Department of Health & Social Care

The government's response to the Science, Innovation and Technology Committee's report: The antimicrobial potential of bacteriophages

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Introduction

The government welcomes the opportunity to respond to the recommendations made in the House of Commons Science, Innovation and Technology Committee's Report 'The antimicrobial potential of bacteriophages' published 3 January 2024 (1).

The report contributes to the wider debate on how bacteriophages, or 'phages', have the potential to be used as an antimicrobial, either in conjunction with, or as an alternative to, antibiotics and as an additional tool to tackle the threat of antimicrobial resistance.

The report recognises the scale of the antimicrobial resistance (AMR) threat and its wide-ranging impacts for humans and animals. The government acknowledges the risk of AMR within the UK and the threat it poses to public health, animal health, food security and the economy.

The government recognises the need to act on AMR to preserve the effectiveness of antimicrobials and save lives. In January 2019, the government published its vision for AMR to be contained and controlled by 2040 (2). The vision recognises that a global problem as significant and complex as AMR requires long-term action to better understand AMR and what works to contain and control it.

In support of the vision, the government also committed to develop a series of 5-year national action plans (NAP) that will prioritise actions and direct resources based on the latest information about the biggest risks, and which interventions are most effective in addressing them.

The current AMR NAP 2019 to 2024 is focused on 3 key ways of tackling AMR:

- reducing the need for, and unintentional exposure to, antimicrobials
- optimising the use of antimicrobials
- investing in innovation, supply and access

The committee's report highlights the threat of AMR and proposes that phages have the potential to play a vital role in responding to it.

The committee's recommendations on the use of phages as an alternative to antimicrobials are split into 4 themes:

- phage safety, efficacy and the UK phage research base
- manufacturing phages

- phage clinical trials
- the clinical use of phages in the UK

The response set out below outlines the government's consideration of each of the recommendations made in the report.

While the committee's recommendations were focused on the health sector, the government is committed to taking a 'One Health' approach to tackling AMR. This response therefore includes consideration of the potential for the use and regulation of phages in animals too.

In line with usual practice, the government response addresses the recommendations made by the committee. The responses have been collated by officials within the Department of Health and Social Care (DHSC) with input from relevant government departments and agencies where necessary.

Summary of the committee's recommendations

Phage safety, efficacy and the UK phage research base

Number	Paragraph	Recommendation
1.	41	We recommend that the Department for Health and Social Care (DHSC), the Medicines and Healthcare products Regulatory Agency (MHRA), the National Institute for Health and Care Excellence (NICE) and National Institute for Health and Care Research (NIHR) should now consider what specific evidence, and to what standard, is needed to fully assess the safety and effectiveness of phages to allow them to be used more widely within the NHS and other UK healthcare settings, including over the long term. DHSC, MHRA, NICE and NIHR should engage with phage researchers to establish a dialogue on these issues. The Phage Knowledge Transfer Network established by Innovate UK to bring together phage stakeholders would be an appropriate forum for this dialogue.
2.	50	We recommend that the government reviews the status of phages within its plans to tackle AMR. We also recommend more specifically that the National Institute for Health and Care Research and the UK Health Security Agency engage with the phage researchers to improve prospects for phage related applications for research funding.
3.	57	We recommend that the DHSC reviews the current funding arrangements for phage translational research and identifies what are the bottlenecks for such research. A review should consider what specific assistance phage translational research requires to increase the prospects of success for funding bids. It

		should also consider whether specific funding is appropriate where it can deliver AMR priorities.
4.	63	We recommend that the DHSC, as the lead department on AMR, reports annually on the progress made on evaluating and developing all phage-related technologies and therapies that affect human, animal or environmental health (referred to as the 'One Health' approach). This should be a joined-up assessment bringing together analyses and data from all relevant departments, regulators, public bodies and funders who are in receipt of public funding for work on phages.
5.	68	We recommend that the DHSC responds to the UK Phage Knowledge Transfer Network's proposals within 6 months of their publication. The department should set out how it will help develop a network for phage-related knowledge sharing and assets such as biobanks. The department should also indicate how phage-related research and development across different sectors might be joined up as part of its overarching 'One Health' approach to tackling AMR.
6.	70	We recommend that information about the clinical use of phages is included within medical training courses and that information about how to access phages or phage expertise is readily available to clinicians and other healthcare staff within each hospital.

