REVIEWS

Review article
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To the question of the relevance of the development and prospects for the use of the bacteriophage *Streptococcus pneumoniae*

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Abstract

Introduction. The prevalence of *Streptococcus pneumoniae* strains causing invasive forms of pneumococcal infection and the growing rates of antibiotic resistance of individual serotypes of the pathogen pose a number of urgent and socially significant tasks the search for new antimicrobial agents for prevention and treatment.

Objective. To analyze the data of scientific publications of domestic and foreign authors on the problems of practical use and prospects for the development of the bacteriophage *S. pneumoniae* drug aimed at the actual serotypes of the pathogen.

Results. Analysis of literary sources in scientific electronic databases and publishing houses eLibrary.Ru, ScienceDirect, Scopus, PubMed, Springerlink, Wiley Online Library, Annual reviews allowed us to summarize information about four isolated lytic bacteriophages of *S. pneumoniae* and their endolysins, as well as about two lysogenic phages, to present data on the clinical efficacy of streptococcal bacteriophage in pneumococcal infection in animals and humans. The results of search queries on the most significant and widespread serotypes of *S. pneumoniae* in the territory of the Russian Federation have established the predominance in the structure of variants 19F, 14, 9V/A, 15 A/F, 6 A/B/C/D, 3 and 23F. Some of them are characterized by a high level of antibiotic resistance and cause invasive forms of the disease, and serotypes 15 A/F/C, 6 C/D are not represented in modern vaccines, which increases the relevance of the development and use of pneumococcal bacteriophage, including intraspecific typing of significant and common serotypes.

Conclusion. Based on the analysis of the current state of the issue of pneumococcal bacteriophages, the information obtained on the circulation of topical strains of *S. pneumoniae* on the territory of the Russian Federation and their serotype landscape, it is concluded that the development of the bacteriophage *S. pneumoniae* drug is relevant as a means of targeted action for the prevention, diagnosis and personalized therapy of human diseases of pneumococcal etiology.

Keywords: *Streptococcus pneumoniae, bacteriophages, phage therapy, phage prophylaxis, phage diagnostics, literature review*

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Обзорная статья
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К вопросу об актуальности разработки и перспективам использования препарата бактериофага *Streptococcus pneumoniae*

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Аннотация

Введение. Распространённость штаммов *Streptococcus pneumoniae*, вызывающих инвазивные формы пневмококковой инфекции, и растущие показатели антибиотикорезистентности отдельных серотипов возбудителя ставят в ряд актуальных и социально значимых задач поиск новых антимикробных средств для профилактики и лечения.

Цель — провести поиск научных публикаций отечественных и зарубежных авторов о проблемах практического использования и перспективах разработки препарата бактериофага *S. pneumoniae* узконаправленного действия на актуальные серотипы возбудителя.

Результаты. Анализ литературных источников в научных электронных базах и издательствах eLibrary.Ru, ScienceDirect, Scopus, PubMed, Springerlink, Wiley Online Library, Annual reviews позволил обобщить сведения о 4 выделенных литических бактериофагах *S. pneumoniae* и их эндолизинах, а также 2 умеренных фагах, представить данные клинической эффективности стрептококкового бактериофага при пневмококковой инфекции у животных и человека. Результаты поисковых запросов о наиболее значимых и распространённых на территории России серотипах *S. pneumoniae* установили преобладание в структуре вариантов 19F, 14, 9V/A, 15 A/F, 6 A/B/C/D, 3 и 23F. Часть из них характеризуется высоким уровнем антибиотикорезистентности и вызывает тяжёлые формы заболевания, при этом серотипы 15 A/F/C и 6 C/D не представлены в составе современных вакцинных штаммов, что повышает актуальность разработки и использования пневмококкового бактериофага, в том числе для внутривидового типирования значимых и распространённых серотипов.

Заключение. На основании анализа современного состояния вопроса о пневмококковых бактериофагах, полученных сведений о циркуляции актуальных штаммов *S. pneumoniae* на территории России и их серотиповом пейзаже сделан вывод об актуальности разработки препарата бактериофага *S. pneumoniae* как средства направленного действия для профилактики, диагностики и персонализированной терапии заболеваний человека пневмококковой этиологии.

