CENTRE HOSPITALIER INTERCOMMUNAL
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Lucie & Raymond AUBRAC

GEEPhage
Phagothérapie

La phagothérapie :une alternative à l'antibio-thérapie ou une prise en charge complémentaire?

ANTIBIOLOR
LE RÉSEAU LORRAIN D'ANTIBIOLOGIE

11ème Journée Régionale d'Infectiologie

CHRU NANCY

Docteur Olivier PATEY
Maladies infectieuses et tropicales
CH Lucie et Raymond Aubrac
« Phagothérapie 2020 »

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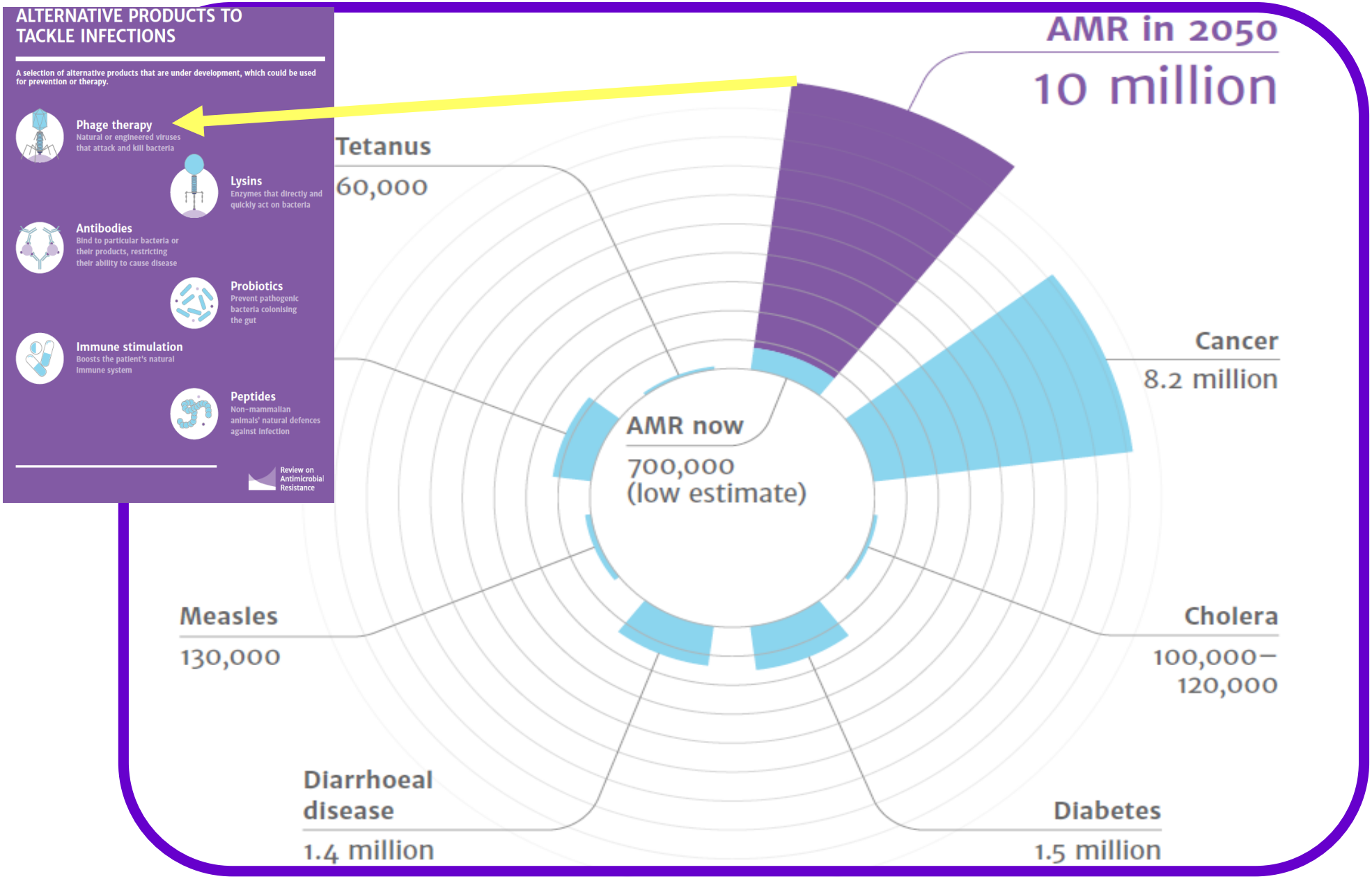
ESTIMATION DU NOMBRE DE DECES DANS LE MONDE

GEEPhage Phagothérapie



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LES DEUX PROTAGONISTES

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Hankin observed *V. cholerae* antibacterial activity in Indian river water (1896)

Bacteriophages characterized and named by d' Hérelle (1917)

Use of phages as molecular biology tools begins (1950s) and continues to present day

Phage genome sequencing begins (1980s) and continues to present day

1890 1900 1920 1940 1960 1980 2000 2010

Anciennes fioles contenant des phages à visée thérapeutique. [B]

Phage institute set up in Tbilisi, Georgia (1923)

Phage lambda (λ) isolated (1951)

Animal studies of Smith and Huggins revitalize phage therapy research in West (1980s)

Fischetti' s group demonstrate in vivo activity of phage lysins (2001)

Phage cocktail for biocontrol of *Listeria* in ready-to-eat meats approved by FDA (2006)

Antibacterial activity against *S. aureus* published by Twort (1915)

Major timelines in th py.

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PHAGE ET BACTERIE

GEEPhage
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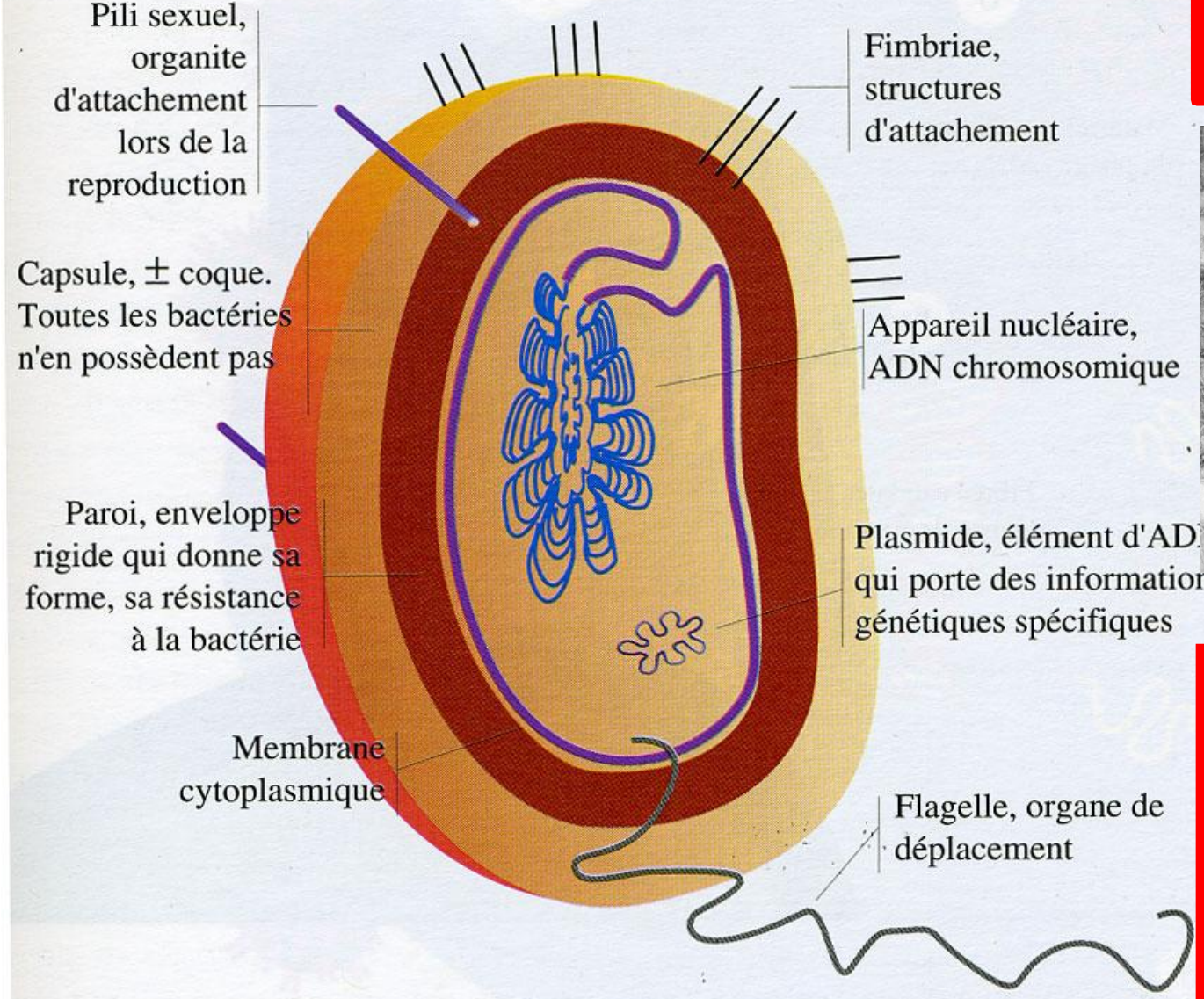
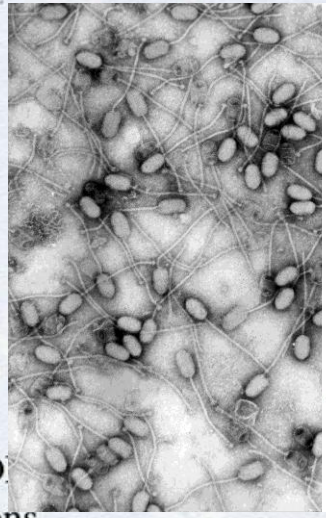
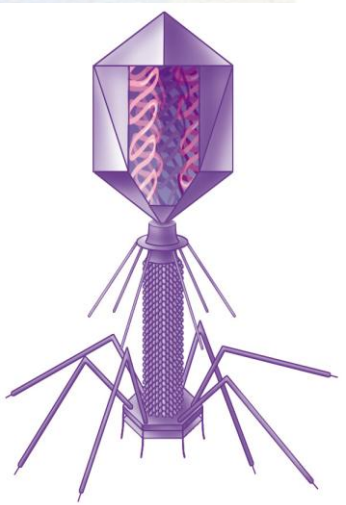
BACTÉRIE
(Taille moyenne : 1 000 nanomètres)



BACTÉRIOPHAGE
(50 nm)





10^{32} bactériophages
(<10% connus)
(< 6 000 φ identifiés)

10^{31} bactéries (20% détruites/24H)

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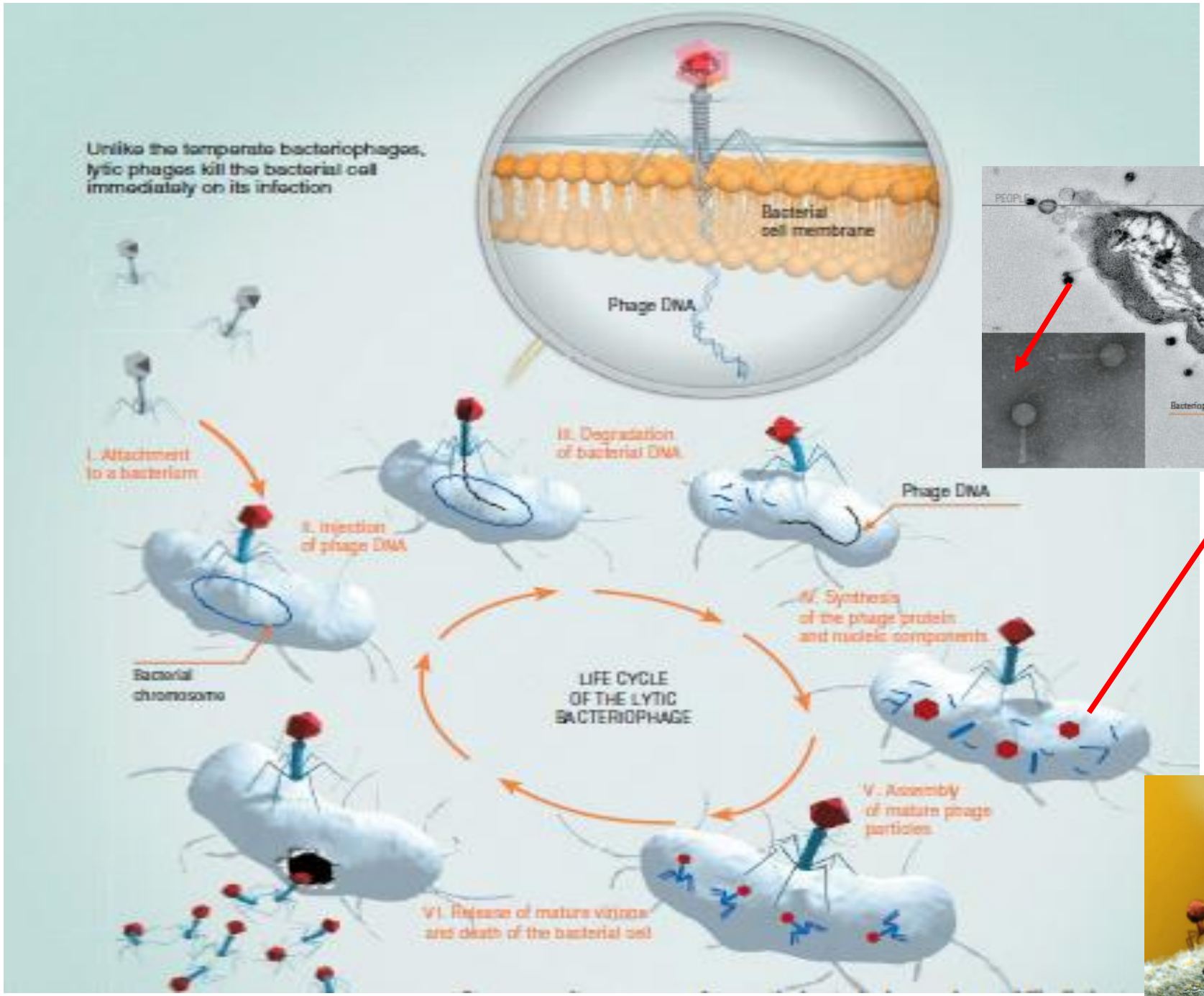
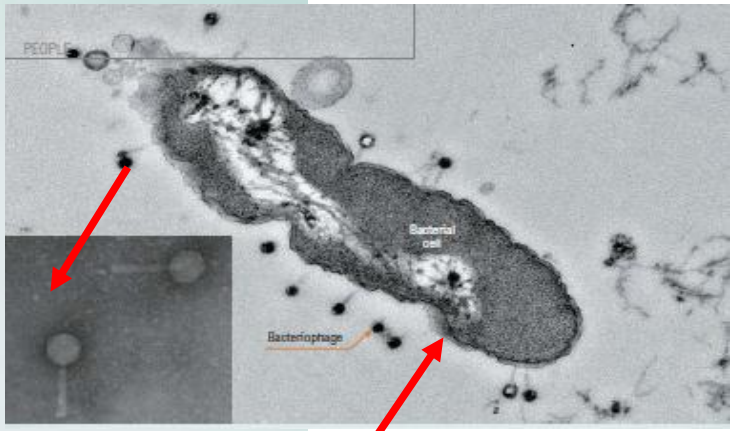
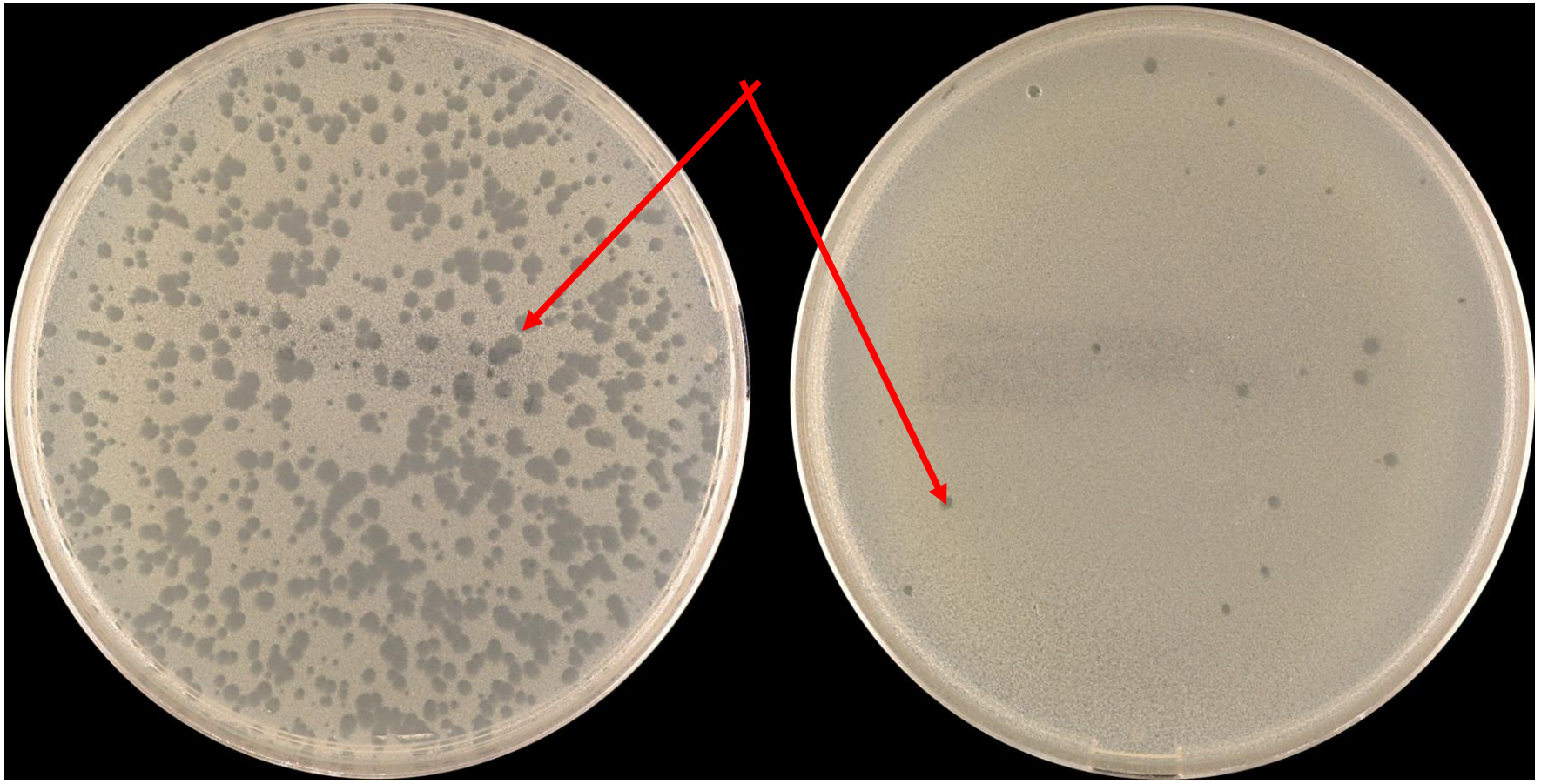
CYCLE LYTIQUE

GEEPhage
Phagothérapie





PHAGE COUNT



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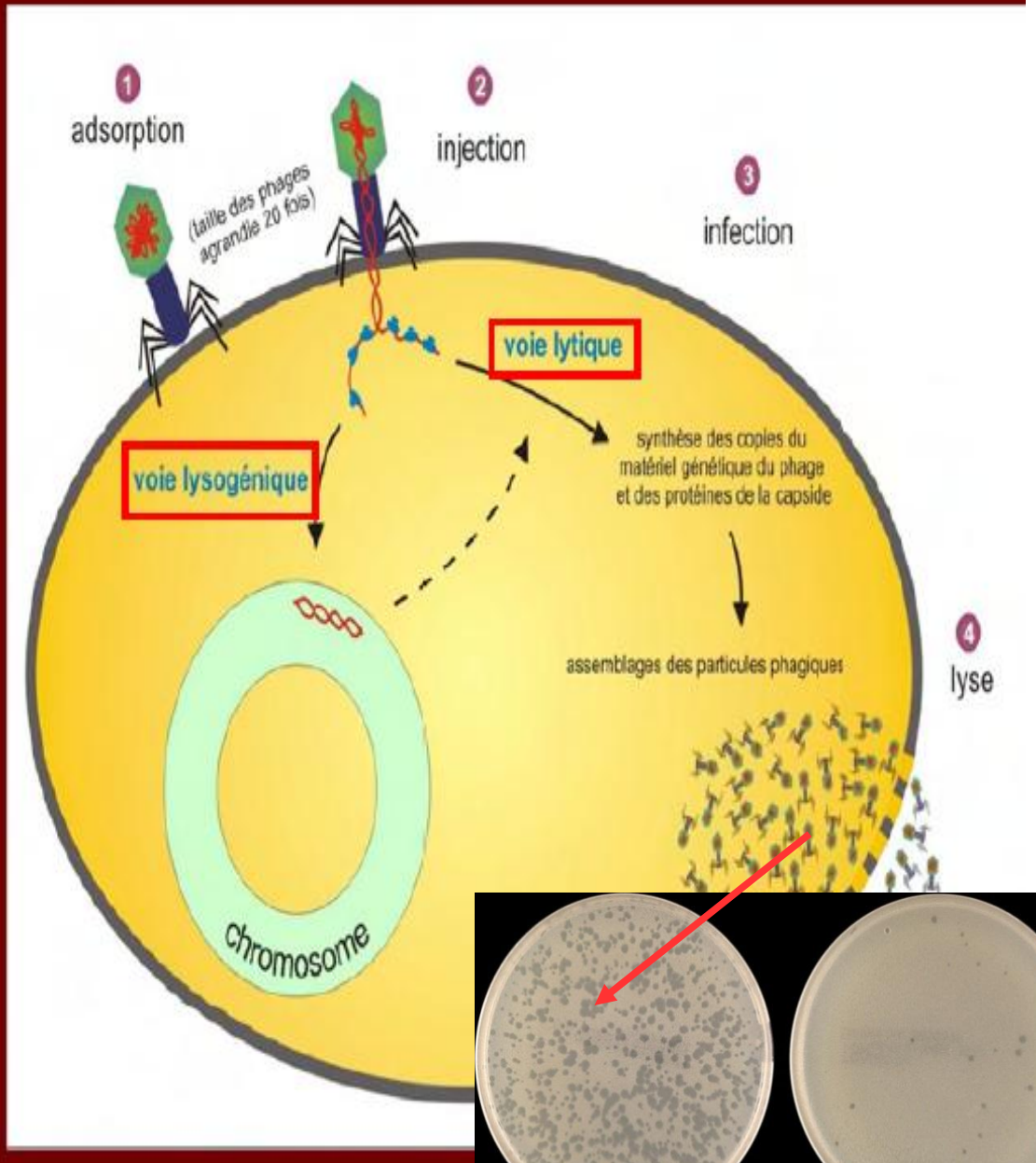
CYCLES DES PHAGES

GEEPhage
Phagothérapie

- **Phages lysogéniques**
  - Véhicules de matériel génétique
  - Transfert du gène de la toxine
  - Vibriophage filamenteux lysogénique CTXΦ
- **Phages lytiques**
  - Multiplication intracellulaire
  - Destruction de la bactérie
  - Plus de 200 bactériophages



