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Exploring perceptions of bacteriophage use in the UK across the One Health spectrum: a roundtable discussion

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Abstract

In 2022, the UK Government launched the My Science Inquiry, an open call for potential topics of inquiry within science and technology. Applied Microbiology International (AMI) recommended bacteriophage as an alternative to antimicrobials, due to the increasingly serious threat of antimicrobial resistance. This resulted in an inquiry and report by the House of Commons Science, Innovation & Technology Committee, for which the government published a response in March 2024. In July 2024, AMI held a closed roundtable discussion, inviting bacteriophage experts across the One Health spectrum and all stages of the phage development pipeline to discuss some of the major barriers to phage therapy implementation within the UK. Overall, the lack of investment, national infrastructure and public awareness regarding phage therapy, its development and its potential, were agreed upon as the key barriers that need to be overcome to more widely implement phage therapy across the UK. Continuation of the Phage Innovation Network was repeatedly recognized as an essential requisite for overcoming these barriers and for ensuring the progress of phage innovation. The aim of this paper is to provide a progressive step for phage therapy, continuing momentum to facilitate their widespread implementation nationally.

Sustainability Statement

The impact of antimicrobial resistance affects all sectors across the One Health spectrum, including human health, animal health, food, and the environment, compromising the achievement of several of the UN Sustainable Development Goals (UN SDGs). As such, it is imperative that the UK Government continues exploring alternatives to traditional antimicrobials. This closed roundtable discussion brought together phage experts from across the One Health spectrum, to raise awareness of the current and future bottlenecks in developing phage therapy in the UK. It is hoped that the recommendations made can help to build momentum and be used to inform decision-making within the UK Government, thereby progressing several of the UN SDGs. These include UN SDG one (no poverty), two (zero hunger), three (good health and wellbeing), six (clean water and sanitation), eight (decent work and economic growth), and fifteen (life on land).

Introduction

In 2022, Applied Microbiology International (AMI) responded to the UK Government's open call for potential topics of inquiry within science and technology for the My Science Inquiry (https://committees.parliament.uk/work/6845/my-science-inquiry/). AMI put forward the suggestion of exploring bacteriophage (phage, viruses which specifically infect and kill bacteria) as an alternative to antimicrobials, to help combat the growing global challenge of antimicrobial resistance (AMR). The bid was successful and resulted in the inquiry (https://committees.parliament.uk/work/7045/the-antimicrobial-potential-of-bacteriophages/) launched by the House of Commons Science, Innovation & Technology Committee in November 2022, leading to a report being published in January 2024 (https://publications.parliament.uk/pa/cm5804/cmselect/cmsctech/328/summary.html). The government published a response (https://www.gov.uk/government/publications/the-antimicrobial-potential-of-bacteriophages-report-government-response/governments-response-to-the-science-innovation-and-technology-committees-report-the-antimicrobial-potential-of-bacteriophages) to that report in March 2024, which though supportive of the continued exploration of antimicrobial alternatives—which includes phage therapy—did not appear to acknowledge the specific support that implementing phage therapy across the UK would require, or whether/how such support would be provided.

With the threat of AMR growing, it is imperative that the UK Government continues exploring alternatives to traditional antimicrobials, to preserve the efficacy of those still in use and to find sustainable solutions to a dwindling supply of treatment options. Although the initial interest in phage therapy shown by the UK government has been promising, continued momentum is necessary to ensure that (i) phages are fully explored as a viable antimicrobial alternative across human, veterinary, and agricultural sectors and (ii) if so, that the infrastructure, know-how and frameworks to support implementation within the UK are put in place in a timely manner.

As such, in July 2024, AMI hosted a closed roundtable event, bringing together a panel of invited participants from across academia, industry, regulatory bodies, as well as potential phage end-users to discuss some of the key questions pertaining to phage therapy implementation within the UK. Though exact metrics are hard to establish, the UK's bacteriophage research landscape is excellent, with a growing

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number of researchers, companies, and publications in this area. Due to the One Health nature of antimicrobial use, and the challenge posed by AMR, participants represented the full One Health spectrum. This paper summarizes the key take-home messages that emerged following the One Health panel's roundtable discussions. The aim of providing this collaborative response from all stages of the phage development pipeline, will serve to highlight to the UK Government that—with support—phage therapy offers a feasible, achievable, and vital means of addressing the serious global threat posed by AMR.

