Génétique de la résistance aux antibiotiques

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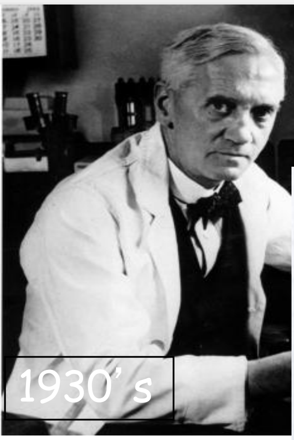
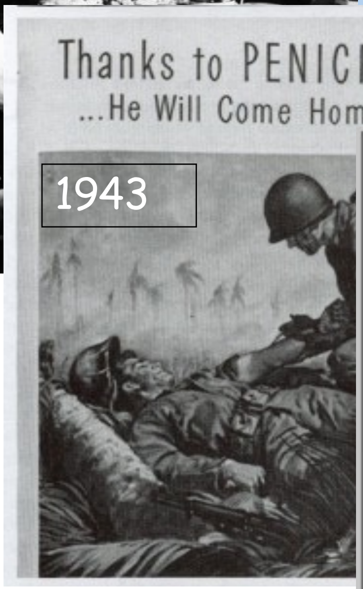

1930' s

Découverte

Premières utilisations



1943

Première résistance

1940

No. 3713, DEC. 28, 1940 NATURE 837

LETTERS TO THE EDITORS

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IN THE PRESENT CIRCUMSTANCES, PROOFS OF "LETTERS" WILL NOT BE SUBMITTED TO CORRESPONDENTS OUTSIDE GREAT BRITAIN.

An Enzyme from Bacteria able to Destroy Penicillin

FLEMING[1] noted that the growth of *B. coli* and a number of other bacteria belonging to the coli-typhoid group was not inhibited by penicillin. This observation has been confirmed. Further work has been done to find the cause of the resistance of these organisms to the action of penicillin.

An extract of *B. coli* was made by crushing a suspension of the organisms in the bacterial crushing mill of Booth and Green[2]. This extract was found to contain a substance destroying the growth-inhibiting property of penicillin. The destruction took place on incubating the penicillin preparation with the bacterial extract at 37°, or at room temperature for a longer time. The following is a typical experiment showing the penicillin-destroying effect of *B. coli* extracts. A solution of 1 mgm. penicillin in 0·8 c.c. of water was incubated with 0·2 c.c. of centrifuged and dialysed bacterial extract at 37° for 3 hours, in the presence of ether, and a control solution of penicillin of equal concentration was incubated without enzyme for the same time. (The penicillin used was extracted from cultures of *Penicillium notatum* by a method to be described in detail later. It possessed a degree of purity similar to that of the samples used in the chemotherapeutic experiments recorded in a preliminary report[3].) The growth-inhibiting activity of the solutions was then tested quantitatively on agar plates against *Staphylococcus aureus*. The penicillin solution incubated with the enzyme had entirely lost its growth-inhibiting activity, whereas the control solution had retained its full strength.

The conclusion that the active substance is an enzyme is drawn from the fact that it is destroyed

B. coli, it was not necessary to crush the organism in the bacterial mill in order to obtain the enzyme from it; the latter appeared in the culture fluid. The enzyme was also found in *M. lysodeikticus*, an organism sensitive to the action of penicillin, though less so than *Staphylococcus aureus*. Thus, the presence or absence of the enzyme in a bacterium may not be the sole factor determining its insensitivity or sensitivity to penicillin.

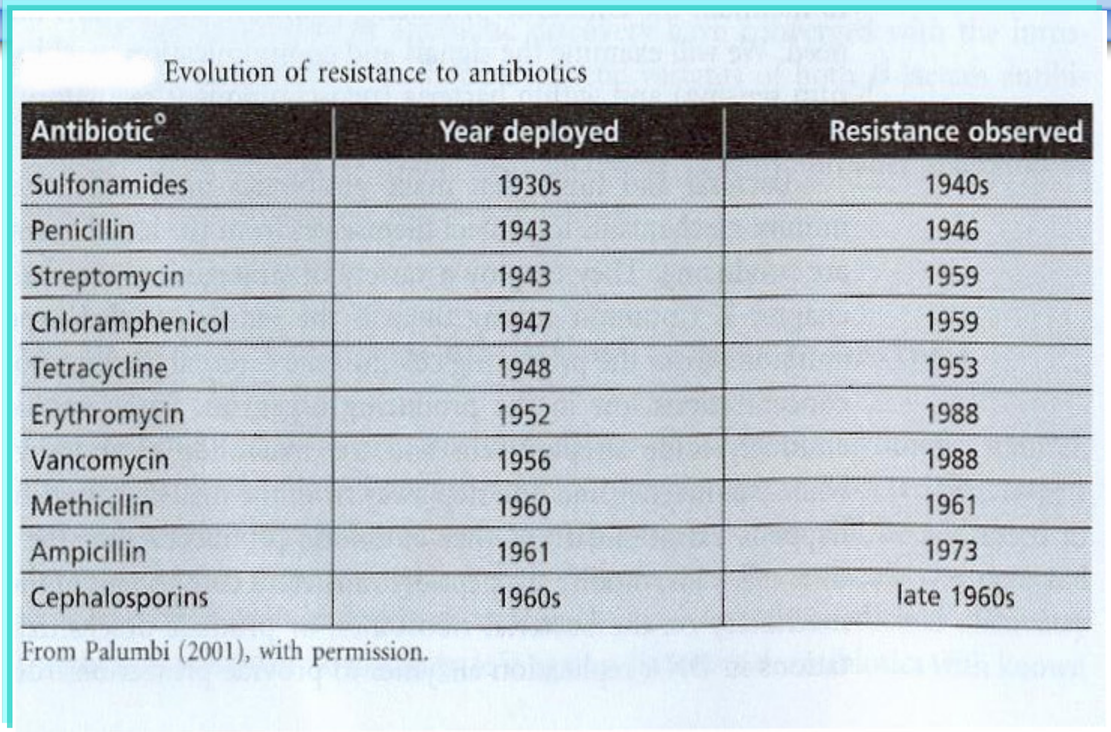
The tissue extracts and tissue autolysates that have been tested were found to be without action on the growth-inhibiting power of penicillin. Prof. A. D. Gardner has found staphylococcal pus to be devoid of inhibiting action, but has demonstrated a slight inhibition by the pus from a case of *B. coli* cystitis. The bacteriostatic action of the sulphonamide drugs is known to be inhibited in the presence of tissue constituents and pus.[4] That the anti-bacterial activity of penicillin is not affected under these conditions gives this substance a definite advantage over the sulphonamide drugs from the chemotherapeutic point of view. The fact that a number of bacteria contain an enzyme acting on penicillin points to the possibility that this substance may have a function in their metabolism.

E. P. ABRAHAM.
E. CHAIN.

Sir William Dunn School of Pathology,
Oxford.
Dec. 5.

[1] Fleming, A., *Brit. J. Exp. Path.*, **10**, 226 (1929).
[2] Booth, V. H., and Green, D. E., *Biochem. J.*, **32**, 855 (1938).
[3] Chain, E., Florey, H. W., Gardner, A. D., Heatley, N. G., Jennings, M. A., Orr-Ewing, J., and Sanders, A. G., *Lancet*, **239** (1940).
[4] MacLeod, C., *J. Exp. Med.*, **72**, 217 (1940).

Evolution de la résistance aux antibiotiques

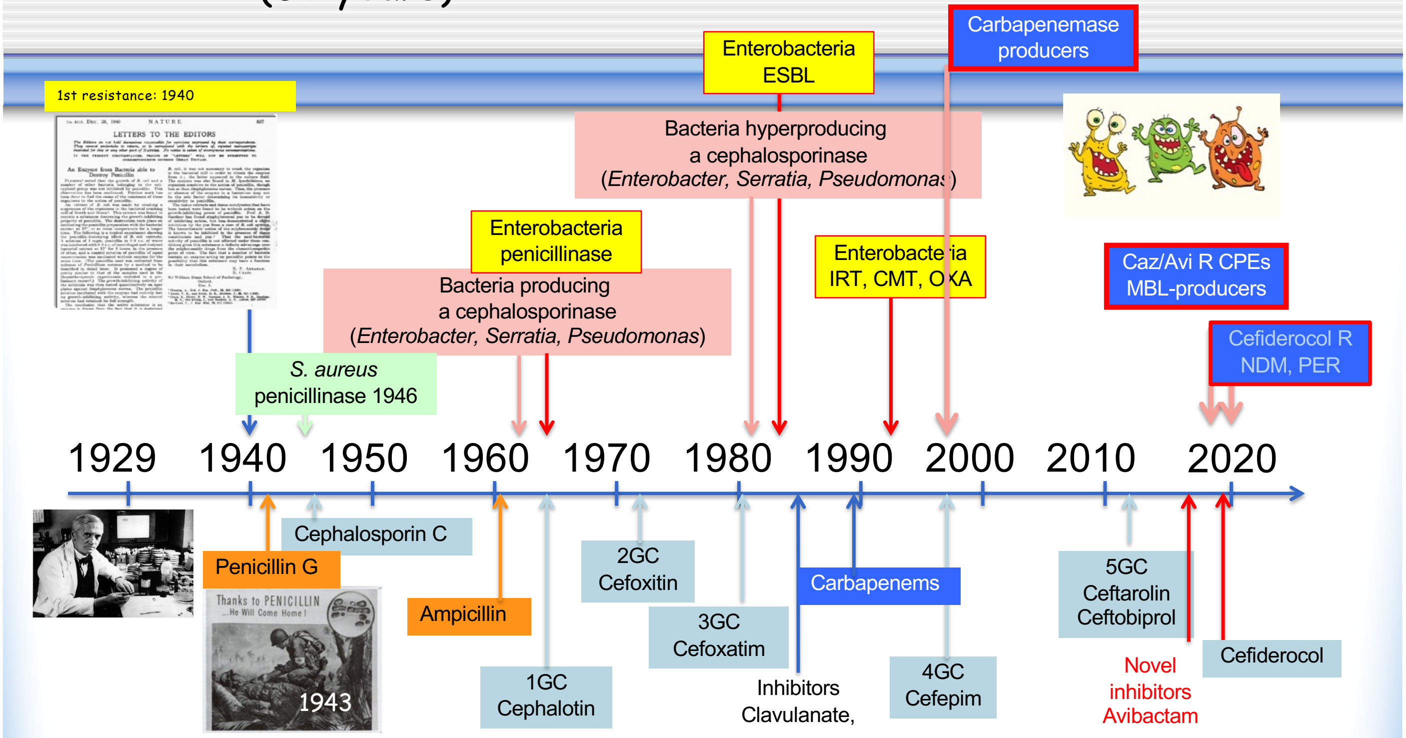


Evolution of resistance to antibiotics

Antibiotic°	Year deployed	Resistance observed
Sulfonamides	1930s	1940s
Penicillin	1943	1946
Streptomycin	1943	1959
Chloramphenicol	1947	1959
Tetracycline	1948	1953
Erythromycin	1952	1988
Vancomycin	1956	1988
Methicillin	1960	1961
Ampicillin	1961	1973
Cephalosporins	1960s	late 1960s

From Palumbi (2001), with permission.

The road to pan-drug resistance
(60 years)



1st resistance: 1940

S. aureus penicillinase 1946

Bacteria producing a cephalosporinase (*Enterobacter, Serratia, Pseudomonas*)

Enterobacteria penicillinase

Bacteria hyperproducing a cephalosporinase (*Enterobacter, Serratia, Pseudomonas*)

Enterobacteria ESBL

Enterobacteria IRT, CMT, OXA

Carbapenemase producers

Caz/Avi R CPEs MBL-producers

Cefiderocol R NDM, PER

Penicillin G

1943

Cephalosporin C

Ampicillin

1GC Cephalotin

2GC Cefoxitin

3GC Cefoxatim

Inhibitors Clavulanate,

Carbapenems

4GC Cefepim

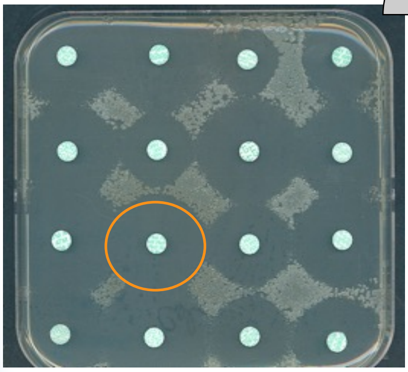
5GC Ceftarolin Ceftobiprol

Novel inhibitors Avibactam

Cefiderocol

Résistances émergentes aux antibiotiques: ß-lactamines

E. coli
de notre enfance

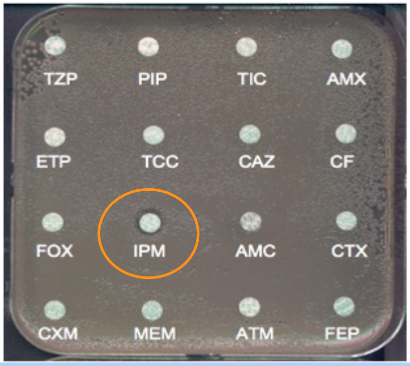


60 ans

Comment?

Ou?

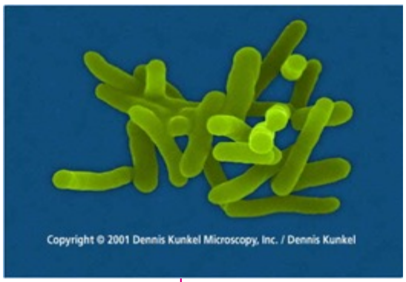
E. coli
des temps modernes



Carbapenemases
Metallo-enzymes (bla_{VIM}, bla_{IMP}, **bla_{NDM}**)
Oxacillinases (**bla_{OXA-48}**)
Class A (bla_{NMCA}, bla_{GES}, and **bla_{KPC}**)

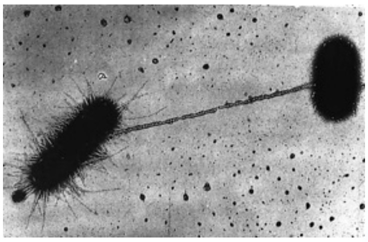
Comment ?
« Evolution » bactérienne aux antibiotiques

Antibiotiques



Mort

It was on a short-cut through the hospital kitchens that Albert was first approached by a member of the Antibiotic Resistance.



Survie

- Hyperproduction
- Hyper. efflux
- Imperméabilité
- Cible

Mutation

Acquisition de gène - échange de matériel génétique
Plasmides, transposons, intégrons

« Bacterial Evolution » to antibiotics

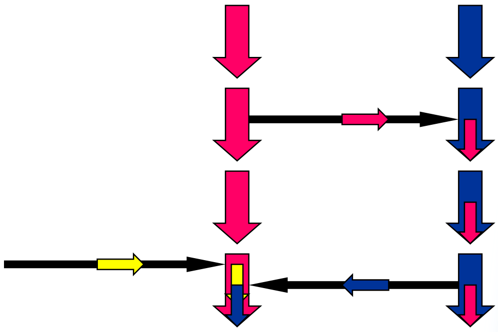
Qualitative change of the genome

- Mutations

Quantitative change of the genome

- gene exchange

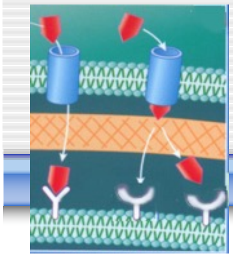
Horizontal evolution

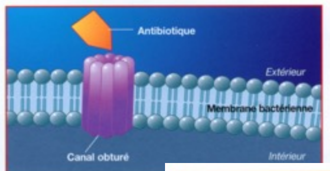


Qualitative and quantitative change of the genome

- Mutations and gene exchange

Résistance aux ß-lactamines Gram négatives

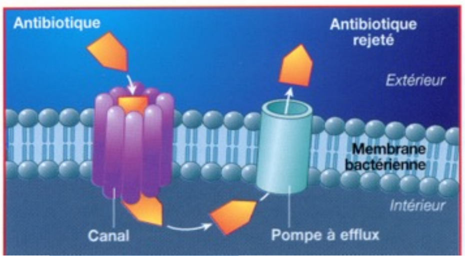




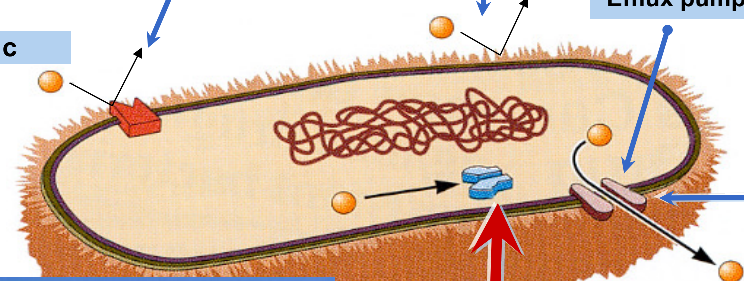
Modification of PBPs

Decrease in permeability

Overexpression Efflux pumps

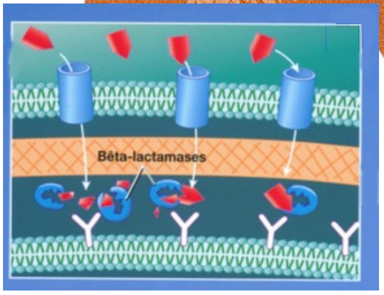


Antibiotic

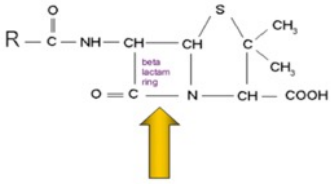


Pumps

Antibiotic

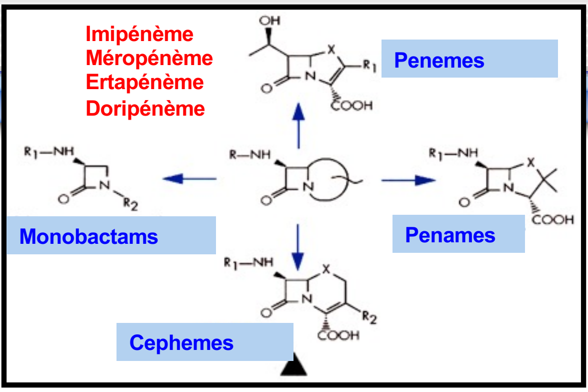


β-Lactamases



Site of penicillinase action
(break in β lactam ring)

Résistance aux ß-lactamines:
ß-lactamases

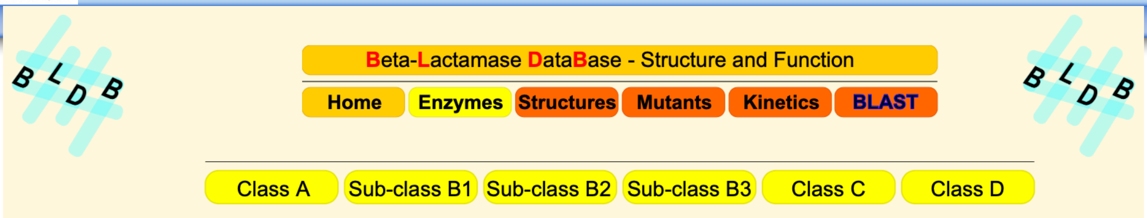


ß-lactamines

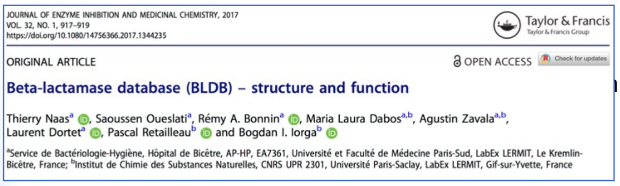
ß-lactamases

	Active site		G		KTG	Groupe	Inhibitors	
A	SXXK 70-73	SXN 130-132	156	Ωloop 164-179	234-236	**Penicillinase**	**clavulanic acid**	**CTX-M** **KPC**
C	SXXK 64-67	YXN		Ωloop 208-213	315-317	**Cephalosporinase**	**Cloxacillin**	
D	SXXK 70-73	YGN 144-146		WxExxL 164-169	216-218	**Oxacillinase**	**no inhibitor**	**OXA-48**
B **Zn++**	61-65	Zn1 ligand His116, 118,196		Zn2 ligand Asp120, Cys221,His263		**Metallo-enzyme**	**EDTA**	**NDM/VIM/IMP**

Beta-Lactamase DataBase (BLDB)



http://www.bldb.eu/



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VOL. 32, NO. 1, 917–919
https://doi.org/10.1080/14756366.2017.1344235

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ORIGINAL ARTICLE

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Beta-lactamase database (BLDB) – structure and function

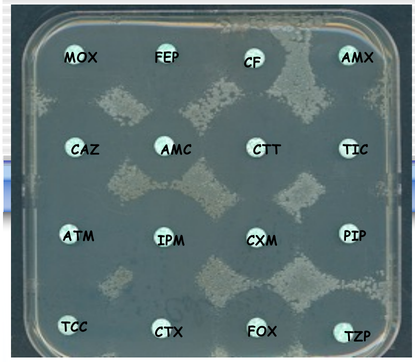
Thierry Naas[a], Saoussen Oueslati[a], Rémy A. Bonnin[a], Maria Laura Dabos[a,b], Agustin Zavala[a,b], Laurent Dortet[a], Pascal Retailleau[b] and Bogdan I. Iorga[b]

