Microbiology Society written evidence to the House of Commons Science and Technology Committee inquiry on the antimicrobial potential of bacteriophages

The Microbiology Society is a membership charity for scientists interested in microbes, their effects and their practical uses. It is one of the largest microbiology societies in Europe with a worldwide membership based in universities, industry, hospitals, research institutes and schools. Microbiology is the study of all living organisms that are too small to be visible with the naked eye. This includes bacteriophages and their bacterial targets.

Our principal goal is to develop, expand and strengthen the networks available to our members so that the science of microbiology provides maximum benefit to society.

We note that our submission reflects the views expressed by 17 members of the Microbiology Society who responded to our call for input. We present evidence provided by our respondents and provide recommendations where appropriate.

Executive Summary

- Current research suggests that phages could be a safe and effective antimicrobial agent. More research is required to support routine prescription of phages in the UK, however there is evidence for the safety and efficacy of phage therapy to support its compassionate use.
- Phages are highly specific, so can target specific pathogens without destroying healthy tissue or microbiomes. They can be used in conjunction with antibiotics to attack pathogens on multiple fronts. This could slow the development of antibiotic resistance and extend the utility of existing antibiotics.
- However, the high specificity of phages poses a challenge for the design of clinical trials, so most are not double-blind or placebo-controlled. Bacteria can evolve resistance to phages as they do to antibiotics. There is also a low risk that phages can pick up and transfer antibiotic resistance genes between bacteria.
- In the UK, phages must be manufactured under Good Manufacturing Practice (GMP) protocol for their compassionate use and for clinical trials. This requirement limits the clinical trials of phages performed in the UK due to the high-cost and lack of manufacturing capability. Other countries (e.g., Belgium, Australia, USA) do not impose a GMP requirement for such use. Aligning with these frameworks by lifting the GMP requirement, or investing in UK GMP manufacturing facilities, would accelerate the clinical trial process and simplify the compassionate use of phages.

- Phage-specific funding calls for both fundamental phage research and interdisciplinary research across academia, industry and clinics would be beneficial.

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

Some current research is outlined below. It is worth noting that while this question specifically addresses use of phages as antimicrobials in humans, use of phages in agriculture, for example to reduce antibiotic use in animals, could be beneficial.

1. **Recent Highlights**

   Phages have been employed in Eastern Europe and Russia for decades. More recently there have been clinical trials in Western Europe, North America and Australia to test the efficacy of bacteriophages[1]:

   a) There are studies investigating phage application in respiratory conditions such as *Mycobacterium abscessus*[2] and *Pseudomonas aeruginosa*[3] that show promising results.

   b) Phage therapy has been successfully employed by the NHS. A cystic fibrosis patient with a drug-resistant infection was treated successfully at Great Ormond Street Hospital[4]. More recently, patients with diabetic foot ulcers were successfully treated and as a result NHS Scotland appointed the UK's first clinical phage specialist[5].

   c) Basic research investigating biological processes exhibited by phages has furthered our understanding of how they interact with human cells[6,7].

2. **Strengths**

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[1] Stacey, H.J., De Soir, S. and Jones, J.D., 2022. The Safety and Efficacy of Phage Therapy: A Systematic Review of Clinical and Safety Trials. *Antibiotics*, 11(10), p.1340.

[2] Dedrick, R.M., Smith, B.E., Cristinziano, M., Freeman, K.G., Jacobs-Sera, D., Belessis, Y., Whitney Brown, A., Cohen, K.A., Davidson, R.M., van Duin, D. and Gainey, A., 2023. Phage Therapy of *Mycobacterium* Infections: Compassionate Use of Phages in 20 Patients With Drug-Resistant *Mycobacterial* Disease. *Clinical infectious diseases*, *76*(1), pp.103-112.

[3] Law, N., Logan, C., Yung, G., Furr, C.L.L., Lehman, S.M., Morales, S., Rosas, F., Gaidamaka, A., Bilinsky, I., Grint, P. and Schooley, R.T., 2019. Successful adjunctive use of bacteriophage therapy for treatment of multidrug-resistant *Pseudomonas aeruginosa* infection in a cystic fibrosis patient. *Infection*, *47*(4), pp.665-668.

