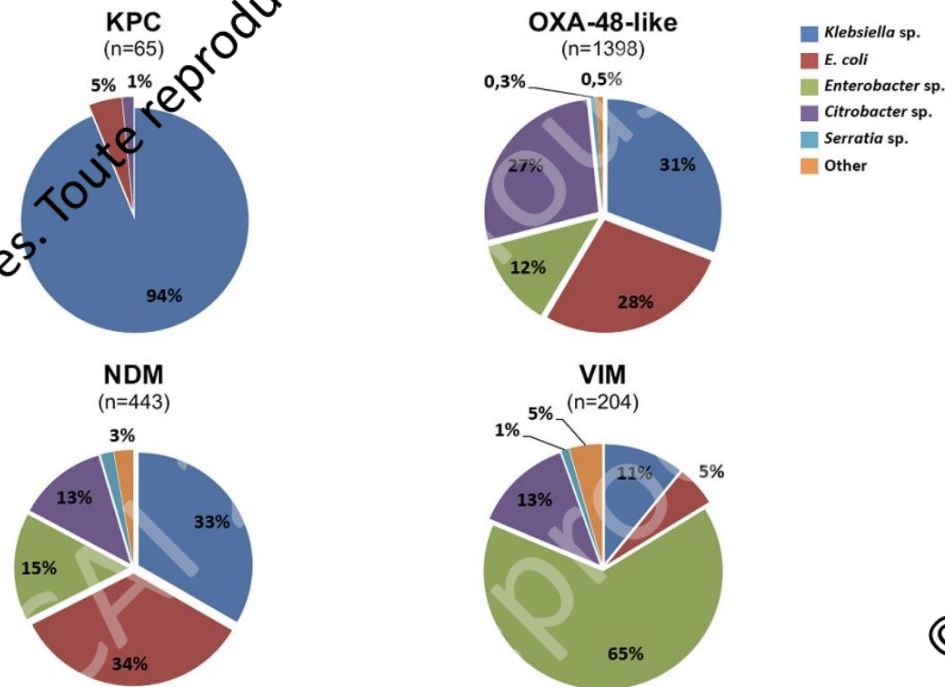
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# CPE in France- 2020

Distribution des EPC par type de carbapénèmase en 2020.

Type de carbanemase	n	%
OXA-48-like	1398	63,3
KPC	65	2,9
NDM	443	20,1
VIM	204	9,2
IMI / NMCA	22	1,0
OXA-48-like + NDM	46	2,1
OXA-48-like + VIM	10	0,6
OXA-48-like + KPC	1	0,05
NDM + VIM	6	0,3
OXA-48-like + NDM + VIM	1	0,05
OXA-23	11	0,5
GES-5	1	0,05
TOTAL	2208	100

Distribution des différentes espèces d'entérobactéries selon le type de carbapénèmase identifié en 2020.



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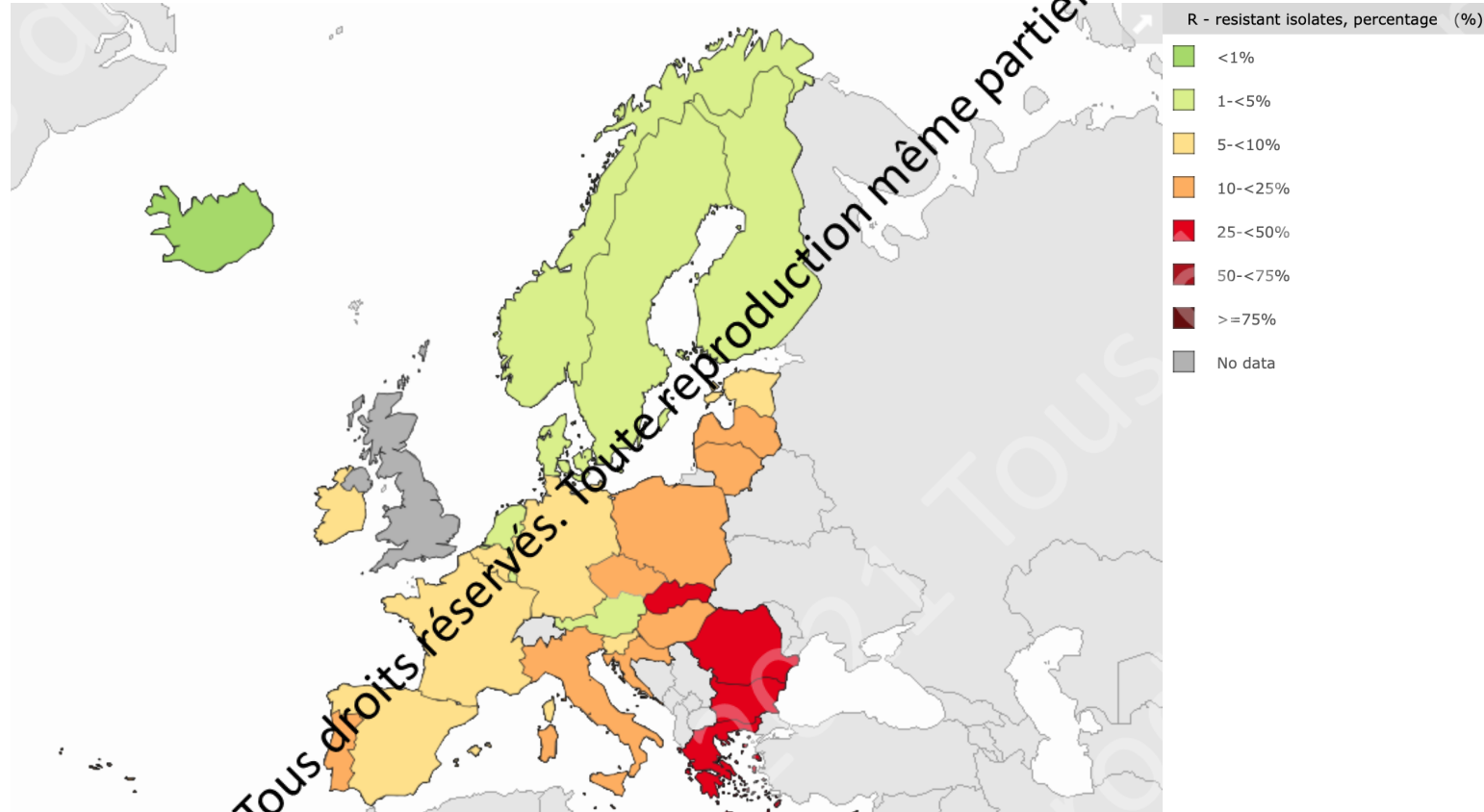
# *Pseudomonas aeruginosa*



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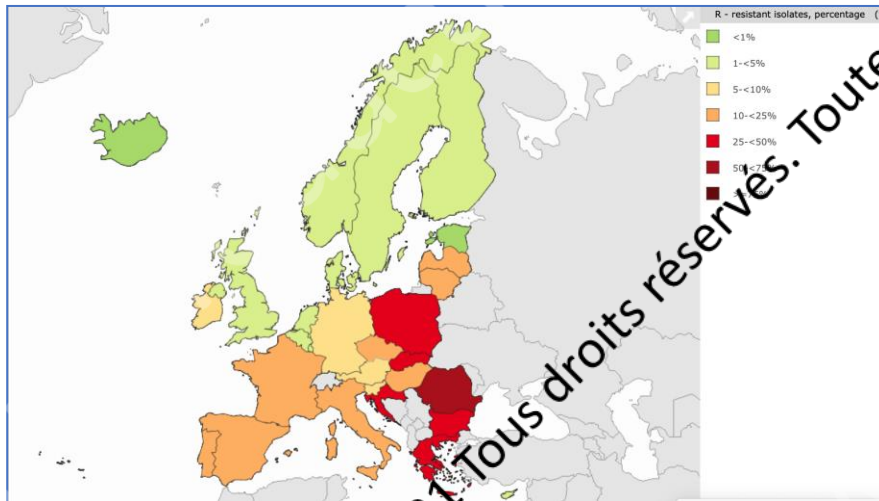
# Multiresistance\* in *P. aeruginosa* (2020)



