Bacilles à Gram négatif de résistance émergentes aux antibiotiques :

Nouveaux antibiotiques et nouvelles stratégies thérapeutiques

Pr. Tristan Ferry, MD, PhD
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Infectious and Tropical Diseases Unit
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Claude Bernard Lyon1 University, Lyon

Centre International de Recherche en Infectiologie, CIRI, Inserm U1111, CNRS UMR5308, ENS de Lyon, UCBL1, Lyon, France

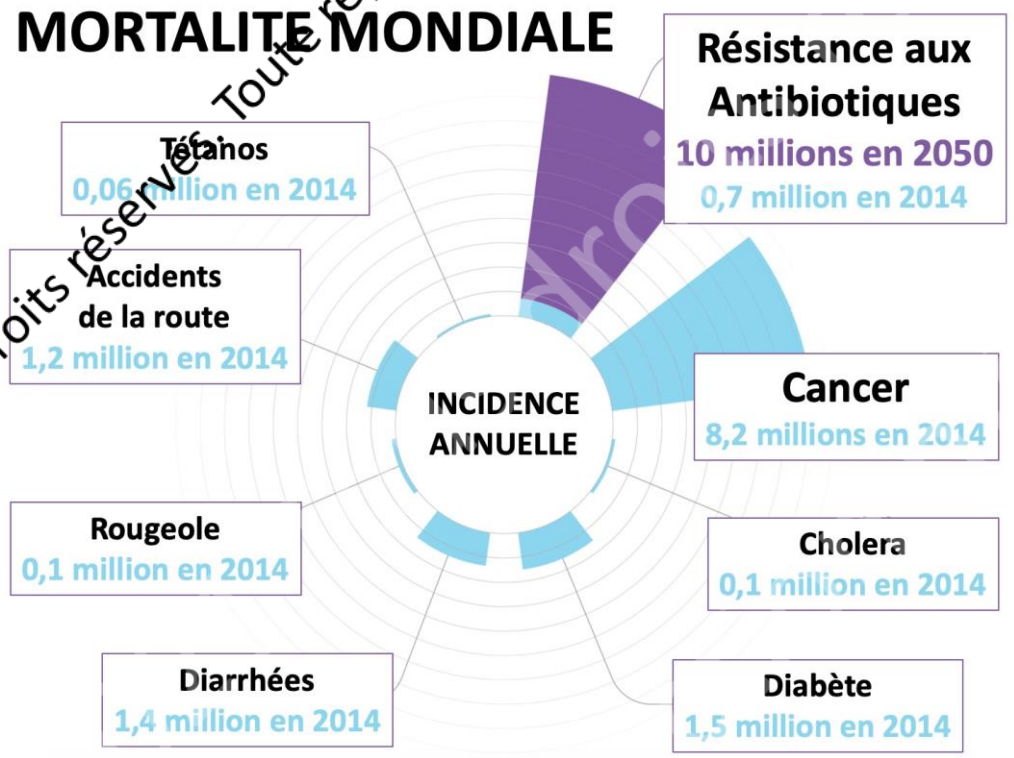
Regional referral center for the management of complex bone and joint infection
Centre de Référence des IOA complexes de Lyon (CRIOAc Lyon)

@FerryLyon

Hokusai, 1931

Antimicrobial resistance is, indeed,
a slow motion tsunami

World Health Organization



Data and statistics

33,000

The number of people who die every year in EU/EEA countries due to an infection with a resistant bacterial strain. Estimate for the whole WHO European Region is currently not available.

World Health Organization
REGIONAL OFFICE FOR Europe

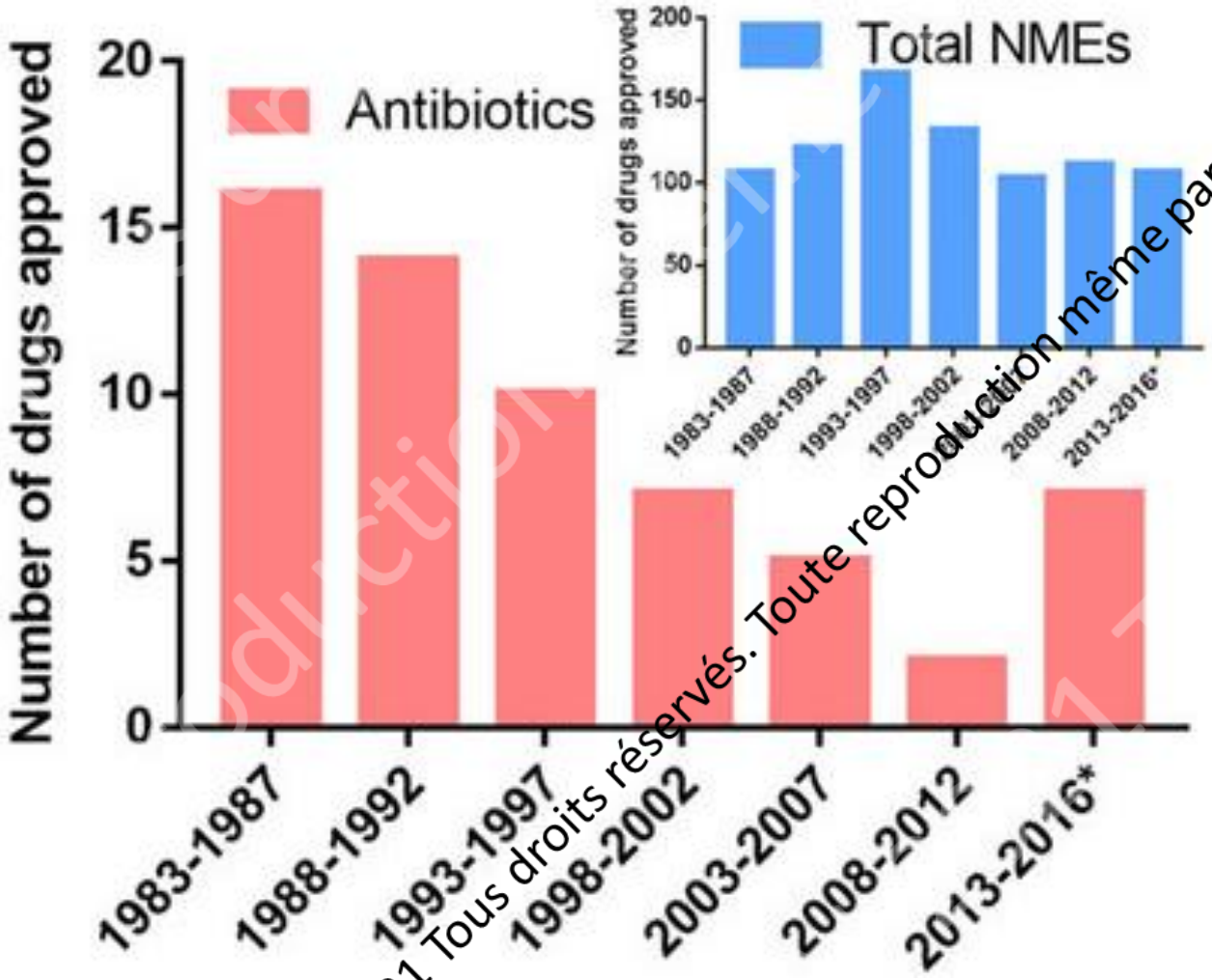
WHO publishes list of bacteria for which new antibiotics are urgently needed

Priority 1: CRITICAL

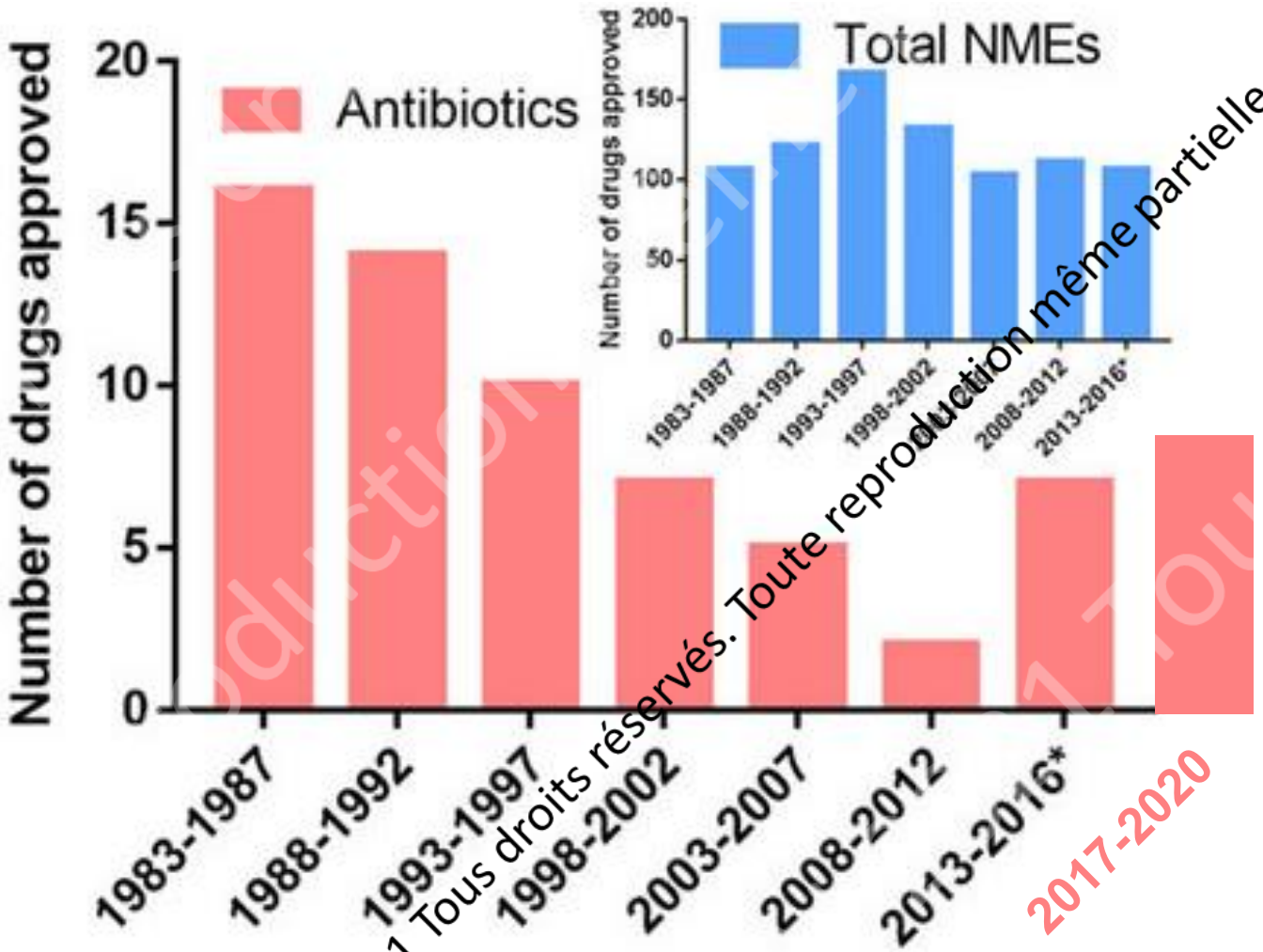
***Acinetobacter baumannii*, carbapenem-resistant**
***Pseudomonas aeruginosa*, carbapenem-resistant**
***Enterobacteriaceae*, carbapenem-resistant, ESBL-producing**

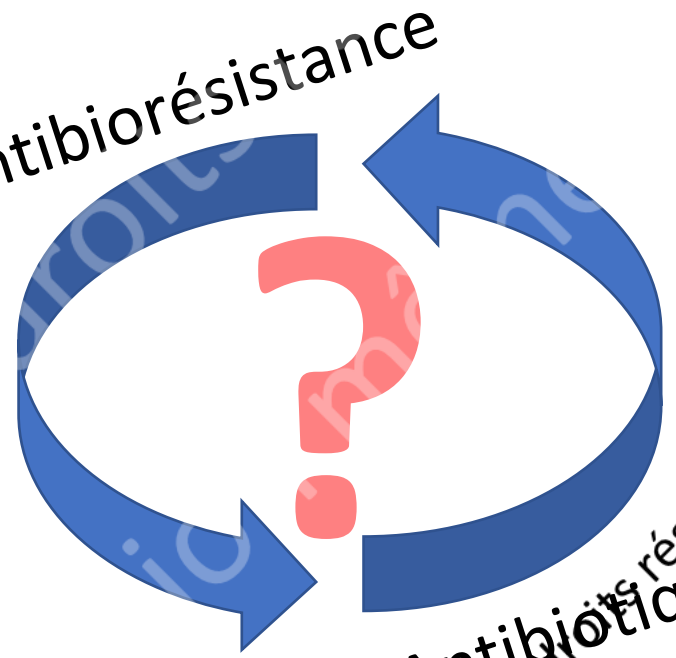
Priority 2: HIGH

***Enterococcus faecium*, vancomycin-resistant**
***Staphylococcus aureus*, methicillin-resistant, vancomycin intermediate and resistant**
***Helicobacter pylori*, clarithromycin-resistant**
***Campylobacter* spp., fluoroquinolone-resistant**
***Salmonellae*, fluoroquinolone-resistant**
***Neisseria gonorrhoeae*, cephalosporin-resistant, fluoroquinolone-resistant**



British Journal of Pharmacology 2017





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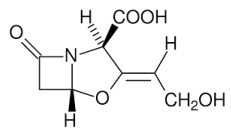
Les nouveaux inhibiteurs de β-lactamase

Inhibiteurs de β-lactamases	β-lactamases						
	BLSE	AmpC entéro	AmpC Pyo	Carbapénémases			
				KPC	MBL	OXA-48	OXA-23 OXA-58
Dérivés de β-lactamines							
Acide clavulanique							
Tazobactam							

Acide clavulanique



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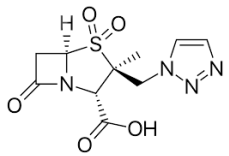

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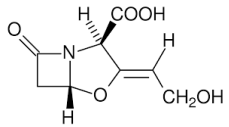
Acide clavulanique							
Tazobactam							
Diazabicyclooctanes							
Avibactam							
Relebactam							
Dérivés de l'acide boronique							
Vaborbactam							

Acide clavulanique



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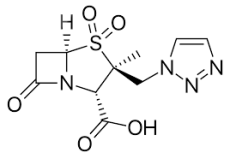

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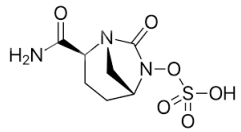

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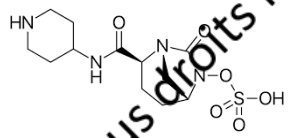
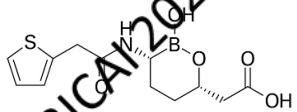


Vaborbactam



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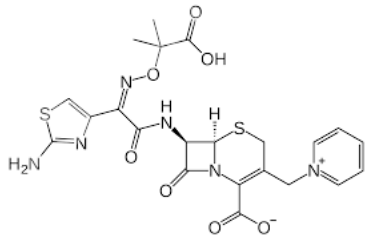
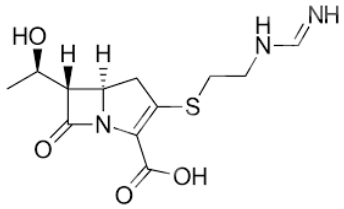
Les nouveaux inhibiteurs de β-lactamase

Anciens antibiotiques

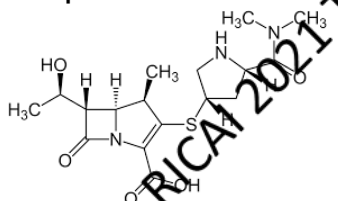
Ceftazidime



Imipénème cilastatine



Méropénème



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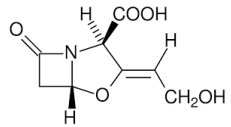

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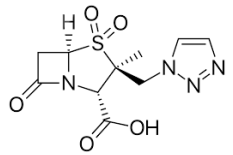

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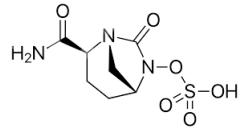

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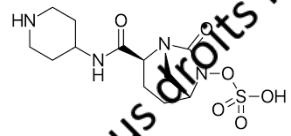

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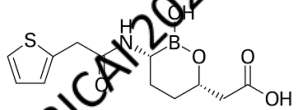

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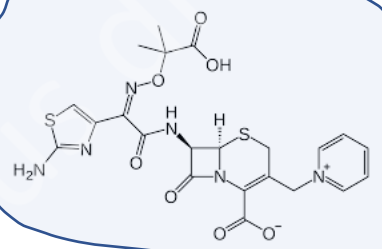
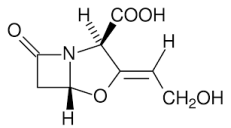


ZAVICEFTA®

Acide clavulanique



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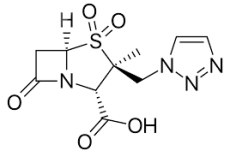
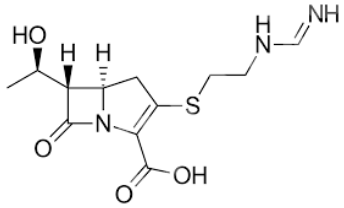


Imipénème cilastatine



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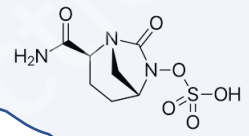

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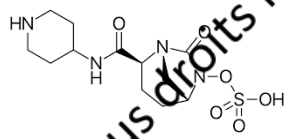

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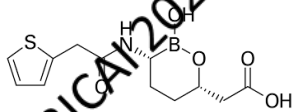
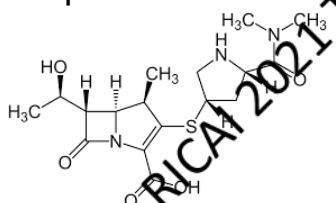


Méropénème



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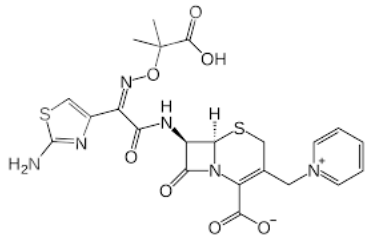

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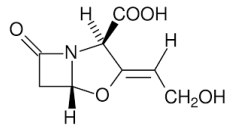

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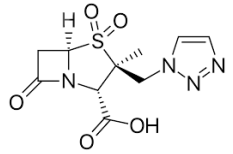

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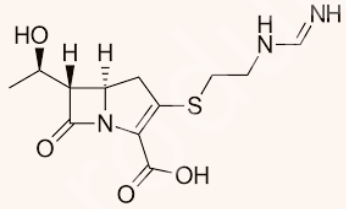

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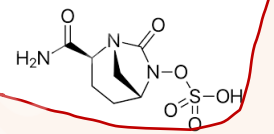

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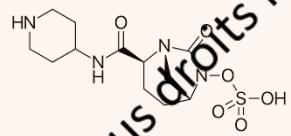

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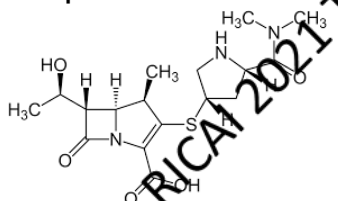

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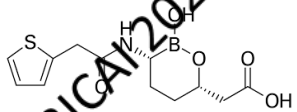

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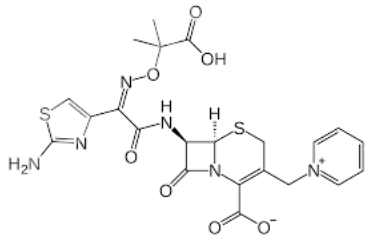

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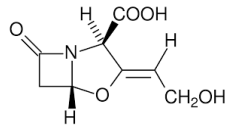

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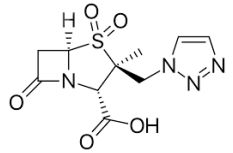
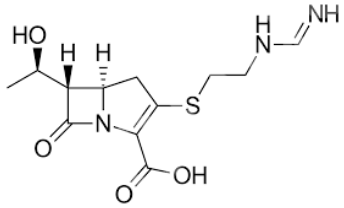


