Phage therapies: Nature's answer to combating superbugs

As antibiotic effectiveness declines, increased clinical trials are being conducted. Cellexus is committed to supporting the development of phage therapies, which use bacteriophages to combat superbugs

ANTIMICROBIALS – including antibiotics, antivirals, antifungals, and antiparasitics – are medicines used to prevent and treat infectious diseases in humans, animals and plants.

So-called superbugs are microbes, typically bacteria, that have become resistant to one or more of the antimicrobial agents that have previously been used to treat them.

For nearly 100 years, antimicrobials have been helping animals and humans live longer, healthier lives. The extensive and frequently inappropriate use of antibiotics has fuelled the significant and rising instances of multi-drug resistant bacteria and antimicrobial resistance (AMR) as a whole.

It is estimated that in 2021, 4.71 million deaths were associated with bacterial AMR, including 1.14 million deaths attributable to bacterial AMR.[1] AMR is now recognised as one of the biggest global public health threats and is predicted to cause the death of ten million people annually by the year 2050,[2] presenting as a leading cause of human mortality.

The threat of AMR is not limited to human health but needs to be viewed in a wider, One Health, context where AMR is impacting the health and productivity of Animals and Crops. The impact of AMR is predicted to cost $1tr by 2030 and cause the world to lose 3.8% of GDP by 2050.[3]

In 2015, the World Health Organization (WHO) committed to a Global Action Plan (GAP) to tackle AMR, from which, as of November 2023, 178 countries have developed AMR National Action Plans (NAPs) aligned with the GAP. A key component of the plans is the development of new antimicrobials of which Bacteriophages (a.k.a. phages) are included as a highly promising solution.

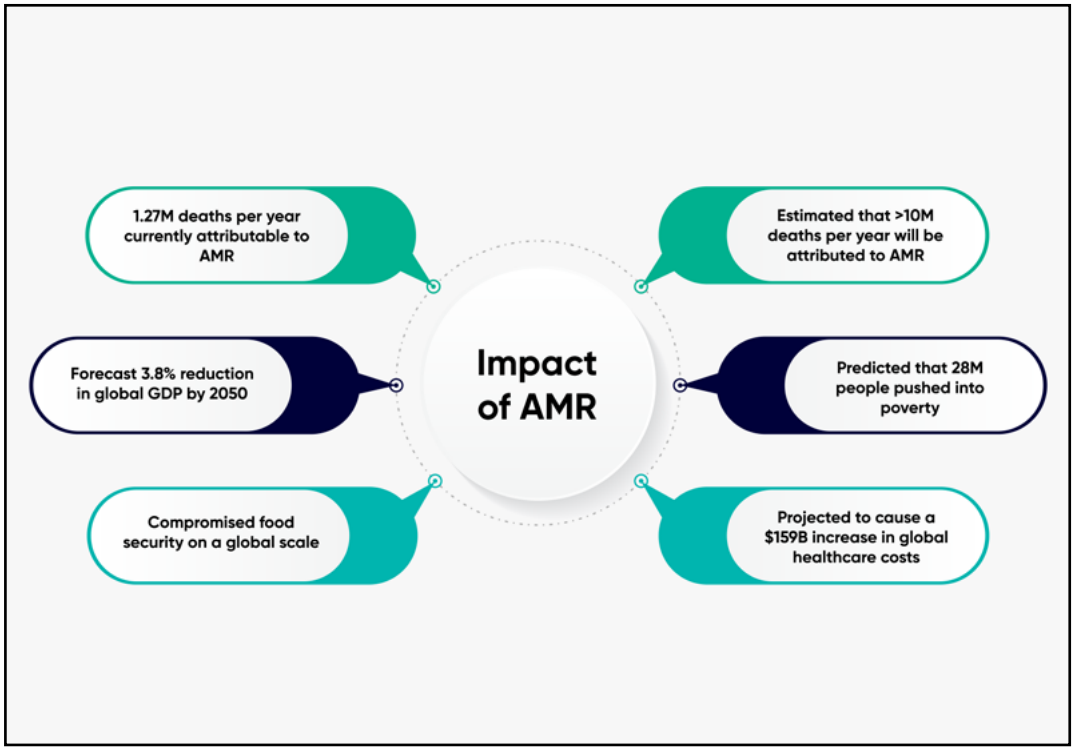


Fig. 1: The impact of AMR is significant and widespread

What are phages?

