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Phage therapy: a new frontier for antibiotic-refractory infections

Phage therapy has the potential to play a key role in the broader response to antimicrobial resistance.

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In this article, Josh Jones explains the potential of phages for treating infections and explores the challenges of implementing their use within healthcare systems.

What are bacteriophages?

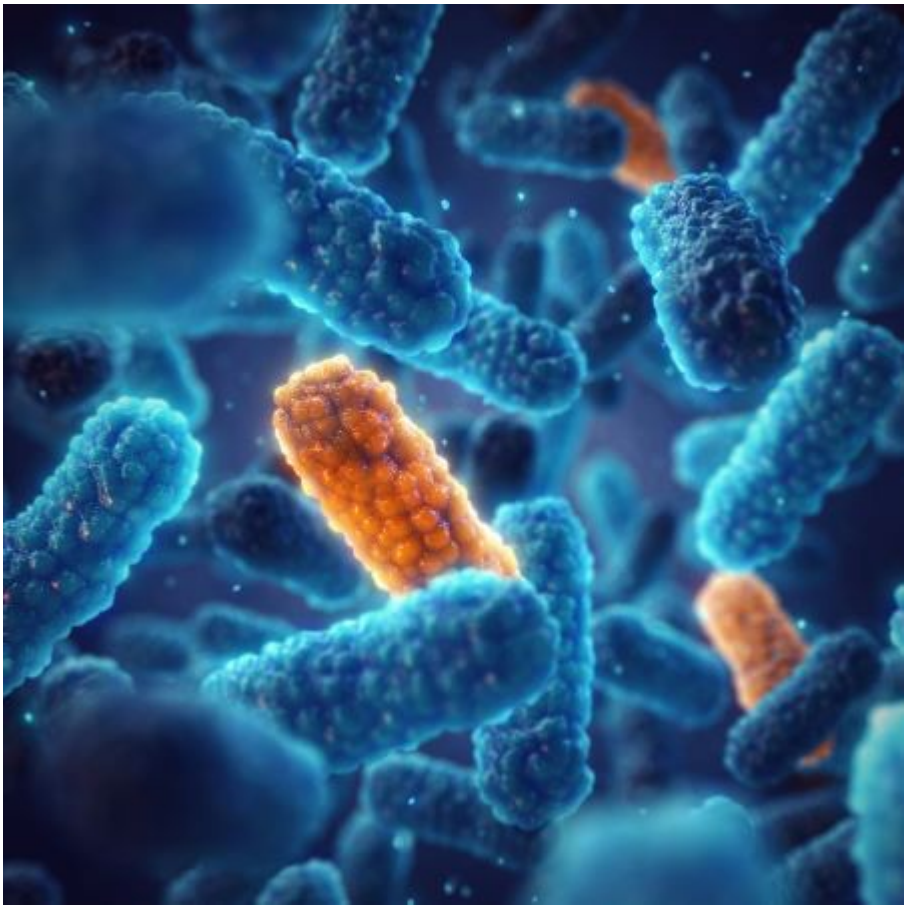
- Bacteriophages (phages) are an extremely diverse group of viruses which infect and kill bacteria and can be used to treat bacterial infection.
- There is a sizeable body of trial and observational evidence supporting the safety of phages. Efficacy requires enough of the right phage(s) to be administered to the right site(s).
- Phages can be used as an unlicensed medicine in cases where licensed alternatives (i.e. antibiotics) are not meeting clinical needs. This is governed by existing local NHS unlicensed medicines policies, with the quality of imported phage products reviewed by the medicines regulator.
- Patients potentially suitable for phage therapy include those with antibiotic-resistant infections, antibiotic-susceptible infections but clinical recalcitrance, those needing an alternative medical option to prevent high risk surgery, or cases where other factors (like allergy, antibiotic intolerance or renal disease) might prevent the use of appropriate antibiotics.
- In-vitro phage susceptibility testing of patient isolates is essential to match the right phage(s) to the patient's bacteria.
- Phages generally come in a suspension that can be administered by a wide range of routes, with the goal typically being administration directly to the site of infection. For example, this could be topical administration for a diabetic foot infection, nebulised for a respiratory infection or intravenous for an endovascular infection.