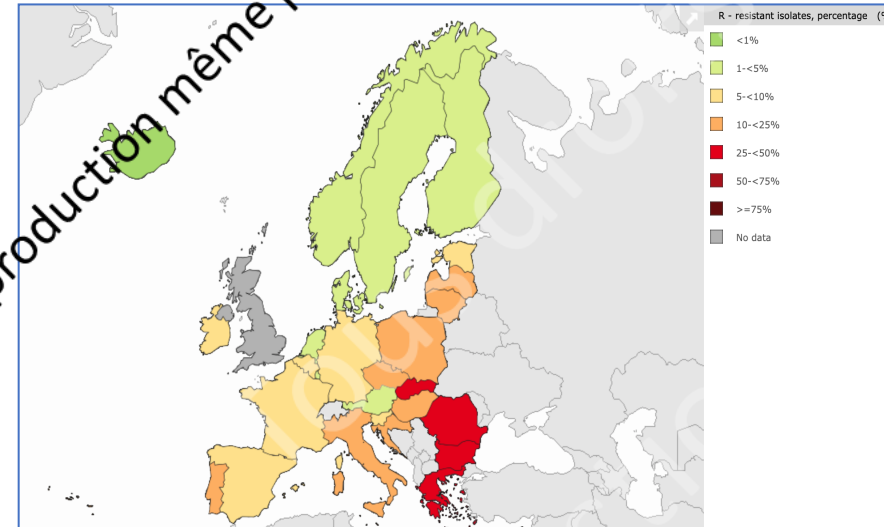
\*Resistance to three or more than three antibiotics or antibiotic families (piperacillin/tazobactam, ceftazidime, aminoglycosides, fluoroquinolones, carbapenems)

# Multiresistance\* in *P. aeruginosa* (2015/2020)

2015



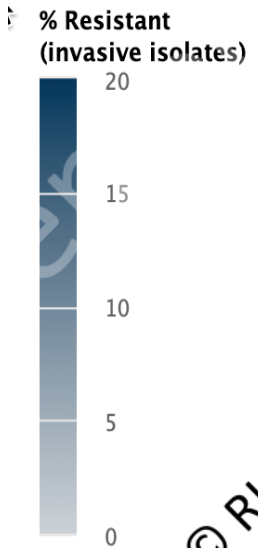
2020



\*Resistance to three or more than three antibiotics or antibiotic families  
(piperacillin/tazobactam, ceftazidime, aminoglycosides, fluoroquinolones, carbapenems)



# Resistance of *Pseudomonas aeruginosa* to Polymyxins



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# *Acinetobacter baumannii*

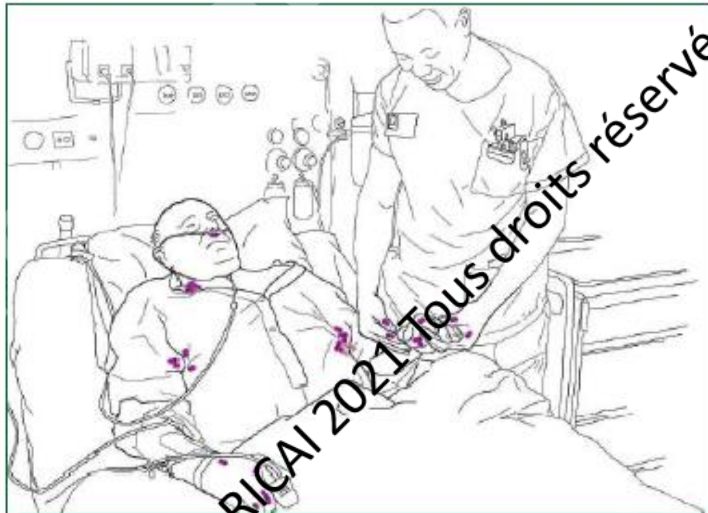
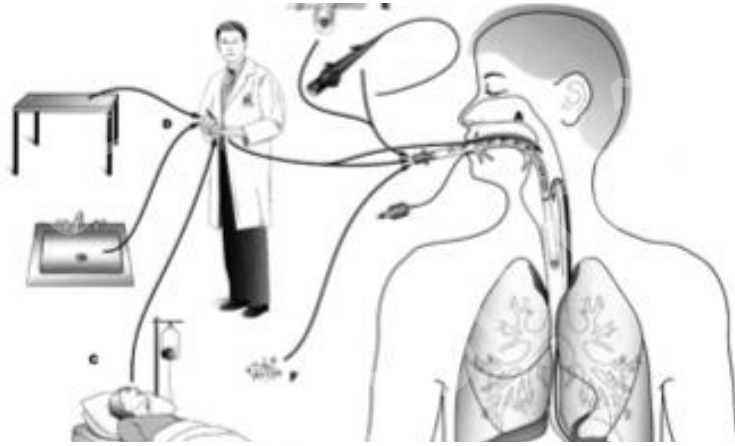
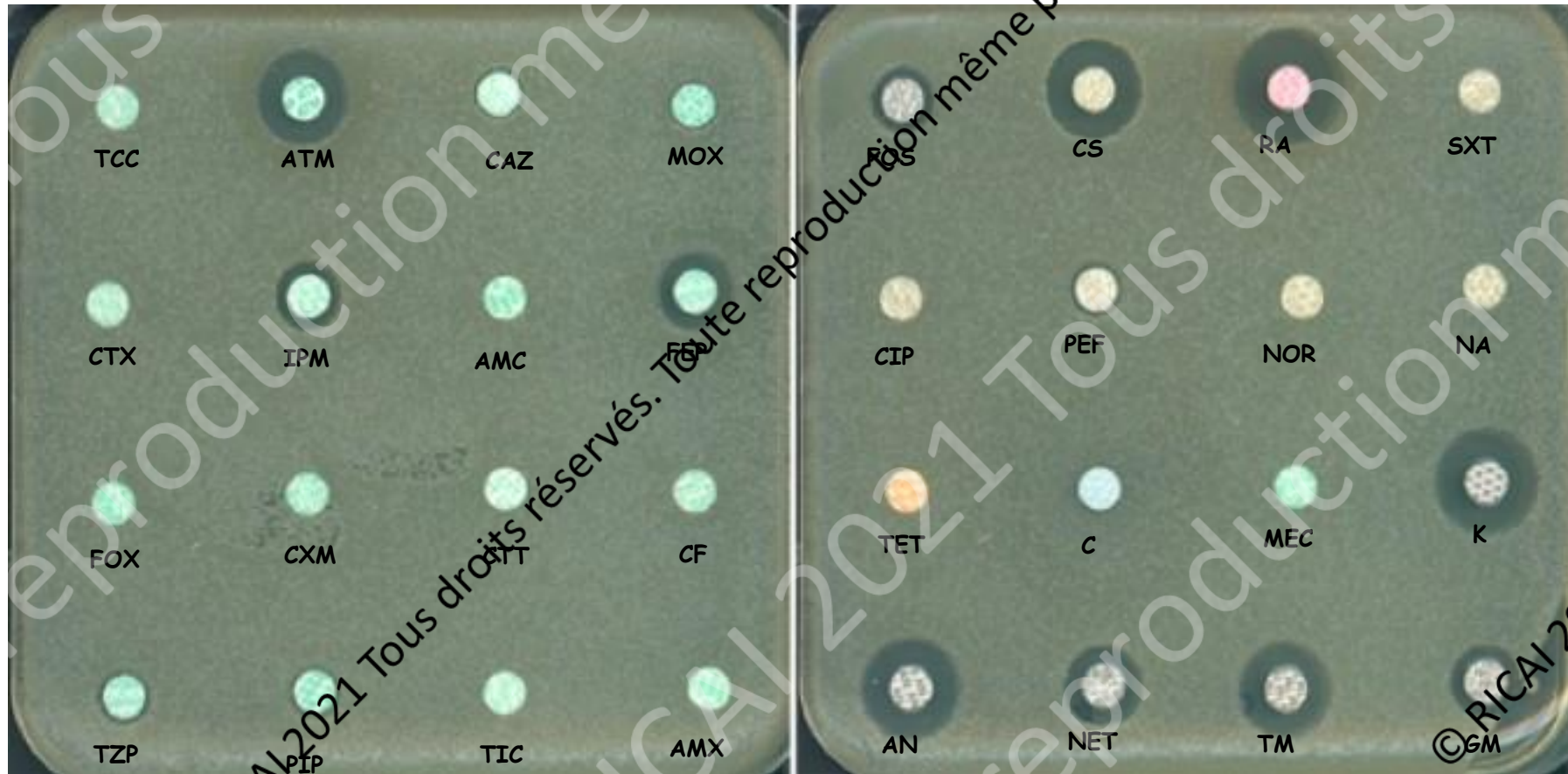


