Written Evidence Submitted by University College London (PHA0034)

The following submission represents the current state of scientific thinking about and evidence on the antimicrobial potential of bacteriophages collated from academics with different disciplinary expertise including clinician-scientists at University College London (UCL). As a multi-faculty, comprehensive university, with hospital partners including Great Ormand Street Hospital, UCLH and the Royal Free, UCL colleagues are well placed to offer recommendations for the advancement of research, regulation and policy to enable the UK to take advantage of the potential of phages to address antimicrobial resistance.

A. Executive Summary

A.1. Antimicrobial resistant bacteria are becoming the new global health challenge and there is renewed interest in 'phage' therapy which uses "good" viruses to attack the culprit "bad" bacteria often causing disease[1].

A.2. Phages were used before the discovery of antibiotics and are now increasingly used in some countries including Australia and Belgium because many bacterial pathogens have become resistant to frontline antibiotics.

A.3. Phages generally target the specific bacterial pathogen so in theory do not harm the "good" bacteria or the body's own cells.

A.4. Modern day phage therapy has been documented usually as case studies in cases of compassionate access to treat chronic or recurrent infections but also in several published early phase clinical trials in humans. These data suggest that they are generally safe to use. Indeed, many of us will already have consumed phages which have been added to food products to kill bacteria to make them safer to eat. Only two out of ten trials assessing efficacy reported statistically significant positive results but all had methodological flaws.

A.5. Phage therapy is far from being a standard therapeutic option in the UK due to the lack of published or registered large scale clinical trials, and is rarely available on compassionate grounds due to regulatory requirements and lack of suitably licensed facilities and necessary expertise.

A.6. Out of the handful of registered clinical trials, none are currently hosted in the UK, despite major advances in biological understanding of phage improving their theoretical prospects, because of organisational, methodological and regulatory complexities associated with their manufacture and clinical evaluation.

A.7. By collaborating with scientists and practitioners in those countries which already have the infrastructure, expertise and experience, the UK could develop its own platforms for using whole phages (or some of their enzymes that kill bacteria) to combat high priority antimicrobial resistant pathogens in clinical environments.

A.8. UK government policies for research priorities and investment in different phage

[1] *The Review on Antimicrobial Resistance*, Chaired by Jim O'Neill (2016). https://amr-review.org/sites/default/files/160518_Final%20paper_with%20cover.pdf

technology platforms could lead to a new antimicrobial revolution generating high skill jobs and hundreds of millions of pounds for the economy. This should not only include their conventional use in the medical field to treat infections. The UK should also harness phages for other uses to improve human health and to address antimicrobial resistance by modulating natural microbial communities (i.e., microbiomes) as probiotics, preservation of foods (instead of using chemicals) and controlling bacterial pathogens in agriculture.

B. How well established is the evidence-base for phages as an antimicrobial for humans? What are their strengths and weaknesses?

B.1. Basic science. Bacteriophages (phages) have been used as antimicrobials for over a century. Their clinical use, and related research and literature, has been concentrated in Eastern European countries for much of this time.

A simple PubMed search using the words "phage" and "therapy", brings more than 10,000 results[2]. There is considerable and growing mechanistic knowledge of and experience with phages in laboratory studies. They are very specific to the bacterial pathogen(s) in question (in contrast with broad spectrum antibiotics) and as such they have theoretically a minimal impact on the microbiome (other populations of bacteria in the human body, including the gut). New avenues of research have opened up, namely phage engineering and the use of phage enzymes that kill the bacteria, e.g., to increase the host range of individual phage to kill more bacterial pathogens and to decrease the bacterium's ability to adapt and become resistant to particular phages. Phages are effective in eradicating a broad range of non-systemic infections in experimental animals.[3]

