



Activity of Bacteriophages against Multidrug Resistant Bacteria

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Tbilisi, Georgia

Emerging Antibiotic-Resistance

- WHO: “Antibiotic resistance - increasingly serious threat to global public health that requires action across all government sectors and society”
- CDC: “Antibiotic resistance has been called one of the world’s most pressing public health problems”

Obama Administration Takes Actions to Combat Antibiotic-Resistant Bacteria | The White House

Posted on September 19, 2014 by jgill

Today, President Obama signed an Executive Order directing key Federal departments and agencies to take action to combat the rise of antibiotic-resistant bacteria. The Administration also released its *National Strategy on Combating Antibiotic-Resistant Bacteria*. In addition, the President's Council of Advisors on Science and Technology (PCAST) is releasing a related report on *Combating Antibiotic Resistance*. The Administration also announced a \$20 million prize, co-sponsored by the National Institutes of Health and the Biomedical Advanced Research and Development Authority, to facilitate the development of rapid, point-of-care diagnostic tests for healthcare providers to identify highly resistant bacterial infections.

TACKLING DRUG-RESISTANT INFECTIONS GLOBALLY: FINAL REPORT AND RECOMMENDATIONS

THE REVIEW ON ANTIMICROBIAL RESISTANCE

CHAired BY JIM O'NEILL

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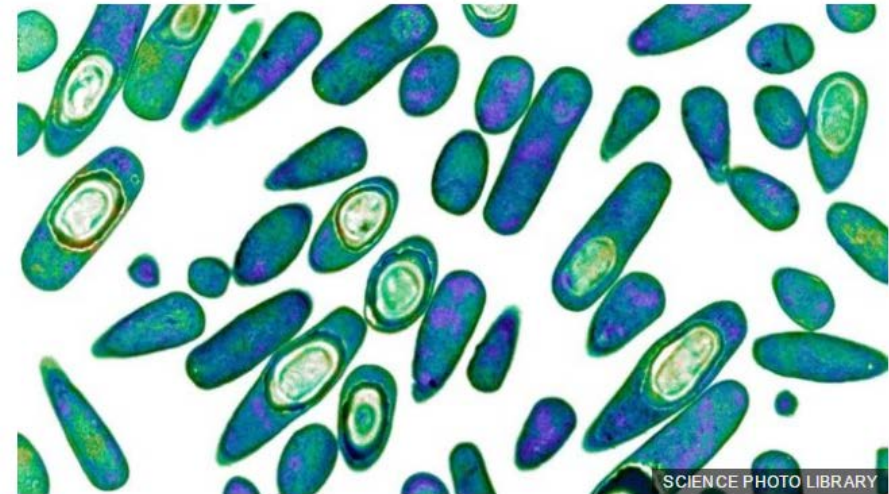
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Global antibiotics 'revolution' needed

19 May 2016 | Health



A global revolution in the use of antimicrobials is needed, according to a government backed report.

Lord Jim O'Neill, who led the **Review on Antimicrobial Resistance**, said a campaign was needed to stop people treating antibiotics like sweets.

Emerging Antibiotic-Resistance

- *If we fail to act, we are looking at an almost unthinkable scenario where antibiotics no longer work and we are cast back into the dark ages of medicine" – David Cameron, UK Prime Minister*
- *We have reached a critical point and must act now on a global scale to slow down antimicrobial resistance" – Professor Dame Sally Davies, UK Chief Medical Officer*

To Your Health

The superbug that doctors have been dreading just reached the U.S.

By **Lena H. Sun and Brady Dennis** May 27 at 7:22 AM



CRE, a family of bacteria pictured here, is considered one of the deadliest superbugs because it causes infections that are often resistant to most antibiotics. (Centers for Disease Control and Prevention/Reuters)



Most Read

- 1 The superbug that doctors have been dreading just reached the U.S.



