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Applications of Phage Therapy in Veterinary Medicine

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Fagterapi och dess Tillämpning inom Veterinärmedicin

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SUMMARY/ABSTRACT

This paper describes some different investigations of phage therapy within veterinary medicine, in treating some of the most common bacterial infections in poultry, cattle and fish. As a red thread, phage therapy is being compared and contrasted with the current standard antibiotic treatment within some common diseases, as well as in general, in the discussion section.

Bacteriophages, also known simply as phages, are bacterial (obligate) parasites or viruses that infect, replicate inside and eventually lyse their host bacterium, letting out hundreds of new phages. Since phages depend on bacteria as their host, they can be used for therapeutic purposes to help the immune system against the pathogens by killing the bacteria.

Salmonellosis is caused by *Salmonella* bacteria and it is one of the most common and important infections transmitted between animals and man (zoonosis). Salmonella phages proved very effective in treating mice and chicken infected with Salmonella with a success rate of 90-100% (Lenev, 2013).

Treatment of rabbits infected with *Vibrio cholera* by phages did not provide any successful results on the rabbit models, in contrast to the successful trial of treating cholera in humans. This is one of the examples how the effect of phage therapy application can vary within different species.

Phages have shown to be effective against *Enterococcus* in mice models, with the pathogen's significant decrease under infective dose; however, a tendency has been found that the earlier the treatment started the better result was obtained.

When tested against *Clostridium difficile*, phages were able to protect the mice models from the disease but the effect did not endure for long. In all the different trials, it remains important to neutralise the gastric acid before administering phages orally, since low pH deactivates them.

In the aquatic sphere, the two principle diseases have been taken up – aeromonosis and pseudomonosis, where phage therapy is still in the mode of trial, but already suggested by some researchers (Kafydova and Grinyova, 2014) to be used for treatment. Phage therapy has shown significant effects on *Pseudomonas pleoglossicida*, and a very promising result has been demonstrated on the *Lactococcus* bacteria, with maximal success and absolute protection of fish against the pathogen.

SAMMANFATTNING

Denna uppsats beskriver några olika undersökningar av fagbehandling inom veterinärmedicin, inom några av de vanligaste bakterieinfektionerna hos fjäderfä, boskap och fisk. Som en röd tråd jämförs fagterapi med den aktuella antibiotikabehandlingen inom några vanliga sjukdomar samt allmänt i diskussionsdelen.

Bakteriofager, även kända som fager, är bakteriella (obligata) parasiter eller virus som infekterar, replikerar inuti och så småningom lyserar deras bakterievärdar och släpper ut hundratals nya fager. Eftersom fager är beroende av bakterier som värdar, kan de användas för terapeutiska ändamål för att hjälpa immunsystemet mot patogenerna, genom att avdöda bakterierna.

Salmonellos orsakas av Salmonella-bakterier och det är en av de vanligaste och viktigaste infektionerna mellan djur och människor (zoonos). Salmonellafager visade sig vara mycket effektiva vid behandling av möss och kaniner, infekterade med salmonella, med en framgångsgrad på 90-100% (Lenev, 2013).

Fagbehandling av kaniner infekterade med *Vibrio cholera* gav inga framgångsrika resultat på kaninmodellerna, i motsats till det framgångsrika försöket att behandla kolera hos människor. Detta är ett exempel på hur fagbehandlingseffekt kan variera inom olika arter.

Fager har visat sig vara effektiva mot *Enterococcus* i mössmodeller, med patogenens signifikanta minskning under infektionsdos; emellertid, har man hittad en tendens: ju tidigare behandlingen började, desto bättre resultat erhölls.

När fager testades mot *Clostridium difficile*, kunde fager skydda musmodellerna från sjukdomen, men effekten varade inte länge. I de olika försöken är det viktigt att neutralisera magsyran före administrering av fager oralt, eftersom lågt pH deaktiverar dem.

I akvatiska världen har de två principiella sjukdomarna upptagits - aeromonos och pseudomonos, där fagbehandling fortfarande är i provtillståndet, men som redan föreslagits av vissa forskare (Kafydova och Grinyova, 2014) som en alternativ behandling. Fagterapi har visat signifikanta effekter på *Pseudomonas pleoglossicida*, och ett mycket lovande resultat har visats på *Lactococcus*-bakterierna, med maximal framgång och absolut skydd av fisk mot patogenen.

