ISSUE 1 | SEPTEMBER 2023

TRIANGULATE HEALTH

AMR NAVIGATOR

SPOTLIGHT ON PHAGE THERAPY

THE SILENT PANDEMIC

‘IT’S ALIVE!’ PATENTING THINGS THAT MOVE

IN THE HEADLINES

Recent developments in phage therapy, from clinical trials to publications and funding grants.

CONTENTS

In this issue, we include insights from an interview with Professor Richard James, Emeritus Professor, University of Nottingham Medical School, founder of the Developing Novel Antibiotics Consultancy, and co-founder of Phage-UK.

TRIANGULATE HEALTH

The silent pandemic

The news of increasing antibiotic resistance is no longer a future concern. Dubbed 'the silent pandemic' by Dame Sally Davies, it is a very current threat to the treatment of routine medical conditions and the survival of patients. Concerns related to antibiotic use and consequential resistance are not new but started to compound during the COVID-19 pandemic. AMR resistance was partly masked by slower tracking of hospital-acquired bacterial infections as resources were diverted to patient care during the pandemic.

AMR could be responsible for a global increase in healthcare costs of ~$300 billion to $1 trillion per year by 2050.

According to a report published in The Lancet, AMR is now the 3rd leading cause of death worldwide behind ischaemic heart disease and stroke. Some of the most commonly resistant pathogens include *E. coli*, *S. aureus*, *K. pneumoniae*, *S. pneumoniae*, *A. baumannii*, and *P. aeruginosa*, which combined were responsible for 929,000 attributable deaths and 3.57 million associated deaths in 2019. Methicillin-resistant *S. aureus* alone, more commonly known as MRSA, was responsible for more than 100,000 attributable deaths in 2019.

An increase in AMR costs could result in a drop in GDP of 1% globally, rising to 5-7% in low- and middle-income countries by 2050.

What causes AMR?

Overuse and inappropriate use of antibiotics is probably the most well-discussed cause. In China, for example, the inappropriate prescription rate has been estimated at ~30%, rising to 50% in India and Kenya. In the US, pharmacists at the Mayo Clinic estimated 30-50% of antibiotics across the US are prescribed inappropriately. Overuse and misuse of antibiotics in agricultural practice have also been linked to increasing antibiotic resistance in human gut microbes. More recent research suggests air pollution is also to blame for as much as 11% of changes in antibiotic resistance levels across the world.

