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ABSTRACT

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PROSPECTS AND PROBLEMS OF DEVELOPMENT, PRODUCTION, AND USE OF BACTERIOPHAGE-BASED MEDICINES

The objective of the study was to investigate the current state of bacteriophages in the fight against multidrug-resistant infections based on international and national scientific publications and to identify the main problems with the use of bacteriophage therapy in medical practice.

Methods: In our research, we used general theoretical methods: historical, documentary, analytical, generalization, comparison, systematization and analytical data processing

Results: The global medical community has been raising the issue of rational use of antibiotics for more than 30 years and is looking for new ways to combat multidrug-resistant (multidrug-resistant) infections. In particular, the WHO report for 2022 “The burden of bacterial antimicrobial resistance in the WHO European region in 2019: a cross-country systematic analysis” indicates that 541 thousand deaths in the European region were caused by multidrug-resistant infections. These fatal infections were caused by *Escherichia coli, Staphylococcus aureus, Klebsiella pneumoniae, Pseudomonas aeruginosa*, *Enterococcus faecium, Streptococcus pneumoniae* and *Acinetobacter baumannii* and their combinations with *S. aureus*. In Ukraine, the problem of multidrug-resistant infections is particularly relevant in connection with the Russian aggression, during which many militaries and civilians were injured. One of the most effective and promising ways to combat multidrug-resistant infectious diseases is the “forgotten” bacteriophage therapy. The interest of the medical community in bacteriophage therapy is evidenced by the large number of scientific publications on this topic. Thus, in 2009 it was about 2600 publications, and in 2024 their number increased to 20800. During this period, a large number of clinical trials were conducted to prove the efficacy and safety of phage therapy against various infectious agents; in Europe and the United States alone, this number reached more

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than 200 phase 1 and phase 2 clinical trials.

The world's largest research center is the Giorgi Eliava Institute of Bacteriophages, Microbiology, and Virology (Tbilisi, Georgia), which has been researching bacteriophages for more than 100 years. These studies have resulted in a number of medicines with bacteriophage "cocktails" that are successfully used to treat wounds from postoperative interventions, injuries and burns. Today, the technologies for treating bacterial infections developed in Georgia are used in medical institutions in Europe (Belgium, England, Germany, France), as well as in Israel and the United States.

Conclusions: Bacteriophage-based medicines are a promising area for the treatment of multidrug-resistant infectious diseases of various etiologies, and are currently used only as a last resort. WHO is collecting evidence on the effectiveness and safety of bacteriophages for the treatment of infectious diseases of various etiologies.

The main problem on the way to the development, clinical trials and introduction of bacteriophage-based medicines into medical practice is the international and national good regulatory practices (GLP, GCP, GMP, etc.) that all researchers and manufacturers of medicines must follow. Such regulatory requirements for drug development are not applicable to drugs containing bacteriophages, and therefore new requirements need to be developed or adapted to ensure that new drugs that can save thousands of lives are finally available.

Keywords: *infectious diseases, antibiotic resistance, phages, phage therapy, drug supply, availability of medicines, good regulatory practices*.

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ПЕРСПЕКТИВИ ТА ПРОБЛЕМИ РОЗРОБКИ, ВИРОБНИЦТВА ТА ЗАСТОСУВАННЯ ЛІКАРСЬКИХ ЗАСОБІВ НА ОСНОВІ БАКТЕРІОФАГІВ

Мета: на основі міжнародних та вітчизняних наукових публікацій дослідити сучасний стан застосування бактеріофагів у боротьбі з мультирезистентними до антибіотиків інфекціями та визначити основні проблеми щодо застосування бактеріофагової терапії у медичній практиці.

Методи: У своїх дослідженнях ми застосовували загально-теоретичні: історичний, методи документальний, аналітичний, узагальнення, порівняння, систематизації та аналітичної обробки даних

Результати: Світова медична спільнота вже більше 30 років піднімає питання раціонального застосування антибіотиків та шукає нові шляхи боротьби з стійкими до дії багатьох антибіотиків (мультирезистентними) інфекціями. Зокрема у звіті ВООЗ за 2022 рік «The burden of bacterial antimicrobial resistance in the WHO European region in 2019: a cross-country systematic analysis» вказується, що 541 тисячі смертей у Європейському регіоні, були спричинені мультирезистентними інфекціями. Причиною цих смертельних інфекцій були *Escherichia coli, Staphylococcus aureus, Klebsiella pneumoniae, Pseudomonas aeruginosa*, *Enterococcus faecium, Streptococcus pneumoniae* і *Acinetobacter baumannii* та їх комбінації із золотистим стафілококом (*S. aureus*). В Україні

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проблема мультирезистентних інфекцій особливо актуальна у зв'язку з російською агресією, під час якої багато військових та цивільних громадян зазнали різних поранень. Одним із ефективних та перспективних напрямків боротьби з мультирезистентними інфекційними захворюваннями є «забута» терапія бактеріофагами. Про зацікавленість медичної спільноти бактеріофаговою терапією свідчать велика кількість наукових публікацій за цією темою. Так, у 2009 році це було близько 2600 публікацій, а у 2024 році їх кількість зросли до 20800. За цей період було проведено велику кількість клінічних досліджень для доведення ефективності та безпеки фагової терапії по боротьбі з різними збудниками інфекцій; тільки у Європі та США ця кількість сягнула більш ніж 200 клінічних досліджень 1 та 2 фаз.