The roundtable was Chaired by James Ebdon, Professor of Environmental Microbiology at the University of Brighton, who delivered the winning 2022 My Science inquiry pitch on phage on behalf of AMI.

Roundtable discussion point 1: Does the lack of a good manufacturing practices (GMPs) facility (or commitment to build one) present the biggest barrier to the implementation of phage therapy on a wider scale in the UK? If so, how can it be overcome?

Though it was largely agreed that a lack of GMP facilities is a barrier to phage implementation in the UK, there were differing and nuanced thoughts on whether it poses the biggest barrier.

Regarding licensed phage products—which must be manufactured to GMP standards—the lack of national GMP facilities does not prevent such products from getting to the market, but it does make it difficult. The reason it does not fully prevent this is due to their potential for manufacture in countries with GMP facilities and subsequent import into the UK for use in clinical trials and the wider product development pipeline. However, though clinical-grade material *can* be imported and used, doing so is very difficult and as such the lack of facilities poses a major barrier to phage implementation on a wider scale in the UK. The cost of outsourcing manufacturing over the long term presents an additional indirect barrier to implementation, as private investment (key to enabling overseas manufacturing) may be reluctant if there are uncertainties about the availability of manufacturing services, which ultimately could affect access to phage products. Additionally, non-cost related issues associated with importing phage products from outside the UK, such as those relating to the stability and reliability of the supply chain, could also pose a barrier to wider-scale implementation.

For unlicensed phage products (i.e. products used on a named patient basis where there are no licensed therapies available as an option for specific patients) the lack of national GMP facilities may not be an obvious barrier to the wider scale implementation for this use in the UK. This is because, while products produced in the UK for unlicensed use must adhere to GMP, non-GMP products of suitable quality can readily be imported for use (with Medicines & Healthcare products Regulatory Agency approval) with a 24-h turnaround for urgent cases (provided necessary accompanying paperwork is completed and correct). However, there can be no adaptation of imported products once in the UK as there is no national GMP facility to do this, meaning they can only be used as supplied. Furthermore, reliance on imported products could create a phage deficit as they are being sourced from suppliers for whom the UK is not the priority market. Encouragingly, the UK's existing regulations provide a suitable framework to enable the use of unlicensed phage therapies within the National Health Service, and this type of activity is being streamlined by the non-profit initiative, UK Phage Therapy (https://www.ukphagetherapy.org/). There are patient safety aspects that require consideration in this scenario; however, because non-GMP phages do come with an increased risk with regards to quality and therefore safety and efficacy, and as such may not represent the best standard for patient care. Therefore, it would be preferable if UK-based GMP manufacturing facilities could be available to support this application.

In summary, while the lack of national GMP facilities does not technically prevent the development or use of phage therapies in the UK, it arguably poses one of the biggest barriers to enabling longer-term development and use on a wider scale. Furthermore, the lack of UK GMP manufacture is restricting the application and advancement of personalized, adaptive phage therapy on a named patient basis since products imported into the UK must be used without alteration to their formulation and could be subject to supply chain issues outside the control of users within the UK. The lost economic opportunities associated with a lack of national facilities also merit consideration, since companies and innovators who develop phage products are forced to source manufacturing outside of the UK.

Roundtable discussion point 2: The antimicrobial subscription model developed by NHS England has been recognized as a potentially relevant model for phage therapies. Do you think that this model could be appropriate in the future?

The antimicrobial subscription model was developed by NHS England to incentivize the development of new antimicrobials. It does so by decoupling revenue from the volume of pharmaceuticals sold such that pharmaceutical companies selling the new antimicrobial will receive a fixed annual fee related to the societal value and how well the product meets Spectrum, Transmission, Enablement, Diversity and Insurance (STEDI) criteria (https://www.england.nhs.uk/long-read/antimicrobial-products-subscription-model-guidance-on-commercial-arrangements/).

As it stands, the NHS England subscription model does not explicitly cover phage and does not lend itself to all types of phage therapy mainly named patient therapeutics; however, the current model could represent an appropriate model for phage cocktail products, and with some adaptation, could be suitable for named patient use also.

Phage banks—collections of pre-characterized phage that can be screened for use in named patient cases or clinical trials—could be factored into the model, e.g. by implementing a fixed payment to access banks. While the model could be adapted accordingly to accommodate this aspect of phage therapy, the issue remains that there is no centralized facility for phage stocks which would be required for this model to work.