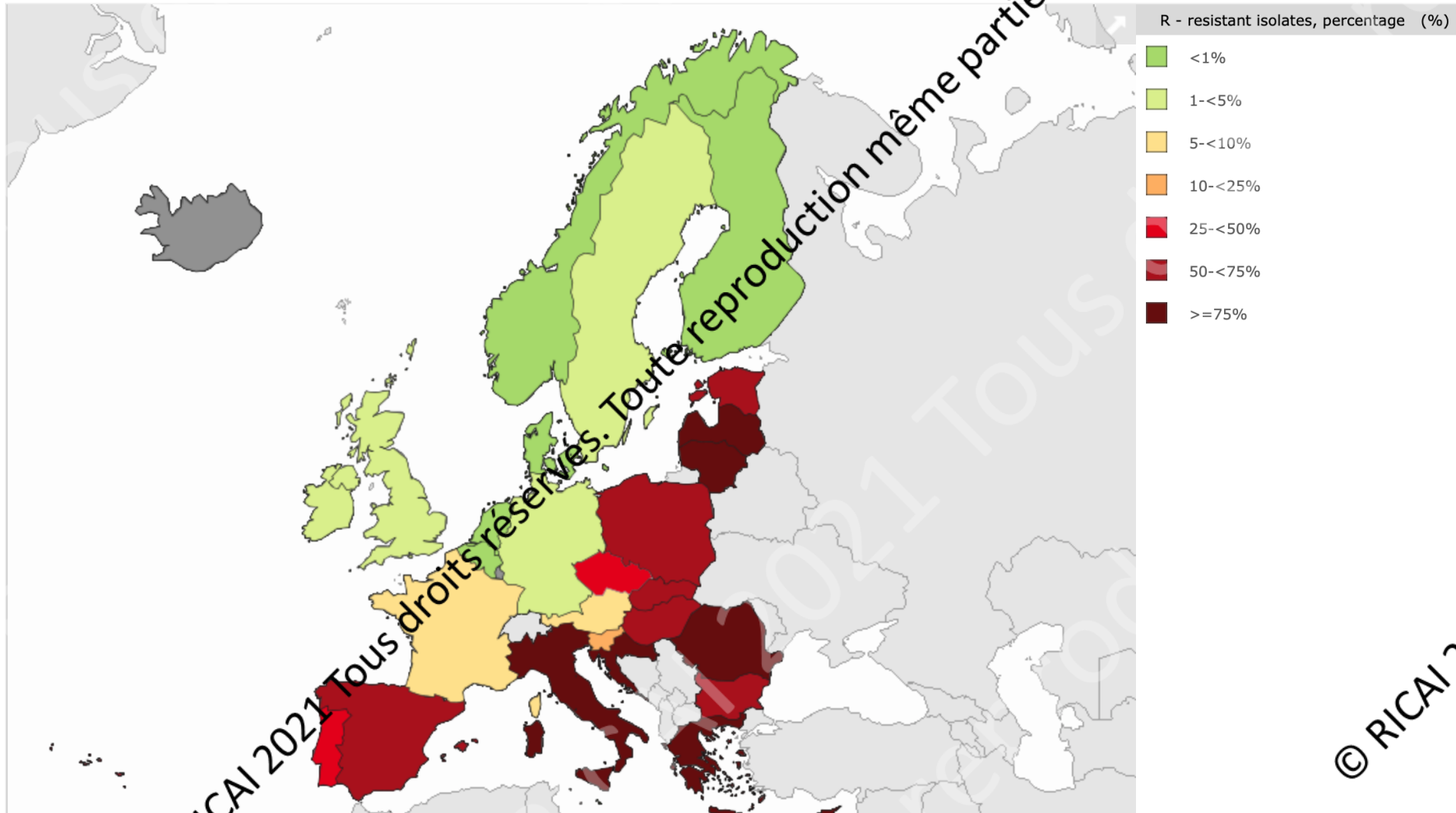
Figure 2: Organism transfer from patient to health-care worker's hands  
Contact between the health-care worker and the patient results in cross-transmission of microorganisms. In this case, Gram-positive cocci from the patient's own flora.

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# Multidrug-resistant *A. baumannii* OXA-23



# Carbapenem resistance *A. baumannii* 2019 (invasive isolates)



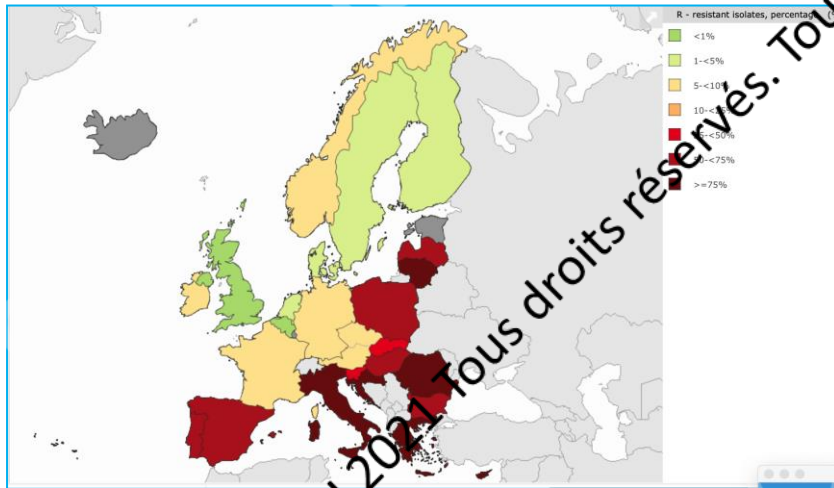
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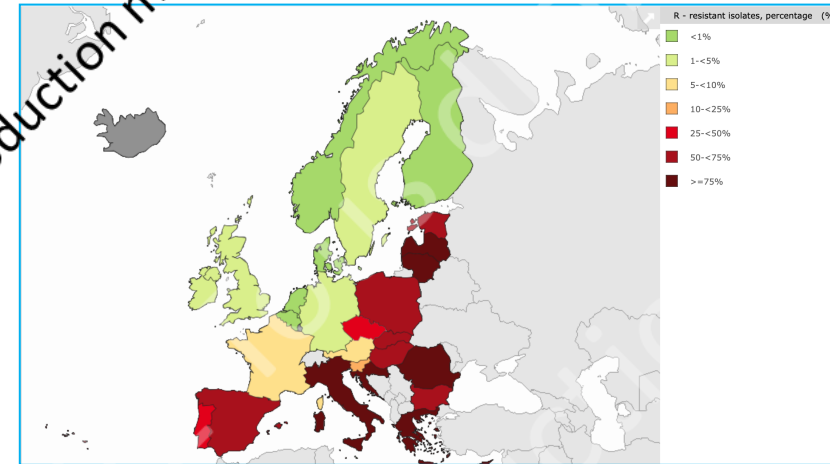
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# Carbapenem resistance *A. baumannii* 2015- 2019 (invasive isolates)

2015



2020



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# Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis