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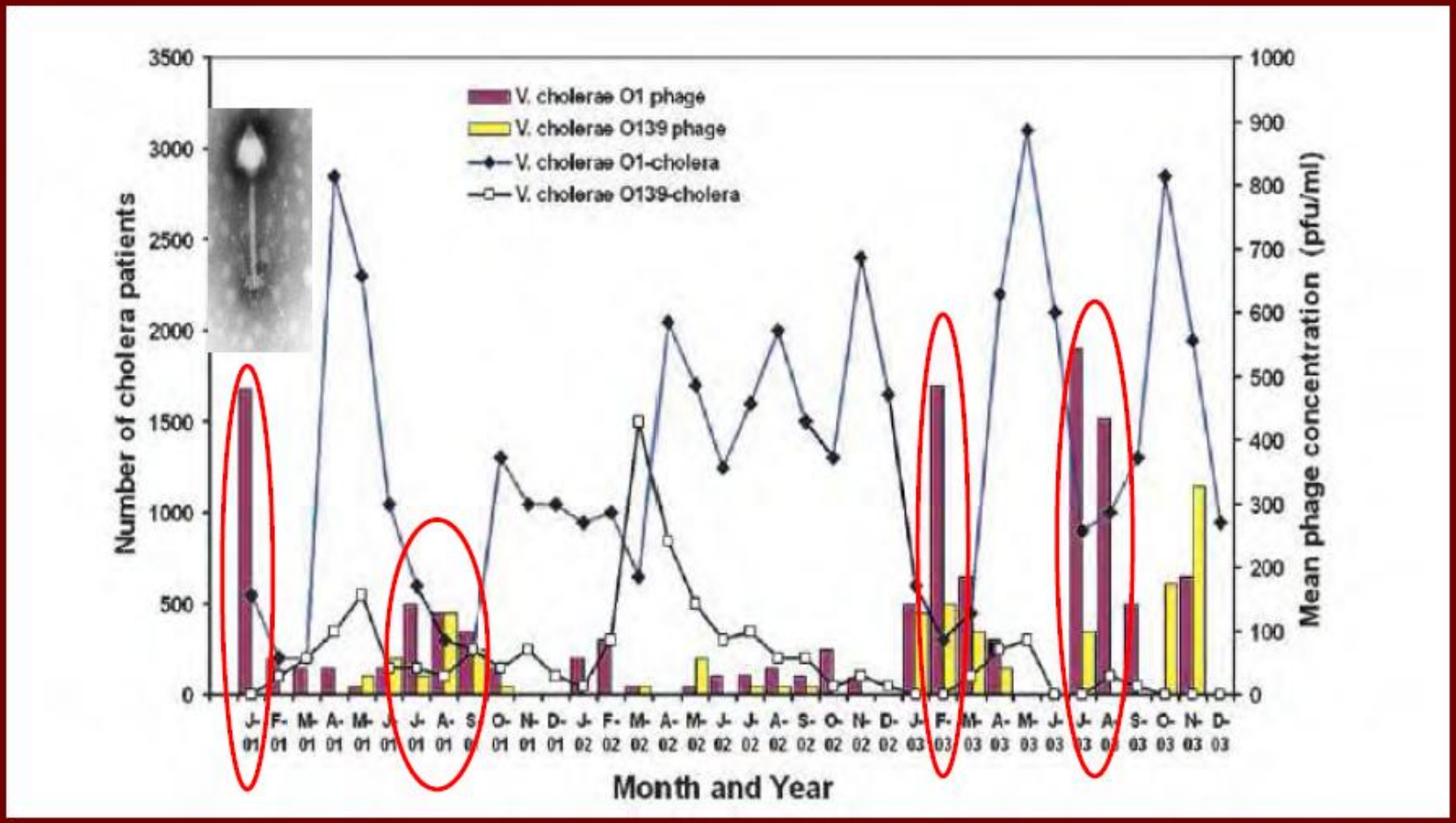
CO-EVOLUTION

GEEPhage Phagothérapie

Seasonal epidemics of cholera inversely correlate with the prevalence of environmental cholera phages

Shah M. Faruque*, Iftekhar Bin Naser†, M. Johirul Islam*, A. S. G. Faruque*, A. N. Ghosh†, G. Balakrish Nair*, David A. Sack*, and John J. Mekalanos‡§



Faruque. PNAS. 2004: 1-6

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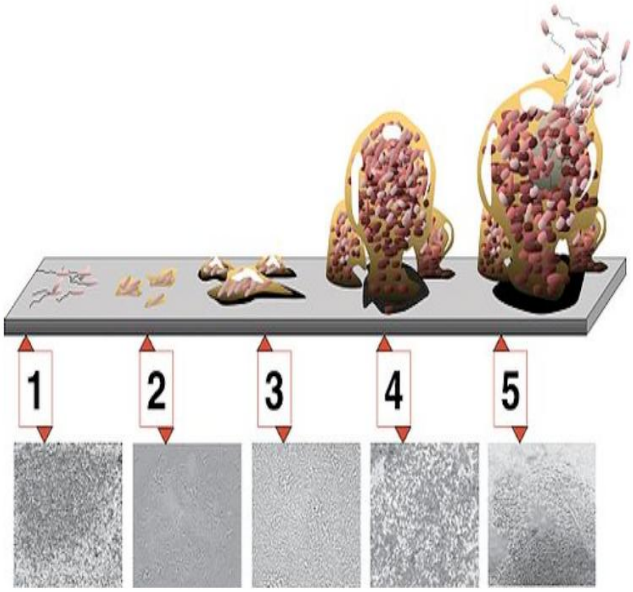
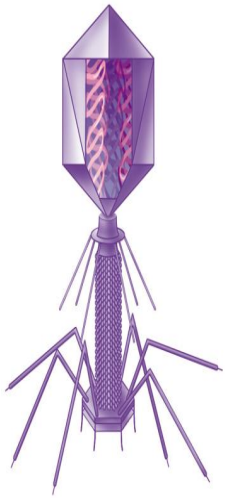
PHAGE ET BIOFILM

GEEPhage Phagothérapie

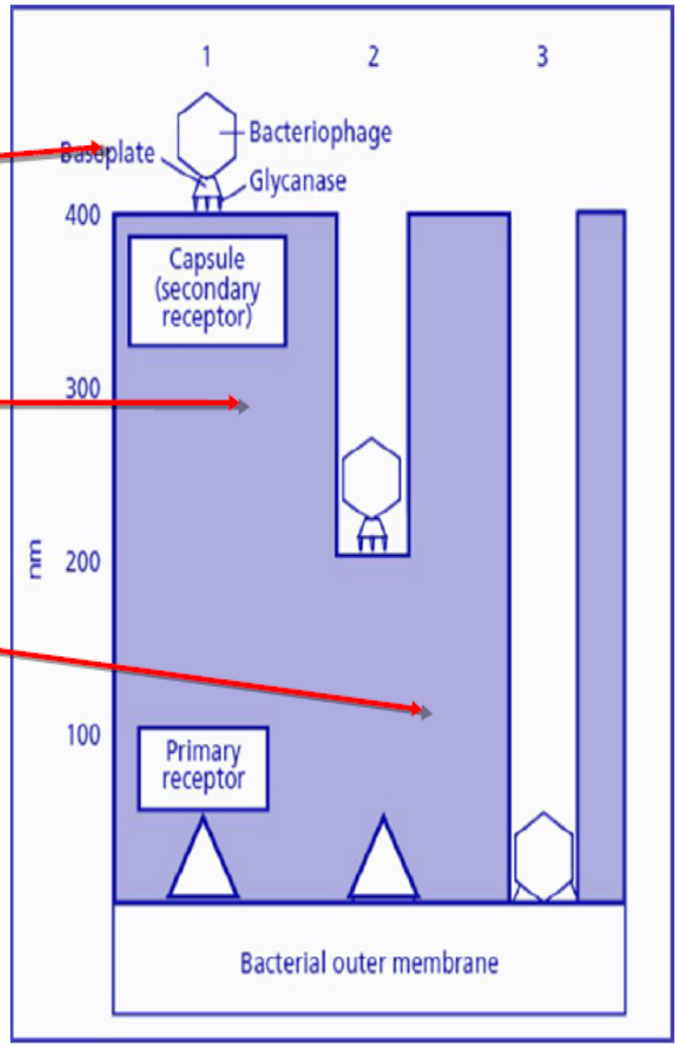


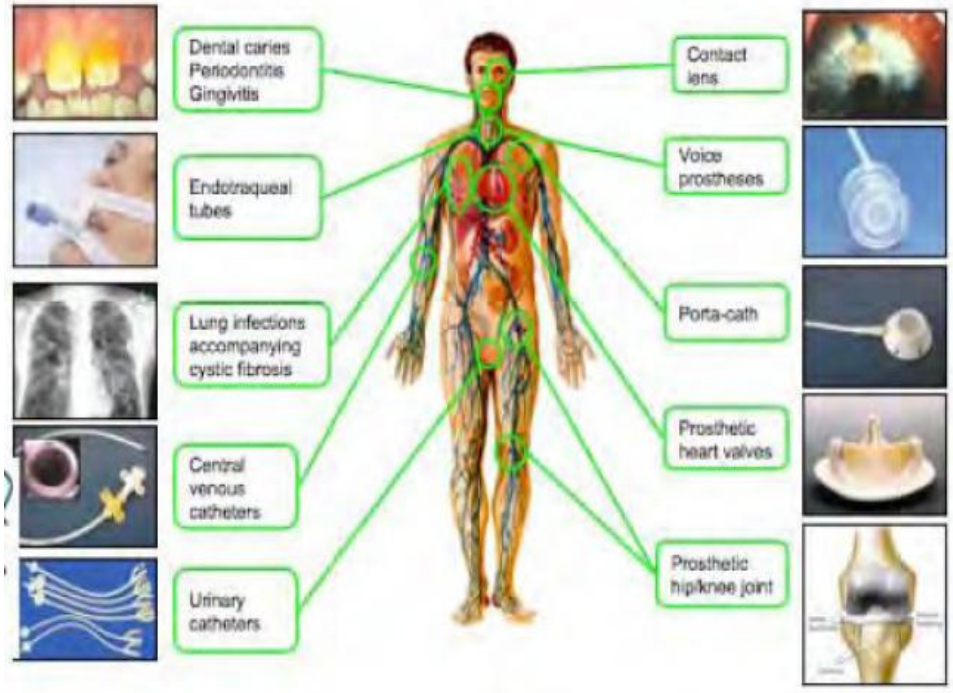


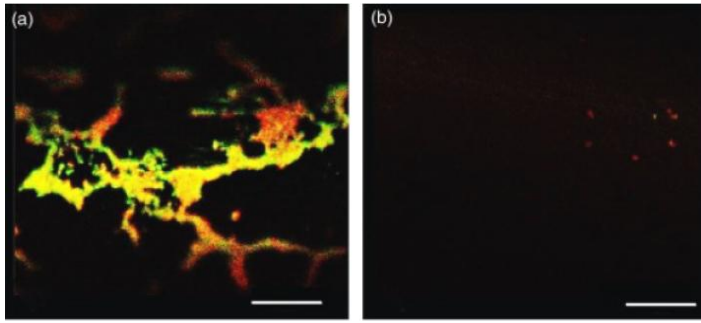
site secondaire

dépolymérase

site primaire







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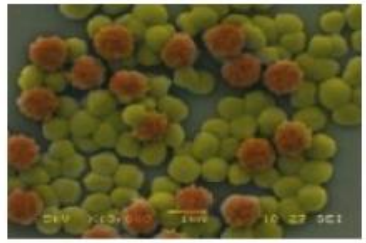
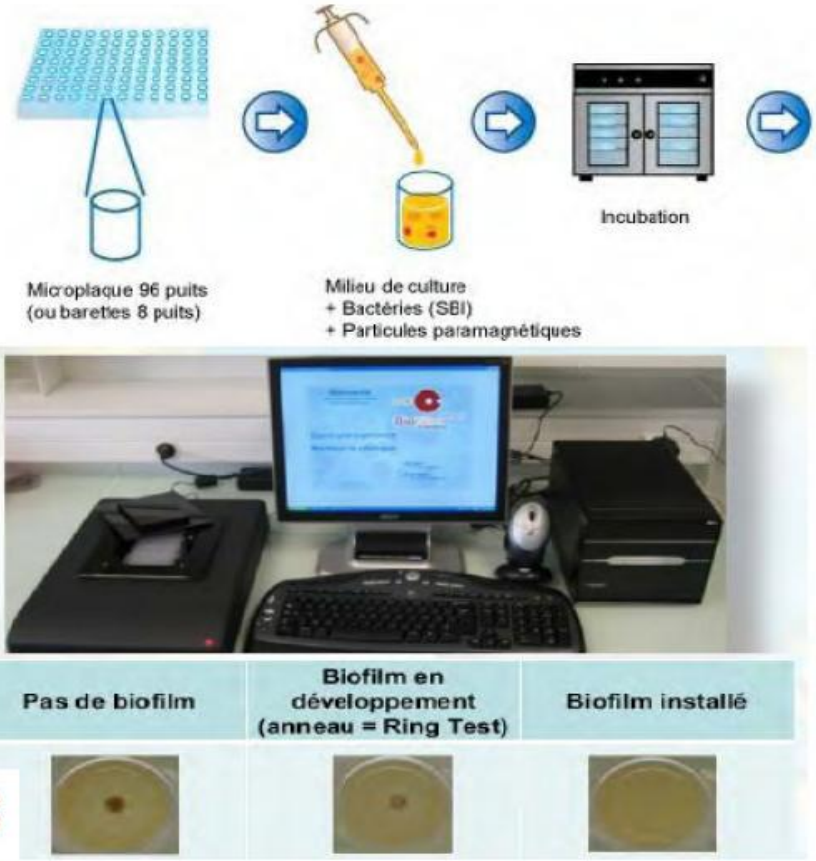
GEEPhage Phagothérapie

ANTIBIO-PHAGO-FILMOGRAMME

Modèles expérimentaux statiques

Biofilm Ring Test (BioFilm Control)

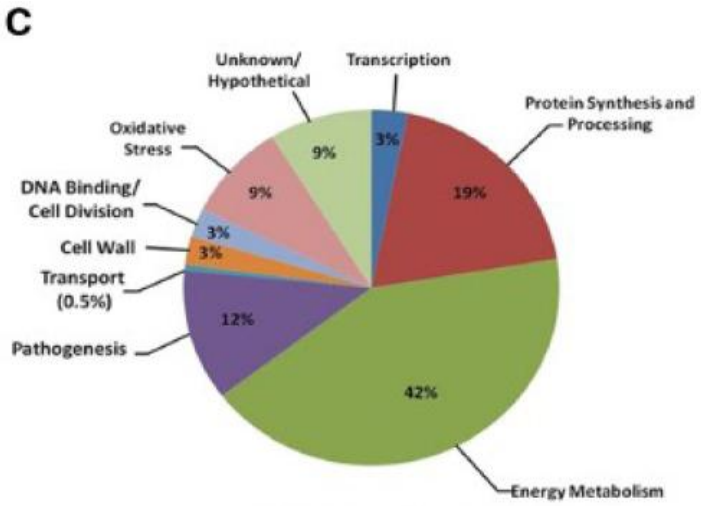




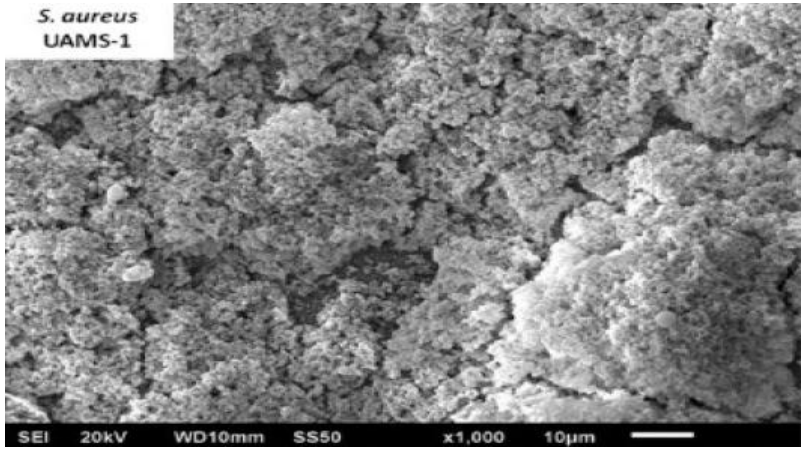
BioFilm Control

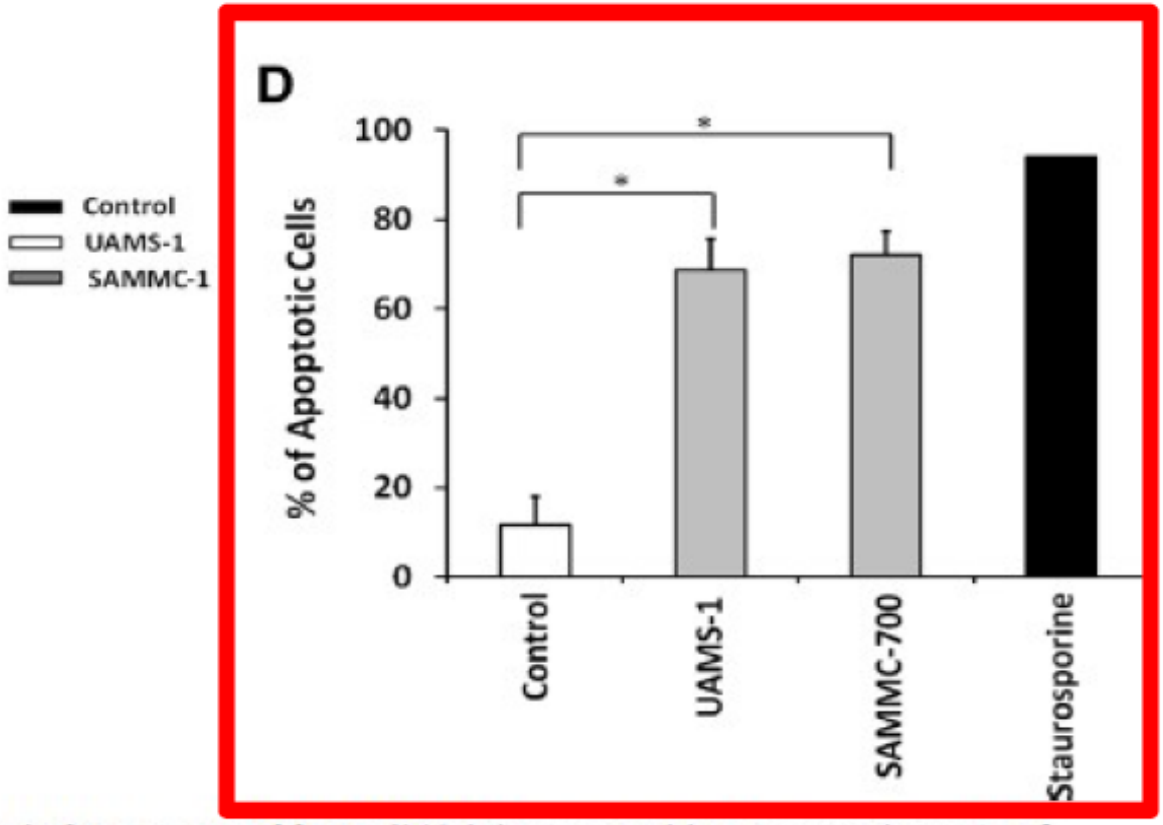
BIOFILM ET OSTEOBLASTOSE

Staphylococcus aureus biofilms decrease osteoblast viability, inhibits osteogenic differentiation, and increases bone resorption



S. aureus SAMCC 700 Biofilm Condition Media





Sanchez *et al. BMC Musculoskeletal Disorders* 2013, **14**:187
http://www.biomedcentral.com/1471-2474/14/187

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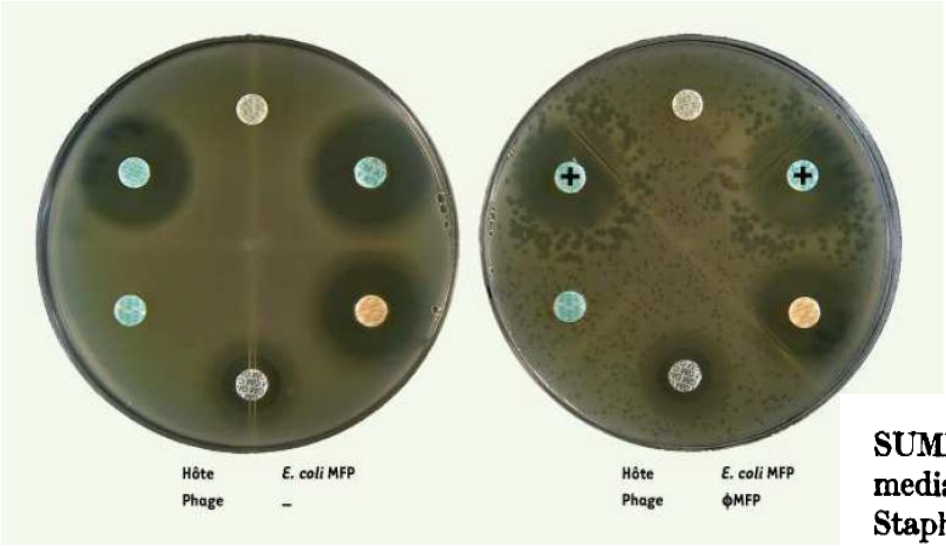
PHAGES ET ANTIBIOTIQUES

GEEPhage Phagothérapie

Phage-Antibiotic Synergy (PAS): β-Lactam and Quinolone Antibiotics Stimulate Virulent Phage Growth



André M. Comeau[1*], Françoise Tétart[1*], Sabrina N. Trojet[1], Marie-Françoise Prère[1,2], H. M. Krisch[1*]

1 Laboratoire de Microbiologie et Génétique Moléculaires, Centre National de la Recherche Scientifique, Université Paul Sabatier-Toulouse, Toulouse, France, 2 Laboratoire de Bactériologie, Institut Fédératif de Biologie, Centre Hospitalier Universitaire de Toulouse, Toulouse, France

The Influence of Antibacterial Substances on the Interaction of Bacteria and Bacteriophages

1. The Influence of Penicillin

By W. J. ELFORD

National Institute for Medical Research, Hampstead, London

SUMMARY: Penicillin in concentrations up to 100 units/ml. in broth or synthetic media has no demonstrable effect, after 20 hr. incubation at 37°, on the activities of Staphylococcus K phage, Coli-phage C 36, Coli-dysentery phage S 13, a Streptococcal phage and a *Bacillus subtilis* phage.

The simultaneous action of penicillin and phage on young cultures of *Staphylococcus aureus* (Oxford) in broth or synthetic medium at 37° produces, under certain conditions, a more rapid lysis than occurs in the presence of penicillin or phage alone.

The phenomenon of accelerated lysis through the joint action of penicillin and phage occurs with other organisms besides *Staph. aureus*, e.g. *B. subtilis* and *Streptococcus pyogenes*, Group C, differing from that with *Staph. aureus* only in degree.

Penicillin does not affect the adsorption of phage by the organisms. When the amount of antibiotic is sufficient to interfere adversely with the growth of the cell then the multiplication of phage decreases. It is suggested that certain balanced intracellular reactions of metabolism are disturbed by the action of penicillin, and as a result, intermediates essential to growth both of cell and phage cease to be available.

A phage-inhibiting substance was demonstrable in certain instances when *Staph. aureus* (Oxford) cultures were lysed by penicillin.

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Co-Therapy Using Lytic Bacteriophage and Linezolid: Effective Treatment in Eliminating Methicillin Resistant *Staphylococcus aureus* (MRSA) from Diabetic Foot Infections

Sanjay Chhibber*, Tarsem Kaur, Sandeep Kaur
Department of Microbiology, Panjab University, Chandigarh, India

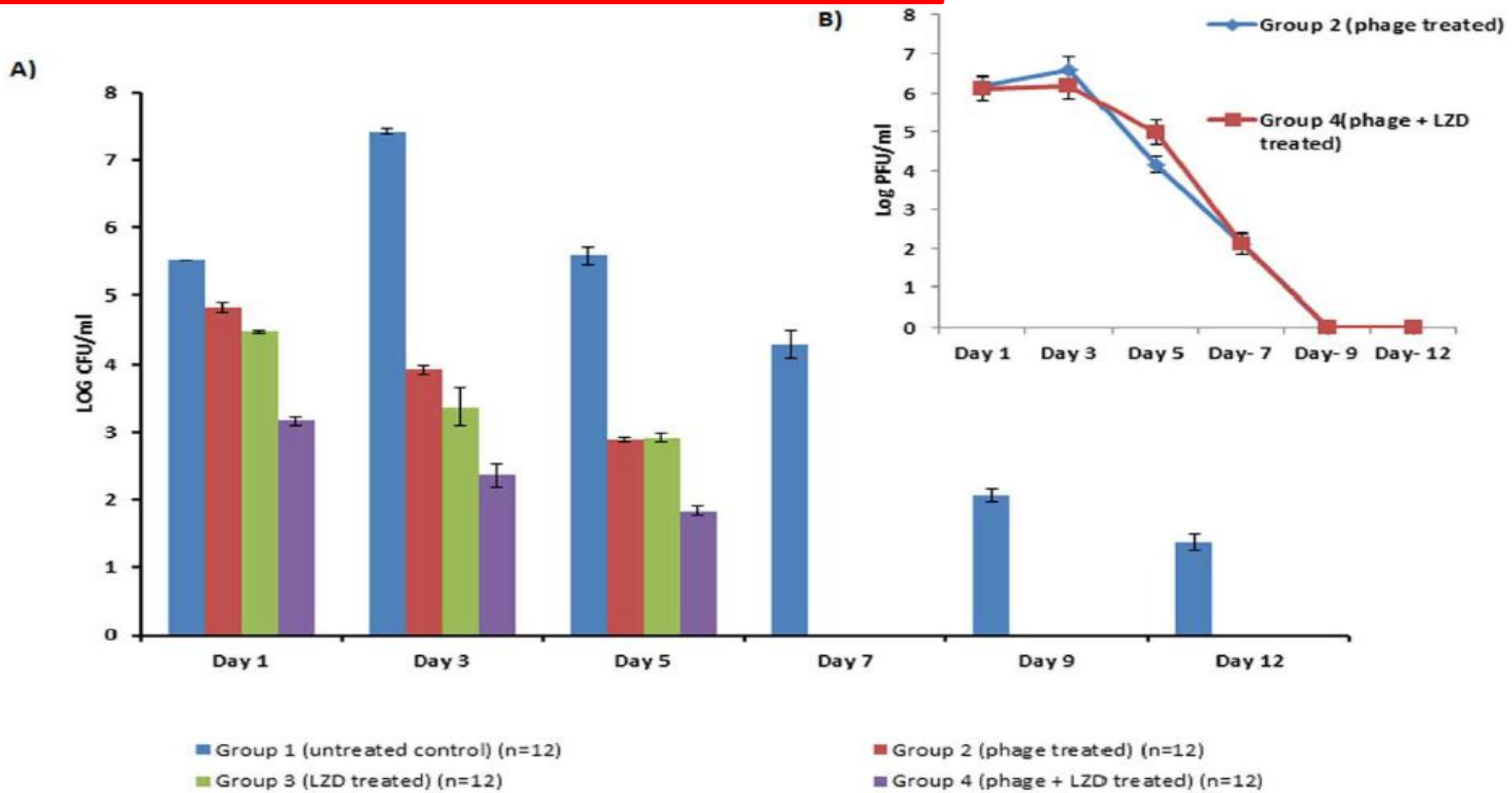

Figure 4. Bacterial load (in terms of Log CFU/ml) in A) Hindpaws of diabetic BALB/c mice following treatment with phage MR-10, linezolid and combination of phageMR-10 and linezolid (25 mg/kg/per oral) and Phage titers(in terms of Log PFU/ml) in B) Hindpaws of phage treated (group 2) and phage + LZD treated (group 4). [Error bars represent the standard deviation (S.D) from four independent values].

