Resistance to polymyxins in *Enterobacteriaceae*

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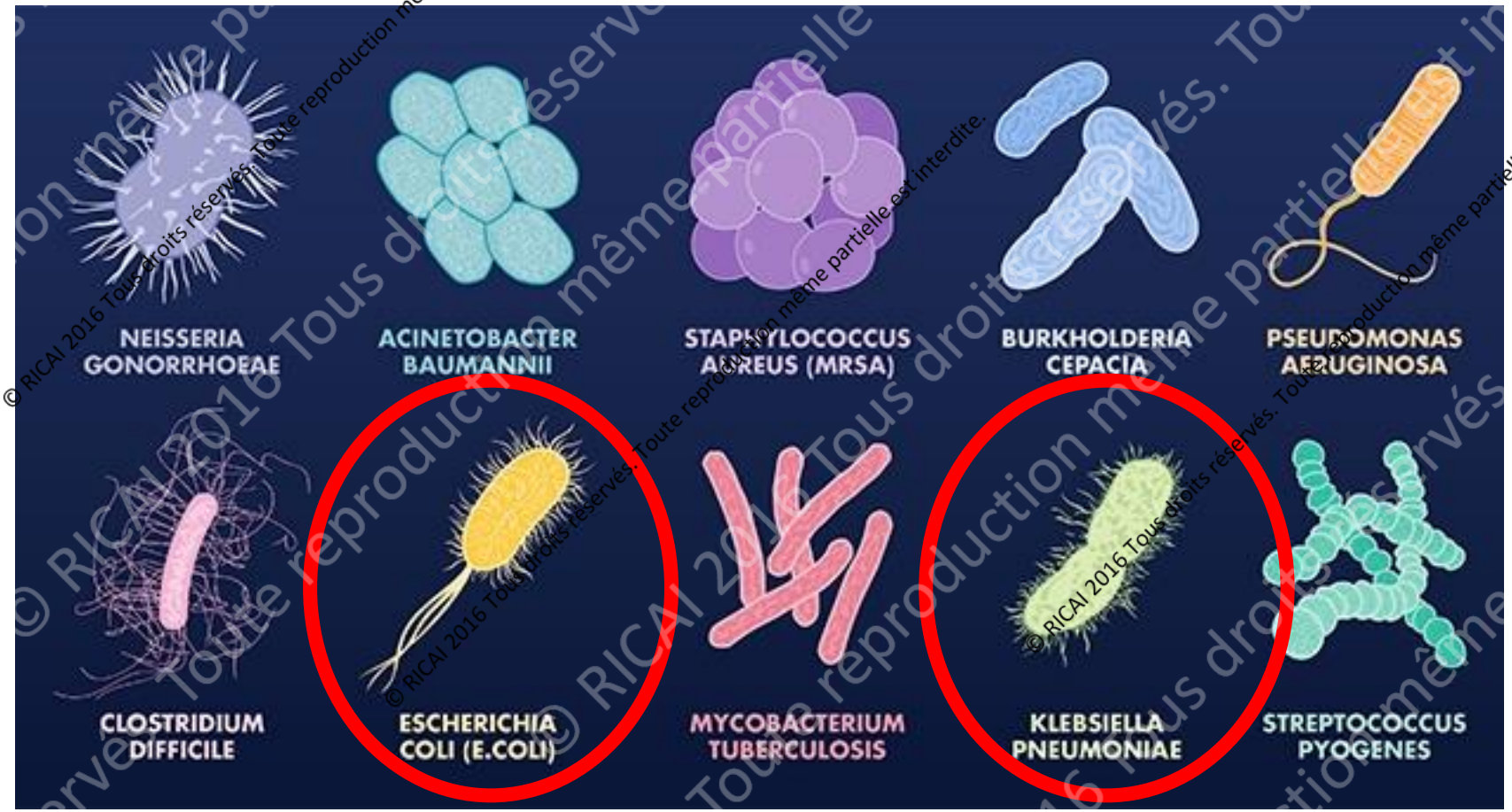
Nationales Referenzlaboratorium zur Früherkennung neuer Antibiotikaresistenzen und Resistenzmechanismen (Switzerland)

Prof. Patrice Nordmann

Most dangerous bacteria…



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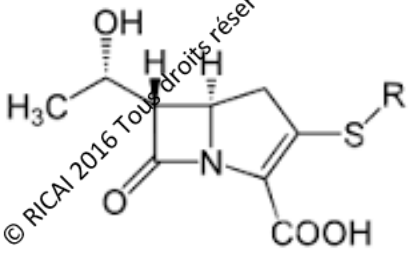
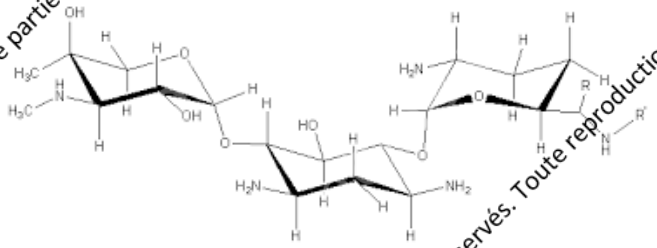
Those emerging antibiotic resistance problems…

Cephalosporins,
Carbapenems



ESBLs
Carbapenemases

Aminoglycosides



16s RNA methylases

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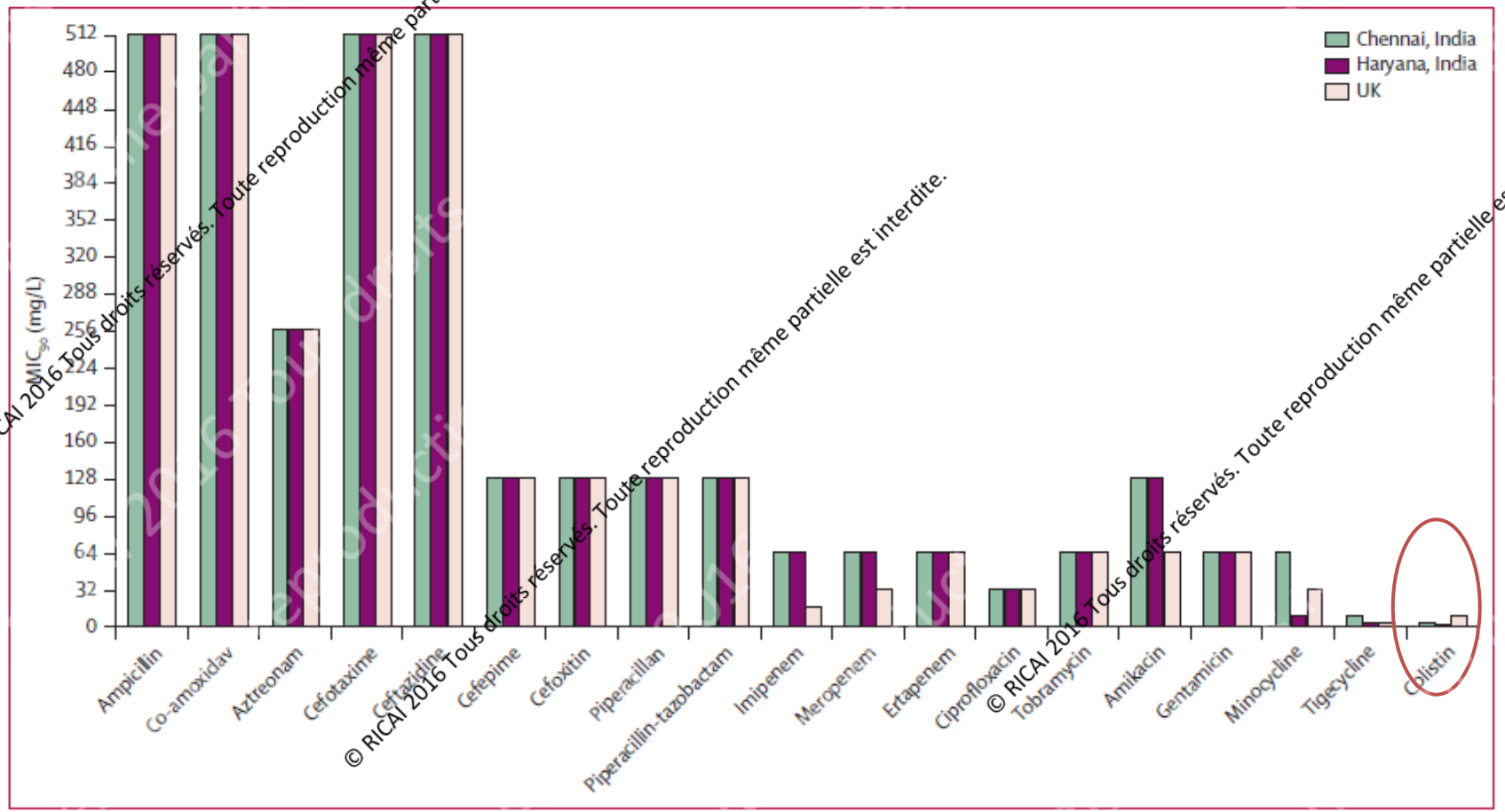
NDM-1 producers in *Enterobacteriaceae*



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Lancet Infect Dis 2010;
10: 597–602

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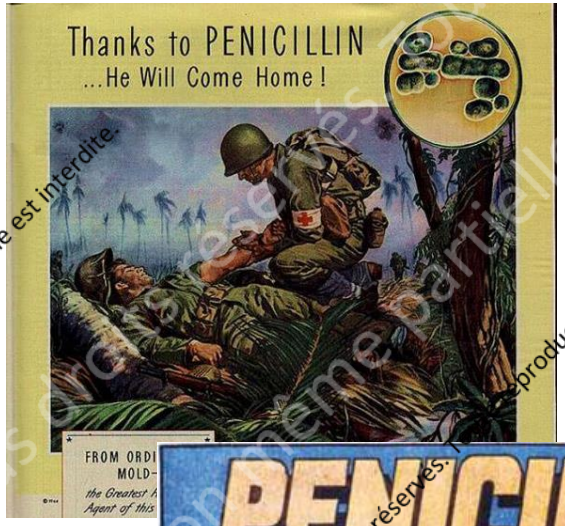

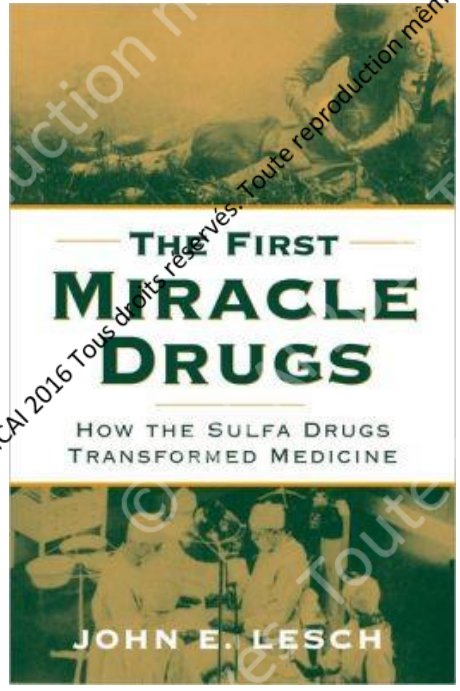

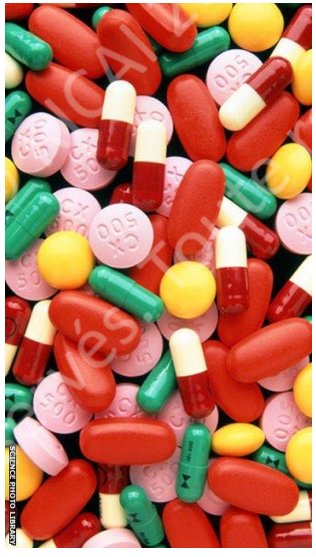

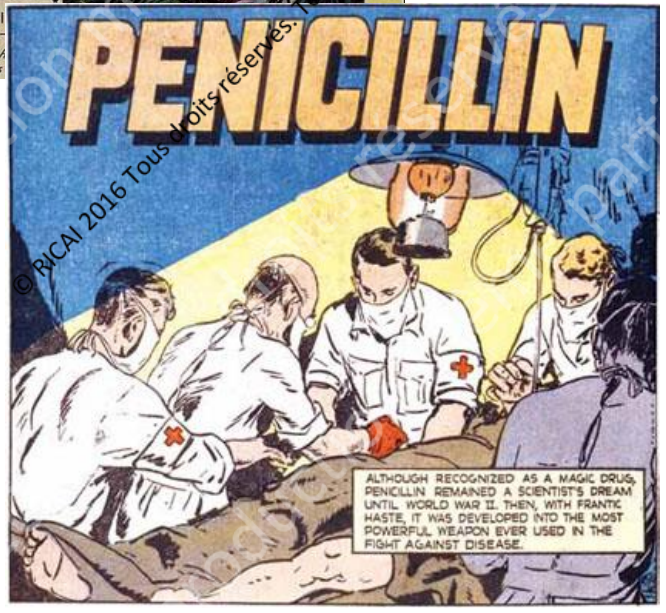

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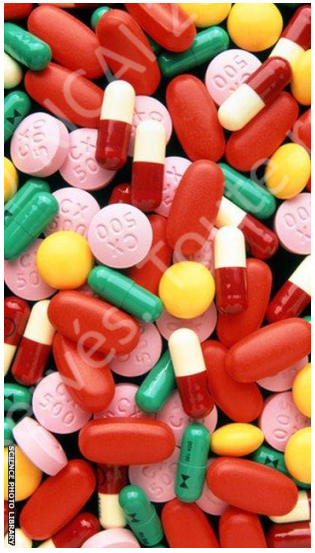
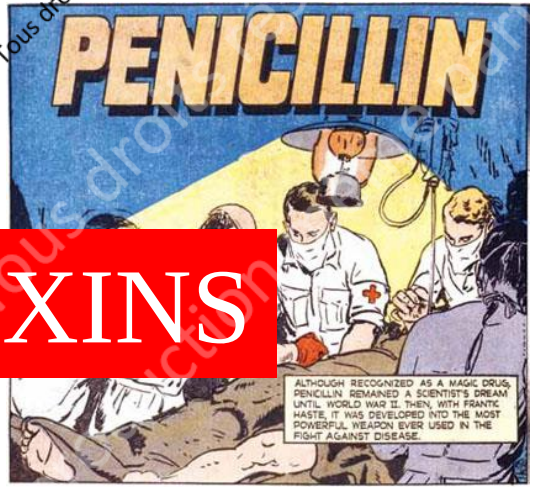
TEMOCILLIN



