

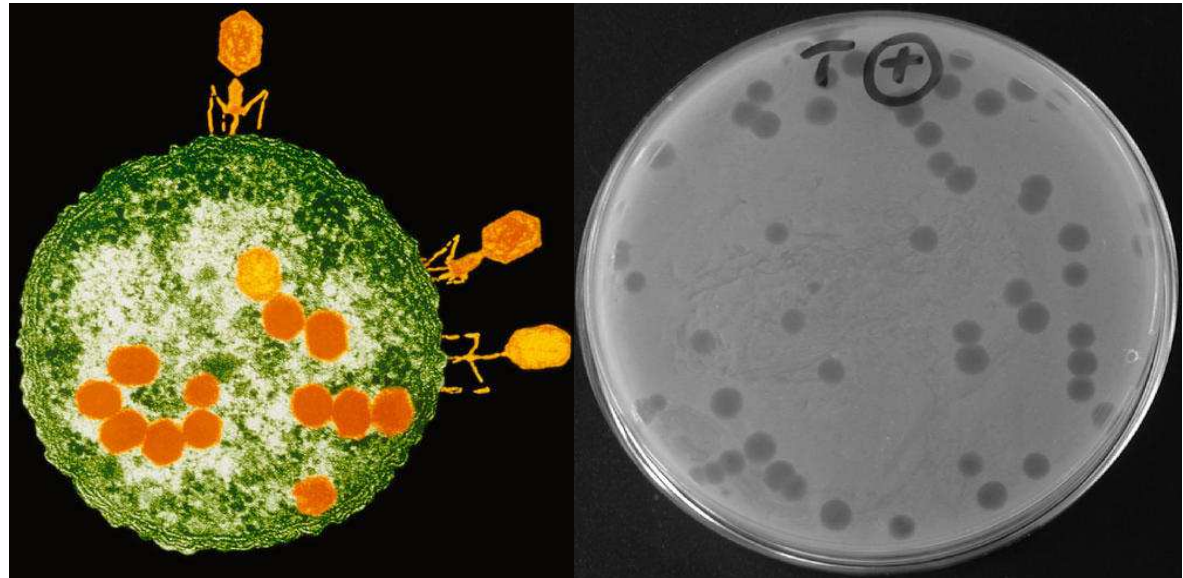
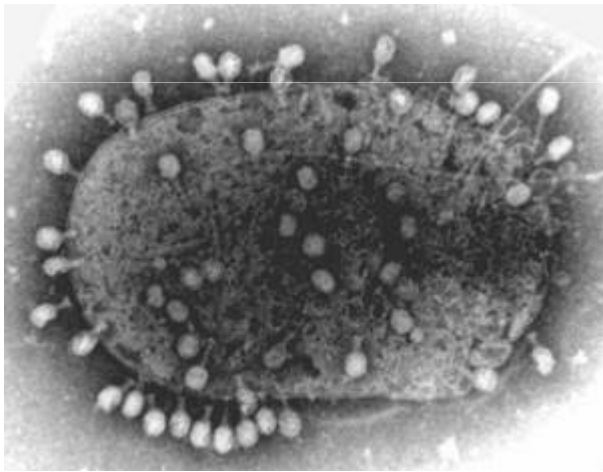


# Le retour de la phagothérapie. Et pourquoi pas...

28.09.2012

Séminaire de Thèse  
Jean-Sébastien Sohier

La **phagothérapie** est l'utilisation de virus bactériophages (phages) lytiques afin de traiter certaines maladies infectieuses d'origine bactérienne.



## Alfred's Story



I first met Alfred Gertler standing on the broad steps outside the Thirteenth Evergreen International Phage Biology Meeting at McGill University. Standing on crutches, he was regaling Rezo Adamia and the other smokers in the group with stories of his catastrophic climbing accident 4 years earlier while working as a musician on a cruise ship. His pulverized ankle had become badly infected, leading to osteomyelitis that was not cleared up by multiple surgeries, an IV pump of an antibiotic for a full year and other available treatments. The bacteria had built a reservoir in his ankle that was so deeply entrenched and well isolated from the circulating antibiotic that no resistance had even developed. The same antibiotic still served to keep the bacteria under control in the rest of his body so long as he spent most of his time in bed, but that constraint was devastating to both his career as a string bass player and to his family life with a pair of preschoolers, and things were getting worse rather than better.

The only option he was now given by his physicians was unthinkable - amputation! And then he had seen an article a few months earlier in the New York Times Magazine about the Republic of Georgia and the use of bacteriophages as antibiotics. The article had mentioned the upcoming International Phage Biology meeting in Montreal, where his parents lived, and he arranged to participate in the meeting, studying all he could in advance and undaunted by being the only nonscientist in attendance. His sincerity and dedication impressed everyone there and he soon made many friends.

Rezo Adamia took a sample of his bacteria back to Tbilisi, where scientists soon confirmed that it was highly sensitive to the Pyophage mixture standardly used in hospitals there as well as to their special single phage against Staphylococcus. For 6 months, he tried to find a physician near his home in Toronto willing to administer the phage, but still was unsuccessful when I called in January, 2001 shortly before I was to leave to give a talk in Bangalore and then visit Tbilisi. We agreed that with such a complex problem, it made much more sense to be treated in Tbilisi, where people had so many years of experience - and our Tbilisi colleagues managed to arrange with Dr. Guram Gvasalia, the best surgeon there, to treat him.

Alfred met me in London, stayed with me at the home of my long-time friend Liana Gachechiladze for a week of evaluation by a phalanx of physicians, and then entered the hospital for 10 days of treatment. There were still open wounds in both sides of his ankle and the phage solution could be pumped through from one side to the other over 24 hours. Phage bioderm was then inserted to gradually release phage over a couple of days, along with enzymes to help break down the scar tissue and let the phage better access the bacteria. Electrical stimulation was used to further enhance the process. Within a few days, the fluid draining from his ankle was free of bacteria!! He headed home 2 weeks later armed with phage and other supplies, with an admonition to have surgery to fuse the ankle and reduce the irritation within about half a year or expect some further trouble.



Alfred soon was back playing his bass in bands, playing with his kids, and generally again picking up the pieces of his life - feeling that a miracle had happened. (He finally had the surgery!) Hopefully there will be more routine mechanisms in place before long for others to follow in his footsteps - and eventually phage therapy will be available around the world for all who need it so desperately.

While in Toronto for the 2007 ASM meeting, I had the wonderful opportunity to see Alfred again and watch him playing. A 2009 conversation showed that his gratitude for the healing power of phages is still very strong.

by Betty Kutter



(<http://blogs.evergreen.edu>)

Cas d'osteomyelite (cheville)

Foyer d'infection inaccessible

Antibio en permanence ou amputation!

Il se renseigne sur internet...

Seul non-scientifique à un congrès sur "phage therapy" ...

Se fait soigner à Tbilissi

**GUERI!**

## "The next phage" (<http://www.popsci.com>)

Dr Wolcott et blessures infectées:

Streptococcus and Staphylococcus multiresistants

Amputation voire mort: (100 000/an aux USA)

**GUERI EN 3 SEMAINES!**

Plusieurs cas *a priori* désespérés soignés

Dr Wolcott se fournit au "Eliava institute" (Tbilissi, Géorgie)

**"La mecque de la thérapie par les phages"**



Can't Look: Dr. Randy Wolcott tends to a patient's wound at his office in Lubbock, Texas John B. Carnett

"That's it?" Brillon asked, after Wolcott dribbled a few drops of the yellowish liquid onto his wound. The stuff was painless. Nothing much happened over the first few days, and Brillon braced himself for another disappointment. But as the week passed, the sore began to fade to a healthier pink, and then a new island of healthy skin emerged, expanding steadily every day. Within three weeks, the wound was completely healed. "You'd better take pictures of this," Brillon told Wolcott, "or nobody is going to believe it."

Brillon's recovery was astonishing, but it wasn't a one-shot deal. Wolcott had also given the phage solution to 10 of his other worst-case patients, and many of them were showing similar results. If phages worked for them, Wolcott reasoned, couldn't they also work for the millions of patients in the U.S. living with infections resistant to antibiotics? His patients, he felt, were proof of it. The real question was whether he could convince the FDA.

As viruses go, phages are relatively benign. They're the most abundant naturally occurring organisms on Earth. They can be found virtually everywhere—in soil, drinking water, sewage. In fact, each one of us naturally has billions of them in our bodies. They prey only on bacteria, never human cells, they rarely spread from person to person, and, perhaps most important, bacteria have trouble becoming immune to them. As living organisms, phages are constantly changing and adapting in tandem with their host bacteria to kill them more effectively. Phage therapy could therefore eliminate the vicious cycle in which bacteria evolve resistance to antibiotics, necessitating the development of new, even more powerful drugs, at which point the process begins all over again.

Bacteriophage therapy, pioneered in Stalin-era Russia, is attracting renewed attention in the West as a potential weapon against drug-resistant bugs and hard-to-treat infections

## Stalin's Forgotten Cure

**TBILISI**—Last December, three woodsmen in the mountains of Georgia stumbled upon a pair of canisters that were, oddly, hot to the touch. The men lugged the objects back to their campsite to warm themselves on a bitterly cold night. That turned out to be a terrible mistake: The canisters, Soviet relics once used to power remote generators, were intensely radioactive and burned two of the men severely. The victims were rushed to the capital, Tbilisi, where doctors plied them with antibiotics but failed to prevent staphylococcus bacteria from invading the deep wounds. Septic shock seemed just around the corner. Then a kinder legacy of the Soviet Union came to the rescue.