Phages are viruses that specifically target and kill bacteria and are the most abundant organisms on Earth. Phages are found in every natural environment, from the human gut to the soil of Antarctica. To put this in context, there are estimated to be 10^{31} phage particles in the world with a biomass of 200 million tonnes.[4]

Evolving alongside bacteria, each phage has typically become specialised to target a specific bacterial strain, and for each bacteria, there will be multiple phages hunting it.

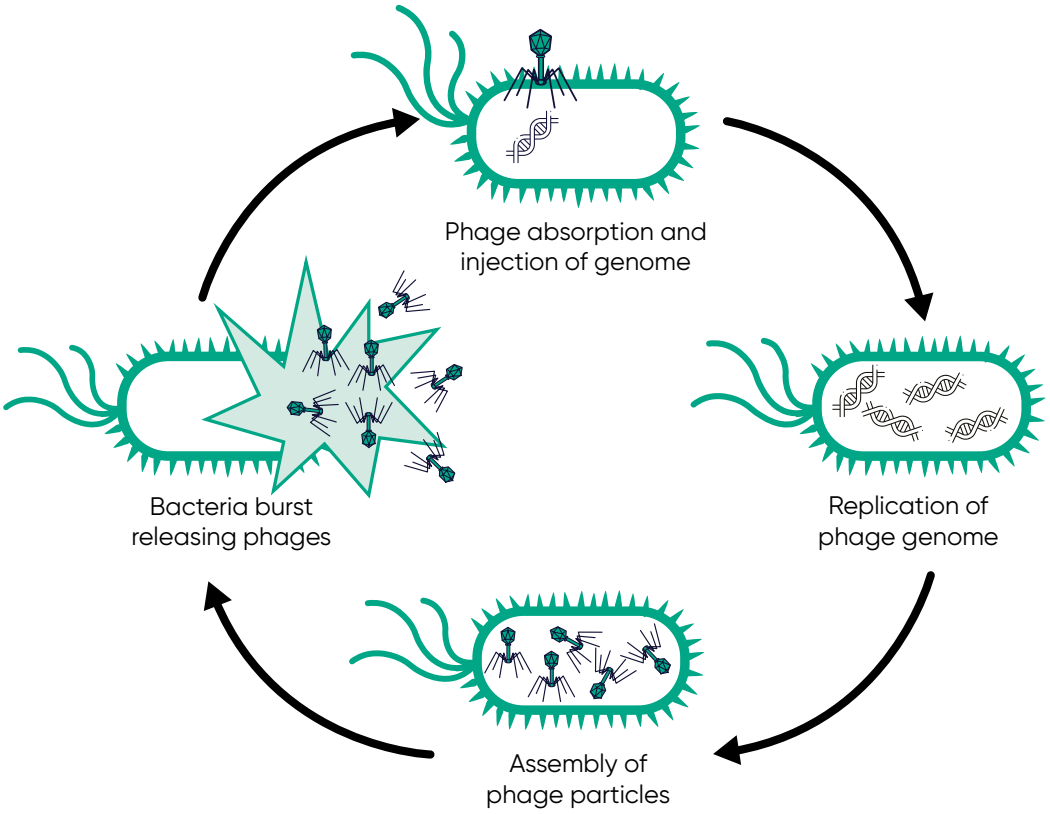


Fig. 2: The lifecycle of a lytic bacteriophage

Phages are hunting bacteria as they need to use the bacterial cellular machinery to replicate. Once a phage finds its target bacterium, it binds to the surface and injects its genetic material into the bacterial cell. The bacteria's cellular machinery is then hijacked to make more phage particles which form inside the bacteria until it bursts, releasing numerous phage to go hunting.

