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The antimicrobial potential of bacteriophages

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Science, Innovation and Technology Committee

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Contacts

All correspondence should be addressed to the Clerk of the Science, Innovation and Technology Committee, House of Commons, London, SW1A 0AA. The telephone number for general inquiries is: 020 7219 2793; the Committee's e-mail address is: commonssitc@parliament.uk.

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Contents

Summary

Antimicrobial resistance (AMR) poses a serious global threat to our ability to treat bacterial infections. New antibiotics have often proved difficult and expensive to develop. This has led to an interest being rekindled in an older form of antimicrobials—bacteriophages (phages)—viruses that 'eat' bacteria. They can treat bacterial infections and reduce resistance to antibiotics by removing barriers—biofilms—which have evolved and reduced antimicrobial effectiveness. Each phage can target individual bacteria, can be combined with multiple phages and antibiotics, and adapted specifically for each individual patient. Phages have been described as a 'personalised medicine'—a group of treatments adapted to each patient.

The further development of phage therapies face significant challenges that will need to be overcome if their potential is to be fully realised. Like many personalised medicines, they currently struggle to meet regulations designed for conventional medicines produced to a single formulation. In the UK phages have not been manufactured to required Good Manufacturing Process (GMP) standards, precluding UK-produced phages from clinical use. The small quantities of phages that have been used in the UK are imported, usually not to GMP standards, and are heavily restricted because they are unlicensed.

Regulators should address these issues at pace. The Medicines and Healthcare Products Regulatory Agency (MHRA) should consider using a 'magistral monograph', as is the case in Belgium, to allow non-GMP phages to be produced in the UK to an acceptable standard for compassionate cases. Regulators should set out what standards will be required for phages to meet clinical trial and GMP standards, reflecting their unique characteristics and specificity for each patient treated. This work should be used to inform regulation of personalised medicine more generally.

This impasse of phages being unlicensed, and therefore their minimal deployment in the UK, has hindered attempts to integrate phages within our health system. With the lack of a route to a return on investment, there has not been significant investment in phage infrastructure. This has stalled a roll out of phage biobanks, a systematic network of phage laboratories to produce specific phage formulations or the manufacturing capability to produce more generic phages for humans and for use in other areas, such as animals and aquaculture.

The Department for Health and Social Care (DHSC) should consider bringing together funders with relevant catapults and innovation centres to build a GMP facility that can be accessed and used by phage innovators, the NHS and those seeking to produce other personalised medicines, such as microbiome products. The DHSC should also set out how it will help develop a network for sharing phage-related knowledge, and assets such as biobanks.

Despite the UK hosting some leading phage researchers and research centres, and acknowledgement of the role they could play, key funders have appeared reticent to back phage research. Whilst research indicates that phages are comparatively safe, further work can address remaining concerns, and develop a body of evidence to demonstrate both their safety and effectiveness. Such research could harness the UK's genomic

research prowess and artificial intelligence to quickly match phages to bacteria and allow manipulation to increase effectiveness. The National Institute for Health and Care Research and the UK Health Security Agency should engage with phage researchers to improve prospects for phage related applications for research funding.

More broadly, the Government should produce a clear statement on the role that phages could play in fighting AMR and how they will be supported.

1 Introduction

1. The starting point for our inquiry into bacteriophages ('phages')—viruses that 'eat' bacteria—is the threat posed by antimicrobial resistance to antibiotics (AMR) and the challenges in developing new approaches to tackle this. AMR occurs when bacteria, viruses, fungi and parasites evolve over time and no longer respond to medicines, making infections harder to treat and increasing the risk of disease spread, severe illness and death.[1] The World Health Organization (WHO), has described AMR as one of the most urgent global health challenges for the next decade, noting that it threatens "to send modern medicine back decades to the pre-antibiotic era, when even routine surgeries were hazardous".[2] We held an evidence session in June 2022 on AMR and have retained an interest in this area.[3]

Our Inquiry

2. Bacteriophages, or 'phages', are viruses that can be used as an antimicrobial, either in conjunction with antibiotics or as an alternative. Phages have the potential to reanimate antibiotics by removing bacterial defences that reduce their effectiveness. They have therefore been seen as having the potential to play a significant key role in addressing AMR. However, the widespread use of phages faces a number of challenges. Our inquiry examined the evidence regarding the safety and effectiveness of phages and the barriers to their development and use, with a focus on their clinical use and application as a medical product. This included looking at UK phage regulation, funding for phage research, and the infrastructure need to translate phages into clinical therapeutics and commercial products. We also looked at comparative approaches to phages in terms of funding, clinical trials, therapies and commercial use to consider what steps the Government, regulators, and those involved in phage research, therapies and commercialisation, can take to ensure that the potential of phages can be properly assessed and exploited.

3. Our inquiry was a result of the successful pitch to the Committee's My Science initiative held in November 2022 by Professor James Ebdon, on behalf of Applied Microbiology International. It followed a one-off evidence session on antimicrobial resistance (AMR) held in June 2022. The inquiry received over 40 pieces of written evidence and held three oral evidence sessions. We heard from academic experts and clinicians from the UK and from around the world, funders, Small and Medium-sized enterprises (SMEs), regulators and government officials. It included a visit to the Santini Lab at University College London (UCL), an Electron Microscope (Birkbeck College and UCL) and a Good Manufacturing Practice (GMP) facility at the Zayed Centre for Research into Rare Disease in Children, Great Ormond Street Hospital.

1 WHO, Antimicrobial resistance, (accessed 14 June 2021).
2 WHO, Urgent health challenges for the next decade, (January 2020).
3 Science and Technology Committee, Oral evidence: Antimicrobial resistance, (HC 231; 322 June 2023). We followed up with subsequent correspondence with the Secretary of State Health and Social Care Minister for Farming, Fisheries and Food.

The scale of the antimicrobial resistance threat

4. In January 2022, the Lancet published an analysis which estimated that AMR had directly caused 1.27 million deaths and played a role in 4.95 million deaths in 2019.[4] In November 2022, the European Centre for Disease Prevention and Control published statistics which estimated that more than 35,000 people a year die from AMR across the EU and EEA,[5] with similar levels of US deaths estimated by the US Centers for Disease Control and Prevention.[6] In April 2019, the ad hoc UN Interagency Coordinating Group on Antimicrobial Resistance suggested that, if unchecked, AMR could lead to 10 million global deaths a year by 2050.[7]

5. In addition, there are concerns over potential associated economic costs with AMR. The OECD has estimated that EU and EEA countries will be spending up to €1.1bn a year on AMR health care if it is not checked, including costs incurred by slower recovery from infection and a higher risk of complications, with up to 569 million extra hospital days annually across EU and EEA countries.[8] Other estimates, which also include the impact of AMR on productivity, project higher costs. In 2017, the World Bank estimated that AMR could cost the world economy between $1 trillion and $3.4 trillion a year by 2030 depending on the mitigations in place.[9] In 2014, the Review on Antimicrobial Resistance estimated that the cumulative global costs of AMR could have cost up to $100 trillion by 2050.[10]

The UK's response to the AMR threat

6. The threat posed by AMR has been acknowledged by the UK Government, which in 2019 published a new 20-year vision for tackling AMR,[11] and a 5-year action plan,[12] building on a previous five year strategy published in September 2013.[13] AMR is also on the UK National Risk Register.[14] More recently, the Government's UK Biological Security Strategy, published on 12 June 2023, stated that AMR could lead to a situation where "certain infections will no longer be treatable and routine medical care may become too

4 The Lancet, Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis, vol 399, issue 10325, (January 2022).

5 European Centre for Disease Prevention and Control, 35 000 annual deaths from antimicrobial resistance in the EU/EEA, (17 November 2022).

6 CDC, COVID-19: U.S. IMPACT ON ANTIMICROBIAL RESISTANCE, (2022). The Report stated that AMR was in danger of deteriorating after its 2019 Report, which had estimated more than 2.8mn AMR infection and more than 35,000 deaths a year.

7 WHO, New report calls for urgent action to avert antimicrobial resistance crisis, (April 2019). See also: The Review on Antimicrobial Resistance, Antimicrobial Resistance: Tackling a crisis for the health and wealth of nations, (December 2014), p 6.

8 OECD, Antimicrobial Resistance: Tackling the Burden in the European Union, (2019), p 12. A report also published in 2019 by the OECD predicted that EU and OECD countries collectively would be spending up to $3.5bn a year on AMR health-related costs. This it estimated would correspond to 10% of healthcare costs caused by communicable diseases. See: OECD, Stemming the Superbug Tide: Just A Few Dollars More, (2019), p 17.

9 World Bank, Drug-Resistant Infections: A Threat to Our Economic Future, (March 2017), p 6.

10 The Review on Antimicrobial Resistance, Antimicrobial Resistance: Tackling a crisis for the health and wealth of nations, (December 2014), p 6. See also: HM Government, Tackling antimicrobial resistance 2019–2024: The UK's five-year national action plan, (January 2019), p 9.

11 HM Government, Contained and controlled: The UK's 20-year vision for antimicrobial resistance, (January 2019).

12 HM Government, Tackling antimicrobial resistance 2019–2024: The UK's five-year national action plan, (January 2019).

13 Department of Health and Department for Environment and Rural Affairs, UK Five Year Antimicrobial Resistance Strategy: 2013 to 2018, (September 2013).

14 HM Government, National Risk Register 2023 edition, (3 August 2023), p 18.

risky leading to significant loss of life".[15] The scale of the risks involved was underlined on 15 November 2023, when the UK Health Security Agency (UKHSA) published estimates which shows that an estimated 58,224 people in England had an antibiotic resistant infection in 2022–a rise of 4% since 2021 (55,792), while deaths due to severe antibiotic resistant infections also increased from 2021 to 2022 from 2,110 to 2,202.[16] The Government has stated that it will publish a new five year National Action Plan for AMR in early 2024.[17]

Approaches to mitigating the AMR threat

7. Several approaches have been advanced to tackle AMR.[18] One is better stewardship of existing antibiotics, to reduce their use and exposure with the aim of reducing resistance or at least slowing the rate of resistance down.[19] For instance, it has been estimated that in the US that one in three antibiotic prescriptions are unnecessary.[20] In the UK, NHS trusts are required to reduce annual antibiotic consumption by at least 1% from a 2018 baseline,[21] and submit total antibiotic consumption data to the UK Health Security Agency (UKHSA).[22] This has led to sizeable reductions in some NHS Trusts, with one Trust reporting a 17.8% reduction between 2018/19 and 2020/2021.[23] However, antibiotic stewardship faces challenges. It requires investment to implement and monitor its impact, and to be effective it needs to be implemented across multiple sectors, including the veterinary sector.[24]

8. Another approach to tackling AMR, is the development of new antimicrobials, using new chemical compounds.[25] The WHO has described progress on this as slow, and lacking innovation,[26] in part due to an absence of interest from pharmaceutical companies because of a dearth of lucrative opportunities for novel antibiotics compared to other types of medicines.[27] Witnesses we heard from also emphasised the problems associated with the development of new antibiotics, especially the financial model associated with developing

15 Cabinet Office, UK Biological Security Strategy, (12 June 2023).
16 UKHSA, Antibiotic resistant infections and associated deaths increase, (15 November 2023). A full analysis can be found here: UKHSA, English surveillance programme for antimicrobial utilisation and resistance (ESPAUR) report, (15 November 2022).
17 Ibid. UKHSA confirmed that the new five year National Action Plan for AMR is expected to be published in early 2024.
18 For a concise overview see: POST, Responding to the challenge of antimicrobial resistance, (April 2021).
19 See for example: HM Government, Tackling antimicrobial resistance 2019–2024: The UK's five-year national action plan, (January 2019), pp 53–70; WHO, Antimicrobial stewardship programmes in health-care facilities in low - and middle-income countries, (2019); Centres for Disease Control and Prevention, Core Elements of Antibiotic Stewardship, (accessed 14 June 2023).
20 Pew, National Survey Reveals Barriers to Outpatient Antibiotic Stewardship Efforts, (August 2020).
21 NHS, NHS Standard Contract 2019/20 Technical Guidance, 2019.
22 This is in line with the UK 2019 to 2024 five-year action plan on antimicrobial resistance.
23 Gloria Kiapi et al., Successful antibiotic stewardship in the electronic era, JAC-Antimicrobial Resistance, vo 5, issue 3, (June 2023).
24 Md Anwarul Azim Majumder et al., Antimicrobial Stewardship: Fighting Antimicrobial Resistance and Protecting Global Public Health, Infect Drug Resist, no 13, (2020).
25 See: Marco Terreni et al., New Antibiotics for Multidrug-Resistant Bacterial Strains: Latest Research Developments and Future Perspectives, Medicine, vol 29, no 9, (May 2021).
26 WHO, Lack of innovation set to undermine antibiotic performance and health gains, (June 2022).
27 Sujata M. Bhavnani et al., A Broken Antibiotic Market: Review of Strategies to Incentivize Drug Development, Open Forum Infectious Diseases, (March 2020), p 2. See also: Financial Times, Non-profits fill gaps in the broken market for antibiotics, (December 2020); Pew, The Antibiotic Market Is Broken—and Won't Fix Itself, (April 2019);

expensive drugs with uncertain and/or limited market to recoup investment.[28] For instance, between 2010 and 2016 only 6 new pharmaceutical antibiotics were approved by the Food and Drug Administration (FDA) for use in the United States.[29] These challenges have led to calls for greater 'push' to support research and development, and enhanced 'pull' to provide incentives for innovators and investors to develop new antimicrobials.[30] Witnesses noted that the UK Government has introduced a new 'subscription-style' approach to address this.[31] This involves paying pharmaceutical companies a fixed annual fee primarily on a health technology assessment of their value to the NHS, as opposed to the volumes used.[32] This aims to incentivise companies to invest in researching and developing at the beginning of their work rather than waiting for later returns.[33] Work is also taking place to develop vaccines to tackle AMR. However, progress has been described as 'challenging'.[34]

9. Finally, there is the effort to identify or develop drugs or therapies that can be used in conjunction with existing antibiotics—to which resistance is feared, is emerging or has developed—to reduce, prevent or disrupt that resistance. Such approaches are referred to as 'antibiotic resistance breakers' (ARBs). ARBs can be used in conjunction with antibiotics by combatting the bacterial resistance mechanisms employed against the latter, allowing lower doses of antibiotics to be used. This is seen as attractive because it could slow the onset of resistance and allow for the alleviation of side effects experienced by patients on antibiotics.[35] Phages arguably have the potential to play a role in all three approaches, offering credible alternatives, potential substitutes or helpful allies in the fight against evolving bacterial infections and their resistance to antimicrobials.

The revival of bacteriophages as an antimicrobial

What are phages?

10. With the growing threat of AMR and the challenges facing other solutions, interest has been rekindled in an antimicrobial approach that predates antibiotics. Lytic Bacteriophages (or 'phages') are viruses that kill bacteria by making them undergo 'lysis' (in other words burst their cell wall or membrane) by binding to the bacteria and injecting

28 Professor Cath Rees, Professor of Microbiology, University of Nottingham (Q14); Greg Merril, Chief Operating Officer, Adaptive Phage Therapeutics (Q156 and Q165); Richard Hebdon, Director Health and Life Sciences, Innovate UK (Q198); Wellcome Trust (PHA0011); AMR Action Fund (PHA0012); Phage-UK (PHA0013); Antibiotic Research UK (PHA0020); Oxford Silk Phage Technologies Ltd (PHA0035). See also: Wellcome Trust, Why is it so hard to develop new antibiotics?, (accessed 23 July 2023).

29 Derek M Lin et al., Phage therapy: An alternative to antibiotics in the age of multi-drug resistance, World J Gastrointest Pharmacol Ther, vol 8, no 3, (August 2017), pp 162–173.

30 See for example: Scott Gottlieb, FDA's Strategic Approach for Combating Antimicrobial Resistance, (December 2018). See also: J Cama et al. To Push or To Pull? In a Post-COVID World, Supporting and Incentivizing Antimicrobial Drug Development Must Become a Governmental Priority, ACS Infectious Diseases, vol 7, no 8, (August 2021); Talha Burki, Push and pull of antibiotic development, (January 2010);

31 Dr Tim Jinks, Head of Infectious Disease Interventions, Wellcome Trust (Q200); Dr Morwenna Carrington, Deputy Director for UK Health Security, Department for Health and Social Care (Q242).

32 GOV.UK, World-first scheme underway to tackle AMR and protect UK patients, (June 2020).

33 NHS England, The Antimicrobial Products Subscription Model: consultation on proposals, (October 2023).

34 See: Francesca Micoli et al., The role of vaccines in combatting antimicrobial resistance, nature Reviews Microbiology, vol 19, (February 2021), pp 287–302.

35 Mark Laws et al., Antibiotic resistance breakers: current approaches and future directions, FEMS Microbiology Reviews, vol 43, issue 5, (September 2019).

their own genetic material (DNA or RNA).[36] The phage virus replicates inside the bacteria by using up the latter's nutrients, making up to 1000 new viral particles in each bacterium to infect others when they in turn burst.

Strengths and weaknesses of phages as an antimicrobial

11. Phages are very species-specific with regard to their hosts and usually only infect a single bacterial species or even specific strains within a species.[37] For this reason, they are seen to have an advantage over antibiotics, which are more indiscriminate in the bacteria they eliminate—good and bad.[38] One potential advantage of phages is their ability to dismantle the biofilm that bacteria have evolved, which inhibits the action of antibiotics.[39] The properties of biofilms and their role in AMR are set out in the box below.

Box 1: Biofilms

Biofilms are structured microbial communities that occur as surface-attached communities or suspended aggregates. They consist of microbial cells (bacteria and/or fungi) embedded in a self-produced extracellular matrix composed of polysaccharides, extracellular DNA and other components. In comparison to planktonic cells (i.e., free-living cells in suspension), cells in a microbial biofilm are much less susceptible to antimicrobial agents and this decreased susceptibility has a considerable impact on the treatment of biofilm-related infections. Biofilm formation is often considered to be the underlying reason why treatment with an antimicrobial agent fails and as an estimated 65%–80% of all chronic infections is thought to be biofilm-related, this presents a serious challenge.

Tom Coenye, Biofilms, Reference Module in Life Sciences, (October 2022)[40]

By removing this biofilm, phages not only infect bacteria in their own right, they can also re-sensitise bacteria to previously ineffective antibiotics, establishing a 'phage-antibiotic

36 Phages can follow two cycles. Lytic phages involves a virus taking control of a host bacterial cell and using it to produce its viral progeny, killing the host in the process. Lysogenic phages involve the virus assimilating a bacterial genome with the host cell's genome to achieve replication without killing the host. Lytic phages are used to treat microbial infections. See: Immunology and Microbiology, Lytic vs Lysogenic – Understanding Bacteriophage Life Cycles, (August 2018); American Society for Microbiology, Phage Therapy: Past, Present and Future, (August 2022).

37 National Library of Medicine (US National Center for Biotechnology Information), Bacteriophages, (September 2022).

38 Catherine Loc-Carrillo and Stephen T Abedon, Pros and cons of phage therapy, Bacteriophage, vol 1 no 2, (March-April 2011), pp 111–114.

39 Biofilms can start forming when a group of microbes sense a given surface and adhere to it. Subsequent colonization and production of an extracellular polysaccharide matrix (EPS) solidify the structure. The EPS matrix substance is sticky and protects the internal surface environment of the bacteria from the external environment. See: American Society for Microbiology, The Role of Bacterial Biofilms in Antimicrobial Resistance, (March 2023).

40 See also: American Society for Microbiology, The Role of Bacterial Biofilms in Antimicrobial Resistance, (March 2023); Philip Bowler et al., Biofilm exacerbates antibiotic resistance: Is this a current oversight in antimicrobial stewardship?, Antimicrobial Resistance & Infection Control, vol 9, (2020).

synergy'.[41] Phages can be used therefore with or without antibiotics,[42] though in clinical interventions, usually the former. In some cases, they do not need repeated administration, as they replicate and can stay in the human body for prolonged periods of time.[43]

12. Phages are generally used as 'cocktails'. This is where a combination of phages is used to target a diversity of bacterial types or to inhibit the growth of bacterial infections, or bacterial resistance to phages. Such cocktails may also include a combination of phages and antibiotics, where there is a positive synergy between the ingredients.[44]

13. However, the use of phages to tackle bacterial pathogens has several weaknesses. It can be difficult and time consuming to identify which pathogen needs to be eradicated, which phage is needed and its dose, strength and ability to maintain specificity. The interrelationship between a phage, the bacterium and its modification after contact with the phage, and the environment, can also be particularly complex and difficult to determine. There are also challenges and costs in formulating and stabilising pharmaceutical-grade phage preparations, varying from phage to phage. In addition, as with antibiotics, there is the possibility of bacteria developing resistance to phages.[45] And, because phages are non-self-antigens—cells that originate outside a host body—they can be recognised by a patient's immune system and their effectiveness can be reduced if attacked.[46] Finally, as with other drugs, there is also a risk of anaphylaxis and an auto immune response in patients who receive phage therapies. We heard, however, that some of these weaknesses might be addressed by better genomic sequencing;[47] an expanded mapping of the range of phages; genetic engineering of phages;[48] and the use of Artificial Intelligence (AI) to match phages to bacterial pathogens.[49] A personalised approach to the use of phages can also address some of these issues. By providing unique combinations of phages, including generic and engineered phages, alongside antibiotics and other medicines, that can be matched and tailored to individual patients, they have the potential to optimise antimicrobial effectiveness, while reducing side effects.