Georgian doctors turned to a therapy virtually unknown in the West: They unleashed the bacteria's natural predators. The doctors covered the open wounds with novel biodegradable patches impregnated with bacteriophages, viruses that infect bacteria. The business card-sized PhageBioDerm patches, recently licensed for sale in Georgia, eliminated the infection, and within a few weeks the woodsmen were stable enough to go abroad for treatment to replace the lost skin.

The episode shows that a unique brand of medicine from the Stalin era is alive and well in this remote corner of the world.



**Irradiated.** Georgian doctors covered this man's radiation burns with patches that released bacteriophages into the wound as they degraded.

ten used as a last-ditch treatment. "The window of opportunity for new antibiotics is rapidly closing," asserts Janakiraman ("Ram") Ramachandran, a former president of AstraZeneca India who 2 years ago launched GangaGen Inc., a phage-therapy start-up in Bangalore.

Although phages offer hope against drug-resistant bacteria and could soon find a role as a treatment for burns, diabetic ulcers, and other open wounds, experts concur that these viral breeds are unlikely to knock antibiotics off their pedestal for most infections. "Phages are certainly not going to replace chemicals," says Alexander Sulakvelidze of Intralytix, a company in Baltimore, Maryland, that's ex-

carpeted with them. "Mother nature gives you an endless source of phages," says Sulakvelidze. And unlike most antibiotics, they are very specific, Kutter says: "Phages can kill off a small fraction of the microbial population and leave the rest intact."

Phages are like minuscule smart bombs that home in on particular bacterial strains. Anecdotal evidence from decades of Soviet practice suggests that this results in far fewer side effects than use of antibiotics. And whereas drugs lose effectiveness as they are metabolized, phages replicate in their hosts, gaining strength in numbers and thus increasing potency.

EBI, the fastest company off the blocks, has completed safety testing in healthy volunteers of a phage against vancomycin-resistant enterococci and plans to launch a clinical trial in patients with VRE in the middle of next year. "We really are living in a brave new world," says Toney Ilenchuk, vice president of Biophage Pharma in Montreal, Canada. He and others are watching EBI closely, because its experiences could determine how quickly the first phage therapies against human diseases reach the market—or whether the approach slips back into obscurity in the Western world.

Many are rooting for a comeback. "We need to do something, have some alternatives to antibiotics," says Diana

(Sciences Mag, 2002)

3 bûcherons tombent en Géorgie sur un objet radioactif qu'ils prennent pour se réchauffer...

Brûlures + Staphylococcus résistant...

"PhageBioDerm"

Prêts pour la greffe en quelques semaines...



(Le monde, 2012)

Caroline Lemaire, Staph aureus prise en charge, en 2008, alors qu'elle s'apprêtait à se faire amputer...**GUERIE!**

- Prof Dublanche: "*plusieurs dizaines de patients à [son] actif*". "*Mon objectif est de traiter les infections graves avec des phages, comme compléments aux antibiotiques, explique-t-il. Jusqu'ici, je n'ai pas déclaré l'importation des phages rapportés de Géorgie et de Russie, ni demandé d'autorisation. Je suis extrêmement prudent car on m'attend au tournant.*"
- Dr Debarbieux (Pasteur): Il travaille notamment sur l'utilisation des phages pour traiter les infections pulmonaires, comme celles dues à la mucoviscidose.

## Les phages, des virus guérisseurs

LE MONDE SCIENCE ET TECHNO | 14.06.2012 à 15h21 • Mis à jour le 25.07.2012 à 10h20

Par Raphaëlle Maruchitch et Anuliina Savolainen (à Tbilissi)

## REVIEW ARTICLE

# Resistance to Antibiotics: Are We in the Post-Antibiotic Era?

Alfonso J. Alanis

*Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana*

## Bad Bugs, No Drugs: No ESKAPE! An Update from the Infectious Diseases Society of America

Helen W. Boucher,<sup>1</sup> George H. Talbot,<sup>2</sup> John S. Bradley,<sup>3,4</sup> John E. Edwards, Jr.,<sup>5,6,7</sup> David Gilbert,<sup>8</sup> Louis B. Rice,<sup>9,10</sup> Michael Scheld,<sup>11</sup> Brad Spellberg,<sup>5,6,7</sup> and John Bartlett<sup>12</sup>

## Metallo- $\beta$ -Lactamases: the Quiet before the Storm?

Timothy R. Walsh,<sup>1\*</sup> Mark A. Toleman,<sup>1</sup> Laurent Poirel,<sup>2</sup> and Patrice Nordmann<sup>2</sup>

*Department of Pathology and Microbiology, University of Bristol, Bristol, United Kingdom,<sup>1</sup> and Service de Bactériologie-Virologie, Hôpital de Bicêtre, Assistance Publique/Hôpitaux de Paris, Faculté de Médecine Paris-Sud, Le Kremlin-Bicêtre, France<sup>2</sup>*

## **Carbapenem resistance in *Enterobacteriaceae*: here is the storm!**

**Patrice Nordmann, Laurent Dortet and Laurent Poirel**

Service de Bactériologie-Virologie, INSERM U914 'Emerging Resistance to Antibiotics', Hôpital de Bicêtre, Assistance Publique/Hôpitaux de Paris, Faculté de Médecine Paris Sud, K.-Bicêtre, 78 rue du Général Leclerc, 94275 Le Kremlin-Bicêtre Cedex, France



Pq on en parle pas ?

→ Raison historique...

Pq ne pas y avoir recours ?

→ Raisons pratiques...

# Les premiers soupçons

- 1896: **ME Hankin**, Eaux du Gange (Inde)

Substance non-identifiée, filtrable et sensible à la chaleur qui réduit le titre de *Vibrio cholerae* en culture de laboratoire.

→ Pourrait limiter l'incidence des épidémies

- 1898: **Gamalea (Russe)**

Observations similaires



Troubled waters? Bathers in the Ganges were thought to be protected from cholera by phage.

# La découverte



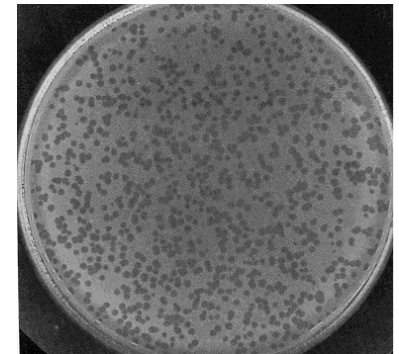
- 1915: **F Twort**, colonies microcoques d'aspect vitreux, un virus?
- 1915-1917: **Félix d'Hérelle**, dysenterie parmi les troupes françaises (*Shigella*)

## “Guérison naturelle”

- Développement vaccin: Filtrats des fèces mélangés avec *Shigella* pour injecter animal et contrôle sur boite, observations de **plaques**.
- Plaques sur boites concomitamment avec l'amélioration de l'état de santé du patient et la fin de l'épidémies
- Nature virale du phénomène: **Bactériophages** (sans convaincre...)



“... in a flash, I had understood: what caused my clear spots was in fact an invisible microbe, a filterable virus, but a virus parasitic on bacteria ... If this is true, the same thing has probably occurred during the night in the sick man ... He should now be cured. In fact, during the night, his general condition had greatly improved ...”





# L'âge d'or...

- 20's: **La thérapie par les phages** devient un paradigme en microbiologie
  - 1919: Hôpital enfant malades: **1<sup>ier</sup> essai clinique**  
(F D'Hérelle)
    - Guérison de la **dysenterie** par ingestion de  $\phi$  en 24h
  - 1920: Infection de la peau par **Staphylocoque**: **1<sup>ière</sup> publi**  
(Maisin, 1921)
    - Régression suite aux injections de  $\phi$  en 48h
  - 1927: Prophylaxie à large échelle: **1<sup>ier</sup> usages en masse**  
(F d'Hérelle et Morison, Asheshov,...)
    - Epidémie de **cholera** en Inde enrayée en 48h (>< 26 jours)

# ...et le début de la fin

- 30's: **Age d'or commercial et politique mais controverses scientifiques...**
  - France: Lab du bactériophage (futur l'Oréal): « Bacté-coli-phage », ...
  - US: Eli Lilly: « Colo lysate », « Entero lysate... », Swan-Meyers, Squibb & Sons
  - Aussi en Allemagne (Antipol), UK, USSR...

## **MAIS:** Efficacité aléatoire et discrédit

- Physiologie du  $\phi$  peu connue (lysogénie...)
- Mauvais diagnostics...
- Préparations (filtrats contenant endotoxines, mercure, chaleur...)
- Etudes peu rigoureuses (cas d'étude, pas de double aveugle...)

=> 1934 et 1941: 2 JAMA reviews:  
**Phages jugés inefficaces**



# Félix d'Hérelle: seul contre tous

- Homme de terrain, autodidacte, indépendant et rebelle. **Opposant** >< **Persuasif**
- **Théorie hérétique:** “Guérison naturelle” résulte d’interactions entre...