Найбільшим світовим науковим центром є Інститут бактеріофагії, мікробіології та вірусології імені Георгія Еліави (Тбілісі, Грузія), у якому більше 100 років не переставали досліджувати бактеріофаги. Результатом цих досліджень є низка лікарських засобів з бактеріофаговими «коктейлями», які успішно застосовуються для лікування ран від післяопераційного втручання, травм та опіків. На сьогодні технології лікування бактеріальних інфекцій, напрацьовані у Грузії, використовуються у лікувальних закладах Європи (Бельгія, Англія, Німеччина, Франція), а також Ізраїлю та США.

Висновки: Лікарські засоби на основі бактеріофагів є перспективним напрямком для лікування мультирезистентних до антибіотиків інфекційних захворювань різної етіології. На сьогодні вони застосовуються тільки як останній спосіб порятунку хворого. ВООЗ збирає доказову базу щодо ефективності та безпеки застосування бактеріофагів для лікування інфекційних захворювань різної етіології.

Основною проблемою на шляху до розробки, клінічних досліджень та впровадження у медичну практику ліків на основі бактеріофагів є міжнародна та національні належні регуляторні практики (GLP, GCP, GMP та ін.), якими повинні керуватися усі дослідники та виробники лікарських засобів. Такі регуляторні вимоги до створення лікарських засобів не можуть бути застосовані до ліків, що містять бактеріофаги, і тому потрібно розробити нові або адаптувати існуючі вимоги для того, щоб нарешті з'явились нові ліки, які зможуть врятувати тисячі життів.

Ключові слова: *інфекційні захворювання, антибіотикорезистентність, фаги, фаготерапія, забезпечення лікарськими засобами, доступність ліків, належні регуляторні практики.*

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INTRODUCTION

The WHO report for 2022 "The burden of bacterial antimicrobial resistance in the WHO European region in 2019: a cross-country systematic analysis", which analyzed the causes of 541 thousand deaths in the European region, indicates that these deaths were caused by antibiotic-resistant infections. Most people died from circulatory system infections (195 thousand), intra-abdominal infections led to the deaths of 127 thousand people, and 120 thousand people died from respiratory infections. The main causative agents of these deadly infections were *Escherichia coli, Staphylococcus aureus, Klebsiella pneumoniae, Pseudomonas aeruginosa*, *Enterococcus faecium,*

Streptococcus pneumoniae, and *Acinetobacter baumannii*, as well as their combinations with *Staphylococcus aureus* [5]. The "Roadmap on antimicrobial resistance for the WHO European Region 2023–2030" (RC73) developed by the WHO calls on European countries to join forces to combat the new pandemic of antibiotic-resistant infections, primarily through the introduction of national strategies for rational antibiotic therapy and the search for new ways to combat infectious diseases. In Ukraine, this is especially relevant in connection with the Russian aggression, during which many soldiers and civilians were injured and often acquired multidrug-resistant infections during evacuation through several medical facilities. One of the most effective and promising ways to combat multidrug-resistant infectious diseases is the “forgotten” bacteriophage therapy, which was first used in the 1930s to treat infectious diseases by the French microbiologist and bacteriophage discoverer Felix d'Erell (1873–1949) and recognized as unpromising at that time due to the penicillin industrial production [1].

Objective: To investigate the current state and directions of the fight against multidrug-resistant infectious diseases, to analyze international publications on the prospects and problems of treatment with phage preparations.

Research methods: information search, analysis, comparative analysis, marketing analysis, graphical, systematization and generalization.

Objects of research: foreign and domestic publications on the stated topic; regulatory documents governing the development, production, and circulation of medicines containing phages.

RESULTS

The research of British microbiologist Alexander Fleming in 1928 marked the beginning of the era of antibiotics. Although penicillin was used as a medicine only during the Second World War, it gave rise to the creation of other antibacterial preparations. In the ten years from 1940 to 1950, streptomycin, erythromycin, vancomycin, chloramphenicol, and many other drugs appeared. Scientific articles were filled with headlines that "humanity has overcome infectious diseases" which were the main cause of death at that time, but a few years later doctors began to talk about resistance – the chronology of antibiotic resistance development is shown in Table 1. Pneumococci "fought" penicillin for more than 20 years, Staphylococcus aureus "overcame" it in 4 years [2], and modern Staphylococci needed 1 year to cope with linezolid and ceftaroline. Table 1 shows the periods from the release of an antibiotic into medical practice and the emergence of information about resistance to it in certain bacteria [3–5].