Imipénème cilastatine



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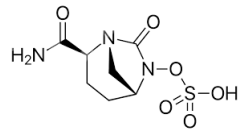

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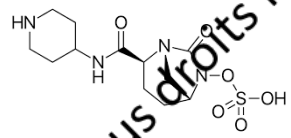
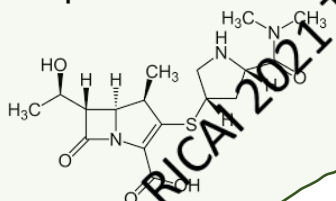
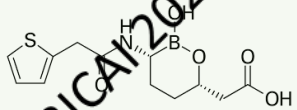


Méropénème



VABOREM®

Vaborbactam



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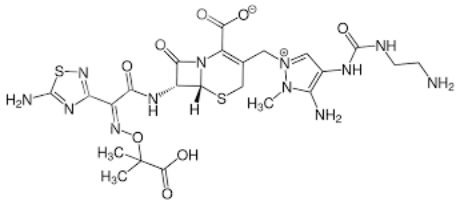
Nouveaux antibiotiques

Ceftolozane



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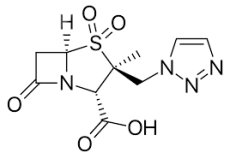
Ancien inhibiteur

Tazobactam



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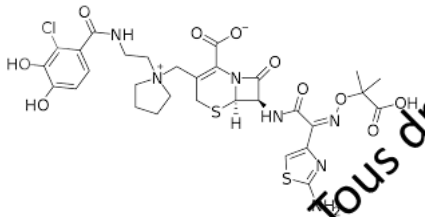

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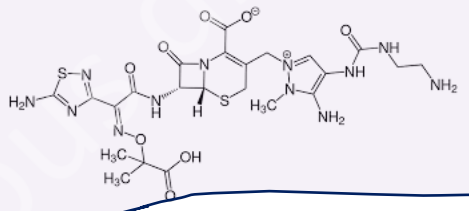
Nouveaux antibiotiques

Ceftolozane



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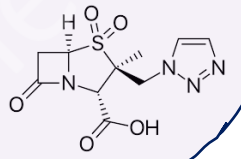
Tazobactam



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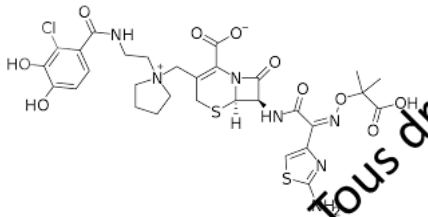

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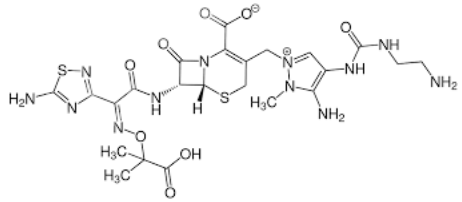

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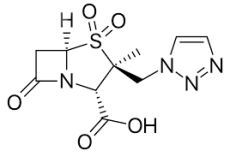
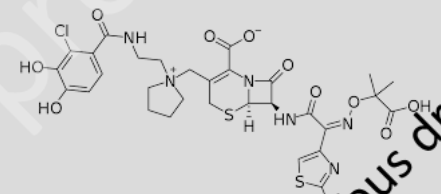
Ancien inhibiteur

Tazobactam



Cefiderocol



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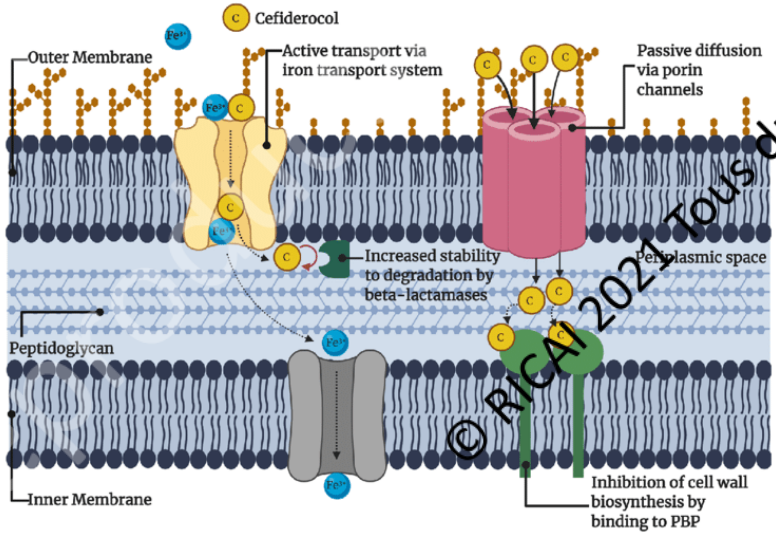

Annals of Pharmacotherapy 2020

Recommended antibiotic treatment options for carbapenem-resistant Enterobacterales (CRE), assuming *in vitro* susceptibility to agents in table, for URINARY TRACT INFECTIONS

Source of Infection	Preferred Treatment	Alternative Treatment (first-line options not available or tolerated)
Cystitis	Oral drug Single-dose of an aminoglycoside Meropenem[1] (standard-infusion): only if ertapenem resistant, meropenem susceptible, AND carbapenemase testing results are either not available or negative.	**Ceftazidime-avibactam** **Meropenem-vaborbactam** **Imipenem-cilastatin-relebactam** **Cefiderocol** Colistin (only when no alternative options are available)
Pyelonephritis or cUTI[2]	**Ceftazidime-avibactam** **Meropenem-vaborbactam** **Imipenem-cilastatin-relebactam** **Cefiderocol** Meropenem[1] (extended-infusion): only if ertapenem resistant, meropenem susceptible, AND carbapenemase testing results are either not available or negative.	Once-daily aminoglycosides

IDSA Infectious Diseases Society of America

V1.0
August 2020

Recommended antibiotic treatment options for carbapenem-resistant Enterobacterales (CRE), assuming *in vitro* susceptibility to agents in table, for OTHER INFECTIONS

Source of Infection	Preferred Treatment	Alternative Treatment (first-line options not available or tolerated)
Infections outside of the urinary tract Resistant to ertapenem, susceptible to meropenem, AND carbapenemase testing results are either not available or negative	Meropenem[1] (extended infusion)	**Ceftazidime-avibactam**
Infections outside of the urinary tract **Resistant to ertapenem, meropenem**, AND carbapenemase testing results are either not available or negative	**Ceftazidime-avibactam** **Meropenem-vaborbactam** **Imipenem-cilastatin-relebactam**	**Cefiderocol** Tigecycline, eravacycline (IAI)
KPC identified (Or carbapenemase positive but identity of carbapenemase unknown[3])	**Ceftazidime-avibactam** **Meropenem-vaborbactam** **Imipenem-cilastatin-relebactam**	**Cefiderocol** Tigecycline, eravacycline (IAI)
Metallo-β-lactamase (i.e., NDM, VIM, or IMP) carbapenemase identified	**Ceftazidime-avibactam** + aztreonam **Cefiderocol**	Tigecycline, eravacycline (IAI)
OXA-48-like carbapenemase identified	**Ceftazidime-avibactam**	**Cefiderocol** Tigecycline, eravacycline (IAI)

Recommended antibiotic treatment options for difficult-to-treat (DTR) *Pseudomonas aeruginosa*, assuming *in vitro* susceptibility to agents in table

Source of Infection	**Preferred Treatment**	**Alternative Treatment** (when first-line options not available/tolerated)
Cystitis	**Ceftolozane-tazobactam** **Ceftazidime- avibactam** **Imipenem-cilastatin-relebactam** **Cefiderocol** or a single-dose of an aminoglycoside	Colistin
Pyelonephritis or cUTI[1]	**Ceftolozane-tazobactam** **Ceftazidime- avibactam** **Imipenem-cilastatin-relebactam** **Cefiderocol**	Once-daily aminoglycosides
Infections outside of the urinary tract	**Ceftolozane-tazobactam** **Ceftazidime- avibactam** **Imipenem-cilastatin-relebactam**	**Cefiderocol** Aminoglycoside monotherapy: limited to uncomplicated bloodstream infections with complete source control[2]

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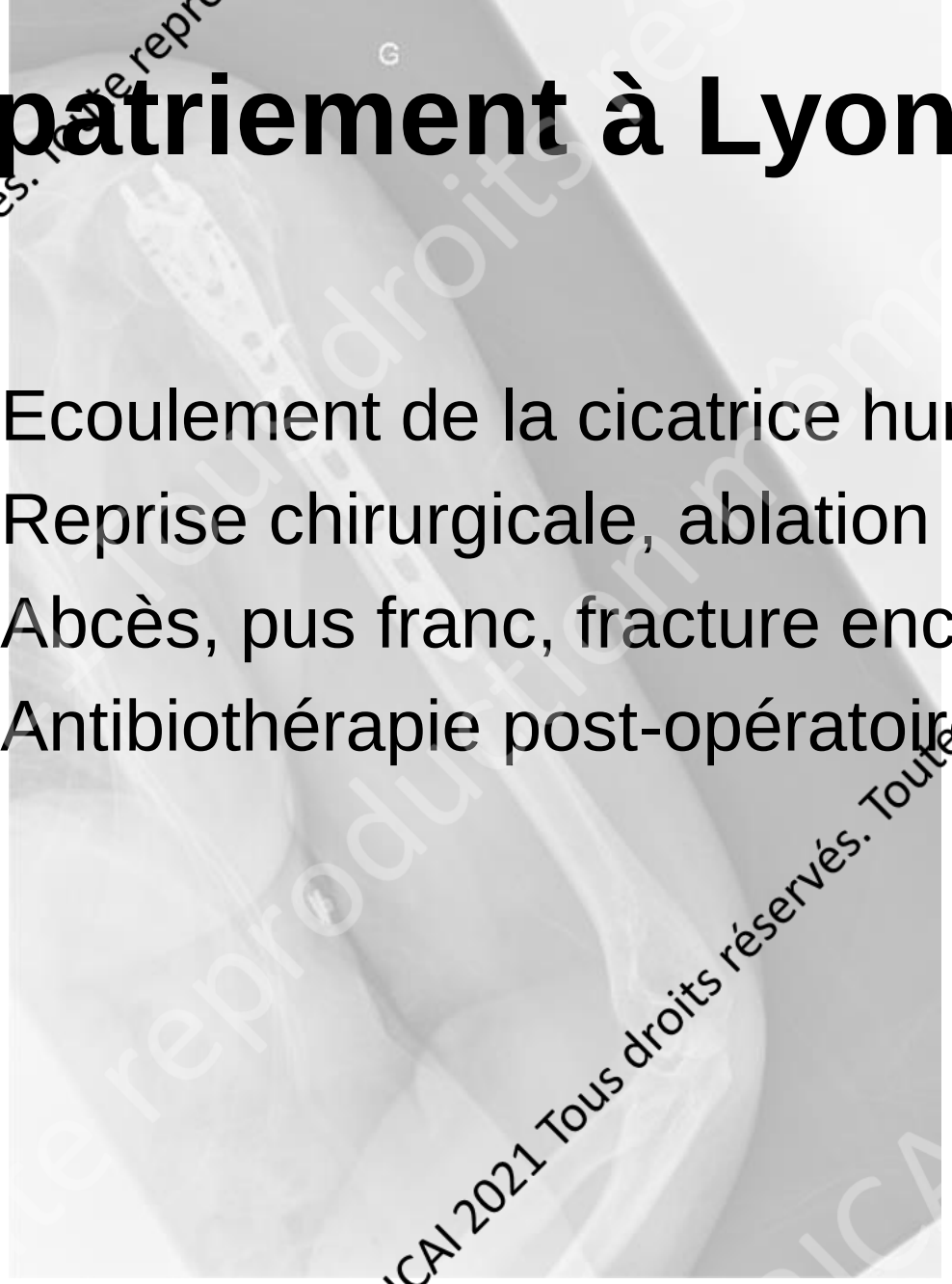
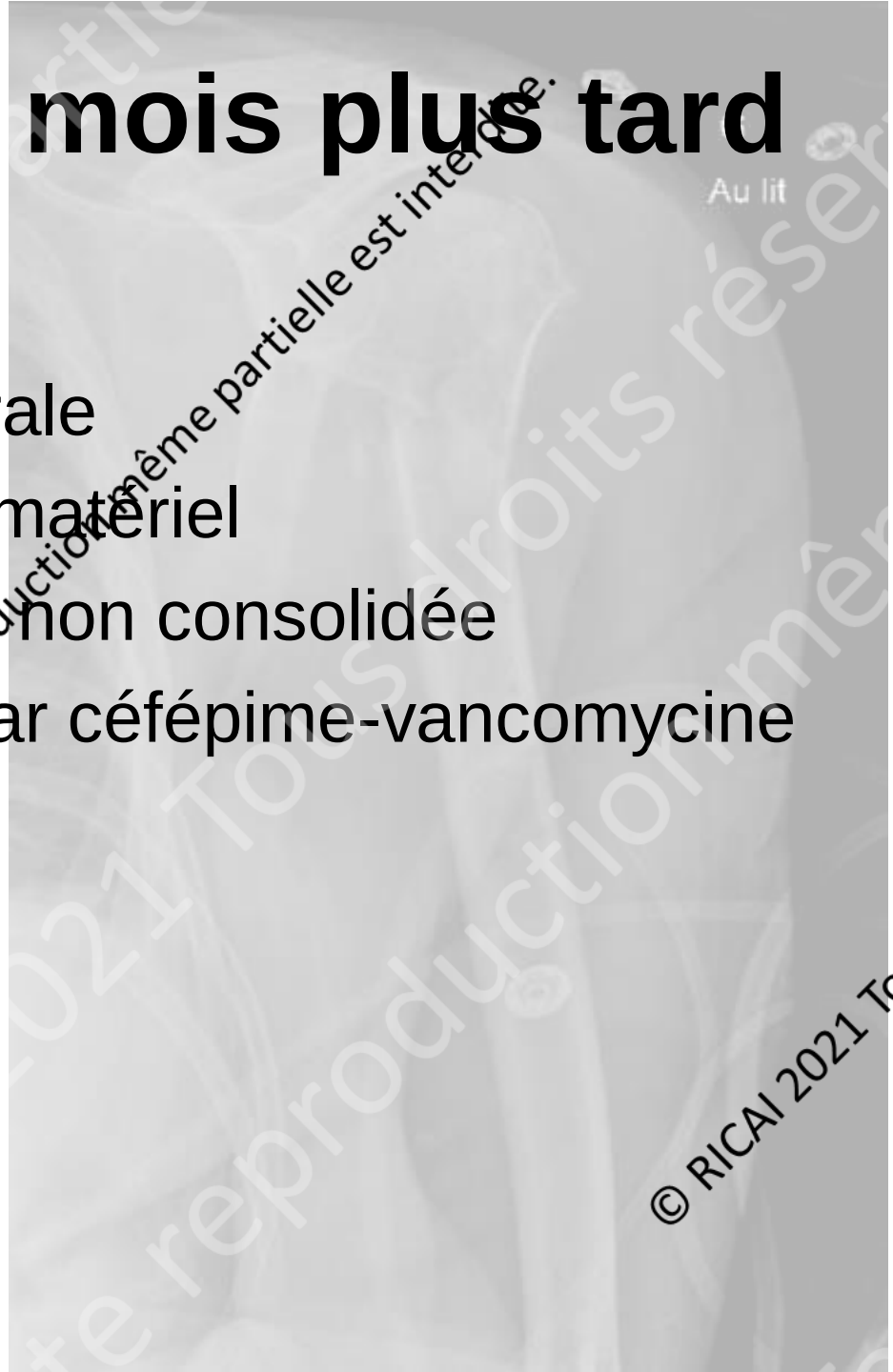
Cas clinique

- Patiente de 70 ans, 45 kg
- Cancer du sein en 2011, HTA
- Fracture humérale gauche lors d'un voyage en Ouzbékistan (AVP)
- Ostéosynthèse en Turquie
- Séjour en réanimation avec pneumonie nosocomiale (traitement par colistine-tigécycline)

Rapatriement à Lyon 1 mois plus tard

- Ecoulement de la cicatrice humérale
- Reprise chirurgicale, ablation du matériel
- Abcès, pus franc, fracture encore non consolidée
- Antibiothérapie post-opératoire par céfépime-vancomycine





	Klebsiella pneumoniae CMI (mg/l)
Ampicilline	R
Amoxicilline	R
Amoxicilline + Ac.Clavulanique	R
Ticarcilline	R
Ticarcilline + Ac. Clav	R
Temocilline	R
Pipéracilline	
Pipéracilline + Tazobactam	
Céfoxitine	R
Céfotaxime	R
Ceftazidime	R
Céfépime	
Aztréonam	R
Ertapénème	R
Imipénème	S
Meropeneme	R
Gentamicine	R
Tobramycine	R
Amikacine	R
Tigécycline	S
Norfloxacine	R
Ciprofloxacine	R
Moxifloxacine	R
Acide Nalidixique	R
Cotrimoxazole	R

R

Fosfomycine (Etest)	S CMI : 64
Aztreonam (Etest)	R CMI : > 256
Cefepime (Etest)	R CMI : 64
Imipeneme (Etest)	S CMI : 0.380
Meropeneme (Etest)	R CMI : > 32
Tobramycine (Etest)	S CMI : 0.250
Tigecycline (Etest)	S CMI : 0.250
Ceftolozane-tazobactam (Etest)	R CMI : > 256
Ceftazidime-Avibactam (Etest)	R CMI : > 256
Colistine (UMIC)	R CMI : 64

CMI par E-test Aztréonam + Ceftazidime/Avibactam : 0.19 mg/L.

Adaptation thérapeutique

- Aztréonam 2g/8h – Ceftazidime/avibactam 2g/8h – Daptomycine

- Aztréonam 2g/8h – Ceftazidime/avibactam 2g/8h – Fosfomycine 3g en 3h/8h

Adaptation thérapeutique

- Aztréonam 2g/8h – Ceftazidime/avibactam 2g/8h – Daptomycine

- Aztréonam 2g/8h – Ceftazidime/avibactam 2g/8h – Fosfomycine 3g en 3h/8h

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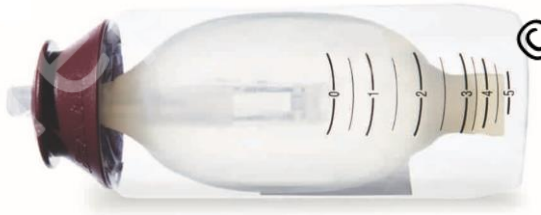
- Aztréonam 3g dans un diffuseur sur 12h – Ceftazidime/avibactam 3g dans un diffuseur sur 12h



Aztréonam + Ceftazidime/avibactam ?

Can Ceftazidime-Avibactam and Aztreonam Overcome β-Lactam Resistance Conferred by Metallo-β-Lactamases in *Enterobacteriaceae*?

