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Il ruolo dei batteriofagi nella lotta alle contaminazioni e alle infezioni batteriche

Raniero Lorenzetti
Biologo U.O.C. Ricerca, Innovazione e Cooperazione Internazionale

11/03/2021

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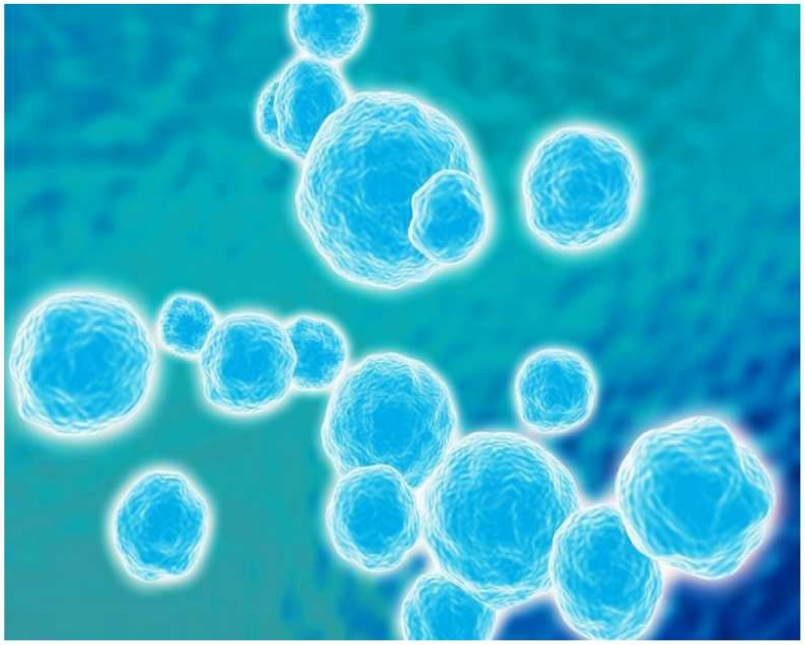
'The world is headed for a post-antibiotic era,' WHO official warns



The methicillin-resistant Staphylococcus aureus bacteria -- better known as MRSA -- is just one example of a pathogen that is making current drugs obsolete, the World Health Organization warns. (Science Photo Library / Getty Images)

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***Cassini et al. Lancet Infect Dis* 2019; 19: 56–66**

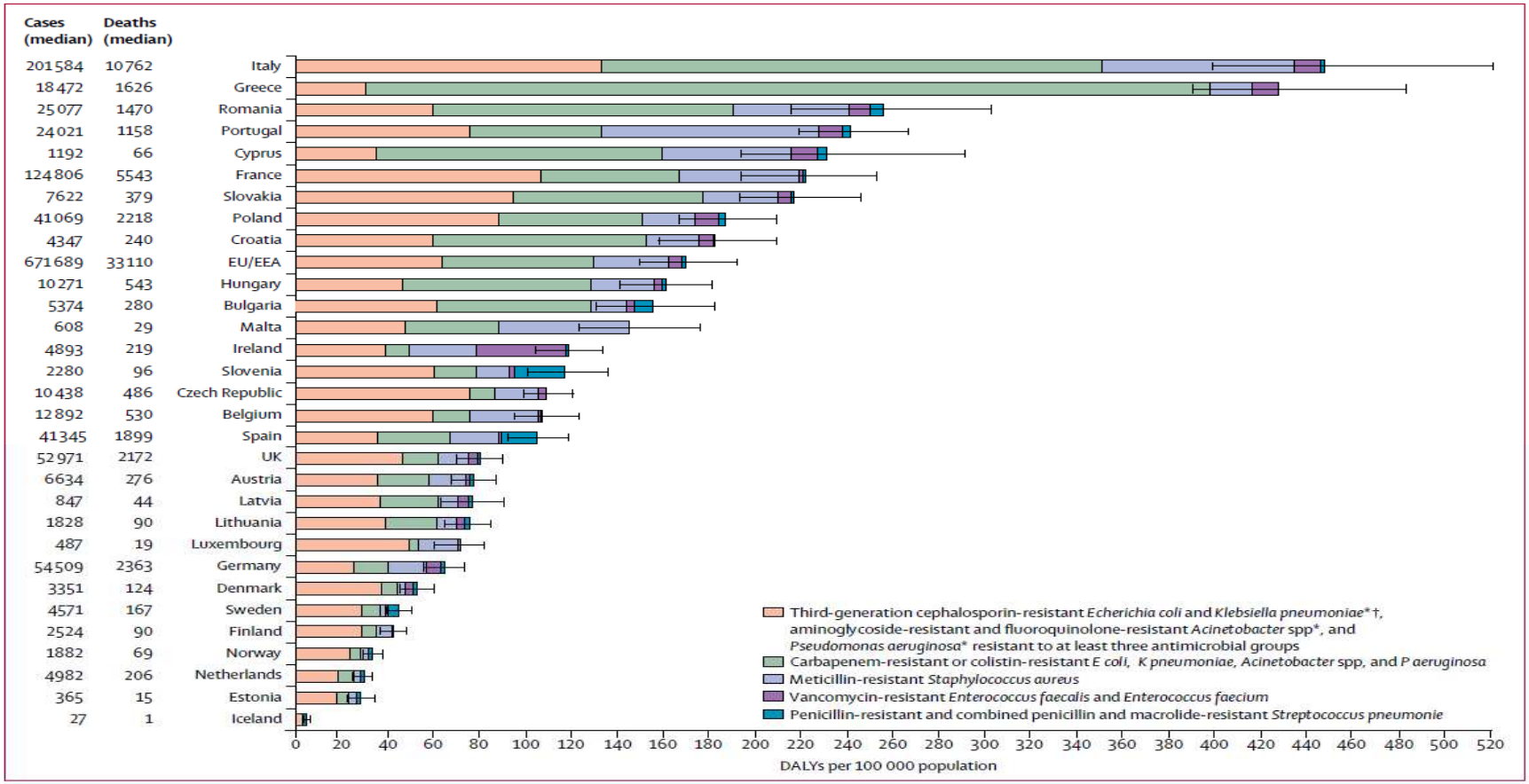

Figure 3: **Burden of infections with antibiotic-resistant bacteria in DALYs, EU and European Economic Area, 2015**
Error bars are 95% uncertainty intervals. Greece did not report data on *S pneumoniae* isolates to the European Antimicrobial Resistance Surveillance Network in 2015. DALY rates are age-standardised to limit the effect of demographic differences across countries; numbers of cases and deaths are not age-standardised. DALYs=disability-adjusted life-years. *Excludes those resistant to carbapenem or colistin. †In 2015, most of the third-generation cephalosporin-resistant *E coli* (88·6%) and *K pneumoniae* (85·3%) isolates reported to the European Antimicrobial Resistance Surveillance Network produced an extended-spectrum β-lactamase.[9]

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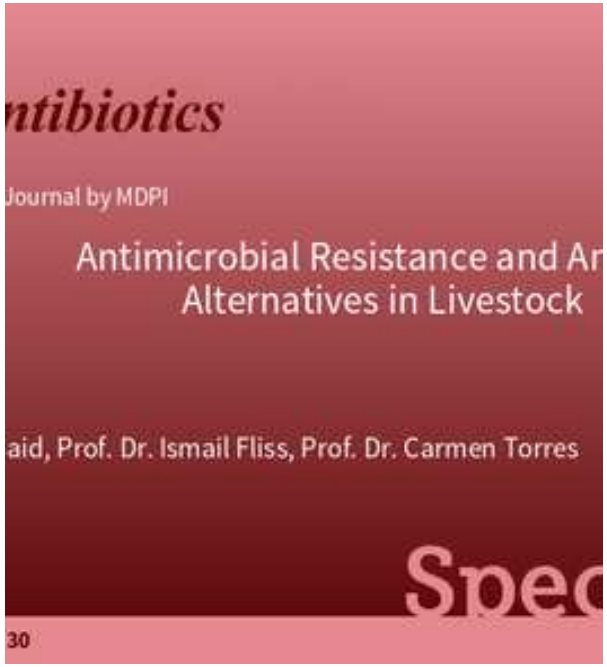
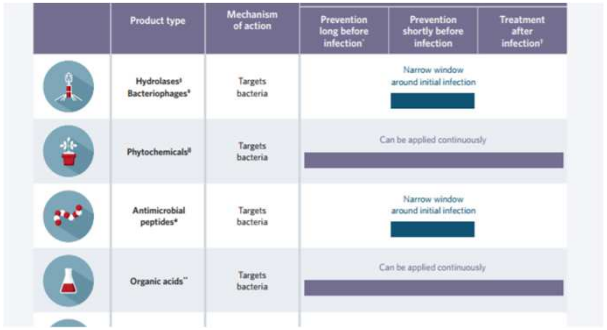
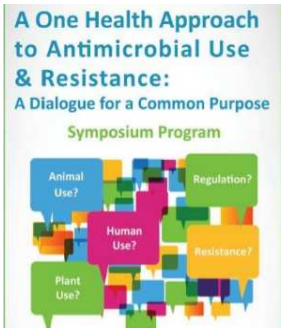
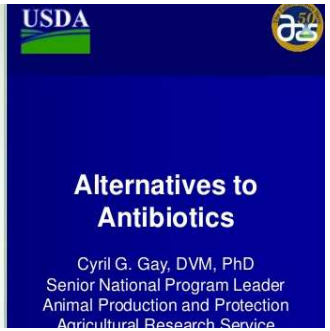