Manufacturing phages

Number	Paragraph	Recommendation
7.	84	We recommend that the DHSC considers bringing together funders with relevant catapults and innovation centres, such as the Centre for Process Innovation, to build a good manufacturing practice (GMP) facility that can be accessed and used by phage innovators, the NHS and those seeking to produce microbiome products. The government should also consider investment in existing spare and disused laboratory space, such as the currently for sale Rosalind Franklin Laboratory, to develop a GMP facility for phage production. In addition, the government should consider why there is a reluctance by pharmaceutical companies to invest in phages, and what steps it can take to address this.
8.	86, 88	We recommend that the MHRA provides guidance on how phage cocktails will be regulated. It should consider the case of influenza vaccines and allow phage permutations to be assessed on the basis of their individual constituent ingredients meeting agreed purity and safety standards and not for each new combination of those ingredients. We recommend that the MHRA produces guidance on how genetically engineered (GE) phages will be regulated and how they will meet GMP. The MHRA should also provide guidance on how extracted phage enzymes will meet GMP requirements.
9.	94	We recommend that the MHRA publishes guidance on how it intends to regulate phages if they are not produced using a

		GMP approach. This should include guidance on what developmental pathways are available to phage innovators.
10.	101	The MHRA should set out how they propose to regulate and ensure clinical safety for each of the scenarios set out in paragraph 100 of the report. This would allow for the narrowing of R&D and production work to prevent wasted effort and allow an agile approach, allowing non-generic phage production for specific patients but GMP production for phages to mitigate the most common bacterial pathogens causing AMR in humans, animals and the environment.

Phage clinical trials

Number	Paragraph	Recommendation
11.	102	The MHRA should also set out more broadly how current clinical trial structures can support the development and regulation of new personalised medicines. This should include an outline of what changes may be required to underpin this emerging and promising area. This should include early and regular engagement by regulators with the sector and a transformative approach to the safety testing and licencing of these exciting products. It should publish this within a year of this report being published.
12.	106	We recommend that the MHRA sets out what standard of phages will be required for UK clinical trials and how GMP will be acquired by UK produced phages if they cannot be assessed by a clinical trial. This guidance should be published within 6 months of the publication of this report.
13.	110	We recommend that the DHSC and the National Institute for Health and Care Research follow up on this amenability to receive applications from phage researchers for clinical trials by engaging with them and supporting them in their applications. Similarly, we recommend that the MHRA offers tailored support for phage applications for clinical trials.
14.	113	We recommend that the MHRA outlines how it will use clinical data from other countries and non-health evidence to inform its decision-making on regulating phages.

The clinical use of phages in the UK

Number	Paragraph	Recommendation
15.	118	We recommend that the DHSC and the MHRA reviews the current rules regarding the clinical use of phages in the UK. This should aim to ensure alignment between domestically produced and imported phages.
16.	129	We recommend that the MHRA revisits the regulation of the clinical use of non-GMP phages produced in the UK for last resort compassionate cases where antibiotics or other antibacterial interventions have failed. The MHRA should review the use of non-GMP phages in such cases in other countries and produce a monograph to govern and ensure their safety

		and purity. The MHRA should publish its review and proposals for a non-GMP phage monograph and any changes that will be required to change necessary regulation to underpin this change. The DHSC should review and report on what changes, if any, will be required to ensure that current guidance and oversight procedures are sufficient for the preparation and use of UK produced non-GMP phages in UK healthcare settings.
17.	131	We recommend that the MHRA reviews how current regulations would govern liability for clinicians and hospitals who used UK non-GMP phages, produced to a magistral monograph. It should consider what changes, if any, could be made to provide greater reassurance regarding liability, where appropriate safety and purity standards were met.
18.	141	We recommend that the government produces a clear statement on its assessment of phages. If it concludes that phages are to play a significant role in fighting AMR, it should produce a comprehensive plan as to how they will be supported and how the necessary infrastructure and regulatory landscape will be created.

Responses to the committee's recommendations

Phage safety, efficacy and the UK phage research base

Recommendation 1

We recommend that the Department for Health and Social Care (DHSC), the Medicines and Healthcare products Regulatory Agency (MHRA), the National Institute for Health and Care Excellence (NICE) and National Institute for Health and Care Research (NIHR) should now consider what specific evidence, and to what standard, is needed to fully assess the safety and effectiveness of phages to allow them to be used more widely within the NHS and other UK healthcare settings, including over the long term. DHSC, MHRA, NICE and NIHR should engage with phage researchers to establish a dialogue on these issues. The Phage Knowledge Transfer Network established by Innovate UK to bring together phage stakeholders would be an appropriate forum for this dialogue.

The MHRA will provide non-binding advisory guidance on the type of quality, safety, and efficacy data needed to evaluate applications for licensed phage products intended for proactive and reactive use in the NHS for common infections.

NICE will continue in its world-leading role in producing evidence-based guidance on the use of medicines. In line with the 2024 voluntary scheme for branded medicines pricing access and growth (3), NICE is committed to considering all new active substances and significant indications (symptoms or conditions needing an intervention).

As the UK regulator for veterinary medicinal products (VMPs), the Veterinary Medicines Directorate (VMD) continues to work to ensure that only good quality, safe and effective veterinary medicinal products are authorised and available in the UK. The VMD is considering its guidance for phage-based VMPs and the minimum UK standards for the quality, safety and efficacy of these novel products including their manufacture in accordance with 'phage adapted' good manufacturing practice (GMP).

