Bacteriophages for chronic infections

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How to pronounce:
Phages rhyme with pages

Personalised phage therapy for pan-resistant Pseudomonas aeruginosa infection

Microbiology
Blood cultures
P. aeruginosa

Catheter-related bacteremia

Microbiology
Aspiration
Bone biopsies
P. aeruginosa
3+/3

Microbiology
Bone biopsies
P. aeruginosa
6+/7

Surgery
8th March 2019
Treatment of infection
Abcess drainage
Discectomy
Debridement
Partial stabilization

Microbiology
Bone biopsies
P. aeruginosa (SCV phenotype)
2+/6

Surgery
14th May 2019
Reconstruction
Debridement
Intersomatic cages
Osteosynthesis
Definite stabilization

Back pain

Phage therapy
Local

Phage therapy
Local

Dec. 2017 | July 2018 | Dec. 2018 | Jan. 2019 | March | April | May | June | July | Aug. | Sept. 2019

Opioids

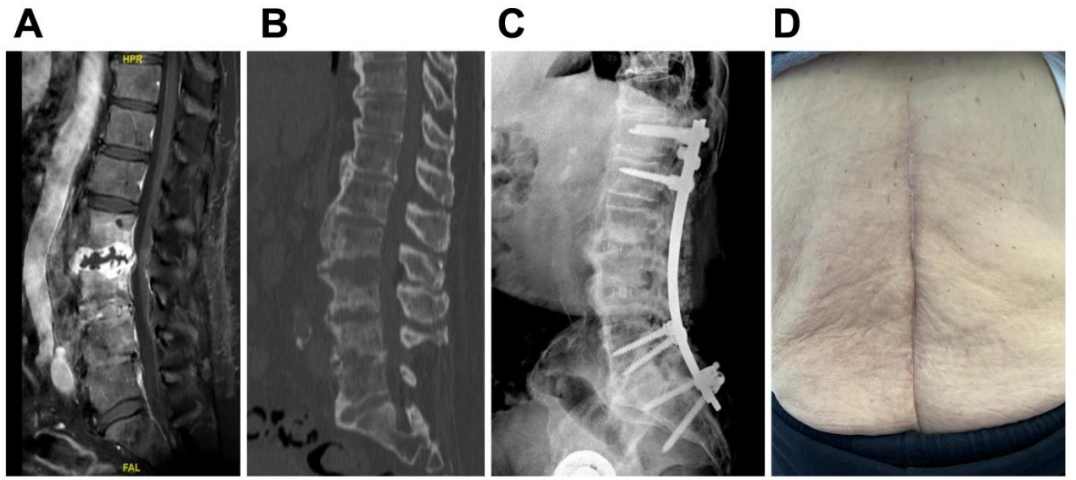
Phage therapy
IV
Duration: 21 days

Antibiotics
IV: Meropenem, Colistin
Duration: 6 days

Antibiotics
Oral: Rifampin
IV: Colistin
Duration: 12 days

Antibiotics
IV: Cefiderocol
Duration: 43 days

Antibiotics
IV: Cefiderocol, Colistin
Duration: 97 days



A Gadolinium T1-weighed MRI of the spine showing L2-L3 disc abscess and L3-L4 spondylodiscitis; **B** CT-scan showing mirror-like bone destruction from either side of the L2-L3 abscess; **C** X-ray performed at the end of the follow-up showing no loosening of the spinal osteosynthesis and the adequate position of the intersomatic cages at L2-L3 and L3-L4 level with anterior bone fusion; **D** Local aspect of the lumbar scar at the end of the follow-up, showing no inflammation nor discharge.

