WRITTEN EVIDENCE SUBMITTED BY QUADRAM INISTITURE BIOSCIENCE (PHA0004)

Quadram Institute Bioscience (QIB) (quadram.ac.uk) receives strategic funding from the Biotechnology and Biological Sciences Research Council to create new interfaces between food science, gut biology, human health and disease, capitalising on the world-class bioscience cluster based on the Norwich Research Park.

Its vision is to understand how food and microbes interact to promote health & prevent disease.

QIB's research programme covers these main areas, where we are looking to answer major fundamental questions:
Microbes in the Food Chain – How can we reduce microbial pathogens in the food chain, and prevent the emergence of antimicrobial resistance?
Gut Microbes and Health – What is a healthy gut, and how is health modulated by our resident gut microbes?
Food Innovation and Health – How can we enhance the quality of food to promote lifelong health?

At QIB, researchers are undertaking projects to establish how bacteriophages contribute to the functioning of the human gut microbiome, how bacteriophages can be used to modulate this microbiome, and how bacteriophages can be used as biocontrol agents in therapy and as antimicrobial agents in the food chain and the environment.

How well established is the evidence base for phages as an antimicrobial for humans?
Phages have been used for 100 years in the treatment of bacterial infections. Most of our current knowledge on routine treatment of human bacterial infections comes from the Eliava Institute of Bacteriophages, Microbiology and Virology in Georgia, host to the Eliava Phage Therapy Centre. In this centre, since 1923, patients have been treated with cocktails of bacteriophages as well as custom bacteriophages tailored to the specific bacterial strain(s) causing the infection. As a result of the perceived success of these treatments, randomised controlled trials for the therapies were never initiated.

In Europe and the USA, the majority of phage therapy cases are conducted under "last resort" regulations, meaning that phages can be administered to patients if all other treatment options are exhausted. This means that case studies are usually limited to very ill patients. Despite this, phage therapy has known many success stories in which patients recovered after phage therapy, usually in combination with antibiotic treatment. A recent systematic review of English scientific literature on phage therapy cases in difficult to treat infections (Uyttebroek et al, 2022), showed that phage application was well tolerated with mild adverse effects lower in prevalence than the control group, with clinical improvement in 79% of patients. This is a very high number, taking into account that at that point in the treatment process all other options had been exhausted, and the only remaining options were amputation, chronic illness or palliative care. In some case studies, however, the treatment was only assessed by the clinical outcome, i.e. patient recovery, and no research samples were taken to assess whether the phage was the main agent of recovery. It is also noted in many case studies that the main aim of phage therapy was patient welfare, not the collection of data for research.

A limitation on the current evidence base is the absence of high-quality clinical trials. The Phagoburn phase I/II clinical trial in France and Switzerland, while set up as a rigorous trial, had a breakdown in the stability of the investigated 12-phage cocktail resulting in a dose applied that was 10,000x lower than expected. The limited success demonstrated should not be considered a failure of phage therapy in itself.

What are their strengths and weaknesses?

Strengths:

- Specificity: phages target specific bacterial strains thus limiting off-target effects on the beneficial microbiota, common after antibiotic use.
- Auto-dosing: phages replicate in bacterial cells and produce new particles that will in turn infect other bacterial cells.
- Self-limiting: when no host bacterial cells are available, phages will be inert particles and degrade.
- Overcoming resistance: while bacteria can become resistant to individual phages, these phages can then in turn develop mutations to overcome such resistance. Bacterial resistance development can be reduced further by using a combination (or cocktail) of phages that target different receptors and have different infection strategies.
- Limiting virulence: phages can be selected so that when bacteria develop resistance, the resulting resistant bacterium is less virulent to humans.
- Limited toxicity: phages are inherently non-toxic to humans.
- Capacity to act on biofilms: phages can be selected for their ability to degrade biofilms which are a barrier to many antibiotics.
- Potential for phage-antibiotic synergy: phages and antibiotics can be selected so that their mode of action and resistance development has a synergistic effect, for example, resistance against the phage can result in increased sensitivity to the antibiotic, or the use of a biofilm-degrading phages allows an antibiotic to work more effectively.
- Natural and ubiquitous: phages are everywhere and humans ingest them by the millions every day.