41 Siyu Liu et al., Phages against Pathogenic Bacterial Biofilms and Biofilm-Based Infections: A Review, Pharmaceutics, vol 14, no 2, (February 2022). See also: Q6 (Professor Martha Clokie, Professor of Microbiology, University of Leicester).

42 Q16 (Professor Martha Clokie, Professor of Microbiology, University of Leicester).

43 See: Nicola Principi et al, Advantages and Limitations of Bacteriophages for the Treatment of Bacterial Infections, Frontiers in Pharmacology, vol 10, May 2019; Catherine Loc-Carrillo1,2 and Stephen T Abedon, Pros and cons of phage therapy, Bacteriophage, vol 1, no 2, March-April 2011.

44 See: Stephen T. Abedon, Katarzyna M. Danis-Wlodarczyk and Daniel J. Wozniak, Phage Cocktail Development for Bacteriophage Therapy: Toward Improving Spectrum of Activity Breadth and Depth, Pharmaceuticals (Basel), vol 14, no 10, (October 2021).

45 See: Dr Morwenna Carrington, Deputy Director for UK Health Security, Department for Health and Social Care (Q249).

46 See: Nicola Principi et al, Advantages and Limitations of Bacteriophages for the Treatment of Bacterial Infections, Frontiers in Pharmacology, vol 10, May 2019; Catherine Loc-Carrillo1,2 and Stephen T Abedon, Pros and cons of phage therapy, Bacteriophage, vol 1, no 2, March-April 2011.

47 See: Zeheng Bai et al., Identification of bacteriophage genome sequences with representation learning, Bioinformatics, vol 8, issue 18, (September 2022); Trever L Thurgood et al., Genome Sequences of 12 Phages That Infect Klebsiella pneumoniae, American Society for Microbiology, vol 9, no 16, (April 2020).

48 See: Joana Azeredo et al., Targeting biofilms using phages and their enzymes, vol 68, (April2021); Barbara Maciejewska et al., Applications of bacteriophages versus phage enzymes to combat and cure bacterial infections: an ambitious and also a realistic application?, Applied Microbioogy Biotechnology, (2018).

49 See for example: Phage AI, Phage Therapy 2.0: Artificial Intelligence & Bioinformatics for Phage Research, (accessed 20 June 2023); Yousef Nami et al., Application of machine learning in bacteriophage research, BMC Microbiology, vol 21, (June 2021).

The use of phages

14. Phages were first discovered 1915, with phage therapy subsequently being used to treat microbial infections during the 1920s particularly in the Soviet Union and other Eastern European countries.[50] In Russia, phage preparations are registered medicines, with dedicated research centres.[51] The country has also intensified its efforts to reduce AMR in its food supply systems and introduced proactive measures to mitigate AMR in clinical and medical settings.[52] In addition, Russia has used phages to treat contaminated water.[53] In Georgia, patients are treated with either manufactured generalised phages,[54] or individualised phages, if the bacteria is resistant to standard phages.[55] Phage products are also used for environmental protection, sanitation and decontamination of different environments contaminated with bacterial pathogens.[56] In Poland, the Phage Therapy Unit (PTU) at the Hirszfeld Institute of Immunology and Experimental Therapy in Wrocław, has treated patients with phages since the 1950s.[57] It was permitted to continue using phages as an experimental treatment regime after joining the EU in May 2004.[58] It has also produced phages for patients across Europe and North America.[59]

15. In the US and Western Europe, the emergence of antibiotics in the 1920s led to dwindling interest in phages,[60] apart from their use as tools for molecular research in the 1950s, until their re-emergence in the 1980s to control bacterial infections.[61] Phages have also begun to be used in the food industry, with the first phage-based product (ListShield) gaining regulatory approval for use to control *L. monocytogenes* (*Listeria*) in meat and

50 See: William C. Summers, The strange history of phage therapy, Bacteriophage, vol 2, no 2, (April 2012); A. V. Letarov, History of Early Bacteriophage Research and Emergence of Key Concepts in Virology, Biochemistry (Moscow), vol 85, pp 1093–1112, (2020); American Society for Microbiology, Phage Therapy: Past, Present and Future, (31 August 22).

51 Ryszard Międzybrodzki et al., Current Updates from the Long-Standing Phage Research Centers in Georgia, Poland, and Russia, Bacteriophages, (February 2018).

52 Russia's Federal Service for the Oversight of Consumer Protection and Welfare has initiated an intensive programme to: prevent food infections; produce agents to avoid contamination in semi-finished food products; produce disinfection for processing medical instruments and premises; set up measures for bacteriophage prevention of infections associated with medical care. See: Bacteriophage News, Russia's programme against antibiotic-resistant bacteria with bacteriophages, (September 2021).

53 See: Bacteriophage News, Irkutsk, Russia – intesti phage used in emergency situation post flooding, (July, 2019).

54 The products include oral prepations made with Intesti, SES, Stasphyocccal, Ferisi and Enko phages. See: Eliava BioPreparations, Products, (accessed 16 June 2023).

55 Bacteriophage News, Phage therapy centers & phage products, (July 2019). The Center pimarily targets Staphylococcus, Streptococcus, Enterococcus, Coli, Proteus and Pseudomonas. However, the Institute houses a library of 600 phages and has facilties to identify the bacteria and match it with the appropriate phage.

56 Eliava Consortium, Elaiva Consortium, (accessed 17 June 2023).

57 Andrzej Górski et al., How Interest in Phages Has Bloomed into a Leading Medical Research Activity in Poland, Viruses, (December 2022).

58 Maciej Żaczek et al., Phage Therapy in Poland – a Centennial Journey to the First Ethically Approved Treatment Facility in Europe, Frontiers in Microbliogy, (June 2020).

59 Andrzej Górski et al., A Thorough Synthesis of Phage Therapy Unit Activity in Poland—Its History, Milestones and International Recognition, Viruses, vol 14, no 6, (June 2022).

60 The first antibiotic—salvarsan—was deployed in 1910. The widespread use of antibiotics increased rapidly after the discovery of penicillin in 1928. See: Matthew I Hutchings et al., Antibiotics: past, present and future, Current Opinion in Microbiology, vol 51, (October 2019).

61 See: Bruce R. Levin and J. J. Bull, Phage Therapy Revisited: The Population Biology of a Bacterial Infection and Its Treatment with Bacteriophage and Antibiotics, The American Naturalist, vol 147, no 6, pp 881–898. This included the work of H Williams Smith and J B Huggins who used phages and antibiotics to control lethal systemic infection of Escherichia coli in experimentally innoculated mice. See: HW Smith and M B Huggins, Successful treatment of experimental Escherichia coli infections in mice using phage: its general superiority over antibiotics, Gen Microbiology, vol 128, no 2, pp 3017.18.

poultry products in 2006.[62] This was after the US FDA in 2006 had approved the use of phages as 'generally safe' to target foodborne bacteria such as *Listeria*,[63] *Salmonella spp.*, and *E. coli*.[64] Witnesses also told us that phages have been increasingly used as a method to detect bacteria.[65]

16. Phages have also begun to be used as a compassionate clinical intervention in cases where antibiotics have failed or are beginning to fail.[66] They have typically been used to treat serious multidrug-resistant bacterial infections that are associated with the following conditions: life- or limb-threatening bacterial infections, mycobacterial infections, complicated urinary tract infections, organ transplantation and implantable hardware, such as cardiac devices or joint replacements.[67] Depending on the type of infection being treated, they can be administered orally, by a nebulizer, topically, intravenously, or intra-rectal.[68] However, the use of phage therapy has been limited to a small number of experimental treatment centres or associated with individual physicians and researchers, such as in Belgium, France and the US.[69] In the UK, they have been used on only 12 occasions in the last four years.[70] The phages in these instances have been allowed by either permissive regulators (e.g. the US), as unlicensed medicinal products (e.g. the UK), or under specific national rules which have allowed them to be prescribed by medical professionals but not manufactured for wider use (e.g. Belgium).[71] A number of these case studies have shown that phage therapy was successful in treating life-threatening

62 See: Lorraine Endersen and Aidan Coffey, The use of bacteriophages for food safety, Current Opinion in Food Science, vol 36, (December 2020); American Society for Microbiology, Phages and Food: Combatting Bacteria From Farm to Fork, (1 June 2003).

63 Elizabeth Martin Kutter et al., Re-establishing a place for phage therapy in western medicine, Future Microbiology, vol 10, no 5, (2015), p 685–686.

64 Derek M Lin et al., Phage therapy: An alternative to antibiotics in the age of multi-drug resistance, World J Gastrointest Pharmacol Ther, vol 8, no 3, (August 2017), pp 162–173.

65 Professor Cath Rees, Professor of Microbiology, University of Nottingham (Q5); Professor Joanne M Santini, Professor of Microbiology, University College London (Q8); Dr Mzia Kutateladze, Director, George Eliava Institute of Bacteriophage, Microbiology and Virology (Q130); Dr Jonathan Pearce, Director of Strategy and Planning at Medical Research Council (Q186); Professor Isabel Oliver, Scientific Officer, UK Health Security Agency (Q221-Q222); Centre for Phage Research at the University of Leicester (PHA0027); Bangor University School of Natural Sciences (PHA0029); UKRI (PHA0041); See: Susanne Meile et al., Reporter Phage-Based Detection of Bacterial Pathogens: Design Guidelines and Recent Developments, Viruses, vol 12, no 9, (August 2020); Jan Paczesny et al., Recent Progress in the Detection of Bacteria Using Bacteriophages: A Review, Viruses, vol 12, no 8, (August 2020).

66 A compassionate intervention refers to the use of a treatment option including an unauthorised medicine made available under specific conditions to patients who have a disease with no satisfactory authorised therapies and who cannot enter clinical trials (European Medicines Agency). See Chapter 5 of this Report.

67 See: UC San Diego School of Medicine, Center for Innovative Phage Applications and Therapeutics, Frequently Asked Questions, (accessed 28 July 2023).

68 For instance, oral applications can be used to treat Typhoid Fever, Dysentery or Cholera. Nebulized phages can be used to treat Tuberculosis. Topical phages for chronic wounds and burns. Intravenous for systemic infections and intra-rectal application for Prostatitis. See: Ali Khalid et al., A Phage Therapy Guide for Clinicians and Basic Scientists: Background and Highlighting Applications for Developing Countries, Frontiers in Microbiology, vol 11, (2020).

69 Shawna McCallin et al., Current State of Compassionate Phage Therapy, Viruses, vol 11, no 4, (April 2012).

70 In the last four years, they were used for 2 cystic fibrosis patients at Great Ormond Street Hospital and for 10 diabetic foot infection patients in 2 Scottish hospitals. See: Joshua D Jones et al., The Future of Clinical Phage Therapy in the United Kingdom, Viruses, vol 15, no 3, (March 2023).

71 For an overview see: Andrzej Górski et al., Phage Therapy: What Have We Learned?, Vruses, vol 10, no 6, (2018).

infections, ranging from successfully clearing infections to improving a patient's outcome, for conditions ranging from cystic fibrosis and pneumonia to prosthetic, bone, joint and urinary tract infections.[72]

Phages and national plans to tackle AMR

17. The potential of phages has been acknowledged by various governments. The US Government's National Action Plan for Combating Antibiotic-Resistant Bacteria, 2020–2025, included phages within a call for accelerated basic and applied research, and the development of new therapeutics.[73] The UK Government similarly stated that there is a need to stimulate more Research and Development into vaccines and alternatives, including phages.[74]

Selection, production and storage of phages

18. The process of phage therapy begins with identifying which phage will be effective in treating a bacterial infection. Sources of phages can include phage banks of existing screened and purified phages or environmental sites, such as wastewater treatment sites. Once acquired, their effectiveness against target bacteria is assessed. A common method is to use a plaque assay, whereby bacteria and bacteriophages are mixed on an agar plate and the plaques are observed to assess whether the phages inhibit bacterial growth.[75] This approach can be used to test multiple candidate bacteriophages and bacterial isolates. The increasing use of genomics,[76] and AI,[77] is also allowing phages to be assessed for their potency and viability, but also their susceptibility to bacterial resistance.

19. Phage production is usually achieved using a double-layer agar method, which allows isolation of individual phages, and then liquid culture of single plaques.[78] A pure phage lysate is obtained by centrifugation and membrane filtration but may also include additional steps, such as dialysis, ultrafiltration, or treatment with organic solvents. A number of tests can be used to verify the absence of toxic components to identify whether additional purification methods might be required, such as specialized filtration, affinity

72 Diana P. Pires et al., Current challenges and future opportunities of phage therapy, FEMS Microbiology Reviews, (2020), pp 687–688. The cases studies spen severa countries including: USA; France; Israel; Belgium, Poland; Georgia; Australia; and, the UK.

73 Federal Task Force on Combating Antibiotic-Resistant Bacteria, National action plan for combating antibiotic-resistant bacteria 2020–2025, (October 2020), p 31. See also Scott Gottlieb's comments in 2018, when as the then FDA Commissioner he noted the need for research to support the development of alternative antimicrobials, including phages.

74 HM Government, Tackling antimicrobial resistance 2019–2024: The UK's five-year national action plan, (January 2019), p 86.

75 Roberto Vázquez et al., Essential Topics for the Regulatory Consideration of Phages as Clinically Valuable Therapeutic Agents: A Perspective from Spain, Microorganisms, vol 10, no 4, (April 2022).

76 For example, the University of Leicester's Microbial Sciences and Infectious Diseases Centre is studying phage genomics on a variety of systems, including *C. difficile*, *Salmonella*, *Escherichia coli*, *Vibrio spp*, *Pseudomonas*, *Helicobacter* and *Cyanobacteria*. This will allow researchers to understand the diversity of genes phage carry and how this alters infection. See also: Shengjian Yuan at al., Genome-scale top-down strategy to generate viable genome-reduced phages, Nucleic Acids Research, vol 50, Issue 22, (December 2022).

77 See: Fixed Phage, AI Revolutionises Bacteriophage Research for Human, Animal, and Harvest Health, (August 2023); Yousef Nami at al., Application of machine learning in bacteriophage research, BMC Microbiology, vol 21, (June 2021).

78 As above.

chromatography, tangential flow filtration and CsCl gradient ultracentrifugation.[79] This approach can be scaled up and optimized to an industrial level by using bioreactors of different sizes, which allow continuous and semi-continuous production.[80]

20. Phages can also be genetically engineered, or produced synthetically, to generate phage variants with unique properties for prophylactic and therapeutic applications.[81] This can be used to increase the purity of phages and to overcome bacterial resistance to phages.

21. Storage of phages varies depending on the type of phage and may range from 4 °C to −80 °C, or in liquid nitrogen (−196 °C).[82] Phages can also be freeze-dried. Additives can be added to prevent or delay the loss of infectivity (e.g. Calcium Chloride and Magnesium Sulphate) along with cryopreservants such as disaccharides (lactose, sucrose, trehalose) or polyethylene glycol, gelatin or Ficoll (an inert and hydrophilic polysaccharide).[83]

Health care and economic opportunities

22. The potential for phages to tackle AMR appears almost limitless. They are the most abundant organisms on earth,[84] with an estimated ten phages for every bacterial cell.[85] As we heard, in theory this abundance could yield enough variety to provide an antimicrobial matched to each particular bacteria.[86] If they were introduced in a more systematic way, they promise to offer savings to healthcare systems where they can avoid the use of more expensive treatments (e.g. specialised antibiotics),[87] or interventions with longer term and more expensive consequences (e.g. amputations).[88] There are also economic opportunities associated with phages. For example, a growing global phage therapy market is estimated to be worth $38mn in 2021–22, and is expected to reach $100.8mn by 2030,[89] with a range of global companies investing in such products, especially in the USA.[90] In February 2023, the Financial Times reported estimates that suggested that the total phage market could

79 See: Centre for Phage Technology, Protocol: Purifying phage by CsCl gradient ultracentrifugation, (accessed 8 November 2023); Evelien M Adriaenssens et al., CIM (R) monolithic anion-exchange chromatography as a useful alternative to CsCl gradient purification of bacteriophage particles, Virology, vol 434, no 2, (October 2012).

80 See also: Dr Clare Trippett on behalf of CPI (INS0047).

81 See: Tayfun Tanir at al., Manufacturing Bacteriophages (Part 1 of 2): Cell Line Development, Upstream, and Downstream Considerations, Pharmaceuticals, vol 14, no 9, (September 2021).

82 See: Tayfun Tanir at al., Manufacturing Bacteriophages (Part 1 of 2): Cell Line Development, Upstream, and Downstream Considerations, Pharmaceuticals, vol 14, no 9, (September 2021).

83 Roberto Vázquez et al., Essential Topics for the Regulatory Consideration of Phages as Clinically Valuable Therapeutic Agents: A Perspective from Spain, Microorganisms, vol 10, no 4, (April 2022).

84 See: Diana P. Pires et al., Current challenges and future opportunities of phage therapy, FEMS Microbiology Reviews, vol 44 (2020), p 684–700; MR Clokie et al. , Phages in nature, Bacteriophage, vol 1, (2011), p 31–45.

85 See: Tom Ireland, The Good Virus, (2023), p 8. He notes that it has been estimated that there could be as many as 10^{31} phages on the planet. See also: Big Think, Phage: The most abundant life form on Earth has a unique license to kill, (16 August 2023).

86 Q14 (Professor Cath Rees, Professor of Microbiology, University of Nottingham).

87 Nicola Principi et al., Advantages and Limitations of Bacteriophages for the Treatment of Bacterial Infections, Frontiers in Pharmacology, vol 10, (May 2019).

88 For example, Healthcare Improvement in Scotland and SHTG, noted that if phage treaments could be proven to be effective and if the proper infratructure was in place to produce and use them for conditions such as diabetic foot infections, they would be a "cost effective use of resources", especially for those at the "higher risk of lower extremity amputation". See: Healthcare Improvement in Scotland and SHTG, Bacteriophage therapy for patients with difficult to treat bacterial infections, (February 2023).

89 Global Newswire, Phage Therapy Market Size [2022-2028] | is Projected to Reach USD 100.8 Million, with 17.6% CAGR | Growth Rate, Share, New Developments, Market Dynamics, Key Players, Revenue, and Expansion Plans, Research | Market Reports World, (April 2022)..

90 InsightAce Analytic, Global Phage Therapy Market, (November 2022).

be as much as $1.1bn,[91] with other analyses indicating that the use of phages in food and beverages were the largest component.[92] In addition, if phages could be manufactured at scale, generic cocktails could be produced to target the most common pathogens cheaply.[93]

The mixed evidential base; observational studies and clinical trials

23. While the interpretation of data from clinical observational studies and trials of phage therapy have been generally encouraging in terms of safety,[94] the picture revealed in terms of clinical effectiveness has been more mixed.[95] The Lancet Infectious Disease journal reported in its review of 59 clinical studies between 2000 and 2021, that of 1,904 patients with chronic and drug resistant infections treated with phages, 79% showed improvement, while 87% of the target bacteria were eradicated in 1,461 of the cases.[96] However, other studies have reported that evidence on the success of phages as an antimicrobial is mixed and complex, noting the control of bacterial infections in some instances, but failures in others.[97]

24. In February 2023, the Scottish national health technology assessment agency (Scottish Health Technologies Group (SHTG)) noted that the published evidence on bacteriophage therapy rested primarily on a heterogeneous collection of small single arm cohort studies,[98] small case series and individual case studies, mainly in combination with conventional antibiotics. The SHTG argued that combination studies made it difficult to identify the specific impact of phages. The SHTG did, however, point to a small number of randomised controlled trials suggesting that bacteriophage therapy may be effective for patients with difficult to treat bacterial infections.[99] Healthcare Improvement Scotland recommended, on the basis of the SHTG analysis, that bacteriophages may be considered as an option to treat people with a specific range of bacterial infections. However, it called for more high-quality research to provide a more accurate estimate of the true effect of bacteriophage therapy in patients with difficult to treat bacterial infections.[100] The Medicines and Healthcare Products Regulatory Agency told us that there are encouraging indications

91 Financial Times, Spread of antibiotic resistance revives interest in bacteria-killing viruses, (8 February 2023). See also: Credence Research, How will an Increase in Anti-Biotic Resistance Infection Supports Market Growth?, (July 2022). The latter estimated that in 2021 In 2021, that the global Bacteriophage Market was valued at $1,172.5mn and is projected to reach at value of $1,441.3mn by 2028.

92 BusinessWire, Global Bacteriophage Market Report 2021–2029: Increasing R&D is Expected to Multiply Revenues - Food & Beverages Display Highest Share, (July 2021).

93 Q13. (Professor Joanne M Santini, Professor of Microbiology, University College London).

94 See for example: Steele, A. et al., The Safety and Efficacy of Phage Therapy for Superficial Bacterial Infections: A Systematic Review, Antibiotics, vol 9, (2020); Saartje Uyttebroek, MD, Safety and efficacy of phage therapy in difficult-to-treat infections: a systematic review, The Lancet Infectious Diseases, (March 2022); Geneviève, J et al., . A systematic review of phage therapy applied to bone and joint infections: an analysis of success rates, treatment modalities and safety, EFORT Open Rev, vol 6, no 19 (December 2021). The latter found out of 51 patients, 4 had a minor adverse event.

95 See: Luigi Marongiu et al., Reassessment of Historical Clinical Trials Supports the Effectiveness of Phage Therapy, Clinical Microbiology Reviews, vol 35, no 4, (September 2022).