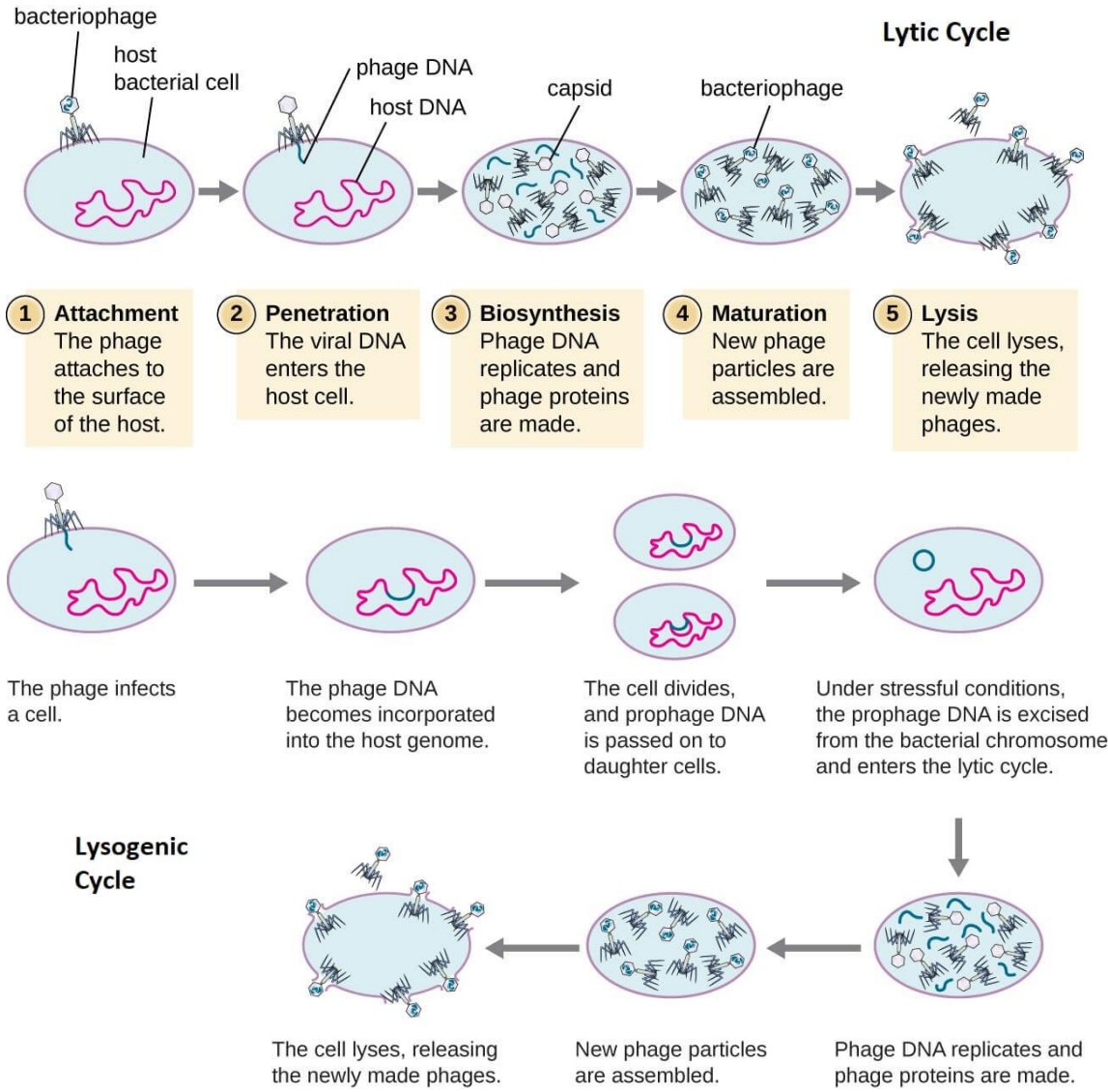
74y Frenchman with malignant melanoma (pembrolizumab) gets a catheter-related MDR-Ps aeruginosa infection in Dec-17 successfully treated with colistin & meropenem

Dec-18 – pan-resistant spinal abscess – AKI with AB. Treated with phages at each surgical episode plus AB

https://www.nature.com/articles/s41467-022-31837-9

🔬 What Are Bacteriophages? “Devour bacteria”

- Viruses that infect and kill bacteria
- Found in abundance in nature—oceans, soil, and the human gut
- Can only reproduce in a bacteria
- Highly specific: each phage targets a particular bacterial strain
- Two life cycles:
  - **Lytic**: destroys bacteria immediately
  - **Lysogenic**: integrates into bacterial DNA (less useful for therapy)
- Used widely in food industry to stop bacterial biofilms on equipment, or extending the shelf-life of food where pathogenic bacteria spoil the food



💊 Why Phages Matter in Human Health

- **Antibiotic Resistance Crisis**
  - Overuse of antibiotics has led to resistant “superbugs”
  - WHO estimates AMR causes over 133,000 deaths annually in Europe
- **Phage Therapy Potential**
  - Targets drug-resistant bacteria
  - Can be tailored to individual infections
  - Minimal disruption to human microbiota
  - Discovered in 1911 but dropped out of favour when antibiotics discovered, except in Russia, Poland & Georgia. Used as off the shelf cocktails or bespoke products
  - As AMR increase phages are being revisited for chronic infections

- **UK Parliamentary Science, Innovation & Technology Committee** made recommendations in Jan-24 on
  - phage safety, efficacy and the UK phage research base
  - manufacturing phages
  - phage clinical trials
  - the clinical use of phages in the UK
- **Scottish Health Technology Group (Feb-23)**
  - Bacteriophage therapy may, at the **discretion of the responsible clinician**, be appropriate management for patients with difficult to treat bacterial infections.
  - Bacteriophage therapy is **not currently licensed** by the MHRA and use must comply with their guidance on the supply of unlicensed medicinal products
  - Use of bacteriophage in Scotland must be **accompanied by the collection of data to monitor the clinical effectiveness and safety** of bacteriophage therapy for specific clinical indications, in order to inform ongoing decision making on the provision of bacteriophage therapy in Scotland.

