Résistances émergentes aux antibiotiques d'impact clinique réel

Bactéries à Gram positif

Frédéric LAURENT

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Centre Internationale de Recherche en Infectiologie – INSERM U1111, CNRS UMR5308, Université Lyon 1, ENS de Lyon - Equipe *"Pathogénèse des infections à staphylocoques"*

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Résistances émergentes aux antibiotiques d'impact clinique réel

Bactéries à Gram positif

en 20 minutes ! …

Bêta-lactamines ?

Macrolides ?

Glycopeptides ?

Fluoroquinolones ?

C5G ?

…… ?

Résistances émergentes aux antibiotiques d'impact clinique réel

Bactéries à Gram positif

en 20 minutes ! …

Bêta-lactamines ?

Macrolides ?

Glycopeptides ?

Fluoroquinolones ?

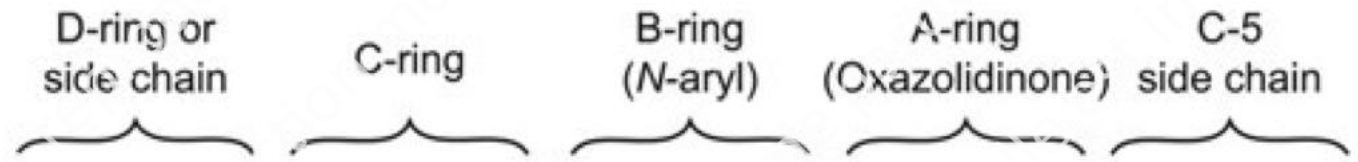
C5G ?

…… ?

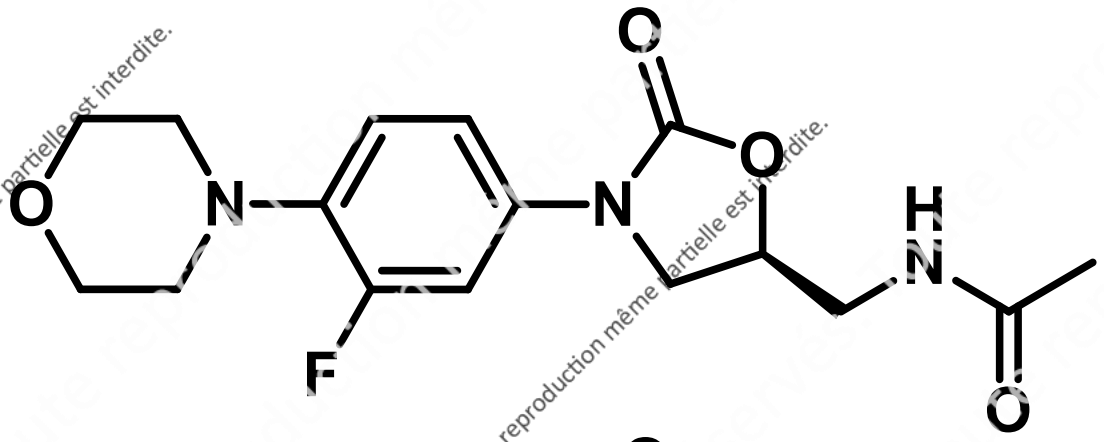
oxazolidinones

Famille qui s'est … et va s'agrandir
Utilisation en expansion
Génériques disponibles
Souches résistantes : épidémies/endémies - locales/nationales/internationales
Nouveaux mécanismes de résistances

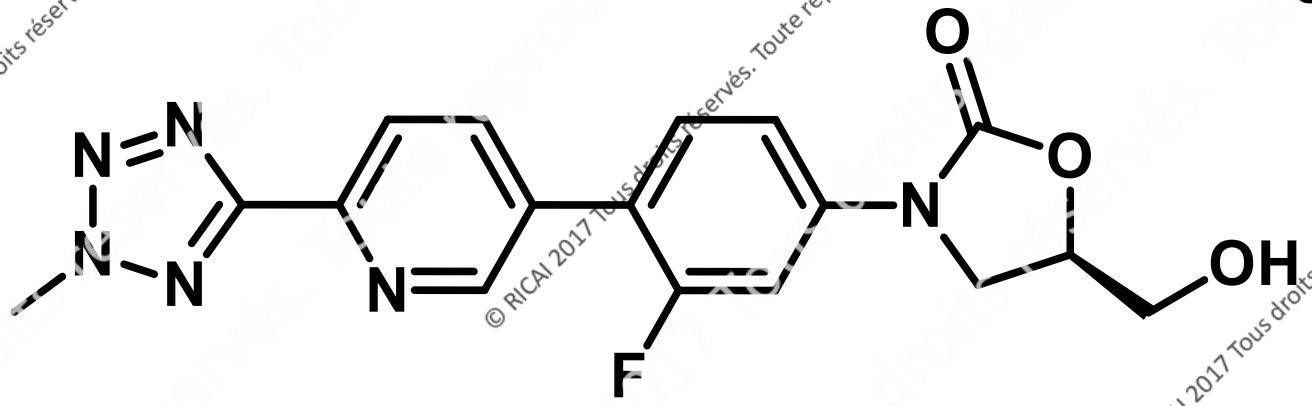
Structure des oxazolidinones



Linézolide
ZYVOXYD®



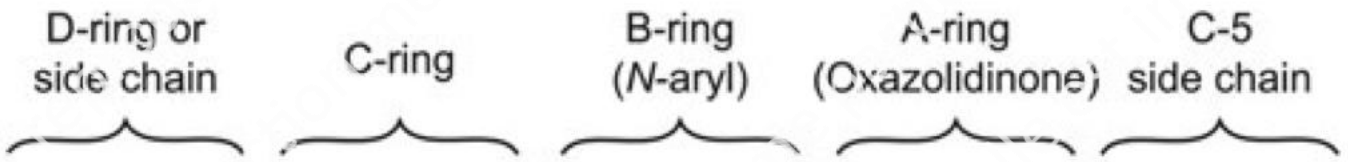
Tédizolide
SIVEXTRO®



Sous forme de phosphate = **Prodrogue** = activation *in vivo* par phosphatases sanguines

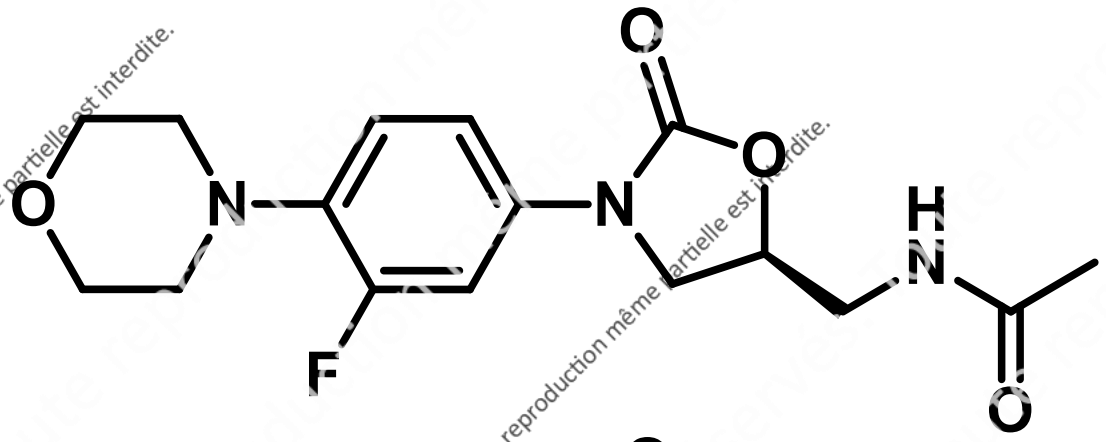
Arnold Louie et al. AAC. 2011;55:3453-3460

Structure des oxazolidinones

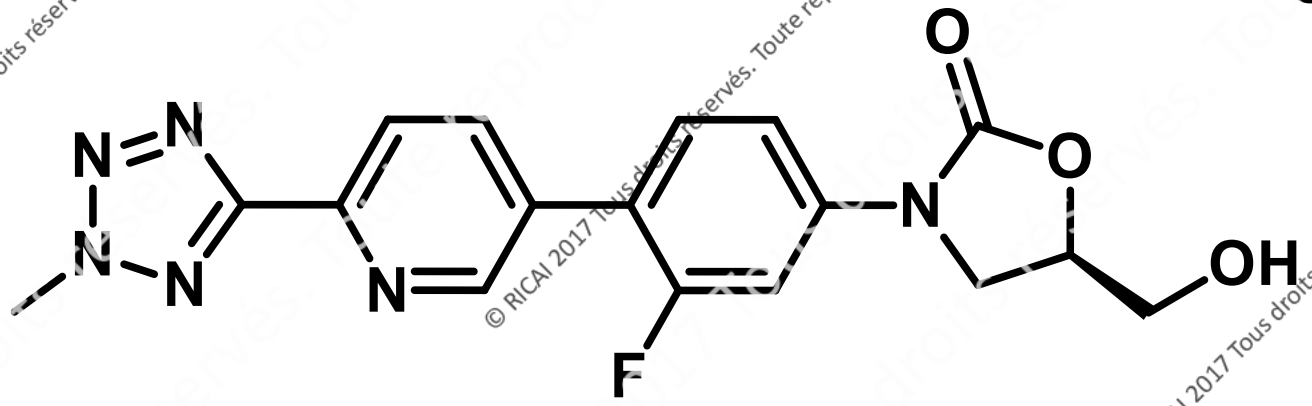


Linézolide
ZYVOXYD®

Forme IV génériquée depuis 2017



Tédizolide
SIVEXTRO®



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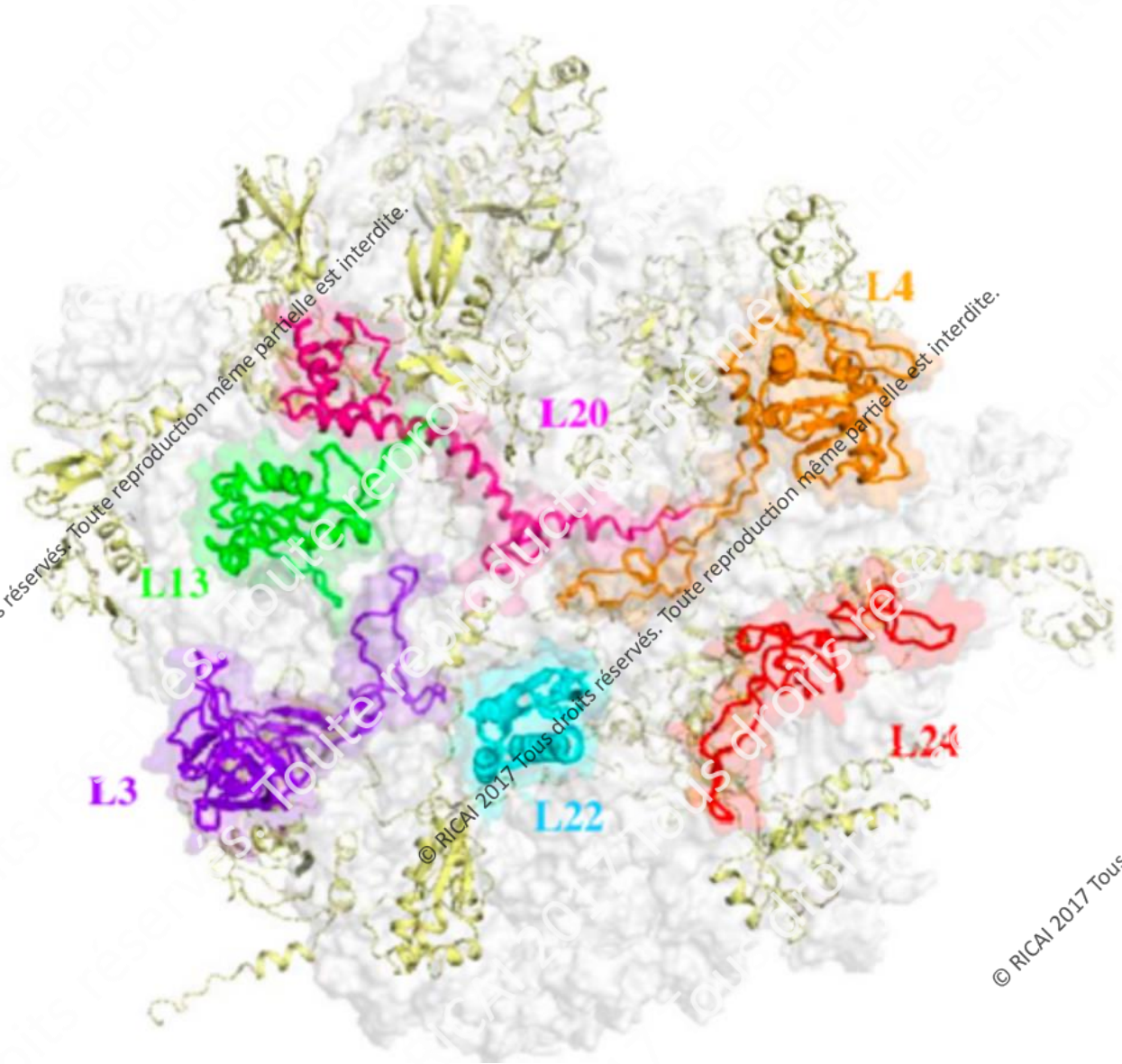
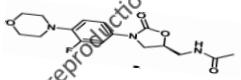
Mécanisme d'action



Ribosome bactérien : ARNr + protéines ribosomales

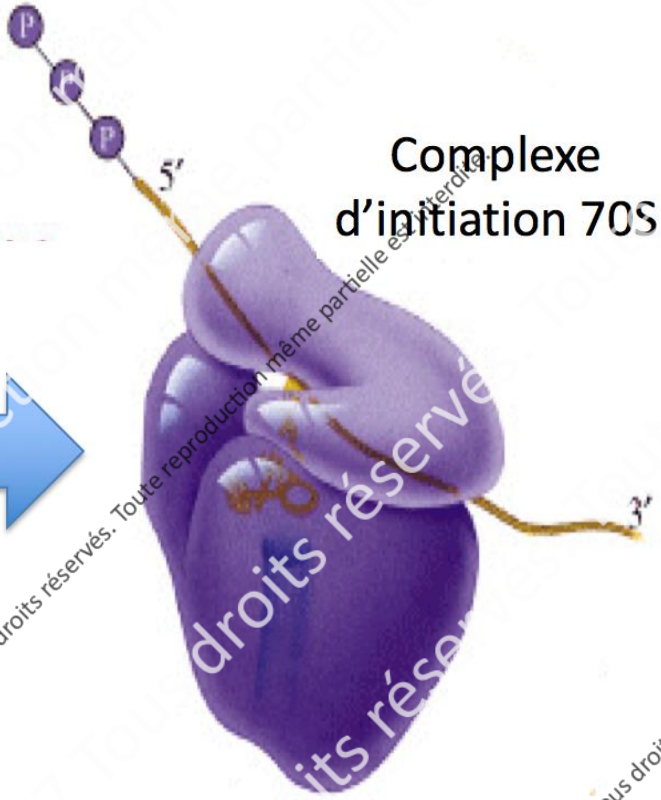
Mécanisme d'action



Sous unité 50S

Complexe d'initiation 30S

Complexe d'initiation 70S



Swaney *et al*. AAC, 1998; Bozdogan *et al*. Int J Antimicrob Agent, 2004

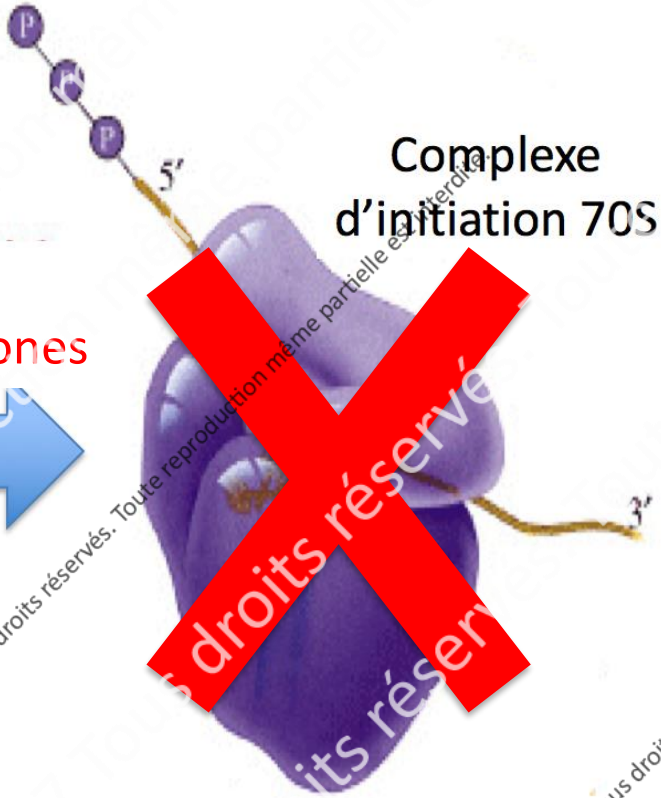
Mécanisme d'action

Sous unité 50S

Oxazolidinones

Complexe d'initiation 30S

Complexe d'initiation 70S



Arrêt des synthèses protéiques

Swaney *et al*. AAC, 1998; Bozdogan *et al*. IJAA, 2004

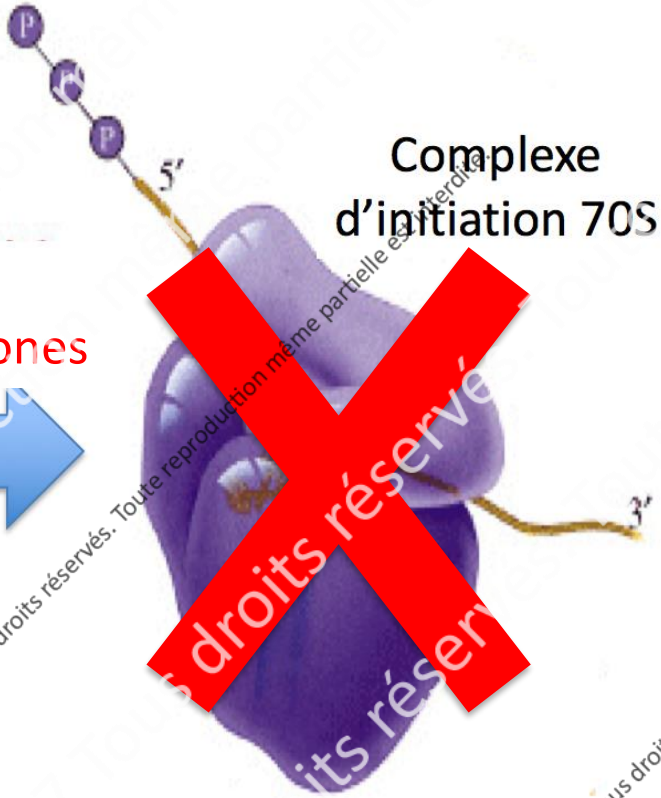
Mécanisme d'action

Sous unité 50S

Oxazolidinones

Complexe d'initiation 30S

Complexe d'initiation 70S

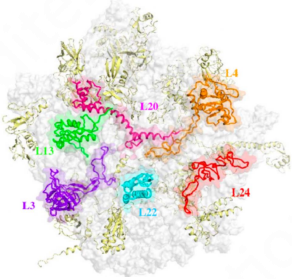


Arrêt des synthèses protéiques

+ si 70S déjà formé = arrêt de translocation de la chaine peptidique

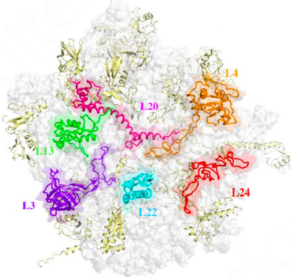
Swaney *et al*. AAC, 1998; Bozdogan *et al*. IJAA, 2004