Weaknesses:

- Specificity: since each individual phage only infects a limited number of bacterial strains (narrow host spectrum), host range tests need to be carried out in the lab before treatment can be started.
- Need for characterisation: the individual phages to be used need to be well-characterised, their genomes sequenced and analysed as well as their life cycles verified, because not all phages are well suited for therapeutic purposes. A subset of phages, called temperate phages, employ the lysogenic life cycle, meaning that they can incorporate their genome into that of the host bacterium. These temperate phages are considered not suited for therapy.
- Potential to invoke immune response: some phages invoke an immune response and are rapidly cleared from the body, thereby limiting their usefulness.
- Lack of IP protection: the traditional pharmaceutical industry has historically shown limited interest in phages because it is hard to protect the IP. In the theoretical case where one single phage was to be developed into a product like an antibiotic and likewise protected by patents, there is nothing stopping others from isolating and developing a different phage that works equally well.
- Stability of phage preparations: not all phage preparations are stable over time and any preparation/formulation will have to be extensively characterised. This weakness can be overcome by only preparing the preparation when the phage treatment will be given.

(references: Loc-Carrillo & Abedon, 2011 [doi: 10.4161/bact.1.2.14590]; Gordillo Altamirano & Barr, 2019 [doi: 10.1128/CMR.00066-18])

What regulatory approaches have been used by other countries for the use of phages and what lessons can the UK learn?

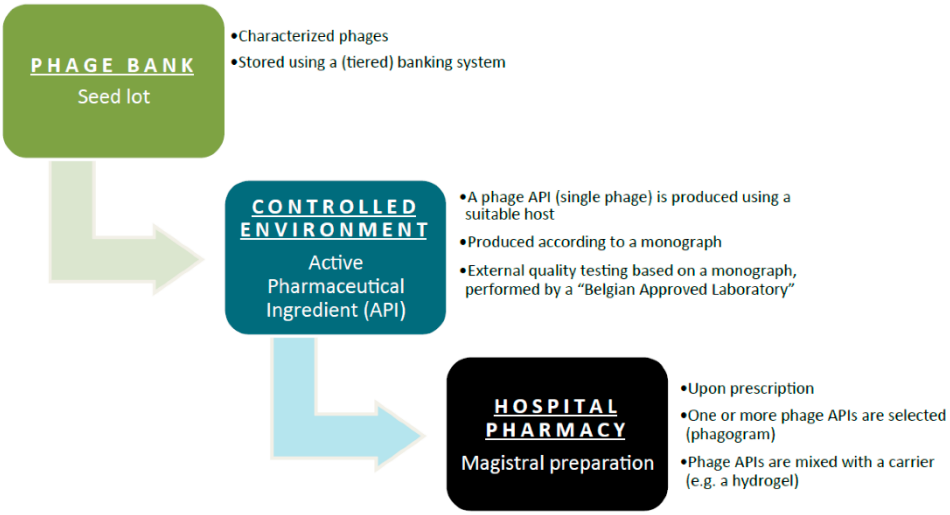
Georgia: phage therapy in all forms allowed. The therapy is administered and regulated by a national research institute, the Eliava Institute in Tbilisi.

USA: Bacteriophages are considered biological products and are regulated by the Center for Biologics Evaluation and Research at the Food and Drug Administration (FDA). Most treatments in the USA have been under the “expanded access to investigational drugs for treatment” route, which is often referred to

as compassionate use. Therapeutic application in humans requires that an investigational new drug application (IND) is submitted to the FDA by a "sponsor", which can be a new IND for the specific treatment alone, or an amendment to an existing IND which was established for research purposes. For more information see Plaut & Stibitz (2021) in Bacteriophages: Biology, Technology, Therapy (doi: 10.1007/978-3-319-41986-2_52).

EU: Phage therapy is allowed under the Declaration of Helsinki, a set of ethical principles – not laws - governing medical research on human subjects (https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/). Article 37 allows for the use of unproven interventions in clinical practice, which should then be the subject of medical research, similar to the guidelines governing phage therapy in the USA. Important to note is that in the EEA, bacteriophages are subject to Directive 2001/83/EC stating that any substance used to treat or prevent disease in humans is a medicinal product and may not be put on the market in the EEA without authorisation of the competent regulatory authorities (Pelfrene et al, 2021 in Bacteriophages: Biology, Technology, Therapy doi: 10.1007/978-3-319-41986-2_51).

Belgium has taken this further into law and has extracted phage therapy from the drug discovery funnel using the principle of magistral preparations, which are described as "any medicinal product prepared in a pharmacy in accordance with a medical prescription for an individual patient" (Pirnay et al, 2018, doi: 10.3390/v10020064). The procedure for phage therapy (see Figure) starts with a Phage Bank of approved and well-characterised phages from which a clinician can prescribe. The phages are then produced at a centralised lab according to a monograph, sent to a hospital pharmacy where they are tested to check whether or not they work on the bacteria (phagogram) and are prepared by the pharmacist for direct application.



Other EU countries: Germany, France and Finland (and potentially other countries) are all looking into the Belgian model for the implementation of phage therapy. This is facilitated by companies that provide services on different aspects of the magistral pipeline but are monitored/regulated by the European Medicines Agency.