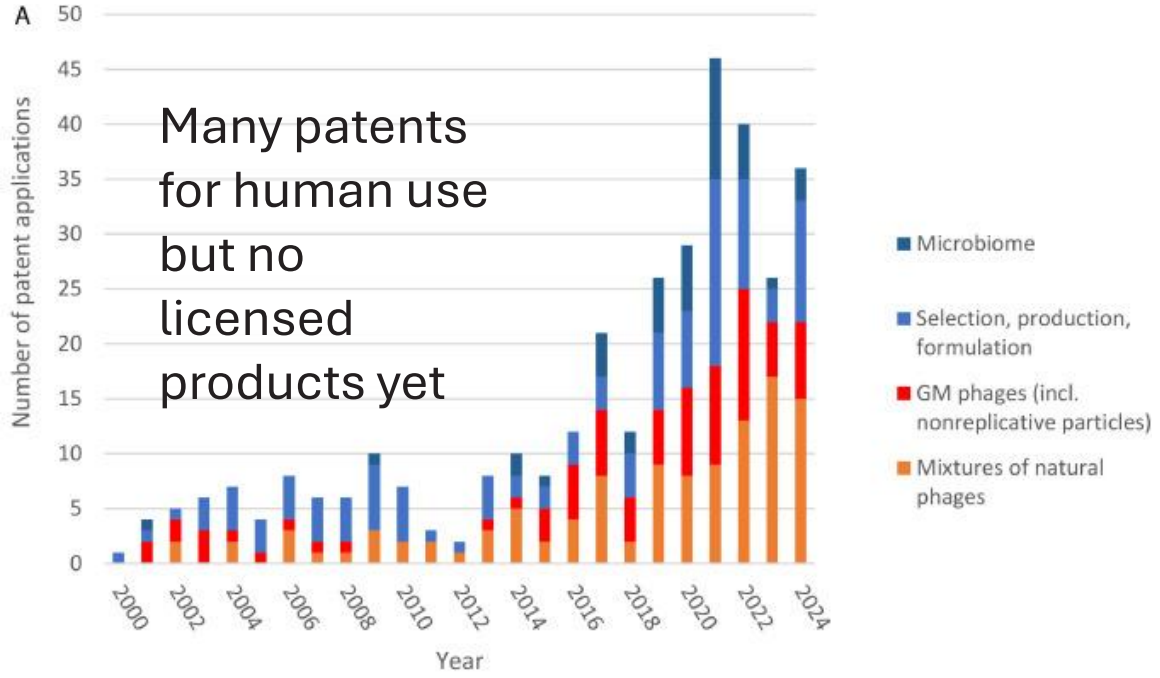
https://www.gov.uk/government/publications/the-antimicrobial-potential-of-bacteriophages-report-government-response/governments-response-to-the-science-innovation-and-technology-committees-report-the-antimicrobial-potential-of-bacteriophages#summary-of-the-committees-recommendations
https://shtg.scot/our-advice/bacteriophage-therapy-for-patients-with-difficult-to-treat-bacterial-infections/

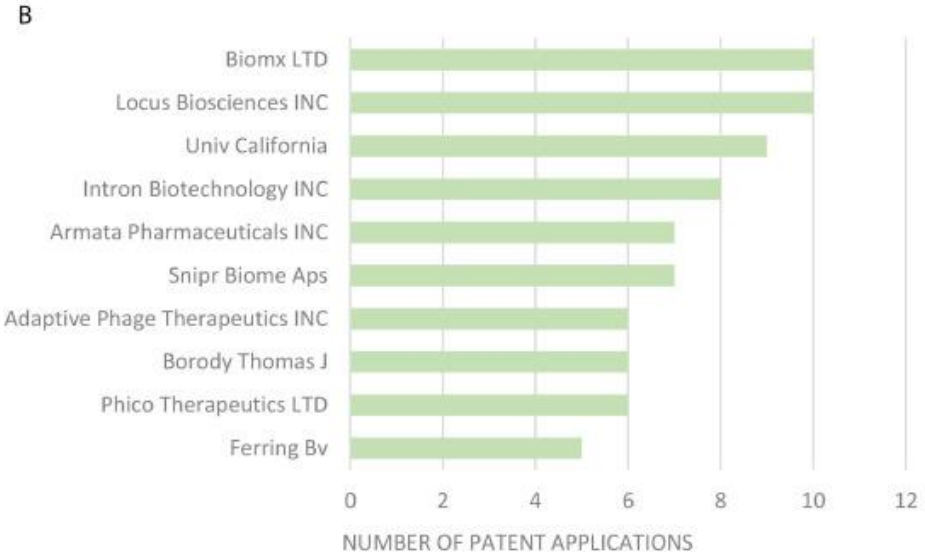
Difference between bacteriophages & antibiotics