Mécanismes de résistance aux oxazolidinones

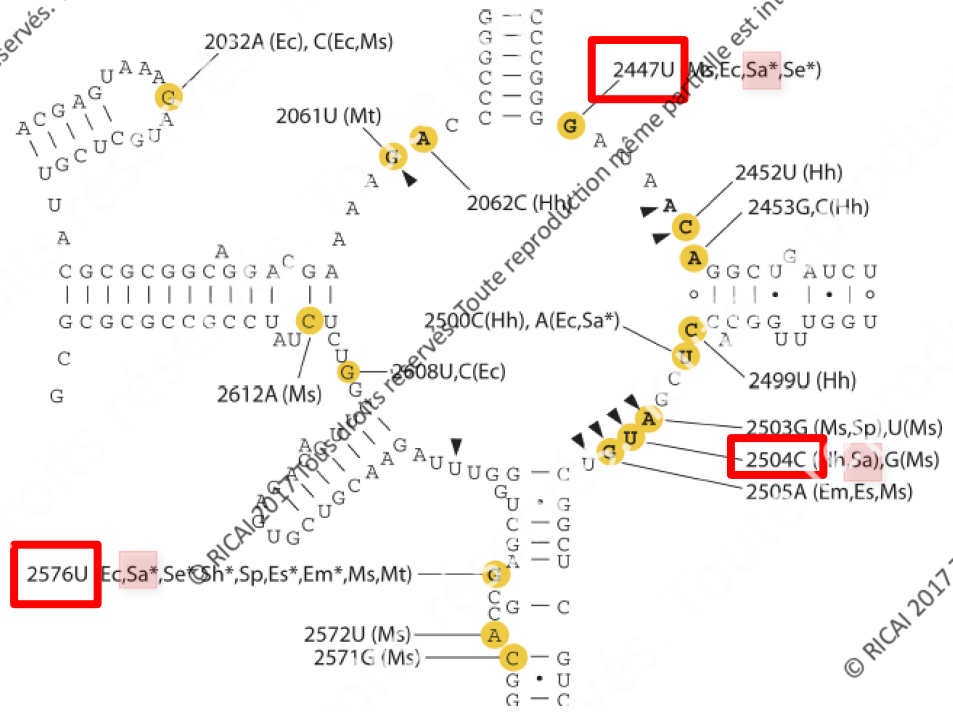


- **Mutations** de l'ARN 23S
- **Mutations** des protéines ribosomales
- **Méthylase** : gène *cfr*
- **ABC transporteur** : gène *optrA*

Mécanismes de résistance aux oxazolidinones



➢ Mutations de l'ARN 23S

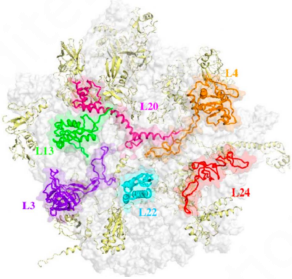


Augmentation CMI fonction du nombre de copies mutées

Strain Background	23S rRNA Gene Mutation	Proportion of Mutant Alleles	MIC (µg/ml) LNZ	MIC (µg/ml) TDZ
ATCC 29213 (MSSA)	wild-type	-	2	0.5
	G2447T	1/6	4	0.5
		2/6	8	1
		2/5	16	2
		3/5	32	4
		4/5	128	8
	T2500A	1/6	4	1
		2/6	8	2
ATCC 33591 (MRSA)	wild-type	-	1	0.25
	G2576T	1/6	4	0.5
		2/6	4	0.5
		3/6	16	1
		4/6	32	2
	T2571C/ G2576T	1/6	2	0.5
		2/6	4	1
		3/6	16	2

Locke et al, AAC 2009

Mécanismes de résistance aux oxazolidinones



- Mutations dans les protéines ribosomales L3, L4, L22

L3:

```
  1 MTKGILGRKI GMTQVFGENG FLIPVTVVEA KENVVLQKKT VEVDGYNAIQ
 51 VGFEDKKAYK KDAKSNKYAN KPAEGHAKKA DAAEKRFIRE FRNVDVDAYE
101 VGQEVSVDTF VAGDVIDVTG VSKGKGFQGA IKRHGQSRGP MSHGSHFHRA
151 PGSVGMASDA SRVFKGQKMP GRMGGNTVTV QNLEVVQVDT ENKVILVKGN
201 VPGPKKGLVE IRTSIKKGNK
```

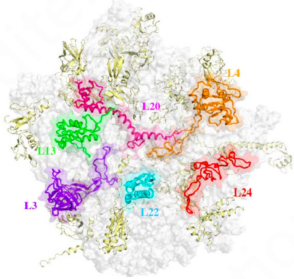
L4:

```
  1 MANYDVLKLD GTKSGSIELS DAVFGIEPNN SVLFEAINLQ RASLRQGTHA
 51 VKNRSAVSGG GRKPWKQKGT GRARQGTIRA PQWRGGGIVF GPTPRSYAYK
101 MPKKMRRLAL RSALSFKVQE NGLTVVDAFN FEAPKTKEFK NVLSTLEQPK
151 KVLVVTEKED VNVELSARNI PGVQVTTAQG LNVLDITNAD SLVITEAAAK
201 KVEEVLG
```

Strain Background	Mutation	MIC LZD (µg/mL)
ATCC 29213 (MSSA)	**WT**	0.5
	L3 (Gly155Arg)	1
	L3 (Gly155Arg + Met169Leu)	2
	L3 (ΔPhe127-His146)	2
ATCC 33591 (MRSA)	**WT**	0.25
	L3 (Gly155Arg)	0.5
	L4 (Lys68Gln)	0.5
	L3 (ΔPhe127-His146)	1

Locke et al, AAC 2009

Mécanismes de résistance aux oxazolidinones

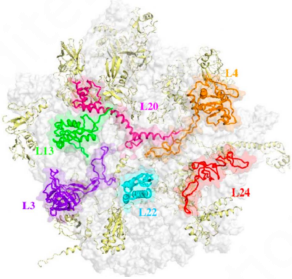


- Mutations de l'ARN 23S
- Mutations dans les protéines ribosomales L3, L4, L22

Strain	Mutation	MIC (µg/mL)		MIC Fold-shift	
		TDZ	LZD	TDZ	LZD
ATCC 29213 (MSSA)	wild-type	0.5	2		
	23S rRNA - T2500A (1/6)	1	4	2	2
	23S rRNA - T2500A (2/6)	2	8	4	4
	L3 - Gly155Arg/Met169Leu	2	8	4	4
	L3 - ΔPhe127-His146	2	8	4	4
ATCC 33591 (MRSA)	wild-type	0.25	1		
	23S rRNA - T2571C/ G2576T (1/6)	0.5	2	2	2
	23S rRNA - T2571C/ G2576T (2/6)	1	4	4	4
	23S rRNA - T2571C/ G2576T (3/6)	2	16	8	16
	L3 - Gly155Arg	0.5	2	2	2
	L3 - ΔPhe127-His146	1	4	4	4

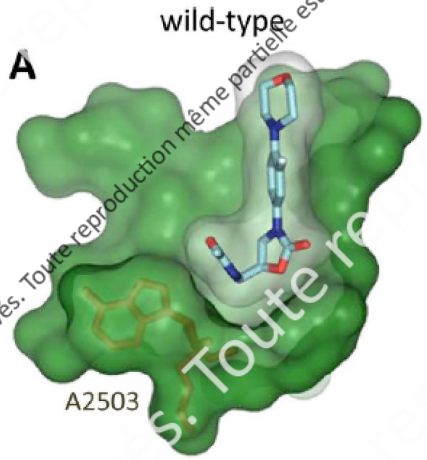
Locke et al. AAC, 2009

Mécanismes de résistance aux oxazolidinones

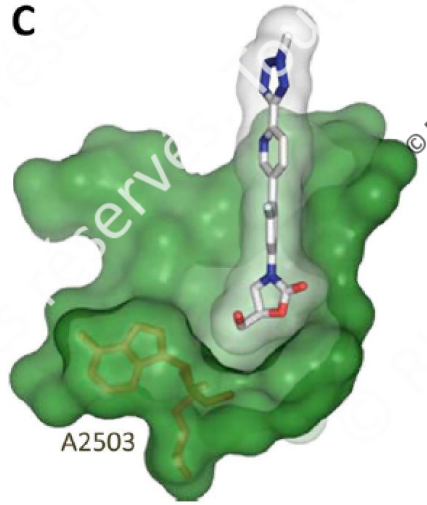


- **Méthylation** du ribosome : gène plasmidique ***cfr***

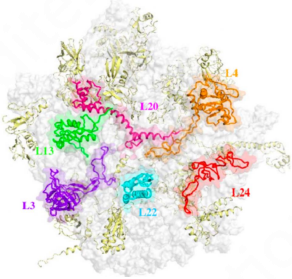
Linézolide



Tédizolide



Mécanismes de résistance aux oxazolidinones



- **Méthylation** du ribosome : gène plasmidique ***cfr***

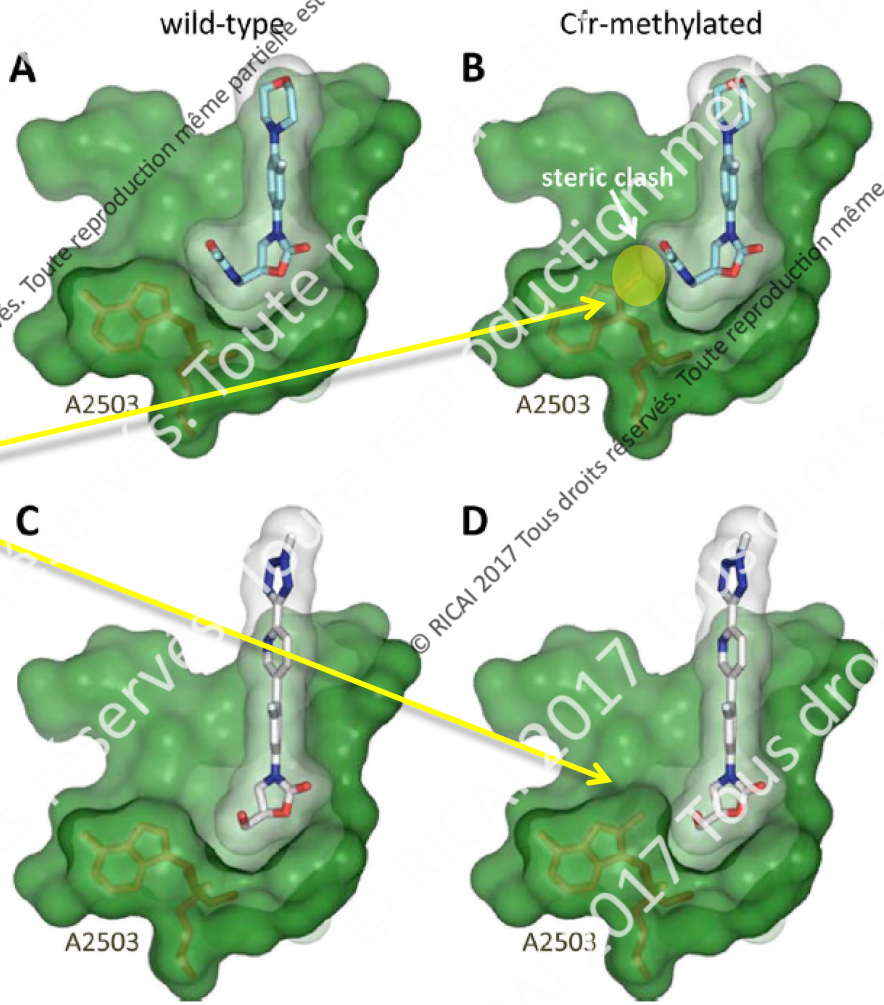
Linézolide

gène cfr

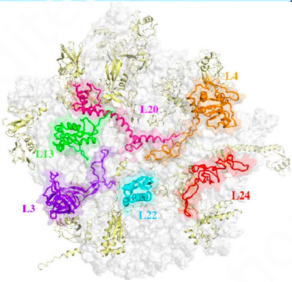
↓

méthylase

Tédizolide



Mécanismes de résistance aux oxazolidinones



➢ **Méthylation** du ribosome : gène plasmidique ***cfr***

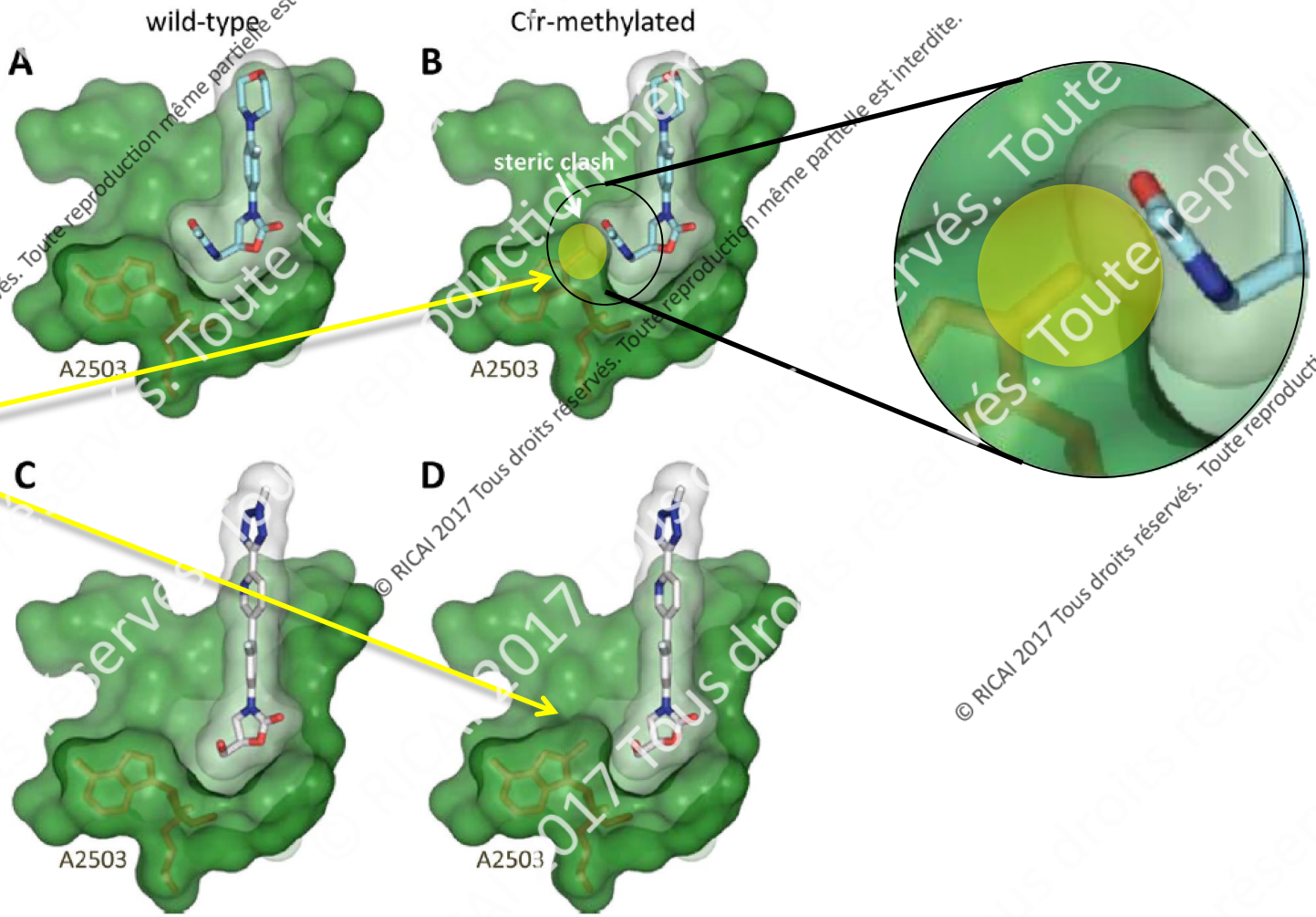
Linézolide

gène cfr

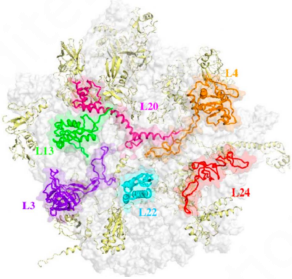
↓

méthylase

Tédizolide



Mécanismes de résistance aux oxazolidinones



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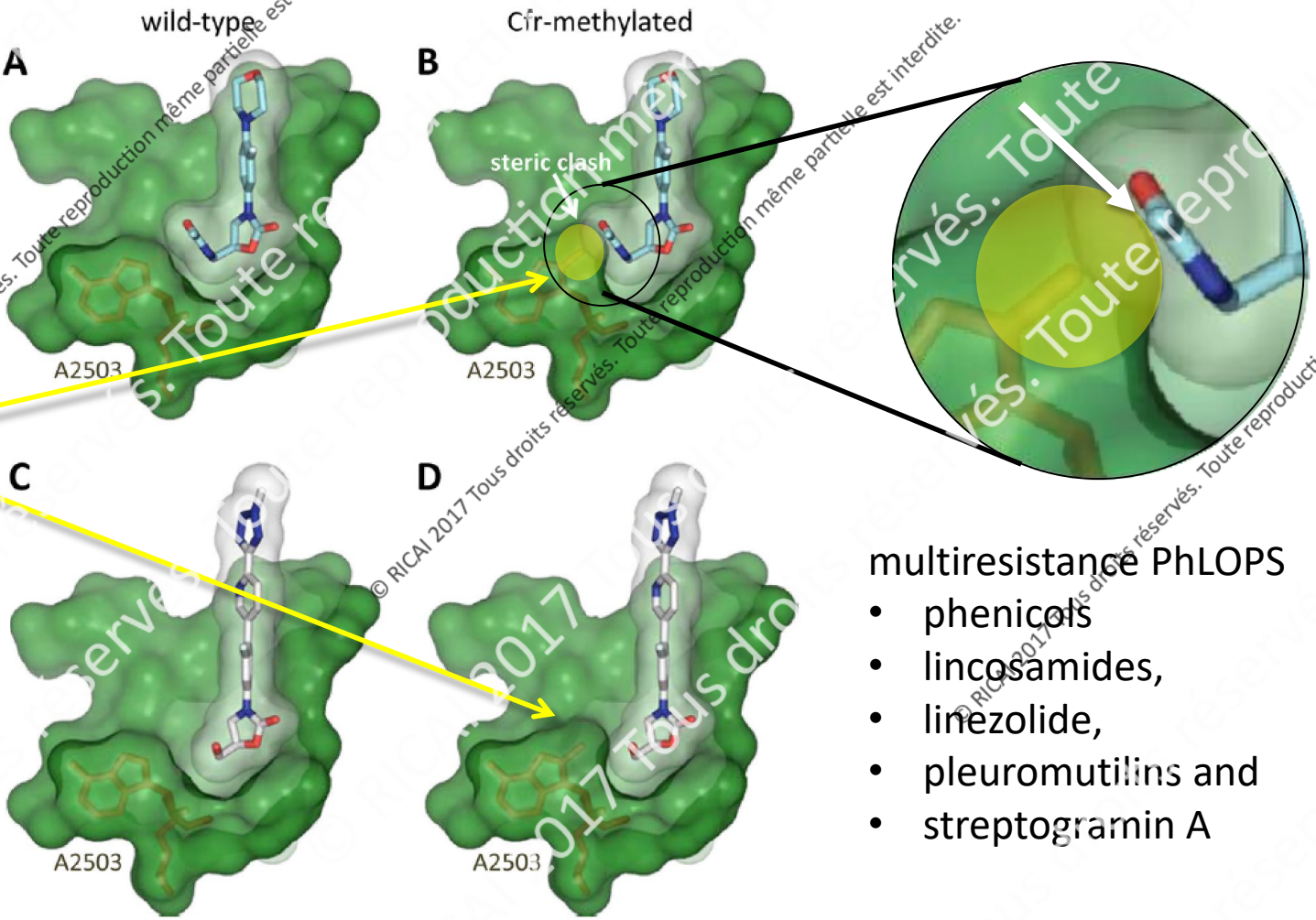
Linézolide

gène cfr

↓

méthylase

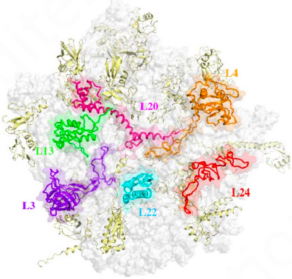
Tédizolide



multiresistance PhLOPS

- phenicols
- lincosamides,
- linezolide,
- pleuromutilins and
- streptogramin A

Mécanismes de résistance aux oxazolidinones



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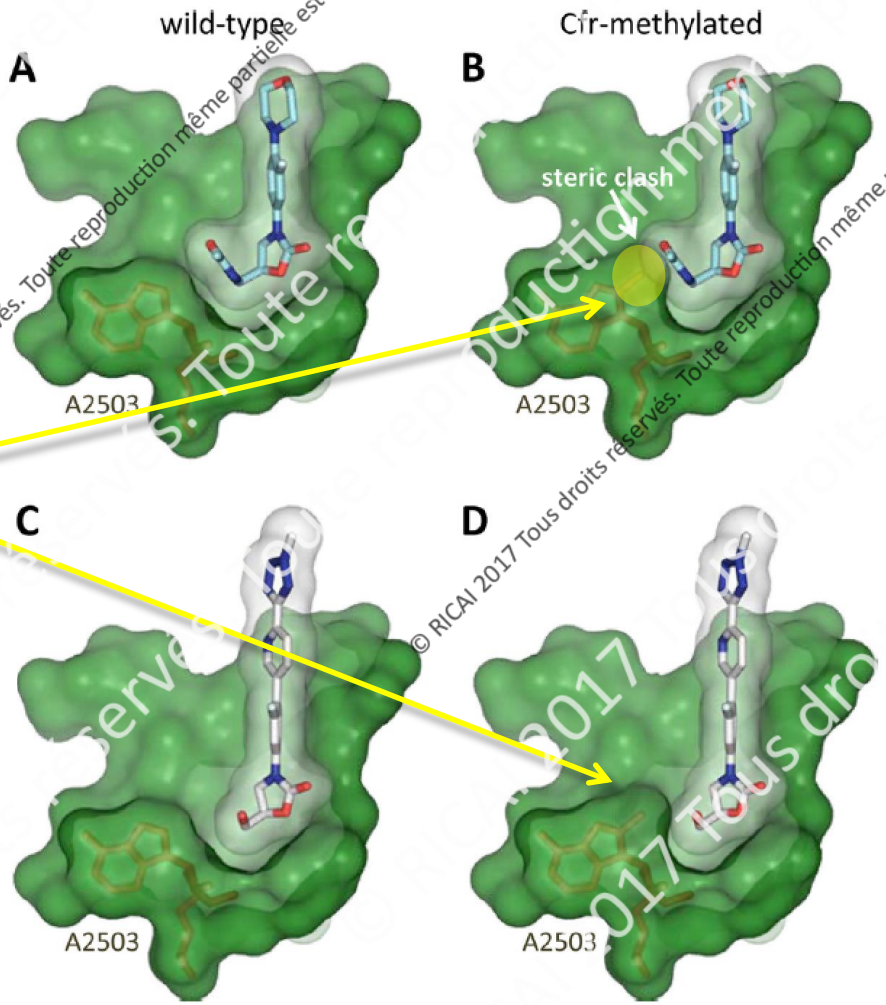
Linézolide

gène cfr

↓

méthylase

Tédizolide



Sous-unité 50S méthylée :