[4] Dedrick, R.M., Guerrero-Bustamante, C.A., Garlena, R.A., Russell, D.A., Ford, K., Harris, K., Gilmour, K.C., Soothill, J., Jacobs-Sera, D., Schooley, R.T. and Hatfull, G.F., 2019. Engineered bacteriophages for treatment of a patient with a disseminated drug-resistant *Mycobacterium abscessus*. *Nature medicine*, *25*(5), pp.730-733.

[5] Ennals, E. (2022, August 27). How an army of "friendly viruses" so small that there are more than 10 million of them in a thimbelful of sea water are leading the NHS's war on superbugs. *The Daily Mail*.

[6] Nguyen, S., Baker, K., Padman, B.S., Patwa, R., Dunstan, R.A., Weston, T.A., Schlosser, K., Bailey, B., Lithgow, T., Lazarou, M. and Luque, A., 2017. Bacteriophage transcytosis provides a mechanism to cross epithelial cell layers. *MBio*, *8*(6), pp.e01874-17.

[7] Van Belleghem, J.D., Dąbrowska, K., Vaneechoutte, M., Barr, J.J. and Bollyky, P.L., 2018. Interactions between bacteriophage, bacteria, and the mammalian immune system. *Viruses*, *11*(1), p.10.

a) Phages are very specific and can target a pathogen without destroying healthy microbiomes. Phages can be used in their naturally occurring form to create personalised medicines. In addition, phages can be optimised either through evolutionary adaptation and/or genetic modification to enhance antimicrobial properties.

b) There is evidence of synergy when phages are used in conjunction with conventional antibiotics[8,9]. Combination treatments could slow the development of resistance in bacteria and extend the utility of existing antibiotics.

c) Exposure to phages can result in resistant bacteria becoming once again susceptible to antibiotics[10,11].

d) Laboratory and clinical trial results to date show no severe toxicity caused by phage therapy[12,13].

e) Phages that target many multi-drug resistant bacteria have been identified and can be isolated from the natural environment at low cost.

f) Phages are self-regulating, so will increase at the site of infection and be cleared from the body once the infection is treated.

g) Due to the abundance of phages in nature, there is an extensive supply of potential alternative phages to be used if/when resistance to a phage develops.

h) Phages encode proteins (e.g., lysins and other enzymes) with antimicrobial properties that can be isolated from the self-replicating phage.

i) The application of multiple phages in 'phage cocktails' can prevent the development of resistance and/or direct the evolution of bacteria to reduce their pathogenicity[14].

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[8] Luo, J., Xie, L., Liu, M., Li, Q., Wang, P. and Luo, C., 2022. Bactericidal Synergism between Phage YC# 06 and Antibiotics: A Combination Strategy to Target Multidrug-Resistant *Acinetobacter baumannii* In Vitro and In Vivo. *Microbiology Spectrum*, *10*(4), pp.e00096-22.

[9] Oechslin, F., Piccardi, P., Mancini, S., Gabard, J., Moreillon, P., Entenza, J.M., Resch, G. and Que, Y.A., 2017. Synergistic interaction between phage therapy and antibiotics clears *Pseudomonas aeruginosa* infection in endocarditis and reduces virulence. *The Journal of infectious diseases*, *215*(5), pp.703-712.

[10] Segall, A.M., Roach, D.R. and Strathdee, S.A., 2019. Stronger together? Perspectives on phage-antibiotic synergy in clinical applications of phage therapy. *Current opinion in microbiology*, *51*, pp.46-50.

[11]Chan, B.K., Sistrom, M., Wertz, J.E., Kortright, K.E., Narayan, D. and Turner, P.E., 2016. Phage selection restores antibiotic sensitivity in MDR *Pseudomonas aeruginosa*. *Scientific reports*, *6*(1), pp.1-8.

[12] Dedrick, R.M., Smith, B.E., Cristinziano, M., Freeman, K.G., Jacobs-Sera, D., Belessis, Y., Whitney Brown, A., Cohen, K.A., Davidson, R.M., van Duin, D. and Gainey, A., 2022. Phage therapy of *Mycobacterium* infections: compassionate-use of phages in twenty patients with drug-resistant mycobacterial disease. *Clinical Infectious Diseases*.