Félix D’Hérelle: ...Bactérie, hôte **et phages.**

- Phage comme SEUL effecteur de la guérison
- Immunité: une conséquence plutôt que la cause de la guérison
- Immunité hétérologue et contagieuse ( $\varphi$ ) >< Immunité homologue
- Il veut un changement de paradigme  
(immunologie classique, i.e. la vaccination, est un “danger public”)



## CLASH avec la communauté scientifique



Metchnikoff et Ehrlich (Nobel 1908), Bordet (Nobel 1919): ...Bactérie, hôte

- Instituts Pasteur (Paris et Brabant): Réputation et crédibilité élevées!
- Phagocytose, chimiothérapie, anticorps et complément
- Pères de l’immunité cellulaire et humorale
- Bordet: théorie enzymatique >< théorie des  $\varphi$
- Bordet: Twort réel découvreur des  $\varphi$  et D’Hérelle, imposteur, est discrédité voire persécuté...

# Félix d'Hérelle: sujet d'étude

- Nouvelle "Arrowsmith" (Sinclair Lewis, Prix Pulitzer)
- L'histoire de la thérapie par les phages...

"... is a notable example of the negative impact an investigator's personality can have on the outcome of a discovery. Surely the prospects of phage therapy in the historical era would have been better served if d'Herelle had possessed some of the personality traits and scientific style of Pasteur".

(Carter, Bull Hist Med, 1991)

# Le Déclin

- 30's: d'Hérelle émigre (fuit) en Géorgie et rejoint le Pr Eliava:

"Only in the Soviet Union is it possible to condemn erroneous methods of prophylaxis, sanctified by time, without fear of insulting the habitual delusions having prescriptive rights. A new social system has the right to afford itself revision of everything that has been obtained as a heritage of the past."  
(Préface de son livre dédié à Staline)

## "(George Eliava) Institute of Bacteriophage"



→ Fournit toute l'URSS (Armée rouge)

- 1937: Eliava, "ennemi du peuple", est exécuté (Aaah l'Amour...)
- 1932: Bayer: **Sulfanilamides**, large spectre (Nobel 1939)  
1ère chimiothérapie largement distribuée...
- 1939: E. Chain produit en quantité la **Penicilline**. (Nobel 1945)  
1er antibiotique largement distribué...

# “Stalin’s cure...”

- 40-45: Pénicilline en essais cliniques sur les soldats, secret militaire.
  - Premier microscope  $e^-$  → preuve de la nature virale du phage (Ruska)
  - Phages utilisés par l’Armée rouge → enjeu stratégique
  - F d’Hérelle n’offre pas ses compétences aux Allemands → assigné à Vichy
  - Usage civil de la pénicilline en 44: **l’ERE DES ANTIBIOTIQUES COMMENCE...**  
**MAIS le problème des résistances se pose de manière immédiate...**  
→ Antibio + Phages : efficaces mais jamais utilisés aux US mais bien à l’Est...
- 1949: Sans jamais avoir changé de discours, F d’Hérelle décède dans l’anonymat malgré plusieurs nominations pour le Nobel.
- 1959: OMS favorise l’usage de la tétracycline pour lutter contre le cholera.

## RIDEAU DE FER

**Chimio(antibio)thérapie à l’Ouest >< Phages à l’Est**

# Renouveau

- 50's aux 90's: Usages, recherches et publications en Géorgie, Pologne, Russie
  - Barrière de la langue
  - Niveau d'exigence différent
  - Preuves d'efficacité (85% en moyenne dans la littérature polonaise), mais **LARGEMENT EMPIRIQUE...**



- 1989: Chute du mur de Berlin
- 1991: Indépendance de la Géorgie
- 80's: Précurseurs à l'Ouest (Smith and Huggins)
- 1996: Gd nom accorde du crédit (J Lederberg, Nobel 58)
- 2009: Traduction de la littérature de l'Est.
- **RESISTANCES aux antibiotiques:**  
**25 000 morts en Europe en 2007** (Bush, 2011)

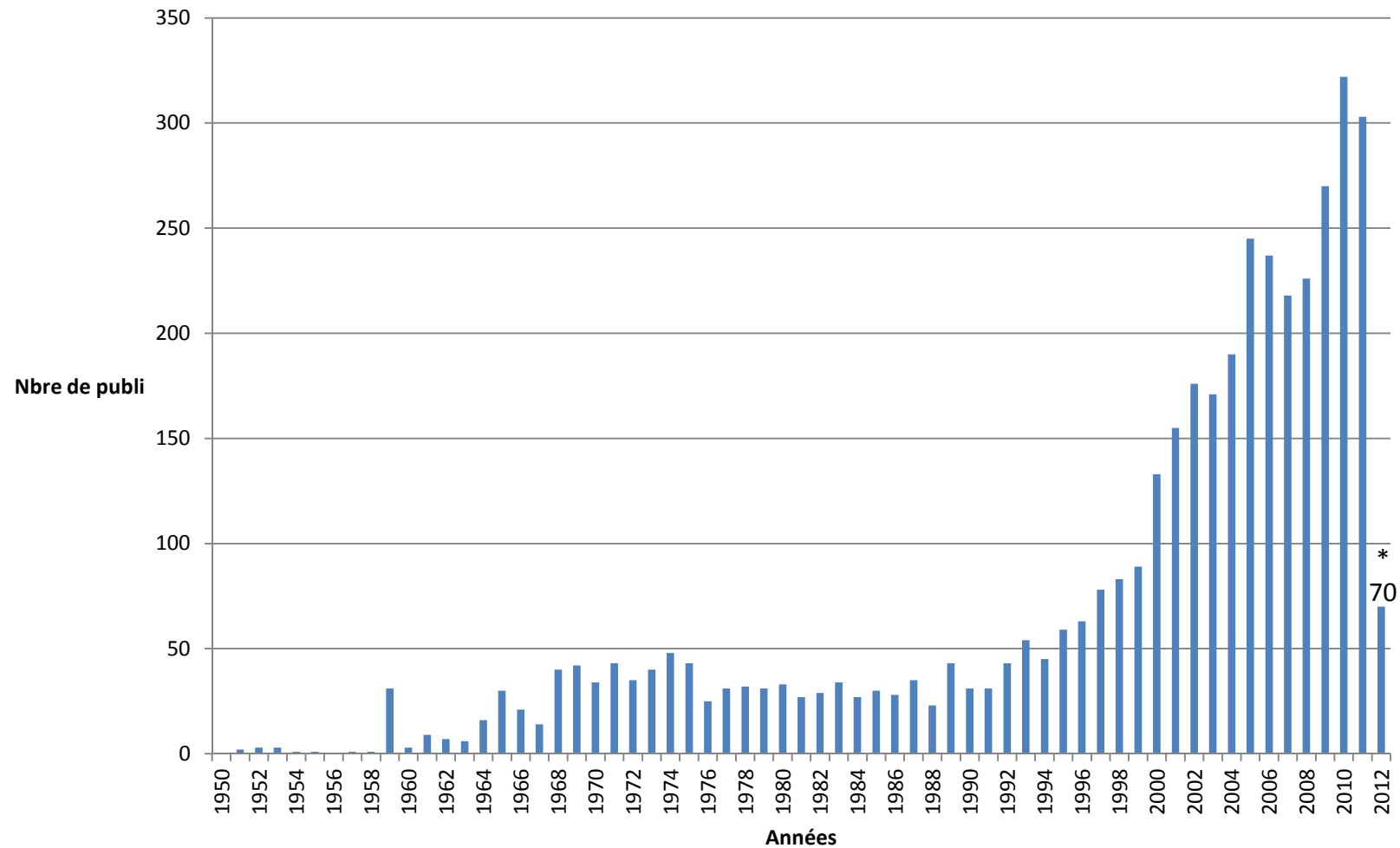
“ While others are still thinking...”  
(N Chanishvili ppt)