- Diminution +++ de l'accessibilité du LZD
- Augmentation ++ CMI

Sous-unité 50S méthylée :

- pas de modification de l'accessibilité du TZD

Mécanismes de résistance aux oxazolidinones

- **Méthylation** du ribosome : gène plasmidique ***cfr***

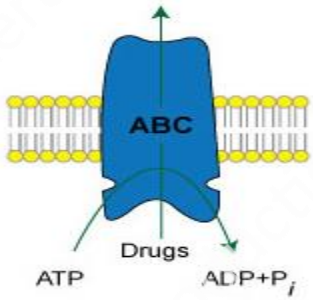
Strain	Reference	Presence of *cfr*	MIC (μg/ml)	
			LZD	TDZ
RN4220(pLI50)	68	−	2	0.5
RN4220(pLXM1)[b]	68	+	8	0.5
CM05Δ[c]	44	−	2	0.5
CM05[c]	68	+	8	0.5
29213	ATCC	−	2	0.5
29213(p42262)[d]	45	+	16	0.5
42262[e]	51	+	16	0.5

[a] MICs (broth microdilution; CLSI) were performed against the oxazolidinone panel (Fig. 1). VAN, vancomycin; RZD, radezolid.
[b] The pLXM1 *cfr*-containing plasmid is isogenic to the empty pLI50 vector.
[c] CM05Δ is isogenic to the CM05 clinical *cfr*-positive strain but lacks *cfr* and one copy of *ermB*.
[d] 29213(p42262) was generated through transformation of ATCC 29213 with the p42262 *cfr*-containing plasmid isolated from strain 42262.
[e] 42262 is a clinical *cfr*-positive isolate from a 2008 hospital outbreak in Madrid, Spain.

Locke et al, AAC 2010

Pas d'impact du gène *cfr* sur les CMI du tédizolide

Mécanismes de résistance aux oxazolidinones



- **ABC transporteur**: nouveau gène *optrA*

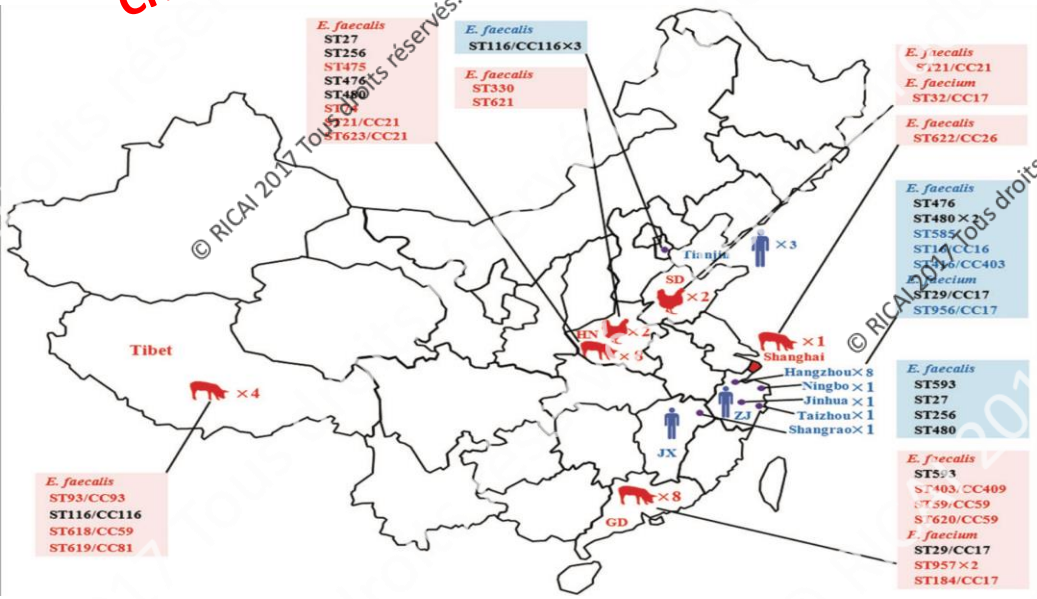
J Antimicrob Chemother 2015; 70: 2182–2190
doi:10.1093/jac/dkv116 Advance Access publication 14 May 2015

Journal of Antimicrobial Chemotherapy

A novel gene, *optrA*, that confers transferable resistance to oxazolidinones and phenicols and its presence in *Enterococcus faecalis* and *Enterococcus faecium* of human and animal origin

Yang Wang[1]†, Yuan Lv[2]†, Jiachang Cai[3]†, Stefan Schwarz[4]†, Lanqing Cui[2], Zhidong Hu[5], Rong Zhang[3], Jun Li[1], Qin Zhao[1], Tao He[1], Dacheng Wang[6], Zheng Wang[1], Yingbo Shen[1], Yun Li[2], Andrea T. Feßler[4], Congming Wu[1], Hao Yu[6], Xuming Deng[6], Xi Xia[7] and Jianzhong Shen[1]*

CHINE



Bacterial isolate	MIC (mg/L) CHL	FFC	LZD	TZD	VAN
Clinical *E. faecalis* E349 (with *optrA*-carrying pE349)	64	64	8	2	1
E. faecalis FA2-2	4	2	2	0.5	1
Transconjugant *E. faecalis* FA2-2-E349	32	64	8	2	1

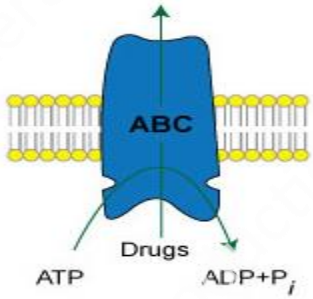
Resistance PhLOPS

- phenicols
- oxazolidinones,
- chloramphenicol

optrA impacte les CMI du LZD et TZD

Mécanismes de résistance aux oxazolidinones

- **ABC transporteur**: nouveau gène *optrA*



J Antimicrob Chemother 2017; **72**: 3245–3251
doi:10.1093/jac/dkx321 Advance Access publication 26 September 2017

Journal of Antimicrobial Chemotherapy

Detection of *optrA* in the African continent (Tunisia) within a mosaic *Enterococcus faecalis* plasmid from urban wastewaters

Ana R. Freitas[1†], Houyem Elghaieb[2†], Ricardo León-Sampedro[3–5], Mohamed Salah Abbassi[2], Carla Novais[1], Teresa M. Coque[3–5], Abdennaceur Hassen[6] and Luisa Peixe[1*]

J Antimicrob Chemother 2017; **72**: 678–683
doi:10.1093/jac/dkw490 Advance Access publication 15 December 2016

Journal of Antimicrobial Chemotherapy

Detection of linezolid resistance due to the *optrA* gene in *Enterococcus faecalis* from poultry meat from the American continent (Colombia)

L. M. Cavaco[1*], J. F. Bernal[2,3], E. Zankari[1], M. León[2,3], R. S. Hendriksen[1], E. Perez-Gutierrez[4], F. M. Aarestrup[1] and P. Donado-Godoy[2,3]

collection de souches de 2010–11

J Antimicrob Chemother 2017; **72**: 614–633
doi:10.1093/jac/dkw488
Advance Access publication 20 December 2016

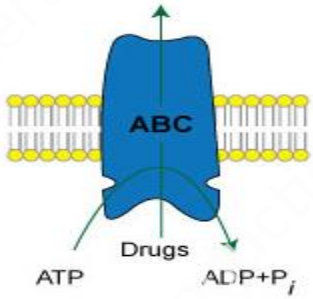
Retrospective analysis of genome sequences revealed the wide dissemination of *optrA* in Gram-positive bacteria

Jinhu Huang[1], Li Chen[1], Zuowei Wu[2] and Liping Wang[1*]

Enterococcus
Streptococcus suis
metagenome de lisier

Mécanismes de résistance aux oxazolidinones

- **ABC transporteur**: nouveau gène *optrA*



J Antimicrob Chemother 2017; **72**: 3245–3251
doi:10.1093/jac/dkx321 Advance Access publication 26 September 2017

Journal of Antimicrobial Chemotherapy

Detection of *optrA* in the African continent (Tunisia) within a mosaic *Enterococcus faecalis* plasmid from urban wastewaters

Ana R. Freitas[1†], Houyem Elghaieb[2†], Ricardo León-Sampedro[3–5], Mohamed Salah Abbassi[2], Carla Novais[1], Teresa M. Coque[3–5], Abdennaceur Hassen[6] and Luisa Peixe[1*]

J Antimicrob Chemother 2017; **72**: 678–683
doi:10.1093/jac/dkw490 Advance Access publication 15 December 2016

Journal of Antimicrobial Chemotherapy

Detection of linezolid resistance due to the *optrA* gene in *Enterococcus faecalis* from poultry meat from the American continent (Colombia)

L. M. Cavaco[1*], J. F. Bernal[2,3], E. Zankari[1], M. Léon[2,3], R. S. Hendriksen[1], E. Perez-Gutierrez[4], F. M. Aarestrup[1] and P. Donado-Godoy[2,3]

collection de souches de 2010–11

J Antimicrob Chemother 2017; **72**: 614–633
doi:10.1093/jac/dkw488
Advance Access publication 20 December 2016

Retrospective analysis of genome sequences revealed the wide dissemination of *optrA* in Gram-positive bacteria

Jinhu Huang[1], Li Chen[1], Zuowei Wu[2] and Liping Wang[1*]

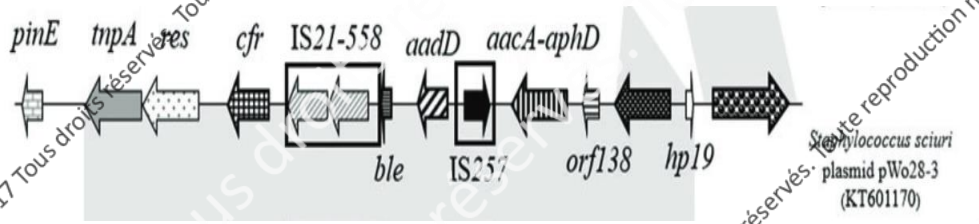
Enterococcus
Streptococcus suis
metagenome de lisier

J Antimicrob Chemother 2016; **71**: 1474–1478
doi:10.1093/jac/dkw040 Advance Access publication 5 March 2016

Journal of Antimicrobial Chemotherapy

Co-location of the oxazolidinone resistance genes *optrA* and *cfr* on a multiresistance plasmid from *Staphylococcus sciuri*

Dexi Li[1], Yang Wang[1], Stefan Schwarz[1,2], Jiacheng Cai[3], Run Fan[1], Jun Li[1,2], Andrea T. Feßler[2], Rong Zhang[3], Congming Wu[1] and Jianzhong Shen[1*]

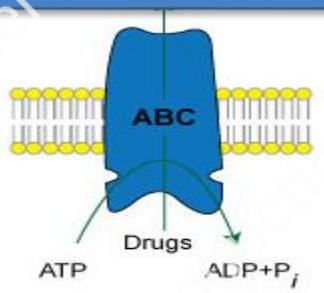


Isolate	CHL	FFC	LZD	TED	TIA	CLI	ERY	TET	SPT	GEN	KAN	NEO	BLE
	MIC (mg/L)												
S. sciuri Wo28-3	128	>512	16	4	128	>256	>128	64	128	64	64	4	8
S. aureus RN4220	8	4	2	0.5	≤0.5	≤0.0625	2	≤0.5	16	0.25	0.25	0.25	0.25
Transformant RN4220/pWo28-3	128	>512	16	4	128	>256	2	≤0.5	16	64	64	4	8

Mécanismes de résistance aux oxazolidinones

Staphylococcus sciuri

- *cfr* seul ou associé à *optr*A
- différents plasmides porteurs



Veterinary Microbiology 210 (2017) 43–46

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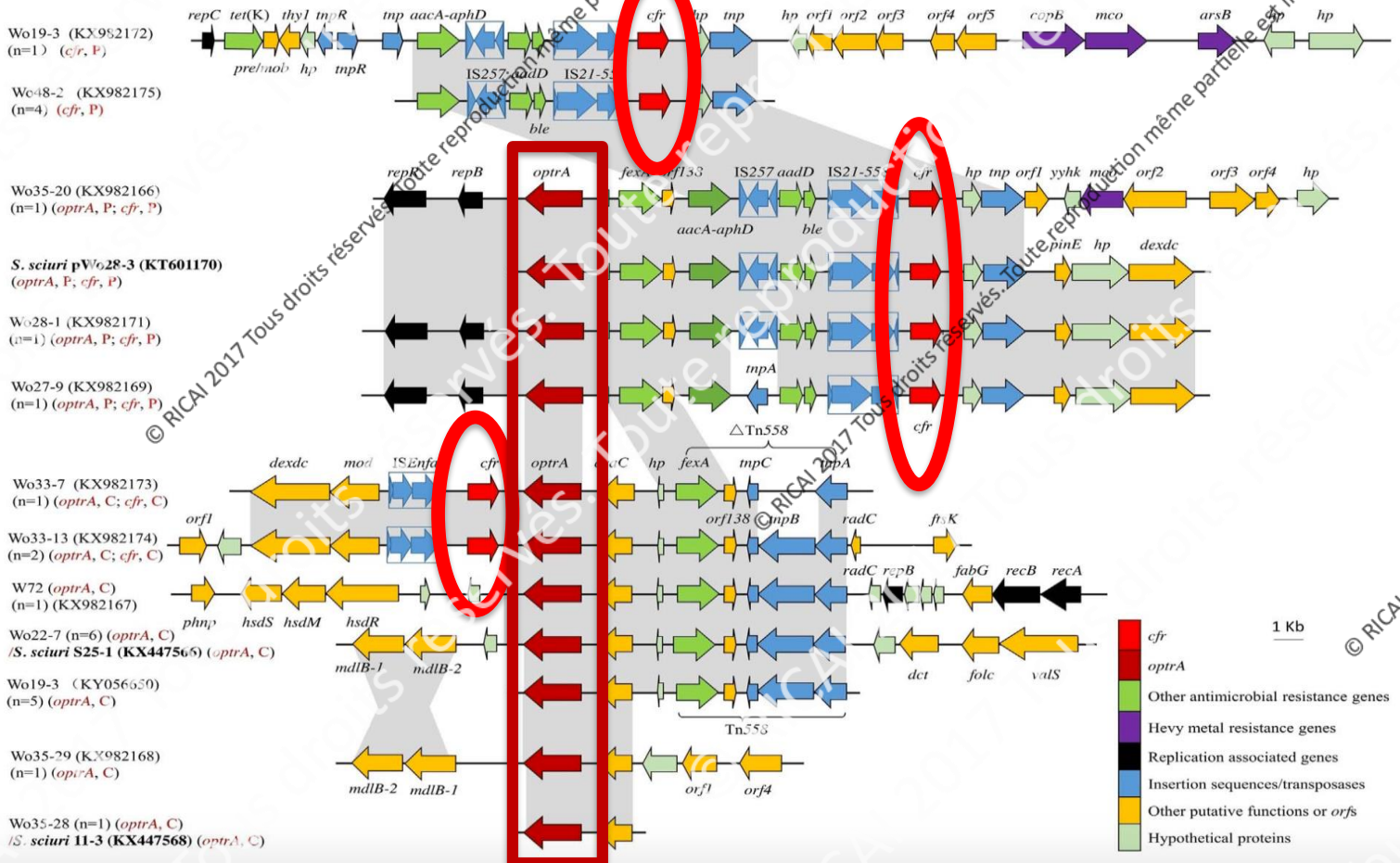
journal homepage: www.elsevier.com/locate/vetmic

Distribution of *optrA* and *cfr* in florfenicol-resistant *Staphylococcus sciuri* of pig origin

Run Fan[a,1], Dexi Li[a,c,1], Andrea T. Feßler[b], Congming Wu[a], Stefan Schwarz[a,b,**], Yang Wang[a,**]

[a] Beijing Advanced Innovation Center for Food Nutrition and Human Health, College of Veterinary Medicine, China Agricultural University, Beijing, 100193, PR China
[b] Institute of Microbiology and Epizootics, Center for Infection Medicine, Department of Veterinary Medicine, Freie Universität Berlin, Robert-von-Ostertag-Str. 7-13, 14163 Berlin, Germany
[c] College of Animal Husbandry and Veterinary Medicine, Henan Agricultural University, Zhengzhou, 450002, PR China

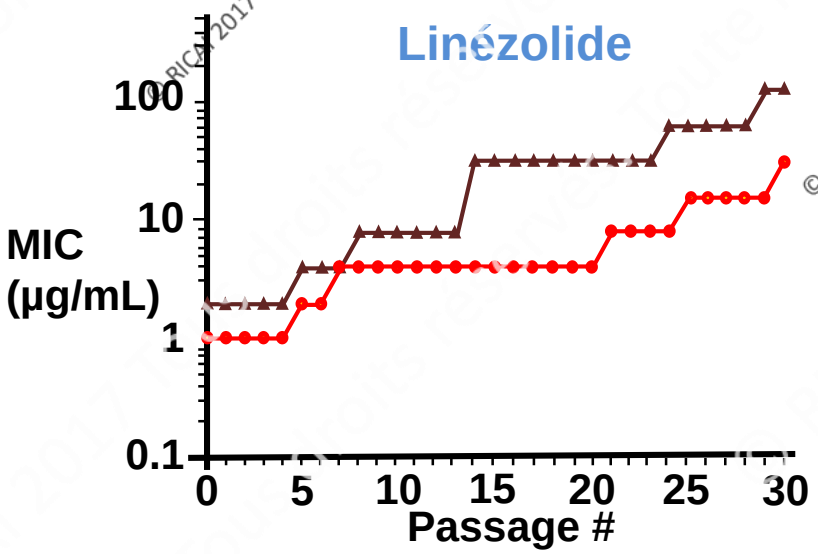


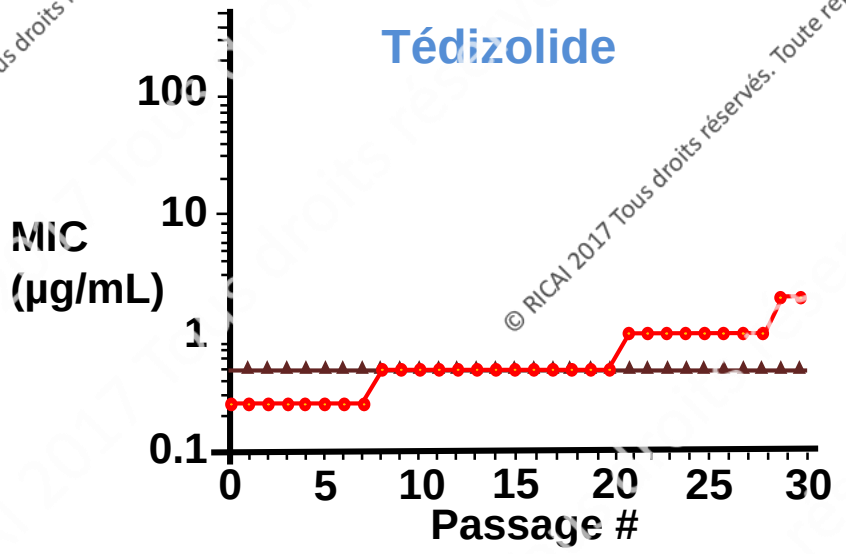
Résistances aux oxazolidinones : sélection, émergence et dissémination

