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Ethical argument for establishing good manufacturing practice for phage therapy in the UK

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ABSTRACT

Antimicrobial resistance (AMR) poses an increasing threat to patient care and population health and there is a growing need for novel therapies to tackle AMR. Bacteriophage (phage) therapy is a re-emerging antimicrobial strategy with the potential to transform how bacterial infections are treated in patients and populations. Currently, in the UK, phages can be used as unlicensed medicinal products on a 'named-patient' basis. We make an ethical case for why it is crucially important for the UK to invest in Good Manufacturing Practice (GMP) for both ongoing unlicensed and future licensed phage therapy. Access to phages produced to GMP (GMP phages) will ensure effective patient care and better outcomes as well as health systems benefits. The UK also has the potential to become a global leader in the timely and cost-efficient manufacturing and supply of a therapy that meets internationally recognised standards.

INTRODUCTION

Bacteriophages (phages) are naturally occurring viruses that infect bacteria and were first used to treat bacterial infections in 1919.[1] Their use declined sharply with two critical and influential American reviews questioning the nature of bacteriophages (not at the time known to be viruses), poor efficacy due to uncontrolled application and inconsistent viability, and the discovery and mass production of antibiotics in the 1940s.[2] However, the current global antimicrobial resistance (AMR) crisis is driving a re-emergence of phage therapy. It has been estimated that by 2050 AMR will contribute to 10 million deaths per year by 2050.[3] Arguably, there is an ethical imperative to ensure innovation and supply of alternative antimicrobials that reduce our use of and reliance on antibiotics.[4]

Phage therapy is a promising alternative antimicrobial strategy. A recent systematic review of observational data reported encouraging findings around safety and efficacy of phage therapy in patients with difficult-to-treat infections.[5] However, although existing clinical trial data are comparatively reassuring regarding safety, efficacy signals have not been consistently demonstrated through clinical trials. This has been considered to reflect mechanistic shortcomings in the trials.[6] More robust trial data are needed and there are several clinical trials of phage therapy ongoing.[7] Nonetheless, the American Antibiotic Resistance Leadership Group and Health Improvement Scotland have recommended the consideration of phage therapy in cases of antibiotic refractory infection.[8 9] Phages have unique advantages relative to antibiotics: they kill bacteria independent of antibiotic resistance, have an extremely promising safety profile, are comparably quick and inexpensive to produce and the diversity of phages means that new phages can be found or developed where resistance occurs.[10] Phages can work synergistically with antibiotics, potentially even resensitising bacteria to antibiotics during combined treatment[11] and can also be used to address antibiotic tolerance, a significant factor in many chronic infections.[11 12] Phage therapy also has the added benefit of reducing the likelihood of opportunistic infections[13] and offers a suitable alternative to patients with antibiotic hypersensitivity.[14]

Phage therapy provides clinicians and microbiologists with a much-needed additional treatment option for the management of difficult-to-treat infections such as diabetic foot infections at high risk of amputation, chronic respiratory infections and prosthetic joint infections. Without phage therapy patients face an empty choice of trialling antibiotics of limited efficacy or undergoing debilitating and costly surgery. Ethically, the introduction of phages enhances patient autonomy by offering meaningful choice, the potential for mitigating harms such as limb loss and poor surgical outcomes, and precious hope to patients and clinicians facing a rapidly narrowing window of treatment and care options. At the population level, phage therapy also has the potential to promote public health by enabling appropriate resource allocation (ie, reducing inappropriate antibiotic use and increasing targeted justified use—which also has the potential to limit AMR).

Phage therapy is being used, although still sporadically and with low patient numbers, for difficult-to-treat infections in the USA, Australia, Israel and several countries across Europe.[15–19] In the UK, the application of phage therapy occurs only on an ad hoc basis, and availability is limited due to procurement difficulties and a lack of sustainable access to phages manufactured according to Good Manufacturing Practice (GMP). This paper first outlines the current practice of phage therapy in the UK and its limitations, followed by the case for why the UK has an ethical obligation to invest in GMP for phage therapy.

ETHICAL CHALLENGES ASSOCIATED WITH CURRENT PRACTICE IN THE UK

Although there are currently no licensed medical phage products, in the UK, phages may be used in certain circumstances as an unlicensed medicinal product. This must be undertaken in accordance with Medicine and Healthcare products Regulatory Agency (MHRA) guidance on an unlicensed ('named patient') basis when licensed alternatives

(eg, antibiotics) are not fulfilling a patient's clinical needs.[20] The use of phages as an unlicensed medicine is challenging, not because of their unlicensed status, as unlicensed medicines are commonplace in the UK, but largely because of pharmacologistics and the National Health Service's (NHS) unfamiliarity around handling and using phages.[21] In future, clinical trials will lead to licensed phage therapy products, however, unlicensed use will almost certainly remain to meet unique clinical needs. Currently, phages imported for use as an unlicensed medicine do not need to be manufactured according to GMP, although such products are subject to careful quality assessment. This practice, although key to providing patients with a much-needed alternative to antibiotics, is far from a best model for patient care.