Overall, there was agreement that the NHS England subscription model should be explored for phage therapies, especially if they are to be implemented on a wider basis, with the necessary adaptions put in place and consideration around how it would work for licensed products.

Roundtable discussion point 3: What do you think are the main challenges from an industry perspective in terms of commercialization?

Commercialization of phage therapy faces several key challenges:

(i) A current lack of investment due to the modest evidence-base around the safety and efficacy of phage (in the Western world) and successful clinical trials.
(ii) A lack of investment due to the absence of success stories on the economic viability and return on investment for phage therapy and other antimicrobial therapies.
(iii) A lack of evidence showing successful scale-up of phage development, formulation, and manufacturing.
(iv) A lack of quality control and industry standards for producing phage therapeutics which in turn could impact public trust.
(v) Concerns around the security of supply for high-quality phage therapeutics (due to the lack of national GMP facilities).
(vi) Concerns around the implications of intellectual property.
(vii) A lack of clarity around regulation.

From an industry perspective, it was agreed that it was the current lack of a financial model to support investment that poses one of the main barriers to the commercialization of phage therapies. Though there was consensus that the confidence of private investors is on the rise as the evidence base grows—and this will hopefully drive a positive feedback loop for further investment—the challenges listed above (and throughout this paper) need addressing to build momentum for commercialization. Knowledge-sharing across different sectors (e.g. between clinical and veterinary use), different parts of the phage pipeline (e.g. between academics and regulators) and different countries (e.g. between the UK and Georgia, where phage therapy is used extensively), is a key step to start addressing these challenges. However, clarity around legislation is also required to support commercial investment.

Roundtable discussion point 4: The government has recommended that the Department of Health and Social Care, Medicines and Healthcare products Regulatory Agency, National Institute for Health and Care Excellence, and National Institute for Health and Care Research should engage with phage researchers to see what evidence is needed to determine the safety and efficacy of phage use within clinical settings. Do you think enough is being done to establish this dialogue and if not, what should be done to promote engagement?

The Phage Innovation Network (PIN) is a sector-agonistic forum run by Innovate UK, that connects different sectors relevant to the development and potential adoption of phage therapies across the UK, including researchers, innovators, industry, funders, regulators, and more (https://iuk.ktn-uk.org/programme/phage-innovation-network/). PIN has been instrumental in the creation of a national phage community through by fostering and encouraging a continuous dialogue between sectors and community members.

There was a strong consensus from across the community that PIN has been pivotal in maintaining this critical dialogue going forward and will continue to be, if supported. However, the network was originally formed to unify the community and catalyze progress, with the aim for the community to eventually lead itself, so by its very nature, PIN will not exist in its current form indefinitely. However, the continuation of PIN was seen as a vital necessity to continue promoting the exploration of phage as an alternative to traditional antimicrobials. It was therefore agreed that continued government support for PIN should be maintained while the more widespread adoption of phage therapy becomes established on a national scale.

Roundtable discussion point 5: The House of Commons (HoC) Science, Innovation and Technology Committees' report suggested that the government should undertake a review into what assistance phage translational research requires to increase the success of funding bids, and whether specific funding is appropriate where it can deliver AMR priorities. The government response indicates that whilst they will not ringfence funding for phage research, they will continue to support the clinical trial pipeline for antimicrobials & alternative therapies. In the absence of ringfenced phage funding, what specific assistance do you think should be given to most effectively bridge the translational phage research 'gap' to break the funding impasse which has existed in the UK?

Public funding sources like PACE AMR (pathways to antimicrobial clinical efficacy) and Innovate UK, currently provide some funding opportunities for phage therapy, and there is potential for funding through programs like the Innovate UK Biomedical Catalyst calls. However, the recent webinar series led by the World Health Organisation in collaboration with the Global AMR Research and Development hub, highlighted that phage therapy receives only ∼2% of public and philanthropic funding for AMR research, even though many projects target high-priority bacterial pathogens (https://www.who.int/europe/news-room/events/item/2024/04/18/default-calendar/webinar---towards-building-the-evidence-for-broader-use-of-bacteriophages-from-an-amr-one-health-perspective).