What opportunities does the UK have for regulatory divergence from the EU on phages, and what would the implications be?

There are many opportunities for divergence since there is not one set of laws regulating phages. EU countries are regulated by the Declaration of Helsinki, but these guidelines are interpreted and put into law by each country independently. As discussed above, the Belgian model, which is taken as an example by

other EU countries, has strict criteria for the choice of phage product. The phage used must be free of toxins and should not be temperate. Furthermore, the competent authority that regulates the access to market of medicinal products is now separate from the European Medicines Agency, where the UK MHRA can make decisions independently.

Opportunities exist in the choice of the individual bacteriophage products. All current phages approved for use in the EU are naturally occurring phages, i.e. isolated directly from the environment and used in their natural state, as well as their natural derivatives. Engineered phages in which the properties have been modified by genetic engineering approaches are currently not used in the EU. This provides an opportunity for the UK to regulate the use of engineered phages. There are many implications to the use of engineered phages, both as risks and opportunities. The risks are the spread of modified phages in the environment and unknown effects of using these phages therapeutically. The opportunities are an increase in the number of infections that can be targeted, i.e. infections for which no suitable natural phages can be found, an increase in the efficacy of treatments if phages can be engineered to be more effective, and the potential for IP protection of engineered phages, which would allow broader interest from pharmaceutical companies into this therapy.

Two engineered phages have been successfully used in the UK in a high-profile phage therapy case in 2019. Isabelle Carnell-Holdaway, who had cystic fibrosis and a persistent lung infection with *Mycobacterium abscessus,* was treated with a cocktail of two temperate phages that were engineered to be virulent in a collaboration between Great Ormond Street Hospital and the University of Pittsburgh (doi: 10.1038/s41591-019-0437-z). The patient recovered from this infection but died in 2022.

What are the major barriers and opportunities relating to the development and deployment of phages in the UK?

Barriers:

- Lack of awareness by clinicians of the existence of phage therapy, its applications and its strengths and weaknesses.
- Lack of dedicated funding.
- Lack of support from pharmaceutical industry.
- Limited number of research groups in the UK investigating clinical applications.
- Insufficient knowledge of the mechanism of action of novel phage.
- Insufficient knowledge of the activity of phage in diverse environments and modes of application.
- Insufficient diversity of phage collections with detailed knowledge of their mechanism of action and host range.
- Insufficient knowledge of optimal combinations of phage.
- Insufficient knowledge of optimal therapy applications.

Opportunities:

- Opportunity for growth of the industry, including the creation of spin-out companies from universities and research institutes.
- Opportunity to create world-leading national capability into phage research.
- Development of new antimicrobials that have the potential to decrease the emergence of resistance against important antibiotic therapies.

How well developed is the UK's phage research and clinical trial pipeline and how could it be improved?

According to publicly available information on clinicaltrials.gov, the UK has no ongoing clinical trials on the use of bacteriophages and does not have any finished trials either, with one planned trial withdrawn due to lack of funding. Compared to the rest of the world, there are 14 completed trials using bacteriophages as an intervention, and a further 14 actively recruiting patients. These aggregate data show that the UK is

behind in its clinical trial pipeline for phages. However, it is unclear what the underlying reasons are for the UK's lagging pipeline.

Improvement is possible in all stages of the clinical trials pipeline. Increased funding into fundamental phage research needs to be linked up with the needs of the clinics and NHS Trusts, in which awareness needs to be raised. Dedicated funding streams could be made available for research into the treatment of difficult-to-treat infections. Incentives for pharmaceutical and other companies to develop a phage therapy branch of their research and development would lead to more products in the pipeline.

To what extent is the UK Government ensuring that phages research and development is adequately funded and supported?

There is currently no dedicated funding stream for phage research. A review of Gateway to Research using the key words "phage OR bacteriophage" shows that in the past five years, 40 research grants have been awarded to 23 institutions. Of these grants, 21 were awarded by BBSRC, eight by MRC, five by Innovate UK, three by UKRI, two by NERC and one by EPSRC. Only 15 of these could be classified as related to human applications, none of which involve product development or clinical trials.

It is our opinion that dedicated funding for phage research aimed at research into clinical applications, the creation of a characterised phage BioBank (or multiple) and support for basic research will be of great assistance to the field.

Bacteriophage research for clinical applications is more advanced in many parts of the EU/EEA. Association status with Horizon Europe is essential for advancing the UK's research status. Continued membership of the Joint Programme Initiative on Antimicrobial Resistance (JPI-AMR) which funds phage research in the context of AMR remains crucial, allowing UK scientists to collaborate with others in Europe.

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