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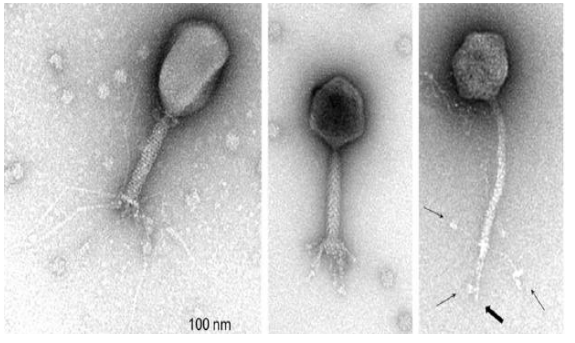
Phagothérapie

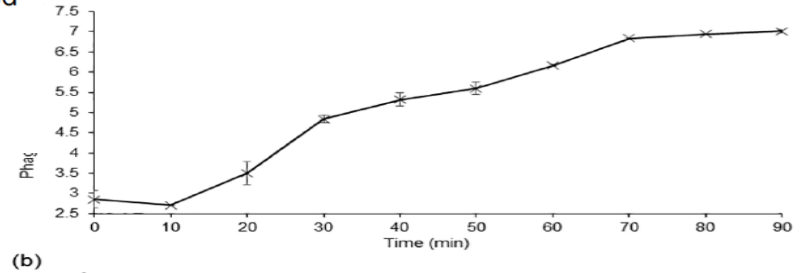
Three New *Escherichia coli* Phages from the Human Gut Show Promising Potential for Phage Therapy

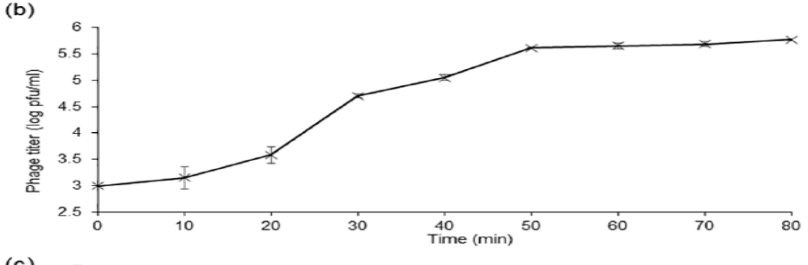
Marion Dalmasso[1,2¤], Ronan Strain[1,2], Horst Neve[3], Charles M. A. P. Franz[3], Fabien J. Cousin[1,2¤], R. Paul Ross[2,4], Colin Hill[1,2]*

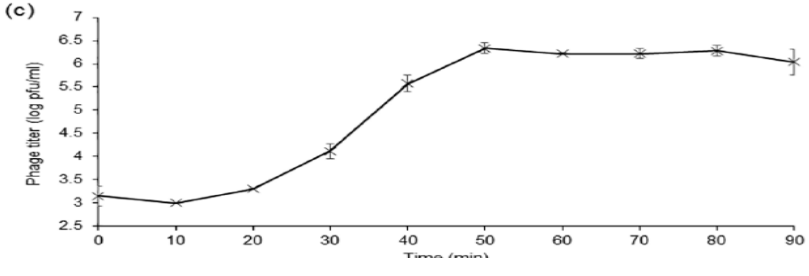
1 School of Microbiology, University College Cork, Cork, Ireland, 2 APC Microbiome Institute, University

With the emergence of multi-drug resistant bacteria the use of bacteriophages (phages) is gaining renewed interest as promising anti-microbial agents. The aim of this study was to isolate and characterize phages from human fecal samples. Three new coliphages, ϕAPCEc01, ϕAPCEc02 and ϕAPCEc03, were isolated. Their phenotypic and genomic characteristics, and lytic activity against biofilm, and in combination with ciprofloxacin, were investigated. All three phages reduced the growth of *E. coli* strain DPC6051 at multiplicity of infection (MOI) between 10^{-3} and 10^{5}. A cocktail of all three phages completely inhibited the growth of *E. coli*. The phage cocktail also reduced biofilm formation and prevented the emergence of phage-resistant mutants which occurred with single phage. When combined with ciprofloxacin, phage alone or in cocktail inhibited the growth of *E. coli* and prevented the emergence of resistant mutants. These three new phages are promising biocontrol agents for *E. coli* infections.









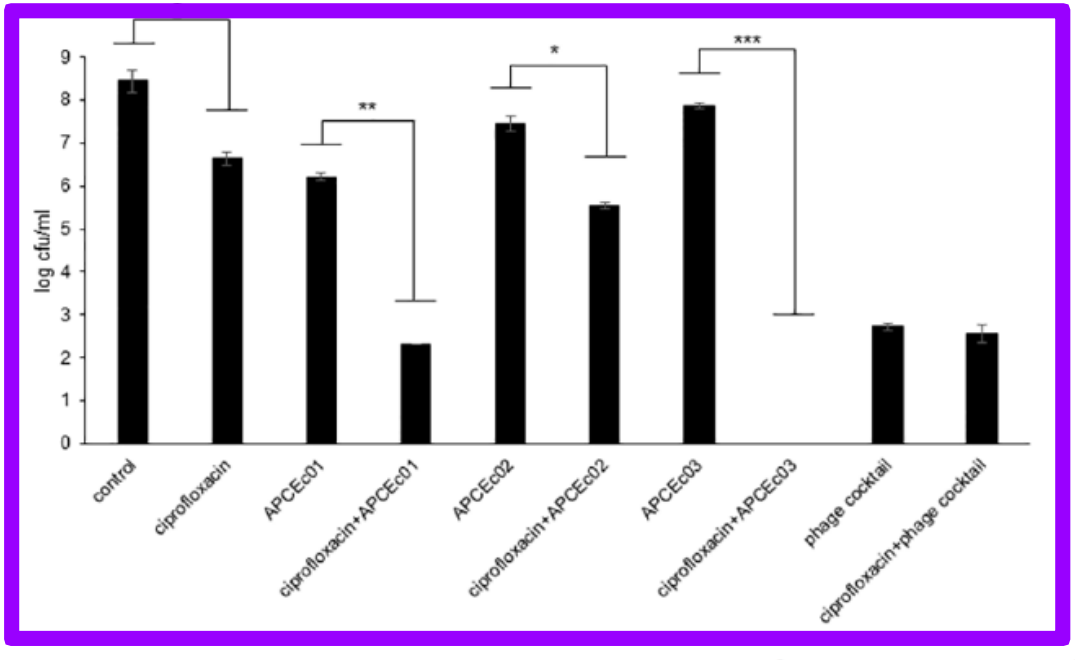


Fig 6. Effect of a combination of ciprofloxacin HCl and phages ϕAPCEc01, ϕAPCEc02, and ϕAPCEc03, alone or in cocktail, on the growth of *E. coli* strain DPC6051. Each condition was tested in

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Phagothérapie

Bacteriophages as Potential Treatment for Urinary Tract Infections

*Wilbert Sybesma[1], Reinhard Zbinden[2], Nino Chanishvili[3], Mzia Kutateladze[3], Archil Chkhotua[4], Aleksandre Ujmajuridze[4], Ulrich Mehnert[1] and Thomas M. Kessler[1]**

[1] Neuro-Urology, Spinal Cord Injury Center and Research, University of Zürich, Balgrist University Hospital, Zürich, Switzerland, [2] Institute of Medical Microbiology, University of Zürich, Zürich, Switzerland, [3] The Eliava Institute of Bacteriophage, Microbiology, and Virology, Tbilisi, Georgia, [4] Tsulukidze National Center of Urology, Tbilisi, Georgia

Background: Urinary tract infections (UTIs) are among the most prevalent microbial diseases and their financial burden on society is substantial. The continuing increase of antibiotic resistance worldwide is alarming so that well-tolerated, highly effective therapeutic alternatives are urgently needed.

Objective: To investigate the effect of bacteriophages on *Escherichia coli* and *Klebsiella pneumoniae* strains isolated from the urine of patients suffering from UTIs.

Material and methods: Forty-one *E. coli* and 9 *K. pneumoniae* strains, isolated from the urine of patients suffering from UTIs, were tested *in vitro* for their susceptibility toward bacteriophages. The bacteriophages originated from either commercially available bacteriophage cocktails registered in Georgia or from the bacteriophage collection of the George Eliava Institute of Bacteriophage, Microbiology and Virology. *In vitro* screening of bacterial strains was performed by use of the spot-test method. The experiments were implemented three times by different groups of scientists.

Results: The lytic activity of the commercial bacteriophage cocktails on the 41 *E. coli* strains varied between 66% (Pyo bacteriophage) and 93% (Enko bacteriophage). After bacteriophage adaptation of the Pyo bacteriophage cocktail, its lytic activity was increased from 66 to 93% and only one *E. coli* strain remained resistant. One bacteriophage of the Eliava collection could lyse all 9 *K. pneumoniae* strains.

Conclusions: Based on the high lytic activity and the potential of resistance optimization by direct adaption of bacteriophages as reported in this study, and in view of the continuing increase of antibiotic resistance worldwide, bacteriophage therapy is a promising treatment option for UTIs highly warranting randomized controlled trials.

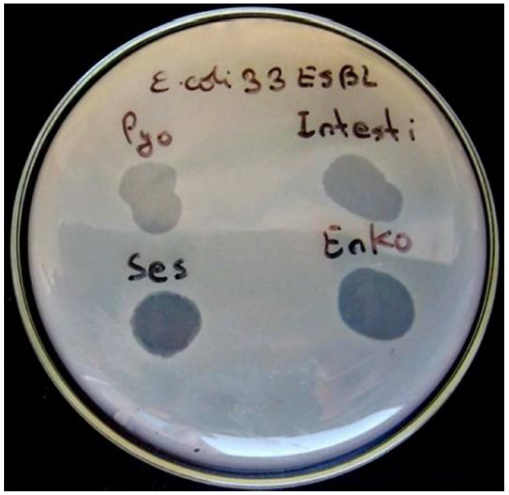

FIGURE 1 | Plaque morphology of *Escherichia coli* strain #33. The figure shows overgrown (partial) lysis (OL) in case of Pyo and Intesti bacteriophages and confluent (complete) lysis (CL) in case of Ses and Enko bacteriophages. All these results are positive.

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PRODUCTION DE PHAGES

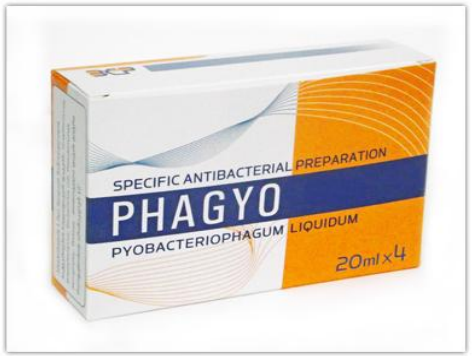
Institute ELIAVA

Staphylococcus phage for intravenous use

Manufacturer:
JSC Biochimpharm
Addres: Gotua str. 3, Tbilisi 0160, Georgia.
Phone: +995 32 2 244777; +995 32 2 244778
Fax: +995 32 2 380895
E-mail: biochimpharm@geophage.ge
Web-site: www.biochimpharm.ge

State Registration No R-001875
Renewal: March 2010

Approved by Order of the Head of Drug Agency of the Ministry of Labour, Health and Social Affairs of Georgia
№ 40/adm, January 29, 2008



Quantitative composition
PHAGESTI is presented as a liquid and 1 ml product contains:
Bacteriophagum Shigella;
Bacteriophagum Salmonella;
Bacteriophagum E.Coli;
Bacteriophagum Proteus (vulgaris, mirabilis);
Bacteriophagum Staphylococcus;
Bacteriophagum Pseudomonas;
Bacteriophagum Enterococcus;
Each quantity not less than - 10^5;

Recommendation dosage scheme for treatment:

Age	Per oral administration	Per rectum (enema)
up to 6 month	5 ml X 1a day	5 ml X 1 a day
6 to 12 month	5 ml X 2 a day	10 ml X 1 a day
1 to 3 years	5 ml X 3 a day	20 ml X 1 a day
3 to 8 years	10 ml X 2-3 a day	30 ml X 1 a day

MICROGEN

Bacteriophages

Pseudomonas aeruginosa bacteriophage

Coliproteic bacteriophage

Staphylococcal bacteriophage

Dysenteric bacteriophage, polyvalent

Klebsiella bacteriophage, polyvalent, purifi...

Klebsiella pneumoniae bacteriophage, purified

Klebsiphage (Klebsiella pneumoniae bacteriophage)

Coli bacteriophage

Proteus bacteriophage

Salmonellosis of ABCDE groups bacteriophage

Streptococcal bacteriophage

Intesti-bacteriophage

Pyopolyphage (pyobacteriophage combined, liquid)

Pyobacteriophage polyvalent, purified®

SEXTAPHAGE ® (pyobacteriophage polyvalent)

INTESTI-BACTERIOPHAGE

solution for oral and rectal use

Mixture of filtrates of phagolysates active against Shigella flexneri 1, 2, 3, 4, 6 serovars and Zonnei, salmonellae of paratyphoid A and B, typhimurium, cholerae suis, infantum, oranienburg, enteritidis; enteropathogenic colibacillus of etiologically significant serovariants, enterococci, staphylococci, Pseudomonas aeruginosa, Proteus vulgaris and mirabilis. Intesti-bacteriophage possesses the ability to specifically lyse the above-mentioned bacteria.

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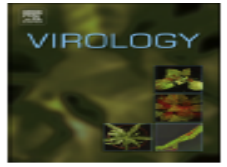
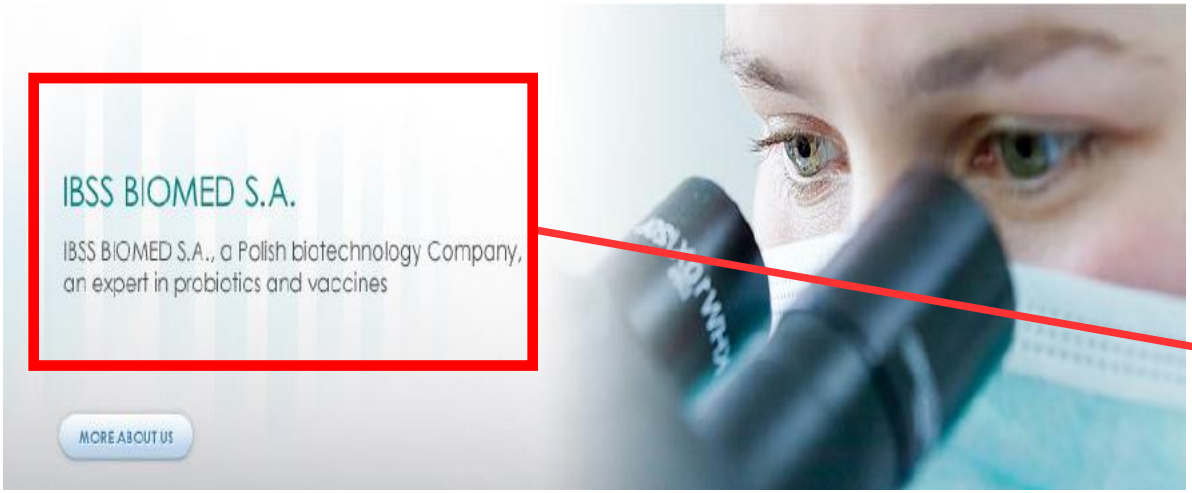


Safety analysis of a Russian phage cocktail: From MetaGenomic analysis to oral application in healthy human subjects

Shawna McCallin [a], Shafiqul Alam Sarker [b], Caroline Barretto [a], Shamima Sultana [b], Bernard Berger [a], Sayeda Huq [b], Lutz Krause [a,1], Rodrigo Bibiloni [a,2], Bertrand Schmitt [a], Gloria Reuteler [a], Harald Brüssow [a,*]

[a] Nestlé Research Centre, Nestec Ltd, Vers-chez-les-Blanc, CH-1000 Lausanne 26, Switzerland
[b] International Centre for Diarrhoeal Diseases Research, Bangladesh (icddr,b), 68 Shaheed Tajuddin Ahmed Sharani, Mohakhali, Dhaka 1212, Bangladesh

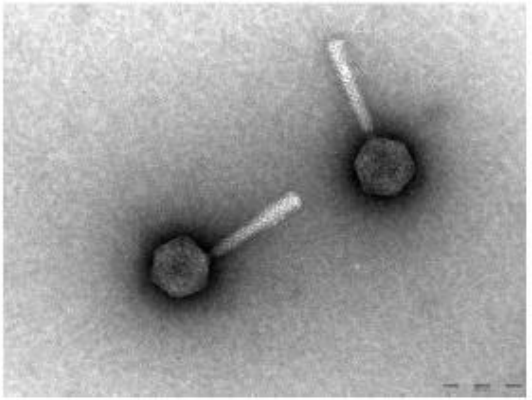


The GMP (Good Manufacturing Practice) System that is in place at the company guarantees that the products manufactured by IBSS BIOMED S.A. fully meet quality and safety standards.

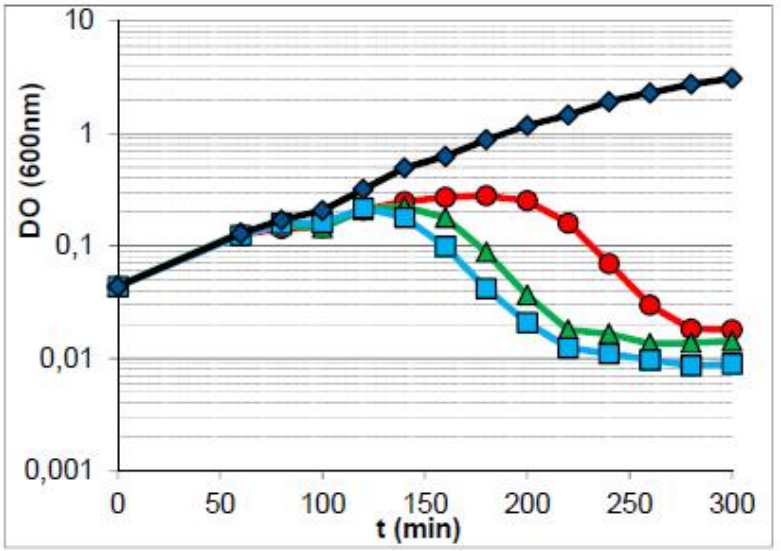
Bacteriophages isolation and characterization

Plaques

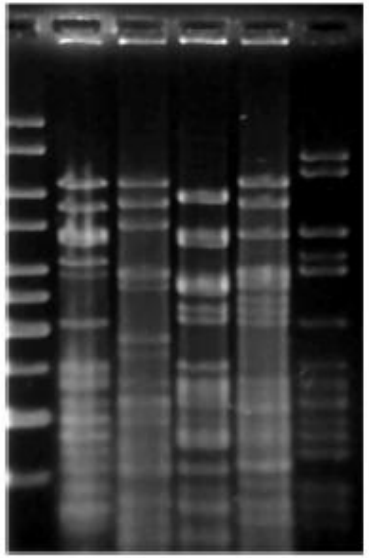
EM



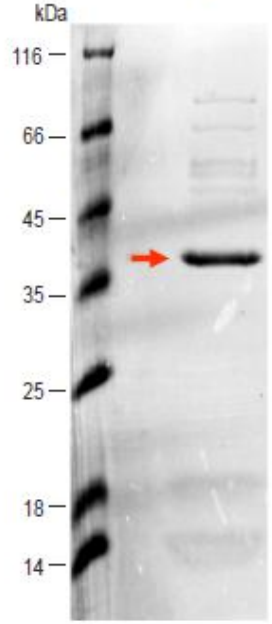
Kinetics parameters



RFLP



Mass Spec



Genome sequencing

↓

Virus classification

↓

Molecular studies

Institut Pasteur

L. Debarbieux

Quality and Safety Requirements for Sustainable Phage Therapy Products

Jean-Paul Pirnay • Bob G. Blasdel • Laurent Bretaudeau • Angus Buckling • Nina Chanishvili • Jason R. Clark • Sofia Corte-Real • Laurent Debarbieux • Alain Dublanchet • Daniel De Vos • Jérôme Gabard • Miguel Garcia • Marina Goderdzishvili • Andrzej Górski • John Hardcastle • Isabelle Huys • Elizabeth Kutter • Rob Lavigne • Maia Merabishvili • Ewa Olchawa • Kaarle J. Parikka • Olivier Patey • Flavie Pouilot • Gregory Resch • Christine Rohde • Jacques Scheres • Mikael Skurnik • Mario Vaneechoutte • Luc Van Parys • Gilbert Verbeken • Martin Zizi • Guy Van den Eede

Table I Expert Consensus Quality and Safety Requirements for Sustainable Phage Therapy Products

A. Production environment

When production activities include the processing of intermediate, bulk or finished phage products exposed to the environment, this must take place in an environment with specified air quality and cleanliness in order to minimize the risk of contamination. The effectiveness of these measures must be validated and monitored. Where intermediate, bulk or finished products are exposed to the environment during processing, without a subsequent microbial inactivation process, an *air quality* with particle counts and microbial colony counts equivalent to those of Grade A as defined in the current European Guide to Good Manufacturing Practice (GMP), Annex 1 and Directive 2003/94/EC is required with a background environment at least equivalent to GMP Grade D in terms of particles and microbial counts. The biosafety level (BSL) is determined by the host bacteria used in the production processes (e.g., BSL-2 for *Pseudomonas aeruginosa*).