[a]Service de Bactériologie-Hygiène, Hôpital de Bicêtre, AP-HP, EA7361, Université et Faculté de Médecine Paris-Sud, LabEx LERMIT, Le Kremlin-Bicêtre, France; [b]Institut de Chimie des Substances Naturelles, CNRS UPR 2301, Université Paris-Saclay, LabEx LERMIT, Gif-sur-Yvette, France

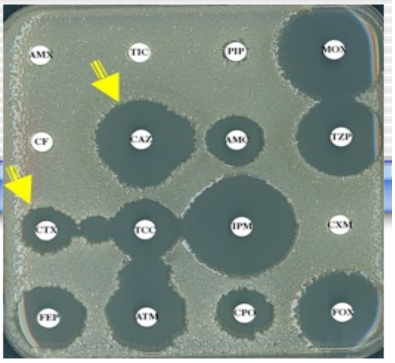
2022

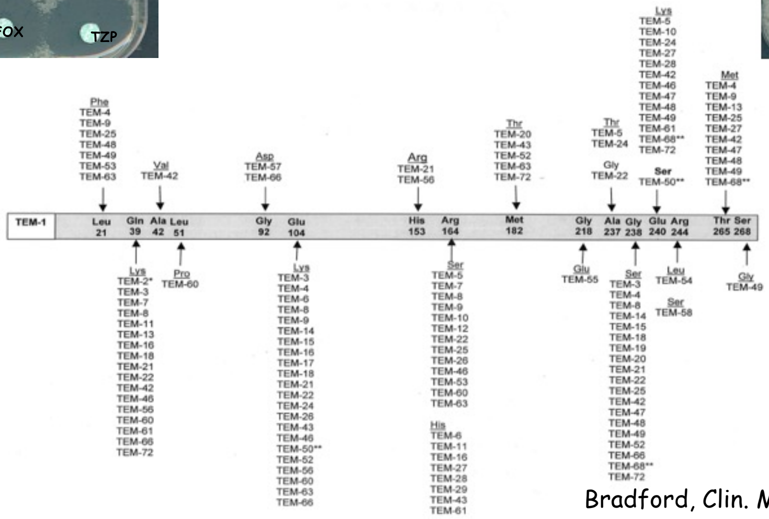
Class	Public version	Increase since 2016
A	1726	X 1.5
B1	557	X 2.7
B2	23	X 1.3
B3	226	X 3.8
C	3620	X 5.8
D	1145	X 2.1
Total	**7490**	**X 2.8**

*Integration of new sequences into BLDB is still ongoing



Role of mutations
The TEM family

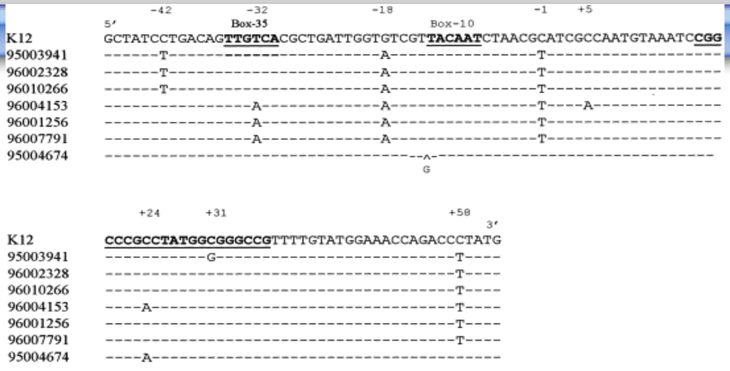




Bradford, Clin. Microbiol.Rev. 2001, 14; 933-51

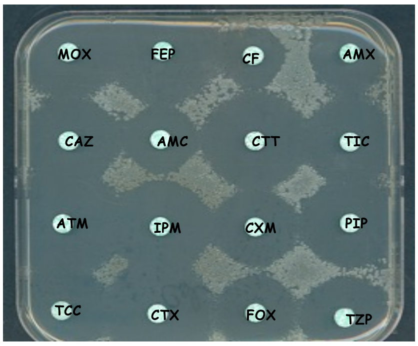
FIG. 1. Amino acid substitutions in TEM ESBL derivatives. The amino acids listed within the grey bar are those found in the structural gene of the TEM-1 β-lactamase (162). The amino acid numbering is according to the scheme of Ambler et al. (5). Substitutions found in TEM-type ESBL derivatives are shown under the amino acids of TEM-1. TEM-type variants may contain more than one amino acid substitution. ∗, TEM-2 is not an ESBL but is included in the figure as a derivative of TEM-1. The Gln39Lys substitution does not contribute to the ESBL phenotype, but a number of ESBLs are derived from TEM-2. ∗∗, TEM-50 and TEM-68 contain amino acid substitutions that are common to both the ESBL and the IRT phenotypes. Only the amino acid substitutions that are common to TEM-type ESBLs are shown in this figure.

Mutations de la région promotrice de *ampC* de *E. coli*

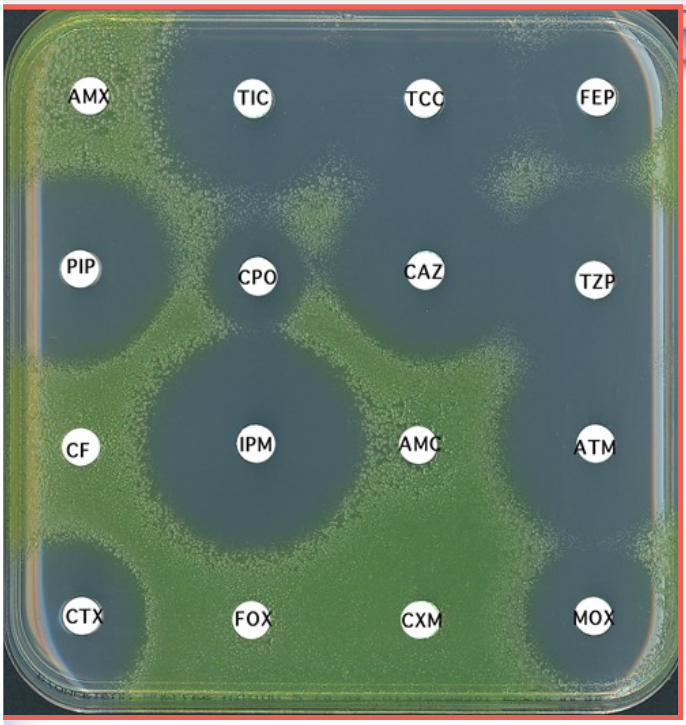


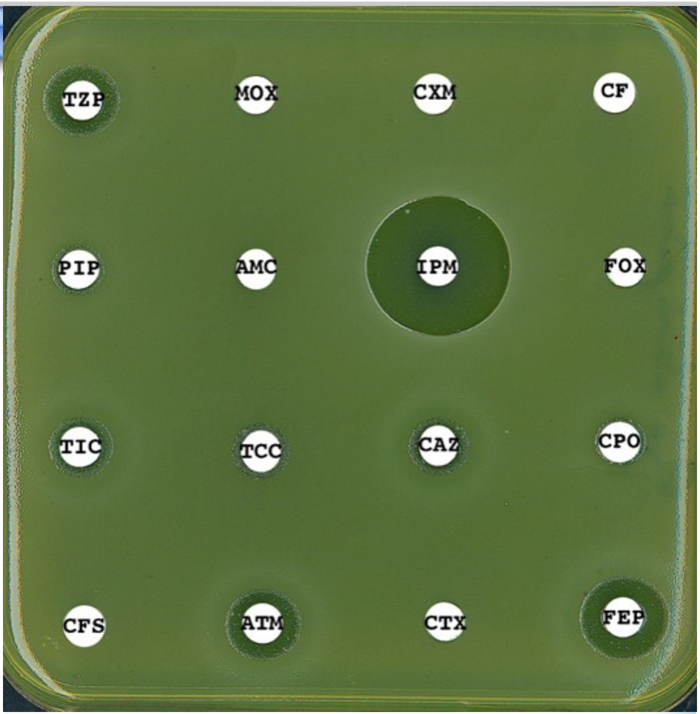
```
                 -42       -32           -18              -1   +5
            5'           Box-35                 Box-10
K12         GCTATCCTGACAGTTGTCACGCTGATTGGTGTCGTTACAATCTAACGCATCGCCAATGTAAATCCGG
95003941    ------T-----------------------A----------------T-------------------
96002328    ------T-----------------------A----------------T-------------------
96010266    ------T-----------------------A----------------T-------------------
96004153    ----------------A-------------A----------------T----A--------------
96001256    ----------------A-------------A----------------T-------------------
96007791    ----------------A-------------A----------------T-------------------
95004674    -----------------------------------^-------------------------------
                                               G

                +24    +31                        +58
                                                     3'
K12         CCCGCCTATGGCGGGCCGTTTTGTATGGAAACCAGACCCTATG
95003941    -----------G--------------------------T----
96002328    --------------------------------------T----
96010266    --------------------------------------T----
96004153    ----A---------------------------------T----
96001256    --------------------------------------T----
96007791    --------------------------------------T----
95004674    ----A--------------------------------------
```

Caroff et al. FEMS Microbiol Lett. 1999: 173(2):459-65.

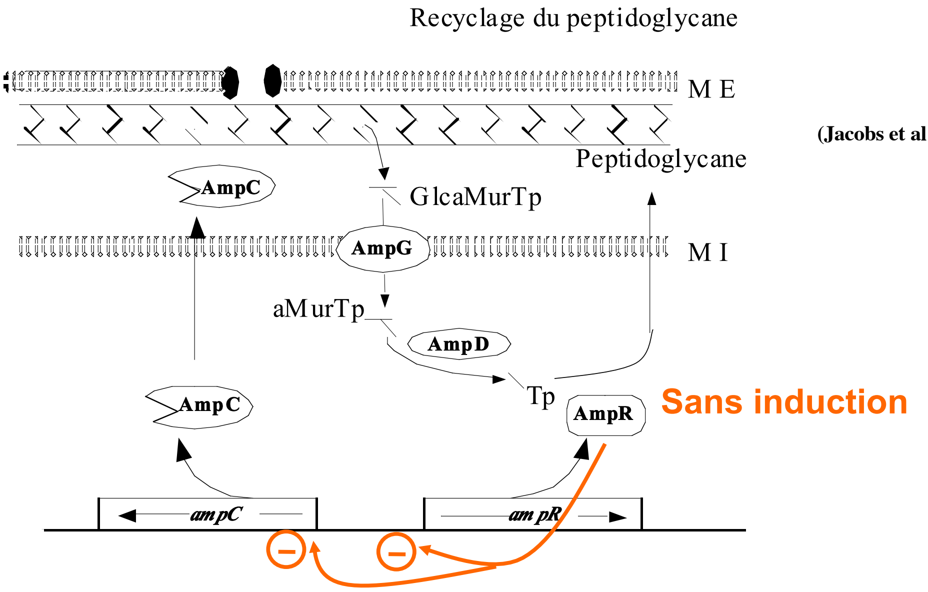


Dérépression de l'expression de céphalosporinase chez *P. aeruginosa*





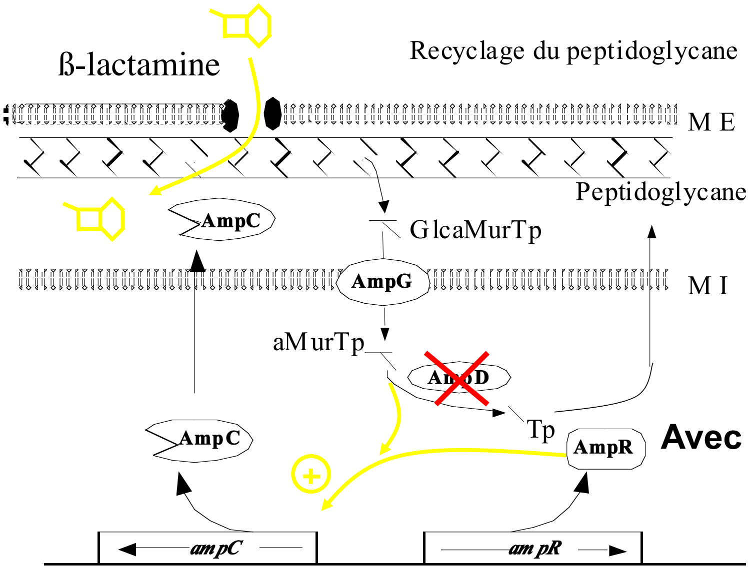
Régulation de l'expression des gènes *ampC (C. freundii, P. aeruginosa…)*



(Jacobs et al., Cell,1997)

Sans induction

Régulation de l'expression des gènes *ampC (C. freundii, P. aeruginosa…)*



(Jacobs et al., Cell,1997)

AMPD muté: hyperproduction de AMPC

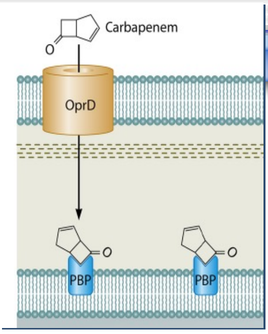
Avec induction

Mutation dans un gène régulateur : hyperproduction de céphalosporinase

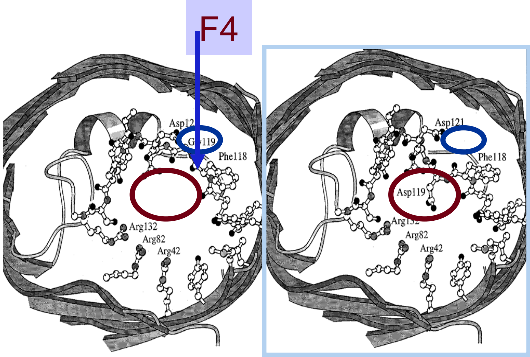
Gram - : *E. cloacae, S. marcescens, P. stuartii, E. aerogenes, H. alvei, M. morganii, C. freundii, P. aeruginosa*

		CMI (µg/ml)		
	AMOX	TIC	CTX	CAZ
Basal	512	16	0.12	0.12
Déréprimé	512	**512**	**32**	**128**

Imperméabilité chez *P. aeruginosa*

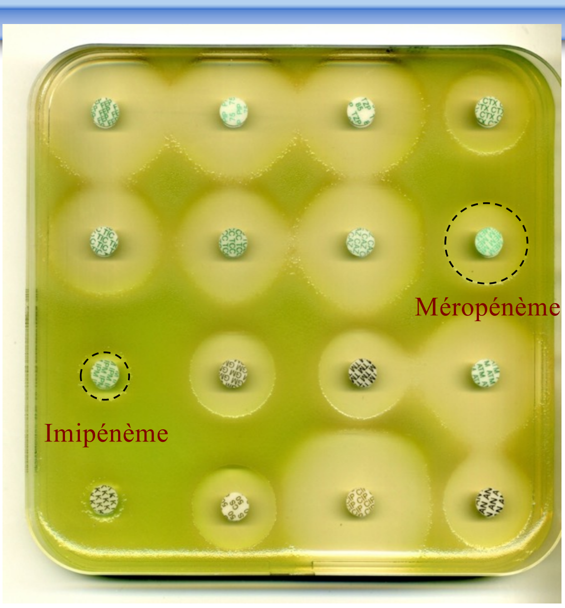


Mutation porine D2, *P. aeruginosa*



Porine sauvage

Porine mutée (G119D)



Courtesy from P. Plésiat

Mutation and carbapenem resistance: combined mechanisms of resistance

Enterobacteriaceae (++Enterobacter spp.)

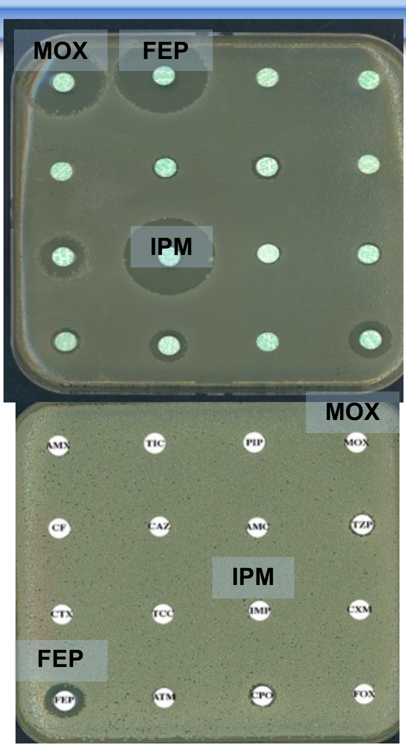
- Overproduced cephalosporinase
- Plasmid-mediated cephalosporinase
- Plasmid-mediated ESBL

Resistance to CIIIG

Decreased OM permeability

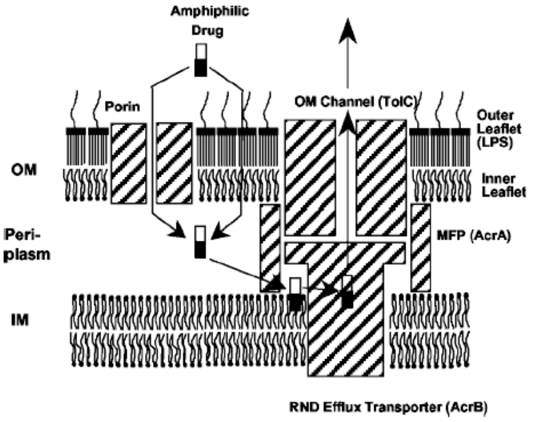
Additional Resistance to carbapenems

Lee EH, Nicolas MH, Kitzis MD, Pialoux G, Collatz E, Gutmann L.
Association of two resistance mechanisms in a clinical isolate of Enterobacter cloacae with high-level resistance to imipenem.
Antimicrob Agents Chemother. 1991, 35:1093-8.



Role of mutations
Active efflux

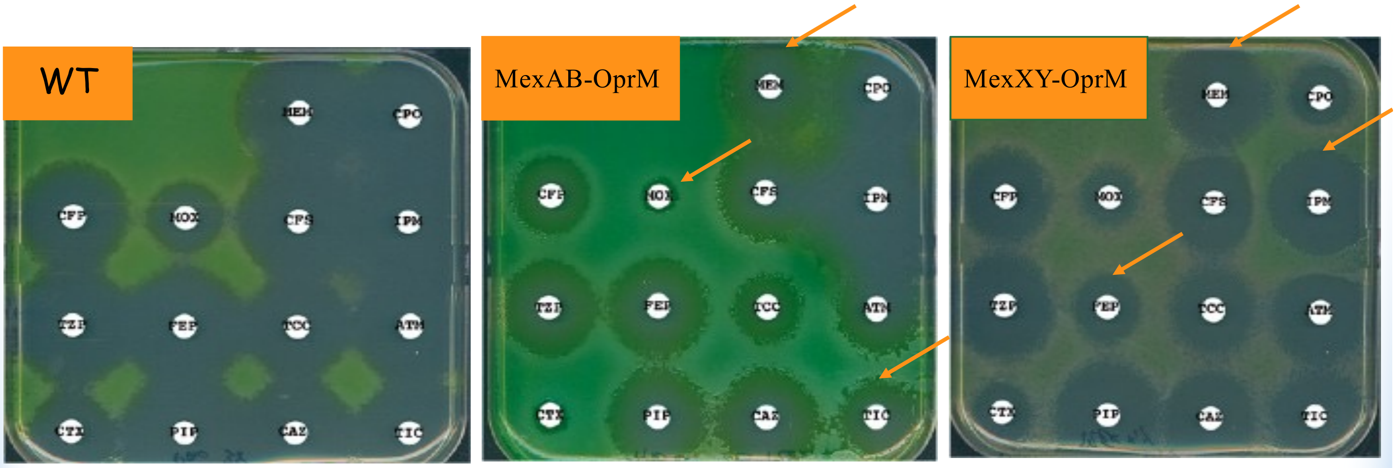
P. aeruginosa :



Efflux systems	Antibiotic resistance
MexAB-OprM	quinolones tetracycline chloramphenicol trimethoprime β-lactams
MexCD-OprJ	quinolones chloramphenicol
MexEF-OprN	quinolones chloramphenicol
MexXY	quinolones erythromycine Aminoglycosides

(AAC 2003: 43 ; 415-7)
(AAC 2003: 43 ; 2624-8)