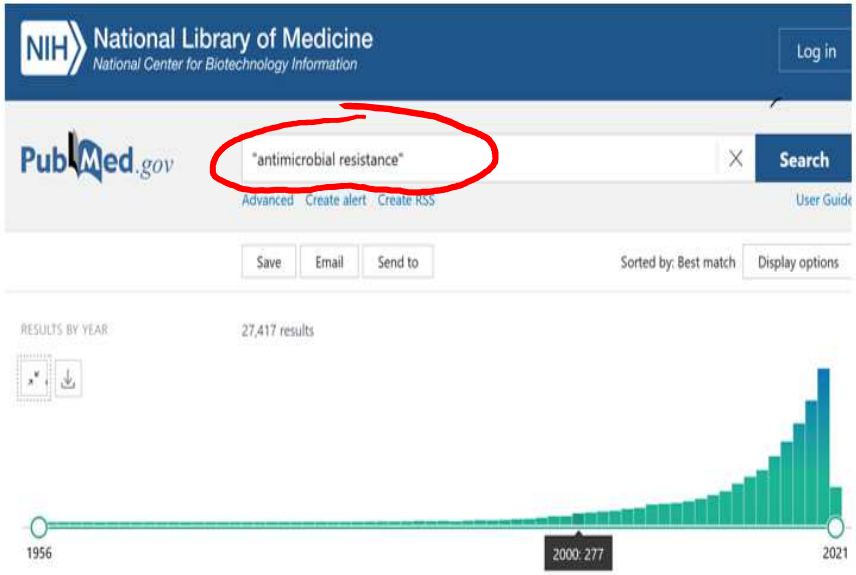






NECESSITA' DI INDIVIDUARE
NUOVE STRATEGIE E NUOVI ANTIMICROBICI

I BATTERIOFAGI E LA FAGOTERAPIA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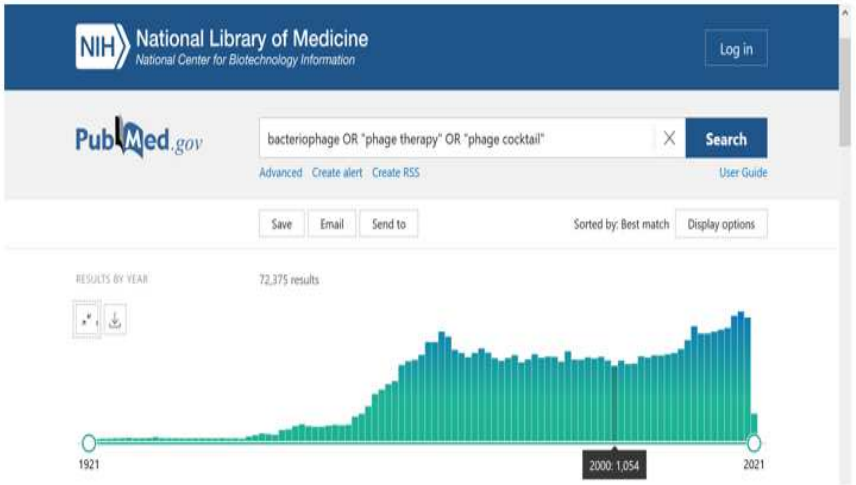
2000: 277
2021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RESULTS BY YEAR
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2000: 1,054
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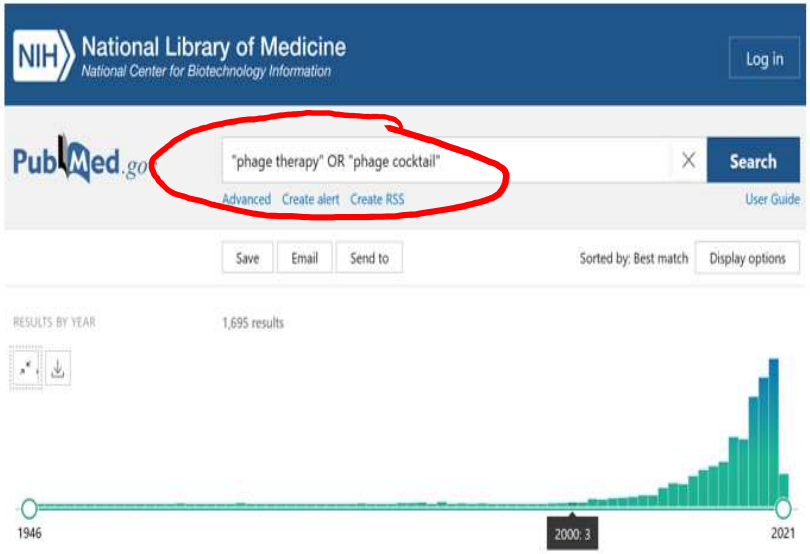
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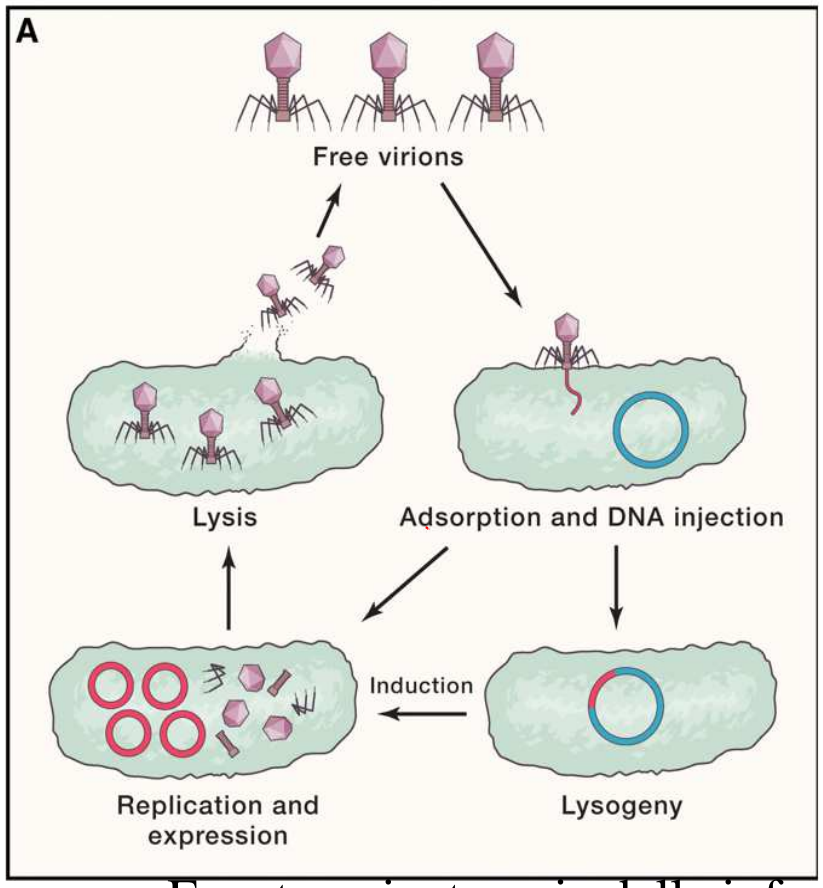

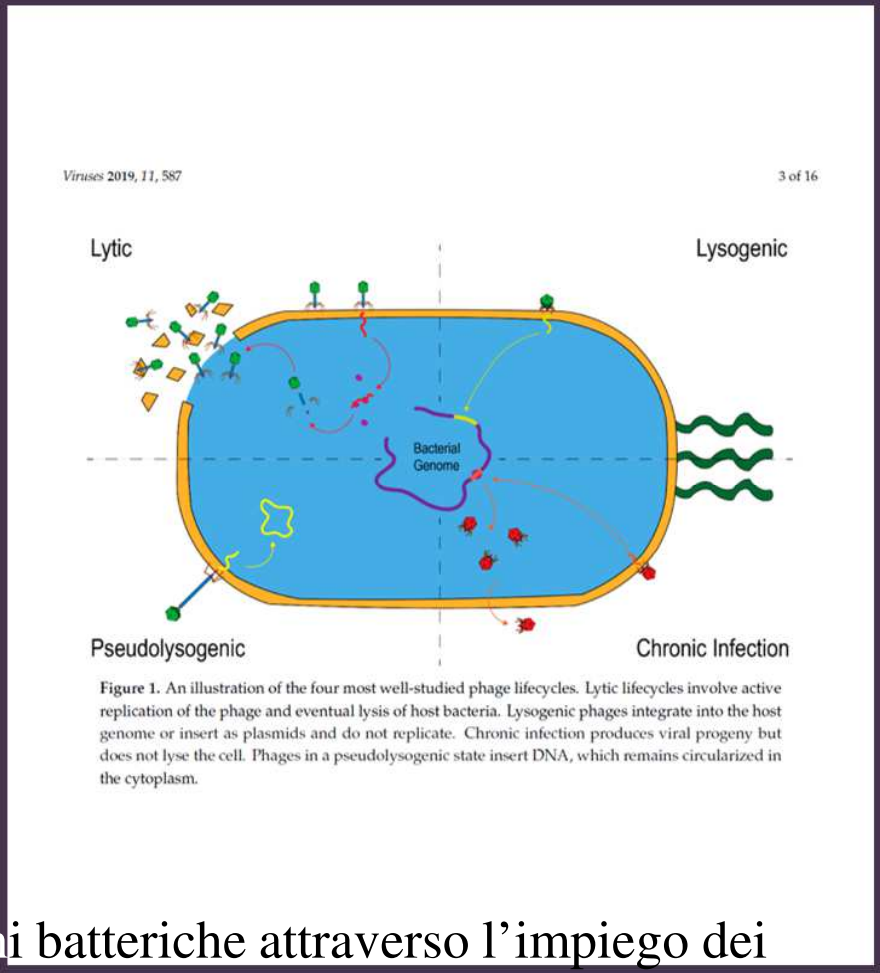

Figure 1. An illustration of the four most well-studied phage lifecycles. Lytic lifecycles involve active replication of the phage and eventual lysis of host bacteria. Lysogenic phages integrate into the host genome or insert as plasmids and do not replicate. Chronic infection produces viral progeny but does not lyse the cell. Phages in a pseudolysogenic state insert DNA, which remains circularized in the cytoplasm.

Fagoterapia: terapia delle infezioni batteriche attraverso l'impiego dei batteriofagi (possibilmente litici…..)

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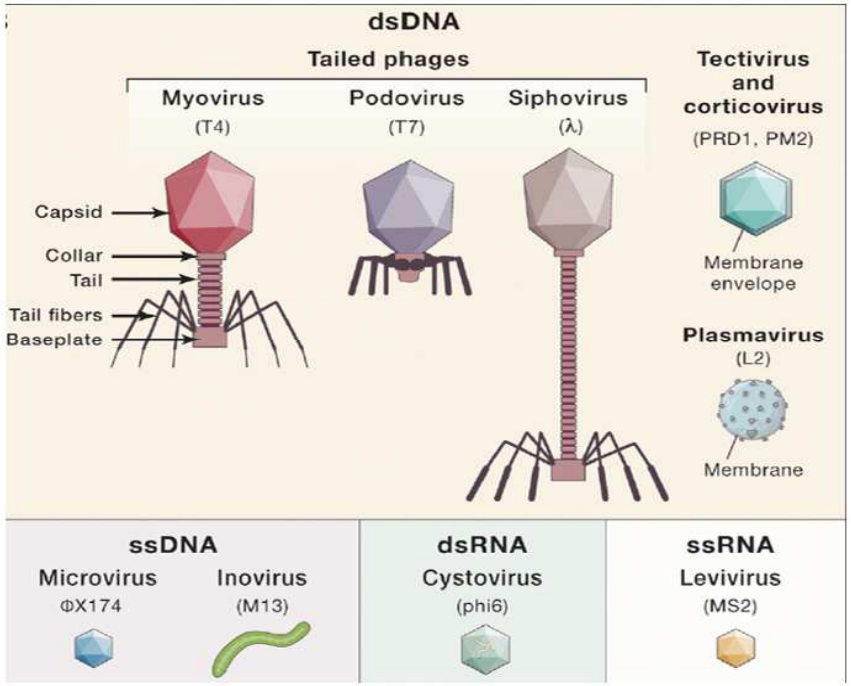
TASSONOMIA

Table 2. Virus order, family, viral examples, features, target species, and related taxonomy.

Order	Family	Bacteriophage	Features	Target Species
Caudovirales	*Myoviridae*	T2, T4, vBSM-A1 [64]	dsDNA, linear [58], NE, contractile tail [60]	*Escherichia coli*, *S. aureus*
	Siphoviridae	λ, T1, T5, ΦAPCM01	dsDNA, linear, NE, non-contractile tail [62]	*S. mutans* [65]
	Podoviridae	T7, vBSP-A2, PFpW-6		*E. coli*, *S. aureus* [64]
Ligamenvirales	*Lipothrixviridae*	TTV1, SIFV	Helical, dsDNA, linear, E, rod-shaped	Thermophilic Archaea
	Rudiviridae	SIRV1, AVF-1	Helical, dsDNA, linear, NE, bottle shaped	Hyperthermophilic Archaea
Non grouped	*Inoviridae*	Fd, pf1, Vf33 [66]	Filamentous, ssDNA, NE, circular	Enterics, *Pseudomonas*, *Vibrio* [67]
	Microviridae	PhiX174	Polyhedral ssDNA [66]	Enterobacteria
	Tectiviridae	PRD1	Linear dsDNA	Gram-negative bacteria
	Corticoviridae	PM2	Highly supercoiled, dsDNA, NE, circular [66]	
	Cystoviridae	Phi6	dsRNA, linear, lipoprotein envelope, spherical	*Pseudomonas* species-specific
	*Levivirida*e	MS2 [66]	Polyhedral ssRNA, linear	Enterics, *Acinetobacter*, *Pseudomonas*
	Ampullaviridae	Acidianus bottle-shaped virus	dsDNA, linear, E, bottle-shaped	Archaea
	Bicaudaviridae	Acidianus two-tailed virus	dsDNA, circular, NE, lemon-shaped	Hyperthermophilic archaea
	Clavaviridae	Aeropyrum pernix bacilliform virus 1.	NE, rod shaped, dsDNA, circular	Aeropyrum pernix
	Fuselloviridae	Sulfolobus spindle-shaped virus 1, SSSV2, SSSV3	Superhelical dsDNA [67], circular	Thermophilic Archaea
	Plasmaviridae	Acholeplasma virus L2	Superhelical dsDNA, E, pleomorphic	Acholeplasma laidlawii
	Globuloviridae	Pyrobaculum spherical virus	Helical, E, dsDNA, linear [62]	Hyperthermophilic archaea, genera Pyrobaculum, and Thermoproteus

NE = non-enveloped; E = enveloped.



Tratto da: Contemporary Phage Biology: From Classic Models to New Insights https://doi.org/10.1016/j.cell.2017.10.045

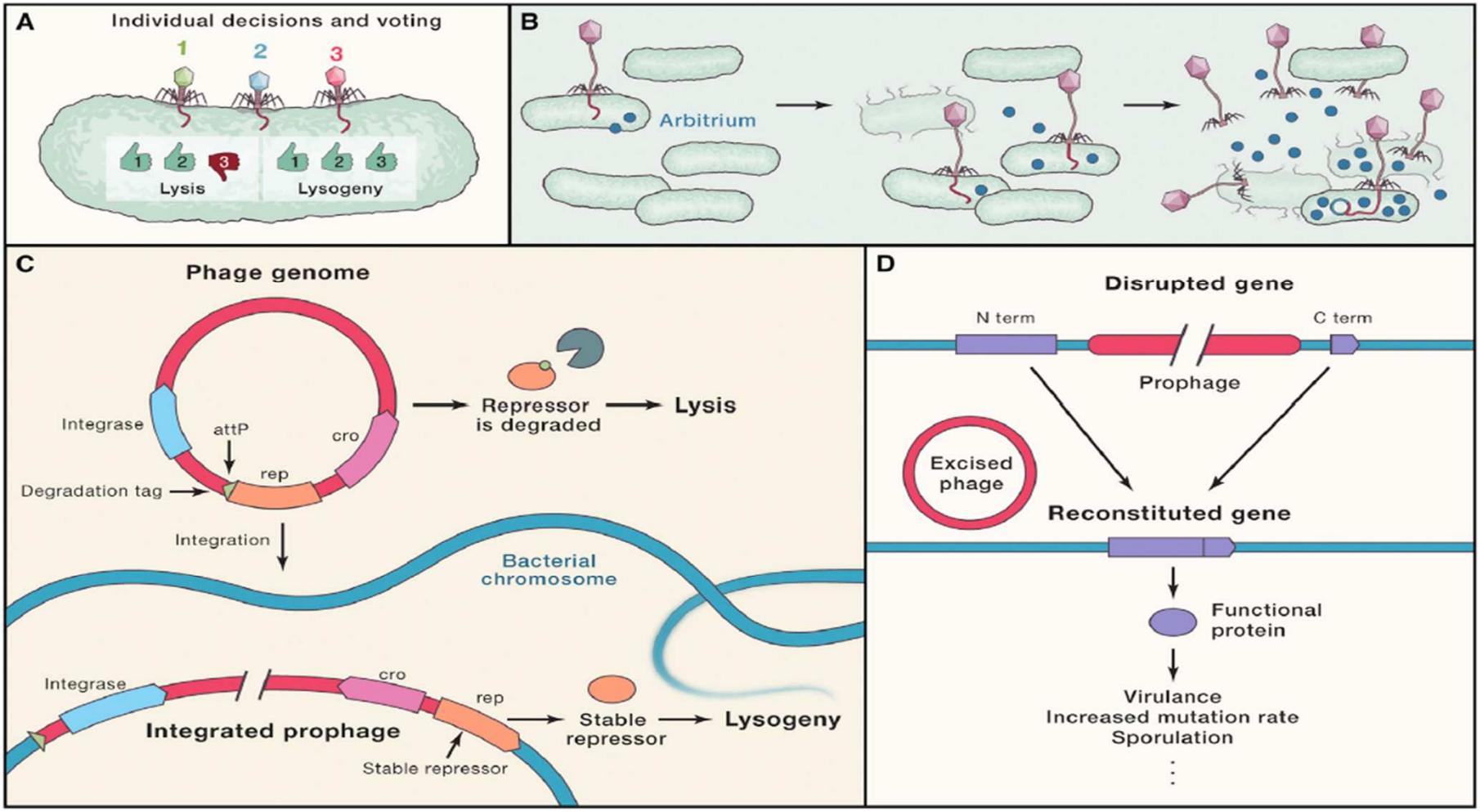


Figure 2. Mechanisms of Phage Lysogeny Decisions Contemporary Phage Biology: From Classic Models to New Insights https://doi.org/10.1016/j.cell.2017.10.04