Global Threat - Antimicrobial Resistance

In the **EUROPEAN UNION**,
antibiotic resistance
causes 25,000 deaths per year
and 2.5m extra hospital days¹



In **INDIA**, over 58,000 babies died
in one year as a result of infection
with resistant bacteria usually
passed on from their mothers²



In the **UNITED STATES**,
antibiotic resistance
causes 23,000+ deaths
per year and >2.0m illnesses⁴



Emerging Antibiotic-Resistance

Bacteria over time have mutated and developed a resistance to many or all antibiotics:

- Methicillin-Resistant *Staphylococcus aureus* (MRSA)
- Vancomycin-Resistant *Enterococcus* (VRE)
Clostridium difficile (C. diff)
- Extended-Spectrum Beta-Lactamase (ESBL)
- Carbapenamase-Producing *Enterobacteriaceae* (CPE)

Emerging Antibiotic-Resistance

US National Action Plan (March 27, 2015)

- Slow the Emergence of Resistant Bacteria and Prevent the Spread of Resistant Infections
- Strengthen National One-Health Surveillance Efforts to Combat Resistance
- Advance Development and Use of Rapid and Innovative Diagnostic Tests for Identification and Characterization of Resistant Bacteria
- **Accelerate Basic and Applied Research and Development for New Antibiotics, Other Therapeutics, and Vaccines**
- Improve International Collaboration and Capacities for Antibiotic-resistance Prevention, Surveillance, Control, and Antibiotic Research and Development

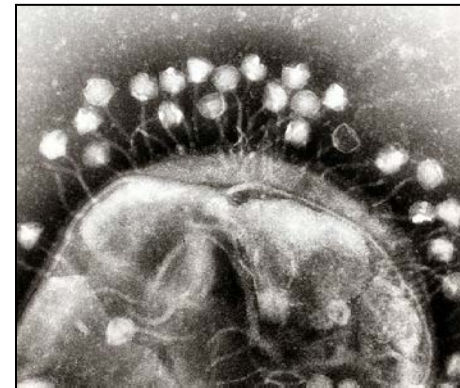
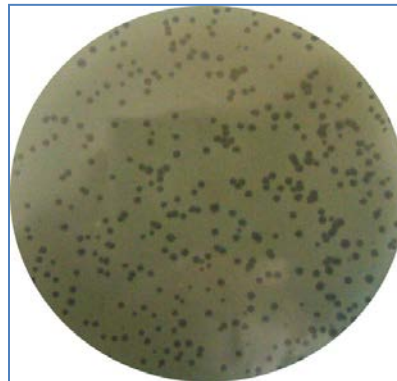
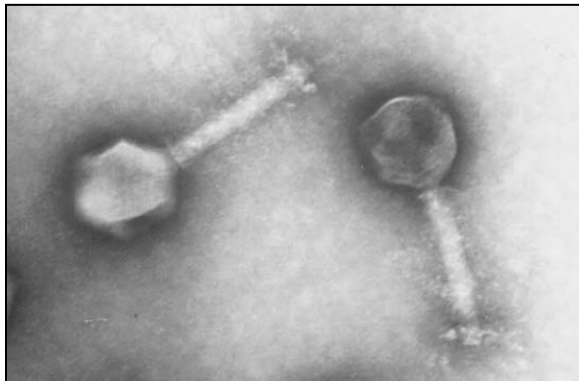
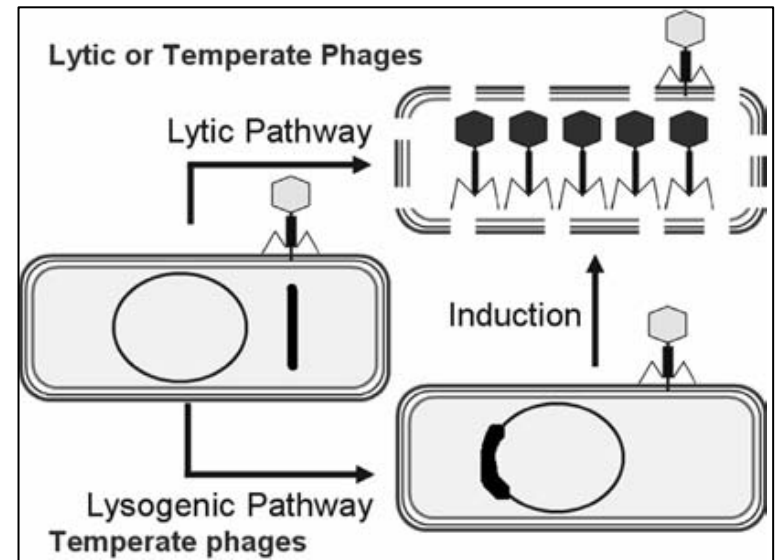
Bacteriophages: An introduction