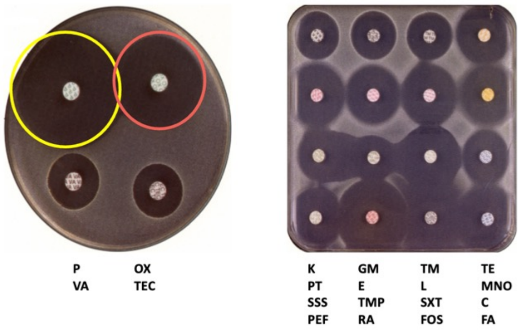
Efflux overexpression

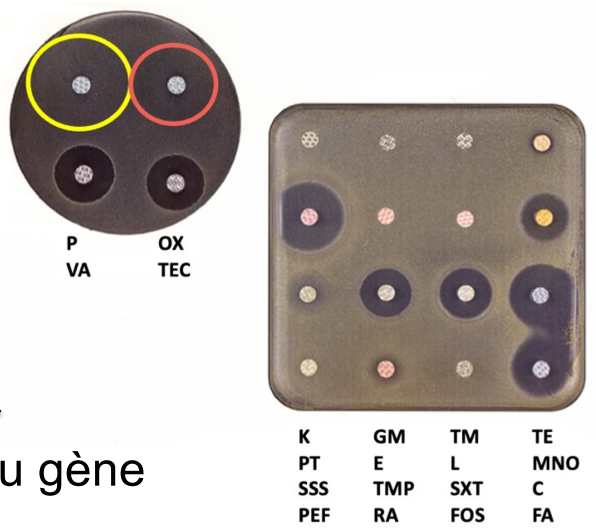


Rôle des PLPs: le cas *S. aureus*

S.aureus
Phénotype sauvage

S. aureus
Phénotype Méti-R

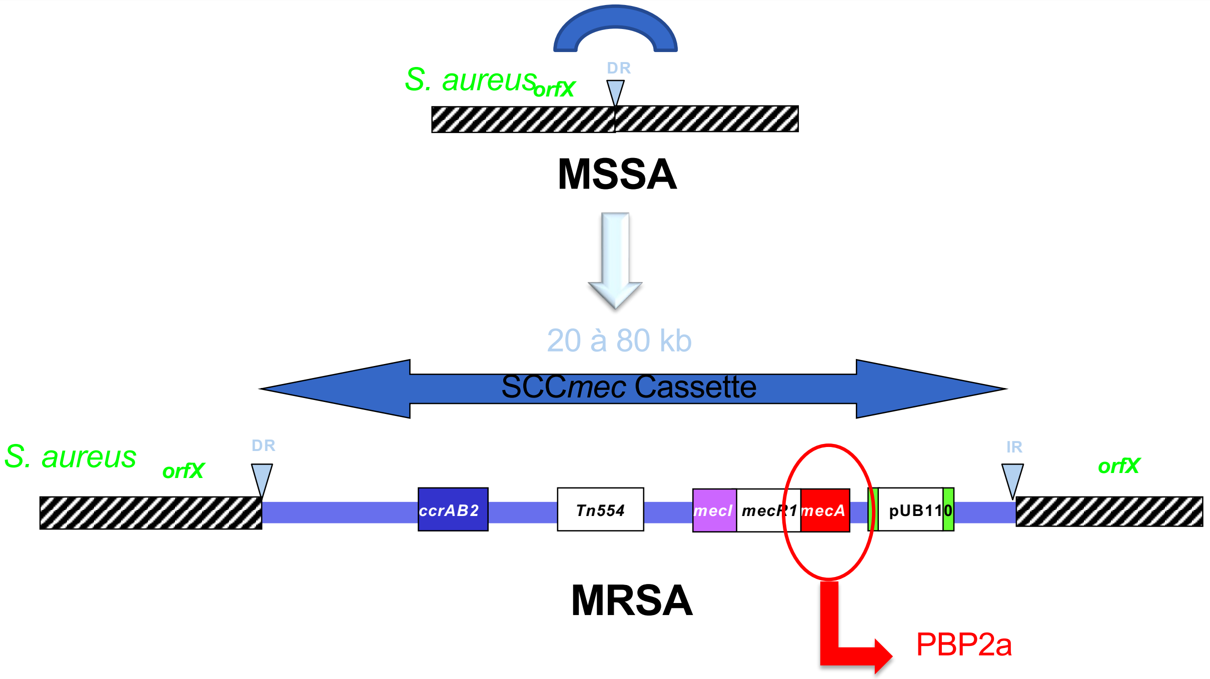




Acquisition du gène
mecA

MSSA – MRSA : SCC*mec* story

Cassette SCC*mec*



Patiño-Navarrete *et al. Genome Medicine* (2020) 12:10
https://doi.org/10.1186/s13073-019-0699-6

Genome Medicine

RESEARCH Open Access

Stepwise evolution and convergent recombination underlie the global dissemination of carbapenemase-producing *Escherichia coli*

Rafael Patiño-Navarrete[1,2], Isabelle Rosinski-Chupin[1,2†], Nicolas Cabanel[1,2], Lauraine Gauthier[1,3,4,5], Julie Takissian[1,5], Jean-Yves Madec[6], Monzer Hamze[7], Remy A. Bonnin[1,4,5], Thierry Naas[1,3,4,5†] and Philippe Glaser[1,2*†]

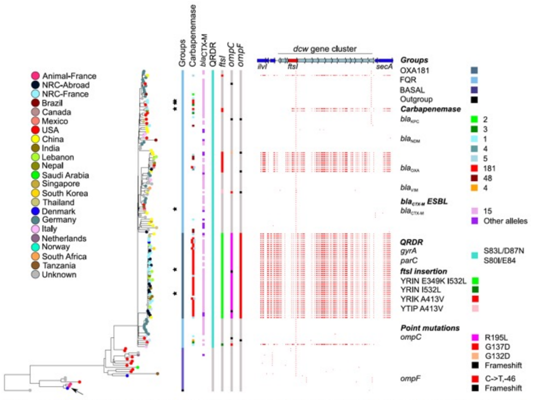


Fig. 1 Core genome phylogeny and genomic features of *E. coli* ST410 isolates. ML phylogeny of 155 *Ec* ST410 nr genomes built with RAxML [39]

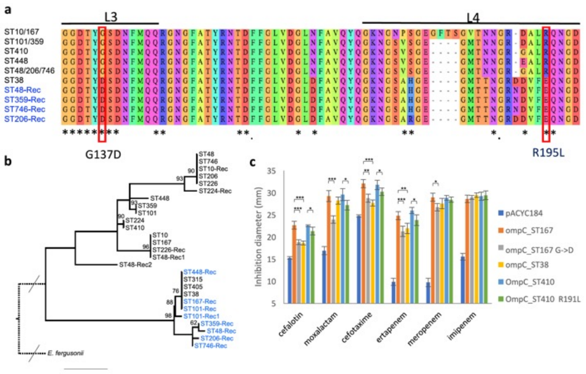
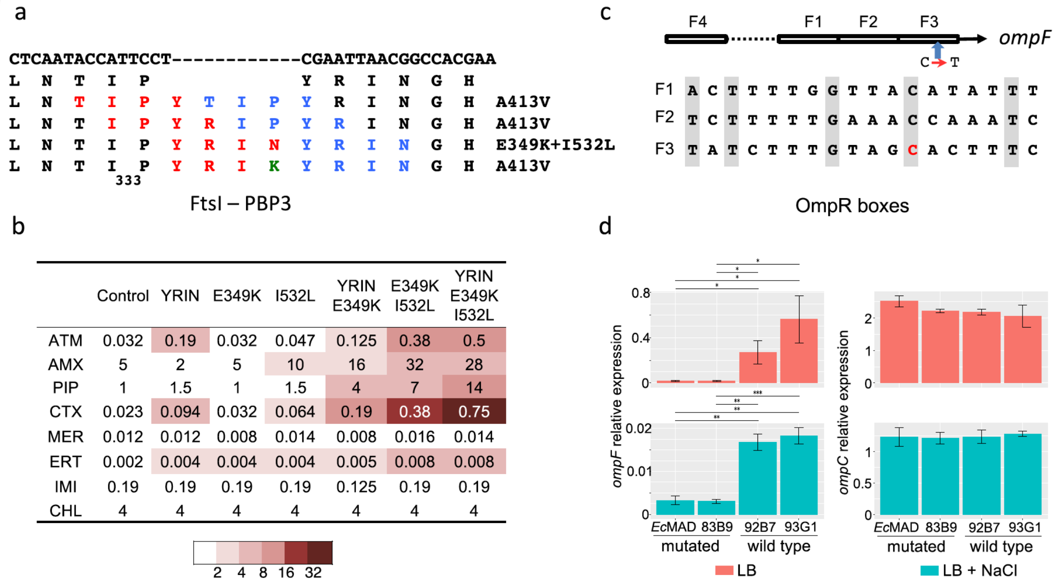


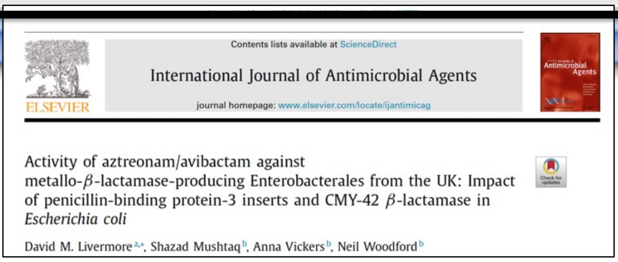
Fig. 2 Mutations and recombination in the *ompC* gene. **a** Alignment of OmpC L3L4 region from ST in which mutations or recombination events



	Control	YRIN	E349K	I532L	YRIN E349K	E349K I532L	YRIN E349K I532L
ATM	0.032	0.19	0.032	0.047	0.125	0.38	0.5
AMX	5	2	5	10	16	32	28
PIP	1	1.5	1	1.5	4	7	14
CTX	0.023	0.094	0.032	0.064	0.19	0.38	0.75
MER	0.012	0.012	0.008	0.014	0.008	0.016	0.014
ERT	0.002	0.004	0.004	0.004	0.005	0.008	0.008
IMI	0.19	0.19	0.19	0.19	0.125	0.19	0.19
CHL	4	4	4	4	4	4	4

Fig. 3 Functional analyses of *ftsI* and *ompF* mutations occurring in the OXA-181 *Ec* ST410 subclade. **a** Mutations identified in *ftsI*. The 4 different

E. coli and aztreonam-avibactam resistance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Activity of aztreonam/avibactam against metallo-β-lactamase-producing Enterobacterales from the UK: Impact of penicillin-binding protein-3 inserts and CMY-42 β-lactamase in *Escherichia coli*

David M. Livermore[a,*], Shazad Mushtaq[b], Anna Vickers[b], Neil Woodford[b]

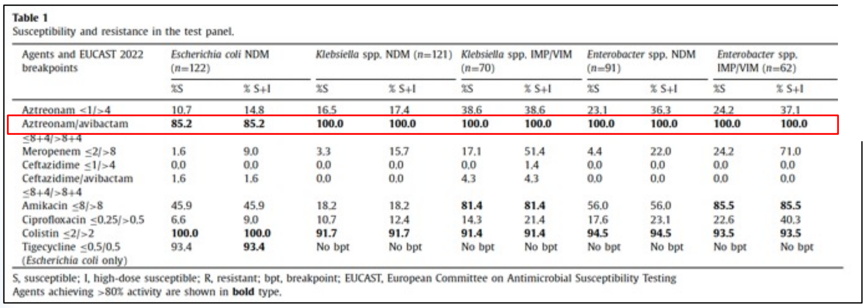
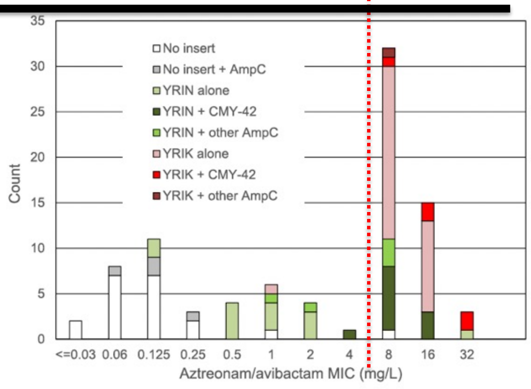


Table 1
Susceptibility and resistance in the test panel.

Agents and EUCAST 2022 breakpoints	*Escherichia coli* NDM (*n*=122)		*Klebsiella* spp. NDM (*n*=121)		*Klebsiella* spp. IMP/VIM (*n*=70)		*Enterobacter* spp. NDM (*n*=91)		*Enterobacter* spp. IMP/VIM (*n*=62)	
	%S	% S+I	%S	% S+I	%S	% S+I	%S	% S+I	%S	% S+I
Aztreonam <1/>4	10.7	14.8	16.5	17.4	38.6	38.6	23.1	36.3	24.2	37.1
Aztreonam/avibactam ≤8+4/>8+4	**85.2**	**85.2**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**
Meropenem ≤2/>8	1.6	9.0	3.3	15.7	17.1	51.4	4.4	22.0	24.2	71.0
Ceftazidime ≤1/>4	0.0	0.0	0.0	0.0	0.0	1.4	0.0	0.0	0.0	0.0
Ceftazidime/avibactam ≤8+4/>8+4	1.6	1.6	0.0	0.0	4.3	4.3	0.0	0.0	0.0	0.0
Amikacin ≤8/>8	45.9	45.9	18.2	18.2	**81.4**	**81.4**	56.0	56.0	**85.5**	**85.5**
Ciprofloxacin ≤0.25/>0.5	6.6	9.0	10.7	12.4	14.3	21.4	17.6	23.1	22.6	40.3
Colistin ≤2/>2	**100.0**	**100.0**	**91.7**	**91.7**	**91.4**	**91.4**	**94.5**	**94.5**	**93.5**	**93.5**
Tigecycline ≤0.5/0.5 (*Escherichia coli* only)	93.4	**93.4**	No bpt	No bpt	No bpt	No bpt	No bpt	No bpt	No bpt	No bpt

S, susceptible; I, high-dose susceptible; R, resistant; bpt, breakpoint; EUCAST, European Committee on Antimicrobial Susceptibility Testing
Agents achieving >80% activity are shown in **bold** type.



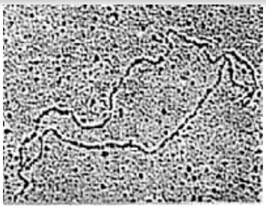
- YRIK alone, and YRIN plus acquired AmpC (mostly CMY-42) are associated with higher MICs towards aztreonam/avibactam (8–16 mg/L , versus 0.03–0.25 mg/L for NDM-producing *E. coli* without insertion.
- Insertions + additional mutations in *ftsI* (PBP3), => MICs 128 mg/L for cefiderocol and 256 mg/L for cefepime/taniborbactam, two other anti-MBLs.

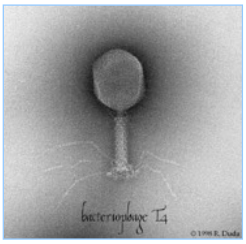
Les transferts d'information génétique

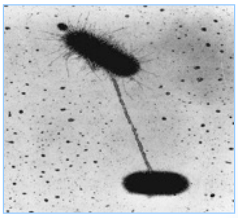
- Transduction et Conversion
  - vecteur : phage
  - spectre d'hôte : intra-espèce
  - efficacité : importante
  - distribution : ubiquitaire
- Transformation
  - vecteur : ADN
  - spectre d'hôte : intra- ou inter-espèce
  - efficacité : importante
  - distribution : restreinte
- Conjugaison
  - vecteur : plasmide
  - spectre d'hôte : inter-espèce
  - efficacité : variable
  - distribution : ubiquitaire

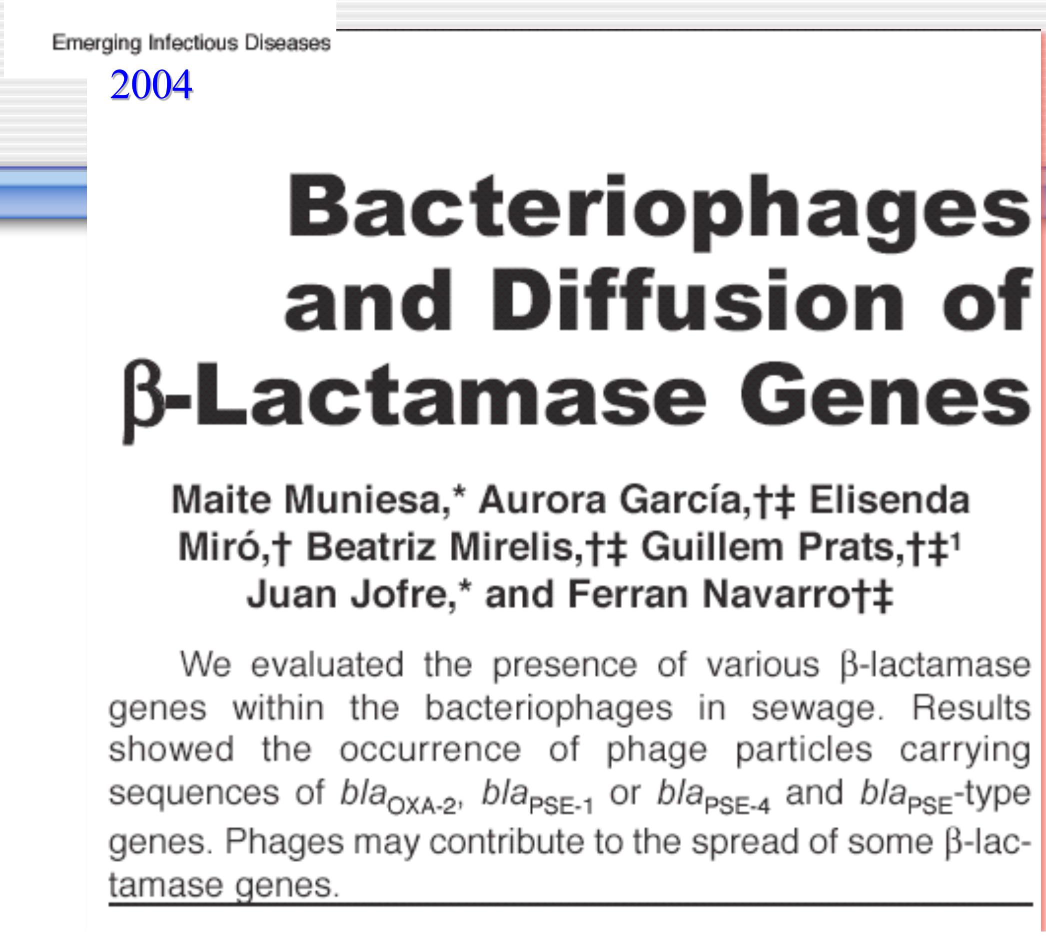
Véhicules du transfert horizontal

- ADN Nu
  - Transformation
  - Spectre d'hôte : intra- and inter- espèce
  - efficacité : élevée
  - distribution : limitée
- Bactériophage
  - Transduction and Conversion lysogénique
  - Spectre d'hôte : intra-espèce
  - efficacité : élevée
  - distribution : ubiquitaire
- Plasmides
  - Conjugaison
  - Spectre d'hôte : intra- and inter- espèce
  - efficacité : variable
  - distribution : ubiquitaire









Emerging Infectious Diseases

2004

Bacteriophages and Diffusion of β-Lactamase Genes

Maite Muniesa,* Aurora García,†‡ Elisenda Miró,† Beatriz Mirelis,†‡ Guillem Prats,†‡[1]
Juan Jofre,* and Ferran Navarro†‡

We evaluated the presence of various β-lactamase genes within the bacteriophages in sewage. Results showed the occurrence of phage particles carrying sequences of bla_{OXA-2}, bla_{PSE-1} or bla_{PSE-4} and bla_{PSE}-type genes. Phages may contribute to the spread of some β-lactamase genes.

La Conversion lysogénique
Certains bactériophages portent dans leur génome les nouveaux caractères apportés.

Protein	Gene	Bactériophage	Bactérie
Gènes de Résistance			
methicillin-R	mecA		*Staphylococcus spp,*
erythromycin-R	erm		*S. epidermidis,*
….			
Toxines extracellulaires			
Diphtérique	tox	beta-phage	*Corynebacterium diphteriae*
Neurotoxin	C1	phage C1	*Clostridium botulinum*
Shiga toxins	stx1-stx2	H-19B	*Escherichia coli (EHEC)*
Enterohemolysin	hly2	PhiFC3208	*E. coli (EPEC)*
Enterotoxine	sea, b,…, m -		*Staphylococcus aureus*
Exfoliative toxine A	eta	phiETA	*S. aureus*
Toxine A, C, I, …	speA, C, I	-	*Streptococcus pyogenes*
Cholérique	ctxAB	CTX-phi	*Vibrio cholerae*
……			

Protéines modifiant l ’ antigénicité

Protéines impliquées dans l ’ invasion

Protéines impliquées dans l ’ adhésion

Protéines impliquées dans la survie intracellulaire

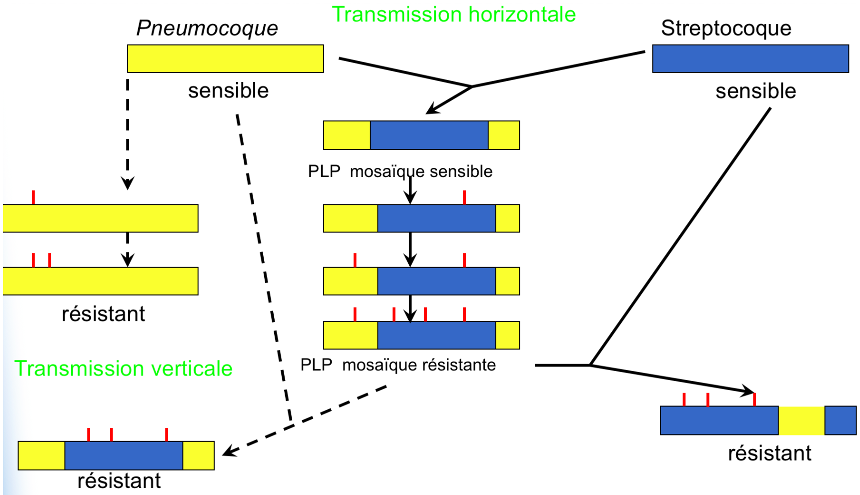
Etc….