Characteristics	Phage Therapy	Antibiotics
Safety	comparatively **safer than antibiotics** as there are minimal side effects to the patients.	well documented adverse reactions to antibiotics eg neurotoxicity, cardiotoxicity, and hepatotoxicity.
Specificity	Phages are **highly specific**, and thus, a phage can only be used for a few bacterial strains.	broad spectrum that can affect more than a single target organism.
Resistance	Resistance against phages can occur, but it is usually **limited to a single target bacteria**.	Antibiotic resistance is common phenomenon, and it is not limited to the targeted bacteria.
Efficiency against biofilms	**can penetrate biofilms** to infect the bacterial population present underneath.	Antibiotics are ineffective against biofilms.
Development	**comparatively easy** as phages obtained from sewage and waste materials with high bacterial density.	Time-consuming and expensive process.
Immune system	Some phages **might interact with the immune system** and result in undesired effects.	Antibiotics do not interact with the immune system of the patients.
Guidelines	There are **no guidelines for the use of phages** as therapeutic agents.	There are specific guidelines for the use of antibiotics by a different organization.
Combination therapy	The **development of combination phage therapy is tough.**	The development of a combination antibiotic therapy is fairly easy.
Administration	The administration of some forms of phage therapy **might be difficult**.	The administration of antibiotics is quite easy.

Clinical Applications

- **Compassionate Use Cases**
  - Life-threatening infections where antibiotics fail.
  - Scotland have recommended it but without funding
  - No licensed products in UK, EU, USA, Canada or Australia
- **Examples of Success**
  - Chronic wound infections
  - Cystic fibrosis-related lung infections
  - Sepsis caused by multidrug-resistant bacteria
  - Chronic bone infections
- **Combination Therapy**
  - Phages + antibiotics = enhanced efficacy