B.2. Clinical trials A recent systematic review of clinical trials included sixteen trials of phage therapy in which 378 patients received phage.[4] Thirteen of the trials reported that phage therapy was safe. The remaining two thirds did not comment on safety while adverse effects in the third were likely due to contaminated phage preparations with bacterial debris. Six of the 16 trials were exclusively safety trials. Only two of the 10 trials testing for efficacy reported positive results. In a small randomised phase 1/2 trial of 24 patients, Wright and colleagues with support from Parexel International treated patients in the UK with chronic otitis caused by *Pseudomonas* with one dose of a six-phage cocktail and reported interim analysis of significant clinical improvements from baseline and statistically significant lower bacterial counts in the phage-treated group compared to the control group.[5] Some information regarding the methods is however missing from the publication. While the trial was stopped early on account of positive results, the larger planned Randomised Control Trial (RCT) was later rejected by the European Medicines Agency (in conversation with trial's co-investigator). More recently, Ooi and colleagues treated patients with chronic rhinosinusitis with a three-phage cocktail for 7 or 14 days and noted that all patients had a reduction in the growth of *S. aureus* and in two of the nine patients bacterial eradication was

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[2] PubMed search (phage + therapy): https://pubmed.ncbi.nlm.nih.gov/?term=phage+and+therapy

[3] Harper DR, Enright MC. Bacteriophages for the treatment of Pseudomonas aeruginosa infections. J Appl Microbiol. 2011 Jul;111(1):1-7. https://doi.org/10.1111/j.1365-2672.2011.05003.x

[4] Stacey, H.J.; De Soir, S.; Jones, J.D. The Safety and Efficacy of Phage Therapy: A Systematic Review of Clinical and Safety Trials. *Antibiotics* **2022**, *11*, 1340. https://doi.org/10.3390/antibiotics11101340

[5] Wright, A.; Hawkins, C.H.; Anggard, E.E.; Harper, D.R. A Controlled Clinical Trial of a Therapeutic Bacteriophage Preparation in Chronic Otitis Due to Antibiotic-Resistant *Pseudomonas aeruginosa*; a Preliminary Report of Efficacy. *Clin. Otolaryngol.* **2009**, *34*, 349–357

achieved.[6] For efficacy to be observed a therapeutic amount must be administered to the right place to treat infections containing enough susceptible bacterial cells.

There are currently two active clinical trials funded by the National Institutes of Health (NIH) on phage therapy[7] and recent clinical studies have been expedited in Europe under national Medical Ethical Committee guidelines. There are nearly 20 current, or recent, clinical trials registered in the USA and four[8] in Europe **There are no active clinical trials using phages in the UK**.

B.3. Observational data from Eastern Europe on treatment of non-systemic human infections, collected over a long period beginning in the 1970s, indicates that good efficacy can be obtainable.[9] A summary of published clinical reports from the past two decades in the USA lists 63 entries[10]. All these cases are ones where the phages were used therapeutically as a last resort for compassionate reasons.[11, 12] In the UK, such use for compassionate access is sparse (two UK patients in a global group of 20[13] and one standalone case[14]) all from imported phage due to regulatory constraints.

B.4.Weaknesses

1. **There is growing clinical evidence** in the scientific literature but from case reports of compassionate access and small clinical trials many of which were not designed to test efficacy, only safety.
2. **Specificity** of phages may also be viewed as a disadvantage as they can be species or even strain specific. This may limit their efficacy in complex infections. However, a way of circumventing this apparent disadvantage is using a “cocktail” of unrelated phages that target a broader group of organisms.
3. **Preparation** of phages may be a limiting factor, but there are companies/institutes in other countries (e.g., USA, Belgium and Georgia) whose production lines are already developed and experienced e.g., in dosing, purification, and delivery. Key to this in the UK is new infrastructure for their production to regulator standards which will differ depending on their final use (see below re: GMP).
4. **Non-standard therapeutic interventions** require exactly the right amount must be administered to the right place to treat infections containing enough susceptible

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[6] Ooi, M.L.; Drilling, A.J.; Morales, S.; Fong, S.; Moraitis, S.; Macias-Valle, L.; Vreugde, S.; Psaltis, A.J.; Wormald, P.-J. Safety and Tolerability of Bacteriophage Therapy for Chronic Rhinosinusitis Due to *Staphylococcus aureus*. *JAMA Otolaryngol.-Head Neck Surg.* **2019**, *145*, 723–729.