Alessandro Cassini, Liselotte Diaz Högberg, Diamantis Plachouras, Annalisa Quattrocchi, Ana Hoxha, Gunnar Skov Simonsen, Mélanie Colomb-Cotinat, Mirjam E Kretzschmar, Brecht Devleeschauwer, Michele Cecchini, Driss Ait Ouakrim, Tiago Cravo Oliveira, Marc J Struelens, Carl Suetens, Dominique L Monnet, and the Burden of AMR Collaborative Group\*

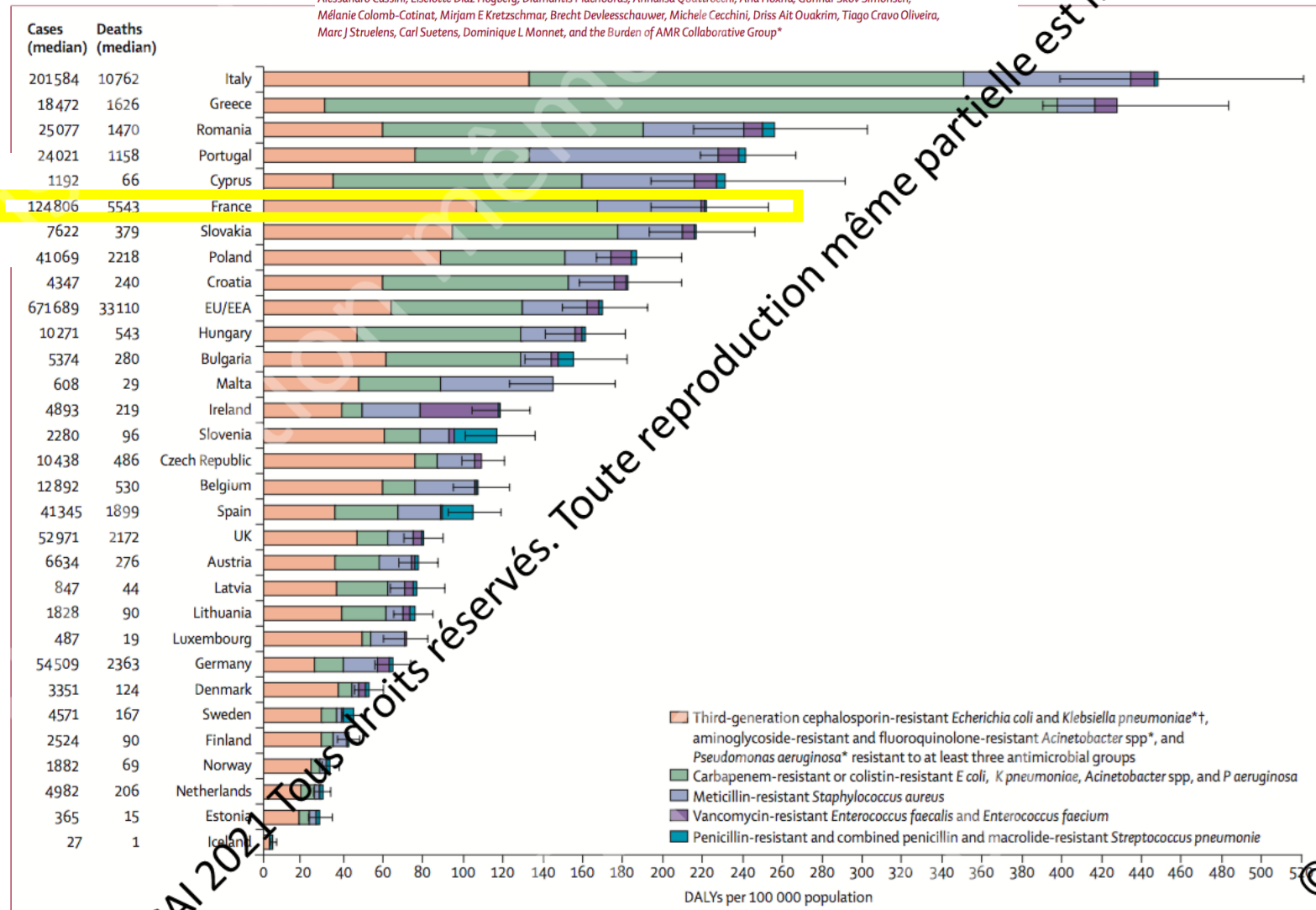


Figure 3: Burden of infections with antibiotic-resistant bacteria in DALYs, EU and European Economic Area, 2015

# Perspectives



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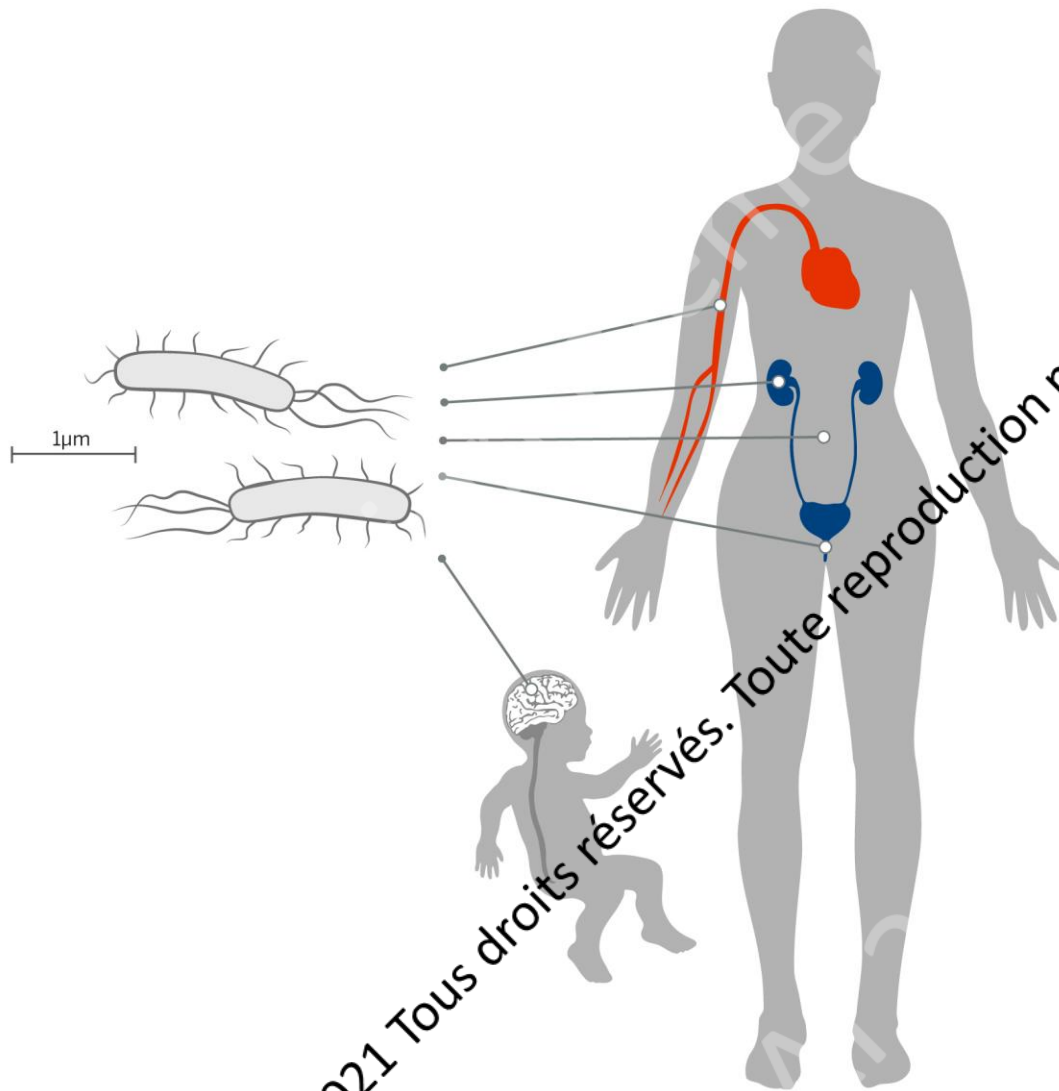
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Source: bioMérieux