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*Bergh O, Børsheim KY, Bratbak G, Heldal M (August 1989). "High abundance of viruses found in aquatic environments". Nature. **340** (6233): 467–68*

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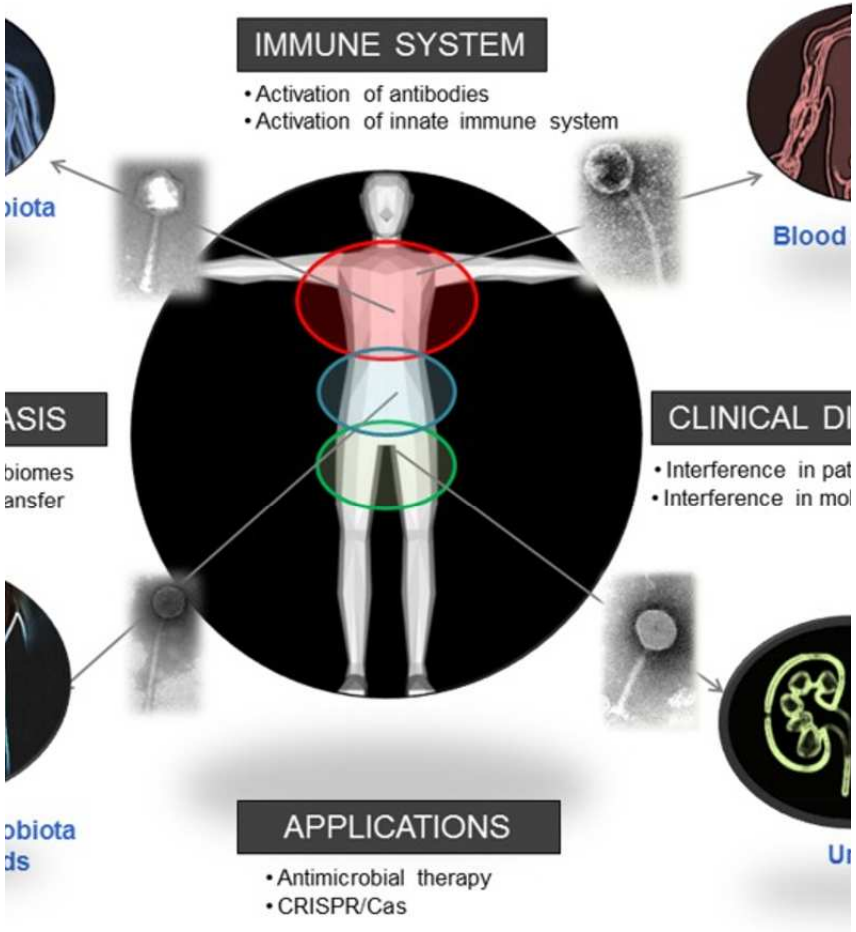

microorganisms

MDPI

Review

The Presence of Bacteriophages in the Human Body: Good, Bad or Neutral?

Marzanna Łusiak-Szelachowska [1,†], Beata Weber-Dąbrowska [1,2,†], Maciej Żaczek [1], Jan Borysowski [3] and Andrzej Górski [1,2,4,*]

1 Bacteriophage Laboratory, Ludwik Hirszfeld Institute of Immunology and Experimental Therapy, Polish Academy of Sciences, 53-114 Wrocław, Poland; marzanna.lusiak-szelachowska@hirszfeld.pl (M.Ł.-S.); beata.weber-dabrowska@hirszfeld.pl (B.W.-D.); maciej.zaczek@hirszfeld.pl (M.Ż.)

2 Phage Therapy Unit, Ludwik Hirszfeld Institute of Immunology and Experimental Therapy, Polish Academy of Sciences, 53-114 Wrocław, Poland

3 Department of Clinical Immunology, Transplantation Institute, Medical University of Warsaw, 02-006 Warsaw, Poland; jborysowski@interia.pl

4 Infant Jesus Hospital, Medical University of Warsaw, 02-005 Warsaw, Poland

* Correspondence: andrzej.gorski@hirszfeld.pl; Tel.: +48-71-370-99-05

† Equal contributed as co-first authors.

Received: 3 December 2020; Accepted: 15 December 2020; Published: 16 December 2020

check for updates

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Sono ovunque, ma occorre anche
un po' di fortuna per trovare quelli giusti

BROWSE PUBLISH ABOUT

PLOS NEGLECTED TROPICAL DISEASES

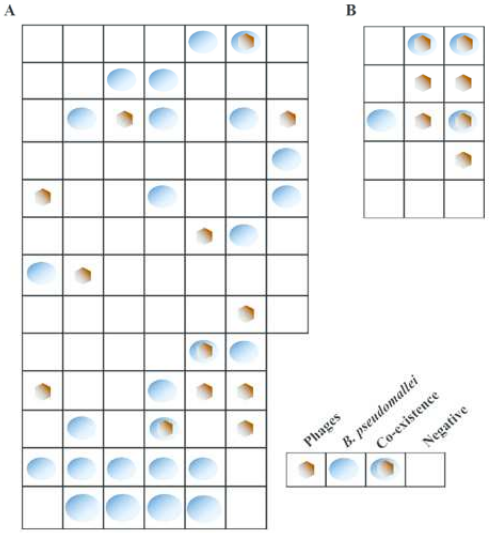
OPEN ACCESS PEER-REVIEWED

RESEARCH ARTICLE

Analyses of the Distribution Patterns of *Burkholderia pseudomallei* and Associated Phages in Soil Samples in Thailand Suggest That Phage Presence Reduces the Frequency of Bacterial Isolation

Patoo Withatanung, Narisara Chantratita, Veerachat Muangsombut, Natnaree Saiprom, Ganjana Lertmemongkolchai, Jochen Klumpp, Martha R. J. Clokie, Edouard E. Galyov, Sunee Korbsrisate

Published: September 26, 2016 • https://doi.org/10.1371/journal.pntd.0005005



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STORIA DEI BATTERIOFAGI


Hankin ME: L'action bactéricide des eaux de la Jumma et du Gange sur le vibrion du choléra.
Annales de l'Inst Pasteur 1896; 10:511–23
Bacteriophage
Bacteriophage. 2011 May-Jun; 1(3): 174–178.
Published online 2011 May 1. doi: 10.4161/bact.1.3.16591
PMCID: PMC3225782
PMID: 22164351
Bacteriophage prehistory
Is or is not Hankin, 1896, a phage reference?
Stephen T Abedon,[*1] Cameron Thomas-Abedon,[1] Anne Thomas,[1] and Hubert Mazure[2]
Author information ▸ Article notes ▸ Copyright and License information Disclaimer
This article has been cited by other articles in PMC.
Abstract
Go to:
We identified 30 actual or presumptive "bacteriophage" references dating between the years 1895 and 1917 and have further explored one of the oldest: Hankin's 1896 study of a bactericidal action associated with the waters of the Ganges and Jumna rivers in India. As Hankin's work took place approximately 20 years prior to the actual discovery of bacteriophages, no claims were made as to a possible phage nature of the phenomenon. Here we suggest that it may be imprudent to assume nevertheless that it represents an early observation of phagemediated bactericidal activity. Our principal argument is that the antibacterial aspect of these river waters was able to retain full potency following "heating" for one-half hour in hermetically sealed tubes, where heating in "open" tubes resulted in loss of antibacterial activity. We also suggest that environmental phage counts would have had to have been unusually high—greater than 10^6/ml impacting a single host strain—to achieve the rates of bacterial loss that Hankin observed.
Key words: Ganges River, history, natural bactericidal activity, presumptive early phage references
Introduction
Go to:
Traditionally, the discovery of bacteriophages is traced to the papers of Twort[1] and d'Hérelle.[2] Several earlier studies, however, hint at the existence of phagelike antibacterial activity. In his collection of phage
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photofvg.it
FVG036201

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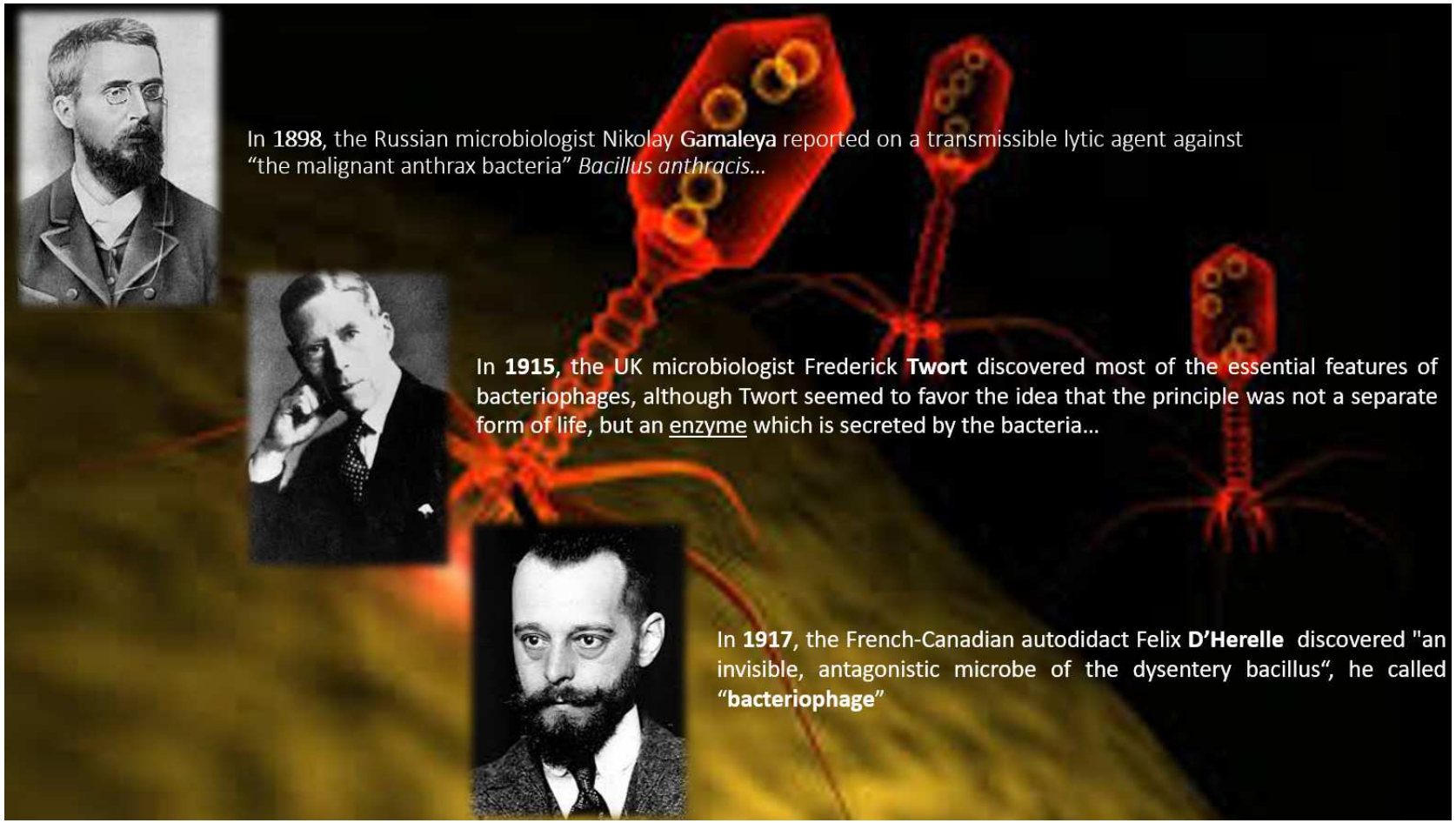

Bacteriophage 2:2, 130–133; April/May/June 2012; © 2012 Landes Bioscience

The strange history of phage therapy

William C. Summers
Yale University; New Haven, CT USA

Since the enlightenment, scientists have enjoyed a self-image as rational actors, guided only by reason, evidence and logic. When the Royal Society of London was founded in 1660 it chose as its motto "nullius in verba" (often translated as "on the word of no one") a reference to Horace's Epistles "Nullius addictus iurare in verba magistri…" (being not obliged swear allegiance to any mast[illegible] 21st century

prophylactic against avian typhosis (*Salmonella gallinarum*) in rural France in 1919 to its widespread use in humans in the pre-antibiotic 1930s, phage therapy was controversial. Some saw it as the panacea for all infectious diseases while others thought it was over-sold and probably worthless.[2,3]