Transformation

- **44 bacterial species including;**
  - *Streptococcus*
  - *Enterococcus*
  - *Staphylococcus*
  - *Enterobacteriaceae*
  - *Pseudomonas*
  - *Acinetobacter*
  - *Haemophilus*
  - *Neisseria*

Résistance du pneumocoque aux ß-lactamines

- ♦ 5 Protéines liant les pénicillines (PLP) de haut poids moléculaire
- ♦ diminution de la sensibilité aux β-lactamines par modifications de plusieurs PLPs
- ♦ Acquisition de gènes par création de structure en mosaïque par recombinaison homologue en association à des mutations ponctuelles



Pneumocoque

sensible

Transmission horizontale

Streptocoque

sensible

PLP mosaïque sensible

résistant

Transmission verticale

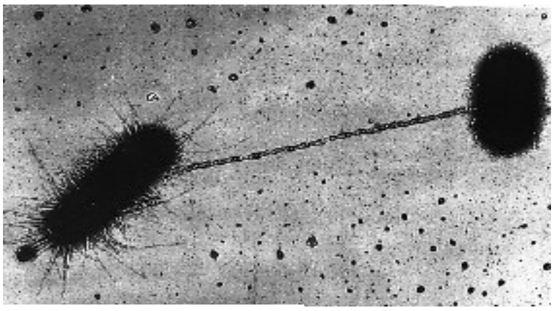
PLP mosaïque résistante

résistant

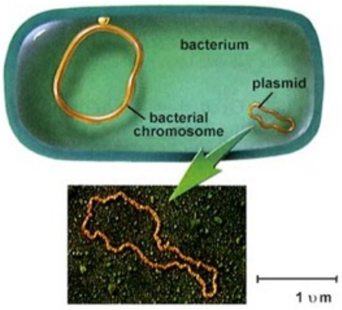
résistant

Principal véhicule du transfert horizontal: La conjugaison

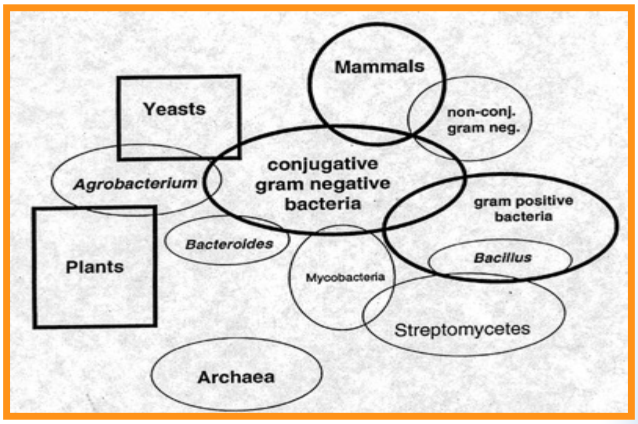
Pont cytoplasmique

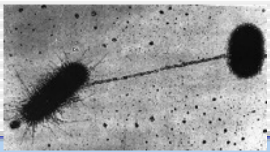


Définition : Processus spécialisé qui implique un transfert unidirectionnel d’ADN d’une cellule donatrice à une cellule réceptrice, par un mécanisme requérant un contact spécifique

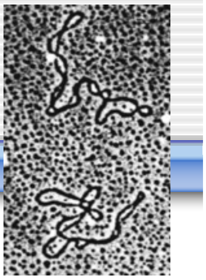


ADN Extra chromosomique se réplicant de manière autonome



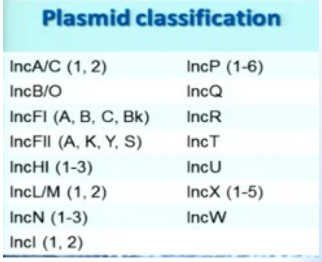


Horizontal gene transfer : The conjugation: Plasmids



1. Extrachromosomal DNA, usually circular-parasite?
2. Usually encode ancillary functions for in vitro growth
3. Can be essential for specific environments: virulence, antibiotics resistance, use of unusual nutrients, production of bacteriocins (colicins), addiction systems (These plasmids produce both a long-lived poison and a short-lived antidote)
4. Must be a replicon - self-replicating genetic unit
5. Plasmid DNA must replicate every time host cell divides or it will be lost

   => partitioning (making sure each progeny cells receives a plasmid)
6. High copy plasmids are usually small; low copy plasmids can be large
7. Partitioning is strictly controlled for low copy, but loose for high copy
8. Plasmid replication requires host cell functions
9. Copy number is regulated by initiation of plasmid replication
10. Plasmids are incompatible when they cannot be stably maintained in the same cell because they interfere with each other's replication.

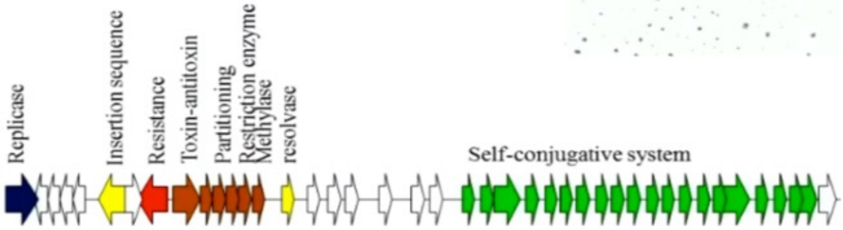


Plasmid classification

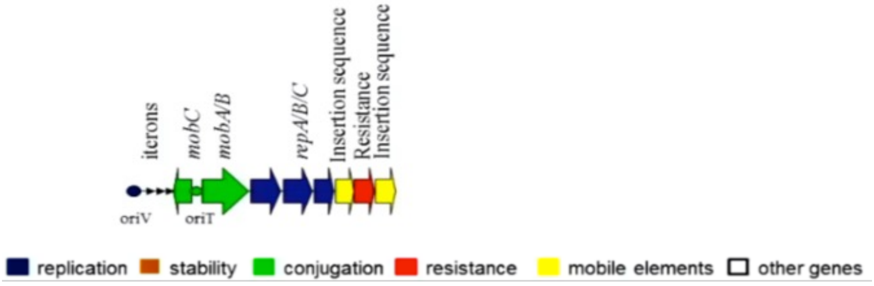
IncA/C (1, 2)	IncP (1-6)
IncB/O	IncQ
IncFI (A, B, C, Bk)	IncR
IncFII (A, K, Y, S)	IncT
IncHI (1-3)	IncU
IncL/M (1, 2)	IncX (1-5)
IncN (1-3)	IncW
IncI (1, 2)	

Plasmid structure and function

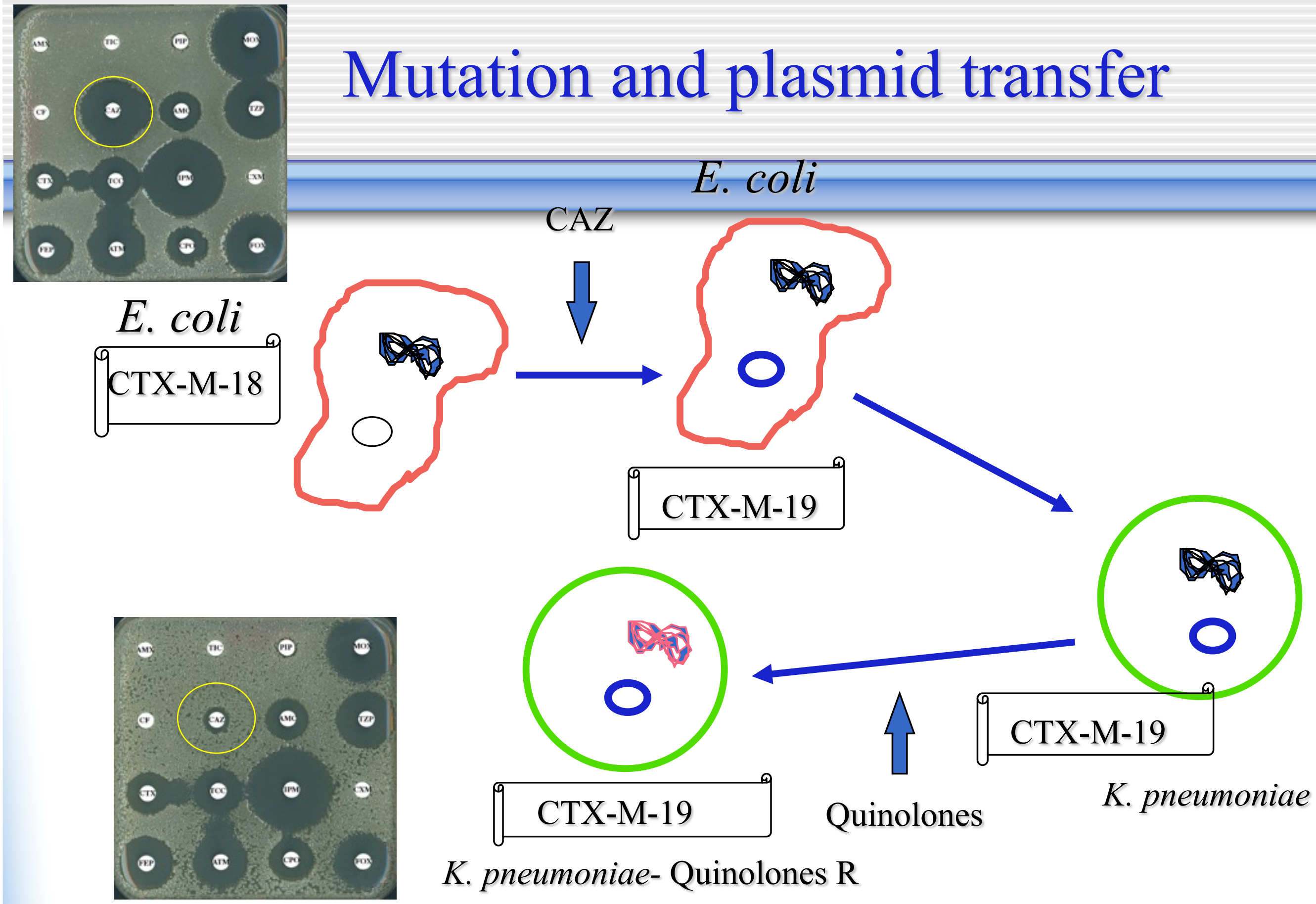
Large (30-300kb) self conjugative plasmids



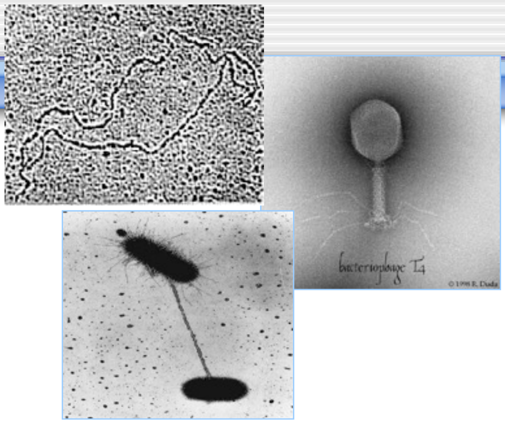
Small (<30kb) mobilizable plasmid



Mutation and plasmid transfer



Limits of horizontal gene transfer



- **Vehicules of transfer:**
  - Nakes ADN nu (transformation)
  - Bacteriophages (transduction)
  - Plasmids (conjugation)
- **Fate of transferred DNA depends on**
  - Replication,
  - Expression,
    - Transcription : promoters
    - Translation : RBS, codon usage.

The solutions: gene capture systems

==> **Homologous Recombinaison:** rate limiting step of the integration after gene transfer : divergence between the sequences

==> **Non Homologous Recombinaison: Gene mobilizing and expression systems:**

-Insertion Sequences and transposons:

- ✓ Composite transposons
- ✓ Tn*3*-type transposons
- ✓ Peculiar Insertion Sequence: IS*Ecp1*
- ✓ The Repeated elements: Res

- mediating plasmid insertion into the chromosome (co-integration)
- inserting only part of a plasmid (transposition)
- providing promoters for gene expression

- ✓ Peculiar Insertion Sequence: ISCR

-The integrons :

Non-homologous recombination – Mobile elements

- Mobile (transposable) genetic elements provide flexibility to the genome; "jumping genes"

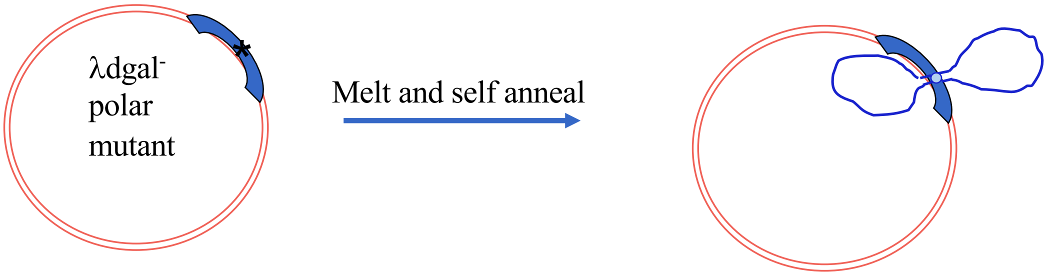
Barbara McClintock,
Nobelprize 1983

Discovery of Transposable DNA elements in bacteria

✓ First noted in 1967 in *E.coli* as cause of polar mutations in;

- *gal* operon (Saedler) and *lac* operon (Shapiro)
- High frequency of spontaneous reversion to *gal* or *lac* +
- DNA of λdgal polar mutant phage analysed by density gradient centrifugation and by homology annealing and EM sizing:

=> Inserts of approx' 800 bps or 1500 bps
=> Named Insertion Sequences IS1 and IS2



✓ Hedges and Jacob (1974) demonstrated 1st Transposon Tn1 (Tn3 related): Amp^r in plasmid RP4

Transposable DNA elements in bacteria

✓ Many elements discovered since first ones

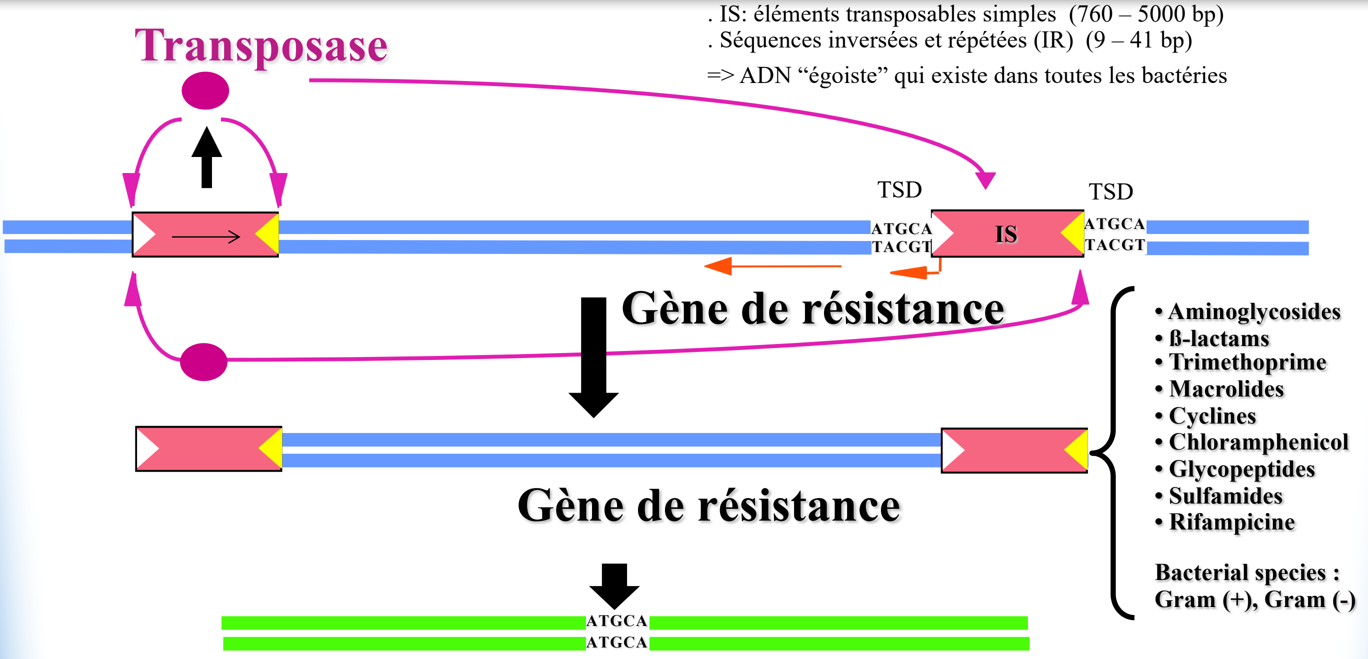
✓ There are four basic types

- The Insertion sequences and their composite elements TYPE I
- The Tn3 family of elements TYPE II
- The transposing bacteriophages (e.g. mu) TYPE III
- The conjugative transposons (e.g. Tn916 carrying tet resistance). Large family found in Gram positive bacteria.

✓ Many features in common but with exceptions

- MUST have precise end recognition EITHER use terminal inverted repeat sequences OR in some cases integrate at specific sequences to produce a consensus sequence for end recognition
- Often generate duplications at target sites

Séquences d'insertion (IS) et Mobilisation de gènes de résistance: transposons composites

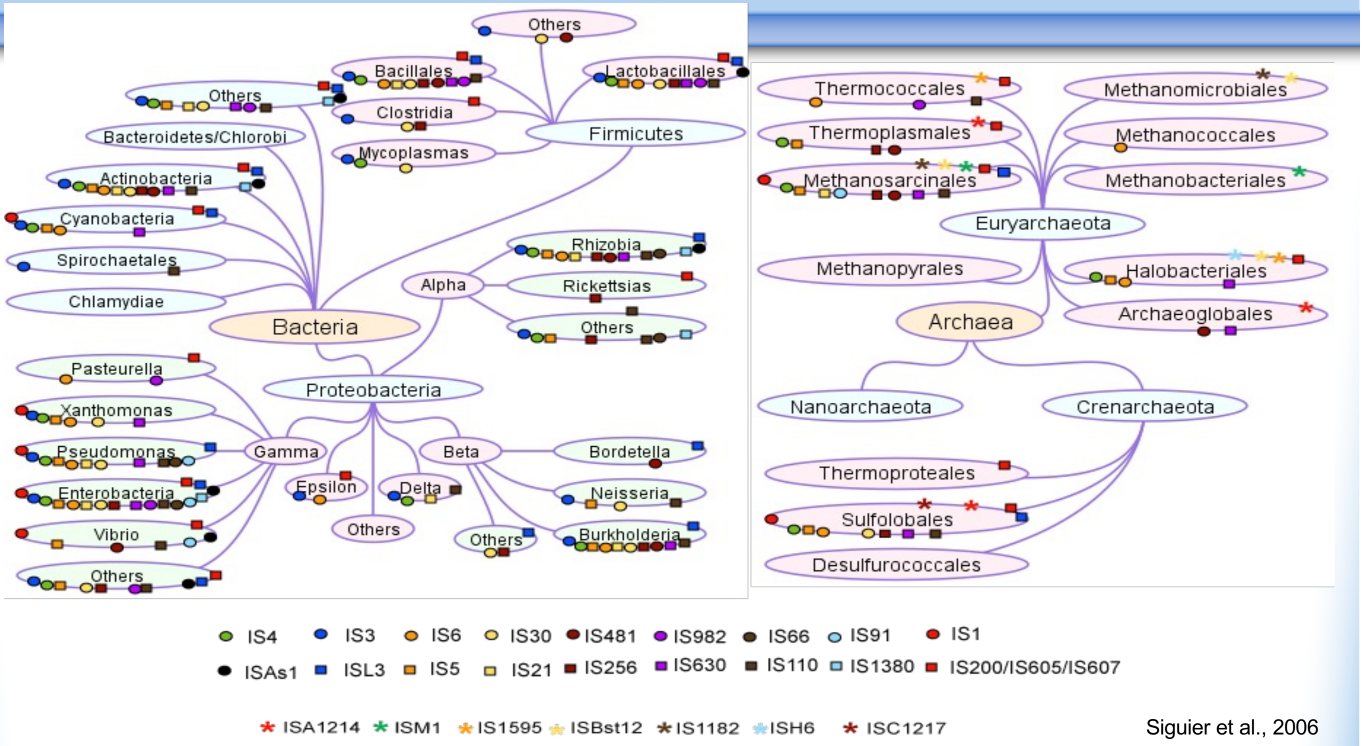


. IS: éléments transposables simples (760 – 5000 bp)
. Séquences inversées et répétées (IR) (9 – 41 bp)
=> ADN "égoiste" qui existe dans toutes les bactéries

- **Aminoglycosides**
- **ß-lactams**
- **Trimethoprime**
- **Macrolides**
- **Cyclines**
- **Chloramphenicol**
- **Glycopeptides**
- **Sulfamides**
- **Rifampicine**

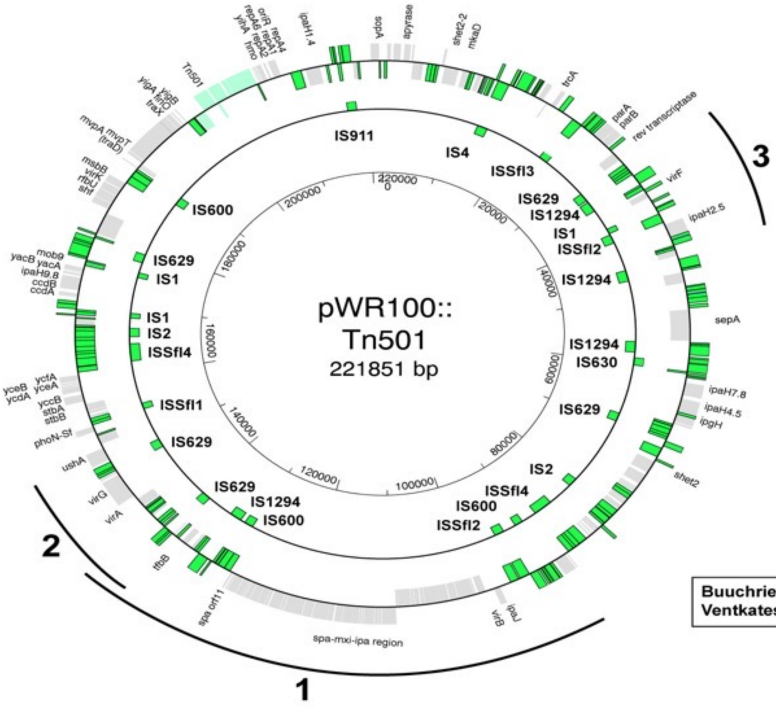
Bacterial species :
Gram (+), Gram (-)

ISs in the Procaryote World



Siguier et al., 2006

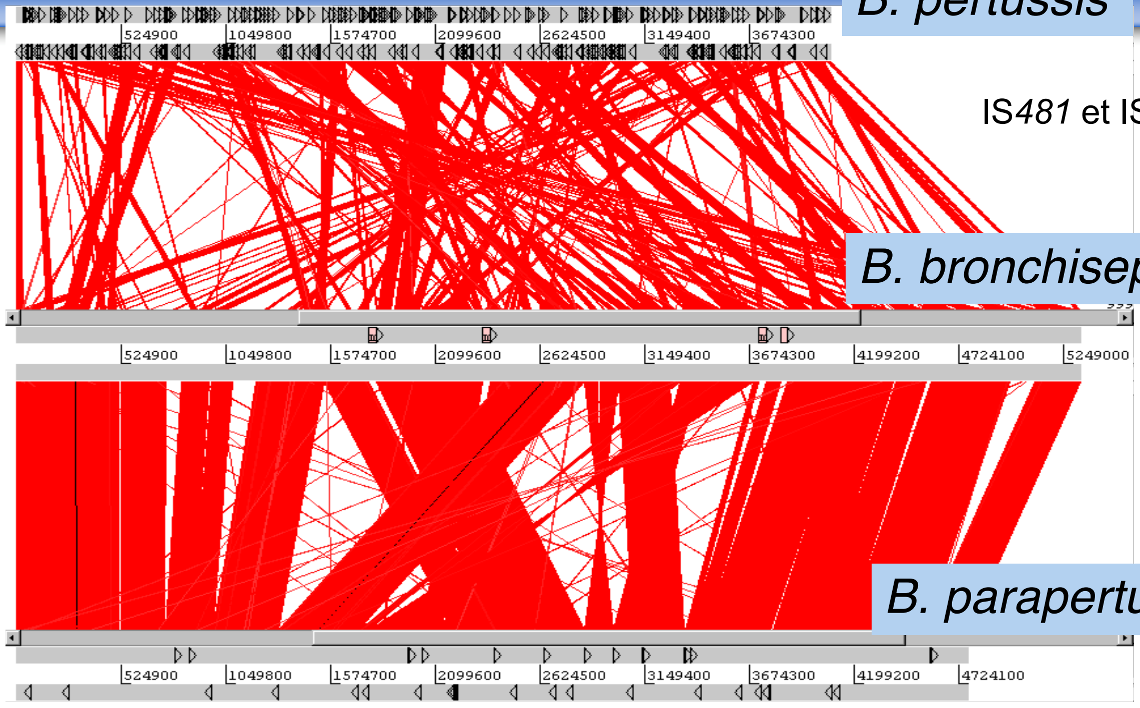
The Shigella flexneri 5a Virulence Plasmid: IS mediated assembly?



