Journée régionale « Maîtrise de la diffusion des BHRe »
Rennes – Mardi 21 mars 2017

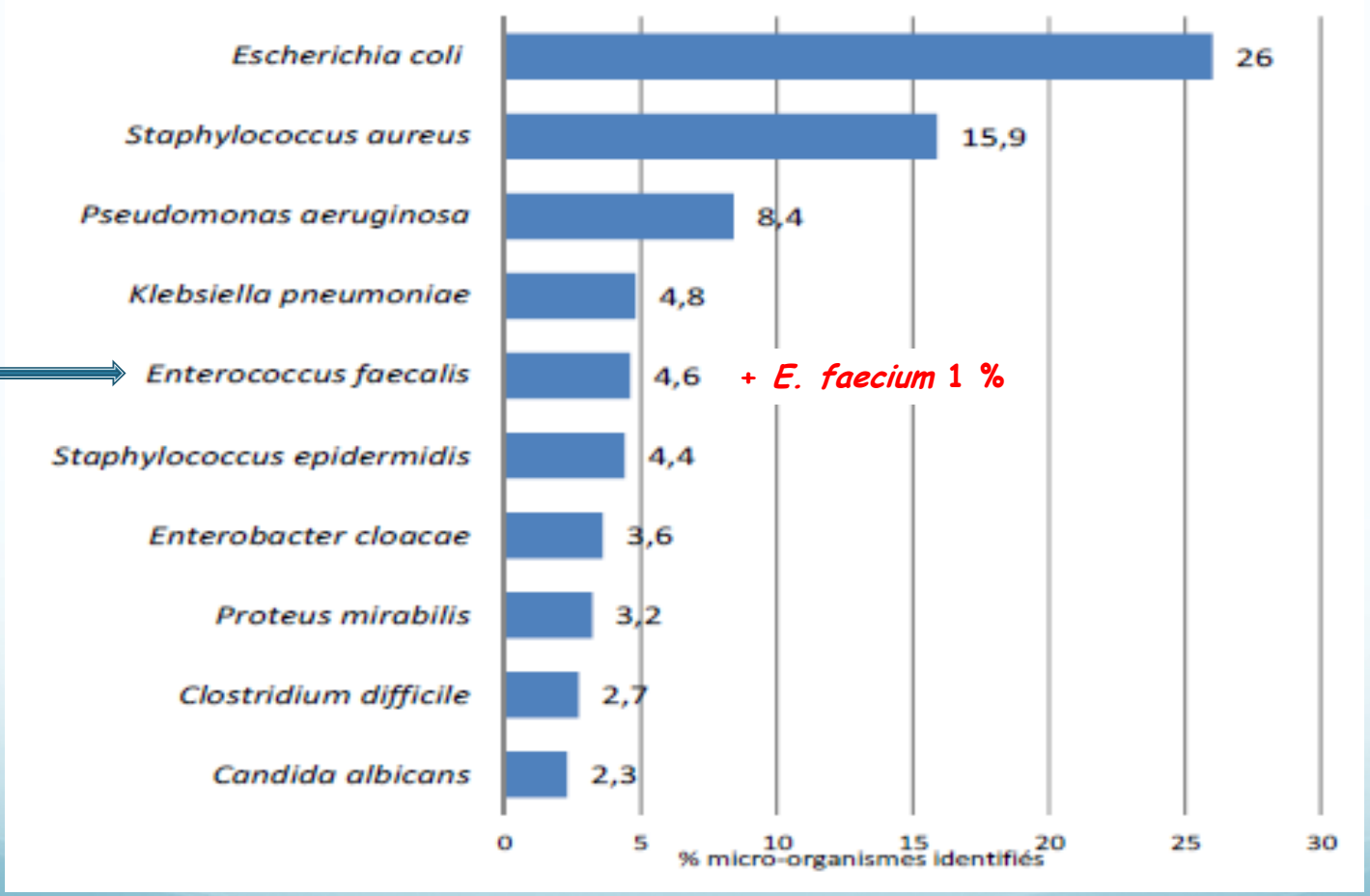
Les ERG : Quelle problématique ? Epidémiologie nationale

Prof. Vincent CATTOIR

Service de Bactériologie-Hygiène hospitalière, CHU de Rennes
CNR de la Résistance aux Antibiotiques (laboratoire associé « Entérocoques »)
Faculté de Médecine, Université de Rennes 1
E-mail: vincent.cattoir@chu-rennes.fr

Infections à entérocoques en France

4ème cause la plus fréquente d'infections liées aux soins en France



http://www.invs.sante.fr/enp2012

Espèces d'entérocoques

2 espèces principales :

	1990	2005	2010
E. faecalis	90 %	80 %	73 %
E. faecium	10 %	20 %	27 %

E. faecalis
Facteurs de virulence

E. faecium
Multi-résistance

Espèces mineures :

E. gallinarum, E. casseliflavus, E. avium, E. durans, E. hirae, E. raffinosus

Entérocoques résistants à la vancomycine (ERV)

PLASMID-MEDIATED RESISTANCE TO VANCOMYCIN AND TEICOPLANIN IN *ENTEROCOCCUS FAECIUM*

ROLAND LECLERCQ, M.D., ELIANE DERLOT, JEAN DUVAL, M.D., AND PATRICE COURVALIN, M.D.

E. faecium strains BM4147 and BM4152 were isolated in 1986 from the feces of two patients with acute leukemia who had not been treated with vancomycin and who had undergone selective digestive tract decontamination with oral kanamycin, sisomicin, nitrofurans, and colistin five days before a bone marrow transplantation. The patients had been hospitalized in a hematology unit where vancomycin was included in a regimen of empirical antibiotic therapy of febrile patients with neutropenia. The strains were isolated as pure cultures from the stools of the patients with neutropenia but did not provoke infection.

VANCOMYCIN-RESISTANT ENTEROCOCCI

SIR,—Vancomycin resistance among gram-positive organisms is rare,[1,2] except in some strains of *Leuconostoc* spp, lactobacilli, and pediococci.[3] Since November 1986, 55 strains of vancomycin-resistant enterococci derived from twenty-two patients with end-stage renal failure or multiple organ failure, including acute renal failure, have been isolated at the Dulwich Public Health Laboratory. The sources of these enterococci included blood (8), intra-abdominal sepsis (8), urine (5), peritoneal fluid (2), pleural fluid (1), and bile (1). Colonisation of four central venous lines was detected at their exit sites. Faecal carriage of resistant organisms was present in some infected patients and in 1 without evidence of infection.

Two patients were infected with both species. All strains are resistant to vancomycin at a concentration in excess of 64 mg/L

Public Health Laboratory,
Dulwich Hospital,
London SE22 8QF

ANNE H. C. UTTLEY
C. H. COLLINS

Antibiotics Reference Laboratory,
Divison of Hospital Infection,
Central Public Health Laboratory,
London NW9

JAY NAIDOO
R. C. GEORGE

Mécanismes de résistance acquise principaux

	Acquise		Intrinsèque
	VanA	VanB	VanC1/C2-3
CMI (mg/l) Vancomycine	>64	4-1000	4-32
Téicoplanine	>32	0,5-2	0,5-2
Expression	ind	ind	ind/const
Localisation	Tn*1546*	Tn*1547*	*chrom.*
Espèces	*E. faecium* multi-R *E. faecalis,* (autres entérocoques)		*E. gallinarum* *E. casseliflvus*