While it is no doubt true that the discovery and wide-spread availability of antibiotics in the immediate post World War era undermined enthusiasm for [illegible] that is not the whole

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George Eliava

- 1918-1921: ospite presso l'Istituto Pasteur, incontra d'Herelle
- 1923: fonda l'Istituto Eliava, a Tbilisi (Georgia) dove promuove la ricerca e l'applicazione della fagoterapia
- 1937: arrestato e giustiziato come nemico del popolo

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- Commercial department at the **Pasteur Institute** (5 preps)
- **German Bacteriophage Society** (dried phages in tablet forms)
- **German company Antipiol** (Enterofagos)
- **Eli Lilly Company** (USA) (7 products based on phages)
- **Swan-Myers** of Abbot Laboratories
- **Squib and sons** (now belongs to Brystol Myers Squibb)
- **Parke, Davis and Company** (now part of Pfizer)

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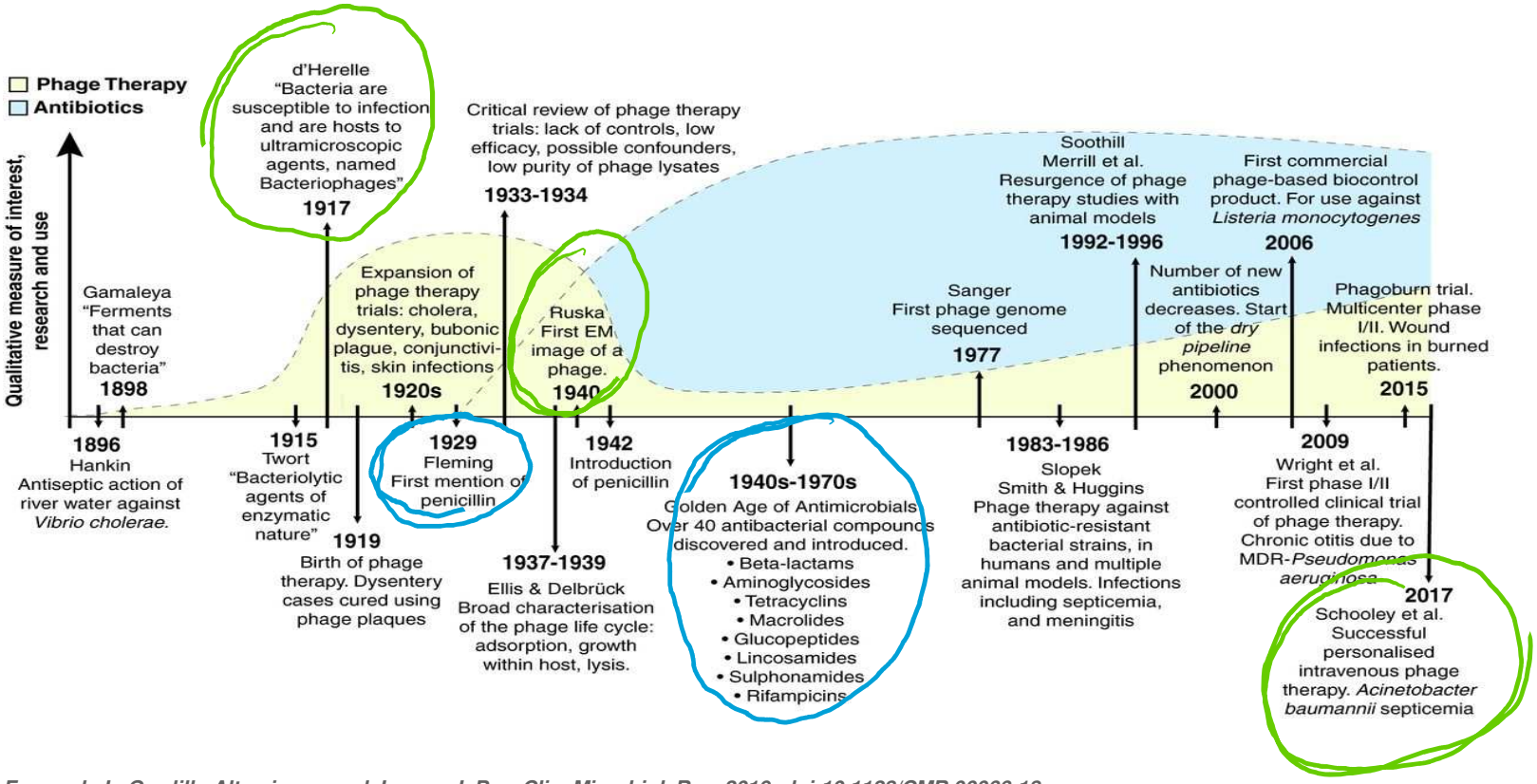
Timeline of major events in the history of research on phages, phage therapy, and antibiotics.



Fernando L. Gordillo Altamirano, and Jeremy J. Barr Clin. Microbiol. Rev. 2019; doi:10.1128/CMR.00066-18

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Eliava Institute of Bacteriophage,
Microbiology and Virology,
founded in 1923 in Tbilisi, Georgia

DAGLI ANNI '40 FINO AD I PRIMI ANNI 2000, SOLTANDO DUE CENTRI RESISTONO AL DECLINO DELL'INTERESSE NELLA FAGOTERAPIA

Ludwik Hirszfeld Institute of Immunology
and Experimental Therapy,
founded in 1952 in Wroclaw, Poland

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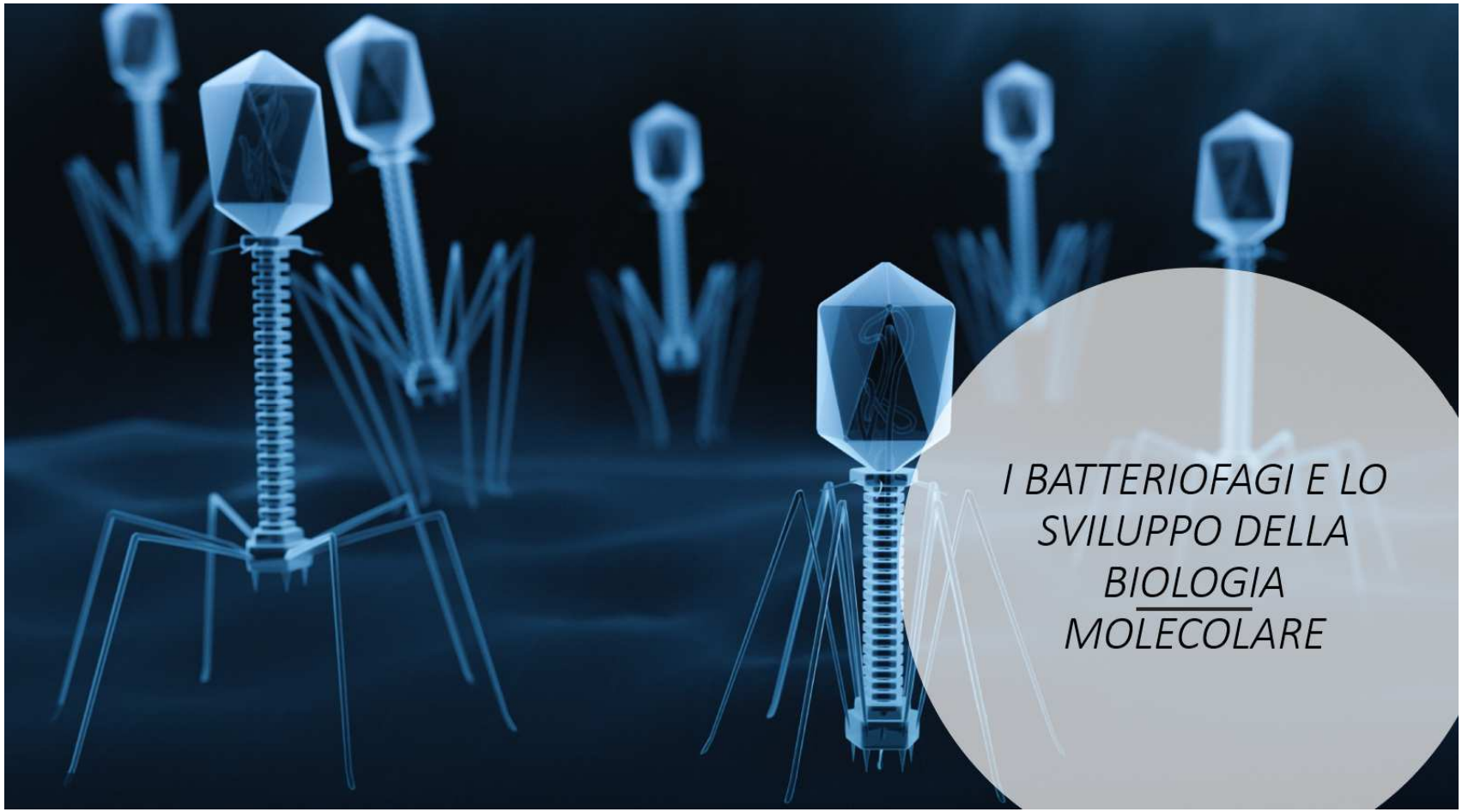
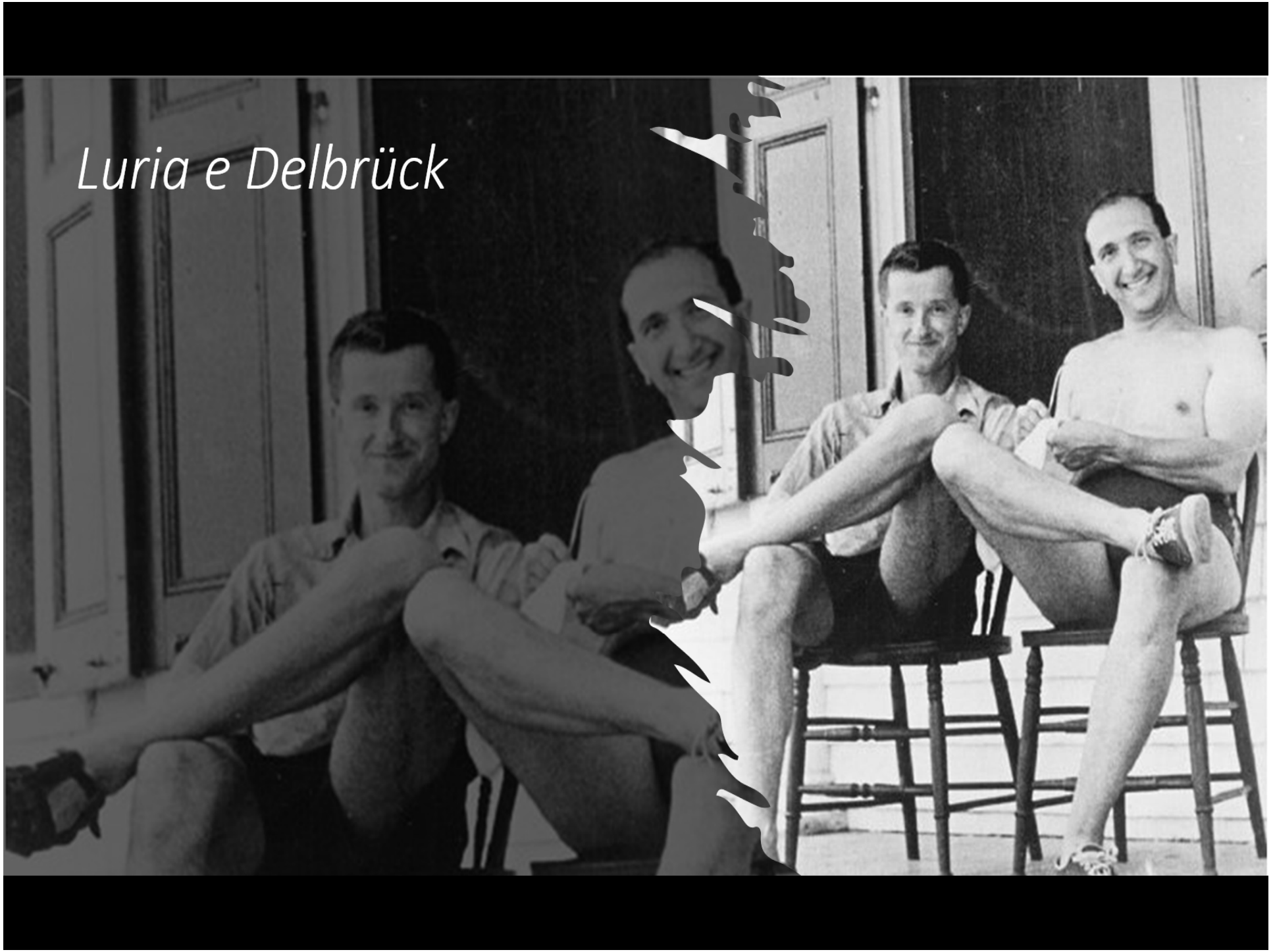


I BATTERIOFAGI E LO SVILUPPO DELLA BIOLOGIA MOLECOLARE


Luria e Delbrück


Harshey e Chase

Lwoff, Jacob e Monod


Hester Zimmer (in Lederberg)
Joshua Lederberg

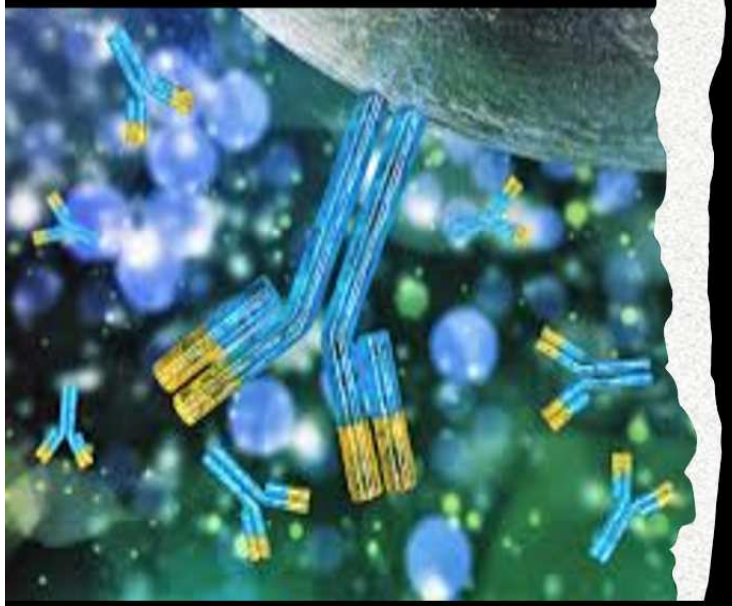
Esther Lederberg and Her Husband Were Both Trailblazing Scientists. Why Have More People Heard of Him?