C. Quality Assurance and Quality Control (QA/QC) specifications

Products/characteristics	Control test	Limits of acceptance	Recommended test procedures
C.1. Host bacteria used in production (stock suspensions)			
The bacterial hosts used in the production process – with the exception of selection, adaptation and efficiency of plating (EOP) and host range determination – should be as safe (or least pathogenic) as feasible.			
Origin	Document pedigree/ history/pathogenicity level	Known origin	Screening of scientific literature, lab books, consignment letters,..
Identification	Identification at the species and strain levels	Matching species and strain identification	• State of the art clinical microbiology techniques • Highly discriminating (molecular/ genomic) typing techniques (e.g., MLST, AFLP, PFGE, Rep-PCR,..)
Most often it will not be possible to find or quickly generate a suitable host bacterium that is free of prophages or phage-like elements, but one should nevertheless strive to use non-lysogenic strains, containing as few phages or other phage-like elements of genetic exchange [11, 12] as possible	• Induction of phages • Host genome screening for phage or phage-like elements	As few spontaneously produced (or by induction) temperate phages, complete prophage sequences or phage-like elements as possible[a]	• *In vitro* induction methods (Mitomycine C [13] or UV induction) • State of the art DNA sequencing and analysis (bioinformatics) procedures
Avoid mutator strains as host bacteria	Screen for mutator strains in case of doubt	No mutator strain	State of the art tests (e.g., fosfomycin and rifampicin Disk Diffusion Tests) [14]
Validated preservation/storage (cryopreservation, freeze-drying,..)	Monitor storage conditions (e.g., temperature)	Variable, depending on the preservation method	Variable (e.g., temperature probes, temperature indicator labels,..)
C.2. Bacteriophages (Master Seed lots)			
Origin		• Known origin	

Pharm Res
DOI 10.1007/s11095-014-1617-7

AmpliPhi Biosciences Corporation
800 East Leigh Street
Richmond, Virginia 23219

AmpliPhi's Bacteriophage Manufacturing Facility Receives cGMP Certification

First cGMP-certified manufacturing facility commissioned to manufacture bacteriophage products for human use

San Diego and Richmond, VA, USA, Ljubljana, Slovenia, and Sydney, Australia, June 3, 2014 – AmpliPhi BioSciences Corporation. (OTCQB: APHB), a global leader in developing bacteriophage-based antibacterial therapies to treat drug resistant infections, announced today that its production facility in Ljubljana, Slovenia, was cleared by JAZMP, the Agency of the Republic of Slovenia for Medicinal Products and Medical Devices, to manufacture bacteriophages under current Good Manufacturing Practices (cGMP) standards. AmpliPhi will produce *Staphylococcus aureus* and *Pseudomonas aeruginosa* bacteriophages to be used in planned human clinical trials.

AmpliPhi Biosciences Announces Dosing of First Patient in Phase 1 Clinical Trial of AB-SA01

San Diego, CA, January 20, 2016 – AmpliPhi Biosciences Corporation (NYSEMKT: APHB), a global leader in developing bacteriophage-based antibacterial therapies to treat drug-resistant infections, today announces it has dosed the first patient in its Phase 1 clinical trial of AB-SA01 for the treatment of *Staphylococcus aureus (S. aureus)* infections in patients with chronic rhinosinusitis (CRS) that fail to respond to standard antibiotic treatment.

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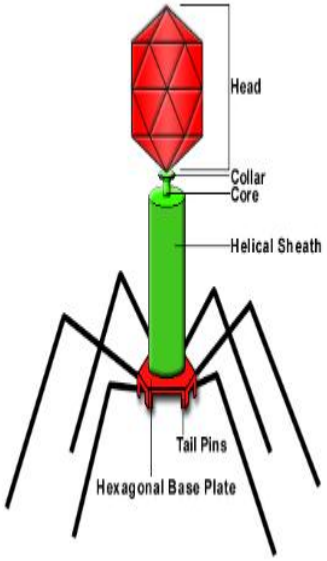
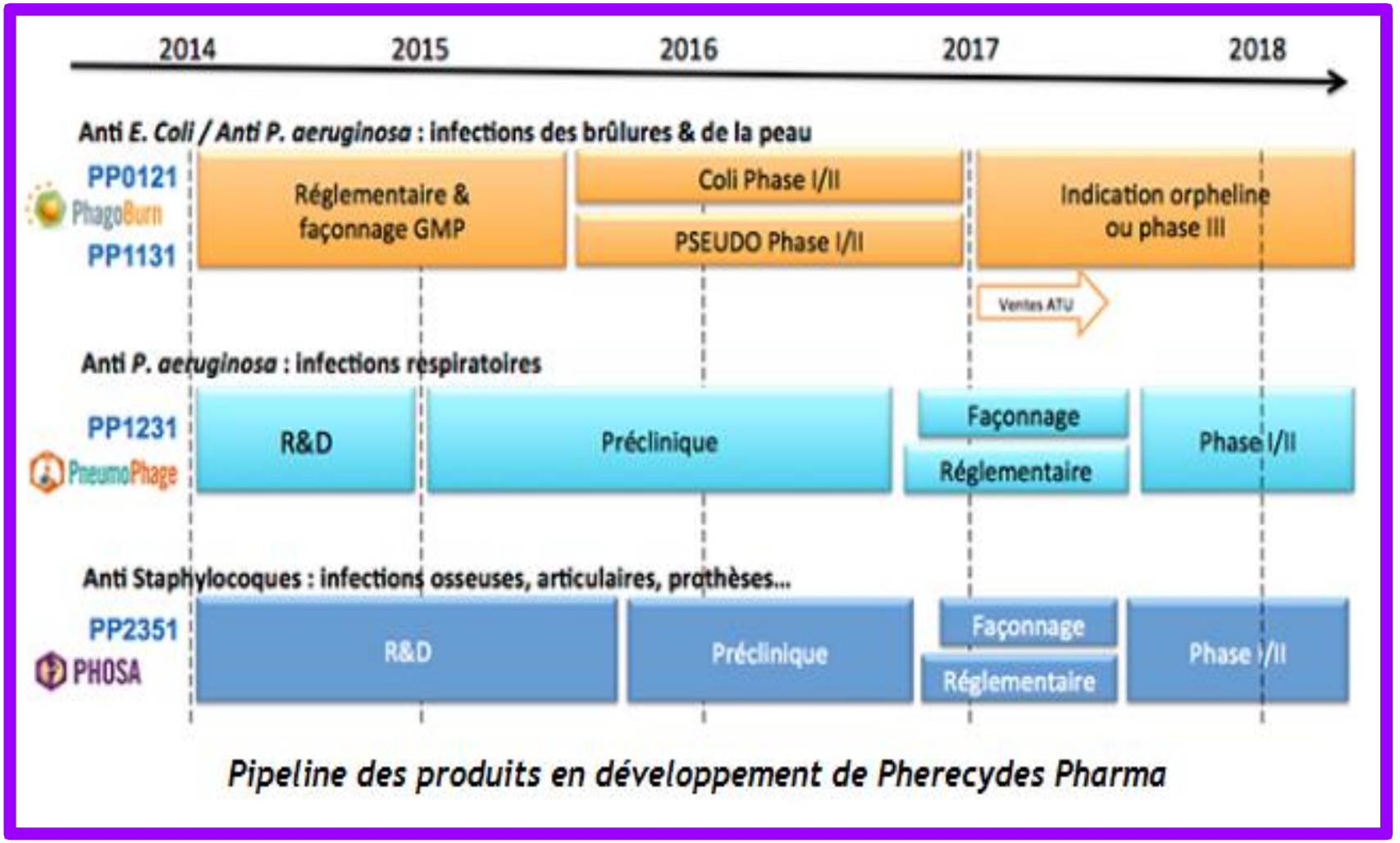
PHERECYDES PHARMA

GEEPhage
Phagothérapie





Pipeline des produits en développement de Pherecydes Pharma

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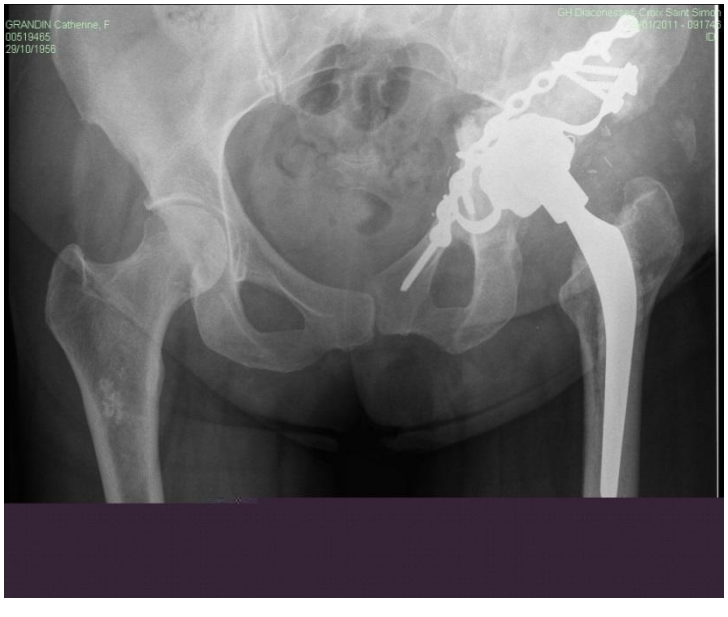
PROJETS
STAPHYLOCOQUES ET OS

PHOSA

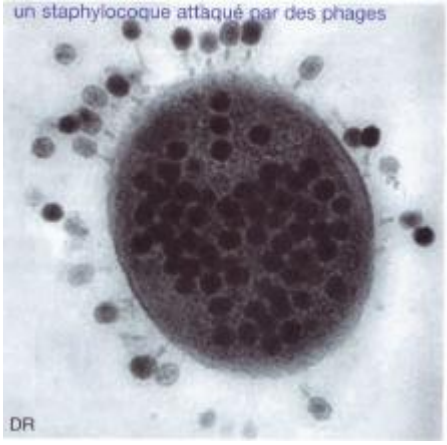
2015-2016

Cocktail de bactériophages pour lutter contre certaines infections bactériennes ostéo-articulaires provoquées par *Staphylococcus (aureus* et *epidermidis*)

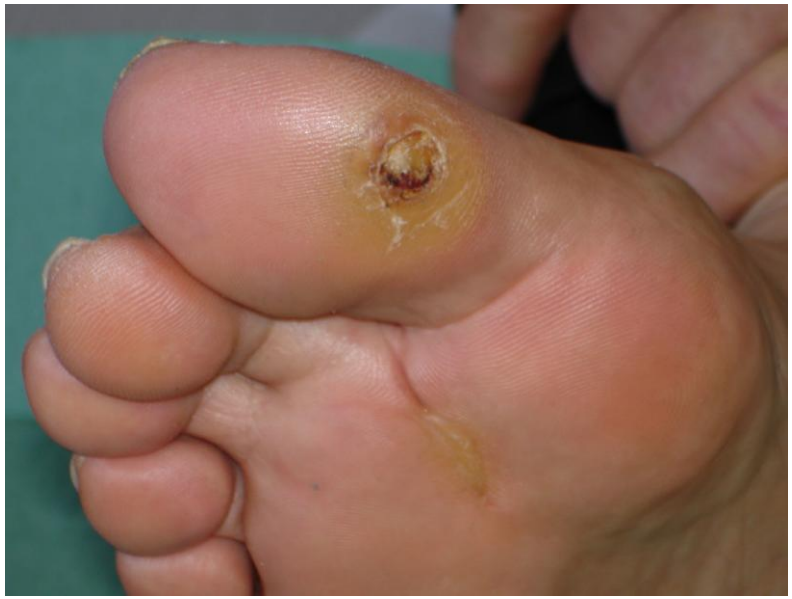
PHAGOS



2017?



PHAGOPIEDS



ansm
Agence nationale de sécurité du médicament et des produits de santé

COMITE SCIENTIFIQUE SPECIALISE TEMPORAIRE

CSST201611011- Phagothérapie

Jeudi 24 mars 2016 de 9h30 à 17h00, en salle A011

DÉCISION DG n° 2016-11

du 13 JAN. 2016 portant création d'un Comité scientifique spécialisé temporaire « Phagothérapie » à l'Agence nationale de sécurité du médicament et des produits de santé

Programme de séance		
	Sujets abordés	**Action** (pour audition, information, adoption ou discussion)
1.	**Introduction**	
1.1	Adoption de l'ordre du jour	Pour adoption
2.	**Dossier thématique**	
2.1	PHAGOTHERAPIE Elaboration d'une position quant aux situations cliniques pouvant justifier d'un accès précoce aux bactériophages, et détermination de prérequis nécessaires pour une mise à disposition précoce des bactériophages	Pour discussion
5.	**Tour de Table**	Pour discussion

Question posée N°1	Quelles sont les situations de besoin ?
Question posée N°2	Quels sont les domaines et les objectifs thérapeutiques à cibler ?
Question posée N°3	Quels sont les pré-requis nécessaires pour une mise à disposition précoce des bactériophages ?

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MODES D'ADMINISTRATION

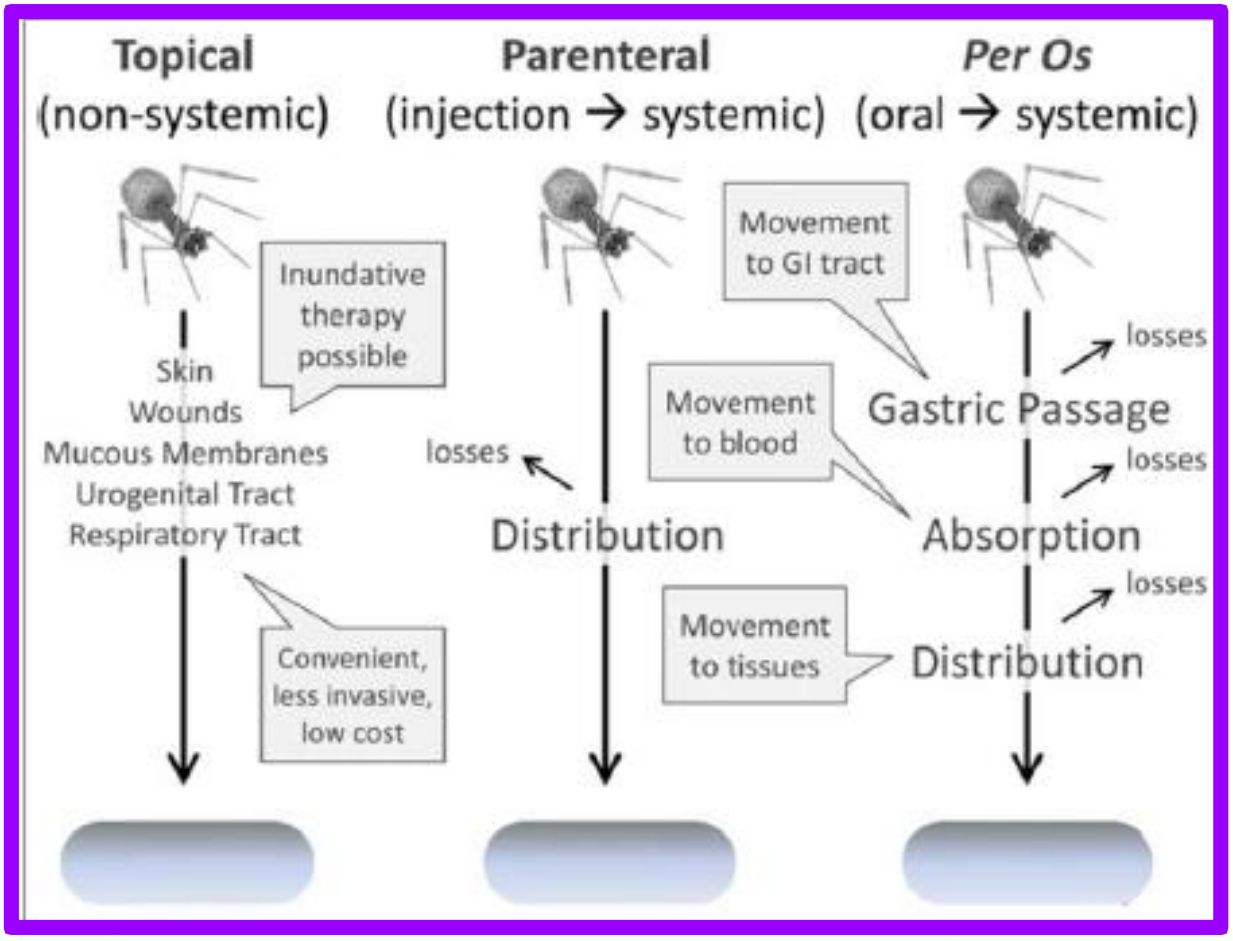
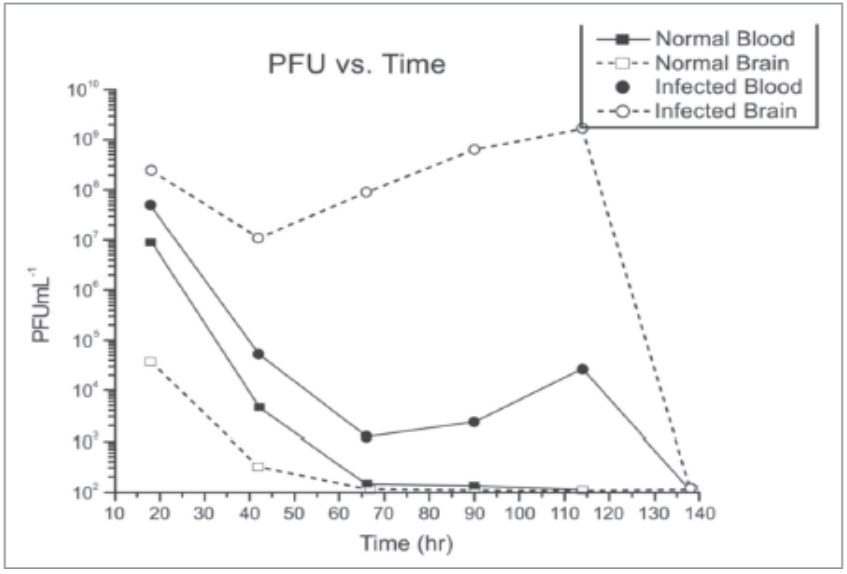
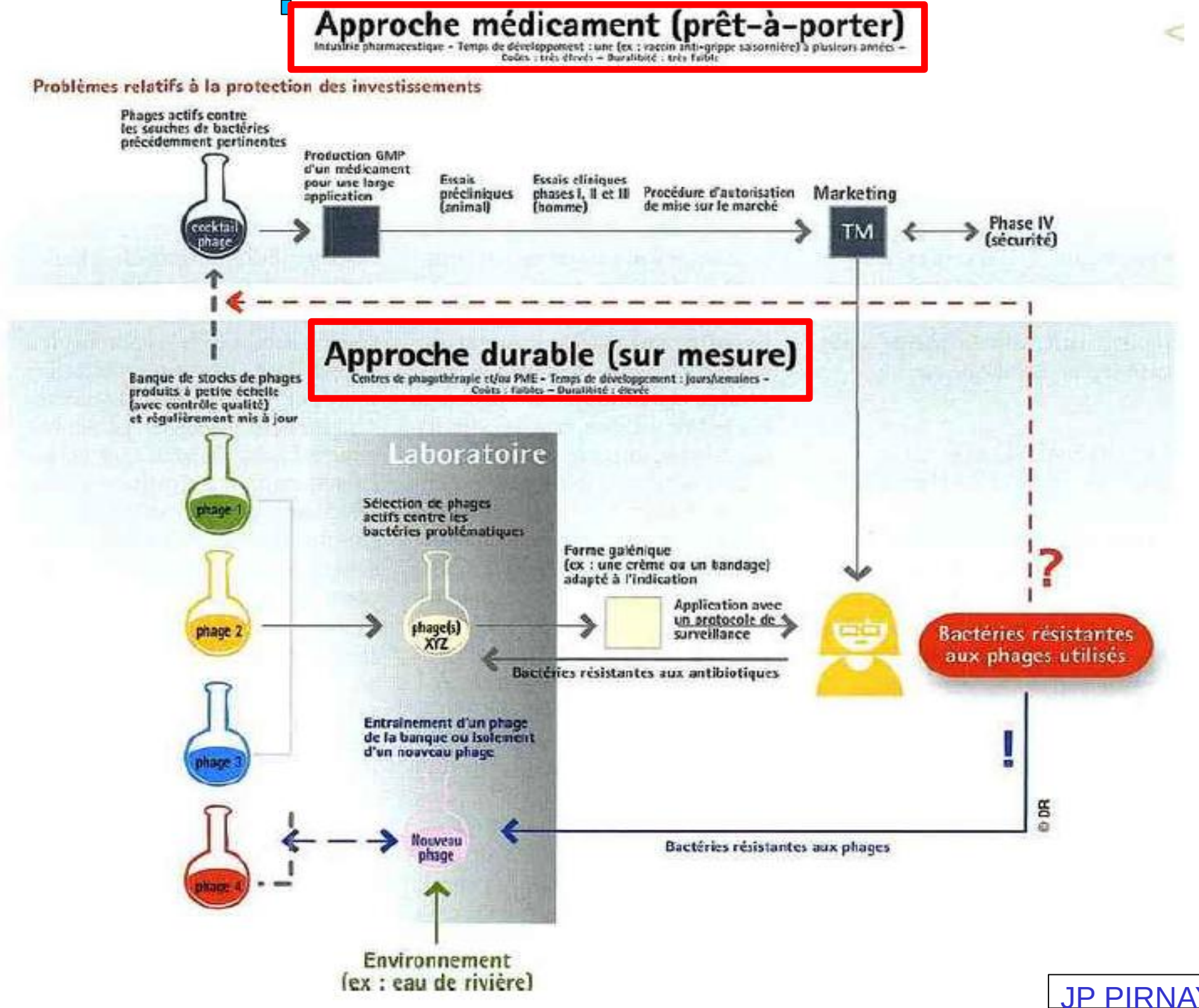


Figure 1. This figure, based on the data in the 1943 mouse studies of Rene Dubos,[78] provides significant insight into why phage therapy works well even in treating infections that antibiotics can't reach. When he injected the mice intraperitoneally with 10^9 phages, they quickly appeared in the blood stream, entering the brain, but they were rapidly cleared. However, if the mice were also injected intracerebrally with *Shigella dysenteriae*, the host for these phages, then 46/64 of the mice survived (as compared with 3/84 in the absence of appropriate viable phage) and the brain level of phage climbed to over 10^9 per gram. Once the bacteria were cleared, phage levels dropped below detection limits.