First, reliance on imported sources of phages poses ethical challenges in terms of equity. Sourcing high-quality phages is difficult, especially for those unfamiliar with phage therapy. Access to phages is currently on an informal basis and driven largely by networking between clinicians and phage laboratories. Consequently, access to phage therapy is not currently equitable, with large variations in clinician awareness and NHS capacity to deliver phages as an unlicensed medicine across the UK.[22] Patients facing the possibility of limb amputation or further surgery due to hard-to-treat infections are currently subject to an unsystematic and decentralised system where Trusts vary in their willingness, time and resource to invest in unlicensed medicines. Patients may also be cared for by clinicians who are unaware of or unable to access phages, resulting in poorer outcomes. Clinicians who are able to access phage therapy may still face significant delays in receiving them.[10] The current large variations in clinical awareness and access to phage therapy in the NHS result in significant unmet needs and inequitable outcomes. These variations need to be tackled to ensure fairer and better management for patients facing acute risk to life or limb or suffering clinically chronic infections.

Second, sourcing and importing phages is unsustainable and is thwarting scalability. Currently, access is through disparate, typically non-commercial, international sources and relies on payment per patient by individual Trusts. The costs associated with obtaining non-commercial phages can vary per patient from free of charge for off-the-shelf phages to around £10 000 for de novo isolation and characterisation of phages. Trusts must carry out lengthy quality assurance assessments for each phage. The process of sourcing phages in this ad hoc manner is time, labour and financially intensive. A local phage therapy source is needed to transform the use of phage therapy from an increasing number of ad hoc cases to a sustainable, equitable and scalable system.

Third, the current use of phages as an unlicensed medicinal product which does not need to be manufactured according to GMP raises important questions of quality, consistency and ultimately safety. The NHS and MHRA have a fundamental responsibility to ensure that quality standards are met for treatments provided to patients. However, the current lack of centralised co-ordination and governance for phage therapies, in addition to importation of phages which have not been manufactured according to GMP, means that patients may be receiving phage preparations of varying quality. This gives rise to concerns that suboptimal quality treatments may be offered to patients, unnecessarily increasing risks of harm, and potentially adversely impacting broader conceptions of an important and necessary treatment. Indeed, there are reports of adverse effects in the literature observed at a high but not lower phage concentration, which has led some to speculate that unknown pyrogens possibly associated with manufacturing may be responsible.[10 11] Adverse effects associated with manufacturing risk jeopardising the reputation of phage therapy and therefore the potential benefits for current and future patients.

In summary, there are very few effective treatment options for antibiotic refractory infections and there is an obligation to improve care options if we can. GMP phages are one option, however, at present phages are not and cannot be provided optimally, safely and equitably as we do not have a sustainable, scalable or equitable source. What is needed is onshore GMP phage manufacturing, where a national central GMP-equipped phage centre provides support to all Trusts for the use of phage therapy, delivering an equitable and sustainable system with minimal delays.[22] Such a system is important not just for current patients but also for future patients and population health, because AMR already poses a huge health burden and this is only likely to increase.

ETHICAL ADVANTAGES OF ONSHORE GMP PHAGE MANUFACTURING

Having outlined the ethical challenges resulting from the current practice of importing non-GMP phages, we provide a critical analysis of the ethical justifications for establishing GMP phage manufacturing in the UK. Arguments include benefits for patient care and outcomes, including the treatment of antibiotic refractory infections, upskilling of practitioners, opportunities for innovation and systematic research, increased preparedness for outbreaks, enhanced antibiotic stewardship, as well as reducing NHS costs from infections, amputations and complex surgical care.

Context and assumptions

Before providing ethical rationale for the importance of GMP to phage manufacturing, it is necessary to provide a brief outline of what we are proposing and the underlying assumptions. A fuller account of our vision for the future of clinical phage therapy in the UK is presented elsewhere[22] and the salient features relevant to this discussion are as follows.