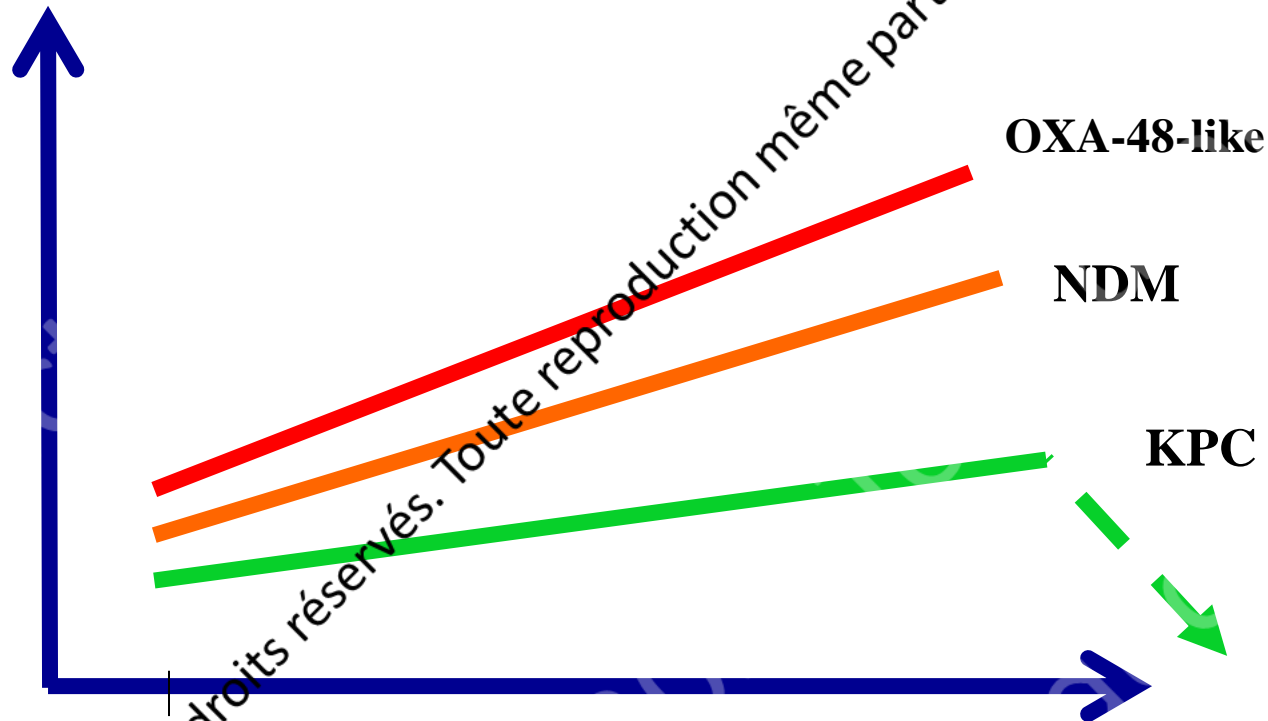
## Most frequent infections caused by *Escherichia coli*

*Escherichia coli* is part of the normal intestinal flora in humans and animals. But when these bacteria appear in areas where they should not be present (e.g. by self-infection) or when a specific disease-causing strain starts circulating between animals, food and humans, it can cause a variety of infections:

- Community and hospital-acquired urinary tract infections.
- Bloodstream infections and intra-abdominal infections such as peritonitis.
- Meningitis in neonates.
- Food-borne infections. For instance, the O157 strain of *E. coli* is known for its ability to secrete the Shiga toxin and cause fever, nausea, vomiting, stomach cramps and potentially fatal diarrhoea.

*E. coli* is increasingly resistant to antibiotics such as quinolones and 3<sup>rd</sup> generation cephalosporins.

# Future spread of carbapenemase producers in *Enterobacterale*



OXA-48: *E. coli* ++, community-acquired, highly transferable plasmid  
NDM: *Enterobacteriaceae*, community- and hospital-acquired  
KPC; *K. pneumoniae*, hospital-acquired

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**Carbapenemase producers are spreading now also in the community; NDM and OXA-48 likes**



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## Difficult detection: *E. coli* OXA-244 (OXA-48-like)



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## Multiple colonization with carbapenem-resistant Gram-negative bacteria acquired in India and transferred to Switzerland

Linda Mueller<sup>1,2</sup> · Cornelia Ottiger<sup>3</sup> · Anthony Demord<sup>1,2</sup> · Laurent Poirel<sup>1,4</sup> · Patrice Nordmann<sup>1,2,4,5</sup>

Strain	β-lactamase resistance determinant			Non β-lactamase resistance determinant 16S rRNA methyltransferase
	Carbapenemase	ESBL	Cephalosporinase	
<i>E. coli</i> (C+I)	NDM-5	CTX-M-15	–	–
<i>K. pneumoniae</i> (C+I)	–	CTX-M-15	–	–
<i>P. rettgeri</i> (C)	NDM-5	–	CMY	ArmA
<i>E. cloacae</i> (C)	NDM-1	CTX-M-15	–	ArmA
<i>P. aeruginosa</i> (C)	VIM-2	–	–	–
<i>A. baumannii</i> (C+I)	NDM-1	–	–	–

C patient colonized, C+I patient colonized and infected (rectal abscess)

# Paving the way to pandrug resistance: *in K. pneumoniae*

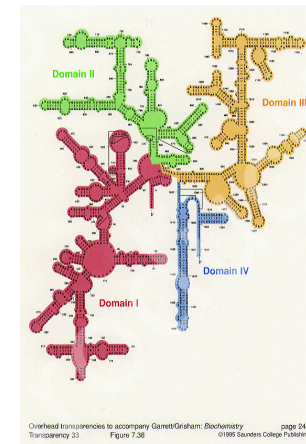
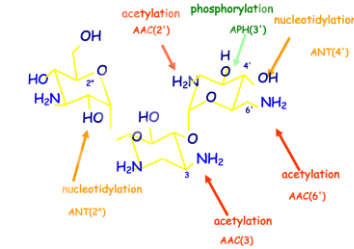
## Methylases conferring resistance to all aminoglycosides ;



**NDM-1**

**RmtF**

Common mechanisms of resistance to aminoglycosides



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## To pandrug resistance with multiple carbapenemases



*K. pneumoniae* ESBL, NDM-1, OXA-232

**Treatment with colistin = additional resistance to colistin !**

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## National survey of colistin resistance among carbapenemase-producing *Enterobacteriaceae* and outbreak caused by colistin-resistant OXA-48-producing *Klebsiella pneumoniae*, France, 2014

A Jayol<sup>1</sup>, L Poirel<sup>1</sup>, L Dortet<sup>2,3,4</sup>, P Nordmann<sup>1,2,5</sup>

1. Emerging Antibiotic Resistance Unit, Medical and Molecular Microbiology, Department of Medicine, University of Fribourg, Fribourg, Switzerland
2. Associated National Reference Centre for Antibiotic Resistance, Le Kremlin-Bicêtre, France
3. Faculty of Medicine, South-Paris University, Le Kremlin-Bicêtre, France
4. Bacteriology-Hygiene unit, Hospital Bicêtre, Assistance Publique /Hôpitaux de Paris, Le Kremlin-Bicêtre, France
5. University of Lausanne and University Hospital Center, Lausanne, Switzerland

Correspondence: Laurent Poirel (laurent.poirel@unifr.ch)

Citation style for this article:

Jayol A, Poirel L, Dortet L, Nordmann P. National survey of colistin resistance among carbapenemase-producing *Enterobacteriaceae* and outbreak caused by colistin-resistant OXA-48-producing *Klebsiella pneumoniae*, France, 2014. *Euro Surveill.* 2016;21(37):pii=30339. DOI: <http://dx.doi.org/10.2807/1560-7917.ES.2016.21.37.30339>

Article submitted on 30 October 2015 / accepted on 04 April 2016 / published on 15 September 2016

