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House of Commons Science and Technology Committee: Realising the antimicrobial potential of bacteriophages

Submission by Applied Microbiology International

How well established is the evidence base for phages as an antimicrobial for humans?

- **What are their strengths and weaknesses?**

There is extensive evidence that highlights phage therapy as an effective antimicrobial treatment for humans, the earliest of which dates back to over 100 years ago. Although the pursuit of bacteriophages as a therapeutic option was dropped by Western society after the emergence of antibiotics, bacteriophages became a common treatment in the Soviet Union, due to the lack of antibiotics resulting from the Cold War[1,2,3].

The strengths of bacteriophages include[2,4,5]:

- They are effective at treating infections caused by susceptible bacteria and bacteria that are resistant to antibiotics.
- They only infect bacterial cells and cause minimal disturbance to the human gut because most bacteriophages only infect a specific bacterial species / strains of a bacterial species. As such, they are unlikely to cause secondary infections (unlike antibiotics which can cause fungal infections due to their effects on the human gut).
- They only infect and replicate in bacterial cells and are not toxic to the human body, animals, plants or the environment.
- A single dose may be effective, therefore reducing the risk of resistance emerging from overuse.
- They can be effective at removing biofilms, which are often the cause of persistent infections.
- They can be used alone, or alongside antibiotics and other drugs.
- Bacteriophage therapy may be more cost-effective than antibiotic use, possibly due to the lower dosage needed.
- Some bacteriophages can infect a range of different bacterial species, which enables them to treat different types of and/or complex infections caused by multiple species of bacteria.
- Bacteriophages are the most abundant biological entity on the planet, therefore there isn't a risk of running out of bacteriophages.

[1] https://doi.org/10.1016/B978-0-12-394438-2.00001-3
[2] https://doi.org/10.4161/viru.25991
[3] Kutter & Sulakvelidze, Bacteriophages - Biology & Applications, 200
[4] https://doi.org/10.3934%2Fmicrobiol.2020014
[5] https://bsac.org.uk/antibiotics-are-failing-could-phage-therapy-hold-the-key-to-stopping-antibiotic-resistant-superbugs/

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The weaknesses of bacteriophages include[2,4,5,6]:

- Although bacteria can become resistant to bacteriophages, bacteriophage use only risks promoting resistance in the target bacterial species, whereas antibiotic use promotes resistance in many bacterial species since antibiotics aren't as specific. Additionally, although bacteria can evolve to become resistant to bacteriophages, bacteriophages can also evolve to overcome bacterial resistance mechanisms.
- They are difficult to isolate on a large scale, and since they often only specifically infect one bacterial species / one strain of a bacterial species, there is often a need to isolate new bacteriophages for different / complex infections.
- Although some bacteriophages can infect a range of different species of bacteria, these bacteriophages are often less potent.
- It may be difficult to find the exact bacteriophage needed to treat an infection, since the bacterial species causing the infection first needs to be recovered to know what bacteriophage is required.
- Some bacteriophage therapeutics may need to be modified over time, due to the natural evolution of bacteria. This could be challenging since current regulations (such as the US FDA and EMA) do not allow for modifications once a finished medicinal product is registered. This could mean that approved bacteriophage therapeutics cannot be improved under any circumstances after approval (under such current legislation).
- There may be uncertainties regarding bacteriophage therapeutics e.g., regarding dosage, the concentration of bacteriophages needed and lengths of treatment. More large-scale clinical trials are needed before bacteriophages can become a standard treatment and their full therapeutic potential recognised.

What regulatory approaches have been used by other countries for the use of phages and what lessons can the UK learn?

There are currently no explicit regulatory guidelines that cover phage therapy and phage-based therapeutic formulations in the European Union or United States[7]. As such, some EU Member States are determining solutions nationally.

Belgium is currently implementing a phage therapy framework that focuses on magistral (master) phage formulations. Magistral formulations are any medicinal product prepared in a pharmacy in accordance with a medical prescription for an individual patient[8]. The Belgian Magistral Phage framework enables the use of non-authorised ingredients (e.g., phages) in magistral treatments, as long as they are

[6] https://doi.org/10.1093/femsre/fuab048
[7] Naureen Z, Malacarne D, Anpilogov K, Dautaj A, Camilleri G, Cecchin S, Bressan S, Casadei A, Albion E, Sorrentino E, Beccari T, Dundar M, Bertelli M. Comparison between American and European legislation in the therapeutical and alimentary bacteriophage usage. Acta Biomed. 2020 Nov 9;91(13-S):e2020023. doi: 10.23750/abm.v91i13-S.10815. PMID: 33170166; PMCID: PMC8023134.
[8] Article 3 of Directive 2001/83 and Article 6 quater, § 3 of the Law of 25 March 1964

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approved by a laboratory that is accredited by the national regulatory authorities[9,10]. The framework therefore allows phage treatments to be prescribed, and pharmacists to prepare individual tailored phage treatments for patients. This framework is expected to be flexible enough to give the ability to modify a phage therapeutic over time (overcoming potential regulatory barriers), while giving preference to patients' safety. It has been suggested that it would also avoid stringent production requirements like Good Manufacturing Practice (GMP) and would facilitate the development of therapeutic phage-based products.

France has issued recommendations for using phage therapeutics under the Temporary Authorisation for Use (ATUn) programme. This programme allows access to non-authorised therapeutics in patients with severe or rare diseases when there is no authorised alternative, and they cannot partake in a clinical trial[11,12].

Poland takes a prominent role in the area of phage research. In 2005, the Phage Therapy Unit (PTU) at the Hirszfeld Institute of Immunology and Experimental Therapy was established and this was the first ethically approved phage therapy treatment facility in Europe[13]. The PTU is internationally recognised and has advanced phage therapy through the extensive planning of clinical trials, making it a model for phage treatment centres around the world[14]. In Poland, phage therapy is considered an ‘experimental treatment’ under the Polish Law Gazette, 2011, item 1634 and article 37 of Declaration of Helsinki.