What is a **Bacteriophage**?

Bacteriophage (phage) - a group of viruses that infect only bacteria, including pathogenic microorganisms

Phages are one of the most abundant microorganisms on earth

Bacteriophages are unique - they solely infect bacteria and are completely innocuous to human, animal, or plant cells



Overall comparison of bacteriophages and antibiotics: Ability to overcome resistant bacteria

- Antibiotics

- Antibiotics are unable to adapt to bacteria which has acquired resistance
- New classes of antibiotics must be elaborated, but eventually bacteria will become resistant to those antibiotics as well

- Bacteriophages

- Bacteriophages evolve alongside the bacteria due to the process by which they destroy the bacteria
- Bacteriophages can be either selected to adapt to resistant bacteria in the event of new bacterial strain
- Phage cocktails can be used to exclude appearance of resistance

Overall comparison of bacteriophages and antibiotics: side effects

- Antibiotics

- Wide range of adverse effects
- Elevated risk of allergic reaction
- Decline in efficacy as a result of increased resistance from bacteria
- Increased danger of side effects in immune-compromised patients

- Bacteriophages

- There have been no reported side effects on humans in over 90 years of treatments
- Bacteriophages are completely harmless to humans, animals or plants
- As a result, there is no danger of over dosage with Bacteriophages

Eliava Institute



- 1916 – Tiflis Pasteur station was transformed to the Central Bacteriological Laboratory
- 1918 – George Eliava became a director of CBL
- 1923 - Inst. Bacteriology has been established by G. Eliava on the base of CBL
- 1930, 1931 - Felix d'Herelle was working at the Institute in Tbilisi
- 1937 – G. Eliava was executed

Research at the Eliava Institute

Research of bacterial strains (including antibiotic-resistant strains) – causative agents of various infections in humans and animals

Creation of phage based remedies against bacterial infections (for humans, animals, plant protection, environmental decontamination)



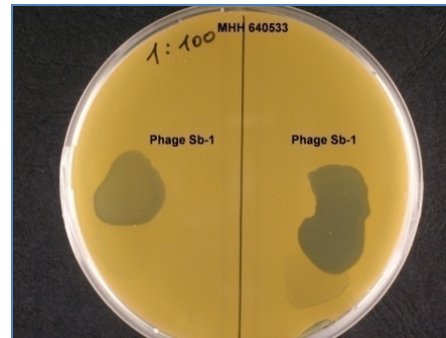
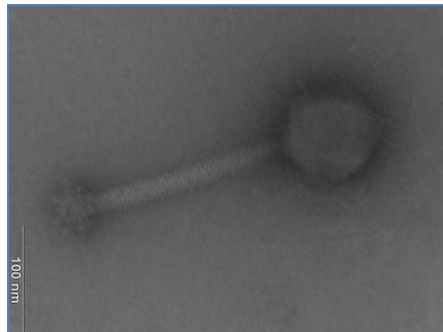
Staph phage against *S. aureus* (MRSA) strains