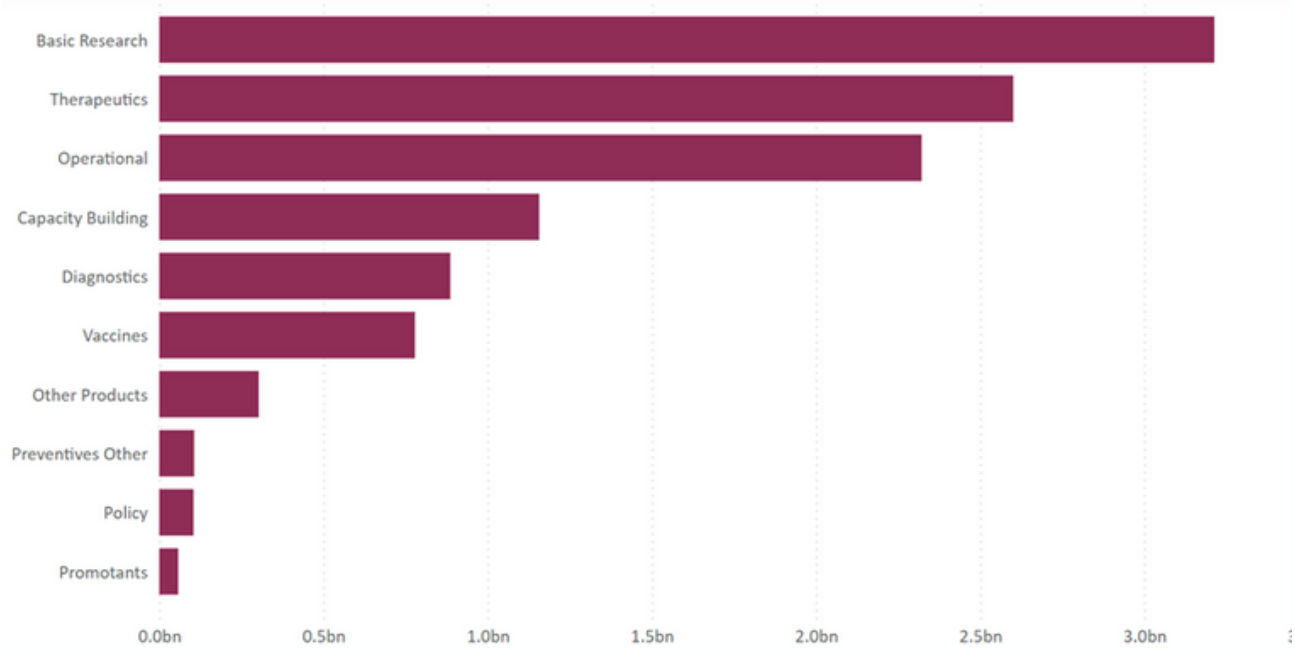
A blast from the past

One of the first steps to avoid overuse of antibiotics is simply having alternatives. Figure 1 outlines the total investments in AMR R&D between 2017 and 2023. It is no surprise that therapeutics have received the largest focus. In this first article, we focus our attention on a non-pharmaceutical therapeutic, phage therapy.

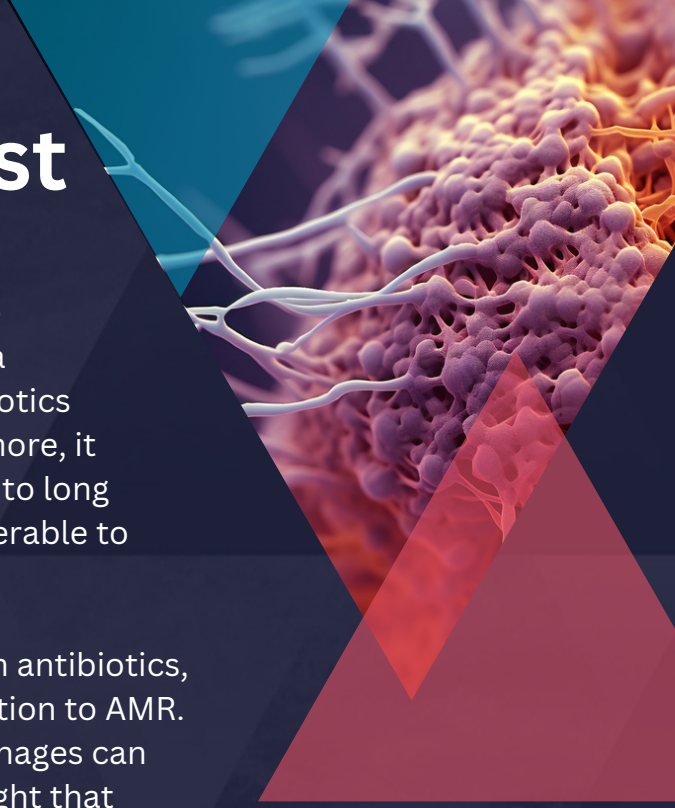
Phage therapy has gained increased interest in the last two to three years as a solution to antimicrobial resistance across the globe. It is a process that makes use of naturally occurring bacteriophage viruses, otherwise known as 'phages' which are not harmful to humans. Instead, they kill the bacteria causing an infection, and are capable of infecting and killing even antibiotic-resistant bacteria.

Professor Richard James describes bacteriocins and phages as an *"opportunity evolution created for us"* whilst simultaneously cautioning the disturbance of the microbiome with conventional antibiotics, especially in young children. While phage therapy has been available to treat bacterial infections since the beginning of the 20th century, the discovery of antibiotics in the 1920s relegated its use to the fringes of modern medicine. However, since 2005, several countries including Australia, Belgium, France, Germany, Georgia, and the US have used phages to treat difficult bacterial infections that have not responded to antibiotics.