FOSFOMYCIN



POLYMYXINS

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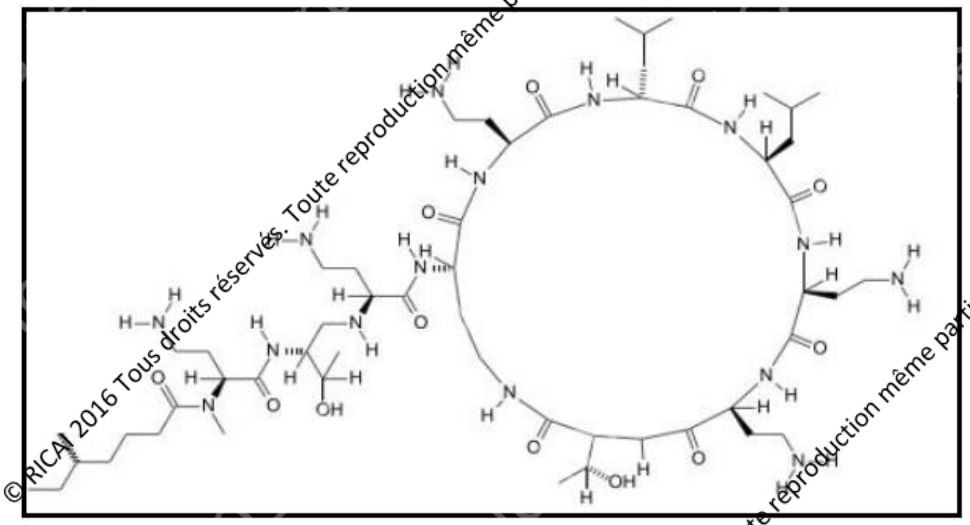
The polymyxins



Colistin

- Colistin, polymyxin B
- Synthesis by *Bacillus polymyxa* spp colistinus
- Discovered in the 1950's

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Spectrum of Activity

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Susceptible bacteria

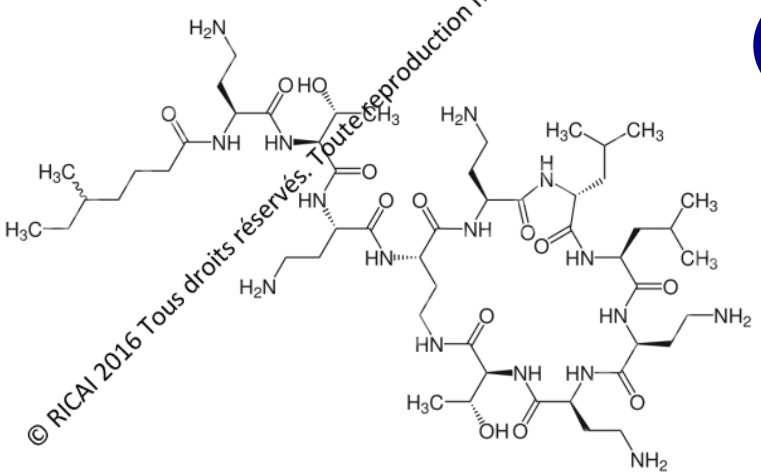
- ***E. coli, Klebsiella spp. Enterobacter***
- ***P. aeruginosa, A. baumannii H. influenzae, Bordetella pertussis***
- ***Salmonella spp., Shigella spp***
- ***Legionella, Stenotrophomonas maltophilia***

Non-susceptible bacteria

- **All gram positives**
- **Gram-negative cocci: *N. gonorrhoeae; N. meningitidis***
- ***Proteus* group, *Serratia* spp; *Burkholderia* spp; *Brucella* spp**
- **Anaerobes**

Mechanism of action

Colistin



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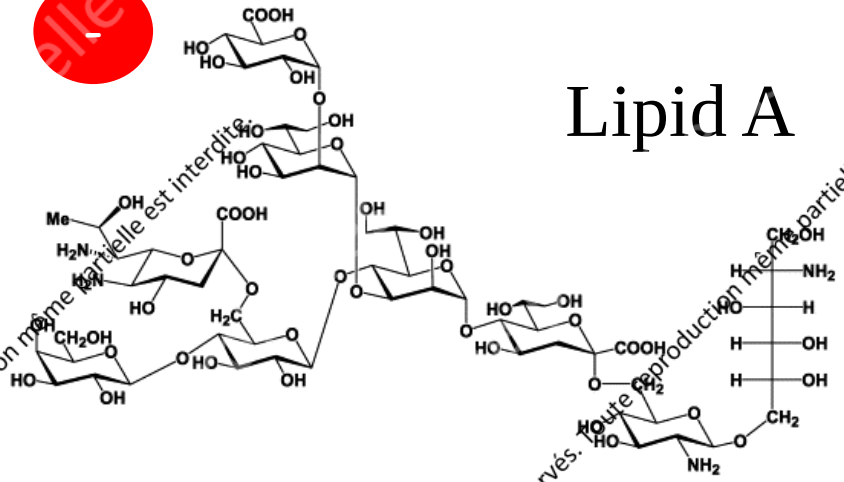
Lipid A



Colistin is a cationic antibiotic that is composed of a cyclic heptapeptide covalently attached to a fatty acyl chain

Lipopolysacharide (LPS) of Gram- negative bacteria is composed by :

- Lipid A
- Core
- Oligosaccharide O

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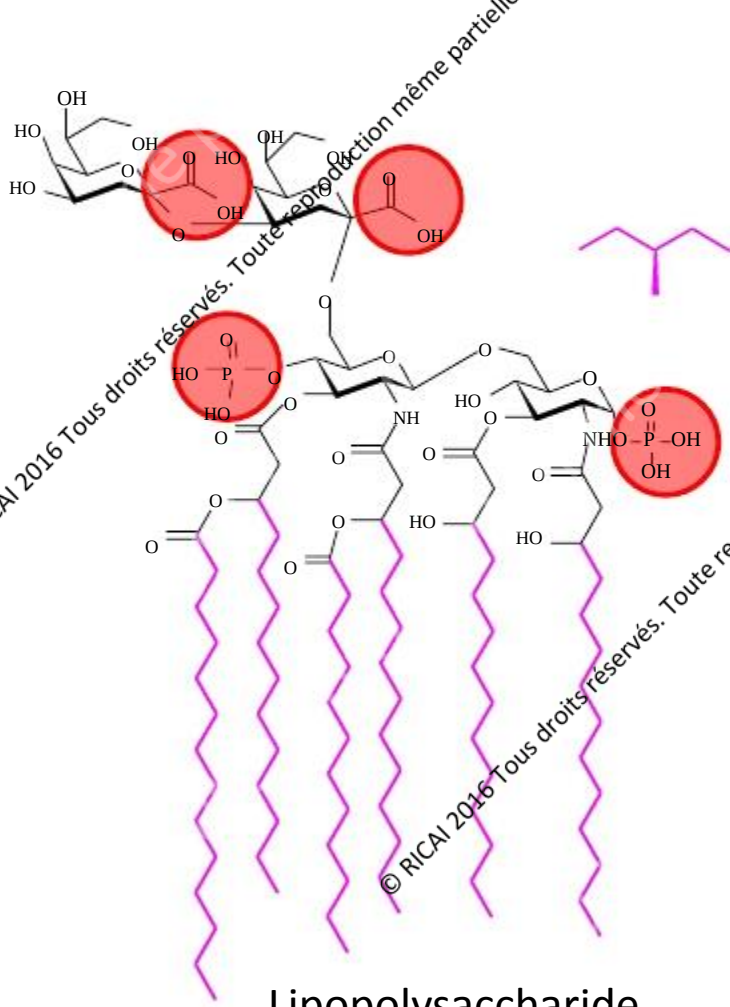
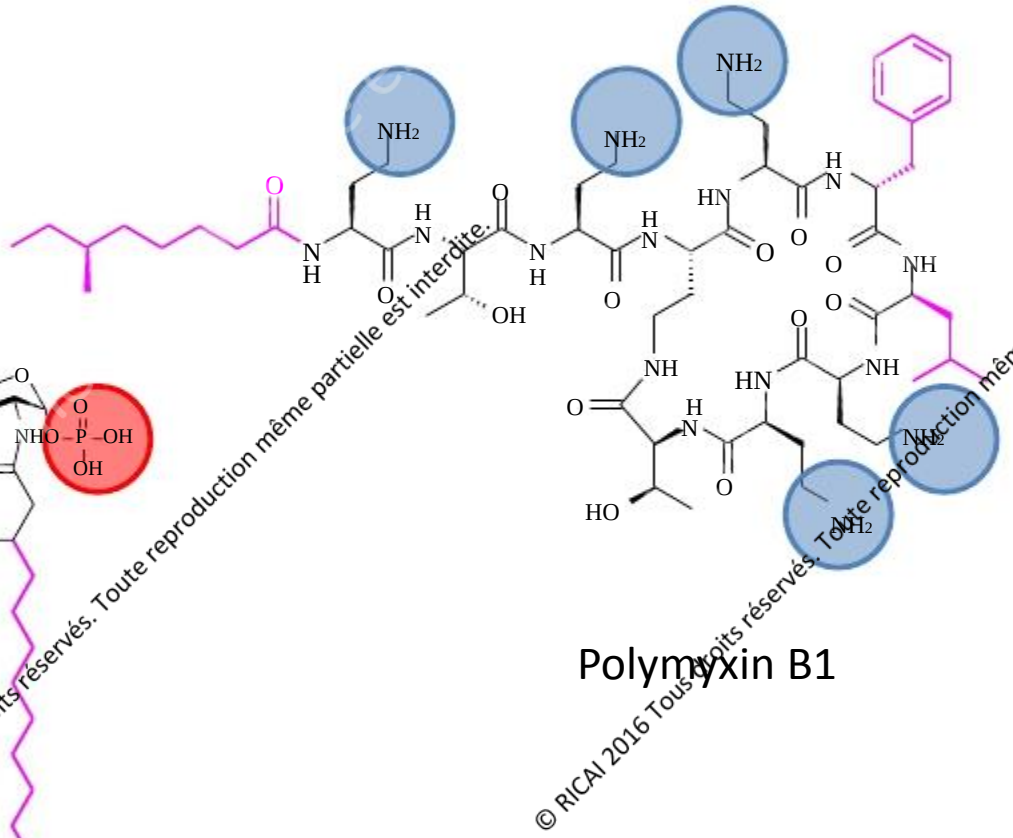
Polymyxins interact with lipopolysaccharide



Lipopolysaccharide



Polymyxin B1

Mares et al. (2009) J. Biol. Chem. 284, 11498

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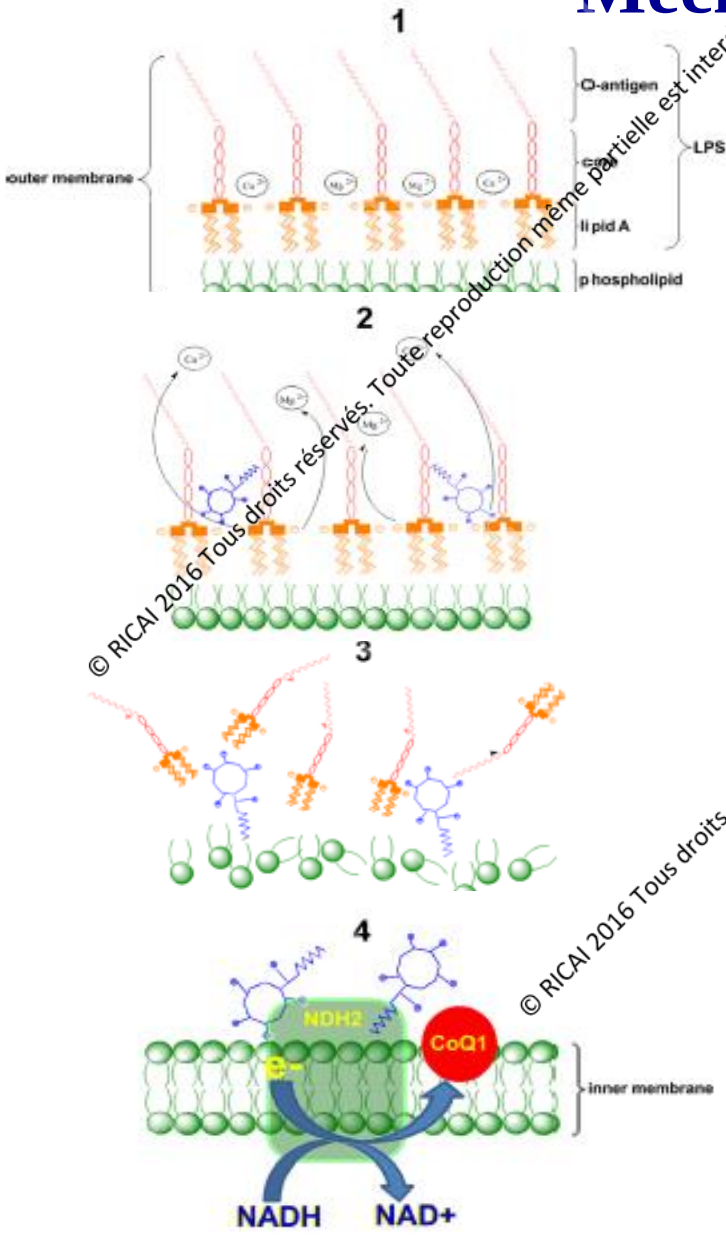
Mechanism of action