Approche médicament (prêt-à-porter)
Industrie pharmaceutique - Temps de développement : une (ex : vaccin anti-grippe saisonnière) à plusieurs années - Coûts : très élevés - Durabilité : très faible
Problèmes relatifs à la protection des investissements
Phages actifs contre les souches de bactéries précédemment pertinentes
cocktail phage
Production GMP d'un médicament pour une large application
Essais précliniques (animal)
Essais cliniques phases I, II et III (homme)
Procédure d'autorisation de mise sur le marché
Marketing
TM
Phase IV (sécurité)
Approche durable (sur mesure)
Centres de phagothérapie et/ou PME - Temps de développement : jours/semaines - Coûts : faibles - Durabilité : élevée
Banque de stocks de phages produits à petite échelle (avec contrôle qualité) et régulièrement mis à jour
phage 1
phage 2
phage 3
phage 4
Laboratoire
Sélection de phages actifs contre les bactéries problématiques
phage(s) XYZ
Forme galénique (ex : une crème ou un bandage) adapté à l'indication
Application avec un protocole de surveillance
Bactéries résistantes aux antibiotiques
Bactéries résistantes aux phages utilisés
?
!
Entraînement d'un phage de la banque ou isolement d'un nouveau phage
Nouveau phage
Bactéries résistantes aux phages
© DR
Environnement (ex : eau de rivière)

JP PIRNAY

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Phagothérapie

NECESSITE DE CREATION D'UNE BANQUE DE BACTERIOPHAGES

DSMZ

P-H-A-G-E.org

Phages for Human Applications Group Europe vzw
Militair Hospitaal Koningin Astrid
C DIS/Site NOH, Blok C, 1ste verdieping
Lokaal 1.391
Bruynstraat 1
1120 BRUSSEL

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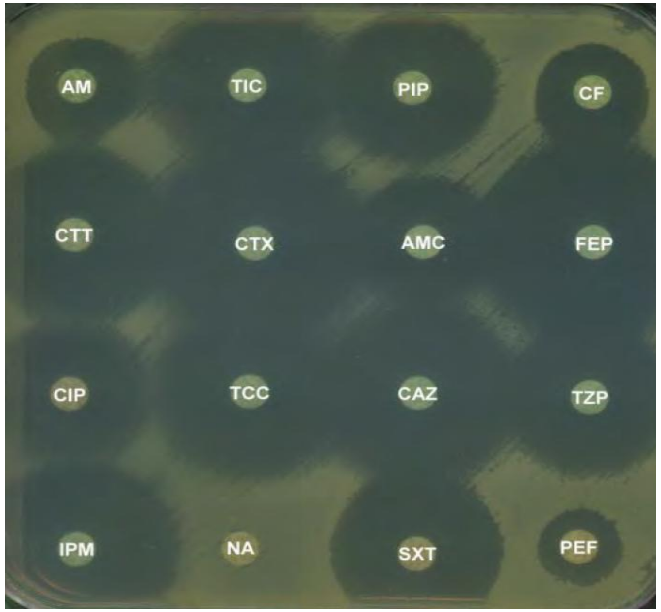
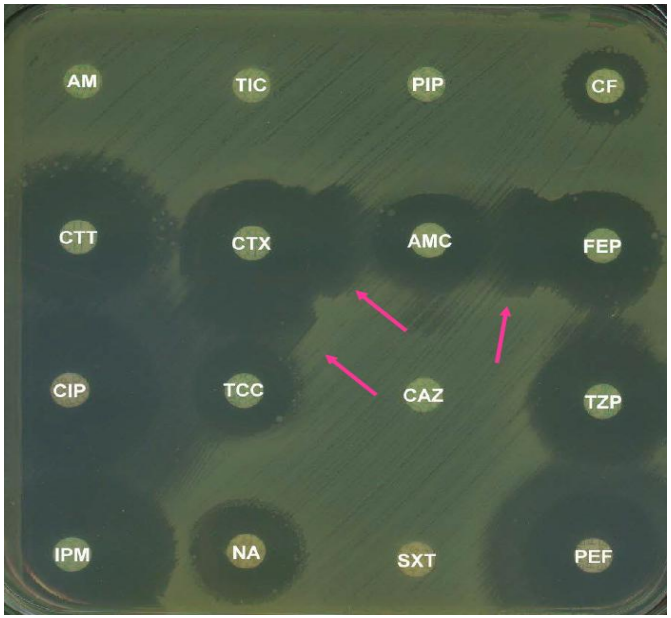
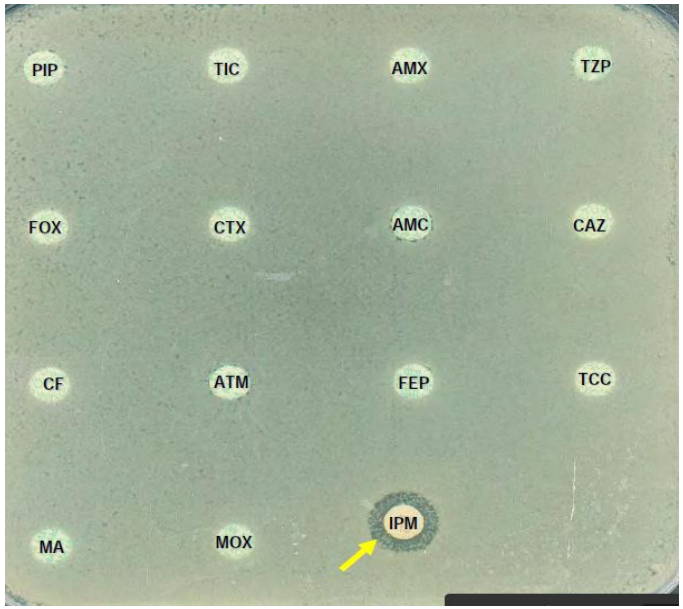
ALTERNATIVES THERAPEUTIQUES

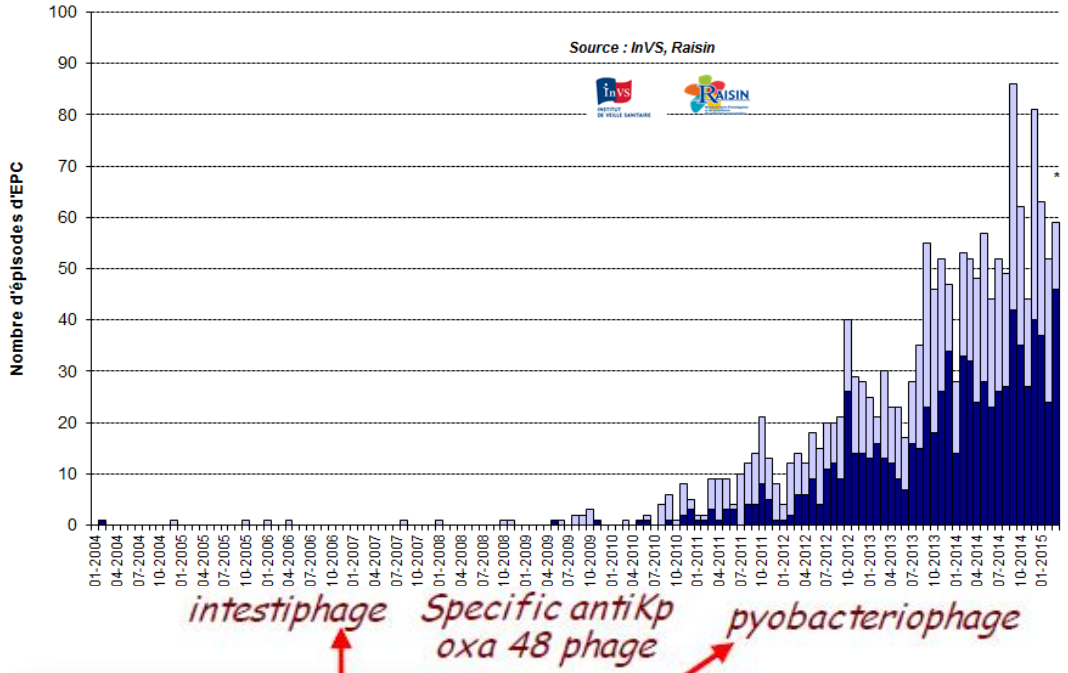




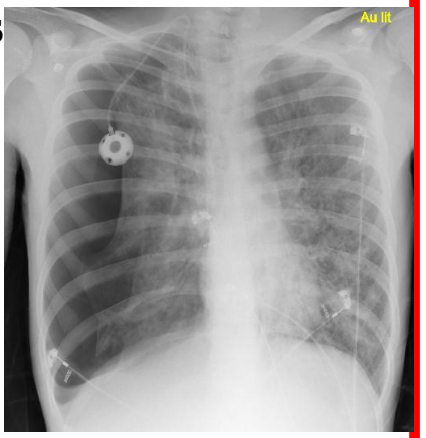


ANTIBIO-RESISTANCE

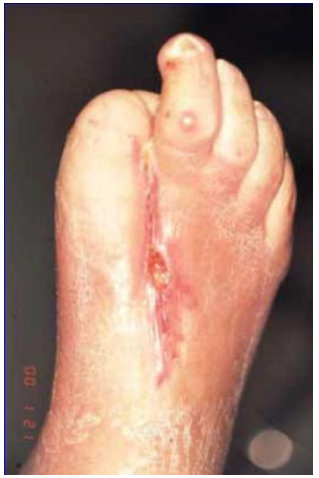
- **EPISODES D'INFECTION A ENTERO-BACTERIES PRODUCTRICES DE CARBAPENEMASE**

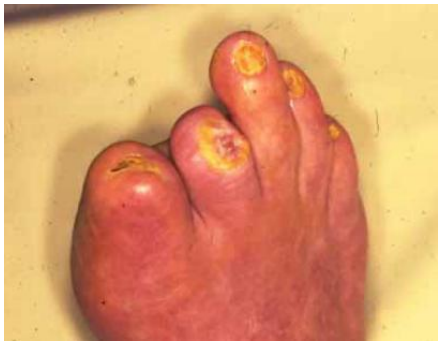


- **MUCOVISCIDOSE: 80% de colonisés à *P.aeruginosa* à 18 ans**



- **DIABETIQUES: une amputation toutes les 30 secondes dans le monde**





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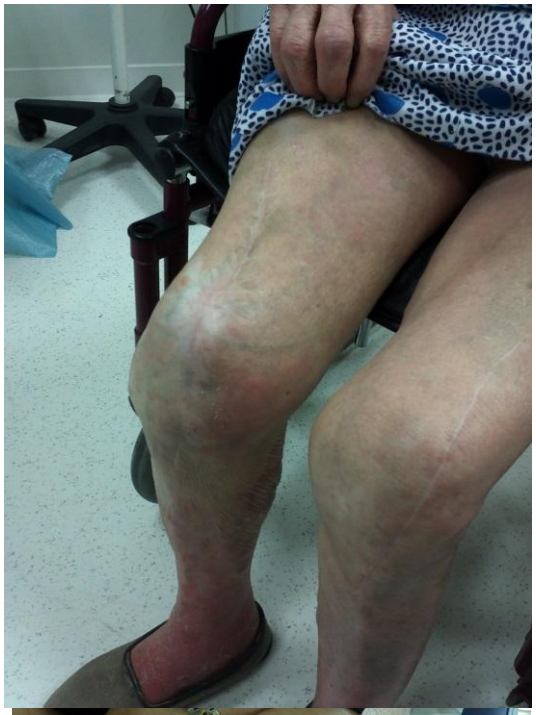
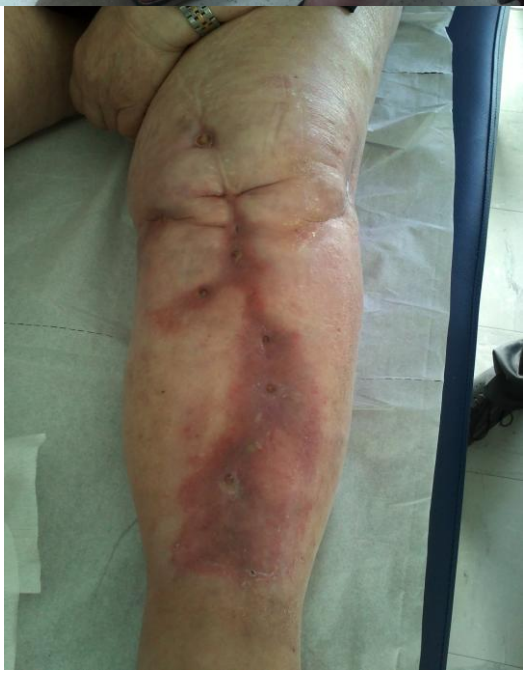
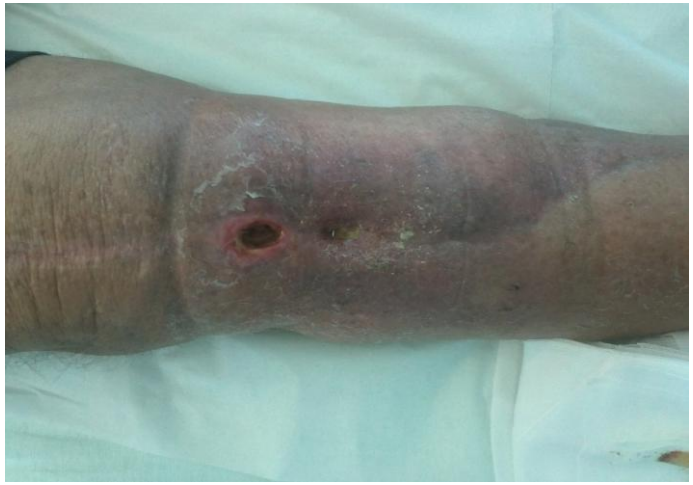
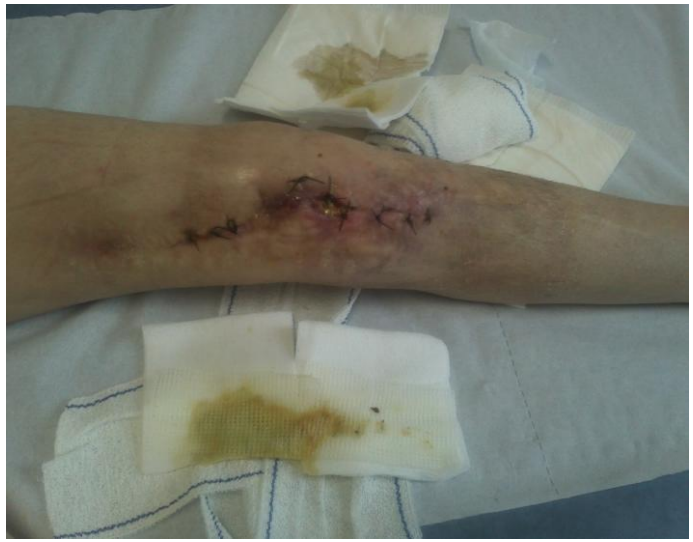
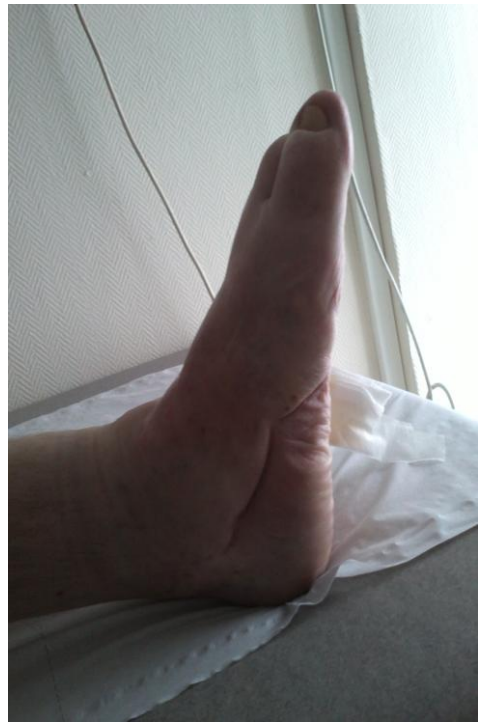
IMPASSES THERAPEUTIQUES

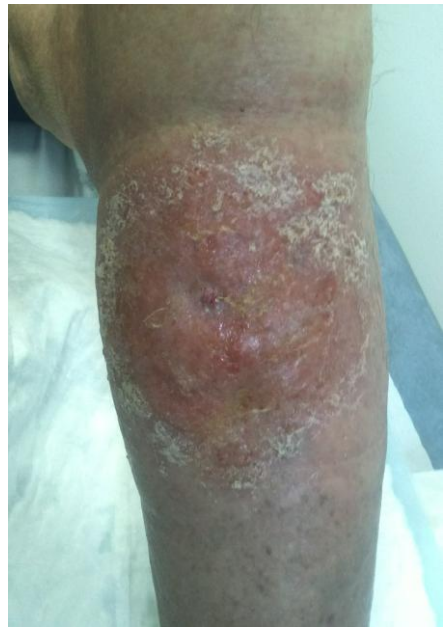












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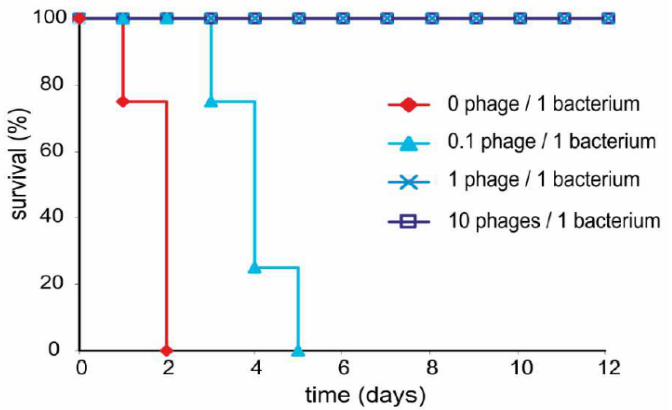
IMPASSES THERAPEUTIQUES
COOPERATION ANTIBACTERIENNE

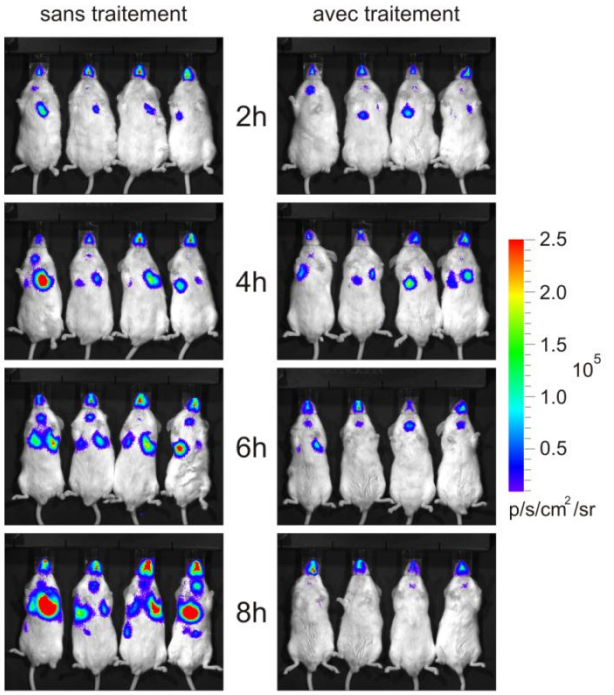
* Action lytique rapide exponentielle des phages
* Action lytique curative et préventive sur les biofilms permettant la libération planctonique des bactéries
* Suppression de l'effet délétère des biofilms (notamment sur l'apoptose des ostéoblastes)
* Effet synergique avec les antibiotiques

Infection pulmonaire aiguë à *P. aeruginosa*

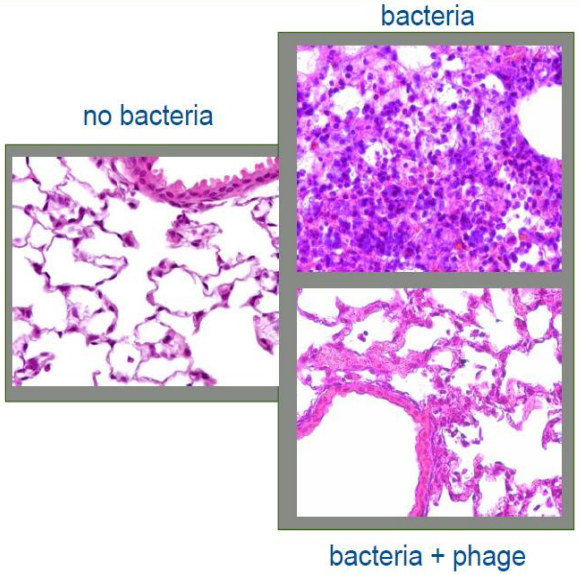
Bacteriophages treatment of lung infection in mice

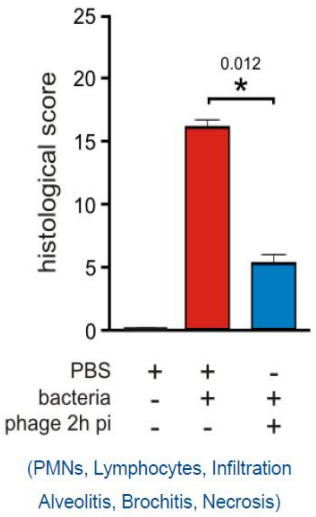
Infection by $1.0x10^7$ bacteria and 2H later different doses of phages





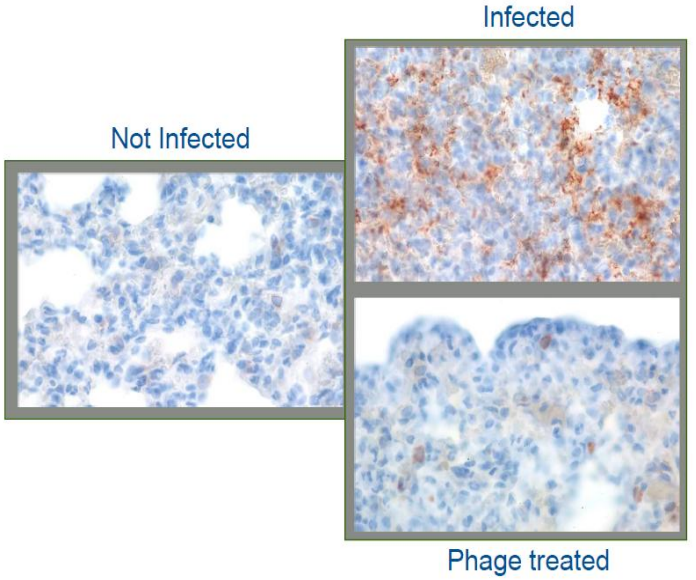
Histology on bacteriophage-treated lungs





(PMNs, Lymphocytes, Infiltration
Alveolitis, Brochitis, Necrosis)

Immuno-histochemistry on bacteriophage-treated lungs



Debarbieux, J. Infect. Dis. 2010, 201: 1096-1104

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Treatment of Highly Virulent Extraintestinal Pathogenic *Escherichia coli* Pneumonia With Bacteriophages*

Nicolas Dufour, MD, MSc[1,2,3,4]; Laurent Debarbieux, PhD[1]; Mélanie Fromentin, MSc[2]; Jean-Damien Ricard, MD, PhD[2,3,4]

GEEPhage Phagothérapie

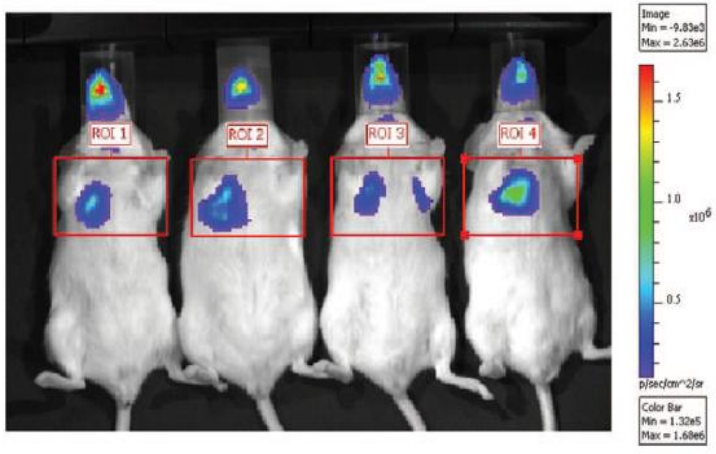
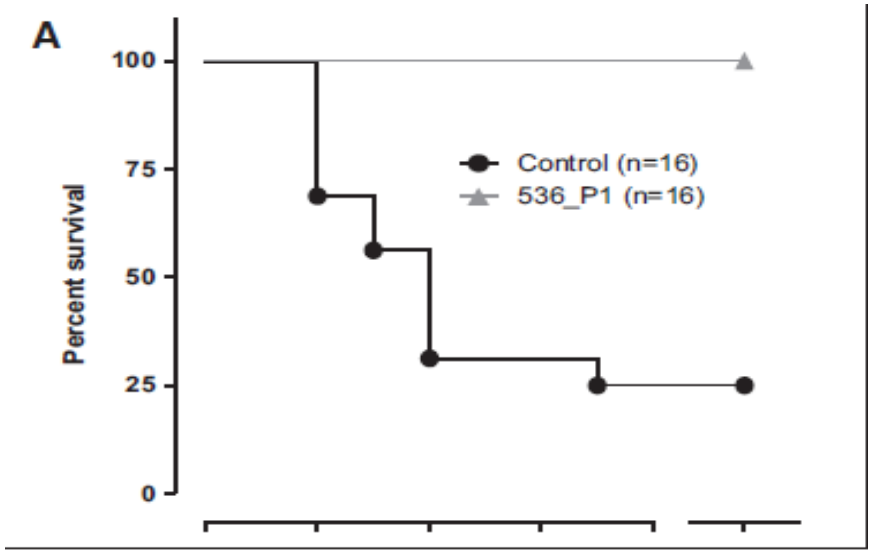
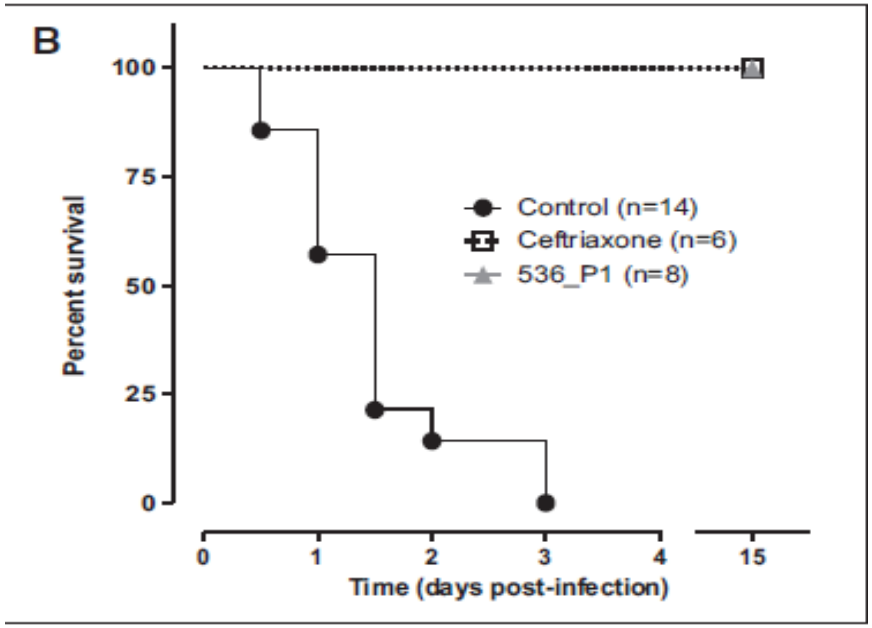


TABLE 1. Bacterial and Bacteriophage Counts on Lung Homogenates and Data Obtained From Bronchoalveolar Lavage Fluids