The government will continue to engage with phage stakeholders, including through the Innovate UK Knowledge Transfer Network (KTN) Phage Innovation Network. The UK Health Security Agency (UKHSA) provides the chair for Phage Innovation Network's scientific advisory board. UKHSA supports the goals of the network in developing phage-based products for use in clinical settings and other sectors, alongside developing links with researchers. The MHRA is working closely with the network to understand how it can support phage research and innovation.

DHSC works closely with NIHR and UK Research and Innovation (UKRI) to monitor the research and clinical trial pipeline for antimicrobials and alternative therapies. Where phage research opportunities are identified, NIHR can engage researchers to encourage and support funding applications. The government is developing the 2024 to 2029 AMR NAP. The NAP will set out the government's research priorities, including innovation of new products for tackling AMR.

Recommendation 2

We recommend that the government reviews the status of phages within its plans to tackle AMR. We also recommend more specifically that the National Institute for Health and Care Research (NIHR) and the UK Health Security Agency (UKHSA) engage with the phage researchers to improve prospects for phage related applications for research funding.

The government is committed to exploring alternative therapies, including bacteriophages, to tackle antimicrobial resistance (AMR). The 2024 to 2029 AMR NAP is being developed in consultation with a range of stakeholders and will include research and innovation priorities. The NAP reflects the broad spectrum of interventions needed to tackle AMR. The government recognises the importance of research into non-traditional therapies that could tackle AMR and that phage therapy is one of the options that merits further exploration.

UKHSA works with researchers both in the UK and internationally to support phage-related research, as described in written and oral evidence provided to the committee. This support aims to improve the chances of successful research funding and translation of phage into clinical use.

Examples of the support offered includes, but is not limited to, the following current activities:

1. Access for researchers to bacterial strain panels, biofilm, and infection models for evaluation of the efficacy of phage and phage-cocktails against clinically relevant bacterial strains. Delivered through an Open Innovation AMR programme and previously supported by an NIHR infrastructure grant (NIHR200658), this enables researchers to work directly with UKHSA to evaluate new approaches and generate data to support grants and funding applications

2. Expertise and novel approaches for the rapid susceptibility profiling of clinical isolates against phage or phage cocktails, to support the development of phage cocktails, the provision of data to clinicians looking to use phage in clinical settings and, in the longer term, aiming to support patient recruitment into clinical trials

3. Studies exploring the synergy and antagonism of phage when used with 'standard of care' antibiotics and looking at the changes in antimicrobial susceptibility and virulence linked to emergence of phage-resistance in WHO priority pathogens

4. Working with others to develop new concepts of use and target product profiles (TPPs) for phage, to support their evaluation and implementation in the clinic

5. Working with others to understand the appropriate regulatory frameworks for the manufacture of phage for clinical use, aligned with the concepts of use for different patient groups. Evaluation of novel methods for GMP that could support future clinical implementation of phage

In addition to these current activities, UKHSA will consider appropriate activity to develop further research partnerships in this area alongside the NIHR Health Protection Research Units (HPRUs).

NIHR offers funding through 'researcher-led' programmes. The researcher-led workstream invites applications in response to calls for research on specific questions, which have been identified and prioritised for their importance to the NHS and patients. Proposals may include primary research, evidence synthesis, or feasibility and pilot studies.

UKRI (across its different councils) also offers substantial funding opportunities for phage research. For example, Innovate UK has recently launched PACE 'Pathways to antimicrobial clinical efficacy' (4) – a £30 million initiative with LifeArc and Medicines Discovery Catapult to accelerate early-stage innovation in AMR, with phage projects within its scope.

The VMD engages with the UK KTN Phage Innovation Network and researchers working on phage based VMP, when approached, providing support to these stakeholders on a product specific basis.

Recommendation 3

We recommend that the Department of Health and Social Care (DHSC) reviews the current funding arrangements for phage translational research and identifies what are the bottlenecks for such research. A review should consider what specific assistance phage translational research requires to increase the prospects of success for funding bids. It should also consider whether specific funding is appropriate where it can deliver AMR priorities.

As stated above, DHSC works closely with the NIHR and UKRI to monitor the research and clinical trial pipeline for antimicrobials and alternative therapies.

DHSC commissions research through NIHR. NIHR does not routinely ringfence funding for specific conditions or research areas but welcomes funding applications for research into any aspect of human health, including bacteriophages. These applications are subject to peer review and judged in open competition, with awards being made on the basis of the importance of the topic to patients and health and care services, value for money and scientific quality. In all disease areas, the amount of NIHR funding depends on the volume and quality of scientific activity.

As outlined in evidence provided to the committee, the Medical Research Council (MRC) received very few applications for phage research in the last decade. However, with the growing interest from the Phage KTN, this inquiry, and the launch of the Centre of Phage Research in Leicester, among other initiatives, there are positive signs for the future of phage research.

NIHR focuses on early translational research, clinical research, and applied health and social care research. NIHR and DHSC are working closely with UKRI to explore approaches to improve capacity for phage research in the UK. Through fora such as the AMR funders forum, research funders including the NIHR can explore possible collaborative approaches to research funding for phages.