Background

Discovered in 1917, phages are naturally-occurring viruses that infect and kill bacteria. Collectively, phages are the most abundant 'living' entity on the planet and can be found wherever bacteria are found. We have co-evolved with, and continue to exist in, constant contact with phages; for example, there are at least as many phages in our gut as there are bacteria.[1] Phages were used to treat bacterial infections in the early 20th century, but limited knowlegde about phages at the time and the mass production of antibiotics led to the demise of phage therapy from Western medicine, although its use persisted in parts of the geopolitical East.[2]

Phages and AMR

Today, the antimicrobial resistance (AMR) crisis is driving renewed global interest in phage therapy, with an estimated 4.95 million deaths worldwide associated with AMR in 2019.[3] Phage therapy has the potential to play a key role in the broader response to AMR, by offering both a viable alternative antimicrobial strategy that can help reduce reliance on traditional antibiotics and a practical alternative treatment option for patients already living with antibiotic refractory infections.



Antimicrobial resistance is a major global health threat.

Growing demand

Although there are no licensed phage therapy products yet, phage therapy is increasingly being used on an unlicensed basis in small, but growing, patient numbers in countries including the USA, Australia, Israel and Belgium.[4–8] Phage therapy has also been used to treat diabetic foot (n = 10), orthopaedic (n = 3) and respiratory (n = 2) infections in the UK.[5,9,10] Survey data supports growing demand for phage therapy in the UK, with 77 clinicians from 2 trusts seeing an estimated 300 potential phage patients over 12 months.[11] The recent UK Parliamentary Science, Innovation and Technology Select Committee inquiry into phage therapy has stimulated further interest.[12]

Advantages

Phages offer a way of killing bacteria independent of antibiotic resistance, with a promising safety profile. Any bacterial species for which phages are available may be considered.

While preformulated phage cocktails may be able to meet most clinical needs, a library of phages can be used to create personalised phage formulations. Currently, most phage preparations come as a suspension of phage particles in a clinically appropriate diluent, such as 0.9% NaCl. Notwithstanding quality assessment, such a phage preparation is suitable for a wide variety of routes of administration. Notably, the use of phages with antibiotics can be synergistic and there is some evidence that adjunctive phage therapy can resensitise bacteria to antibiotics.[8] Of particular relevance to chronic infections, some phages encode enzymes which can degrade biofilms, the polysaccharide matrices considered to play a key role in many chronic infections.[13] Moreover, as phages are not human pathogens, they are suitable for use in patients with immunodeficiency.[14]

Another advantage of phage therapy is that such is the specificity of phages that the commensal flora is left largely intact,[15] reducing adverse effects associated with the loss of commensal organisms, such as the acquisition of opportunistic pathogens.