Table 1 – **Development chronology of antibiotic resistance to some bacteria**

No.	Medicine	Year of antibiotic introduction into medical practice	Year of antibiotic resistance detection	Bacterium*
1	Penicillin	1943	1965	*R. Pneumococci spp.*
2	Tetracycline	1950	1959	*R. Shigella spp.*
3	Erythromycin	1953	1968	*R. Streptococcus spp.*
4	Methicillin	1960	1962	*R. Staphylococcus spp.*
5	Gentamicin	1967	1979	*R. Enterococcus spp.*
6	Vancomycin	1972	1988	*R. Enterococcus spp.*
			2002	*R. Staphylococcus spp.*
7	Imipenem	1985	1998	*R. Enterobacteriaceae spp.*
8	Ceftazidime	1985	1987	*R. Enterobacteriaceae spp.*
9	Levofloxacin	1996	1996	*R. Pneumococci spp.*
10	Linezolid	2000	2001	*R. Staphylococcus spp.*
11	Daptomycin	2003	2004	*PDR* Acinetobacter spp.*
14	Ceftaroline	2010	2011	*R. Staphylococcus spp.*

*Note: *R (resistant) – resistance; PDR (pandrugresistant) – multiresistance*

This rapid adaptability of infectious bacteria to antibiotics has led to a significant slowdown in the development of new effective antibiotics: over the past 30 years, only 2 new classes of antibiotics have been developed to combat gram-negative bacteria: cyclic lipopeptides and oxazolidinones [6].

The website of the Center for Public Health of Ukraine also contains a lot of information on the careful

and rational use of antibiotics. One of the warnings indicates that if antibiotics stop working, 3 out of 10 cases of pneumonia will be fatal; out of 1000 women in labor, 5 will not survive the delivery; and only 25% of tuberculosis patients will have a chance to live [7].

The introduction of new methods of treatment of infectious diseases is very important in Ukraine, especially during the war, when doctors are faced with a large number of wounded soldiers and civilians who, during evacuation from the wounding area, "collect" a whole collection of antibiotic-resistant bacteria. Therefore, infectious diseases often cause severe complications and death of the wounded, so improving the treatment of infectious diseases to prevent complications and death of our military and civilian compatriots is very important today. Hospital-acquired (nosocomial) infections include diseases of an infectious nature that affect a patient during a hospital stay or after a visit to a medical facility for diagnosis or treatment. About 20% of hospital-acquired infections are multidrug-resistant. The risk of infection in hospitals in developing countries ranges from 12% to 40% [8]. This is a problem that haunts hospitals around the world, taking lives of patients and complicating the treatment process.

According to the WHO [9], the list of pathogens of hospital-acquired infections includes the following:

- *Acinetobacter baumannii*
- *Enterobacteriaceae*
- *Mycobacterium tuberculosis*
- *Salmonella typhi*
- *Shigella spp.*
- *Enterococcus faecium*
- *Pseudomonas aeruginosa*
- *Neisseria gonorrhoea*
- *Staphylococcus aureus*.

The above information shows that antibiotic resistance is a global challenge today. Fig. 1 shows the statistics of detection of bacteria with multiple antibiotic resistance in patients from Ukraine and European countries [10].

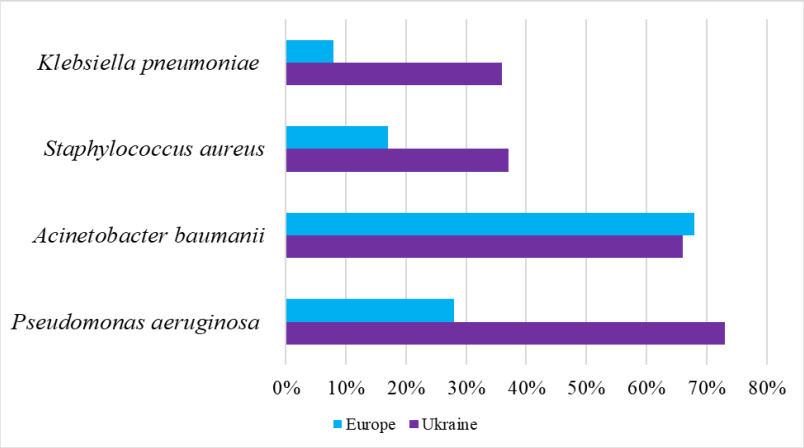


Fig. 1. Statistics on antibiotic resistance of the most common pathogens [10]
Note: statistics are based on trials with the most effective antibiotics for each strain

Bacteriophages are viruses that selectively infect certain types of bacteria and archaea; they multiply only in these bacteria, breaking them down and leaving the "good bacteria" unharmed, unlike antibiotics. Bacteriophages, derived from the terms "bacterium" and the Greek "φάγος" (meaning "eater" or "glutton"), are bacterial viruses capable of dissolving microorganisms. The cycle of bacteriophage reproduction at the expense of a bacterium is shown in Fig. 2.

To date, microbiologists have identified 13 families, more than 140 genera, and over 5300 species of bacteriophages. They are obligate intracellular parasites of bacteria, so the name of the host bacterium is included in the nomenclature of phages (dysentery, diphtheria, staphylococcal, salmonellosis, etc.). The modern classification of bacteriophages is based on their virion structure. Each virion contains a capsid (protective shell) and nucleic acid. Most bacteriophages, known as tailed bacteriophages, have an icosahedral head and a spiral tail whose ends have the ability to attach to specific molecules on the surface of the target cell. The head contains genomic DNA, and the tail serves as a channel for infection of the host cell. In some cases, the tail may be short or even absent.