In vitro screening: 467 MRSA from the UK collection -98.5%

54 MRSA and 38 toxin-producing (not MRSA) from German Strain and Culture collection (**DSMZ**) – 99%

56 MRSA from NYU – 95%

100 MRSA from Royal College of Surgeon (Ireland) – 97%



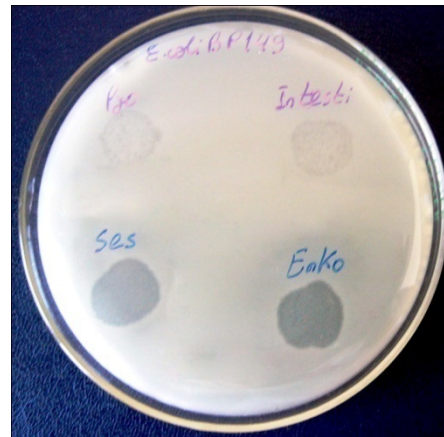
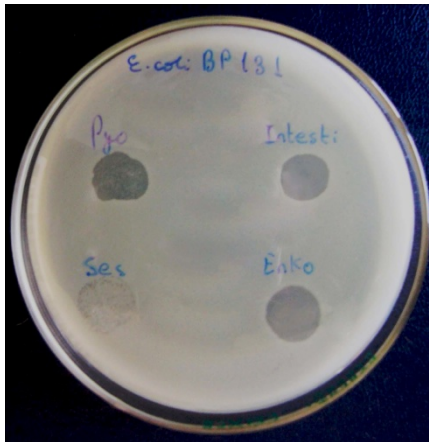
L. Kvachadze, N. Balarjishvili, T. Meskhi, E. Tevdoradze, N. Skhirtladze, T. Pataridze, R. Adamia, T. Topuria, E. Kutter, Ch. Rohde, M. Kutateladze Evaluation of lytic activity of Staphylococcal bacteriophage Sb-1 against freshly isolated clinical pathogens, **Microbial Biotechnology**, 2011, doi: 10.1111/j.1751-7915.2011.00259.x

Phages against β -lactamase-producing *E. coli* and *Klebsiella*

100 *E. coli* from Royal College of Surgeon (Ireland)

41 *E. coli* and 9 *Klebsiella* from Balgrist University Hospital
(Switzerland)

Pyophage, Intestiphage, SES, Encophage, lab phages were tested

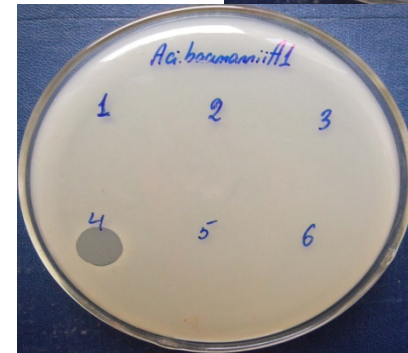


D. Hughes, D. Bolkvadze, et al, The susceptibility of extended beta-lactamase (ESBL)-producing *E. coli* to commercial and laboratory bacteriophages. **J. Antimicrobial Chemotherapy**, 2013, doi:10.1093/jac/dkt453

W. Sybesma, N. Chanishvili, M. Kutateladze et al, Bacteriophages as potential treatment for urinary tract infections. **Frontiers in Microbiology**, 2016, doi: 10.3389/fmicb.2016.00465

Phage against various pathogens

- 71 bacterial strains of *Acinetobacter baumannii* (from Vietnam, Iraq, Switzerland, Bulgaria, Germany, Turkey, China) – laboratory phages reveal **94%** of activity
- 63 *Enterococcus spp.* from Hong Kong:
84% - susceptible to the commercial phages
100% - susceptible to lab phages
- 123 strains of *Klebsiella spp.* (from Switzerland, China, Singapore)
93% activity of lab phages





Eliava Biopreparations

Pyo-Phage (*Staphylococcus, E. coli, Streptococcus, Pseudomonas, Proteus*)