Steven Marshall,[a] Andrea M. Hujer,[a,b] Laura J. Rojas,[a,b,c] Krisztina M. Papp-Wallace,[a] Romney M. Humphries,[d] Brad Spellberg,[e] Kristine M. Hujer,[a,b] Emma K. Marshall,[a] Susan D. Rudin,[a,b] Federico Perez,[a] Brigid M. Wilson,[a] Ronald B. Wasserman,[f] Linda Chikowski,[g] David L. Paters[h] Alejandro J. Vila,[i] David van Duin,[j] Barry N. Kreiswirth,[k] Henry F. Chambe[r] Vance G. Fowler, Jr.,[m] Michael R. Jacobs,[n] Mark E. Pulse,[o] William J. Weiss,[o] Robert A. Bonomo[a,b,c,p]

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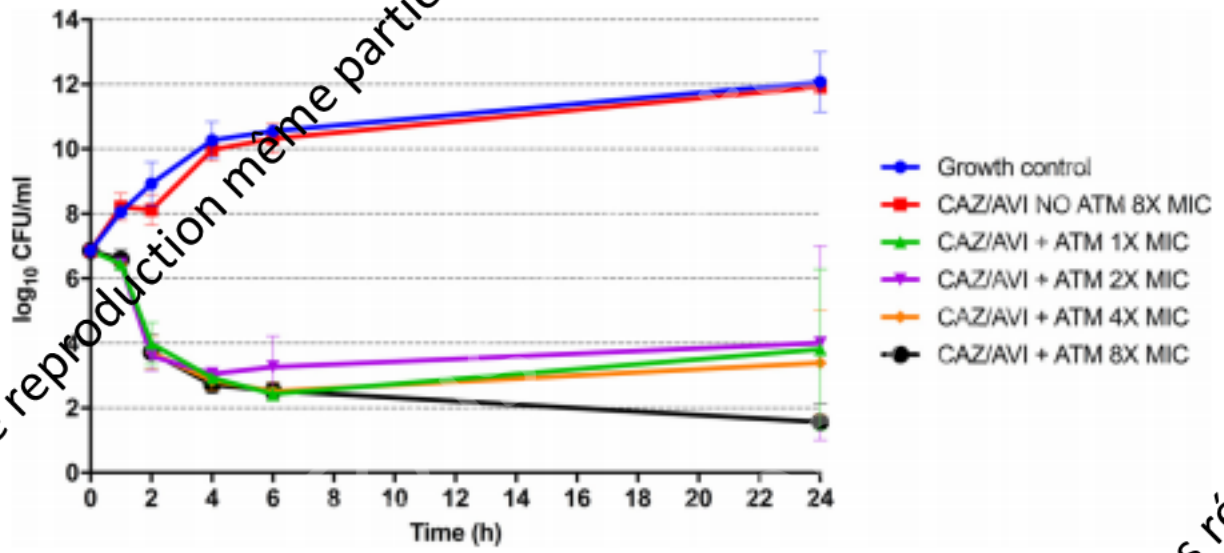

FIG 2 Time-kill curve for *K. pneumoniae* isolate 1.41. ATM concentrations were held constant at 8 μg/ml for all combinations, with two exceptions: (i) the growth control (no antibiotics added) and (ii) CAZ-AVI with no ATM at 8× the MIC. Various ceftazidime-avibactam (CAZ-AVI) concentrations were added corresponding to 1× (1 μg/ml CAZ plus 0.25 μg/ml AVI), 2× (2 μg/ml CAZ plus 0.5 μg/ml AVI), 4× (4 μg/ml CAZ plus 1 μg/ml AVI), and 8× (8 μg/ml CAZ plus 2 μg/ml AVI) the MIC of the combination CAZ-AVI plus ATM obtained by agar dilution (1 μg/ml). Three replicates were conducted for each of the conditions reported in the time-kill assay.

K. Pneumoniae NDM-1, CTX-M-15, OXA, SHV, TEM

Aztréonam +

?

Aztreonam plus Clavulanate, Tazob
Treatment of Infections Caused by
Producing Gram-Negative Bacteria

Cécile Emeraud,[a,b,c,d] Lelia Escaut,[e] Athénaïs Boucly,[d,f,g] Nicolas Fortin
Laurent Dortet[a,b,c,d]

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TABLE 2 MICs and categorization according to CLSI breakpoints for antimicrobials on MBL-producing *Enterobacteriaceae*, MBL-producing *P. aeruginosa*, and *S. maltophilia*

		MICs (mg/liter) by treatment[a]						
Enterobacteriaceae sp.	β-Lactamases	ATM	CZA	C/T	AMC	ATM+ CZA	ATM+ C/T	ATM+ AMC
E. coli	NDM-1 + OXA-1 + OXA-10 + CMY-16 + TEM-1	32	>256	>256	96	0.125	24	8
E. coli	NDM-1 + CTX-M-15 + TEM-1	>256	>256	>256	12	1	>256	2
E. coli	NDM-1 + OXA-1 + OXA-2 + CTX-M-15 + TEM-1	>256	>256	>256	24	2	>256	8
E. coli	NDM-1 + CTX-M-15 + TEM-1	>256	>256	>256	32	6	>256	8
E. coli	NDM-4 + CTX-M-15 + OXA-1	>256	>256	>256	96	6	>256	4
E. coli	NDM-4 + CTX-M-15 + CMY-6	>256	>256	>256	>256	6	>256	24
E. coli	NDM-5 + TEM-1 + CTX-M-15	>256	>256	>256	96	8	>256	64
E. coli	NDM-6 + CTX-M-15 + OXA-1	>256	>256	>256	16	1	>256	2
E. coli	NDM-7 + ESBL	>256	>256	>256	96	4	>256	32
K. pneumoniae	NDM-1 + CTX-M-15 + SHV-11 + OXA-1	>256	>256	>256	12	0.125	24	0.38
K. pneumoniae	NDM-1 + CTX-M-15 + CMY-4 + OXA-1	>256	>256	>256	32	0.75	>256	16
K. pneumoniae	NDM-1 + CTX-M-15 + OXA-1 + OXA-9 + TEM-1 + SHV-28 + SHV-11	>256	>256	>256	32	0.25	>256	3
K. pneumoniae	NDM-1 + OXA-1 + SHV-11	>256	>256	>256	12	0.047	0.094	0.094
K. pneumoniae	NDM-1 + OXA-1 + CTX-M-15 + TEM-1 + SHV-28 + OXA-9 + CMY-6	>256	>256	>256	16	0.047	3	0.25
K. pneumoniae	NDM-1 + TEM-1 + CTX-M-15 + SHV-12 + OXA-9	>256	>256	>256	12	0.125	96	1
K. pneumoniae	NDM-1 + TEM-1 + CTX-M-15 + SHV-12 + OXA-9	>256	>256	>256	12	0.125	96	0.5
K. pneumoniae	NDM-1 + TEM-1 + CTX-M-15 + SHV-11 + OXA-1	>256	>256	>256	12	0.064	8	0.38
Salmonella enterica	NDM-1 + CTX-M-15 + TEM-1 + OXA-1 + OXA-9 + OXA-10	>256	>256	>256	16	0.125	16	0.5
E. coli	VIM-1 + CTX-M-3	>256	>256	>256	16	0.125	24	0.5
E. coli	VIM-4 + ESBL	16	>256	>256	24	1.5	24	16
K. pneumoniae	VIM-1 + SHV-5	>256	>256	>256	>256	0.25	192	1.5
K. pneumoniae	VIM-1 + SHV-12	>256	>256	>256	16	0.125	4	0.25
K. pneumoniae	VIM-1 + ESBL	>256	>256	>256	>256	12	16	12
K. pneumoniae	VIM-1 + SHV-5	16	>256	>256	>256	6	12	32
K. pneumoniae	VIM-1 + TEM-1 + SHV-5	96	>256	>256	>256	96	64	48
K. pneumoniae	VIM-1 + SHV	>256	>256	>256	24	0.25	8	0.75
K. pneumoniae	VIM-1 + SHV	>256	>256	>256	12	0.125	2	0.38
K. pneumoniae	VIM-19 CTX-M-3 + TEM-1 + SHV-1	6	32	>256	16	0.047	2	1.5
Enterobacter cloacae	VIM SHV-70	256	128	>256	48	0.094	0.25	0.19
E. cloacae	VIM + CTX-M-15 + TEM-1 + SHV-31	64	>256	>256	64	1	64	32
Citrobacter freundii	VIM-2 + TEM-1 + ESBL	16	16	>256	32	0.25	2	24
C. freundii	VIM-2 + TEM-1 + OXA-9 + OXA-10	32	24	>256	32	1.5	16	24
E. coli	IMP-8 + SHV-12	128	>256	>256	24	0.19	2	0.38
K. pneumoniae	IMP-8 + SHV-12	>256	48	>256	12	0.094	32	0.25
E. cloacae	IMP-8 + SHV-12	12	>256	>256	24	0.032	0.064	0.094
E. cloacae	GIM-1 + ESBL	12	>256	48	24	0.5	8	16
Enterobacter hormaechei	TMB-1 + overexpressed Case[b]	64	64	32	32	0.5	12	12
C. freundii	TMB-1 + overexpressed Case	64	96	32	12	0.125	12	12
K. pneumoniae	NDM-1 + OXA-181 + SHV-11 + TEM-1 + CTX-M-15 + OXA-1	64	>256	>256	48	0.094	8	2
K. pneumoniae	NDM-1 + OXA-181 + SHV-27 + CTX-M-15 + TEM-1 + OXA-1	128	>256	>256	96	0.25	16	3
K. pneumoniae	NDM-1 + OXA-181 + SHV-11 + CTX-M-15 + OXA-1	256	>256	>256	>256	0.19	32	3
K. pneumoniae	NDM-1 + OXA-181 + SHV-11 + TEM-1 + CTX-M-15 + OXA-9	>256	>256	>256	>256	0.19	>256	12
K. pneumoniae	NDM-1 + OXA-181 + SHV-2 + CTX-M-15 + OXA-1	>256	>256	>256	32	0.125	32	1.5
C. freundii	NDM-1 + OXA-181 + OXA-1 + OXA-9 + OXA-10 + CTX-M-15 + TEM-1	>256	>256	>256	64	0.75	>256	12
E. coli	NDM-1 + OXA-48 + ESBL	32	>256	>256	48	0.094	12	8
E. coli	NDM-1 + OXA-48 + ESBL	>256	>256	>256	>256	0.75	>256	4
E. coli	NDM-1 + OXA-48 + ESBL	>256	>256	>256	>256	1	>256	4
K. pneumoniae	NDM-1 + OXA-232 + ESBL	64	>256	>256	>256	0.094	24	4
E. coli	NDM-1 + OXA-232 + ESBL	>256	>256	>256	>256	1	>256	8
E. coli	NDM-5 + OXA-232 + ESBL	>256	>256	>256	96	1	>256	64
S. maltophilia		>256	>256	>256	32	2	128	2
S. maltophilia		>256	>256	6	96	1.5	6	2
S. maltophilia		>256	>256	>256	>256	4	>256	4
S. maltophilia		>256	16	72	16	1	8	2
S. maltophilia		>256	>256	>256	>256	0.75	24	0.75
P. aeruginosa	VIM-2 + overexpressed cephalosporinase	16	24	>256	>256	8	12	16
P. aeruginosa	IMP-2 + overexpressed cephalosporinase	12	>256	>256	>256	6	12	24
P. aeruginosa	IMP-1 + overexpressed cephalosporinase	128	>256	>256	>256	96	48	64

Aztréonam + Ceftazidime/avibactam ?

TABLE 2 MICs and categorization according to CLSI breakpoints for antimicrobials on MBL-producing *Enterobacteriaceae*, MBL-producing *P. aeruginosa*, and *S. maltophilia*

		MICs (mg/liter) by treatment[a]						
Enterobacteriaceae sp.	β-Lactamases	ATM	CZA	C/T	AMC	ATM+ CZA	ATM+ C/T	ATM+ AMC
K. pneumoniae	NDM-1 + CTX-M-15 + SHV-11 + OXA-1	>256	>256	>256	12	0.125	24	0.38
K. pneumoniae	NDM-1 + CTX-M-15 + CMY-4 + OXA-1	>256	>256	>256	32	0.75	>256	16
K. pneumoniae	NDM-1 + CTX-M-15 + OXA-1 + OXA-9 + TEM-1 + SHV-28 + SHV-11	>256	>256	>256	32	0.25	>256	3
K. pneumoniae	NDM-1 + OXA-1 + SHV-11	>256	>256	>256	12	0.047	0.094	0.094
K. pneumoniae	NDM-1 + OXA-1 + CTX-M-15 + TEM-1 + SHV-28 + OXA-9 + CMY-6	>256	>256	>256	16	0.047	3	0.25
K. pneumoniae	NDM-1 + TEM-1 + CTX-M-15 + SHV-12 + OXA-9	>256	>256	>256	12	0.125	96	1
K. pneumoniae	NDM-1 + TEM-1 + CTX-M-15 + SHV-12 + OXA-9	>256	>256	>256	12	0.125	96	0.5
K. pneumoniae	NDM-1 + TEM-1 + CTX-M-15 + SHV-11 + OXA-1	>256	>256	>256	12	0.064	8	0.38
Salmonella enterica	NDM-1 + CTX-M-15 + TEM-1 + OXA-1 + OXA-9 + OXA-10	>256	>256	>256	16	0.125	16	0.5
E. coli	VIM-1 + CTX-M-3	>256	>256	>256	16	0.125	24	0.5
E. coli	VIM-4 + ESBL	16	>256	>256	24	1.5	24	16
K. pneumoniae	VIM-1 + SHV-5	>256	>256	>256	>256	0.25	192	1.5
K. pneumoniae	VIM-1 + SHV-5	>256	>256	>256	16	0.125	4	0.25
K. pneumoniae	VIM-1 + ESBL	>256	>256	>256	>256	12	16	12
K. pneumoniae	VIM-1 + SHV-5	16	>256	>256	>256	6	12	32
K. pneumoniae	VIM-1 + TEM-1 + SHV-5	96	>256	>256	>256	96	64	48
K. pneumoniae	VIM-1 + SHV-5	>256	>256	>256	24	0.25	8	0.75
K. pneumoniae	VIM-1 + SHV-5	>256	>256	>256	12	0.125	2	0.38
K. pneumoniae	VIM-19 + CTX-M-3 + TEM-1 + SHV-1	6	32	>256	16	0.047	2	1.5

ATM, aztreonam; CZA, ceftazidime-avibactam; C/T, ceftolozane-tazobactam; AMC, amoxicillin-clavulanate

Aztréonam + Ceftazidime/avibactam ?

Ceftazidime-Avibactam and Aztreonam, an Interesting Strategy To Overcome β-Lactam Resistance Conferred by Metallo-β-Lactamases in *Enterobacteriaceae* and *Pseudomonas aeruginosa*

Benjamin Davido,[a] Lesly Fellous,[b] Christine Lawrence,[c,d] Virginie Maxime,[e]
Martin Rottman,[d,f] Aurélien Dinh[a]

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Susceptibility testing showing with ellipsometry the effect of the synergistic combination of CAZ-AVI and ATM. The combination (middle strip) was tested by first applying an ATM strip to the Mueller-Hinton (MH) agar, removing it after 5 min, and then applying a CAZ-AVI strip on the exact same location and placing back the ATM strip to read the susceptibility to ATM in the presence of AVI (and CAZ). *K. pneumoniae* NDM-1/OXA-48 from patient 1.

Ceftazidime/avibactam alone or in combination with aztreonam against colistin-resistant and carbapenemase-producing *Klebsiella pneumoniae*

Aurélie Jayol[1–4], Patrice Nordmann[1–3,5], Laurent Poirel[1–3]* and Véronique Dubois[4,6]

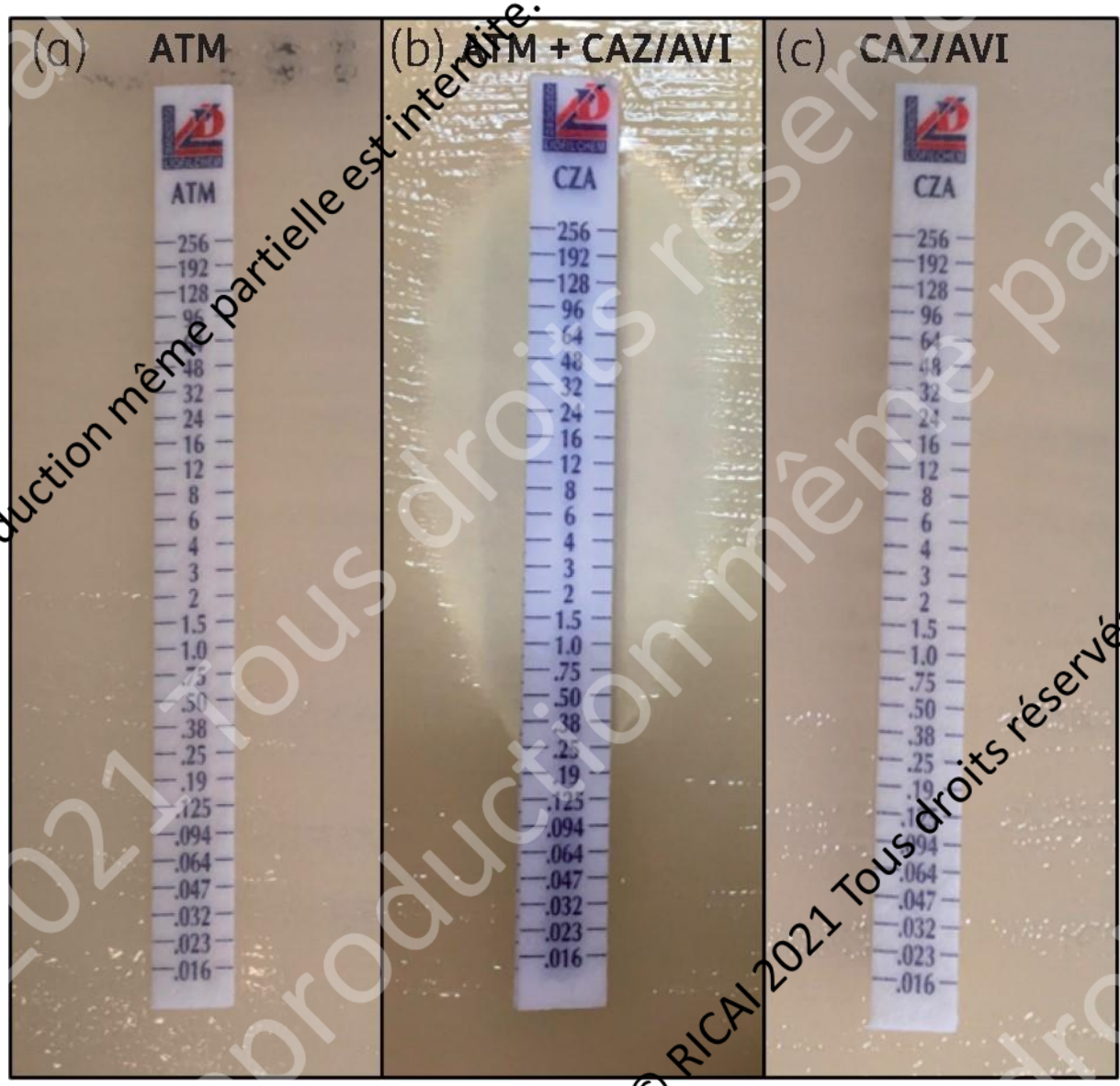
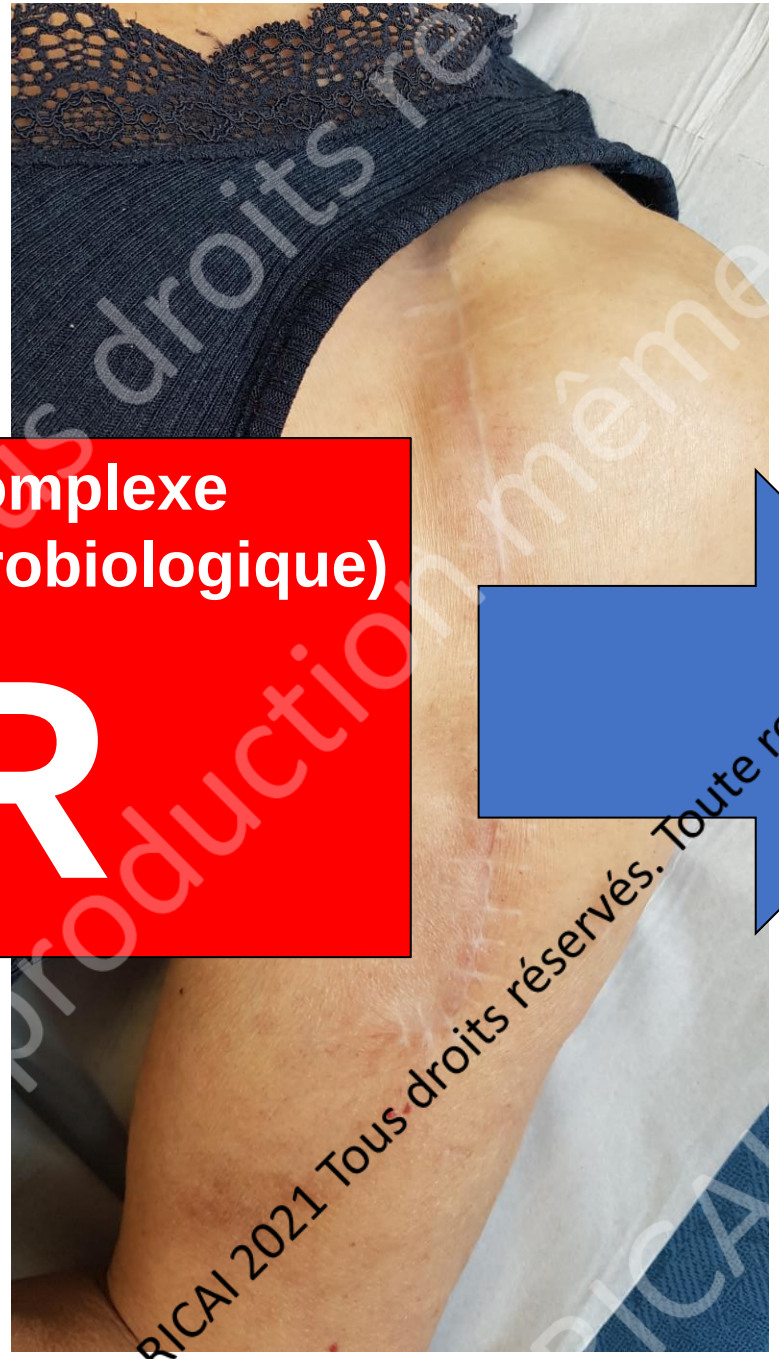


Figure 1 Example of synergistic combination of ceftazidime/avibactam (CAZ/AVI) and aztreonam (ATM) for an NDM + ESBL-producing *K. pneumoniae*. Susceptibility testing of ATM alone (a), combination of CAZ/AVI with ATM (b) and CAZ/AVI alone (c).