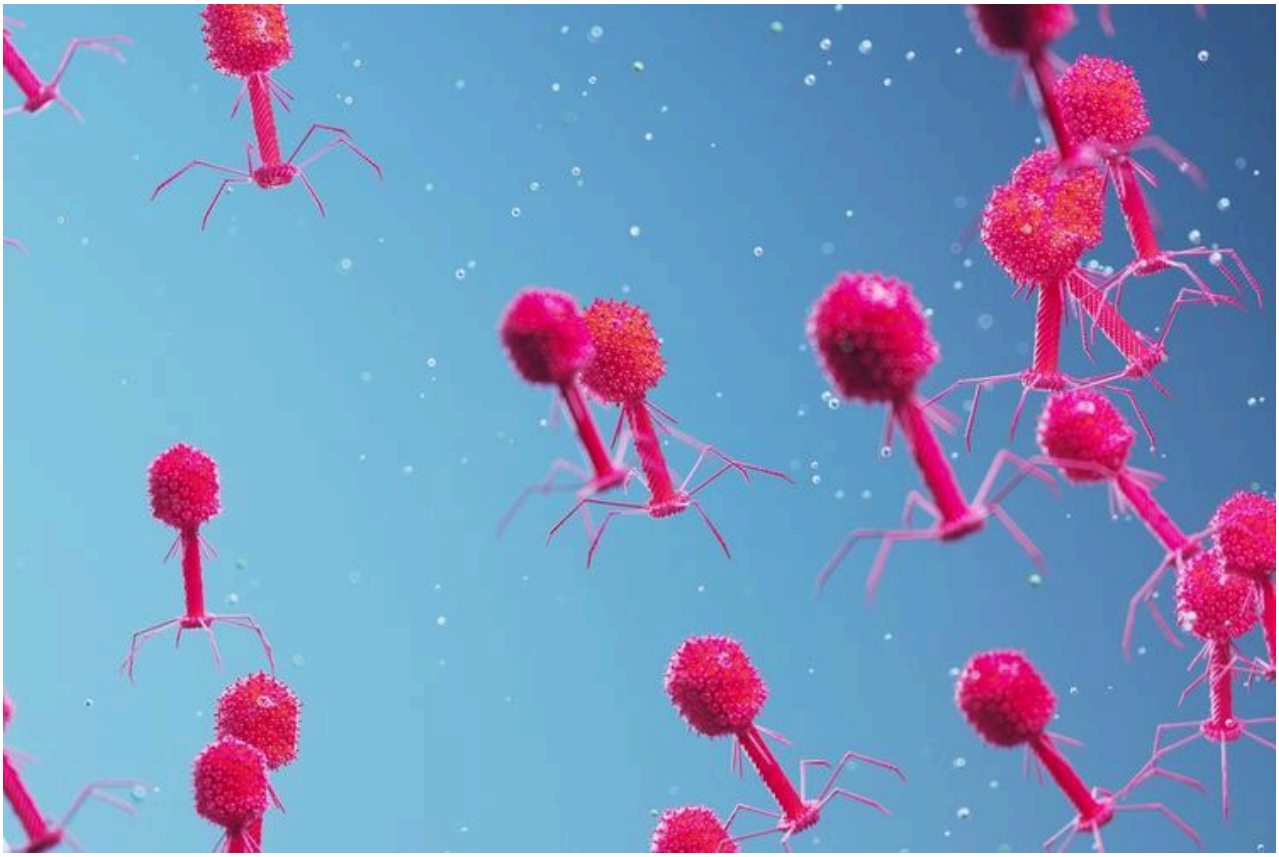
Challenges

While the specificity of phages is advantageous, it also creates challenges. For example, depending on the bacterial species in question, finding phage(s) that can kill your bacteria of interest may be difficult. Also, in many cases, several different types of phages will be needed to ensure suitable target coverage, for example in a polymicrobial infection, and to mitigate the development of bacterial resistance. Nevertheless, the diversity of phages means that bacterial resistance or neutralising immune response to phages can be overcome with different phages.

Safety and efficacy

Clinical and safety trials consistently demonstrate that the use of naturally occurring phages for therapy, by various routes of administration, is safe.[16,17] Regarding efficacy, the clinical case data are compelling. A 2022 systematic review of cases treated with phages since the year 2000 found that bacterial eradication was achieved in 87% of 1,461 patients – most of whom had failed antibiotic therapy.[17]

However, efficacy has been challenging to consistently demonstrate in trials, although this is likely to reflect methodological challenges rather than biological shortcomings.[16] Successful phage therapy requires the administration of enough of the right phages to the right place at the right time during infection, which has been challenging for trials to consistently achieve. However, where this has been achieved, efficacy signals have been observed.[16]



Research in phage therapies is making significant progress.