Status of phage therapies and challenges

Despite having been discovered and used as therapeutics long before the discovery of antibiotics, phage therapy was largely discounted once antibiotics became available. Antibiotics surpassed phage therapy as they provided broad-spectrum effectiveness against a wide range of bacteria and were cheap and easily administered.

Now that antibiotics are losing their efficacy, eyes are turning back to phage therapy as a solution. With the ready availability of high throughput laboratory techniques, such as genetic sequencing and advanced bioinformatics, the preparation of safe and effective phage therapies is more easily achieved. The past decade has seen a significant increase in the number of phage-based clinical trials undertaken, indicating the renewed interest in phage.

Despite this, many challenges remain, requiring a coordinated effort from a variety of stakeholders, not limited to researchers and clinicians but also funders, regulatory bodies, and governments.[5]

The development of tools to streamline the isolation, analysis and production of phage will be integral to the widespread implementation of phage therapy. At Cellexus, we are committed to providing phage scientists with a culture platform that is perfect for overcoming the unique challenges of producing phage and supporting their vital work to combat AMR.

The CellMaker system delivers exceptional performance and process benefits and focuses on the three key aspects of resource utilisation, regulatory compliance, and reliability.

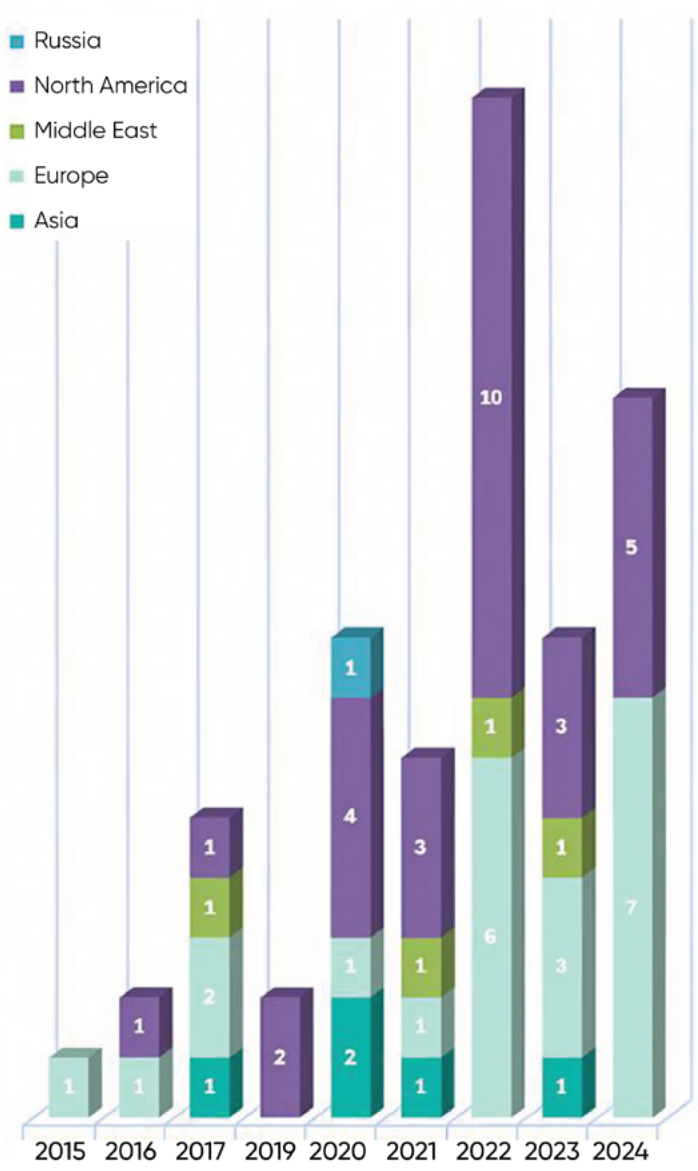
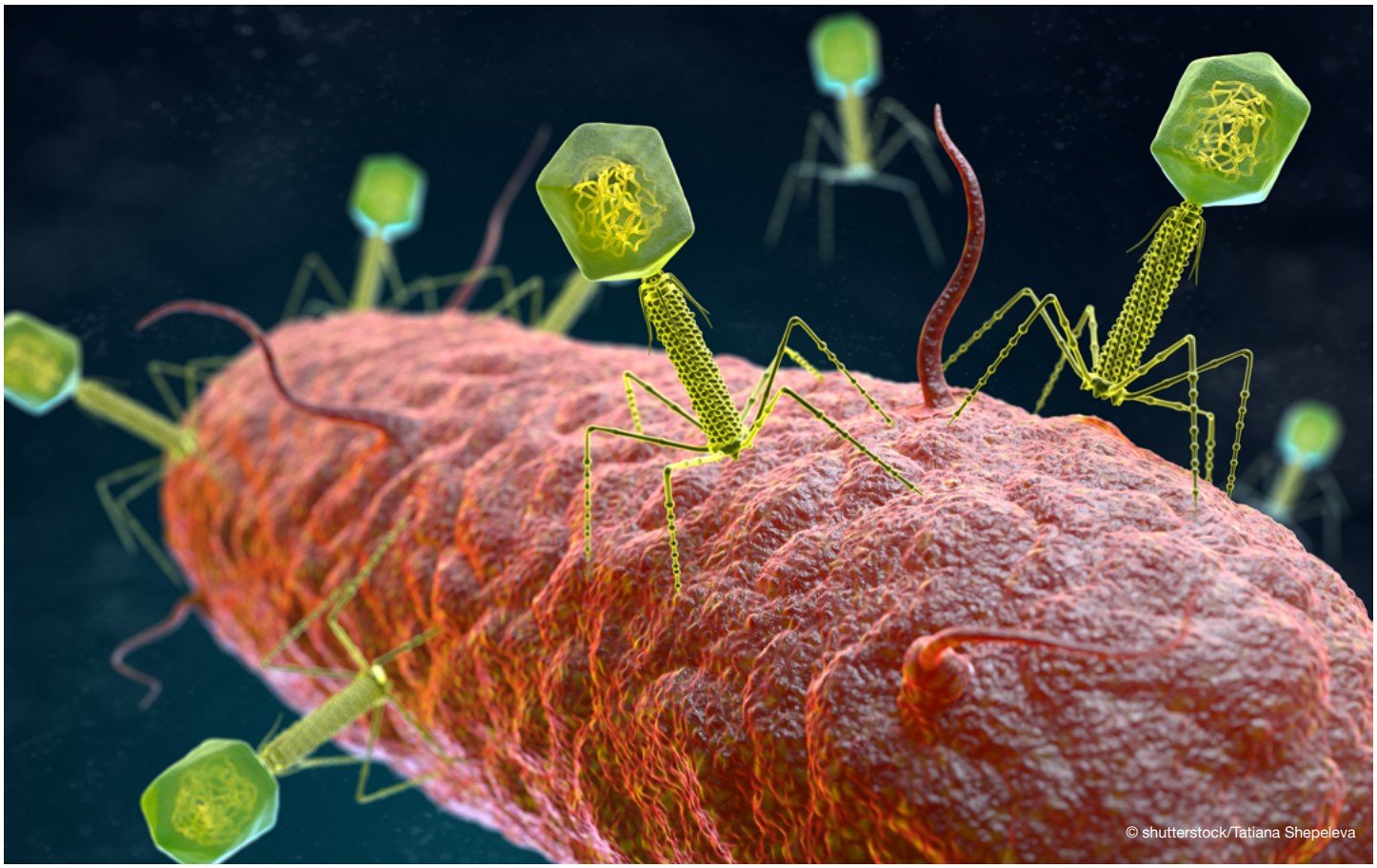


Fig. 3: Number of clinical trials initiated by geographic region. Data sources: www.clinicaltrials.gov and www.EudraCT.ema.Europa.eu.