J Antimicrob Chemother 2018



IOA Complexe
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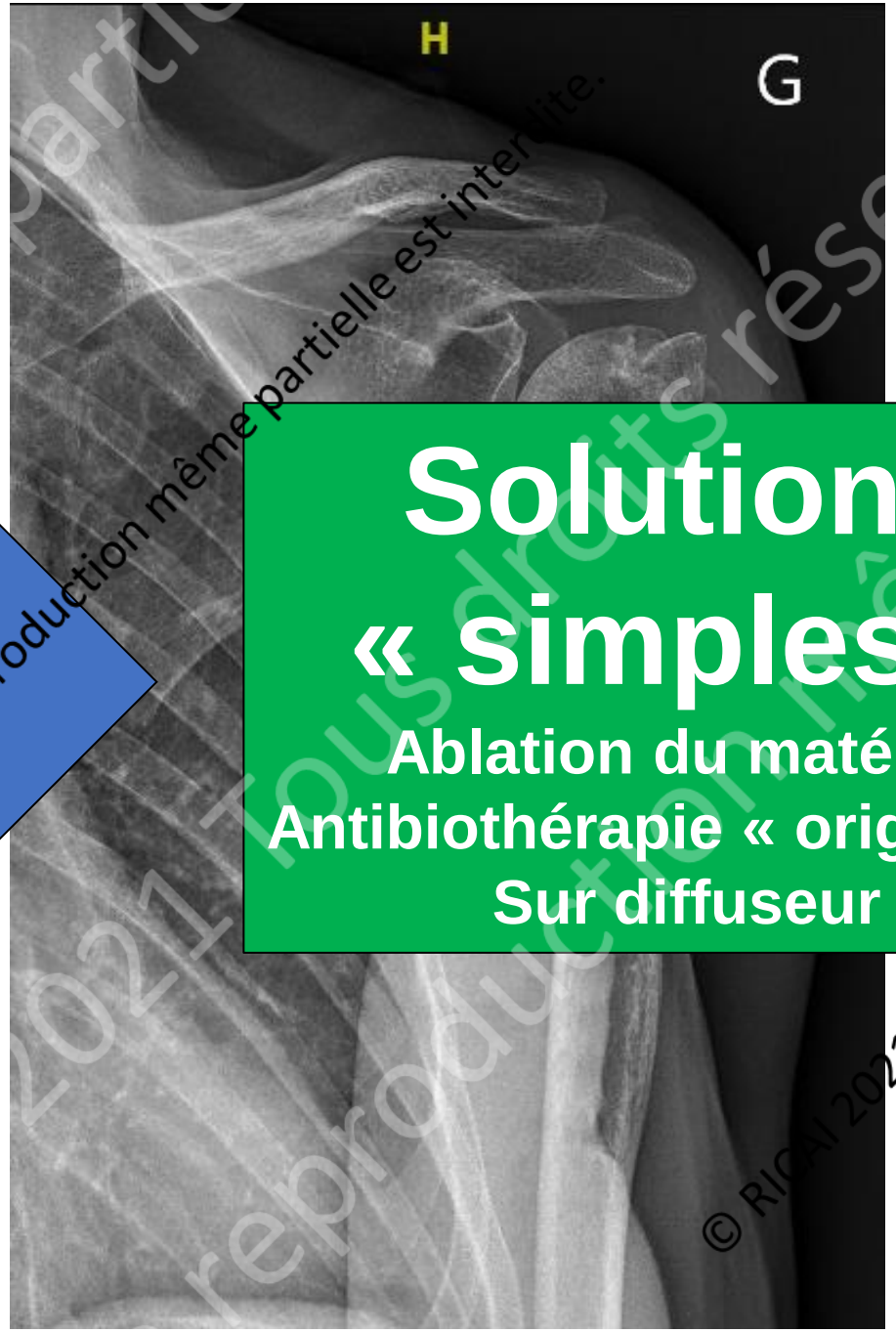

Solutions « simples »

Ablation du matériel
Antibiothérapie « originale »
Sur diffuseur

Bacilles à Gram négatif de résistance émergentes aux antibiotiques :

Nouveaux antibiotiques et nouvelles stratégies thérapeutiques

Pr. Tristan Ferry, MD, PhD
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Claude Bernard Lyon1 University, Lyon

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Regional referral center for the management of complex bone and joint infection
Centre de Référence des IOA complexes de Lyon (CRIOAc Lyon)

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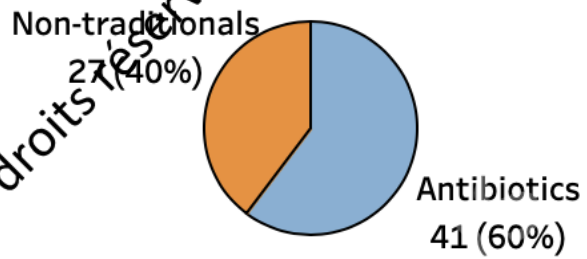
2020 ANTIBACTERIAL AGENTS IN CLINICAL AND PRECLINICAL DEVELOPMENT

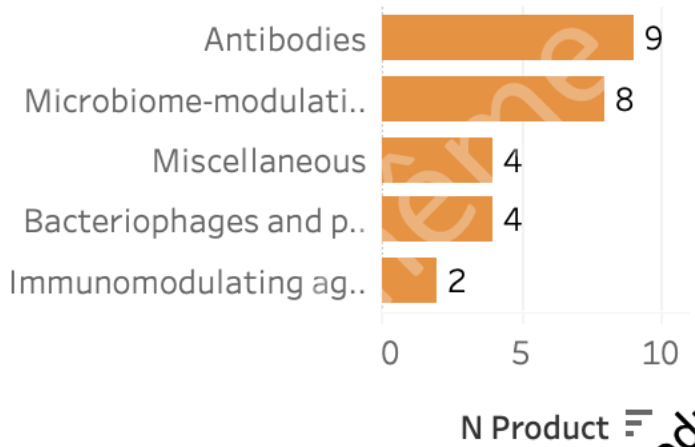
an overview and analysis

World Health Organization

A.1. Products by type



A.2. No. of non traditional products by category



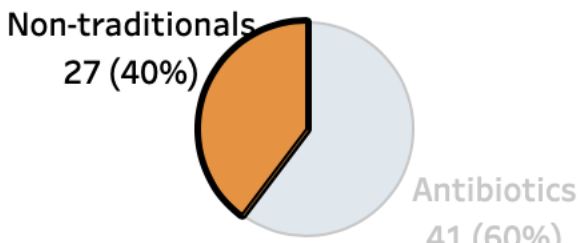
A.3. Products by pathogen category and phase

Pathogen category	Phase I	Phase II	Phase	Unkno..	Total
Priority pathogens	18	15	9	1	43
Mycobacterium tuberculosis	3	9			12
Clostridium difficile	3	8	2		13
Total	24	32	11	1	68

B. Expected activity against priority pathogens

	Critical priority pathogens					Other priority pathogens								
Active?	Acinetobac baumannii	Pseudomor aeruginosa	Enteroba..	All critical priority pathogens	Subtotal	Gram-positive priority p..	Neisseria gonnorhoea	Helicobact pylori	Staphyloco aureus	Enterococc faecium	Streptococ pneumonia	Campyloba spp.	Subtotal	Total
Yes	7	7	14	3	31	17	3	2	17	3	2	2	21	38
Possibly	3	3	3	2	6	1	1	1	1	1			2	8
No	12	17	10	17	18	3	7	8	3	7	7	8	10	20

A.1. Products by type



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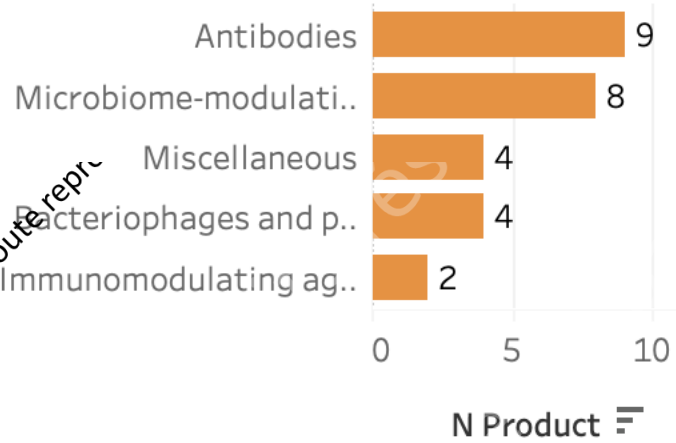


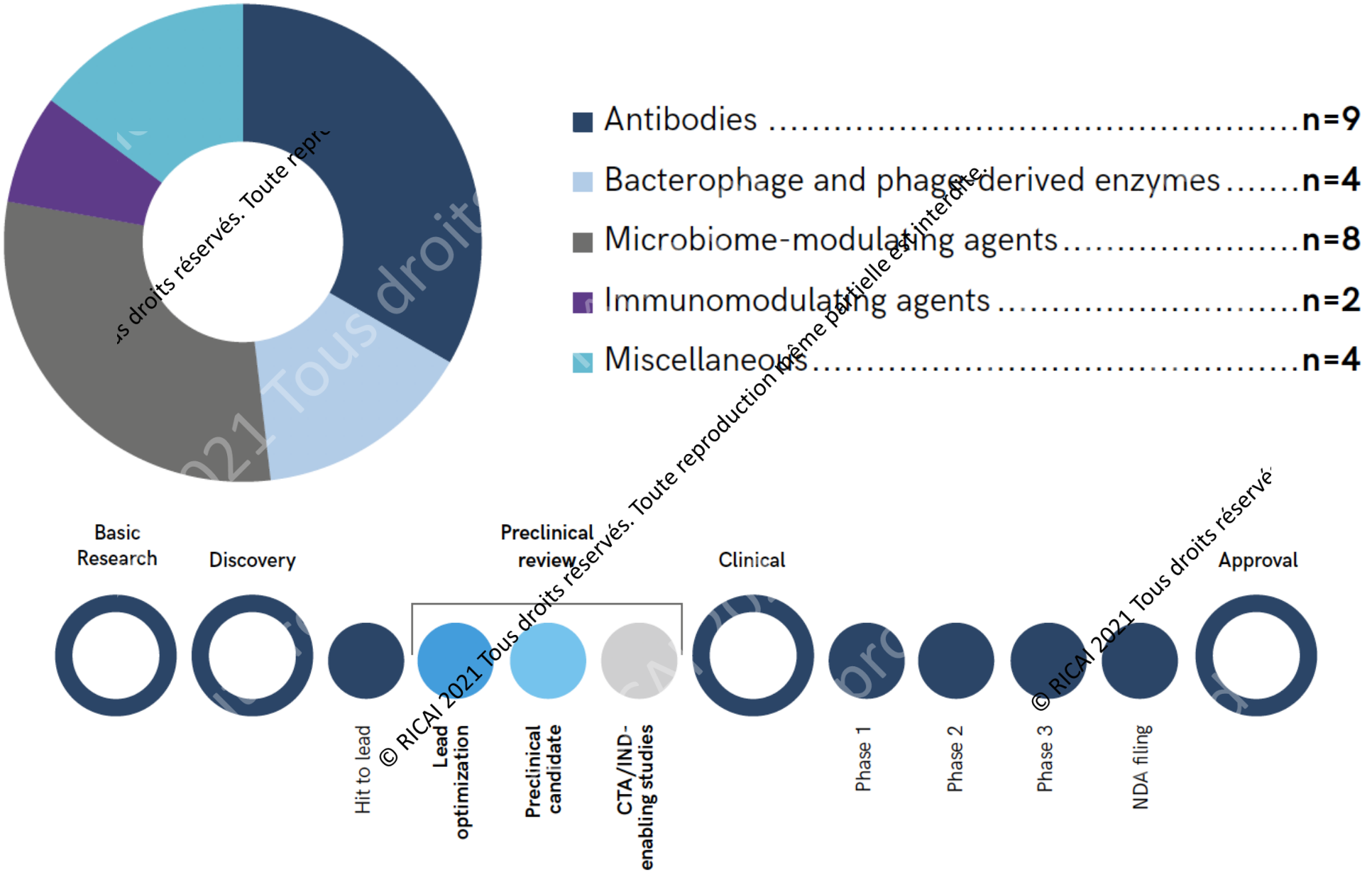
A.3. Products by pathogen category and phase

Pathogen category	Phase I	Phase II	Phase	Unkno..	Total
Priority pathogens	4	11	3	1	19
Clostridium difficile..	2	5	1		8
Total	6	16	4	1	27

B. Expected activity against priority pathogens

Active?	Critical priority pathogens					Other priority pathogens								Total
	Acinetobac baumannii	Pseudomor aeruginosa	Enteroba..	All critical priority pathogens	Subtotal	Gram-positive priority p..	Neisseria gonnorhoe	Helicobact pylori	Staphyloco aureus	Enterococc faecium	Streptococc pneumonia	Campyloba spp.	Subtotal	
Yes	1	5	6	1	13	10	1	1	10	6	1	2	12	19

Fig. 7. Number of non-traditional antibacterials in the clinical pipeline.



Name (synonym)	Phase	Antibiotic class	Route of administration (developer)	Expected activity against priority pathogens
CF-301 (exebacase)	3	Phage endolysin	iv (ContraFect)	*S. aureus*
SAL-200 (tonabacase)	2a	Phage endolysin	iv (iNtRON Biotechnology, Roivant Sciences)	*S. aureus*
PhageBank	1/2	Phage bank (process)	oral (Adaptive Phage Therapeutics and US Department of Defense)	*E. coli*, *K. pneumoniae*
LBP-EC01	1b	CRISPR-Cas3-enhanced phage	iv (Locus Bioscience)	*E. coli*, *K. pneumoniae*

Traitement adjuvant dans les bactériémies à *S. aureus*

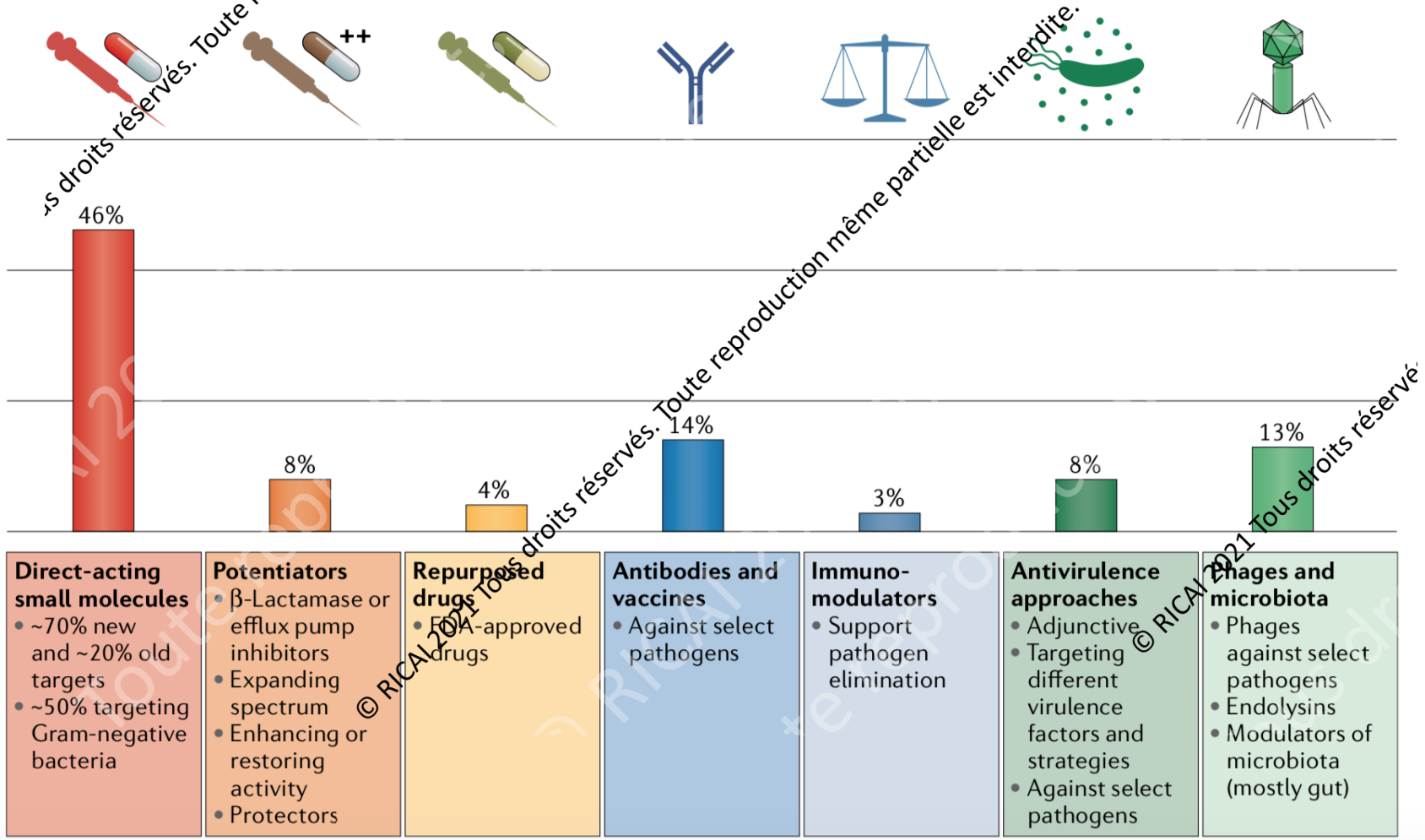
Name (synonym)	Phase	Antibiotic class	Route of administration (developer)	Expected activity against priority pathogens
CF-301 (exebacase)	3	Phage endolysin	iv (ContraFect)	*S. aureus*
SAL-200 (tonabacase)	2a	Phage endolysin	iv (iNtRON Biotechnology, Roivant Sciences)	*S. aureus*
PhageBank	1/2	Phage bank (process)	oral (Adaptive Phage Therapeutics and US Department of Defense)	*E. coli*, *K. pneumoniae*
LBP-EC01	1b	CRISPR-Cas3-enhanced phage	iv (Locus Bioscience)	*E. coli*, *K. pneumoniae*

Traitement vs placebo dans les colonisations ou infections urinaires

Name (synonym)	Phase	Antibiotic class	Route of administration (developer)	Expected activity against priority pathogens
CF-301 (exebacase)	3	Phage endolysin	iv (ContraFect)	*S. aureus*
SAL-200 (tonabacase)	2a	Phage endolysin	iv (iNtRON Biotechnology, Roivant Sciences)	*S. aureus*
PhageBank	1/2	Phage bank (process)	oral (Adaptive Phage Therapeutics and US Department of Defense)	*E. coli*, *K. pneumoniae*
LBP-EC01	1b	CRISPR-Cas3–enhanced phage	iv (Locus Bioscience)	*E. coli*, *K. pneumoniae*
+				
Phagos (PHRC 2015)	1/2	Bacteriophage cocktail	Local (Pherecydes)	*S. aureus*
PhagoPied (PHRC 2015)	1/2	Bacteriophage cocktail	Local (Pherecydes)	*S. aureus*
PhagoDAIR	1/2	Bacteriophage cocktail	Local (Pherecydes)	*S. aureus*

