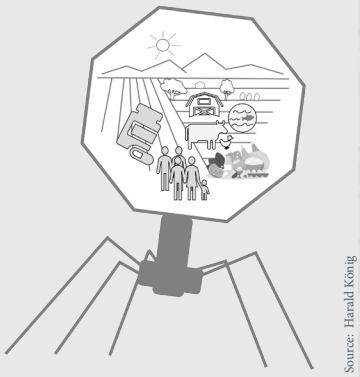
TAB OFFICE OF TECHNOLOGY ASSESSMENT AT THE GERMAN BUNDESTAG

Bacteriophages in medicine, agriculture and food industry – application perspectives, innovation and regulatory issues



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Summary

- In view of the major challenges to the health of humans, animals and the environment (One Health), especially due to antibiotic resistance, phages represent a relevant option – the potential of which should be investigated and exploited more intensively.
- Under the current framework conditions, however, it seems to be unlikely that the use of phages for therapeutic purposes in medicine or for applications in agriculture and the food industry will become established in the EU or in Germany better or on a larger scale than it has been so far.
- To achieve this, it would be necessary to make the legal framework conditions more suitable and flexible, to create special approval programmes and economic incentive structures (e. g. for novel antimicrobial drugs) and to promote research and development activities on phages in a more targeted way.
- A more intensive exchange on these issues between politics, science, industry, regulatory authorities and – in the case of phage therapy – stakeholders from the health system, such as health insurance companies and patient representatives, should be strived for. This could be the starting point both for tangible practice-oriented steps to design regulations at the national level and for initiatives to make regulation at the EU level more flexible.

What is involved

Bacteriophages (or phages for short) are viruses that can specifically attack and destroy certain bacteria. They are considered the most abundant biological entities on earth and, together with bacteria, are found in all habitats – including in animals and humans (with large numbers especially in their intestinal tract). Phages were discovered over 100 years ago and have been investigated and used as an option to fight bacterial infections – especially in humans, but also in animals and plants. In some countries of the former Soviet Union or Poland, phages have been used continuously as approved drugs or for personalised or experimental treatments of chronic and antibiotic-resistant infections in human medicine. In contrast, phages were hardly used for medical purposes in western industrialised countries for a long time after antibiotics became available in the 1940s.

Particularly in view of the worldwide growing **problem of antibiotic resistance** for human, animal and environmental health, phages are once again being discussed as a relevant option for combating pathogenic bacteria or bacterial infections in medicine as well as in agriculture and the food industry. Hence, approximately from the beginning of the 2000s, phages were taken into consideration again by researchers, physicians, patients and some young biotechnology companies for the **treatment of infections that respond poorly or even not at all to antibiotics**. In 2019, in Germany alone, more than 45,000 people died in association with antibiotic-resistant infections, i. e. on average one person every 12 minutes. In western industrialised countries, however, there is no phage preparation yet that is approved as a drug. And currently, phages can only be used under exceptional conditions in individual cases when available drugs have failed. Also, bacteriophages are increasingly being investigated for use in agriculture and the food industry. In these sectors, some commercial preparations are available or usable – but mainly outside the EU.

However, the special properties of phages compared to synthetic or chemical substances pose particular challenges for both the development and approval of effective drugs and commercial products to fight bacteria along the food chain.

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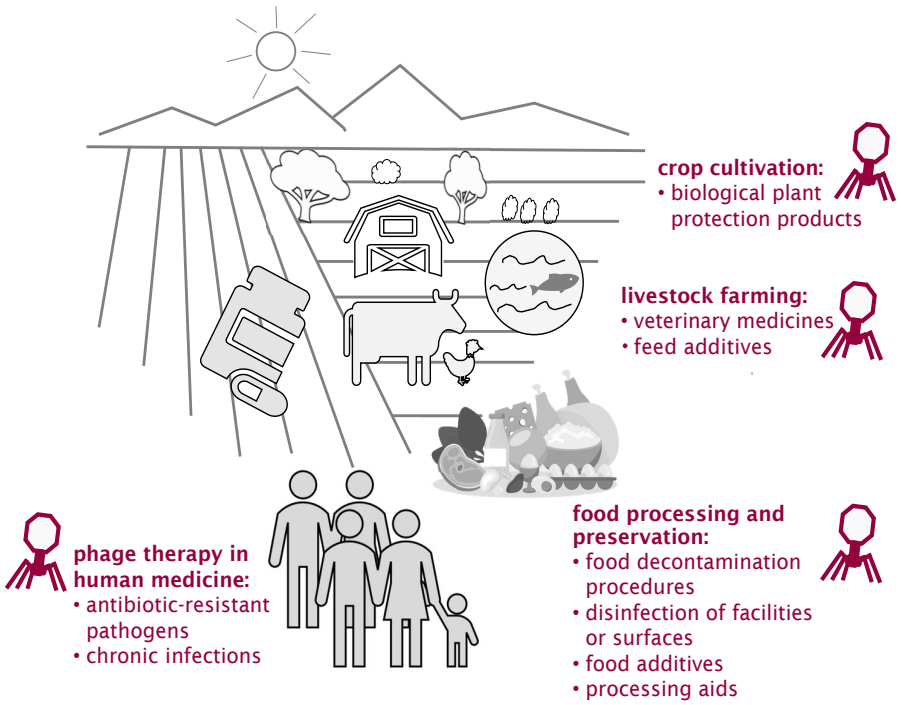
In order to better explore the existing multifaceted potential of phages in these areas and to be able to use it to a greater extent in the future, legal and innovation policy issues would have to be addressed in addition to scientific and technological questions.