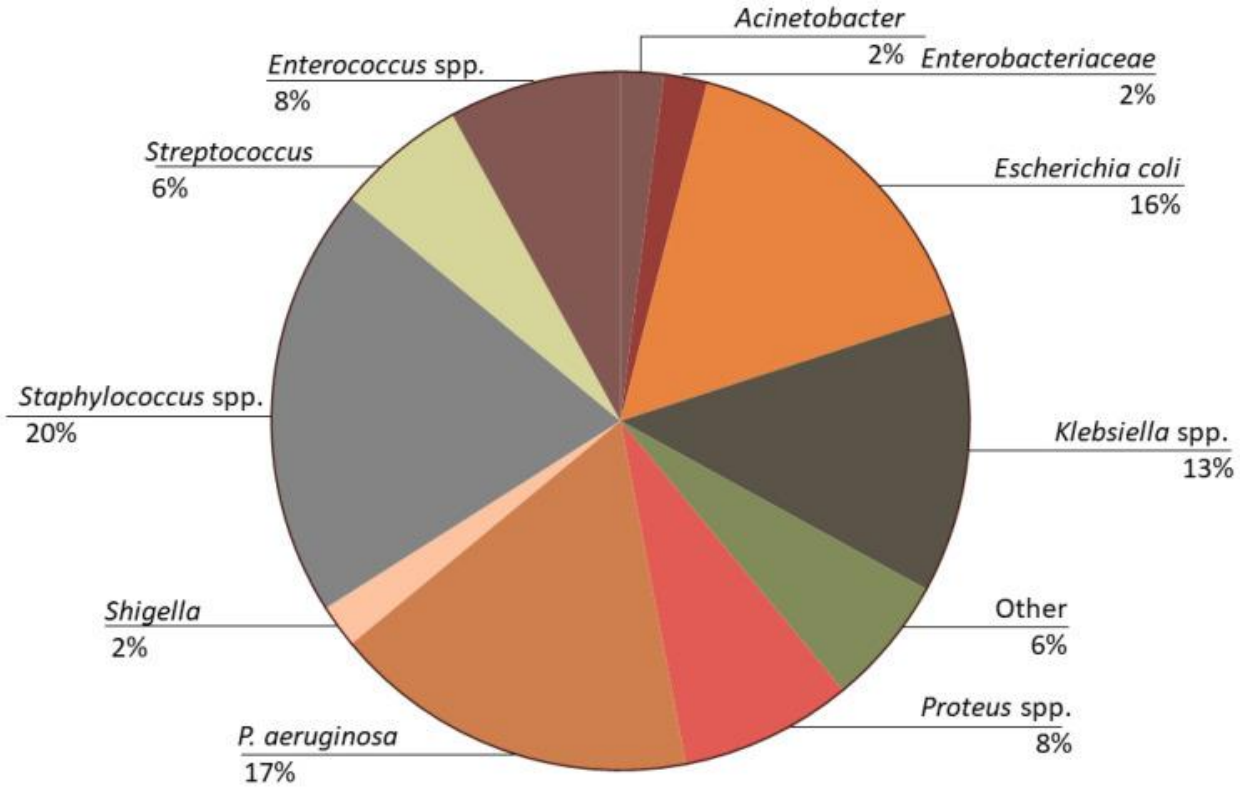


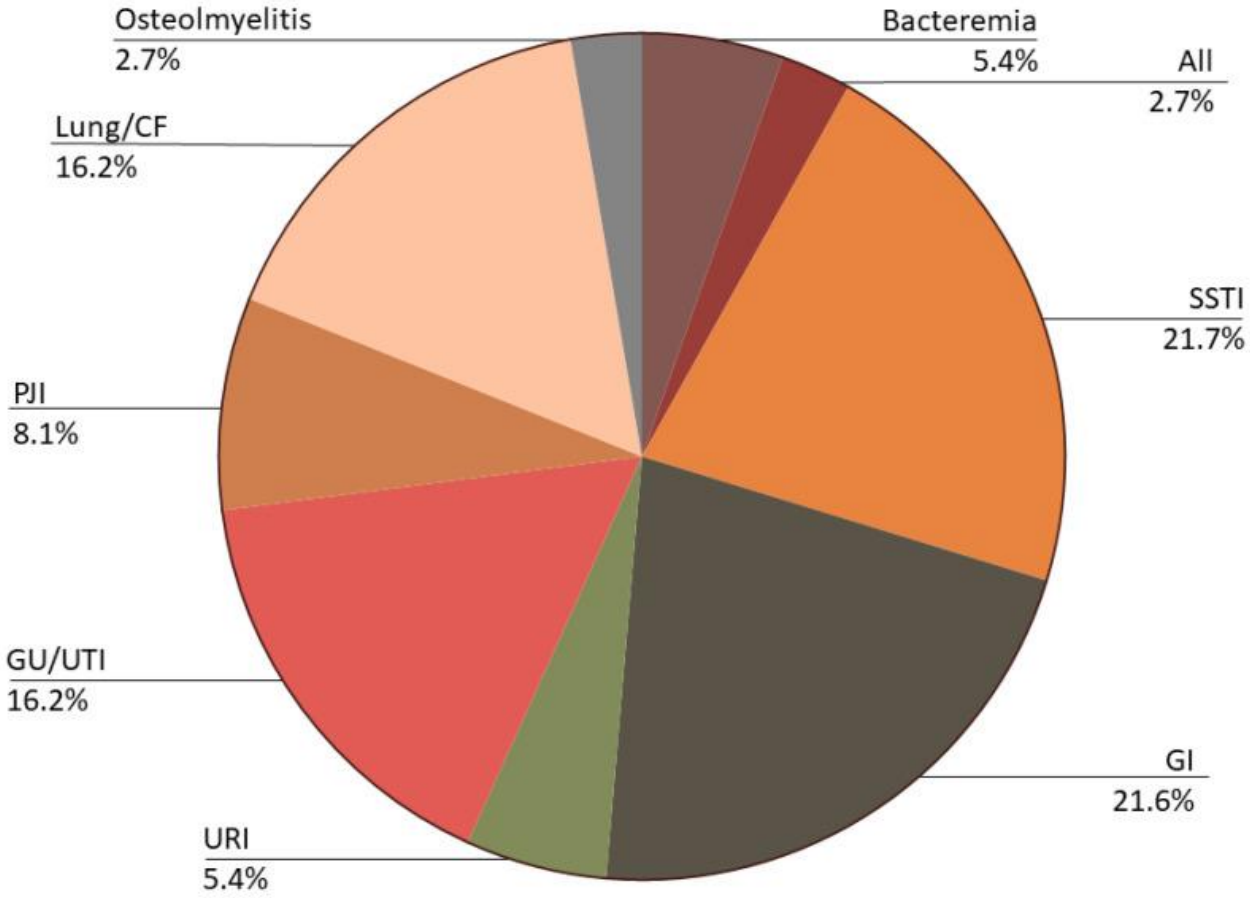
Safety and Efficacy of clinical trials

- Phages do **not** infect human cells, but can cause **endotoxin release** from bacterial lysis similar to beta-lactams and immune response with neutralising antibodies
- 13 trials since 2000 for safety (6) & efficacy (7):
  - 6 oral, 3 topical & 4 intra-nasal / aural / vestibular.
  - 11/13 used cocktails
  - 302 subjects - 6/13 in healthy adults / children
  - All 13 concluded that phage were safe and without phage-related side-effects
- **Pseudomonas chronic otitis externa** – single dose (6-phage cocktail) showed improvements & lower bacterial counts vs controls
- **Chronic sinusitis by Staphylococci** treated 7 or 14 days of 3-phage cocktail – all improved & 2 eradicated
- All **others failed to show a benefit**, possibly due to poor trial design
  - Complex UTI by mixed pathogens
  - Chronic venous leg ulcers
  - Pseudomonas in burns (2)
  - E.coli diarrhoea
- 1st 100 patients treated by Belgian Military Hospital case series from 12 EU countries (incl UK) showed 77% improvement & 61% bacterial eradication.
- UK study of Staph aureus Diabetic Foot at high risk of amputation showed. 9/10 improved.