96 Saartje Uyttebroek, MD, Safety and efficacy of phage therapy in difficult-to-treat infections: a systematic review, The Lancet Infectious Diseases, (March 2022).

97 Yan D. Niu et al., Efficacy of Individual Bacteriophages Does Not Predict Efficacy of Bacteriophage Cocktails for Control of Escherichia coli O157, Frontiers in Microbiology, vol 12, (February 2021).

98 A single-arm trial is a sample of individuals with a targeted medical condition that is given the experimental therapy and then followed over time to observe their response. See: Scott R. Evans, Clinical trial structures, J Exp Stroke Transl Med, vol 3, no 1, (February 2010).

99 Healthcare Improvement Scotland and SHTG Advice on health technologies, Bacteriophage therapy for patients with difficult to treat bacterial infections: Recommendations for NHS Scotland, (February 2023).

100 Healthcare Improvement Scotland, Innovative therapy to combat hard-to-treat infections approved for Scotland, (3 February 2023).

that phages were safe and effective, with "anecdotes in the literature that where patients had been treated … that have shown good efficacy". However, they also stated that robust clinical data at scale is required to reach an authoritative conclusion to regulate and allow their wider use.[101]

25. An increasing number of clinical trials have started to strengthen the evidence base. For instance, between 2015 and 2017, the first randomised phage study, funded by the EU—the PHAGOBURN clinical trial—used a cocktail of phages,[102] to treat about 30 burns patients in Belgium, France and Switzerland, which indicated that they could be effective if a patient's bacterial strain is sensitive to the phages employed.[103] Currently there are 45 open phage trials listed on clinicaltrials.gov.[104]

Regulatory uncertainty and manufacturing costs

26. Another major challenge for the development and use of phages has been the lack of manufacturing capability mainly because current regulatory processes appear unsuited to phages. Phages have been classified in most western countries as a pharmaceutical product requiring exacting manufacturing processes, notably the globally recognised Good Manufacturing Practice (GMP) standard which seeks to ensure that pharmaceuticals are consistently produced and controlled according to quality standards.[105] This approach to phages requires an approval process that has been characterised as "complex, costly and time intensive".[106] The British Standards Institution has stated that the costs of GMP "are measured in the multimillion pounds per annum for a typical medium or large pharma company".[107]

27. Because a phage is a biological entity, often used in cocktails with other phages and other agents, such as antibiotics, and with the potential for genetic modification of the phages used, establishing GMP has been seen as a challenge because of the potential multiple variables. This complexity also results from the fact that phage treatments are tailored to address specific bacterial infections and personalised for individual patients. This has been contrasted with GMP for a fixed pharmaceutical product, such as an antibiotic or paracetamol where the ingredients are established.[108] One implication of this has been that GMP might be required for each phage, and each combination of phages, which might be changeable depending on each patient. Dr Pirnay, for instance told us:

101 Q211.
102 For a definition of a phage cocktail see paragraph
103 European Commission, Phages, a bacteria killer with a twist..., (July 2019). For a
104 Nicole Marie Hitchcock et al., Current Clinical Landscape and Global Potential of Bacteriophage Therapy, Viruses, vol 15, no 4, (April 2023). See also: See: ClinicalTrial.gov (accessed 15 June 2023).
105 See: International Society for Pharmaceutical Engineering, Good Manufacturing Practice (GMP) Resources, (accessed 23 June 2023).
106 Sebastian Leptihn and Belinda Loh, Complexity, challenges and costs of implementing phage therapy, FUTURE MICROBIOLOGY, vol 17, no 9, (April 2022). See also: Laurent Bretaudeau et al., Good Manufacturing Practice (GMP) Compliance for Phage Therapy Medicinal Products, Frontiers in Microbioogy, vol 11, (June 2020).
107 BSI and Poseidon, Getting More Value from Logistics Quality, (July 2021).
108 Roberto Vázquez et al., Essential Topics for the Regulatory Consideration of Phages as Clinically Valuable Therapeutic Agents: A Perspective from Spain, Microorganisms, vol 10, no 4, (April 2022). See also: Professor Cath Rees, Professor of Microbiology, University of Nottingham (Q26).

> As you might know, phages are very specific to which bacteria they infect. Sometimes, phages need to be trained, for instance, to be more efficient. If every time this means that it is another medicine product that needs to be produced according to GMP, this is technically impossible.[109]

28. Similarly, Dr Kutateladze, stated that phages are:

> … biological products, not a chemical formula that can be produced again and again. After time, when we have new bacterial strains with new mechanisms of antibiotic resistance, we can update our commercial product. This is very challenging for the GMP standards. You have to update your procedure again and again.[110]

29. This means that if phages are to be used more widely, they will need a flexible and personalised medicine licencing regime that allows a unique combination of phages, generic and engineered, often with antibiotics, that can be produced for individual patients. Such a licencing regime would allow the optimal use of phages and the regulatory certainty required for them to be produced and manufactured.

30. In addition, natural phages maybe difficult to patent, though unique combinations of phages and engineered phages might be more amenable to intellectual property protection.[111] This has been seen as a major disincentive for pharmaceutical companies to invest in phage manufacturing, and also in clinical trials with an uncertain return on investments. Some of our witnesses therefore suggested a dual approach to the production of phages, with large scale GMP production for generic phages, and an individualised approach for patients requiring specific combinations of phages and antibiotics.[112]

Phages: personalised medicine trailblazers

31. Many of the challenges that phages face also apply to other forms of 'personalised medicine'. For example, microbiome therapeutics seek to alter a patient's microbiota to fight disease. The latter includes additive therapy which adds microbial strains or microbial consortia, subtractive therapy which removes lethal pathogens, and modulatory therapy that modifies or manipulates host microbiome interactions. As with phages, microbiome therapeutics require a regulatory framework and clinical trial structure that addresses both safety and the specificity of therapeutics prepared for individual patients. Phages are therefore arguably one of the first trailblazers for a wider trend of personalised medicine. While this inquiry has sort to work through issues facing phages, our findings will have relevance for the wider emerging field of personalised medicine.

109 Q118.

110 Q131.

111 Daniel De Vos et al., Phage Therapy in Europe: Regulatory and Intellectual Property Protection Issues, Phage Therapy: A Practical Approach, (October 2019). See also: Professor Joanne M Santini, Professor of Microbiology, University College London (Q30).

112 Dr Josh Jones, Clinical Phage Specialist, NHS Tayside (Q61); Dr Jean-Paul Pirnay, Head of the Laboratory of Molecular and Cellular Technology, Queen Astrid Military Hospital, Brussels (Q134); Dr Mzia Kutateladze, Director, George Eliava Institute of Bacteriophage, Microbiology and Virology (Q134); Professor Robert Schooley, Professor of Division of Infectious Diseases at UC San Diego School of Medicine (Q147); Fixed Phage LTD (PHA0033). See also: Joshua D Jones et al., The Future of Clinical Phage Therapy in the United Kingdom, Viruses, vol 15, no 3, (March 2023). Laurent Bretaudeau et al., Good Manufacturing Practice (GMP) Compliance for Phage Therapy Medicinal Products, Frontiers in Microbiology, vol 11, (June 2020).

2 Safety, Efficacy, and the UK's phage research base

32. Witnesses told us that the UK has a number of leading experts on phages, several phage centres and biobanks and a small number of clinicians who have used phages to treat bacterial infections (usually, as mentioned, as a last resort).[113] However, the evidence we took indicated that there are weaknesses in the UK's support for phages, in terms of research funding, nationwide phage infrastructure, and the networks needed to pull together existing assets and research resources. We also heard that this has created issues for UK-based phage SMEs, while a lack of communication on the potential benefits of phage treatments and products has led to a low level of awareness amongst clinicians and the public. This chapter explores these issues and potential solutions if the potential of phages is to be supported by a joined-up UK approach spanning various sectors, and that engages healthcare professionals and the public.

Establishing the safety of phages

33. The majority of the evidence we took reflected much of the existing literature,[114] and found that phages are generally safe.[115] UKRI, for instance, stated that clinical trials and studies had established that phage therapy is safe, though it noted that there are no current global standards for assessing safety.[116] However, a few studies have reported transient adverse events or side effects during phage therapy, which include inflammation, flushing, hypotension, and fever,[117] with serious events being extremely rare.[118]

34. The Phage Research Centre at the University of Leicester maintained that genomic information is also expanding knowledge of phages and illustrating their safety.[119] Professor Martha Clokie told us that "we do not have to worry about their overall safety",[120] while Dr Josh Jones, the first NHS phage specialist, and Dr James Soothill, who has used

113 Professor Martha Clokie, Professor of Microbiology, University of Leicester (Q20); Professor Cath Rees, Professor of Microbiology, University of Nottingham (Q25); Department of Health and Social Care (DHSC), UK Health Security Agency (UKHSA), and Medicines and Healthcare products Regulatory Agency (MHRA) (PHA0007); AMR Action Fund (PHA0012); Microbiology Society (PHA0015); Centre for Phage Research at the University of Leicester (PHA0027); Bangor University School of Natural Sciences (PHA0029); CF Syndicate in AMR (PHA0030); University of Nottingham (PHA0039); Phage-UK (PHA0013);

114 See: Saartje Uyttebroek, MD, Safety and efficacy of phage therapy in difficult-to-treat infections: a systematic review, The Lancet Infectious Diseases, (March 2022); Geneviève, J et al., . A systematic review of phage therapy applied to bone and joint infections: an analysis of success rates, treatment modalities and safety, EFORT Open Rev, vol 6, no 19 (December 2021); Steele, A. et al., The Safety and Efficacy of Phage Therapy for Superficial Bacterial Infections: A Systematic Review, Antibiotics, vol 9, (2020).

115 See: Professor Graham Hatfull (Professor at University of Pittsburgh, Pittsburgh PA 15260 USA) (PHA0001); University of California of San Diego, Center for Innovative Phage Applications and Therapeutics (PHA0003); AMR Action Fund (PHA0012); Phage-UK (PHA0013); Microbiology Society (PHA0015); UK Phage Therapy (PHA0017); Antibiotic Research UK (PHA0020); Adaptive Phage Therapeutics Inc (PHA0023); Centre for Phage Research at the University of Leicester (PHA0027); Oxford Silk Phage Technologies Ltd (PHA0035); Bangor University School of Natural Sciences (PHA0029); Jason Clark (Chief Scientific Officer at Fixed Phage LTD) (PHA0038); UKRI (PHA0041).

116 UKRI (PHA0041).

117 See: Ka Mun Chung et al., The Safety of Bacteriophages in Treatment of Diseases Caused by Multidrug-Resistant Bacteria, Pharmaceuticals, vol 16, issue 10, (August 2023).

118 See: Dan Liu et al., The Safety and Toxicity of Phage Therapy: A Review of Animal and Clinical Studies, Viruses, vol 13, no 7, (July 2021).

119 Centre for Phage Research at the University of Leicester (PHA0046).

120 Q11.

phage therapy at Great Ormond Street Hospital, both said that they were "very confident" that they were safe to be used as a clinical intervention.[121] International phage experts also confirmed that in their view, phages are safe to be used as a clinical intervention.[122] However, Professor Iredell told us that it is still important to track the safety of phages and to look for adverse reactions.[123]

35. Other witnesses were more cautious. A number told us that though initial assessments indicated that phages are safe, more robust clinical data and evidence is required to establish that they are safe enough to develop into a medical treatment.[124] Researchers at the University of Nottingham also noted that while phages are generally considered to be safe, more research is required to examine the "synergy or antagonism between phages and the mammalian immune system",[125] while Antibiotic Research UK and others suggested a need for a greater understanding of the long-term impact of phages within humans.[126] This includes the risk of anaphylaxis and auto immune responses.

The efficacy of phages

36. The evidence we took offered mixed views on the effectiveness of phages. The Department for Health and Social Care, UK Health Security Agency and MHRA stated that the effectiveness of compassionate use studies is "encouraging", which suggested that "phage therapy can resolve even complex and difficult-to-treat infections in patients with severe disease", with a "clear case" for phages to be included in the Government's AMR strategy.[127] Dr Morwenna Carrington, Deputy Director for UK Health Security, Department for Health and Social Care, told us that "bacteriophages are definitely part of our armoury".[128]

37. Microbiology International stated that there is "extensive evidence that highlights phage therapy as an effective antimicrobial treatment for humans",[129] while the Microbiology Society and others believed that there is enough evidence to indicate that phages could be effective therapies for compassionate use cases, with more research needed to underpin routine prescriptions.[130] The Centre for Phage Research, University of Leicester, stated that purified phages, correct dosage and the use of genotyping had increased the effectiveness of phages.[131] Professor Clokie told us that the phages used to

121 Q59 and Q59.
122 Q121 (Dr Mzia Kutateladze,Director, George Eliava Institute of Bacteriophage, Microbiology and Virology); Q158 (Greg Merril, Chief Operating Officer, Adaptive Phage Therapeutics); Q164 (Naomi Zak, Founder, BiomX).
123 Q149.
124 See: Dr Marc Bailey, Chief Science, Research & Innovation Officer, at the Medicines and Healthcare products Regulatory Agency (MHRA) (Q211); Professor Isabel Oliver, Scientific Officer, UK Health Security Agency (Q222); Dr Morwenna Carrington, Deputy Director for UK Health Security, Department for Health and Social Care (DHSC) (Q240).
125 University of Nottingham (PHA0039). See also: Antibiotic Research UK (PHA0020).
126 Antibiotic Research UK (PHA0020). See also: Dr Gwen Knight (Associate Professor at London School of Hygiene and Tropical Medicine), and Prof Jodi Lindsay (Professor at St George's University of London) (PHA0021).
127 Department of Health and Social Care (DHSC), UK Health Security Agency (UKHSA), and Medicines and Healthcare products Regulatory Agency (MHRA) (PHA0007).
128 Q248.
129 Applied Microbiology International (PHA0010)
130 Microbiology Society (PHA0015); AMR Action Fund (PHA0012); Jason Clark (Chief Scientific Officer at Fixed Phage LTD) (PHA0038); UKRI (PHA0041).
131 Centre for Phage Research at the University of Leicester (PHA0027).

treat infected birds in her laboratory had shown that they are effective,[132] while Dr Josh Jones pointed to a review of 2,241 patients treated with phages that indicated 80% had seen a medical improvement.[133]

38. However, some of the evidence suggested that more strict clinical trials were required to augment the existing observational clinical data on efficacy.[134] This included arguments that phage science and phage antimicrobial technology is still at an early stage and needs to be advanced further.[135] The National Physical Laboratory more specifically called for an evaluative mechanism that could measure the specifics of phage therapies so that results could be reproduced consistently.[136] Other contributors called for more specific research, as detailed below, that could establish effectiveness, taking into account issues such as dosage,[137] the best medical regimens, the use of genetic engineering,[138] and phage combinations in cocktails or with antibiotics.[139]

39. **The safety of phages has been well established mainly on the basis of observational evidence drawn from specific clinical interventions. However, as with all medicines, robust clinical trial data is important to provide and develop assurances around all aspects of patient safety, including the long-term impact of phages, especially their interaction with human immune systems, such as anaphylaxis and auto immune response.**

40. **Clinical data indicates that in many cases phages have been observed to reduce bacterial infections in patients. We also heard that their use in animals has also been shown to be effective. However, further clinical trials are required to prove the consistent effectiveness of phages. Such studies need to include analysis of the impact of different phage cocktails as well as phage/antibiotic combinations.**

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.***

132 Q11.

133 Q59. See: Uyttebroek S et al., Safety and Efficacy of Phage Therapy in Difficult-to-Treat Infections: A Systematic Review, Lancet Infectious Diseases, vol 22, no 8, (August 2022).

134 Dr Tim Jinks, Head of Infectious Disease Interventions, Wellcome Trust (Q208); Dr Jonathan Pearce, Director of Strategy and Planning at Medical Research Council (Q207); Richard Hebdon, Director Health and Life Sciences, Innovate UK (Q206); Dr Marc Bailey, Chief Science, Research & Innovation Officer at Medicines and Healthcare products Regulatory Agency (Q211); Professor Isabel Oliver, Scientific Officer, UK Health Security Agency (Q221); UK Phage Therapy (PHA0017).

135 Wellcome Trust (PHA0011); Antibiotic Research UK (PH0020).

136 National Physical Laboratory (PHA0014).

137 Professor Graham Hatfull (Professor at University of Pittsburgh, Pittsburgh PA 15260 USA) (PHA0001); Antibiotic Research UK (PHA0020).

138 Quadram Institute Bioscience (PHA0004).

139 Quadram Institute Bioscience (PHA0004).

UK foundational phage research: work still to be done

42. Several witnesses, such as Professor Clokie, told us that despite the history of research into phages going back over a hundred years, there are still gaps in our understanding.[140] Those identified in our evidence and elsewhere included:

- the occurrence and degree of synergy between bacteriophage therapy and antibiotics *in vitro* in terms of effectiveness;[141]
- the interaction between phages and host immune systems and the impact on host antibodies, including the impact of endotoxins released when bacterial cells are lysed;[142]
- the movement of phages within the human body and ability to target the specific organs or parts of the body;[143]
- the stability of phage preparation (e.g. their vulnerability to changes in temperature and pH balance);[144]
- detailed knowledge of the breadth of phages, their bacterial host range, modes of action and effectiveness;[145]
- the possible transfer of material between phages and bacteria, including the introduction of resistant bacterial genes from animals, humans and food;[146]
- isolating phage genes and enzymes to reduce risk of contamination of unwanted materials from phages;[147]
- the safety and efficacy of genetically engineering phages or adapting phages to reduce potential immunogenic response and/or 'weaponising' them, to take advantage of bacteria weaknesses;
- more knowledge relating to the optimal combination of phages;[148]
- the most effective regimens of administering phages, including the length and type of treatment.[149]

140 Q11.
141 University of Nottingham (PHA0039). See also: Professor Graham Hatfull (Professor at University of Pittsburgh) (PHA0001); Applied Microbiology International (PHA0010).
142 Centre for Phage Research at the University of Leicester (PHA0046); See also: Professor Graham Hatfull (Professor at University of Pittsburgh) (PHA0001); Applied Microbiology International (PHA0010).
143 Centre for Phage Research at the University of Leicester (PHA0046).
144 As above.
145 Quadram Institute Bioscience (PHA0004).
146 Microbiology Society (PHA0015). See also: Q24; Antibiotic Research UK (PHA0020); Dr Gwen Knight (Associate Professor at London School of Hygiene and Tropical Medicine), and Prof Jodi Lindsay (Professor at St George's University of London) (PHA0021); Centre for Phage Research at the University of Leicester (PHA0046); Dr Shan Goh et al (PHA0028); Bangor University School of Natural Sciences (PHA0029); University of Nottingham (PHA0039); UKRI (PHA0041).
147 Q17 (Professor Joanne M Santini, Professor of Microbiology, University College London).
148 As above. See also: University College London (UCL) (PHA0034); University of Nottingham (PHA0039); Professor Graham Hatfull (Professor at University of Pittsburgh) (PHA0001). See also: University College London (UCL) (PHA0034); Applied Microbiology International (PHA0010).
149 Applied Microbiology International (PHA0010). See also: Professor Graham Hatfull (Professor at University of Pittsburgh) (PHA0001).

- the potential impact of chemicals, such as Caesium Chloride, which is used to purify phages on the human body.[150]

43. We were told that that the UK is well placed to address these gaps. For instance, the Phage Research Centre (University of Leicester) told us that UK excellence in genomic sequencing could be harnessed by phage researchers to answer many of these questions, provided that appropriate funding is available.[151] Professor Cath Rees similarly noted that advances in both genomic sequencing and bioinformatics offered the opportunity to focus on many of these issues.[152] Researchers from University College London also maintained that fundamental research is important to underpin calls for clinical trials and to inform translational research that can lead to applications to address AMR.[153]

44. Many contributors to our inquiry called for more funding for phage research. Phage-UK, for instance, stated that phage research in the UK had "been poorly funded and relied largely on internal investment by universities" rather than external research grants.[154] UKRI acknowledged that there had been limited specific funding calls for phages and that phage-based projects had to compete with other bids within the general AMR portfolio. However, UKRI said that, between 2015 and 2021, the Medical Research Council had invested £2.43mn in phage research projects, while between 2017 and 2022, the Biotechnology and Biological Sciences Research Council (BBSRC) had invested £4.7mn in research relevant to the use of phages, of which £1.6m was specifically focused on phages, including research aimed at understanding their biology.[155]

45. The Microbiology Society and the Centre for Phage Research at the University of Leicester and others argued that there should be specific funding calls for phage research, especially for fundamental research on phage biology and phage interactions, alongside interdisciplinary research across academia, industry and clinics.[156]

46. However, several witnesses, including several funders and the DHSC questioned whether dedicated funding for phages is appropriate. Dr Tim Jinks, Head of Infectious Disease Interventions at the Wellcome Trust, told us that the Wellcome Trust believed a portfolio approach to AMR is appropriate and that it was "not seeing sufficient evidence to prioritise one particular modality over another",[157] and that ring-fenced funding risked creating "a particular distortion in the innovation ecosystem".[158] However, he noted that Wellcome had funded phage research and had predominantly funded genetically engineered and modified phages as an innovative approach within the AMR space.[159] He

150 Centre for Phage Research at the University of Leicester (PHA0027).
151 Centre for Phage Research at the University of Leicester (PHA0046).
152 Q19.
153 University College London (UCL) (PHA0034).
154 PHAGE UK (PHA0013). See also: Dr Shan Goh et al (PHA0028).
155 UKRI (PHA0041). For instance, the BBSRC funded research into bacteriophages and Escherichia coli O157:H7 in the UK. See: Daniel A. Yara et al., Comparison of Shiga toxin-encoding bacteriophages in highly pathogenic strains of Shiga toxin-producing Escherichia coli O157:H7 in the UK, Microbal Genomics, (February 2020).
156 MICROBIOLOGY SOCIETY (PHA0015) and Centre for Phage Research at the University of Leicester (PHA0027). See also: Antibiotic Research UK (PHA0020); Dr Gwen Knight and Professor Jodi Lindsay (PHA0021).
157 Q193.
158 Q195.
159 Q194.

also noted that Wellcome supported two international AMR projects—CARB-X,[160] and the AMR Action Fund[161]—which support a diverse range of antimicrobial approaches, including phages.