<http://www.eliava-institute.org/>



# Résistances et regain d'intérêt

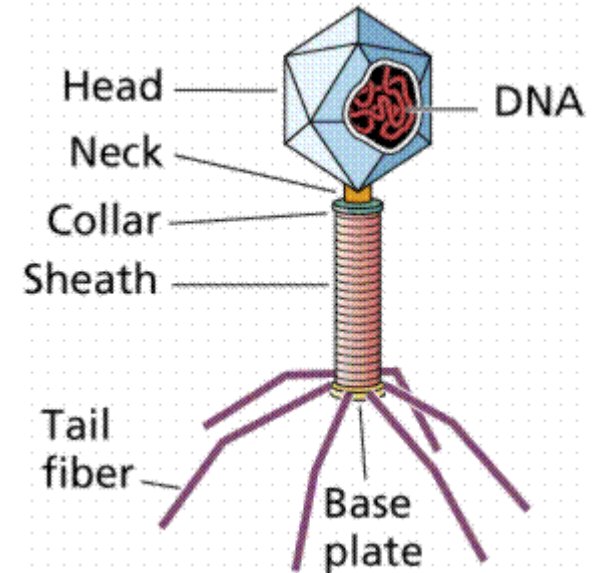
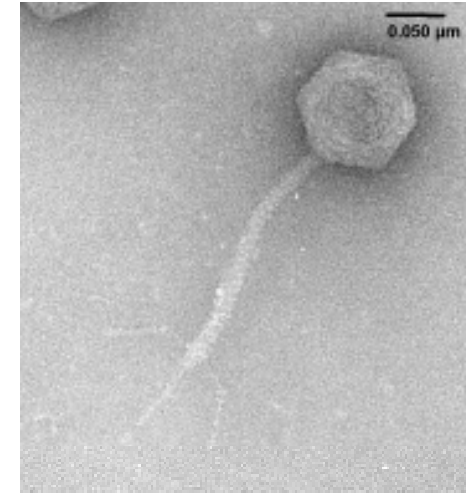
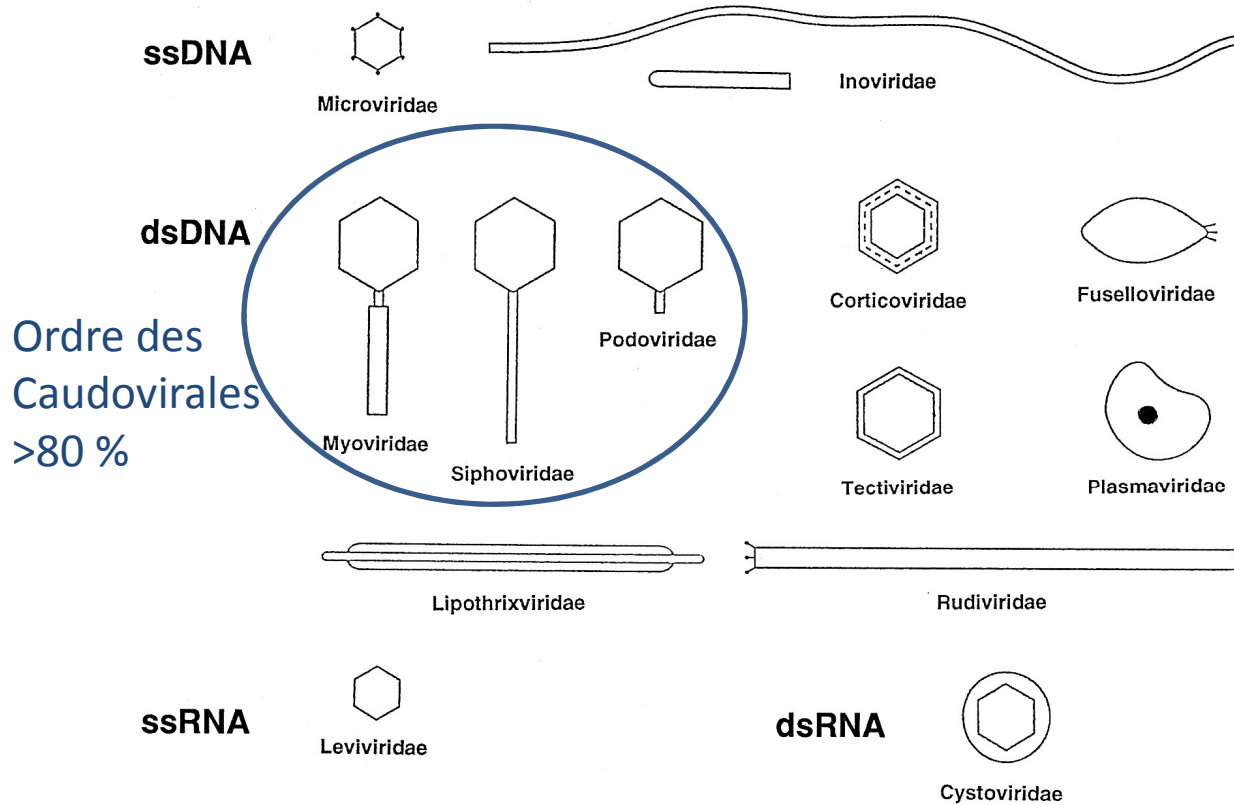
## Titres contenant "Phage + therapy"





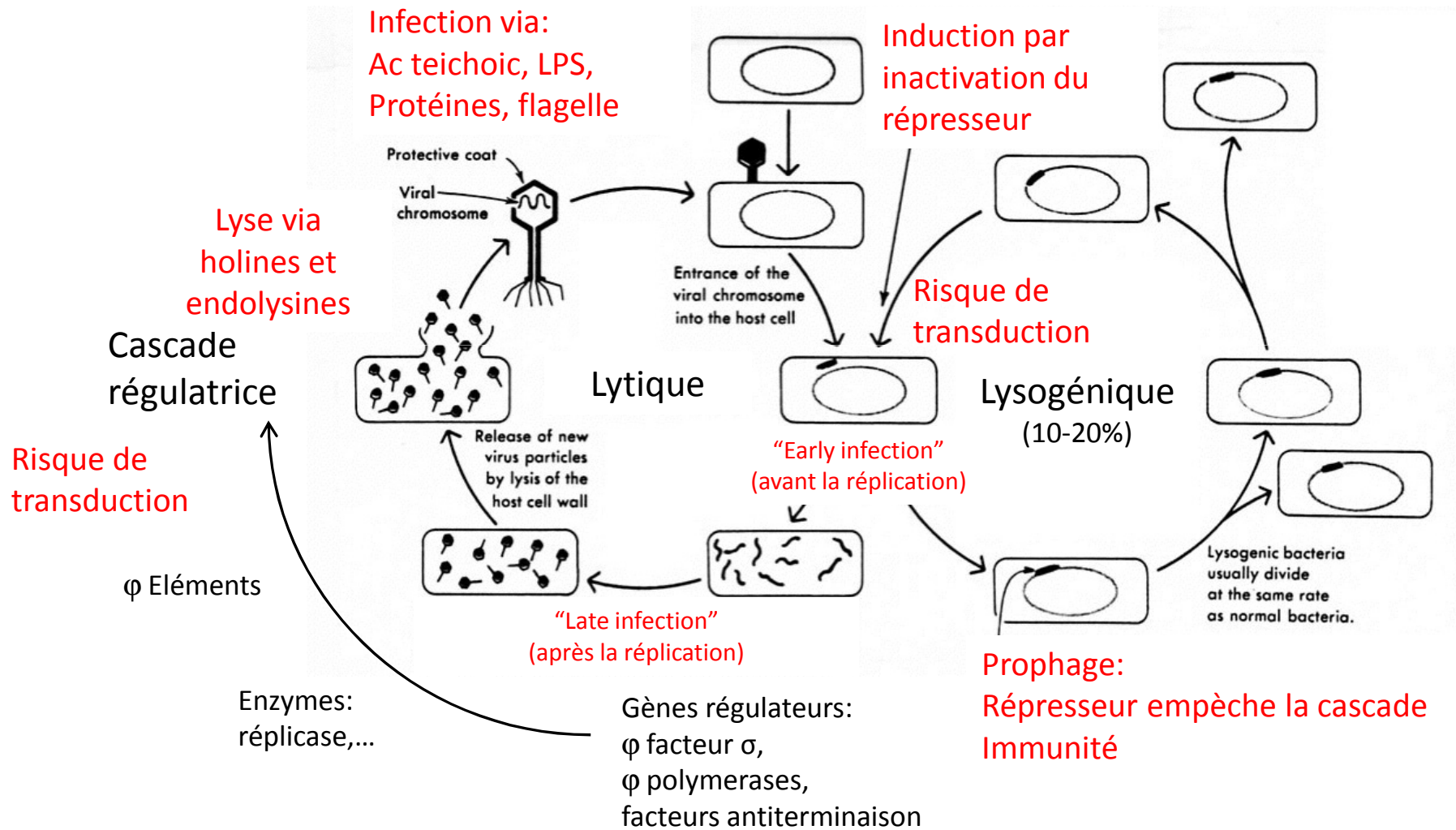
# Structure des phages

19 familles reconnues actuellement



(<http://www.thebacteriophages.org>)

# Lytique et lysogénique



# Dangereux?

- Ubiquitaire: Nous sommes en permanence porteurs de phages et nous en consommons constamment.
- $10^8$  souches de phages et  $10^8$  phages par ml d'eau de surface
- On estime le nombre total de particules phagiques sur terre à  $4-6 \times 10^{31}$  => 10 x le nombre de procaryotes

*(Bergh. 1989. Nature 340: 467-468; Whitam et al. 1998. PNAS 95: 6578-6583)*

- Aucune infection eucaryotique à phage n'a pu être rapportée à ce jour.
- Aucune séquence d'ADN de phage n'a pu être détectée dans le génome humain (>< séquences de rétrovirus – 8-10 %)