INTRODUCTION

Antibiotic resistance has been an alarming issue in the recent decades, subject to much discussion within the humane medical sphere, as well as in veterinary medicine. The ongoing debate exposes the fact that bacterial strains continually develop resistance towards the existing antibiotics by the means of adaptive mutations, and that new types of antibiotics are not introduced (Golkar et al., 2014). By trying to find a solution for this problem, acceptable alternatives to antibiotics have to be found, e.g. an antibacterial agent that would be able to surpass this constant bacterial resistance development, for example bacteriophages.

Phage therapy has been known since the end of 19th century, but with the discovery and rise of antibiotics, the interest in bacteriophages faded away in some countries. However, in recent decades an interest in phage therapy has returned, this time viewed from another perspective.

This literature review aims to elucidate the application of phage therapy in veterinary medicine, considering its advantages and disadvantages. This paper takes up certain bacterial diseases of some of the most common animal species in relation to phage therapy. A general overview of the current condition of antibiotic treatment of these pathologies has also been discussed. Moreover, phage therapy is to be evaluated as a potential future compliment or even alternative to antibiotics, at least considering the mentioned diseases within veterinary medicine.

MATERIAL AND METHODS

Literature, in this study, has been found using, Pubmed, and other scientific databases. The focus was placed on the international origin of the sources and their specificity in bacteriophageal research. Such search terms as "bacteriophages", "phage therapy", "phage treatment of aquatic organisms" have been used.

LITERATURE REVIEW

BACTERIOPHAGEAL BIOLOGY

Bacteriophages (etymology: “bacteria” and greek “phagos” – consuming) can be viewed as obligate parasites for bacteria. These viruses received this functional name, since they invade bacteria and “consume” their cells, replicate within them and leave the cell with all their copied “progeny” usually by lysing the bacteria. Bacteriophages (sometimes abbreviated to “phages”) can be found in many different environments, such as soil, water, glacier, etc. The important condition being that bacteria also be found there, since phages cannot live without bacterial hosts. It has been noticed that phages effectively infect enteric bacteria, such as *E. coli, Shigella, Salmonella typhimurium,* etc. Bacteriophages are unique microorganisms, they are also known as “good viruses”, their survival dependence on bacteria, which are sensitive to phages, including

even most pathogenic and virulent strains thereof, gives rise to a distinctive treatment technique known as phage therapy (Efremova and Nikolaeva, 2013) (Sherbenkov, 2013).

Being a virus, a phage has a viral structure: genetic material (single or double stranded RNA or DNA), surrounded by a capsid (protein coat). Its size ranges approximately from 20 nm to 200 nm (up to 800 nm long within the filiform) (Tets et al., 2002). Larger size phages are usually constructed as icosahedrons with spiral symmetry tail. Phages are more resistant to both physical and chemical influence than bacteria; for example, they can endure pH ranging from 5 to 8, neither are they deactivated by ethanol, phenol, cyanide or chloroform. However, boiling, acids, formalin and UV-light, can destroy them. (Bykov et al., 1998)

The potential magnitude of phage therapy effect can be imagined if one considers how phages replicate. It is similar to how any virus replicates: the viral genome enters the cell and the genetic information within the virus redirects the cell to produce many new copies of the virus. Subsequently, the phages are released from the lysed bacterial cell and the newly formed phages can infect a multitude of other bacteria in the vicinity. All this provides phages with an extraordinary bactericidal potential, rendering them to be powerful therapeutic agents against bacterial diseases (Sulakvelidze and Kutter, 2012)

BACTERIOPHAGEAL CLASSIFICATION

Today bacteriophages are usually classified into 13 families, over 140 genii, more than 5300 types of phages. They can be distinguished by shape, structure, nucleic acid and by its interaction with microbial host. Phages are also distinguished by size: small, medium, large; shape: filiform, spherical; phages with and without head and/or tail, etc.

Furthermore, phages can be differentiated into virulent (productive infection, where the phage replicates in the cell and leaves it afterwards) and temperate (reductive infection, where the phage integrates its genome into the cell, becoming a prophage and rendering the cell lysogenous). The lysogenous cell carries the genes of the prophage, which can anytime leave the bacterial chromosome and start replicating and then its progeny leave the cell by lysing it (Bykov et al., 1998) (Korotyayev and Babichev, 2002).