In terms of shape, bacteriophages can be filamentous, spherical, or even sperm-like. In terms of size, they can be small, medium, or large. Typically, the size of a phage particle is between 20 and 200 nm, the diameter of the head is on average 60–100 nm, and the length of the process can be between 100 and 200 nm.

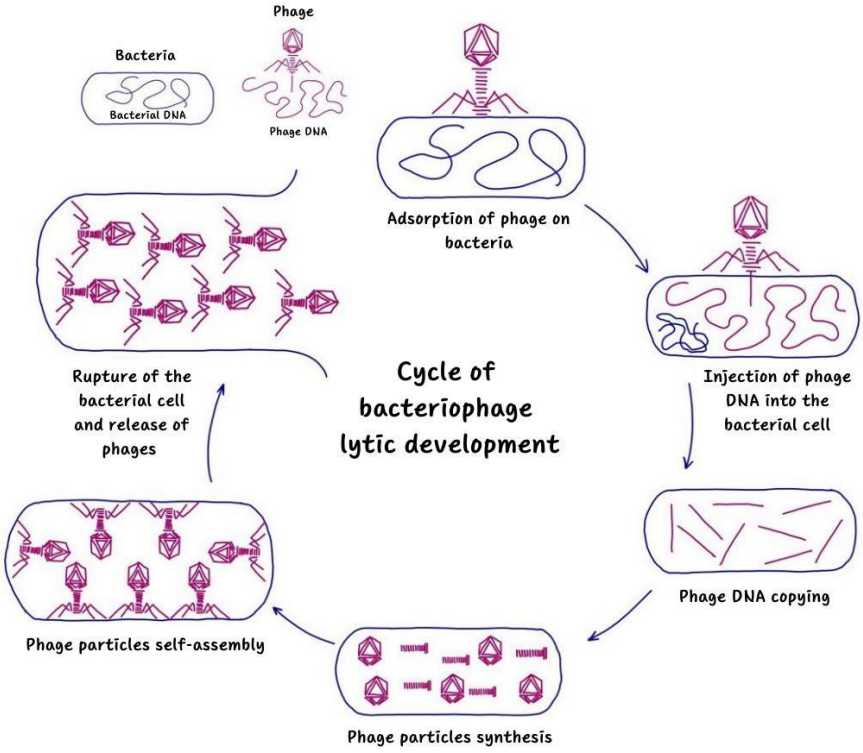


Fig. 2. Scheme of the process of lytic reproduction of bacteriophages

Most bacteriophages have double-stranded genomic DNA, but some may have single-stranded DNA or even double- and single-stranded RNA (Table 2).

The basis for the effectiveness of phage therapy is the determination of sensitivity of the particular pathogen to phage (Table 3), so it is mandatory to determine the sensitivity of a staphylococcus isolated from a particular patient to the staphylococcal bacteriophage. The phages are injected directly into the site of infection, which determines the dose and route of administration (topically, compresses, tampons, injections, orally, rectally etc.); the duration of the treatment course can be from 5 to 15 days, and repeated, if necessary, in 7–14 days. The most

Table 2 – **Bacteriophages classification**

Family	Morphology	Nucleic acid
Myoviridae	Non-enveloped contractile tail	Linear dsDNA
Siphoviridae	Long non-enveloped non-contractile tail	Linear dsDNA
Podoviridae	Short non-enveloped non-contractile tail	Linear dsDNA
Tectiviridae	Non-enveloped isometric shape	Linear dsDNA
Corticoviridae	Non-enveloped isometric shape	Cyclic dsDNA
Lipothrixviridae	Enveloped rod shape	Linear dsDNA
Plasmaviridae	Enveloped pleomorphic shape	Cyclic dsDNA
Rudiviridae	Enveloped rod shape	Linear dsDNA
Fuselloviridae	Non-enveloped lemon shape	Cyclic dsDNA
Inoviridae	Non-enveloped filamentous shape	Linear ssDNA
Microviridae	Non-enveloped isometric shape	Cyclic ssDNA
Leviviridae	Non-enveloped isometric shape	Linear ssDNA
Cystoviridae	Enveloped spheric shape	Segmented dsDNA

Table 3 – **Bacteriophages advantages**

Characteristics	Phages preparations	Antibiotics
Specificity	Highly specific – only target bacteria are affected	A wide range of bacteria, including normal flora, are affected
Allergic reactions / Individual intolerance	Not recorded	Observed in 12% of patients
Use for preventive purposes	Possible, no negative consequences	Numerous negative consequences are caused
Distribution throughout the body	Concentrate in the infection focus	Spread throughout the body
Risk of resistance development	Minimal risk when using combination medicines	High risk
Impact on enzyme systems of the body	Not recorded	Significant impact
Compatibility with other medicines	Fully compatible	Restrictions exist
Effectiveness against biofilms	Effective	The vast majority are not effective

reasonable use of bacteriophages is observed in cases where the infection is caused by antibiotic-resistant strains. Combination therapy of bacteriophages with antibiotics can be used. To date, there are no contraindications to the use of phage medicines. Modern research continues to reveal the potential of phages as a primary and complementary therapy in the treatment of antibiotic-resistant infectious diseases.