Variable	Uninfected Animals	2 Hr Post Infection (Without Treatment)	6 Hr Post Infection		16 Hr Post Infection	
			PBS (Control)	536_P1 (Treatment)	PBS (Control)	536_P1 (Treatment)
Bacterial count (lung homogenate, CFU/g)	NA	1.0×10^8 [4.5×10^7; 1.6×10^8]	8.3×10^6 [5.2×10^6; 1.0×10^7]	4.3×10^5 [2.0×10^5; 1.3×10^6][a]	4.8×10^8 [2.1×10^8; 5.5×10^8]	2.4×10^6 [2.1×10^5; 1.8×10^7][a]
Bacteriophage count (lung homogenate, PFU/g)	NA	NA	0	8.8×10^8 [2.6×10^8; 1.4×10^9]	0	1.1×10^{10} [2.5×10^9; 1.5×10^{10}][b]
Bronchoalveolar lavage fluid analysis						
Total nucleated cell count (cells/mL)	$1.3\times10^6\pm2.3\times10^5$	NA	3.1×10^6 ($\pm9.7\times10^5$)	3.9×10^6 ($\pm9.4\times10^5$)	1.0×10^7 ($\pm2.3\times10^6$)	1.0×10^7 ($\pm4.5\times10^6$)[b]
Ratio of polymorphonuclears/ monocyte-macrophages (%)	4.2/95.8 (± 1.5)	NA	93.2/6.8 (± 2.7)	92.2/7.8 (± 4.2)	96.8/3.2 (± 1.8)	91.8/8.2 (± 4.8)[a]
Percentage of phagocytes with engulfed bacteria (%)	NA	NA	NA	NA	26.6 (± 6.8)	0.6 (±0.2)[a]
Total protein (µg/mL)	74 (± 6)	NA	140 (± 59)	208 (± 44)	320 (± 62)	304 (± 76)[b]
LDH activity (fold change compared with noninfected condition)	1	NA	1.3 (± 0.3)	1.3 (± 0.2)	3.9 (± 0.7)	3.1 (± 0.6)[b]
KC/CXCL-1 (pg/mL)	24 (± 12)	NA	14,816 (± 3,720)	17,729 (± 2,531)	14,927 (± 1,044)	3,487 (± 1,264)[a]

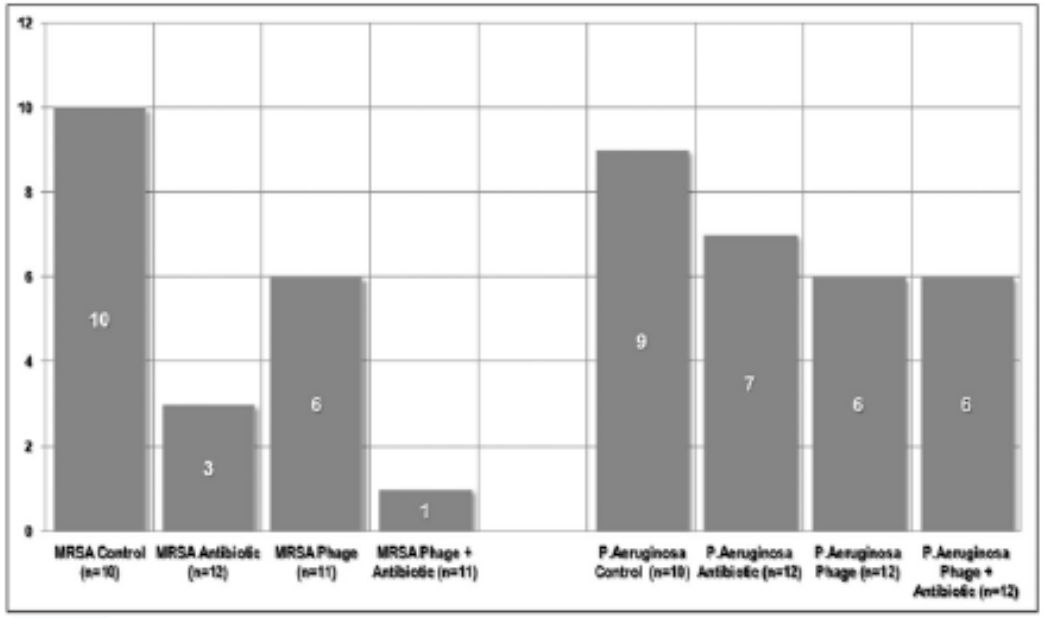




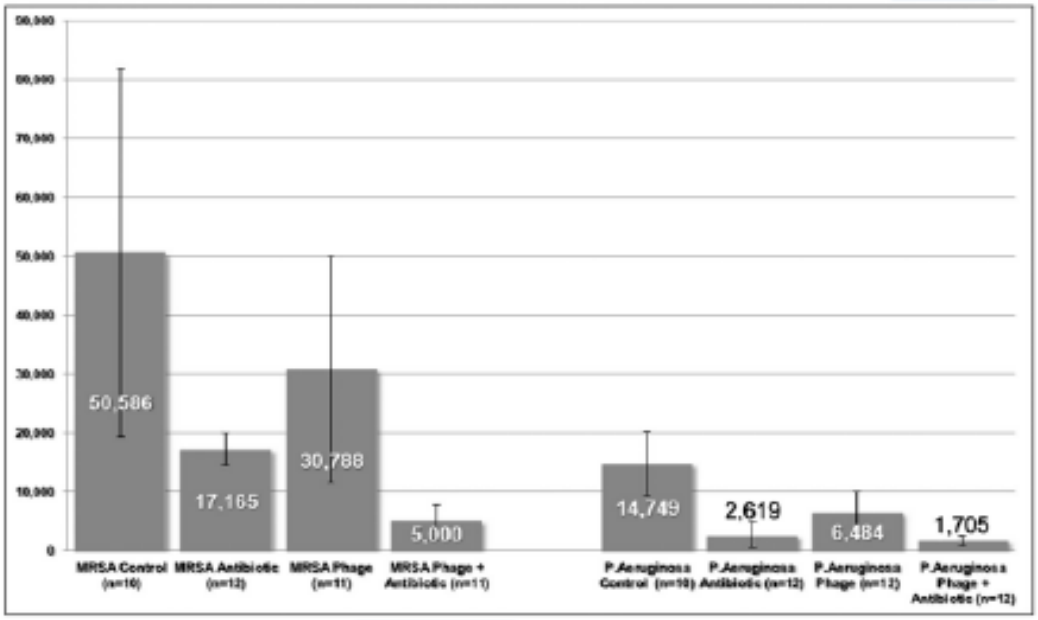
Bacteriophage Therapy in Implant-Related Infections

An Experimental Study

Model of tibial infection in rats
MRSA and Pseudomonas human infection strains



Number of subjects with positive gram staining



Quantitative culture counts

Ylmaz C et al. J Bone Joint Surg Am.2018

AmpliPhi Biosciences Corporation
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F-274

Efficacy of a Bacteriophage Cocktail in a *Staphylococcus aureus* Mouse Pneumonia Model is Comparable to Vancomycin

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ABSTRACT

Background: A cocktail of four bacteriophages was constructed, which together has broad activity against a panel of clinically relevant and diverse *Staphylococcus aureus* isolates. The efficacy of this cocktail was evaluated vs. vancomycin (Van) in a *S. aureus* lung infection model.

Methods: Neutropenic ICR mice were inoculated intranasally (IN) with 6.98 log10 CFU in 50 µL of TSB. At 2 hrs postinfection, 50 µL phage cocktail was administered IN to three dosage groups (n=5) of mice consisting of $2X10^{10}$, $2X10^{9}$, and $2X10^{8}$ PFU/mL per phage. A second identical dose was administered IN at 6 hrs postinfection. The multiplicity of infection (MOI) of each of the 4 phages in the cocktail was ~ 50, ~5 and ~0.5 at the 2 hr time point (first administration). Van (100 mg/kg) was administered subcutaneously at 2 hr and 6 hr postinfection to a 4th group. The remaining groups were infected, but untreated. One group of control mice was euthanized at 2 hrs post-infection and all other mice were euthanized at 24 hrs and CFU/lung pair determined.

Results: Administration of phage cocktail resulted in *S. aureus* titers of 6.08, 6.16 and 7.8 mean log10 CFU/ lung pair for the $2X10^{10}$, $2X10^{9}$ and $2X10^{8}$ PFU/mL treatment groups, respectively. The two highest phage treatment groups and Van demonstrated a significant reduction ($p < 0.0001$) in lung CFU vs. the 24 hr nontreated control, with mean log10 CFU/lung pair decreases of 3.1 , 3.02, and 3.63 (Van), respectively. The $2X10^{8}$ PFU/mL treatment group did not achieve statistical significance vs. the 24 hr nontreated control ($p=0.074$). Twenty seven *S. aureus* colonies recovered from the murine lung infection model demonstrated similar sensitivity to the individual phages and to the 4 phage cocktail when compared to the starting strain.

Conclusions: The two highest doses of the phage cocktail exhibited efficacy that was comparable to Van in a *S. aureus* lung infection model. No evidence of recovery of phage resistant isolates was observed. These results demonstrate the potential therapeutic utility of phage therapy in bacterial lung infections.

BACKGROUND

- The rising tide of bacterial resistance to antibiotics has driven a renewed interest in novel therapies that can circumvent traditional mechanisms of resistance
- This clinical challenge has sparked a re-examination of the potential of bacteriophage (phage) therapy.

METHODS

Table 1. *S. aureus* Neutropenic Lung Model

Group	# Mice	Test Article	Route	Dose OR Titer (BID)	CFU Assessed (Time)
1	5	Phage	IN	$1x10^{8}$ PFU/phage	24 hr
2	5			$1x10^{9}$ PFU/phage	
3	5			$1x10^{7}$ PFU/phage	
4	5	Vancomycin	SC	100 mg/kg	24 hr
5	5	Untreated	–	–	24 hr
6	5		–	–	2 hr

- Mice were immunocompromised with 150 mg/kg cyclophosphamide on day -4 and 100 mg/kg on day -1
- Inoculum of 6.98 log_{10} CFU *S. aureus* UNT144-3 in 50 µL was delivered intranasally to female ICR mice
- Infection controls received 50 µL PBS-Mg diluent at 2 hrs and 6 hrs post infection
  - Mean bacterial lung titers were 7.24 log10 CFU/lung pair at 2 hrs
  - Increased to 9.18 log_{10} CFU/lung pair at 24 hrs
- A 4-phage cocktail was administered 2 hrs and 6 hrs post-infection using 3 dosing levels. 100 mg/kg vancomycin was administered SC at 2 hrs and 6 hrs post-infection
- 50 µL doses of phage mix were administered such that each mouse received $1X10^{9}$ PFU per phage, $1X10^{8}$ PFU per phage, or $1X10^{7}$ PFU per phage at each time point, according to its dosage group.
- At the time of the first administration of 50 µL phage mix, there were 1.74 x 10^{7} CFU/lung pair. Thus, the multiplicity of infection was ~50, ~6 and ~0.6 for the 3 dosage groups at the 2 hrs time point when the first phage mix dose was administered.

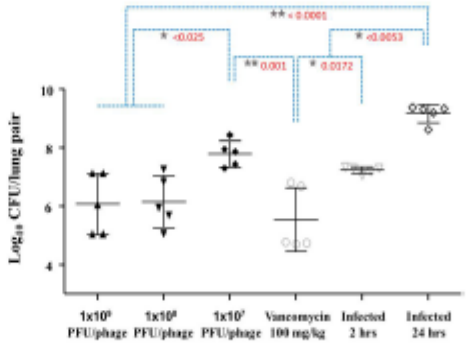
RESULTS

- In infected, untreated controls, the mean log CFU/lung pair titers increased ~ 2 logs between 2 hrs and 24 hrs post-infection **(Table 2)**.
- Administration of the two highest phage cocktail concentrations resulted in 3 log_{10} CFU reductions compared to the 24 hrs control group and 1 log_{10} CFU reductions compared to bacterial titers at 2 hrs post-infection

Table 2. Evaluation of 4 phage cocktail vs vancomycin

Dose OR Titer	CFU Assessed (Time)	Mean ± SD log_{10} CFU/ Lung Pair
$1x10^{8}$PFU/phage BID	24 hrs	6.08 ± 1.04
$1x10^{9}$ PFU/phage BID	24 hrs	6.16 ± 0.89
$1x10^{7}$ PFU/phage BID	24 hrs	7.8 ± 0.45
Vancomycin	24 hrs	5.55 ± 1.1
Infected, untreated	24 hrs	9.18 ± 0.32
Infected, untreated	2 hrs	7.24 ± 0.12

Figure 1. Efficacy of 4 phage cocktail in *S. aureus* lung model: statistical analysis of dosing groups



RESULTS

- **Figure 1** shows a comparison of the different treatment groups that demonstrated statistical significance as determined by ANOVA analysis (Tukey's multiple comparisons test).
- The $1x10^{8}$ PFU/phage and $1x10^{9}$ PFU/phage treatment groups demonstrated a significant reduction in lung CFU vs the 24 hrs non-treated control ($P < 0.0001$ for both). These two treatments were similar to the vancomycin-treated group.
- Although the $1x10^{7}$ PFU/phage treatment group also suggested a trend towards decreased lung counts, statistical significance vs the 24 hrs non-treated control was not achieved ($P=0.0745$).
- Twenty seven *S. aureus* colonies recovered from the murine lung infection model demonstrated similar sensitivity to the individual phages and to the 4-phage cocktail when compared to the starting strain.

CONCLUSIONS

- A *S. aureus* 4-phage cocktail administered at the two highest dosage levels demonstrated efficacy similar to vancomycin in a *S. aureus* lung model of infection.
- > 3 log reductions in mean CFU/lung pair were observed when compared to the 24 hrs untreated control, and > 1 log reductions were observed vs the 2 hrs untreated control.
- MOI values of ≥ 6 PFU per phage at the time of first administration were necessary for efficacy. An MOI of 0.6 was ineffective.
- These data support the potential utility of phage cocktails as a therapeutic agent for *S. aureus* lung infections.

ACKNOWLDEGEMENTS

We thank K. Božnik, Z.Kalcic and A. Alegro for technical assistance in phage production.

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Bacteriophage therapy for the treatment of *P. aeruginosa* infections in cystic fibrosis patients

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AmpliPhi Biosciences[1], Department of Paediatric Respiratory medicine, Royal Brompton Hospital, London[2], Imperial College London[3]

INTRODUCTION

Chronic lung infections caused by *Pseudomonas aeruginosa* (PA) are a major cause of morbidity and mortality in cystic fibrosis (CF) patients. In some cases effective antibiotic therapy is no longer available, with multi-drug resistant (MDR) forms of these bacteria becoming increasingly challenging to treat. Thus, new alternative means of controlling MDR PA infections are urgently needed. Bacteriophage (phage) therapy is a potential therapeutic tool for the treatment of bacterial infections. However, due to the specific nature of phages, questions have been raised about the clinical practicality of bacteriophage based products and their ability to be effective against a range of clinical isolates.

We have previously reported in the development of three prototype phage mixes and shown that phages are efficacious in reducing both bacterial load and inflammation in a murine lung infection model [1]. In this study, we have expanded the in vitro testing and developed a bacteriophage mix (AB-PA01) active against relevant clinical PA isolates collected from around the world. In addition, we demonstrated the efficacy of AB-PA01 in vivo in a murine lung infection model.

METHODS

In vitro testing: Lytic bacteriophages were isolated from environmental sources in Australia and England and their activity screened against a reference collection of 67 *P. aeruginosa* from CF patients. A prototype combination of four phages was then developed and tested for its activity against 429 global CF and non-CF clinical isolates collected between 2007 to 2015. Isolates included were both antibiotic susceptible/resistant and mucoid/non-mucoid.

In vivo testing: Immunocompetent CD-1 female mice were inoculated intranasally (IN) with 6.26 $\log_{10}$ CFU in 50 µL of TSB. At 2 hrs post-infection (PI), 50 µL 4-phage mix was administered IN to three dosage groups (n=5) of mice consisting of $7.5x10^9$, $7.5x10^8$, and $7.5x10^7$ PFU/mL per phage (for a total of $1.5x10^9$, $1.5x10^8$, or $1.5x10^7$ PFU administered). A second identical dose was administered IN at 6 hrs PI. Meropenem (25 mg/kg) was administered subcutaneously at 2 hrs and 6 hrs PI to a fourth group. A fifth group was infected, but treated with the phage diluent. All mice were euthanized at 24 hrs and CFU/lung pair determined. Statistical analysis was performed using Tukey's multiple comparisons test (Graphpad Prism 6, $p < 0.05$).

RESULTS

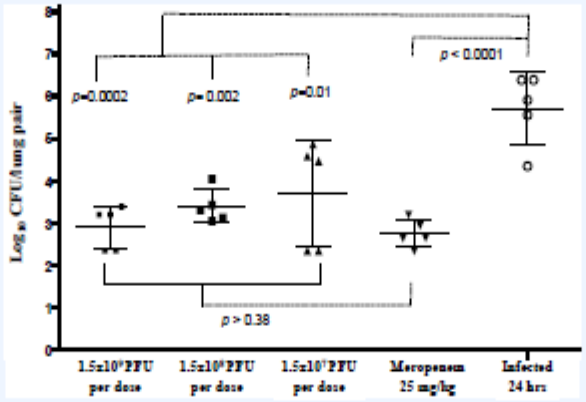
AB-PA01 Phage Mix Host Range

Phages were isolated from a variety of environmental sources in Australia and the UK, using different protocols as previously described [2]. Four phages were selected based on the spectrum of activity against a reference panel of 67 distinct CF isolates, with the number of isolates targeted by ≥2 phages considered an important selection criteria. The overall activity of the selected 4-phage mix **AB-PA01** is summarised in Table 1.

Number of Isolates	Area (Year of Isolation)	Type	AB-PA01 % of Activity	% of Isolates sensitive to ≥2 phages in mix
67*	UK/AU/USA (2012-13)	CF	95.5%	87.5%
120	UK (2012-13)	CF	85.0%	95.0%
60	AU (2007-2013)	CF	93.3%	98.2%
40	USA (2014)	CF	87.5%	91.4%
82	UK (2015)	CF	81.7%	92.5%
60	USA/EU/AU (2013)	Non-CF	83.3%	80.0%
369	Total CF Isolates		87.8%	93.2%
429	Total Isolates (CF + Non-CF)		87.2%	91.4%

Table 1 Activity of AB-PA01 against global CF and non-CF *P. aeruginosa* isolates. Phage mix (10^8 PFU/ml) was used to spot onto *P. aeruginosa* lawns. Each strain was considered sensitive if more than 20 plaques were observed. *Reference panel used for phage selection composed of 67 distinct CF strains that included well characterized CF epidemic clones. UK: United Kingdom; AU: Australia; USA: The United States of America. % of activity=[no. sensitive isolates/total no. of isolates tested] x 100

Murine Lung Infection Model



CONCLUSIONS

- Four phages were isolated and combined into a effective prototype phage mix capable of infecting *P. aeruginosa* clinical isolates collected around the world. The developed 4-phage mix was shown to infect both antibiotic susceptible/resistant and mucoid/non-mucoid CF strains.
- This study has shown that AB-PA01 has a broad range of activity addressing concerns that the specificity of phages could make this therapy impractical in the clinical environment. However, it is likely that, like the flu vaccines, these broad spectrum preparations will need to be reformulated overtime as the bacterial populations evolve.
- AB-PA01 administered at the three dosage levels demonstrated efficacy similar to meropenem in a *P. aeruginosa* murine lung model of infection. However, there seems to be a non-significant trend suggesting a possible dose-dependent effect.
- In addition, we have confirmed the usability of AB-PA01 for:
  - ✓ Clinical use (exclusively lytic, efficacious in vivo)
  - ✓ Nebulisation (no significant decreases in titre were observed)
  - ✓ GMP Manufacturing (long-term stability, current process optimisation)

The use of phages as therapeutic tools continues to be a viable option for the treatment of PA infections in CF patients. AmpliPhi Biosciences, in collaboration with the Brompton Hospital, plan to evaluate the safety and efficacy of AB-PA01 in CF patients.

REFERENCES

1.Pabary, R., Singh, C., Morales, S., Bush, A., Alshafi, K, Bilton, D, Alton, E., Smithyman, A., Davies, J. (2015).Anti-Pseudomonal bacteriophage reduces infective burden and inflammatory response in murine lung. *Antimicrobial Agents* and Chemo. 60 (2): 744-51.

2. Kutter, E. and Sulakvelidze, A. (2005). Bacteriophages: Biology and Applications. Boca Raton, FL: CRC Press.

ACKNOWLEDGEMENTS

We would like to thank our colleagues: G. Mearns, D. Rankin, R. Cole for performing the phage testing. K Boždnik, Z. Kalcic and A. Alegro for technical assistance in phage production William Weiss and the UNTHSC Pre-Clinical Services team for performing the animal work and Dr Karen Shaw for providing experimental input.

*Author's Contact details: Sandra Morales, spm@ampliphibio.com, +61 (2) 9905 7634. *AmpliPhi Biosciences is a public US company focused on the development of bacteriophage-based treatments*

Phage therapy of staphylococcal chronic osteomyelitis in experimental animal model

Chandan Kishor[1,†], Raghvendra Raman Mishra[2,†], Shyam K. Saraf[1], Mohan Kumar[3], Arvind K. Srivastav[4] & Gopal Nath[2]

Background & objectives: Methicillin resistant *Staphylococcus aureus* (MRSA) are the commonest cause of osteomyelitis. The aim of this study was to evaluate the role of an alternative therapy *i.e.* application of *S. aureus* specific bacteriophages in cases of osteomyelitis caused by MRSA in animal model.

Methods: Twenty two rabbits were included in this study. The first two rabbits were used to test the safety of phage cocktail while the remaining 20 rabbits were divided into three groups; group A (n=4) to assess the establishment of osteomyelitis; group B (n=4) osteomyelitis developed but therapy started only after six weeks; and group C (n=12) osteomyelitis developed and therapy started after three weeks. Groups B and C rabbits were treated with four doses of cocktail of seven virulent bacteriophages at the interval of 48 h. Comparison between three groups was made on the basis of observation of clinical, radiological, microbiological, and histopathological examinations.

Results: Experimental group rabbits recovered from the illness in the subsequent two weeks of the therapy. Appetite and activity of the rabbits improved, local oedema, erythema and induration subsided. There were minimal changes associated with osteomyelitis in X-ray and histopathology also showed no signs of infection with new bone formation. Control B group rabbits also recovered well from the infection.

Interpretation & conclusions: The present study shows a potential of phage therapy to treat difficult infections caused by multidrug resistant bacteria.