[13] Liu, D., Van Belleghem, J.D., de Vries, C.R., Burgener, E., Chen, Q., Manasherob, R., Aronson, J.R., Amanatullah, D.F., Tamma, P.D. and Suh, G.A., 2021. The safety and toxicity of phage therapy: a review of animal and clinical studies. *Viruses*, *13*(7), p.1268.

[14] Gurney, J., Brown, S.P., Kaltz, O. and Hochberg, M.E., 2020. Steering phages to combat bacterial pathogens. *Trends in microbiology*, *28*(2), pp.85-94.

j) Phages are effective at destroying bacterial biofilms, which are responsible for the vast majority of infectious diseases in humans and which can protect bacteria against antibiotics[15,16].

3. **Weaknesses**

a) Bacteria can evolve resistance to phages as they do when exposed to antibiotics. Determining the efficacy of applying phages to repeat infections requires further experimental data.

b) Phages have a number of genes with unknown function[17]. Whether these genes can cause unforeseen interactions *in vivo* is unknown.

c) Unlike antibiotics, phage specificity requires the correct phages to be matched to an infecting pathogen. Identifying potential phages can take days to weeks and requires access to large phage biobanks. Compared to mass-produced antibiotics, phage therapy is labour intensive and not currently suitable for treating fast-progressing infections.

d) The high specificity of phages poses a challenge for standard design of clinical trials and most clinical studies have not been double-blind, placebo-controlled studies. More research is needed ahead of widespread use.

e) Phage therapy can only be deployed if the causative agent is known. For some infections, particularly those with multiple bacterial pathogens, this can pose a challenge with current diagnostics.

f) Some phages are difficult to store due to susceptibility to degradation by light, heat, pH and other external factors.

g) It is unclear how phages are distributed to different organs when inside the human body. Organ cells may respond in different ways making it difficult to determine clinical dosages[18]. However, the self-replicating nature of phages at the site of infection reduces the need for precise dosing.

h) Understanding of the immunogenicity of phages is limited and some studies have identified low levels of interaction with the immune system[7]. While they do not appear to trigger a strong immune response, the initial application can trigger antibody production in the patient's immune system. It is possible a second

[15] Yadav, M.K., Song, J.J., Singh, B.P. and Vidal, J.E., 2020. Microbial biofilms and human disease: a concise review. *New and future developments in microbial biotechnology and bioengineering: Microbial biofilms*, pp.1-13.

[16] Parasion, S., Kwiatek, M., Gryko, R., Mizak, L. and Malm, A., 2014. Bacteriophages as an alternative strategy for fighting biofilm development. *Polish Journal of Microbiology*, *63*(2), p.137.

[17] Hatfull, G.F. and Hendrix, R.W., 2011. Bacteriophages and their genomes. *Current opinion in virology*, *1*(4), pp.298-303.

[18] Podlacha, M., Grabowski, Ł., Kosznik-Kawśnicka, K., Zdrojewska, K., Stasiłojć, M., Węgrzyn, G. and Węgrzyn, A., 2021. Interactions of bacteriophages with animal and human organisms—safety issues in the light of phage therapy. *International Journal of Molecular Sciences*, *22*(16), p.8937.

application of the same phage could elicit a stronger immune response. More research is needed.

i) Measures are needed to ensure patients are treated with virulent phages (that effectively destroy the target bacteria by bursting them open) and not temperate phages (that incorporate their DNA into the bacterial chromosome forming a 'prophage' that can help bacterial survival). When the bacterial host cell is under threat, prophages are triggered into a replicative cycle and act like virulent phages. Standardised procedures established in other countries can readily discriminate between virulent and temperate phages and could be adopted to reduce this risk[19].

j) There is a low risk that phages could transfer useful DNA from one bacteria to another. They can do this by mistakenly packaging bacterial DNA into their heads when they replicate, and sometimes incorporating bacterial DNA into their genome. If such DNA includes genes that encode antimicrobial resistance or virulence, there is a risk of transfer of these traits when infecting the next bacterial cell[20]. It is worth noting that this risk is also posed by antibiotics, which can cause temperate phages within the patient's own microbiome to switch to a lytic cycle[21].