Overall, the UK is a great place for innovative clinical research, as the NIHR has recently invested almost £948 million to strengthen the research infrastructure supporting clinical trial capacity over the next 5 years. This includes funding for the NIHR Biomedical Research Centres and NIHR Clinical Research Facilities. This funding supports the government ambition to create a patient-centred, pro-innovation and digitally enabled clinical research environment. The aim is to ensure the clinical research environment can

improve health and make the UK one of the best places in the world to design and deliver all research.

Recommendation 4

We recommend that the Department for Health and Social Care (DHSC), as the lead department on AMR, reports annually on the progress made on evaluating and developing all phage-related technologies and therapies that affect human, animal or environmental health (referred to as the ‘One Health’ approach). This should be a joined-up assessment bringing together analyses and data from all relevant departments, regulators, public bodies and funders who are in receipt of public funding for work on phages.

The government recognises the importance of exploring a range of different approaches to develop a comprehensive response to AMR domestically, internationally and across sectors. The government recognises the importance of research into non-traditional therapies, such as phages, as a potential part of the toolkit for tackling AMR. The government will continue to work with partner organisations to monitor the AMR clinical and research pipeline, including the growing evidence base for phage therapy, in line with the 'One Health' approach to tackling AMR.

The government is committed to taking a holistic approach to tackling AMR and is reluctant to prioritise any one technology in terms of funding or reporting. For this reason, the government will not produce annual reports that focus exclusively on phages. The government will, however, regularly review progress in delivering its 5-year AMR NAP 2024 to 2029, which will include, but will not be limited to, phages.

Recommendation 5

We recommend that the Department for Health and Social Care (DHSC) responds to the UK Phage Knowledge Transfer Network’s proposals within 6 months of their publication. The department should set out how it will help develop a network for phage-related knowledge sharing and assets such as biobanks. The department should also indicate how phage-related research and development across different sectors might be joined up as part of its overarching ‘One Health’ approach to tackling AMR.

The government welcomes the valuable insights and recommendations put forward by the UK KTN Phage Innovation Network and acknowledges the importance of establishing a robust network for phage-related knowledge sharing and the management of assets like biobanks. The government is supportive of the important role the network has played convening phage stakeholders and of the network’s ambitious plans to focus on GMP manufacturing, as well as engaging with regulators on the use of phages in humans.

The government does not plan to publicly respond to the UK KTN Phage Innovation Network's report but will consider its recommendations and proposals as part of the wider evidence base for phage therapy. The government recognises the urgency of this matter and understands the potential impact that a well co-ordinated phage-related research and development network can have on tackling AMR across various sectors. As more scientific evidence becomes available, the government will further consider how the use of phages may support achievement of the UK's 20-year vision for AMR.

In 2023, UKRI launched a funding call for transdisciplinary networks related to 'Tackling Infections' (5). This offered up to £650,000 per project to networks looking to generate research questions to address key areas of unmet need, identify and prepare for future challenges, increase collaboration and use a transdisciplinary approach. This call closed on 5 December 2023 and applications are currently being evaluated. It is expected that innovative alternatives or improvements to antibiotics will be a common theme emerging in responses to the call. It is hoped that phage researchers can make full use of these networks, anticipating future research calls in the AMR space.

Biobank infrastructure is eligible for UKRI funding through a range of routes that support research partnerships and infrastructure, particularly the MRC's partnership grant schemes. The partnership grant scheme is designed to support novel partnerships between diverse groupings of researchers.

AMR is a broad and wide-ranging issue with many competing priorities for research. DHSC, NIHR and the UKRI are members of the UK AMR Funders Forum. The forum supports co-ordination of all activities relating to AMR research, including phage research where appropriate. It aims to improve research impacts on national and international policies and activities. The forum brings together 21 different groups from across government departments, UKRI and charity partners. It assesses gaps in research evidence, product development and research translation. It identifies opportunities for research collaboration including workshops, training, and research funding calls. This approach is aligned with the UK 20-year vision for AMR, the 5-year AMR NAP and the UKRI tackling infection's strategic theme. The forum is chaired and managed by the MRC.

The VMD supports continued and joined up communication on phage-related work between VMD and MHRA, alongside other UK regulatory authorities such as the Health and Safety Executive (HSE) and the Food Standards Agency (FSA), as part of the government's 'One Health' approach to tackling AMR.

Recommendation 6

We recommend that information about the clinical use of phages is included within medical training courses and that information about how to access phages or phage expertise is readily available to clinicians and other healthcare staff within each hospital.

The government supports the principle of education and training on the clinical use of phage, as well as access to phage therapies and expertise, for medical and veterinary professionals as and when relevant. However, the standard of medical training is the responsibility of the General Medical Council (GMC) and the standard of veterinary training is the responsibility of the Royal College of Veterinary Surgeons (RCVS), both of which are independent statutory bodies.

Furthermore, UK medical and veterinary schools determine the content of their own curricula which have to meet the standards set by the respective regulatory bodies, the GMC and RCVS, which provides monitoring to ensure that the standards are maintained.