45% ISs
26 complete

Buuchrieser et al. 2000
Ventkatesan et al. 2001

The *Bordetellae:* IS expansion



B. pertussis

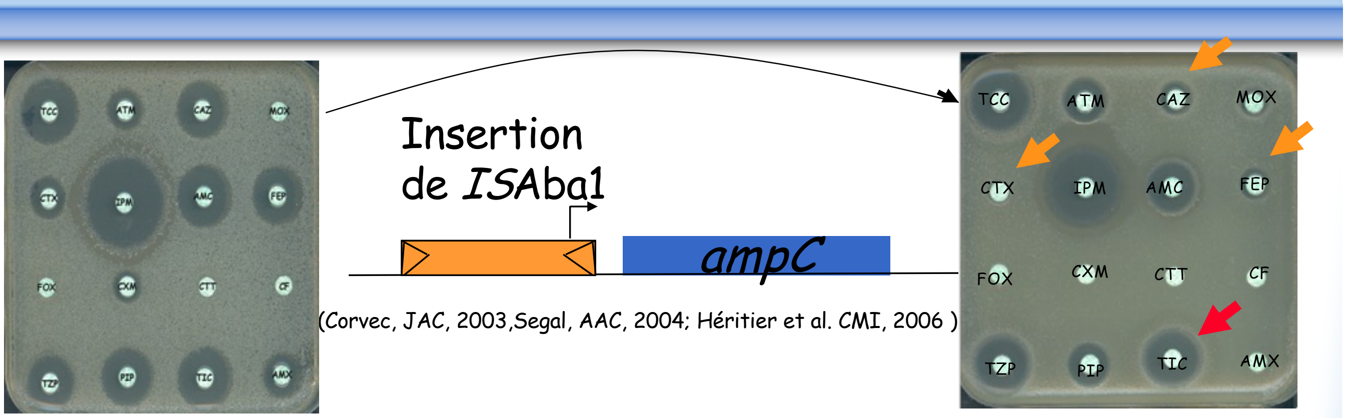
IS*481* et IS*1001*

B. bronchiseptica

B. parapertussis

Parkhill et al., 2003

Cephalosporinase hyperproduction in *A. baumannii*

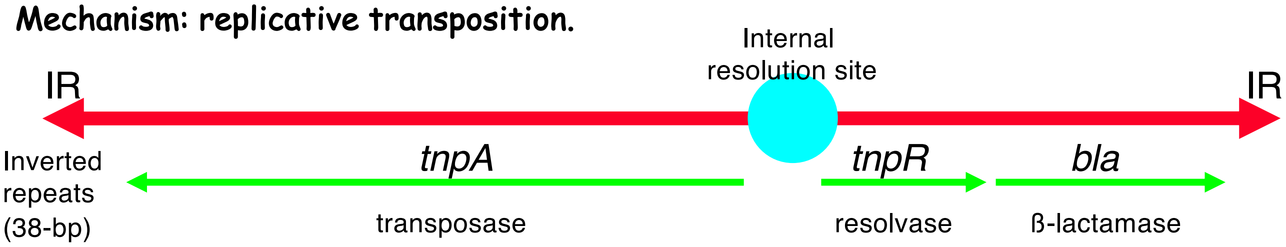


(Corvec, JAC, 2003,Segal, AAC, 2004; Héritier et al. CMI, 2006)

(Turton et al., FEMS Microbiol lett., 2006))

Mobilisation of resistance genes: noncomposite (simple) transposons

Class II transposons (non-composite): Flanked by 2 IR (e.g. Tn3, phage Mu).
Mechanism: replicative transposition.



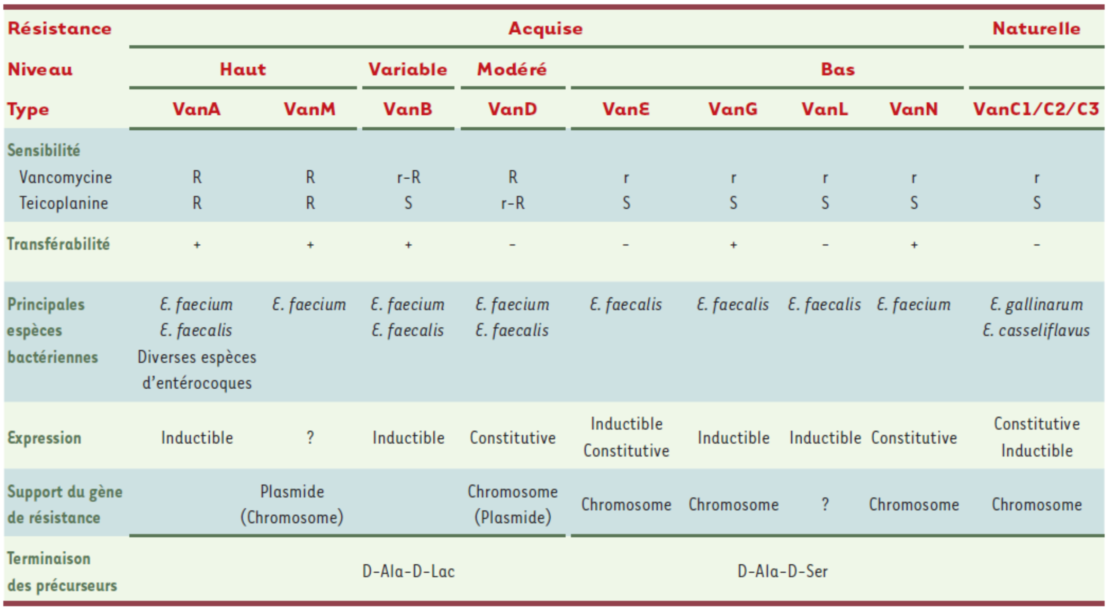
Gram negative

- . Tn*3* (4.9 kb, Ap)
- . Tn*4* (20 kb, Ap, Sm, Su)
- . Tn*1721* (10 kb,Tc)

Gram positive

- . Tn*551* (5.3 kb, Em)
- . Tn*917* (5.2 kb, Em)

Résistance chez les entérocoques



Résistance	**Acquise**								**Naturelle**
Niveau	**Haut**		**Variable**	**Modéré**	**Bas**				
Type	**VanA**	**VanM**	**VanB**	**VanD**	**VanE**	**VanG**	**VanL**	**VanN**	**VanC1/C2/C3**
Sensibilité									
Vancomycine	R	R	r-R	R	r	r	r	r	r
Teicoplanine	R	R	S	r-R	S	S	S	S	S
Transférabilité	+	+	+	-	-	+	-	+	-
Principales espèces bactériennes	*E. faecium* *E. faecalis* Diverses espèces d'entérocoques	*E. faecium*	*E. faecium* *E. faecalis*	*E. faecium* *E. faecalis*	*E. faecalis*	*E. faecalis*	*E. faecalis*	*E. faecium*	*E. gallinarum* *E. casseliflavus*
Expression	Inductible	?	Inductible	Constitutive	Inductible Constitutive	Inductible	Inductible	Constitutive	Constitutive Inductible
Support du gène de résistance	Plasmide (Chromosome)			Chromosome (Plasmide)	Chromosome	Chromosome	?	Chromosome	Chromosome
Terminaison des précurseurs	D-Ala-D-Lac				D-Ala-D-Ser				

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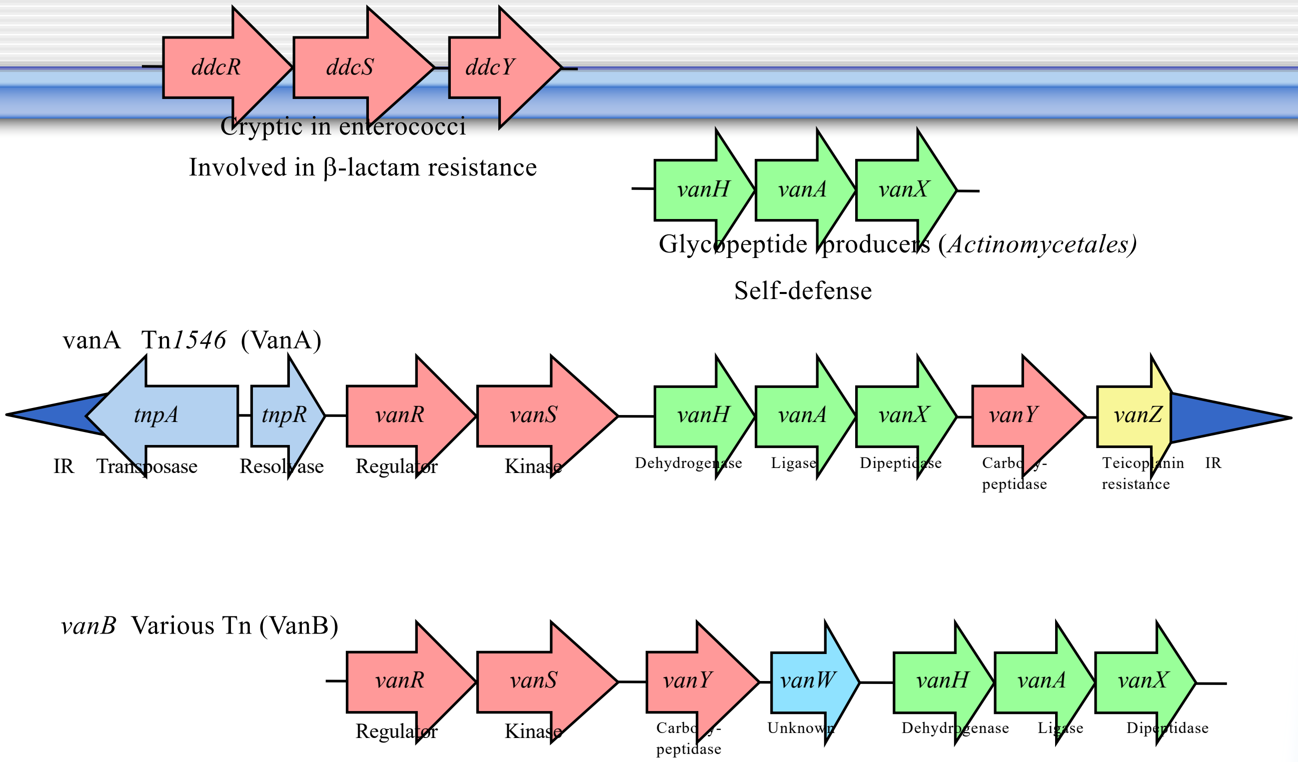
van gene clusters have a modular organization revealing multiple origins



Cryptic in enterococci

Involved in β-lactam resistance

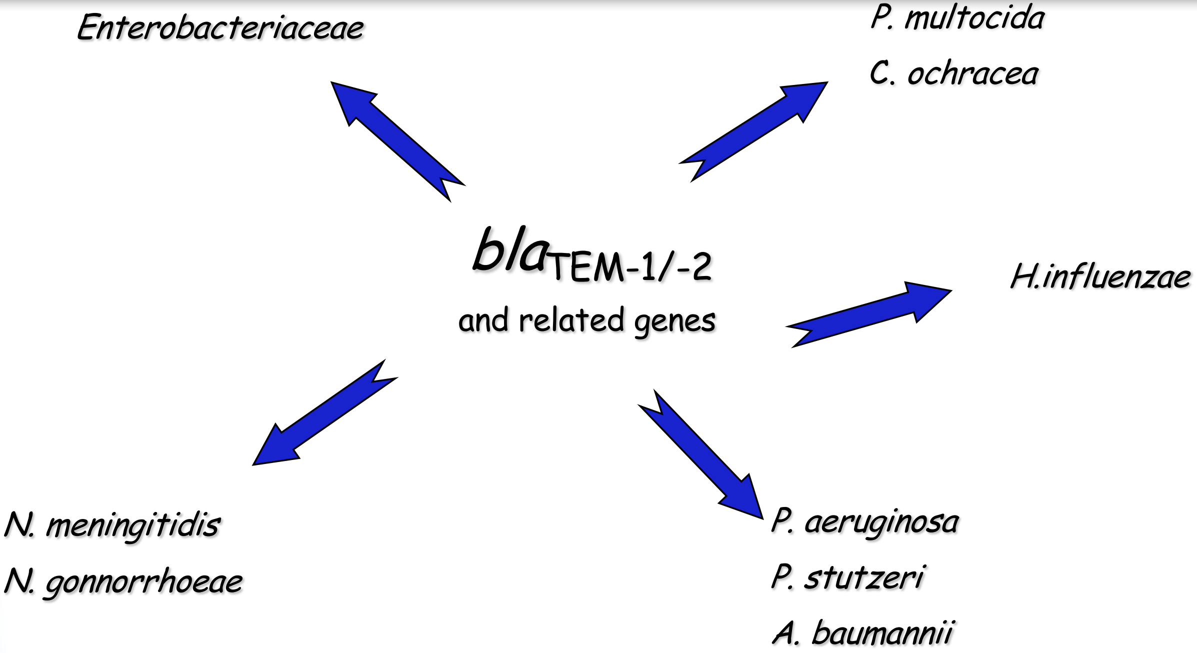
Glycopeptide producers *(Actinomycetales)*

Self-defense

vanA Tn*1546* (VanA)

vanB Various Tn (VanB)

Genes without frontiers : $\mathit{bla}_{\text{TEM-1/-2}}$ and derivatives



$\mathit{bla}_{\text{TEM-1/-2}}$
and related genes

Enterobacteriaceae

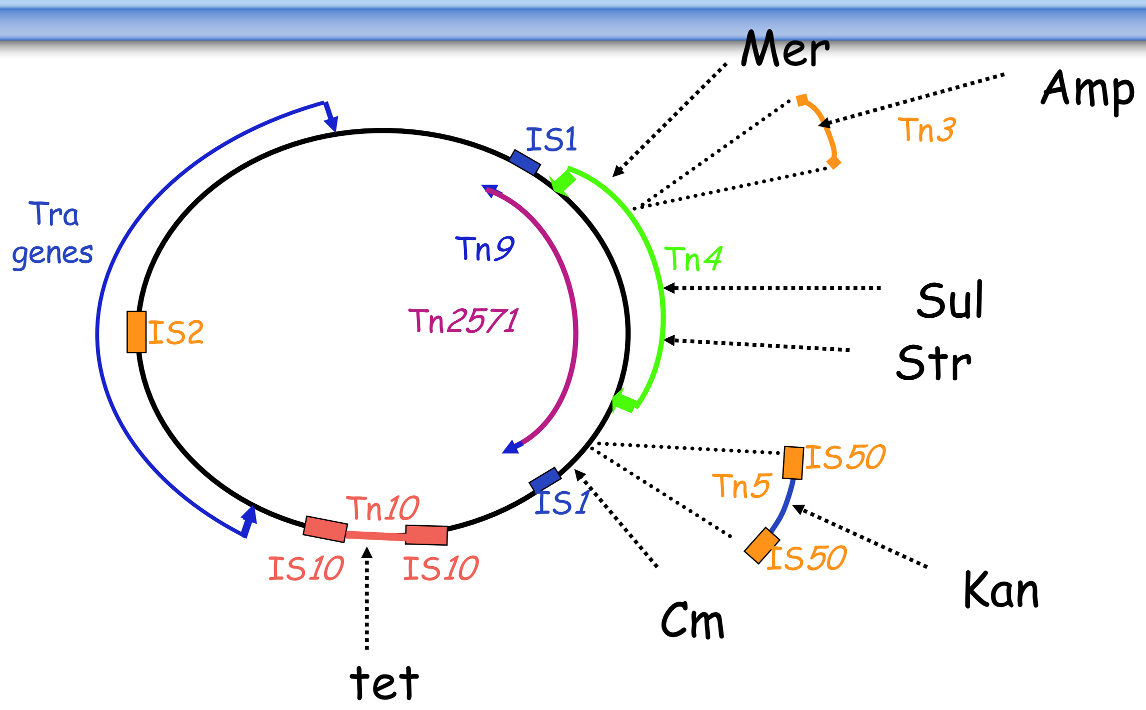
P. multocida
C. ochracea

H.influenzae

N. meningitidis
N. gonnorrhoeae

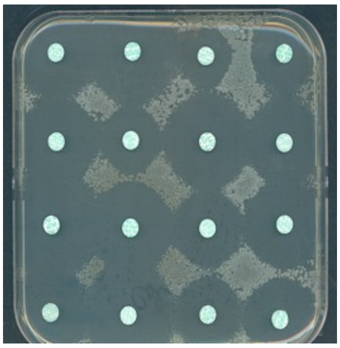
P. aeruginosa
P. stutzeri
A. baumannii

R1 plasmid (100-kbp): an example of resistance accumulation mediated by transposable elements



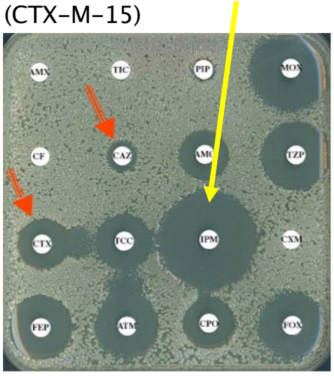
Multi-resistance and therapeutic dead-ends
Escherichia coli, our best friend and our worst enemy

E. coli
of our
youth



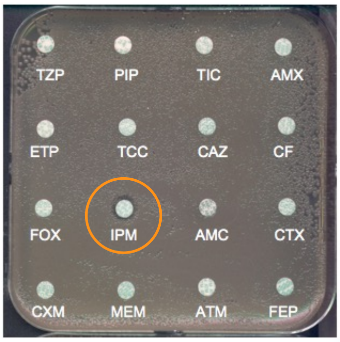
E. coli
of modern
days

ESBL (CTX-M-15)



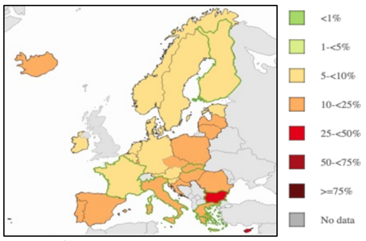
E. coli
of
tomorrow

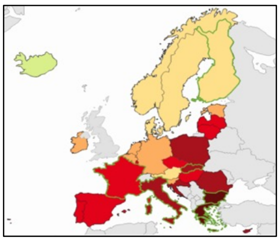
Carbapenemases
KPC, OXA-48, NDM, VIM, IMP



Enterobacterales resistant to 3GC

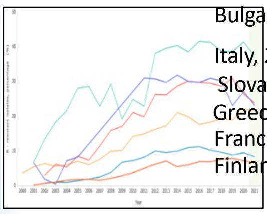
Bacteraemia in Europe (ECDC)



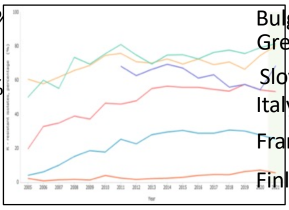


E. coli
- **0.8%** in 2002
- **8.3%** in 2021

K. pneumoniae
- **6.1%** in 2006
- **25.4%** in 2021



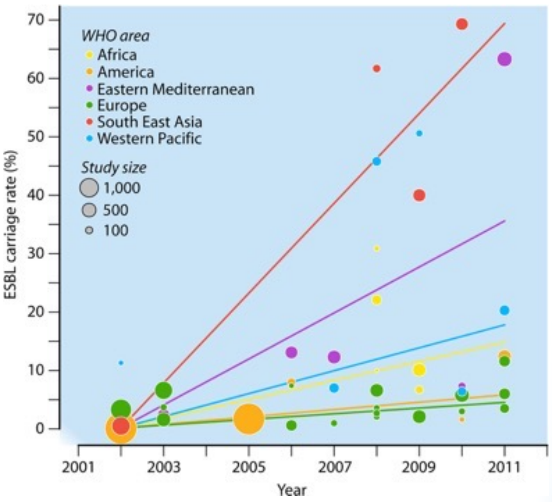
Bulgaria, 37.3 %
Italy, 23.8%
Slovakia 23.1 %
Greece, 21.7 %
France, 8.3%
Finland, 6.6 %



Bulgaria, 81.1 %
Greece, 80.4 %
Slovakia 68.4%
Italy, 53.3%
France, 25.4 %
Finland, 5.6 %

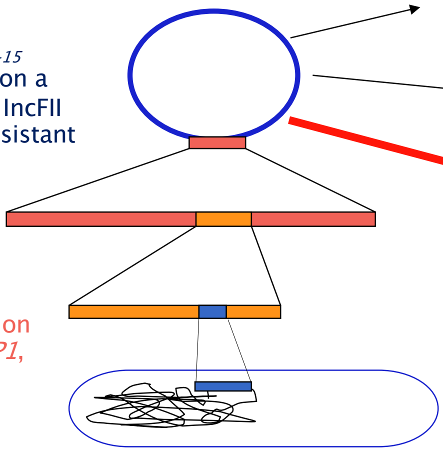
Dissemination of CTX-M-type ESBLs

Healthy carriage of ESBL-Enterobacterales



Woerther, et al. *Clin Microbiol Rev* 2013;26:744–58

CTX-M: Le secret de cette ‘success story’



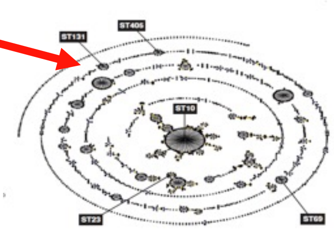
bla$_{CTXM-15}$
present on a
plasmid IncFII
multi-resistant

Mobilisation
Par IS*ECP1*,
ISCR…

Kluyvera sp.