4. **Balancing Risk**

It is important to note that the risks posed by many of these weaknesses become less significant when phage therapy is considered as a last resort treatment under compassionate use.

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

International Models

5. **UK**

In the UK, the Medicines and Healthcare products Regulatory Agency (MHRA) classifies phages as 'unlicensed specials'. UK manufacture of unlicensed specials must be done under Good Manufacturing Practice (GMP). GMP is the area of quality assurance which ensures that medicinal products are consistently produced and controlled according to quality standards. This requires a defined manufacturing procedure, a combination of physicochemical and biological tests and stringent production facilities. Whilst chemical products can be manufactured to this standard, phages are biological agents therefore it is more difficult to meet quality requirements such as stability and consistency. The MHRA

[19] Hyman, P., 2019. Phages for phage therapy: isolation, characterization, and host range breadth. *Pharmaceuticals*, *12*(1), p.35.

[20] Enault, F., Briet, A., Bouteille, L., Roux, S., Sullivan, M.B. and Petit, M.A., 2017. Phages rarely encode antibiotic resistance genes: a cautionary tale for virome analyses. *The ISME journal*, *11*(1), pp.237-247.

[21] McGannon, C.M., Fuller, C.A. and Weiss, A.A., 2010. Different classes of antibiotics differentially influence *Shiga* toxin production. *Antimicrobial agents and chemotherapy*, *54*(9), pp.3790-3798.

does not require imported unlicensed specials to be manufactured under GMP, and previous use of phages in the UK (see point 1b) used phages which were manufactured abroad. There are not currently any GMP facilities for phage production in the UK. UK Phage Therapy[22] is a novel non-profit organisation aiming to act as a specialist clinical phage centre able to manufacture phages under GMP protocol, however this initiative is in its preliminary stages and has not yet been fully established. With current technology, GMP manufacture of personalised phages for a single patient under compassionate use is cost- and time-prohibitive.

6. **Europe**

   Phages are currently classed as medicinal products in Europe, a label designed for industrial pharmaceuticals which cannot be customised for individual patients.

   The Declaration of Helsinki[23] allows for the compassionate use of unlicensed medicines where proven treatments have been exhausted, provided the intervention is made the object of research designed to evaluate its safety and efficacy. This is how phage therapy is employed through much of Europe and the Western world on a case-by-case basis. The UK is a signatory to the Declaration of Helsinki.

7. **Australia**

   A new Standardised Treatment and Monitoring Protocol (STAMP) for phage therapy has been approved in Australia that regulates the process of phage therapy rather than a specific phage product[24]. It does not require phages to be made under GMP for their use in clinical trials. The lifting of the GMP requirement in Australia accelerates the clinical trial process and makes a personalised medicine approach feasible for compassionate use.

8. **Belgium**

   The Belgian regulatory framework for phage therapy is the most advanced in the EU and is effective in allowing for routine personalised treatment using magistral (a medical product prepared in a pharmacy in accordance with a medical prescription for an individual patient) phage preparations.

   Since 2007, phages have been used sporadically to treat infections in the Queen Astrid Military Hospital in Brussels[25]. In 2018, the production and characterisation of phages suitable for magistral preparations was approved by the Belgian health authority[26]. This

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[22] *UK phage therapy*, *UK Phage Therapy*. Available at: https://ukphagetherapy.org/ (Accessed: December 20, 2022).

[23] World Medical Association. (2001). World Medical Association Declaration of Helsinki. Ethical principles for medical research involving human subjects. *Bulletin of the World Health Organization, 79* (4), 373 - 374. World Health Organization.

[24]Bacteriophage News (2022) Stamp protocol approved for phage therapy in Australia, *Bacteriophage News*. Available at: https://www.bacteriophage.news/stamp-protocol-phage-therapy-in-australia/ (Accessed: December 16, 2022).

[25]Djebara, S., Maussen, C., De Vos, D., Merabishvili, M., Damanet, B., Pang, K.W., De Leenheer, P., Strachinaru, I., Soentjens, P. and Pirnay, J.P., (2019). Processing phage therapy requests in a Brussels military hospital: Lessons identified. *Viruses*, *11*(3), p.265.