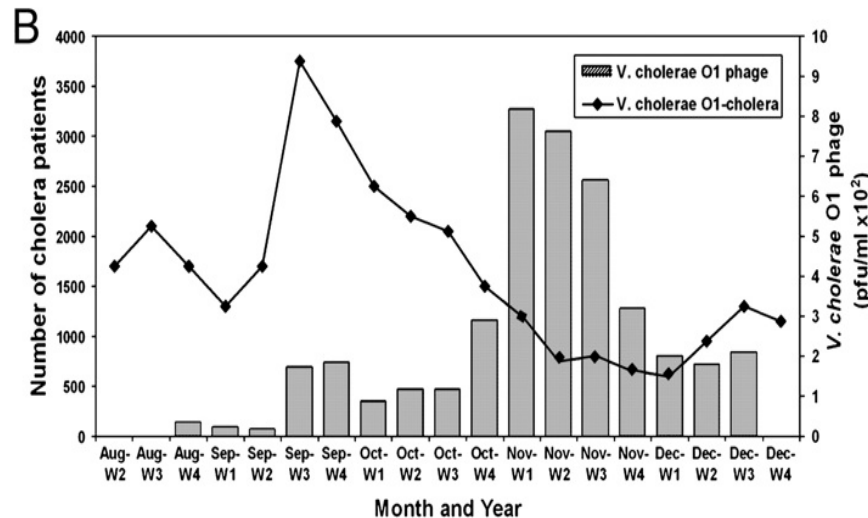
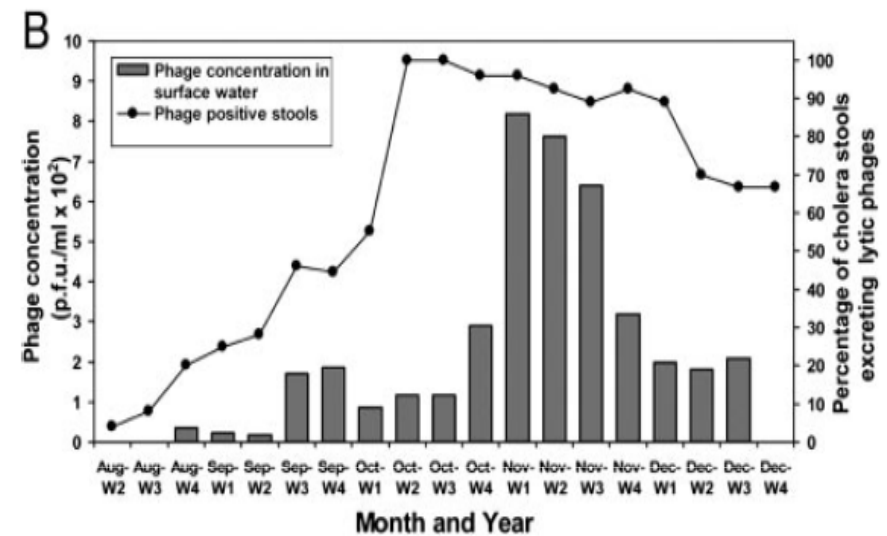
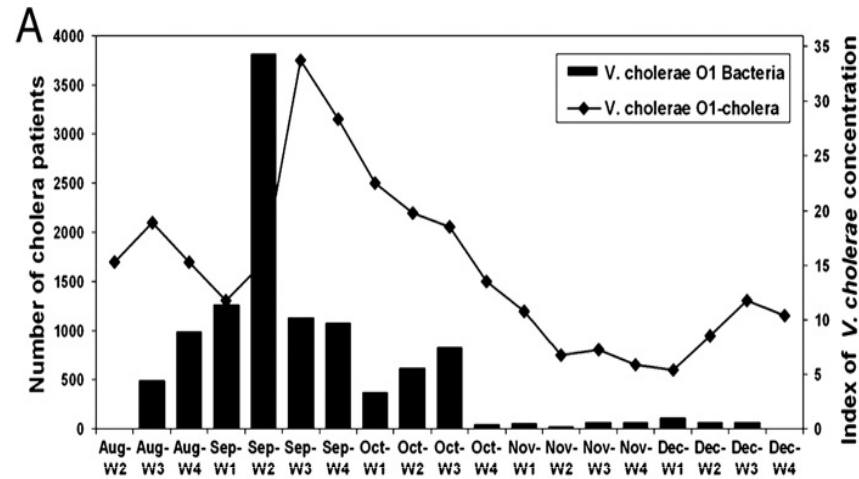
*(Mi et al, Nature 403, 785-789, 2000).*

- Utilisés depuis des dizaines d'années à l'Est...(orale, topicale, iv, aérosol,...)

# Dangereux?

- Différents tests d'innocuité réalisés: **SAFE**
  - Staphage lysate  
(Delmont laboratories, Sulakvelidze and Barrow, 2005)
  - FDA phase I: Ulcère veineux  
(wound care center Lubbock, Rhoads *et al.*, 2009)
  - FDA phase I/II: Otites chroniques  
(*P. aeruginosa*, Whright *et al.*, 2009)
  - Grands brûlés  
(Hopital Reine Astrid, Merabishvili *et al.*, 2009)
  - Nestlé  
(Bruttin, 2005 et test à grande échelle au Bangladesh actuellement)

# Phages ↔ Bactéries



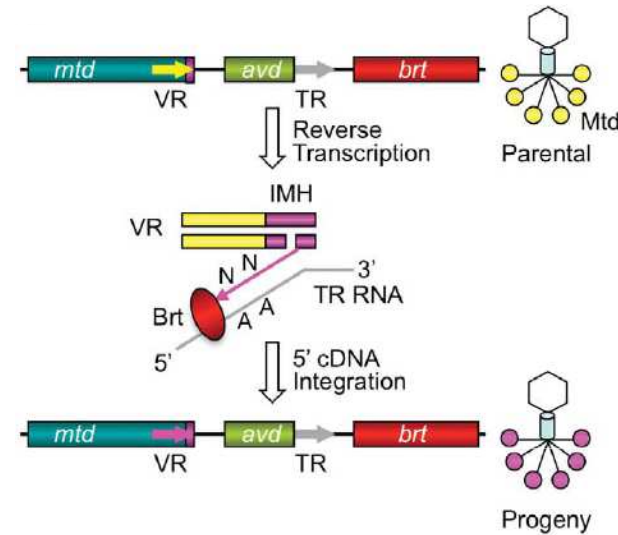
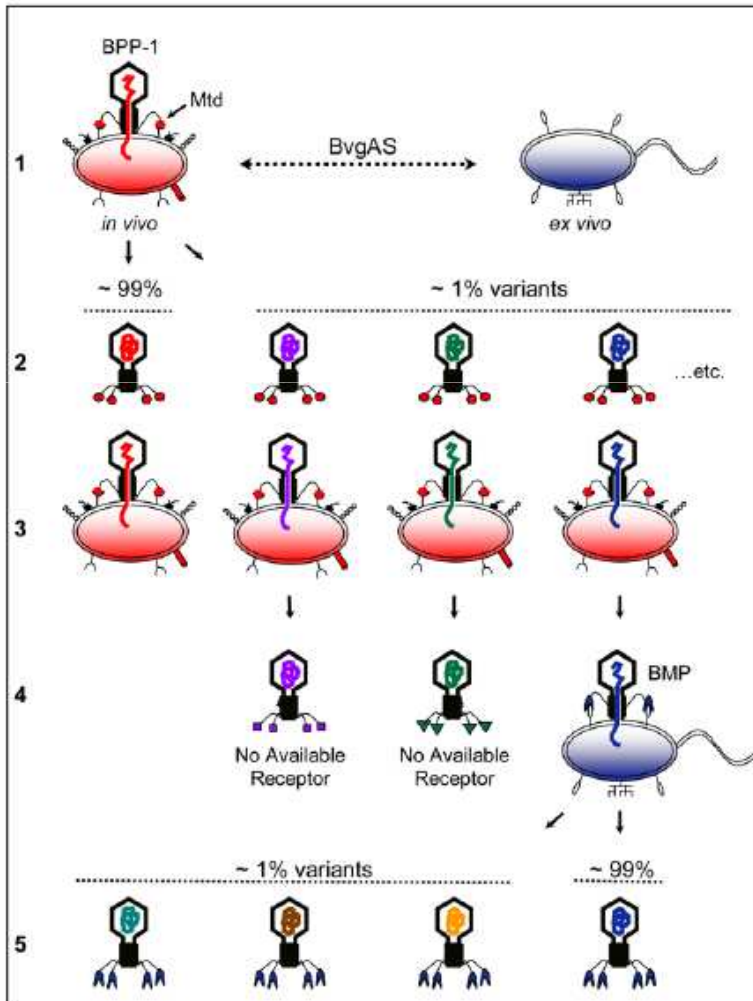
“Host-mediated **phage amplification during the cholera** epidemic likely contributed to increased environmental phage abundance, **decreased load of environmental *V. Cholerae*** **and**, hence, the collapse of the epidemic”

=> La prédation *in vivo* contrôle l'épidémie.  
Félix d'Hérelle avait raison...

Mais aussi: Territorialité, CoEvolution (transduction), ...

# Diversity Generating Retroelement

Phage BPP-1 de *Bordetella pertussis*



- *mtd*: major tropism determinant (lectin like)
- VR: Variable Repeat
- TR: invariable Template Repeat
- *brt*: RT (mutagenisante adénine dépendante)
- IMH: Initiation of Mutagenic Homing (site cible probable d'une endonucléase, hairpin,...)