The global preclinical antibacterial pipeline

Ursula Theuretzbacher[1], Kevin Outterson[2,3], Aleks Engel[4] and Anders Karlén[5]*



NATURE REVIEWS | MICROBIOLOGY
2020

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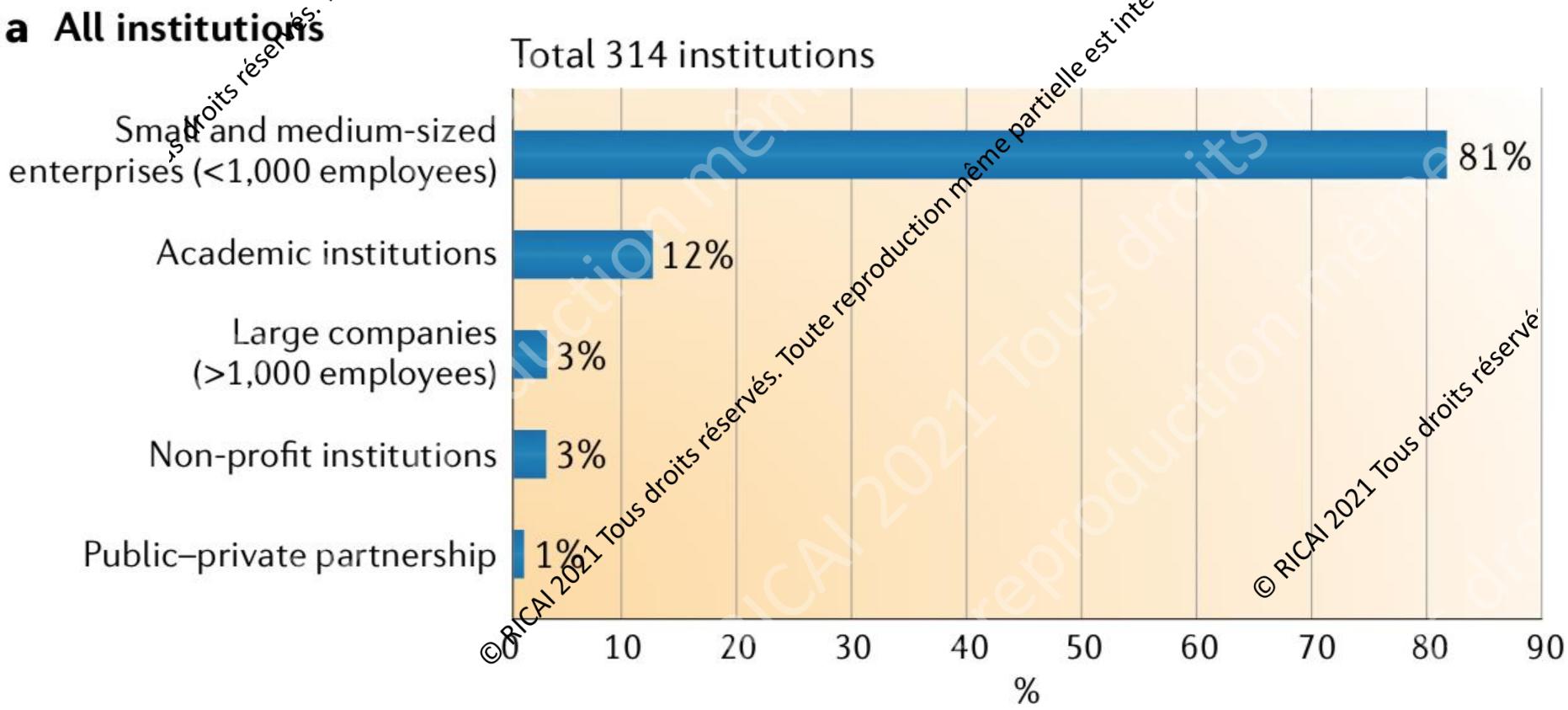

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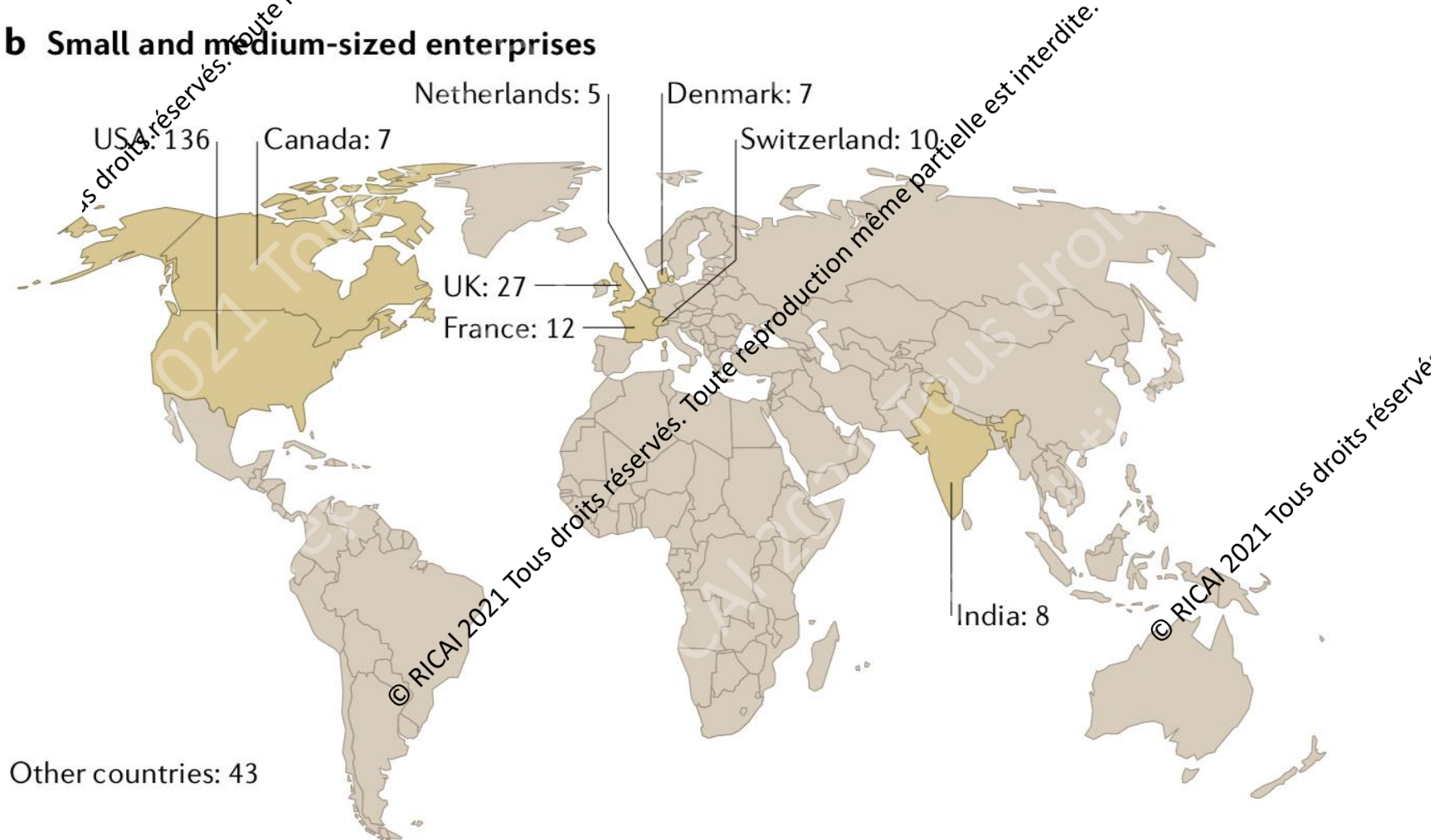

NATURE REVIEWS | MICROBIOLOGY
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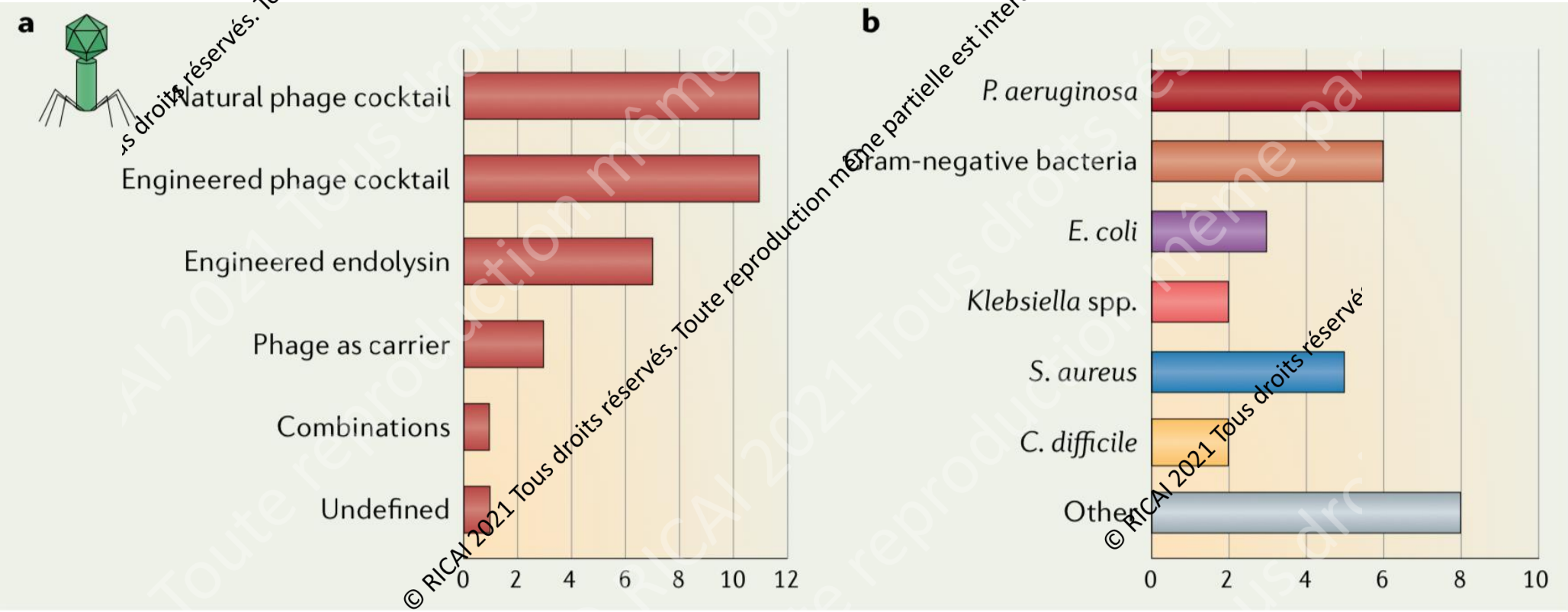


NATURE REVIEWS | MICROBIOLOGY
2020

ESGNTA

ESCMID STUDY GROUP FOR NON-TRADITIONAL ANTIBACTERIAL THERAPY

European Society of Clinical Microbiology and Infectious Diseases

Inauguration Committee Members

Prof. Ran NIR-PAZ
Hadassah-Hebrew University Medical Center
Clinical Microbiology and infectious Diseases
Israël

Prof. Tristan FERRY
Hospices Civils de Lyon
Infectious Diseases
France

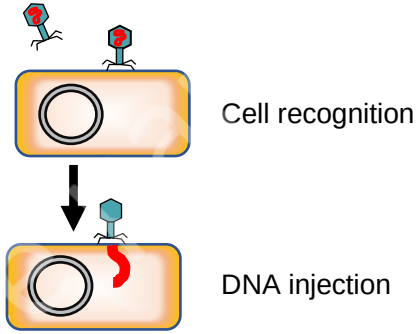
Prof. Patrick SOENTJENS
Department of Clinical Sciences
Institute of Tropical Medicine, Antwerp
Belgium

Prof. Zuzanna DRULIS-KAWA
University of Wroclaw
Department of Pathogen Biology and Immunology
Poland

Prof. Joana AZEREDO
Universidade do Minho
Engenharia Biológica
Portugal

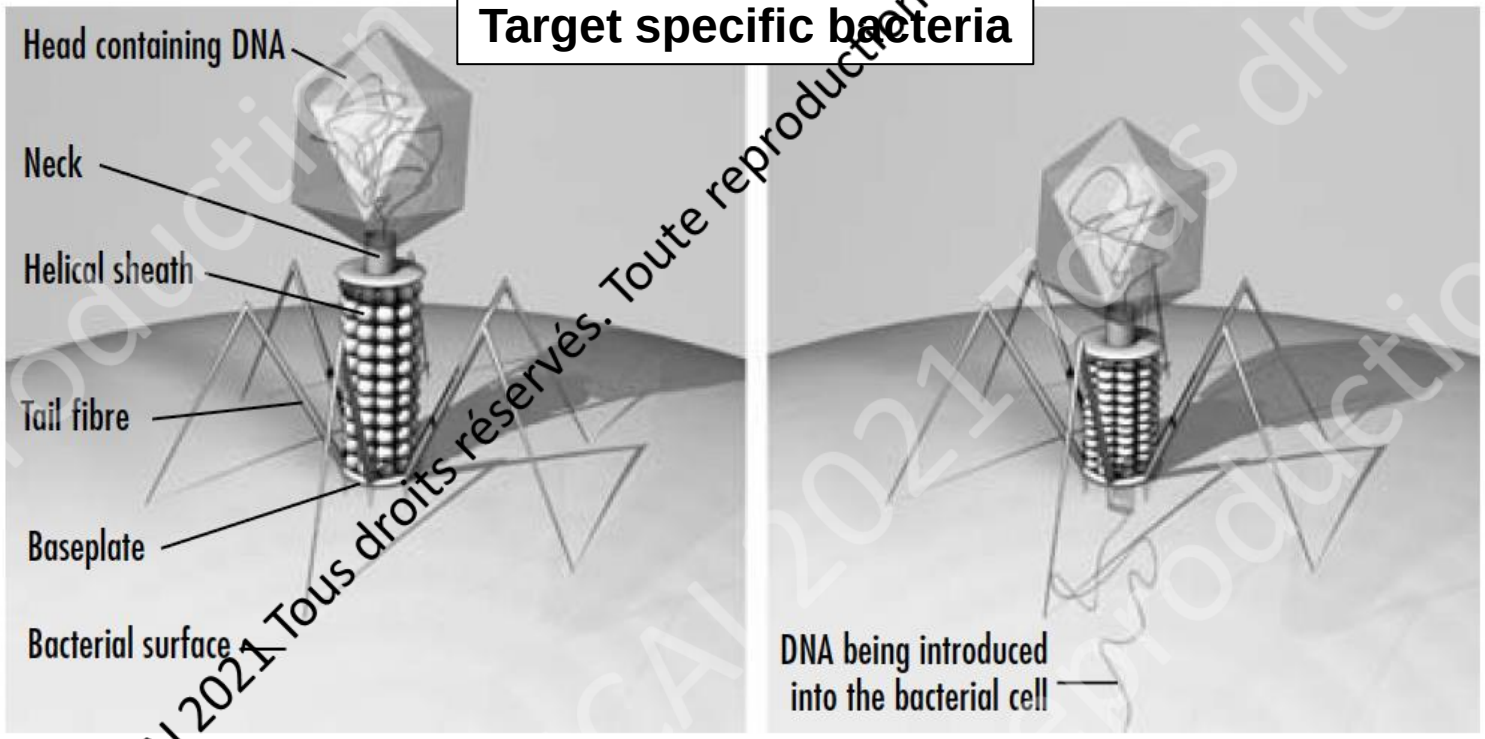
- Creating standards
- Support knowledge exchange
- Designing, initiating and supporting clinical trials
- Discuss with EMA about monography for phages
- Creating an register & database for phage therapy
- …