[26] Pirnay, J.P., Verbeken, G., Ceyssens, P.J., Huys, I., De Vos, D., Ameloot, C. and Fauconnier, A., 2018. The magistral phage. *Viruses*, *10*(2), p.64.

means that a physician in Belgium can prescribe phages, and a pharmacist can prepare a tailor-made phage cocktail which does not have to be manufactured under GMP.

9. **Poland**

   In Poland, phage therapy is classed as an experimental treatment regime rather than a medicinal product so can be more easily prescribed when other treatments fail[27]. This simplifies the compassionate use of phages.

   This classification means that phage use is permitted under certain conditions, including approval by a bioethics commission, when other available treatment has failed. The Hirszfeld Institute of Immunology and Experimental Therapy produces tailored phage therapy products to physicians and has a continuously expanding phage collection.

10. **Georgia**

    In Georgia, phage therapy is a standard medical treatment, and they are a leading nation in terms of bacteriophage research and production.

    Phage products are classed as pharmaceuticals and require a marketing authorisation similar to other pharmaceutical products**.** The George Eliava Institute of Bacteriophages, Microbiology and Virology produces over-the-counter phage preparations and products for clinicians. There is strong public trust in the treatment and it is routinely employed. We can learn from their efficient manufacturing and commercialisation process, and how phages came to be widely accepted by the Georgian public.

11. **USA**

    Phage therapy is regulated by the Food and Drug Administration (FDA) and can be employed as a last-resort treatment in the USA. Phages do not need to be manufactured under GMP for this purpose. In addition, products entering phase I clinical trials are not required to be manufactured under GMP, accelerating development and enabling the gathering of safety data across a large population.

    In 2010, the US Naval Medical Research Centre Biological Defence Research Directorate launched an initiative to explore the use of phage therapy, and in 2016 it funded the development of Adaptive Phage Therapeutics which now acts as large phage bank.

12. **Key takeaways**

    Waiving the requirement for GMP manufacture of phages for compassionate use could align the UK with other successful international frameworks. For broad use and new off-the-shelf phage products to be feasible, significant investment is needed for a UK GMP manufacturing facility. Alternatively, GMP requirements could be lifted and a regulatory body established to monitor phages to an appropriate standard.

[27] Żaczek, M., Weber-Dąbrowska, B., Międzybrodzki, R., Łusiak-Szelachowska, M. and Górski, A., 2020. Phage therapy in Poland–a centennial journey to the first ethically approved treatment facility in Europe. *Frontiers in Microbiology*, *11*, p.1056.

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

13. Phage therapy falls under the scope of the EU regulatory framework on biological medicinal products. This means that a marketing authorisation is required for each personalised phage cocktail based on detailed pharmaceutical and clinical documentation. This is inflexible and time consuming. Approving collections of phages rather than individual formulations and establishing a new definition for phages for medical use would expedite this process and allow more flexibility in treatment design.
14. The EU regulatory framework requires all medicinal products entering phase I clinical trials to be manufactured under GMP. Since adopting this framework, there have been no clinical trials of phages performed in the UK due to the high-cost barriers and the lack of manufacturing capability.
15. The EU regulatory framework does not account for the ability of phages to evolve. Any modification of phage composition requires an entirely new marketing authorisation. Divergence from this in UK regulation could simplify the process of modifying phage cocktails. It is, however, important to note that even small evolutionary changes can alter the function of a phage. There would therefore need to be a system in place to ensure genomic information is collected and shared in accessible databases. More research of phage genomes would help to inform legislation.
16. In the EU, Genetically Engineered (GE) phages need to comply with EU Genetically Modified Organism legislation before clinical trials can occur. This legislation is complex, varies across countries and leads to significant delays. There is therefore potential for regulatory divergence in the UK to simplify the use of GE phages in clinical trials and as a last resort treatment. However, without the EU market for any final GE product it would be more difficult to commercialise.