47. Dr Jonathan Pearce, Director of Strategy and Planning at the MRC, also did not support ringfencing funding for phage research.[162] Dr Morwenna Carrington, Deputy Director for UK Health Security, Department for Health and Social Care, also told us that her department would "not want to specify or earmark specific research funding for bacteriophages over and above some of the other [AMR] research priorities".[163] She pointed out that research funding for AMR could be accessed through a number of streams other than UKRI, including through the National Institute for Health and Care Research and the UK Health Security Agency.[164]

48. **Phages have been used as therapy for over a hundred years, and much of the fundamental science relating to phages is understood. However, there is still more that the global and UK research communities can learn. Further research will be able to establish key issues such as long-term interactions between phages and human hosts and how phages can be engineered to maximum effect, to work alone or in combination with antibiotics. Such research will help hone phage therapeutics and clinical practice. The UK is well placed to conduct this research as it has a number of leading phage research centres and academics, and access to world class genomic sequencing and bioinformatic resources and experts.**

49. **However, the apparent reticence of funders to commit to phages is despite a general acceptance in the evidence we took that phages show promise and need more research alongside clinical trials. It is important to understand and reflect on the reasons for this. The recently established Innovate UK Phage Knowledge Transfer Network may provide such a forum for funders and phage researchers to discuss these matters.**

50. ***Because phages have had relatively limited recent research funding from public sources, 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. Without proper support, the full potential of phages will not be realised within the Government's AMR strategy.***

160 CARB-X is a global non-profit partnership accelerating antibacterial products to address AMR. It has a diverse portfolio of new antibiotics, vaccines, rapid diagnostics and other products. It has funded a number of bacteriophage projects. For example, it funded Eligo Bioscience in Paris to produce a genetically engineered phage to selectively eliminate extended-spectrum beta-lactamase-producing (ESBL) and *Carbapenem-resistant E. coli* and *K. pneumoniae* (CRE).

161 The AMR Action Fund invests in companies that are developing therapeutics for priority pathogens. Among its portfolio is Adaptive Phage Therapeutics, who submitted written evidence and gave oral evidence to the Committee.

162 Q184.

163 Q232.

164 Q232.

UK translational phage research: much more to do

51. Several witnesses explained how phages can be translated into phage treatments and therapies,[165] and as a form of personalised medicine.[166] The latter includes developing technology and expertise to match a patient's infection to a pre-screened cocktail of phages.[167] We also heard that the country of Georgia had a number of generic phage products.[168] Other witnesses noted that there are also opportunities for translating phages into products to control bacteria pathogens in food, livestock and other agricultural purposes.[169] For example, in the USA phage products are available on the market for use in agriculture and food production, and are regulated by the Food and Drug Administration (FDA) having received 'Generally Recognised As Safe' (GRAS) status.[170]

52. However, we were told that while the UK had made some progress in translating phage research into clinical and commercial applications, it is still limited compared to other countries,[171] with a noticeable "translational gap".[172] This is despite the availability of leading phage experts and access to molecular genetics, sequencing and computational biology tools that could be used to ensure phages developed for therapy were safe and effective.[173] Professor Clokie told us that the 'translational gap' ran contrary to the UK's general ability to translate science into applications.[174] David Browning, CEO of Fixed Phage Ltd, also stated that his company is doing its early studies on diabetic foot products in Australia and not the UK because it is able to access "first-class" knowledge and capability and Australian Government funds to help translate research into products.[175]

53. There were particular calls for better funding for translational research.[176] For instance, the CF (cystic fibrosis) Syndicate in AMR stated that though the UK has strong phage expertise, this had "yet to be translated into more medical research and translation into patient therapies", because they do not accord with "funding and research council priorities".[177] Professor Rees told us that this is because research council funders believe that phage therapies are not "novel" and that companies should be supporting such work. She called for funding that "supported those early stages to get that fundamental

165 Jason Clark (Chief Scientific Officer at Fixed Phage LTD) (PHA0038).
166 Microbiology Society (PHA0015); UK Phage Therapy (PHA0017); Centre for Phage Research at the University of Leicester (PHA0027); Dr Shan Goh (Senior Lecturer in Microbiology at University of Hertfordshire) (PHA0028); Bangor University School of Natural Sciences (PHA0029).
167 Bangor University School of Natural Sciences (PHA0029).
168 UKRI (PHA0041).
169 University of Nottingham (PHA0039); Microbiology Society (PHA0015); Roslin Institute, University of Edinburgh (PHA0019); Centre for Phage Research at the University of Leicester (PHA0027); Bangor University School of Natural Sciences (PHA0029); Fixed Phage LTD (PHA0033); University College London (UCL) (PHA0034); UKRI (PHA0041).
170 UKRI (PHA0041).
171 See: Phage-UK (PHA0013).
172 See: CPI (PHA0047); Jason Clark (Chief Scientific Officer at Fixed Phage LTD) (PHA0038).
173 Centre for Phage Research at the University of Leicester (PHA0027); UKRI (PHA0041).
174 Q20.
175 Q104.
176 See: Professor Graham Hatfull (Professor at University of Pittsburgh) (PHA0001); National Physical Laboratory (PHA0014); Jason Clark (Chief Scientific Officer at Fixed Phage LTD) (PHA0038); Centre for Phage Research at the University of Leicester (PHA0046). PHAGE UK (PHA0013); Bangor University School of Natural Sciences (PHA0029).
177 CF Syndicate in AMR (PHA0030).

movement from the lab to the application, that would benefit UK industry in the long term and help us to build that sector".[178] Fixed Phage Ltd also called for more government support in this area to support UK phage SMEs.[179]

54. The MRC did not favour ringfencing funding for phage translational research or phage research in general. Dr Jonathan Pearce, MRC's Director of Strategy and Planning, told us that the Council supported a portfolio AMR approach and accepted the highest quality applications for funding.[180] He noted that if the phage research is relevant to human health, applications could be made through the Developmental Pathway Funding Scheme,[181] which supports the development of pre-clinical and early clinical investigations.[182] He stated that few applications for phage research had been made—only 2 out of 1,600 applications were related to phages—and had not met the quality threshold to be accepted.[183] However, he said that the establishment of a Phage Knowledge Transfer Network by Innovate UK in November 2022, will provide a good opportunity to engage with the phage researchers to "to identify the key research questions that need to be addressed in order to prosecute successful clinical investigations".[184]

55. The DHSC, UKSA and MHRA also noted that the UK Health Security Agency (UKHSA) is conducting research to evaluate phages, and is overseeing an open-innovation early-stage antimicrobial discovery and evaluation process, that included phages.[185] Professor Isabel Oliver, Scientific Officer, UK Health Security Agency, told us that she thought there is a need for "targeted funding" for phage translational research.[186]

56. **We were disappointed to hear that there is a translational phage research "gap" in the UK. We agree that funding, and especially public funding, should be awarded with care. However, we are concerned that, despite being included in the Government's AMR strategy, if not properly supported, the potential of phages to deliver therapeutics and commercial outputs will remain untested and untapped. There is a particular danger that translational phage research will be trapped in an impasse where it will miss out on research funding because it has not been able to prove its credibility, because of a lack of previous funding.**

57. ***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.***

178 Q25.

179 Jason Clark (Chief Scientific Officer at Fixed Phage LTD) (PHA0038). Currently there are only a small number of phage companies listed on the UK Companies House website.

180 Q183.

181 The Developmental Pathway Funding Scheme, funded by the MRC, has a total fund £30mn to award grants to develop and test novel therapeutics, medical devices, diagnostics and other interventions.

182 Q183.

183 Q183 and Q190.

184 Q189.

185 See: UKHSA, Antimicrobial Resistance: Open-innovation in early stage antimicrobial discovery and evaluation, (October 2021). This suggested that suitable projects might include " Kinetic studies on bacteriophage-kill in relation to antibiotic synergy and resistance emergence". It also noted that its facilities at Porton Down could be used.

186 Q229.

'One Health', AMR and phages

58. The World Health Organisation describes 'One Health' as "an integrated, unifying approach that aims to sustainably balance and optimize the health of people, animals and ecosystems".[187] It promotes collaboration across sectors, such as health, food, water, energy and environment, to protect health and address health challenges such as the emergence of infectious diseases and AMR.[188] The One Health approach is incorporated into the UK Government approach to AMR; it is referred to in both the 2018 and 2023 UK Biological Security Strategies;[189] and underpins the Government's tracking of AMR across animals, humans and the environment.[190] We have looked at One Health, as part of our inquiry into 'Emerging diseases and learnings from covid-19'.[191]

The role of phages in delivering One Health

59. The role that phages can play in a One Health approach to AMR was emphasised by Dr Morwenna Carrington, Deputy Director for UK Health Security, Department for Health and Social Care. She noted that the Government is "very keen" to look at not just human health applications of phages but also other cases, such as in agriculture, where, for example, they had been "proven to be efficacious, in tackling bacterial infections in poultry flocks".[192] She added that phages can play a number of roles in addressing the threat from AMR in food, zoonotic infections, specific patient groups (e.g. diabetic foot) and bespoke last-resort cases.[193]

60. These views were supported by others.[194] For instance, Dr Tim Jinks, Head of Infectious Disease Interventions, Wellcome Trust, noted that there are "significant opportunities" in seeing phages in the context of a "one health issue cutting across to animals, plants and the environment … where phage might deliver real benefit much sooner".[195] Dr Jonathan Pearce, Director of Strategy and Planning at the Medical Research Council, also noted that there are opportunities for phages to manage foodborne pathogen spread,[196] be used in diagnostics and in therapeutics, both in animals and in humans. He pointed to collaboration with the BBSRC to ensure that phages are considered across both human and animal health areas.[197]

187 WHO, One Health, (accessed 9 July 2023). See also: UN, Tripartite and UNEP support OHHLEP's definition of "One Health", (December 2021).
188 The WHO's One Health Joint Action Plan (2022–2026) includes the prevention of AMR as one of its six actions. See: WHO, One health joint plan of action (2022–2026): working together for the health of humans, animals, plants and the environment, (October 2022).
189 HM Government, UK Biological Security Strategy, (2018) and HM Government, UK Biological Security Strategy, (2023).
190 See: HM Government, UK One Health Report - Joint report on antibiotic use and antibiotic resistance, 2013–2017, (January 2019).
191 See: Commons Science, Innovation and Technology Committee, Oral evidence: Emerging diseases and learnings from covid-19, (HC 1303; 14 June 2023)
192 Q231.
193 Q239.
194 See: UKRI (PHA0041); Phage Research Centre, Leicester (PHA0046); Roslin Institute, University of Edinburgh (PHA0019); University College London (UCL) (PHA0034).
195 Q208.
196 See also: University College London (UCL) (PHA0034).
197 Q186.

61. Professor Cath Rees, Professor of Microbiology at the University of Nottingham, and others,[198] emphasised the role of phages in reducing bacterial pathogens in animal stock (e.g. *Campylobacter* in poultry), in food (*E. coli*) and noted the diagnostic ability of phages to detect bacterial pathogens.[199] She argued that the development of phages as a preventative measure and one outside human health could help open up the viability of phages as a technology and human therapeutic. David Browning, Chief Executive Officer, Fixed Phage Ltd, concurred and told us that his company is working across the One Health space (aquaculture, food safety, animal and human health) and that this combined approach will ultimately help develop the science and technology to underpin phage therapeutics.[200] We were also told that a cross sector approach is a key focus of Innovate UK's Phage Knowledge Transfer Network, which was set up in November 2022.[201]

Progress on using phages across One Health

62. Dr Morwenna Carrington told us that the Government is monitoring progress in tackling AMR across the One Health space and that DHSC is the lead department on AMR. However, she acknowledged that though phages are mentioned in the Government's Five-Year AMR Action Plan, the DHSC is at a "relatively early stage despite now entering year four of the five-year national action plan … in terms of monitoring progress".[202]

63. **The Government, the World Health Organisation and a number of the witnesses we heard from have highlighted the importance of a "One Health" approach to tackling AMR across sectors including human and animal health, the food supply chain, and the environment. The Department of Health and Social Care (DHSC) and others told us that phages could play an important role in delivering this approach. However, the DHSC acknowledged that they were at an early stage of tracking progress on phages. We believe it is important that—if phages are to play a meaningful part in a 'One Health' approach to tackling AMR—progress is reported in a timely and comprehensive manner. *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.***

Building and linking phage expertise

64. The UK has a number of leading phage experts and several phage research centres, including the Centre for Phage Research at the University of Leicester,[203] and research

198 Roslin Institute, University of Edinburgh (PHA0019); University College London (UCL) (PHA0034).
199 Q24.
200 Q80.
201 Richard Hebdon, Director Health and Life Sciences, Innovate UK (Q204).
202 Q230.
203 The Centre, launched in May 2023, is establishing a UK Phage Biobank, working with modellers, bioinformaticians and structural biologists to establish a mechanistic understanding of phages to ensure the most optimal phages are developed, whilst addressing clinical and agricultural needs by developing treatments. See: University of Leicester, Centre for Phage Research, (accessed 20 June 2023).

groups, such as those at the University of Nottingham (Phage Biotechnology),[204] and University College London (Santini Laboratory).[205] The University of Exeter also hosts a number of research groups looking at phages,[206] and established the Citizen Phage Library, to provide clinicians with suitable phages to treat drug-resistant bacterial infections.[207] The National Collection of Type Cultures, hosted at the UK Health Security Agency, also has a collection of over 100 characterised bacteriophages, which are available for scientists to use.[208] We were also told that several of the UK's phage research centres and groups have established links with their local hospitals,[209] and medical schools.[210]

65. However, we were told that the UK's phage assets and expertise are fragmented and not joined up.[211] Stephanie Lesage, Co-Founder/Director and Chief Executive Officer, Oxford Silk Phage Technologies Ltd, while praising the UK's academic phage research base, told us that there is work to be done to increase collaboration and the visibility of the various phage research groups across the UK.[212] Professor Santini contrasted this with Australia where there is a linkup between all hospitals and well-characterised phage bio-banks, which allows the sharing of phages for compassionate use cases and a network—Phage Australia—which brings together phage researchers and clinical scientists.[213]

66. Some steps have been taken to address this. In November 2021, Phage-UK was set up to build a network of clinicians to centralise expertise and to connect clinicians to the right research groups, companies and institutes to facilitate the logistics of phage therapy administration.[214] More recently, in November 2022, Innovate UK established a Phage Knowledge Transfer Network, tasked with bringing together key UK stakeholders and phage specialists across different sectors, and outlining the challenges that need to be addressed to establish the use of phage-based technologies across different sectors. It will also produce a report and roadmap with key targets to focus research and development and is engaging with regulators and policy makers.[215]

67. **For the potential benefits of phages to be fully explored and, if possible, exploited in the UK, with competitive advantage, it is important that existing phage-related assets are properly aligned and integrated, connecting the various sectors, institutions, and actors so they can draw on shared resources, information, data, and expertise. This will also allow the development of additional shared assets, such as phage**

204 The group has specific expertise to characterise the action of bacteriophages at molecular and physiological levels, to understand the impact of phages on bacterial population dynamics, in both biotic and abiotic environments. It also has experience of developing novel technologies for detection and eradication of bacteria. See: University of Nottingham, Phage Biotechnology, (accessed 20 June 2023).

205 UCL, Bacteriophages, (accessed 20 June 2023).

206 See for example: University of Exeter, Phage structure captured for the first time, to benefit biotech applications, (15 May 2023); University of Exeter, Research brings scientists a step closer to harnessing viruses to fight antibiotic resistance, (October 2021).

207 Citizen Phage Library, Developing therapeutic phages to fight antimicrobial resistance with Citizen Science, (accessed 20 June 2023).

208 UKHSA, Bacteriophages, (accessed 21 June 2023).

209 Q20 and Q23. For example, UCL is partnered with three hospitals including Great Ormond Street Hospital, University College Hospital and the Royal Free Hospital. See also: Professor Cath Rees, Professor of Microbiology, University of Nottingham (Q23).

210 Q23.

211 Q20 and Q23 (Professor Martha Clokie); Dr Gwen Knight (Associate Professor at London School of Hygiene and Tropical Medicine), and Prof Jodi Lindsay (Professor at St George's University of London) (PHA0021).

212 Q85.

213 Q23. See: Phage Australia, About Us, (accessed 1 July 2023).

214 Phage-UK, OUR MISSION, (accessed 2 July 2023).

215 Innovate UK, Innovate UK KTN Launches Phage Innovation Network, (21 November 2022).

biobanks, as well as encouraging new relationships between universities, hospitals, the pharmaceutical industry, and other stakeholders. We were concerned to hear that the UK's phage expertise and resources are 'fragmented'. We therefore welcome Innovate UK's Phage knowledge transfer initiative to bring phage stakeholders together to produce a roadmap to deliver a sustainable and integrated network for the transfer and sharing of phage-related knowledge for the benefit of all.

68. ***We recommend that the Department for Health and Social Care responds to the UK's Phage Knowledge Transfer Network's proposals within six 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.***

Awareness of phages and phage therapy

69. Another key issue facing the wider use of phages, is low levels of awareness amongst clinicians. For instance, an article published in 2023 noted that across the UK there were large variations in clinicians' awareness of phages and phage treatments.[216] We were told that this included a lack of understanding of the routes and barriers associated with compassionate-use phage therapy in the UK.[217] Professor Clokie suggested that one way of addressing this would be embedding phages within medical training courses.[218]

70. **If phages are to be used more widely within the UK's healthcare system it is important that healthcare professionals are aware that they are an antimicrobial alternative, especially when antibiotics have failed or are failing.** ***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.***

71. In terms of the public, we were told that surveys indicated that there is a high awareness of AMR, but low levels of awareness of phages. Furthermore, when it is explained that phages are viruses, the public are wary if not sceptical.[219] However, it was suggested that explaining that phages could fight bacterial infections and be used to make antibiotics more effective, could make phages more acceptable to the public.[220] This suggested a need for better communication and education regarding phages as part of a One Health approach to addressing AMR. The Phage Citizen Science Project, based at the Exeter Science Centre, is an example of an outreach resource that can be used to explain and promote the use of phages to the public, including school children.[221] The Citizen Phage Library, based at the University of Exeter, which works with the Exeter Science Centre,

216 Joshua D. Jones et al., The Future of Clinical Phage Therapy in the United Kingdom, Viruses, vol 15, no 3, (2023).
217 Microbiology Society (PHA0015).
218 Q9 and Q23.
219 Miss Sophie McCammon (Graduate Research Assistant at University of Exeter), Professor Susan Banducci (Director of Research at University of Exeter), Doctor Vicki Gold (Senior Lecturer at University of Exeter), and Doctor Kirils Makarovs (Lecturer at University of Amsterdam) (PHA0006)
220 See: Sophie McCammon et al., Phage therapy and the public: Increasing awareness essential to widespread use, PLoS One, vol 18, no 5, (2023).
221 Exeter Science Centre, Phage Therapy Citizen Science Project, (accessed 17 June 2023).

is promoting a broader understanding of phages, including recruiting members of the public to use sampling kits to identify and isolate phages to add to the Citizen Phage library.[222] The Library is also promoting phages with local doctors.[223]

72. **The public will need to be convinced that phages are safe and effective. This will be key if phages are to play a role in addressing AMR in healthcare and as part of a One Health approach to addressing AMR across various sectors, such as the food industry and the environment. Careful and transparent promotion of phages' antimicrobial ability to reduce or eradicate bacterial pathogens and re-weaponise antibiotics, would help make their use more acceptable.**

222 Citizen Phage Library, A great weekend at the Sidmouth Science Festival, (October 2021).

223 Citizen Phage Library, Developing therapeutic phages to fight antimicrobial resistance with Citizen Science, (accessed 17 June 2023).

3 Manufacturing phages

73. One of the major obstacles to the wider use of phages that was mentioned in most of the evidence we took is the need for phage production to meet Good Manufacturing Practices (GMP) standards. GMP describes the minimum standards that a medicines' manufacturer must meet in their production processes.[224] GMP is supported by the World Health Organisation (WHO) which produces guidance on it how it should be applied.[225] The box below outlines the key components of GMP:

Box 2: Good Manufacturing Practices (GMP)

Good manufacturing practice (GMP) is a system for ensuring that pharmaceutical products are consistently produced and controlled according to quality standards. It is designed to minimize the risks involved in any pharmaceutical production that cannot be eliminated through testing the final product.

The main risks are: unexpected contamination of products, causing damage to health or even death; incorrect labels on containers, which could mean that patients receive the wrong medicine; insufficient or too much active ingredient, resulting in ineffective treatment or adverse effects. GMP covers all aspects of production; from the starting materials, premises and equipment to the training and personal hygiene of staff.