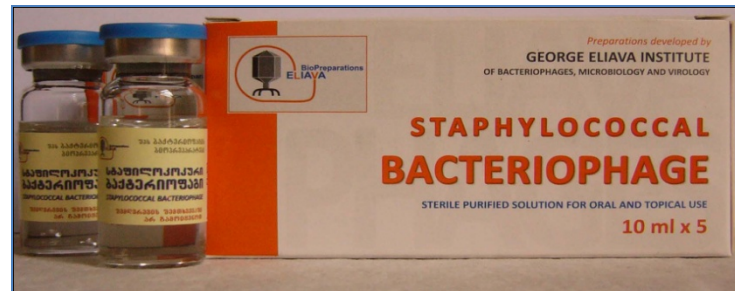
Intesti phage (*Shigella, Salmonella, entero-pathogenic E. coli Proteus, Enterococci, Staphylococci and Pseudomonas aeruginosa*)

Enkophage (*Salmonella spp., Shigella spp., entero-pathogenic E. coli, Staphylococcus spp.*)

SES phage (*Staphylococcus spp., Streptococcus spp., E. coli*)

Fersis (*Staphylococcus spp., Streptococcus spp.*)

Staphylococcal monophage





Eliava Phage Therapy International Center



Urologist
Gynecologist
Pediatrician
Infectious disease specialist
Therapist

Eliava Phage Therapy International Center

(2014-2016, April)

- **3422** visits for phage treatment
- Phage preparations were sent to **447** patients abroad
- **52** Foreign Patients were treated, (France, USA, Romania, Canada, Norway, Denmark, China, Bulgaria, Italy, Germany, Austria, New Zealand, Lebanon, Russia, Uruguay)
- **32** Foreign patients (treatment on distance)

Frequently occurring diseases in our clinic:

Urologic diseases	Prostatitis
	Urethritis
	Cystitis and other inflammatory diseases of the urinary tract
Gynecological Diseases	Vaginitis
	Colpitis
	Other inflammatory diseases
Internal medicine and Pediatrics	Gastrointestinal tract diseases: gastroduodenitis, enteritis, colitis, irritable bowel syndrome, and others that cause frequent diarrhea or constipation
	Respiratory system diseases: sinusitis, bronchitis, bronchiectasis
	Cystic fibrosis
	Skin and soft tissue diseases

Why Phage Therapy?

- Serious problems of antibiotic-resistance
- Phage therapy – **ecologically safe approach** (do not affect normal microflora)
- No resistance with multi-component phage preparation
- 90 years of successful experience of using phages for therapy, prophylaxis and diagnostics in FSU
- **No serious side effects** have been reported from the Eliava Institute phages, despite use in **hundreds of thousands of people since it was introduced**

Why Phage Therapy?

- **Phages are available and easy to apply** (different forms: tablets, in liquid, suppositories etc.)
- **Compatible with the other therapy** (other antibacterial remedy, vaccine, probiotics)
- **Stable preparations** (no cold storage and long shelf life)
- **Cost effective** (in comparison to antibiotics)

Clinical application

Case 1: Chronic infection

Patient: J.O. , Male 70 years old

Diagnosis - chronic gastroenterocolitis

Complaints: frequent diarrhea, bloating, abdominal pain in the lower half of epigastrium; diarrhea, with increased frequency of defecation (3-4 times per day)

Clinical investigations: confirmed gastritis, duodenitis, gastro and duodenogastral reflux and spastic colitis

Bacteriological analysis : *Klebsiella spp.* - 10^7 cfu/ml (No commercial phage available).

E. coli: 2×10^8 pfu/ml (hemolytic - 20%)

Susceptibility: SES and ENKO phages, autophage for *Klebsiella* prepared

Phage treatment: *Per os* for two weeks in combination with probiotics

Results: Repeat analysis revealed: complete eradication of pathogens, recovery in the normal microflora; Patient's subjective condition dramatically improved - bowel movements were normalized, no pain or bloating

Clinical application

Case 2: Chronic infection

Patient: M.SH., male, 39 years old (Germany), approached EPTC in 2015

Diagnosis - Maxilla sinusitis

Complaints: pain on face and forehead, pus excreta from nose, was diagnosed in 2004, last 5 years regular antibiotic-therapy and pain-killers

Bacteriological analysis: *Streptococcus mitis*, *Enterococcus durans*, *Staphylococcus aureus*