Epidémies

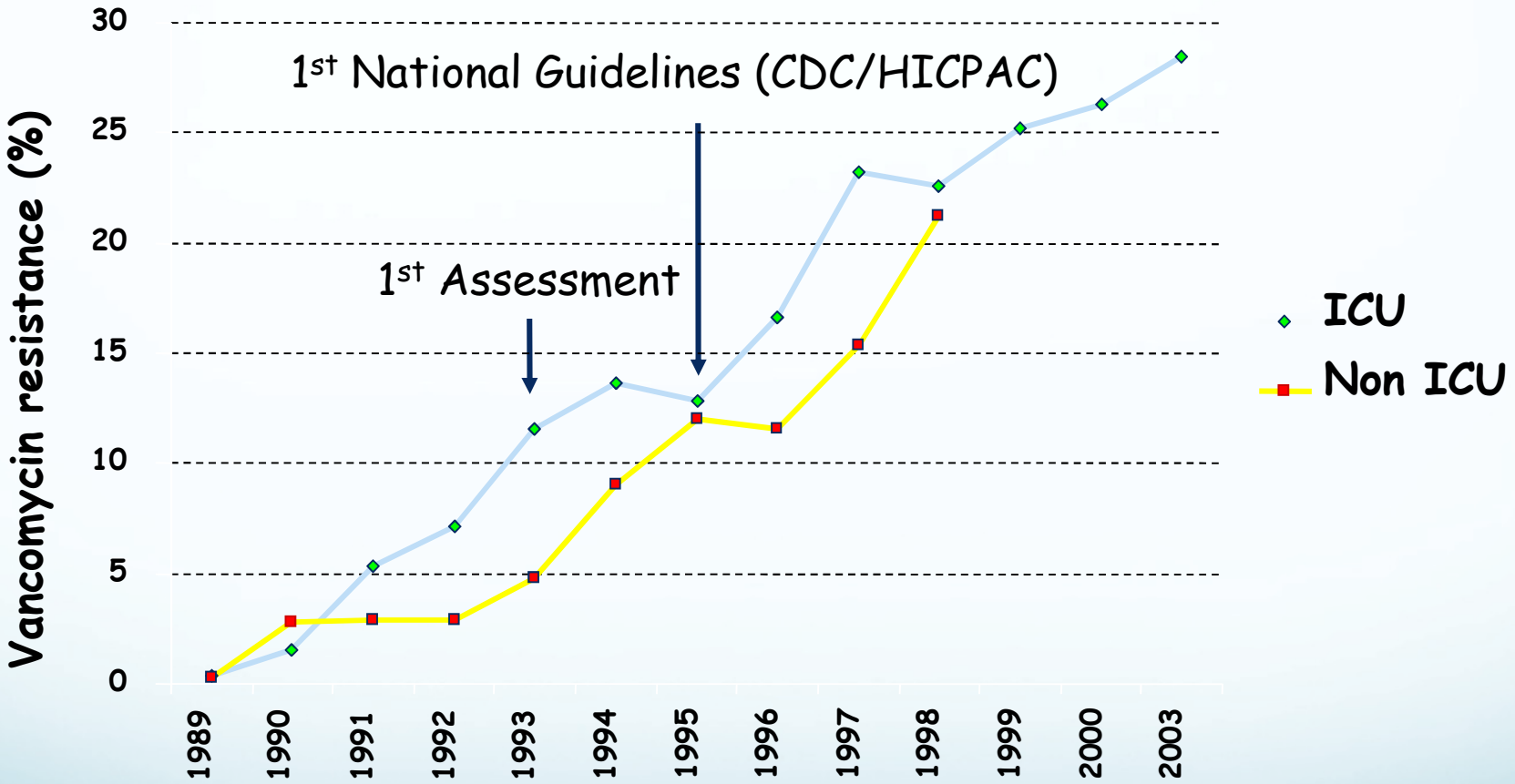
+++ ++ +/-

Alphabet Van

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				

Cattoir & Leclercq, MS 2010

Emergence aux Etats-Unis



First cases of VRE = *E. faecalis* in 1987 (Saint Louis, MO)
First outbreaks = *E. faecium* in 1989 (New York City, NY)

Source : NNIS system, CDC
Sahm et al., *AAC* 1989
Frieden at al., Lancet 1993

Comparaison Europe/Etats-Unis (1990)

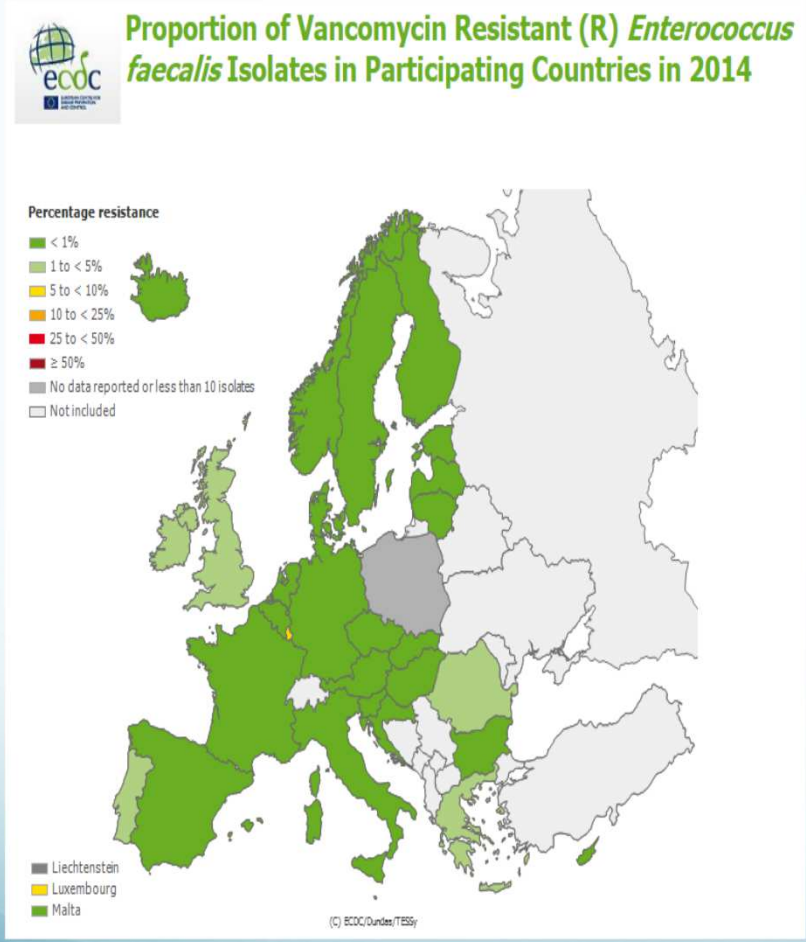
	Europe	US
Prevalence	Low (<1 %) (exceptions)	High (>25 %) (local variations)
Hospital outbreaks	Uncommon (sporadic cases)	Frequent (outbreaks)
Species, genotype	*E. faecium vanA*	*E. faecium vanA* and others (*vanB*, *E. faecalis*)
Multidrug resistance	Variable	Ampi, Genta
Reservoir	GIT (community, animals)	GIT (hospitals)
Growth factors	Avoparcin (before 1997)	-

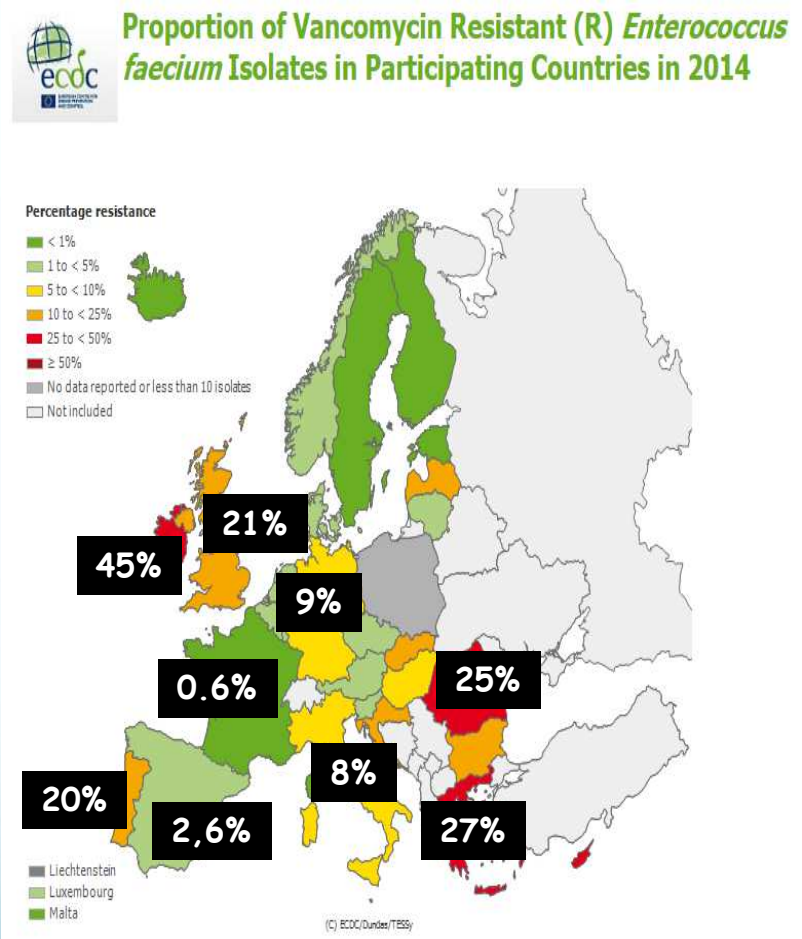
Actuellement aux Etats-Unis

	Percent of all *Enterococcus* healthcare-associated infections resistant to vancomycin	Estimated number of infections	Estimated number of deaths attributed
Vancomycin-resistant *Enterococcus faecium*	77%	10,000	650
Vancomycin-resistant *Enterococcus faecalis*	9%	3,100	200
Vancomycin-resistant *Enterococcus* (species not determined)	40%	6,900	450
Totals		20,000	1,300