Ключевые слова: *Streptococcus pneumoniae, бактериофаги, фаготерапия, фагопрофилактика, фагодиагностика, литературный обзор*

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Introduction

Infections of pneumococcal etiology have become an urgent issue for many countries. Under certain conditions, the *Streptococcus pneumoniae* pathogen can cause infectious diseases and life-threatening conditions in humans, including pneumonia, ear infection, sinusitis, meningitis, sepsis, endocarditis, arthritis, and others.[1] The high-risk groups include children, elderly people, patients with chronic cardiovascular, respiratory, and liver diseases, functional or anatomical asplenia, diabetes, immunodeficiencies, head injuries, spinal cord injuries, etc. [1, 2]. Reduction of incidence and mortality caused by pneumococcal pneumonia remains one of the top-priority goals in clinical and preventive medicine [3]. Wide geographic distribution of *S. pneumoniae* and its ability to develop antibiotic-resistant strains [4–9] show very clearly the need for development of new antimicrobial agents. As specified in the Action Plan for Implementation of the Strategy for Prevention and Restriction of Antimicrobial Resistance in Russia till 2030[2],

[1] MSD Manuals. Professional version. Pneumococcal Infections. URL: https://www.msdmanuals.com/ru/профессиональный/инфекционные-болезни/грамположительные-кокки/пневмококковые-инфекции

[2] RF Government Executive Order, No. 604-r "On Approval of the 2019–2024 Action Plan for Implementation of the Strategy for Prevention and Restriction of Antimicrobial Resistance in the Russian Federation till 2030". Moscow, 2019.

the top-priority biotechnological projects include development of bacteriophage-based agents. Thanks to their specificity, high antimicrobial activity, ability to get accumulated in the affected area, ability to cross biological barriers, bacteriophages are seen as promising candidates targeting prevailing strains of *S. pneumoniae*.

Main points

The studies addressing the isolation of pneumococcal bacteriophages trace their roots back to the Urals, to the Perm Institute of Epidemiology and Microbiology of the People's Commissariat of Public Health of Russia (presently NPO Biomed, Branch of Microgen, Perm). In 1935, postgraduate student A.M. Rodigina, using the sensitive bacterial culture of *S. pneumoniae*, was able to isolate the streptococcal bacteriophage for the first time [10]. Under the supervision of Professor P.I. Chistyakov, 3 series of experiments were conducted with 16 laboratory animals (rabbits) to study the prospects for using bacteriophages in ophthalmology in treatment of corneal ulcer. The solution containing clinically virulent strains of pneumococci was injected into each rabbit's cornea to cause development of an ulcer. In the experimental group, the animals received subconjunctival injections and/or ample washing of their corneas with the obtained phage lysate; as a result, in all cases the ulcerative process stopped, and the animals started recovering. In the control group of animals, the disease lasted longer and was complicated by iritis, hypopyon, and panophthalmitis. Thus, for the first time, the clinical efficacy of the new antimicrobial agent was demonstrated using a biological model. However, the bacteriophage did not have target specificity.

At present, Russia is the world leader in production of bacteriophage-based agents, including streptococcal bacteriophages. NPO Microgen offers a wide range of monovalent and polyvalent phages. One of its products, Streptococcal Bacteriophage is a filtrate of phage lysates of different *Streptococcus* species. The commercial product Sextaphage (INN Pyobacteriophage) is a mixture of phage lysates of *Staphylococcus*, *Streptococcus*, *Proteus* (*Proteus vulgaris*, *Proteus mirabilis*), *Pseudomonas aeruginosa*, *Escherichia coli*, *Klebsiella pneumoniae*. The Complex Pyobacteriophage (INN Pyobacteriophage) includes phages targeting *Staphylococcus*, *Enterococcus*, *Streptococcus*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Klebsiella oxytoca*, *Escherichia coli, Proteus vulgaris, Proteus mirabilis*. The combination of bacteriophages increases the effectiveness of empiric therapy; however, it can have a strong effect on the resident microflora.

The human upper respiratory tract is one of the most important biotopes and has diverse microbial associations. According to the findings reported by Belyaev et al. who conducted a study involving all age groups of the population, streptococci are the dominant species in the oral cavity [11]. These findings are supported by the study conducted by Belyaeva et al. who confirmed the key role of *Streptococcus* (75.2%) in the microbiocenosis of the nasopharyngeal cavity [12]. It was found that the disturbance in the microbial community structure led to development of active infectious processes [11–13]. Fujimori et al. found that patients were at high risk of being infected with virulent strains of Group A β-hemolytic Streptococcus (*S. pyogenes*) at low levels of α-hemolytic streptococci in the oral cavity [14, 15]. The researchers explained this phenomenon by the ability of most of the α-hemolytic streptococci to produce bacteriocins inhibiting the growth of *S. pyogenes* [18].