1. Fixation

2. Displacement of divalent cation (Ca^{2+} et Mg^{2+})

3. Destabilisation of the outer membrane of Gram negatives

4. Penetration throughout the inner membrane and inhibition of the respiratory enzymes NDH2

Falagas et *al*, Clin Infect Dis. 2005
Deris et *al*, J Antibiot. 2013

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Toxicity

- Nephrotoxicity
- Neurotoxicity
  - Parasthesia, visual alteration, ataxia, neuromuscular blockade
  - Reversible on stopping CMS
  - Cases are mild & infrequent

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Colistin use : hospital acquired pneumonia (HAP) & Ventilator associated pneumonia (VAP)

Rationale for inhaled colistin: delivery of antibiotic directly to the infection site with the intention of achieving selective targeting minimizing systemic exposure & potential adverse effects

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Polymyxins.. now

- Last resort antibiotic for MDR Gram negatives :
  - *Klebsiella* / carbapenemase producers
  - *Acinetobacter* multi-R
  - *Pseudomonas* multi-R
- In association
- Loading dose
- Twice a day 12 h; uncertain PK/PD

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Colistin use

Mostly in veterinary medicine (prophylaxis and metaphylaxis)

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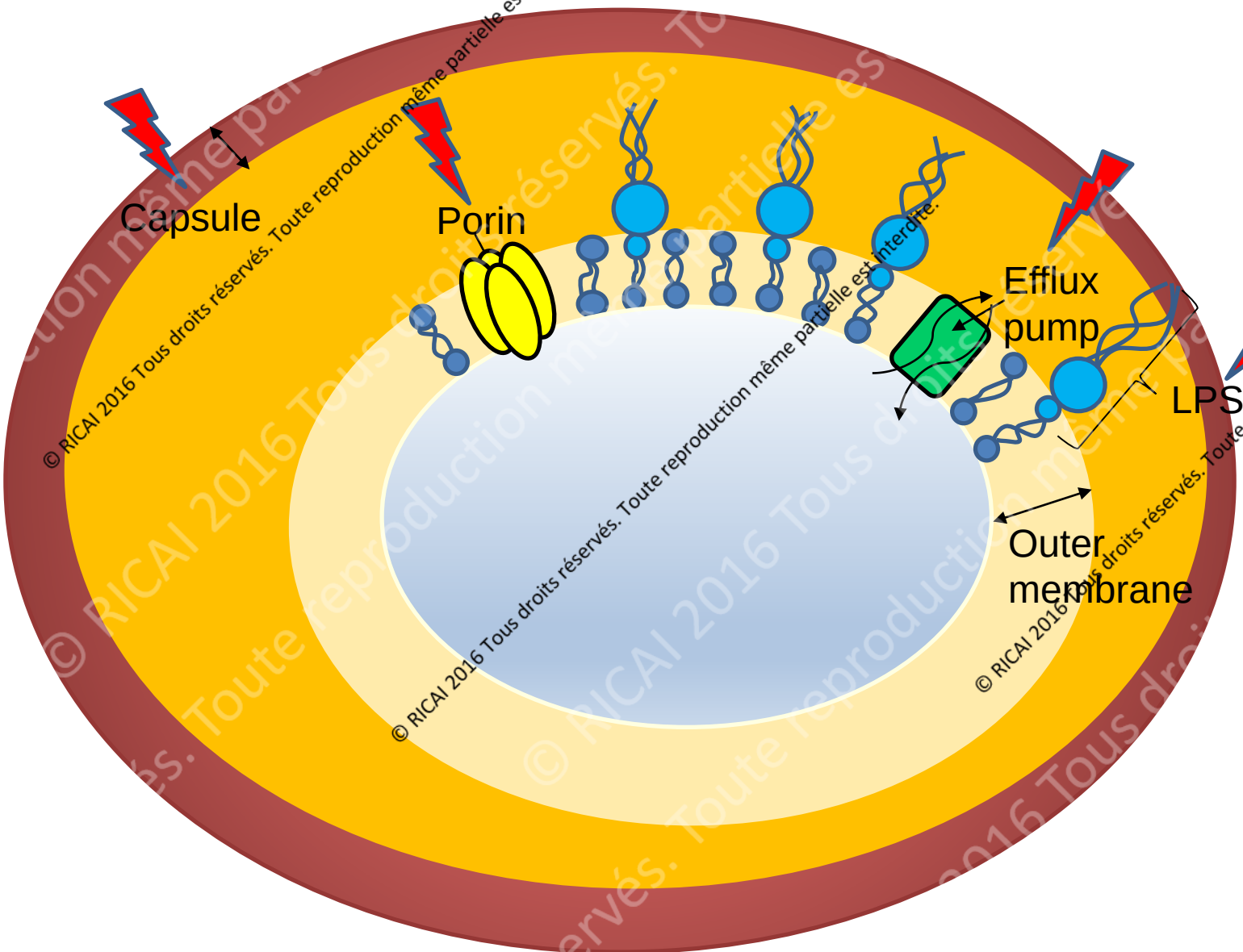
Multiple and combined chromosomal mechanisms of colistin resistance



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Role of LPS in polymyxin resistance

❖ Loss of LPS :

Inactivation of lipid A biosynthesis genes (*lpxA*, *lpxC* and *lpxD*) cause loss of LPS and prevent the interactions of polymyxins with its binding sites on the LPS, described in *A. baumannii*

❖ LPS modifications : the main mechanism of resistance to colistin :

Addition of 4-amino-4-deoxy-L-arabinose (LAra4N) and or phosphoethanolamine (pEtN) to lipid A ➔ Increase of positive charges ➔ decreased affinity for LPS

Synthesis of L-Ara4N and pEtN mediated by PmrA / PmrB, PhoP / PhoQ, and *mgrB* gene

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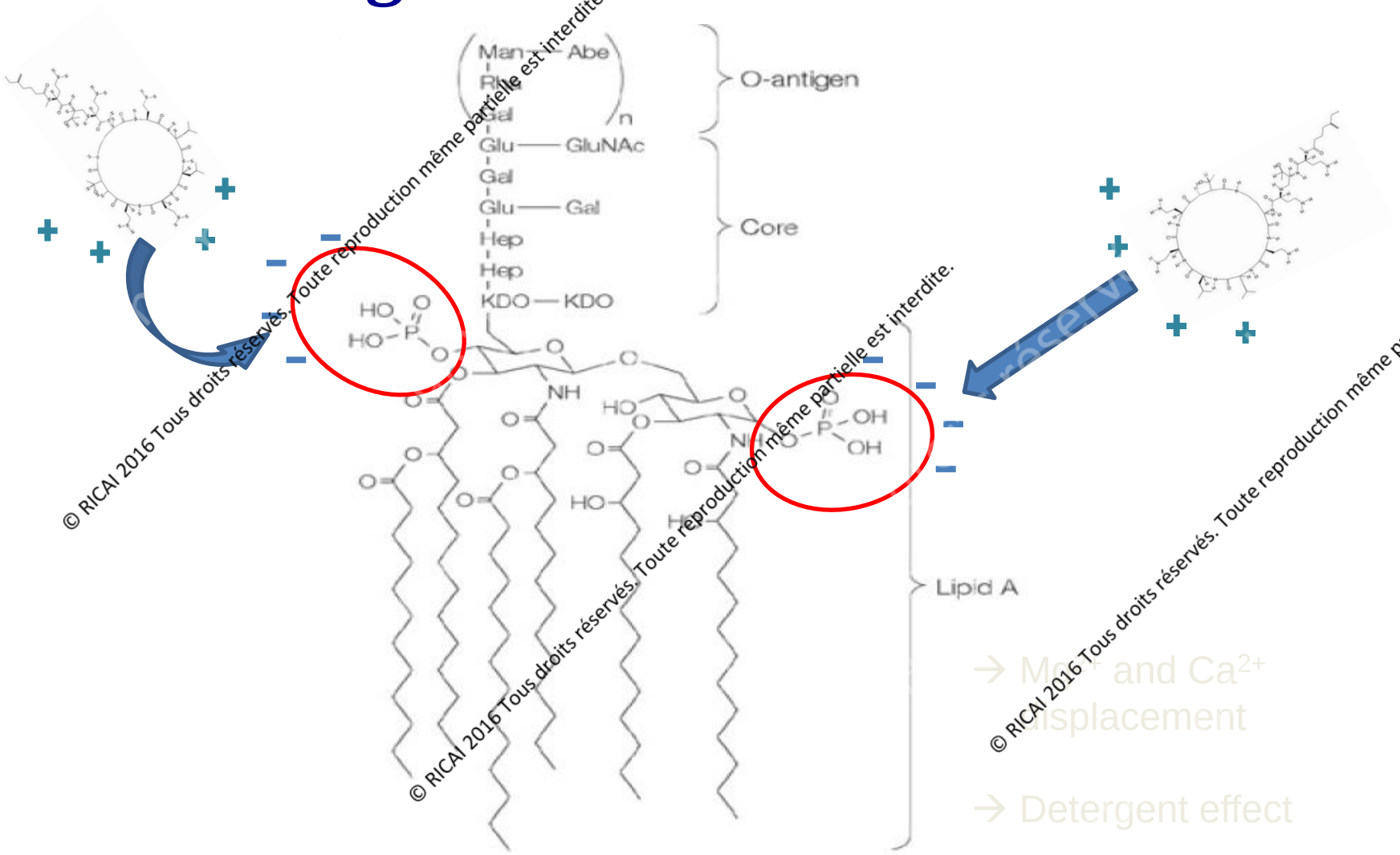
Target of colistin : LPS



→ Mg^{2+} and Ca^{2+} displacement

→ Detergent effect

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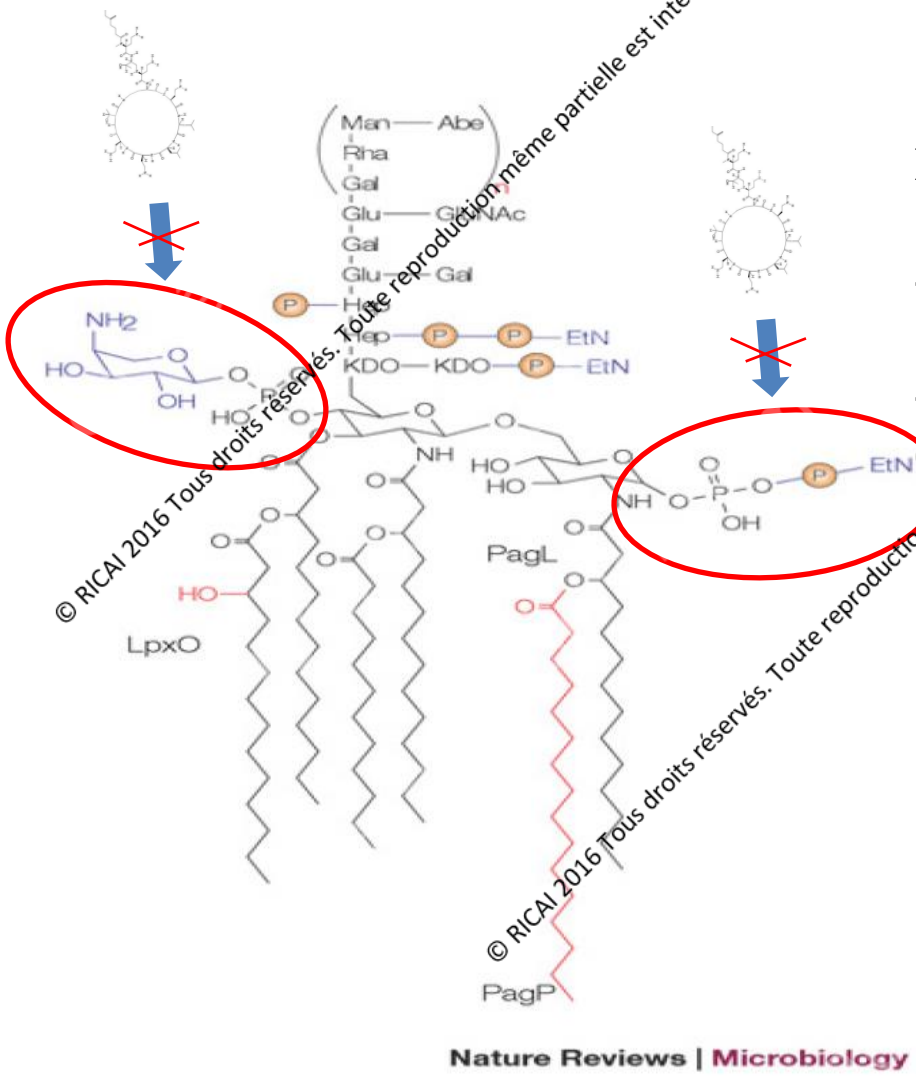
Modification of the chemical structure of the LPS