Figure 1: Total investments (USD) by research area in AMR R&D between 2017-2023. *Source: Global AMR R&D HUB*



A blast from the past



Phage therapy can be both quick and inexpensive to produce, making it an appealing alternative to the development of novel antibiotics. It can be used as a stand-alone treatment or in combination with antibiotics to increase the effectiveness of treatment. Furthermore, it is less toxic to the body's natural bacteria—contrary to long courses of antibiotics which can leave patients vulnerable to re-infection.

Phages are also less likely to develop resistance than antibiotics, making phage therapy a potentially sustainable solution to AMR. Although resistance to phages can still occur, new phages can be used or even trained to attack bacteria. It is thought that with the correct personalised phage solution, the chance of resistance is low.

Phage therapy in practice

Phage therapy to treat multi-drug resistant tuberculosis

Phage therapy has the potential to be used for a range of health issues affected by AMR, including multi-drug resistant tuberculosis (MDR-TB), which is a growing public health problem in several countries. In 2021, 450,000 MDR-TB cases were reported, which is projected to increase up to 15% by 2040.

Currently, 20% of MDR-TB patients die each year during lengthy antibiotic courses of between four and twelve months. As MDR-TB requires longer antibiotic treatment courses than drug-responsive cases, phage therapy may have potential. Phage therapy offers a much shorter treatment duration of 6-8 weeks. One systematic review found the effectiveness of phage therapy to treat multidrug-resistant bacteria to be 85%.

Phage therapy to treat post-operative infections

Post-operative infections, or surgical site infections are the main cause of revision surgery, amputations, and reinfections. These complications are costly to health systems and amounted to GBP£962 million (about 0.9% of the entire NHS budget) in the UK between 2014-2016. Furthermore, evidence from Qatar estimates the cost per patient for amputations to be around USD$89,808 per patient, a significant economic burden on health systems.

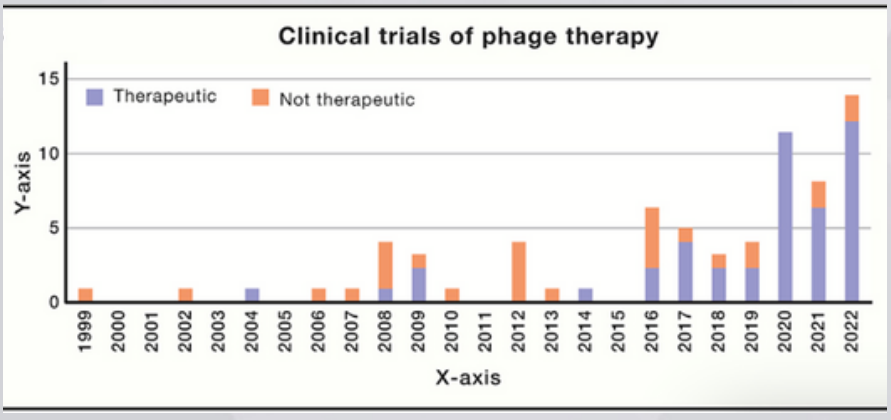
Phage therapy has the potential to reduce the burden of post-operative infections. One systematic review found phage therapy had a 71% success rate in the post-operative management of complicated infections. Phage therapy was generally well tolerated with only minor adverse events reported. This finding was supported by another systematic review, which found 79% of post-operative infections treated with phage therapy had a clinical improvement.

In the headlines

A recent flurry of activity in the phage space has partly been driven by Steffanie Strathdee, an epidemiologist who became an influential figure in the battle against superbugs when phage therapy saved her husband's life. A little over a year later, Strathdee used Twitter to hunt for phages to treat a patient with cystic fibrosis whose infection was no longer responding to antibiotics. A US based biology PhD student and a startup consultant who saw the tweet were inspired to start a Phage Directory in 2017. The directory includes a library of different phages used to treat specific pathogens as well as serving as a platform for collaboration. In the same year, the WHO published a priority list of multidrug-resistant bacteria, which includes carbapenem-resistant *Acinetobacter baumannii* and various strains of the *Enterobacteriaceae* family including *E. coli*. *Acinetobacter baumannii* has been successfully treated by phage therapy and a clinical trial is currently underway to examine if genetically engineered phages can be used to successfully treat E. coli. Researchers in the UK have produced a Citizen Phage Library, aiming to isolate new phages and encourage members of the public to become phage hunters (using sample kits provided at outreach events to collect bacteria).