Résistances aux oxazolidinones : sélection, émergence et dissémination

Pression de sélection et sélection de mutants résistants

Strain	Antibiotique Selection	Frédquence de Mutations 23S	
		Linézolide	Tédizolide
S. aureus ATCC 29213 (MSSA)	2× MIC	2.0×10^{-9}	1.1×10^{-10}
	4× MIC	ND	$<4.5\times10^{-10}$
S. aureus ATCC 33591 (MRSA)	2× MIC	3.0×10^{-9}	1.9×10^{-10}
S. aureus USA300-0114 (MRSA)	4× MIC	ND	$<4.5\times10^{-10}$
E. faecalis ATCC 29212 (VanS)	4× MIC	$<5.7\times10^{-11}$	$<5.7\times10^{-11}$
E. faecalis ATCC 700802 (VanR)	4× MIC	$<6.1\times10^{-11}$	$<6.1\times10^{-11}$
S. pyogenes ATCC 49399	4× MIC	$<1.0\times10^{-10}$	$<1.0\times10^{-10}$
S. agalactiae ATCC 13813	4× MIC	$<3.1\times10^{-10}$	$<3.1\times10^{-10}$





Résistances aux oxazolidinones : sélection, émergence et dissémination

Pression de sélection et sélection de **mutants** résistants

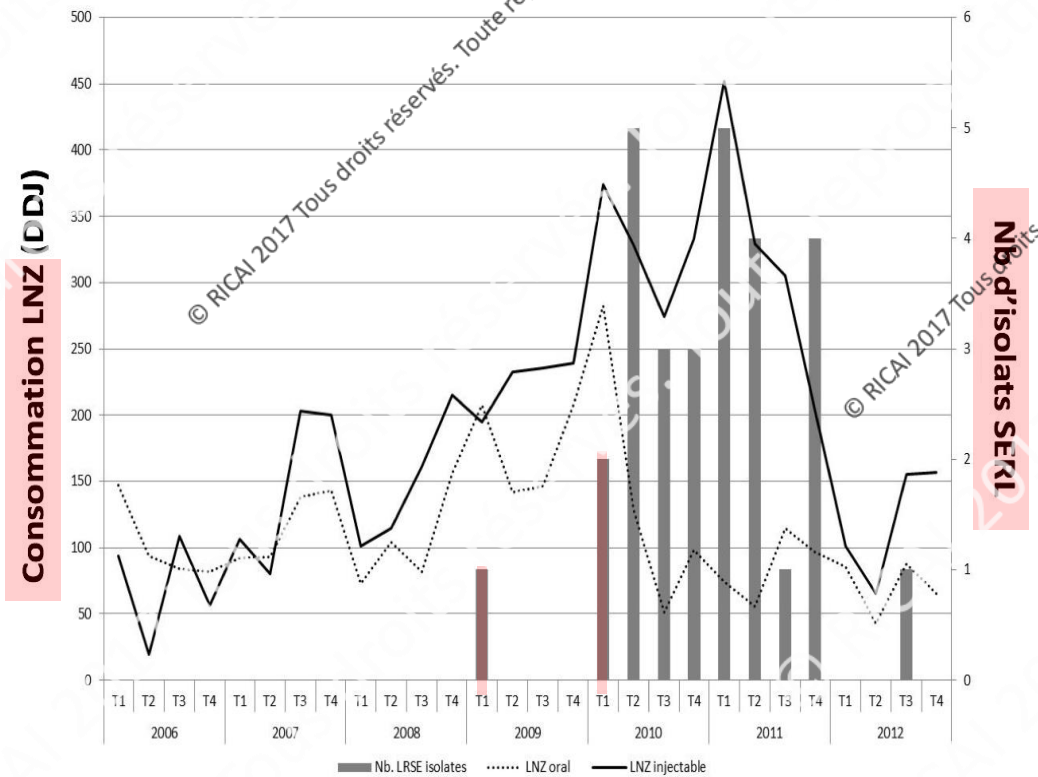
- **Toulouse – Hôpital Rangueil et Hôpital Purpan, 2009-2012**
- Hémoculture (n=30), plaie (n=4), urines (n=3), liq peritoneal (n=1), liq pleural (n=1)
- 39 souches de ***S. epidermidis*** ST2 – **Meti-R KTG fus Van - co CMI linézolide > 256 mg/L** (SERL)

  23S : mutation T2504A (2/6)

  L3: Gly152Asp, Asp159Glu, Ala160Pro

  cfr- / optrA-

Emergence et diffusion locale



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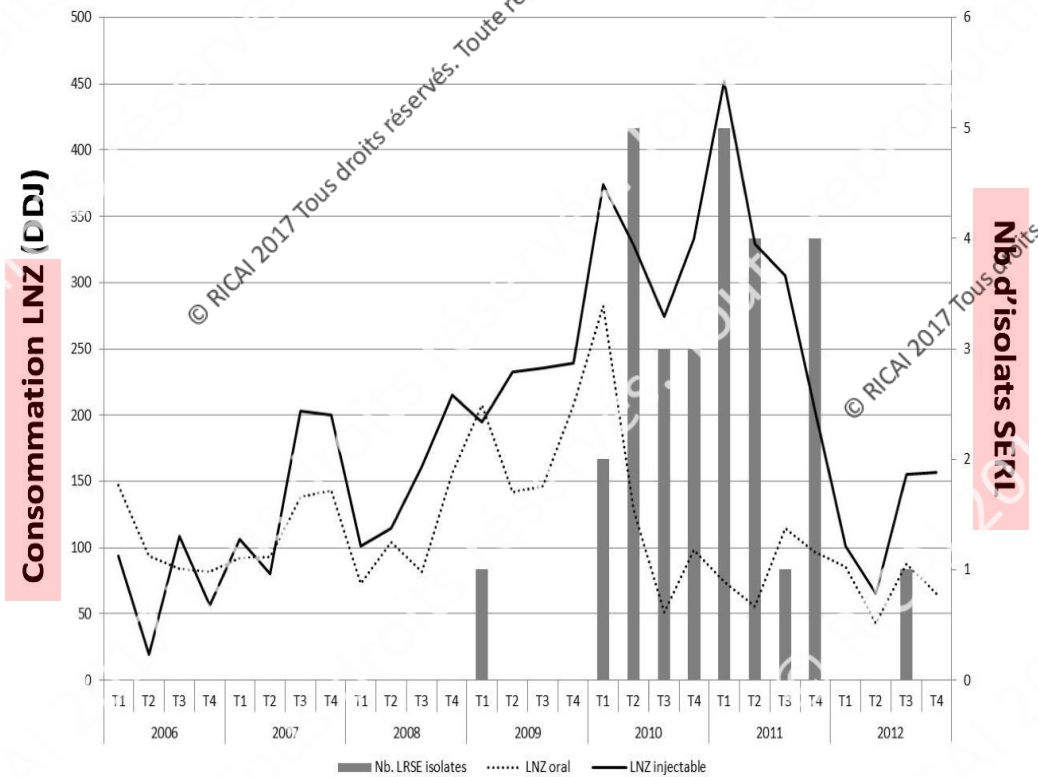

Diffusion nationale

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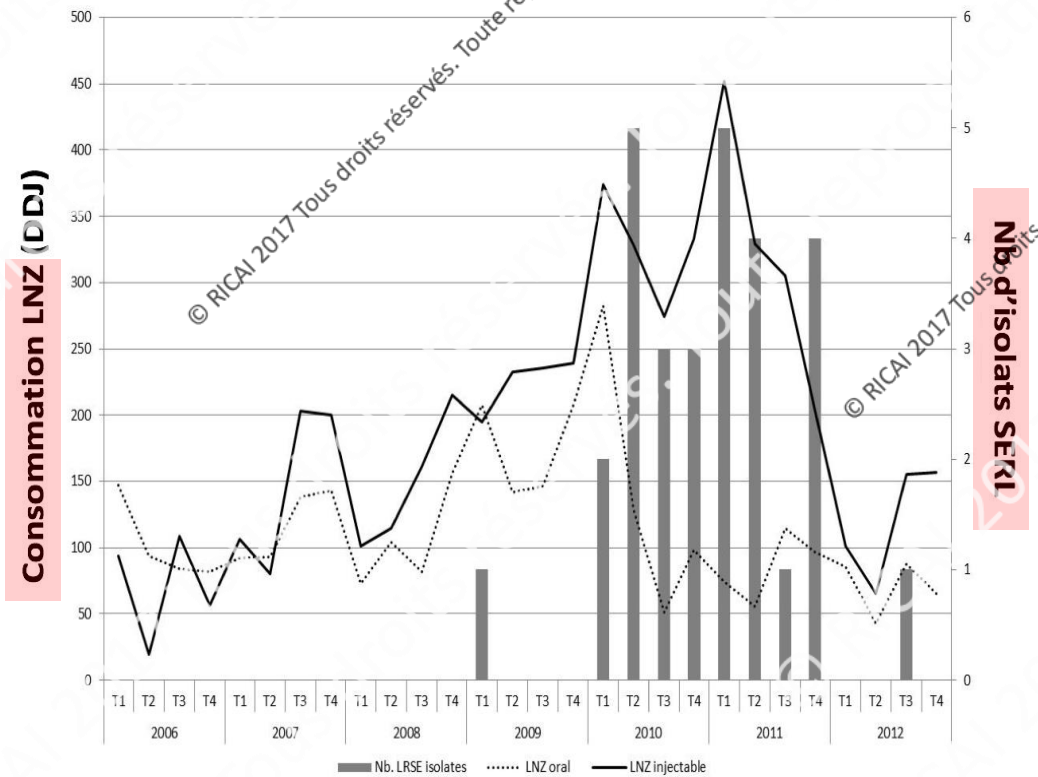

Diffusion nationale

Résistances aux oxazolidinones : sélection, émergence et dissémination

Pression de sélection et sélection de mutants résistants

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M. Butin[1,2]*, P. Martins-Simões[1–3], B. Pichon[4], D. Leyssene[5], S. Bordes-Couecou[5], H. Meugnier[1–3], C. Rouard[6], N. Lemaitre[7], F. Schramm[8], A. Kearns[4], T. Spiliopoulou[9], H.-L. Hyyryläinen[10], O. Dumitrescu[1–3], F. Vandenesch[1–3], C. Dupieux[1–3] and F. Laurent[1–3]

Table 1. Clinical, epidemiological and demographic data for nine LZR *S. capitis* cases from France

Isolate	Setting	Date of isolation	Site	Age	Sex	Comorbidities	Prior linezolid therapy	Time to isolation of LZR *S. capitis* (days)
ST20130790	ICU 1	14/05/2013	blood	63	M	colic cancer	yes	11
ST20131315	ICU 1	23/06/2013	blood	59	M	cerebral haemorrhage	yes	8
ST20140272	ICU 1	30/01/2014	catheter	69	M	chronic respiratory failure	no	–
ST20142047	ICU 1	29/11/2014	catheter	43	M	pancreatitis	no	–
ST20150040	ICU 1	27/12/2014	wound	78	M	cerebral stroke	no	–
ST20140480	ICU 2	24/08/2013	blood	55	M	chronic respiratory failure	yes	42
ST20140482	ICU 2	23/11/2013	blood	56	M	chronic respiratory failure	yes	42
ST20140578	ICU 3	18/03/2014	peritoneal	74	M	pancreatitis	yes	32
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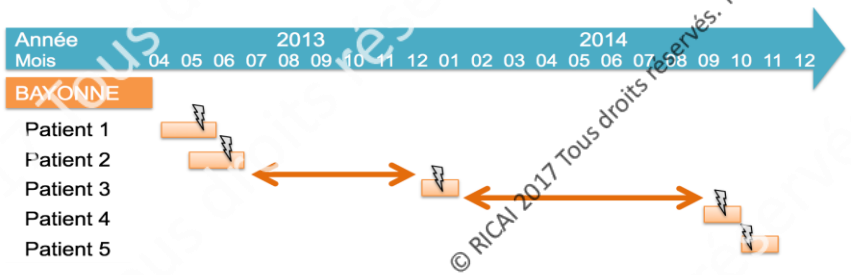

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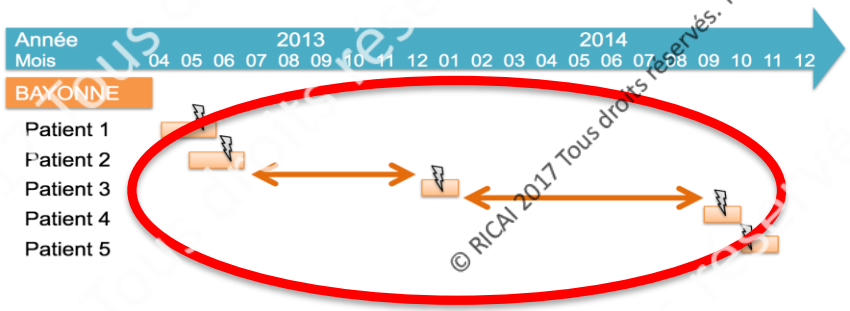

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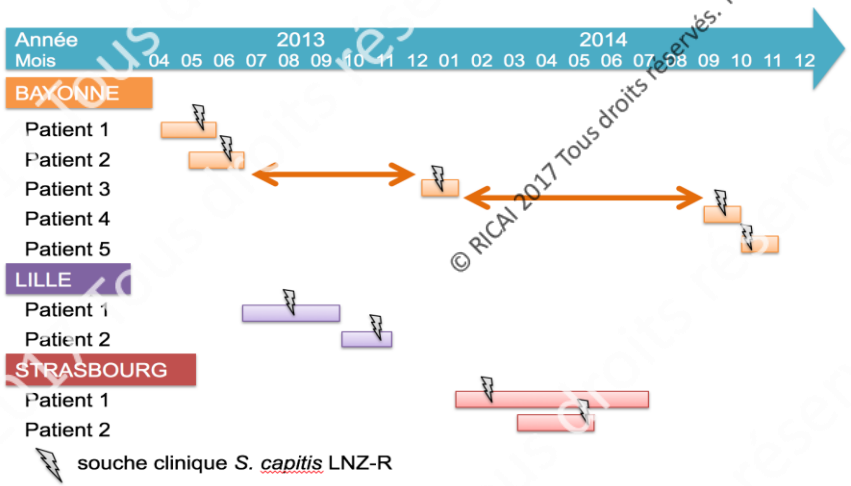

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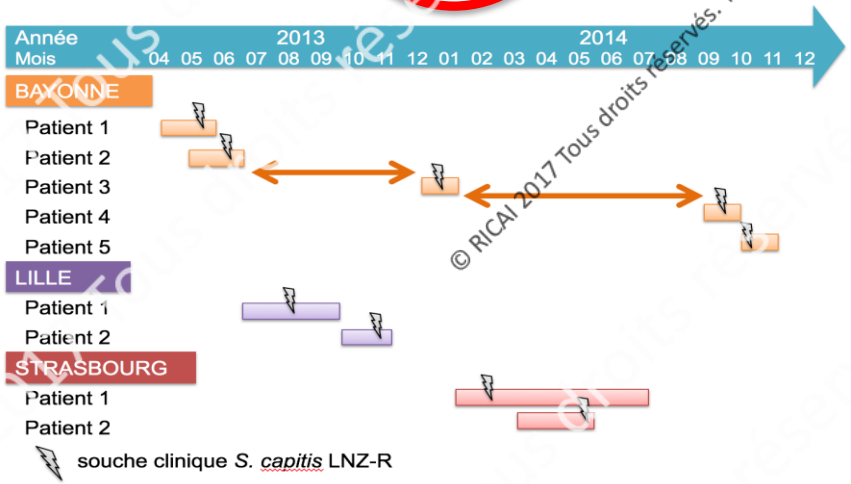

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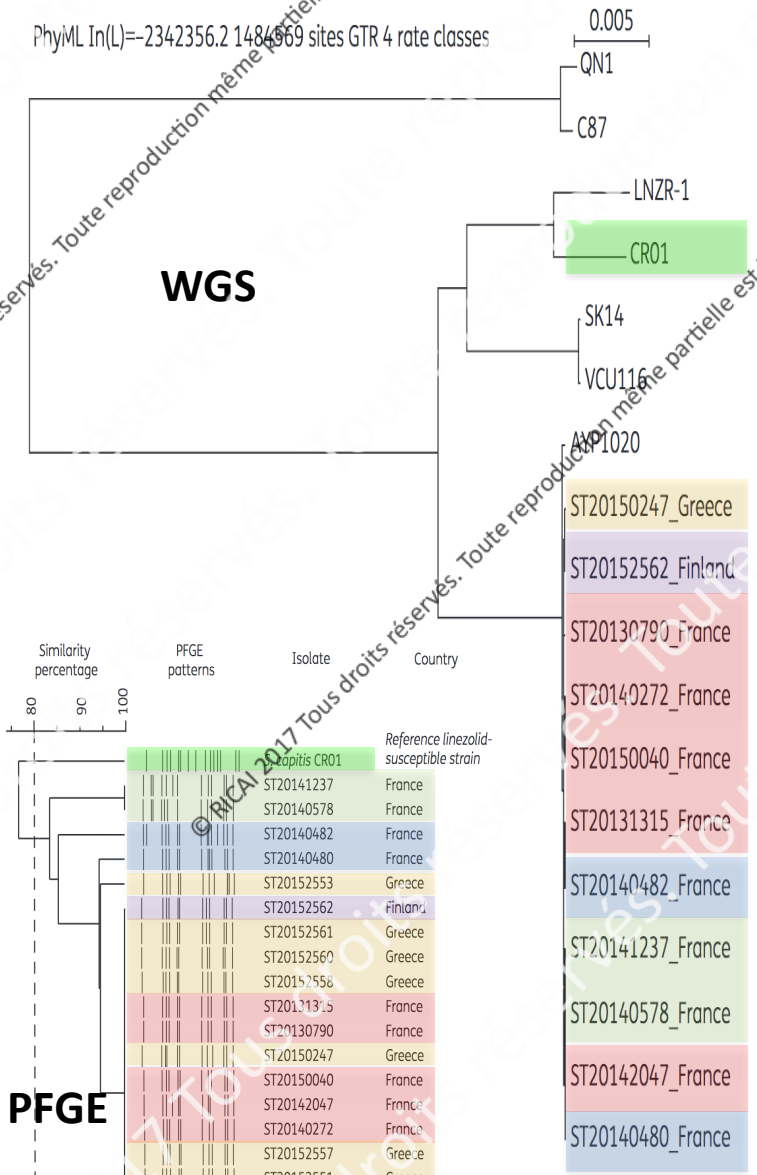

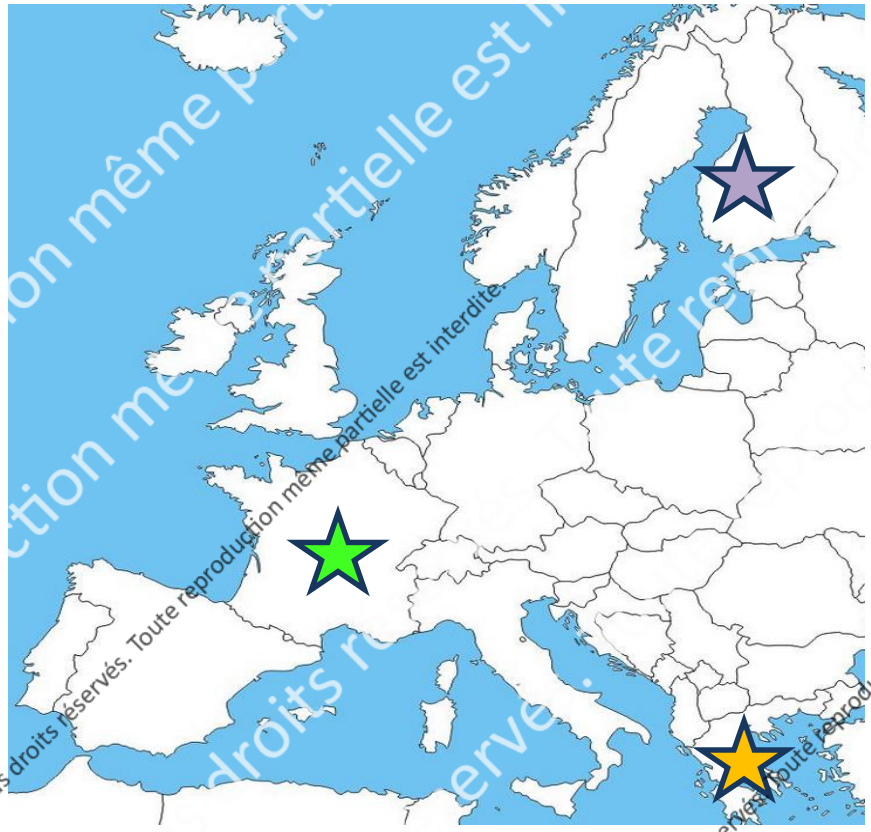

Au final : espèce *S. capitis*

- espèce classiquement non pathogène
- acquisition de mutations
- transmission sans pression de sélection
- maintien longtemps comme colonisant/contaminant
- endémique (sur plusieurs années)
- large diffusion géographique ! voie de dissémination ?

