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Introduction to the Special Issue: Variable Viruses – The Past, Present, and Future of Bacteriophage Research

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For over a century, bacteriophages have exerted a profound influence on the evolution of microbiology, epidemiology, drug development, and clinical medicine (1-8). However, far from being stable, phages have proven to be incredibly variable entities. Variability in this context has multiple biological and social meanings. It refers to the "pluribiotic" way in which phage genomes are always changing, evolving according to their interactions with bacteria and more broadly with the ecosystems in which they participate (9). It also refers to the multiple forms of knowledge that have been developed to account for and attempt to grasp the specificities of these biological entities. Finally, it refers to the diverse nature of the projects that phages are subjects of from molecular biology to evolution, ecology, human health, biocontrol, animal health, etc. This biosocial variability is reinforced by the different scales through which phages can be thought of and the infrastructures via which they are mobilised: in laboratories working on coevolution or interaction mechanisms, in collections of microorganisms that may or may not be shared between research teams, in ecosystems whose scales are themselves variable, from the microbiota of a mouse to the major biogeochemical cycles, in clinical trials, in uses in the agri-food industry, in the multiple regulations on which they depend, or in the recommendations and reports issued by international agencies (10).

Finding ways of decoding these interconnected biosocial variables is of key scientific and societal importance during a time of resurgent public and commercial interest in bacteriophage applications, breakthroughs in synthetic biology and artificial intelligence, and mounting concern about inequalities of access to resulting benefits. Doing so requires an interdisciplinary approach that crosses the science-culture divide. While life sciences methodologies are ill-suited to assess the wider socio-economic contexts structuring phages' mobilisation as biomedical objects, social scientists and humanities scholars struggle to grasp the full technical, biological, and conceptual complexity of working with and researching phages.

In this special issue, we bring together experts from across the humanities and social and biomedical sciences to think collectively about the past, present, and future of bacteriophage research and infrastructures. Originating in a Wellcome Trust and CNRS-sponsored workshop at University College Dublin in early 2023, the assembled articles offer multidisciplinary reflections on path dependencies shaping the production, circulation, and uses of knowledge about phages in the four thematic areas of: (1) Ecology & Evolution; (2)

Surveillance & Diagnosis; (3) Phage Collections & Communities; and (4) Phage Therapy Models and Markets.

In article one on Ecology & Biocontrol, Brives et al. conduct an interdisciplinary review of the potential of phage-based applications in light of current knowledge about phage evolution and ecologies. Although phages have been used for over a hundred years across numerous fields with varying degrees of success, many currently talked about applications in antibacterial therapy, biocontrol, and biotechnology are still only in early development stages. The authors argue that gaining an improved understanding of phages' ecology and evolutionary dynamics is crucial to understanding both the benefits and limits of these applications as well as potential negative downstream effects across different ecological milieus. They highlight that the history of the industrialisation of antimicrobials and the rise of antimicrobial resistance (AMR) is rich in warnings: it reminds us both of the potential of micro-organisms to evolve – a process in which phages play an important role – and how the material, scientific, economic and political infrastructures that have emerged around existing antimicrobials (11, 12) have crystallised specific types of relationships between humans and microbes. When it comes to imagining new applications with phages, it is important to consider what we know and what we do not know about phages and their ecologies, as well as the way in which our current antibiotic infrastructures constrain the development of innovations.

In article two, Kirchhelle et al. reconstruct phages' often-neglected use as bacterial diagnostics and surveillance tools and discuss their current renaissance in the fields of clinical diagnosis and environmental surveillance across both high- and low-income contexts. The authors highlight how phages played an important role in mapping 20th century microbial environments, helped shape modern microbiological infrastructures, and how new phage-based molecular and genomic surveillance systems are offering unprecedented insights into microbial environments. They also note that many current breakthrough technologies depend on the repurposing and recycling of older phage collections and applications that originated during the Cold War. In highlighting the importance of 20th century technologies and infrastructures for 21st century science, the authors call for a broadening of narrow understandings of scientific innovation as consisting solely of molecular novelty to encompass processes of repurposing and tinkering (13). This also entails paying more attention to preserving existing microbial and phage collections as well

as microbiological know-how. However, the authors also warn about the dangers of naively repurposing historical phage collections, technologies, and infrastructures without paying due attention to structurally embedded socio-economic, cultural, and geopolitical biases.