Like many female scientists, Esther Lederberg saw her achievements overshadowed by a man's. Now there's a movement to tell their stories

By Katy Steinmetz

April 11, 2019 6:22 AM EDT

Esther Lederberg is standing on an ornate carpet in Stockholm, wearing a ruched gown and a rather serious expression. It's an unusual getup for the pioneering scientist, who more often wore a lab coat and a wry grin. But it is also an unusual night. The year is 1958, and Lederberg, 35 years old, has been invited to a tony ceremony in Sweden not as a bacterial geneticist but as a wife. Alongside other spouses, she will look on while three men—her first husband, her mentor and another



George Smith

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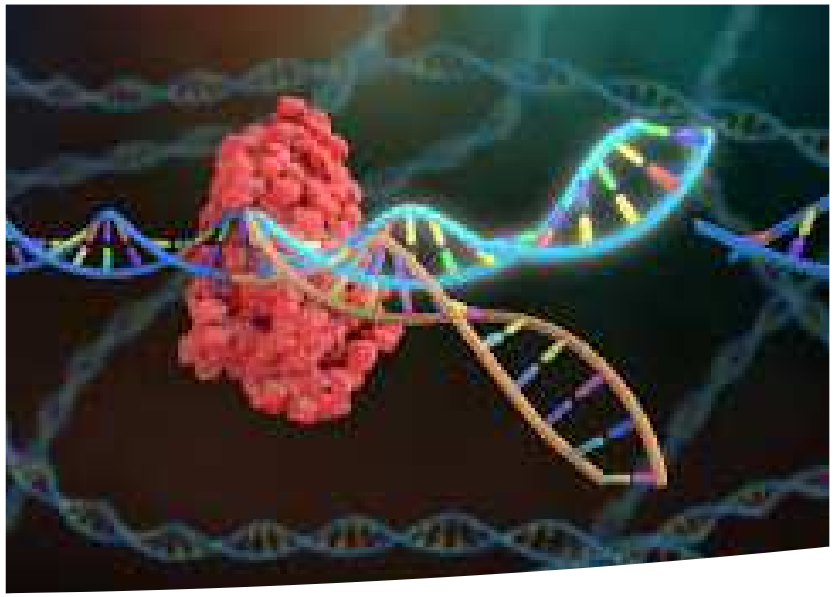

Charpenitier e Doudna e l'editing genetico
CRISPR-Cas

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IL REVIVAL DELLA FAGOTERAPIA

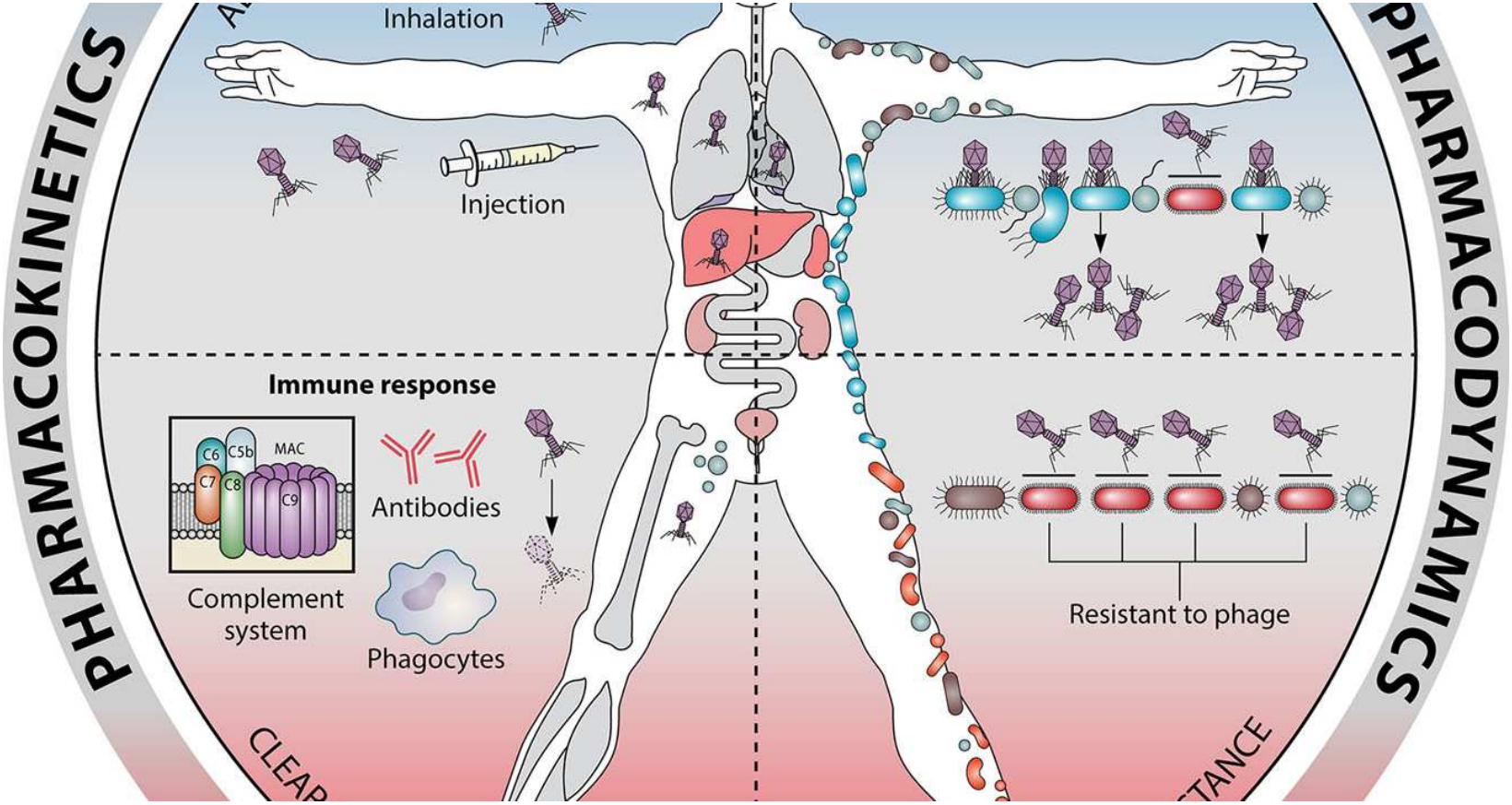

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TABLE 1 Advantages, disadvantages, and similarities of phage therapy compared to antibiotic therapy

Advantages	Similarities	Disadvantages
Specificity: does not kill the microbiota	Administration requires a neutralized-pH environment	Specificity: causative bacterium must be identified beforehand, narrow spectrum of action
Self-limitation: once the bacterial host is killed, it ceases to function	Therapeutic success depends on variables such as time of treatment initiation	Induction of phage-neutralizing antibody production (clinical relevance to be determined)
Available for patients with antibiotic allergies	Activity is influenced by the immune system of the patient	Significantly smaller body of evidence and correctly designed clinical trials supporting its effectiveness
Safety: no effects on mammalian cells	Versatility in routes of administration	Lack of a specific regulatory framework, and legal issues regarding intellectual property
Exponential reproduction allows for lower doses	Occurrence of bacterial resistance to the therapeutic agent	
Evolution: if resistance arises, phages mutate alongside bacteria		
Antibiofilm activity		
Simple and inexpensive to produce		
Ubiquity		

Down

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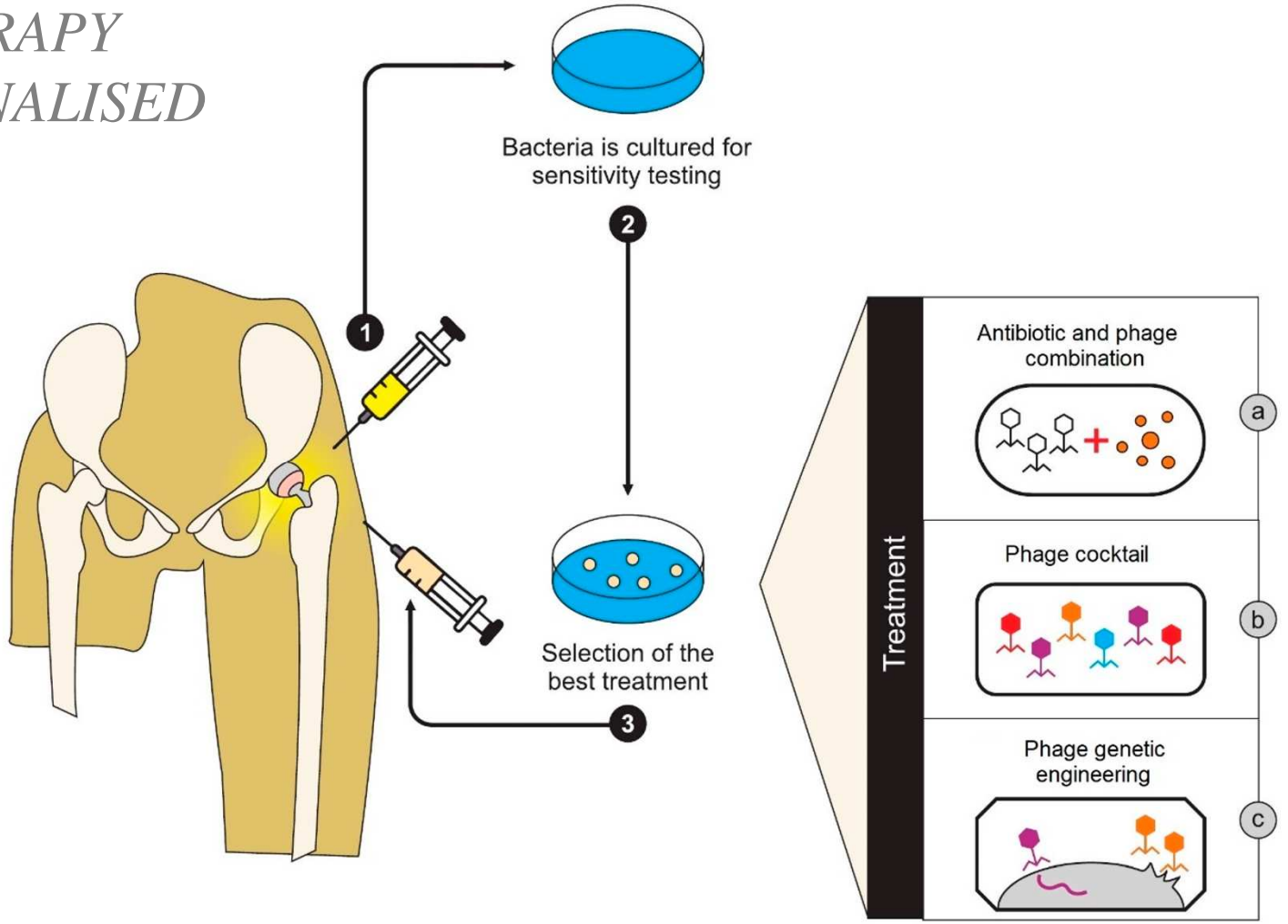
PHAGE THERAPY AND PERSONALISED MEDICINE