Resources

CellMaker is designed to make the most of the resources (time, space and money) you have available.

CellMaker is the ideal solution for producing phage at very high titres (concentrations), frequently 10-100x higher than can be achieved using other types of bioreactor. Being able to produce phage at much higher titres reduces the production cost through the use of smaller culture volumes. Producing phage at higher concentrations also removes and/or reduces costly and time-consuming downstream processing steps.

The higher yield is attributed to the unique airlift mixing technology, which provides highly effective gas and nutrient exchange to support bacterial growth but without the mechanical forces associated with conventional bioreactors, which can damage cells and phage alike.

The patented CellMaker airlift bioreactors are single-use, which practically eliminates the risk of cross-contamination during the cell culture process and reduces the burden of process validation.

CellMaker single-use bioreactors maximise laboratory productivity by minimising bioreactor turnaround time. Practically a turn-key solution, CellMaker can be ready to use in a matter of minutes and negates the cleaning, assembly and sterilisation processes normally

Fig. 4: A CellMaker can be made ready to produce something completely different within minutes by simply putting a new bioreactor bag into the CellMaker Enclosure, filling it with media and pressing go!

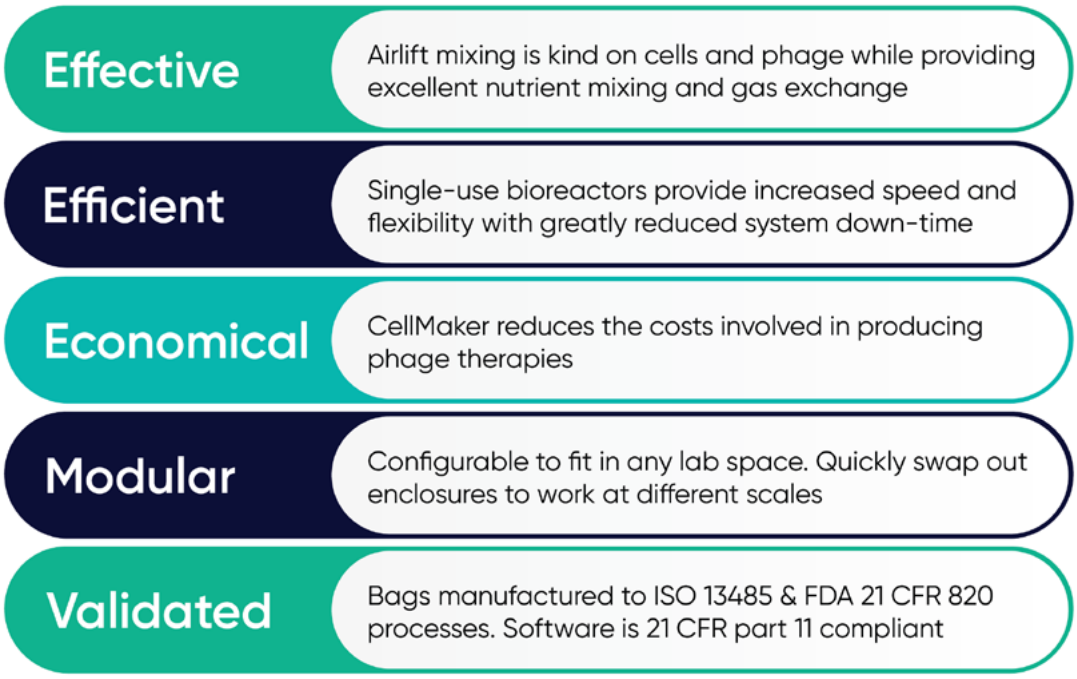


Fig. 5: Summary of CellMaker benefits

associated with reusable bioreactors, making them a more sustainable solution.[6]