Publications supporting phage therapy have started to pop up in high impact journals such as Cell, The Lancet and The Lancet Infectious Diseases. In a recent paper, Strathdee and colleagues demonstrate that the last three years have seen more activity in phage therapy than previous years (Figure 2). Out of a total 44 therapeutic clinical trials reported between 2016 and 2022, 29 were posted since the start of 2020.

Figure 2: Clinical trials of phage therapy.
Source: Strathdee et al. 2023



Local country governments and government funded health bodies are also stepping up. The UK Parliaments, Science, Innovation and Technology Committee set up an inquiry to investigate phage therapy, with its final report due end of summer 2023. In the US, the National Institute of Health recently awarded USD$2.5 million to 12 global institutes to investigate phage therapy. In Belgium, a phage therapy framework is being developed and the Belgian Ministry of Social Affairs and Public Health have written their own laws to enable phages to be prepared in pharmacies according to a medical prescription for an individual patient. This nimble strategy is flexible enough to allow the exploration of evolving bacteriophages whilst providing individualised therapies for patients as they need them.

TRIANGULATE HEALTH

‘It’s alive!’
Patenting things that move

Because phages are living organisms, they are difficult—but probably not impossible—to patent. Professor James, who is also a member of the advisory committee of CARB-X—a non-profit organisation with a mission to create a diverse portfolio of antibacterial products with regulatory approval—talked of the intellectual property (IP) complications. *“Native phages, found in living organisms, are very difficult to patent, whereas for genetically engineered phages and phages produced through cell-free synthesis, IP is possible”.*

Similarly, in May 2023, The Economist wrote an article about the potential of phage therapy but cited a lack of industry interest due to IP obstacles. The Economist suggested phage financing mechanisms might become more appealing to industry partners if the manufacturing process can be patented rather than the end product or phages themselves. Genetically engineering phages rather than using those that occur naturally was also suggested. The infamous CRISPR technique has been used with great success in phage genome engineering.

Table 1: Examples of commercial phage products on the market or in development.
Source: Huang et al. 2022, Gencay et al. 2023

Company	Product	Stage of trial	On the market
Adaptive Phage Therapeutics	Bacteriophages from phage bank to treat various infections	Phase 1/2 clinical trials for Diabetic Foot Osteomyelitis (DFO), Prosthetic Joint Infection (PJI), and Cystic Fibrosis-related Lung Infection	Early access for some critically ill patients where standard-of-care antibiotics failed
SNIPR Biome	CRISPR engineered bacteriophage to treat E. coli	Interim results available from ongoing phase 1 clinical trial (SNIPR001)	No
Pherecydes Pharma	Phage cocktail to treat bone and joint infections caused by S.aureus	Phase I/II trials	No
AmpliPhi	Treatment for C. difficile	Pre-phase 1	No
MicroMir	Topical gel to prevent bacterial skin infections	NA	Yes – only in Russia

‘It’s alive!’ Patenting things that move

While phage therapy holds great promise, its implementation into mainstream medicine requires further research and planning. Many practical complications relate to phage licencing. In most countries, phages can only be used as an unlicensed product in special circumstances when usual care—namely antibiotics—have failed. Until regulatory pathways open up, widespread use of phage therapy will remain constrained. Phage products are being developed for plants, animals, humans, and the environment but none are approved for human use in the US or UK. Only in Russia, Georgia, and a few other countries are phage products available to buy. Examples of commercial phage ventures in development or on the market are provided in Table 1.

It is also worth noting that pharmaceutical regulations are not fixed, they move as science evolves. Some regulators—such as the Food and Drug Administration (FDA) in the US—have already acknowledged the regulatory barriers to phage therapy.