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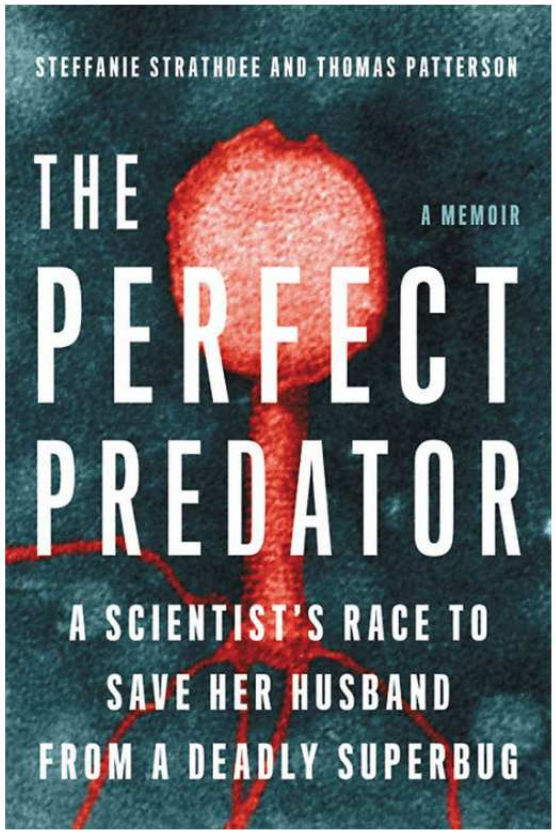

The Observer
Medical research

Steffanie Strathdee: 'Phages have evolved to become perfect predators of bacteria'

Zoë Corbyn

Sat 15 Jun 2019 16.00 BST

369 114

▲ Steffanie Strathdee and her husband, Thomas Patterson. His picture shows the superbug that nearly killed him; hers the phage that saved his life. Photograph: Courtesy of Steffanie Strathdee / UC San Diego Health

In 2015, the scientist's husband was almost killed by an antibiotic-resistant superbug, until she found a cure that is now saving others

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LA PRESSE ACTUALITÉS INTERNATIONAL DÉBATS AFFAIRES SPORTS AUTO ARTS CINÉMA SOCIÉTÉ GOURMAND VOYAGE

National Politique Grand Montréal Régional Justice et faits divers Santé Éducation Enquêtes Insolite Environnement

ELISABETH ZINGG
AGENCE FRANCE-PRESSE

Publié le 29 février 2016 à 10h47

Après 49 interventions et une infection nosocomiale résistante aux traitements qui ne lui laissait que l'amputation comme perspective, Christophe, qui a craint pour sa vie, a réussi à sauver sa jambe grâce à une méthode oubliée depuis l'avènement des antibiotiques: des virus mangeurs de bactéries.

Pour aboutir à ce résultat, le Français Christophe Novou, dit Picot, 47 ans, a dû se rendre en Géorgie, l'un des très rares pays de l'ex-bloc soviétique où la phagothérapie est encore proposée.

Depuis une quinzaine d'années, cette thérapie ancienne fait pourtant l'objet d'un regain d'intérêt dans des pays comme les États-Unis, la Belgique ou la France, parallèlement au développement de l'antibiorésistance, c'est-à-dire la résistance croissante des microbes aux antibiotiques, un défi à l'échelle de la planète.

En novembre dernier, l'Organisation mondiale de la santé (OMS) a averti que si rien

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Health | Coronavirus

Phage therapy: 'Viral cocktail saved my daughter's life'

By James Gallagher
Health and science correspondent, BBC News

8 May 2019

Isabelle Carnell-Holdaway is now 17 and learning to drive

Top Stories

France reverses stance on AstraZeneca vaccine
Older French patients can now get the jab, which had been initially limited to those aged under 65.
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US warned of 'potential fourth surge' of Covid-19
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Hundreds of kidnapped Nigerian schoolgirls freed
2 hours ago

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Eight-year-old becomes youngest pro Fortnite gamer

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LE SOIR+ Belgique Monde Économie Sports Culture Opinions

Première mondiale: un «bon» virus sauve un enfant greffé du foie

Un enfant greffé hépatique souffrant d'une infection résistante aux antibiotiques a été traité par phagothérapie intraveineuse pendant 85 jours aux Cliniques universitaires Saint-Luc à Bruxelles. C'est une première mondiale.

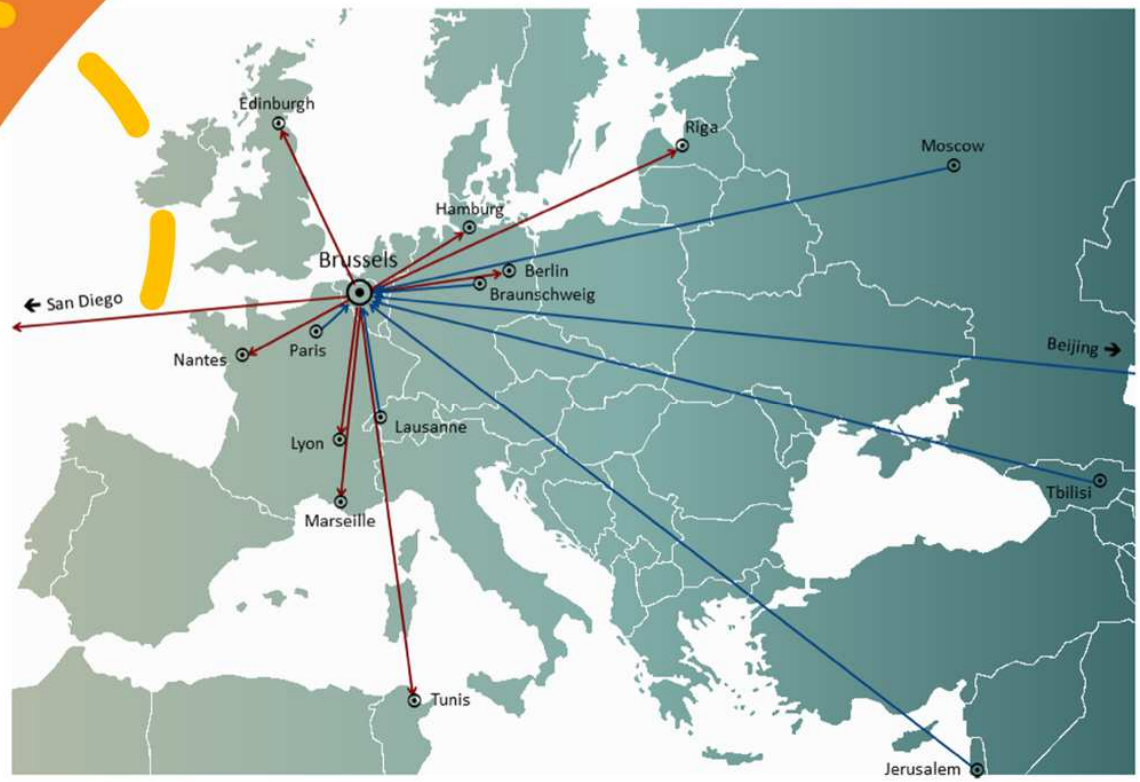

FIGURE 1 | International transfers of phages from (red arrows) and to (blue arrows) the Queen Astrid Military Hospital (QAMH) in Brussels in view of clinical applications over the period 2015–2020. On the national level, phages were dispatched from the QAMH to five university hospitals (not shown). In addition, the selection of matching phages often encompassed the transfer of the patients' bacterial isolates, and five international patients (two from France, two from the Netherlands, and one from Tunisia) were transferred to Brussels for phage therapy.

Clin Infect Dis. 2020 Jul 23;ciaa705. doi: 10.1093/cid/ciaa705. Online ahead of print.

Phage Therapy for Limb-threatening Prosthetic Knee Klebsiella pneumoniae Infection: Case Report and In Vitro Characterization of Anti-biofilm Activity

Edison J Cano [1 2], Katherine M Caflisch [2 3], Paul L Bollyky [4], Jonas D Van Belleghem [4], Robin Patel [1 2 5], Joseph Fackler [6], Michael J Brownstein [6], Bri'Anna Horne [6], Biswajit Biswas [7], Matthew Henry [7 8], Francisco Malagon [7], David G Lewallen [9], Gina A Suh [1]

Affiliations + expand

PMID: 32699879 DOI: 10.1093/cid/ciaa705

Abstract

Background: Prosthetic joint infection (PJI) is a potentially limb-threatening complication of total knee arthroplasty. Phage therapy is a promising strategy to manage such infections including those

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ATTIVITA' CLINICA PRESSO IL GEORGE ELIAVA INSTITUTE

Eliava Phage Therapy International Center

- **300+** Foreign patients were treated at the clinic (from France, Canada, USA, Romania, Norway, Denmark, China, Bulgaria, Italy, Germany, Austria, New Zealand, Switzerland, United Kingdom, Lebanon, Russia, Ecuador, Uruguay, Cameroon, India)
- Number of foreign patients doubled in 2016, tripled in 2017
- Several TV documentaries have been produced by media from various countries

2012-2018
9140 visits

Frequently occurring diseases in our clinic:

Urologic and Gynecologic Diseases	Prostatitis
	Urethritis
	Vaginitis
	Cystitis, other inflammatory diseases of the urinary tract
Surgical infections	Chronic wounds
	Diabetic foot ulcers
	Prosthetic associated infections
Internal Medicine, ENT and Pediatrics	Gastrointestinal tract diseases: antibiotic associated diarrhea, irritable bowel syndrome, small intestine bacterial overgrowth syndrome and infectious diarrhea
	Respiratory system diseases: sinusitis, otitis, tonsillitis, bronchitis, bronchiectasis, pneumonia
	Cystic fibrosis
	Skin and soft tissue diseases
Frequent Bacterial Pathogens	*Staphylococcus, E.coli, Enterococcus, Pseudomonas, Proteus, Enterobacter, Klebsiella,* MDR bacteria, nosocomial infections

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APPLICAZIONI IN AMBITO AGROZOOTECNICO

Review | Open Access | Published: 12 December 2019

Veterinary use of bacteriophage therapy in intensively-reared livestock

Adriano Gigante & Robert J Atterbury

Virology Journal **16**, Article number: 155 (2019) | Cite this article

Abstract

Zoonoses are infectious diseases transmitted directly or indirectly between animals and humans. Several important zoonotic pathogens colonize farm animals asymptomatically, which may lead to contamination of the food chain and public health hazards. Moreover, routine sampling of carcasses at retail by government authorities over the past 20 years suggests the prevalence of antibiotic resistance in foodborne pathogens has increased. If this continues, antibiotics may be ineffective against such pathogens in the future and alternative approaches, such as phage therapy, may be necessary. Intensive livestock farming is the only realistic way of meeting the demand for meat from an increasing global population and growth in middle class consumers in developing countries, particularly in Asia. This review elaborates on the use of phages to control zoonotic pathogens in intensively-reared

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Gastroenterology and Hepatology News

Richard Peek and K. Rajender Reddy, Section Editor

FDA Approves Use of Bacteriophages to be Added to Meat and Poultry Products

In the *Federal Register* of August 18, 2006, the US Food and Drug Administration (FDA) announced that it had approved the use of a bacteriophage preparation made from 6 individually purified phages (LMP-102) to be used on ready-to-eat (RTE) meat and poultry products as an antimicrobial agent against *Listeria monocytogenes*. The ruling came in response to a food additive petition submitted in 2002 from Intralytix, Inc. (Baltimore, MD), the biotech company that produces the bacteriophage.

This marks the first time the FDA has regulated the use of a phage preparation as a food additive. However, phages are currently approved in the United States for pesticide applications, including use on crops. Although not currently permitted in the United States, phages are used in other countries in antibiotic therapy regimens.

toxic components from the host organism are effectively removed from the final phage product. To ensure safety, the regulation specifies that the additive must test negative for *L monocytogenes*, and the *L monocytogenes* toxin, listeriolysn O, must not be present at detectable levels, where the limit of detection is 5 hemolytic units per milliliter.

The phage preparation will be used in meat and poultry processing plants for spray application to the surface of RTE meat and poultry products, such as lunch meats and hot dogs, to kill *Listeria*. "The phage preparation will be applied to the surface of RTE meat and poultry products at a level not to exceed 1 mL per 500 cm^2 food surface just prior to packaging. These foods can become contaminated with *Listeria* during production, but unlike fresh meat and poultry, these foods are consumed without additional cooking that would kill the bacteria, thereby increasing the risk to Listeriosis, an in-

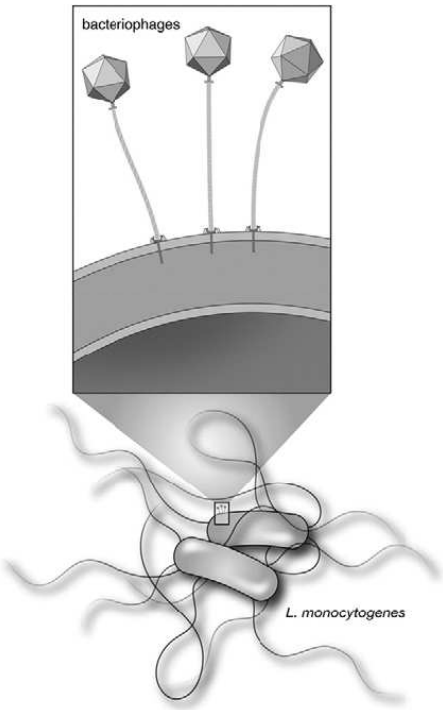

Figure 1. Bacteriophages.