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

Actuellement en Europe

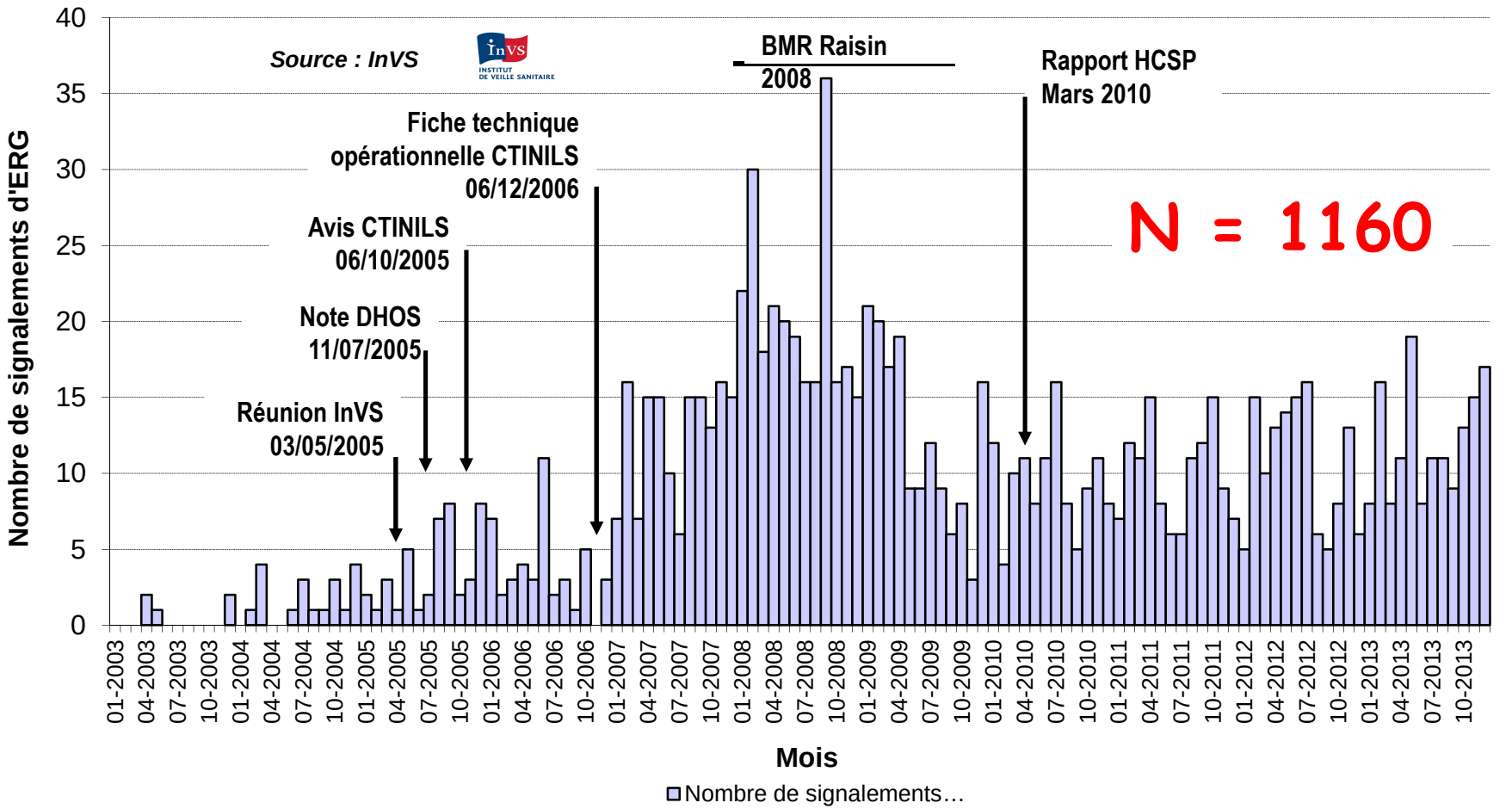




*Only blood isolates

Source: EARS-Net, ECDC

Signalements des ERV en France (2003-2013)



Signalement ERV = Un évènement :

. Un seul cas de colonisation ou infection

. Epidémie

Courtesy from S. Vaux (InVS)

Bilan des signalements (2003-2013)

- 1160 signalements de
  - 2560 cas *
  - Répartition des infections ou colonisations en fonction des sites (1198 sites décrits)
    - Colonisation : 945 (79%)
    - Infection : 253 (21%)
    - Ratio infection / colonisation : 0,27

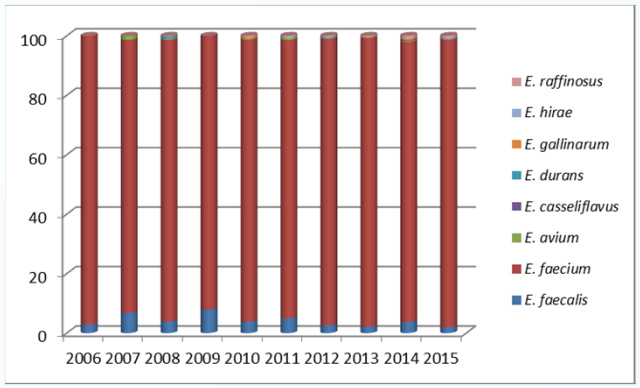
- Répartition par espèce (en nombre de signalements) :
  - *E. faecium* : 1060 (91%)**
  - *E. faecalis* : 106 (9%)**

- 289 épisodes de cas groupés (> 1 cas) * : 25% des signalements
  - Etendue : de 2 à 55 cas

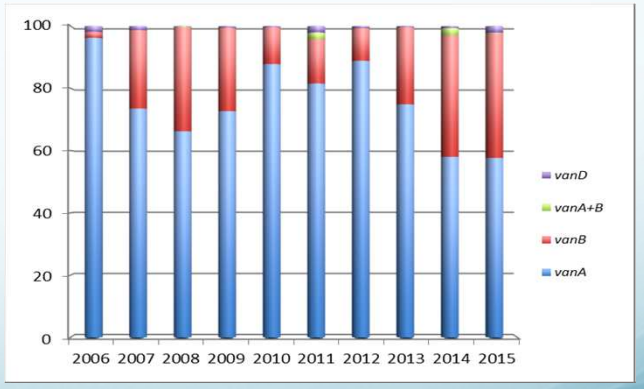
* Données obtenues lors du signalement
** 6 signalements impliquent *E. faecium* et *E. faecalis*

Courtesy from S. Vaux (InVS)

Souches d'ERV reçues au CNR (2006-2015)