Detailed, written procedures are essential for each process that could affect the quality of the finished product. There must be systems to provide documented proof that correct procedures are consistently followed at each step in the manufacturing process - every time a product is made.

World Health Organisation, Medicines: Good manufacturing practices, (2015)

74. In some countries, non-GMP phages have been allowed either for compassionate use in last resort cases or as prescribed medicines within the jurisdiction of that country. The UK has not allowed the use of any domestically produced non-GMP phages either for clinical use or in clinical trials. However, irrespective of national approaches, GMP certification has been seen as a requirement for phage products to be exported. For instance, while the EU has permitted non-GMP phages to be used within individual Member States and exchanged between them on individual compassionate grounds,[226] it has not allowed commercial non-GMP phages to be exported between them.[227] A key obstacle in setting up new GMP production in the UK and elsewhere has been what we were told are the very high costs of qualifying design, equipment, installation and processes alongside the lack of a pathway for a return on such an investment in phages. Currently, world-wide there are only four phage GMP facilities, in Slovenia, Portugal, Norway and the United States.[228] This chapter will explore these issues and possible solutions.

224 See: European Medicines Agency, Good manufacturing practice, (accessed 14 June 2023).

225 WHO, Medicines: Good manufacturing practices, (November 2015).

226 See Chapter 5 for an overview of different approaches within the EU and elsewhere.

227 Phages are classified as biological medicinal products within the EU and are regulated under Directive 2001/83/EC (as amended). This requires that products given to patients (1) follow the gradual evaluation through clinical trials before obtaining a Market Authorization, and (2) are manufactured in compliance with the Good Manufacturing Practice (GMP) rules. See European Commission, EudraLex - Volume 4 - Good Manufacturing Practice (GMP) guidelines, (accessed 20 July 2023). See also: Virustatic (PHA0032).

228 CPI (PHA0047).

Support for GMP phage production

75. The majority of the evidence we took argued in favour of phage production being required to meet the GMP standard though, as noted in Chapter Five, many witnesses thought that non-GMP phages produced in the UK should be used on compassionate grounds in last resort cases where antibiotics had failed, in lieu of GMP-compliant products ('GMP phages'). Dr Josh Jones argued that UK GMP phages would allow clinical trials to start in the UK because UK regulators require that GMP phages are used for trials.[229] UK GMP phage production would also help catalyse UK phage businesses and allow UK phages to be exported as a commercial products, because GMP is a globally recognised standard.[230] It would also ensure a high-quality source of phages for biobanks, and for use at scale in the NHS, providing reassurance to pharmacists and clinicians.[231] Others noted that phages produced to a GMP standard would increase general UK resilience to AMR across sectors, and in the event of a future AMR health emergency.[232] Dr Jones also told us that GMP phage manufacturing could allow off-the-shelf phages within 5 to 10 years.[233]

76. Dr Morwenna Carrington, Deputy Director for UK Health Security, DHSC, also said GMP is key to developing phage exports.[234] Professor Isabel Oliver, Scientific Officer, UK Health Security Agency, told us that the UK "probably" needed to invest in national phage manufacturing capacity".[235]

77. However, some disagreed. Dr Jean-Paul Pirnay and Dr James Soothill maintained that GMP is not required to provide clinical phages because they are a form of personalised medicine produced in small quantities that do not require commercial mass production.[236] They suggested that because phages need to be tailored for each patient in terms of combination for each cocktail, dosage, alteration and use alongside antibiotics, this would not lend itself to the strict requirements of GMP. Dr Pirnay advocated instead an approach used in Belgium that allows a medical doctor to personalize patient treatments to specific needs and to make medications available that do not exist commercially.[237] Both Dr Pirnay, Dr Soothill and others suggested that phages should be publicly funded and provided by a state healthcare service to treat bacterial infections, because they might not be commercially viable and provided a public good.[238]

78. **The set of consensus high standards for pharmaceutical production, known as Good Manufacturing Practice (GMP), should continue to be required in the UK for high quality phages manufactured for generic products targeting the most common bacterial pathogens. It should also underpin the production of phage biobanks to be accessed at short notice by clinicians providing assurance to both clinicians and patients that phages from biobanks will be of the highest standard of safety and purity. Access to phages manufactured to GMP standards will also allow microbiology**

229 Q42.
230 CPI (PHA0047); UK Phage Therapy (00045).
231 Q42 and Q58. Dr Josh Jones, UK Phage Therapy (00045).
232 CPI (PHA0047).
233 Q61.
234 Q245. See also: Jason Clark (Chief Scientific Officer at Fixed Phage LTD) (PHA0038).
235 Q229.
236 Q117 and Q36. See also: Professor Tristan Ferry (Professor of Medicine at Hospices Civils de Lyon and Université Claude Bernard Lyon 1) (PHA0037).
237 Jean-Paul Pirnay at al., The Magistral Phage, Viruses, vol 10. No 2, (February 2018). See Chapter 5 for an overview of the Belgian magistral monograph approach to using non-GMP phages.
238 See also: Antibiotic Research UK (PHA0020).

laboratories to deal with less common pathogens and tailor phages to be more effective for individual patients when a more agile precision medicine approach is required. However, there may still be a place for non-GMP phages in instances when non-banked phages are needed at short notice for compassionate use as a last resort and can be produced via collaboration between a physician and pharmacist—as in Belgium.

Cost of GMP manufacturing

79. One of the key obstacles to establishing a GMP manufacturing capability in the UK is the initial cost and the lack of a clear profit model for businesses to invest in such facilities, because as Professor Rees told us, there is not a market big enough to support such investment.[239] Stephanie Lesage, Co-Founder/Director and Chief Executive Officer, Oxford Silk Phage Technologies Ltd, told us that it would initially cost £170,000 for each individual phage to be produced to the GMP standard, though costs would decrease once the upfront costs of building GMP facilities had been met.[240] Dr Josh Jones told us that it would cost £500,000 to treat between 100 to 200 patients with a single batch of GMP phage contract-manufactured in the EU.[241] However, he stated if there was a UK-based phage GMP facility it could reduce the cost to "a couple of pounds" for each patient as economies of scale increased.[242]

80. The Centre for Process Innovation—an independent technology innovation centre and a founding member of the UK Government's High Value Manufacturing Catapult[243]—agreed and suggested that one way of addressing the costs of building a GMP facility would be to construct a GMP facility for a range of microbiome products including phages. This, it argued, would help mitigate the potential risk associated with the financial viability of manufacturing phage therapies alone.[244] This approach, providing resources and assets that can be supported by catapults—private not-for-profit Research and Technology Organisations (RTOs) working with innovators, government, and industry[245]—is a concept that we have seen working successfully in other sectors, such as the UK's space and satellite sector.[246]

81. Dr Josh Jones also suggested that the cost of setting up a GMP facility could be offset by the savings from using phages to treat AMR infections in hospitals. He suggested that if phage therapy was routinely used in the NHS, it could save between £150m and £200m a year from reduced diabetic foot and hip/knee infection costs alone, by avoiding interventions, such as amputations and other surgery.[247] He also argued that it could lead

239 Oxford Silk Phage Technologies Ltd (OSPT) (PHA0035) and Q21. See also UKRI (PHA0041).
240 Q90.
241 Q45.
242 Q74.
243 See: Centre for Process Innovation, About CPI: From innovation to commercialisation, (accessed 13 October 2023).
244 Fixed Phage LTD (PHA0033); CPI (PHA0047). See also: Q48; Fixed Phage LTD (PHA0033).
245 Nine Catapults were set up by the Government in 2011 with funding from Innovate UK. The Government has confirmed £1.6bn Catapult core funding for the next five years (April 2023 – March 2028). See: DSIT, 2023 Update to the 'Catapult Network Review': An update on developments since the Catapult Network Review April 2021, (September 2023).
246 See: House of Commons Science and Technology Committee, UK space strategy and UK satellite infrastructure, (HC 100; November 2022), pp 50–52. The role of clusters and the use of shared resources was also highlighted in our evidence session's on the role of technology and innovation in the covid-19 recovery held between April 2021 and July 2022 in Belfast, Glasgow, West Midlands, Manchester and Westminster.
247 Dr Josh Jones, UK Phage Therapy (00045).

to savings from not requiring expensive new antibiotics.[248] For instance, one study found that as older antibiotics fail because of AMR, the cost of a 14-day treatment course for methicillin-resistant *Staphylococcus aureus bacteremia* (MRSA) with a newly approved drug was found to be 6 to 60 times higher than that of older drugs, while the cost of a 14-day course for carbapenem-resistant *Enterobacterales* or *MDR Pseudomonas aeruginosa* was doubled with new drugs.[249] A GMP facility could also produce phages for non-health sectors, such as food and animals, which could be used to cross-subsidise health-related phages.[250]

82. Dr Morwenna Carrington, Deputy Director for UK Health Security, DHSC, told us that that the department is "really interested in the potential for bacteriophages to deliver cost savings to the NHS" though these were "quite complex to estimate".[251]

83. **One of the main obstacles to establishing Good Manufacturing Practice (GMP) facilities in the UK is the cost and the reluctance of pharmaceutical firms to invest in phages and antimicrobials more generally because of an uncertain return on investment compared to other medicines and drugs. However, investing in a small, or shared multi-use, GMP facility is one possible solution to ensure that such capacity could be run cost effectively. The allocation of public funds to establish a GMP facility could be offset by savings delivered to the NHS, by avoiding wasted antibiotics and unnecessary surgery resulting from AMR. Such a facility could also supply phages to non-health sectors which could be used to cross-subsidise healthcare phages.**

84. ***We recommend that the Department for Health and Social Care 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,[252] 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.***

A flexible GMP approach to the use of phages

85. The Microbiology Society and others suggested that there is a danger that a marketing authorisation might be required for each personalised phage combination which would be inflexible and time-consuming. They suggested that this needed to be addressed to allow more flexibility in treatment design.[253] Several witnesses suggested that one approach might be to treat phages like flu vaccines, which allowed the combination of each vaccine to be modified to address new flu strains.[254] This would allow a phage cocktail to be

248 As above.

249 Dafna Yahav et al., Cost Analysis of New Antibiotics to Treat Multidrug-Resistant Bacterial Infections: Mind the Gap, Infect Dis Ther, vol 10, no 1, (March 2021), pp 621–630.

250 University of Nottingham (PHA0039).

251 Q239.

252 BBC News, UK's first Covid mega lab for sale, (9 November 2023); Business Live, Former Covid-19 testing site the Rosalind Franklin Laboratory goes on the market in 'unique opportunity' for life sciences sector, (6 November 2023). The Laboratory was still listed on RightMove as of 19 December 2023.

253 Microbiology Society (PHA0015); Fixed Phage LTD (PHA0033); AMR Action Fund (PHA0012).

254 See: David Browning, Chief Executive Officer, Fixed Phage Ltd (Q94).

updated, as long as the individual phages were demonstrated to be safe and of a high quality.[255] Dr Marc Bailey, Chief Science, Research & Innovation Officer, MHRA, said that he saw merit in this approach, as long as each phage had been properly characterised and their individual purity could be guaranteed.[256]

86. ***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.***

Genetically engineered phages and GMP

87. As noted in previous chapters, witnesses told us that genetically engineered (GE) phages,[257] and the extraction of phage enzymes can help reduce the risk of using unknown genes,[258] and address bacterial resistance to phages.[259] We heard that phages that have been imported—often from Belgium and San Diego—[260] and genetically engineered are already being used in the UK,[261] and elsewhere,[262] though they had not met the GMP requirement. Several witnesses told us that GE phages and phage enzymes, if they met regulatory standards, might interest big pharmaceutical companies as they would be easier to patent than natural phages.[263] The Wellcome Trust highlighted that it predominantly funds research involving genetically engineered phage, because it sees this as an innovative approach to the phage space.[264] However, we heard that UK GE phages

255 See: Greg Merril, Chief Operating Officer, Adaptive Phage Therapeutics (Q162).

256 Q219.

257 One key approach is phage genome editing based on the CRISPR–Cas system. See for example: Xueli Zhang et al., CRISPR–Cas9 Based Bacteriophage Genome Editing, Microbiology Spectrum, (July-August 2022); Benjamin A. Adler et al., Broad-spectrum CRISPR-Cas13a enables efficient phage genome editing, Nature Microbiology, vol 7, (October 2022); Yilmaz Emre Gencay et al., Engineered phage with antibacterial CRISPR–Cas selectively reduce E. coli burden in mice, Nature Microbiology, (May 2023).

258 Q17 and Q26. See also: University College London (PHA0034).

259 See: Professor Robert Schooley (Professor of Division of Infectious Diseases at UC San Diego School of Medicine) (Q147 to Q148); Wellcome Trust (PHA0011); Phage-UK (PHA0013); Dr Shan Goh (Senior Lecturer in Microbiology at University of Hertfordshire) et al. (PHA0028); University College London (PHA0034); Fixed Phage LTD (PHA0033).

260 This includes phages from the Division of Infectious Diseases at UC San Diego School of Medicine and the Queen Astrid military hospital (QAMH) in Brussels, Belgium.

261 Dr James Soothill (Consultant Microbiologist at Great Ormond Street Hospital Laboratory Medicine) Q52. A 15-year-old cystic fibrosis patient with a disseminated *Mycobacterium abscessus* infection was treated with a three-phage cocktail following bilateral lung transplantation. Effective lytic phage derivatives that efficiently kill the infectious *M. abscessus* strain were developed by genome engineering and forward genetics. Intravenous phage treatment was well tolerated and associated with objective clinical improvement including sternal wound closure, improved liver function, and substantial resolution of infected skin nodules. See: Rebekah M. Dedrick et al., Engineered bacteriophages for treatment of a patient with a disseminated drug resistant Mycobacterium abscessus, Nat Med, vol 25, no 5, (May 2019).

262 Professor Robert Schooley (Professor of Division of Infectious Diseases at UC San Diego School of Medicine) (Q147 to Q148); Professor Jonathan Iredell (Senior Staff Specialist Infectious Diseases and Microbiology et al. (PHA0008).

263 Professor Joanne M. Santini, Professor of Microbiology at University College London (Q26 and Q30); Professor Jon Iredell, Director, Centre for Infectious Diseases and Microbiology at The Westmead Institute for Medical Research (Q151);

264 Dr Tim Jinks, Head of Infectious Disease Interventions, Wellcome Trust, (Q194).

will need additional regulatory approval,[265] which was confirmed by the MHRA who told us that they might be classified as advanced therapy medicinal products (ATMPs), which require separate legislative requirements.[266]

88. **For phages to be effective they will need to keep pace with bacterial resistance and be amenable to adaptation for individual patients. Genetically engineered (GE) phages may be one way of ensuring this. GE phages have already been used in the UK and elsewhere. However, if they are to be produced commercially, GE phages will need to be aligned with GMP. *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.***

89. We were also told that if GE phages gained regulatory approval in the UK it would lead to regulatory divergence from the EU,[267] as the EU has strict regulations on genetically modified organisms.[268] Several witnesses suggested that this would offer the UK a competitive advantage over the EU in developing and exploiting a key growth area for phages.[269] Others argued that commercialising UK GE phages would be difficult if this is not aligned with the EU's regulatory frameworks.[270] However, it is worth noting that the UK government has already initiated regulatory divergence from the EU in relation to gene editing and precision breeding techniques.[271] The Genetic Technology (Precision Breeding) Act 2023 will allow technologies such as gene editing to adapt the genetic code of plants, in the first instance.[272]

90. **If the UK government supports the commercial production of genetically engineered (GE) phages, it will inevitably lead to regulatory divergence from the EU. However, we believe this divergence offers the UK an opportunity that should be pursued. This should be part of a clear regulatory and safety licensing regime for phages, if phages are to be exploited for competitive advantage.**

Other routes for phage therapies

91. Contributors pointed to other possible routes for the clinical use of non-GMP phages.[273] The Innovative Licensing and Access Pathway (ILAP) aims to accelerate the time to market for a medicine, facilitating patient access to medicines. The criteria for the pathway, includes identifying that a condition is life-threatening or seriously debilitating and/or that there is a significant patient or public health need. The medicine should also be an advanced therapy medicinal product (ATMP), a new, or repurposed, chemical or

265 See: Richard Hebdon, Director Health and Life Sciences, Innovate UK (Q208); Dr James Soothill (Consultant Microbiologist at Great Ormond Street Hospital) (PHA0009).
266 Department of Health and Social Care (DHSC), UK Health Security Agency (UKHSA), and Medicines and Healthcare products Regulatory Agency (MHRA) (PHA0007).
267 Centre for Phage Research at the University of Leicester (PHA0027); Phage-UK (PHA0013); Dr James Soothill (Consultant Microbiologist at Great Ormond Street Hospital) (PHA0009); CF Syndicate in AMR (PHA0030).
268 European Commission, GMO legislation, (accessed 28 July 2023).
269 Centre for Phage Research at the University of Leicester (PHA0027); Phage-UK (PHA0013); CF Syndicate in AMR (PHA0030).
270 Microbiology Society (PHA0015).
271 See: House of Commons Library, Genetic Technology (Precision Breeding) Act 2023, (March 2023).
272 See: Food Standards Agency, Precision breeding, (November 2023).
273 CF Syndicate in AMR (PHA0030); Jason Clark (Chief Scientific Officer at Fixed Phage LTD) (PHA0038).

biological entity or novel drug/device combination. There are a number of entry points for such medicines, depending on the data available and its stage of development, and can be based on non-clinical data.[274]

92. The Early Access to Medicines Scheme, aims to give patients with life threatening or seriously debilitating conditions access to medicines that do not yet have a marketing authorisation when there is a clear unmet medical need. This requires a scientific opinion that describes the risks and benefits of the medicine based on data gathered from the patients who will benefit from the medicine. The opinion supports the prescriber and patient to make a decision on whether to use the medicine before its licence is approved.[275]

93. The DHSC, MHRA and UKHSA noted that the MHRA will take a risk-proportionate approach so "that UK patients have the fastest possible access to innovative bacteriophage therapies for which quality, safety and efficacy had been shown".[276] They stated that the MHRA is open to working with phage innovators through its Innovation Accelerator and Innovation Office, and relationships with health technology bodies, such as the National Institute for Health and Care Excellence (NICE). This would include advice on how they could meet regulatory conditions and navigate routes such as ILAP.[277] Dr Marc Bailey, Chief Science, Research & Innovation Officer, MHRA, told us that the MHRA is particularly open to regulatory flexibility in relation to phages.[278] However, several contributors argued that clarity is required to ensure that phage innovators have clarity on what is required from each pathway.[279]

94. **We welcome the willingness of the MHRA to adopt a flexible approach to accelerating the authorisation of the use of phage therapies and its offer to work with phage innovators to support their development. However, the MHRA should provide clarity on how different pathways for developing phages, such as the Innovative Licensing and Access Pathway, and other flexible regulatory approaches will work in practice and how they will align with GMP and non-GMP phage for compassionate use in last resort cases. *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.***

274 GOV.UK, Innovative Licensing and Access Pathway, (accessed 17 July 2023).
275 GOV.UK, Apply for the early access to medicines scheme (EAMS), (accessed 14 July 2023).
276 Department of Health and Social Care (DHSC), UK Health Security Agency (UKHSA), and Medicines and Healthcare products Regulatory Agency (MHRA) (PHA0007)
277 As above.
278 Q208.
279 AMR Action Fund (PHA0012); University College London (UCL) (PHA0034).

4 Phage clinical trials

95. One of the major obstacles facing the use of phages as a medical intervention, is a lack of clinical trials in which the effects of new therapies are tested on selected patients in controlled circumstances. Clinical trials are important because they move the knowledge base from observed, qualitative and anecdotal information to replicable, verifiable and quantifiable data. They are key to medical products gaining regulatory approval for clinical use after meeting high standards of assurance and effectiveness required for human therapies and treatments in terms of safety and impact (i.e. going beyond individual compassionate use reports).[280] In the UK, there have been no clinical trials involving phages since 2009,[281] with the main challenges being the requirement for clinical trials to use only phages produced to GMP standards and a lack of research funding (as referred to in earlier chapters). This chapter will explore these issues and potential solutions.

What are clinical trials?

96. Clinical trials are studies that are used to test the safety and efficiency of human medicines before they can be licensed for use.[282] They usually fall into three phases, though on occasion a fourth phase trial may be used.[283] The various phases of a clinical trial are set out in the box below:

280 Antibiotic Research UK (PHA0020).

281 See: Jason Clark (Chief Scientific Officer at Fixed Phage LTD) (PHA0038); Phage-UK (PHA0013); University College London (PHA0034). See also: Joshua D Jones et al., The Future of Clinical Phage Therapy in the United Kingdom, Viruses, vol 15, no 3, (March 2023).

282 See: NHS, Clinical Trials, (accessed 19 June 2023).

283 As above. Phase four trials See: Jason Clark (Chief Scientific Officer at Fixed Phage LTD) (PHA0038).

Box 3: The phases of a clinical trial

Phase 1 trials:

- A small number of people, who may be healthy volunteers, are given the medicine.
- The drug is being trialled in human volunteers for the first time.
- Researchers test for side effects and calculate what the right dose might be to use in treatment.
- Researchers start with small doses and only increase the dose if the volunteers do not experience any side effects, or if they only experience minor side effects.

Phase 2 trials:

- The new medicine is tested on a larger group of people who are ill. This is to get a better idea of its effects in the short term.

