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## **Between Centralisation and Fragmentation – the past, present, and future of phage collections.**

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### **Abstract**

Despite over a century of collecting bacteriophages, there has been a persistent lack of interest in systematically cataloguing resulting phage banks. The result was a situation in which the ongoing growth of phage infrastructures was paralleled by an increasing fragmentation of knowledge about collections' contents – and existence. Over the last two decades, renewed interest in phage therapy and phage biology has further exacerbated confusion amidst a rapid increase in the number of large and small phage collections and an ongoing dearth of coordination and standardized cataloguing. Whatever the modalities (isolated phages or genomes), the time has undoubtedly come to create sustainable, interconnected, and equitable phage banking infrastructures. This article reviews both the history and current status of microbial collections, provides a non-exhaustive overview of relevant phage collections, and reflects on the challenges and potential of centralizing

therapeutically relevant collections ahead of likely paradigm shifts caused by synthetic biology and artificial intelligence.

**Keywords:** Bacteriophages, Microbial Culture Collections, Phage Banks, Cataloguing, Centralization.

## **Introduction**

Microbial culture collections and phage banks are an essential infrastructure underpinning modern microbiology and biotechnology. However, despite decades of systematised use of phages for research, epidemiological, and therapeutic purposes, and the ongoing surge of interest in new antibacterial applications, there is no comprehensive international inventory of phage banks. Phage collections do have some specific features that need to be highlighted. Due to the very nature of phages and their long co-evolutionary relationships with bacteria, each phage isolated, identified and then stored in a bank is the result of specific interactions with a given bacterium. A phage that enters a collection is therefore a snapshot, at time, of a relationship between that phage and the host bacterium from which it was isolated (1) (see also Brives et al. in this issue). This is why a collection of phages is now systematically accompanied by the collection of bacteria used to isolate them. This is an important detail when it comes to coordinating efforts to produce centralized collections. Here, we review the history of phage banks and microbial culture collections (Part One), provide an overview of current phage banks (Part Two), and finally reflect on the potential of centralizing therapeutically relevant collections of phages (Part Three).

### **From curiosities to essential resources – a history of phage collecting.**

Questions over the degree to which phage collections should be centralized have been regularly debated since bacteriophages' discovery. While university and industrial culture collections of bacteria and fungi such as the Prague Král collection emerged during the 1890s, the 20<sup>th</sup> century saw growing international recognition of the strategic and economic importance of reliable access to well-described microbial material (2, 3). After World War One, there was a boom in the foundation, professionalization, and interlinkage of culture collections across high-income countries (4). For example, the National Collection for Type Cultures (NCTC) in Britain was created in 1920 to secure reliable access to reference strains.<sup>[1]</sup> In the US, the American Type Culture Collection (ATCC) was founded in 1925 and initially supported by the Rockefeller Foundation to consolidate existing microbial collections and support the development of American biomedical research and industry (5). In Japan, multiple smaller industrial and public microbial culture collections emerged as part of intensifying efforts to find, optimize, and preserve valuable microbial strains (6).

Despite excitement about their therapeutic applications, phages initially played a marginal role in the early growth of culture collections. Many different centers around the world turned to local environments and clinics when it came to isolating phages with diagnostic or therapeutic value. Meanwhile, systematized collection efforts were hampered by controversies about phages' viral or enzymatic nature, difficulties in identifying different phages, and lack of interest in cataloguing existing collections by international research and

health bodies. Consequently, scattered phage collections were maintained in academic and industrial laboratories with varying storage and exchange protocols (7, 8).

A significant increase in the coordination and systematization of phage collection efforts occurred during the 1940s, after the viral status of phages was confirmed. This increase was driven both by phages' use in molecular biology and the advent of bacteriophage-typing – the use of defined sets of phages to phenotype and monitor high-priority bacterial pathogens. In parallel to the post-war expansion of classic microbial culture collections, significant public health interest in phage-typing led to an international proliferation of dedicated phage banks (4). Founded at the Fourth International Congress of Microbiology in Copenhagen in 1947, the International Committee for Enteric Phage Typing (ICEPT) played a crucial role in standardizing protocols for the description, storage, and distribution of international reference sets of enteric-specific phages (9). ICEPT's success inspired the creation of similar phage-typing networks for other pathogens such as *Staphylococcus aureus*. Amidst the contemporary decline of commercial phage therapy ventures in North America and Western Europe (10) (see also Kirchhelle et al. in this special issue), public health phage bank curators such as Kaare Lilleengen and Pierre Nicolle also provided phages and technical know-how to molecular biologists (11)<sup>[2]</sup> and to physicians and veterinarians engaging in phage therapy.<sup>[3]</sup> In communist and socialist countries, public health and research institutes such as the Hirsfeld Institute in Poland, the East German Centre for Experimental Epidemiology, the Eliava Institute in Georgia, and Moscow's Gamaleya Institute also served as important repositories for typing and therapeutic phages (9).