MOLECULAR MECHANISMS OF PHAGE THERAPY

After having penetrated the bacterial cell, the phage inserts its genetic material into the cell to replicate it, in order to produce up to 300 new phage particles, whose complete lytic cycle (from the moment of absorption into the cell to its exit in cellular lysis) lasts for 30-40 min. (Marina, 2011). Lysosyme from the phages dissolves the bacterial cell wall, thus letting the phage virions leave the microbe, in order for them to further infect and lyse other phage sensitive bacteria. Thus, in a very short time, a single phage can multiply to produce millions of phages, all with the potential to kill bacteria and further subsequent magnification of phage shall then occur. Nevertheless, phages are self-limiting, that is when no target bacteria is around no replication occurs and the phages will eventually denaturise and disintegrate.

The phages vary in specificity, being type-specific (lysing certain types of bacteria within one species), monovalent (lysing bacteria of only one species) and polyvalent (lysing bacteria of different species within a genus). Virulent phages are lytic, implying that they lyse the cell upon replication and formation of new phages, whereas temperate phages are lysogenic, meaning that they hijack the bacterial genome and force it to produce their viral proteins.

Transduction is a process of gene transportation between bacteria, carried out by phages. One big concern in using phages in therapy is the risk of spreading virulence genes between bacteria. Temperate phages can integrate into the bacterial chromosome and sometimes they can take with them genes close to their integration site. By this mechanism, many temperate phages carry virulence genes in their genome, e.g. the Shiga toxin carrying phages causing *E. coli* to become the feared STEC strains, triggering very severe food poisonings (Martinez-Castillo and Muniesa, 2014). Thus, it is important to use only virulent phages in phage therapy.

PHAGE THERAPY IN VETERINARY MEDICINE

Phage therapy has been used in veterinary science since the beginning of the 20th century. In 1919 phages were first used in France against bird typhoid fever. *Salmonella gallinarum*, as well as their bacteriophages, were isolated from the infected chicken and when tested, phages proved to be effective against *Salmonella gallinarum*. The first trial model for testing phage therapy was mice salmonellosis, mainly caused by *Salmonella typhimurium*. Phages were both administered intraperitoneally and orally, where the latter did not give a positive bactericidal result and the former only decreased microbial spread insignificantly (Topley, et al., 1925). This trial failed most probably because the right type of phage was not used, since later scientists managed to infect typhoid bacteria *in vitro* successfully with a well-chosen anti-tiphoid phage (Fisk, et al., 1938). Many subsequent experiments in treating rabbits, Guinee pigs, mice and rats, infected with streptococci and staphylococci have not shown to be effective (Compton, 1930). Nevertheless, there are multiple evidence of successful phage treatment of streptococcal meningitis in rabbits (Kolmer and Rule, 1933) (Eaton & Bayne-Jones , 1934) *E.coli* cystitis in rabbits and Guinee pigs (Larkum, 1926), *Salmonella dysenteriae* encephalitis in mice (Dubos, et al., 1943) (Sulakvelidze and Kutter, 2012).

Today phages are used in both human and veterinary medicine. Among their advantageous characteristics, such as their specificity on bacteria, qualifies them for use in phage therapy. Modern phage medicine is based upon virulent phages of a broad range of action that are active against antibiotic resistant bacteria. The latter phenomenon (antibiotic resistance development) has in recent decades led to less efficient bacterial disease treatment, as well as to an increase of persistent infections and latency (Pimenov, et. al., 2006). Antibiotics usage today is narrowed down as much as possible, in order to avoid, or at least, decelerate resistance growth, which provides more importance of the ecologically safe phage therapy as a modern anti-epizootic treatment, which is to be opted for (Lenev, 1992) (Sulakvelidze and Kutter, 2012).