It is important to note that there are no regulatory barriers to the appropriate use of phage therapy in the UK. Paradoxically, non-GMP phages may be imported for unlicensed use, whereas phages produced in the UK must be made to GMP. Our proposal to ensure patient access to phages is not to compromise on quality by enabling the use of locally produced non-GMP phages but to establish onshore GMP phage manufacturing. This is to enable a consistent supply of phages and to expand access beyond a limited number of cases.

GMP phage production is expensive and investment in this area has historically been limited. This is partly because of the existing disincentives around antimicrobial production but also reflects that phages are natural entities, and therefore, cannot reliably be protected through patenting, although other aspects of a formulation could be protected.[23 24] Moreover, naturally occurring phage therapies can be easily copied, or partially reverse-engineered by isolating viable phages from a product or preparation. Therefore, if a company invests in developing a phage product, there is little perceived protection. Globally there are currently only a handful of GMP production facilities with experience producing phages, including just two in Europe—arguably too few to meet growing demand or be adequately responsive to clinical needs.[25 26] This reflects the financial, rather than technical, challenges of GMP phage production. It is against this background, and given the potentially significant public impact of a mature phage therapy infrastructure, that it is

imperative for the production and development to be supported through public funding. In the analysis below, we outline how GMP phage production is cost saving and critical for better patient outcomes.

Onshore GMP production would involve a centralised and coordinated production and delivery process. Although investment is required to establish infrastructure, personnel and processes, once fully established this will afford significant advantages.

Better for patients

Onshore GMP phage production is key to benefiting patients by enabling equitable and timely access to phages tailored to the UK's bacterial ecology. Advantages of onshore infrastructure include responsive access for patients suffering time-sensitive and difficult-to-treat infections, a bank of phages selected for activity against local bacterial strains and quality reassurance provided by oversight from the MHRA. While we envisage that the majority of patient need will be met by preformulated licensed cocktails, GMP infrastructure will enable the timely and responsive preparation of personalised formulations from GMP phage stocks. Timely provision of phages, without delays associated with importation, will not only improve outcomes and allow the application of phages in acute settings but also mitigate harms such as ongoing recalcitrant infections, inappropriate antibiotic use, avoidable surgery and deaths. A centralised and coordinated system will also afford patients fairer access, instead of the current ad hoc practice.

Better for clinicians

Through a nationally established programme with a centralised GMP-equipped point of focus, clinical teams will be better able to advocate for their patients and access high-quality GMP phages, overcoming the need for time consuming phage sourcing at the Trust level. A centralised system will also have the added advantage of being able to support training and education of individual staff and teams resulting in upskilling across Trusts on the use and implementation of phage therapy. Such a system will also provide better infrastructure for research, enabling greater opportunity for individual clinicians and teams to undertake site specific and/or multisite research to improve patient care. This improved access, training and research will improve patient care.

Better for the healthcare system

Onshore production facilitates the provision of quality-assured phages in a timely, cost-effective and integrated manner. A substantial number of patients could benefit from off-the-shelf and personalised phage therapy, with phages having the potential to one day be used at a magnitude comparable to that of antibiotics and for phages to potentially replace antibiotics in some circumstances. GMP phage production offers a sustainable and secure source of antimicrobial therapy that limits our reliance on antibiotics and thereby mitigates AMR. Nationally, it also has the potential to expand our armoury against threats to our biosecurity and enchance our medicines security, giving the UK antimicrobial resilience when supplies of antibiotics are interrupted. We are facing increasing outbreaks of bacterial pathogens, such as the recent Streptococcus A infection.[27] With increasing levels of AMR, there is a risk that we will have fewer options for how to respond to such crises.

Construction of a GMP-equipped phage manufacturing centre, capable of delivering phage therapy at scale to the NHS, could cost up to around £20–30 million. However, this will not only be offset by but could offer savings to the NHS of an estimated £179.7 million/year, even if only diabetic foot, hip and knee infection costs are considered.[28] This figure greatly underestimates the potential savings as it does not include other major infection types that could benefit from phage therapy such as surgical site infections, prosthetic or implant-related infections, urinary tract infections, chronic respiratory infections, for example, in cystic fibrosis, Chronic Obstructive Pulmonary Disease (COPD), bronchiectasis or infections in immunosuppressed patients. With contract manufacturing of a single batch of GMP phage currently costing hundreds of thousands of pounds, public investment in GMP production facilities could deliver long-term savings relative to repeated importation of contract manufactured phages. Onshore phage production is important as many patients will require personalised formulations and local production will negate costs and logistical delays associated with importation, the latter being potentially detrimental to patients. Moreover, the onshore location of such a facility is important to enable close working with the NHS, supporting the delivery of personalised phage therapy, phage resistance surveillance and broader use of phage therapy in the NHS.