In addition to time and money, space is typically a limiting factor within cell culture suites. CellMaker is a small-footprint, modular system that can be configured to fit into practically any laboratory. With a single Controller, one or two 8L and/or 50L Enclosures can be controlled, providing scalability from 1.5L to 100L with minimal lab space required.

Regulatory

Manufactured within ISO Class VII cleanrooms to ISO 13485:2016 validated and FDA 21 CFR 820 compliant, the CellMaker bioreactor bags provide the regulatory compliance required for rapid translation from research to therapeutic production. The ability to quickly initiate the production of therapeutic phage will be vital to respond effectively to outbreaks of antimicrobial-resistant pathogens.

Underpinning the operation of the system is the intuitive and highly usable CellMaker software which provides full control and logging of the cell culture process. The CellMaker software can operate either in research mode or in a 21 CFR Part 11 compliant GMP manufacturing mode as required.

Reliability

CellMaker sets new standards in bioreactor reliability. Repeatedly assembling and disassembling bioreactors is not only costly but can lead to vessel damage, seal failures and process issues. CellMaker removes all of these potential sources of batch failure. With few moving parts and no vessel assembly or maintenance requirements, CellMaker is always ready to be used. With each and every CellMaker bioreactor bag being rigorously inspected and pressure tested after manufacture, you can rest assured that CellMaker will not let you down.

Leading the way

Cellexus is at the forefront of phage production technology and is developing the CellMaker platform to further support the rapidly evolving requirements of phage scientists. We are always keen to discuss specific requirements and work with partners to overcome particular challenges, please do not hesitate to contact us if you would like to explore how CellMaker could help your workflow.

References

1. GBD 2021 Antimicrobial Resistance Collaborators. Global burden of bacterial antimicrobial resistance 1990-2021: a systematic analysis with forecasts to 2050. *Lancet*. 2024 Sep 28;404(10459):1199-1226. doi: 10.1016/S0140-6736(24)01867-1. Epub 2024 Sep 16. PMID: 39299261; PMCID: PMC11718157.

2. O'Neill, J. (2014) Antimicrobial Resistance: Tackling a Crisis for the Health and Wealth of Nations. *The Review on Antimicrobial Resistance*, 20, 1-16.

3. WORLDBANK - Jonas, O.B.; Irwin, A.; Berthe, F., Cesar, J., Le Gall, F.G.; Marquez, P.V.. (2017). *Drug-resistant infections: a threat to our economic future* (Vol. 2): final report (English). HNP/Agriculture Global Antimicrobial Resistance Initiative Washington, D.C.: World Bank Group.

4. Chevallereau, A., Pons, B.J., van Houte, S. et al. (2022). Interactions between bacterial and phage communities in natural environments. *Nat Rev Microbiol* 20, 49–62. https://doi.org/10.1038/s41579-021-00602-y

5. Strathdee, S.A., Hatfull, G.F., Mutalik, V.K., Schooley, R.T.. (2023) Phage therapy: From biological mechanisms to future directions. *Cell*. 2023 Jan 5;186(1):17-31. doi: 10.1016/j.cell.2022.11.017. PMID: 36608652; PMCID: PMC9827498

6. Whitford, W.G., Petrich, M.A., Flanagan, W.P.. (2019). *Environmental Impacts of Single-Use Systems, Single-Use Technology in Biopharmaceutical Manufacture*, Second Edition, John Wiley & Sons, Inc.

Gareth Bolitho
Commercial Director
Cellexus International Ltd
+44 (0)1382 666357