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Phages for Food Safety: Regulatory Approvals

Date	Agency	Phage preparation	Target application
2006, August	FDA, 21 CFR 172.785	ListShield (LMP-102)	RTE meats
2006, October	FDA, GRN 198	Listex	cheese
2007, January	USDA, FSIS Directive 7120.1	*E. coli* O157:H7 targeted	hides of livestock
2007, March	USDA, FSIS Directive 7120.1	*Salmonella*-targeted	hides of livestock
2007, June	FDA, GRN 218	Listex	foods, generally
2008, July	USDA, FSIS Directive 7120.1	*Salmonella*-targeted	feathers of live poultry
2010, September	Health Canada	Listex	RTE meat, dairy, fish
2011, February	FDA, FCN 1018	EcoShield	ground beef
2012, August	FSANZ	Listex	meat, seafood, cheese, RTE foods
2013, February	FDA, GRN 435	SalmoFresh	poultry, fish, fruits, vegetables
2013, December	FDA, GRN 468	Salmonelex	pork and poultry
2014, August	Health Canada	SalmoFresh	poultry, fish, fruits, vegetables
2014, August	Israel Ministry of Health	SalmoFresh	poultry, fish, fruits, vegetables
2014, August	Israel Ministry of Health	ListShield	RTE meats
2014, August	Israel Ministry of Health	EcoShield	ground beef
2014, December	FDA, GRN 528	ListShield	fruits, vegetables, dairy, fish
2016, July	FDA, GRN 603	SalmoPro	poultry
2017, March	FDA, GRN 672	ShigaShield	RTE meat, fish, fruits, vegetables, dairy

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PHERECYDES PHARMA

PROJET D'INTRODUCTION EN BOURSE

À l'avant-garde du combat contre les infections bactériennes.

EN SAVOIR PLUS

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FIXED PHAGE

ABOUT US | APPLICATIONS | CASE STUDIES | INVESTORS | NEWS | CONTACT

- ANIMAL HEALTH
- HARVEST HEALTH
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- HUMAN HEALTH
- PROCESS HEALTH

ENABLING THE POTENTIAL OF PHAGE

https://www.fixed-phage.com/antibacterial-solutions/

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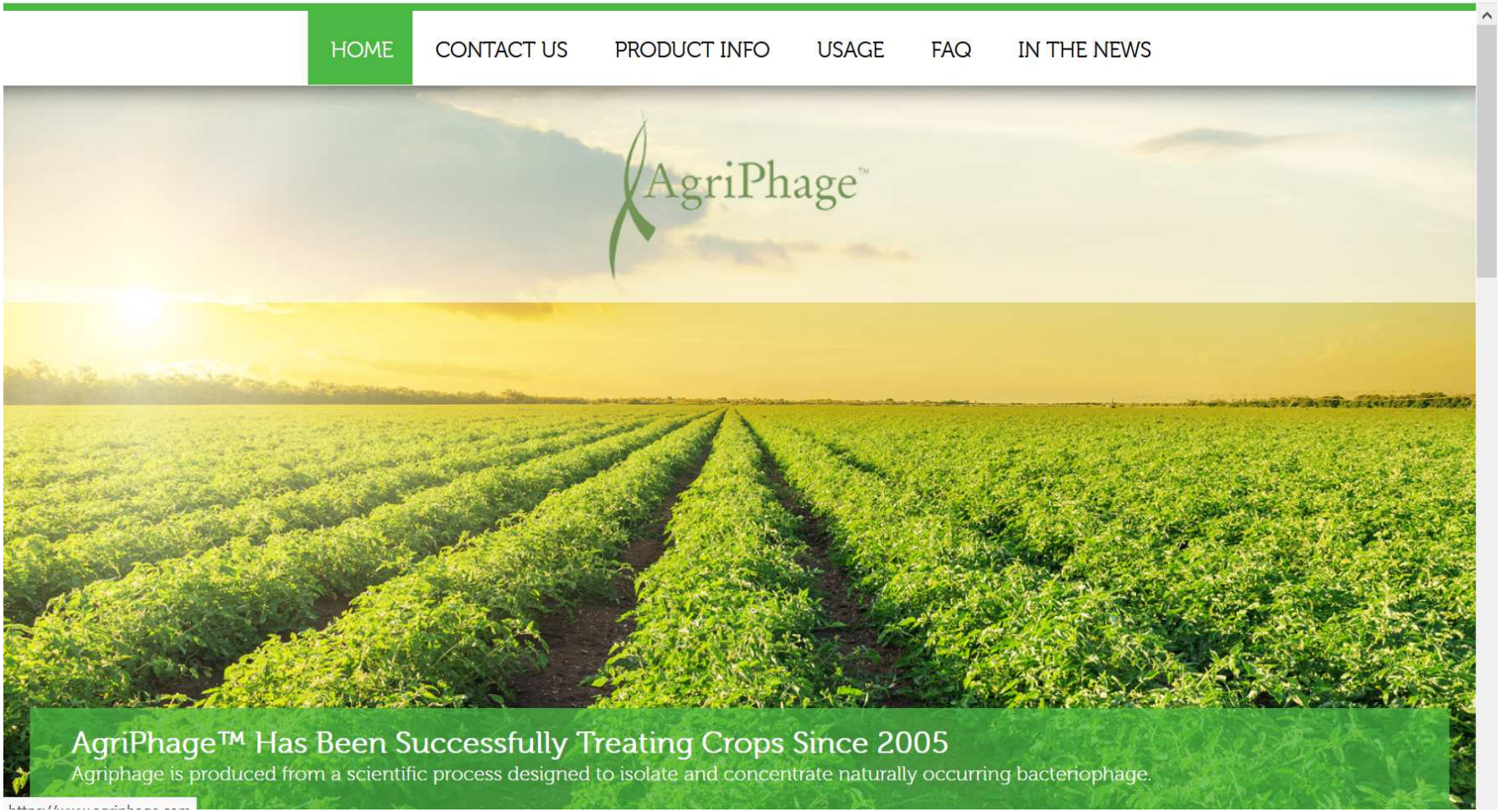

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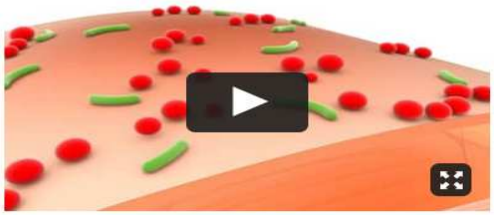
MICREOS FOOD SAFETY
MICREOS HUMAN HEALTH

Welcome to the world of Micreos...

Bacteria are all around us. Most of them are good and protect us, but some can cause irritation or infection. Antibiotics do not distinguish between good and bad bacteria and their use can lead to side effects and resistance. This renders them unsuitable for long-term use. As they have been broadly used - often inappropriately - the emergence of antibiotic-resistant 'superbugs' is now a global concern. On the other hand it has become evident that our microbiome, comprising billions of beneficial bacteria, is necessary for our health and should be left intact.

Micreos develops the world's first *targeted* antibacterial products, set to replace antibiotics. The company is viewed as global leader spearheading this exciting new field. With Micreos endolysin technology, for the first time we can kill only the *unwanted* bacteria - including antibiotic resistant strains - while preserving the *beneficial* bacteria, essential for our health. In addition, scientists do not expect emergence of resistance against endolysins, based on their working mechanism. **This unlocks a completely new approach in dealing with the bacteria around us - also enabling preventive daily therapy against only unwanted bacteria for as long as needed.**



Micreos' Staphefekt SA.100 is an enzyme (endolysin), which kills only *Staphylococcus aureus*, including MRSA. It is suitable for daily maintenance therapy, for inflammatory skin conditions such as eczema, rosacea, psoriasis and inflammatory acne and has already had a life changing impact for thousands of people. It is marketed under the Gladskin brand. For further background information on SA.100 fact sheets are available. Micreos next generation

Staphefekt

gladskin
bacterial skin balance

SALMONELEX

LISTEX

Micreos 'Alternative to antibiotics' chosen as Europes most relevant innovation 2018 at Finals Ideas from Europe, April 24 2018
Watch: Winning Pitch

October 29, 2020

L'Oréal signs license agreement with Dutch biotech Micreos, world leader in targeted bacterial biotechnology

PRESS RELEASE - FOR IMMEDIATE RELEASE

Clichy / The Hague, 29 October 2020 – L'Oréal and Micreos announced today the signature of a license agreement to join their expertise in biotechnology and the skin microbiome, the community of bacteria and microorganisms that live on the skin. Under the terms of the agreement, Micreos will give L'Oréal access to its endolysin, a type of active protein in the cosmetic field. With this technology, it is possible for the first time to target only unwanted bacteria in the skin flora - responsible for many skin problems - while sparing the good ones.

For 15 years, L'Oréal's Research & Innovation has been cooperating with scientific institutions and conducting clinical studies to better understand the role of the skin microbiome. "The agreement with Micreos opens up a very promising field in high-tech cosmetics", says Laurent Attal, Executive Vice-President Research & Innovation of L'Oréal.

Micreos develops new biological therapies based on phage and endolysin technology. Micreos CEO Mark Offerhaus: "We expect this partnership to be ground-breaking. L'Oréal has been a leader in skincare for decades. Micreos is at the forefront of targeted bacterial biotechnology. We pair our strengths and millions stand to benefit". Micreos' pharma development program includes endolysins that all target Staphylococcus bacteria, which cause or aggravate a broad range of health issues, including skin conditions.

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2020

LOréal signs license agreement with Dutch biotech Micreos, world leader in targeted bacterial biotechnology
PRESS RELEASE - FOR IMMEDIATE RELEASE Clichy / The

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HOME RESULTS PACKS RIVISTE RESEARCH*EU NOTIZIE ED EVENTI PROGETTI E RISULTATI A PROPOSITO DI NOI ACCEDI

HORIZON 2020

Know your enemy: systematic discovery of Salmonella anti-Phage Defences for the improved design of phage therapeutics

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HORIZON 2020

GMP manufacturing & GLP diagnostic: Towards a personalised phage therapy against antimicrobial resistance

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HORIZON 2020

Constructing a ‘Eubiosis Reinstatement Therapy’ for Asthma

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HORIZON 2020

An effective and environmentally friendly solution to control fire blight disease caused by Erwinia amylovora in pome fruit crops

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NORMATIVA

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@nmvi Oggi
L'informazione Veterinaria Online

PREVENZIONE

La Corte europea è favorevole ai fagi anti-Listeria

28 Ottobre 2019

In assenza di un quadro giuridico, la Corte di giustizia europea consente alle aziende alimentari l'uso dei fagi anti-Listeria su tutti i cibi pronti

Dopo la pronuncia della Corte di Giustizia Europea, il Parlamento europeo raccomanda alla Commissione europea di regolamentare, con urgenza, l'impiego dei fagi per la prevenzione della Listeria a beneficio del consumatore europeo. Casus belli: l'impiego di Listex™, prodotto dall'azienda di scienze della vita Micreos Food Safety, con sede a Wageningen (Paesi Bassi). Questa tecnologia- nata del 2006 negli USA e utilizzata in alcuni Paesi Nord Europei, non è mai stata regolamentata dall'Unione Europea (draft regulation qui). Ma ora l'avvallo della Corte del Lussemburgo impone un intervento legislativo.

Il fago anti-Listeria Listex™- I fagi (batteriofagi) che uccidono specificamente la Listeria possono essere usati durante la trasformazione agro-alimentare per prevenire la diffusione di questi batteri mortali nel cibo. Listex, prodotto dall'azienda di scienze della vita Micreos Food Safety, con sede a Wageningen, è

ATTUALITÀ

EV PALAZZO TRECCHI, STANGA: VALUTIAMO TEST RAPIDI

Per le attività di formazione delle "comunità a basso rischio" sono disponibili test antigenici rapidi. Il Direttore di EV: "Li stiamo considerando per i Veterinari non vaccinati". >>

APICOLTURA, AUMENTANO DURATA E

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WMA DECLARATION OF HELSINKI – ETHICAL PRINCIPLES FOR MEDICAL RESEARCH INVOLVING HUMAN SUBJECTS

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964
and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

9th July 2018

Policy Types

Declaration

Archived Versions

» DoH-Jun1964

» DoH-Oct1975

» DoH-Oct1983

» DoH-Sept1989

» DoH-Oct1996

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

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DIRETTIVA 2001/83/CE DEL PARLAMENTO EUROPEO E DEL CONSIGLIO

del 6 novembre 2001

recante un codice comunitario relativo ai medicinali per uso umano

Articolo 3

La presente direttiva non si applica a quanto segue:

1) ai medicinali preparati in farmacia in base ad una prescrizione medica destinata ad un determinato paziente (detti formula magistrale);

2) ai medicinali preparati in farmacia in base alle indicazioni di una farmacopea e destinato ad essere fornito direttamente ai pazienti che si servono in tale farmacia (detti formula officinale);

3) ai medicinali destinati agli esperimenti di ricerca e di sviluppo;

4) ai prodotti intermedi destinati ad ulteriore trasformazione da parte di un fabbricante autorizzato;

5) ai radionuclidi utilizzati in forma preconfezionata;

6) al sangue intero, al plasma né agli emoplasti di origine umana.

PHAGE ACTIVE PHARMACEUTICAL INGREDIENTS

DEFINITION

Phage active pharmaceutical ingredients (APIs) are pharmaceutical raw materials containing naturally occurring bacteriophages (phages in short), which are viruses that infect bacteria. Phages are composed of proteins that encapsulate a DNA or RNA genome, and may have relatively simple or elaborate structures. Phages replicate within a bacterium following the injection of their genome into its cytoplasm.

Phage APIs are intended for use as active ingredients of phage magistral preparations for *in vivo* treatment of bacterial infections (phage therapy).