Tzannetis et al. pointed out the effect some strains of oral streptococci had on staphylococci [17]. Using the deferred antagonism technique, they found that certain species of streptococci, including *S. mutans*, *S. sanguis,* and *S. mitior,* had the highest inhibitory activity against strains of staphylococci, while the lowest activity was demonstrated by *S. milleri* and *S. salivarius.* On the whole, nasal strains of streptococci were more sensitive to "natural" inhibitors than oral ones, thus providing grounds for conclusion about an important protective function of oral streptococci. Bisgaard et al. found that *S. pneumoniae, H. influenzae,* and *M. catarrhalis* are the main microbial factor contributing to development of bronchial asthma in children during the first 5 years of life when the above species colonize the oral cavity in neonates with absent representatives of the normal flora [18]. Dysbiosis of the oral microbiome in adults taking antibiotics prompted development of dental periodontitis and caries [19, 20]. Broad-spectrum antimicrobial agents caused serious disturbance of the balance within the microbial community and resulted in the loss of significant symbiotic bacteria, which in normal conditions inhibit pathogen colonization, and these factors should be addressed when administering personalized therapy.

There are not many examples of phage therapy administered for human pneumococcal infection, and most of them relate to using therapeutic compounds with a streptococcal component. Akimkin et al. found that Streptococcal Bacteriophage (NPO Microgen) demonstrated a positive effect in team-working individuals with streptococcal infection [21]. After the preventive treatment by irrigating the oropharyngeal cavity with the bacteriophage solution (1.5–2.0 ml 2 times a day), the production of streptococci in the study group decreased 2.4 times, primarily, due to the reduction in the proportion of *S. pneumoniae*. In the control group, the levels of bacterial cultures, on the contrary, increased 2.8 times. The incidence among the people who received the bacteriophage decreased 1.8 times, while in the control group, it increased 1.4 times.

At present, the complete genome sequence of pneumococcal bacteriophages Dp-1 and MM-1 (the

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family *Siphoviridae*), Cp-1 and SOCP (the family *Podoviridae*), and phage EJ-1 (the family *Myoviridae*) has been identified. In 2017, the phage MS1 with the syntenic genome compared to the related phage Dp-1 and with an average nucleotide identity 73.3% (on 62.3% of aligned sequences) was obtained [22]. Cp-1, SOCP, Dp-1, and MS1 are lytic phages, whereas MM-1 and EJ-1 are temperate phages, which can integrate their genome into the genome of the bacterial cell. The embedded gene can be passed on to daughter cells when they divide. The bacteria carrying phage genomes integrated into their own genomes are defined as lysogenic bacteria, and the integrated phage is known as a prophage. The host-parasite microbial association will exist until stress conditions lead to induction of the prophage from the bacterium genome, triggering the transition of the bacteriophage to the lytic cycle. It is known that prophages (or their remnants) are well-represented in the *S. pneumoniae* genome. According to the latest estimates, they are carried by up to 90% of bacterial isolates [23].

The phage Dp-1 of the family *Siphoviridae*, which was isolated by McDonnell et al. from patients with mild symptoms of the upper respiratory tract infection, was the first described pneumococcal bacteriophage [24]. The phage having an icosahedral capsid structure (69.8 ± 1.2 nm) with a long non-contractile tail (169.9 ± 3.6 nm long, 19.6 ± 2 nm), lytic development cycle [25] was described as the first phage of gram-positive bacterium, which contains lipids (8.5% of the dry weight) [26]. The researchers pointed out high sensitivity of Dp-1 to organic solvents and, consequently, its low stability (chloroform is actively used for preservation and extended storage of the phage lysate). The first step of the infection process involving the bacteriophage is adsorption of phage particles on the bacterial cell surface through interaction of the phage with specific receptors. For its adsorption, the phage Dp-1 requires residues of phosphorylcholine, which is present in teichoic acids of all gram-positive bacteria [27]. Choline-binding proteins (Cbps) are noncovalently bound to phosphorylcholine, one of them being the CpbA protein, the main pneumococcal adhesin [28, 29]. Choline-binding lytic enzymes, including LytA (N-acetylmuramoyl-I-alanine amidase) also attach to phosphorylcholine. Being a major autolysin, LytA causes the lysis of bacterial cells and promotes film formation [30]. The key role of choline residues in adhesion of the phage Dp-1 was confirmed by Lopez et al. using *S. pneumoniae* cultures, where choline in the culture medium was replaced by other amino alcohols (ethanolamine, N-monomethylaminoethanolamine, N-dimethylaminoethanolamine) [27]. Pneumococci in media supplemented with ethanolamine and N- monomethylaminoethanolamine demonstrated much lower rates of phage adsorption. At the same time, the increased concentration of Dp-1 and the incubation time did not have any significant effect on the adsorption rate. The researchers pointed out that *S. pneumoniae* strains grown in media with ethanolamine recovered their ability to adsorb the phage in the presence of choline.