Stacey 2022Antibiotics https://pmc.ncbi.nlm.nih.gov/articles/PMC9598614/
Pirnay 2024 Nature https://www.nature.com/articles/s41564-024-01705-x

Current (45) clinical trials are mainly targeting ESKAPE organisms and skin & soft tissue or gastrointestinal infections

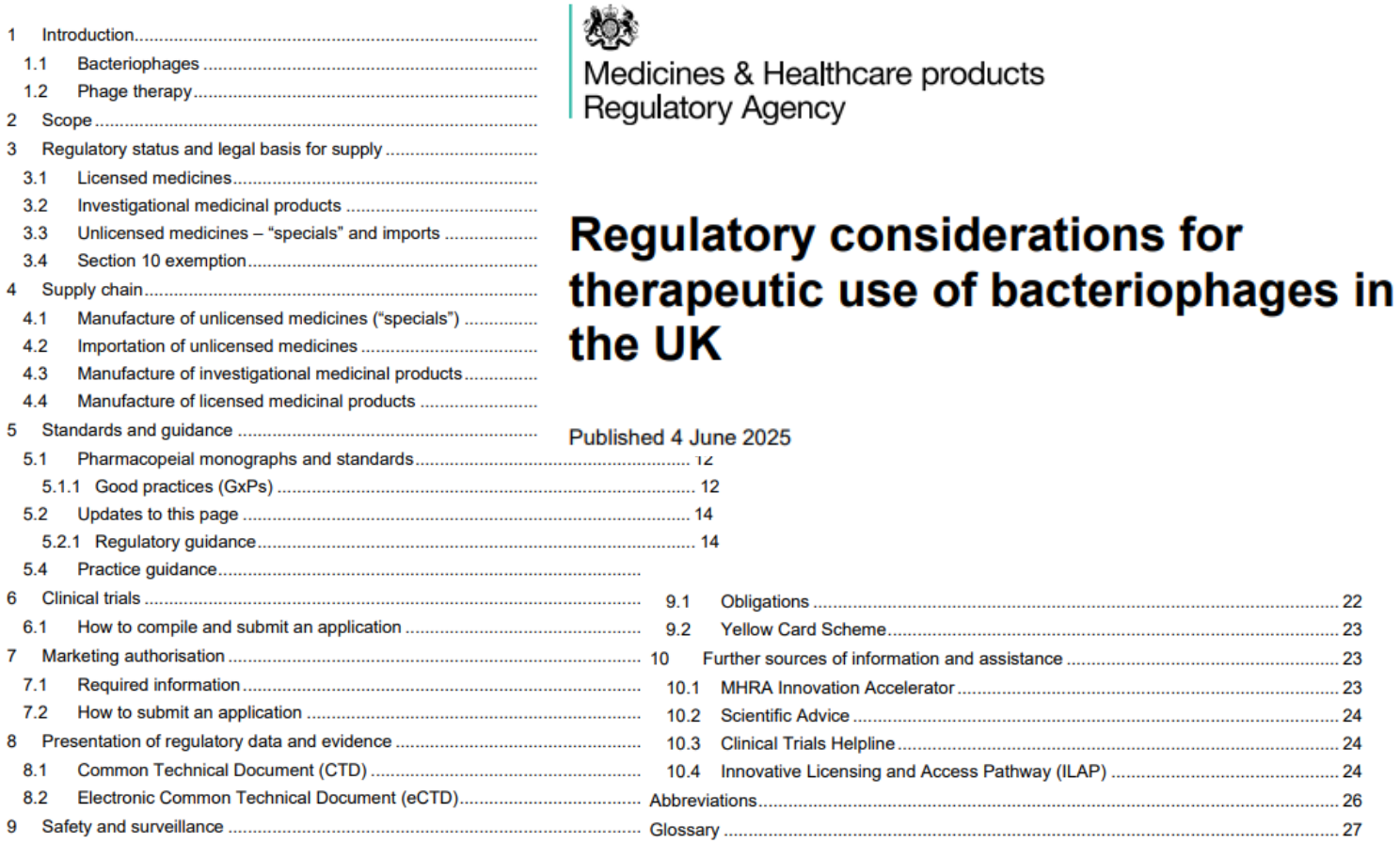




Hitchcock 2023 Viruses https://pmc.ncbi.nlm.nih.gov/articles/PMC10146840/

Challenges and Limitations

- Regulatory hurdles—lack of standardized approval pathways eg susceptibility testing, BP/EU monographs
- Need for more clinical trials to prove efficacy and safety, especially dosing
- Potential for bacterial resistance to phages (neutralizing antibodies)
- Manufacturing and storage complexities (shelf-life) – only 5 GMP sites in EU