The WHO European Office (WHO/Europe), together with the Global Antimicrobial Resistance Research and Development (R&D) Fund, conducts research and collects evidence on the practical use of phages in the treatment of antimicrobial-resistant diseases [11].

Bassoon therapy began to gain popularity at a frantic pace. Fig. 3 shows the growth of interest of the scientific community, which is expressed in the number of published articles in different periods of time [12].

Fig. 4 shows a map with countries that use phage therapy and/or are studying the possibility of using bacteriophages in medicine.

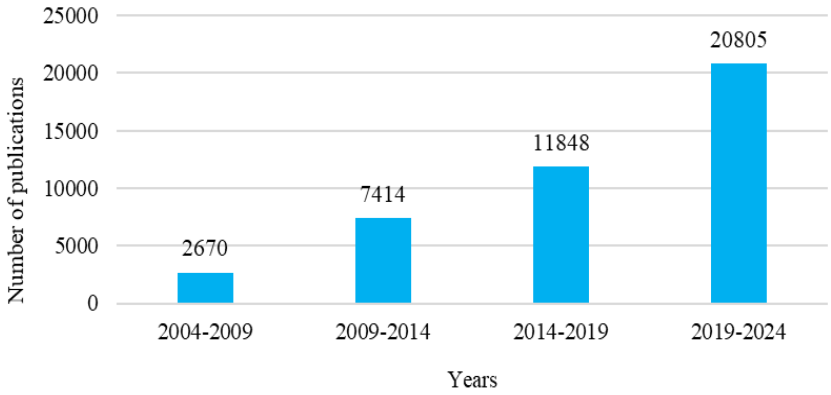


Fig. 3. Statistical data of publications of studies on the use of phages in medical practice [12]

Another evidence that confirms the interest and spread of the phage therapy idea is the 85 active clinical trials. Table 4 shows some of the clinical trials that have been conducted recently and have proven the efficacy and safety of bacteriophage-based medicines [13].

The world's leading scientific institution for the research and practical application of bacteriophages today is the Giorgi Eliava Institute of Bacteriophagy, Microbiology and Virology (Tbilisi, Georgia), which has one of the world's largest funds of therapeutic bacteriophages. The history of this scientific institution began in 1923 when Georgian bacteriologist Giorgi Eliava, a student of the "father" of phages Felix d'Erell, established a bacteriological institute where they began to study phages and to use them to fight infectious diseases, which laid the foundation for phage therapy. Felix d'Erell also planned to move to Georgia, but it did not come true – in 1937, Georgy and his wife were shot as "enemies of the people" [14].

Fig. 4. Countries studying or using phage therapy

Table 4 – **List of clinical trials on the use of bacteriophages**

Title	Country	Start date	Status	Patients number	Phase
Therapy with bacteriophage TR-102 for diabetic foot ulcers	Israel	22.03.2021	Completed 05.09.2022	20	1,2
Research on bassoon therapy for cystic fibrosis at Yale University	USA	29.03.2021	Completed 22.06.2023	8	1,2
A study evaluating the safety and tolerability of inhaled AP-PA02 in subjects with chronic lung infections caused by *Pseudomonas aeruginosa* and cystic fibrosis	USA	22.12.2020	Completed 14.12.2022	29	1,2
Safety, tolerability, and pharmacokinetics of LBP-EC01 in patients with *E. coli* lower urinary tract colonization	USA	30.12.2019	Completed 19.11.2020	36	1
Bacteriophages for the treatment of urinary tract infections in patients undergoing transurethral resection of the prostate	Georgia	02.06.2017	Completed 14.12.2018	97	2,3
Clinical trial to demonstrate safety and efficacy of DUOFAG®	Czech Republic	27.10.2023	Search for participants	52	1,2
A study to evaluate the safety, phage kinetics, and efficacy of inhaled AP-PA02 in subjects with non-cystic fibrosis of bronchiectasis and chronic pulmonary infection caused by *Pseudomonas aeruginosa*	USA	10.01.2023	Search for participants	60	2
Phagotherapy for prosthetic joint infections caused by *Staphylococcus aureus* treated with DAIR	France	16.06.2022	Search for participants	64	2
Bacteriophage treatment of tonsillitis	Uzbekistan	02.10.2020	Active	128	3

Today, the Institute continues its active scientific and medical work as the Eliava Consortium, an association of the Georg Eliava Institute of Bacteriophages, Microbiology and Virology and the Eliava Foundation, which includes the following subsidiaries [15]:

- Eliava Diagnostic Center is a diagnostic center that performs bacterial, virological, immunological, serological, biochemical, molecular and clinical tests.

- Eliava Phage Therapy Center is one of the few centers in the world dedicated to phage therapy. It provides assistance in the fields of pediatrics, urology, gynecology, otolaryngology, dermatology and offers outpatient surgical consultations based on bacteriophages in the treatment strategy.

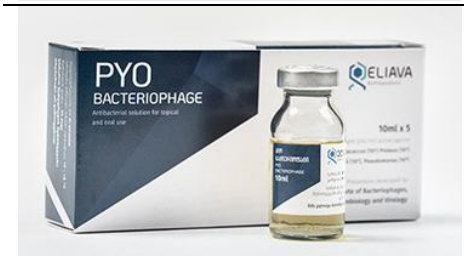
- Eliava Biopreparations is a company that produces phage-based finished pharmaceuticals and extemporaneous medicines for individual therapy.