Modifications :

-Addition of phosphoethanolamine (pEtN)

-Addition of 4-amino-4-deoxyl-L-arabinose (Ara4N)

➔Adaptation against hostile environment

➔Lower affinity for cationic molecules such as colistin

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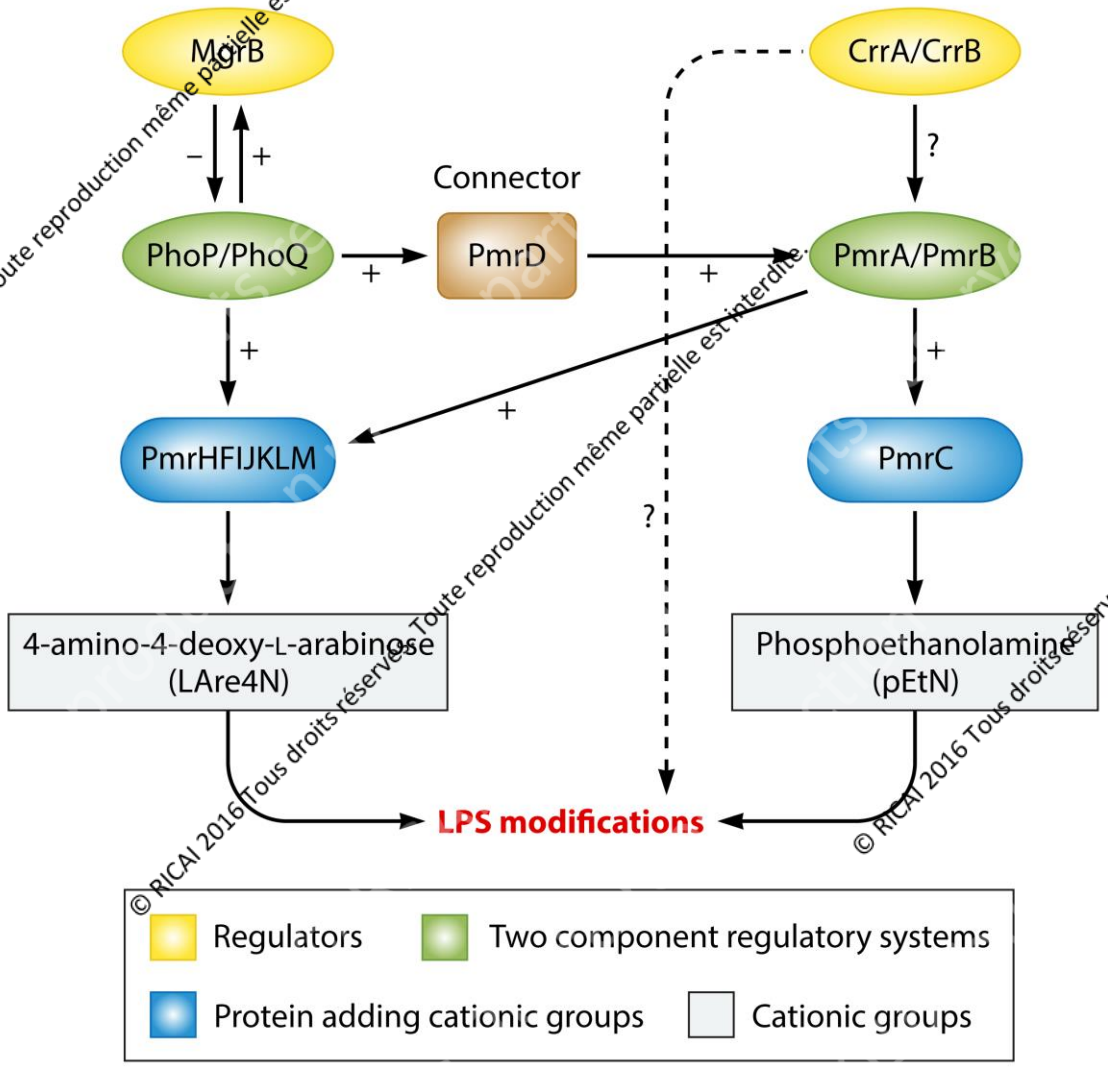
Modification of the LPS structure



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Acquired resistance to colistin in *K. pneumoniae*

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Resistance to Colistin Associated with a Single Amino Acid Change in Protein PmrB among *Klebsiella pneumoniae* Isolates of Worldwide Origin

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INSERM U914, South-Paris Medical School, K.-Bicêtre, France[a]; Medical and Molecular Microbiology Unit, Department of Medicine, Faculty of Science, University of Fribourg, Fribourg, Switzerland[b]; Hôpital Fribourgeois-Hôpital Cantonal de Fribourg, Fribourg, Switzerland[c]; Department of Clinical Microbiology, Ampath National Laboratory Services, Milpark Hospital, Johannesburg, South Africa[d]; International Center for Medical Research and Training, CIDEIM, Cali, Colombia[e]; Medical Microbiology Department, School of Medicine, Istanbul Medipol University, Istanbul, Turkey[f]

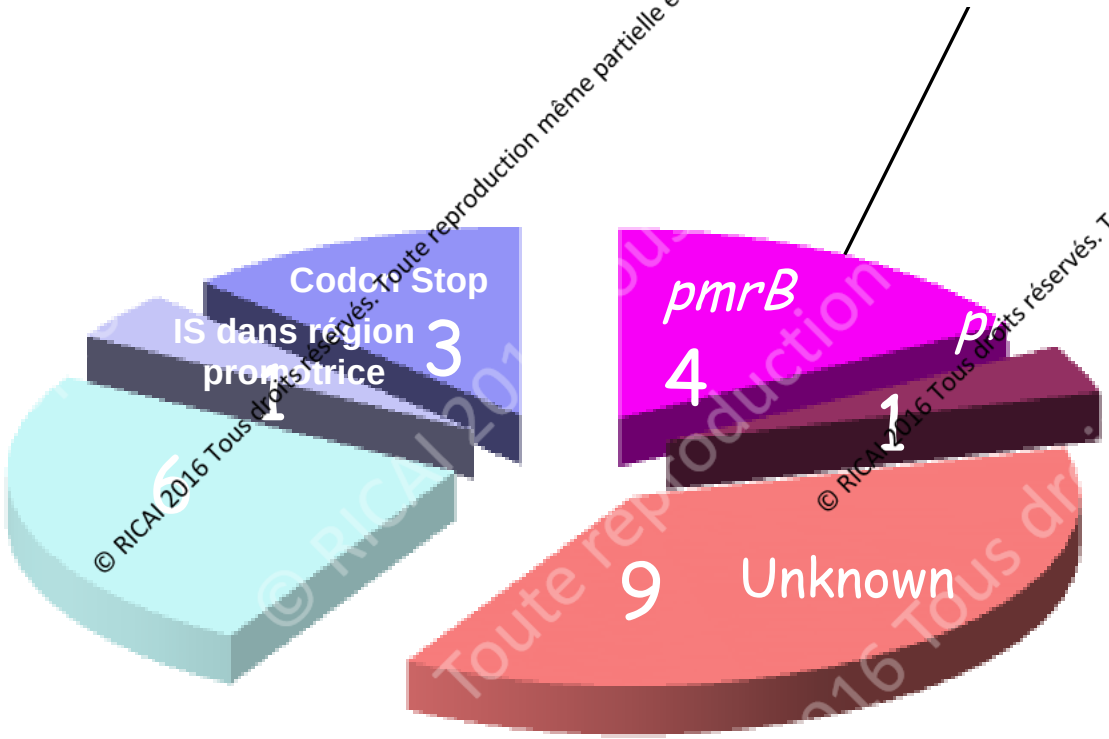
Journal of Antimicrobial Chemotherapy Advance Access published September 3, 2014

J Antimicrob Chemother
doi:10.1093/jac/dku323

Journal of Antimicrobial Chemotherapy

The *mgrB* gene as a key target for acquired resistance to colistin in *Klebsiella pneumoniae*

Laurent Poirel[1,2], Aurélie Jayol[2], Séverine Bontron[1], Maria-Virginia Villegas[3], Melda Ozdamar[4], Salih Türkoglu[4] and Patrice Nordmann[1,2,5]*



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High rate of colistin resistance among patients with carbapenem-resistant *Klebsiella pneumoniae* infection accounts for an excess of mortality

A. Capone[1], M. Giannella[1], D. Fortini[2], A. Giordano[3], M. Meledandri[4], M. Ballardini[4], M. Venditti[5], E. Bordi[6], D. Capozzi[7], M. P. Balice[8], A. Tarasi[9], G. Parisi[10], A. Lappa[10], A. Carattoli[2], N. Petrosillo[1] and on behalf of the SEERBIO-GRAB network

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Colistin resistance superimposed to endemic carbapenem-resistant *Klebsiella pneumoniae*: a rapidly evolving problem in Italy, November 2013 to April 2014

M. Monaco[1,2], T Giani[2,3], M Raffone[1,4], F Arena[3], A Garcia-Fernandez[1], S Pollini[3], Network EuSCAPE-Italy[5], H Grundmann[6], A Pantosti (annalisa.pantosti@iss.it)[1], G M Rossolini[7,8]

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2. MM and TG have equally contributed to this work
3. Department of Medical Biotechnologies, University of Siena, Siena, Italy
4. Federico II University Hospital, Neaples, Italy
5. The network EuSCAPE-Italy participants are listed at the end of this article
6. Department of Medical Microbiology, University of Groningen, University Medical Center Groningen, the Netherlands
7. Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy
8. Clinical Microbiology and Virology Unit, Florence Careggi University Hospital, Florence, Italy

Citation style for this article:
Monaco M, Giani T, Raffone M, Arena F, Garcia-Fernandez A, Pollini S, Network EuSCAPE-Italy, Grundmann H, Pantosti A, Rossolini GM. Colistin resistance superimposed to endemic carbapenem-resistant Klebsiella pneumoniae: a rapidly evolving problem in Italy, November 2013 to April 2014. Euro Surveill. 2014;19(42):pii=20939. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20939

Article submitted on 08 October 2014 / published on 23 October 2014

Consecutive non-replicate clinical isolates (n=191) of carbapenem non-susceptible Enterobacteriaceae were collected from 21 hospital laboratories across Italy from November 2013 to April 2014 as part of the European Survey on Carbapenemase-producing Enterobacteriaceae (EuSCAPE) project. *Klebsiella pneumoniae* carbapenemase-producing *K. pneumoniae* (KPC-KP) represented 178 (93%) isolates with 176 (43%) respectively resistant to colistin, a key drug for treating carbapenamase-producing Enterobacteriaceae. KPC-KP colistin-resistant isolates were detected in all participating laboratories. This underscores a concerning evolution of colistin resistance in a setting of high KPC-KP endemicity.

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Kp KPC-2

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

Tommaso Giani,[a] Fabio Arena,[a] Guendalina Vaggelli,[b] Viola Conte,[a] Adriana Chiarelli,[a] Lucia Henrici De Angelis,[a] Rossella Fornaini,[c] Maddalena Grazzini,[d] Fabrizio Niccolini,[d] Patrizia Pecile,[b] Gian Maria Rossolini[a,b,e,f]

Department of Medical Biotechnologies, University of Siena, Siena, Italy[a]; Clinical Microbiology and Virology Unit,[b] Hospital Pharmacy Unit,[c] and Hospital Medical Direction,[d] Florence Careggi University Hospital, Florence, Italy; Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy[e]; Don Carlo Gnocchi Foundation, Florence, Italy[f]

We describe a large hospital outbreak (93 bloodstream infections) of colistin-resistant *Klebsiella pneumoniae* carbapenemase (KPC)-producing *K. pneumoniae* isolates which was mirrored by increased colistin consumption. The outbreak was mostly traced to the clonal expansion of an *mgrB* deletion mutant of an ST512 strain that produced KPC-3.