**During mutagenic homing, adenine residues are converted to random nucleotides in a unidirectional, reverse transcriptase-dependent transposition process from a donor template repeat (TR) to a recipient variable repeat (VR).**

ANTIBIOTIQUES	BACTERIOPHAGES
MECANISMES D'ACTION DIFFERENTS	
<b>STATIQUE</b>	Naturel => "Evolving antibiotics"
Métabolisés => Doses multiples	Multiplication expo <i>in situ</i>
Dose sublétales et résistances...	Effet tout ou rien: 1 $\phi$ tue 1 bactérie
SPECTRE LARGE (quoique...) - Traitements <i>a priori</i> possible  - Résistances → Concerne plusieurs souches → Intérêt d'utiliser au + vite les + spécifiques...  - Effets secondaires (mycoses <i>Candida</i> , allergies, toxicité...)	SPECTRE (très) ETROIT - Traitements <i>a priori</i> inefficaces → "Cocktail"  - Résistances → Uniquement pour la souche ciblée → Usage de "cocktail" → Screening sur mesure en 1 semaine  - Aucun effet secondaire avéré
Inefficaces lorsque biofilm	Depolymerase spécifiques
Traverse la BBB difficilement	Traverse la BBB
Coûts élevés de développement	Développement bon marché
Impact écologique	<i>A priori</i> nul

# Désavantages

- Lysogénie (potentiel de transduction)  
→ Nécessité de séquencer
- Résistance et évolution  
→ Nécessité de réactualiser, combinaison phages/antibiotiques
- Spectre étroit  
→ Nécessité de connaître la souche infectieuse
- Préparation (coût) et dosage (batch to batch reproducibility)
- Relarguage d'endotoxines?, Pharmacocinétique?,  
Immunogénicité et anticorps neutralisants?  
Impact écologique si utilisés en masse?
- Phage=Virus: Appréhension négative



# Synergie: Phages/antibiotiques

Table 1. Effectiveness of staphylococcal phage preparation against staphylococcal sepsis, septic infection of the lungs and osteomyelitis<sup>a</sup>

Diagnosis	Phage therapy only				Phage with antibiotics				Antibiotics only			
	Total number (N)	Complete recovery	Improvement	No effect	Total number (N)	Complete recovery	Improvement	No effect	Total number (N)	Complete recovery	Improvement	No effect
Sepsis	46	19 41%	6	21	40	31 78%	4	5	96	22 23%	22	52
Lung infection	60	21	25	14	61	31	24	6	55	10	21	24
Osteomyelitis and arthritis	9	9	–	–	51	51	–	–	60	60	–	–

<sup>a</sup>Soviet data on phage therapy trials from the Eliava Institute [22]. In a series of clinical trials in the 1970s, the therapeutic effectiveness of the staphylococcal phage preparation against different infectious diseases was evaluated, from which some results are listed here.

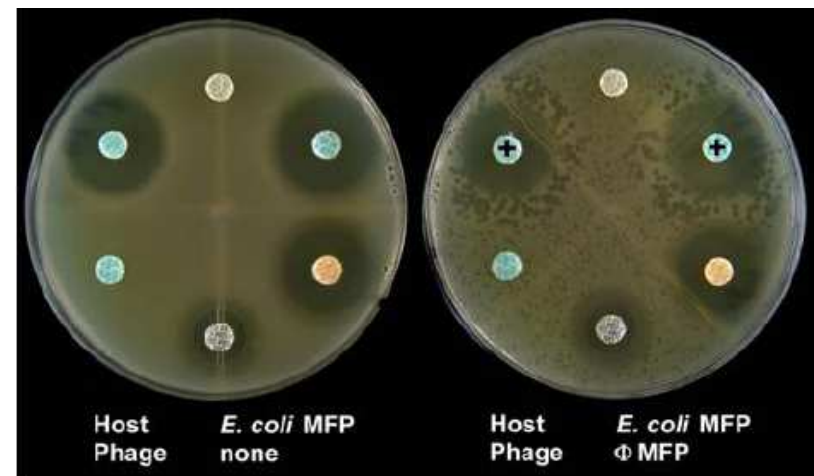
- PAS: Phage Antibiotic Synergy

→ Plaques + grande à proximité des  $\beta$ -lactams et quinolone(+)

→ Concentration subléthale en  $\beta$ -lactam ou quinolone (><division)

→ Induction de filaments dont l'état physiologique est plus favorable à la multiplication des phages (grandes plaque)

→ Fonction écologique dans la régulation des populations microbiennes?



(Kutateladze, Adamia, 2010) (Comeau, et al. 2007)

# Biofilm: Synergie phages/antibiotiques

- **Phages:**

Polysaccharide depolymerase  
SPECIFIQUE

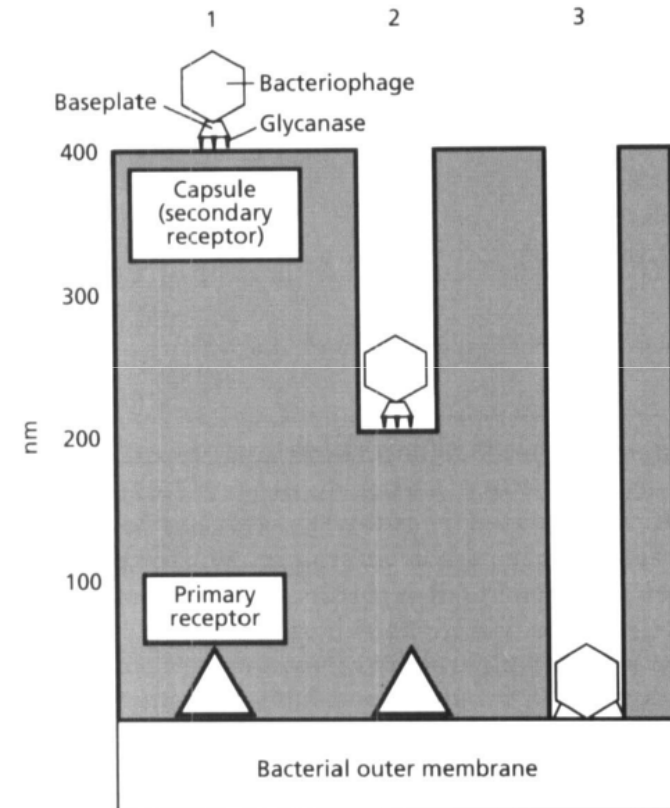
Mais:

- Efficacité ↓ ↑ Age du biofilm
- Probabilité faible d'interaction sur les 2 récepteurs

- **Phages + Antibiotiques:**

Synergie sur les biofilm mature

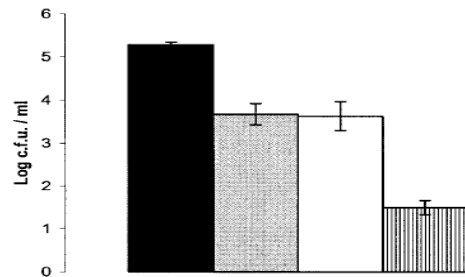
- Action des depolymerases = voies d'entrée pour les antibiotiques
- Préviens l'apparition des résistances



# Biofilm: prophylaxie

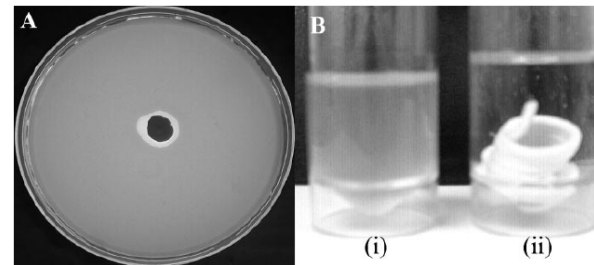
- Broad spectrum phage K vs MRSA strains:

**Lavage des mains**

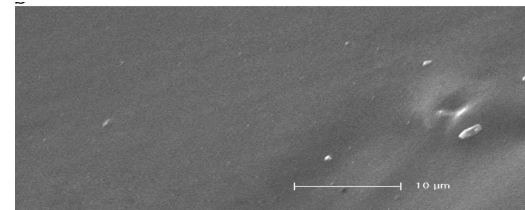
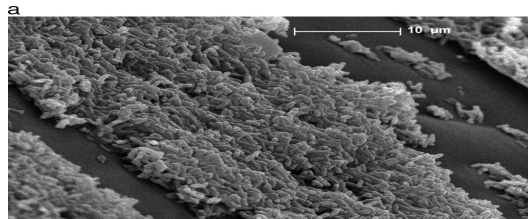


Bact susp / Unwashed / -φ / +φ

**Crème +φ**

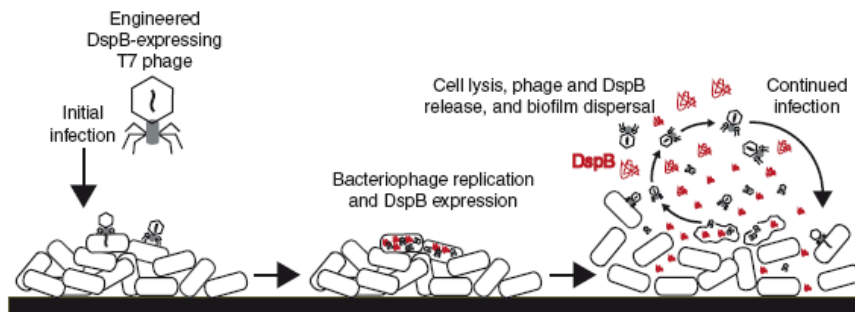


- Hydrogel-coated catheter with *P. aeruginosa* phages to prevent biofilm formation



(99.9% reduction CFU)