92-97 % d'*E. faecium*
2-8 % d'*E. faecalis*

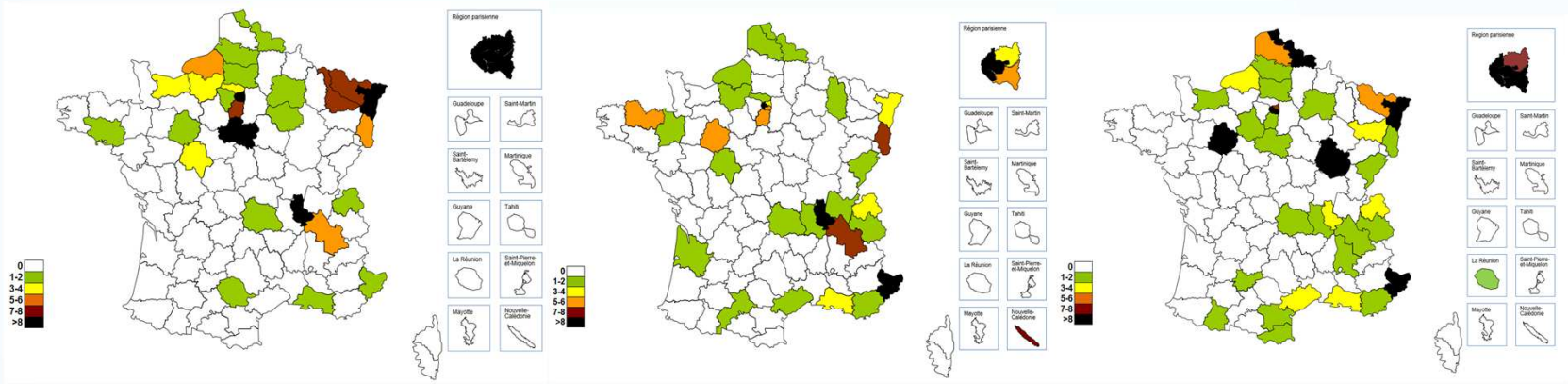


58-96 % de *vanA*
2-40 % de *vanB*
0,1-2 % de *vanD*

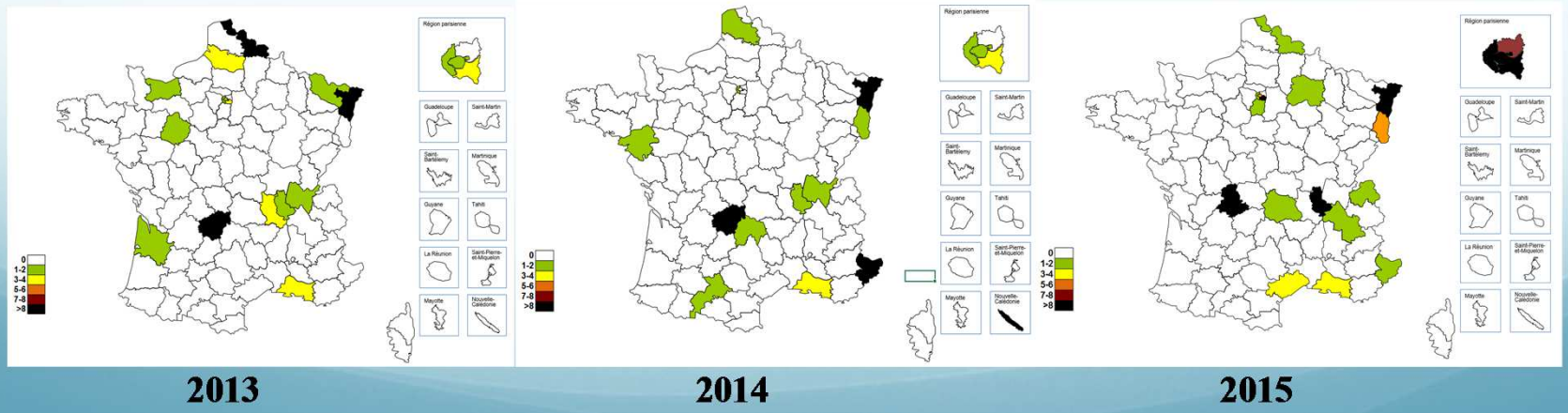
Données CNR (2015)

Epidémies à ERV en France (2013-2015)

E. faecium vanA(+)



E. faecium vanB(+)



Données CNR (2015)

Shift vers *E. faecium*

Table 1. Prevalence of *van* genotypes according to enterococcal species from 2006 to 2008

	No. of isolates									
	2006			2007			2008			
Enterococcal species	*vanA*	*vanB*	*vanD*	*vanA*	*vanB*	*vanD*	*vanA*	*vanB*	*vanD*	total
E. faecium	86	2	1	91	37	0	386	251	1	855
E. faecalis	4	0	0	8	0	0	22	7	0	41
E. avium	0	0	0	0	0	1	2	0	0	3
E. durans	0	0	0	0	0	0	2	0	0	2
E. hirae	0	0	0	0	0	0	0	1	0	1
Total	90	2	1	99	37	1	412	259	1	902