The analysis of the genome of phage Dp-1 was conducted by Sabri et al. [31]. The phage was 56,506 bp in length and included 156 interactions and 72 open reading frames. Its G+C content was 40.3%, being close to the *G+C* (39%) content in the genome of *S. pneumoniae*. The genome sequence of *Dp-1* is deposited to the GenBank database under accession number HQ268735[3]. The researchers found that most of the Dp-1 genes are homologous to genes of other phages of gram-positive bacteria — both virulent and temperate. For example, the researchers identified the remote homology between the cluster gene (*orf23*) of the phage Dp-1 and the terminase large subunit gene fragment (*orf37)* of the temperate phage EJ-1. The scaffold protein Gp41 (the researchers called the protein of the phage Dp-1 glycoprotein 41) encoded by *orf41* was homologous to the capsid protein Gp23 of the *Staphylococcus aureus* phage *88* and the conserved domain of the scaffold protein Gp20 of the *Lactobacillus* phage *mv4.* The discovered phenomenon gives an illustrative example of the consequences caused by the genetic exchange between phage populations, which takes place through bacterium-host communities.

The next lytic phage of *S. pneumoniae*, which was isolated from the oropharynx of healthy children by Ronda et al., was the phage Cp-1 of the family *Podoviridae* [32]. Morphologically, the phage consists of an elongated hexagonal capsid (65.8 ± 1.1 nm long and 42.1 ± 1.7 nm wide) with a short non-contractile tail (19.3 ± 1 nm long, 7.5 ± 1.2 nm wide) [25]. The researchers pointed out that the phage was stable in storage. The ability of Cp-1 to infect not only *S. pneumoniae*, but also *S. oralis* was mentioned by Ronda et al. [33]. The genome of Cp-1 consists of a linear, double-stranded DNA with a terminal protein covalently linked to its 5' ends. The phage DNA is replicated by a protein-primed mechanism. The genome has 19,343 base pairs. The total content of *G+C* in the Cp-1 DNA is 38.8%, thus correlating with the total content (39%) of *G+C* in the *S. pneumoniae* genome. A total of 28 reading frames have been identified. For the adhesion to the surface of the cell wall, both the phage Cp-1 and the phage Dp-1 needs choline residues [34]. The genomic sequence of the phage Cp-1 under the number Z47794 is deposited to GenBank[4]. Interestingly, when sequencing the phage Cp-1 from the Félix d'Hérelle collection, Ouennane et al. received the nucleotide sequence that

[3] National Library of Medicine. Streptococcal phage Cp-1, complete genome.
URL: https://www.ncbi.nlm.nih.gov/nuccore/HQ268735

[4] National Library of Medicine. Streptococcal phage Cp-1, complete genome.
URL: https://www.ncbi.nlm.nih.gov/nuccore/Z47794

was different from the phage Cp-1 Z47794 sequence [27]. As a result, the Cp-1 from the Félix d'Hérelle collection was renamed as SOCP and registered with GenBank as the phage KJ617393.1[5]; its genome includes 19,347 bp (Cp-1 Z47794 has 19,343 bp). The lysis capability of the phages Dp-1 and SOCP of *S. mitis* has been identified [27].