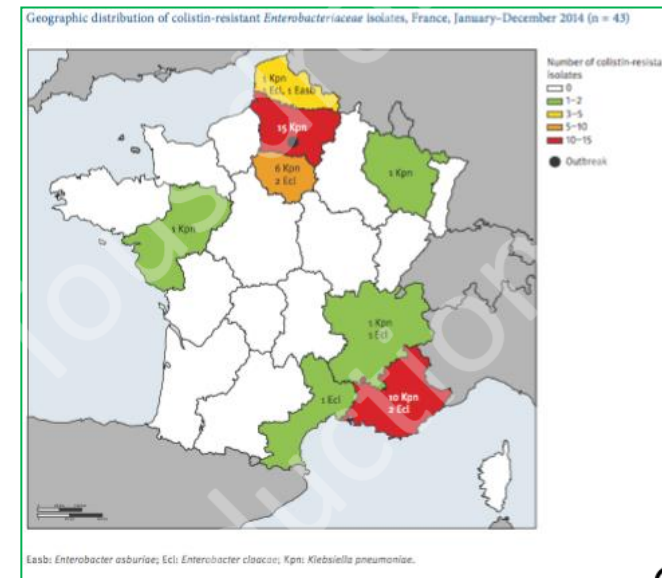
From January 2014 to December 2014, 972 consecutive non- replicate carbapenemase-producing *Enterobacteriaceae* isolates from colonised or infected patients were collected at the Associated French National Reference Centre as part of the French national survey on antimicrobial resistance. It included 577 *Klebsiella* spp. (59%), 236 *Escherichia coli* (24%), 108 *Enterobacter* spp. (11%), 50 *Citrobacter* spp. (5%), and a single *Salmonella* spp. isolate (0.1%). Of 561 *K. pneumoniae* isolates, 35 were found to be resistant to colistin (6.2%). PFGE analysis revealed a clonal outbreak involving 15 *K. pneumoniae* isolates belonging to sequence type ST11, recovered in a single hospital in the Picardie region in northern France. Those clonally related isolates showed variable levels of resistance to colistin, ranging from 4 to 64 mg. They harboured the *bla*<sub>OXA-48</sub> carbapenemase gene and the *bla*<sub>CTX-M-15</sub> extended-spectrum beta-lactamase gene. Among the 91 *Enterobacter cloacae* isolates, seven were resistant to colistin and produced different types of carbapenemases. Surprisingly, none of the *E. coli* and *Citrobacter* spp. isolates showed resistance to colistin. This national survey including carbapenemase-producing isolates recovered in 2014 reported a high rate of colistin resistance in *K. pneumoniae* and *E. cloacae* (6.2% and 7.7%, respectively) in France.

currently almost unknown in most parts of the world. In Italy, an increase in carbapenemase-producing *Enterobacteriaceae* has been noted in the past years, but the situation remains unknown in France [1]. The lack of information about the prevalence of colistin resistance among multidrug-resistant enterobacterial isolates derives from several reasons: (i) so far, there has been limited interest in that field, (ii) methods used for determination of colistin susceptibility are not adequate, and (iii) the lack of well-defined breakpoints does not allow precise determination of prevalence. However, the recent identification of a plasmid-borne colistin resistance determinant (MCR-1) raised a very serious concern in that resistance to colistin might widely disseminate [2].

The aim of this study was to evaluate retrospectively the prevalence of colistin resistance among a collection of CPE strains recovered in France during a period of one year and to analyse the phenotypic, genotypic features and clonality of the colistin-resistant isolates.

### Methods

#### Carbapenemase-producing *Enterobacteriaceae* isolates



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Letter to the Editor

# Hypervirulent *Klebsiella pneumoniae* ST23 producing OXA-48 in Switzerland

Dominique S. Blanc<sup>1, 2</sup>, Laurent Poirel<sup>2, 3, 4</sup>, Mathias Van Singer<sup>1</sup>, Gilbert Greub<sup>5</sup>, Patrice Nordmann<sup>2, 3, 4, 5</sup>

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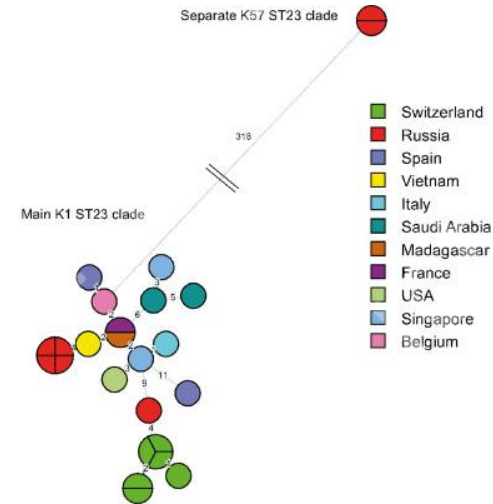
Sir,

The population of *Klebsiella pneumoniae* (Kp) is composed of genetically diverse strains that may be gathered in two distinct groups: classical Kp associated with nosocomial infections and less common hypervirulent Kp (hvKp) associated with more severe and aggressive infections, often recovered from healthy and community-residing individuals [1]. First reported from East Asia, the hvKp strains were generally quite susceptible to antibiotics. However, hvKp like classical Kp may also be reservoirs of several antibiotic resistance determinants, including the problematic carbapenemases (mostly of the KPC and OXA-48 types [1, 2]). Such association of high-level virulence and high-level resistance explains the high threat made by the circulation of those strains in the community. Those latter belong to a relatively small number of clonal backgrounds and therefore sequence types (STs), as shown through multilocus sequence typing (MLST) with sequence type (ST) ST23 being the most prevalent clone worldwide and particularly in China [1, 2]. A warning on possible emergence of hvKp ST23 producing carbapenemases in EU/EEA has been published very recently [3].

Here, we report the case of a 25 years-old Russian patient who had been firstly hospitalized in Russia for multiple orthopedic trauma. He was then hospitalized at the University hospital of Lausanne in 2018 for treatment of several bone injuries and bone infection. Upon admission, but along the entire year of his hospitalization, a total of 6 Kp isolates (namely Kp1 to Kp6) were identified while screening for carbapenemase producing isolates in his rectal flora by using the selective SuperCarba medium (CHROMagar mSuperCABA, CHROMagar, Paris France)

Table 1. Genetic features associated with the different *K. pneumoniae* isolates.

Strain	ST type	$\beta$ -lactamase content	Other resistance determinants	Colistin resistance determinants	Virulence determinants <sup>a</sup>
Kp1	ST23	OXA-48, CTX-M-15, TEM-1, SHV-11	dfrA14, sul2, QnrB1	MgrB stop codon	<i>rmpA2</i> , <i>ybt1</i> , <i>iuc1</i> , <i>cb2</i>  <i>strA</i> , <i>strB</i>
Kp2	ST23	OXA-48, CTX-M-15, TEM-1, SHV-11	dfrA14, sul2, QnrB1	MgrB stop codon	<i>rmpA2</i> , <i>ybt1</i> , <i>iuc1</i> , <i>cb2</i>  <i>strA</i> , <i>strB</i>
Kp3	ST23	OXA-48, CTX-M-15, TEM-1, SHV-11	dfrA14, sul2, QnrB1	MgrB wild-type	<i>rmpA2</i> , <i>ybt1</i> , <i>iuc1</i> , <i>cb2</i>  <i>strA</i> , <i>strB</i>
Kp4	ST23	OXA-48, SHV-11		MgrB wild-type	<i>ybt1</i> , <i>cb2</i>
Kp5	ST23	OXA-48, CTX-M-15, TEM-1, SHV-11	dfrA14, sul2, QnrB1	MgrB wild-type	<i>ybt1</i> , <i>cb2</i>  <i>strA</i> , <i>strB</i>
Kp6	ST23	OXA-48, CTX-M-15, TEM-1, SHV-11	dfrA14, sul2, QnrB1	MgrB wild-type	<i>ybt1</i> , <i>cb2</i>  <i>strA</i> , <i>strB</i>



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**Risk Assessment: Emergence of hypervirulent *Klebsiella pneumoniae* ST23 carrying carbapenemase genes in EU/EEA countries**