Better for UK phage science

Infrastructure development and upskilling of clinical and research staff presents the UK with an important opportunity to become a global leader in GMP phage production, use and research. Although the evidence is growing for the use and efficacy of phage therapy, there is an opportunity for establishing world leading research in clinical phage therapy as well as opportunities for developing therapeutic innovation that are commercially attractive and of international standing. Onshore access to GMP phages will also help encourage UK-based clinical trials, with the UK currently notably absent from this space. As AMR poses an increasing threat to patient care as well as population health, GMP phage offers a vital safeguard by minimising ineffective use and targeting effective use of antibiotics, thus minimising further development of AMR. Investing in onshore GMP phage manufacture and an associated research infrastructure, including a national phage library, will provide the UK with an essential and effective lever within its national strategy to contribute to global efforts to tackle AMR.

Furthermore, the UK has the opportunity to become a world leader in the cross-sector phage space. Although requiring substantial investment to establish the necessary infrastructure, training and research, the outputs will meet commercial and clinical needs. As GMP phage meets internationally recognised standards, it is a commercially attractive and high-quality pharmaceutical product, which will benefit both the UK economy and patients. Countries such as Belgium and Australia that have established non-GMP phage production have limited commercial phage activities.

COUNTERARGUMENTS AND RESPONSES

As with all therapies which are not currently in widespread use and for which the evidence base is evolving, there should be ongoing consideration of emerging ethical issues and appropriate monitoring of safety and efficacy to contribute to the evidence base and inform future use. There is a compelling body of literature supporting the safety of phage therapy and we acknowledge that, despite strong clinical evidence, more clinical trial evidence is needed around efficacy. However, when considering use in circumstances where licensed therapeutics are not meeting clinical needs the risk/benefit balance would appear to be favourable.

Proponents for the broader use of non-GMP phages may argue that establishing an onshore GMP centre and system will be burdensome in terms of time and cost and that such costs may be circumvented by the continued use of non-GMP phages as unlicensed medicines. However, as we have explored, while the existing system works on a small scale it is not sustainable, scalable or equitable. Although the initial GMP manufacturing setup could take 2–3 years, once established the processes will be time-saving and stocks of GMP phages will be readily available to meet even pressing clinical needs. Although patients will not have quick and immediate access to phages produced to GMP until the infrastructure and systems are in place, the long-term benefits include a higher and more consistent production quality, and therefore, standards for patient care. While manufacturing and delivery capabilities are being established, we propose centralisation of the current ad hoc system of using imported non-GMP phages to allow consistent quality assessment and at least improve equity. Interim centralisation will provide a foundation on which the subsequent site-specific phased introduction of GMP phage supply and application can be delivered to ensure sustainable transformation from non-GMP to GMP phages nationally and across all NHS Trusts.

Current UK regulations stipulate that medicines produced in the UK, including phages, must be produced in accordance with GMP. To ensure a commercially thriving phage sector and, most importantly, to ensure a consistently high-quality source of phages for use at scale in the NHS, GMP must be adhered to. It is anticipated that the vast majority of clinical needs will be met by off the shelf licensed GMP products or personalised formulations of GMP stocks. There may be a minority of patients, for example, those with rare bacteria, for whom GMP products may not be financially viable but the highest possible standard of quality should always be the goal. The quality of GMP also provides sufficient reassurance to pharmacists and other NHS staff charged with overseeing medicines governance. We do not believe that the requirement for adherence to the highest possible quality manufacturing standards precludes realising the potential of personalised phage therapy, including the use of phages 'trained' against a patient's specific bacterial pathogen. It should be kept in mind that the current GMP regulations have generally evolved in response to extreme adverse events resulting from lax regulations or poor compliance, for example, the thalidomide tragedy.[29] Although the phages themselves are inherently safe, any harms caused to patients that are caused by poor manufacture or quality control of phage batches risk not only compromising patient welfare but potentially setting back the field of phage therapy for years to come.[29]

CONCLUSION

Ethical implementation that ensures sustainable, equitable and secure access to GMP phage will require political support and buy in. Our analysis provides ethical and pragmatic justifications for GMP phage predicated on improved patient safety, economic savings to the NHS, prospects for biosecurity, commercial benefits and securing the opportunity to become a world leader in the cross-sector phage space. Systems transformation of this kind, which are both therapeutic and preventative, require assessment similar to public health interventions (such as for mitigating cardiovascular risk) where economic modelling takes into account discounting for future benefits for individual and population health. Accomplishing lasting change that carries benefit nationally and globally will need patience and courage, and our analysis shows there are sound ethical reasons for doing so.

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