This funding gap is particularly pronounced in the intermediate stage of developing phage therapeutics, a crucial stage lasting 2–3 years that involves process development scale up and GMP manufacture for clinical trial use. This is because this stage often does not qualify for public funding as it does not necessarily involve a step-change in innovation, and private investment is lacking since it tends to focus on the initial innovation stage of phage development, or the commercialization of an end product.

A lack of awareness and understanding amongst funders on the different stages of phage development is considered the root cause of this funding issue. This lack of understanding is thought to be a common problem across drug discovery in general. Educating funders by sharing socio-economic analyses of phage development and use, could be an important means of increasing future investment. Named patient success stories from around the world and examples of successful phage use in the veterinary field are already available to start building investor confidence.

There is clearly a need for more growth-focused funding to support the intermediate development stage of phage therapy, to bridge the gap between initial innovation and end-product development. Specific assistance should therefore be targeted at this stage of the phage development pipeline going forward. For products that progress to clinical trials (human or veterinary medicines), this links back to the need to access GMP manufacturing facilities.

Roundtable discussion point 6: Since phage have the potential to be deployed across the One Health spectrum including in the human, animal, food, and environmental sectors. Does this present the opportunity to have an integrated, joined-up approach to phage development? If so, what is needed for this to be done?

According to the World Health Organisation, the term 'One Health' refers to 'an integrated, unifying approach that aims to sustainably balance and optimize the health of people, animals, and ecosystems. It recognizes that the health of humans, domestic and wild animals, plants, and the wider environment (including ecosystems) are closely linked and interdependent' (https://www.who.int/health-topics/one-health#tab=tab_1).

A One Health approach to phage development and use is deemed crucial for good health across all sectors, since use in one will inherently have consequences in the others. However, this approach is made slightly more complicated by the different needs (in relation to phage therapy), regulatory and funding frameworks, and economic models for therapy development currently in place between sectors. Thus, a 'one size fits all' approach to phage was deemed inappropriate, with the need to add nuance and flexibility to existing frameworks and models noted as essential, to avoid stifling innovation and market development. A harmonized, joined-up approach to ensure that these changes are implemented is therefore essential.

There was a broad agreement that the wider phage community needs to be the driver of these changes, by taking a concerted bottom-up approach. Initiating this dialogue with regulators and funders, increasing their awareness of the nuance needed for frameworks, and models relating to phage development and use, is paramount for good stewardship. The central voice of PIN was suggested as an ideal vehicle/tool for facilitating this joined-up dialogue across the phage pipeline. The added benefit of increased knowledge-sharing between phage users from such an approach was also recognized as a driver of phage innovation and implementation, since better dialogue facilitates faster progress, generating more success stories to bolster confidence of investors.

Roundtable discussion point 7: Could the One Health approach to tackling AMR help promote the utility and potential of phage to the public? If so, how can careful and transparent promotion of phage be ensured across different sectors to the public and avoid sending mixed messages which can confuse, or worse, scare?

AMR threatens the effective prevention and treatment of a wide range of pathogen infections and there has been growing interest in new antimicrobials to combat this (Chakravorty S. *Anti microbial resistance: a silent progressive pandemic. J Intern Med* 2021;15:1–3.). There is an opportunity to refresh and strengthen public dialogue around the One Health concept and AMR in general, whilst introducing the concept of phage. There is a fine balance between enabling necessary debates within the scientific community on the safety and efficacy of phage, whilst avoiding the risk of negative perceptions within the public over unanswered scientific questions.

A carefully considered dialogue will not only better educate the public on these important concepts but will also be critical for building public trust; a cornerstone for enabling wider phage implementation. The risk of not taking the utmost care with this dialogue could be devasting for the progression of phage within the UK, as the historic impact of misinformation can be seen for genetically modified (GM) crops and more recently for the COVID-19 pandemic. In particular, not overpromising on results was noted as a critical lesson to be taken on board for phage, learned from the past communications used for antibiotics.

Developing appropriate public educational materials to initiate this dialogue is needed; it is essential to utilize real-world learning opportunities within these materials—such as Georgia's extensive and successful history with phage therapy (https://link.springer.com/referenceworkentry/10.1007/978-3-319-41986-2_31)—to demonstrate safe and responsible use, and the inclusion of these materials in the academic curricula of relevant fields (e.g. veterinary and medical training) will further bolster public confidence. A coordinated approach around educational materials, will help to reduce the risk of confusion and speculation that can arise from conflicting information.