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Isolate	Country	No. of 23S mutated copies[a]	Antimicrobial susceptibility: LZD MIC	ERY	TET	OFX	SXT	RIF	FUS	VAN (MIC)	TEC (MIC)	DAP (MIC)
ST20130790	France	3/6	12.0	S	S	I	R	R	R	S (2.0)	S (4.0)	R (2.0)
ST20131315	France	5/6	64.0	S	S	R	R	R	R	S (3.0)	R (6.0)	R (2.0)
ST20140272	France	5/6	>256.0	S	S	S	S	S	R	S (2.0)	R (6.0)	R (2.0)
ST20142047	France	3/6	>256.0	R	S	R	I	R	R	S (2.0)	S (1.5)	S (1.0)
ST20150040	France	5/6	>256.0	I	S	R	I	R	R	S (1.0)	S (1.0)	S (0.5)
ST20140480	France	5/6	>256.0	S	S	R	S	R	S	S (2.0)	S (0.5)	R (2.0)
ST20140482	France	5/6	>256.0	S	S	R	S	R	S	S (1.5)	S (0.38)	S (1.0)
ST20140578	France	4/6	>256.0	S	S	R	I	R	S	S (2.0)	S (3.0)	S (1.0)
ST20141237	France	4/6	>256.0	I	I	R	S	R	S	S (2.0)	R (6.0)	S (1.0)
ST20150247	Greece	unknown	8.0	S	S	R	R	R	R	S (1.5)	S (0.38)	S (0.75)
ST20152551	Greece	unknown	48.0	S	S	R	R	R	R	S (1.5)	S (0.5)	R (1.5)
ST20152552	Greece	unknown	>256.0	S	S	R	R	R	R	S (1.5)	S (0.38)	S (1.0)
ST20152553	Greece	unknown	>256.0	S	S	R	R	R	R	S (1.5)	S (0.5)	S (0.75)
ST20152554	Greece	unknown	24.0	S	S	R	R	R	R	S (1.5)	S (0.5)	S (1.0)
ST20152555	Greece	unknown	32.0	S	S	S	S	S	S	S (1.5)	S (0.5)	R (1.5)
ST20152556	Greece	unknown	>256.0	S	S	R	R	R	R	S (1.5)	S (0.38)	R (1.5)
ST20152557	Greece	unknown	32.0	S	S	R	R	R	R	S (1.5)	S (0.5)	R (1.5)
ST20152558	Greece	unknown	24.0	S	S	R	R	R	R	S (1.25)	S (0.38)	R (1.25)
ST20152560	Greece	unknown	32.0	S	S	R	R	R	R	S (1.5)	S (0.5)	R (1.5)
ST20152561	Greece	unknown	32.0	S	S	R	R	R	R	S (1.0)	S (0.25)	R (1.5)
ST20152562	Finland	unknown	96.0	S	S	R	S	R	R	S (1.5)	S (0.38)	R (1.5)

Résistances aux oxazolidinones : sélection, émergence et dissémination

Acquisition de gènes de résistance

Résistances aux oxazolidinones : sélection, émergence et dissémination

Acquisition de gènes de résistance

J Antimicrob Chemother 2016; **71**: 587–592
doi:10.1093/jac/dkv391 Advance Access publication 11 December 2015

Journal of Antimicrobial Chemotherapy

Horizontal gene transmission of the *cfr* gene to MRSA and *Enterococcus*: role of *Staphylococcus epidermidis* as a reservoir and alternative pathway for the spread of linezolid resistance

Fabio Cafini[1,2*], Le Thuy Thi Nguyen[2,3], Masato Higashide[4], Federico Román[5], José Prieto[5] and Kazuya Morikawa[2]

Expérience de conjugaison avec plasmide pSCFS7/cfr+
. *S. epidermidis* SE45 : 100% MRSA et fréq 8.6×10^{-5}
. *S. epidermidis* SE50 : <50% MRSA et fréq 5.2×10^{-9}

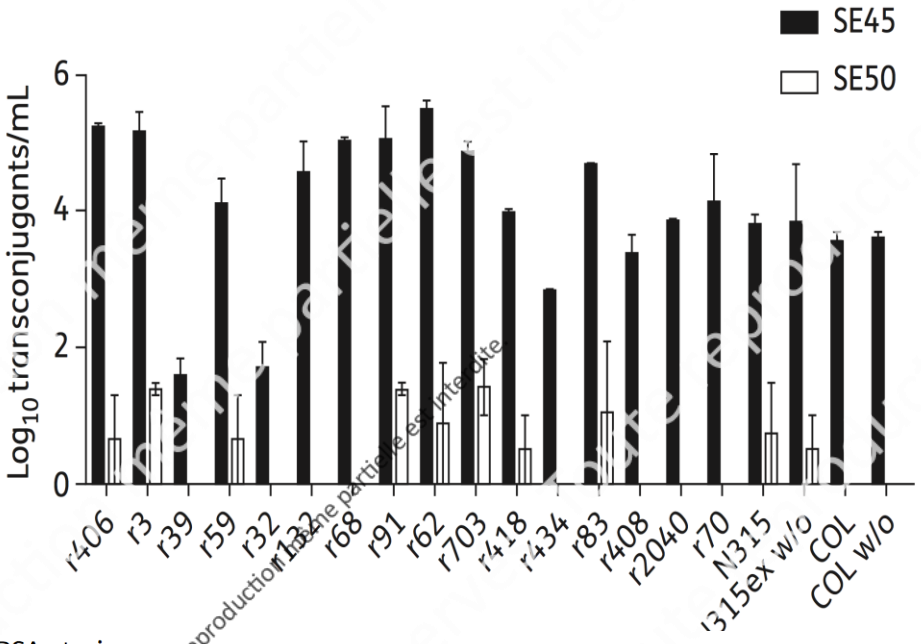

Table 1. Investigation of HGT mechanisms involved in *cfr* transmission in MRSA strains

HGT	Donor	Recipient	Frequency
Conjugation	N315-45	COL	1.00×10^{-6}
	N315-45	Mu50	1.29×10^{-5}
Transduction	N315-45	N315	6.88×10^{-10}
	N315-45	COL	1.00×10^{-11}
	N315-45	Mu50	3.68×10^{-10}
Transformation	plasmids (COL-45)	N2-2.1	under the limit of detection
	whole DNA (COL-45)	N2-2.1	under the limit of detection

- Conjugaison SCN- SA : possible mais variable
- Une fois présent chez *S. aureus* transfert efficace inter *S. aureus* ++
  par conjugaison et transduction mais pas tranformation

Résistances aux oxazolidinones : sélection, émergence et dissémination

Acquisition de gènes de résistance

4 *S. epidermidis* ST2 cfr+

1 *S. aureus* cfr+

2 *S. epidermidis* ST2 cfr+

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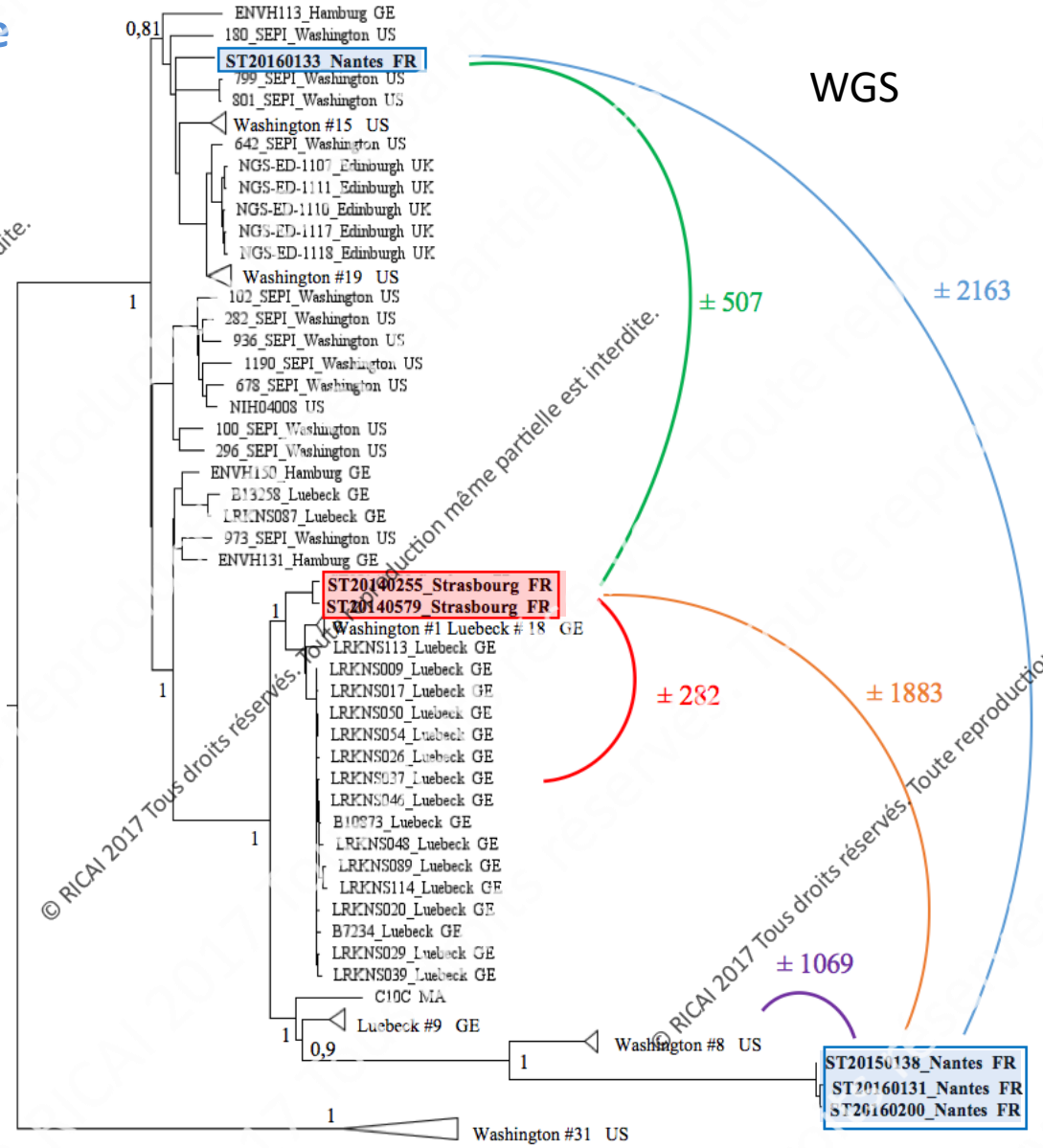

Résistances aux oxazolidinones : sélection, émergence et dissémination

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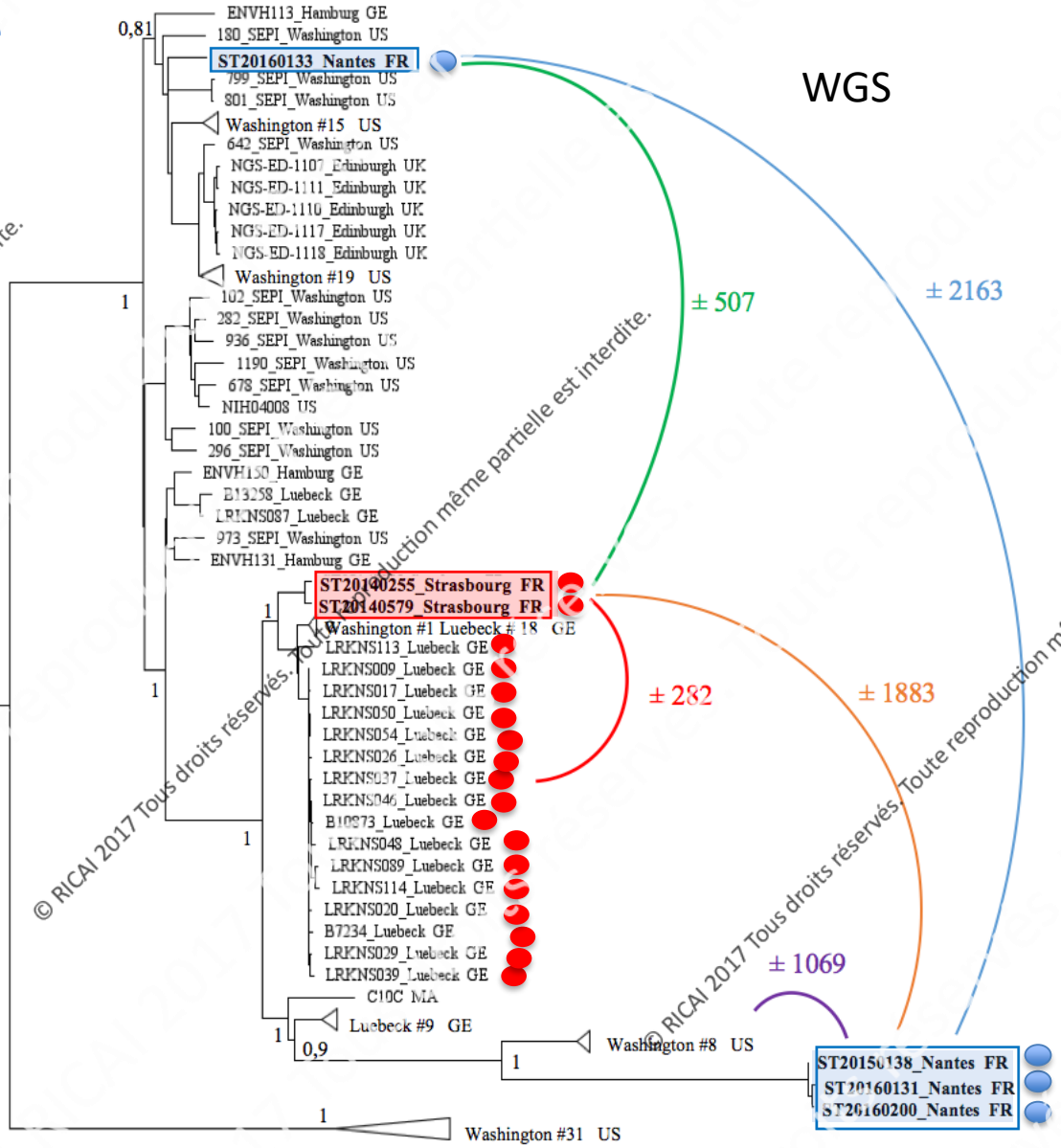
Isolate	Region	plasmid	Identity	Coverage
SA_ST20151386	Nantes	pSA737	100%	99%
SE_ST20140255	Strasbourg	p12-02300	93%	99%
SE_ST20140579	Strasbourg	p12-02300	93%	99%
SE_ST20150138	Nantes	pSA737	100%	99%
SE_ST20160200	Nantes	pSA737	100%	99%
SE_ST20160133	Nantes	pSA7373	99%	99%
SE_ST20160131	Nantes	pSA747	100%	99%

pSA 737 = décrit Ohio

p12-02300 = décrit allemagne

WGS



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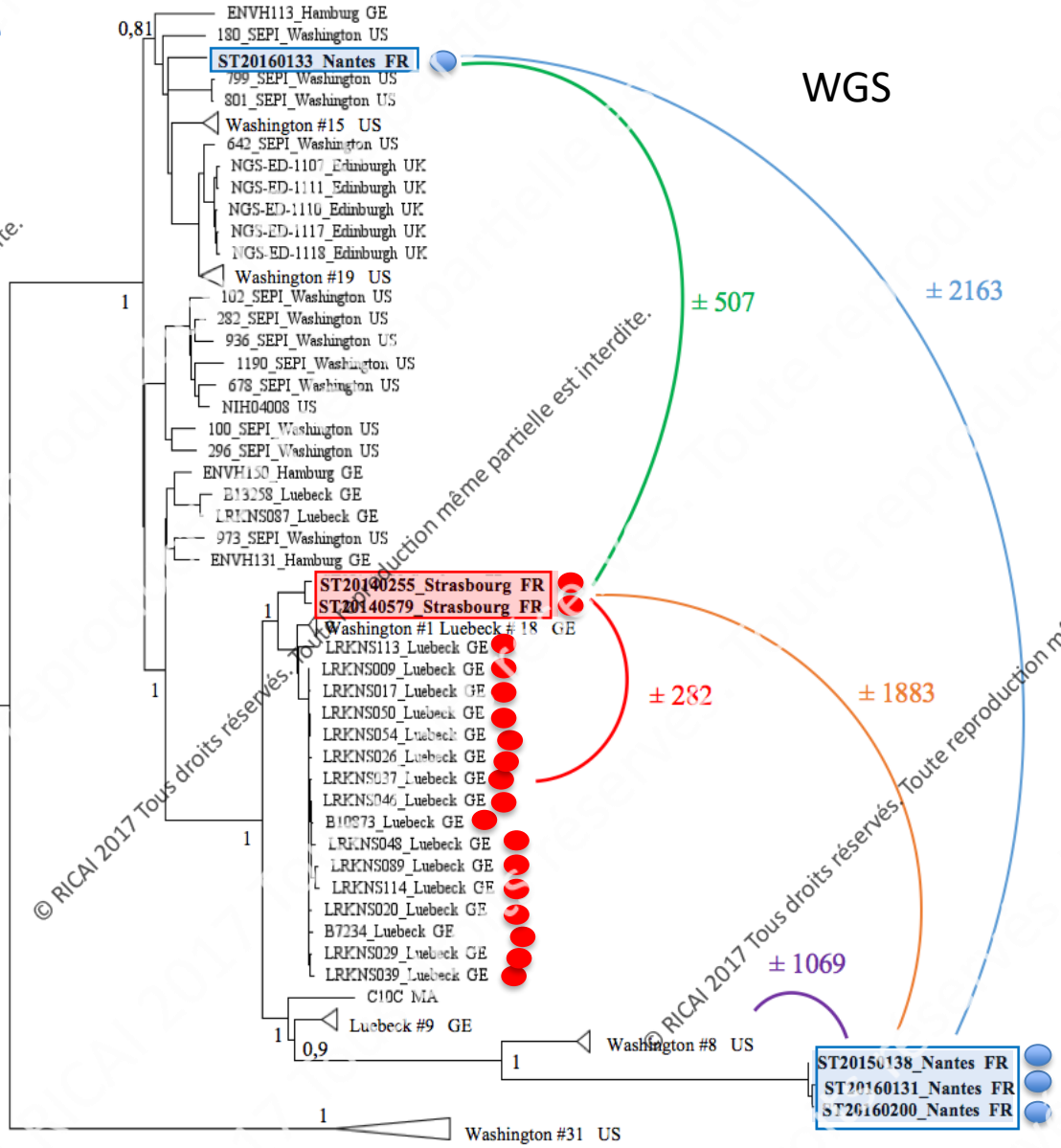