The GMC standards require the curriculum to be formed in a way that allows all medical students to meet the GMC's outcomes for graduates by the time they complete their medical degree, which describe the knowledge, skills and behaviours they have to show as newly registered doctors. The GMC co-ordinates all stages of medical education to ensure that medical students and newly qualified doctors are equipped with the knowledge, skills and attitudes essential for professional practice.

The training curricula for postgraduate doctors in training is set by the relevant Royal College and must meet the standards set by the GMC. While curricula do not necessarily highlight specific advances for doctors to be aware of, they instead emphasise the skills and approaches that a doctor must develop to ensure accurate and timely diagnoses and treatment plans for their patients.

Manufacturing phages

Recommendation 7

We recommend that the Department for Health and Social Care (DHSC) considers bringing together funders with relevant catapults and innovation centres, such as the Centre for Process Innovation, to build a GMP facility that can be accessed and used by phage innovators, the NHS and those seeking to produce microbiome products. The government should also consider investment in existing spare and disused laboratory space, such as the currently for sale Rosalind Franklin Laboratory, to develop a GMP facility for phage production. In addition, the government should consider why there is a

reluctance by pharmaceutical companies to invest in phages, and what steps it can take to address this.

The government acknowledges that challenges in the manufacturing of phage materials in the UK are considered by a range of stakeholders to be a barrier to the development and use of phage therapies in the UK.

A number of capital grant programmes have been delivered by the Office for Life Sciences (OLS) to incentivise life sciences manufacturers to invest in the UK:

- the Medicines and Diagnostics Manufacturing Transformation Fund
- the Life Sciences Innovative Manufacturing Fund
- the Biomanufacturing Fund

Since 2022, OLS capital grants programmes have helped secure investments at 11 manufacturing sites and delivered £416 million joint public and private investment, creating and securing over 1,400 jobs. The recent announcement of a transformative £520 million fund over 5 years (2025 to 2030) (6) will further support ambitions to ensure the UK remains one of most attractive locations for life sciences manufacturing investments. These investments complement the highly regarded research and development ecosystem in the UK, which includes a high-quality science base and network of manufacturing innovation centres, such as the forthcoming Oligonucleotide Manufacturing Innovation Centre of Excellence.

The government will consider the case for development of a GMP facility to support phage innovators by undertaking engagement with key stakeholders including relevant funders and research organisations.

The committee’s report makes a strong case for the development of manufacturing capability to underpin the future evaluation and implementation of phage in the clinic. The provision of such manufacturing capacity, as part of future UK infrastructure within the public sector, would provide significant impetus for the future development of phage therapy across the 'One Health' agenda. Generating phage under GMP will be essential for the translation of some, if not all phage therapies, subject to some of the considerations by MHRA on whether magistral preparations would be suitable for compassionate use cases. Any such activity would require targeted, strategic investment to develop, establish and maintain such facilities and ensure they meet regulatory standards.

Development of a GMP phage manufacturing facility in an appropriate location as part of UKHSA’s scientific estate is not a proposal that government can commit to funding at present. UKHSA has expertise and specialist capabilities to partner and engage in phage

manufacturing but does not have the suitable laboratory capacity to act as a GMP facility for phage production.

The OLS maintains strong relationships with pharmaceutical companies and engages frequently with them through multiple routes, such as the Life Sciences Council and its expert sub-groups, as well as bilateral conversations with individual stakeholders. OLS will use the available engagement routes to consider why there is a reluctance by companies to invest in phages, and what steps can be taken to address this.

As phage technology is in its infancy, engagement with industry to understand the issues for commercialisation will be important. The MHRA provides information on how new medicines products are considered for licencing. The route to market for all medicines is also set out by NHS England (NHSE) in the NHS commercial framework for new medicines (7).

NHSE has devised a novel approach - the subscription model - as a positive, proactive and world-leading step to commercially incentivise antimicrobial drug development. However, there are complex manufacturing and regulatory challenges that create unique challenges for phage products. Working with MHRA and NICE, NHS England has committed as part of the current UK AMR NAP to consider whether the scheme may be relevant to other innovative antimicrobial products including, for example, bacteriophages. If the antimicrobial subscription model is deemed appropriate for phage products in the future, work will be undertaken to review and revise eligibility and award criteria to enable assessment of the effectiveness of phage products.

Recommendation 8

We recommend that the MHRA provides guidance on how phage cocktails will be regulated. It should consider the case of influenza vaccines and allow phage permutations to be assessed on the basis of their individual constituent ingredients meeting agreed purity and safety standards and not for each new combination of those ingredients. We recommend that the MHRA produces guidance on how GE phages will be regulated and how they will meet GMP. The MHRA should also provide guidance on how extracted phage enzymes will meet GMP requirements.

The MHRA is developing non-binding advisory guidance for the licensing requirements for phage products, which will include input from the public. This guidance will be updated in consultation with the phage research and development community as the products and associated methods and technologies mature and in the light of regulatory experience.