The phage MM1 was the first sequenced temperate phage of *S. pneumoniae*. Obregón et al. found that its 40,248 bp long genome was organized by 53 open reading frames and had at least 5 functional clusters (lysogenic, replication, structural, packaging, lytic). The DNA of mature phage particles is terminally redundant and contains the covalently linked protein with 5' ends. The average content of *G+C* in the phage MM1 DNA was 38.4%, thus being comparable with the nucleotide proportion in the genome of its host – *S. pneumoniae* (39%). The comparison of the MM1 genome with genomes of other bacteriophages also revealed their similarity with phages infecting gram-positive bacteria [35].

The electron microscopy of the phage MM1 showed that it belonged to the family *Siphoviridae*. Morphologically, the phage has an icosahedral capsid structure (60 nm in diameter) with a long non-contractile tail (160 nm long) [36]. The site-specific recombination resulting in the phage integration into the bacterial genome is mediated by the phage integrase. The process involves recognition and recombination of specific DNA sequences located in the genomes of the bacterium and the phage. These attachment sites are known as attB and attP (the bacterial attachment site and the phage attachment site). The phage integrated into the bacterial cell is flanked by two hybrid sites – attL and attR. The reverse induction of the prophage involves recombination between attL and attR into attB and attP. Gindreau et al. identified and deposited attB, attP, attL and attR sequences to GenBank under accession numbers AJ400631, AJ400629, AJ400632, and AJ400630 [36]. It has been found that prophage genes frequently have a "phenotypical" effect on the host bacterium. In 2006, Loeffler et al. studied lysogenic and non-lysogenic strains of *S. pneumoniae* [37]. They used the temperate phage MM1-1998 (the alignment of the MM1-1998 sequence with that of MM1 showed the identity of more than 99.8%). Lysogenic strains of *S. pneumoniae* demonstrated better adherence to inert surfaces (glass, plastics) and biological tissues (cell cultures from the nasopharyngeal cavity of animals). In their study, the researchers proved that the presence of a prophage in a bacterial cell results in its phenotypical modification, along with increased virulence and activation of adaptation mechanisms.

[5] National Library of Medicine. Streptococcal phage SOCP, complete genome.
URL: https://www.ncbi.nlm.nih.gov/nuccore/KJ617393

Another temperate phage of *S. pneumoniae*, which was best described, was the phage EJ-1 isolated from a clinical isolate of *S. pneumoniae* 101/87 [38]. The phage EJ-1 (induced from a bacterial cell using mitomycin C) was isolated from the strain of *S. pneumoniae*, which was obtained from the blood of a patient with atypical pneumonia. The strain was characterized by resistance to bile and optochin; it was not suitable for serotyping and had the *lytA* gene, which is specific for all strains of *S. pneumoniae* [39]. The temperate phage EJ-1 with a capsid of 57 nm in diameter had a long contractile tail of 130 nm in length; later the phage was assigned to the family *Myoviridae*. Its genome did not contain covalently linked proteins. In 2004, Romero et al. deposited the whole genome sequence of EJ-1 (42,935 bp long) to GenBank; the sequence was organized by 73 open reading frames and, at least, by 5 functional clusters [40]. The average content of *G+C* in the DNA of phage EJ-1 was 39.6%, being comparable (39%) with the content of *G+C* in the *S. pneumoniae* genome [41].

The studies of pneumococcal bacteriophages continued, being focused on biochemical processes induced by the bacteriophage in the bacterial cell, where the important and final stage is the destruction of the bacterial cell wall and release of mature phage particles. It is known that the bacterial lysis is primarily the result of production of specific phage-encoded enzymes. Two different types of lytic enzymes were found in pneumococcal phages, including amidases and lysozyme. All of them degrade murein by cleaving the glycosidic bond between N-acetylglucosamine and N-acetylmuramic acid or between the lactic group of N-acetylmuramic acid and amino group of L-alanine. The Cpl-1 enzyme encoded by the phage Cp-1 is lysozyme, and Pal, Mml, and Ejl enzymes encoded by phages Dp-1, MM1, and EJ-1 are amidases. Lytic enzymes of phages have a two-domain structure, where the C-terminal domain specifically recognizes and binds choline in the bacterial cell wall, while the N-terminal domain is responsible for bond cleavage in the peptidoglycan [42, 43]. The distinctive feature of the cell lysis by the bacteriophage with double-stranded DNA is the production of the holin protein that forms lesions in the cytoplasmic membrane. This way, murein hydrolases gain access to the murein layer of the cell wall. As a rule, the gene encoding holin and the gene encoding endolysin are located in the phage genome in sequence. In the genome of the phage Cp-1, the products of genes 21 and 22 are lysozyme and holin, respectively. This lysis mechanism is known as the holin-lysozyme lysis strategy [44, 45].