The phage life

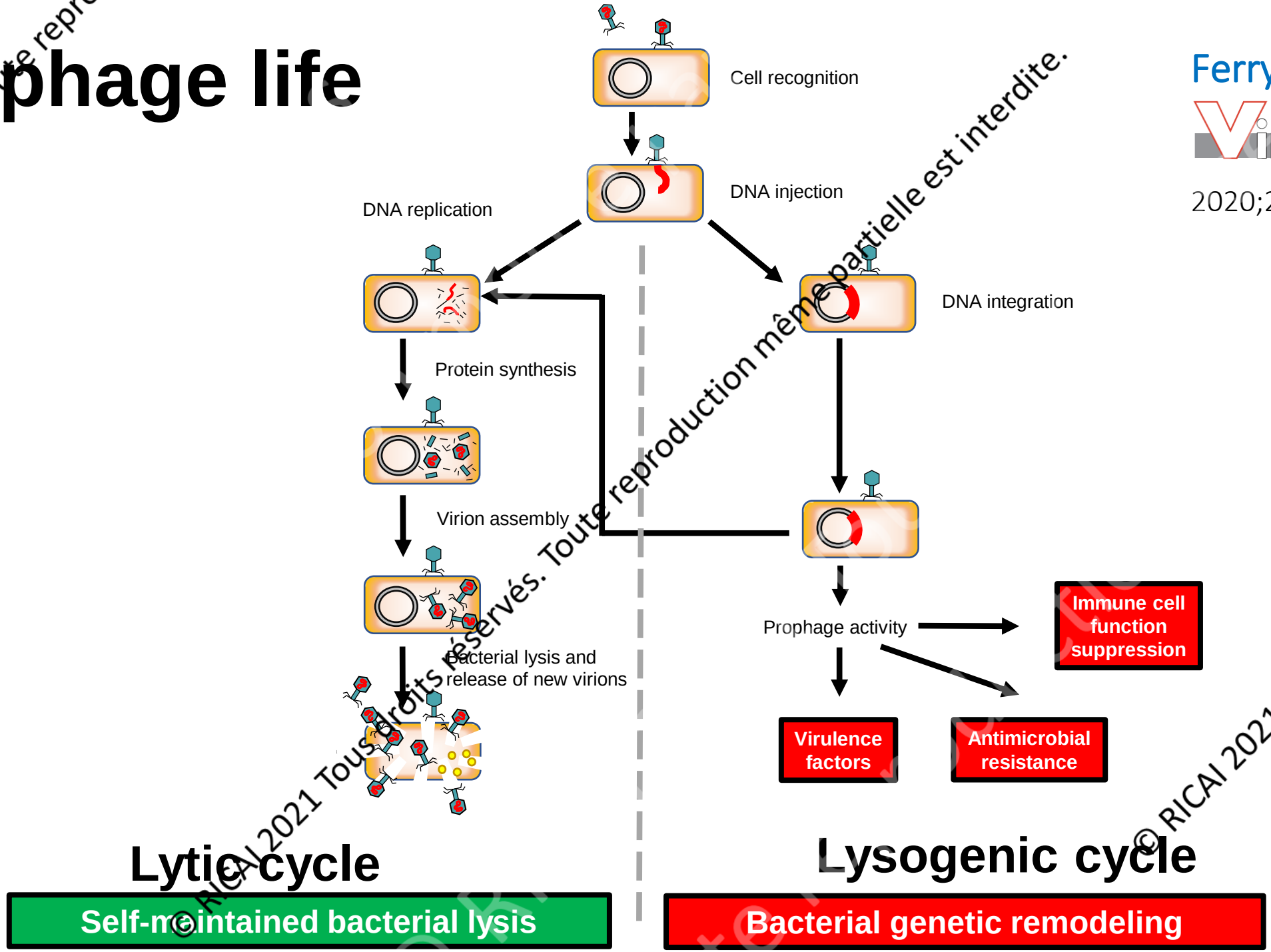


Ferry T. et al.
Virologie
2020;24(1):49-56

Environmental viruses
Target specific bacteria



The phage life



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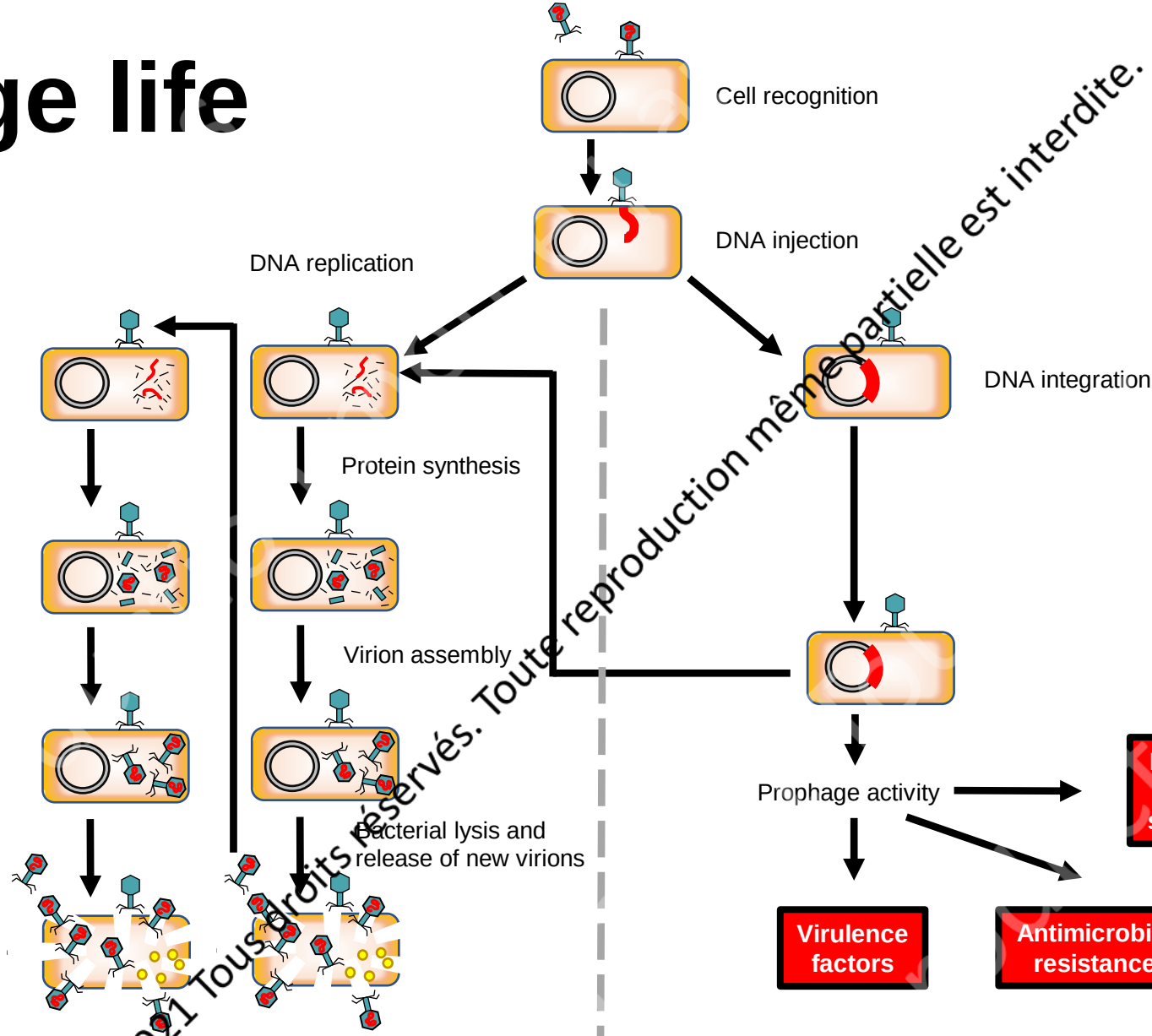

Lytic cycle

Self-maintained bacterial lysis

Lysogenic cycle

Bacterial genetic remodeling

The phage life

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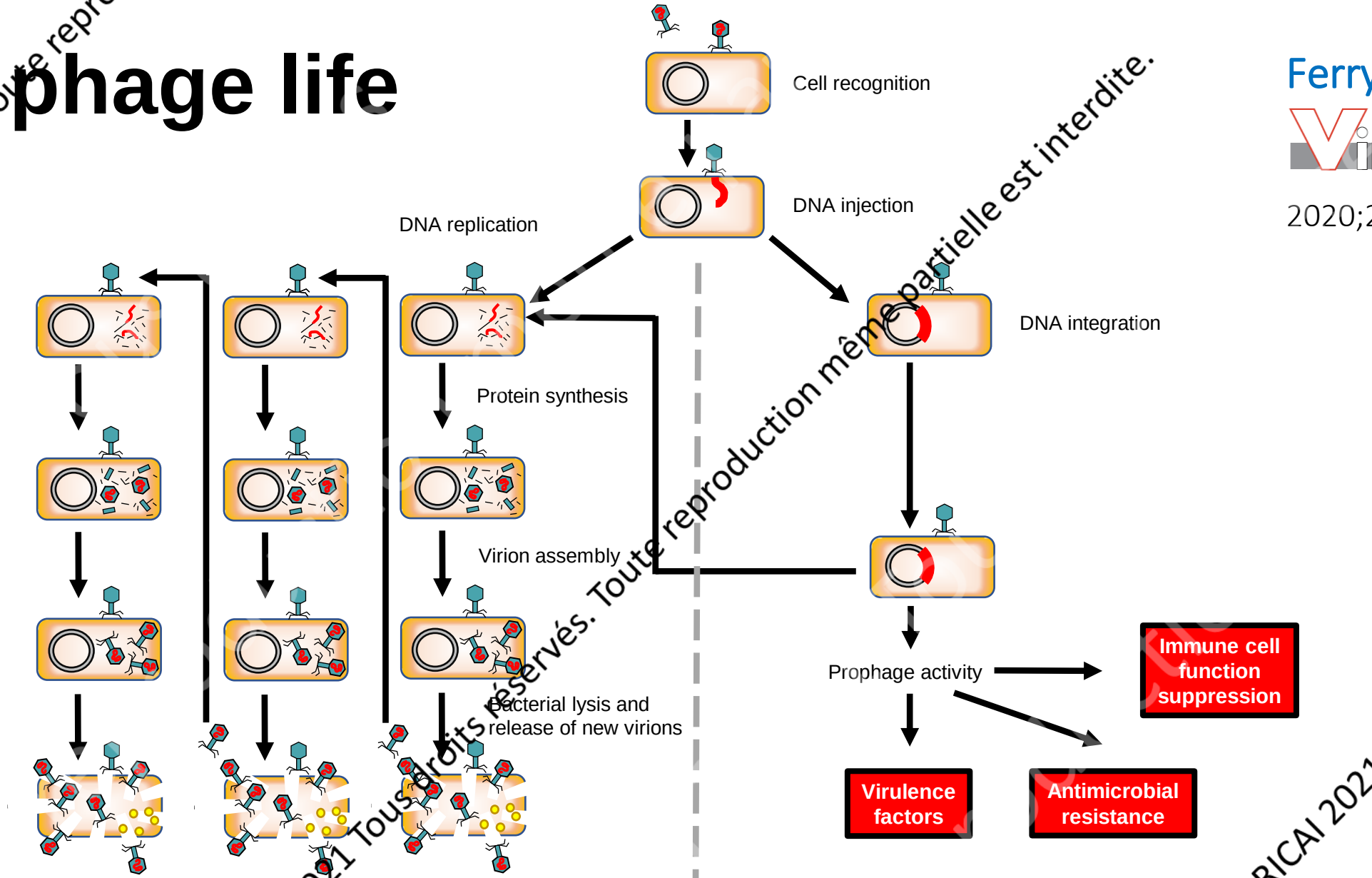


Lytic cycle

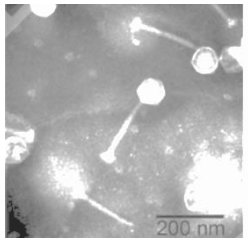
Self-maintained bacterial lysis

Lysogenic cycle

Bacterial genetic remodeling

Only lytic phages have to be used

S. aureus being lysed by the Sa2 phage



Bacterial DNA appeared in green

Courtesy Pascal Mazuin
Luciano Marraffini Lab
THE ROCKEFELLER UNIVERSITY

The Journal of Infectious Diseases

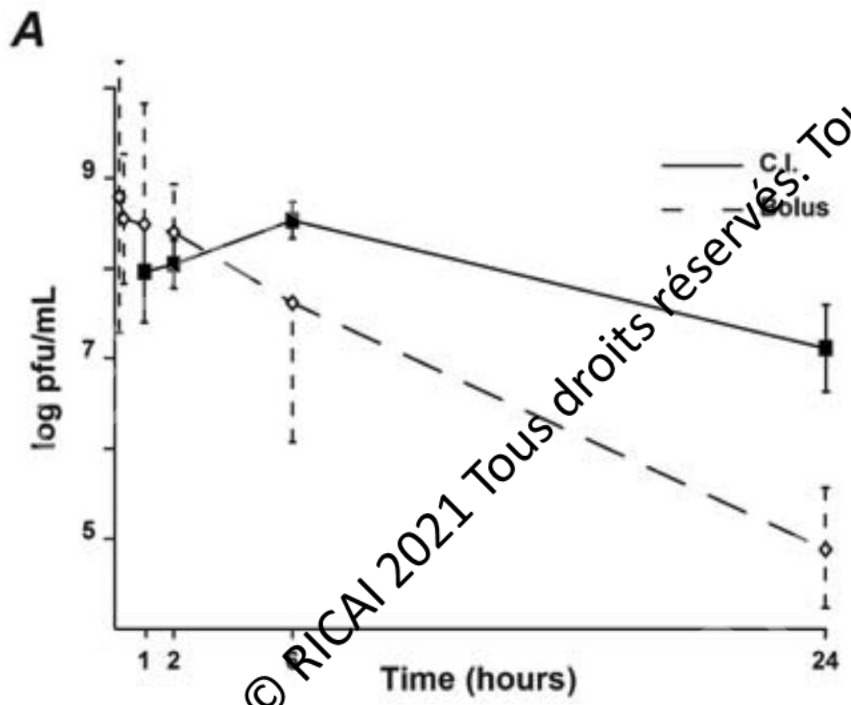
MAJOR ARTICLE

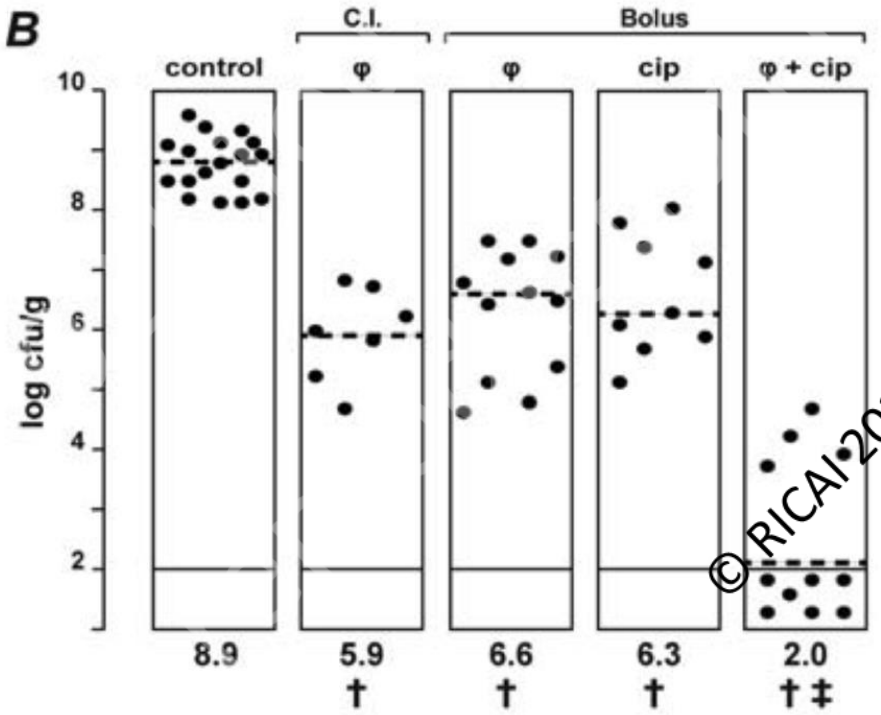
Synergistic Interaction Between Phage Therapy and Antibiotics Clears *Pseudomonas Aeruginosa* Infection in Endocarditis and Reduces Virulence

Frank Oechslin,[1] Philippe Piccardi,[1] Stefano Mancini,[1] Jérôme Gabard,[3] Philippe Moreillon,[1] José M. Entenza,[1] Gregory Resch,[1] and Yok-Ai Que[2]

[1]Department of Fundamental Microbiology, University of Lausanne, and [2]Department of Intensive Care Medicine, Bern University Hospital, Switzerland; and [3]Pherecydes Pharma, Romainville, France

2015





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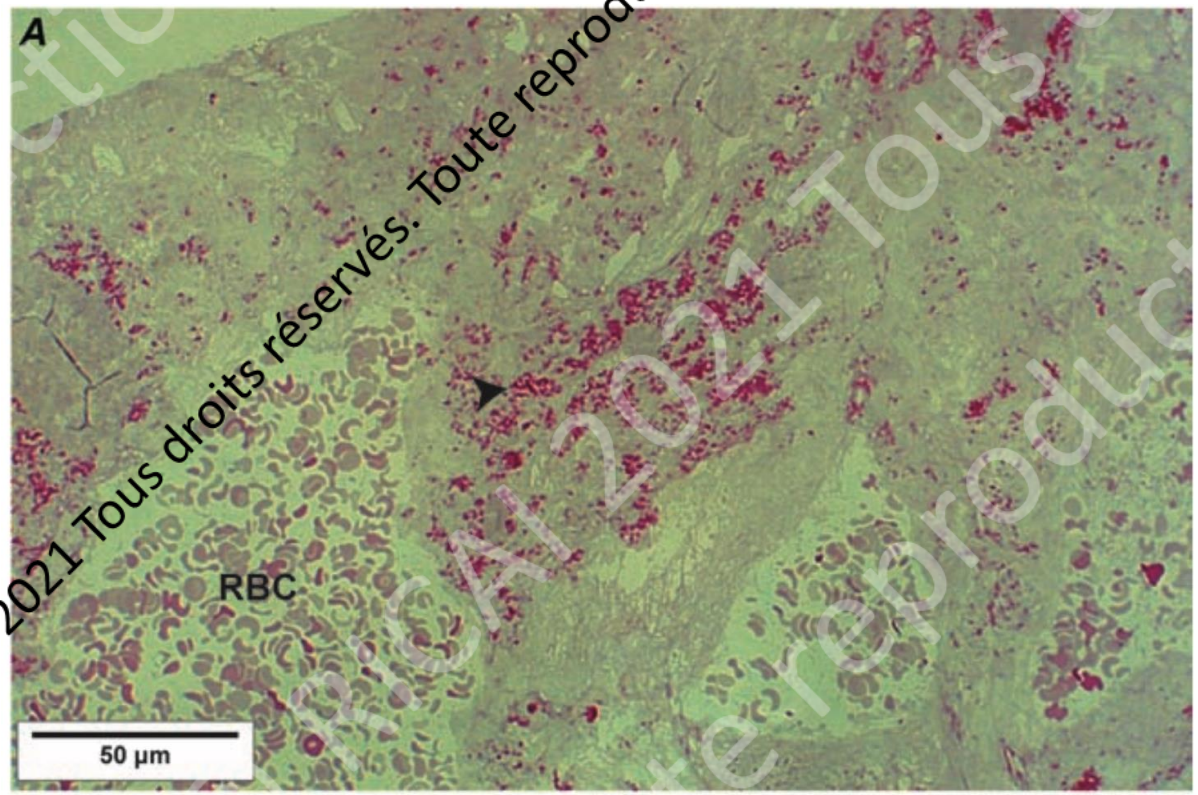

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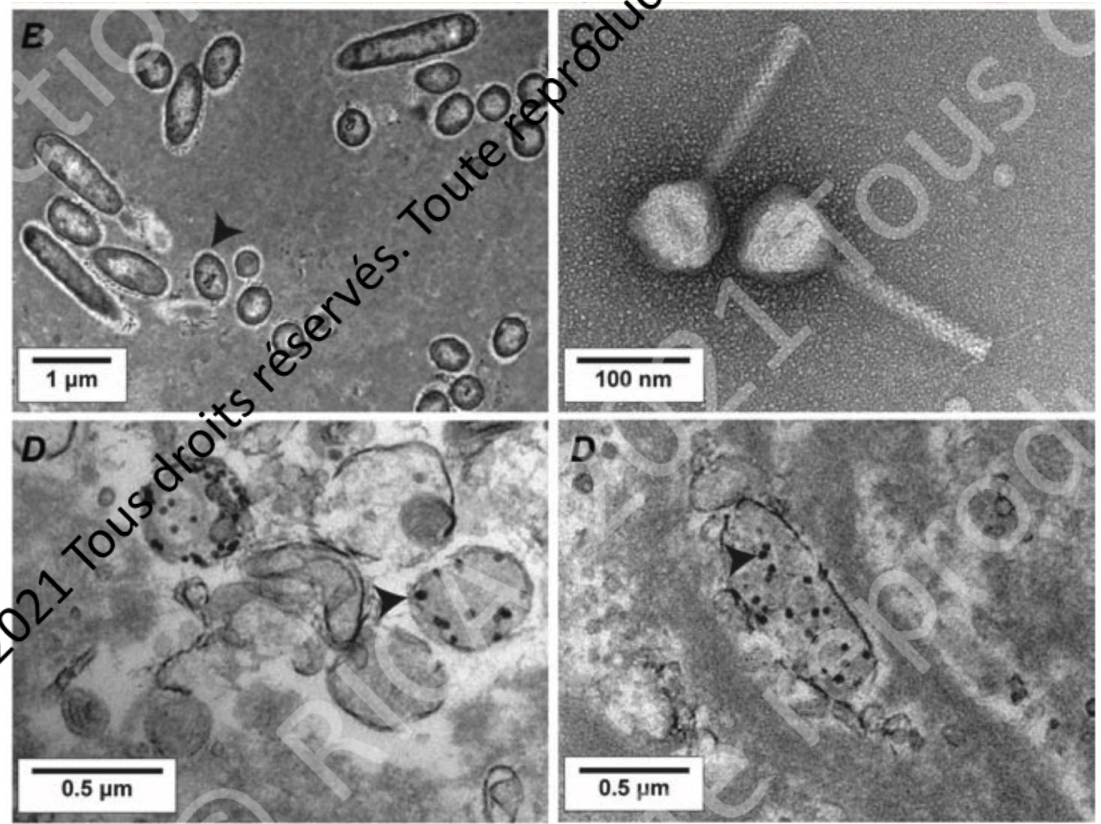
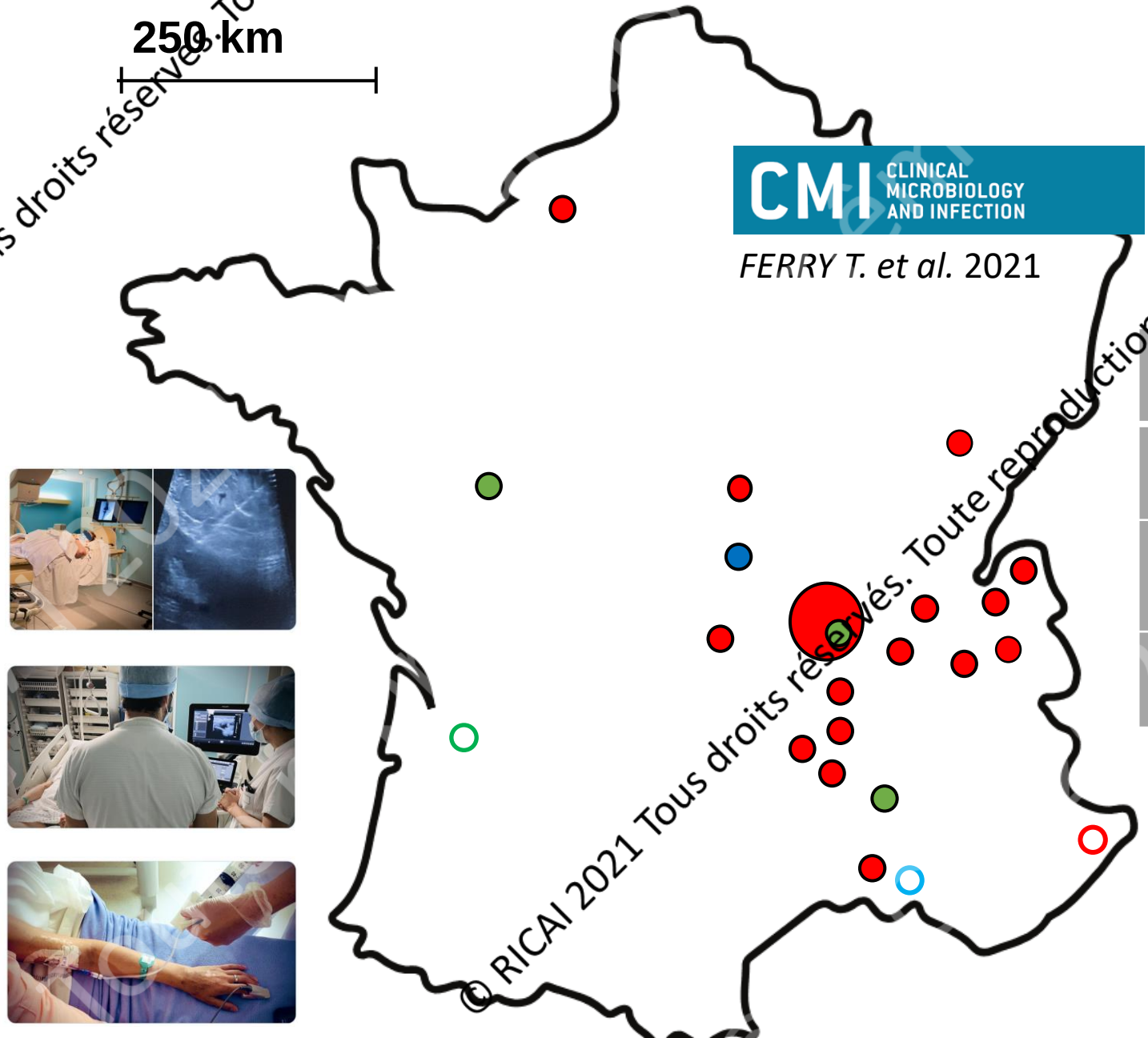