SALMONELLA IN POULTRY

Salmonella remains to be a large problem for both human and veterinary medicine. WHO classifies Salmonellosis as epidemiologically the most severe zoonosis to eradicate, especially considering the fact of intense antibiotic resistance development (Pimenov, et. al., 2005). Poultry farms are the primary source of salmonella dispersion. Salmonellosis of all serovars contributes with a severe socioeconomic damage (Kaftyreva et al., 2008). Phages have exceptional possibilities, since they can be used in the different parts of the food chain, from such prophylactic means as sanitation in farms to treating carcasses in the slaughterhouse (Lenev, 1992). Phages that are used against *Salmonella typhimurium* are typically isolated from bird faeces in poultry farms and dovecotes. *Salmonella typhimurium* phage (type B1 Siphoviridae) isolates have shown maximal lytic activity against *Salmonella enterica* (Pimenov, 2013). *Salmonella enteritidis* is the dominant salmonella strain for both chicken and humans (Kuzmin, 1995) (Michael, 2010). It has been shown in an experiment on salmonella infected mice and rabbits that 90-100% of the animals were saved from death, as compared to 0-10% in the control group (Lenev, 2013). Thereafter, these phages were successfully used in poultry farms, dovecotes and zoos. In conclusion, the typhimurium phage and the bivalent salmonella phage are successfully introduced into veterinary praxis and are recommended to veterinary specialists, thereby proving to be promising anti-epizootic medicals (Pleshakova and Stepanov, 2013). In another phage therapy experiment in broiler poultry, from the pathologic material from broiler chicken, 11 *Salmonella enteritidis* strains have been isolated in the first day, and on day 29, no strains were detected, while the control group had all the 11 strains for 32 days. In addition, average daily body mass gain in the experimental group was 0.7 g/chicken higher than in the control group, and the productivity index was 9.4 times the index of the control group. As a result, it can be concluded that phage therapy eradicates salmonella, increases average daily mass gain, as well as the final mass at slaughter together with the productivity index (Pleshakova and Stepanov, 2013).

ESCHERICHIA COLI INFECTIONS IN BOVINE CATTLE AND SWINE

Bacteriophages are known for being effective against *Enterobacteriaceae* in general and *E. coli* in specific (Huff, et al., 2003). An experiment has been done on escherichiosis in piglets, where T4 phage from the *Myoviridae* family was used (minimum of 10^5 phages/g body mass were applied) providing with up to 100% protection, in all dosages; the optimal dosage has been determined to be triple treatment with 10^9 phages/1-month old piglets (Skoblikow and Zimin, 2013).

Experiments have been set on calves and lambs, orally infected by $3x10^9$ *E. coli* type O9:K30.99.57 and none of the 9 phage treated calves, with the dosage of 10^{11} phages, got diseased, as compared to the control group, where 93% died. While the phages were unable to eradicate the *E. coli* completely, it could decrease the amount of bacteria to a level below the pathogenic threshold; almost no phagoresistant mutated *E. coli* have been determined (Smith and Huggins, 1983).

Investigations have also shown that the low pH of the gastric acid had to be neutralised, in order to preserve the phages given orally, which could easily be done by sodium bicarbonate (given prior to phage therapy) or milk (Smith and Huggins, 1983).

In yet another experiment, calves were orally infected by 10^{10} $K1^+$ *E. coli* within 2 hours after delivery, which caused a severe septic reaction within the next 18-36 hours; thereafter, they were obviously euthanized; however, 3 out of 4 infected calves in the phage-treated group remained healthy after 8 hours and the 4^{th} one was only slightly sick. R-phages (10^{10} PFU) were inoculated intramuscularly 8 hours after the oral inoculation with bacteria into the thigh (Barrow et al., 1998).

VIBRIO CHOLERAE IN RABBITS

In an experiement, 10 *V. cholerae* phages (B1 – B10) were tested (10^{10} – 10^{11} phages/ml) against *V. cholerae* using an *in vivo* rabbit model. They were injected together with 10^8 CFU ATCC 51352 *V. cholerae* into the rabbit intestines; however, neither prophylactic nor therapeutic effect has been noticed, in contrast to the successful human cholera phage treatment, subsequently taken up and discussed by Summers, 1999. Researchers surmise that this could have occurred since certain components in the rabbit intestines inhibit phage activity (Sarkar et al., 1996) (Sulakvelidze and Kutter, 2012).

ENTEROCOCCUS FAECIUM IN MICE

Phage therapy was tested against vancomycin-resistant *Enterococcus* on mice models, by infecting the mice with 10^9 CFU *Enterococcous faecium*. A single *intraperitoneal* injection 45 min after bacterial infection of $3x10^9$ phages protected all the mice, whereas when the treatment was postponed until disease peaked (18-24 hours after infecting), only 50% could be saved from death. In both cases, the amount of pathogen has significantly decreased in the blood (Biswas et al., 2002) (Sulakvelidze and Kutter, 2012).

CLOSTRIUDIUM DIFFICILE IN HAMSTERS

Phages were extracted and isolated from lysogenous *C. difficile* to be tested on 26 hamsters, who were gastrically infected by 1 ml 10^3 CFU/ml *C. difficile*. The phage-treated group received 1 ml 10^8 phages directly, and additional phage doses were administered after each 8 hours in two of the groups. All animals in the control group died within 96 hours after being infected, whereas all the hamsters in the treated group, except for one individual, survived the infection, although phages were not noted to have a prolonged effect. It has been concluded that phage therapy can be effective against pathogenic *C. difficile*, but it remains important to neutralise gastric acid when administering phages orally, in order for them not to get deactivated (Ramesh et al., 1999) (Sulakvelidze, 2012).