[7] See *NIH awards grants to support bacteriophage therapy research* (2021). https://www.nih.gov/news-events/news-releases/nih-awards-grants-support-bacteriophage-therapy-research and *NIH-supported clinical trial of phage therapy for cystic fibrosis begins* (2022). https://www.nih.gov/news-events/news-releases/nih-supported-clinical-trial-phage-therapy-cystic-fibrosis-begins

[8] Clinical trial numbers: NCT03140085; NCT00945087; NCT05369104; NCT02116010

[9] Furfaro LL, Payne MS and Chang BJ (2018) Bacteriophage Therapy: Clinical Trials and Regulatory Hurdles. Front. Cell. Infect. Microbiol. 8:376. https://doi.org/10.3389/fcimb.2018.00376

[10] *Considerations for the Use of Phage Therapy in Clinical Practice* (2022). https://journals.asm.org/doi/10.1128/aac.02071-21

[11] See *Phage Therapy of Mycobacterium Infections: Compassionate Use of Phages in 20 Patients With Drug-Resistant Mycobacterial Disease* (2023). https://academic.oup.com/cid/article/76/1/103/6604409 and *Current State of Compassionate Phage Therapy* (2019) https://www.mdpi.com/1999-4915/11/4/343

[12] *Considerations for the Use of Phage Therapy in Clinical Practice* (2022). https://journals.asm.org/doi/10.1128/aac.02071-21

[13] *Phage Therapy of Mycobacterium Infections: Compassionate Use of Phages in 20 Patients With Drug-Resistant Mycobacterial Disease* (2023). https://academic.oup.com/cid/article/76/1/103/6604409

[14] *First use of pioneering phage virus therapy to treat patient with cystic fibrosis* (2019). https://www.gosh.nhs.uk/news/first-use-pioneering-phage-virus-therapy-treat-patient-cystic-fibrosis/

bacterial cells which can be challenging and subject to variability amongst individual patients. **New avenues for research may improve the prospects for treating populations of patients.**

5. **Resistance**, phage resistance is one of the most challenging barriers to overcome. There is however progress in this field. Circumventing bacterial resistance to phages can be overcome by 1) engineering new phages with the ability to combat bacterial resistance, 2) using cocktails of genetically unrelated phages that target the pathogen(s) of interest, 3) using some of the phage's enzymes instead of whole phages which is probably most efficient. Examples of such enzymes includes lysins that break open (lyse)/kill the bacteria.

Recommendation:
The UK should move forward with enabling and formalising compassionate access to develop standardised therapies and design clinical trials for evaluation on larger populations of patients infected with pathogens of concern.

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

C.1. USA

The USA currently adopts two main approaches to the use of phages: compassionate use for patients with severe infections when there is no therapeutic alternative; and a clinical trial route. In addition, it is evident that regulatory authorities are open to the use of phages for control of infection and have specific guidelines for their preparation as therapies and have registered several clinical trials sponsored by industry.

To benefit human health more widely, the United States Food and Drug Administration (FDA) approved LMP-102 (a bacteriophage) as a food additive to target and kill *Listeria monocytogenes*. LMP-102 was approved in 2006 for treating ready-to-eat poultry and meat products. In October of that year, the FDA also approved the use of bacteriophages on cheese to kill the *Listeria monocytogenes* bacteria, giving them GRAS status (Generally Recognized as Safe)[15].

C.2. Europe

Many different countries are well ahead of the UK on research and clinical use of phages:

- The compassionate use and clinical trial routes are also used in many European countries, in particular Belgium[16], France, Germany and Italy. Belgium is implementing a pragmatic phage therapy framework that centres on the magistral preparation of tailor-made phage medicines, which is proving successful in the treatment of niche infections such as non-systemic MRSA.
- PhagoBurn is a European Research & Development (R&D) project funded by the European Commission on the clinical use of bacteriophages.