Poirel, et al.
Antimicrob Agents Chemother 2005

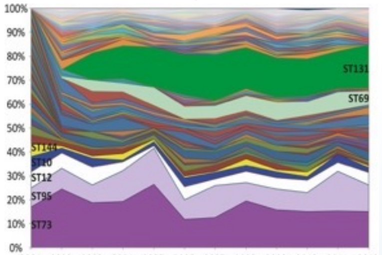
Diffusion
E. coli O25:H4-ST131
(group B2)



How to prevent this diffusion?

Coque, et al. *Emerg Infect Dis* 2008
Clermont, et al. *J Antimicrob Chemother* 2008
Nicolas-Chanoine, et al. *J Antimicrob Chemother* 2008
Leflon-Guibout, et al. *J Clin Microbiol* 2008

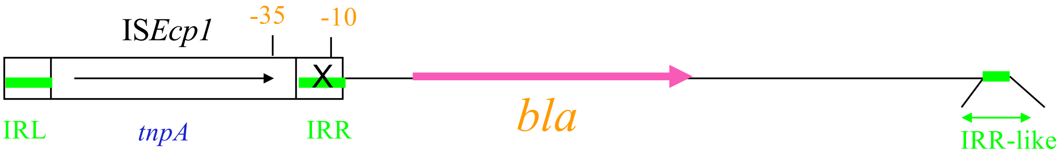
Population of invasive *E. coli* in England



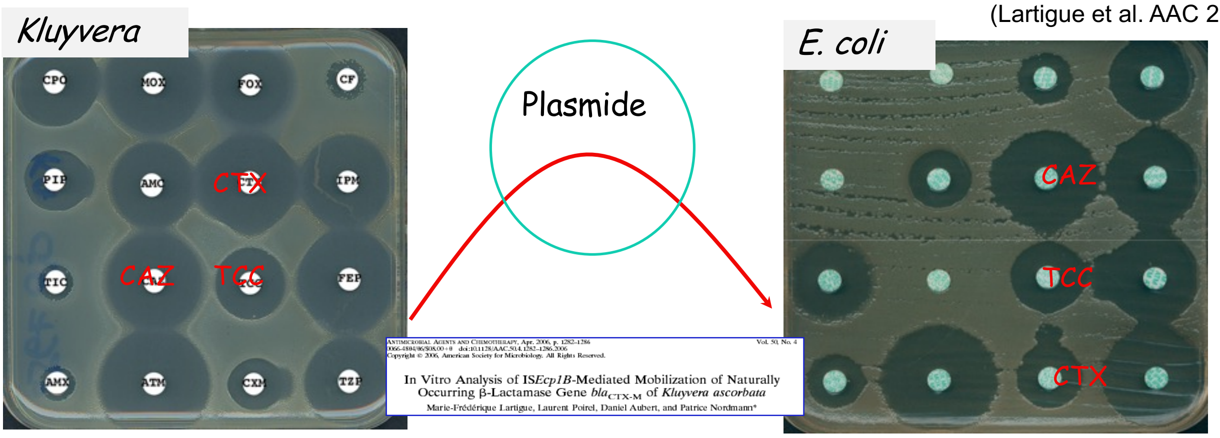
Kallonen T, et al. *Genome Res* 2017

What triggered the emergence? Where did it happen?

Single IS-mediated gene mobilization IS*Ecp1*



(Lartigue et al. AAC 2006)



ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Apr. 2006, p. 1282–1286 Vol. 50, No. 4
0066-4804/06/$08.00+0 doi:10.1128/AAC.50.4.1282–1286.2006
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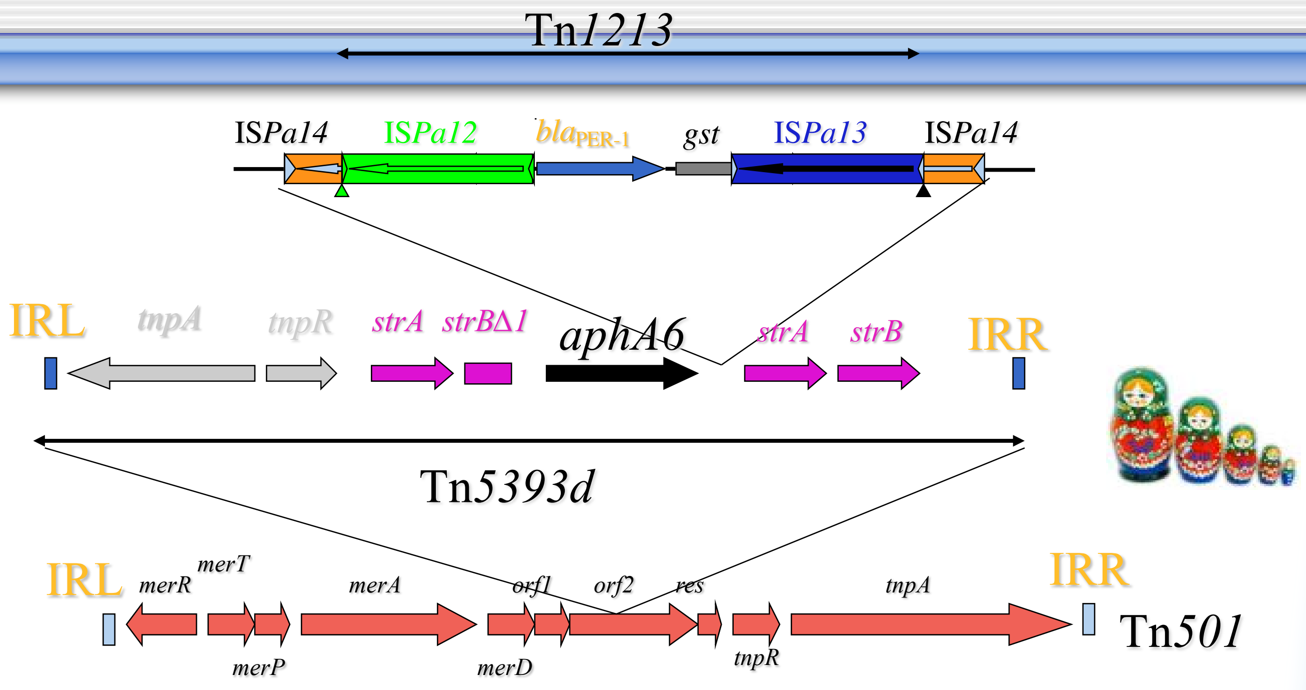
In Vitro Analysis of IS*Ecp1B*-Mediated Mobilization of Naturally Occurring β-Lactamase Gene *bla*$_{CTX-M}$ of *Kluyvera ascorbata*

Marie-Frédérique Lartigue, Laurent Poirel, Daniel Aubert, and Patrice Nordmann*

Genetic environment of *bla*$_{PER-1}$



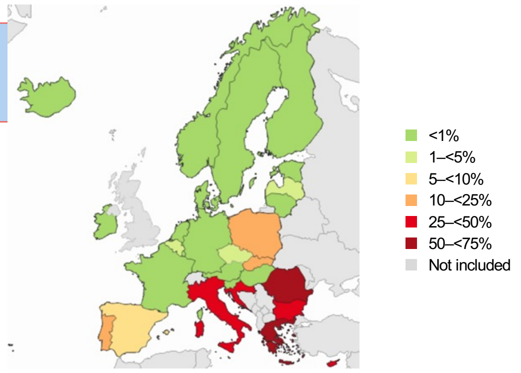
Alcaligenes faecalis, Italy

Mantengoli & Rossolini, AAC 2005

Multi-resistance and therapeutic dead-ends

Bacteremia with *K. pneumoniae* resistant to carbapenem in Europe 2021 (ECDC)

E. coli
France: 0.1%
Greece: 1.1%
Slovakia: 0.0%

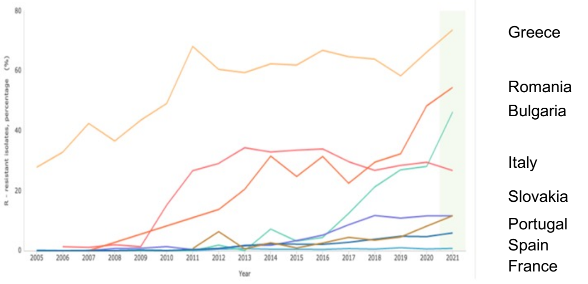


0.8 %	5.9 %	11.6 %	11.7 %	26.7 %	46.3 %	54.5%	73.7 %
France	Spain	Portugal	Slovakia	Italy	Bulgaria	Romania	Greece

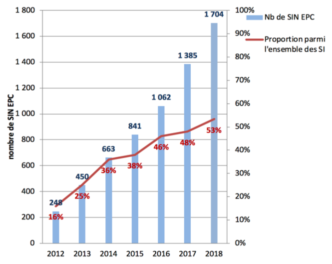
CRE remain susceptible to colistin only (plus newer molecules), but frequent resistance described in Italy and Greece (15 to 25 %)

=> pan-resistance, therapeutic dead-ends
=> high mortality rates (30-70%)

Evolution of CRE, Bacteremia



CPE Notification, France



Colomb-Cotinat M, Med Mal Infect. 2020

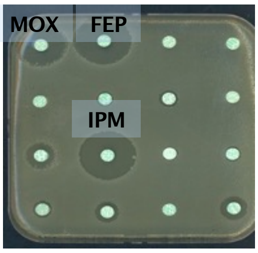
CRE: Résistance aux carbapénèmes chez les entérobactéries

1) Diminution de la perméabilité de la membrane externe + β-lactamase avec faible niveau d'hydrolyse des carbapénèmes

Résistance aux C3G
Mais
Sensibilité aux carbapénèmes

Lee EH, Nicolas MH, Kitzis MD, Pialoux G, Collatz E, Gutmann L. AAC 1991, 35:1093-8

Résistance aux carbapénèmes
par
Diminution de perméabilité



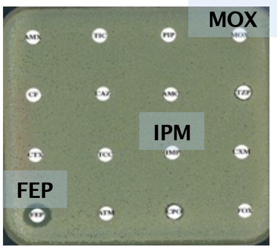
après
21 jours: imipénème
en monothérapie

International Journal of Antimicrobial Agents

Short communication

In vivo selection of imipenem-resistant *Klebsiella pneumoniae* producing extended-spectrum β-lactamase CTX-M-15 and plasmid-encoded DHA-1 cephalosporinase

Gaelle Cuzon, Thierry Naas, Michele Guibert, Patrice Nordmann

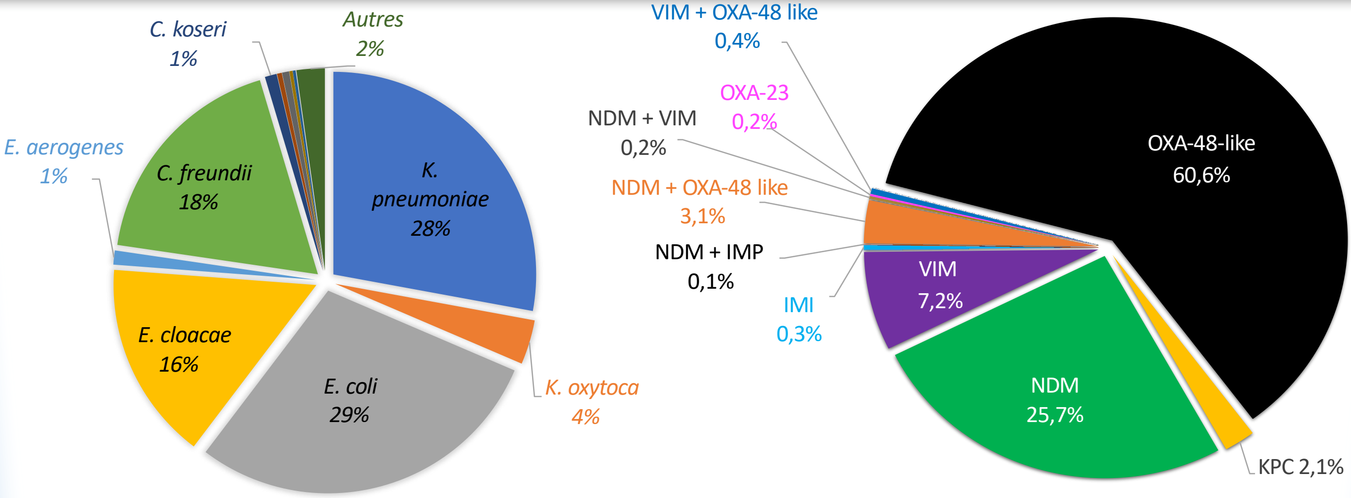


Important pour le traitement, **MAIS pas de** dissémination épidémique,
=> coût en terme de fitness des mutations chromosomiques

2) Carbapénèmases (Entérobactéries productrices de Carbapénèmases)

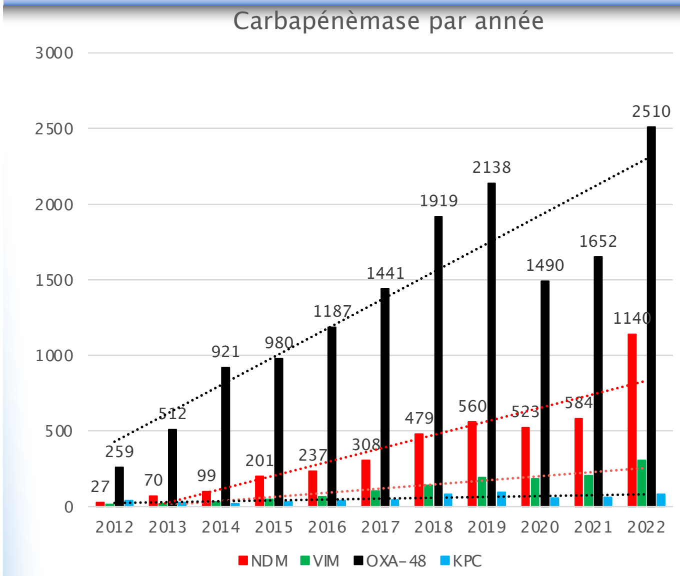
- Hautement épidémique => clones à hauts risques
- Plasmidique
- Difficile à détecter (PAS toujours BMR ou résistant aux carbapénèmes)

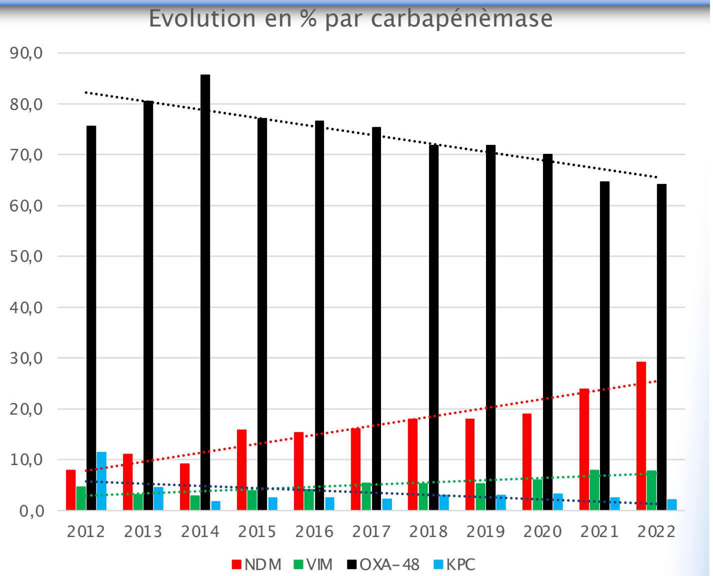
Distribution of CPEs in France 2022 per species per mechanism of carbapenem resistance



36,7% de MBLs

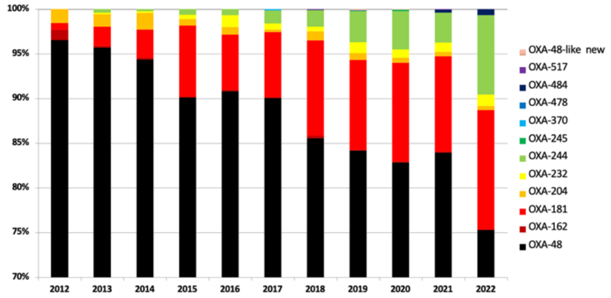
Evolution de l'épidémiologie des EPC (France 2012–2022)



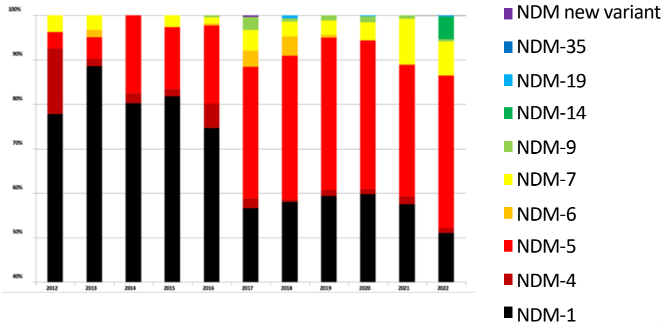


Diversification des Carbapénèmases

OXA-48 like



NDM- like



OXA-244
(n=210)

97,6% *E. coli* (ST38)

OXA-181
(n=316)

39,8% *E. coli* (ST410>ST940)
26,6% *K. pneumoniae* (ST11)
21,9% *C. freundii*

NDM-5
(n=345)

77,3% *E. coli* (ST167, 405, 410, 361)
13,0% *K. pneumoniae*

NDM-1
(n=513)

49,3% *K. pneumoniae* (ST147)
21,8% *E. cloacae*
12,7% *C. freundii*
9,7% *E. coli*

Secrets de la diffusion de KPC ?
Tn*4401:* Is it going to be as efficient as TEM?


ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Apr. 2008, p. 1257–1263 Vol. 52, No. 4
0066-4804/08/$08.00+0 doi:10.1128/AAC.01451-07
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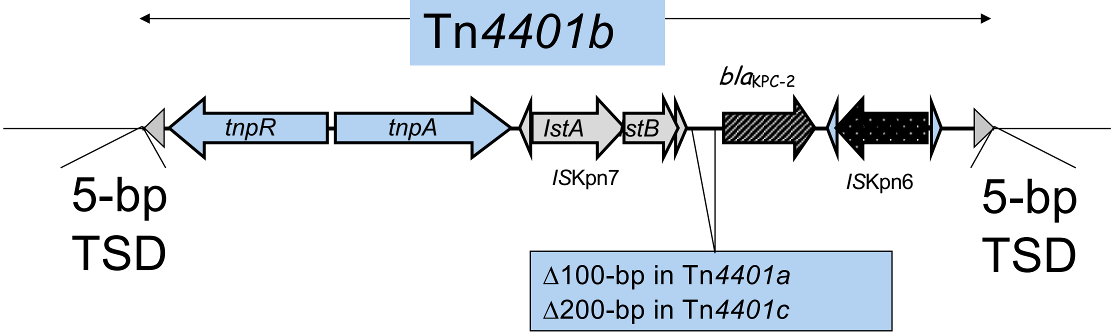
Genetic Structures at the Origin of Acquisition of the β-Lactamase *bla*$_{KPC}$ Gene[▽]

Thierry Naas,[1]†* Gaelle Cuzon,[1]† Maria-Virginia Villegas,[2] Marie-Frédérique Lartigue,[1] John P. Quinn,[3] and Patrice Nordmann[1]



Tn*4401* transposes at high frequency (10^{-5}) without target specificity (Cuzon, Naas, et al. AAC 2011)

What is the secret of KPC's success story ?

bla$_{KPC}$-bearing plasmids


Worldwide Diversity of *Klebsiella pneumoniae* That Produces β-Lactamase *bla*$_{KPC-2}$ Gene[1]

Gaëlle Cuzon, Thierry Naas, HaVy Truong, Maria-Virginia Villegas, Karin T. Wisell, Yehuda Carmeli, Ana. C. Gales, Shiri Navon-Venezia, John P. Quinn, and Patrice Nordmann

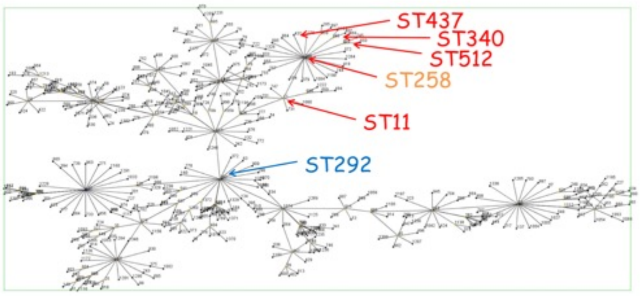
- *bla*$_{KPC}$ located on Tn*4401*
- Incompatibility groups:
  - **IncFII**
  - **IncN**
  - IncX
  - **IncL/M**
  - IncA/C
  - IncFIB
  - ColE

Dissémination chez les Enterobacterales
P. aeruginosa
A. baumannii

The plasmids carrying *bla*$_{KPC}$ are diverse

Clonal structure of KPC-producing *K. pneumoniae*

- Clonal Complex 292 (encompassing ST258, ST11, ST437 and ST512 among others) is by far the most common



RÉSISTANCE À L'ASSOCIATION CEFTAZIDIME/AVIBACTAM

KPC-39-Mediated Resistance to Ceftazidime-Avibactam in a *Klebsiella pneumoniae* ST307 Clinical Isolate AAC, 2021, 65: e01160-21

Agnès B. Jousset,[a,b,c,d] Saoussen Oueslati,[a,c] Cécile Emeraud,[a,b,c,d] Rémy A. Bonnin,[a,b,c] Laurent Dortet,[a,b,c,d] Bogdan I. Iorga,[e] Thierry Naas[a,b,c,d]

Different phenotypic expression of KPC β-lactamase variants and challenges in their detection

Saoussen Oueslati[1], Linda Tlili[1], Cynthia Exilie[1], Sandrine Bernabeu[1,2], Bogdan Iorga[3], Rémy A. Bonnin [1,4], Laurent Dortet[1,2,4] and Thierry Naas [1,2,4]*

J Antimicrob Chemother 2020; 75: 769–771

Unravelling ceftazidime/avibactam resistance of KPC-28, a KPC-2 variant lacking carbapenemase activity

Saoussen Oueslati[1], Bogdan I. Iorga [2], Linda Tlili[1], Cynthia Exilie[1], Agustin Zavala[2], Laurent Dortet[1,3,4], Agnès B. Jousset[1,3,4], Sandrine Bernabeu[1,3], Rémy A. Bonnin [1,4] and Thierry Naas [1,3,4]*

J Antimicrob Chemother 2019; 74: 2239–2246

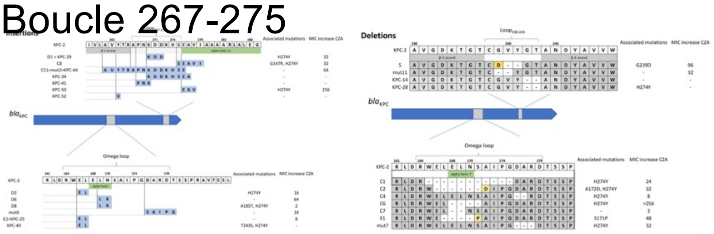
AMERICAN SOCIETY FOR MICROBIOLOGY Antimicrobial Agents and Chemotherapy®

MECHANISMS OF RESISTANCE

KPC Beta-Lactamases Are Permissive to Insertions and Deletions Conferring Substrate Spectrum Modifications and Resistance to Ceftazidime-Avibactam

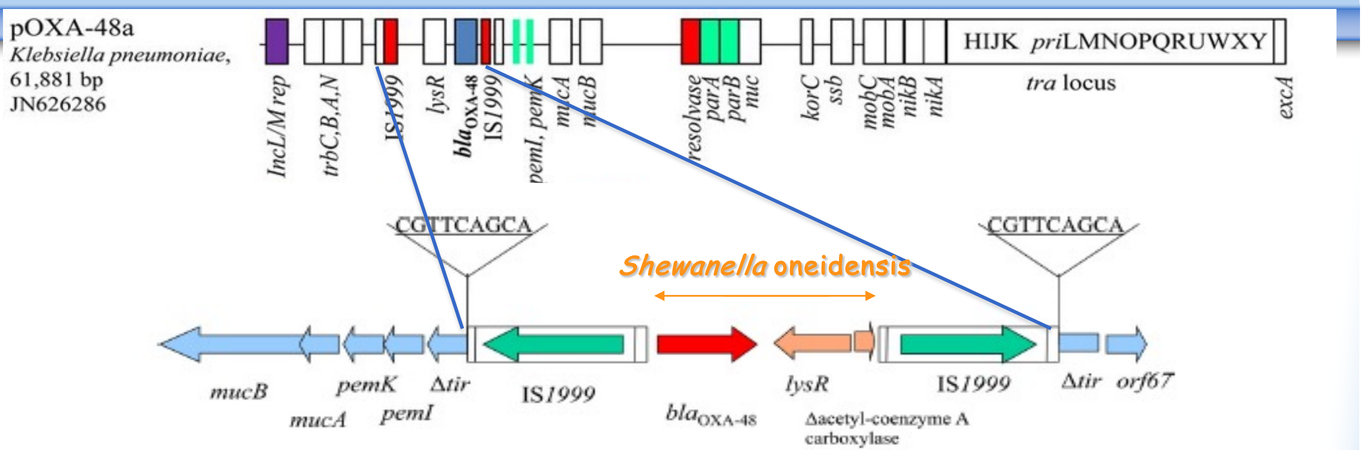
Claire Amaris Hobson,[a] Stéphane Bonacorsi,[a,b] Hervé Jacquier,[a,c] Alaksh Choudhury,[a] Mélanie Magnan,[a] Aurélie Cointe,[a,b] Béatrice Bercot,[a,c] Olivier Tenaillon,[a] André Birgy[a,b]

Boucle 267-275



Boucle Oméga
164-179

Diffusion de OXA-48 liée à un plasmide de type Inc L/M et Tn*1999*

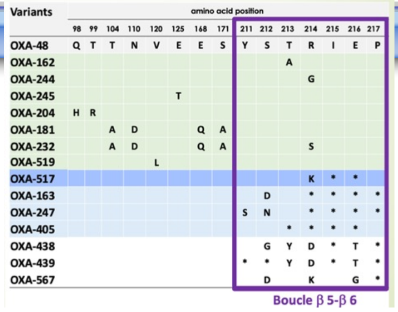


Aubert, Naas et al. J Bac, 2006

- Faible fréquence de transposition **MAIS**
- Haute fréquence de conjugaisons rates (3.3 x 10^{-3})
- => diffusion de plasmides dans de nombreux pays et espèces: "plasmide épidémique"

Carrer *et al* – AAC 2010
Poirel *et al* – AAC 2011
Potron et al. AAC, 2014

Hydrolytic diversity of OXA-48 variants



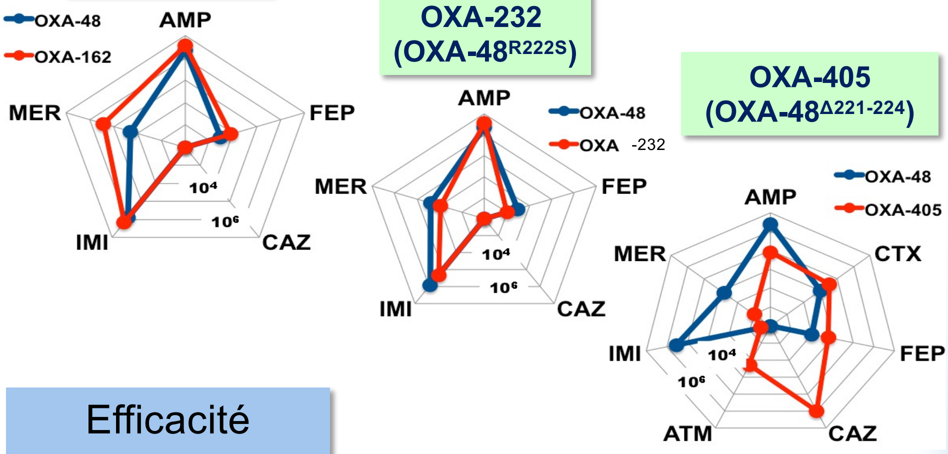
Variants	98	99	104	110	120	125	168	171	211	212	213	214	215	216	217
OXA-48	Q	T	T	N	V	E	E	S	Y	S	T	R	I	E	P
OXA-162											A				
OXA-244												G			
OXA-245						T									
OXA-204	H	R													
OXA-181			A	D			Q	A							
OXA-232			A	D			Q	A				S			
OXA-519					L										
OXA-517												K	*	*	
OXA-163										D		*	*	*	*
OXA-247									S	N		*	*	*	*
OXA-405											*	*	*	*	
OXA-438										G	Y	D	*	T	*
OXA-439									*	*	Y	D	*	T	*
OXA-567										D		K		G	*

amino acid position

Boucle β 5-β 6

OXA-405
OXA-48

Loop β5 – β6



OXA-162 ($OXA\text{-}48^{T221A}$)

OXA-232 ($OXA\text{-}48^{R222S}$)

OXA-405 ($OXA\text{-}48^{\Delta 221\text{-}224}$)

Efficacité catalytique k_{cat}/K_M ($M^{-1} \cdot s^{-1}$)

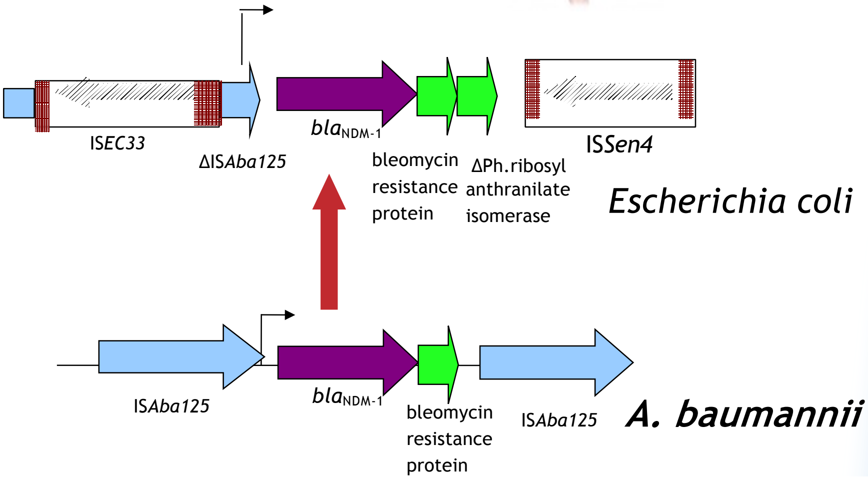
NDMs, the worse scenario?

K. pneumoniae, *E. coli* and in *E. coli* ST131

- E. coli: 1st human bacterial pathogen
- 1st community-acquired pathogen
- 1st cause of urinary tract infections and diarrhea

⇒ High prevalence Indian sub-continent (c.a 300 millions carriers, South East Asia, North African countries

⇒ In France, 16.6% of CPEs



NDM-1: Rapidely evolving carbapenemase

- NDM-1: (41 variants , and 16 in metagenomic data)

	28	32	36	69	74	88	95	130	152	154	200	222	233	264
NDM-1	P	R	G	G	A	V	D	D	E	M	G	G	A	R
NDM-2	A	.	.	.	.	.	.	.	.	.	.	.	.	.
NDM-3	.	.	.	.	.	.	N	.	.	.	.	.	.	.
NDM-4	.	.	.	.	.	.	.	.	.	L	.	.	.	.
NDM-5	.	.	.	.	.	L	.	.	.	L	.	.	.	.
NDM-6	.	.	.	.	.	.	.	.	.	.	.	.	V	.
NDM-7	.	.	.	.	.	.	.	N	.	L	.	.	.	.
NDM-8	.	.	.	.	.	.	.	G	.	L	.	.	.	.
NDM-9	.	.	.	.	.	.	.	.	K	.	.	.	.	.
NDM-10	.	S	D	S	T	.	.	.	.	.	R	.	.	.
NDM-11	.	.	.	.	.	.	.	.	.	V	.	.	.	.
NDM-12	.	.	.	.	.	.	.	.	.	L	.	D	.	.
NDM-13	.	.	.	.	.	.	N	.	.	L	.	.	.	.
NDM-14	.	.	.	.	.	.	.	G	.	.	.	.	.	.
NDM-15	.	.	.	.	.	.	.	.	.	L	.	.	V	.
NDM-16	.	.	.	.	.	.	.	.	.	.	.	.	.	H

http://www.bldb.eu/

Increased Hydrolysis of carbapenems (2x)

Double, tripple, …. variants

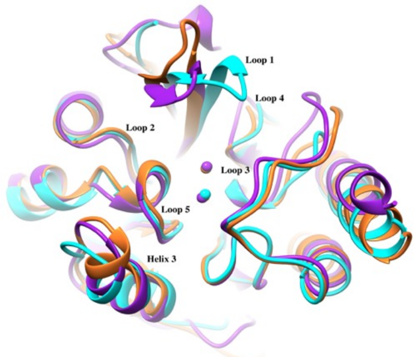
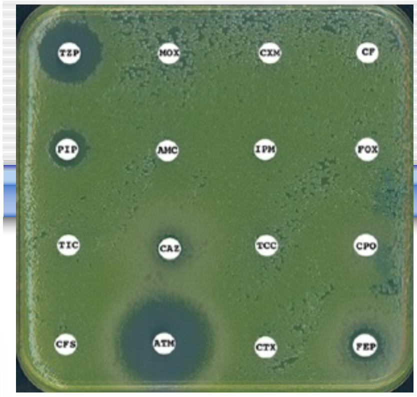
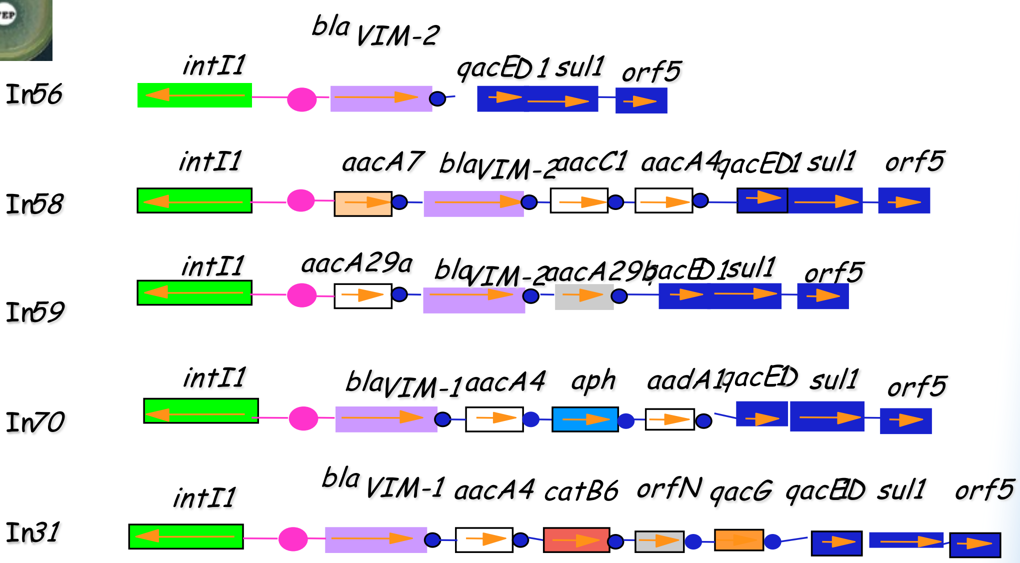


Figure 3. Superposition of NDM-1 (orange, PDB code 4EXS), VIM-4 (purple, PDB code 2WHG) and IMP-1 (cyan, PDB code 1DD6) X-ray structures, showing the important regions reported to interact with substrates. The zinc ions are represented as small spheres.

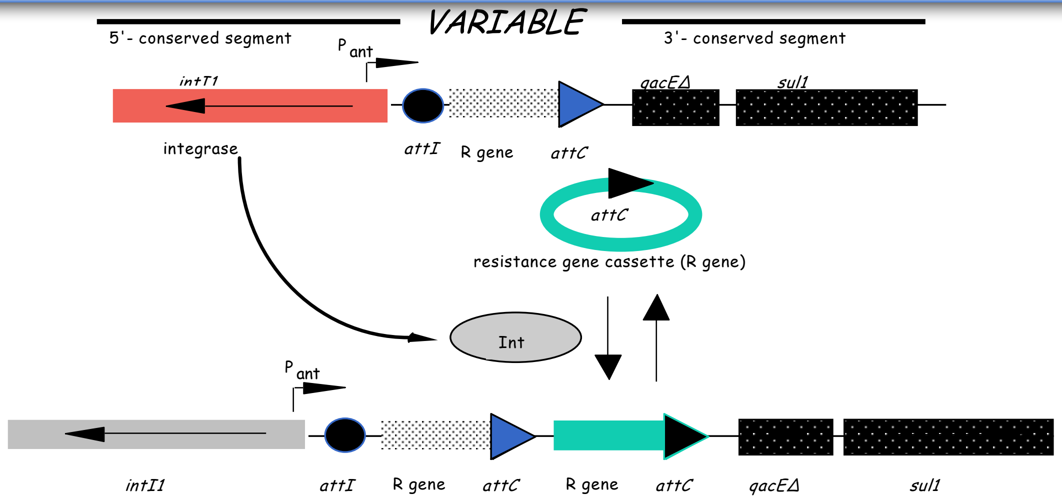
And
IMP (95)
VIM (80)
GIM (2)
DIM (1)
KHM (1)
SIM (2)
SPM (1)
TMB (2)



Integrons carry also VIM, IMP, GES, BEL, …



Integrons as a source of Multidrug resistance



- Consequences : co-resistance ; co-expression ; co-selection

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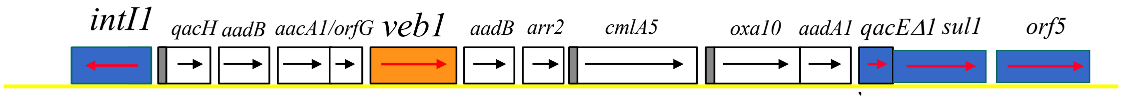
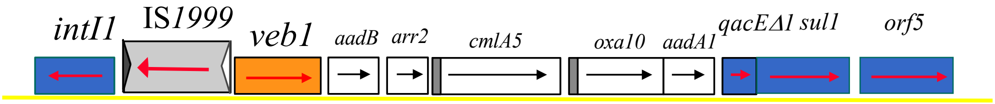
Structure of *veb1* containing integrons

Enterobacteriaceae



P. aeruginosa



⇒*bla*$_{VEB-1}$ is integron-located
⇒IS*1999* increases *bla*$_{VEB-1}$ expression in *P. aeruginosa*

(Naas, Mikami *et al.*, J. Bacteriol. 2001; Aubert, Naas, Nordmann, J. Bacteriol. 2003)