Genetic modifications influence which regulatory frameworks will apply during phage manufacture. This will be clarified in the MHRA non-binding advisory draft guidance.

Genetically engineered (GE) bacteriophages are most likely to be a constituent of licensed products, and, therefore, subject to GMP (all licensed products are currently subject to GMP). It is unlikely that GE phages will be used in named patient or compassionate use cases due to the time needed to engineer and validate them.

Phage-derived proteins and other materials sit under the biologicals regulatory framework alongside products such as monoclonal antibodies, cytokines, and recombinant coagulation factors.

The requirements of a fit-for-purpose regulatory framework for phage-based medicines are already under consideration by the VMD. This includes the consideration of guidance for the manufacturers and developers of phage-based VMPs. Existing requirements and risk assessments for formulations of VMPs, including genetically modified organisms (GMOs), will be reviewed to ensure they are appropriate for VMPs containing GE phages. However, there is little concern regarding the functionality of the existing framework, given that genetically modified viral vaccines have been successfully and safely authorised in the UK for many years for use in animals.

Recommendation 9

We recommend that the MHRA publishes guidance on how it intends to regulate phages if they are not produced using a GMP approach. This should include guidance on what developmental pathways are available to phage innovators.

All medicines including unlicensed medicines must be manufactured to GMP standards. The MHRA's non-binding advisory guidance which is under development is expected to provide more information on the manufacture of bacteriophage-based medicinal products. Compassionate use medicinal products can be imported into the UK via notification to the MHRA. The manufactured products are subject to review to ensure applicable GMP equivalence of the manufacture.

Developmental pathways are not needed for these products as the phages do not need to be ‘developed’ apart from training on clinical samples. Any development following their initial use (adoption into a phage bank or developed as part of a licensed product) would no longer be for compassionate use and would therefore fall within the remit of existing regulatory frameworks.

It is expected that phage based VMPs will be manufactured to phage adapted GMP. Guidance regarding these requirements is under consideration.

Recommendation 10

The MHRA should set out how they propose to regulate and ensure clinical safety for each of the scenarios set out in paragraph 100 of the report. This would allow for the narrowing of R&D and production work to prevent wasted effort and allow an agile approach, allowing non-generic phage production for specific patients but GMP production for phages to mitigate the most common bacterial pathogens causing AMR in humans, animals and the environment.

With regards to licensed phage therapeutic products, MHRA non-binding advisory guidance for licensed products is in development and is scheduled to undergo public consultation in 2024.

Due to the specific nature of bacteriophage products, any guidance on safety tests for phage-based VMPs should ensure studies are carried out with representative mono- or multi-phage preparations. Accordingly, it will also need to consider how extrapolation between comparable strains of bacteriophages may be possible. This may be based on representative in vitro or in vivo test parameters or scientific justifications. The VMD is already considering these specific requirements as part of its wider consideration of guidance for phage-based VMPs.

Specific scenarios set out in paragraph 100 of the report, followed by responses

The individual phage strains specific to the bacteria they seek to inhibit could be limitless and impossible to test in advance.

Where new phage strains are needed, manufacture should occur in compliance with GMP standards, including unlicensed medicines.

Unique formulations of phages in conjunction with other drugs, to target infection in individual patients with specific microbiota might not be anticipated in traditional clinical trials.

Formulations of medicinal products must be assessed for safety. It is recommended that there is engagement with the MHRA Clinical Investigations and Trials team to ensure that the appropriate safety evidence is available for assessment.

In the future, pre-tested generic phages that have met regulatory standards may not be able to inhibit bacterial growth necessitating adaptation which maybe beyond inflexible regulations.

The GMP and Clinical Trials Regulations exist to ensure the safety of the patient. The regulations include frameworks and processes to ensure that when a medicinal product is changed there is assessment of the implications of the change for the efficacy and safety of the product. The planned guidance will provide information on the requirements for those seeking to adapt an existing medicinal product.

The specificity required to target a particular infection in a single human could require gene editing of phages, with current regulations implying that each new formulation would require full clinical trials each time, which would not be timely cost effective efficient or possible in terms of generating clinical data if each use ins unique.

Urgent, patient-specific compassionate use largely excludes gene editing due to time pressures (if there is no time pressure it can be made to GMP), while formulation is a pharmacy issue, and clinical trials are not relevant in this case.

The use of double-blind clinical trials and control groups would be problematic if they related to a unique combination of phages produced for a single patient.

Unique combinations for patients would fall under named-patient use, for which GMP requirements remain appropriate. The prescribing physician is responsible for the decision on the benefit risk balance of these medicines in an individual patient and they are not subject to the requirement for clinical trials or assessment by MHRA.

Phage clinical trials

Recommendation 11

The MHRA should also set out more broadly how current clinical trial structures can support the development and regulation of new personalised medicines. This should include an outline of what changes may be required to underpin this emerging and promising area. This should include early and regular engagement by regulators with the sector and a transformative approach to the safety testing and licencing of these exciting products. It should publish this within a year of this report being published.