PHAGE THERAPY IN AQUACULTURES

Aquatic organisms are also prone to many bacterial diseases, such as aeromonosis and pseudomonosis, thus requiring antibiotic treatment, to escape economically harmful effect (increased mortality, decreased growth, etc.) on aquatic farms. Considering the problem of the progressively growing antibiotic resistance within bacteria, phage therapy can therefore find its application even here (Nasibullin et al., 2013).

Aeromonas bacteria are a common pathogen within aquatics, causing aeromonosis, which is a dangerous disease encountered in aquacultures. Since many bacterial strains from the *Aeromonas* family can give rise to aeromonosis, its treatment is not easy to issue. (Nasibullin et al., 2013).

Today the standard treatment against aeromonosis is usually antibiotics, iodine-containing compounds and formalin (Revenko, 1978); however, these treatment agents are not safe for the fish by inhibiting their intestinal microflora, exerting a hepatotoxic and nephrotoxic effects, as well as killing the saprophytes that are so important for the ecology. Gradually, bacteria develop antibiotic resistance via multiple mutations. Phage therapy can be used for treating aeromonosis. Among the advantages of phage therapy towards standard treatment, it can be noted that phages

are not toxic to the animal (e.g. immune system does not get inhibited and the bacterial flora is not damaged) and the phages are only active against one specific pathogen time (high specificity), no other microbes. Therefore, phage therapy has clear advantage in being used for treatment of aeromonosis.

Another notable aquatic bacteria is *Flavobacterium psychrophilum*, a thin filiform gram-negative bacteria, causing BCWD (bacterial coldwater disease), also known as RTFS (rainbow trout fry syndrome), which is spread worldwide. Possessing three serotypes, this microbe has proved to be epizootic for fish exposed for stress, with mortality varying from 1-90%. It has been established that *F. psychrophilum* can both be transferred vertically and horizontally, where the vertical transfer occurs via roe infection, which makes it crucial to test both the spawner and the fertilised roe for the bacteria, before incubating it (Iida and Mizokami, 1996) (Nyman and Wiklund et al., 2000) (Dzuba, 2012).

The standard treatment is comprised of antibiotics; however, the problem of antibiotic resistance, mainly due to the development of a protective biofilm, is growing in relevance. The bacterium still remains sensitive to tetracycline and erythromycin, somewhat less sensitive to oxolinic acid, and even less so to gentamycin and streptomycin, whereas all bacteria strands appeared to be resistant towards kanamycin. (Sundell and Wiklund, 2011) (Ustimenko, 2012). There is ongoing research on how phage therapy can be used for the treatment of RTFS. (Zolotukhin et al., 2013)

Yet another fish disease to consider is pseudomonosis, characterised by such symptoms as fatigue, haemorages on gills and fins, dislocation of the scales, exophthalmos, etc., causing significant harm to aquacultures (Nasibullin et al., 2013) (Grinyova et al., 2013). Antibiotics are currently used against *Pseudomonas*. Phage therapy, being highly specific towards the microbe, with its lytic activity, is suggested as a means for treatment of pseudomonosis, (Vasilev et al., 2013).

Phage therapy has been shown to work on *Lactococcus garvieae*, by intraperitoneally infecting sea king fish fry and, thereupon, injecting *L. garviae* phages *i.p.* As a result, 100% of the fishes that undergone phage therapy survived, whereas only 10% of the fishes in the control group survived. (Nakai et al., 1999)

Pseudomonas plecoglossicida is yet another opportunistic aquatic pathogen, inter alia, causing haemorragic ascites in fish. In a Japanese 2-week investigation, fish were infected orally with *P. plecoglossicida* (10^7 CFU/g) and thereupon fed with respective phages (10^7 BFU/g). After the first week the fishes in the control groups started to die, eventually rendering 65% mortality, whereas in the phage treated groups mortality did not exceed 23%. Laboratory experiments were neatly confirmed by a natural treatment session of *P. plecoglossicida* in a pond, which decreased the daily mortality rate to 5%, making it three times less after 14 days, as compared to the control groups (Sulakvelidze and Kutter, 2012).

DISCUSSION

Today, phages regain their usage within human and veterinary medicine and new medicals are being created based on phages. They are usually compared to antibiotics, since both are the main treatment agents against bacterial diseases. Their efficiency is expressed in several aspects, such as their compatibility with other pharmaceuticals, their natural origin, and the fact that they are not known to cause allergies or addiction (Sulakvelidze et al., 2001).