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

A Jayol [1], L Poirel [1], L Dortet [2 3 4], P Nordmann [1 2 5]

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

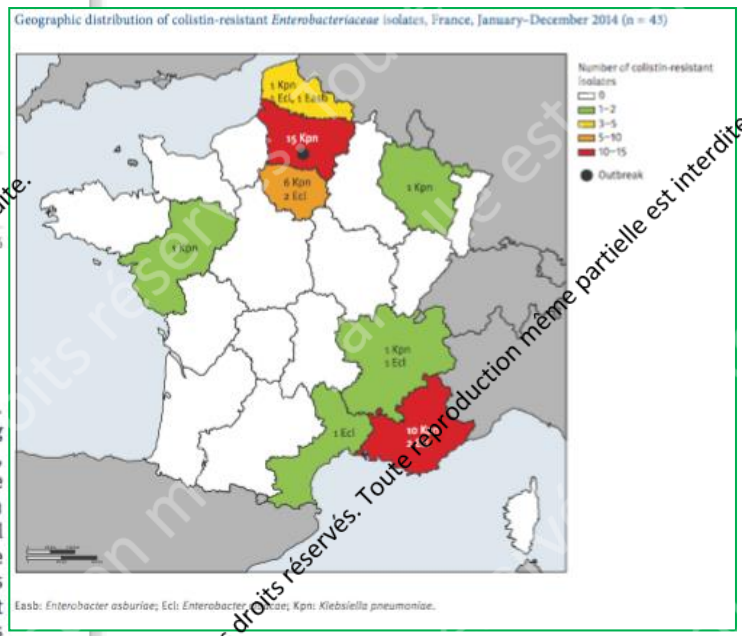
From January 2014 to December 2014, 972 consecutive non-replicate carbapenemase-producing *Enterobacteriaceae* isolates from colonised or infected patients were collected at the Associated French National Reference Centre as part of the French national survey on antimicrobial resistance. It included 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/L. They harboured the bla_{OXA-48} carbapenemase gene and the $bla_{CTX-M-15}$ 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 polymyxin 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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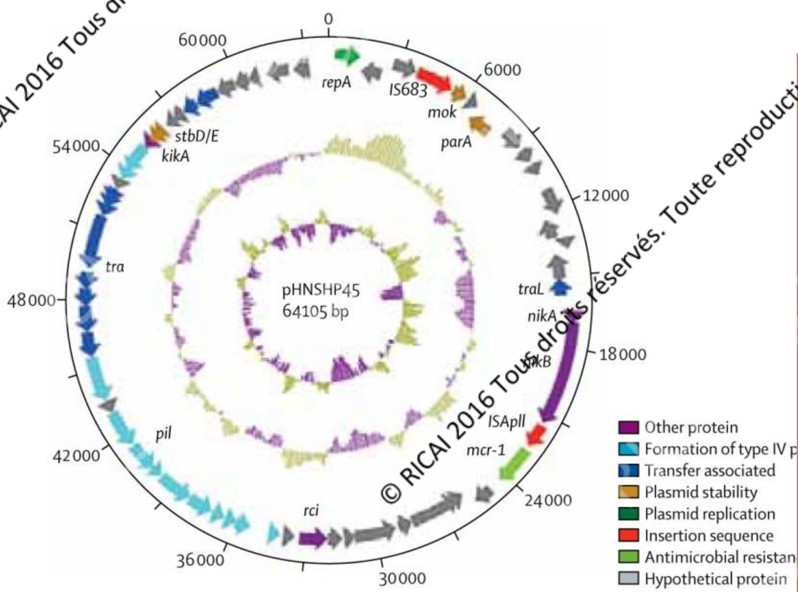
Lancet Infect Dis, Nov 28, 2015

Plasmid-mediated resistance to colistin

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



	Year	Positive isolates (%)/number of isolates
Escherichia coli		
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
Klebsiella pneumoniae		
Inpatient	2014	3 (0·7%)/420

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

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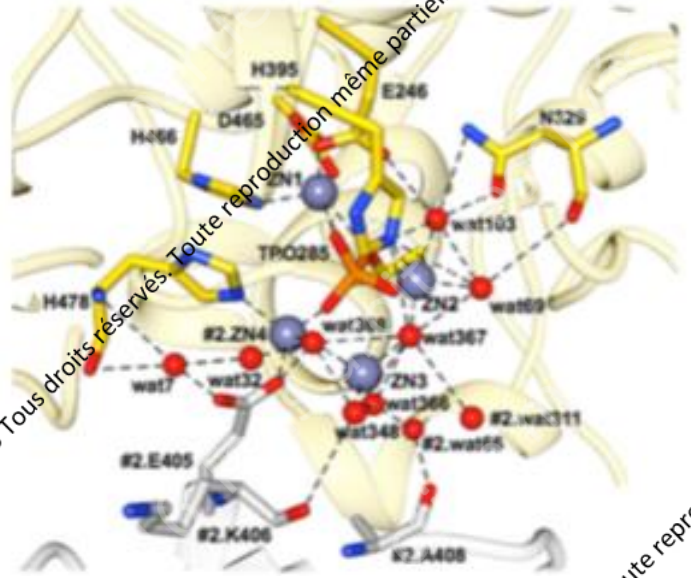
The MCR-1 protein is a phosphoethanolamine transferase



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Stojanoski *et al. BMC Biology* _####################_
DOI 10.1186/s12915-016-0303-0

BMC Biology

RESEARCH ARTICLE Open Access

Structure of the catalytic domain of the colistin resistance enzyme MCR-1

Viatko Stojanoski[1,2], Banumathi Sankaran[3], B. V. Venkataram Prasad[1], Laurent Poirel[4], Patrice Nordmann[4,5] and Timothy Palzkill[1,2*]

Abstract

Due to the paucity of novel antibiotics, colistin has become a last resort antibiotic for treating multidrug resistant bacteria. Colistin acts by binding the lipid A component of lipopolysaccharides and subsequently disrupting the bacterial membrane. The recently identified plasmid-encoded MCR-1 enzyme is the first transmissible colistin resistance determinant and is a cause for concern for the spread of this resistance trait. MCR-1 is a phosphoethanolamine transferase that catalyzes the addition of phosphoethanolamine to lipid A to decrease colistin affinity. The structure of the catalytic domain of MCR-1 at 1.32 Å reveals the active site is similar to that of related phosphoethanolamine transferases. The putative nucleophile for catalysis, threonine 285, is phosphorylated in cMCR-1 and a zinc is present at a conserved site in addition to three zincs more peripherally located in the active site. As noted for catalytic domains of other phosphoethanolamine transferases, binding sites for the lipid A and phosphatidylethanolamine substrates are not apparent in the cMCR-1 structure, suggesting that they are present in the membrane domain.

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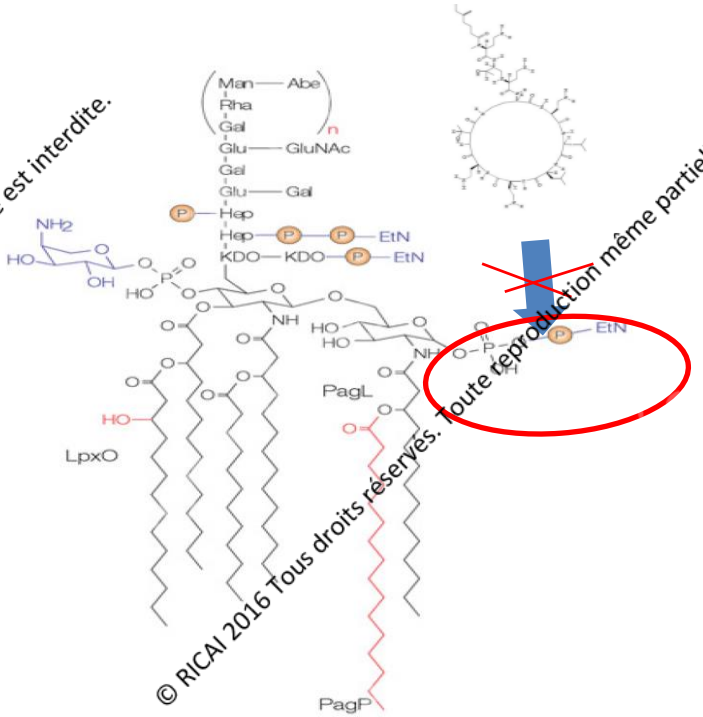
Colistin



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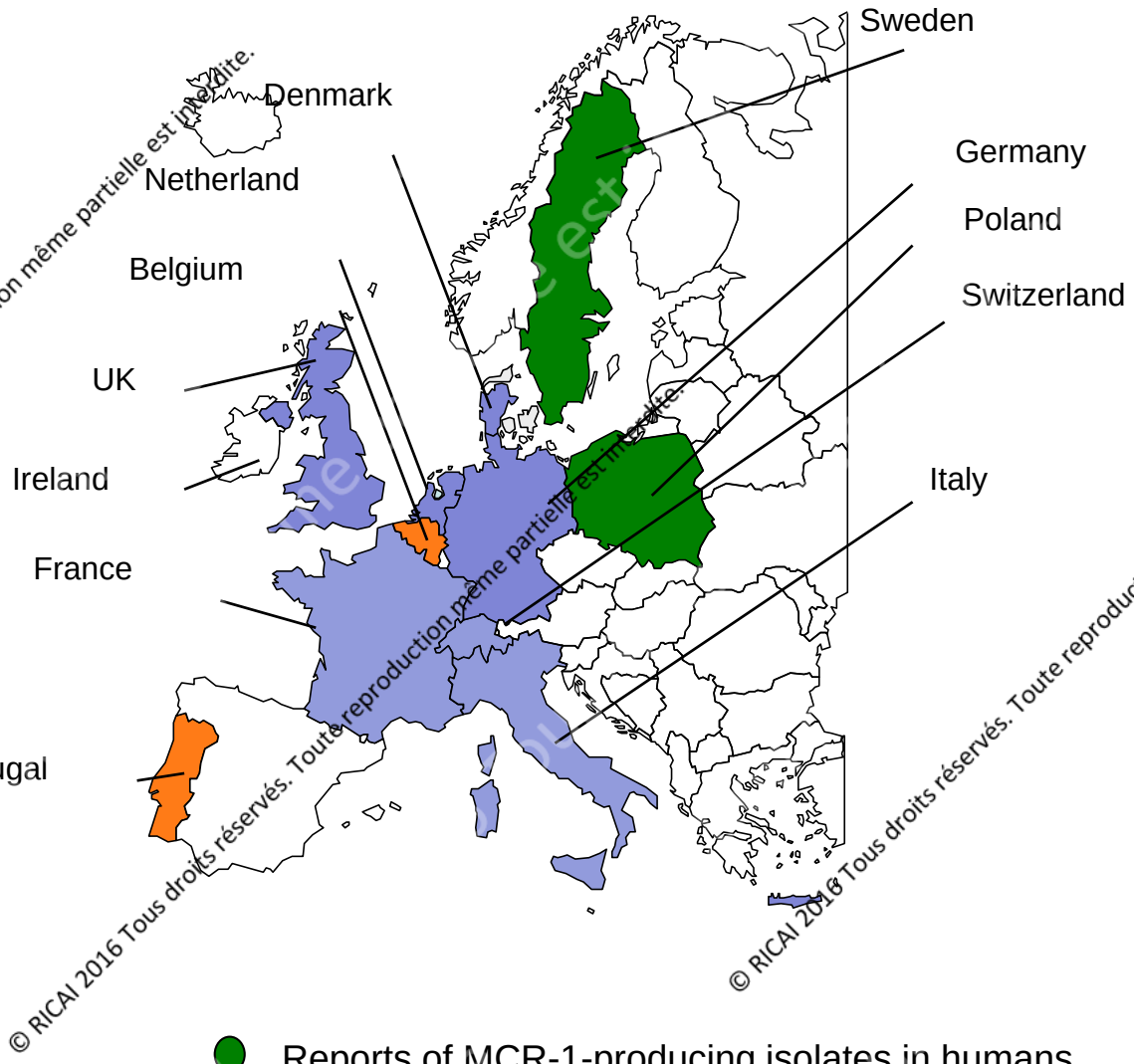
Nature Reviews | Microbiology

LPS

MCR-1



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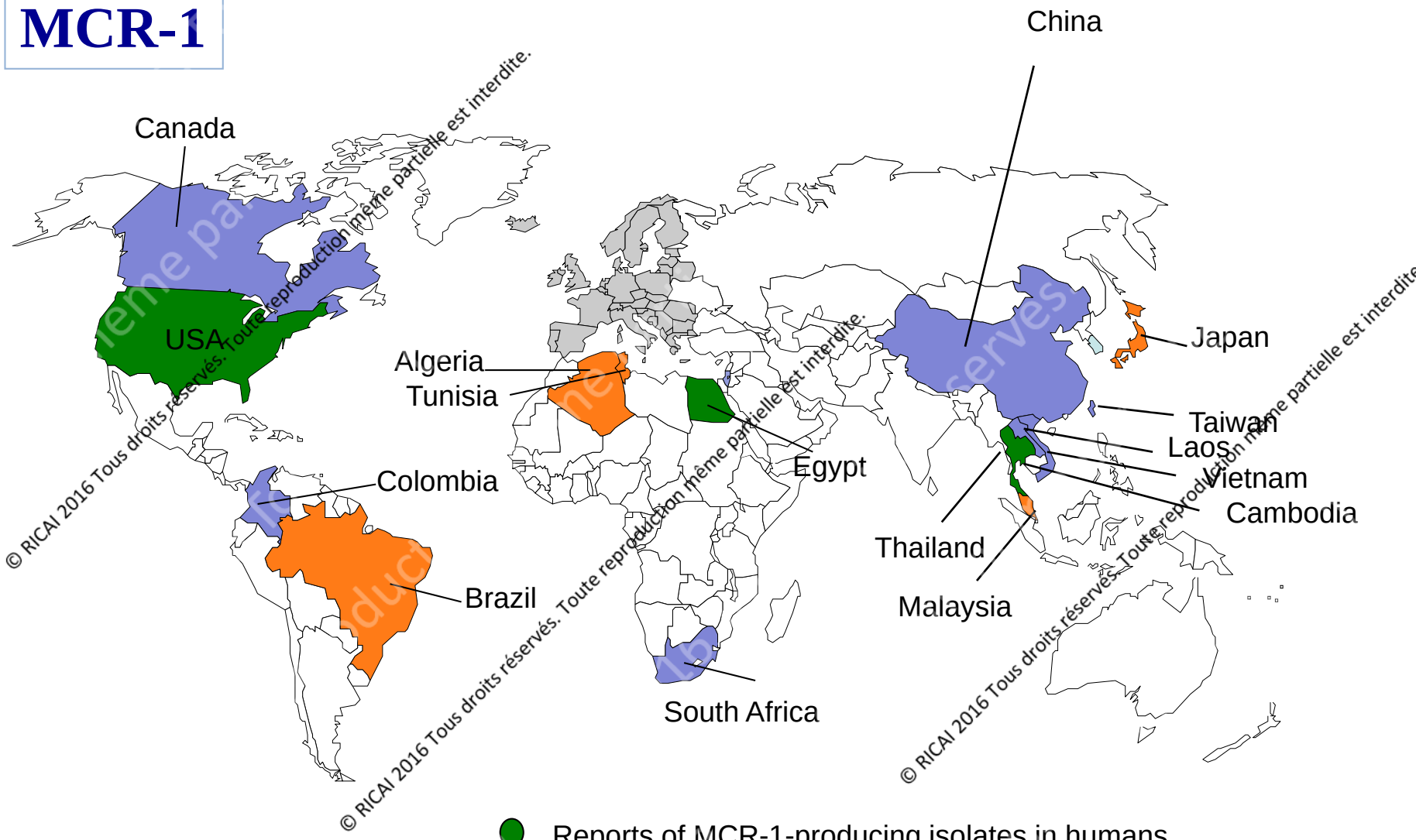
- Reports of MCR-1-producing isolates in humans
- Reports of MCR-1-producing isolates in animals
- Reports of MCR-1-producing isolates in both humans and animals