- Eliava Authorized Pharmacy is an authorized pharmacy that has the right to sell bacteriophage-containing products.

These companies have 6 products sold in authorized multipurpose pharmacies, which allows the use of one phage cocktail to treat infections caused by different pathogens. Table 5 shows the list of drugs and their composition.

Today, the WHO is actively collecting evidence on the use of bacteriophages. Below are the cases of therapy using ready-made cocktails based on bacteriophages and extemporaneously produced with the selection of the most effective phage for a particular patient.

Table 5 – **Combined phage-containing preparations produced by Eliava Biopreparations [16]**

Photo of the product	Name and composition of the product
	Bacteriophages for: *Staphylococcus* (*S. aureus, S. epidermidis*), *Streptococcus* (*S. pyogenes, S. sanguis, S. agalactiae*) Excipients: nutrient medium, NaCl solution (0.9%), quinazoline as a preservative.
	Bacteriophages for: *Staphylococcus aureus, Streptococcus spp., E. coli, Pseudomonas aeruginosa, Proteus spp.* Excipients: nutrient medium, NaCl solution (0.9%), quinazoline as a preservative.
	Bacteriophages for: *Shigella, Salmonella, E. coli, Proteus, Staphylococcus, Pseudomonas aeruginosa, Enterococcus.* Excipients: nutrient medium, NaCl solution (0.9%), quinazoline as a preservative.
	Bacteriophages for: *Shigella, Salmonella, E. coli, Staphylococcus*. Excipients: nutrient medium, NaCl solution (0.9%), quinazoline as a preservative.
	Bacteriophages for: *Staphylococcus aureus.* Excipients: nutrient medium, NaCl solution (0.9%), quinazoline as a preservative.
	Bacteriophages for: *Staphylococcus, Streptococcus, E. coli.* Excipients: nutrient medium, NaCl solution (0.9%), quinazoline as a preservative.

Case 1: The patient is a 68-year-old man. He has a wound on the anterior surface of the left thigh after skin grafting. The area from which the skin was removed did not heal due to infection, despite antibiotic treatment. Testing revealed *Pseudomonas aeruginosa*. The antibiotic susceptibility of the isolated strain showed multiresistance. Testing the sensitivity of the isolated bacteria to commercial preparations containing bacteriophages (bacteriophage PIO and bacteriophage INTESTI) gave a positive result. PIO bacteriophage and INTESTI bacteriophage were prescribed. It was recommended to use both phage cocktails orally (10 ml once a day), and PIO bacteriophage also topically (10 ml of PIO bacteriophage was applied to sterile gauze, which was applied to the wound, once a day). The course of treatment lasted 20 days, followed by a 14-day break and another 20 days of treatment. After the initial treatment, the tissue began to regenerate, the redness of the skin subsided, and granulation tissue was formed (Fig. 5). Antibiotics in combination with phage therapy were not used [17].

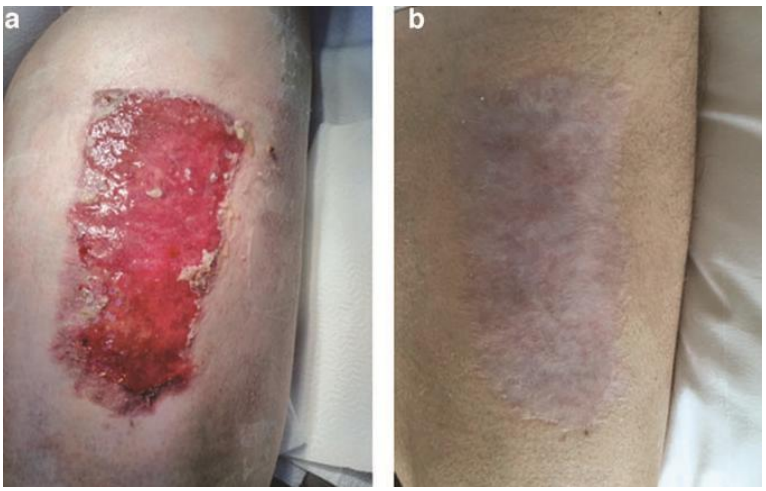


Fig. 5. Photos of the wound before (a) and after treatment (b) [17]

Case 2: The patient is a 56-year-old man. He developed nodular lesions on his left arm, as well as weight loss, night sweats, and fatigue. Comorbidities included stage II chronic kidney disease, myxomatous mitral valve prolapse requiring mitral valve repair, and seronegative arthritis affecting the hands, wrists, knees, and ankles diagnosed in 2019, as well as peripheral neuropathy of unknown etiology which was concurrent with arthritis. Testing revealed multiresistant *Mycobacterium chelonae*. An *ex tempora* drug containing an individually selected bacteriophage was prescribed and administered intravenously. The course of treatment was 6 weeks in combination with antibiotics. After the use of the phage, side effects were observed.