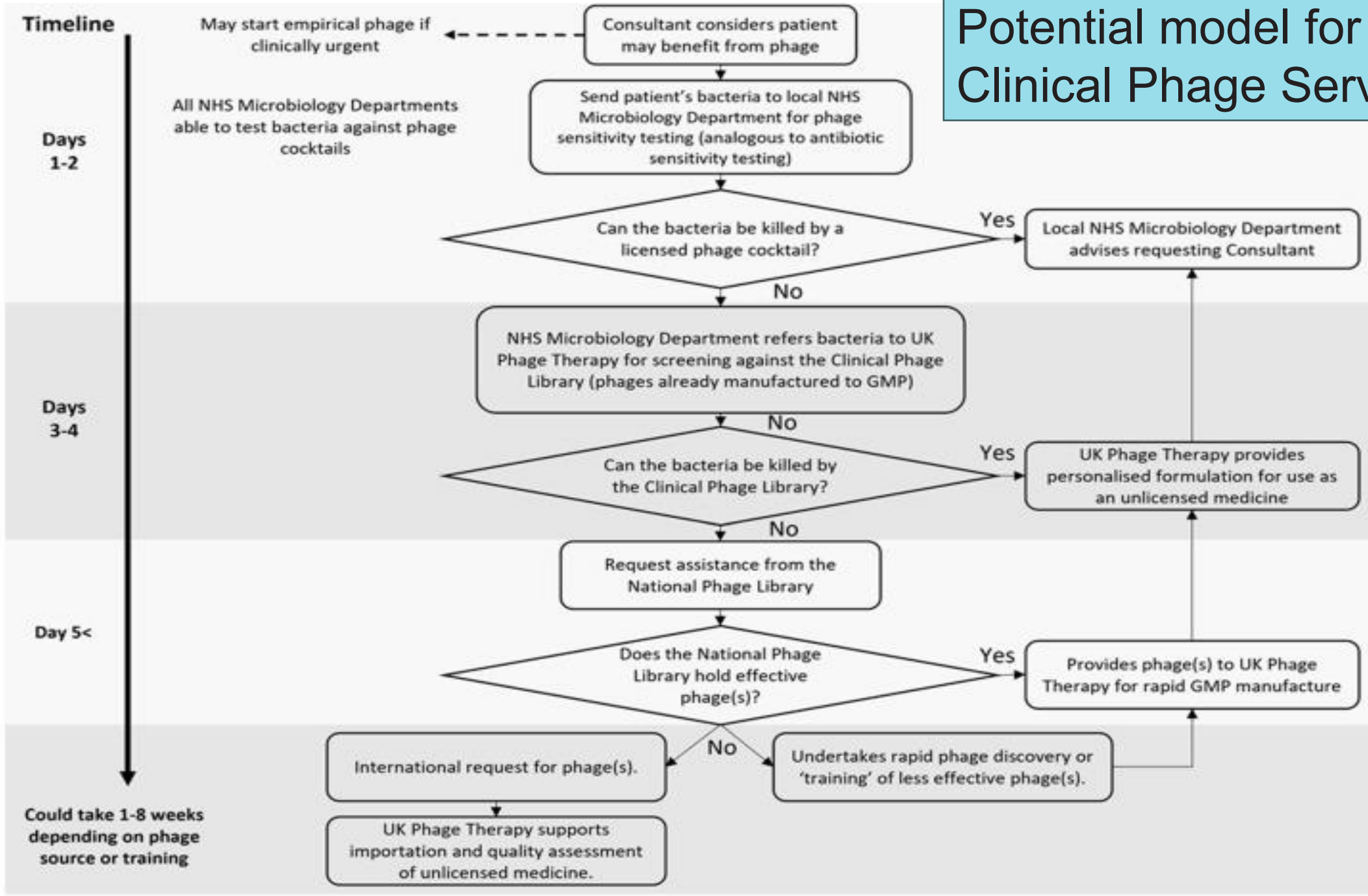
Medicines & Healthcare products Regulatory Agency

Regulatory considerations for therapeutic use of bacteriophages in the UK

Published 4 June 2025

https://www.gov.uk/government/publications/regulatory-considerations-for-therapeutic-use-of-bacteriophages-in-the-uk