MCR-1

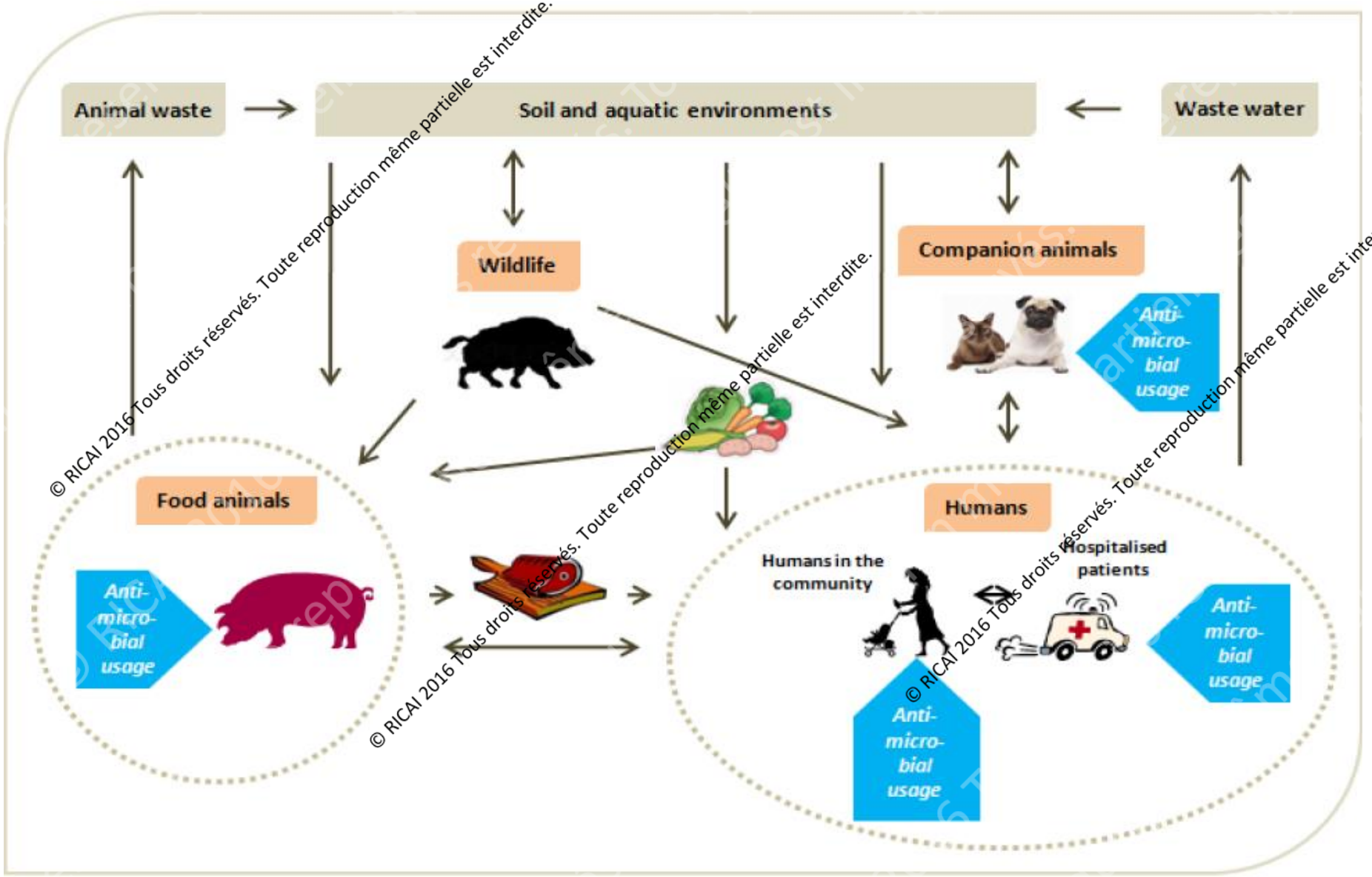


Reports of MCR-1-producing isolates in humans

Reports of MCR-1-producing isolates in animals

Reports of MCR-1-producing isolates in both humans and animals

MCR-1= a one-health approach



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RÉPUBLIQUE FRANÇAISE

MARS

Message d'Alerte Rapide Sanitaire

MINISTERE DES AFFAIRES SOCIALES DE LA SANTE ET DES DROITS DES FEMMES
DIRECTION GENERALE DE LA SANTE
SOUS-DIRECTION VEILLE ET SECURITE SANITAIRE

DATE : 02/09/2016 **REFERENCE :** MARS N°2016_12

OBJET : ENTEROBACTERIES PORTEUSES DU GENE MCR-1 DE RESISTANCE PLASMIDIQUE A LA COLISTINE

Pour action

☑ Etablissements hospitaliers ☐SAMU / Centre 15

Service(s) concerné(s) :

Pour information

☑DGOS ☑ARS ☑ InVS ☑ InSP

☐DGCS ☑ARS de Zone ☐ANSM ☐Autre :

Des souches d'entérobactéries porteuses du gène *mcr-1* de résistance plasmidique à la colistine émergent dans le monde. Décrites initialement en Chine, de telles souches ont été isolées dans d'autres pays (dans l'environnement, la nourriture, chez les animaux, mais aussi chez l'homme) en Europe (Espagne, Royaume Uni notamment), au Canada et aux Etats-Unis.

En France ultramarine, dans le cadre d'une analyse rétrospective, le Centre national de référence de la résistance aux antibiotiques a signalé à Santé publique France la première détection de deux souches d'*Escherichia coli* BLSE porteuses du gène *mcr-1*, isolées de prélèvements cliniques en 2014 en Nouvelle-Calédonie.

L'émergence et la diffusion de cette résistance représente un risque pour la santé publique. La colistine est l'un des rares antibiotiques encore actifs sur les souches d'entérobactéries productrices de carbapénémases (EPC). Le caractère plasmidique et donc hautement transférable entre bactéries de cette résistance accroît considérablement le risque de voir apparaître à terme des souches de *E. coli* et très probablement d'entérobactéries totalement résistantes à tous les antibiotiques, conduisant à des impasses thérapeutiques.

La détection de ce mécanisme de résistance peut poser des difficultés. En routine, la recherche de la résistance à la colistine n'est généralement pas réalisée en première intention et/ou réalisée avec des méthodes d'antibiogramme non adaptées à la détection de ce nouveau mécanisme. De plus, la présence d'un gène *mcr* doit être confirmée à l'aide de techniques moléculaires, non commercialisées à ce jour, qui sont les seules permettant un diagnostic de certitude.

Dans ce contexte et dans l'attente de recommandations spécifiques à venir du Haut conseil de la santé publique, nous vous demandons :

- de rechercher une résistance phénotypique à la colistine pour toute entérobactérie :
  1. Résistante aux céphalosporines de troisième génération ou aux carbapénèmes, à l'exception des entérobactéries naturellement résistantes à la colistine comme les souches appartenant aux genres *Morganella, Proteus, Serratia et Providencia* ;
  2. Et isolée chez un patient rapatrié ou ayant des antécédents récents d'hospitalisation à l'étranger ou dans les départements et territoires d'Outre-Mer ;
- d'adresser ces souches résistantes à la colistine au Centre national de la résistance aux antibiotiques (site de Clermont-Ferrand) pour recherche du mécanisme de résistance à l'aide de méthodes moléculaires.

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MCR-1 worldwide

Team	Species	Plasmid(s)	IncGroup	Origin	Country
Stoesser (Uk)	*E. coli*	-1 plasmid -ISApl1+ -IS1294 +	IncA	Feces, human	UK, 2012
Suzuki (Jp)	*E. coli, Salmonella*	-5 plasmids -Ca 60kb	IncI2	Animal	Japan
Herman Goosens (Be)	*E. coli*	-9 plasmids -ISApl1 +	ND	Rectal swabs pigs	Viet-nam
Petrillo (It)	*E. coli*	-6 plasmids -ISApl1 +/-	ND	Chicken/water/food / pig feces	Malaysia
Madec/Nordmann (Fr, CH))	*E. coli*	-1 plasmid -60-200kb ?	IncHI2	Animal	France, 2005
Goosens (Be)	*E. coli*	-1 plasmid -Ca 80kb -dfrA1, tetA, Aph3'', aadA1	IncX1	Animal	Belgium
Nordmann (CH)	*E. coli*	ISApl1 +, 60kb	ND	Human (urine)	Switzerland
Falgenhauer	*E. coli*	-1 plasmid -ISApl1 + -*bla*KPC +	IncX4, IncHI2	Swine, human	Denmark

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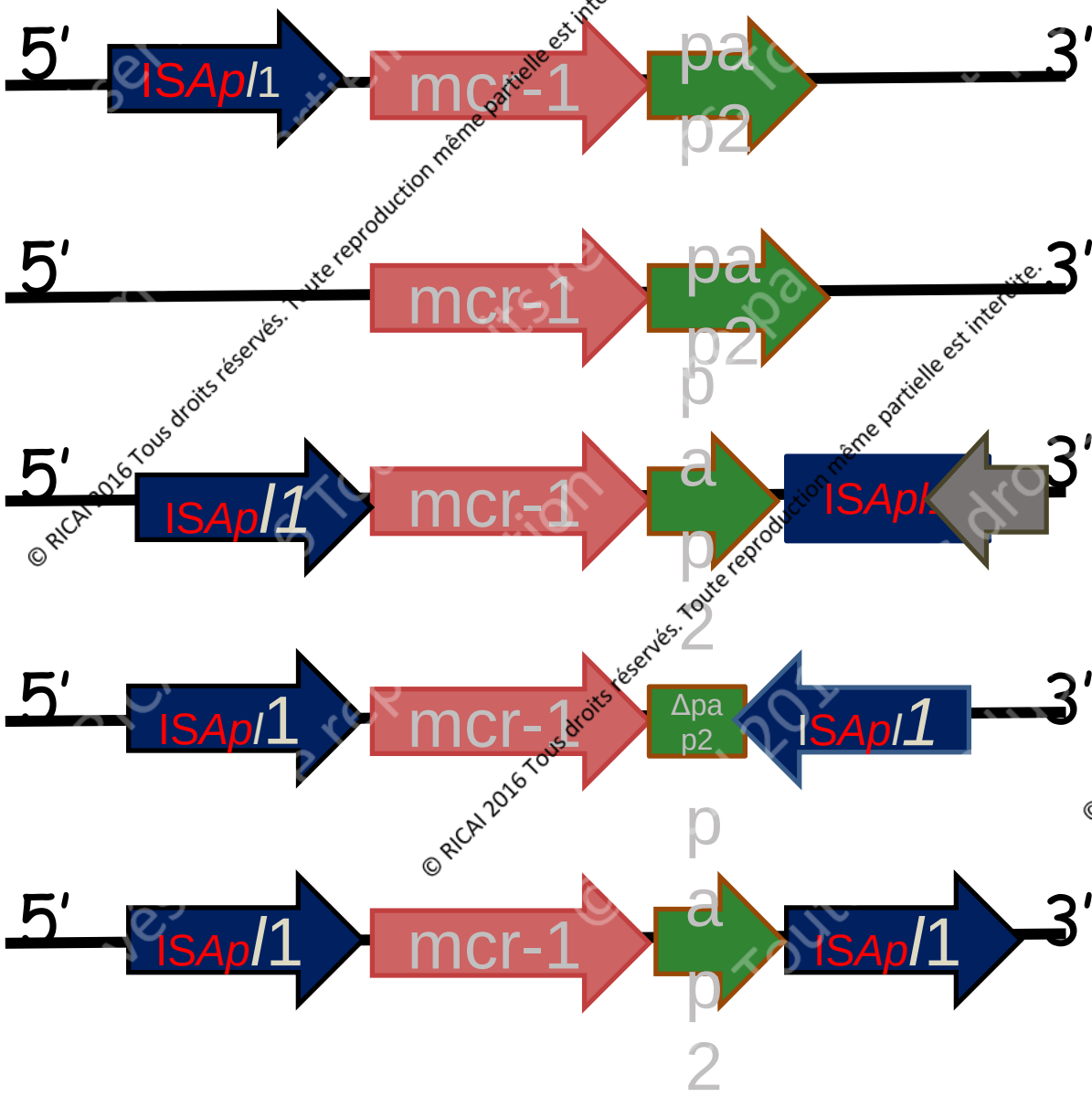
The *mcr-1* gene: genetic features