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

17. **Research**
    a) *Barriers*
        i. Knowledge on phage gene functions and interactions with organ cells is limited (see points 3b and 3g).
        ii. It is difficult to obtain funding for phage research (see points 20-22).
        iii. There is a lack of clinical trial data (see point 3d).
    b) *Opportunities*
        i. More basic research to strengthen our understanding of phage genomics and gene function, and phage interaction with antibiotics, will help when predicting outcomes and determining dosages. Strength is building in this

area, for instance with the establishment of new bioinformatics pipelines for more accurate predicting of phage gene function.

ii. The Innovate UK Knowledge Transfer Network has launched the Phage Innovation Network[28] to bring together expertise in phage therapy. This presents an opportunity for the UK government to easily access a wealth of expertise.

18. **Clinical**

a) *Barriers*

i. There is a lack of awareness among clinicians of the routes and barriers for compassionate phage therapy. When faced with a patient who may benefit from compassionate phage therapy, identifying and navigating the complex regulatory requirements is extremely time consuming.

ii. Currently, the nature and level of data clinicians are able to collect when phages are used compassionately is established on a case-by-case basis[29]. This means that clinicians can be prohibited from collecting data that would not be routinely collected during treatment (such as patient immune response to the phages and the efficacy of bacterial clearance). This limits the lessons that can be learnt about effective phage treatment.

iii. Diagnostic limitations in clinical settings hinders the ability to identify appropriate target pathogens in some cases (see point 3e).

iv. Limited understanding of phage interactions with organ cells, the immune system and antibiotics hinders the ability to determine dosage and formulation (see point 3g).

v. Public perception of phages could act as a barrier and use would require careful communication[30]. However, recent research shows that public perception towards phage therapy is positive[31]. Public expectations need to be managed, as what is successful in one case may not be applicable to all cases due to the high specificity of phages.

b) *Opportunities*

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[28] *Innovate UK KTN launches Phage Innovation Network* (2022) *Innovate UK KTN*. Available at: https://ktn-uk.org/news/innovate-uk-ktn-launches-phage-innovation-network/ (Accessed: December 15, 2022).

[29] *Early Access to Medicines Scheme (EAMS): Task Group and principles* (2016) *GOV.UK*. Available at: https://www.gov.uk/government/publications/early-access-to-medicines-scheme-eams-how-the-scheme-works/early-access-to-medicines-scheme-eams-task-group-and-principles (Accessed: January 11, 2023).

[30] Jones, E.H., Letarov, A.V. and Clokie, M., 2020. Neat science in a messy world: the global impact of human behavior on phage therapy, past and present. *PHAGE*, *1*(1), pp.16-22.

[31] Macdonald, K.E., Stacey, H.J., Harkin, G., Hall, L.M., Young, M.J. and Jones, J.D., 2020. Patient perceptions of phage therapy for diabetic foot infection. *PloS one*, *15*(12), p.e0243947.

i. A single point of contact centre for clinical phage therapy in the UK would prevent the complex regulatory effort undertaken for compassionate use of phages being replicated by individual hospitals.

ii. Phage therapy has the potential to improve health outcomes, reducing the number of patients on long term antibiotic usage, thus saving money and safeguarding antibiotic stocks. For clinicians treating patients under compassionate use, phage therapy is an additional tool in their arsenal.

iii. Exposure to phages can result in resistant bacteria becoming susceptible to antibiotics, increasing the utility of existing antibiotics (see point 2c). Co-administration could be further optimised through additional funding to identify phage-antibiotic synergies.

iv. The UK currently houses several large-scale phage banks with well characterised genomes which target World Health Organisation priority pathogens for novel antimicrobials. Support for developing standardised manufacturing protocols would enable rapid access to, and development of, suitable phage products.

v. The NHS has paved the way for phage therapy use in the UK with the treatment of diabetic foot ulcers (see point 1b) and the appointment of more clinical phage specialists throughout the UK will further facilitate this.