Encouragingly, there are around 20 active clinical trials of phage therapy internationally, providing hope that more robust trial data are on the horizon.[18] Additionally, in 2022, the American Antibacterial Resistance Leadership Group published a recommendation that unlicensed phage therapy be considered in cases of difficult-to-treat infection, with a similar recommendation from Health Improvement Scotland following a year later.[19,20]

Health Improvement Scotland's recommendation identified potentially suitable patients as being:

- those with antibiotic resistance or antibiotic sensitivity but clinical recalcitrance
- those needing an alternative medical option to prevent high risk surgery

- those where other factors (like allergy, antibiotic intolerance or renal disease) might prevent the use of appropriate antibiotics.

This is a sizeable and diverse patient population, including those with chronic bone/joint, respiratory or urinary tract infections. Clinicians can already consider phage therapy for such patients, with the use of phages falling under existing local NHS unlicensed medicines policies. The existence of unlicensed medicines policies in all trusts, the ease with which phages can be transported and the lack of specialist clinical expertise required for administration mean that we can logistically consider phages as we would any new type of antimicrobial, with all trusts equally capable of using them.

However, despite growing demand and no regulatory barriers, the use of phage therapy in the UK remains limited, largely reflecting practical barriers in obtaining phage therapy.[21]

Barriers to success

Historically, phage therapy has struggled to gain traction in Western medicine. This partly reflects a largely successful reliance on antibiotics, general disincentives around antimicrobial production and some commercial challenges unique to phage therapy. For example, phage therapy currently generally relies on naturally occurring phages, which has created concerns aroundissues of intellectual property. Although naturally occurring phages will undoubtedly remain in use, there is increasing commercial interest in engineered phages, which were 4th in the World Economic Forum's 2023 list of top 10 emerging technologies.[22]

Phage production has also been a challenge. Phages produced in the UK must be made in accordance with Good Manufacturing Practice (GMP), which is expensive and has proven commercially intractable despite compelling ethical and financial arguments.[23] For example, the few available health economic analyses of phage therapy have found phage therapy to deliver savings over standard care.[19,24] Cursory estimates suggest that widespread use of licensed phage cocktails could yield annual savings for the NHS of almost £180 million on diabetic foot care alone.[25] The recent UK Parliamentary Science, Innovation and Technology Select Committee inquiry's report recognised the need for the UK to establish GMP phage production. There are signs these challenges will be surmounted in the coming years, paving the way for phage therapy potentially to transform the way we treat bacterial infections.

The future

There are opportunities for phage therapy to be integrated into all stages of care. In future, preformulated commercial phage cocktails will be used in primary and secondary care settings, much as antibiotics are today. NHS microbiology departments will test the susceptibility of

patient isolates against these. While current phage susceptibility testing remains based on classical microbiological techniques, high-throughput real-time platforms are coming through. These can yield more diagnostic information while reducing result turnaround time and associated labour. As licensed medicines, preformulated phage cocktails would not have to be reserved for the most serious infections and could be used to treat routine infections or even prophylactically.

While in many circumstances phages are likely to be used alongside antibiotics, there are scenarios in which phages might be used alone. For example, a more favourable side effect profile may see patients electing for phage therapy rather than antibiotics; equally, and in contrast with unlicensed use, licensed products may be used as an alternative antimicrobial to reduce reliance on antibiotics or even to reduce costs. Even with licensed phage cocktails on the market, there will remain patients whose clinical needs are not covered by licensed products. In these cases, an isolate of their pathogen will be sent to a centralised clinical phage lab for susceptibility testing against a larger phage library and the generation of a personalised phage product. The ability to rapidly prepare and deliver bespoke phage products is a facet of phage therapy that could significantly enhance the UK's broader medicines security and biosecurity.

Conclusion

Phage therapy has the potential to transform the way we treat bacterial infections, improving outcomes for patients while possibly delivering substantial cost savings. Health Improvement Scotland has already recommended phage therapy for the treatment of difficult-to-treat infections. Currently, phage therapy may be considered for use as an unlicensed medicine in cases where licensed alternatives are not meeting clinical needs – a sizeable and diverse group of patients. In future, we can expect to see greater use of unlicensed phage products, licensed phage products coming to market and clinical phage therapy established as a new subspecialty in laboratory medicine.

References available on our website.

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