Implementation of a Phage Therapy Center in a CRIOAc



CMI CLINICAL MICROBIOLOGY AND INFECTION

FERRY T. et al. 2021

HCL HOSPICES CIVILS DE LYON — PHAGE*in*LYON — FONDATION HCL HOSPICES CIVILS DE LYON

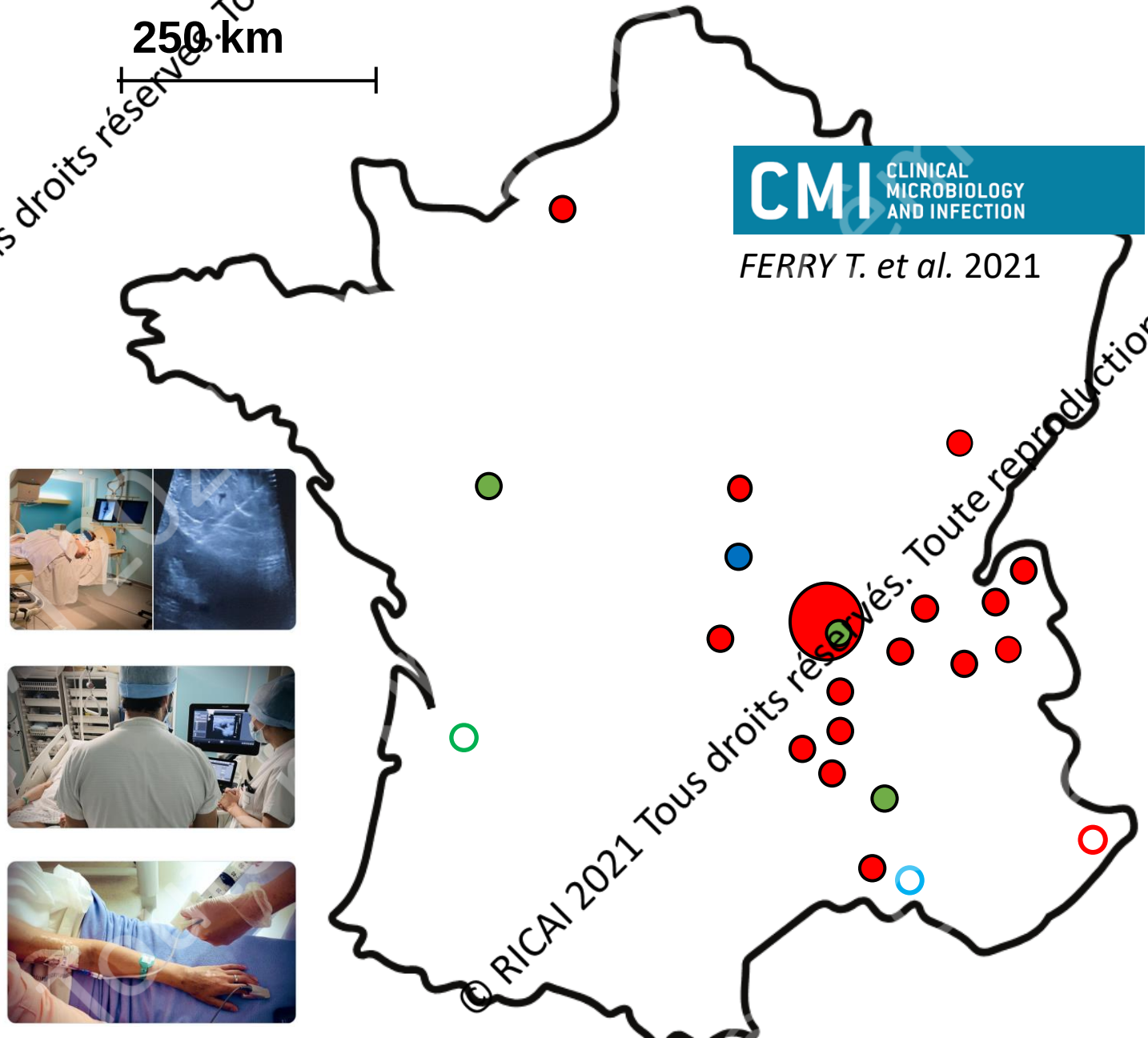
Lyon 1 — CRIOAc LYON — ciri Centre International de Recherche en Infectiologie

Number of patients	2017	2018	2019	2020	Total
Managed in CRIOAc Lyon	557	594	647	520	**2318**
For whom a phagogram was performed	7 (1.2%)	10 (1.7%)	17 (2.6%)	23 (4.4%)	**57 (2.4%)**
For whom phage therapy was done	4 (0.7%)	2 (0.3%)	8 (1.2%)	7 (1.3%)	**21 (0.9%)**

Under the supervision of ansm

BJI **Endocarditis** **Pneumonia**

Implementation of a Phage Therapy Center in a CRIOAc



CMI CLINICAL MICROBIOLOGY AND INFECTION

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HCL HOSPICES CIVILS DE LYON — PHAGE*in*LYON — FONDATION HCL HOSPICES CIVILS DE LYON

Lyon 1 — CRIOAc LYON — ciri Centre International de Recherche en Infectiologie

30 patients in Lyon since 2017

- 27 with phages from PHERECYDES PHARMA
- 3 with phages from MHKA HMRA

- 26 **BJI** (including **22 PJI**)
- 3 **endocarditis**
- 1 **VAP + bacteremia**

+ 3 patients managed outside Lyon

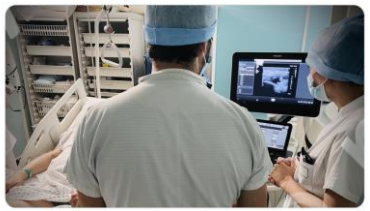
Under the supervision of ansm

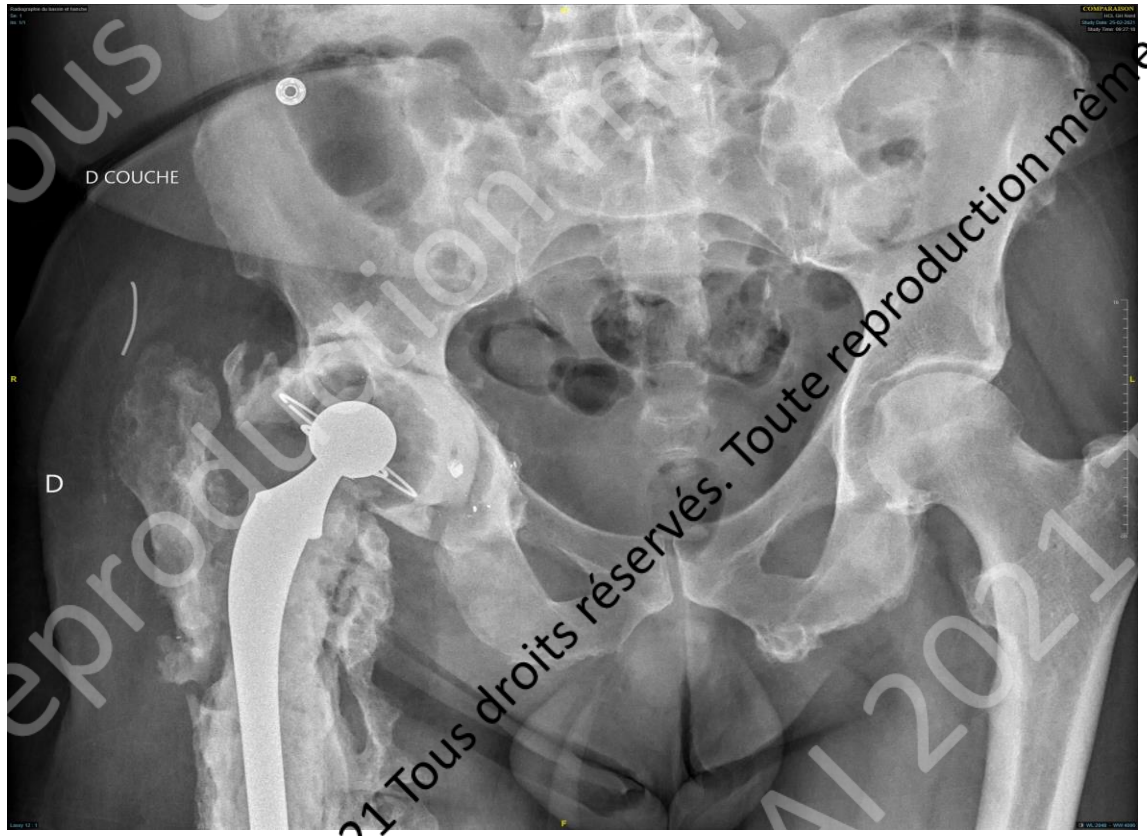
BJI **Endocarditis** **Pneumonia**

Implementation of a Phage Therapy Center in a CRIOAc

13 patients (43%)

treated for *P. aeruginosa* severe infection





- 11 with phages from PHERECYDES PHARMA
- 2 with phages from MHKA HMRA

- 10 **BJI** (including **8 PJI**)
- 2 **endocarditis**
- 1 **VAP + bacteremia**

Under the supervision of ansm

BJI **Endocarditis** **Pneumonia**

Implementation of a Phage Therapy Center in a CRIOAc

13 patients (43%)

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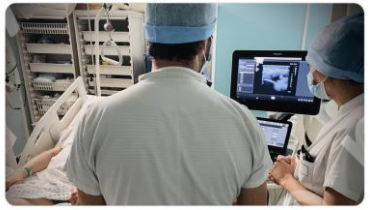
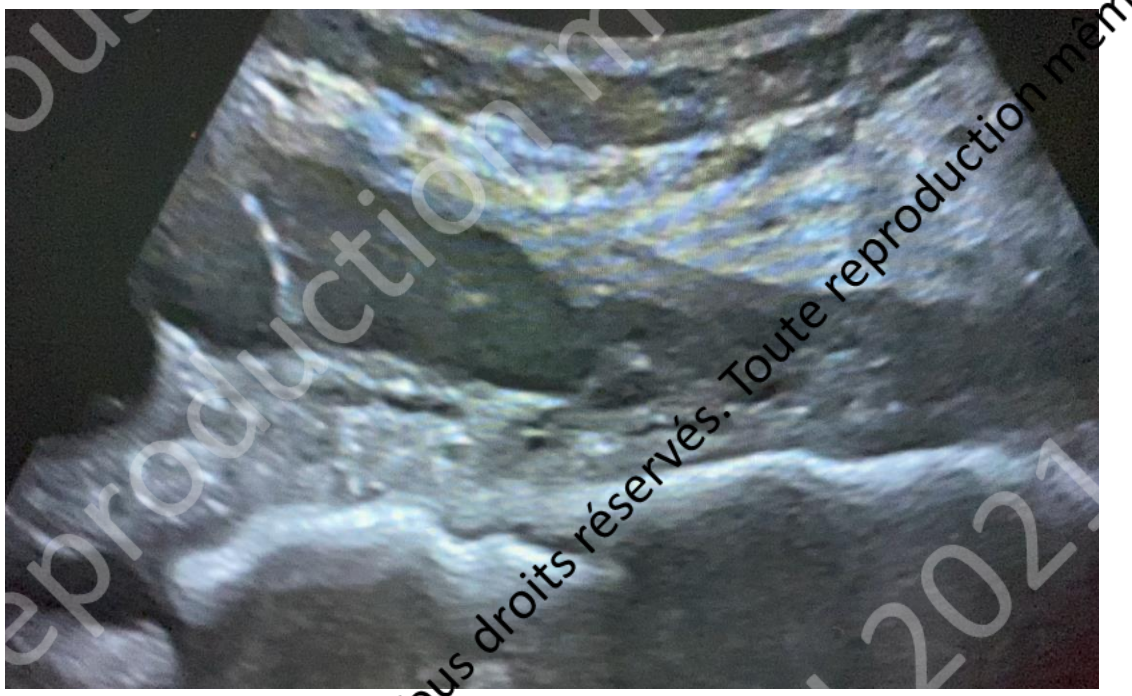




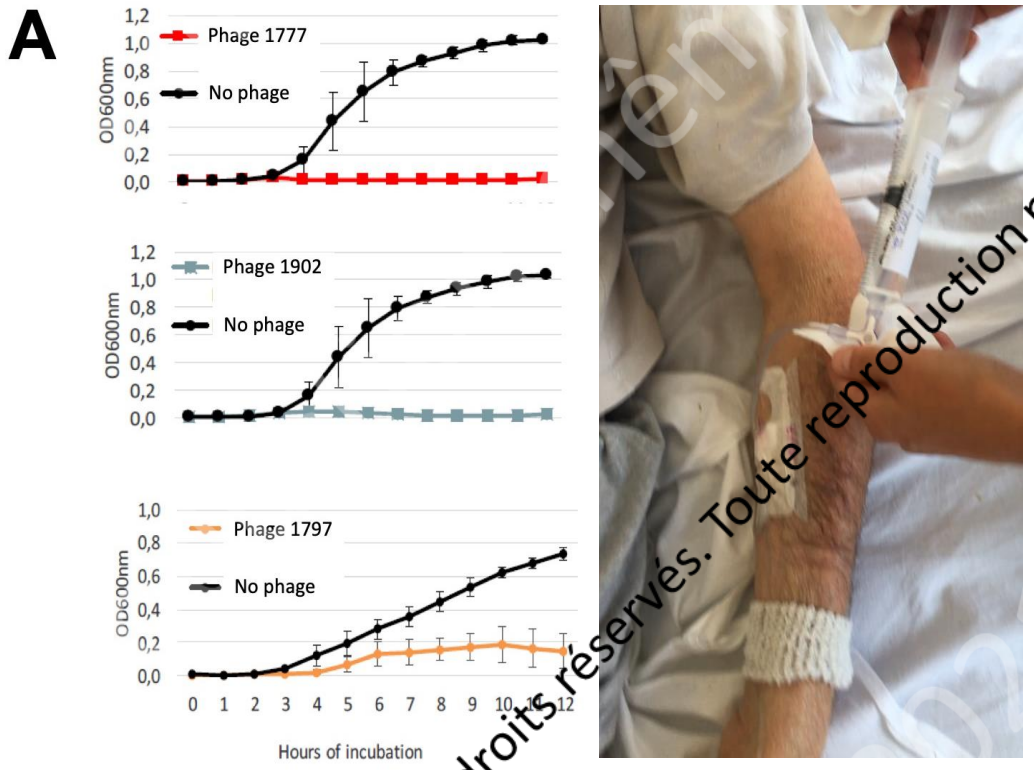
- 11 with phages from PHERECYDES PHARMA
- 2 with phages from MHKA / HMRA

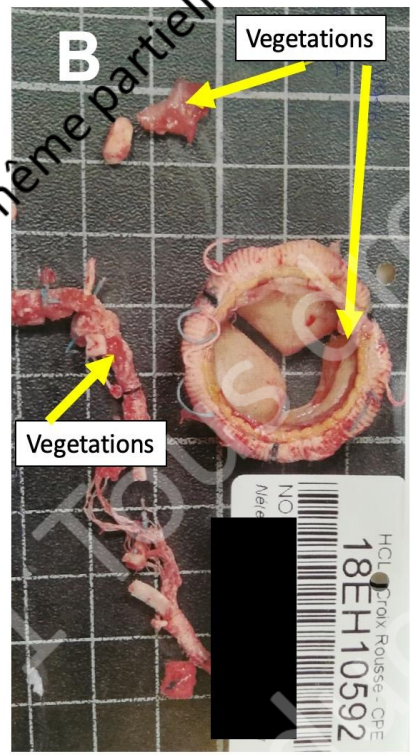
- 10 **BJI** (including **8 PJI**)
- 2 **endocarditis**
- 1 **VAP + bacteremia**

Under the supervision of ansm

BJI **Endocarditis** **Pneumonia**

Intravenous administration of personalized cocktail of bacteriophages as salvage therapy in combination with ceftazidime/avibactam in patients with relapsing *P. aeruginosa* bacteremia: Lesson learned from two cases





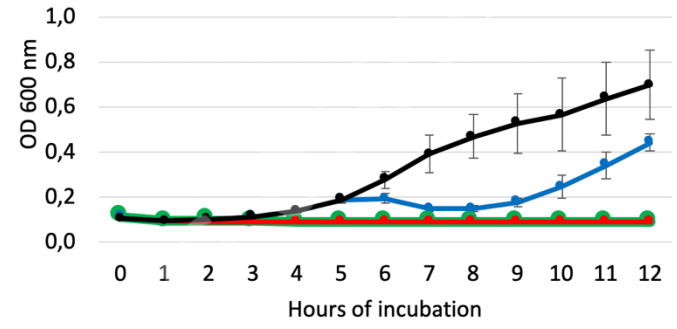
30th ECCMID
Paris, France
18 –21 April 2020

PHERECYDES PHARMA

HCL HOSPICES CIVILS DE LYON

Conclusions: **The type of filter used for the magistral preparation and the duration of the perfusion influenced the phage titer, as the titer in the patient's blood.** Personalized GMP bacteriophage therapy has the potential to be used as salvage therapy of *P. aeruginosa* intravascular implant infections.