MHRA is committed to supporting innovation, with early and regular engagement with the sector. Clinical trial legislation is in the process of being reviewed, with accompanying guidance to be published in 2024. Stakeholder engagement will be central to this process.

The Lord O'Shaughnessy review into commercial clinical trials in the UK (8) was commissioned by the government to offer recommendations on how commercial clinical

trials can help the life sciences sector unlock UK health, growth and investment opportunities. The government welcomes the recommendations from this review, including accelerating new and innovative ways to deliver trials.

The government has committed to establish clinical trial acceleration networks, with funding to be used to deliver innovative, efficient and effective approaches for clinical trials.

Recommendation 12

We recommend that the MHRA sets out what standard of phages will be required for UK clinical trials and how GMP will be acquired by UK produced phages if they cannot be assessed by a clinical trial. This guidance should be published within 6 months of the publication of this report.

Quality, safety, and efficacy standards for licensed phages will be defined the MHRA's draft non-binding advisory guidance on phage regulation, which is intended to be published for public consultation later this year. Engagement with the MHRA clinical trials team to discuss clinical trial design is recommended for many products. Phages used in named-patient use will need to meet GMP standards but do not require clinical trials or a marketing authorisation.

Recommendation 13

We recommend that the Department of Health and Social Care (DHSC) and the National Institute for Health and Care Research (NIHR) follow up on this amenability to receive applications from phage researchers for clinical trials by engaging with them and supporting them in their applications. Similarly, we recommend that the Medicines and Healthcare Products Regulatory Agency (MHRA) offers tailored support for phage applications for clinical trials.

In addition to the above commitment to engage with the UK KTN Phage Innovation Network and other stakeholders on phage research, the NIHR offers an NIHR Research Support Service for phage researchers. This provides free and confidential advice to develop funding applications within the remit of the NIHR, including clinical, applied health and social care research, and post-award advice to award holders. Access to support, advice and expertise is available for all researchers across England applying to NIHR research programmes or research training awards as well as to non-NIHR funders such as charities.

When considering applications to NIHR for funding, researchers should review the 'remit pages'. The most suitable programme for phage research would depend on the research

area, the scale of the study, and whether it will generate new evidence or build upon existing evidence. There is scope for significant further 'basic' phage research, which would be best supported by the UKRI councils. For clinical trials specifically, there are 2 large NIHR programmes offering funding: the Efficacy and Mechanism Evaluation (EME programme) and the Health Technology Assessment (HTA) programme.

The EME programme funds studies into the efficacy of new approaches to disease prevention and treatment. It supports clinical trials and other studies that test how interventions may work in practice. This programme is co-funded with the MRC and is predominantly focused on evidence generation for areas where there is sufficient proof of concept data. A specialist team is available for specific queries about the process from researchers.

The HTA programme funds research into the clinical- and cost-effectiveness of treatments and tests. HTA research compares new technology to the current standard interventions to see which works best, where there is already evidence to show a new technology is effective. Health technology covers any method used to promote health, prevent and treat disease and improve rehabilitation or long-term care. 'Technologies' in this context are not confined to new drugs or equipment, but include procedures, devices, tests, settings of care, screening programmes and any intervention used in the treatment, prevention or diagnosis of disease. They should be currently used in the NHS, or likely to be used if supported by the results of the research. Technologies being evaluated should have had some assessment of efficacy already. Researchers can receive support in advance of their application.

The MHRA's draft guidance on the licensing requirements for phage therapeutic products will recommend that sponsors engage with MHRA at the earliest opportunity to obtain clarity regarding requirements for clinical trials, including Good Clinical Practice requirements. The MHRA will provide scientific advice but cannot design clinical trials on behalf of product developers.

The VMD encourage all stakeholders looking to develop phage based VMPs and wishing to conduct UK clinical trials to contact the VMD for support and advice. The UK framework for veterinary clinical trials is currently fit for purpose and would allow the authorisation of trials involving phage based VMPs.

Recommendation 14

We recommend that the MHRA outlines how it will use clinical data from other countries and non-health evidence to inform its decision-making on regulating phages

The MHRA has mutual recognition agreements with several competent authorities to expedite market approval in the UK for products approved in other territories (9). The International Recognition Procedure (IRP) introduced on 1 January 2024 allows the MHRA to recognise the decision-making of 7 trusted reference regulators. The MHRA conducts a targeted assessment of IRP applications and retains the authority to make a sovereign decision.

The clinical use of phages in the UK

Recommendation 15

We recommend that the Department of Health and Social Care (DHSC) and the Medical and Healthcare products Regulatory Agency (MHRA) reviews the current rules regarding the clinical use of phages in the UK. This should aim to ensure alignment between domestically produced and imported phages.

As previously described, the MHRA intends to publish non-binding advisory phage guidance for public consultation in 2024.