The patient reported diarrhea after each dose, but noted no fever, chills, respiratory, gastrointestinal, or neurologic symptoms. He remained hemodynamically stable with stable laboratory values. During phage therapy, specific antibodies to phages were detected in the blood, but this did not interfere with treatment. After 6 weeks, the symptoms of infection disappeared (Fig. 6) [18].

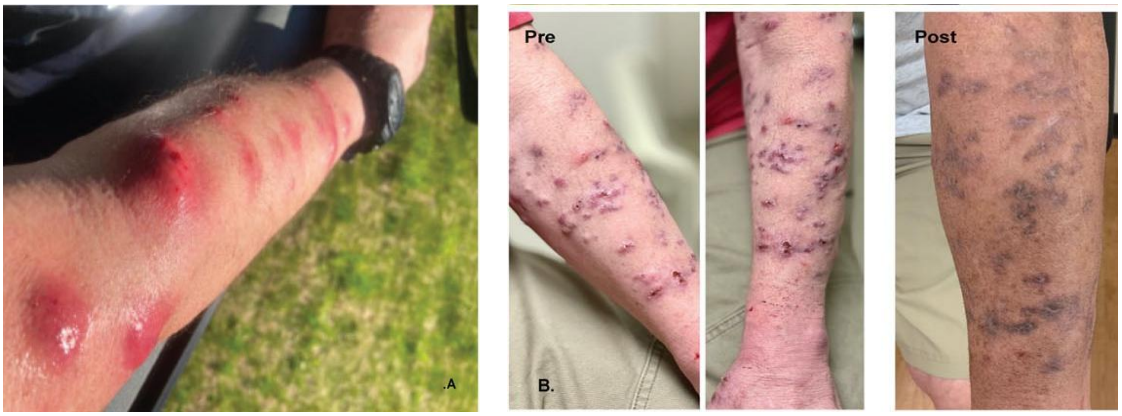


Fig. 6. A – wound before phage therapy, B – wound after phage therapy [18]

Case 3: The patient is a 68-year-old man. He developed necrotizing pancreatitis complicated by a pseudocyst of the pancreas, which was infected with multiresistant *Acinetobacter baumannii* during treatment. Antibiotic susceptibility testing revealed that the isolated *Acinetobacter baumannii* bacterium was resistant to all available antibiotics, and no synergy tests yielded positive results. It was decided to start treatment with individually selected bacteriophage-containing medicines; the list, as well as the method of administration and duration of treatment, are given in Tables 6 and 7, respectively. The treatment lasted 257 days, but the patient made a full recovery [19].

Table 6 – **List of bacteriophage preparations**

Phage	Source of isolation	Family
AB-Navy1	Waste waters	Myoviridae
AB-Navy4	Waste waters	Myoviridae
AB-Navy71	Waste waters	Myoviridae
AB-Navy97	Waste waters	Myoviridae
AbTP3F1	Waste waters	Podoviridae
AC4	Environment	Myoviridae
C1P12	Environment	Myoviridae
C2P21	Environment	Myoviridae
C2P24	Environment	Myoviridae

Table 7 – **Method of administration and duration of treatment with bacteriophage preparations**

Phage cocktail	Cocktail composition	Method of administration	Duration of treatment	Dosage
FPC	AC4, C1P12, C2P21, C2P24	Intracavitary	18 weeks, starting from day 109	N/A
FIV	AB-Navy1, AB-Navy4, AB-Navy71, AB-Navy97	Intravenous	16 weeks, starting from day 111	5×10^9 PFU
FIVB	AB-Navy71, AbTP3F1	Intravenous	2 weeks starting from day 221	5×10^9 PFU

Current state of the bacteriophage market in Ukraine

Today, according to the State Register of Medicines of Ukraine [20], two medicines in the form of phage "cocktails" are registered in Ukraine acting on several pathogens of the most common infectious diseases (see Table 8).

In today's environment, when the antibiotic resistance problem is becoming increasingly relevant, phage therapy can be an effective alternative or complement to traditional treatments. Bacteriophages have a narrow spectrum of action, which allows targeting specific pathogens without affecting the beneficial microflora of the body. This makes their use safer and minimizes the risk of developing dysbiosis.

In addition, bacteriophages can be used not only to treat but also to prevent infections. For example, they can be used in dentistry for the comprehensive treatment and prevention of oral infections, stomatitis, periodontal disease and other diseases, to reduce the number of pathogenic bacteria in the mouth. This is especially important in pediatric practice when the use of antibiotics can lead to severe adverse reactions. The effectiveness of the use of medicines in the form of gels containing phages for the treatment of chronic catarrhal gingivitis, hypertrophic gingivitis, and chronic periodontitis in adults has been proven. Bacteriophages in liposomal membranes can be components not only of therapeutic gels and ointments but also of toothpastes and can be used to prevent many oral diseases [21]. In combination with other safety and hygiene measures, phages can help to significantly reduce the level of bacterial contamination and thus prevent outbreaks of infectious diseases.