96%

4%

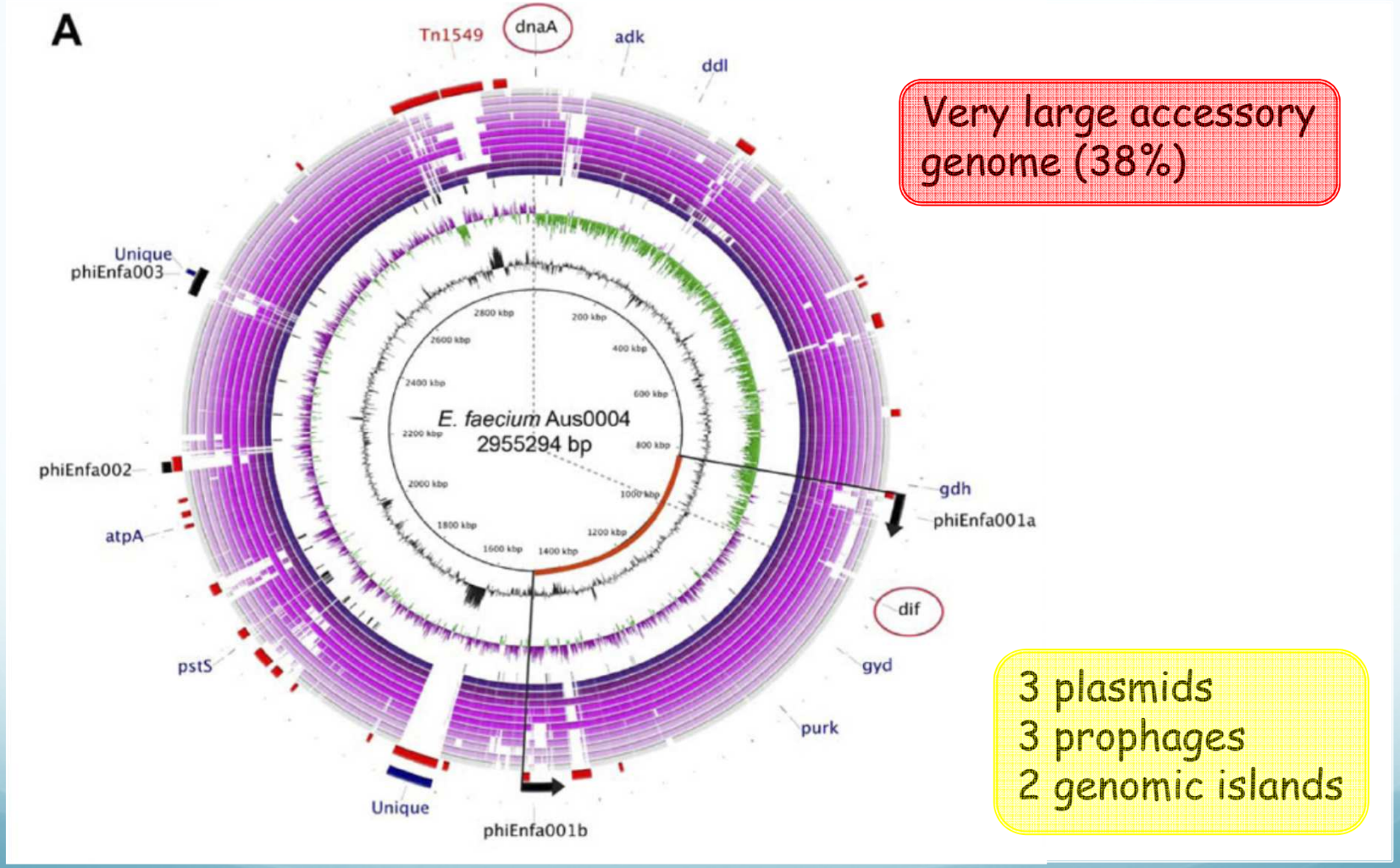
<1%

E. faecium
66% *vanA*
34% *vanB*
<1% *vanD*

E. faecalis
83% *vanA*
17% *vanB*

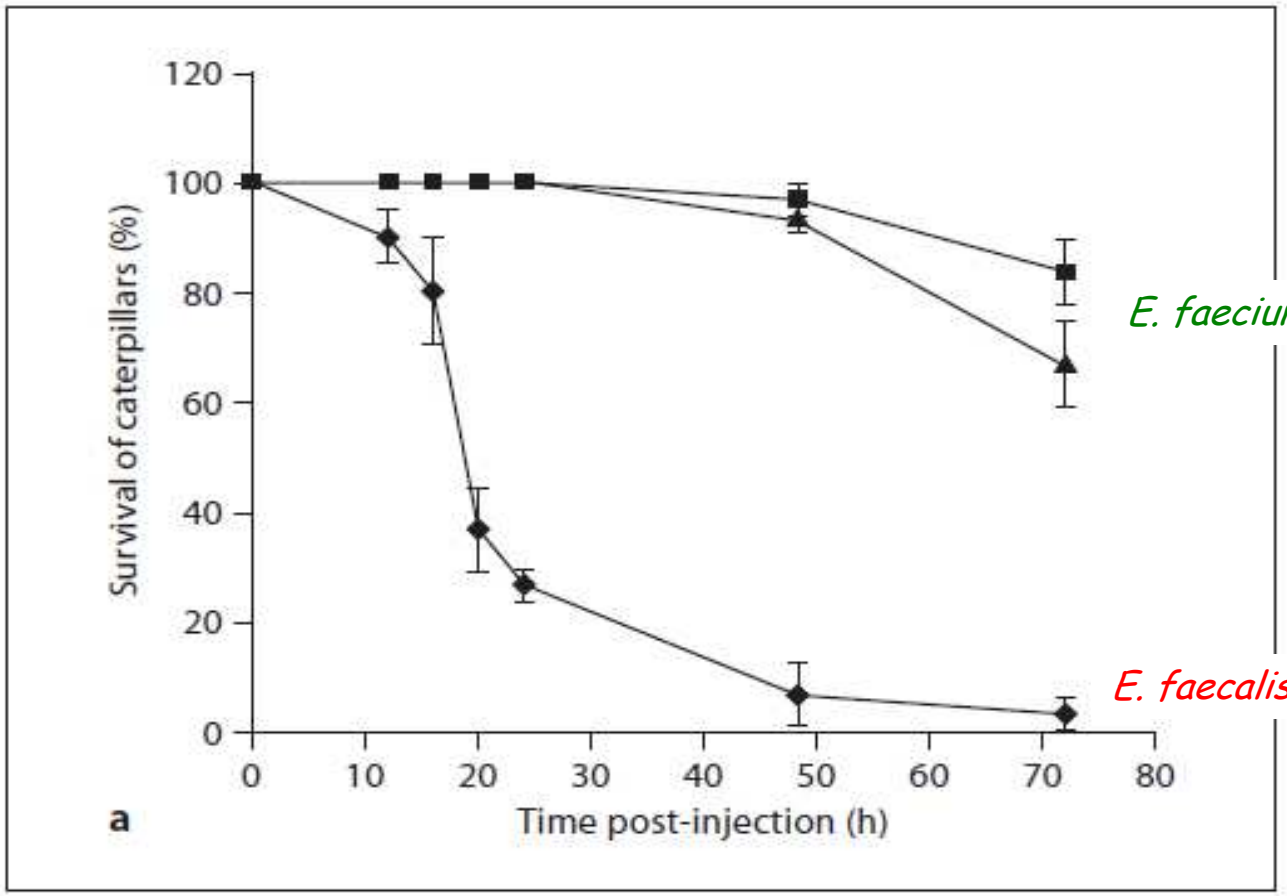
Bourdon et al., JAC 2011

Grande plasticité génomique



Lam et al., JB 2012

Grande persistance chez l'hôte



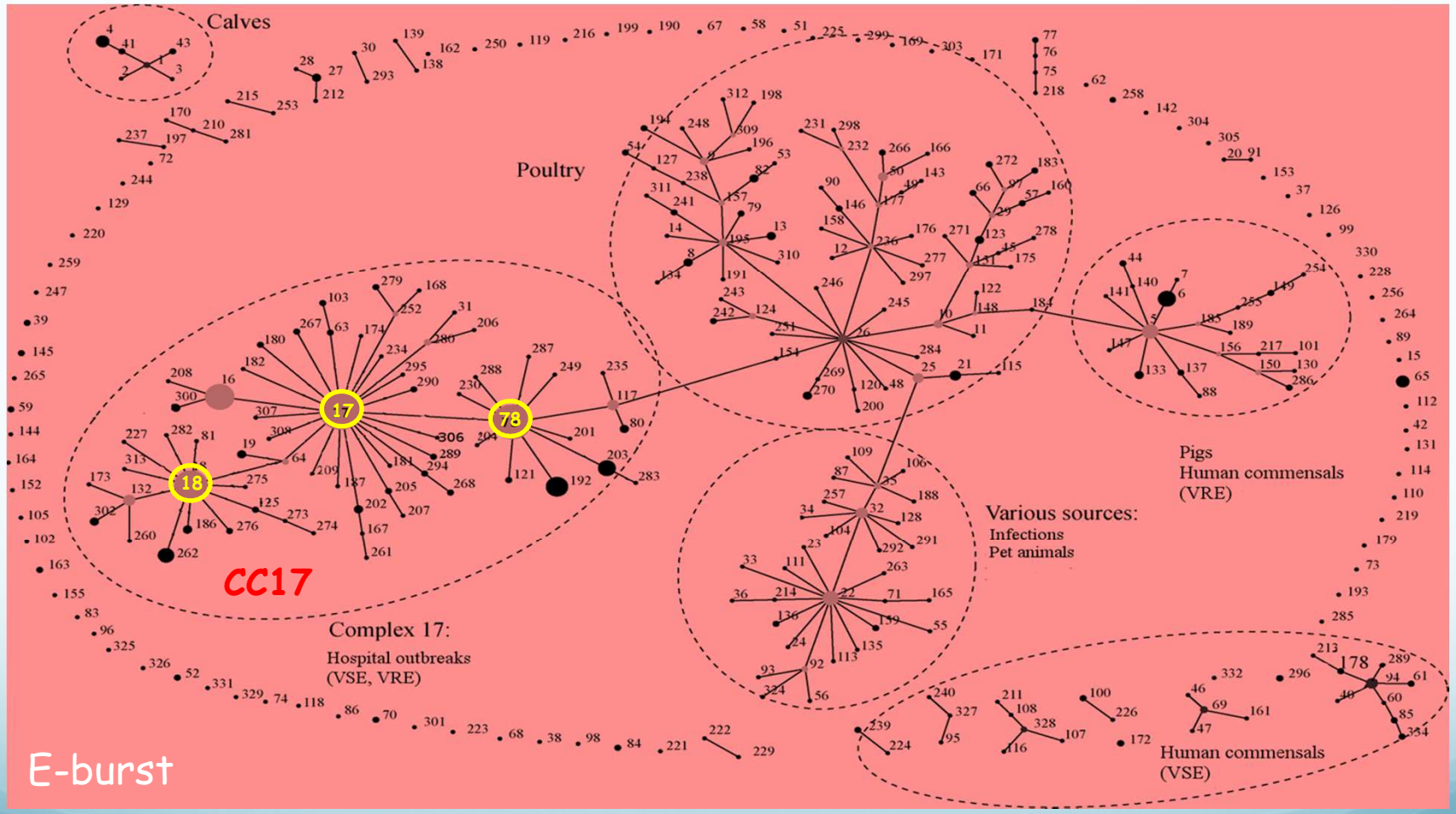
E. faecium : Low mortality rate

E. faecalis : High mortality rate

Fig. 1. a Survival of *Galleria* caterpillars following *E. faecalis* JH2-2 (♦), non-CC17 *E. faecium* HM1070 (■) and CC17 *E. faecium* 1,231,410 (▲) injections. Larvae were inoculated using 2×10^6 (±0.7) CFU.