Table. Bacteriophage therapy of acute and chronic osteomyelitis in rabbit model

Group A	3rd wk	4th wk	5th wk	6th wk	7th wk onwards
1	C1,R1	C1,R2,H1	Two rabbits scarified on day 5 in 4th week		
2	C1,R2	C1,R2,H1			
3	C1,R2	C1,R2,	C1,R3	C1,R3,H1	Two rabbits sacrificed on day 5 in 6th week
4	C1,R2	C1,R2	C1,R2	C1,R3,H1	
Group C	Phage given to all the 12 rabbits on days 1,3,5,7 of 3rd week				
1	C1,R2,H1	This rabbit sacrificed on day 5 in 3th week			
2	C1,R2	C2,R2,H2	Three rabbits sacrificed on day 5 in 4th week		
3	C1,R1	C2,R2,H2			
4	C1,R2	C2,R2,H2			
5	C1,R1	C2,R2	C2,R5,H3	Four rabbits sacrificed on day 5 in 5th wk	
6	C1,R2	C2,R2	C2,R5,H3		
7	C1,R2	C2,R2	C2,R5,H3		
8	C1,R2	C2,R2	C2,R2,H2		
9	C1,R2	C2,R2	C2,R5	C2,R5,H3	Four rabbits sacrificed on day 5 in 6th week
10	C1,R1	C2,R2	C2,R5	C2,R5,H3	
11	C1,R2	C2,R2	C2,R2	C2,R5,H3	
12	C1,R2	C2,R2	C2,R2	C2,R2,H3	
Group B					Phage therapy given on days 1,3,5,7 after 6th week. These rabbits were not sacrificed and observed for 8 weeks**
1	C1,R1	C1,R2	C1,R3	C1,R3	C2R3
2	C1,R1	C1,R2	C1,R3	C1,R3	C2R3
3	C1,R2	C1,R3	C1,R3	C1,R4	C2R4
4	C1,R2	C1,R2	C1,R3	C1,R3	C2R3

Culture: C1, positive culture; C2, negative culture; Radiograph: R1-cortical erosion; R2, cortical erosion, sclerosis, osteolysis; R3, cortical erosion, osteolysis, sclerosis and sequestrum formation; R4, cortical erosion, osteolysis, sequestrum formation and arthritis of the knee; R5, new bone formation with decreased osteolysis. Histopathology: H1, marked inflammation and necrosis; H2, minimal inflammation and necrosis; H3, no inflammation, minimal necrosis and new bone formation.
All four rabbits of group B were kept for long term observation to see changes in clinical and radiological features

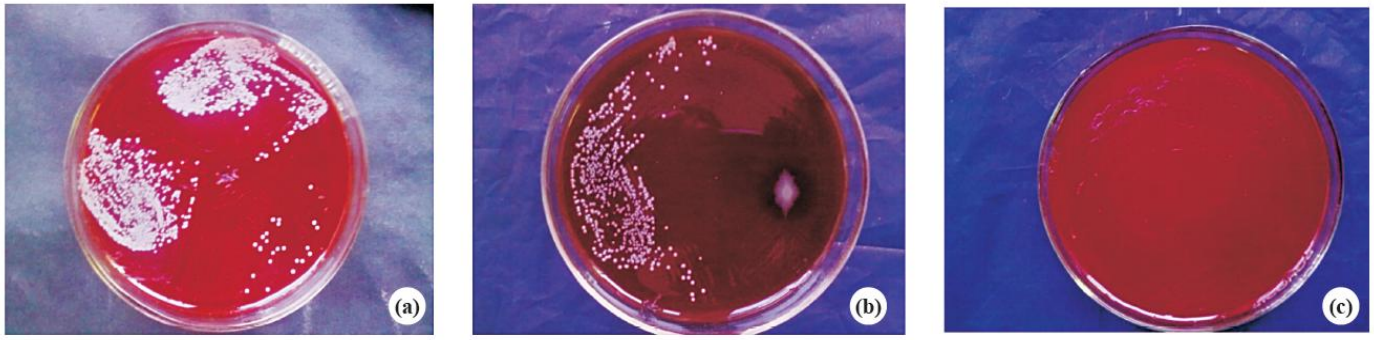
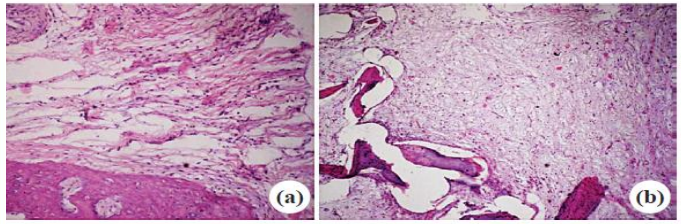


Fig.2. Pus culture showing positive result in 2nd **(a)** and 5th **(b)** week, negative result in 7th week **(c)** in group B rabbits.



4. Histopathological slides of group C rabbits showing minimal mmation at 3rd week **(a)** and no inflammation with new ıation at 6th week **(b)**. Stain H & E, magnification 10x.

Indian J Med Res 143, January 2016, pp 87-94

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GEEPhage Phagothérapie

Service de santé des armées

Votre vie, notre combat

SEVENTH FRAMEWORK PROGRAMME

PhagoBurn

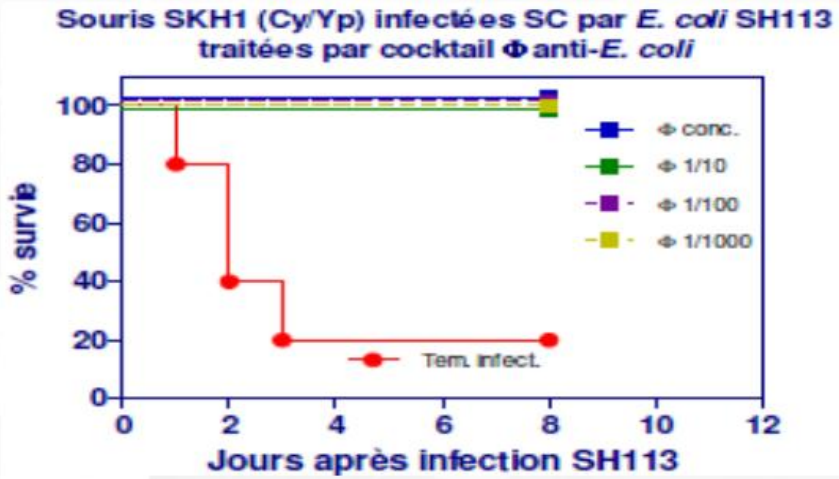
Liberté • Égalité • Fraternité
RÉPUBLIQUE FRANÇAISE
MINISTÈRE DE LA DÉFENSE

BURNED AND INFECTED MICE

Jour	-3	-2	-1	0	1	2	3	4
	1,5mg Cy	Burn	1,5mg Cy	Infection	1,5mg Cy			
Mode injection	IP	Yperite	IP	**SC** 10^7cfu	IP			
PHAGE				SC 6h post-infection				

Conclusions PP0121

- No treatment Survival rate : 20%
- Treated J0 (infection+6h) via SC :SR = 100%
- Dilution of cocktail = 10^5 PFU



P. Jault

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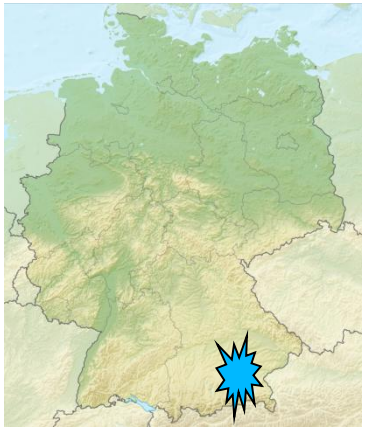
Lucie & Raymond AUBRAC

GEEPhage
Phagothérapie

QUE FAIRE EN FRANCE ET EN EUROPE ?

Expertise limitée dans l'Union Européenne:

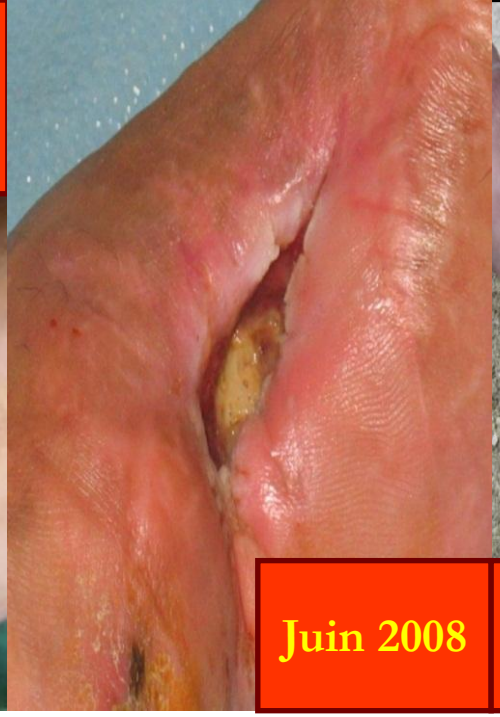
- en France
- en Belgique
- en Allemagne
- en Pologne
- en Roumanie



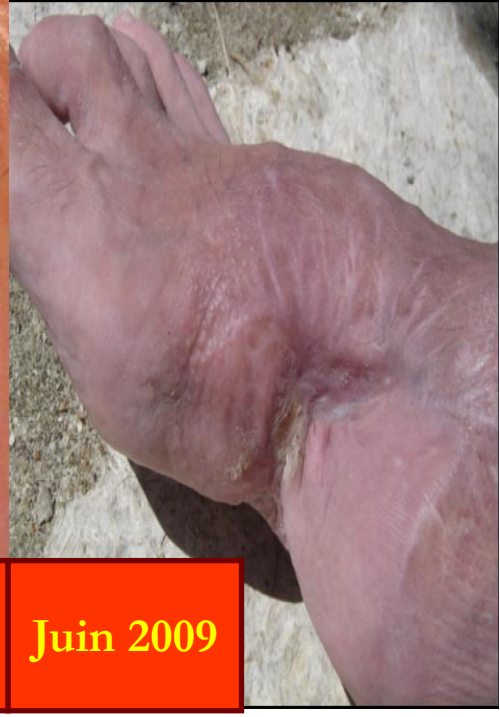
et produits limités

Cas 1: Homme de 45 ans co-infecté VIH/VHC
Polytraumatisme le 10 février 2005 (37 fractures)
avec ostéite chronique du pied à SARM à J30

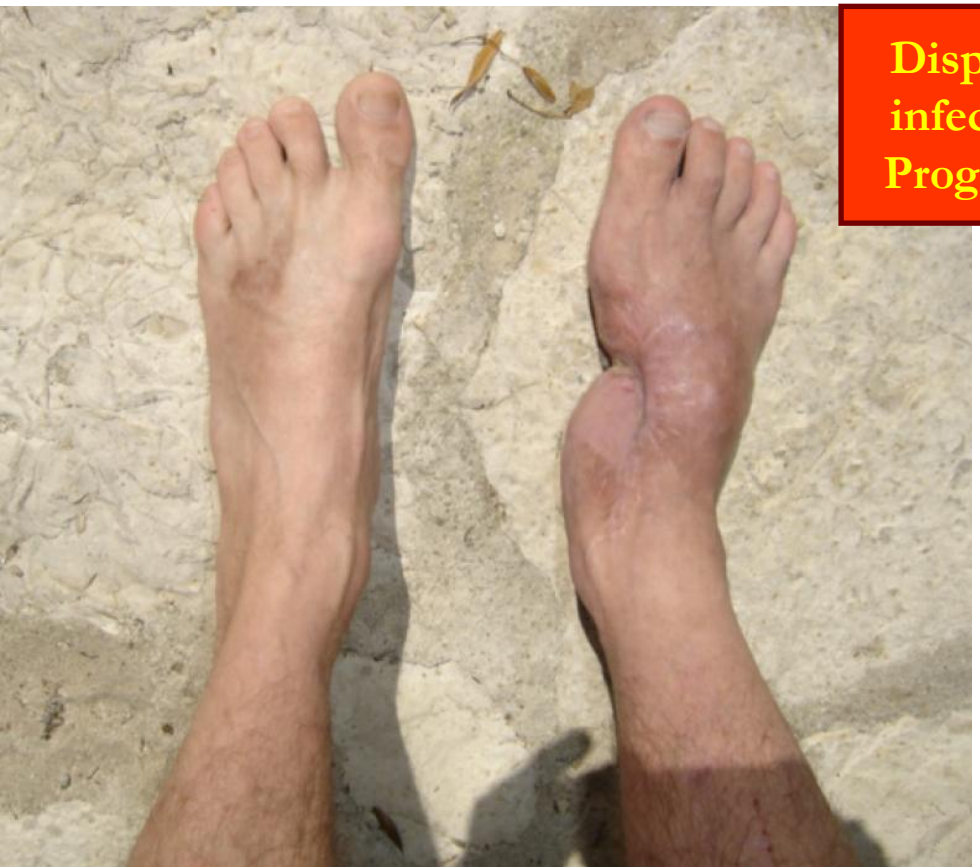
Intervention avec Phagothérapie en mars 2008



Juin 2008

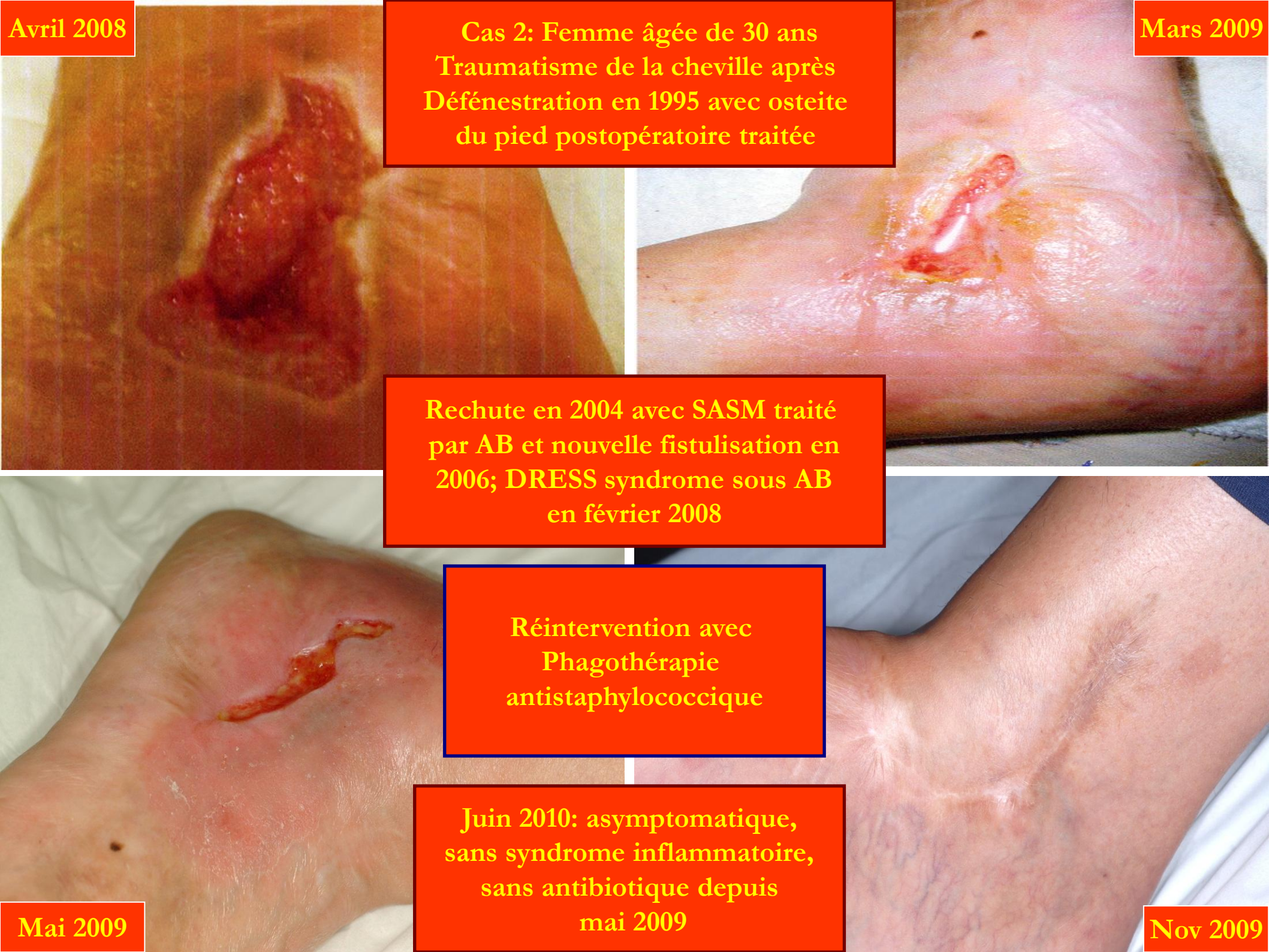


Juin 2009



Disparition des signes infectieux et fermeture Progressive de la plaie

Eté 2009


Avril 2008
Cas 2: Femme âgée de 30 ans
Traumatisme de la cheville après
Défénestration en 1995 avec osteite
du pied postopératoire traitée
Mars 2009
Rechute en 2004 avec SASM traité
par AB et nouvelle fistulisation en
2006; DRESS syndrome sous AB
en février 2008
Réintervention avec
Phagothérapie
antistaphylococcique
Juin 2010: asymptomatique,
sans syndrome inflammatoire,
sans antibiotique depuis
mai 2009
Mai 2009
Nov 2009

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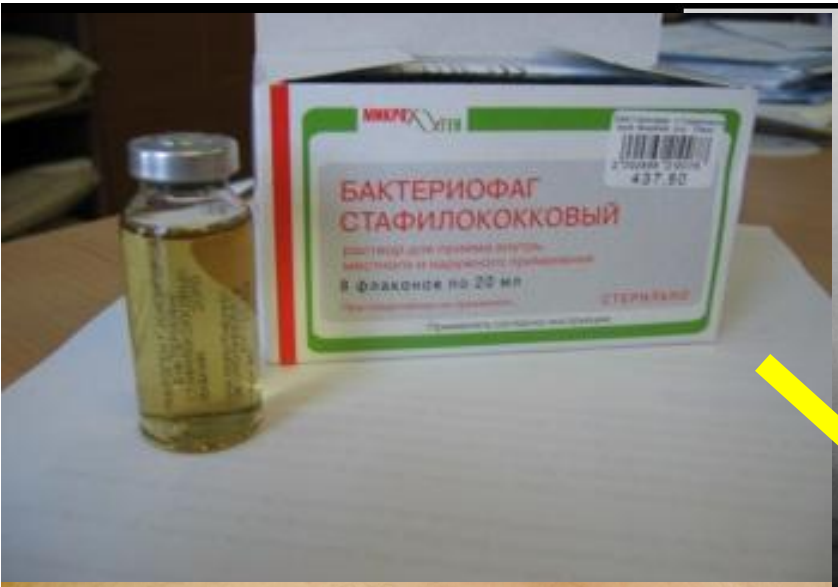
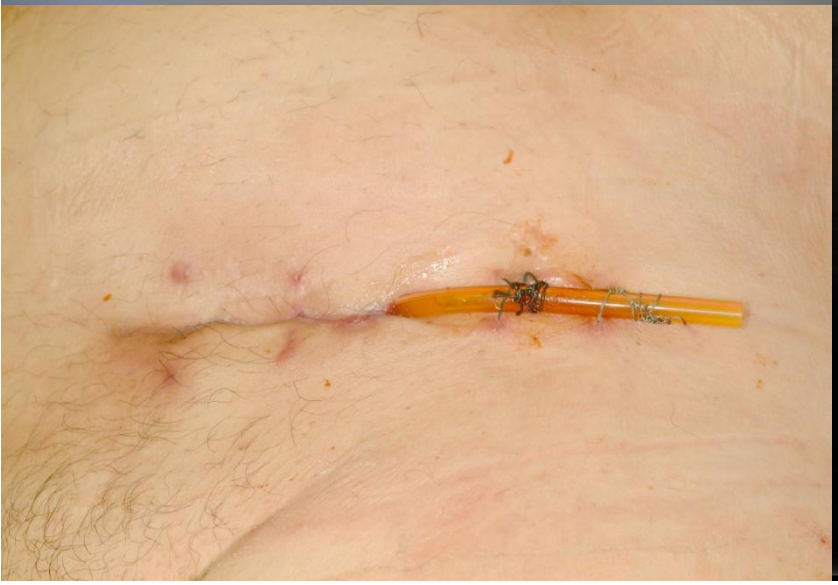
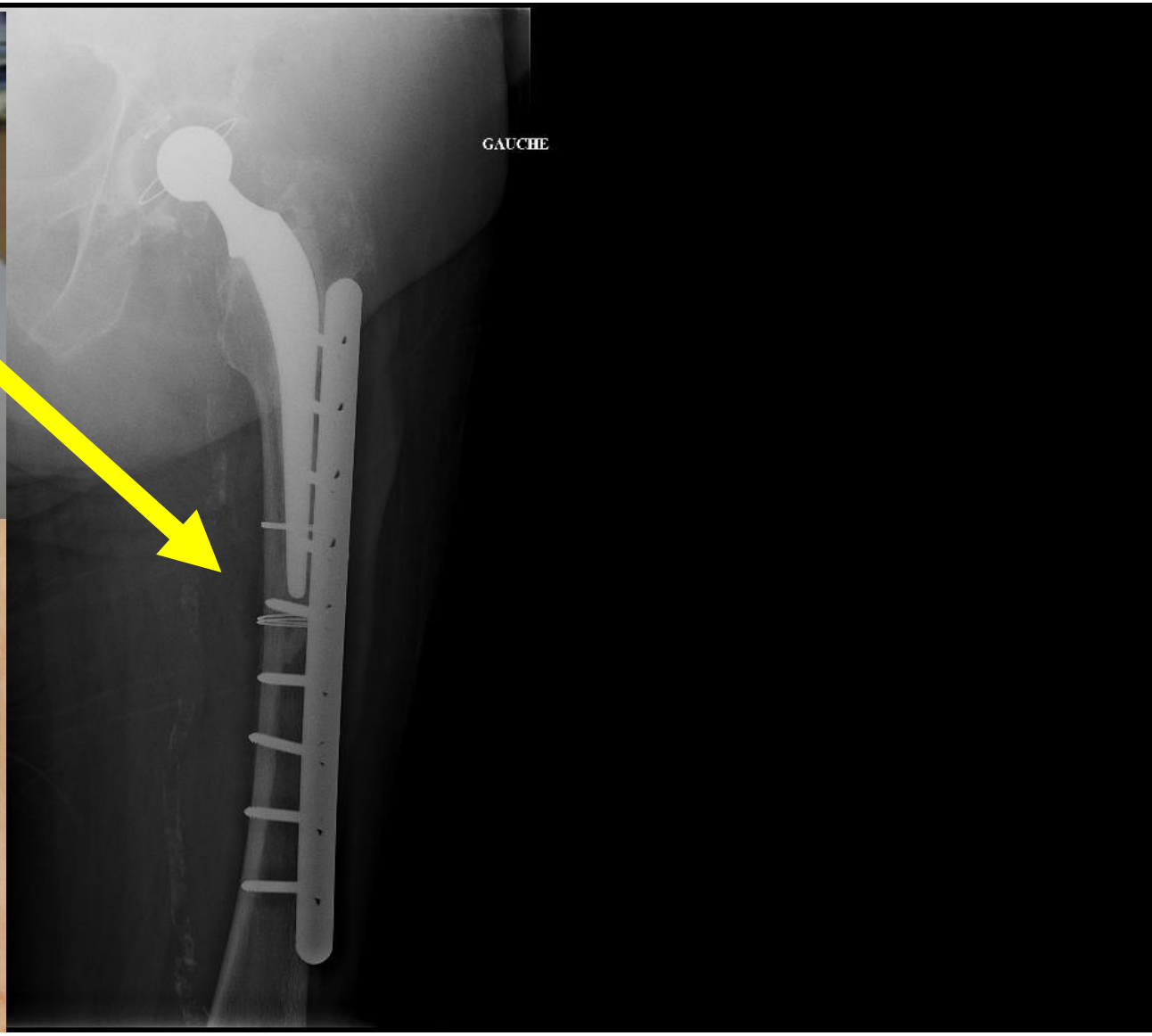
GEEPhage
Phagothérapie







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GEEPhage
Phagothérapie

QUE FAIRE?