C.3. Australia

Phage Australia is a national network of phage researchers and clinicians whose main aim is to share phages for the treatment of bacterial infections at Australian hospitals. They have developed a standardised protocol for the administration and monitoring of phage therapy

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[15] *Science and Regulation of Bacteriophage Therapy* (2021). https://www.fda.gov/media/159400/download

[16] *Processing Phage Therapy Requests in a Brussels Military Hospital: Lessons Identified* (2019). https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6466067/

under a clinical trial framework, known as STAMP[17] (Standardised Treatment and Monitoring Protocol for Adults and Paediatric Patients) (CTRN 12622000181707).

Recommendations:

- The regulation of phages in the UK is currently uncertain, although one small trial in 2009[3] was approved by the MHRA, and there is recent precedent from the US FDA amongst other regulators.
- The standard rules associated with Good Manufacturing Practice (GMP) which cover all medical products in the UK should be reviewed by the MHRA and specific guidelines for phages drafted.

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

D.1. The MHRA does not have guidelines specifically for the preparation of phages as human therapies. Such preparation requires different facilities and expertise from the manufacture of pharmaceuticals, yet these are both currently regulated under GMP of medicines. Specific guidance could be informed by work already done at the US FDA and Phage Australia.

D.2. The UK has many unique opportunities. The first would be to set up an initiative, similar to Phage Australia, involving all UK hospitals for the sharing of phages initially for compassionate use during which therapies can be developed and standardised for research. The second opportunity is to set up a programme to manage the collection of phage, to produce therapies to regulatory standard such as GMP, and to gather robust clinical evidence of efficacy e.g., in clinical trials with MHRA approval and oversight. In addition, there are different university groups, associated with teaching hospitals, already undertaking basic research on phages. It could, therefore, be possible to develop a network to lead on the research and clinical implementation of phage therapy.

Recommendations:

- The UK should develop a “Phage Australia” platform linking all UK hospitals and research groups to facilitate the sharing of phages for compassionate use and enabling clinical trials.
- It will be important for the Government to prioritise research into, and funding to ensure, effective collaboration. This would unhook the latent potential that exists within the UK already. With the right investment from government, for example UCL and partners have all the expertise to lead such initiatives.

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

E.1. Barriers

Regulatory context and lack of facilities

The greatest current barrier is the default MHRA requirement for Good Manufacturing Practice (GMP) production of phages (or lack of coordinated expertise and facilities with

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[17] *Standardised treatment and monitoring protocol to assess safety and tolerability of bacteriophage therapy for adult and paediatric patients (STAMP study): protocol for an open-label, single-arm trial* (2022). https://pubmed.ncbi.nlm.nih.gov/36600337/

suitable manufacturing licenses). A lack of guidelines specifically for phages means that they are treated as medicines (similar to biologics or pharmaceuticals). Currently, there is no UK facility able to produce phages under GMP, so the few cases of phage therapy which have been realised have relied on phages produced in overseas laboratories and imported.

Lack of specific funding to make phage a research priority
There has only recently been an increase in quality research papers on individual cases of phage treatment on grounds of compassionate access from which we can develop therapies. This means that as yet there isn't enough data to create a meaningful evidence-base for future clinical trials. It's clear from the cases of compassionate access and clinical trials that efficacy of phage therapy varies between individuals. This is not surprising and will be improved by the increased use of the technology as is the case for other drug treatments.

Absence of animal models for testing efficacy
Currently there are no suitable animal 'models' for testing efficacy of phages despite their use in veterinary medicine and laboratory studies.

E.2. Opportunities
Finding a pathway to clinical use that addresses current regulatory hurdles opens up significant opportunities for phage therapy. We don't need to reinvent the wheel as there are clear guidelines from Australia, Belgium and the USA on the specific production and use of phages in clinical practice.

The UK has an opportunity to ensure the design of an appropriate phage research and therapy landscape not only for clinical practice but more broadly for microbiome control (e.g., as probiotics), agriculture and food preservation. For example, research should focus on better understanding of the correct dosage and formulation (topical, versus intravenous, versus aerosol etc), appropriate combination with antibiotics, and the number of phages to use (cocktail versus single phage). Expanding our therapy to also include designer or engineered phages with broadened bacterial killing ability (i.e., host range) and the use of phage enzymes will provide further opportunities for investment from pharmaceutical companies. Recent national trials on COVID (i.e., RECOVERY) have demonstrated that the UK clearly has the ability to generate good quality trials and lead the way on new treatment discovery. Without this foundation, the UK faces a future in which it will need to buy expensive formulations from the USA or Europe.