- 3 clones différents de *S. epidermidis*
- dissémination d'un plasmide à Nantes

Résistances aux oxazolidinones : sélection, émergence et dissémination

Acquisition de gènes de résistance

AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy

First Report of *cfr*-Carrying Plasmids in the Pandemic Sequence Type 22 Methicillin-Resistant *Staphylococcus aureus* Staphylococcal Cassette Chromosome *mec* Type IV Clone

Anna C. Shore,[a,b] Alexandros Lazaris,[a] Peter M. Kinnevey,[a] Orla M. Brennan,[a] Gráinne I. Brennan,[a,b] Brian O'Connell,[b,c] Andrea T. Feßler,[d] Stefan Schwarz,[d] David C. Coleman[a]

European Journal of Clinical Microbiology & Infectious Diseases
August 2017, Volume 36, Issue 8, pp 1527–1529 | Cite as

Clinical case of *cfr*-positive MRSA CC398 in Belgium

Authors | Authors and affiliations

H. Paridaens, J. Coussement, M. A. Argudín, B. Delaère, T.-D. Huang, Y. Glupczynski, O. Denis

Occurrence of *cfr*-mediated multiresistance in staphylococci from veal calves and pigs, from humans at the corresponding farms, and from veterinarians and their family members

Christiane Cuny[a], Phillippe Arnold[b], Julia Hermes[c], Tim Eckmanns[c], Jaishri Mehraj[d,e], Sonja Schoenfelder[f], Wilma Ziebuhr[f], Qin Zhao[g], Yang Wang[g], Andrea T. Feßler[h], Gérard Krause[d,i], Stefan Schwarz[h], Wolfgang Witte[a,*]

Résistances aux oxazolidinones : sélection, émergence et dissémination

Epidémie/endémie multi-espèces, multi-clones, multi-mécamismes, multi-supports dans un contexte de surconsommation avec infection et colonistaion

J Antimicrob Chemother
doi:10.1093/jac/dkx370

Journal of Antimicrobial Chemotherapy

Long-lasting successful dissemination of resistance to oxazolidinones in MDR *Staphylococcus epidermidis* clinical isolates in a tertiary care hospital in France

Laurent Dortet[1,2]*†, Philippe Glaser[4,5]†, Najiby Kassis-Chikhani[6], Delphine Girlich[2–4], Philippe Ichai[7], Marc Boudon[7], Didier Samuel[7], Elodie Creton[2–4], Dilek Imanci[8], Rémy Bonnin[2–4], Nicolas Fortineau[1–4] and Thierry Naas[1–4]

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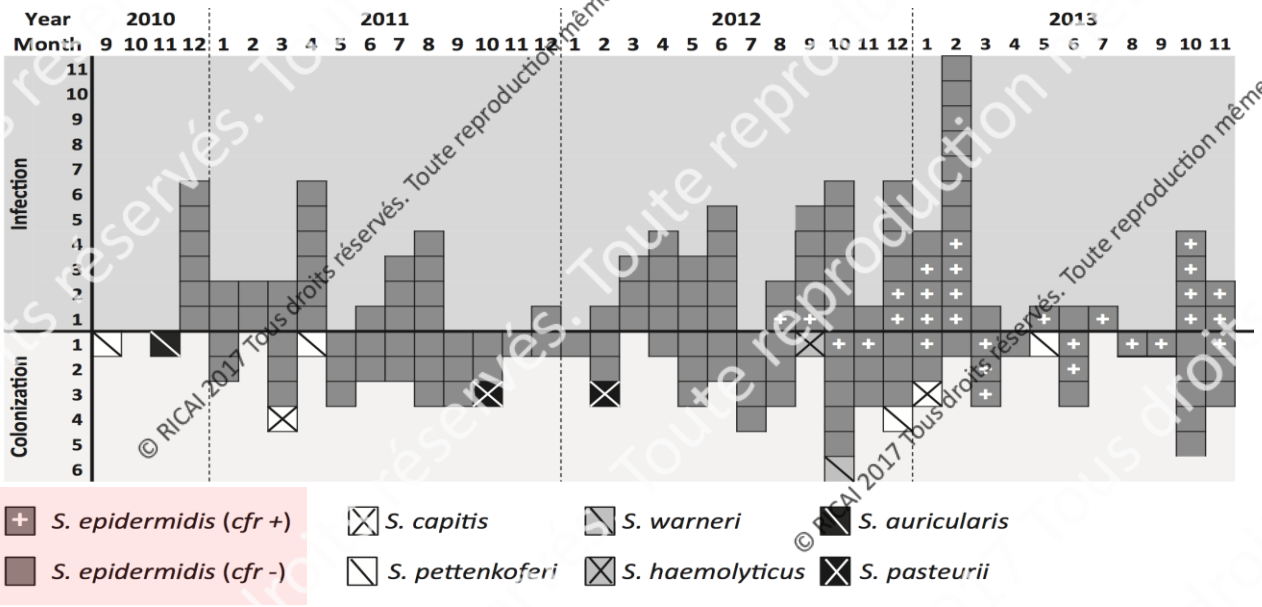

121 patients !

..... 169 souches !

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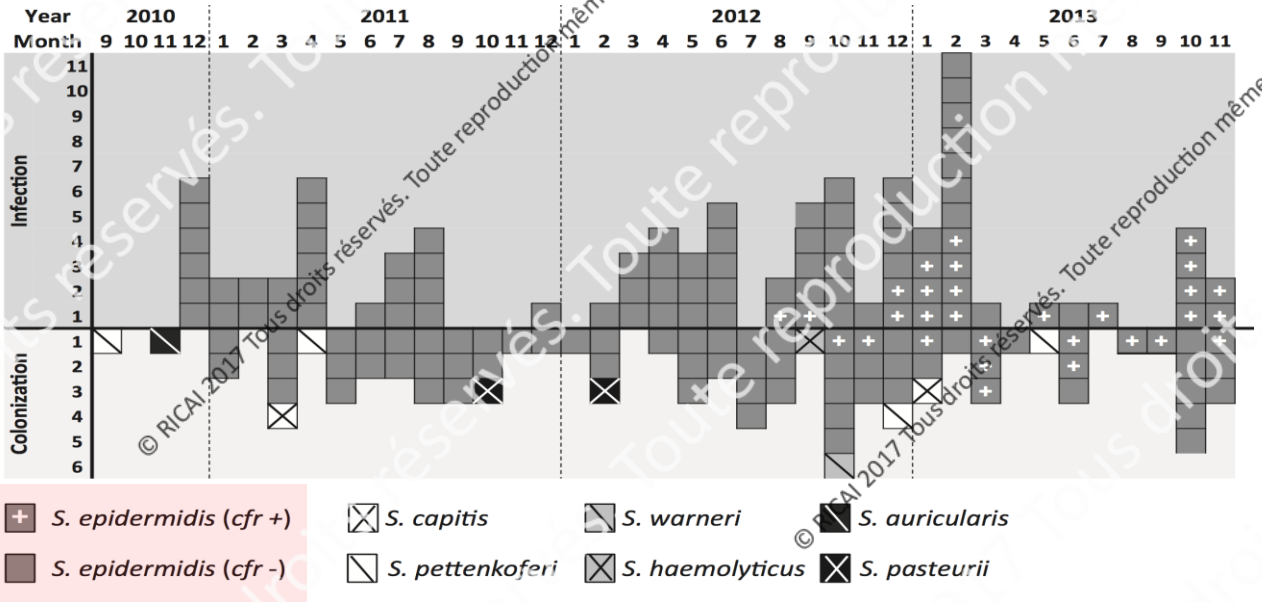

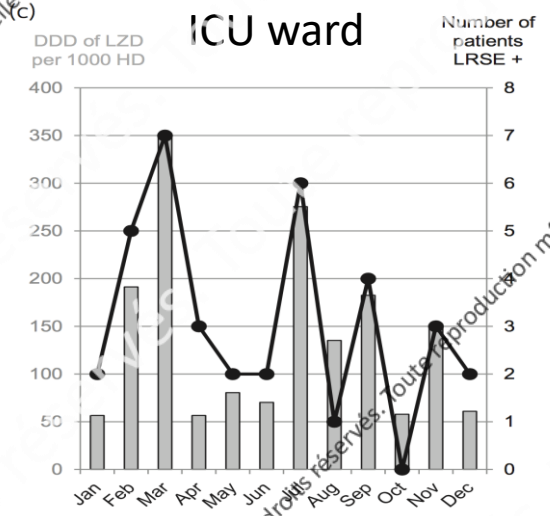

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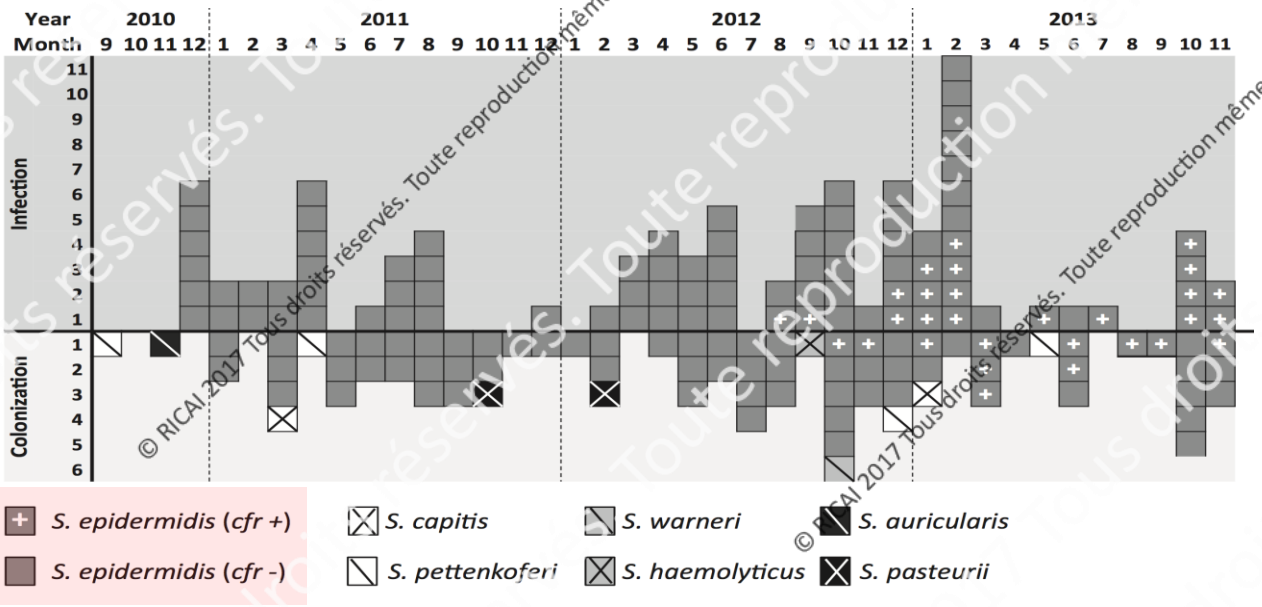

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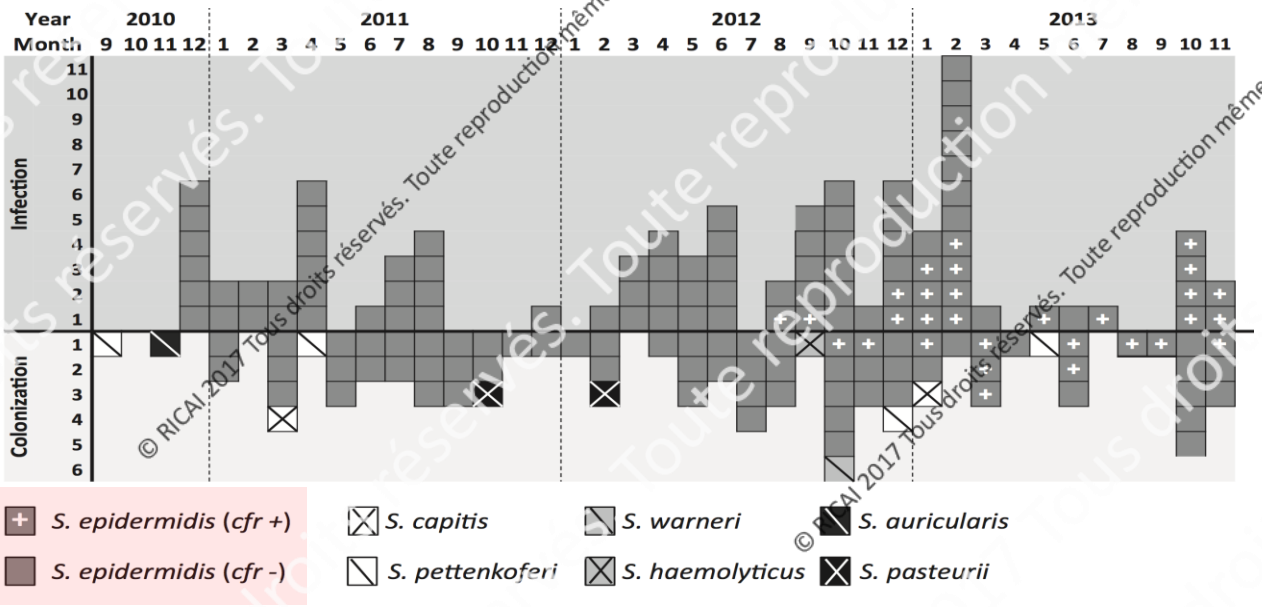

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S. epidermidis :

ST2	ARN23S (5/5) + L3 +/- cfr (7%)	des plasmides communs
ST5	ARN23S (1/6) + L3 + L4 +/- cfr (91%)	
ST22	ARN23S (4/5) + L3	

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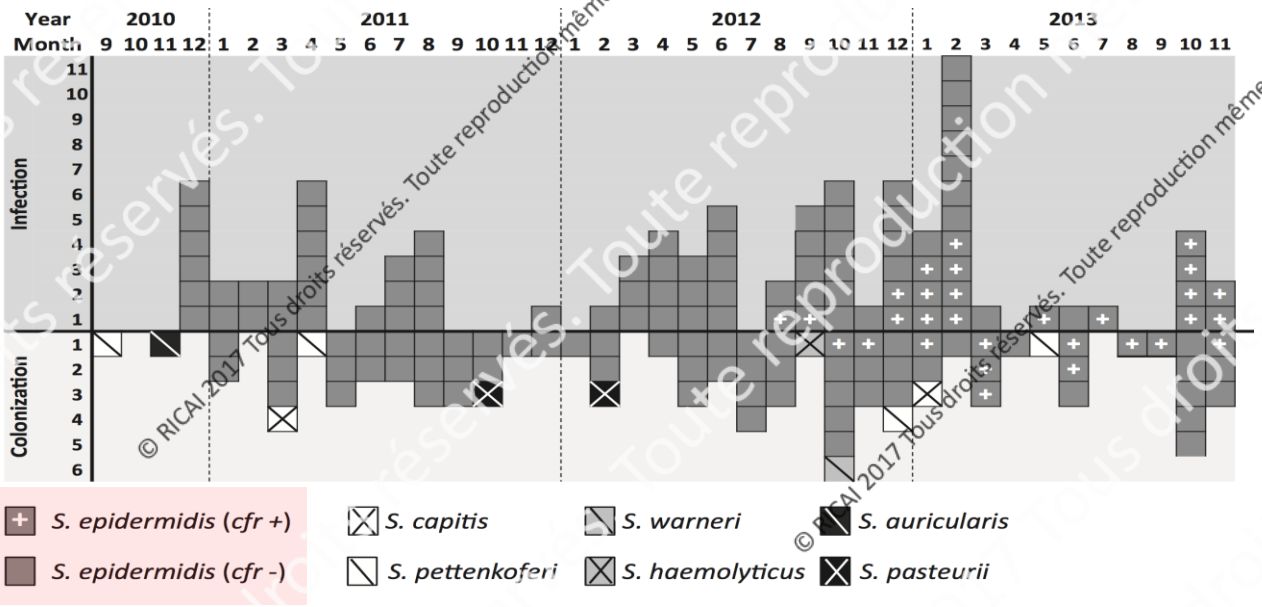

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Démonstration du transfert possible des plasmides *cfr+* entre SCN

Résistances aux oxazolidinones : sélection, émergence et dissémination

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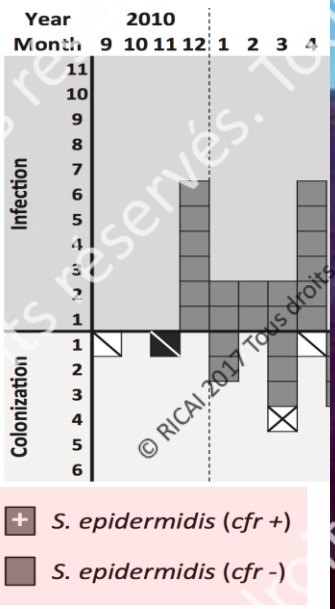

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S. epidermid

des plasmides communs

Démonstration du transfert possible des plasmides *cfr+* entre SCN

Oxazolidinones : take home message …

- Oxazolidinones = une famille importante pour les Gram positifs multirésistants

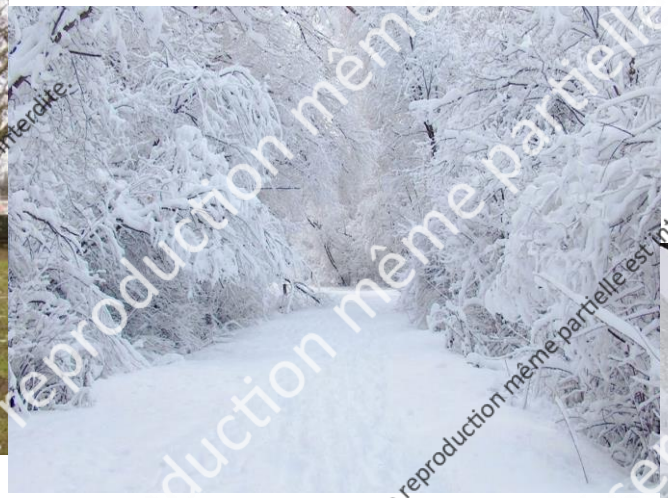
- **Diversité** des mécanismes de résistances
  dont certains restent à identifier

- Inquiétante :
  - **émergence** de clones résistants
  - **maintien** endémique de clones résistants
  - **diffusion** de clones résistants (échelle locale/nationale/inetrnationale)

- Pression de sélection : rôle majeur = **surveillance des consommations**

- Avoir un œil sur … Nos amis les bêtes !