19. **Regulatory**

a) *Barriers*

i. Much of the current phage regulation requires genetic purity. As phages are biological agents there are natural levels of diversity making them difficult to regulate within existing frameworks. A new definition for phages that considers their biological nature would be beneficial.

ii. Current UK regulation requires phages to be made under GMP protocol (see point 5). As a domestic GMP manufacturing infrastructure has not yet been established, this makes the use of phages expensive and time consuming. Investing in a domestic infrastructure to manufacture phages under GMP protocol is essential to avoid this barrier. Alternative solutions include lifting the GMP requirement completely for compassionate use (see point 12). Alternative regulatory measures could be adapted from those used by other countries (e.g., Australia, Belgium or the USA; see points 7, 8 and 11).

b) *Opportunities*

i. Identifying regulation that exists for other biological agents (e.g., therapeutic antibodies[32]) could help when building regulatory frameworks.

[32] Beck, A., Wurch, T., Bailly, C. and Corvaia, N., 2010. Strategies and challenges for the next generation of therapeutic antibodies. *Nature reviews immunology*, *10*(5), pp.345-352.

ii. Removing regulatory barriers could incite investment and boost the UK biotechnology industry.

iii. By implementing effective domestic frameworks, the UK can avoid importing expensive phage formulations.

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

The current pipeline from phage research through to clinical trial is undeveloped in the UK. According to ClinicalTrials.gov[33], only two clinical trials on phage therapy have been initiated, one of which was withdrawn before completion.

17. Currently, clinical efficacy and toxicology testing of phages is not standardised. A standard route looking at resistance relative to pathogenicity would simplify this process. Proactively involving microbiologists in clinical trials could further pre-empt problems such as resistance emergence.

18. Currently there are many isolated groups within academia working on phages. The communication between groups is lacking, and the academic research does not feed well into clinical practice. A collaborative effort between these groups and a centralised point for collaboration and resources would be beneficial. A national reporting system would further optimise collaboration and prevent duplication of clinical research.

19. A centralised phage bank would improve understanding and accessibility of phage data and make it easier to identify gaps in phage collections for use in clinical trials.

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

There is a lack of phage specific funding calls in the UK. This means that phage therapy research applications are often unsuccessful. Phage specific funding calls and increased investment in infrastructure is necessary.

20. The UK Government supports agencies which fund phage research. However, very few of the funds are available solely for phage research, so applications are often outcompeted. Most phage research is therefore funded through university grant schemes, which are limited in both resources and scope. Phage-specific funding calls (like those currently undertaken in the EU[34]) would increase phage therapy research funding. For the successful

[33] *Home - ClinicalTrials.gov*. Available at: https://clinicaltrials.gov/ct2/ (Accessed: December 21, 2022).

[34] *Priority Programme "New Concepts in Prokaryotic Virus-Host Interactions – From Single Cells to Microbial Communities"* (2020) *Deutsche Forschungsgemeinschaft*. Available at: https://www.dfg.de/foerderung/info_wissenschaft/2020/info_wissenschaft_20_48/index.html (Accessed: December 20, 2022).

development of phage therapy, funding is needed for fundamental research on phage biology and phage interactions, alongside interdisciplinary research across academia, industry and clinics.

21. More government investment in UK based infrastructure would be beneficial. UK Phage Therapy[35] is a novel non-profit organisation aiming to act as a specialist clinical phage centre (see point 5). Government support for initiatives such as this, as well as enterprises that seek to further phage therapy innovation, would further accelerate the progression of phage therapy. Additionally, increased investment in infrastructure to rival those established in other countries (see points 7-11) would be beneficial.

22. Funding currently prioritises human focused phage research. However, phage therapy can be applied in alternative areas (e.g., food security and animal welfare) with fewer regulatory hurdles. Increased funding for research institutions and businesses interested in the wider use of phages could reduce the reliance on antibiotics in non-clinical settings.

Final remarks

The 2016 Jim O'Neill review on AMR highlighted bacteriophages as a hope for the future[36], so we greatly welcome this inquiry reaching out to the phage community. The Microbiology Society is well placed to support its members and the wider scientific community to address and raise awareness of AMR and provide expert microbiological opinion and evidence for policymakers on topics such as this to combat this global issue. We wish to send a message of support to the UK Government and would welcome the opportunity to inform future projects.

[35] *UK phage therapy*, *UK Phage Therapy*. Available at: https://ukphagetherapy.org/ (Accessed: December 20, 2022).

[36] O'Neill, J., 2016. Review on antimicrobial resistance: tackling drug-resistant infections globally: final report and recommendations