Successful translation of phage therapy from experimental settings to clinical application depends on the ability to manufacture phages at a quality and scale that meets demand. This necessitates discussion and collaboration between the government, NHS and phage experts as wider scale clinical use of phages will involve navigation of complexities including optimising production processes and ensuring quality control.

Recommendation 16

We recommend that the Medicines and Healthcare products Regulatory Agency (MHRA) revisits the regulation of the clinical use of non-GMP phages produced in the UK for last resort compassionate cases where antibiotics or other antibacterial interventions have failed. The MHRA should review the use of non-GMP phages in such cases in other countries and produce a monograph to govern and ensure their safety and purity. The MHRA should publish its review and proposals for a non-GMP phage monograph and any changes that will be required to change necessary regulation to underpin this change. The Department for Health and Social Care should review and report on what changes, if any, will be required to ensure that current guidance and oversight procedures are sufficient for the preparation and use of UK produced non-GMP phages in UK healthcare settings.

All medicines are required to be manufactured to GMP but may be provided outside of the marketing authorisation framework as unlicensed medicines on an individual patient basis.

In the UK, all imported unlicensed medicines including those that may incorporate bacteriophages are currently subject to review to ensure that they have been manufactured at equivalent standards to, or in compliance with, GMP regulations.

New non-binding advisory guidance is under development by MHRA. The production of a monograph will be deferred until MHRA has gained experience from writing the non-binding advisory guidance.

Recommendation 17

We recommend that the MHRA reviews how current regulations would govern liability for clinicians and hospitals who used UK non-GMP phages, produced to a magistral monograph. It should consider what changes, if any, could be made to provide greater reassurance regarding liability, where appropriate safety and purity standards were met.

Regulation for pharmacy practice is beyond the remit of MHRA and any liability on the use of an unlicensed medicine currently rests with the prescriber.

Recommendation 18

We recommend that the government produces a clear statement on its assessment of phages. If it concludes that phages are to play a significant role in fighting AMR, it should produce a comprehensive plan as to how they will be supported and how the necessary infrastructure and regulatory landscape will be created.

The government previously set out its position on the use of phages to tackle AMR in the written evidence that was submitted to the inquiry in April 2023 (10). This reaffirmed the government commitment to exploring phage therapy as an alternative to antibiotics. While current evidence on phage therapy is promising, more robust data is required to fully understand the role phages could play in combatting AMR. The government continues to work closely with partners to understand, and support, the growing evidence base for bacteriophage therapy.

The government is developing the 2024 to 2029 AMR national action plan (NAP). The NAP will recognise the importance of exploring a range of different research areas, including phages, to develop a comprehensive therapeutic suite for treating and managing infections in humans and animals.

There are several barriers to the development and deployment of phage therapy including quality assurance, supply chain adequacy, financial approvals, health, safety and containment, and usage guidelines, some of which were highlighted in the committee's report and by contributors to this paper.

The government will not produce a further statement on its assessment of phages at this time or publish a roadmap that depicts how phage manufacture and regulation will be embedded in the UK. The government will continue to seek, monitor and evaluate developments made in phage therapy research and use of phage therapies as part of reviewing progress on the wider government AMR programme.

References

1. The antimicrobial potential of phages - parliament.uk (https://committees.parliament.uk/work/7045/the-antimicrobial-potential-of-bacteriophages/)

2. Contained and controlled: the UK's 20-year vision for antimicrobial resistance – GOV.UK (https://www.gov.uk/government/publications/uk-20-year-vision-for-antimicrobial-resistance)

3. 2024 voluntary scheme for branded medicines pricing, access and growth - GOV.UK (https://www.gov.uk/government/publications/2024-voluntary-scheme-for-branded-medicines-pricing-access-and-growth)

4. Pathways to antimicrobial clinical efficacy (PACE) - UKRI (https://www.ukri.org/what-we-do/browse-our-areas-of-investment-and-support/pathways-to-antimicrobial-clinical-efficacy-pace/)

5. Tackling Infections – UKRI (https://www.ukri.org/what-we-do/browse-our-areas-of-investment-and-support/tackling-infections/)

6. 2023 Autumn Statement – GOV.UK (https://www.gov.uk/government/publications/autumn-statement-2023)

7. NHS commercial framework for new medicines - NHS.UK (https://www.england.nhs.uk/publication/nhs-commercial-framework-for-new-medicines/)

8. Commercial clinical trials in the UK: the Lord O'Shaughnessy review - final report - GOV.UK (https://www.gov.uk/government/publications/commercial-clinical-trials-in-the-uk-the-lord-oshaughnessy-review/commercial-clinical-trials-in-the-uk-the-lord-oshaughnessy-review-final-report#executive-summary)

9. Guidance: International Recognition Procedure - GOV.UK (https://www.gov.uk/government/publications/international-recognition-procedure/international-recognition-procedure)

10. Written Evidence submitted by DHSC, UKHSA and MHRA to the SITC's Inquiry: the antimicrobial potential of phages (https://committees.parliament.uk/work/7045/the-antimicrobial-potential-of-bacteriophages/publications/written-evidence/?page=2)

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