There are no known serious counter-indications and side effects when using phages, as compared to the multiple side effects, allergies, and secondary infections caused by antibiotic treatment (Yao and Moellering, 1995). Furthermore, an evident advantage is their positive effect against antibiotic-resistant bacteria, implying that even though phage-resistant bacteria come about, being resistant to a certain phage; they remain susceptible to other phages within the target range, as compared to antibiotics, where resistance to antibiotics is not limited to targeted bacteria. As some authors point out, possessing a broad-spectrum activity results in selection for many resistant bacterial species, not just for resistant mutants of the targeted bacteria (Salyers and Amabile-Cuevas, 1997); phages having a narrow-spectrum activity specifically select for resistant mutants of the targeted microbe, not selecting for resistance in other species. Phages are biotic viruses and their natural origin leads to the hypothesis that phages can potentially be selected against every antibiotic-resistant or phage-resistant bacterium by their ongoing adaptive capacity. In other words, viruses, being microorganisms, can always overcome the resistance that bacteria develop against them, constantly “manufacturing a newer key to the new lock”. In addition, their high specificity is beneficial, implying that a phage infects and thereby kills only a certain bacterial species, no other microorganisms, as compared to antibiotics that target both pathogens and normal microflora. This results in microbial disequilibrium and dysbacteriosis, which may lead to serious secondary infections, which do not develop after phage therapy (Chernomordik, 1989). Moreover, phages replicate at the site of infection, thus being abundantly available where needed, requiring less frequent phage administration for optimal therapeutic effect, as compared to antibiotics, which get metabolised and eliminated from the body and do not necessarily concentrate at the site of infection, unless being tropic to the respective tissue (Smith and Huggins, 1982).

However, phages are also known to have their respective limitations. As mentioned above, phages are highly specific bactericidal agents, which can both be an advantage, namely that phages only target certain bacterial species, not killing unwanted microbes, yet simultaneously it is a disadvantage. It is known that bacterial strains of the same species may structurally differ within the species; due to this morphic variety, phages does not always succeed targeting bacteria within the same species.

Another important consequence of the phages' high specificity is that the bacterial species must be identified prior to initiating phage therapy, as compared to antibiotics that are generally more effective than phages, when the identity of the etiologic pathogen is not yet known. Antibiotics simultaneously affect many bacterial strains; however, at the same time bacteria are more prone to develop resistance against them. Some authors reported certain side effects for therapeutic phages *in vivo,* which they surmise might have been evoked by the liberation of endotoxins from lysed bacteria (Cislo et al., 1987) (Slopek et al., 1987), also because these side effects are common for antibiotic therapy as well (Prins et al., 1994) (Sulakvelidze et al., 2001). Additionally, phages have not currently been discovered for all the known pathogenic bacteria, implying that phage therapy cannot access treating diseases caused by those bacterial species, without the respective phage against them. Specialised transduction, which has previously been described in this paper, is another difficulty that can disturb phage therapy. Finally, the host's immunity can pose a potential threat to phages, recognising them as foreign, but phages usually operate fast and manage to infect bacteria, escaping the immunity.

Considering both the strong and the weak sides of phages, as compared to antibiotics, in some countries phages are viewed as a secondary choice in humane medicine, to be used in cases where the stage is not acute and the condition is not death-threatening, or to be used as additives to the principal antibacterial (usually antibiotic) therapy. In the future, bacteriophages are most probably going to be a compliment to antibiotics, perhaps even used in synergy with them, due to the progressively increasing antibiotic resistance problem that is overwhelming. The following table is from a website and the activity of the functional range of these medicals cannot be validated. The phage medicals in this table can be purchased e.g. on this Russian website: https://www.medsovet.info/

Bacteria	**Phage therapy**
Staphylococcus	Staphage, pyophage, intestiphage
Streptococcus	Streptophage (liquid), pyopolyphage (tablets)
E. coli	Polyvalent pyophage, coliproteal phage
Enterococcus	Intestiphage
Pseudomonas aeruginosa	*Pseudomonas aeruginosa* phage (liquid)
Klebsiella pneumoniae	Polyvalent pyophage (liquid, purified)
Proteus vulgaris et mirabilis	Proteal phage (liquid), pyopolyphage (tablets)

Figure 1. Prescribed phage therapy against some common bacterial infections

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