17 Mar 2021

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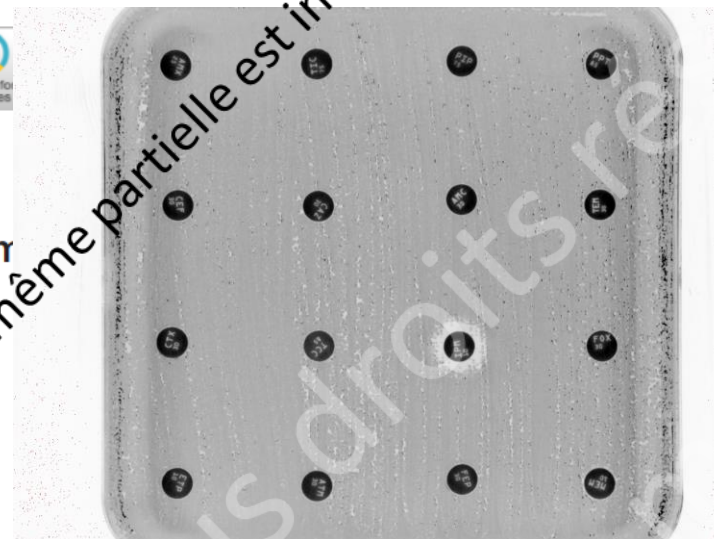


# Phenotypic, Biochemical, and Genetic Analysis of KPC-41, a KPC-3 Variant Conferring Resistance to Ceftazidime-Avibactam and Exhibiting Reduced Carbapenemase Activity

Linda Mueller<sup>a,b,c</sup> Amandine Masseron<sup>a</sup> Guy Prod'Hom<sup>c</sup> Tatiana Galperine<sup>d</sup> Gilbert Greub<sup>c</sup> Laurent Poirel<sup>a,b,e</sup> Patrice Nordmann<sup>a,b,c,e</sup>

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<sup>c</sup>Institut for Microbiology, University Hospital Center and University of Lausanne, Lausanne, Switzerland  
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<sup>e</sup>INSERM European Unit (IAME, France), University of Fribourg, Fribourg, Switzerland

**ABSTRACT** A novel KPC variant, KPC-41, was identified in a *Klebsiella pneumoniae* clinical isolate from Switzerland. This  $\beta$ -lactamase possessed a 3-amino-acid insertion (Pro-Asn-Lys) located between amino acids 269 and 270 compared to the KPC-3 amino acid sequence. Cloning and expression of the *bla*<sub>KPC-41</sub> gene in *Escherichia coli*, followed by determination of MIC values and kinetic parameters, showed that KPC-41, compared to those of KPC-3, has an increased affinity to ceftazidime and a decreased sensitivity to avibactam, leading to resistance to ceftazidime-avibactam once produced in *K. pneumoniae*. Furthermore, KPC-41 exhibited a drastic decrease of its carbapenemase activity. This report highlights that a diversity of KPC variants conferring resistance to ceftazidime-avibactam already circulate in Europe.



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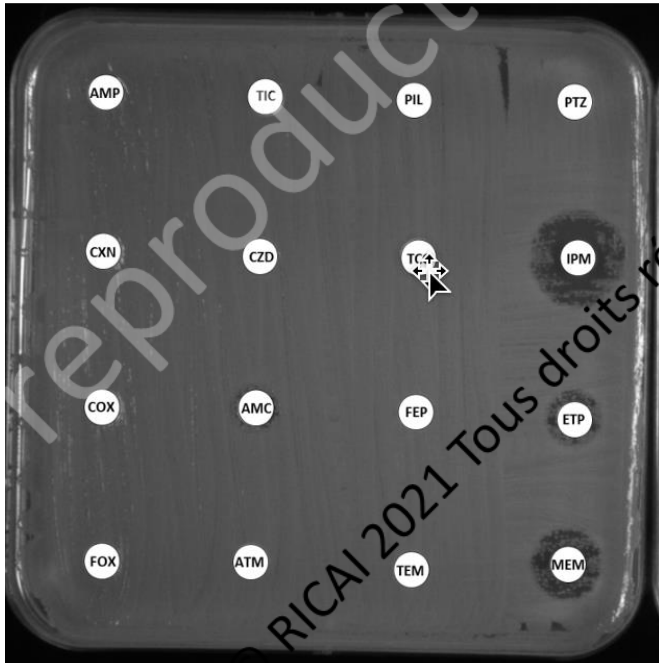
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### Genetic Features Leading to Reduced Susceptibility to Aztreonam-Avibactam among Metallo- $\beta$ -Lactamase-Producing *Escherichia coli* Isolates

Mustafa Sadek,<sup>a</sup> Marco Lunas,<sup>a</sup> Laurent Poirel,<sup>a,b,c</sup> Patrice Nordmann<sup>a,b,c</sup>



PBP-3 insertion+ NDM-5+ cephalosporinase CMY-2-like

TABLE 1 MICs and insertions in the PBP3 sequence of MBL-producing *E. coli* isolates

Strain	ST	Metallo- $\beta$ -lactamase	Other $\beta$ -lactamase(s)	Origin of isolation <sup>a</sup>	MIC ( $\mu$ g/ml) <sup>b</sup>					PBP3 insertion sequence <sup>c</sup>
					ATM	ATM-AVI	CAZ	CAZ-AVI	IMI	
R-3058	ND	NDM-5	CMY-42	Angola	32	16	>256	>256	32	YRIN
R-461	ND	NDM-1	CMY-42	France	32	16	>256	>256	64	YRIN
R-3038	ND	NDM-5	CMY-42	Angola	32	8	>256	>256	16	YRIN
R-3031	ND	NDM-5	CMY-42	Angola	128	8	>256	>256	32	YRIN
N-185	ND	NDM-5	CMY-42	Switzerland	32	8	256	256	16	YRIN
N-590	167	NDM-5	CMY-42	Switzerland	64	8	>256	>256	32	YRIN
N-1013	361	NDM-5	CMY-42	Switzerland	128	8	>256	>256	64	YRIN
N-1076	940	NDM-5	CMY-42, TEM-1B	Switzerland	64	8	>256	>256	32	YRIN