Phase 3 trials:

- Carried out on medicines that have passed phases 1 and 2.
- The medicine is tested in larger groups of people who are ill, and compared against an existing treatment or a placebo to see if it's better in practice and if it has important side effects.
- Trials often last a year or more and involve several thousand patients.

Phase 4 trials:

- The safety, side effects and effectiveness of the medicine continue to be studied while it's being used in practice.
- Not required for every medicine.
- Only carried out on medicines that have passed all the previous stages and have been given marketing licences – a licence means the medicine is available on prescription.

NHS, Clinical trials, (accessed 11 October 2023)[284]

Good clinical trials will use a placebo and/or control group where a random selection of trial subjects is given an inactive 'placebo' facsimile of the active medicine, or continue to receive an existing 'standard' treatment, as a way of double-checking the attribution of impacts and effects to the medicine being trialled.

284 See also: UKRI MRC Clinical Trials Unit, What is a clinical trial?, (accessed 11 October 2023); National Institutes of Health, NIH Clinical Trials and You, (October 2022); WHO, Clinical Trials, (accessed 11 October 2023).

Global phage clinical trials

97. We were told that globally, there has been relatively few phage clinical trials,[285] although more have been conducted recently.[286] Between 2005 and 2021 there were at least 13 modern global clinical or safety trials that took place. Of these, four were phase I clinical trials, two were phase I/II trials, while the others were not designated.[287] In 2022, a further 18 global phage clinical trials were initiated. As of March 2023, there are 45 clinical trials listed on clinicaltrials.gov,[288] of which 25 are phase I or phase II clinical trials, with 14 combined phase I and phase II trials, five are phase III trials, with no phase IV trials.[289] No clinical trials have taken place in the UK since 2009.[290]

Focus of global phage clinical trials

98. The phages being trialled focus on a range of bacterial infections. A large proportion of the trials involve the application of phages for either skin and soft tissue infections, or gastrointestinal infections.[291] Other applications include for: genitourinary tract infections; lung infections (including those in patients with cystic fibrosis); bacteraemia; osteomyelitis; upper respiratory tract infections; prosthetic joint infections; and, for non-healing wounds or infections of bones, upper respiratory tract, and where extensive antibiotic regimens failed or the use of a targeted drug was ineffective.[292] The key bacterial pathogens being targeted include *E. coli*, *Klebsiella spp.*, *Staphylococcus spp.*, *P. aeruginosa* and *Streptococcus spp.*[293]

Challenges for phage clinical trials

99. One particular challenge for phages is that they are not a single compound such as antibiotics or paracetamol.[294] Several contributors noted that the high specificity of phages for treating patients poses a challenge for the standard design of clinical trials, based around consistency and double-blind and placebo-controlled studies.[295] Each patient needs specific phages based around the various bacterial strains infecting them and their own characteristics, which can differ between patients. Some phages might work well in one patient but not another, requiring further adaption.[296] In addition, treatments

285 See: Professor Graham Hatfull (Professor at University of Pittsburgh, (PHA0001); Quadram Institute Bioscience (PHA0004); Dr James Soothill (Consultant Microbiologist at Great Ormond Street Hospital) (PHA0009); Applied Microbiology International (PHA0010);

286 AMR Action Fund (PHA0012); Professor Graham Hatfull (Professor at University of Pittsburgh, (PHA0001); Microbiology Society (PHA0015); Antibiotic Research UK (PHA0020).

287 Helen J. Stacey et al., The Safety and Efficacy of Phage Therapy: A Systematic Review of Clinical and Safety Trials, Antibiotics (Basel), vol 11, no 10. These included: Bangladesh and/or Switzerland (6), the United States (2), France and/or Belgium (2), Australia (1), Georgia (1) and the UK (1). Other evidence point to 14 completed trials (Quadram Institute Bioscience (PHA0004)). See also: ClinicalTrial.gov (accessed 15 June 2023).

288 ClinicalTrials.gov is a registry of clinical trials. It is run by the United States National Library of Medicine at the National Institutes of Health, and holds registrations from over 444,000 trials from 221 countries.

289 Nicole Marie Hitchcock et al., Current Clinical Landscape and Global Potential of Bacteriophage Therapy, Viruses, vol 15, no 4, (April 2023). See also: See: ClinicalTrial.gov (accessed 15 June 2023).

290 Joshua D. Jones et al., The Future of Clinical Phage Therapy in the United Kingdom, Viruses, vol 15, no 3, (March 2023).

291 As above.

292 As above.

293 As above.

294 Q7.

295 Microbiology Society (PHA0015).

296 Dr James Soothill (Consultant Microbiologist at Great Ormond Street Hospital) (PHA0009).

require a broad-spectrum antibiotic with phage as an adjunct therapy, which complicates separating out the specific action of phages.[297] Testing phages alone without antibiotics would therefore not represent real world use, and threaten their evaluation as an effective clinical intervention.[298] This suggests that for phages to be truly effective they are going to have to be subject to a more bespoke licensing regime for clinical trials.

100. **Our evidence suggests that current regulations for clinical trials and the manufacturing of medicines are unlikely to be effective for phages as they are for other drugs or antibiotics. This is because the current regulatory approach to testing and manufacturing medicines is based on a single consistent formulation being shown to have a demonstrable effect. This does not accord with the optimal use of phages which require considerable flexibility in terms of the specificity required for individual patients. There are a number of different medical scenarios where the current regulations will struggle to cope with this need for specificity that mitigates against generic testing. These include:**

- **the requirement for individual phage strains that are specific to the species and even strain genotype of the bacteria they seek to inhibit, which could be almost limitless and impossible to test in advance;**
- **the need for multiple unique formulations of phages, often in conjunction with antibiotics and other drugs, to target infections in individual patients with specific microbiota, which might not be anticipated in traditional clinical trials;**
- **in the future, pre-tested generic phages that have met regulatory standards may not be able to inhibit bacterial growth, necessitating adaptation which may be beyond inflexible regulations;**
- **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 significant clinical data if each use is unique;**
- **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.**

101. ***The MHRA should set out how they propose to regulate and ensure clinical safety for each of the scenarios set out above. 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.***

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***

297 Antibiotic Research UK (PHA0020).

298 See: Andrzej Górski et al., Phage Therapy: Towards a Successful Clinical Trial, Antibiotics (Basel), vol 9, no 11, (November 2020),

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.

Breaking the impasse in the UK

The GMP requirement

103. There have been no phage clinical trials in the UK since 2009. Professor Jo Santini, Dr Josh Jones and Dr James Soothill represented many witnesses in stating that the GMP requirement for phages is holding back clinical trials.[299] Dr Tripett, Chief Technologist at the CPI, an independent technology innovation centre, stated that without clinical trials—because of a lack of GMP phage manufacturing facilities—new therapeutic products will not be able to go on the commercial open market, with innovative companies and leading academics being "forced to go outside of the UK for product manufacture to go into clinical trials".[300] Professor Jo Santini also told us that the UK's approach on clinical trials and need for GMP to undertake them is holding back the UK from being a leader in phages.[301]

104. Stephanie Lesage, Co-Founder/Director and Chief Executive Officer, Oxford Silk Phage Technologies Ltd, suggested that one way of breaking this impasse would be the use of non-GMP phages, in early-stage clinical trials if they are produced to the necessary quality and purity standards.[302]

105. **One of the major obstacles to phage clinical trials in the UK has been the requirement for GMP phages. However, regulators require that for phages to achieve GMP standards they must themselves have first been subject to clinical trials. This impasse is stalling the development of phages in the UK. The Department of Health and Social Care should consider investing in a small GMP facility which would solve one part of the problem. However, it would not solve the issue of UK GMP requiring clinical trials that in themselves had to use GMP phages. Clarity is needed on how this conundrum can be solved.**

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 six months of the publication of this report.***

Funding phage clinical trials

107. As noted in previous chapters, a major problem for UK clinical trials is the lack of funding, especially from pharmaceutical companies because of a clear profit pathway. This is because clinical trials are expensive, especially when they move to phase II and phase III trials. Some clinical trials are funded by charities looking at specific diseases. For example, Antibiotic Research UK is funding research into non-phage antibiotic resistant

299 Q21; Q42; Q55. See also: CPI (PHA0047).
300 CPI (PHA0047).
301 Q20.
302 Q91.

breaker drugs, with a view to move towards large-scale clinical trials.[303] Funding for clinical trials can also be accessed through the MRC and the National Institute for Health Research (NIHR), the latter being funded by the DHSC. For instance, the NIHR will help fund life science companies to carry out clinical evaluations.[304] There are therefore opportunities for UK public funding of phage clinical trials.

108. The evidence we took indicated that in other countries phage clinical trials have been funded by governments. For instance, we were told that some clinical trials in the United States are funded by the FDA.[305] The US National Institutes of Health also recently awarded its first tranche of funding, $2.5mn to 12 institutes around the world to support research on bacteriophage therapy. Naomi Zak, Co-founder of BiomX, an Israeli-based phage SME, told us that her company's current clinical trial, which has moved into phase II, had received some funding from the Israeli Government.[306] Fixed Phage Ltd, a UK phage SME, argued that grant funding is more likely to encourage funding from private investors and pharmaceutical companies.[307]

109. Dr Morwenna Carrington, Deputy Director for UK Health Security, DHSC, told us that the NIHR had put a lot of effort in building clinical trial infrastructure and would "welcome applications from researchers and companies to conduct clinical trials on bacteriophages because it is evidence that we think we sorely need".[308]

110. **The funding of clinical trials, especially later trials, has proved an obstacle for phages. We were pleased to hear that the National Institute for Health and Care Research would welcome applications from phage researchers and companies to access public funding to conduct clinical trials.** ***We recommend that 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 Medicines and Healthcare Products Regulatory Agency offers tailored support for phage applications for clinical trials.***

Using clinical data from other countries and using non-health phage data

111. Several contributors to our inquiry argued that the UK should use clinical data from other countries, and from non-health sectors—such as food and animals—to assess the efficacy and safety of phages in health care.[309] For example, studies from Eastern Europe, where phages have been used more extensively, have provided substantial evidence of the

303 See: Antibiotic Research UK, Antibiotic Resistance Breakers (ARBs), (accessed 20 June 2023).

304 This includes a number of funding streams. For instance, the Invention for Innovation stream allows life science companies to access translational funding that supports the development of innovative medical technologies from demonstrated proof-of-principle to clinical evaluation. It aims to de-risk early stage projects that have a strong potential for commercialisation and acceptance for use in the NHS, and to make them attractive to follow-on funders and investors. The Efficacy and Mechanism Evaluation stream funds studies that test the clinical efficacy of novel or repurposed interventions, where proof of concept in humans has already been achieved. See: NIHR, Apply for funding, (accessed 20 June 2023).

305 Q20.

306 Naomi Zak (Co-Founder at BiomX) (PHA0042).

307 Fixed Phage LTD (PHA0033).

308 Q242.

309 See: University of Nottingham (PHA0039).

efficacy of phages to treat certain infections with no adverse effects reported.[310] Though much of these studies do not meet the current rigorous standards for clinical trials, it has been argued that this still represents a substantial body of work that could be used as part of the evidence to underpin phages in the UK.[311] Similarly, research has indicated that phages have shown some success and promise in controlling bacterial infections in poultry,[312] cattle[313] pigs,[314] aquaculture,[315] and the food industry.[316] This research might also be used to strengthen wider evidence to indicate the safety and effectiveness of phages.

112. Dr Marc Bailey, Chief Science, Research & Innovation Officer, MHRA, told us that the MHRA is open to using clinical data from other countries, as long as those providing the data were in compliance with UK requirements and collected data at a sufficient level of quality.[317] He also explained that the MHRA would consider data from non-health sectors, such as food and agriculture, to fill in some gaps, though the higher standards for evidence required for human therapeutics remained.[318]

113. **We are pleased that the MHRA is open to using phage data from a variety of sources as long as it is of sufficient quality.** ***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.***

310 Dianna P Pireset al., Current challenges and future opportunities of phage therapy, FEMS Microbiology Reviews, (May 2020);

311 See: Alexander Sulakvelidze et al., Bacteriophage Therapy, Antimicrobial Agents and Chemotherapy, vol 45, no 3, (March 2021); Angharad Steele et al., The Safety and Efficacy of Phage Therapy for Superficial Bacterial Infections: A Systematic Review, Antibiotics (Basel), vol 9, no 11, (November 2020).

312 See for example: Anisha M. Thanki et al., A bacteriophage cocktail delivered in feed significantly reduced Salmonella colonization in challenged broiler chickens, Emerging Microns and Infections, vol 12, no 1, (June 2023); S. Mosimann et al., Efficacy of phage therapy in poultry: a systematic review and meta-analysis, Poultry science, vol 100, issue 12, (December 2021); Katarzyna Żbikowska et al., The Use of Bacteriophages in the Poultry Industry, Animals (Basel), vol 10, no 5, (May 2020).

313 See: Mengting Guo et al., Bacteriophage Cocktails Protect Dairy Cows Against Mastitis Caused By Drug Resistant Escherichia coli Infection, Front. Cell. Infect. Microbiology, (June 2021);

314 Rosa Loponte et al., Phage Therapy in Veterinary Medicine, Antibiotics, vol 10, (April 2021); Seo, B.J et al., Evaluation of the broad-spectrum lytic capability of bacteriophage cocktails against various Salmonella serovars and their effects on weaned pigs infected with Salmonella Typhimurium, Journal of Veterinary Medical Science, vol 80, (2018).

315 See for example: Justyna D. Kowalska et al., Growing Trend of Fighting Infections in Aquaculture Environment—Opportunities and Challenges of Phage Therapy, Antibiotics, vol 9, issue 6, (June 2020); Seon Young Park et al., Recent Insights into Aeromonas salmonicida and Its Bacteriophages in Aquaculture: A Comprehensive Review, J. Microbiol. Biotechnol, vol 30, no 10, (October 2020); Yolanda J. Silva et al., Phage Therapy as an Approach to Prevent Vibrio anguillarum Infections in Fish Larvae Production, PLS ONE, (December 2014).

316 See for example: American Society for Microbiology, Phages and Food: Combatting Bacteria From Farm to Fork, (June 2023); Mark Garvey, Bacteriophages and Food Production: Biocontrol and Bio-Preservation Options for Food Safety, Antibiotics, (September 2022); Lorraine Endersen and Aidan Coffey, The use of bacteriophages for food safety, Current Opinion in Food Science, vol 36, (December 2020).

317 Q217.

318 Q218.

5 The Clinical use of phages in the UK

Clinical use of phages in the UK: the current situation

114. Currently, in the UK, only phages that have been produced to GMP standards are allowed to be used for a clinical intervention or as a medicine. As there are no UK GMP manufacturing facilities to produce phages, this means that no domestically produced phages can be used in the UK. In the few instances where they have been used,[319] they have been imported as an unlicensed 'special' medicine,[320] for last resort compassionate cases where other therapies and interventions to address bacterial infections have failed. The MHRA notes that 'specials' are:

> … unlicensed medicinal products for human use which have been specially manufactured or imported to the order of a doctor, dentist, nurse independent prescriber, pharmacist independent prescriber or supplementary prescriber for the treatment of individual patients.[321]

And that:

> An unlicensed medicinal product may only be supplied in order to meet the special needs of an individual patient and should not be supplied where an equivalent licensed medicinal product can meet the special needs of the patient.[322]

115. To be imported, 'specials' must conform to The Human Medicines Regulations 2012, which note that at least 28 days' notice needs to be given before an intended import, with stipulations limiting medicines to no more than 25 single treatments, of no more than three months of treatments.[323] However, the majority of the phages that have been imported, mainly from Belgium or the USA, though compliant with the 2012 regulations, have not been produced to GMP standards.[324] We were told that one option could be to arrange a contract with one of the few phage EU GMP facilities to supply a batch of GMP phages.[325] However, we were told that this would cost in the region of £500,000 for one batch of phage to treat between 100 and 200 patients.[326]

319 In the last four years two cystic fibrosis patients at Great Ormond Street Hospital, and ten diabetic foot patients in two Scottish Hospitals received phage therapy. See: Joshua D Jones et al., The future of Clinical phage Therapy in the United Kingdom, Viruses, no 15, (March 2023).

320 Unlicensed 'specials' are unlicensed medicinal products for human use which have been specially manufactured or imported to the order of a doctor, dentist, nurse independent prescriber, pharmacist independent prescriber or supplementary prescriber for the treatment of individual patients. An unlicensed medicinal product may only be supplied in order to meet the special needs of an individual patient and should not be supplied where an equivalent licensed medicinal product can meet the special needs of the patient.

321 MHRA, The supply of unlicensed medicinal products ("specials"): MHRA Guidance Note 14, (2023), p 4.

322 As above, p 6.

323 See Schedule 4 of The Human Medicines Regulations 2012.

324 Dr Josh Jones Q57. The EU allows the use of non-GMP phages within Member states and to be exchanged between Member states for individual compassionate cases. However, it does not permit the export of commercial non-GMP phages.

325 One such company is JAFRAL, based in Slovenia, which produces GMP and non-GMP phages including Escherichia phages, Acinetobacter phages, Pseudomonas phages, Staphylococcus phages and Clostridium phages. Another is MB Pharma, based in the Czech Republic.

326 Dr Josh Jones (Q45 and Q74).

116. We heard that the restrictions on UK-produced phages have created several issues for patients, clinicians and the NHS:

- access to imported phages is erratic, down to the goodwill of individual laboratories and clinicians, and not sustainable in the long run.[327]
- the import of phages which are limited to a maximum of 25 doses of treatments to be used within three months is expensive (see above), as is the costs for patients who may decide to go abroad to access phage treatments.[328]
- the time taken to agree the import of phages (at least 28 days) is delaying their use for patients who are seriously ill.[329]
- the lack of domestically produced phages is inhibiting the development of UK clinical phage expertise and knowledge about phages.[330]
- the lack of UK-produced phages is retarding the development of UK clinical regulation.[331]

117. David Browning and Stephanie Lesage, the CEOs of two UK-based phage SMEs—Fixed Phage Ltd and Oxford Silk Phage Technologies Ltd—both told us that allowing the use of UK-produced non-GMP phages for compassionate use, would increase confidence in private investors that phages are a technology worth investing in.[332]

118. **The current situation whereby in the absence of UK GMP facilities only phages imported from abroad can be used, which may themselves be non-GMP, is irrational and discriminatory. This is a costly approach based on a fragile supply chain, which is denying very ill patients rapid access to a therapy that is allowed in some other jurisdictions. It is also hindering the UK's clinical development and evaluation of phages and holding back the strengthening of expertise across the UK's health system. There is also a knock-on impact on the UK's phage innovators. The greater compassionate use of phages in the UK in cases of last resort would be more likely to give the opportunity to demonstrate their potential, which could encourage more investment in clinical trials and GMP facilities, to drive forward the commercial use of phages in the UK and exports. *We recommend that the Department of Health and Social Care and the Medical and Healthcare products Regulatory Agency 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.***

327 Dr Josh Jones (Q42–43). See also: DEPARTMENT OF HEALTH AND SOCIAL CARE (DHSC), UK HEALTH SECURITY AGENCY (UKHSA), MEDICENES AND HEALTHCARE PRODUCTS REGULATORY AGENCY (MHRA) (PHA0007).

328 Mrs Abigail Halstead (PHA0022). Mrs Halstead is a cystic fibrosis (CF) patient with a chronic lung infection which she is seeking to eradicate with phage therapy. She noted that travelling to the US for treatment would involve "a huge expense … complicated from an insurance perspective". See also: Antibiotic Research UK (PHA0020).

329 PHAGE UK (PHA0013)

330 Dr Jean-Paul Pirnay, Head of the Laboratory of Molecular and Cellular Technology, Queen Astrid Military Hospital, Brussels (124); Oxford Silk Phage Technologies Ltd (OSPT) (PHA0035). See also: Joshua D Jones et al., The future of Clinical phage Therapy in the United Kingdom, Viruses, no 15, (March 2023).

331 Oxford Silk Phage Technologies Ltd (OSPT) (PHA0035).

332 Q109.

The clinical use of non-GMP phages in compassionate use cases

119. As noted, most witnesses we heard from agreed that the ideal end point should be the production of GMP standard phages. However, most witnesses thought that in lieu of this, consideration should be given to the use of non-GMP UK produced phages in qualifying cases.[333] The evidence we took pointed to a wide range of countries that allow the use of non-GMP phages in such cases and that lessons could be learnt from practice in these countries.[334]

Use of non-GMP clinical phages in Belgium

120. Dr Jean-Paul Pirnay told us that in Belgium a 'magistral approach is used' whereby phages are produced to a three-page monograph which "describes how to produce a phage and to perform quality control", which were less stringent than GMP but signed off by a clinician.[335] This approach is set out in the box below.

333 See: University of Nottingham (PHA0039); University of Nottingham (PHA0039); PROFESSOR JOHNATHAN IREDELL et al. (PHA0008); PHAGE UK (PHA0013); MICROBIOLOGY SOCIETY (PHA0015);

334 Centre for Phage Research at the University of Leicester (PHA0027); Professor Jo Santini (Q20). See also: University of Nottingham (PHA0039); MICROBIOLOGY SOCIETY (PHA0015); Antibiotic Research UK (PHA0020); Centre for Phage Research at the University of Leicester (PHA0027).

335 Q117. For an overview of the magistral approach see: Jean-Paul Pirnay, The Magistral Phage, Viruses, vol 10, no 2, (February 2018); Gilbert Verbeken and Jean-Paul, European regulatory aspects of phage therapy: magistral phage preparations, Current Opinion in Virology, vol 52, (February 2022).