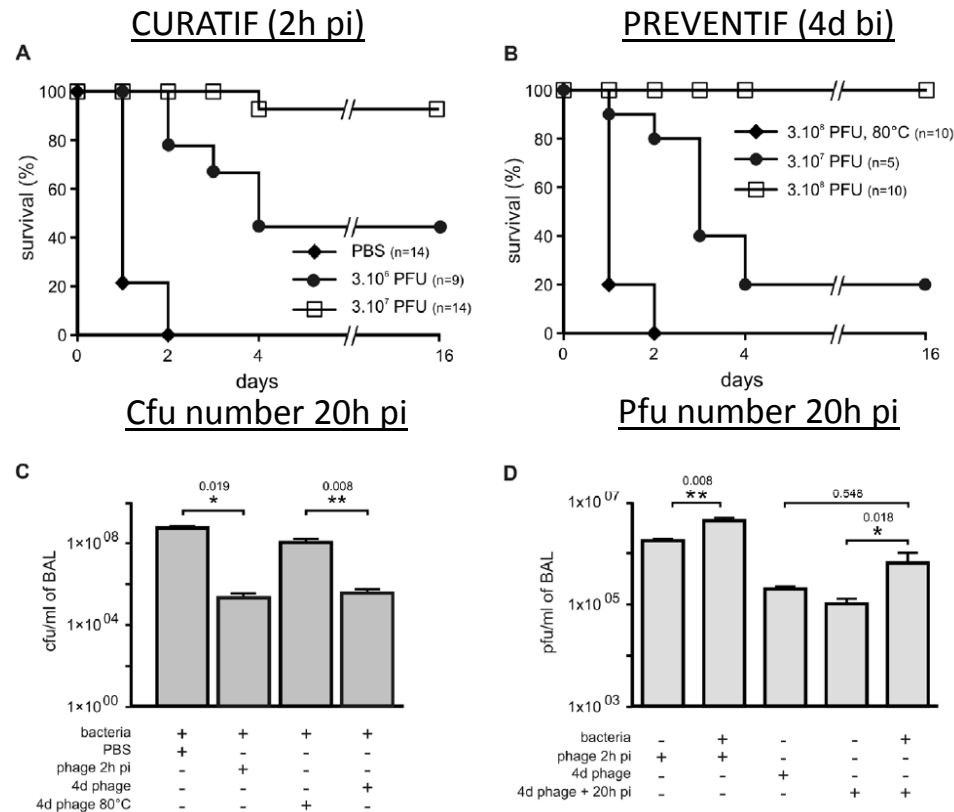
- Biologie synthétique (T7 based): relarguage de DspB qui empêche l'adhésion



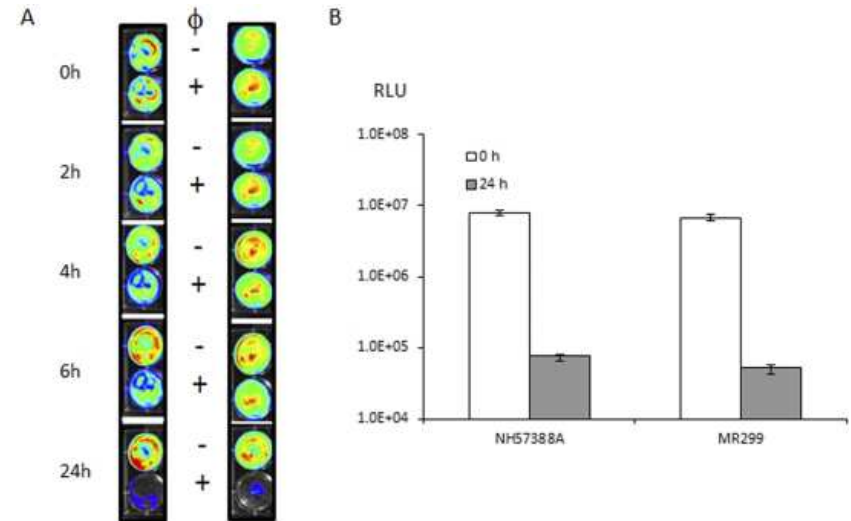
(99.9% reduction CFU)

(O'Flaherty, *et al.* 2005) (Fu, *et al.* 2010) (Lu and Collins 2007)

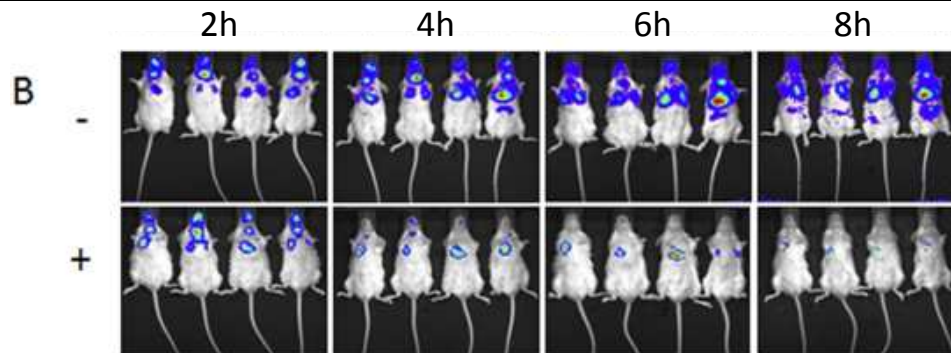
# Cystic Fibrosis



## Biofilms non-mucoïde et mucoïde

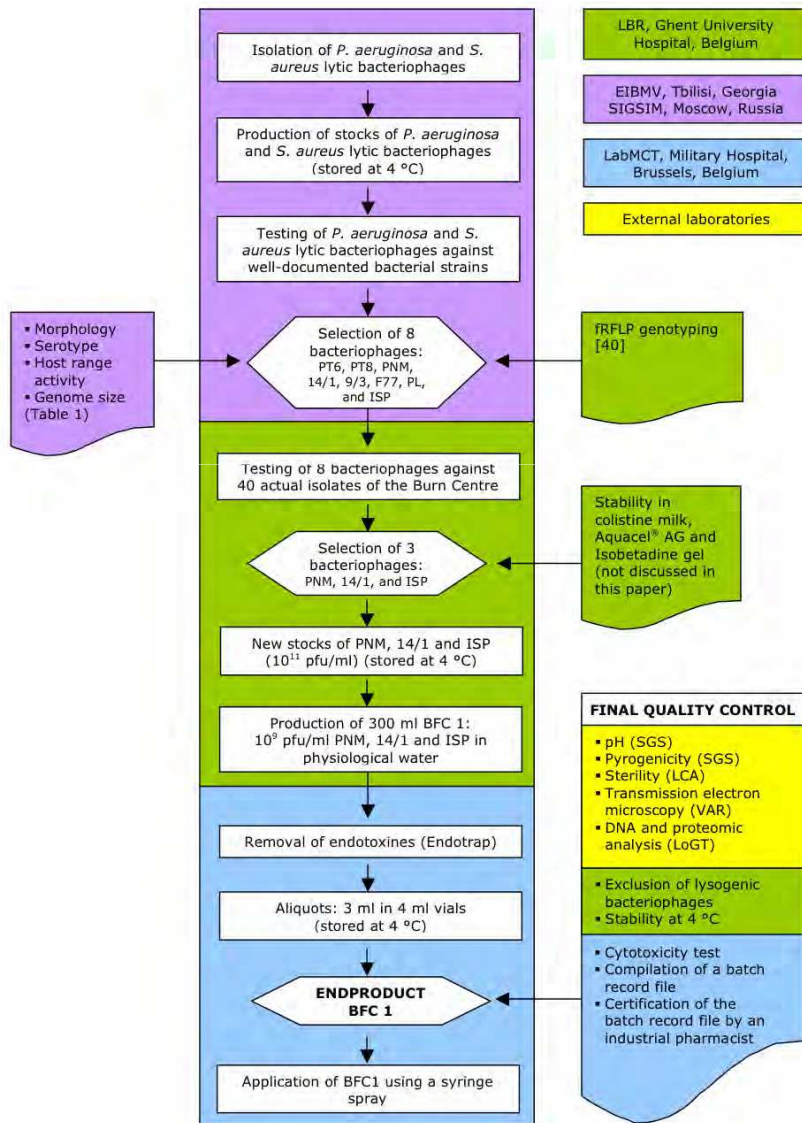


- *lux*-tagged *P. aeruginosa* mucoid and non-mucoid strains on CF bronchial epithelial cells
- Cocktail de 2 phages



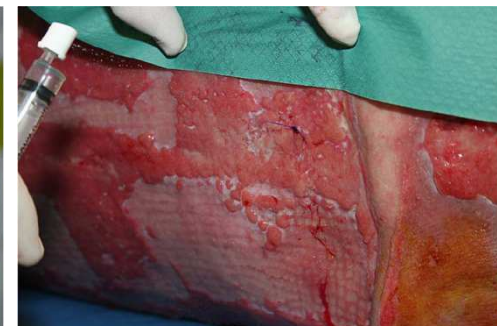
(Morello, *et al.* 2011) (Alemayehu, *et al.* 2012)

# En Belgique...



Hopital Militaire Reine Astrid: **LabMCT et al** (DeVos, Pirnay)

- Cocktail dirigé contre *P. aeruginosa* et *S. aureus*
- Une production “GMP-like” à petite échelle:
  - Stabilité
  - Pyrogenicité
  - Stérilité
  - Cytotoxicité
  - Séquençage DNA et protéomique *in silico*
  - Microscopie électronique (pureté)
- Pas d'effet néfaste



(Merabishvili, et al., 2009)