Phage-encoded enzymes, which specifically destroy cell walls of bacteria, are studied addressing the problem of antibiotic resistance. In 2003, Jado et al. studied the enzyme, Cpl-1 lysozyme, encoded by the phage Cp-1, and the enzyme, Pal amidase, encoded by the phage Dp-1 [46]. They used the strain of *E. coli*, which carried pCIP100 or pMSP11, as a producer of

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both enzymes. The effect of Cpl-1 and Pal was tested using the mouse model for pneumococcal sepsis. After the animals had been intraperitoneally infected with *S. pneumoniae* and had received one dose (10 minutes after the infection) of Cpl-1 or Pal injected into their abdominal cavity, during one day, the researchers observed the dose-dependent therapeutic effect resulting in the reduction of clinical symptoms of the disease. All the animals who received 40 μg of Cpl-1 or 40 μg of Pal recovered completely. The combination of two phage lytic enzymes produced a synergistic effect. Using the identical biological model, the researchers observed that the infection process stopped developing one hour after the infection and combined intraperitoneal injection of 2.5 μg Cpl-1 and Pal (the total dose of components equal to 5 μg was 8 times lower than the mono-component dose of 40 μg). The single dose of 5 μg of either of the two above enzymes, when injected separately after the injection of live culture of *S. pneumoniae*, resulted in death of the animals. The recovery effect in the experimental group of animals was also observed with the later (2 hours after the infection) inoculation of lytic enzymes, which were later called enzybiotics. As opposed to antibiotics, which require the presence of the active substance in the constant pharmacological concentration reachable at strict dosing intervals, the one-dose enzybiotic injection was sufficient to inhibit the growth of clinical isolates of *S. pneumoniae*. The researchers see these unique substances as promising candidates for antimicrobial therapy [46].

The combined use of antibiotics and enzybiotics is one of the most promising strategies in the fight against infectious diseases of humans and animals. The identical mouse model of pneumococcal bacteremia demonstrated a synergistic effect of the antibiotic daptomycin and enzybiotic Cpl-1 combination [47]. Mice were injected intraperitoneally with *S. pneumoniae* D39 and all of them died within 72 hours. Among the mice that received one-dose injection of daptomycin (0.4 mg/kg), the survival rate on the 7th day of the experiment was 35%. When inoculated with Cpl-1 (0.4 mg/kg), all the animals died within 72 hours. The combined intraperitoneal injection of daptomycin and Cpl-1 (0.4 mg/kg of each) increased the survival rate to 80%. The survived animals did not have any signs of infection and gained weight as quickly as the uninfected mice. When the dose of Cpl-1 was increased 2.5 times (from 0.4 to 1.0 mg/kg), while the dose of daptomycin remained the same (0.4 mg/kg), the survival rate in the 7th day reached 95%. The researchers found that the treatment with the Cpl-1 and daptomycin combination, in addition to the pronounced clinical effect, prevented the production of daptomycin-resistant strains of *S. pneumoniae.* Thus, the treatment of animals with antibiotic and enzybiotic was highly efficient.

Harhala et al. were the first to conduct experimental studies of safety and toxicity of two endolysins of Dp-1 and Cp-1 phages, using the human cell culture [48]. During the first stage, the researchers performed gene expression profiling using microarrays for two cell lines: FaDu (human pharynx squamous cell carcinoma, ATCC HTB-43) and SC (human peripheral blood macrophages, ATCC CRL-9855). The cell lines were further cultured in media containing 0.5 μM Pal or Cpl-1 for 6 hours. The DNA microarray analysis showed no statistically significant changes in gene expression in either cell line. In addition, using blood samples collected from 6 healthy human donors, the researchers did not find any potential effects of endolysins on the complement system *ex vivo*. The complement activation was assessed via the classic, alternative, and lectin pathways. The biological mouse model was further used to evaluate the specific immune response after a single-dose application of each of Pal or Cpl-1 enzymes. The evaluation period was 50 days. The IgG induction was characterized by a slow increase in the antibody titer until day 30, then the titers leveled off. The changes in IgG production were typical of the immune response of the tested biological model to substances having a proteinaceous nature. The animals did not demonstrate any adverse physical and behavioral changes or high IgE titers associated with hypersensitivity and allergic reactions; pro-inflammatory cytokine levels remained constant; there were no significant changes in the fecal microbiome; however, related bacteria from the *S. mitis* group were sensitive to Cpl-1 and Pal. The performed studies found that enzybiotics had no significant effect on cellular and systemic functions of small animals' organism, thus supporting the need for pharmacokinetic and pharmacodynamic studies in larger mammals and primates**.**