Phages as bacteria killers for fighting pathogens in a targeted manner

Due to some special **properties**, bacteriophages are particularly suitable to specifically combat bacterial pathogens that are otherwise difficult or impossible to deal with – especially antibiotic-resistant germs. Thus, their effectiveness is generally **not impaired by antibiotic resistance mechanisms**. At the same time, possible bacterial resistance to phages can make bacteria sensitive to antibiotics again, and phages can act **synergistically in combination with antibiotics**. Moreover, some phages can be used for **fighting bacteria in biofilms**, which play an important role in difficult-to-treat infections in medicine as well as in the food processing industry. In biofilms, bacteria are embedded in a mucus-like matrix they produce themselves, which can protect them from antibiotics or disinfectants. Finally, phages generally show a very **high host specificity** (each phage species infects only certain bacteria), so that harmful side effects on non-pathogenic bacteria in the body or in soils can be avoided or reduced.

Possible use of phages in medicine as well as in agriculture and the food industry



Applications in medicine – phage therapy

Bacterial infections are often caused by several pathogens or pathogen strains in a patient-specific composition. For this reason, and due to the development of possible bacterial phage resistance, effective phage preparations must contain mixtures of different phages (phage cocktails) or ideally be prepared individually for each patient with regard to their composition. Thus, phage therapy comprises two different basic types of approaches:

- **Treatments with phage preparations** the composition of which is **defined in advance and which can be kept available for certain indications (off-the-shelf)** as well as
- **personalised therapies** with preparations specifically tailored to patients or their pathogen strains, which are composed of phages derived from special phage collections (phage biobanks) and/or specifically (newly) isolated phages.

Positive results obtained so far on the efficacy and safety of phage therapies have come almost exclusively from case studies or series of **case studies of individual patients (often with no further treatment options left)** with difficult-to-treat chronic and/or antibiotic-resistant infections who were treated with phage preparations specifically tailored to the pathogens. In addition, larger clinical **trials** were conducted **in former Soviet Union countries such as Georgia and Russia**. However, these studies did not meet the criteria of randomised, blinded clinical trials using placebo or standard treatments for comparison (randomised controlled trials), i. e. the study design required for proof of efficacy and safety as well as for marketing approval of (most) drugs and treatments in the EU or the USA. In Germany, a number of successful treatments of antibiotic-resistant infections have been carried out and published within a framework for compassionate use (»individuelle Heilversuche«) by few (mostly university) hospitals. However, only few **randomised clinical trials** have been conducted so far, i. a. in France, Great Britain and Switzerland. In fact, these studies with predefined phage cocktails did not show any serious undesirable side effects, but – with the exception of one relatively small study – they were also unable to prove the efficacy of the therapeutic approaches. However, all of these unsuccessful studies had conceptual, practical or technical problems in their implementation, e. g. a lack of examining

the actual causes of infection and/or the phage susceptibility of the pathogens.

Even if efficacy still has not been proven by larger clinical trials in compliance with modern standards: **Results from preclinical studies as well as clinical experience**, especially from case studies of patients who no longer responded to other treatments, suggest that phages might be an important **option for treating difficult-to-treat and/or antibiotic-resistant infections**. This is especially true for phage preparations that are tailored to the individual patient's needs and the respective pathogens or that are used together with antibiotics. A number of new clinical trials, including the first studies using personalised phage cocktails tailored to patients' pathogens as well as genetically modified (upgraded) phages, have been initiated since 2021. The vast majority of these studies are sponsored by biotechnology companies and are conducted in the USA (also by most of the European companies).

Applications in agriculture and the food industry

The common goal of bacteriophage application in agriculture and the food industry is to replace or reduce problematic chemical substances such as plant protection products, veterinary medicines and antibiotics as well as disinfectants. Similar to human medicine, mixtures of different phages are usually used for applications in this field.