# Prêt-à-Porter ou Sur-mesure?

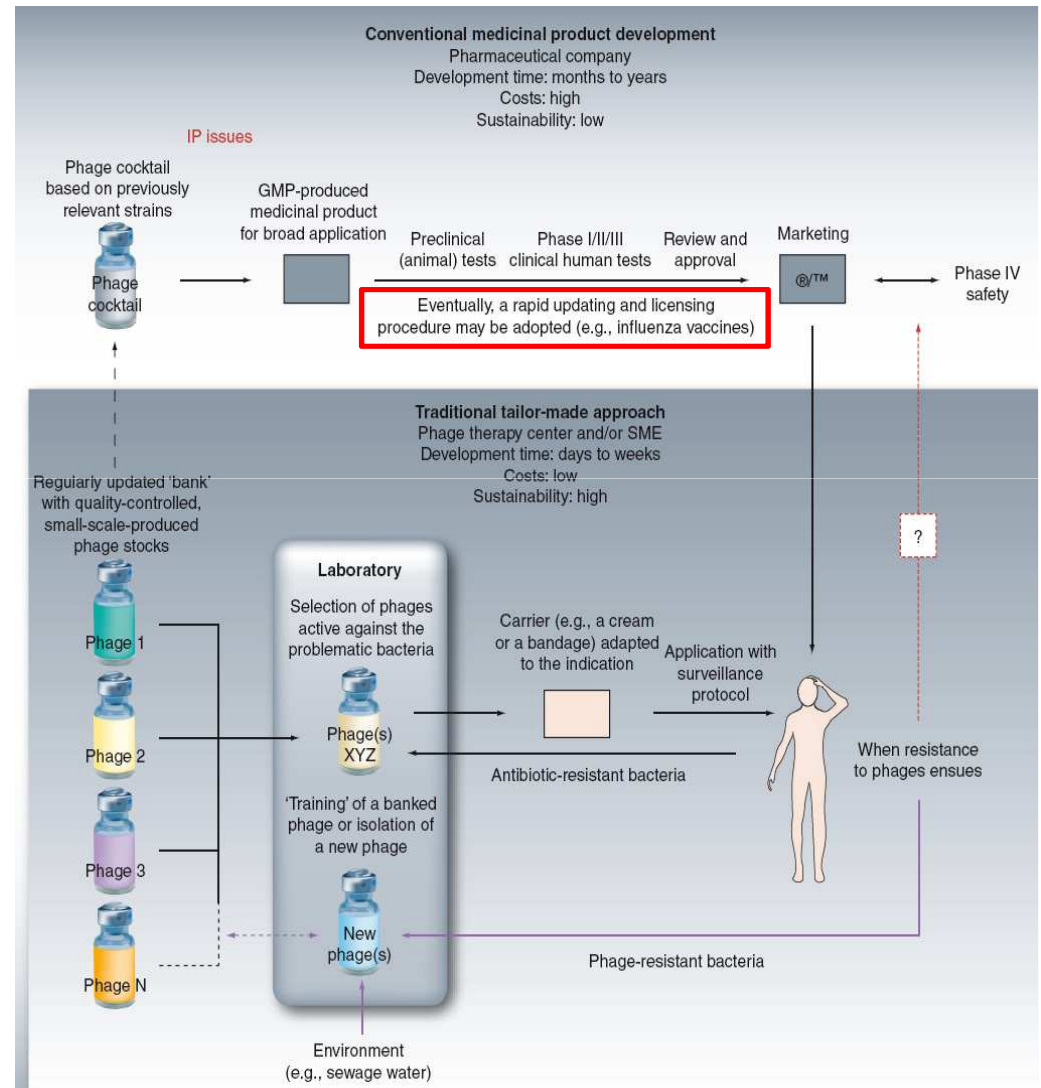
- Phagothérapie durable = “Sur-mesure” à court terme
  - Sources des phages:
    - Environnement (eaux usées)
    - Echantillons cliniques (patient(s))
    - Banques (Géorgie et Pologne)
  - Préparations doivent être actualisées...

⇒ Incompatible avec les systèmes de régulations actuels (FDA, EMA)

- IP et Investissements
  - Procédé connu depuis longtemps
  - Substance biologique
  - Domaine public à “reviewer” énorme (communisme...)

⇒ Modèle économique incompatible

**Obstacles pour le développement de thérapies tant pour un usage commercial que pour un usage de bonne foi.**  
**(ex. Pays en voie de développement)**



# Agences de Régulations

- **EMA: Biological product guidelines**

Différentes sous catégories de médicaments (Biologicals, radiopharmaceuticals, herbal, homeopathic, advanced therapy) ...mais aucune n'est réellement adaptée aux phages et à leur utilisations. (idéalement sur-mesure...)

L'EMA n'envisage pas d'en créer une nouvelle (Lobbying en cours...) mais comment envisager dans l'Union Européenne les produits proposés par l'institut polonais de Wroclaw ?

=>Utilisation sporadique en dehors de toute régulation:

→ Déclaration de Helsinki (cas désespérés, consentement, comité d'éthique)...

→ Usage compassionnel

- **FDA: Vaccines and related products guidelines**

Utilisation approuvée en tant qu'additif alimentaire (Intralix: Listeria)

# Préparations commerciales

	Product	Description	Company	Website
Agriculture et élevage	AgriPhage™	Targets bacterial spot or bacterial speck on crops, with specific formulations for strains of <i>Xanthomonas campestris</i> pv. <i>vesicatoria</i> or <i>Pseudomonas syringae</i> pv. <i>Tomato</i>	Omnilytics <b>Amériques (BIO aux USA) et Asie</b>	<a href="http://www.phage.com">http://www.phage.com</a>
	BioTector	Animal feed for control of <i>Salmonella</i> in poultry	CheilJedang Corporation <b>Corée et Inde (remplace les antibiotiques)</b>	<a href="http://www.cj.co.kr/">http://www.cj.co.kr/</a>
Décontaminants alimentaires et de surface	EcoShield™	Targets <i>Escherichia coli</i> O157:H7 contamination in foods and food processing facilities	Intralytix	<a href="http://www.intralytix.com">http://www.intralytix.com</a>
	ListShield™	Targets <i>Listeria monocytogenes</i> contamination in foods and food processing facilities	Intralytix <b>FDA-, USDA-, and EPA-approved</b>	<a href="http://www.intralytix.com">http://www.intralytix.com</a>
	LISTEX™ P100	A food processing aid that targets <i>L. monocytogenes</i> strains on food products	EBI Food Safety <b>Europe (Bio) et USA (FDA 2006, GRAS)</b>	<a href="http://www.ebifoodsafety.com">http://www.ebifoodsafety.com</a>
Diagnostique	MRSA/MSSA Blood culture test	Determining of <i>Staphylococcus aureus</i> methicillin resistance or susceptibility directly from blood cultures	Microphage <b>Identification bactérienne et test de susceptibilité</b>	<a href="http://microphage.com">http://microphage.com</a>
	MRSA Screening test	Identifies methicillin-resistant <i>Staph. aureus</i> (MRSA) for use in Infection Control programs	Microphage	<a href="http://microphage.com">http://microphage.com</a>
	MicroPhage MRSA/MSSA test	Differentiation of methicillin-resistant (MRSA) and methicillin-susceptible (MSSA) <i>Staph. aureus</i>	Microphage	<a href="http://microphage.com">http://microphage.com</a>
	FASTPlaque-Response™	Rapid detection of rifampicin resistance in smear-positive sputum specimens containing <i>M. tuberculosis</i>	Biotech Laboratories/Lab21	<a href="http://www.biotec.com">http://www.biotec.com</a>
	FASTPlaqueTB™	Rapid detection of <i>Mycobacterium tuberculosis</i> in human sputum samples	Biotech Laboratories/Lab21 <b>Pays en voie de développement (rapide et peu cher)</b>	<a href="http://www.biotec.com">http://www.biotec.com</a>

(Monk *et al.*, 2010)



# Sites web

Pour une utilisation raisonnée des bactériophages



## PHAG ESPOIRS

ACCUEIL | LES BACTÉRIOPHAGES, "CÉKOISSA"? | QUI SOMMES-NOUS? | LES ACTIONS DE PHAGESPOIRS | COMMENT NOUS AIDER? | COMMENT NOUS CONTACTER?

**Catégories**

- Congrès et manifestations scientifiques
- Interactions Phages-Bactéries
- Non classé
- Presse

**Liens**

GEEPHAGE  
Institut Eliava  
P.H.A.G.E.  
unBlog.fr

**Visiteurs**

Il y a 1 visiteurs en ligne

**Des programmes de recherche lancés sur les bactériophages – PHAGESPOIRS, pour promouvoir la recherche!**

Posté par Jérôme Larché le 30 janvier 2012

Article paru dans l'Indépendant (26 janvier 2012)



Font size Bigger | Reset | Smaller | Search...

HOME | GOALS | BECOME A MEMBER | MEETINGS | LITERATURE | NEWS | LINKS | CONTACT | EXECUTIVE BOARD

## P.H.A.G.E. PHAGES FOR HUMAN APPLICATION GROUP EUROPE

**JULY THE 20TH, DO NOT MISS OUR IMPORTANT AFTERNOON ON CLINICAL PHAGOTHERAPY AT VOM 2012 REGISTER HERE**

Mercredi, 04 Juillet 2012



**GEEPhage**  
Phagothérapie

LE BACTÉRIOPHAGE  
SON RÔLE DANS L'IMMUNITÉ

*L. Pasteur*  
18.6.1944

GEEPhage | Actualité | Contacts

identifhez-vous

Merci

*"Qui ne voit que le passé est borgne, qui oublie le passé est aveugle."*