Recommendation: The UK has the ability to generate good quality data through compassionate access use of phages that is not only important for rare cases but where data can also feed into well motivated and designed interventions to be evaluated in large clinical trials. The UK should find an acceptable organisational and regulatory pathway to clinical use that is adapted specifically for phages (and their enzymes) rather than as any other medication. This would provide significant opportunities for the involvement of the pharmaceutical industry in developing this therapy.

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

F.1. The UK's current research pipeline

The UK has a growing number of phage research laboratories and a handful of cases where phages were used for compassionate access including at UCL partner GOSH[18] and promising evidence from the one very small clinical trial[3]. There are also a growing number of physicians, research ethicists and SMEs interested in using or developing phage therapies. However, a lack of financial support, regulatory guidelines and organisational coordination means that progress has been slow. Current lack of regulatory guidelines means that the phages used in the few compassionate access cases were sourced from overseas. This has not only slowed down the development of phage therapy but has no doubt put lives at risk possibly evening leading to deaths. There is currently no clinical trial pipeline in the UK for phages or their products.

F.2. Research pipeline improvements

Priority funding needs to be made available to boost the number and variety of research projects undertaken in this field. A much better evidence base is needed, with key issues for study including, for example, dosing frequency and amount, duration of therapy, mode of delivery, clarity on measurement of hard clinical outcomes - all of which require a well-characterised patient population.

Alongside funding, it will also be necessary to develop clear guidelines to coordinate and streamline the research process to optimise the research and avoid duplication. The UK can look to Phage Australia for an example of a focussed resource that can coordinate all the different research groups and hospital facilities to optimize the research and clinical outputs. In addition, Belgium provides a template for attracting commercial partners to expedite clinical trials.

Recommendations:

- Government funding e.g., through the Research Councils needs to be made available to boost the number and variety of research projects undertaken in this field.
- An industrial strategy may need incentives to move phage therapy beyond compassionate access.
- Alongside funding, the MHRA should also develop clear guidelines to streamline the research process and a national network to optimise the research and avoid duplication.
- Lastly new infrastructure is essential and this requires approved and licensed facilities for the large-scale production of phages (and their enzymes) for their clinical use.

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

G.1. In contrast to countries such as the USA, Belgium and Australia, which are forging ahead with phage research and development, there is very limited support in the UK. While

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[18] *First use of pioneering phage virus therapy to treat patient with cystic fibrosis* (2019). https://www.gosh.nhs.uk/news/first-use-pioneering-phage-virus-therapy-treat-patient-cystic-fibrosis/ https://www.gosh.nhs.uk/news/first-use-pioneering-phage-virus-therapy-treat-patient-cystic-fibrosis/

the MRC and BBSRC have some funds available, the councils' tendency is to take an unfavourable view of early-stage phage therapy, possibly based on unsubstantiated negative beliefs surrounding the utility of the technology.

The UK funders have not advertised any specific funds to support major phage research and development, putting the UK at a huge disadvantage compared to the other countries already making advances. Not only is this deficit a risk to our future competitiveness in the field, but it is currently exacerbating the inevitable challenges of catching up to those in the lead, particularly in the USA and Europe. Funds are needed to facilitate both basic research on phages, their production and use in therapeutics including compassionate access for rare cases as well as more widely in clinical trials.

Recommendation: There are **four essential requirements** for the use of phages (and their enzymes) for therapeutics, **1) clear regulatory guidelines from the MHRA** for the use of phages (and their enzymes) for therapeutics, **2) government and industry funding for the development of platforms** that allow for the large-scale production of phages, **3) government funding for a UK-wide network** similar to Phage Australia for the sharing of phages for individual cases of compassionate access, **4) a MHRA and government supported standardised research platform** for clinical trials of standardised therapies and **5) government and industry investment** that will allow 1-4 to be realised.

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[19] https://www.ucl.ac.uk/research/domains/microbiology