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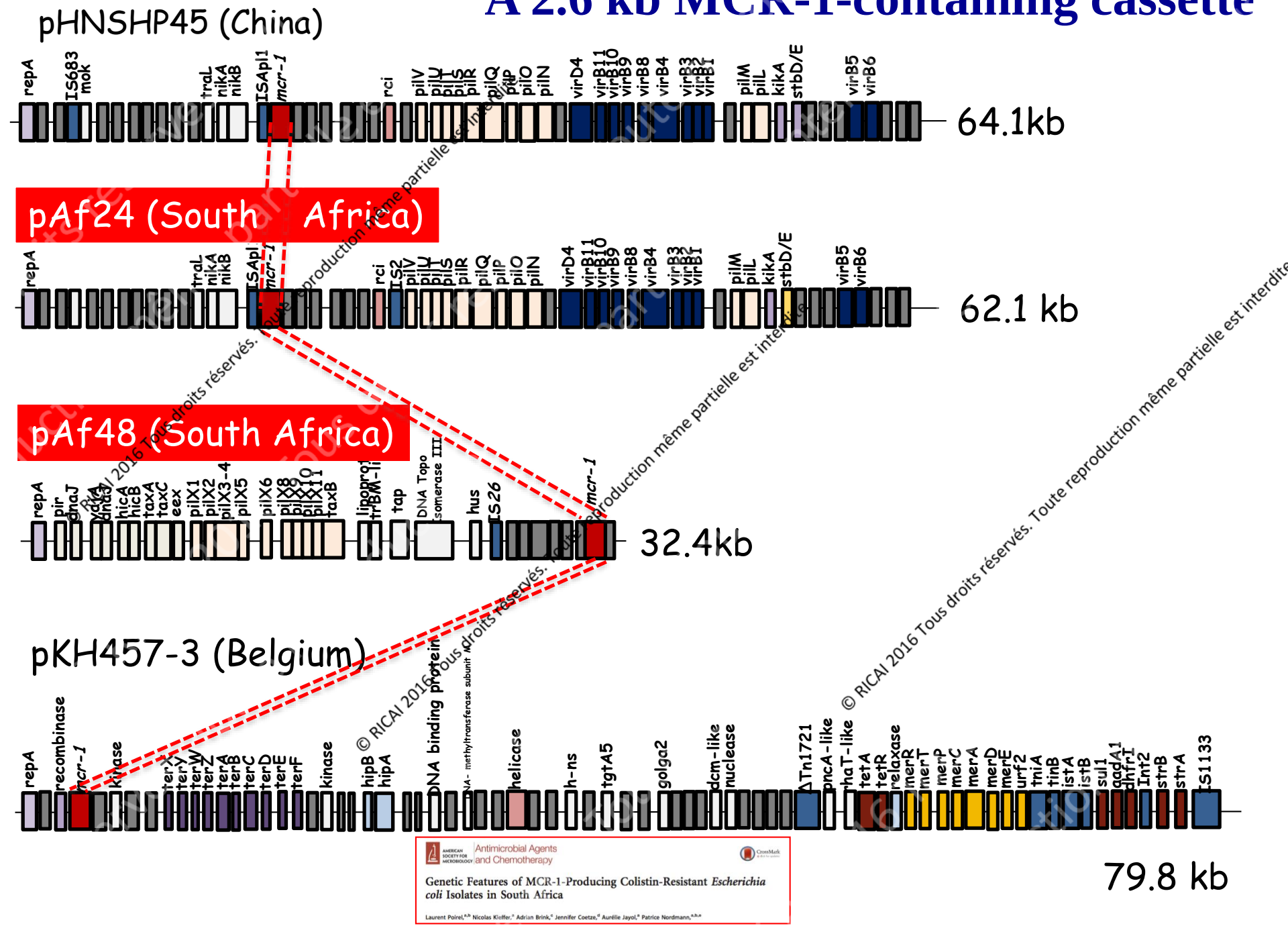
A 2.6 kb MCR-1-containing cassette



Antimicrobial Agents and Chemotherapy

Genetic Features of MCR-1-Producing Colistin-Resistant *Escherichia coli* Isolates in South Africa

Laurent Poirel,[a,b] Nicolas Kieffer,[a] Adrian Brink,[c] Jennifer Coetze,[d] Aurélie Jayol,[a] Patrice Nordmann,[a,b,e]

The *mcr-1* gene: the origin, *Moraxella spp.*

- Moraxella sp are commensal for animals and humans
- Amino acid identity among the MCR-like proteins
- MCR-1 like proteins confercolistin resistance

	MCR-1	MCR-2	MCR-*porci*	MCR-*osloensis*	MCR-*lincolnii*	MCR-*catarrhalis*
MCR-2	81%					
MCR-*porci*	64%	63%				
MCR-*osloensis*	63%	64%	59%			
MCR-*lincolnii*	59%	60%	60%	59%		
MCR-*catarrhalis*	59%	60%	99%	59%	99%	

- The mobile element **ISApl1** was found in *M. porci*
- The **IncX4** replicon marker was found in *M. lacunata*

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Plasmid-mediated colistin resistance; a nightmare ?

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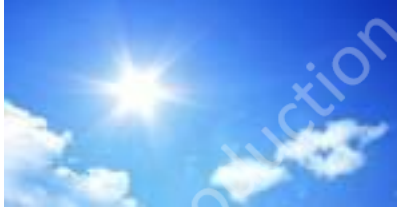

MCR-1: an optimistic point of view

- MCR-1 still, by far, mostly located in animal isolates
- MCR-1 is located in *E. coli*; very few MCR- producing *K. pneumoniae*
- MCR-1 isolates still susceptible to many other antibiotics
- Plasmid conjugation rate of *mcr-1* plasmids: low
- Prevalence of MCR- producing isolates still low; not a true emerging resistance gene: identified already as early as in 2005.
- Very low amount of colistin use in humans (600-fold less than in animals); a very light driving force for selecting resistance to polymyxins in humans
- Low level resistance may indicate a possibility to treat patients with polymyxin-containing antibiotics

Nordmann P, Poirel L. CMI, 2016, 22:398-400

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Eur J Clin Microbiol Infect Dis
DOI 10.1007/s10096-016-2739-0

LETTER TO THE EDITOR

August 2016

Screening of plasmid-mediated MCR-1 colistin-resistance from bacteremia

P. Nordmann[1,2,3] · L. Assouvie[1,2] · G. Prod'Hom[3] · L. Poirel[1,2] · G. Greub[3]

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257 Enterobacteriaceae isolates-bacteremia,CHUV, Lausanne, 2015

MCR producer; n = 0

MCR-1: a pessimistic point of view

- Plasmid-mediated colistin resistance exists
- Severe infections may be due to MCR-1 positive isolates
- Identification worldwide in the environment, animals and humans
- The main target is *E. coli*: the main bacterial species exchanged between animals and humans; same trend as for CTX-Ms ?
- Further extensive spread from *E. coli* to *K. pneumoniae* ?
- Identification on several plasmid backbones: simulateneous events of translocation worldwide
- Driving force; polymyxins as growth promoters, prophylaxis and metaphylaxis in animals
- Low level resistance: difficult detection; silencious diffusion
- Plasmid-mediated colistin resistance and carbapenemase may co-exist

Nordmann P, Poirel L. CMI, 2016, 22:398-400

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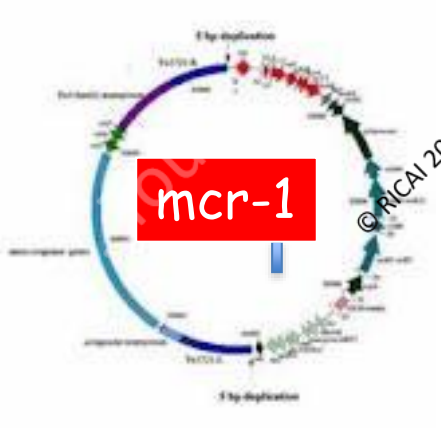
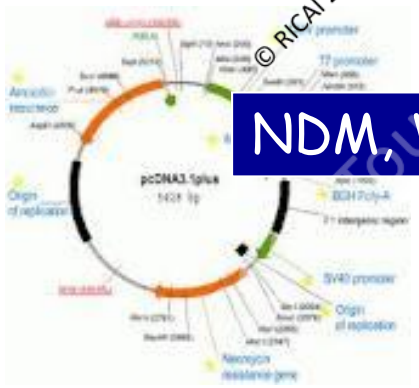
Transfer of plamid-mediated colistin resistance *mcr-1* gene to carbapenamase producers ?

E. coli



?

K. pneumoniae



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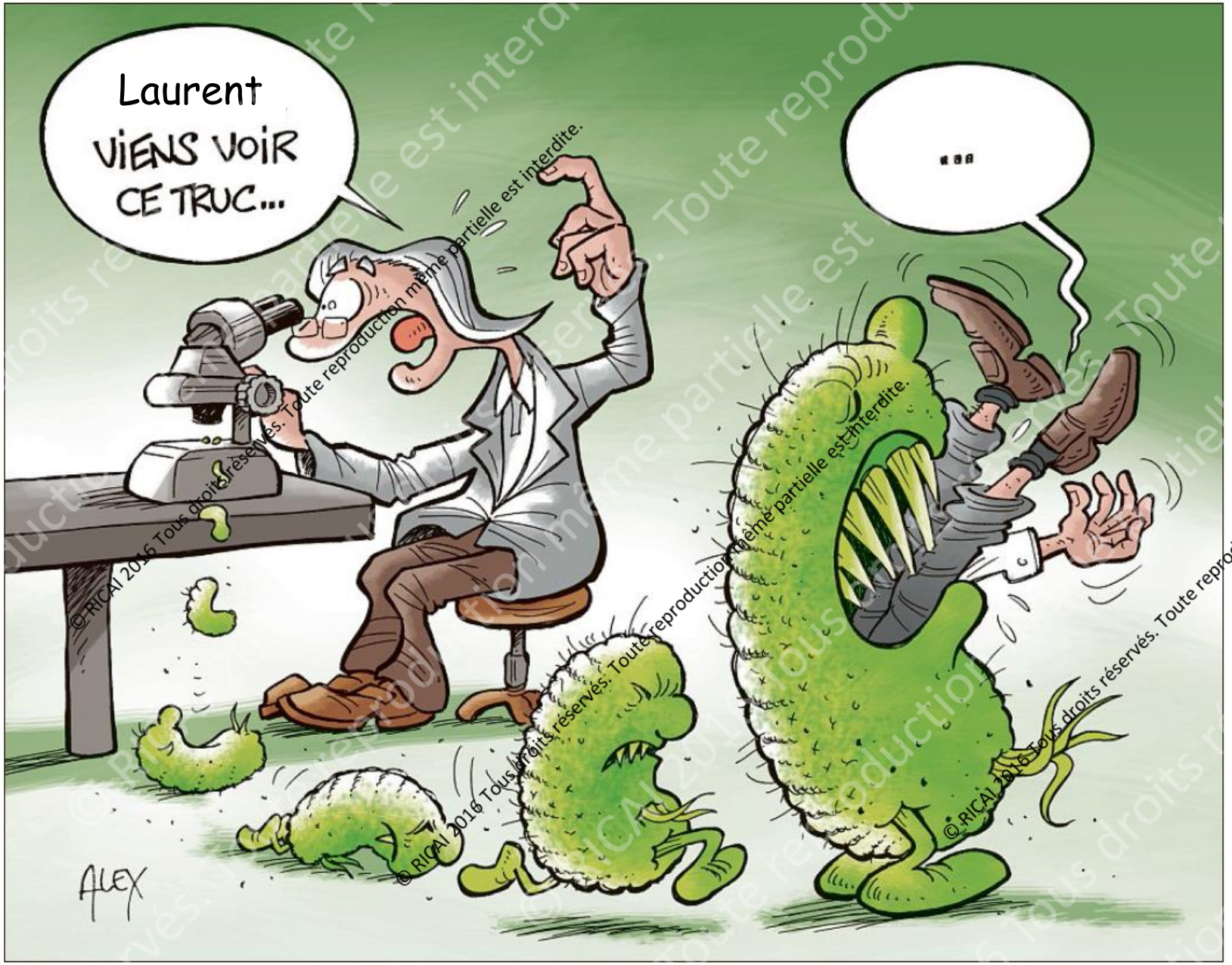

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Emergence of plasmid-mediated carbapenem and colistin resistance in *E. coli* in Europe