Phage APIs are available as aqueous physiological solutions containing natural lytic phages (e.g., saline or glucose solutions) that may contain a buffer or as dried or freeze-dried powder. As active ingredients of magistral preparations, they are intended to be diluted or reconstituted and/or combined with the necessary excipients, in a hospital pharmacy officina, immediately before use on a named patient basis. Dosage forms may consist of capsules, creams, ointments, liquid preparation for oral use, cutaneous application, inhalation or parenteral administration, etc. The excipients needed to formulate these dosage forms must allow the required phage activity during the intended

***De novo* phage isolation.** Natural phages are generally isolated from environmental samples such as sewage and river water or from clinical samples. Usually, the sample, culture medium and phage sensitive host bacteria (typically 10^7-10^8 colony forming units (cfu)) are mixed in a sterile container and incubated under appropriate conditions (typically at 37°C for 1-3 h). If justified, a small volume of chloroform is added and the container is further incubated at 4°C for a short period of time (typically for 1 h). Host bacteria are removed using membrane filtration (0.2-0.5 µm) or by centrifugation. Usually, phages are isolated on bacteriophage sensitive bacteria following the 'double agar overlay method'. Phage lysate is mixed with lukewarm (typically 45°C) culture medium containing 0.5-1% agar and a suspension of bacteriophage sensitive host bacteria (typically 10^7-10^9 cfu/ml) in a sterile container. This mixture is transferred to a sterile cell culture container with culture medium containing 1-3% agar and incubated under appropriate conditions (typically at 37°C for 12-36 h). The resulting plaques ('clear' zones formed in a lawn of bacterial cells due to lysis by phages) with different morphology are transferred to sterile culture media in sterile containers and incubated under appropriate conditions (typically at 37°C for 1-3 h). If justified, a small volume of chloroform is added and the containers are further incubated at 4°C (typically for 1 h). For each container, a dilution series (typically log(0) - log(-8)) is made in sterile containers filled with culture medium. A part from each dilution is mixed with lukewarm

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viruses

MDPI

Communication

The Magistral Phage

Jean-Paul Pirnay [1,*], Gilbert Verbeken [1], Pieter-Jan Ceyssens [2], Isabelle Huys [3], Daniel De Vos [1], Charlotte Ameloot [4] and Alan Fauconnier [4,5]

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2 Bacterial Diseases, Unit Antibiotic Resistance, Scientific Institute of Public Health, Rue Engelandstraat 642, 1180 Brussel, Belgium; pieterjan.ceyssens@wiv-isp.be
3 Department of Pharmaceutical and Pharmacological Sciences, KU Leuven, O&N2, Herestraat 49, Box 521, 3000 Leuven, Belgium; isabelle.huys@pharm.kuleuven.be
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5 Culture In Vivo ASBL, rue du Progrès, 4, boîte 7, 1400 Nivelles, Belgium
* Correspondence: jean-paul.pirnay@mil.be; Tel.: +32-2-264-4844

Received: 15 January 2018; Accepted: 3 February 2018; Published: 6 February 2018

Abstract: Since time immemorial, phages—the viral parasites of bacteria—have been protecting Earth's biosphere against bacterial overgrowth. Today, phages could help address the antibiotic resistance crisis that affects all of society. The greatest hurdle to the introduction of phage therapy in Western medicine is the lack of an appropriate legal and regulatory framework. Belgium is now implementing a pragmatic phage therapy framework that centers on the magistral preparation (compounding pharmacy in the US) of tailor-made phage medicines.

Keywords: antibiotic; antimicrobial resistance; magistral preparation; compounding pharmacy; phage therapy; regulatory framework; personalized medicine

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REGOLAMENTO (UE) 2019/6 DEL PARLAMENTO EUROPEO E DEL CONSIGLIO

dell'11 dicembre 2018

relativo ai medicinali veterinari e che abroga la direttiva 2001/82/CE

Articolo 2

Ambito di applicazione

6. Oltre ai prodotti di cui al paragrafo 1 del presente articolo, il capo VII si applica anche a:

b) medicinali veterinari preparati in farmacia o da una persona autorizzata a tal fine dalla normativa nazionale, conformemente a una prescrizione veterinaria per un singolo animale o un piccolo gruppo di animali («formula magistrale»);

c) medicinali preparati in farmacia conformemente alle indicazioni di una farmacopea e destinati a essere forniti direttamente all'utilizzatore finale («formula officinale»). Tale formula officinale è soggetta a una prescrizione veterinaria nel caso di utilizzo in animali destinati alla produzione di alimenti.

Articolo 106

Impiego dei medicinali

1. I medicinali veterinari sono utilizzati conformemente ai termini dell'autorizzazione all'immissione in commercio.

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REGOLAMENTO (UE) 2019/6 DEL PARLAMENTO EUROPEO E DEL CONSIGLIO

dell'11 dicembre 2018

relativo ai medicinali veterinari e che abroga la direttiva 2001/82/CE

Articolo 113

Impiego non previsto dai termini dell'autorizzazione all'immissione in commercio in specie animali terrestri destinate alla produzione di alimenti

1. In deroga all'articolo 106, paragrafo 1, qualora non esistano medicinali veterinari autorizzati in uno Stato membro per un'indicazione riguardante una specie animale terrestre destinata alla produzione di alimenti, il veterinario responsabile può, sotto la sua diretta responsabilità personale e, in particolare, al fine di evitare sofferenze inaccettabili, trattare in via eccezionale l'animale in questione con il seguente medicinale:

a) un medicinale veterinario autorizzato nello Stato membro interessato o in un altro Stato membro ai sensi del presente regolamento, per l'impiego nella stessa specie o in un'altra specie animale terrestre destinata alla produzione di alimenti per la stessa indicazione o per un'altra indicazione;

b) in mancanza di un medicinale veterinario di cui alla lettera a) del presente paragrafo, un medicinale veterinario autorizzato nello Stato membro interessato, ai sensi del presente regolamento, in una specie animale non destinata alla produzione di alimenti per la stessa indicazione;

c) in mancanza di un medicinale veterinario di cui alle lettere a) o b) del presente paragrafo, un medicinale per uso umano autorizzato ai sensi della direttiva 2001/83/CE o al regolamento (CE) n. 726/2004; oppure

d) in mancanza di un medicinale di cui alle lettere a), b) o c) del presente paragrafo, un medicinale veterinario preparato estemporaneamente, conformemente ai termini di una prescrizione veterinaria.

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REGOLAMENTO (UE) 2019/6 DEL PARLAMENTO EUROPEO E DEL CONSIGLIO

dell'11 dicembre 2018

Articolo 114

Impiego di medicinali per specie acquatiche destinate alla produzione di alimenti

1. In deroga all'articolo 106, paragrafo 1, qualora non esistano medicinali veterinari autorizzati in uno Stato membro per un'indicazione riguardante una specie acquatica destinata alla produzione di alimenti, il veterinario responsabile può, sotto la sua diretta responsabilità personale e, in particolare, al fine di evitare sofferenze inaccettabili, trattare in via eccezionale gli animali in questione con i seguenti medicinali:

a) un medicinale veterinario autorizzato, ai sensi del presente regolamento, nello Stato membro coinvolto o in un altro Stato membro per l'impiego nella stessa o in un'altra specie acquatica destinata alla produzione di alimenti e per la stessa indicazione o per un'altra indicazione;

b) in mancanza di un medicinale veterinario di cui alla lettera a) del presente paragrafo, un medicinale veterinario autorizzato, ai sensi del presente regolamento, nello Stato membro interessato o in un altro Stato membro per l'impiego in una specie terrestre destinata alla produzione di alimenti e contenente una sostanza indicata nell'elenco stabilito ai sensi del paragrafo 3;

c) in mancanza di un medicinale veterinario di cui alle lettere a) o b) del presente paragrafo, un medicinale per uso umano autorizzato ai sensi della direttiva 2001/83/CE o del regolamento (CE) n. 726/2004 e contenente una sostanza indicata nell'elenco stabilito ai sensi del paragrafo 3 del presente articolo; oppure

d) in mancanza di un medicinale di cui alle lettere a), b) o c) del presente paragrafo, un medicinale veterinario preparato estemporaneamente, conformemente ai termini di una prescrizione veterinaria.

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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

10 October 2019
EMA/CVMP/461776/2017
Committee for Medicinal Products for Veterinary Use

CVMP Reflection paper on promoting the authorisation of alternatives to antimicrobials in the EU

Draft

Adopted by CVMP for release for consultation	10 October 2019
Start of public consultation	18 October 2019
End of consultation (deadline for comments)	30 April 2020

Gap	Activity No	Activity	Responsible *(and others involved)*	Timescale	Resource impact	Challenges, comments
		Regulatory requirements for bacteriophages	EMA CVMP	Short term	Initial reflection already on work programme for ADVENT	Similar regulatory and scientific challenges exist for authorisation of bacteriophages as human medicines. Need to consider if specific guidance for bacteriophage products, in line with the new Annex II of Regulation (EU) 2019/6, are required.
		Regulatory requirements for novel biologically active molecules that kill bacteria but are not classic pharmaceutical antibiotics (e.g. lysins, peptides, lysozymes and other enzymes), including requirement related to MRLs	EMA CVMP	Medium-long term	Would require including in the work programme of relevant CVMP WPs Relevant topic for ADVENT	ADVENT is working on this topic.

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LO STUDIO DELLA FAGOTERAPIA NELL'IZSLT

- *Sono stati sottoscritti 2 accordi di collaborazione (con IZSPLV e George ELIAVA Institute) in tema di «fagoterapia».*
- *Sono stati avviati 3 progetti di ricerca (due correnti ed un FEAMP) che prevedono la sperimentazione d della fagoterapia*

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frontiers in Microbiology

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Phage Therapy in the Year 2035

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The emergence of multidrug resistant bacteria in both community- and hospital-acquired infections is recognized as a major public health threat. Phage therapy is increasingly mediatized and researched as an additional tool for combatting antibiotic resistant infections. However, phages exhibit a number of properties that differ from antibiotics and hamper their development as pharmaceutical products and their application in therapy. This paper advocates a paradigm shift in the development and application of infectious disease therapeutics to cater for personalized phage therapy, which could be realized by the year 2035. More specifically, it presents a sustainable and ethical supply chain of instant synthetic phages, based on a community effort, supported and steered by public health organizations, and managed by a platform

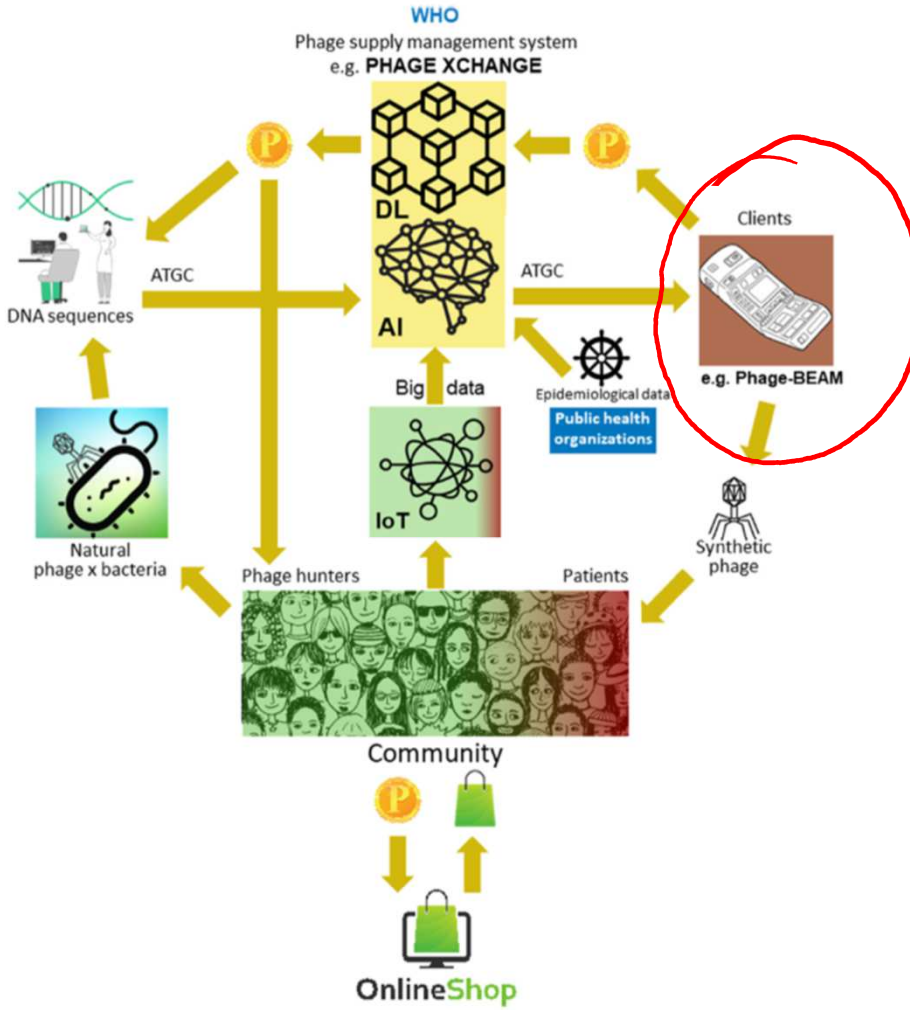

FIGURE 2 | Vision of how the phage supply chain might be organized in 2035. AI, artificial intelligence; ATGC, DNA sequence; BEAM, bedside energized anti-microbial; DL, distributed ledger; IoT, Internet of Things; P, PhageCoin; WHO, World Health Organization.

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