Création rapide de structures de « référence » au niveau de l'Union Européenne avec missions bien définies comme nous le réclamons depuis plusieurs années avec PHAGE.org

Existence de:

- CNR par germes
- CNR par pathologies: Infections ostéo-articulair complexes
- CNR Maladies rares

Situation particulière de la phagothérapie car:

- il s'agit d'une thérapeutique
- s'appliquant à de nombreuses pathologies d'organe
- destinée à traiter de nombreuses infections souvent nosocomiales
- devant tenir compte de l'expérience de l'antibiothérapie

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« TOURISME MEDICAL »

SE SOIGNER EN GEORGIE

69 Sanavardo Street 0104 Tbilissi Georgia

Alain LAVIT

Tél : 00995 322 981 995

Mail : contact@sesoignerengeorgie.com

Sommaire

Quantités	Prestations	Prix en €/UNITE	Prix en €/TOTAL
2	**Vols Paris 14h15 Tbilissi 02h55-Bagages inclus**	240,77 €	481,54 €
1	**Transfert Aller- Aéroport**	0 €	0 €
1	**15 Transferts Appartement-Institut Eliava**	200 €	200 €
21	**Jours Appartement à Tbilissi**	48 €	1008 €
1	**Analyse Institut Eliava**	120 €	120 €
15	**Accompagnateur francophone pour 15 jours**	28 e	420 €
1	**Traitement Phagothérapie 3 semaines à L'Institut Eliava**	3630 €	3630€
1	**Transfert Appartement - aéroport pour 2 personnes**	0 €	0
2	**Vols retour Tbilissi 06h20 - Paris 13h25 Bagages inclus**	0,00 €	0,00 €
Option	**Massage bains turcs privatisés-Transferts inclus**	50€	0
Option	**Journée de visite de Tbilissi avec guide + transferts + restaurant**	96€	0
Option	**Dîners chez l'habitant (transferts inclus)**	30€	
		Prix total	**5 859,54€**

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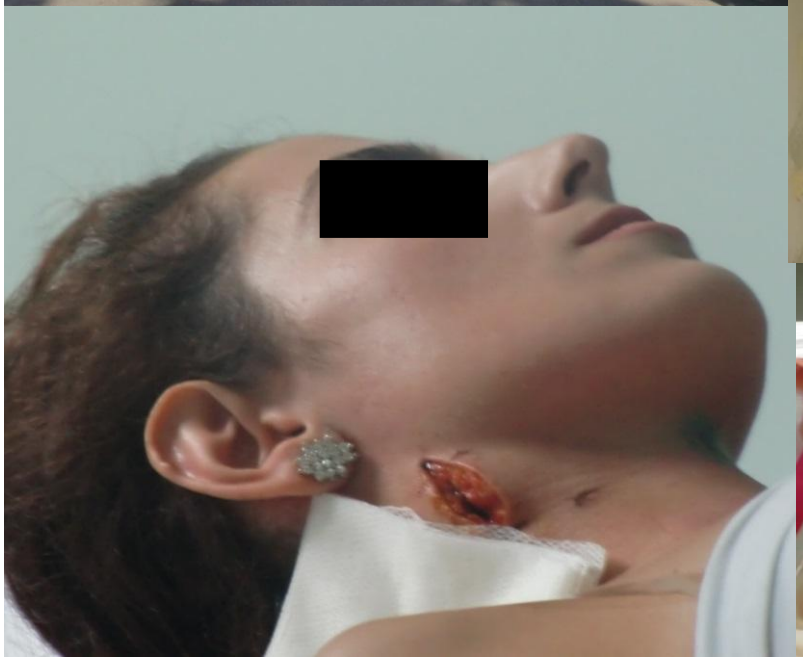

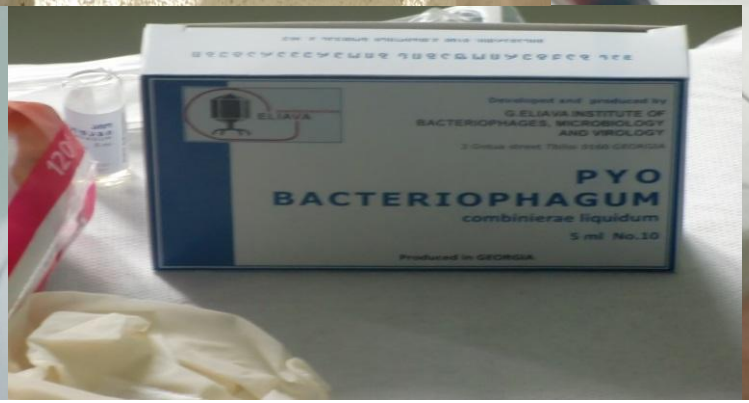

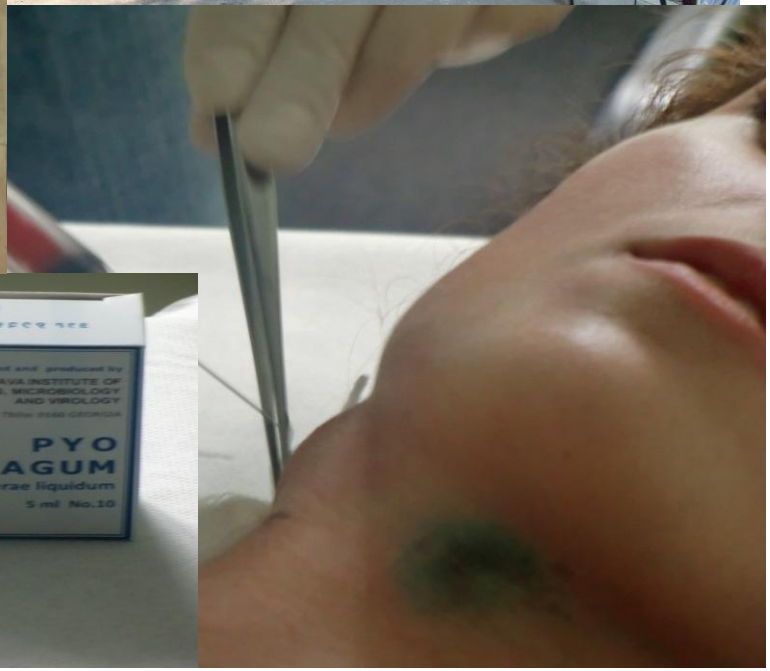

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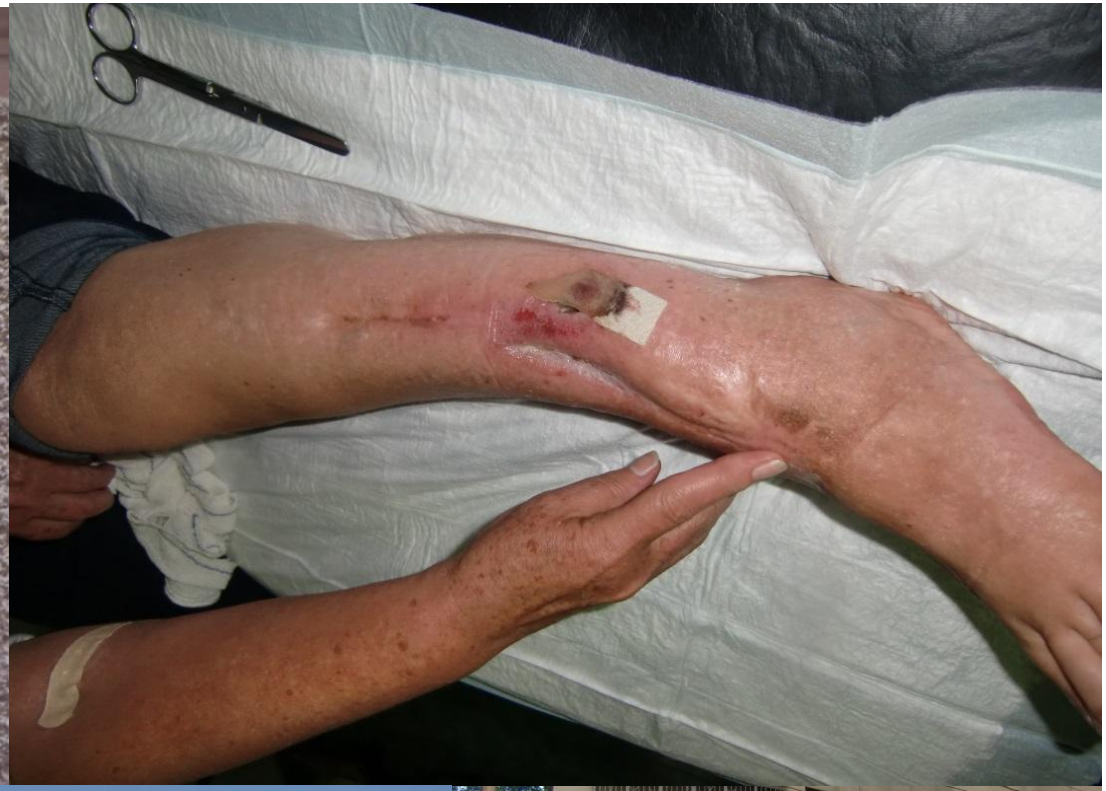

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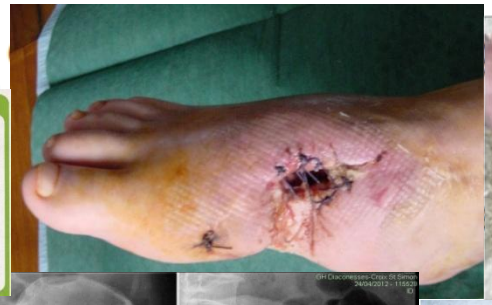
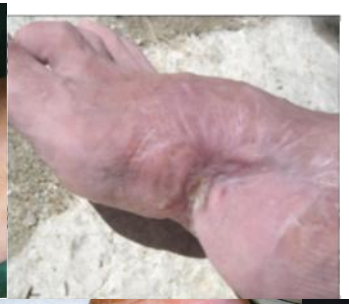
MISSIONS D'UN CNR

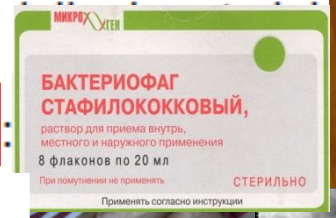
GEEPhage Phagothérapie

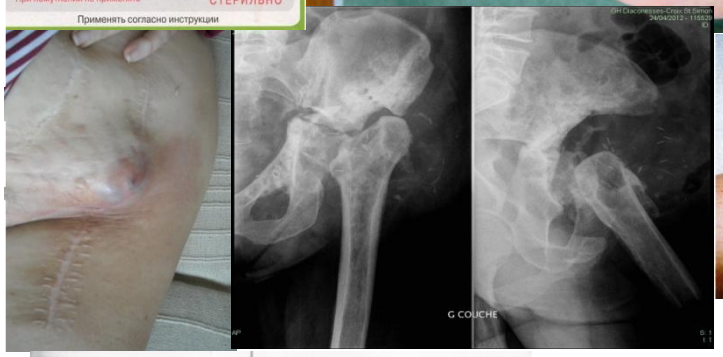
1. **Mission de prise en charge de recours**

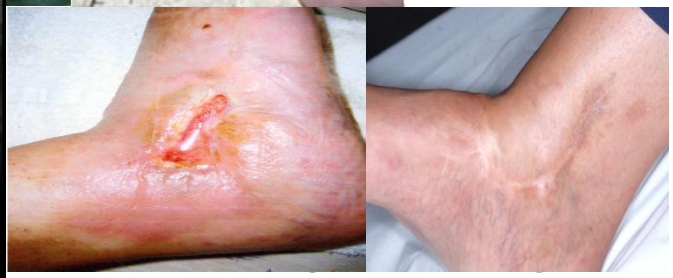




2 **Mission de coordination**







3 **Mission d'expertise**

4 **Mission d'enseignement**

Phage conference in Tbilisi, Georgia in the beginning of the 1930's: Alexander Tsulukidze (presenting), Felix D'Herelle, Simon Amirajibi, and George Eliava (at the table).

5 **Mission de recherche**

PHOSA

Cocktail de bactériophages pour lutter contre certaines infections bactériennes ostéo-articulaires provoquées par *Staphylococcus (aureus* et *epidermidis)*

PHAGOTHERAPIE 2020

Association Loi 1901

L'association PHAGOTHERAPIE 2020 a pour objet de développer un cadre spécifique pour une utilisation régulée de la phagothérapie.

Pour ce faire, l'association se fixe pour objet de :

- susciter et promouvoir par tout moyen la recherche sur la phagothérapie,
- centraliser et diffuser les connaissances scientifiques,
- coordonner les initiatives et les activités des organismes publics, des chercheurs, des industriels et des soignants,
- favoriser les actions et décisions en matière sanitaire,
- évaluer l'intérêt de la phagothérapie et de la phagoprophylaxie,
- définir les modalités pratiques d'utilisation de la phagothérapie (besoins, composition, indications),
- accompagner les patients désireux de bénéficier de la phagothérapie.

PHAGOTHERAPIE 2020

Association Loi 1901

BUREAU

CONSEIL

ADMINISTRATION

CONSEIL SCIENTIFIQUE

COMMISSIONS SPECIALISEES

- SPECIFIQUES D'ORGANES
- MEDICO ECONOMIQUE
- ETHIQUE
- COMMUNICATION
- ECOSYSTEMES ENVIRONNEMENT
- REGLEMENTAIRE
- RECHERCHE

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GEEPhage
Phagothérapie

EQUIPES MULTIDISCIPLINAIRES

CLINICIENS, MICROBIOLOGISTES, ECOLOGISTES
PHARMACIENS, CHERCHEURS, JURISTES
VETERINAIRES, SOCIETE CIVILE, ETHIQUE

COOPERATION EUROPEENNE : RESEAU DE CNR

P-H-A-G-E.org

Phages for Human Applications Group Europe vzw
Militair Hospitaal Koningin Astrid
C DIS/Site NOH, Blok C, 1ste verdieping
Lokaal 1.391
Bruynstraat 1
1120 BRUSSEL

Natural bacteriophages against multidrug resistant (MDR) bacteria

Patey O[1]., Breuil J.[2], Alavidze Z[3]., Mingot N[2]., Dublanchet A. [1,2]

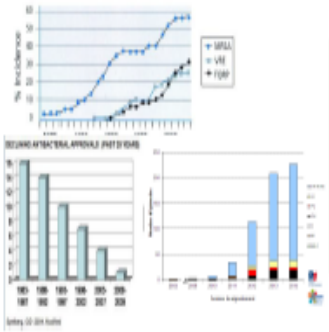
1. Department of infectious and tropical diseases 2. Laboratory of microbiology, Villeneuve Saint Georges Hospital, France 3. Georges Eliava Institute, Tbilisi Georgia

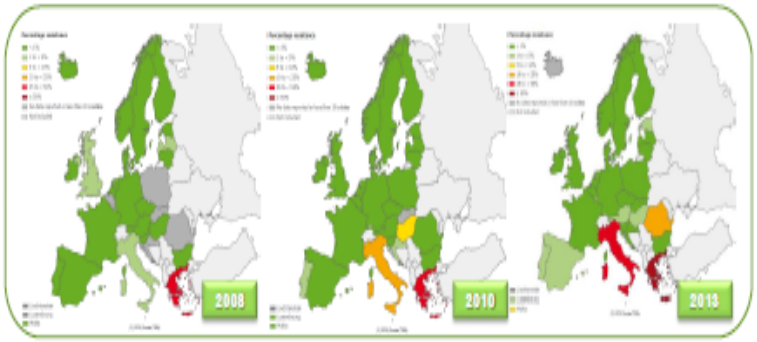
Introduction

Phages were discovered in 1915 by F. W. Twort and F. d'Herelles who isolated and used them for the first time in 1919 for the treatment of dysenteria. Since that time, many bacterial infection have been treated with phages around the world. They were replaced by antibiotics in Western Europe, but continued to be used in East Europa.

During the last years we observed a dramatic increase of MDR bacteria, especially carbapenemase producing enterobacteria , associated with nosocomial outbreaks.

Such an outbreak due to a multidrug resistant strain of oxa 48 producing *Klebsiella pneumoniae (K. pneumoniae)* occurred at Villeneuve Saint Georges Hospital in 2010-2011 with 3 waves (table I)





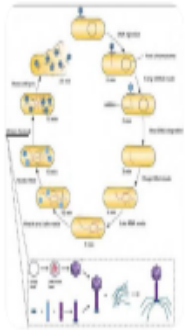


Table1 :Outbreak in Villeneuve Saint Georges Hospital

WAVES	1	2	3
CASES	10	2	2
DEATH	7	0	0
CONTACTS	283	56	37

14 patients with this strain were identified (with or without infection).and 283 contacts. The *K. pneumoniae* oxa 48 was sent to the Georges Eliava Institute, Tbilissi, Géorgia, for the isolation of a specific lytic phage.

Results

Antibiotic susceptibility of the epidemic strain of our hospital:

K. pneumoniae strain was multidrug resistant, being only susceptible to colimycine and of intermediate susceptibility to Amikacine and tygecycline.

Phage efficacy

All our isolates were susceptible to the specific phage.

This efficacy was found for 3 of the 4 French clonal strains. Commercialy available phages cocktails

Comments

These results show a great efficacy of the specific anti *K pneumoniae* phage isolates of Eliava Institute against our epidemic strain. Other French epidemic strains of *K. pneumoniae* oxa 48 were also sensitive but such an efficacy was not found with 3 commercially available

Matérial ar

Phage isolation

One ml bacteria
and 10ml concer
hours . Centrifu
recovered using
To test the sens
Bacterial strain
LB or TSB agar

Phage products

Three commerc
2 polyvalent ph
and one contain

Strains

All the 14 *K.pne*
clonal *K.pneum*
Center, Kremli
outbreak in Bas

Phage effica

To test the pha
Muller Hinton agar on which a *K.pneumoniae* dilution of 0,2 Mc Farland had been spread by swabbing.
The test was interpreted after 24 hours.

and
firm
it of
hage
for
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help
of

National and European Authority and international health organisation (WHO) should be more implicated to develop research and trial with phages.

strains of K. pneumoniae send to our microbiological Laboratory.

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GEEPhage
Phagothérapie

Des hôpitaux débordés par tuberculeux d'Europe de l'E

Par Yves Mamou - le 23/01/2013

INFO LE FIGARO - Depuis quelques mois, des dizaines de Géorgiens, Tchétchènes et Russes, atteints d'une tuberculose ultrarésistante, débarquent en France. Outre le coût élevé de leur prise en charge, le risque de contagion inquiète les autorités sanitaires.

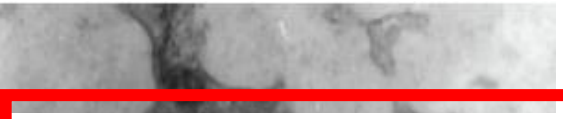
Une réponse: les PHAGES

TB: the return of the phage. A review of fifty years of mycobacteriophage research

INT J TUBERC LUNG DIS 3(3):179–184

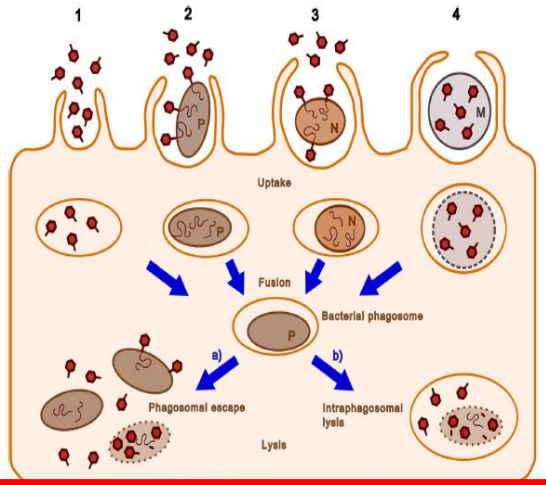
R. McNerney

Department of Infectious and Tropical Diseases, London School of Hygiene & Tropical Medicine, London, UK



A Question of Attire: Dressing Up Bacteriophage Therapy for the Battle Against Antibiotic-Resistant Intracellular Bacteria

Anita Nieth · Cyprien Verseux · Winfried Römer



Effect of mycobacteriophage to intracellular mycobateria *in vitro*

PENG Li, CHEN Bao-wen, LUO Yong-ai and WANG Guo-zhi

A12. ISOLATION AND CHARACTERIZATION OF SIX NOVEL MYCOBACTERIOPHAGES AND INVESTIGATION OF THEIR ANTIMICROBIAL POTENTIAL IN MILK

Lorraine Endersen[1], Aidan Coffey[1]*, Horst Neve[2], Olivia McAuliffe[3], R. Paul Ross[3] and Jim O'Mahony[1]

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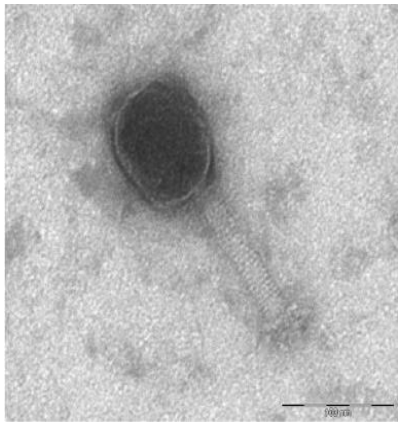
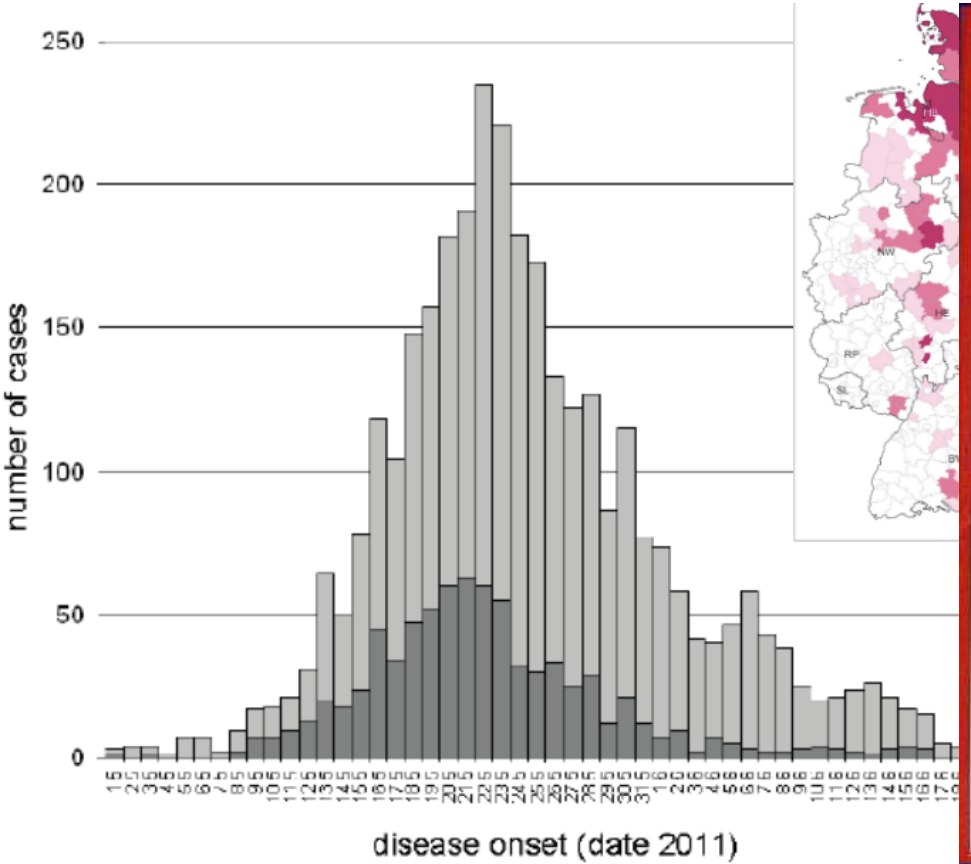
Phagothérapie

Selection and Characterization of a Candidate Therapeutic Bacteriophage That Lyses the *Escherichia coli* O104:H4 Strain from the 2011 Outbreak in Germany



Maia Merabishvili[1,2,3], Daniel De Vos[1], Gilbert Verbeken[1], Andrew M. Kropinski[4,5], Dieter Vandenheuvel[6], Rob Lavigne[6], Pierre Wattiau[7], Jan Mast[8], Catherine Ragimbeau[9], Joel Mossong[9], Jacques Scheres[10,11], Nina Chanishvili[2], Mario Vaneechoutte[3], Jean-Paul Pirnay[1]*

1 Laboratory for Molecular and Cellular Technology, Queen Astrid Military Hospital, Brussels, Belgium, **2** Eliava Institute of Bacteriophage, Microbiology and Virology, Tbilisi, Georgia, **3** Laboratory of Bacteriology Research, Ghent University, Ghent, Belgium, **4** Laboratory for Foodborne Zoonoses, Public Health Agency of Canada, Ontario, Canada, **5** Department of Molecular and Cellular Biology, University of Guelph, Guelph, Ontario, Canada, **6** Laboratory of Gene Technology, KU Leuven, Heverlee, Belgium, **7** Unit of Highly Pathogenic & Foodborne Zoonoses, Veterinary and Agrochemical Research Centre, Brussels, Belgium, **8** Electron Microscopy Unit, Veterinary and Agrochemical 8 Research Centre, Brussels, Belgium, **9** Surveillance and Epidemiology of Infectious Diseases, Laboratoire National de Santé, Luxembourg, Luxembourg, **10** Maastricht University Medical Centre, Maastricht, The Netherlands, **11** European Centre for Disease Prevention and Control, Stockholm, Sweden



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Phages for Human Applications Group Europe vzw
Militair Hospitaal Koningin Astrid
C DIS/Site NOH, Blok C, 1ste verdieping
Lokaal 1.391
Bruynstraat 1
1120 BRUSSEL
P-H-A-G-E.org

JP PIRNAY

ansm
Agence nationale de sécurité du médicament et des produits de santé

Mars 2014

La transplantation de microbiote fécal et son encadrement dans les essais cliniques

TMF= coprophagie médicalement assistée .

•Dilutions (non standardisée): 50 à 60 g de selles/ 200 à 300ml de solutions (eau, sérum salé, lait,...). Moyens Techniques variables.

10 9 bactéries par gramme de selles
10 à 100 fois plus de bac-tériophages

1. Généralités et Cadre réglementaire applicable

En France

- Selon le Code de la santé publique
  - ➢ Pas de statut particulier pour le microbiote fécal
  - ➢ Art.L. 5111-1 = définition d'un médicament
  - ➢ OR microbiote fécal utilisé à visée curative DONC considéré comme un MEDICAMENT
- Stade précoce de développement + Pas d'AMM DONC cadre législatif applicable aux
  - ➢ Préparations magistrales et hospitalières
  - ➢ Mdcts expérimentaux destinés à 1 essai clinique
  - ➢ Art. L. 5121-1 et L. 5121-1-1 du Code de la SP

Au niveau international

- Hétérogénéité sur le statut du microbiote fécal
- USA : médicament
- UE : Tissu (Royaume-Uni, Danemark et Pays-Bas)