Lebreton et al., JMMB 2012

MLST et *sequence types* (ST)



Top et al., FEMS IMM 2008

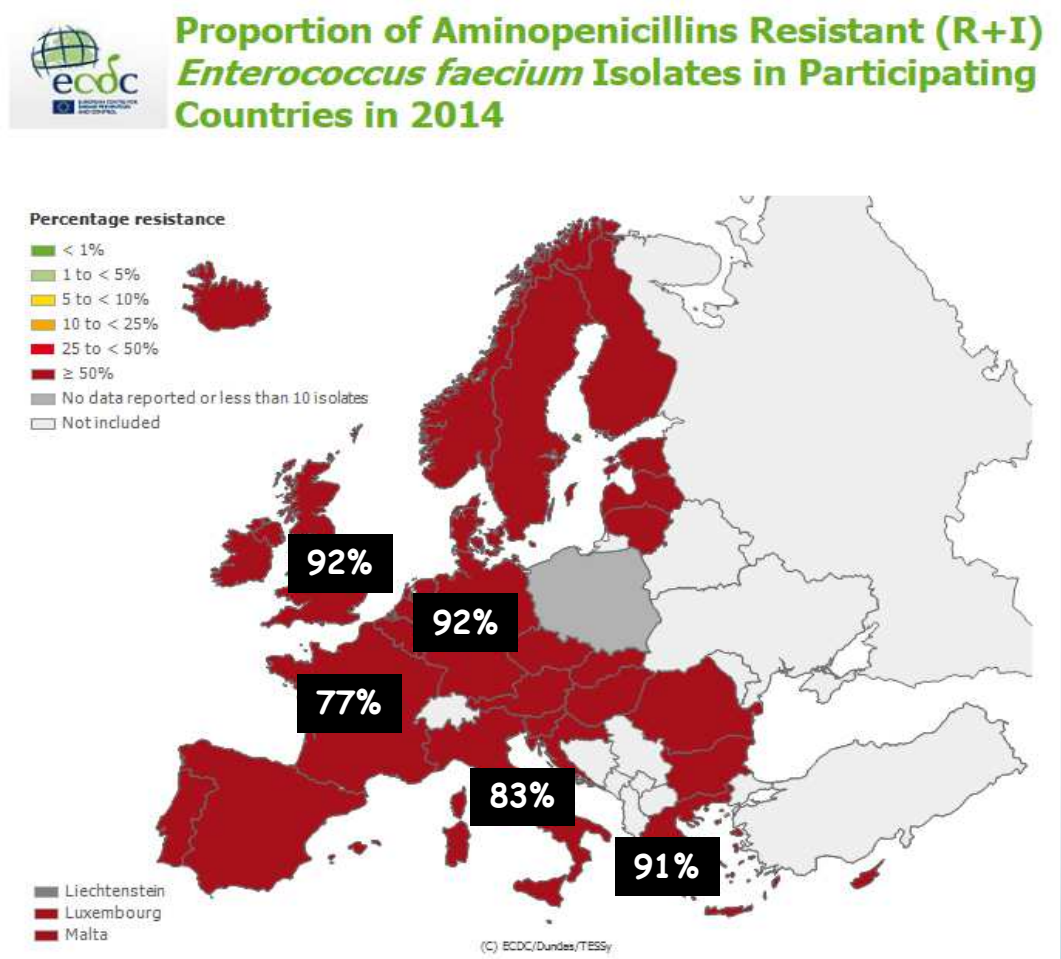
Souches CC17

- Subpopulation of hospital-adapted clones of *E. faecium* that have subsequently acquired resistance to vancomycin

- *CC17* isolates share common characteristics:
  - HLR to ampicillin and fluoroquinolones
  - Presence of a pathogenicity island, harbouring virulence genes (*esp* et hyl_{Efm})
  - Presence of the specific IS*16*

Homan et al., JCM 2002
Willems et al., EID 2005
Leavis et al., PLoS Pathogens 2007

Résistance à l'ampicilline



95-98 % Ampi-R in Vanco-R *E. faecium*

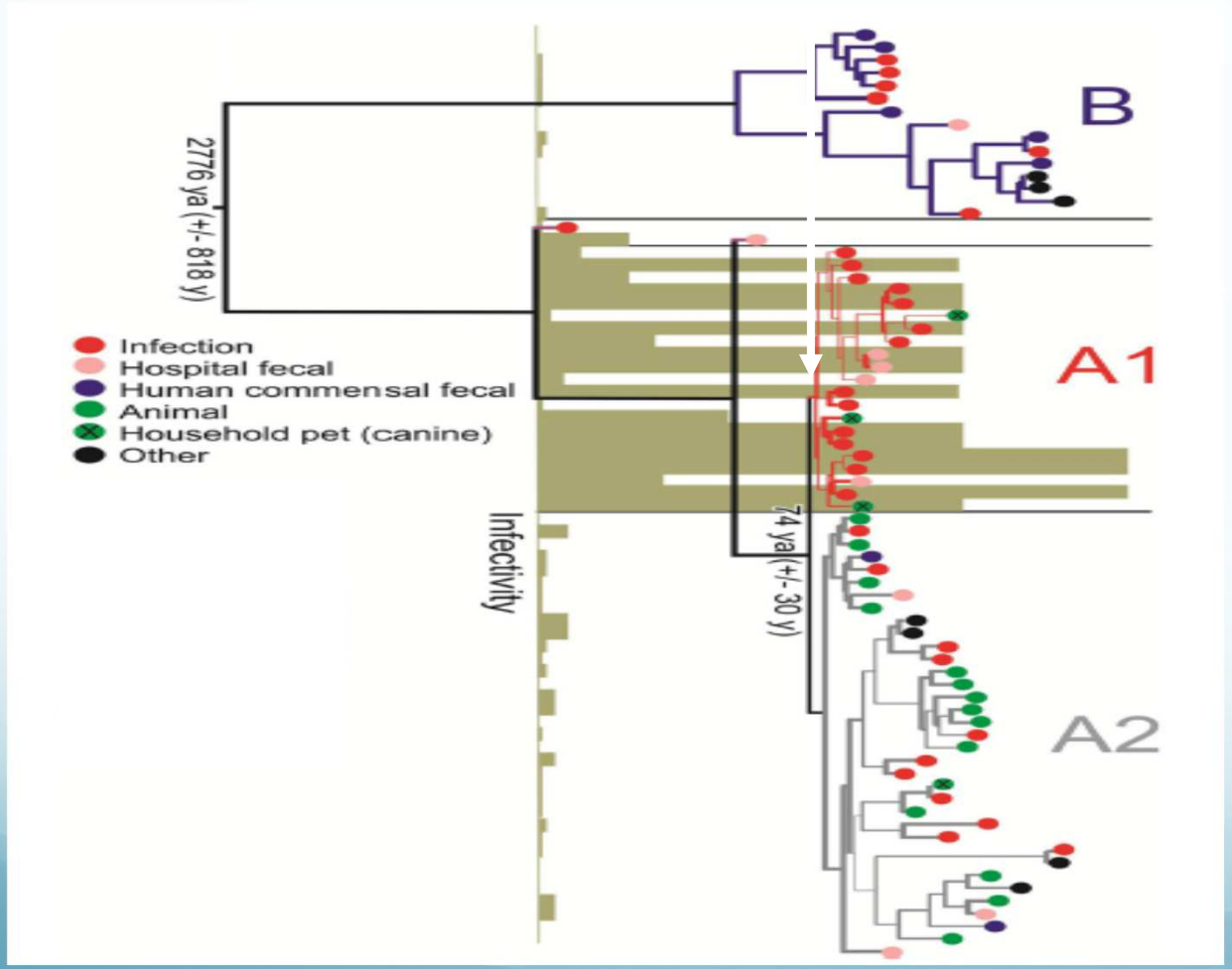
No Ampi-R *E. faecalis*
(except in the US, Lebanon, Argentina)

Sources : EARS-Net, ECDC
NRC France

Lignées génétiques (clades)

Urbanization
Hygienic practices
Animal domestication

Introduction of ATB
(clinical medicine,
agriculture)



Human (commensal)

Human (hospital, *CC17*)