Oxazolidinones : take home message …



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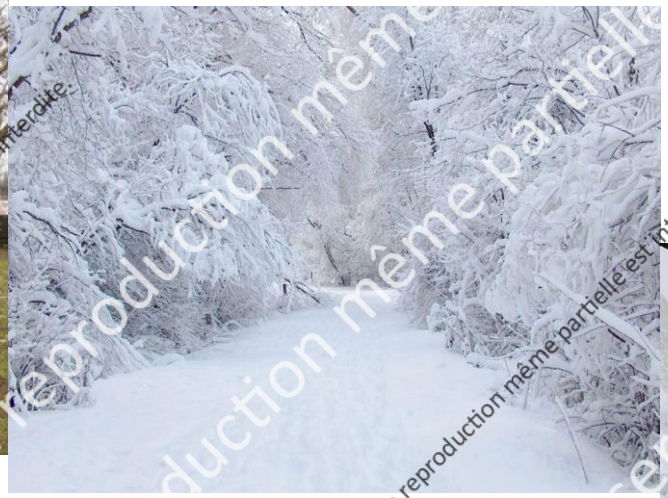
STAPHYLOCOQUES
Centre National de Référence

Oxazolidinones : take home message …



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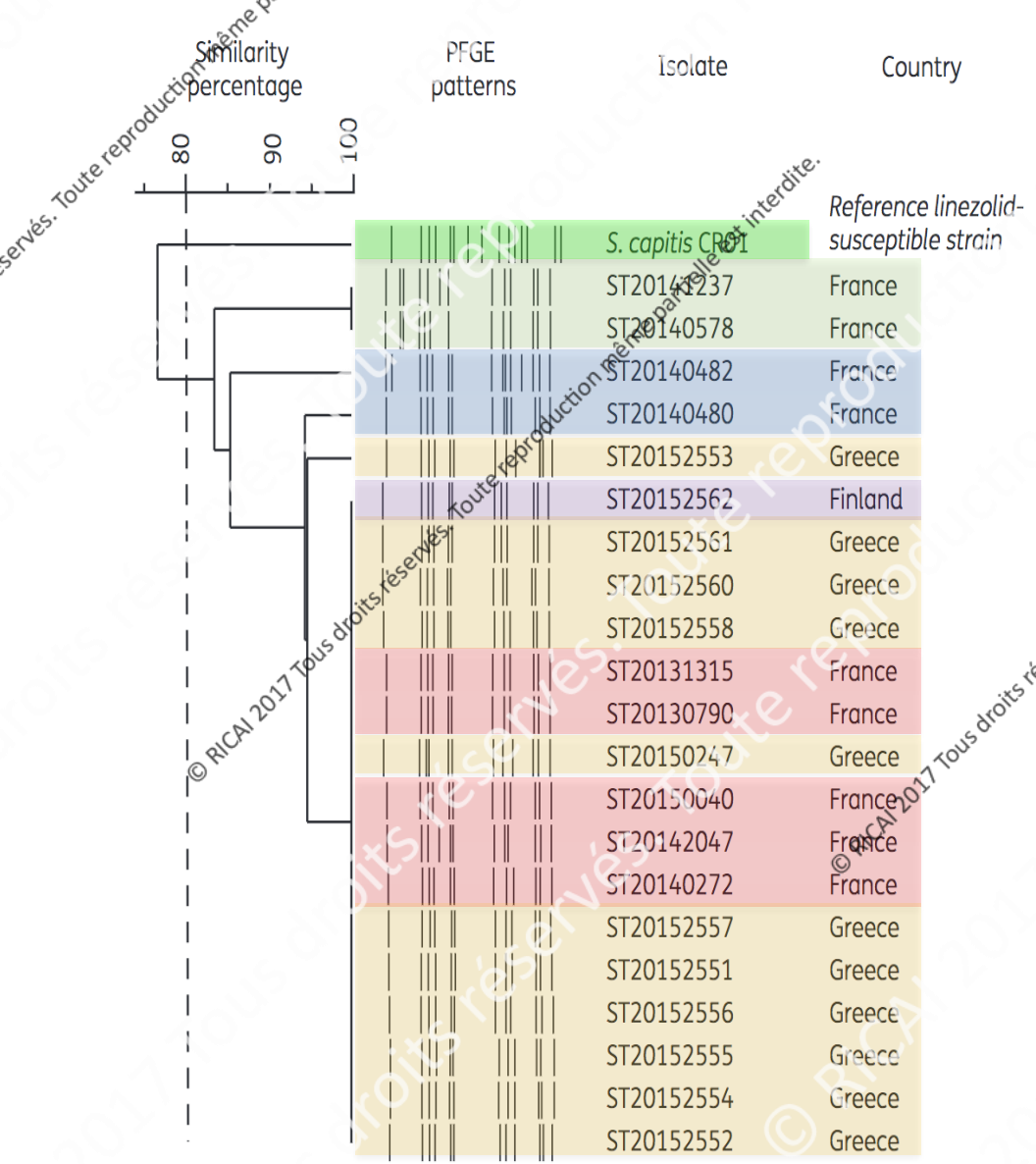
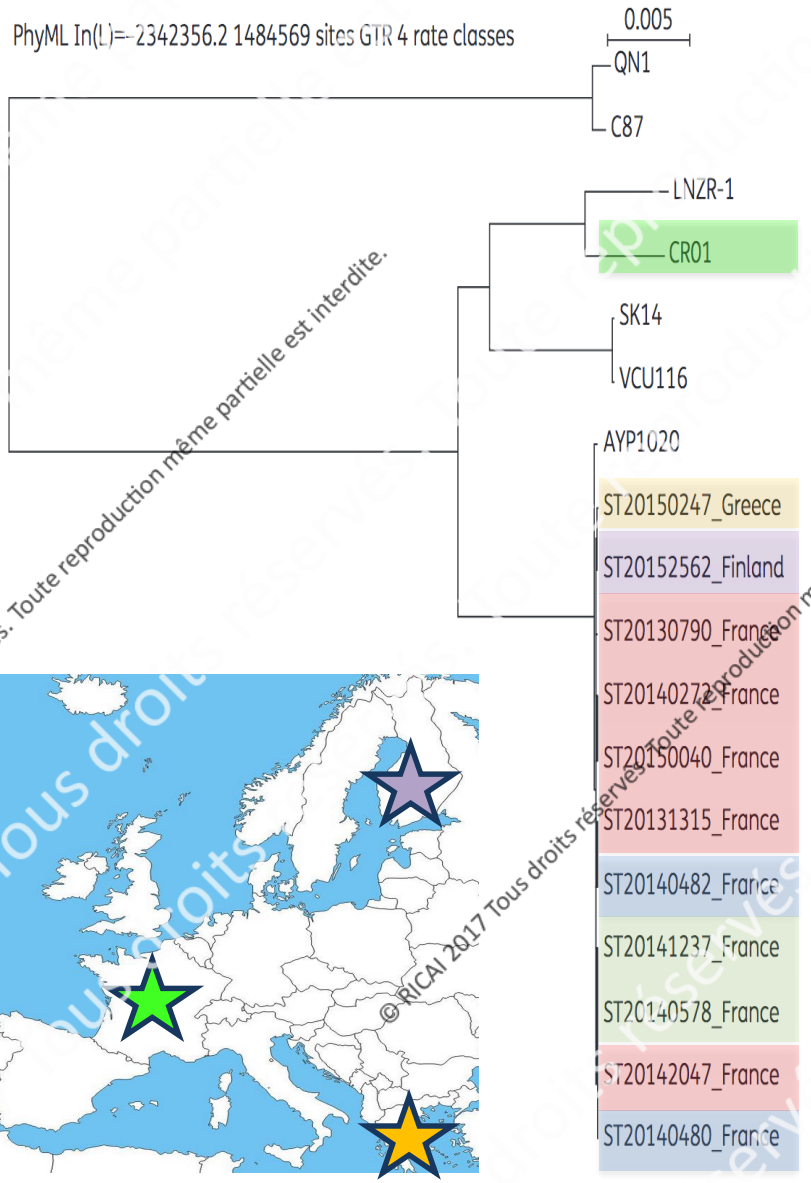
Merci de votre attention …

Résistances aux oxazolidinones : sélection, émergence et dissémination





Mécanismes de résistance aux oxazolidinones

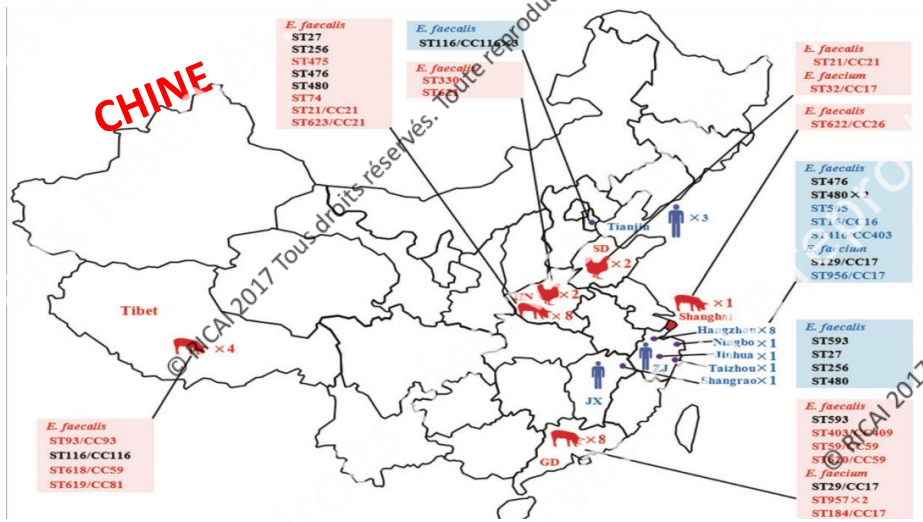
- **ABC transporteur**: nouveau gène *optrA* avec efflux

J Antimicrob Chemother 2015; **70**: 2182–2190
doi:10.1093/jac/dkv116 Advance Access publication 14 May 2015

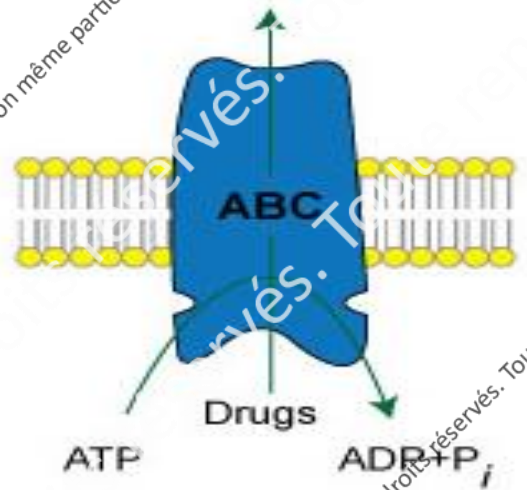
Journal of Antimicrobial Chemotherapy

A novel gene, *optrA*, that confers transferable resistance to oxazolidinones and phenicols and its presence in *Enterococcus faecalis* and *Enterococcus faecium* of human and animal origin

Yang Wang[1]†, Yuan Lv[2]†, Jiachang Cai[3]†, Stefan Schwarz[4]†, Lanqing Cui[2], Zhideng Hu[5], Rong Zhang[3], Jun Li[1], Qin Zhao[1], Tao He[1], Dacheng Wang[6], Zheng Wang[1], Yingbo Shen[1], Yun Li[2], Andreas T. Feßler[4], Congming Wu[1], Hao Yu[6], Xuming Deng[6], Xi Xia[7] and Jianzhong Shen[1]*



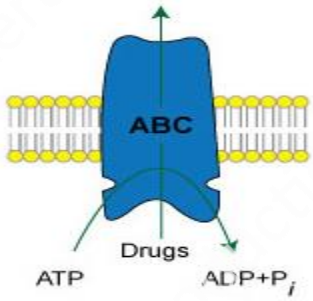
Bacterial isolate	MIC (mg/L)				
	CHL	FFC	LZD	TZD	VAN
Clinical *E. faecalis* E349 (with *optrA*-carrying pE349)	64	64	8	2	1
E. faecalis FA2-2	4	2	2	0.5	1
Transconjugant *E. faecalis* FA2-2-E349	32	64	8	2	1



Mécanismes de résistance aux oxazolidinones

- **ABC transporteur**: nouveau gène *optrA*

Impact du gène *optrA* sur les CMI du LZD et TZD



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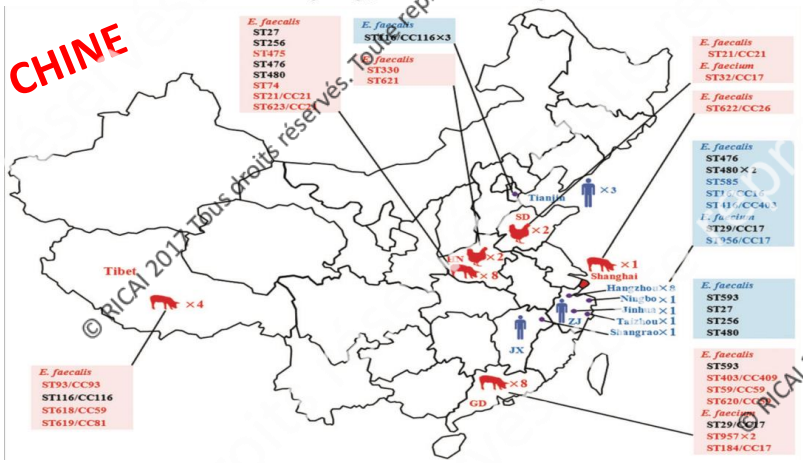

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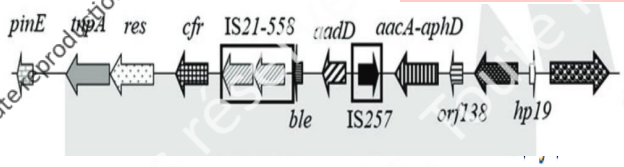
J Antimicrob Chemother 2016; **71**: 1474–1478
doi:10.1093/jac/dkw040 Advance Access publication 6 March 2016

Journal of Antimicrobial Chemotherapy

Co-location of the oxazolidinone resistance genes *optrA* and *cfr* on a multiresistance plasmid from *Staphylococcus sciuri*

Dexi Li[1], Yang Wang[1], Stefan Schwarz[1,2], Jiachang Cai[3], Run Fan[1], Jun Li[1,2], Andrea T. Feßler[2], Rong Zhang[3], Congming Wu[1] and Jianzhong Shen[1]*



Isolate	CHL	FFC	LZD	TED	TIA	CLI	ERY	TET	SPT	GEN	KAN	NEO	BLE
S. sciuri Wo28-3	128	>512	16	4	128	>256	>128	64	128	64	64	4	8
S. aureus RN4220	8	4	2	0.5	≤0.5	≤0.0625	2	≤0.5	16	0.25	0.25	0.25	0.25
Transformant RN4220/pWo28-3	128	>512	16	4	128	>256	2	≤0.5	16	64	64	4	8

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Journal of Antimicrobial Chemotherapy

Detection of *optrA* in the African continent (Tunisia) within a mosaic *Enterococcus faecalis* plasmid from urban wastewaters

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p12-02300:

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Journal of Antimicrobial Chemotherapy

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Article Contents

Abstract

Linezolid resistance in clinical isolates of *Staphylococcus epidermidis* from German hospitals and characterization of two *cfr*-carrying plasmids

Jennifer Bender; Birgit Strommenger; Matthias Steglich; Ortrud Zimmermann; Ines Fenner; Carmen Lensing; Dorantschimeg Dagwadordsch; Alexander S. Kekulé; Guido Werner; Franziska Layer

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Published: 03 March 2015 **Article history**

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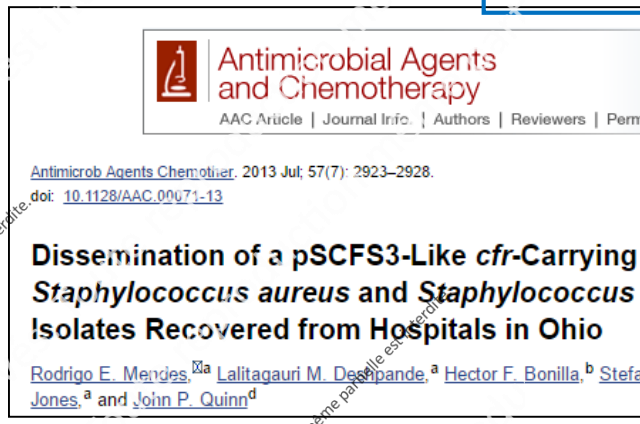


Antimicrobial Agents and Chemotherapy

AAC Article | Journal Info. | Authors | Reviewers | Perm

Antimicrob Agents Chemother. 2013 Jul; 57(7): 2923–2928.
doi: 10.1128/AAC.00071-13

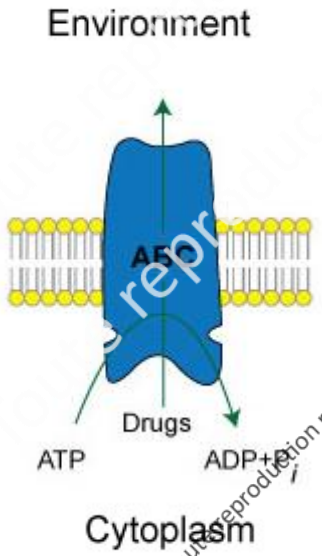
Dissemination of a pSCFS3-Like *cfr*-Carrying *Staphylococcus aureus* and *Staphylococcus* Isolates Recovered from Hospitals in Ohio

Rodrigo E. Mendes,[a] Lalitagauri M. Deshpande,[a] Hector F. Bonilla,[b] Stefa Jones,[a] and John P. Quinn[d]

Isolate	Region	plasmid	Identity	Coverage
SA_ST20151386	Nantes	pSA737	100%	99%
SE_ST20140255	Strasbourg	p12-02300	93%	99%
SE_ST20140579	Strasbourg	p12-02300	93%	99%
SE_ST20150138	Nantes	pSA737	100%	99%
SE_ST20160200	Nantes	pSA737	100%	99%
SE_ST20160133	Nantes	pSA7373	99%	99%
SE_ST20160131	Nantes	pSA747	100%	99%

Non-ribosomal resistance mechanisms: *optrA*

- Oxazolidinone/phenicol transferable resistance gene



- First description in enterococci (China, 2015)
- ABC transporter confering resistance to phenicols, linezolid and tedizolid

- **Li et al, *JAC* 2016: Co-location of *optrA* and *cfr* on a single plasmid in a *S. sciuri* isolate**

Mesure de l'activité : concentrations critiques

EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING

European Society of Clinical Microbiology and Infectious Diseases

New EUCAST breakpoints, April 2015

The following three agents, all indicated for the treatment of acute bacterial skin and skin structure infections in adults, have recently been given marketing approval by EMA. The breakpoints for these agents will be included in the next version of the EUCAST breakpoint tables (January 2016).

Tedizolid

Organism group	Breakpoint (mg/L)	
	S ≤ (mg/L)	R > (mg/L)
Staphylococcus spp.	0.5	0.5
Enterococcus spp.	IE	IE
Streptococcus groups A,B,C,G	0.5	0.5
Viridans group streptococci (*Streptococcus anginosus* group only)	0.25	0.25

"IE" indicates that there is insufficient evidence that the species in question is a good target for therapy with the agent. An MIC with a comment but without an accompanying S, I or R

Miscellaneous agents	MIC breakpoint (mg/L)		Disk content (µg)	Zone diameter breakpoint (mm)	
	S ≤	R >		S ≥	R <
Linezolid	4	4	10	19[B]	19[B]

Activité du linezolide et du tedizolide

CMI 50

CMI 90

Zurenko et al. Annals of Clinical Microbiology and Antimicrobials 2014, 13:46
http://www.ann-clinmicrob.com/content/13/1/46

ANNALS OF CLINICAL MICROBIOLOGY AND ANTIMICROBIALS

RESEARCH Open Access

Use of linezolid susceptibility test results as a surrogate for the susceptibility of Gram-positive pathogens to tedizolid, a novel oxazolidinone

Gary Zurenko[1*], Paul Bien[2], Mekki Bensaci[3], Hina Patel[3] and Grace Thome[3]

Organism grouping (no. tested)	Cumulative number (%) of isolates inhibited at MIC value (μg/ml)								
Antimicrobial agent	**≤0.06**	**0.12**	**0.25[a]**	**0.5**	**1**	**2**	**4**	**8**	**>8**
S. aureus (7187)									
Tedizolid	17 (0.2)	550 (7.7)	*5024(69.9)*	**7163 (99.6)**	7175 (99.8)	7180 (99.9)	7184 (99.9)	7186 (99.9)	7187 (100)
Linezolid	–		7 (0.1)	29 (0.4)	1580 (21.9)	***6813 (94.7)***	7167 (99.7)	7170 (99.7)	7187 (100)
Staphylococcal species (non-*S. aureus*)[b] (674)									
Tedizolid	30 (4.5)	323 (47.9)	*597 (88.5)*	**664 (98.5)**	669 (99.2)	669 (99.2)	673 (99.8)	674 (100)	674 (100)
Linezolid	–	–	6 (0.9)	163 (24.1)	*575 (85.3)*	**660 (97.9)**	668 (99.1)	669 (99.2)	674 (100)
Enterococcus spp. (1241)									
Tedizolid	8 (0.6)	71 (5.7)	*701 (56.4)*	**1224 (98.6)**	1237 (99.6)	1240 (99.9)	1241 (100)	1241 (100)	1241 (100)
Linezolid	–	–	5 (0.4)	39 (3.1)	544 (43.8)	***1219 (98.2)***	1237 (99.6)	1238 (99.7)	1241 (100)
Streptococcus spp. (1600)									
Tedizolid	80 (5.0)	790 (49.3)	***1592 (99.5)***	1600 (100)	1600 (100)	1600 (100)	1600 (100)	1600 (100)	1600 (100)
Linezolid	–	–	56 (3.5)	474 (29.6)	***1516 (94.7)***	1599 (99.9)	1600 (100)	1600 (100)	1600 (100)
Streptococcus anginosus group[c] (91)									
Tedizolid	35 (38.4)	*75 (82.4)*	**91 (100)**	91 (100)	91 (100)	91 (100)	91 (100)	91 (100)	91 (100)
Linezolid	–	–	35 (38.4)	*67 (73.6)*	**91 (100)**	91 (100)	91 (100)	91 (100)	91 (100)

Abbreviations: MIC minimum inhibitory concentration, MIC_{50} MIC required to inhibit growth of 50% of isolates, MIC_{90} MIC required to inhibit growth of 90% of isolates.
Italics indicate MIC_{50}.
Bolding indicates MIC_{90}.
[a]An MIC value of 0.25 was the lowest MIC value tested for linezolid. Linezolid results should be read as ≤0.25 μg/ml.[b]Includes isolates of *S. capitis* (28), *S. caprae* (4), *S. cohnii* (2), *S. epidermidis* (405), *S. haemolyticus* (52), *S. hominis* (56), *S. intermedius* (7), *S. lugdunensis* (47), *S. pasteuri* (1), *S. pettenkoferi* (1), *S. saprophyticus* (28), *S. schleiferi* (6), *S. simulans* (14), *S. warneri* (12), *S. xylosus* (2), and unspeciated coagulase-negative *Staphylococcus* spp. (9).
[c]Includes isolates of *S. anginosus*, *S. intermedius*, and *S. constellatus*.