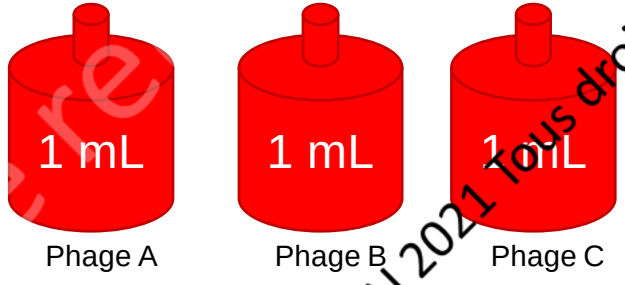
PHAGE*in*LYON team



Phagogram
Selection of active bacteriophages

Active GMP

***S. aureus* Bactériophages**



ID Clinic

HCL HOSPICES CIVILS DE LYON

Lab

HCL HOSPICES CIVILS DE LYON

CRIOAC LYON

ADJUVANT INNOVATIVE ANTI-INFECTIVE AGENTS
OPTIMAL SEPTIC SURGERY
TARGETED AND OPTIMAL ANTIMICROBIAL THERAPY
MULTIDISCIPLINAR MEETING

Surgery

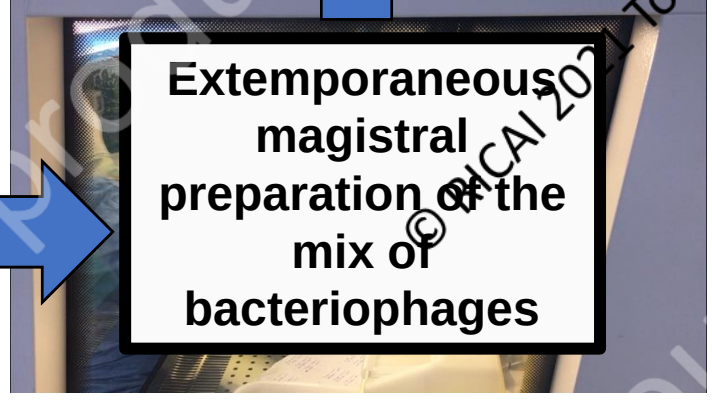
HCL HOSPICES CIVILS DE LYON

Under the supervision of

ansm
Agence nationale de sécurité du médicament et des produits de santé
French Health Authority

Pharmacy

HCL HOSPICES CIVILS DE LYON



Extemporaneous magistral preparation of the mix of bacteriophages

PHAG-ONE

Réunion de Lancement
Mercredi 8 Septembre 2021

7 Workpackages – 10 partenaires

Programme PHAGEinLYON

HCL Hospices Civils de Lyon – Fondation HCL

Université de Lyon

CIRI Centre International de Recherche en Infectiologie

leti CEA tech

Centre Emile Durkheim

MIVEGEC Maladies Infectieuses et Vecteurs : Écologie, Génétique, Évolution et Contrôle

UVSQ Université Paris-Saclay

LBBE Laboratoire de Biométrie et Biologie Évolutive

CNR Résistance aux Antibiotiques

Staphylocoques Centre National de Référence

TRIPHARM®

CRIOAc Lyon

HCL Hospices Civils de Lyon – IAI CBPN Institut des Agents Infectieux

HCL Hospices Civils de Lyon

www.chu-lyon.fr

Ministère de l'Enseignement Supérieur, de la Recherche et de l'Innovation – Liberté Égalité Fraternité

anr

PHAG-ONE

Réunion de Lancement
Mercredi 8 Septembre 2021

7 Workpackages – 10 partenaires

Isoler, tester, caractériser, produire, purifier et libérer
des lots pharmaceutiques
de **phages thérapeutiques académiques**
à coût maîtrisé utilisables en clinique chez l'Homme

3 pathogènes cible
Staphylococcus aureus / Staphylococcus epidermidis / Escherichia coli

HCL HOSPICES CIVILS DE LYON
www.chu-lyon.fr

Organisation du projet PHAG-ONE

WP7 : Etude socio-antropologique

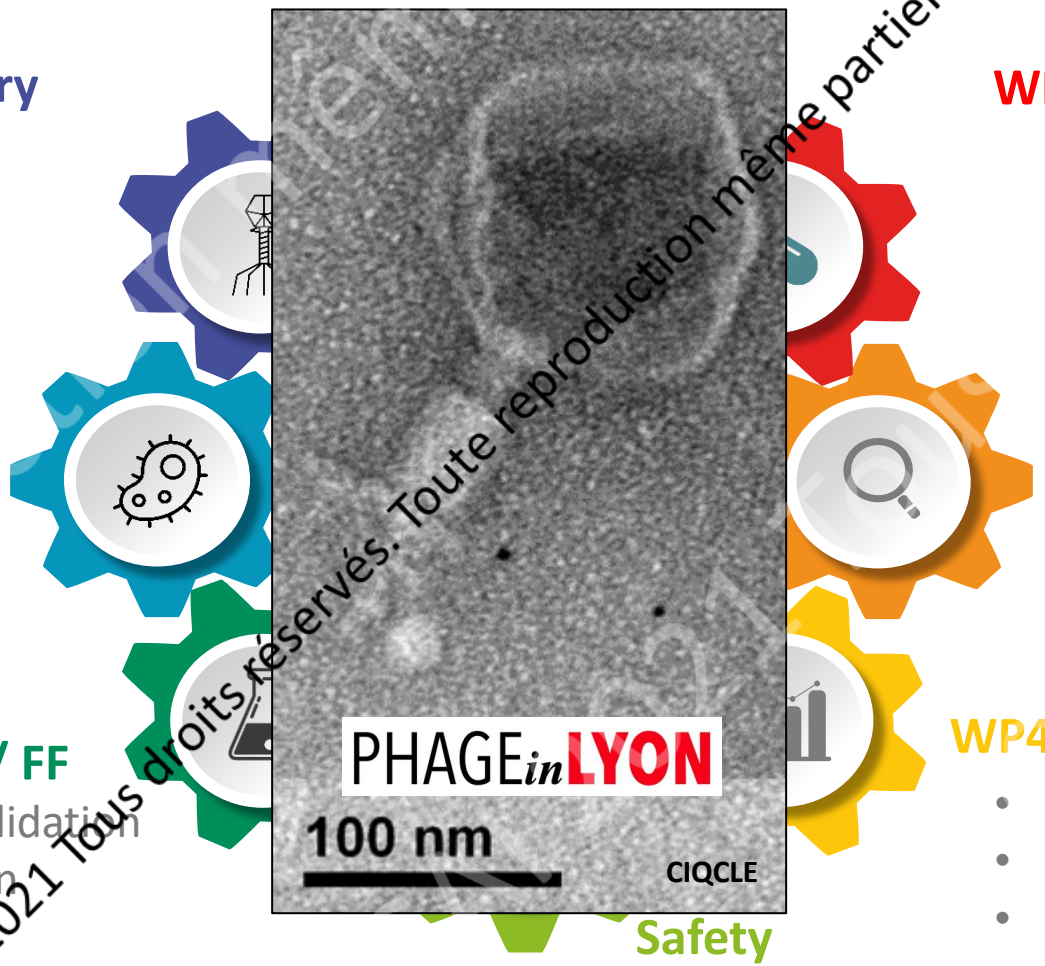
- Epistémologie / Suivi de l'émergence d'une innovation biomédicale
- Perception/Suivi/Accompagnement chez grand public-décideurs-politiques

WP1 : Phage discovery

- Isolement
- Caractérisation
- Entrainement

WP2 : USP

- Sélection souche de production
- Développement et validation process amplification phagique
- Contrôles qualité



WP6 : Utilisation clinique

- Référentiels
- Etudes de cohorte
- Essais cliniques

WP5 : Diagnostic

- Titration
- Phagogramme

WP3 : DSP / FF

- Développement et validation process de purification
- Contrôles qualité
- Libération de lots
- Formulation / Stabilité

WP4 : Efficacité / PK-PD

- Modèle Lapin - Tissu Cage
- Modèle Lapin - Infection sur prothèse
- Etude PK/PD *in vitro* et *in vivo*

Safety

- Tolerance
- Toxicité

FRIPHARM®

PHARMACIE À USAGE INTÉRIEUR (PUI) – HÔPITAL EDOUARD HERRIOT– UCBL -ISPBL

FRI PHARM

PRODUCTION de médicaments hospitaliers, non disponibles sur le marché, ou pour le traitement de maladies orphelines ; production de médicaments expérimentaux adaptés au protocole de recherche clinique (mise en insu …)

CONTRÔLES QUALITÉ des matières premières à usage pharmaceutique et des préparations hospitalières. Centre de référence pour contrôles des eaux de dialyse (endotoxines). **ETUDES DE STABILITÉ** selon la méthodologie ICH.

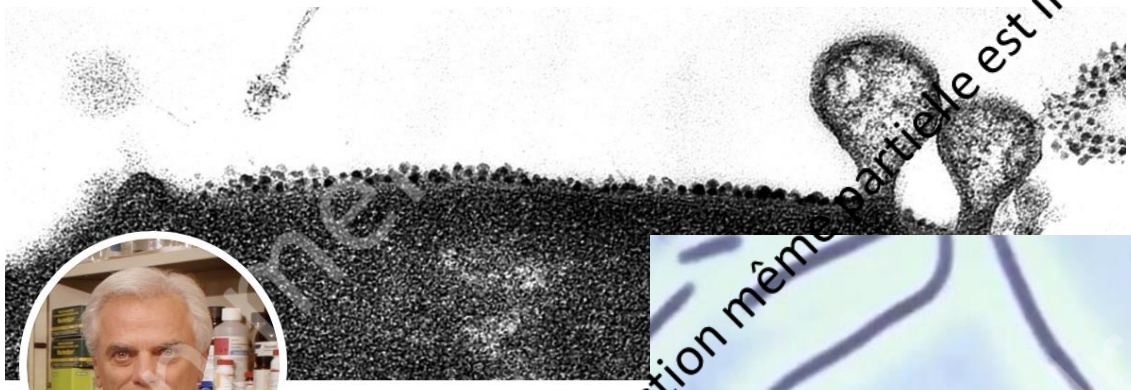
RECHERCHE ET DEVELOPPEMENT de nouvelles préparations adaptées à des besoins cliniques spécifiques ou adaptées aux exigences du protocole de recherche clinique.

FRI PHARM RECHERCHE CLINIQUE

EXPERTISE TECHNIQUE et REGLEMENTAIRE de la gestion des essais cliniques associée à la fabrication/contrôles des médicaments expérimentaux (essais institutionnels).

HCL HOSPICES CIVILS DE LYON

Lysines de bactériophages



Vincent A Fischetti
@microbephage

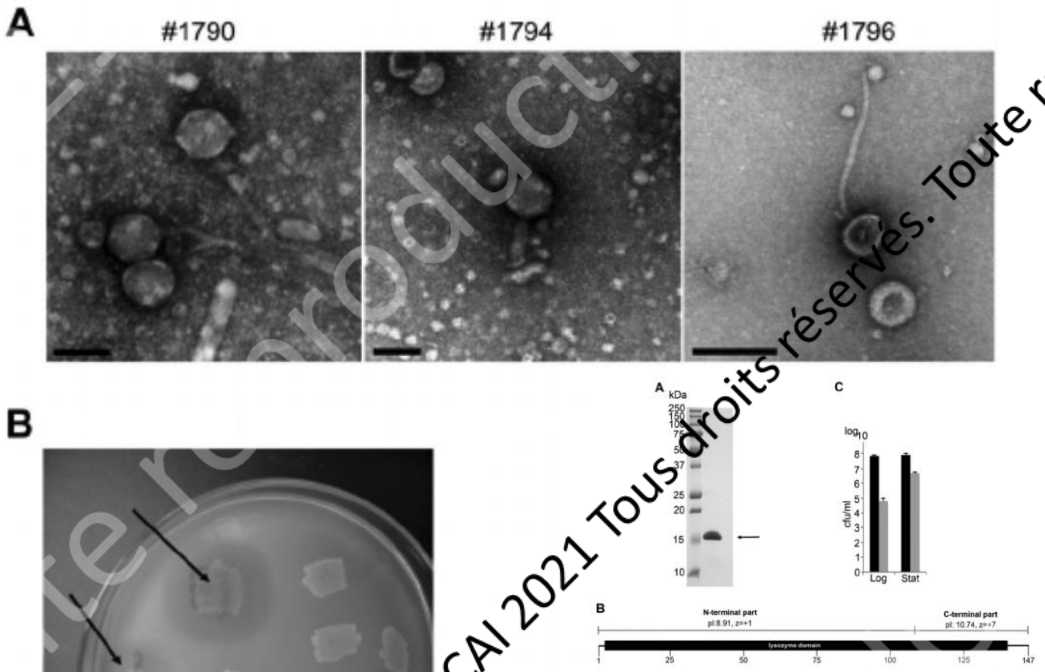
Tristan Ferry Lyon University Hospitals
@FerryLyon

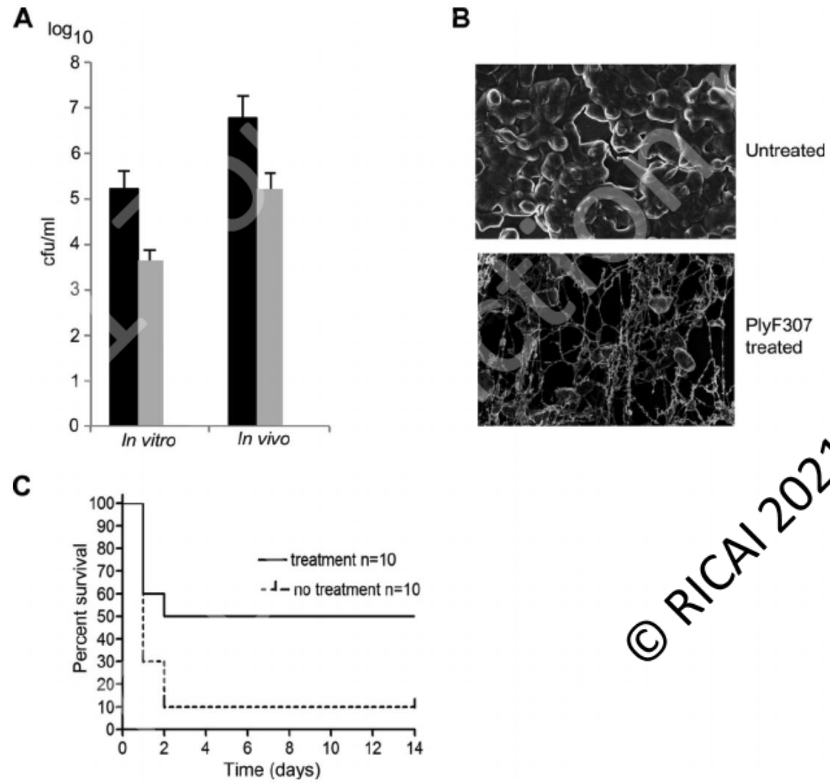
Incredible talk of Pr. Vincent A. Fischetti @microbephage @IDWeek2019 about the great potential of #bacteriophage #lysins to induce bacterial explosion... and disappearance! It's good to hear that he discovered lysins that are active against #multidrugresistant #ESKAPE pathogens!

Novel Phage Lysin Capable of Killing the Multidrug-Resistant Gram-Negative Bacterium *Acinetobacter baumannii* in a Mouse Bacteremia Model

Rolf Lood,[a] Benjamin Y. Winer,[a]* Adam J. Pelzek,[a]* Roberto Diez-Martinez,[a,b] Mya Thandar,[a] Chad W. Euler,[a,c] Raymond Schuch,[a]* Vincent A. Fischetti[a]

Laboratory of Bacterial Pathogenesis and Immunology, The Rockefeller University, New York, New York, USA[a]; Molecular Microbiology and Infection Biology Department, Host-Parasite Interplay in Pneumococcal Infection Group, Centro de Investigaciones Biológicas, Madrid, Spain[b]; Department of Medical Laboratory Sciences, School of Arts and Sciences, Hunter College, CUNY, New York, New York, USA[c]

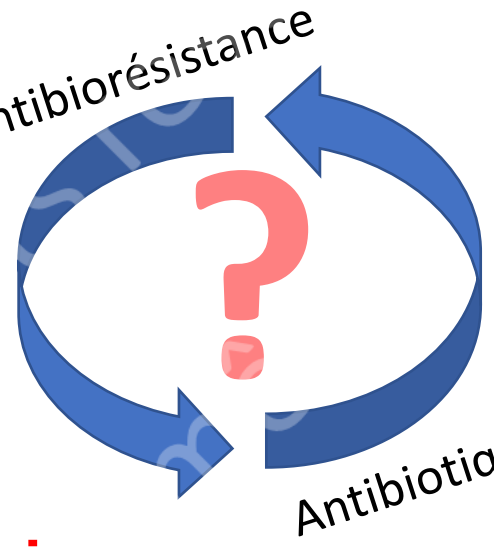




Antimicrob Agents and Chemother 2015

Conclusion

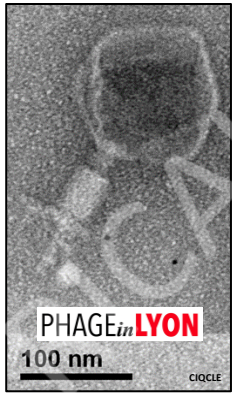
- **Nouveaux inhibiteurs de β-lactamase à disposition**
  - En combinaison avec des “vieux” antibiotiques
- **Nouveaux antibiotiques**
  - En combinaison avec des “vieux” inhibiteurs
  - Céphalosporine siderophore



Evaluation clinique, AMM

Positionnement en fonction des pathogènes et des pathologies

- **Développement des thérapies non traditionnelles (definition OMS)**
  - Bactériophages
    - Industriels
    - Académiques
  - Lysines de phages
  - Groupe ESCMID



ESGNTA
ESCMID STUDY GROUP FOR NON-TRADITIONAL ANTIBACTERIAL THERAPY
European Society of Clinical Microbiology and Infectious Diseases

PHAGEinLYON

Lyon BJI Study group

Coordinator: Tristan Ferry

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FONDATION HCL HOSPICES CIVILS DE LYON

Coordinators: Tristan Ferry and Frédéric Laurent

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Lyon 1

CRIOAc LYON

ciri Centre International de Recherche en Infectiologie

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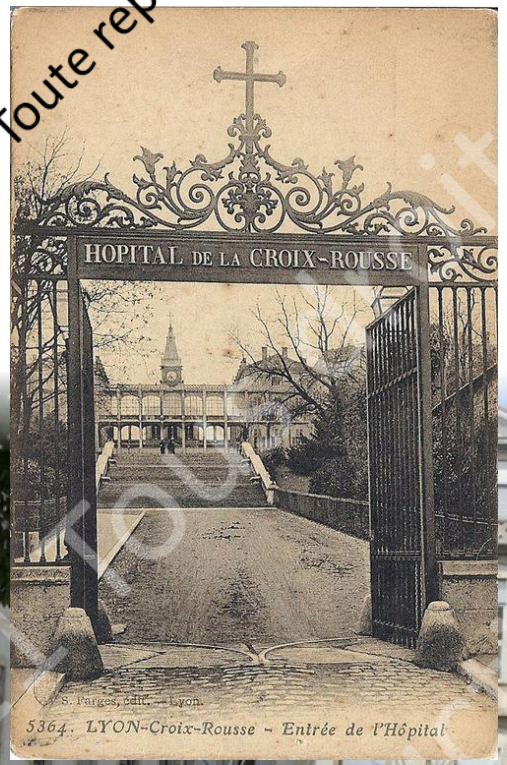
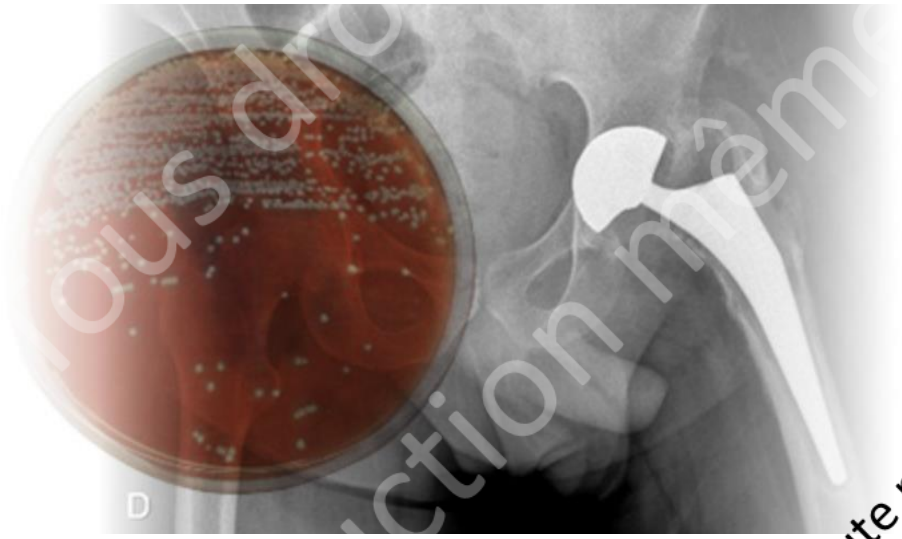
Croix-Rousse Hospital



http://www.crioac-lyon.fr



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- All thesis in pdf
- All recommendations
- **Newsletter**

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