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**Globalization**

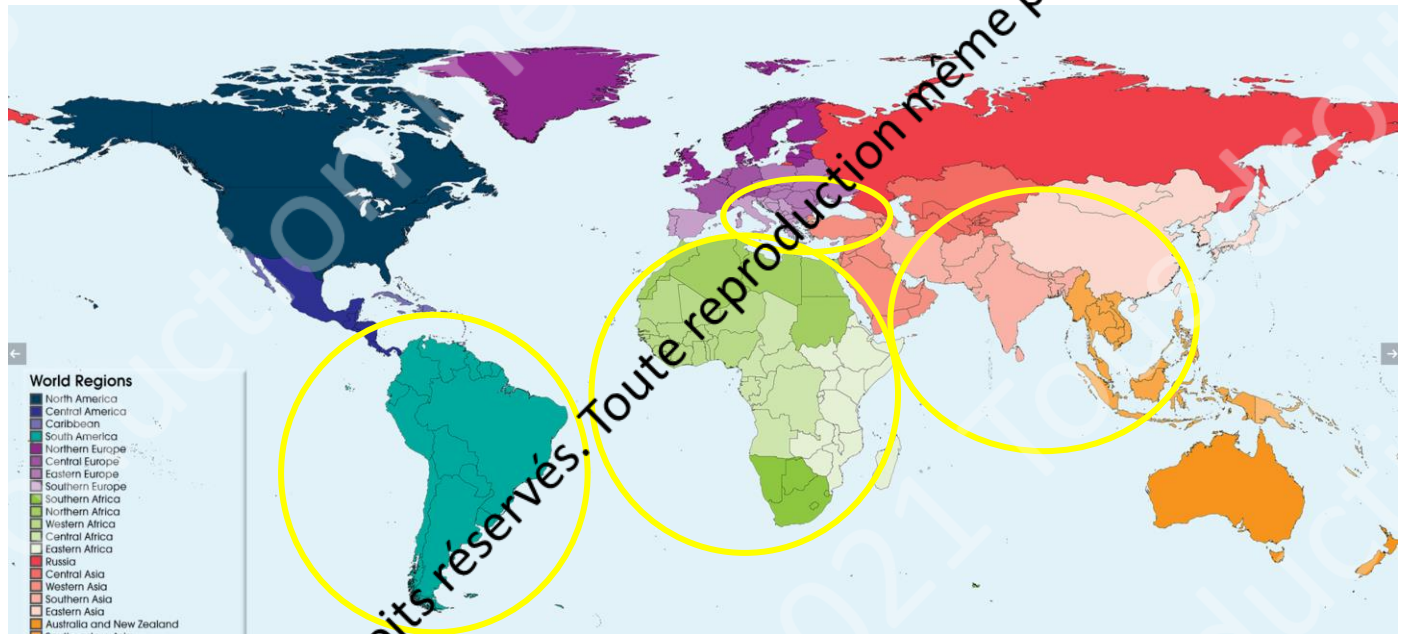


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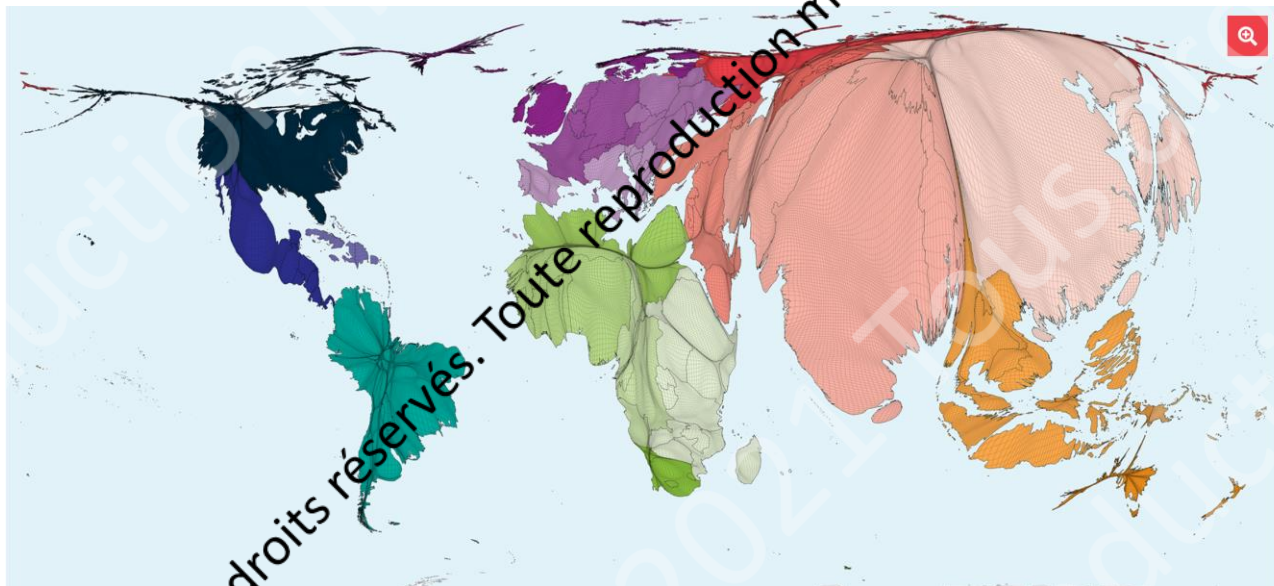
### Which world regions at the origin of MDR bacteria?



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# Worldwide population, 2020



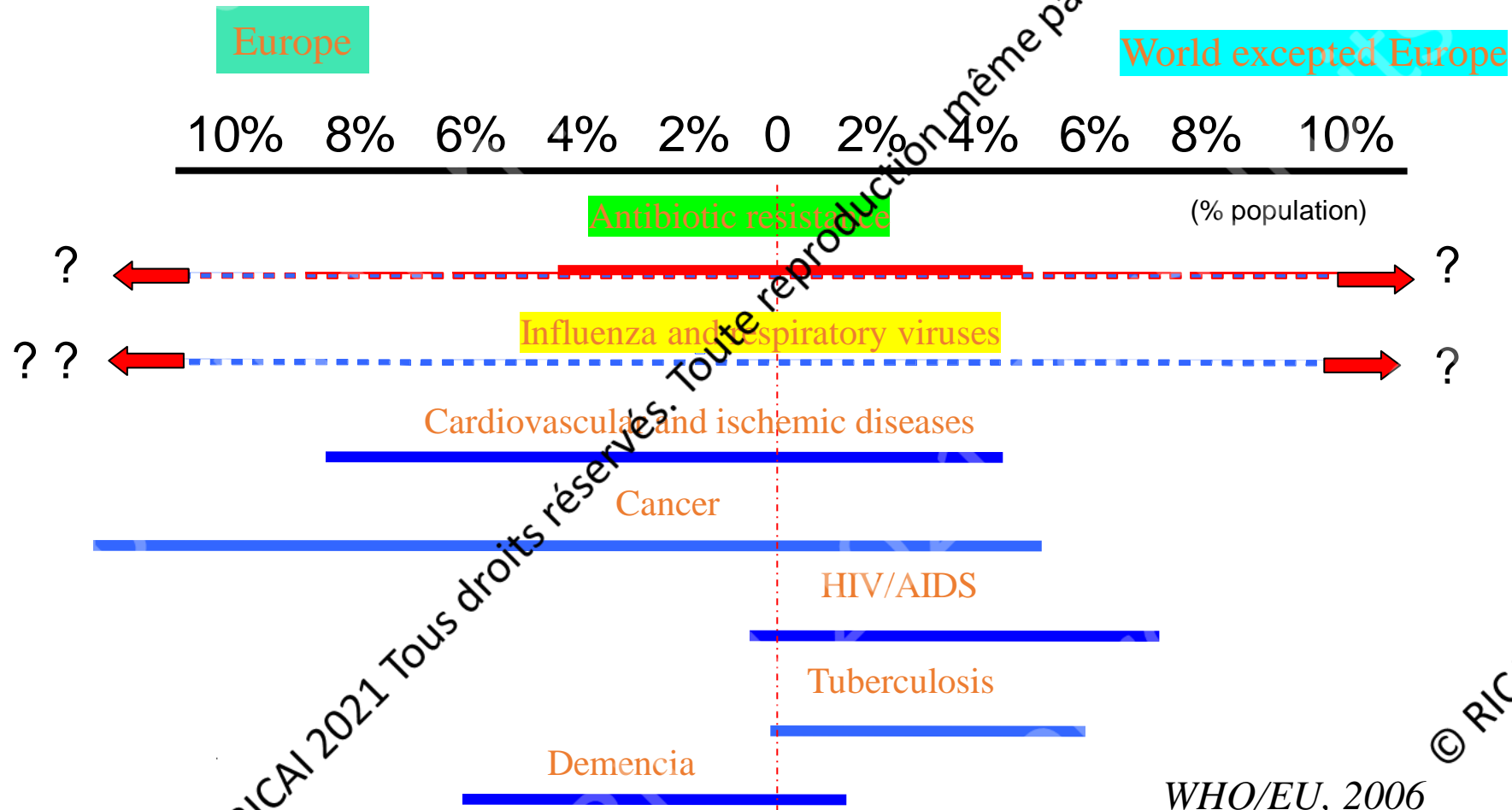
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# Are predictions right ?

## Prediction of mortality for 2016



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WHO/EU, 2006

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# Swiss Medical Weekly

Formerly: Schweizerische Medizinische Wochenschrift

An open access, online journal • [www.smw.ch](http://www.smw.ch)

Viewpoint | Published 18 November 2020 | doi:10.4414/sm.w.20402

Cite this as: Swiss Med Wkly. 2020;150:w20402

## Crisis of emerging antibiotic resistances mirroring that of the COVID-19 in the age of globalisation

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The important things  
are invisible for the eyes

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# Multiple and simultaneous outbreaks occurring worldwide

## Genomics of NDM producers