Activité du linezolide et du tedizolide

Mécanismes de résistance aux oxazolidinones

- Mutations de l'ARN 23S

Strain Background	23S rRNA Gene Mutation	Proportion of Mutant Alleles	MIC (µg/ml) tedizolid	MIC (µg/ml) linezolid
ATCC 29213 (MSSA)	wild-type	-	0.5	2
	G2447T	1/6	0.5	4
		2/6	1	8
		2/5	2	16
		3/5	4	32
		4/5	8	128
	T2500A	1/6	1	4
		2/6	2	8
ATCC 33591 (MRSA)	wild-type	-	0.25	1
	G2576T	1/6	0.5	4
		2/6	0.5	4
		3/6	1	16
		4/6	2	32
	T2571C/G2576T	1/6	0.5	2
		2/6	1	4
		3/6	2	16

Locke et al, AAC 2009

Activité du linézolide et du tédizolide

Mécanismes de résistance aux oxazolidinones

- Mutations des protéines ribosomales

Strain Background	Mutation	MIC (µg/mL)
ATCC 29213 (MSSA)	-	0.5
	L3 (Gly155Arg)	1
	L3 (Gly155Arg + Met169Leu)	2
	L3 (ΔPhe127-His146)	2
ATCC 33591 (MRSA)	-	0.25
	L3 (Gly155Arg)	0.5
	L4 (Lys68Gln)	0.5
	L3 (ΔPhe127-His146)	1

Locke et al, AAC 2009

Activité du linézolide et du tédizolide

Mécanismes de résistance aux oxazolidinones

- Mutations de l'ARN 23S
- Mutations des protéines ribosomales

Strain[a]	Source or reference	Resistance mechanism[b]	MIC (μg/ml)[a]	
			LZD	TZD
29213	ATCC		2	0.5
29213-1	43	23S (G2447T ×3)	32	4
29213-2	43	23S (T2500A ×2)	8	2
29213-3	43	L3 (ΔPhe127-His146)	8	2
33591	ATCC		1	0.25
33591-1	43	23S (G2576T ×3)	16	2
33591-2	43	23S (G2576T/T2571C ×3)	16	2
33591-3	43	L4 (Lys68Gln)	2	0.5
NRS127	NARSA[d]	L3 (ΔSer145)	8	1

[a] ATCC 29213 and ATCC 33591 isogenic mutant panels were generated through selection in the presence of LZD and/or TR-700. NRS127 is an LZD[r] clinical isolate.
[b] Mutations in 23S rRNA genes (and mutant allele copy number) or in the ribosomal protein L3 or L4 are shown.
[c] MICs (broth microdilution; CLSI) were determined against the oxazolidinone panel (Fig. 1). VAN, vancomycin; RZD, radezolid.
[d] Network of Antimicrobial Resistance in *Staphylococcus aureus*.

Locke et al, AAC 2010

Activité du linezolide et du tedizolide

Table 1. Tedizolid MIC distribution and MIC_{90} values for tested isolates

Strain	TZD—number (cumulative percentage) inhibited at MIC (mg/L)							TZD MIC_{90} (mg/L)	TZD MIC range (mg/L)	LZD MIC_{90} (mg/L)	LZD MIC range (mg/L)
	≤0.063	0.125	0.25	0.5	1	2	4				
MRSA											
hVISA (n=120)	7 (5.8)	18 (20.8)	55 (66.7)	38 (98.3)	2[a] (100)	— (100)	— (100)	0.5	0.03–1	4	0.25–8
VISA (n=100)	7 (7)	52 (59)	25 (84)	16 (100)	— (100)	— (100)	— (100)	0.5	0.03–0.5	4	0.125–4
DNS (n=75)	— (0)	23 (30.7)	38 (81.3)	14 (100)	— (100)	— (100)	— (100)	0.5	0.125–0.5	2	1–4
LR[b] (n=7)	1 (14.3)	1 (28.6)	2 (57.1)	— (57.1)	3 (100)	— (100)	— (100)	NA	0.063–1	NA	8–16
VRE											
E. faecium (n=120)	— (0)	6 (5)	51 (47.5)	32 (74.2)	25 (95)	3 (97.5)	3 (100)	1	0.125–4	4	1–32
E. faecalis (n=100)	1 (1)	29 (30)	69 (99)	1 (100)	— (100)	— (100)	— (100)	0.25	0.063–0.5	2	0.25–2
LR *E. faecium* (n=10)	— (0)	— (0)	— (0)	— (0)	4 (40)	3 (70)	3 (100)	NA	1–4	NA	8–32
DNS *E. faecium* (n=25)	— (0)	— (0)	11 (44)	3 (56)	8 (88)	2 (96)	1 (100)	NA	0.25–4	NA	1–32

TZD, tedizolid; LZD, linezolid; NA, not applicable.

[a]These two hVISA isolates were LR, with linezolid MIC values of 8 mg/L.

[b]The three isolates with tedizolid MICs of 1 mg/L did not possess the *cfr* gene.

Activité du linezolide et du tedizolide

Organism	Total Studies	n	Weighted Average MIC_{90} (µg/ml)		Ratio MIC_{90} Linezolid/ Tedizolid
			Tedizolid	Linezolid	
MSSA	6	1389	0.46	2.19	4.76
MRSA	10	1588	0.52	2.72	5.23
MSCoNS	4	165	0.44	2.35	5.34
MRCoNS	4	319	0.37	2.36	6.38

Activité du linezolide et du tedizolide

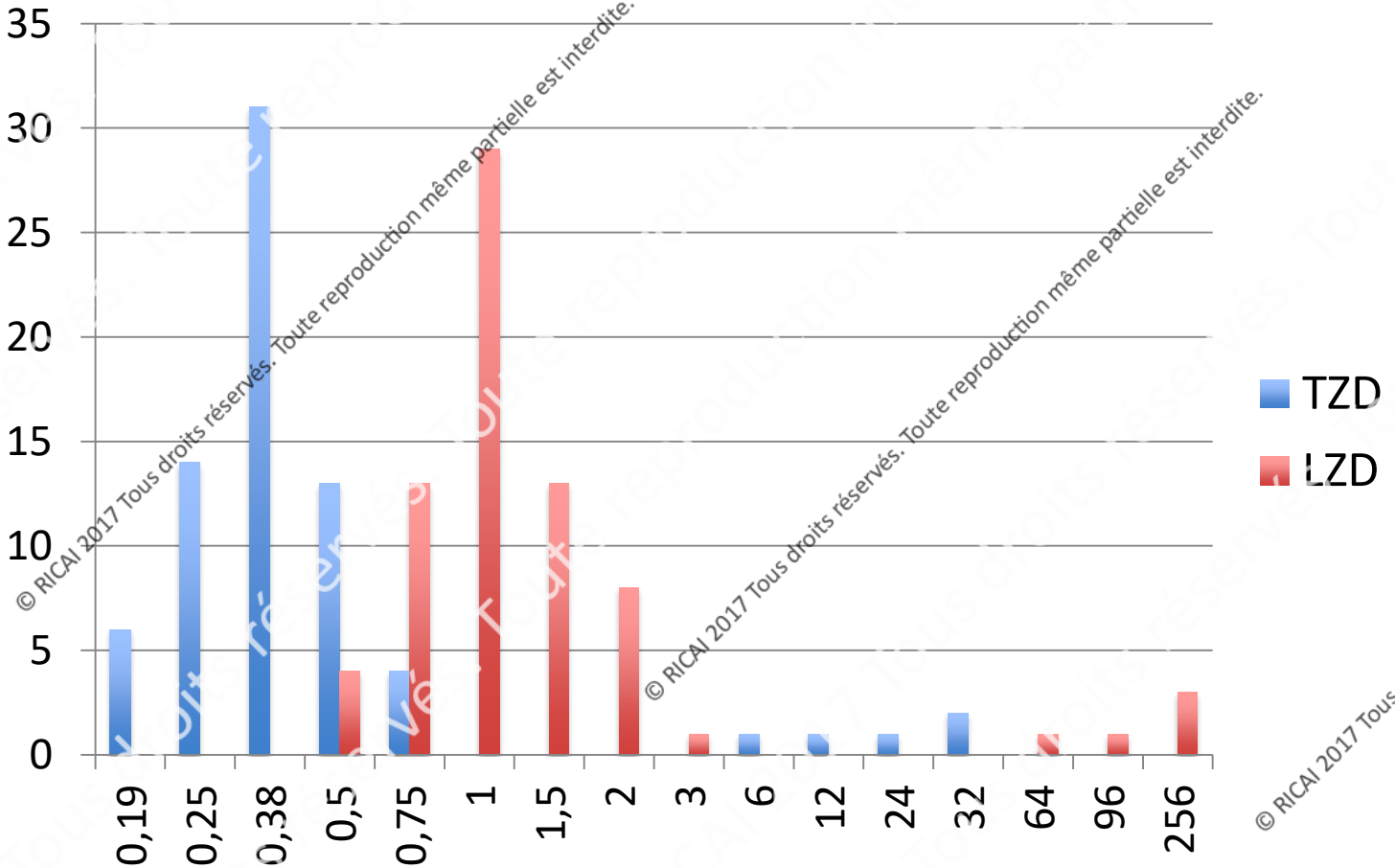
Organism	Total Studies	n	Weighted Average MIC_{90} (µg/ml)		Ratio MIC_{90} Linezolid/ Tedizolid
			Tedizolid	Linezolid	
MSSA	6	1389	0.46	2.19	4.76
MRSA	10	1588	0.52	2.72	5.23
MSCoNS	4	165	0.44	2.35	5.34
MRCoNS	4	319	0.37	2.36	6.38

MRSA Genotype	N	Tedizolid (µg/mL)		Linezolid (µg/mL)	
		MIC Range	MIC_{90}	MIC Range	MIC_{90}
ST5-MRSA-II (USA100)	10	0.25 - 0.5	0.5	1 – 2	2
ST36-MRSA-II (USA200/ EMRSA16)	10	0.125 – 0.5	0.5	0.5 – 4	2
ST8-MRSA-IV (USA300)	10	0.25 – 0.5	0.5	2 – 4	4
ST1-MRSA-IV (USA400)	10	0.5	0.5	2 – 4	4
ST8-MRSA-IV (USA500)	10	0.25 – 0.5	0.5	2	2
ST5-MRSA-IV (USA800)	10	0.25 – 0.5	0.5	1 – 2	2
ST22-MRSA-IV (EMRSA15)	10	0.25 – 0.5	0.5	1 – 2	2
ST80-MRSA-IV (EU community)	10	0.25 – 0.5	0.5	2 – 4	2
ST247-MRSA-I (Iberian)	11	0.25 – 0.5	0.25	1 – 2	2
ST239-MRSA-III (Brazilian)	10	0.125 – 0.5	0.5	1 – 2	2

Premières données françaises

Souches staphylocoques françaises de **GISA**

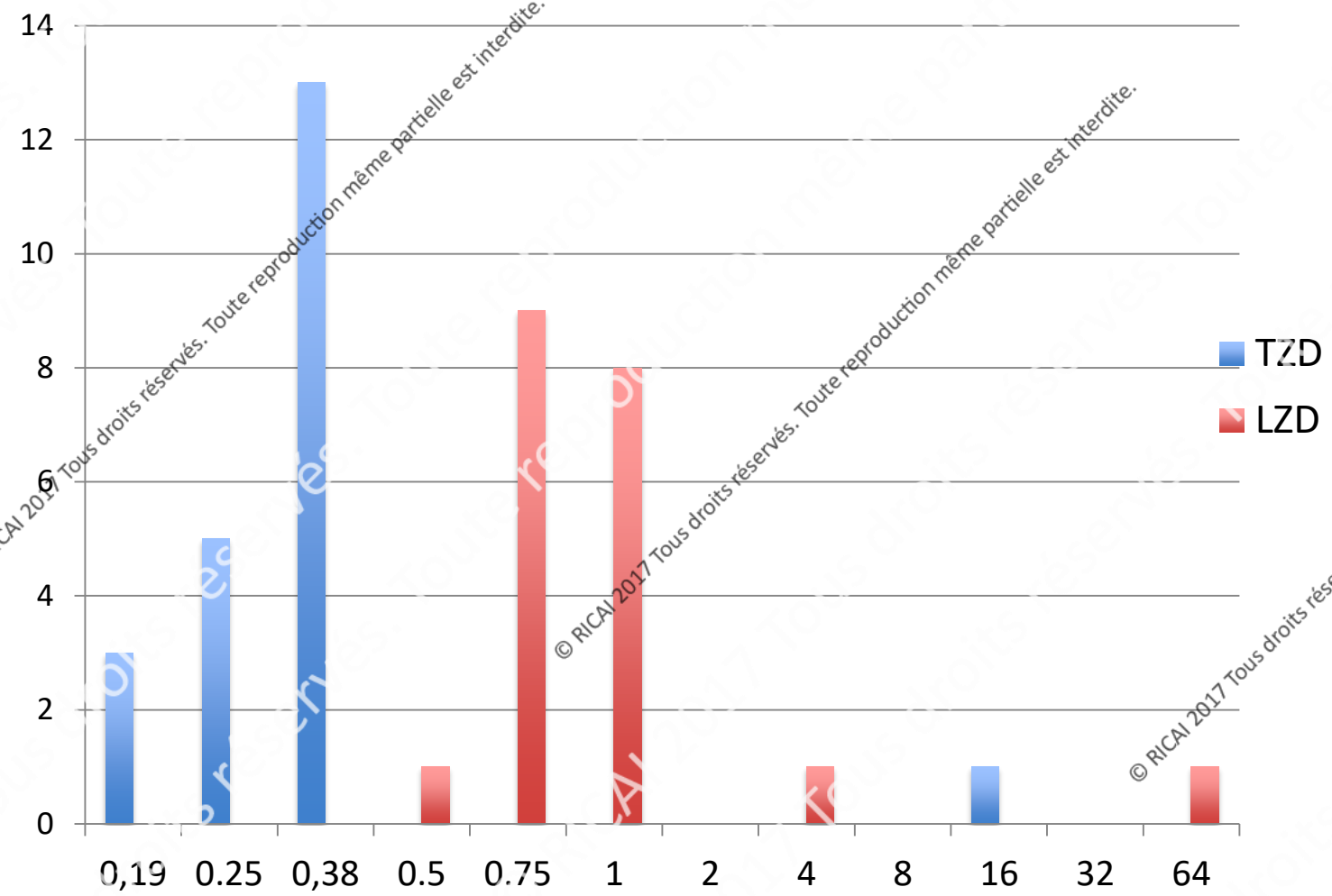
n=73



Premières données françaises

Souches staphylocoques français **daptomycine-R**

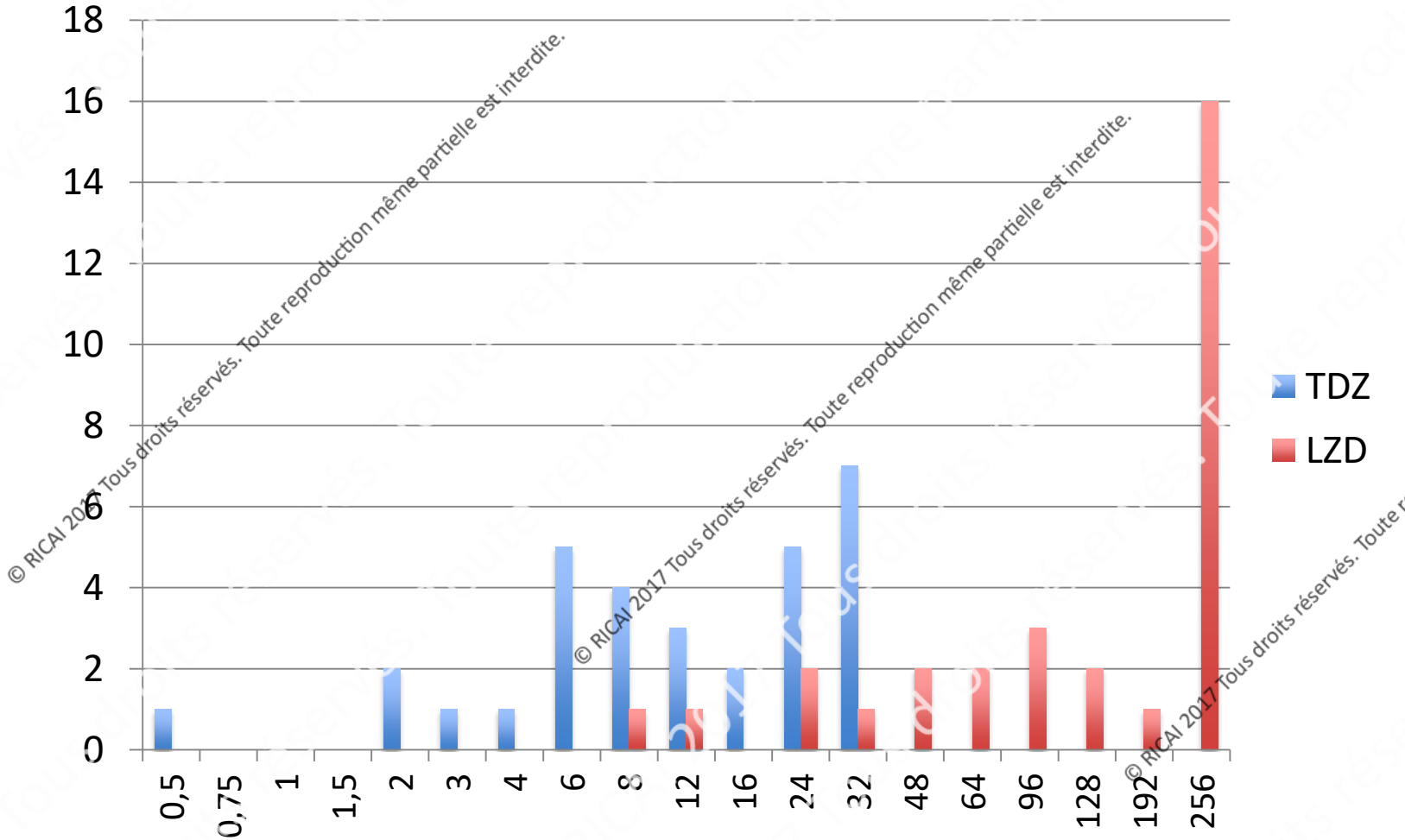
n=28



Premières données françaises

Souches staphylocoques françaises **Linézolide-R mutation ribosomale**

n=31



Premières données françaises

Souches staphylocoques françaises **Linézolide-R *cfr+***

				CMI TDZ	CMI LZD
S. epidermidis	SCN RM	*cfr+*	mutation G/2576/T	6	256
S. cohnii	SCN RM	*cfr+*	mutation G/2576/T	2	256
S. epidermidis	SCN RM	*cfr+*	GISA	0,38	1
S. epidermidis	SCN RM	*cfr+*	mutation G/2576/T	3	256
S. aureus	SARM	*cfr+*	-	0,5	12

Conclusion

- Oxazolidinones = la seule véritable nouvelle famille depuis 30 ans
- Alternative pertinente et efficace sur les staphylocoques
- Tedizolide
  - Profil d'activité microbiologique intéressant
  - Modifications structurales améliorant
    - ✓ le rythme d'administration
    - ✓ la stabilité face aux mécanismes de résistance

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SympoStaph
26 et 27 octobre 2016

Des infections staphylococciques à la biologie du microorganisme

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