- Patient from Switzerland, December 2015

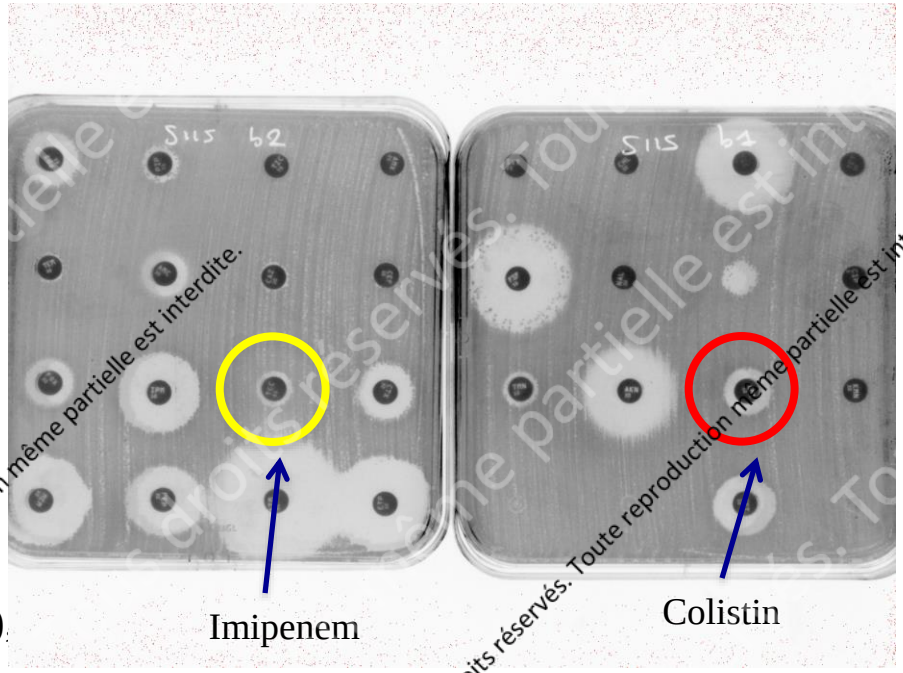
- No history of travel abroad

- No colistin-based treatment

- Urinary tract infection-Community-acquired

- *E. coli* isolate being resistant to carbapenems, fluoroquinolones, aminoglycosides (except amikacin), chloramphenicol, trimethoprim-sulfamethoxazole, and colistin

- Metallo-ß-lactamase VIM-1 + phosphoethanolamine transferase MCR-1



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L. Poirel, N.Kieffer, N Liassine, P. Nordmann;
Lancet Infect Dis, 2016, Jan 7

The future

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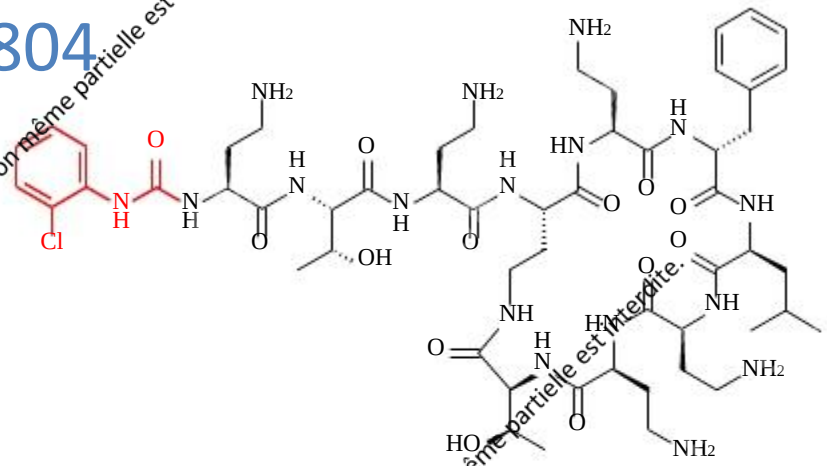
Future; novel colistin –like molecules

Cubist CB-182,804



In vitro activity

Strain	n	CB-182,804		Polymyxin B	
		MIC_{50}	MIC_{90}	MIC_{90}	MIC_{90}
E.coli	3049	2	4	1	1
K.pneumoniae	1155	2	4	1	2
P.aeruginosa	679	2	8	1	2
A.baumannii	407	2	4	1	2

Quale *et al.* (2012) Microb. Drug Resist. 18, 132.

Cytotoxicity vs LLC-PK1:

Cmpd	IC_{50}(µg/ml)
PMB	318
CB-182,804	>1,000

WO2010/075416

Improved toxictiy but at the expense of *in vitro* activity

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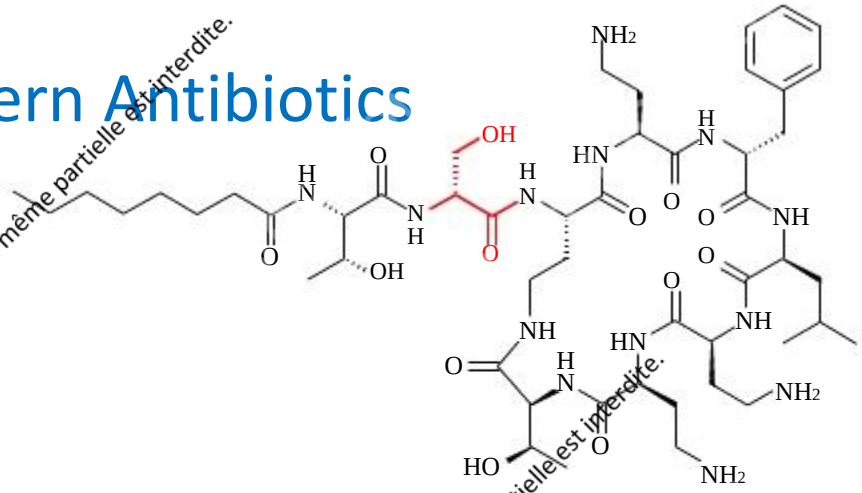
Novel colistin –like molecules

NAB739 – Northern Antibiotics Cantab



In vitro activity

Microorganism	n	NAB739		PolymyxinB	
		MIC50	MIC90	MIC50	MIC90
E.coli	51	1	2	0.5	2
K.pneumoniae	50	2	2	0.5	1
P.aeruginosa	49	4	8	1	2
A.baumannii	49	16	16	1	2

Cytotoxicity (HK2):

Compound	IC50(µg/ml)
PMB	13
NAB739	337

Vaara & Vaara (2013) Int. J. Antimicrob. Agents 41., 292.

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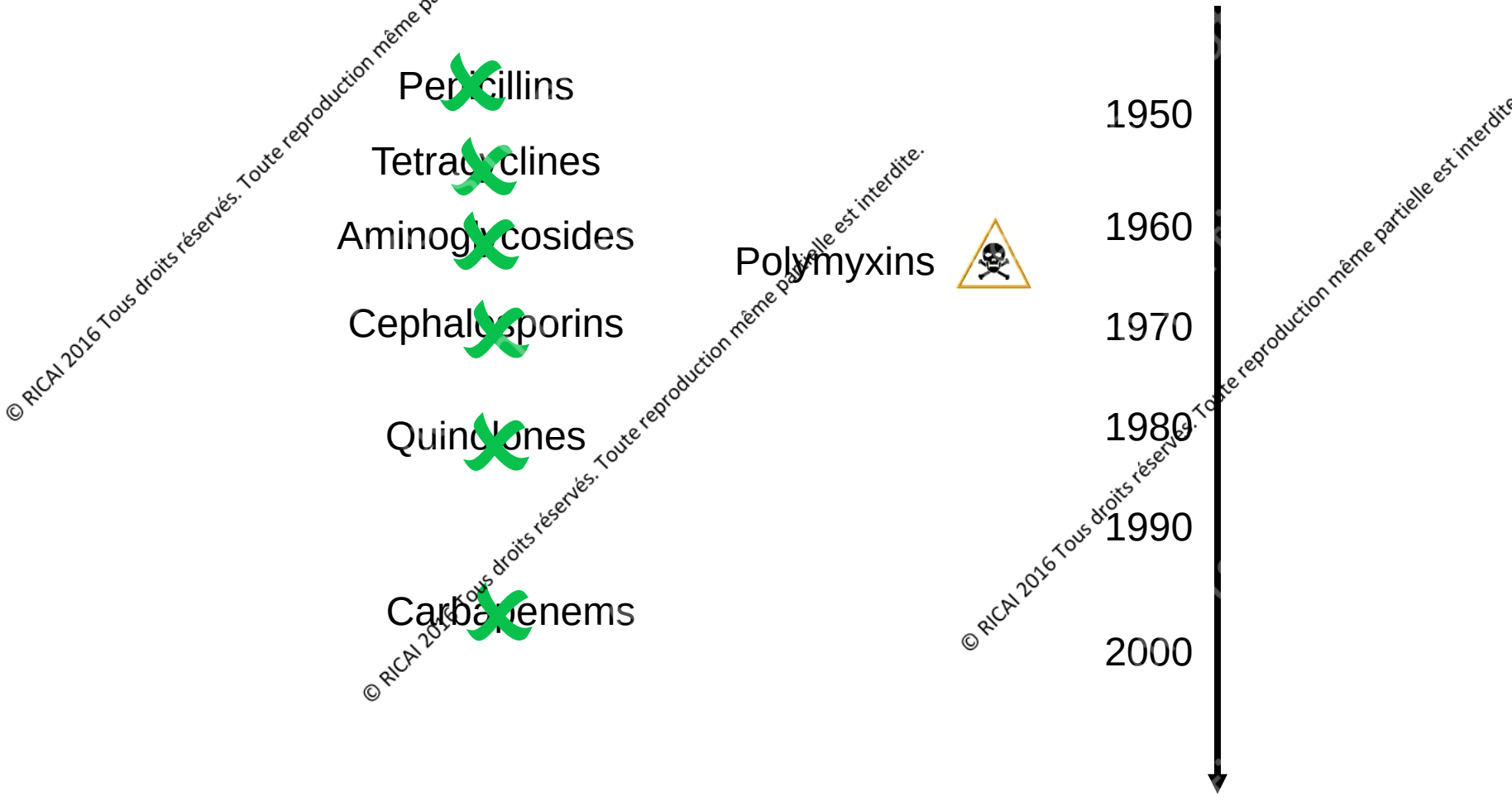
Rise of Antimicrobial Resistance in Gram-negative bacteria



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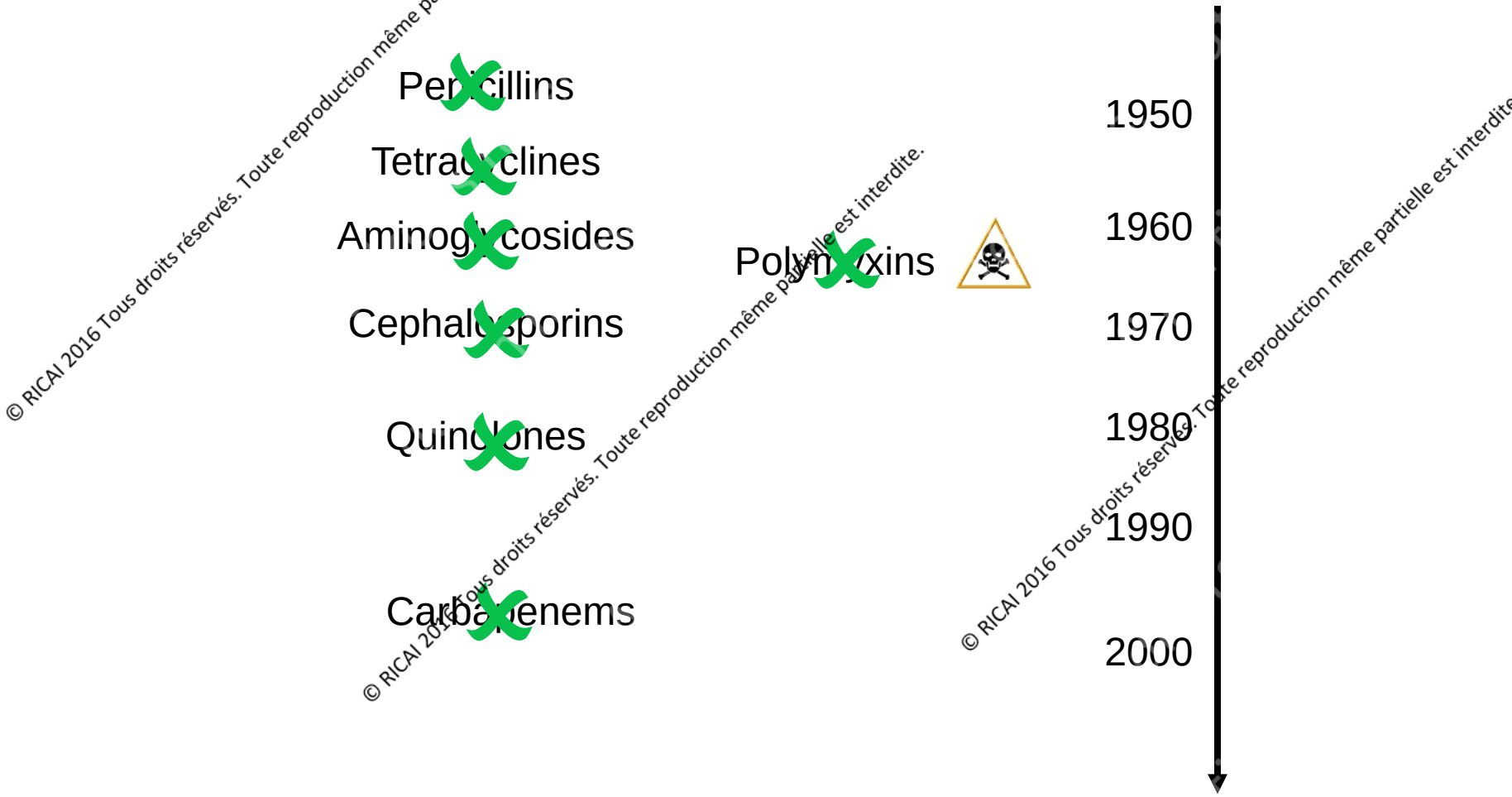
Rise of Antimicrobial Resistance in Gram-negative bacteria



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Conclusion

- Chromosome and plasmid-mediated colistin resistance are now identified, in particular in *E. coli and K. pneumoniae*
- Novel polymyxin-like molecules are under development
- Rapid diagnostic technique for identification of colistin resistance is needed.

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