Roundtable discussion point 8: The government finishes their response to the HoC report by saying it will not produce a further statement on its assessment of phage at this time or publish a roadmap that depicts how phage manufacture and regulation will be embedded in the UK. What is the main reason thought to be causing hesitancy and how can it be overcome?

Though initially the government narrative appears discouraging, their willingness to engage with the phage community to date and the new commitments made within the updated National Action Plan (NAP) on AMR suggest progress can still be made.

The lack of successful clinical trials was suggested as the main reason for the perceived hesitancy to commit to exploring phage further. An increase of successful trials could therefore significantly shift policymaker's perceptions towards phage therapy as a viable antimicrobial alternative. Another reason suggested for the perceived hesitancy included a lack of the necessary infrastructure for developing and commercializing phage therapy on a wider scale. Building a stronger case for phage therapy by showing its alignment with the UK's NAP and government areas of research interest (ARIs) could help to further drive commitment from investors and encourage the government to reassess its stance to become more advocating of phage use.

It is clear the phage community will need to work together to keep phage on the agenda of policymakers.

Roundtable discussion point 9: With the recent general election, how can positive momentum around the development of phage be kept from being lost and how can the phage community ensure that the gaze of new Government remains firmly fixed on phage?

The need to continue pushing phage as an antimicrobial alternative worth exploring, to ensure the progress made to date is not wasted, was fundamentally agreed upon. It is clear from looking at previous parliamentary activities that phages have not garnered much attention in the past; searches in Hansard—the official report of all parliamentary debates—show a minimal number of references to phage and there has been a lack of phage-related briefs from the Parliamentary Office for Science and Technology. This indicates the newfound engagement on phage is likely not enough to keep them at the top of policymaker agendas. Ongoing advocacy is therefore a necessary pursuit for the phage community.

Forums such as PIN were highlighted as being key to this advocacy role. Engagement from foundations and charitable entities through their parliamentary communication channels to further support messaging around phage will also help maintain the dialogue that has been started. The need to establish new, and maintain and strengthen existing, relationships with government are therefore clear, as well as the need to make full use of the multiple routes for getting evidence to de-

cision makers. Coordination and collaboration between such entities will be paramount to ensure maximum opportunities for engagement.

Conclusion

The global AMR crisis and resulting need for new antimicrobial alternatives is undeniable. The potential of bacteriophage as a viable alternative (or even complementary treatment) to traditional antimicrobials is strongly recognized in countries such as Georgia and is increasingly being acknowledged in the UK and globally. Though key steps have been taken to start exploring their more widespread adoption nationally, several challenges—namely, a lack of commercial investment, national infrastructure, and public awareness—must first be overcome to make this a reality.

The discussions held within this roundtable show the willingness of the UK's phage community to collaborate on and problem-solve the issues standing in the way of wider phage adoption. The central voice provided for this community by the PIN was emphatically and repeatedly noted as an essential requisite for ensuring the progress of phage innovation and development continues unabated. This network provides a single point-of-contact for policymakers and others to turn to regarding phage, a vital resource in an increasingly complicated landscape of science, innovation, and technology. The Centre for Phage Research in Leicester is also another anchor—building up critical mass and facilitating the standardization of phage banks that will be accessible to UK phage researchers and innovators.

The aim of AMI in writing this paper is to provide a supportive platform for the wider adoption of phage, in particular by building and maintaining positive momentum (in light of the recent 2024 General Election) and in the hope that the incumbent government recognizes the need to support phage therapy as part of the answer to the threat of AMR. The opinions on the perceived barriers, bottlenecks, and potential impasses raised within this paper hopefully provide a useful starting point for facilitating the widespread implementation of phage therapy across the UK One Health spectrum. The roundtable discussion has highlighted where efforts should be focused to further drive innovation and ensure that vital progress made to date, is not squandered, but built upon in coming years.

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Author contributions

Lucky Cullen (Conceptualization [lead], Project administration [equal], Writing – original draft [equal], Writing – review & editing [equal]), Daisy Neale (Conceptualization [equal], Project administration [lead], Writing – original draft [lead], Writing – review & editing [equal]), and Helen Kinchin (Conceptualization [supporting], Project administration [equal], Writing – original draft [equal], Writing – review & editing [equal]).

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Data availability

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