Potential model for a UK Clinical Phage Service

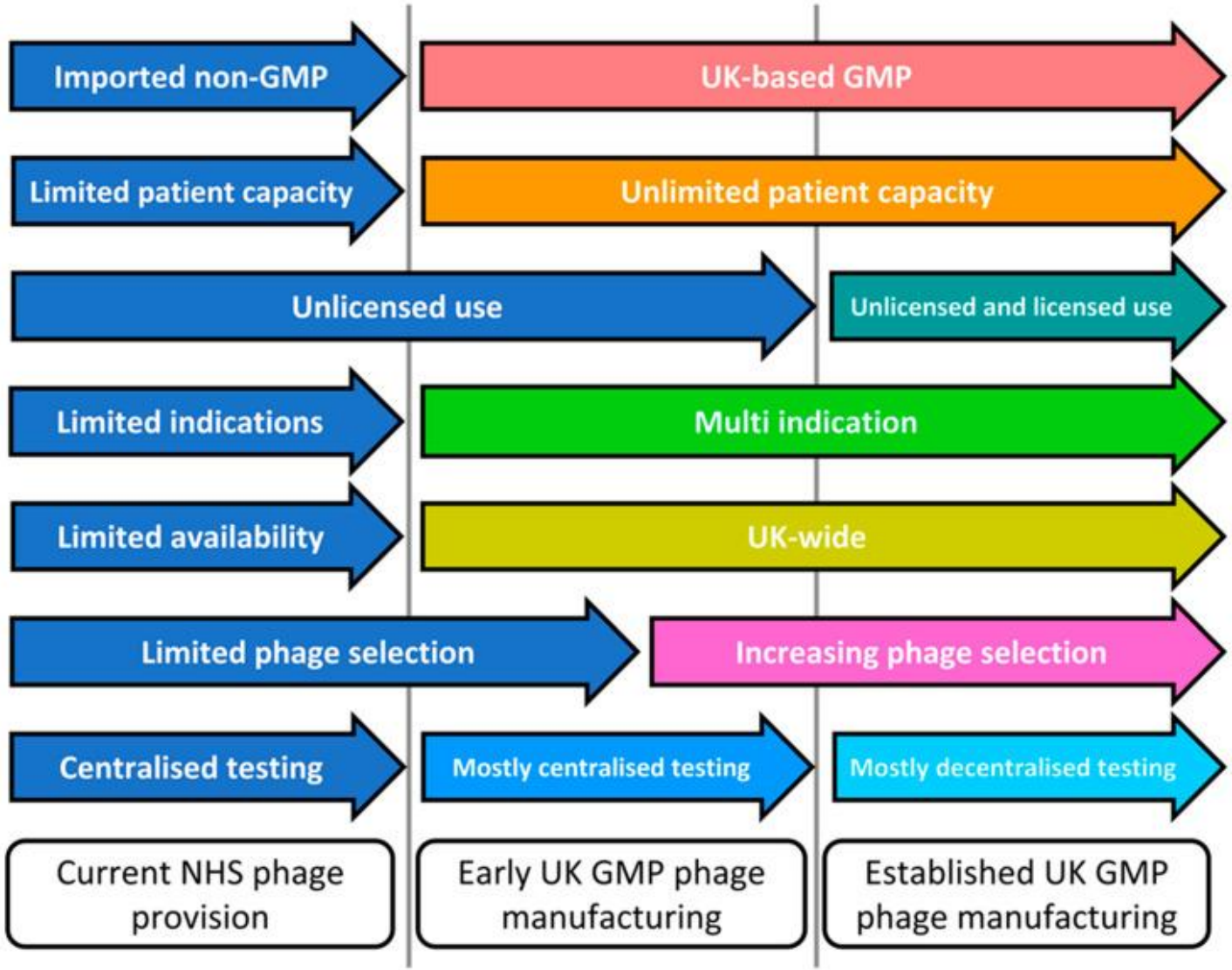


Aseptic considerations of bacteriophages

- Where is the preferred place for preparation and administration?
  - In operating theatre within the sterile field prior to administration
  - Phages are sterile-filtered and sterility-tested, so the main risk is open handling/mixing.
  - Pooling multiple phages into one syringe should be formally risk assessed (SPS ATMP tools) and if required, ideally done in a pharmacy aseptic unit compliant with QAAPS/Section 10 standards.
- How do you clean a laminar flow cabinet?
  - Chlorine-releasing agents probably needed but no standard
  - Follow the SOP in any clinical trial
- How do you dispose of equipment used for administration
  - Disposables are treated as contaminated clinical waste (yellow/orange bags and sharps).

Summary of Bacteriophage Therapy

- Bacteriophages have been used for more than a century
- Routinely used in the food industry
- Have a potential role in chronic infections non-responsive to antibiotics
- Phages are bacterial strain specific
- Limited or no patient harm
- Limited evidence from RCTs but many currently underway
- **No licensed products** currently available
- Very limited use in patients with no remaining treatment options
- MHRA guidance on obtaining phages
- Plans for a UK Phage Therapy Service led by UKHSA
- Phage therapy will be coming but timescales unclear



https://pubmed.ncbi.nlm.nih.gov/36992430/