Regulatory issues in the use of bacteriophages

The main requirements for medicines are efficacy, safety, and quality. These basic requirements are ensured by a number of good pharmaceutical practices: preclinical studies – by Good Laboratory Practice (GLP), clinical studies – by Good Clinical Practice (GCP), manufacturing – by Good Manufacturing Practice (GMP), quality and safety control when the medicinal product is already on the pharmaceutical market – by Good Pharmacovigilance Practice (GPP).The entire complex of good regulatory practices in the world is regulated by international guidelines, directives, recommendations. In Ukraine it is implemented by a number of regulatory documents, including the Laws of Ukraine, Resolutions of the Cabinet of Ministers of Ukraine, Orders of the Ministry of Health of Ukraine etc. The introduction of such a pool of documents into the country's regulatory framework allows us to be sure that high-quality, effective and safe medicines are used in medical practice. The authors took part in international conferences on the phages use in medical practice in Tbilisi (Georgia) and Lyon (France), where almost all speakers voiced regulatory issues related to this group

Table 8 – **Medicinal products based on bacteriophages registered in Ukraine**

Authorization No. and EXP	Name	Composition	Manufacturer
UA/15974/01/01/ unrestricted from 11.01.2022	PYOPHAGE® BACTERIOPHAGE POLYVALENT solution; 10 ml in a glass vial; 4 vials in a contoured cell pack	1 ml of the preparation contains specific bacteriophages in concentration at least 1×10^5 phage particles for the following types of microorganisms: *Streptococcus pyogenes, Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa, Proteus vulgaris, Proteus mirabilis*	PHARMEX GROUP LLC, Ukraine, for NEO PROBIO CARE INC., Canada (all stages of production; batch production), Ukraine/Canada Private Joint Stock Company “Infusion”, Ukraine, for NEO PROBIO CARE INC., Canada (all stages of production, secondary packaging, control, batch release), Ukraine/Canada LLC “NEOPROBIOCARE-UKRAINE” (production of the series), Ukraine
UA/15970/01/01/ unrestricted from 16.05.2022	INTEGIFAG® BACTERIOPHAGE POLYVALENT solution; 10 ml in a vial; 4 vials in a contour cell pack; 1 contour cell pack	1 ml of the preparation contains specific bacteriophages in concentration at least 1×10^5 phage particles for the following types of microorganisms: Shigella flexneri, *Shigella sonnei, Salmonella enterica, Escherichia coli, Proteus vulgaris, Proteus mirabilis, Enterococcus faecalis, Staphylococcus aureus, Pseudomonas aeruginosa*	PHARMEX GROUP LLC, Ukraine, for NEO PROBIO CARE INC., Canada (all stages of production; batch production), Ukraine/Canada Private Joint Stock Company “Infusion”, Ukraine, for NEO PROBIO CARE INC., Canada (all stages of production, secondary packaging, control, batch release), Ukraine/Canada LLC “NEOPROBIOCARE-UKRAINE” (production of the series), Ukraine

of medicines. The development, clinical trials, and industrial production of medicines containing phages require a separate approach to prove efficacy, safety, and quality for many reasons, including the following:

1. "Sewage substance" – the largest number of phages is found in sewage, and the selection of effective and safe phages for a specific patient or group requires separate regulation.
2. Should we give preference to phage "cocktails" or mono-preparations in the development?
3. Over time, bacteria "get adapted" to a particular phage; how often should the phage "strain" be updated? Is it necessary to conduct clinical trials again in this case? Is it enough to determine the sensitivity to bacteria in their culture?
4. Is it possible to update only one type of phages in a "cocktail", or is it needed to update them all?
5. When to start phage treatment? (Today, in many countries, this treatment is used too late "compassionate use").
6. What are the main indicators of phage therapy effectiveness? Will traditional pharmacodynamics and pharmacokinetics be useful for characterizing phage preparations?
7. The "efficacy" indicators used for vaccines (increase in the number of antibodies to a particular infection) are also not suitable for phage preparations, because phages do not contribute to the emergence of antibodies to the infection.

This is far not a complete list of problems voiced by conference participants. These problems need to be addressed today, as doctors see significant potential and benefits from the use of this medical technology being forgotten for almost 100 years.

CONCLUSIONS

Although phage therapy originated in the "pre-antibiotic" period, for many years it was forgotten and not used for human treatment. Today, it is of great interest to researchers, doctors, and pharmaceutical manufacturers. In the former Soviet Union, thanks to Georgian bacteriologists, phage-based medicines were researched and developed to treat dysbiosis in children and adults, treat oral infections and postoperative infections. Today, the WHO, international professional associations of surgeons, traumatologists, and dentists are increasingly turning to phage-based medicines to treat antibiotic-resistant infections.

Phage-based drug development is more of a personalized pharmacy, when a drug is prepared for a

specific patient or group of people. To date, such technologies have been implemented in clinical hospitals in Georgia, Belgium, Germany, Israel, the United States, and France.

The industrial production of mono- and multi-phage preparations is promising not only for the treatment of resistant infectious diseases, but also for the prevention of infections.

The production, development and use of phage-based medicines requires improvement of international and national regulatory policies for such medicines, which are quite promising in the current environment.

AUTHOR CONTRIBUTIONS

All authors substantively contributed to the drafting of the initial and revised versions of this paper. They take full responsibility for the integrity of all aspects of the work.

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ARTIFICIAL INTELLIGENCE DISCLOSURE

The authors confirm that they did not use artificial intelligence technologies in the current paper.

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