Phage collections' evolving role as crucial biomedical resources is the subject of article three by Resch et al. The article begins by tracing phage banks' historical origin in the early 20th century. It notes collections' importance as repositories and enablers of therapeutic, epidemiological, and biological research (8, 14). The article also highlights the challenge of maintaining these critical resources in the face of uncertain funding, shifting societal demands, new technologies, and a greater international focus on making resources accessible beyond the Global North. While the last four decades have seen decreasing state funding for established phage banks, new intellectual property regimes and commercial interest in phages as therapeutics and diagnostics have created alternative revenue streams and led to a proliferation of new collections. Unfortunately, coordination between collections is poor. Despite over a century of collecting, there is no comprehensive catalogue of relevant phage banks. To remedy this situation, the authors provide a noncomprehensive overview of some of several key phage banks. They also reflect on the potential of coordination and centralisation of fragmented collections to better serve researchers, clinicians, and businesses. The article ends by underlining the ongoing difficulty of securing sustained long-term funding for critical phage infrastructures, assessing the potential of new *in silico* approaches to phage design to supersede physical phage banks, and discussing the related need for updated international guidance on phage storage and accessibility.

Article four by Turner et al. turns to the biological, organisational, epistemic, and economic challenges facing both non-profit and for-profit phage therapy ventures. The authors highlight the significant potential of tailored *à la carte* phages or phage cocktail-based *prêt-à-porter* approaches to treat and manage a wide range of bacterial infections amidst rising AMR (15). However, they also note that the specificity of phage-host interactions and varying trial protocols pose problems when it comes to comparing and generating sufficient evidence for regulatory licensing. Significant uncertainty also remains about the use of phages in conjunction with other antimicrobials and in the context of complex microbial biofilms. The authors warn that despite the promise of further breakthroughs due to artificial intelligence and synthetic phage design, phage therapy continues to face considerable socio-economic challenges. In response to the ongoing crisis

of commercial investment in antimicrobial innovation and the absence of established licensing pathways, a decentralised network of non-profit institutions has started successfully offering personalised *à-la-carte* and *prêt-à-porter* phage preparations to patients at the local and regional level (15, 16). However, so far, non-profit initiatives remain localised and geographically concentrated in the Global North. Meanwhile, the planetary nature of the AMR challenge requires more scalable solutions. The authors assess the potential of for-profit phage innovation and services to fill this gap by reviewing recent international funding and coordination initiatives for commercial phage innovation and reviewing the technological challenges experienced by a Danish phage biotech. They note that in the absence of substantial commercial reinvestment, the nascent ecosystem of for-profit phage ventures will continue to require sustained support from public and non-profit funders. The article ends by reflecting on how alternative systems of intellectual property management, public development partnerships, and public phage manufacturing might be harnessed to expand global access to phage therapy.

In her epilogue, PHAGE editor Martha Clokie reflects on the articles and on her recent experience in setting up the UK National Phage Centre at the University of Leicester and advising on a UK House of Commons report on phage therapy. For Clokie, a major danger for the current renaissance of interest in phage biology and applications lies in siloed research approaches, lack of sustainable finance for critical research infrastructures such as phage banks, and treating phages' as a simple antibiotic *ersatz*. Avoiding these cliffs requires actively embracing the biological and social complexity of phage research and simultaneously realising phages' potential in both high- and low-income contexts.

The articles of the special issue are uniform in underscoring the accelerating importance of phage research and applications across all three One Health Domains. However, they also highlight persistent biological, epistemic, and socio-economic tensions concerning the specificity of phage-host interactions, strategic misalignment between decentralised and centralised modes of phage research, and injustices resulting from the historic concentration of biomedical resources and associated intellectual property in the Global North. These tensions are unlikely to disappear anytime soon and may well be exacerbated by current advances in genomics, synthetic biology, and artificial intelligence. In view of their biosocial complexity, developing appropriate scientific, ethical, and regulatory frameworks within

which to manage them will require regular and intensive further interdisciplinary stocktakes of all areas of phage research.

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