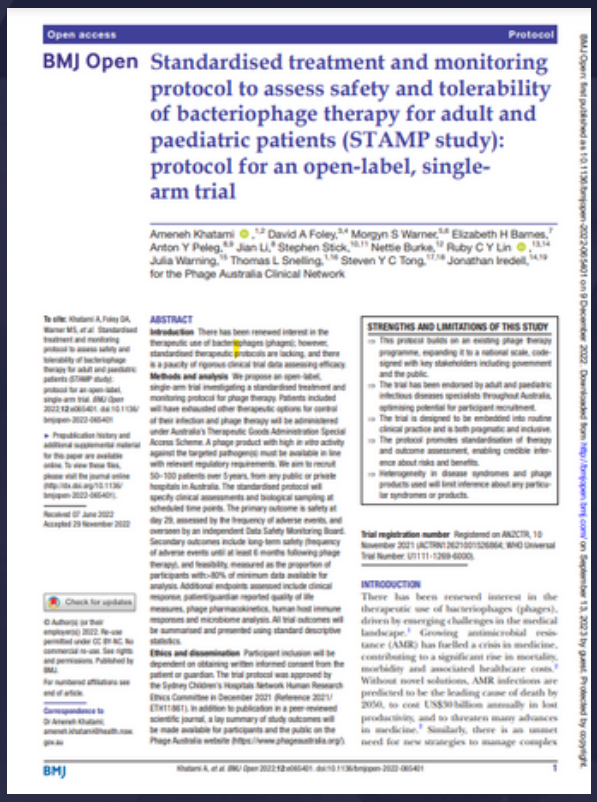
Experiences from countries using phage therapy will be important to move the needle and reduce the regulatory burden. Advocacy from patient groups should not be underestimated as a tool to garner influence and generate investment to showcase that phage therapies are effective and acceptable to patients. This approach has shown success in US. The story of one patient—narrated by the patient’s mother—who died from a superbug infection, caught the attention of medical teams and organisations like the Centre for Innovative Phage Applications and Therapeutics (IPATH). As this patient may have benefited from phage therapy, the story generated enough awareness to provide USD$100,000 to IPATH and a total USD$5.5 million earmarked for research.

“There are some products in agriculture where regulations are much lighter, so companies may be tempted to come through the agricultural route to try and build up their knowledge and expertise, and start selling products with the hope of moving into human health.” ***Professor Richard James***

Phage and frugality

The licensing process in many countries adds further complications—and costs—for phages. Currently as an unlicensed product, they can only be used in special circumstances rather than as an alternative treatment to reduce antibiotic use, to save money, or for clinical convenience. This makes it difficult to justify phage therapy as an efficient clinical alternative to antibiotics, particularly as decision making for special circumstances is often time consuming–a luxury which patients often do not have. Professor James states, *"In the UK there is an absurd situation where if a phage is imported you can use it to treat a patient, but if it's manufactured in the UK, it has to be in a GMC facility which costs half a million pounds for one phage, and for a cocktail of three, treble the price."* The Good Manufacturing Practice (GMP) standards restrict where and how often phages can be produced, as it is unlikely smaller laboratories producing phages on a per-patient basis have GMP certification—which is a long, complex, and expensive process.

Figure 3: The STAMP protocol developed in Australia, a potential alternative to the GMP approach. *Source: Khatami et al. 2022*



Open access Protocol

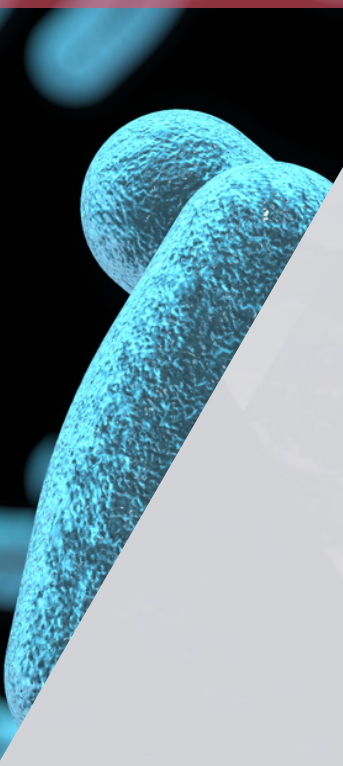
BMJ Open

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

Professor James states the UK is currently trying to adopt an approach developed by Australia, called the STAMP (Standardised Treatment and Monitoring Protocol for Adults and Paediatric Patients) protocol.