In **livestock farming**, phage preparations can be used not only as veterinary medicines but also as feed additives. In particular, this is intended to reduce the contamination with pathogens of food derived from these animals. Some bacteriophage preparations are already being marketed in countries outside the EU for use in the main livestock species of pigs, chickens, cattle as well as in aquaculture. Overall, since the vast majority of plant protection products are used against insects, fungi and weeds, phage applications in **crop cultivation** can only make a small contribution to saving pesticides – in quantitative terms. However, certain plant species can be particularly severely affected by bacterial pathogens and irreversibly damaged. This especially applies to fruit trees. In order to be able to preserve the infested plants, only copper and antibiotics are available – both of which are ecologically very problematic and the use of which is tightly regulated. Similar to veterinary medicine, there are only very few phage preparations already commercialised or in development for fighting bacterial plant diseases. So far, no phage preparation has been approved for use as a plant protection product or biopesticide in the EU. Only once, a regionally limited use of a phage preparation against fire blight in fruit trees was permitted under strict conditions. When used on plants, phages can be rapidly inactivated in the field – for example by UV radiation or desiccation. This is one of the reasons why the use of bacteriophages as biocontrol agents is considered to have better chances in non-outdoor crop cultivation (e. g. greenhouses, vertical farming or hydroponics).

In **food processing and preservation**, phages can be used for fighting pathogens that can spread to humans and cause foodborne infections and for preserving food for longer periods of time. Food of animal origin (meat, fish and seafood, milk and dairy products, eggs), but also vegetables – especially in ready-to-eat form – are particularly at risk of being contaminated with pathogenic bacteria. The four main food law categories in the EU concerning possible phage applications are the use as a method of decontamination of food, disinfection of facilities, surfaces, etc. in food production or storage, as food additives or as processing aids (used in the production process and remaining in the product without having any further function there). Phage preparations are commercially available for the treatment of freshly cut, ready-to-eat fruit and vegetables, for use in meat processing and for cheese production. However, due to the lack of approval under food law, they are not yet allowed to be used in the EU – unlike in the USA, Canada, Israel or Switzerland.

In the EU, phage preparations without labelling or approval can only be used as processing aids in food processing. Reliable figures on the actual use are not available.

Challenges and options for action in medicine

Without successful clinical trials as a prerequisite for marketing authorisation of phage preparations, they can still only be used within the framework of exceptional regulations for special need cases, i. e. for compassionate use treatments or after medical prescription and compounding in pharmacies (magistral formula) for individual patients.

In addition to **scientific and technical issues** – which can be addressed through the funding of various R&D activities and specific research programmes – there are also **regulatory challenges** with regard to the successful development of phage therapies with marketing approval. These are based on a relatively inflexible framework for approval in the EU that is largely geared towards invariable combinations of active pharmaceutical ingredients and standard therapies. Under the current regulations, for example, the necessary regular updates of phage cocktails – i. a. to counter phage resistance – would require costly and lengthy new applications for marketing authorisation. On the other hand, there are **economic challenges**: The high R&D costs for the most promising (personalised) phage therapies with a particular potential benefit – i. e. for infections that are difficult or even impossible to treat conventionally with antibiotics – would have to be recouped by the treatment of relatively small

groups of patients. This is why both **adjustments to the EU regulatory framework and economic incentive schemes for new antimicrobial drugs** are likely to be required to encourage or enable a broader and more diverse development of phage products with marketing approval than has been the case so far.

However, the necessary adjustments at the EU level could be lengthy or even fail. Or possible regulatory adjustments could prove to be too inflexible to also enable forms of treatment for which new phages would have to be isolated on a patient-specific basis. This is why, in parallel, it seems advisable to develop **possible exceptions under EU law in Germany** already now in such a way that – in cases of special need – phage therapies will become available to a larger number of patients than has been the case up to now. For this, particularly a **practice-oriented adaptation according to the Belgian model** might make an important contribution in order to facilitate the treatment of individual patients with (magistral) phage preparations produced individually in specialised pharmacies.

Challenges and options for action in agriculture and the food industry

In addition to the scientific and technical problems that need to be solved with regard to the development of phage preparations for practical application, the legal framework conditions – which are still mostly geared towards individual, defined chemicals – are considered to be a major obstacle. The resulting **requirements for the approval of phage products are often unclear** and pose major challenges, especially for small and medium-sized companies – which currently are the major players in the development of commercial applications.

TAB report no. 206

Bakteriophagen in Medizin, Land- und Lebensmittelwirtschaft – Anwendungsperspektiven, Innovations- und Regulierungsfragen

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This is why **political initiatives or support** are primarily needed to **review regulation in all areas of application** and, if necessary, to develop it further by **adding specific guidelines on phages**. The starting point for this might be corresponding guidelines in the new Veterinary Medicinal Products Regulation. Clarifying the conditions for use might enable various applications both in agricultural production (veterinary medicines and plant protection products) and in post-harvest food processing and preservation. In addition, the funding of longer-term research initiatives and networking activities – involving research institutions, companies and applying enterprises – might contribute to setting up capacities and competencies. Last but not least, such initiatives should also take into account research on safety issues, such as in particular the potential spread of phage resistance as a result of a broad use of bacteriophages.

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