Animal

Lebreton et al., MBio 2013

Réservoirs de la résistance

1 hospitalized patient infected by VRE

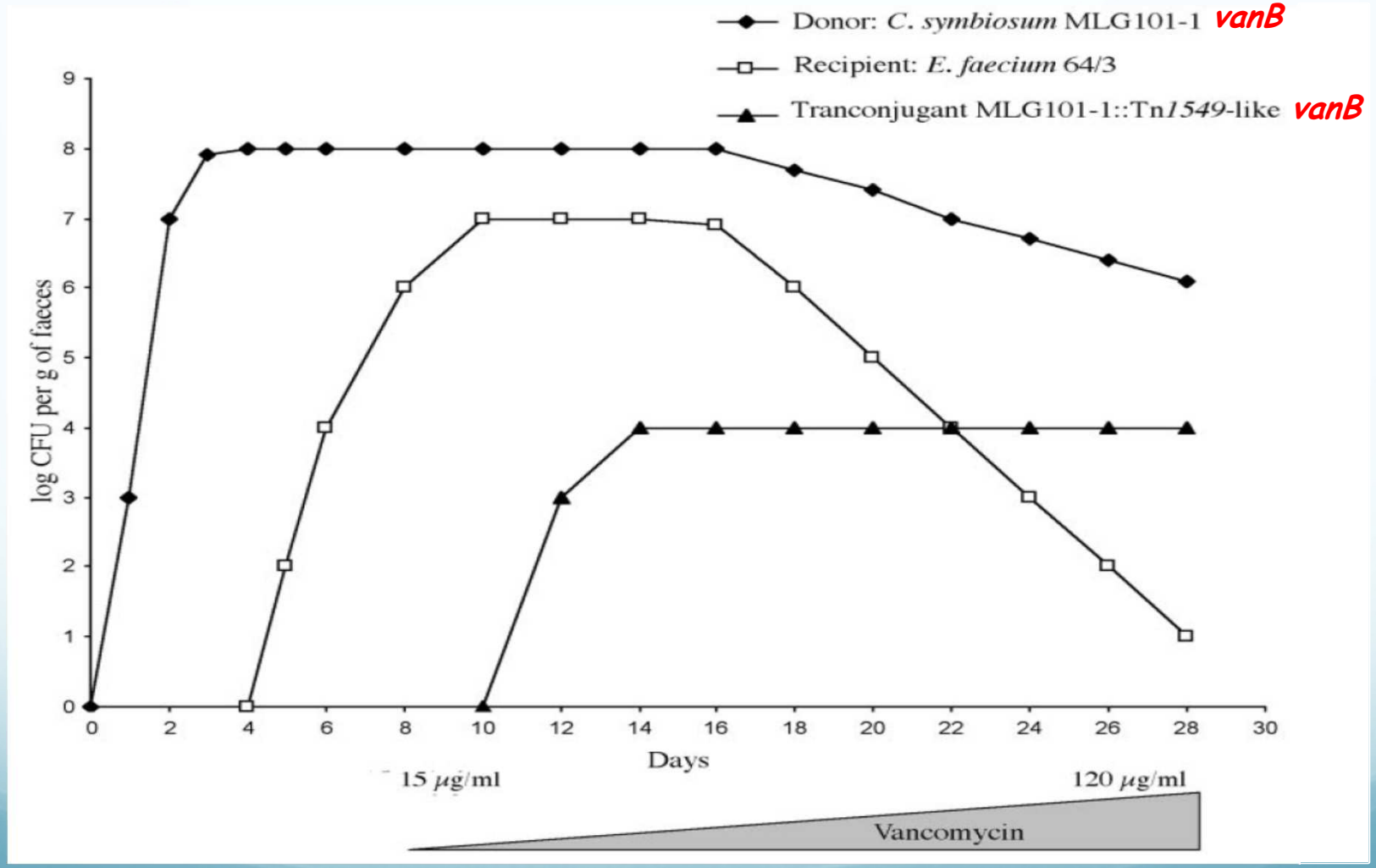
2-10 contact patients faecal carriers

- ✓ Very large reservoir: animals (ducks, chickens, pigs, horses, cows, goats, cats, dogs…), urban and hospital wastewaters, food products (meats, vegetables, cheese)

- ✓ *van* genes identitied in Gram-positive anaerobes:
  - *vanB*: *Clostridium* spp., *Eggerthella lenta*, *Ruminococcus* spp.
  - *vanD*, *vanG*: *Ruminococcus* spp.

Cattoir & Leclercq JAC 2013; Stinear et al., Lancet 2011 ; Ballard et al., AAC 2005; Domingo et al., AAC 2007

Transfert *in vivo* de la résistance



Launay et al., AAC 2006

Détection moléculaire de la résistance

Detection of VRE by PCR and from 804 rectal swabs

Cepheid Xpert™ *vanA*/*vanB* assay	Culture	
	Positive	Negative
vanA or *vanB* (+)	11	116
vanA (+)	8	4
vanB (+)	3	112
vanA and *vanB* (−)	0	677

Sensitivity, specificity, and PPVs and NPVs (and their 95% confidence interval) of the Cepheid Xpert™ *vanA*/*vanB* assay compared with culture as the reference standard

Result	Value (%) of Cepheid Xpert™ *vanA*/*vanB* assay (95% CI)			
	Sensitivity	Specificity	PPV	NPV
vanA or *vanB* (+)	100 (70–100)	85.4 (82.7–87.7)	8.7 (4.8–15.0)	100 (99.3–100)
vanA (+)	100 (62.8–100)	99.5 (98.7–99.9)	66.7 (38.8–86.5)	100 (99.4–100)
vanB (+)	100 (38.2–100)	85.6 (82.9–87.8)	2.6 (0.6–7.7)	100 (99.3–100)

Serious concern with *vanB*: anaerobes?

Bourdon et al., DMID 2010

Transfert de la résistance chez *S. aureus*

❖First description in 2002 (Michigan, US) of *vanA* operon acquisition in MRSA

❖A limited number of clinical isolates (n=35):

Continent	Country	No.
North America	US	13
South America	Brazil	1
Asia	India Iran Pakistan	16 3 1
Europe	Portugal	1

All MRSA *vanA* (+)

❖Risk factors: chronic skin ulcers, vancomycin exposure, MRSA/VRE co-colonization/co-infection

Chang et al., NEJM 2003, Sievert et al., CID 2008; Melo-Cristino et al. Lancet 2013; Moravvej et al., IJAA 2013; Limbago et al., JCM 2014; Rossi et al., NEJM 2014

Résistance aux nouveaux antibiotiques

In vitro susceptibility of Gram-positive pathogens in the US and Europe (2009-2013)

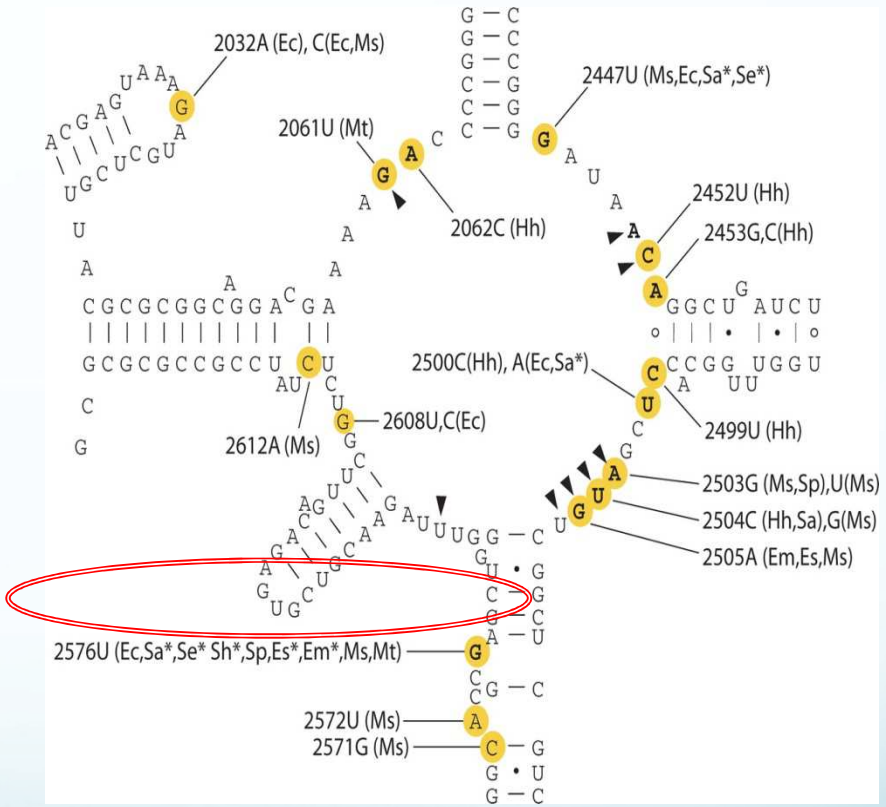
Organism	Drug	Range (mg/L)	MIC_{50} (mg/L)	MIC_{90} (mg/L)	CLSI %S	CLSI %I	CLSI %R
Enterococcus faecium (n = 372)	Tedizolid	0.03 to 4	0.25	0.5	–	–	–
	Linezolid	0.12 to 32	2	2	99.2	0.0	0.8
	Ampicillin	≤0.12 to >16	>16	>16	16.7	0.0	83.3
	Daptomycin	≤0.06 to >4	2	4	97.0	0.0	3.0
	Levofloxacin	0.25 to >32	>32	>32	14.2	1.9	83.9
	Tigecycline	≤0.008 to 1	0.06	0.12	98.1	0.0	1.9
	Vancomycin	≤0.25 to >32	>16	>32	45.2	0.5	54.3