What opportunities does the UK have for regulatory divergence from the EU on phages, and what would the implications be?

An opportunity for the UK comes not necessarily as a result of divergence from the EU but rather from having an NHS. Having the NHS could help the UK Government to incentivise phage funding, e.g. through the adoption of novel funding structures such as those already being used to fund new investment in conventional antibiotics. For example, NHS England in collaboration with the National Institute for Health and Care Excellence and the Department of Health and Social Care (DHSC) has selected the first antimicrobial drugs to be purchased via the UK’s innovative, novel ‘subscription-style’ payment model[15], where instead of paying for individual packs of antimicrobials, healthcare funders make an annual payment based on the health benefits to patients and the value to the NHS. This would de-link the price paid from the volumes sold and such an approach could work very well with phage-based products.

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[9] Pirnay JP, Verbeken G, Ceyssens PJ, et al. The magistral phage. Viruses 2018; 10(2): 64.
[10] Verbeken G, De Vos D, Vaneechoutte M, Merabishvili M, Zizi M, Pirnay JP. European regulatory conundrum of phage therapy. Future Microbiol 2007; 2(5): 485-91.
[11] https://doi.org/10.1093/femsre/fuaa017
[12] https://www.europeanpharmaceuticalreview.com/article/156994/frances-temporary-authorisation-atu-programme-reform-implications/
[13] https://doi.org/10.3389/fmicb.2020.01056
[14] Gill J and Young RF. Therapeutic applications of phage biology: history, practice, and recommendations, in Emerging Trends in Antibacterial Discovery: Answering the Call to Arms, eds A. A. Miller and P. F. Miller (Norfolk: Caister Academic Press), 2011, 367–410.
[15] https://www.england.nhs.uk/blog/how-the-nhs-model-to-tackle-antimicrobial-resistance-amr-can-set-a-global-standard/

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What are the major barriers and opportunities relating to the development and deployment of phages in the UK?

Current barriers include the lack of a funding structure needed to secure the long-term support, development and maintenance of phage biobank facilities (academic institutions, biotech spin-outs and/or big pharmaceutical/biotech) for producing therapeutic phage preparations purified to GMP. There are also regulatory barriers as mentioned already, which have arisen from the classification of phages as biological substances, which means they fall under the remit of pharmaceutical legislation. In the EU, this means a marketing authorisation would be needed for any phage therapeutic to be industrially produced. There are stringent requirements that must be met through this regulatory pathway (e.g., GMP compliance), that are costly and are therefore a barrier to production. Additionally, there are regulatory barriers relating to the potential need to update phage therapeutics overtime, which reduces the ability to produce patient-specific treatments[9].

Other potential barriers relate to intellectual property rights of the final formulated products, since unlike conventional antibiotics (chemical compounds), phage-based formulations cannot be patented in both the US and EU[7] due to reliance on a form of life, or their constituents such as DNA or RNA. Therefore, it will be necessary to extend patents to phage-related organisms/genes for therapeutic purposes.

Planning for a UK phage biobank(s) could build upon work already underway as part of the UK Bacteriophage Centre Project (and similar to the centre of excellence for Cell and Gene Therapy Catapult established in 2012).

Precedent in EU law, patents were extended to genes isolated from their natural environments but they did not rule out patents for gene sequencing technologies, altered genes, or novel methodologies for using existing genes or organisms for therapeutic purposes[1617].

How well developed is the UK's phages research and clinical trial pipeline and how could it be improved?

Researchers at the University of Exeter (Dr Ben Temperton) have been developing a large library of phages for therapeutic use through citizen science initiative[18] and to date they have supplied phages to Belgium, Canada and Switzerland. They are also actively hunting phages for two UK hospitals; however, they have no regulatory route to use them currently.

NHS Tayside have received initial funding to create a Bacteriophage Unit within their health board, starting in February 2022. A report outlining the operations of the service and business case are required to be submitted to NHS National Services Scotland 6 months after the service has begun. Scottish Health Technologies

[16] Anomaly J. The future of phage: Ethical challenges of using phage therapy to treat bacterial infections, Public Health Ethics 2020; 13 (1): 82–8.
[17] Pirnay JP, Verbeken G, Rose T, et al. Introducing yesterday's phage therapy in today's medicine. Future Virol 2012; 7: 379-90.
[18] https://citizenphage.com

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Group's work will be used alongside data collected by the service to inform a decision regarding continued funding[19].

Additionally, phage perception studies have already been carried out to determine what diabetic foot infection patients think about phage therapy.

To what extent is the UK Government ensuring that phages research and development is adequately funded and supported?

There is considerable scope for the UK Government to increase phage funding, since historically (during the last 20 years) much funding for phage work has come from EU Framework funds, the Bill & Melinda Gates Foundations and from the UK water industry (where phages have been used to test the removal efficacy of treatment technologies and as tracers of groundwater contamination).

Globally, investments (public and philanthropic) in phage AMR R&D across all One Health sectors are estimated at 214 million USD since 2017. Over three quarters of this funding volume is for human health related projects. The UK is a key funder of phage related research in terms of funding volume (~10% of all phage related funding) but further funding required. As a comparison, the US contributes approximately 30% of funding for phage-related AMR R&D within the Dashboard. Funders of phage research in the UK include Biotechnology and Biological Sciences Research Council, Medical Research Council, Innovate UK, Wellcome Trust, Global AMR Innovation Fund (GAMRIF).

About Applied Microbiology International

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Word count: 1972

[19] https://shtg.scot/our-advice/bacteriophage-therapy/