Susceptibility: FERSIS phage, Intesti phage

Phage treatment: *Per os* and local wash-out by phages for two weeks

Results: Patient's subjective condition dramatically improved, drastic decrease of excreta, no need in painkillers

Clinical application

Case 3: Chronic infection

Patient: V.B., 48 years, female, (France), approached EPTC in 2016

Diagnosis: Systemic scleroderma, bacterial infection of low part of left leg (stump)

Bacteriological testing: *Staphylococcus aureus*

Susceptibility: SES phage, Staphylococcal phage

Phage treatment: Phage application locally in liquid and ointment for 15 days



Clinical application

Case 4: Post operational infection

Patient: F.B., 58 years, female (US)

Diagnosis: Post operational wound infections, Pyoderma, Nasal furunculosis

Complaints: pain, swelling, redness around the wound and nostril

Bacteriological analyses: *S. aureus (MRSA)*, *E. coli*

Susceptibility: Staphylococcal phage, Fersis phage

Phage treatment: Phage applications locally

Result: after 15 days – complete granulations and epitalization of chronic wounds

Phage therapy gets revitalized

The rise of antibiotic resistance rekindles interest in a century-old virus treatment.

Sara Reardon

03 June 2014 | Corrected: 04 June 2014

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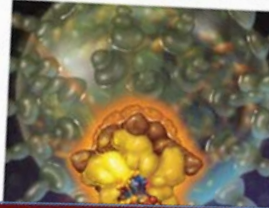
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Bacteriophage Boom?

Researchers are putting a fresh crop of phage-based products to agricultural and medical use, on farms and in early-stage clinical trials.

By Jyoti Madhusoodanan | September 29, 2014

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The search for alternatives to antibiotics has led many scientists to a treatment practice that's been on the fringes of modern medicine for nearly a century. Bacteriophages—viruses that infect and kill bacteria—were first used in 1919 to treat a wide range of infections.

Phage therapy fell out of favor with the advent of antibiotics; the practice has only persisted in some European countries as an experimental treatment. However, earlier this year, phage therapy was highlighted as one of seven approaches to "achieving a coordinated and nimble approach to antibiotic development."

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Antibiotic alternatives rev up bacterial arms race

From predatory microbes to toxic metals, nature is inspiring new ways to treat infections.

Sara Reardon

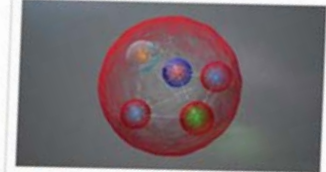
27 May 2015

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More than eight decades have passed since Alexander Fleming's discovery of a fungus that produced penicillin — a breakthrough that ultimately spawned today's multibillion-dollar antibiotics industry. Researchers are now looking to nature with renewed vigour for other ways of fighting infection.

Few new antibiotics are in development, and overuse of existing ones has created resistant strains

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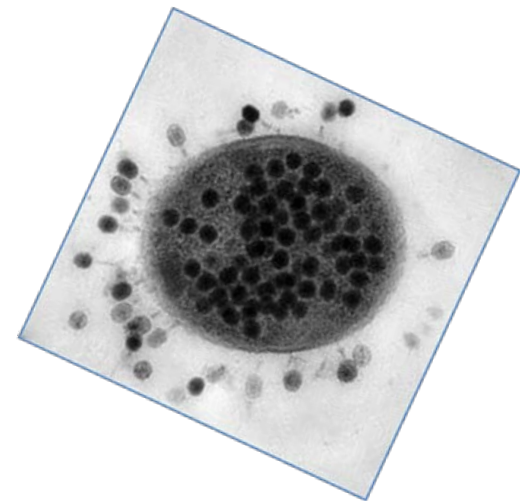
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Challenges



- Virus!!!!
- Lack of knowledge and understanding in Public
- Limited clinical trials performed according to the International standards
- Biological product – should be updated time by time
- Big pharma influence



THANK YOU

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