No resistance to linezolid, daptomycin and tigecycline in *E. faecalis*

Bensaci & Sahm, DMID 2016

Résistance aux oxazolidinones

Résistance principalement acquise par **mutations ribosomales**
(sélection *in vitro* à basse fréquence, 10^{-9}-10^{-11})



Résistance transférable liée à :

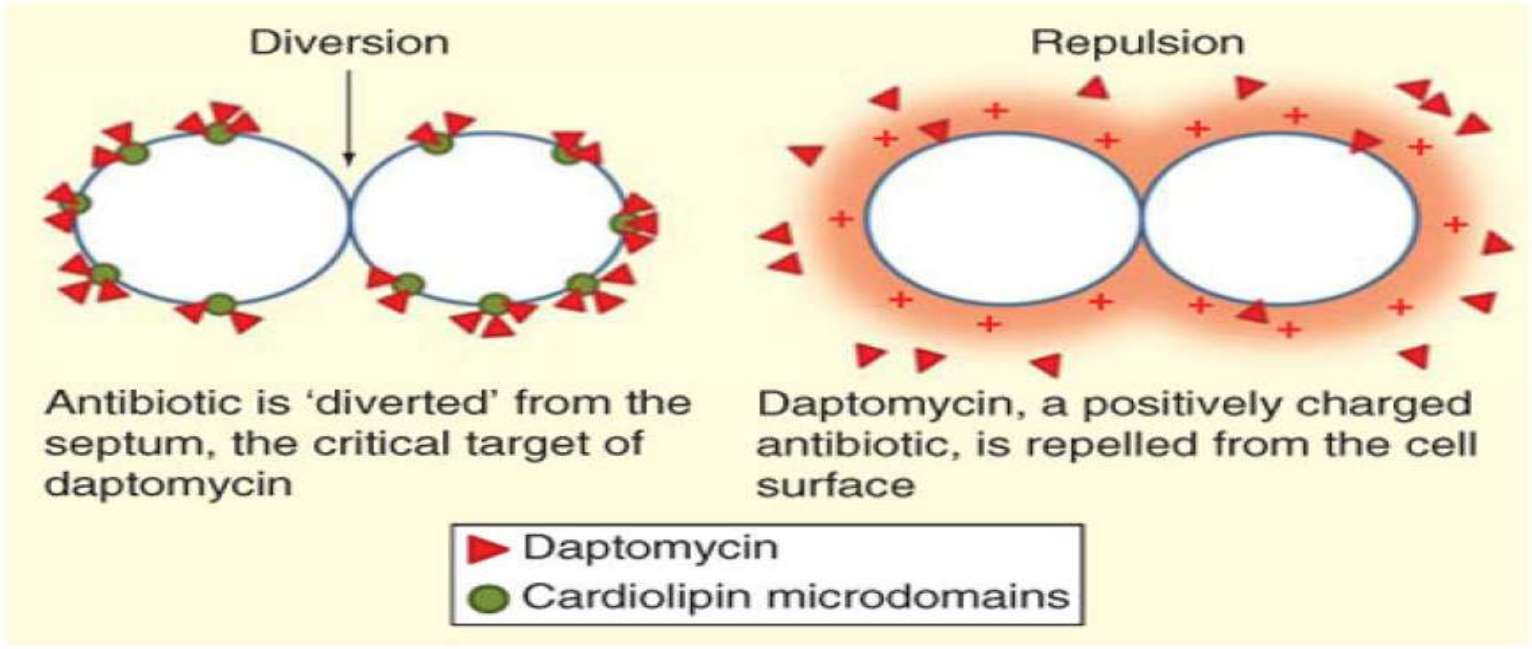
-gène *cfr* → R croisée $PhLOPS_A$

-gène *optrA* → R croisée PhO

Résistance au LIN rare mais émergence de 5 souches *optrA*(+) isolées en France (2014-2016) dont 4 *E. faecium* et 1 *E. faecalis*

Résistance à la daptomycine

E. faecalis | *E. faecium*



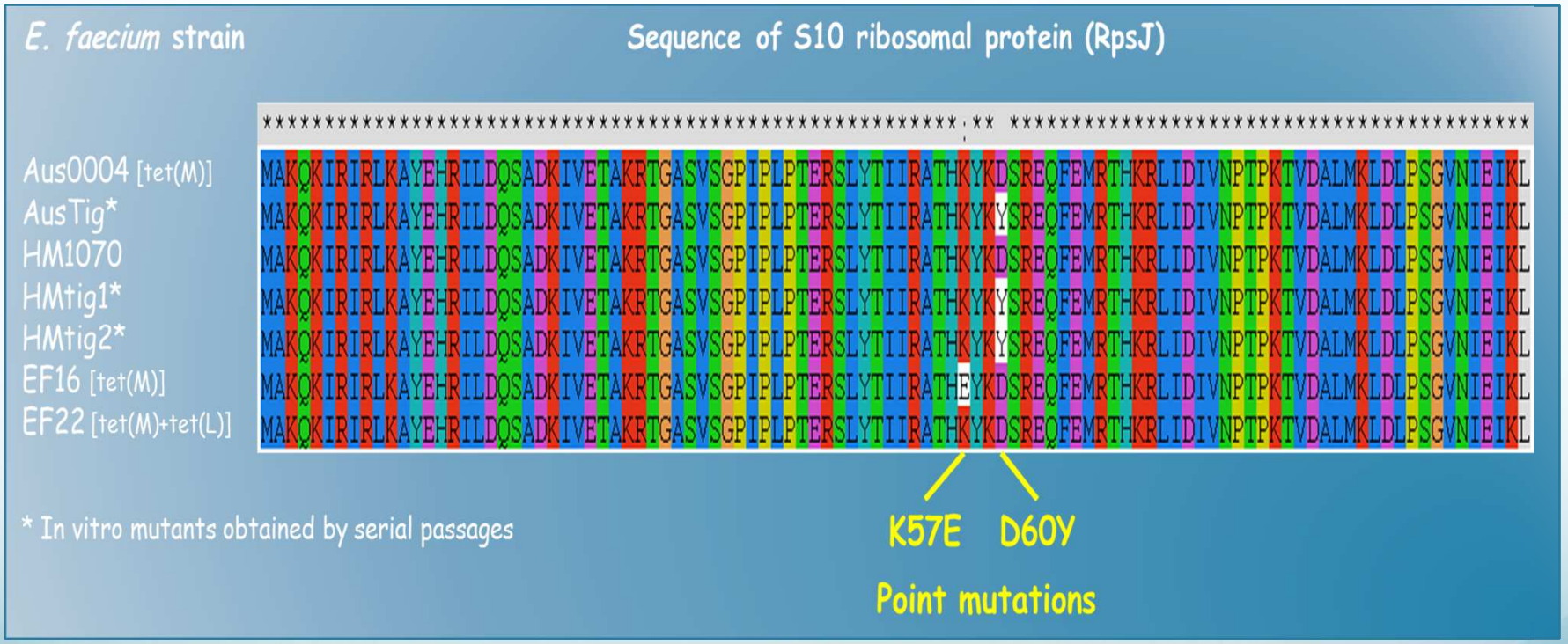
Redistribution des domaines cardiolipine par mutations dans *liaFSR*, *cls* et *gpdD*

Répulsion électrostatique par mutations dans *yycFG* et *cfa* +/- mutations dans *cls* et *liaFSR*

-Résistance à DAP rapportée plusieurs fois sous traitement
-Aucune souche clinique R en France à ce jour

Résistance à la tigécycline

Résistance par mutation chromosomique dans le gène *rpsJ* (pas de résistance transférable)



Seulement 2 souches R rapportées en France

Cattoir et al., AAC 2015

-Prévalence faible des ERV en France
-Souches de portage
-Pas de transfert au SARM
-Résistance aux nouveaux ATB rare

-Remplacement d'*E. faecalis* par *E. faecium*
-Difficulté de détection des souches *vanB*(+)
-Emergence de la résistance au linézolide (surveillance +++)