Box 4: The Belgian Magistral Monograph

A 'magistral' preparation is defined within the European Union as "any medicinal product prepared in a pharmacy in accordance with a medical prescription for an individual patient". It must meet several conditions. First, the medicinal product needs to be prepared in a pharmacy. Second, it needs to be prepared in accordance with a medical prescription. Thirdly, the prescription needs to be for an individual patient. Finally, the medicinal product must be supplied directly by the pharmacy to the patients being treated.[336] This will allow pharmacies to prepare limited stocks of products in advance of receipt of a prescription for an individual patient.[337]

The monograph used in Belgium is a three-page document which a pharmacist must follow to evidence how the phage(s) were produced. It sets out the quality of the phage active pharmaceutical ingredient (API) to be used for the preparation of the medicinal product. Every stock of the phage therapy medicinal product is then tested by a Belgian approved laboratory to confirm the phage(s) comply with the phage API monograph(s), issuing a certificate of analysis that approves its use. A pharmacist then uses the certified phage stock for preparing a customized medicinal product based on the prescription of a physician.[338]

More specifically, the monograph states what ingredients are included (phage and non-phage), what equipment was used, how quality was ensured, and contamination avoided, and what tests were carried out. The approved laboratory identifies the quantity of phages and bacteria present (bioburden),[339] bacterial endotoxin levels, pH and, where relevant, water content and residual chloroform of phage. The monograph also stipulates how the phage should be stored, its shelf life and how it should be labelled.[340]

The final part of the process is where one or more phages are selected and mixed (e.g. a phage cocktail) with a carrier, such as a hydrogel.[341]

121. Dr Pirnay told us that this is a pragmatic approach adapted to phages and their specificity for individual patients.[342] He stated that this is funded free for patients at the point of delivery by the Belgian state. He estimated that the phages themselves, including quality control, cost about €50, with extra costs for treatment and consultations.[343] He also told us that the use of non-GMP phages allowed lessons to be learnt on why phage therapies work sometimes but not others, whilst tracking issues such as phage synergies with antibiotics, bacterial resistance to phages and their impact on immune systems of patients.[344]

336 This approach was set out by Article 3(1) of the Medicines Directive 2001/83/EC, and a subsequent ruling of the European Court of Justice in 2015 (Joined Cases C – 544/13 and C – 545/13 Abcur). For an overview see: H PA Scheepers et al., Legislation on the preparation of medicinal products in European pharmacies and the Council of Europe Resolution, Eur J Hosp Pharm, vol 24, no 4, (July 2017).

337 Covington, EU Pharma Legislation Review Series: Pharmacy and Hospital Exemptions, (April 2023).

338 Diana P Pires et al., Current challenges and future opportunities of phage therapy, FEMS Microbiology Reviews, vol 44, issue 6, (November 2020), pp 884–700.

339 See: Tim Sandle, Bioburden determination, Pharmaceutical Microbiology, (2016), pp 81–91.

340 See: GENERAL MONOGRAPH – VERSION 1.0 Phage active pharmaceutical ingredients and Phage Directory, Belgium's new brand of phage therapy, issue 8, (December 2018).

341 See: Phage Directory, Belgium's new brand of phage therapy, issue 8, (December 2018).

342 Q118.

343 Q115 and Q128.

344 Q124.

122. The Belgian magistral approach to phages is being considered by the European Pharmacopoeia (EP).[345] The EP is a source of official quality standards for medicines and their ingredients, and seeks to harmonise national laws on the manufacture, circulation and distribution of medicines in Europe. It was established by the Council of Europe, and the EU and the UK are signatories.[346] The EU requires all manufacturers of medicines or substances for pharmaceutical use to apply the EP quality standards in order to be able to market and use these products in Europe.[347]

Use of non-GMP clinical phages in France

123. In France, phages are used under a similar magistral-type preparation, mainly provided by a private company—Pherecydes Pharma—to a hospital pharmacist for finalisation of a cocktail, under the supervision of the national authority, the National Agency for the Safety of Medicines and Health Products (ANSM).[348] The ANSM validates the use of phages through a committee of experts on the appropriateness of the use of phages in treating an infection.[349] Professor Tristan Ferry, Infectious Disease Physician and Professor of Medicine, Lyon University Hospital, stated that in addition to those provided by Pherecydes Pharma, phages are also acquired from the Queen Astrid military hospital in Brussels. He added that these phages, which were non-GMP but produced using the magistral approach (see above), are trained for individual patients, with 53 patients being treated in his hospital, 35 of which had prosthetic limb infections.[350]

Use of non-GMP clinical phages in the USA

124. Non-GMP Phages in the US are allowed under the FDA's Emergency Investigational New Drug (eIND) pathway, which allows access to non-approved drugs or biological products.[351] This is on the basis that a physician has determined that the product may be urgently needed for the patient's serious or life-threatening condition, no satisfactory alternative therapy is available, and the patient cannot receive the product through any existing clinical trials or expanded access protocols.[352] Professor Robert Schooley told us that in the USA, the FDA deem phages as "safe" and was "probably one of the greater facilitators of making it possible to get phages to patients".[353] He said that this had also been achieved by frequent interactions with Government. This had resulted in a pre-regulatory approval situation, where non-GMP phages are permitted in compassionate cases, with patients not charged.[354] Phages are provided by academic laboratories funded by various sources. He noted that if the phages are already accessible, phage therapy could

345 See: Council of Europe, Public consultation on new general chapter on phage therapy active substances and medicinal products for human and veterinary use in Pharmeuropa 35.2, (4 April 2023).
346 EUR-Lex, European Pharmacopoeia, (accessed 6 July 2023).
347 European Union Directive 2001/82/EC and Directive 2001/83/EC (as amended) state the legally binding character of European Pharmacopoeia texts for Marketing Authorisation Applications (MAA). All manufacturers of medicines or substances for pharmaceutical use therefore must apply the European Pharmacopoeia quality standards in order to be able to market and use these products in Europe.
348 Oxford Silk Phage Technologies Ltd (OSPT) (PHA0035). See: https://ansm.sante.fr/.
349 Charlotte Brives and Jessica Pourraz, Phage therapy as a potential solution in the fight against AMR: obstacles and possible futures, Palgrave Communications, vol 6, (May 2020).
350 Professor Tristan Ferry, Infectious Disease Physician and Professor of Medicine, Lyon University Hospital (PHA0036).
351 Alan Fauconnier, Phage Therapy Regulation: From Night to Dawn, Viruses, vol 11, no 4, (April 2019).
352 FDA, Emergency Investigational New Drug (EIND) Applications for Antiviral Products, (March 2020).
353 Q151.
354 Q141.

be delivered within two to four days. If a phage is not readily accessible, it could take weeks or months to match and find the right one. He recommended that hospitals need easy access to large phage libraries, and the ability to engineer phages would speed up the process.[355]

Use of non-GMP clinical phages in Australia

125. Professor Iredell, said that in Australia, non-GMP phages were also used in compassionate cases, often intravenously.[356] Phage treatments are allowed through the Clinical Trial Approval (CTA) scheme for an unapproved therapeutic,[357] if enrolled as a trial under the Australian Standardised Treatment and Monitoring Protocol for Adults and Paediatric Patients (STAMP).[358] Patients qualify to receive treatment under the special access scheme (compassionate access) where an infectious disease specialist has certified that all other treatment strategies have been attempted.[359] He suggested that public health systems could horizon scan to predict the most likely bacterial pathogens which could encourage phage production and a pathway to GMP production. In addition, he thought that types of infections might also be more predictable, such as prosthetic device infections, which might also encourage industry investment.[360]

Use of non-GMP clinical phages in Poland

126. The evidence we received also pointed to a similar approach in Poland, which follows Belgium's magistral approach whereby phage therapy is considered an 'experimental treatment' under Polish law.[361] In 2005, the Phage Therapy Unit (PTU) at the Hirszfeld Institute of Immunology and Experimental Therapy in Poland was established and is internationally recognised as an advanced phage therapy centre. Phage cocktails are selected from phage biobanks at institutes such as the PTU for individual patients under the care of a qualified physician.[362] Phages are agreed by a Bioethics Commission, when other available treatments have failed.[363] Over 700 patients have been treated at the PTU since 2005,[364] and we heard that such treatments had been successful.[365]

355 Q141 and Q148.
356 Q149.
357 Australian Department of Health and Aged Care, Clinical trials, (accessed 22 June 2023).
358 See: UKRI (PHA0041). See also: Ameneh Khatami et al., Standardised treatment and monitoring protocol to assess safety and tolerability of bacteriophage therapy for adult and paediatric patients (STAMP study): protocol for an open-label, single-arm trial, BMJ Open, vol 12, iss 12, (2022).
359 Professor Jonathan Iredell (Senior Staff Specialist Infectious Diseases and Microbiology; Professor Medicine and Microbiology; Director Phage Australia at Westmead Hospital and Western Sydney Local Health District; University of Sydney) et al. (PHA0008).
360 Q150 and Q151.
361 MICROBILOGY INTERNATIONAL (PHA0010); University of Nottingham (PHA0039); PHAGE UK (PHA0013); Dr Shan Goh et al. (PHA0028). See also: Andrzej Górski et al., Thorough Synthesis of Phage Therapy Unit Activity in Poland-Its History, Milestones and International Recognition, Viruses, vol 14, no 6, (May 2022); Maciej Żaczek et al., Phage Therapy in Poland – a Centennial Journey to the First Ethically Approved Treatment Facility in Europe, Frontiers in Microbiology, vol 11, (June 2020).
362 University of Nottingham (PHA0039); PHAGE UK (PHA0013;
363 MICROBIOLOGY SOCIETY (PHA0015). See also: Maciej Żaczek et al., Phage Therapy in Poland – a Centennial Journey to the First Ethically Approved Treatment Facility in Europe, Frontiers in Microbiology, vol 11, (June 2020).
364 Maciej Żaczek et al., Phage Therapy in Poland – a Centennial Journey to the First Ethically Approved Treatment Facility in Europe, Frontiers in Microbiology, vol 11, (June 2020).
365 SIMON JONES (PHA0005)

How are unlicensed medicines governed in the UK?

127. There are several sources for guidance on the preparation and use of unlicensed specials for individual patients within the UK, which could be adapted and aligned with the 'magistral' monograph used by other countries. For instance, the General Pharmaceutical Council produces guidance for pharmacies preparing unlicensed specials including risk assessments, regular audits, reactive reviews, recall procedures and record keeping.[366] The General Medical Council also issues guidance on prescribing specials.[367] Within hospitals, Drug and Therapeutics Committees are responsible for approving, monitoring and appraising all unlicensed medicines. Such committees 'risk assess' that their use is justified, informed by the 'clinical information' provided by the requesting clinician and the hospital's Quality Controller who assesses the risks associated with the special.[368]

128. **We believe that the UK should allow the compassionate use of non-GMP phages produced in the UK for last resort medical cases where other medical approaches have failed or are failing. This would bring the UK in line with several EU countries, and the USA and Australia. The UK can learn from these countries in ensuring that phages are produced to a high standard, albeit not to the exacting standard of GMP. Using monographs, as is the case in Belgium, that stipulate safety and purity standards, would be an ideal starting place. It could build upon existing guidance for the use of unlicensed specials (products that have not been assessed by the regulatory authority for safety, quality and efficacy in the same way as licensed products) within UK clinical settings and oversight procedures within hospitals.**

129. ***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.***

Liability for the use of non-GMP phages

130. The prescribing and dispensing of unlicensed medicines, such as non-GMP phages, comes with additional professional responsibilities for the prescriber and the clinician, and hospital using them. Without a marketing authorisation (MA) gained through GMP, there is no MA holder to take responsibility for any adverse reactions associated with the medicine's use and this means any liability rests with the prescriber.[369] The MHRA notes that the prescriber's responsibility and potential liability are increased when prescribing

366 General Pharmaceutical Council, Guidance for registered pharmacies preparing unlicensed medicines, (August 2018).

367 GMC, Prescribing unlicensed medicines, (April 2021).

368 Portsmouth Hospitals University Trust,UNLICENSED MEDICINAL PRODUCTS POLICY, (May 2022).

369 Antibiotic Research UK (PHA0020). See also: Gemma Donovan et al., Special unlicensed medicines: what we do and do not know about them, British Journal of General Practice, vol 65, (December 2015).

unlicensed medical products.[370] Several contributors to our inquiry noted that this might be an obstacle to the use of non-GMP phages.[371] Dr Josh Jones told us that liability issues around the use of non-GMP phages would have to be addressed to reassure hospitals and clinicians they would not be unduly liable.[372]

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.***

Phages as a precision medicine

132. The US Food and Drugs Administration (FDA) defines precision medicine as "an innovative approach to tailoring disease prevention and treatment that takes into account differences in people's genes, environments, and lifestyles" with the aim of "targeting the right treatments to the right patients at the right time".[373] Because the clinical use of phages involves their matching and tailoring to individuals and the pathogens that they have been affected by, they have been seen by many as lending themselves to a precision medicine approach.[374] In addition, their ability to eliminate target pathogenic bacteria without adversely affecting the microbiota,[375] has been seen as "perfectly in accord with the philosophy of precision medicine".[376] Much of the evidence we took supported this view.[377] Dr Jean-Paul Pirnay and Dr Schooley both told us that their clinical approaches are both in accordance with a precision or personalised approach.[378]

133. A precision medicine approach could also move beyond compassionate use cases if phages could be produced to GMP standards or if regulations were adapted to take into account their peculiarities. It could allow a mix of generic off-the-shelf phages for common bacterial pathogens to treat and prevent infections whilst allowing the administration of non-generic and modified phages for more difficult-to-treat infections bespoke for individual patients.[379] Dr Mzia Kutateladze, Director, George Eliava Institute of Bacteriophage, Microbiology and Virology, for example, told us that this dual approach to treating common and more rare bacterial infections is successfully used by her Institute.[380]

370 MHRA, The supply of unlicensed medicinal products ("specials"): MHRA Guidance Note 14, (2023), p 21.
371 Antibiotic Research UK (PHA0020) and PHAGE UK (PHA0013).
372 Q45.
373 FDA, Precision Medicine, (accessed 27 June 2023).
374 See: Belinda Loh and Sebastian Lepihn, A Call For a Multidisciplinary Future of Phage Therapy to Combat Multi-drug Resistant Bacterial Infections, Infectious Microbes & Diseases, vol 2, no 1, (March 2020). See also: Dr Jason Clark, Chief Scientific Officer, Fixed Phage Ltd (PHA0038); Ms Stephanie Lesage, CEO, Oxford Silk Phage Technologies Ltd (PHA0043); Fixed Phage LTD (PHA0033); Adaptive Phage Therapeutics Inc (PHA0023).
375 'Microbiota' are the range of microorganisms that stimulate the immune system, break down potentially toxic food compounds, and synthesize certain vitamins and amino acids. See: Harvard TH Chan Public School of Health, The Nutrition Source: The Microbiome, (accessed 20 July 2023).
376 Andrzej Górski et al., Phage Therapy: Towards a Successful Clinical Trial, Antibiotics Basel, vol 9, no 11, (November 2020).
377 MICROBIOLOGY SOCIETY (PHA0015); UKRI (PHA0041); Phage Research Centre, Leicester (PHA0046); CPI (INS0047); PHAGE UK (PHA0013); UK PHAGE THERAPY (PHA0017); Dr Shan Goh et al (PHA0028); Bangor University School of Natural Sciences (PHA0029); CF Syndicate in AMR (PHA0030).
378 Q133 and Q147.
379 University of Nottingham (PHA0039). See also: Joshua D Jones et al., The Future of Clinical Phage Therapy in the United Kingdom, Viruses, no 15, (March 2023).
380 Q123.

Professor Robert Schooley, Professor of Division of Infectious Diseases at UC San Diego School of Medicine, also supported this approach, arguing that it would be possible to develop a cocktail from prepared phages that could hit a wide spectrum of pathogens, whilst engineering phages for those that needed personalised treatment.[381]

Delivering phages as a precision medicine in the UK

134. However, we were told that for phage precision medicine to work it will need infrastructure, expertise and regulatory certainty.[382] David Browning, Chief Executive Officer, Fixed Phage Ltd, and others noted that it would need access to big phage libraries from which genetically sequenced phages could be drawn to be used in cocktails, with AI and diagnostic technology being used to quickly match libraries with individual patients.[383] Dr Jean-Paul Pirnay, also suggested that the development and use of AI and synthetic biology-based technology could be used to synthetise phages at treatment sites.[384] This approach could, if successful, speed up diagnostics to identify bacterial pathogens within 1–2 days before matching them to appropriate phages held in biobanks and allowing NHS microbiology departments to tailor them to individual patients at pace.[385]

135. Some of the infrastructure needed to deliver this is already taking shape in the UK. For example, the Centre for Phage Research at the University of Leicester is planning to host a phage biobank.[386]Institutions, such as University College London (UCL), are developing facilities to modify phages or extract their enzymes that could contribute to a personalised approach.[387] Phage research expertise is also spread across the UK, including major centres at the University of Exeter, the University of Nottingham, the London School of Hygiene and Tropical Medicine and St George's University of London. The relationship between UCL and Great Ormond Street Hospital, who are using phages, also indicates that different parts of the UK's phage network can be linked up.

136. In addition, Dr Josh Jones, the UK's first NHS phage specialist, based at NHS Tayside with a phage laboratory,[388] has indicated how phages can be successfully used in the NHS, with phages reducing bacterial infection in patients, for example in cases of diabetic toe and after artificial hip replacements.[389] However, Dr Jones told us that funding for his

381 Q141 and Q147. See also: Antibiotic Research UK (PHA0020). The latter noted that phages could be used earlier in treating infections related to prosthetic joint infections and diabetic feet, particularly when it was known that antibiotics might be more vulnerable to AMR and where phages could re-sensitise a bacterial pathogen.

382 University of Nottingham (PHA0039); Bangor University School of Natural Sciences (PHA0029).

383 Q96. See also Adaptive Phage Therapeutics Inc (PHA0023); University of Nottingham (PHA0039).

384 Jean-Paul Pirnay, Head of the Laboratory of Molecular and Cellular Technology at Queen Astrid Military Hospital, Brussels (PHA0044). See also: Jean-Paul Pirnay, Phage Therapy in the Year 2035, vol 3, no 11, (June 2020).

385 Joshua D Jones et al., The Future of Clinical Phage Therapy in the United Kingdom, Viruses, no 15, (March 2023).

386 University of Leicester, University launches pioneering new centre to study bacteriophages to combat antibiotic resistant bacteria, (16 May 2023).

387 Professor Joanne M Santini, Professor of Microbiology, University College London (Q24).

388 Healthcare Improvement Scotland and SHTG, Bacteriophage therapy for patients with difficult to treat bacterial infections, (February 2023).

389 Matthew J. Young, MD et al., Phage Therapy for Diabetic Foot Infection: A Case Series, Clinical Therapeutics, (11 July 2023).
NHS Tayside, Virus used to treat joint infection in UK-first at Ninewells Hospital, (3 July 2023); BBC News, Hopes phage therapy can offer patient lifeline, (7 July 2023).

position only extends to the end of this year, 2023.[390] Several UK SMEs, such as Fixed Phage Ltd, are also developing phage kits and other technologies, so each hospital will be able to put together required phage combinations at speed to a high level of purity on site.[391]

137. However, we heard that there are a number of gaps that will need to be addressed if the UK is to drive forward a more comprehensive personalised phage offer. In addition to the now familiar problem of the absence of GMP production facilities to produce licensed phages for generic therapies and credible phage biobanks, these gaps included:

- the lack of a long-term pipeline of NHS clinical and laboratory expertise to develop phage therapies;[392]
- a need to invest in AI-based genomic sequencing to quickly detect bacterial pathogens and match them to applicable phages;[393]
- a requirement for stable and accessible storage facilities for phages, which need to be stored at between -80°C and 4°C, or freeze dried;[394] and
- a need for phage transportation infrastructure to move phages safely between biobanks, phage centres, microbiology laboratories and hospitals;[395]

138. Professor Isabel Oliver, Scientific Officer, UK Health Security Agency, agreed that there is a "need for targeted funding for phage infrastructure".[396] Dr Morwenna Carrington, Deputy Director for UK Health Security, DHSC, told us that although her Department had no plans to invest in phage biobanks, she agreed with others that they would be "a useful part of the toolbox to facilitate bringing bacteriophages forward".[397] However, Dr Jonathan Pearce, Director of Strategy and Planning at Medical Research Council (MRC), did state that the MRC would look at applications to "provide funding for biobanking and other features".[398]

139. A number of contributors told us that phage infrastructure in other countries depended on varying degrees of both government and private sector funding, such as in the US,[399] Israel,[400] Georgia,[401] Belgium,[402] and Norway[403]. UKRI noted that there were opportunities to develop phages in the UK and make it a "global hub for research, development, and innovation in the phage sector" if GMP manufacturing capacity and biobanks of well-characterised phages were established. It argued that this would benefit from the "communication of a clear, supportive stance on the development and adoption

390 Q39.
391 Mr David Browning, Chief Executive Officer, Fixed Phage Ltd (Q 99).
392 CF Syndicate in AMR (PHA0030); University College London (PHA0034); Fixed Phage Ltd (PHA0038).
393 Mr David Browning, Chief Executive Officer, Fixed Phage Ltd (Q 96); Stephanie Lesage, Co-Founder/Director and Chief Executive Officer, Oxford Silk Phage Technologies Ltd (Q97).
394 Fixed Phage LTD (PHA0033); Department of Health and Social Care (DHSC), UK Health Security Agency (UKHSA), and Medicines and Healthcare products Regulatory Agency (MHRA) (PHA0007).
395 Centre for Phage Research at the University of Leicester (PHA0027).
396 Q229.
397 Q243. See also: UKRI (PHA0041).
398 Q209.
399 Greg Merril (Chief Operating Officer at Adaptive Phage Therapeutics), Dr Hans Petter Kleppen (Chief Science Officer at ACD Pharma) (Q155 and Q157).
400 Naomi Zak (Founder at BiomX) (Q164).
401 Dr Mzia Kutateladze, Director, George Eliava Institute of Bacteriophage, Microbiology and Virology (Q127).
402 Dr Jean-Paul Pirnay, Head of the Laboratory of Molecular and Cellular Technology, Queen Astrid Military Hospital, Brussels (Q129).
403 Dr Hans Petter Kleppen (Chief Science Officer at ACD Pharma) (Q174).

of phage-based technologies in the UK from the UK government".[404] Richard Hebdon, Director, Health and Life Sciences, Innovate UK, noted that Innovate UK's Phage Knowledge Transfer Network is currently reviewing the UK's phage landscape, including key assets, and its strengths and weaknesses.