The polysaccharide capsule plays a key role in *S. pneumoniae* evasion of the host immune response. It is a major pathogenicity factor in the microorganism, and it inhibits the phage entry into the bacterial cell by restricting the access to the receptor, as was proven by the laboratory tests performed by Leprohon et al. [49]. The researchers compared unencapsulated (R6) and encapsulated (D39) *S. pneumoniae* strains by their sensitivity to the phage. The unencapsulated (capsule-free) strain R6 has been used as a classical laboratory strain since 1950s; the absence of the capsule makes it avirulent and safe to work with. The parental strain for R6 is R36A (a derivative of the strain D39), which was isolated through 36 successive passages of D39 in the medium containing rabbit antiserum [50]. Unlike the strain R6, the encapsulated (capsular) strain D39 initially demonstrated the resistance to the phages SOCP and Dp-1. The D39 inactivation for the gene *cps2C* resulted in a reduction in the capsule size and in sensitivity developed by the strain D39 to the phages SOCP and Dp-1, similarly to the strain R6. Thus, the researchers assumed that the capsule of *S. pneumoniae* can affect the resistance of the host cell to the lytic phage. A num-

ber of factors have an effect on the expression level of the *S. pneumoniae* capsule [51, 52]. In 1998, two main phenotypes of *S. pneumoniae* were characterized and defined as transparent and opaque; the latter had enhanced virulence and the content of capsular polysaccharide that was 1.2–5.6 times as high as its content in the transparent phenotype [53]. The transparent phenotype had a 2.1–3.8-fold increase in the cell wall teichoic acid. The detected differences were confirmed by the tests where *S. pneumoniae* was grown in a medium containing a radioactive isotope of choline ([^{3}H] choline) component of teichoic acid, which is known as the only choline reservoir in the pneumococcus bacterial cell. At the same time, the expression level of the *S. pneumoniae* capsule is not stable and provides conditions, under which the phage infection will not be continuously inhibited by the capsule. Therefore, encapsulated pneumococcus strains are also not protected against phagolysis.

Currently, more than 90 serotypes of *S. pneumoniae* have been identified by the biochemical structure of the capsular polysaccharide, demonstrating high plasticity and recombination variability of the pathogen genome, which contribute to development of resistance to antibiotics. Therefore, serotyping of *S. pneumoniae* based on capsular polysaccharides is important for intraspecific identification of the microorganism, for evaluation of the severity of the infection process and for identification of antimicrobial resistance [54, 55]. Studies of prevalent serotypes of *S. pneumoniae* in specific regions and in individual groups of population, depending on the age, practical application of antibiotics, clinical manifestations of infection, demographic characteristics, vaccination coverage of the population, and the composition of vaccine strains, are significant for the personalized approach to treatment and prevention of pneumococcal infection [56, 57]. The results of the studies conducted in different countries show that more than 80% of the most severe invasive pneumococcal infections are caused by 20 main serotypes, with 13 of them causing up to 70–75% cases of serious manifestations. Representatives of serotypes 23, 19, and 6 are characterized by high resistance to the main classes of antibiotics [55, 58]. Invasive infection in children under 5 years of age is most frequently caused by serotypes 4, 6, 9, 14, 18, 19, and 23, while in other age groups the dominant serotypes are serotypes 4, 6, 9, 12, 14, 19, and 23 [55, 59, 60]. Special attention should be given to the information about serotypes 19F, 14, 9V/A, 15 A/F, 6 A/B/C/D, 3, and 23F circulating in Russia [61–64]; some of them are not included in the currently available vaccines (15 A/F/C, 6 C/D, 9A). Some of them are associated with specific clinical forms. For example, serotypes 3 and 14 tend to cause pneumonia and pleurisy leading to lung tissue destruction [5, 65]; serotypes 3 and 19F are responsible for acute otitis media in children. Beloshitsky et al. have found that serotypes 23F, 14, 19F, and 3 can cause severe clinical meningitis and lead to fatal outcomes [66].