"This protocol sets out a plan to make, test, and use phages, and many interested clinicians in the UK are adapting the STAMP protocol to treat patients with phages. The eventual plan is to present this protocol to UK regulators as an alternative to the current and expensive, Good Manufacturing Practice (GMP) approach."

Phage and frugality



Understanding the direct costs of phage therapy—and determining cost-effectiveness—is often difficult, as the costs vary depending on both the type of infection and the pathogen causing the infection. In addition, finding the right phage to kill the bacteria can also be challenging and likely to influence the costs. While 'off-the-shelf' phage solutions seem like a practical option, personalised phage solutions are often needed for multi-drug resistant patients and other special cases. Personalisation requires advanced diagnostics to screen bacterial pathogens against a range of phages. This needs laboratories and unique expertise, not often available in general hospitals and local laboratories.

The cost of outpatient care for treating sinusitis cases with phage therapy has been estimated at USD$4,000-6,000 per procedure. Another study estimated a range of USD$8,000-20,000 to treat orthopaedic conditions such as osteomyelitis, diabetic foot conditions, and ulcers with phage therapy. However, as the cost per case for treating MDR-TB with usual care has been reported to be USD$182,186, increasing to USD$347,324 with the inclusion of societal costs, phage therapy has the potential to be cost-saving.

"Companies can make phage 'cocktails' effective against a large variety and number of pathogens."

Cost-effectiveness analyses could further help determine what a justified price might look like for phage therapy to be implemented into a health system in a sustainable way. It may also help companies develop an interest in phage. Professor James remains curious about how companies can help develop phage therapy. *"In a sense, phage therapy comes in two categories, the personalised phage approach, that takes the pathogen and the patient, and tests the pathogen to see which phage it is susceptible to. This is a public sector approach and does not make sense as a commercial venture. Then there are off-the-shelf options, which have more commercial potential. Companies can make phage 'cocktails' effective against a large variety and number of pathogens."*

To the future...

AMR represents one of the greatest threats to modern medicine. Effective antimicrobials, in particular antibiotics, have been the cornerstone of modern health systems and societies since their invention but it is clear that new technologies are urgently needed to respond to this emerging health crisis.

Phage therapy has the potential to become a powerful tool in the arsenal of health systems as AMR continues to rise. However, current regulatory complications have made phage therapy a less attractive investment for pharmaceutical companies and funders.

If phage therapies are to be a viable response to AMR, regulatory change is urgently needed so products can be licensed in more countries, with off the shelf solutions stocked in hospitals and pharmacies, but also personalised solutions available for complicated, unlicensed cases. Having some products readily available gives responding clinicians and patients more options when antibiotic treatment fails, increasing the chance of survival.

Next issue

Professor James advised us that the true effectiveness and costs of phage therapy may be difficult to determine without incorporating the parallel pathway of diagnostics, including rapid identification, the equivalent of antibacterial sensitivity testing, for phages. In the next issue, we explore diagnostic options, including rapid, whole genome sequencing, to identify the pathogen, predict sensitivity resistance to conventional antibiotics, bacteriocins or phages. Such solutions would help companies and public sector organizations to personalise AMR treatment approaches.

Useful links

AMR

- One Health: 10 ways to tackle antimicrobial resistance
- Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis
- Drug-resistant Infections: A Threat to Our Economic Future

Phage Therapy

- Targeting Phage Therapy 2023 showcased the progress and possibilities of phage therapy in future
- Phage Therapy: Past, Present and Future
- Recent advances in bacteriophage-based therapeutics: Insight into the post-antibiotic era
- Phage Therapy in the Era of Multidrug Resistance in Bacteria: A Systematic Review
- Phage therapy: From biological mechanisms to future directions
- Spread of antibiotic resistance revives interest in bacteria-killing viruses
- How to battle superbugs with viruses that “eat” them
- Phage Directory
- Citizen Phage Library
- The Magistral Phage