Integrons

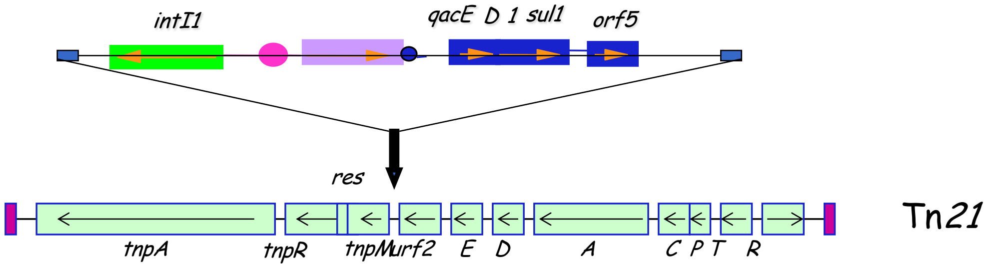
Species

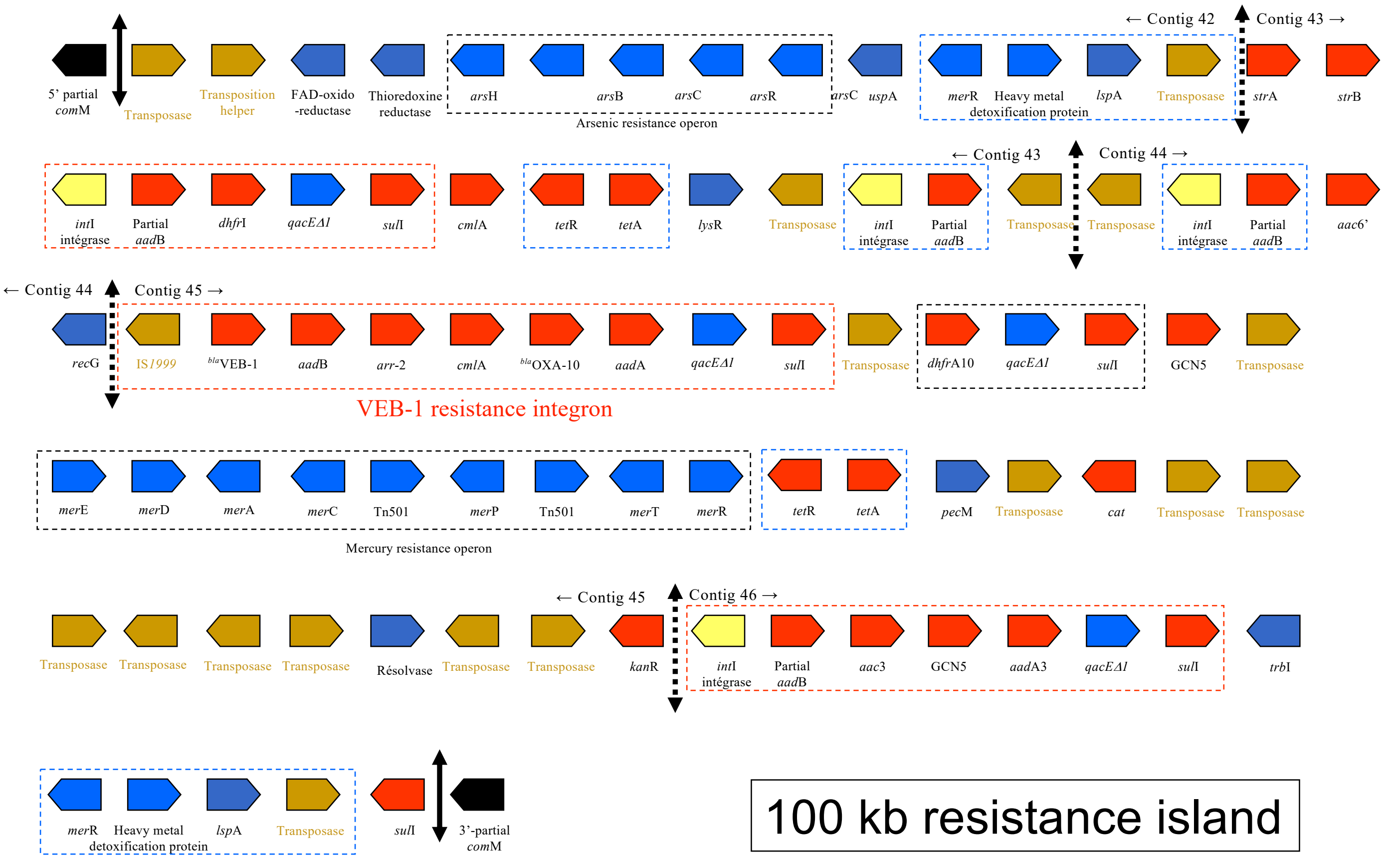
Enterobacteriaceae
P. aeruginosa, *P. putida*, *P. cepacia*
Acinetobacter sp., *Alcaligenes* spp.
Campylobacter spp. ; *Shewanella* sp.
Vibrio cholerae, *Vibrio* spp.
Corynebacterium glutamium,
C. striatum

Resistance gene famillies

β-lactamines
Aminoglycosides
Chloramphenicol
Erythromycine
Rifampicine
Trimethoprime
Sulfamides
Antiseptiques

Integrons and transposons



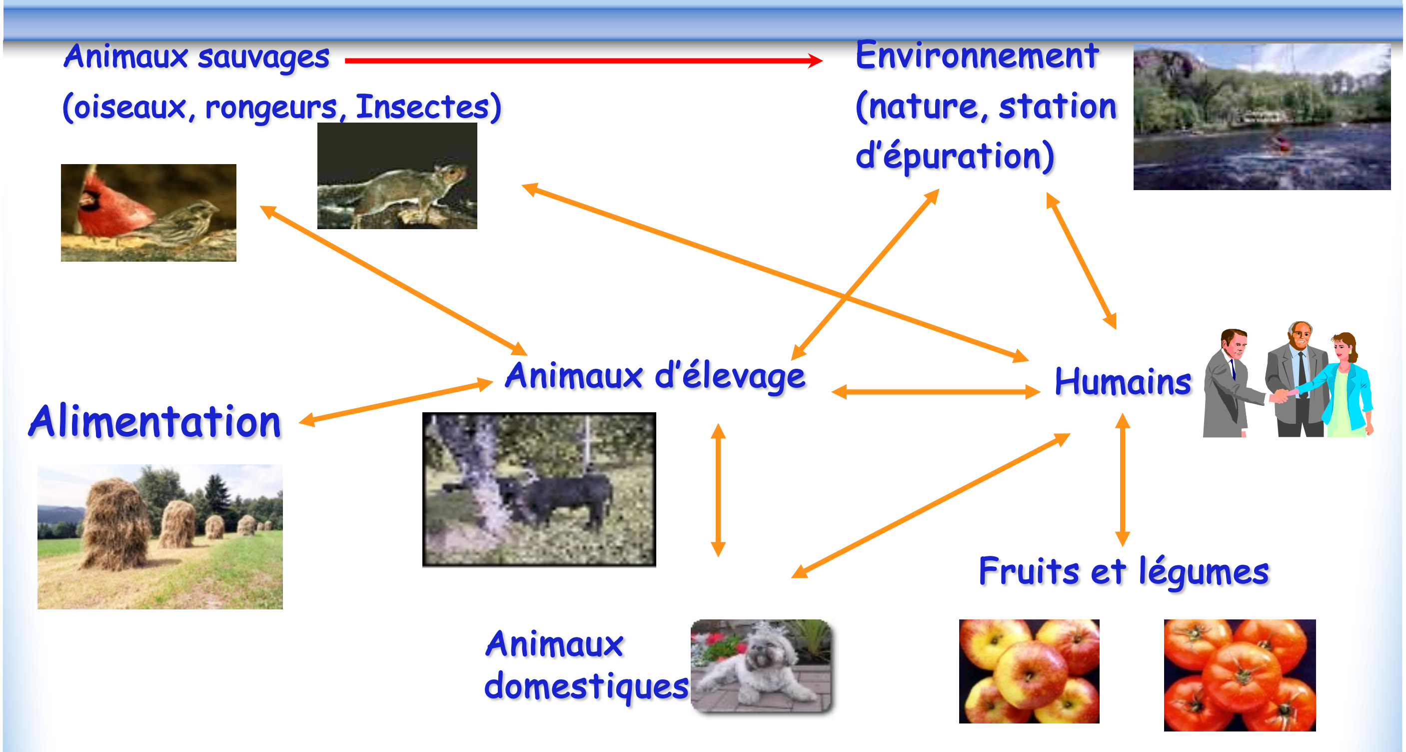


100 kb resistance island

(Fournier et al., PLoS Genetics, 2006)

Ou ?

Pool de gènes de résistance aux antibiotiques



Animaux sauvages (oiseaux, rongeurs, Insectes)

Environnement (nature, station d'épuration)

Animaux d'élevage

Humains

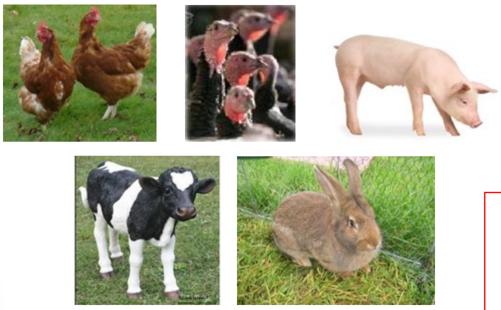
Alimentation

Fruits et légumes

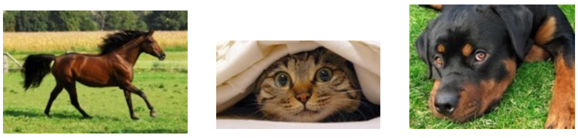
Animaux domestiques

E. coli- producteur de BLSE: ou êtes vous?

Livestock



Pets

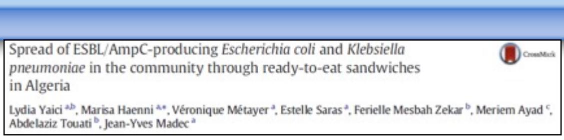


ESBL producing *E. coli* isolates Everywhere: “one health” problem

Environment

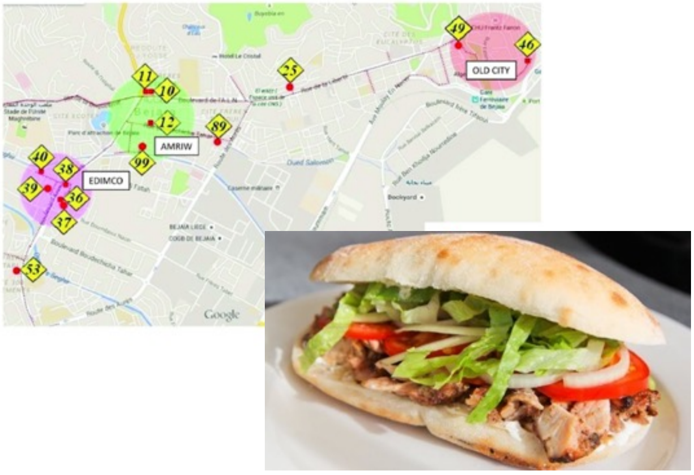
Wild animal and insects

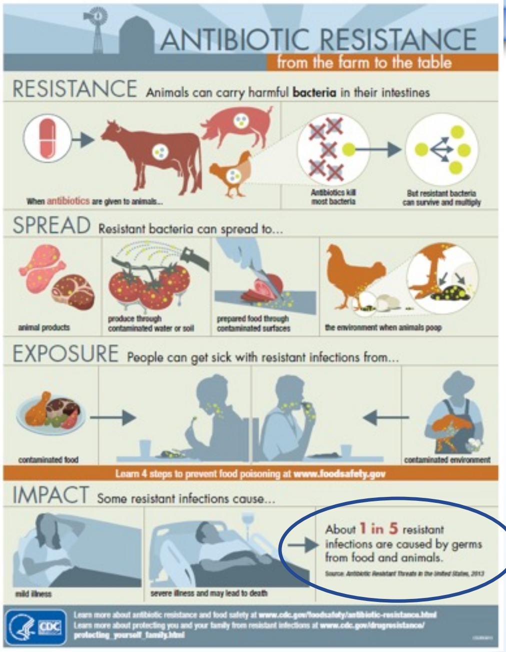
E. coli- producteur de BLSE: Etes vous comestibles?



Spread of ESBL/AmpC-producing *Escherichia coli* and *Klebsiella pneumoniae* in the community through ready-to-eat sandwiches in Algeria

Lydia Yaici [a,b], Marisa Haenni [a,*], Véronique Métayer [a], Estelle Saras [a], Ferielle Mesbah Zekar [b], Meriem Ayad [c], Abdelaziz Touati [b], Jean-Yves Madec [a]





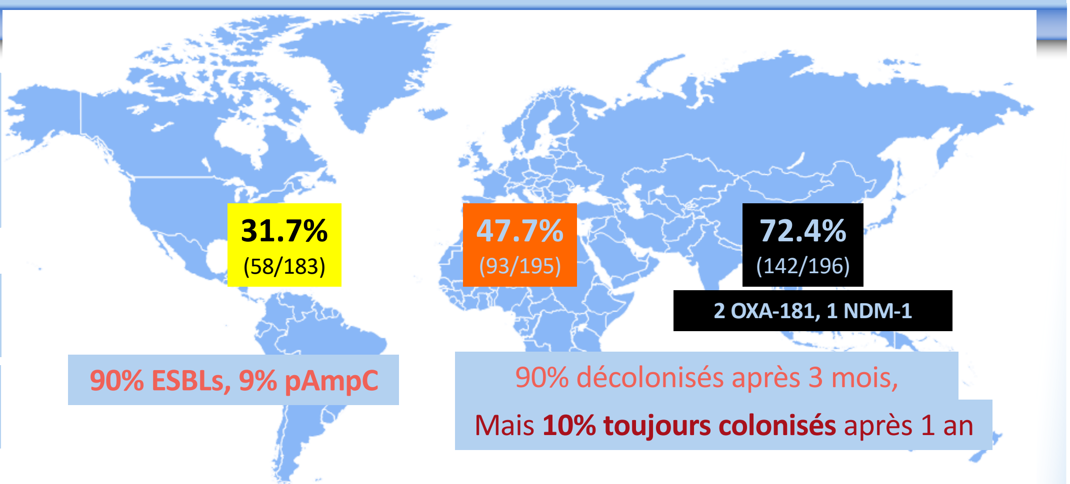
Epidemiology des ESBLs: L'étude VOYAG-R : tourisme et BMR

(E. Ruppé, Clin Infect Dis 2015)

574 voyageurs en zone intertropicale : dépistage négatif avant départ

Tous ont passé d'excellentes vacances!

Mais: 51% ont rapporté un souvenir (n=293)


31.7%
(58/183)

47.7%
(93/195)

72.4%
(142/196)

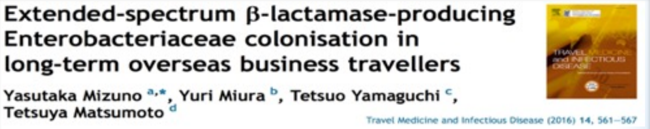
2 OXA-181, 1 NDM-1

90% ESBLs, 9% pAmpC

90% décolonisés après 3 mois,
Mais **10% toujours colonisés** après 1 an

Carriage before trip: 154/2001 = **7.7%**
Acquisition rate after trip: 633/1847 = **34.2%**
Transmission of ESBL-E to a non-travelling family member = **12%**

Arcilla MS, et al. *Lancet Infect Dis* 2017;17:78–85


Extended-spectrum β-lactamase-producing Enterobacteriaceae colonisation in long-term overseas business travellers

Yasutaka Mizuno [a,*], Yuri Miura [b], Tetsuo Yamaguchi [c], Tetsuya Matsumoto [d]

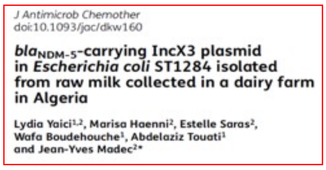
Travel Medicine and Infectious Disease (2016) 14, 561–567

45% acquisition during travel (South-East Asia+)

Ou sont les EPCs?

Dans les pays à forte prévalence (Magreb)

Dans les pays à faible prévalence (Allemagne)


J Antimicrob Chemother
doi:10.1093/jac/dkw160

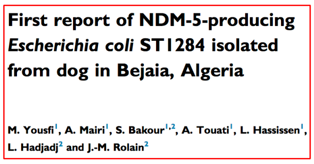
bla_{NDM-5}-carrying IncX3 plasmid in *Escherichia coli* ST1284 isolated from raw milk collected in a dairy farm in Algeria

Lydia Yaici[1,2], Marisa Haenni[2], Estelle Saras[2], Wafa Boudehouche[1], Abdelaziz Touati[1] and Jean-Yves Madec[2*]


J Antimicrob Chemother
doi:10.1093/jac/dkx124

KPC-3-producing ST167 *Escherichia coli* from mussels bought at a retail market in Tunisia

Yosra Mani[1]†, Wejdene Mansour[1,2]†, Hedi Mammeri[3–5], Erick Denamur[4–6], Estelle Saras[7], Noureddine Boujâafar[1,8], Olfa Bouallègue[1,9], Jean-Yves Madec[7*] and Marisa Haenni[7]


First report of NDM-5-producing *Escherichia coli* ST1284 isolated from dog in Bejaia, Algeria

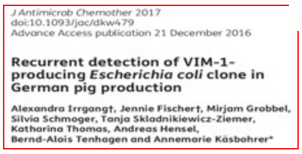
M. Yousfi[1], A. Mairi[1], S. Bakour[1,2], A. Touati[1], L. Hassissen[1], L. Hadjadj[2] and J.-M. Rolain[2]


J Antimicrob Chemother 2012
doi:10.1093/jac/dks108
Advance Access publication 27 March 2012

***Escherichia coli* producing VIM-1 carbapenemase isolated on a pig farm**

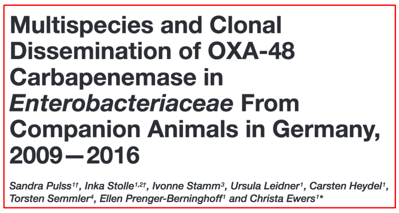
Jennie Fischer[1], Irene Rodríguez[1], Silvia Schmoger[1], Anika Friese[2], Uwe Roesler[2], Reiner Helmuth[1] and Beatriz Guerra[1*]

Mais aussi….


J Antimicrob Chemother 2017
doi:10.1093/jac/dkw479
Advance Access publication 21 December 2016

Recurrent detection of VIM-1-producing *Escherichia coli* clone in German pig production

Alexandra Irrgang†, Jennie Fischer†, Mirjam Grobbel, Silvia Schmoger, Tanja Skladnikiewicz-Ziemer, Katharina Thomas, Andreas Hensel, Bernd-Alois Tenhagen and Annemarie Käsbohrer*


Multispecies and Clonal Dissemination of OXA-48 Carbapenemase in *Enterobacteriaceae* From Companion Animals in Germany, 2009—2016

Sandra Pulss[1†], Inka Stolle[1,2†], Ivonne Stamm[3], Ursula Leidner[1], Carsten Heydel[1], Torsten Semmler[4], Ellen Prenger-Berninghoff[1] and Christa Ewers[1]*

21,569 isolats, 137 (0.64%) OXA-48 +

Aucune chez les animaux d'élevage

Animaux de compagnie
chiens (120/3182; 3.8%),
chats (13/792; 1.6%),
cochon d'inde (1/43; 2.3%),
rat (1/23; 4.3%),
souris (1/180; 0.6%),
lapin (1/144; 0.7%).

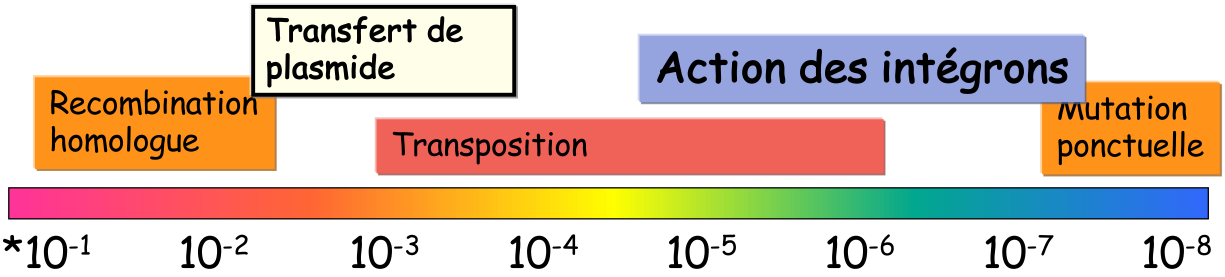
La trousse à outil des bactéries

Class of pieces	Genes and sequences		Function
Operative	Resistance genes	*mecA*	PBP2a (methicillin resistance in *S. aureus*)
	Regulatory genes	*mecR*	*mecA* regulation expression
Translocative	Integrases	*int*	*attC* recognition in class 1 integrons
	Resolvases	TnpR	*res* sequence recognition in Tn *3*-like transposons
	Invertases	*inv*	Specific recombination sequence
	Transposases	ORF513	CTX-M and AmpC capture (?)
Dispersive	Conjugation genes	*oriT*	Plasmid conjugation
	Incompatibility genes	*inc*	Plasmid interference
	Integration sequences	*res*	Recombination in Tn3 -like transposons
	Insertion sequences (IS)	IS 10	Recombination and integration (*tet* genes)

F. Baquero. Nature Rev Microbiol 2004; 2:510-17

Conclusion:
La trousse à outil des bactéries: Evolution efficace

Le role relatif des différents outils génétiques dont dispose la bactérie



Transfert de plasmide

Recombination homologue

Transposition

Action des intégrons

Mutation ponctuelle

$^*10^{-1}$ 10^{-2} 10^{-3} 10^{-4} 10^{-5} 10^{-6} 10^{-7} 10^{-8}

Fréquence élevée
Diversité faible

Fréquence faible
Diversité élevée

* fréquence par cellule par génération

CONCLUSIONS

- Bactéries utilisent de nombreux outils génétiques pour évoluer dans un environnement hostile.

 Pour tout nouveau gène de résistance => nouvel élément mobile associé

- Difficile de prévenir ces évènements génétiques
  - car on se sait pas ou ils se produisent
  - ils sont inhérent au mode de vie de la bactérie,

Mais possibilité de prévenir la diffusion (indentification rapide, hygiène, antibiotiques, …)

==> Concentration des mécanismes de résistance => « Superbugs » hyper-épidémique et difficile à éradiquer.

Différentes stratégies de diffusion, mais même résultat
=> gènes de résistance, éléments mobile, plasmides et souches épidémiques