Bacterial strains within a species or subspecies can have specific sensitivity to phages; therefore, bacteriophages can be used successfully to target a specific biovar, serovar, or phagovar. One of the serious problems in the fight against pneumococcal infection comes from the complexity of laboratory diagnostics of *S. pneumoniae*, including interspecific identification of the pathogen, which is an important element in the monitoring of the epidemic process. The main difficulty in the assessment of the serotype landscape of *S. pneumoniae* arises from the lack of typing techniques that are highly specific, sensitive, reproducible, and inexpensive.

Currently, the best-known methods of serotyping of *S. pneumoniae* are the Neufeld quelling reaction, latex agglutination test, and PCR-based serotyping. Sometimes, researchers using these methods observed cross-reactions with antigens of the representatives within the family *Streptococcaceae* (*S. oralis*, *S. mitis,* and others) and even between families (*Escherichia coli*, *Klebsiella*, etc.) [67]. The large-scale vaccination against pneumococcal infection has caused changes in circulating serotypes. In their work published in 2021, Nikitina et al. reported the decreasing effectiveness of the PCR-based capsular serotyping of *S. pneumoniae* over the last 5 years (2016–2021) from 100% to 41.6% [68].

The bacteriophage-based intraspecific identification of microorganisms dates back to the 1960s. One of the first species of microorganisms typed into phagovars was *S. aureus*, and the international set of Davidson diagnostic staphylococcal phages was used [69, 70]. For many years, phage typing of *S. aureus* helped efficiently evaluate epidemic outbreaks caused by staphylococcal food-born toxicoinfections at public catering facilities and nosocomial infections at healthcare facilities. Different levels of the lysing ability were identified in listeriophages [71]. The bacteriophage lysis of some serotypes was observed during the intraspecific identification of *Enterobacter cloacae* [72]. The results of the research on phenotyping of *Acinetobacter baumannii*, including the specific activity of Acinetobacter bacteriophage, were published by Fedotova et al. [73]. The researchers were the first to identify the specificity of Acinetobacter bacteriophage to the individual sequence-type of *A. baumannii* (ST 1167). The development and implementation of alternative laboratory-based strategies of intraspecific typing by using bacteriophages will improve the quality of *S. pneumoniae* identification and take a priority place in solving molecular, biological, and epidemiological problems, having a significant potential for studying new factors of virulence, pathogenicity, and antibiotic resistance of microorganisms. These strategies will make it possible to gain insight into phylogenetic relationships within the circulating microbial population of pneumococci and, consequently, to develop effective epidemic con-

trol and prevention measures against pneumococcal infection, including preventive vaccination. One of the focus areas is development of a set of bacteriophages specifically targeting prevalent serotypes or genotypes of *S. pneumoniae*.

Conclusion

The fight against pneumococcal infection by improving tools and methods of specific prevention, diagnostics, and treatment is of high significance for preserving health and the quality of life of the population. Therefore, the development of the new antimicrobial agent, Bacteriophage Pneumococcus, targeting individual serological variants of clinical isolates of *Streptococcus pneumoniae*, which circulate in Russia, is of great importance and fits into the Strategy for Scientific and Technological Development of the Russian Federation[6] regarding transition to personalized medicine, high-tech health care and health protection technologies, which also involves the rational use of pharmaceutical products (first of all, antibacterial products). Scientific studies in this area will help identify new patterns of circulating prevalent serological variants of *S. pneumoniae* in different regions. A significant contribution to the understanding of the biology of the pathogen will be made by unique collections of strains of *S. pneumoniae* and strains of bacteria-producers of pneumococcal bacteriophages as well as by the new targeted lytic phages of *S. pneumoniae*. The analysis of their structural and functional patterns will expand the theoretical framework of microbiology for the further development of a new group of promising therapeutic, diagnostic, and preventive products having a fundamental national economic significance. The development of innovative therapeutic, preventive, and diagnostic *S. pneumoniae* bacteriophage-based agents will contribute significantly to the reduction in the circulating strains of microorganisms having multiple drug resistance and in the consumption of antibiotics and will improve the quality of laboratory diagnostics. The phage-based solutions will have exceptional social significance for patients' rehabilitation from consequences of post-covid pneumococcal infection; it will help decrease the incidence and mortality caused by infectious diseases, will help preserve health and quality of life, will improve the demographic situation in the country.

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