140. **If the antimicrobial use of phages is to move beyond ad hoc compassionate cases, the Government and its agencies should reflect on what role they are to play in the fight against AMR. At the moment, phages are referred to in the AMR strategy, as one approach amongst others. However, we believe that the Government and its agencies should make a more definitive and positive statement on phages. Clarity is imperative for research funding decisions and for private investment in commercial phages.**

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.***

404 UKRI (PHA0041).

Conclusions and recommendations

Safety, Efficacy, and the UK's phage research base

1. The safety of phages has been well established mainly on the basis of observational evidence drawn from specific clinical interventions. However, as with all medicines, robust clinical trial data is important to provide and develop assurances around all aspects of patient safety, including the long-term impact of phages, especially their interaction with human immune systems, such as anaphylaxis and auto immune response. (Paragraph 39)

2. Clinical data indicates that in many cases phages have been observed to reduce bacterial infections in patients. We also heard that their use in animals has also been shown to be effective. However, further clinical trials are required to prove the consistent effectiveness of phages. Such studies need to include analysis of the impact of different phage cocktails as well as phage/antibiotic combinations. (Paragraph 40)

3. *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.* (Paragraph 41)

4. Phages have been used as therapy for over a hundred years, and much of the fundamental science relating to phages is understood. However, there is still more that the global and UK research communities can learn. Further research will be able to establish key issues such as long-term interactions between phages and human hosts and how phages can be engineered to maximum effect, to work alone or in combination with antibiotics. Such research will help hone phage therapeutics and clinical practice. The UK is well placed to conduct this research as it has a number of leading phage research centres and academics, and access to world class genomic sequencing and bioinformatic resources and experts. (Paragraph 48)

5. However, the apparent reticence of funders to commit to phages is despite a general acceptance in the evidence we took that phages show promise and need more research alongside clinical trials. It is important to understand and reflect on the reasons for this. The recently established Innovate UK Phage Knowledge Transfer Network may provide such a forum for funders and phage researchers to discuss these matters. (Paragraph 49)

6. *Because phages have had relatively limited recent research funding from public sources, 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. Without proper support, the full potential of phages will not be realised within the Government's AMR strategy. (Paragraph 50)

7. We were disappointed to hear that there is a translational phage research "gap" in the UK. We agree that funding, and especially public funding, should be awarded with care. However, we are concerned that, despite being included in the Government's AMR strategy, if not properly supported, the potential of phages to deliver therapeutics and commercial outputs will remain untested and untapped. There is a particular danger that translational phage research will be trapped in an impasse where it will miss out on research funding because it has not been able to prove its credibility, because of a lack of previous funding. (Paragraph 56)

8. *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.* (Paragraph 57)

9. The Government, the World Health Organisation and a number of the witnesses we heard from have highlighted the importance of a "One Health" approach to tackling AMR across sectors including human and animal health, the food supply chain, and the environment. The Department of Health and Social Care (DHSC) and others told us that phages could play an important role in delivering this approach. However, the DHSC acknowledged that they were at an early stage of tracking progress on phages. We believe it is important that—if phages are to play a meaningful part in a 'One Health' approach to tackling AMR—progress is reported in a timely and comprehensive manner. *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.* (Paragraph 63)

10. For the potential benefits of phages to be fully explored and, if possible, exploited in the UK, with competitive advantage, it is important that existing phage-related assets are properly aligned and integrated, connecting the various sectors, institutions, and actors so they can draw on shared resources, information, data, and expertise. This will also allow the development of additional shared assets, such as phage biobanks, as well as encouraging new relationships between universities, hospitals, the pharmaceutical industry, and other stakeholders. We were concerned to hear that the UK's phage expertise and resources are 'fragmented'. We therefore welcome Innovate UK's Phage knowledge transfer initiative to bring phage stakeholders together to produce a roadmap to deliver a sustainable and integrated network for the transfer and sharing of phage-related knowledge for the benefit of all. (Paragraph 67)

11. *We recommend that the Department for Health and Social Care responds to the UK's Phage Knowledge Transfer Network's proposals within six 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.* (Paragraph 68)

12. If phages are to be used more widely within the UK's healthcare system it is important that healthcare professionals are aware that they are an antimicrobial alternative, especially when antibiotics have failed or are failing. *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.* (Paragraph 70)

13. The public will need to be convinced that phages are safe and effective. This will be key if phages are to play a role in addressing AMR in healthcare and as part of a One Health approach to addressing AMR across various sectors, such as the food industry and the environment. Careful and transparent promotion of phages' antimicrobial ability to reduce or eradicate bacterial pathogens and re-weaponise antibiotics, would help make their use more acceptable. (Paragraph 72)

Manufacturing phages

14. The set of consensus high standards for pharmaceutical production, known as Good Manufacturing Practice (GMP), should continue to be required in the UK for high quality phages manufactured for generic products targeting the most common bacterial pathogens. It should also underpin the production of phage biobanks to be accessed at short notice by clinicians providing assurance to both clinicians and patients that phages from biobanks will be of the highest standard of safety and purity. Access to phages manufactured to GMP standards will also allow microbiology laboratories to deal with less common pathogens and tailor phages to be more effective for individual patients when a more agile precision medicine approach is required. However, there may still be a place for non-GMP phages in instances when non-banked phages are needed at short notice for compassionate use as a last resort and can be produced via collaboration between a physician and pharmacist—as in Belgium. (Paragraph 78)

15. One of the main obstacles to establishing Good Manufacturing Practice (GMP) facilities in the UK is the cost and the reluctance of pharmaceutical firms to invest in phages and antimicrobials more generally because of an uncertain return on investment compared to other medicines and drugs. However, investing in a small, or shared multi-use, GMP facility is one possible solution to ensure that such capacity could be run cost effectively. The allocation of public funds to establish a GMP facility could be offset by savings delivered to the NHS, by avoiding wasted antibiotics and unnecessary surgery resulting from AMR. Such a facility could also supply phages to non-health sectors which could be used to cross-subsidise healthcare phages. (Paragraph 83)

16. *We recommend that the Department for Health and Social Care 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. (Paragraph 84)

17. *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.* (Paragraph 86)

18. For phages to be effective they will need to keep pace with bacterial resistance and be amenable to adaptation for individual patients. Genetically engineered (GE) phages may be one way of ensuring this. GE phages have already been used in the UK and elsewhere. However, if they are to be produced commercially, GE phages will need to be aligned with GMP. *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.* (Paragraph 88)

19. If the UK government supports the commercial production of genetically engineered (GE) phages, it will inevitably lead to regulatory divergence from the EU. However, we believe this divergence offers the UK an opportunity that should be pursued. This should be part of a clear regulatory and safety licensing regime for phages, if phages are to be exploited for competitive advantage. (Paragraph 90)

20. We welcome the willingness of the MHRA to adopt a flexible approach to accelerating the authorisation of the use of phage therapies and its offer to work with phage innovators to support their development. However, the MHRA should provide clarity on how different pathways for developing phages, such as the Innovative Licensing and Access Pathway, and other flexible regulatory approaches will work in practice and how they will align with GMP and non-GMP phage for compassionate use in last resort cases. *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.* (Paragraph 94)

Phage clinical trials

21. Our evidence suggests that current regulations for clinical trials and the manufacturing of medicines are unlikely to be effective for phages as they are for other drugs or antibiotics. This is because the current regulatory approach to testing and manufacturing medicines is based on a single consistent formulation being shown to have a demonstrable effect. This does not accord with the optimal use of phages which require considerable flexibility in terms of the specificity required for

individual patients. There are a number of different medical scenarios where the current regulations will struggle to cope with this need for specificity that mitigates against generic testing. These include:

- the requirement for individual phage strains that are specific to the species and even strain genotype of the bacteria they seek to inhibit, which could be almost limitless and impossible to test in advance;
- the need for multiple unique formulations of phages, often in conjunction with antibiotics and other drugs, to target infections in individual patients with specific microbiota, which might not be anticipated in traditional clinical trials;
- in the future, pre-tested generic phages that have met regulatory standards may not be able to inhibit bacterial growth, necessitating adaptation which may be beyond inflexible regulations;
- 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 significant clinical data if each use is unique;
- 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. (Paragraph 100)

22. *The MHRA should set out how they propose to regulate and ensure clinical safety for each of the scenarios set out above. 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.* (Paragraph 101)

23. *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.* (Paragraph 102)

24. One of the major obstacles to phage clinical trials in the UK has been the requirement for GMP phages. However, regulators require that for phages to achieve GMP standards they must themselves have first been subject to clinical trials. This impasse is stalling the development of phages in the UK. The Department of Health and Social Care should consider investing in a small GMP facility which would solve one part of the problem. However, it would not solve the issue of UK GMP requiring clinical trials that in themselves had to use GMP phages. Clarity is needed on how this conundrum can be solved. (Paragraph 105)

25. *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 six months of the publication of this report.* (Paragraph 106)

26. The funding of clinical trials, especially later trials, has proved an obstacle for phages. We were pleased to hear that the National Institute for Health and Care Research would welcome applications from phage researchers and companies to access public funding to conduct clinical trials. *We recommend that 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 Medicines and Healthcare Products Regulatory Agency offers tailored support for phage applications for clinical trials.* (Paragraph 110)

27. We are pleased that the MHRA is open to using phage data from a variety of sources as long as it is of sufficient quality. *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.* (Paragraph 113)

The Clinical use of phages in the UK

28. The current situation whereby in the absence of UK GMP facilities only phages imported from abroad can be used, which may themselves be non-GMP, is irrational and discriminatory. This is a costly approach based on a fragile supply chain, which is denying very ill patients rapid access to a therapy that is allowed in some other jurisdictions. It is also hindering the UK's clinical development and evaluation of phages and holding back the strengthening of expertise across the UK's health system. There is also a knock-on impact on the UK's phage innovators. The greater compassionate use of phages in the UK in cases of last resort would be more likely to give the opportunity to demonstrate their potential, which could encourage more investment in clinical trials and GMP facilities, to drive forward the commercial use of phages in the UK and exports. *We recommend that the Department of Health and Social Care and the Medical and Healthcare products Regulatory Agency 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.* (Paragraph 118)

29. We believe that the UK should allow the compassionate use of non-GMP phages produced in the UK for last resort medical cases where other medical approaches have failed or are failing. This would bring the UK in line with several EU countries, and the USA and Australia. The UK can learn from these countries in ensuring that phages are produced to a high standard, albeit not to the exacting standard of GMP. Using monographs, as is the case in Belgium, that stipulate safety and purity standards, would be an ideal starting place. It could build upon existing guidance for the use of unlicensed specials (products that have not been assessed by the regulatory authority for safety, quality and efficacy in the same way as licensed products) within UK clinical settings and oversight procedures within hospitals. (Paragraph 128)

30. *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.* (Paragraph 129)

31. *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.* (Paragraph 131)

32. If the antimicrobial use of phages is to move beyond ad hoc compassionate cases, the Government and its agencies should reflect on what role they are to play in the fight against AMR. At the moment, phages are referred to in the AMR strategy, as one approach amongst others. However, we believe that the Government and its agencies should make a more definitive and positive statement on phages. Clarity is imperative for research funding decisions and for private investment in commercial phages. (Paragraph 140)

33. *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.* (Paragraph 141)

Formal minutes

Wednesday 22 November July 2023

Greg Clark, in the Chair

Dawn Butler

Tracey Crouch

Katherine Fletcher

Stephen Metcalfe

Carol Monaghan

Draft Report (*The antimicrobial potential of bacteriophages*), proposed by the Chair, brought up and read.

Ordered, That the draft Report be read a second time, paragraph by paragraph.

Paragraphs 1 to 141 read and agreed to.

Summary agreed to.

Resolved, That the Report be the First Report of the Committee to the House.

Ordered, That the Chair make the Report to the House.

Ordered, That embargoed copies of the Report be made available, in accordance with the provisions of Standing Order No. 134.

Adjournment

Adjourned till Wednesday 29 November 2023 at 9.20am.

Witnesses

The following witnesses gave evidence. Transcripts can be viewed on the inquiry publications page of the Committee's website.

Wednesday 08 February 2023

Professor Martha Clokie, Professor of Microbiology, University of Leicester; **Professor Cath Rees**, Professor of Microbiology, University of Nottingham; **Professor Joanne M. Santini**, Professor of Microbiology, University College London Q1–35

Dr James Soothill, Consultant Microbiologist, Great Ormond Street Hospital Laboratory Medicine; **Dr Josh Jones**, Clinical Phage Specialist, NHS Tayside Q36–75

Ms Stephanie Lesage, Co-Founder/Director and Chief Executive Officer, Oxford Silk Phage Technologies Ltd; **Mr David Browning**, Chief Executive Officer, Fixed Phage LTD Q76–111

Wednesday 15 March 2023

Dr Jean-Paul Pirnay, Head of the Laboratory of Molecular and Cellular Technology, Queen Astrid Military Hospital, Brussels; **Dr Mzia Kutateladze**, Director, George Eliava Institute of Bacteriophage, Microbiology and Virology Q112–136

Professor Robert Schooley, Professor of Division of Infectious Diseases, UC San Diego School of Medicine; **Professor Jon Iredell**, Director, Centre for Infectious Diseases and Microbiology, The Westmead Institute for Medical Research Q137–154

Greg Merril, Chief Operating Officer, Adaptive Phage Therapeutics; **Dr Hans Petter Kleppen**, Chief Science Officer, ACD Pharma; **Naomi Zak**, Founder, BiomX Q155–181

Wednesday 26 April 2023

Dr Tim Jinks, Head of Infectious Disease Interventions, Wellcome Trust; **Dr Jonathan Pearce**, Director of Strategy and Planning, Medical Research Council; **Richard Hebdon**, Director Health and Life Sciences, Innovate UK Q182–209

Professor Isabel Oliver, Scientific Officer, UK Health Security Agency; **Professor Mark Sutton**, Scientific Leader in Healthcare Biotechnology, UK Health Security Agency; **Dr Marc Bailey**, Chief Science, Research & Innovation Officer, Medicines and Healthcare products Regulatory Agency Q210–229

Dr Morwenna Carrington, Deputy Director for UK Health Security, Department for Health and Social Care Q230–249

Published written evidence

The following written evidence was received and can be viewed on the inquiry publications page of the Committee's website.

PHA numbers are generated by the evidence processing system and so may not be complete.

1 AMR Action Fund (PHA0012)

2 Adaptive Phage Therapeutics, Inc. (PHA0023)

3 Antibiotic Research UK (PHA0020)

4 Applied Microbiology International (PHA0010)

5 Bangor University School of Natural Sciences (PHA0029)

6 CF Syndicate in AMR (PHA0030)

7 CPI (PHA0047)

8 Centre for Phage Research at the University of Leicester (PHA0027, PHA0046)

9 Clark, Jason (Chief Scientific Officer, Fixed Phage LTD) (PHA0038)

10 Department of Health and Social Care (DHSC); UK Health Security Agency (UKHSA); and Medicines and Healthcare products Regulatory Agency (MHRA) (PHA0007)

11 Ferry, Professor Tristan (Professor of Medicine, Hospices Civils de Lyon and Université Claude Bernard Lyon 1) (PHA0037)

12 Fixed Phage LTD (PHA0033)

13 Goh, Dr Shan (Senior Lecturer in Microbiology, University of Hertfordshire); Mullany, Professsor Peter (Professor of Molecular Microbiology, UCL Eastman Dental Institute); Timms, Dr Andy (Lecturer in Biomedical Science, University of Hertfordshire); Gundogdu, Dr Ozan (Assistant Professor, London School of Hygiene & Tropical Medicine); and Baines, Dr Simon (Principal Lecturer in Microbiology, University of Hertfordshire) (PHA0028)

14 Great Ormond Street NHS Trust (PHA0040)

15 Halstead, Mrs Abigail (PHA0022)

16 Hatfull, Professor Graham (Professor, University of Pittsburgh, Pittsburgh PA 15260 USA) (PHA0001)

17 Iredell, Professor Jonathan (Senior Staff Specialist Infectious Diseases and Microbiology; Professor Medicine and Microbiology; Director Phage Australia, Westmead Hospital and Western Sydney Local Health District; University of Sydney); Khatami, Dr Ameneh (Staff Specialist; Senior Lecturer; Deputy Director Phage Australia, Childrens Hospital Westmead; University of Sydney); Lin, Assoc Professor Ruby (Deputy Director Phage Australia, Westmead Institute for Medical Research); Stick, Professor Stephen (Director Wal-Yan Centre and Professor Childrens Respiratory Health, Telethon Kids/ Royal Childrens Hospital Perth; University of Western Australia); Peleg, Professor Anton (Professor and Director, Dept Infectious Diseases, Alfred Hospital and Monash University); Tong, Professor Steven (Staff Specialist Infectious Diseases; Co-Head Translational and Clinical Research, Victorian Infectious Diseases Service; Doherty Institute/ University of Melbourne); and Warner, Dr Morgyn (Acting Director Microbiology; Infectious Diseases physician, Pathology South Australia; Queen Elizabeth and Royal Adelaide Hospitals) (PHA0008)

18 Jones, Dr Josh (Clinical Phage Specialist, NHS Tayside) (PHA0018)

19 Jones, Mr Simon (PHA0005)

20 Knight, Dr Gwen (Associate Professor , London School of Hygiene and Tropical Medicine); and Lindsay, Prof Jodi (Professor, St George's University of London) (PHA0021)

21 Lesage, Ms Stephanie (CEO, Oxford Silk Phage Technologies Ltd) (PHA0043)

22 McCammon, Miss Sophie (Graduate Research Assistant, University of Exeter); Banducci, Professor Susan (Director of Research, University of Exeter); Gold, Doctor Vicki (Senior Lecturer, University of Exeter); and Makarovs, Doctor Kirils (Lecturer, University of Amsterdam) (PHA0006)

23 Microbiology Society (PHA0015)

24 National Physical Laboratory (PHA0014)

25 Oxford Silk Phage Technologies Ltd (PHA0035)

26 Phage-UK (PHA0013)

27 Pirnay, Dr Jean-Paul (Head of the Laboratory of Molecular and Cellular Technology, Queen Astrid Military Hospital, Brussels) (PHA0044)

28 Quadram Institute Bioscience (PHA0004)

29 Roslin Institute, University of Edinburgh (PHA0019)

30 Soothill, Dr James (Consultant Microbiologist, Great Ormond Street Hospital) (PHA0009)

31 UK Phage Therapy (PHA0017, PHA0045)

32 UKRI (PHA0041)

33 University College London (UCL) (PHA0034)

34 University of California of San Diego, Center for Innovative Phage Applications and Therapeutics (PHA0003)

35 University of Nottingham (PHA0039)

36 Virustatic Ltd (PHA0032)

37 Wellcome Trust (PHA0011)

38 Zak, Naomi (Co-Founder, BiomX) (PHA0042)

List of Reports from the Committee during the current Parliament

All publications from the Committee are available on the publications page of the Committee's website.

Session 2023–24

Number	Title	Reference
1st Special	The governance of artificial intelligence: interim report: Government response to the Committee's Ninth report of Session 2022–23	HC 248

Session 2022–23

Number	Title	Reference
1st	Pre-appointment hearing for the Executive Chair of Research England	HC 636
2nd	UK space strategy and UK satellite infrastructure	HC 100
3rd	My Science Inquiry	HC 618
4th	The role of Hydrogen in achieving Net Zero	HC 99
5th	Diversity and Inclusion in STEM	HC 95
6th	Reproducibility and Research Integrity	HC 101
7th	UK space strategy and UK satellite infrastructure: reviewing the licencing regime for launch	HC 1717
8th	Delivering nuclear power	HC 626
9th	The governance of artificial intelligence: interim report	HC 1769

Session 2021–22

Number	Title	Reference
1st	Direct-to-consumer genomic testing	HC 94
2nd	Pre-appointment hearing for the Chair of UK Research and Innovation	HC 358
3rd	Coronavirus: lessons learned to date	HC 92

Session 2019–21

Number	Title	Reference
1st	The UK response to covid-19: use of scientific advice	HC 136
2nd	5G market diversification and wider lessons for critical and emerging technologies	HC 450

Number	Title	Reference
3rd	A new UK research funding agency	HC 778