There were also significant improvements in the cataloguing of relevant phage collections. In the field of public health, designation of key phage-typing hubs as reference laboratories by the World Health Organization (WHO) from 1948 onwards upgraded phage banks' prestige and facilitated exchange on their contents (9). Cataloguing of non-medical collections also improved following the Eighth International Congress of Microbiology's 1962 resolution to abandon earlier attempts to establish a central international culture collection in Lausanne in favor of a decentralized information-gathering approach (2). Established in 1963, the World Federation of Culture Collections (WFCC) regularly collected and published information on microbial and phage collections in the fields of research, public health, and industry (2, 9, 12).

Starting in the 1970s, the advent of molecular biology and new intellectual property regimes for biological materials led to significant changes for culture collections and phage banks. The developments were a mixed blessing. On the one hand, collections benefited from new revenue streams resulting from the nascent biotech industry. Their macroeconomic significance was also enhanced following the 1977 Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure and the 1982 US Supreme Court *Diamond vs. Chakrabarty* decision on the patenting of human-made organisms (13, 14). Meanwhile, parallel improvements of information technology reduced cataloguing costs (15). On the other hand, curators had to navigate a significant increase in new bureaucratic requirements as well as legal barriers when it came to exchanging information on these biological materials. They also had to compensate for an accelerating reduction of traditional revenue streams caused by a relative loss of public health interest in phage typing and existing phage banks amidst the rise of molecular typing – with some collections facing existential threats by the end of the 1990s (13).<sup>[4]</sup>

### **State of the field – important phage collections throughout the world.**

Over the past two decades, renewed interest in phage therapy and phage biology has led to growing interest in older phage banks as well as a proliferation of new laboratories working with phages. The result has been a rapid increase in the number of small and large phage collections but a relative lack of coordination and standardisation. In the ongoing absence of a comprehensive international list of relevant collections, the extent of the described boom can be gaged from a survey of phage isolates infecting the high-priority pathogen *Pseudomonas aeruginosa*. Conducted on August 23<sup>rd</sup>, 2023, a PubMed search (Aug 23<sup>rd</sup>, 2023) using “*Pseudomonas aeruginosa* AND phage therapy” and parallel search for *Pseudomonas* phage genomes on the NCBI Virus database ([https://www.ncbi.nlm.nih.gov/labs/virus/vssi/#/virus?SeqType\\_s=Nucleotide&VirusLineage\\_s=Bacteriophage,%20all%20taxids](https://www.ncbi.nlm.nih.gov/labs/virus/vssi/#/virus?SeqType_s=Nucleotide&VirusLineage_s=Bacteriophage,%20all%20taxids)) identified 632 references. Subsequent manual analysis of these references revealed the isolation of *P. aeruginosa* phages with therapeutic potential in at least 37 different countries (Australia, Belgium, Brazil, Canada, China, Denmark, Egypt, Finland, France, Georgia, Germany, Greece, India, Iran, Iraq, Ireland, Israel, Italy, Ivory Coast, Japan, South Korea, Malaysia, Mexico, Netherland, New Zealand, Pakistan, Philippines, Poland, Portugal, Russia, Serbia, Spain, Switzerland, Taiwan, Thailand, UK, and the USA) from the five continents (Africa, America, Asia, Europe, Oceania). Although *P. aeruginosa* is a major clinical target, the situation described for this pathogen can likely be applied to some extent to other bacterial species, particularly those belonging to the ESKAPE family (16). It is therefore likely that several hundreds, if not thousands, of different phages with therapeutic potential are available worldwide.

To make optimal use of these resources, greater coordination and information exchange between phage researchers is highly desirable. In the following, this article draws on the participating authors' expertise to provide a non-exhaustive alphabetical overview of important international phage collections and their respective size. The listed collections are partly service supply culture collections or Bioresource Centers (BRCs), a term that refers to collections with mandatory standards, implemented quality control procedures such as two accepted long-term preservation methods, and in possession of long-term funding. Although funding arrangements differ substantially, BRCs act as custodians of phage diversity, deliver phages for a fee, and may also use their holdings for in-house or external research.

**Australia.** To date >5,000 phages were isolated across the Phage Australia network (<https://www.phageaustralia.org/biobank>). The combined bacterial/phage bank at Westmead Institute for Medical Research is the largest in Australia. It hosts a collection of >300 isolated and curated phages targeting *E. coli*, *Klebsiella pneumoniae* and other coliforms, vancomycin-resistant *Enterococcus*, as well as phages targeting *P. aeruginosa* and *S. aureus* imported from around the world, including partners from Belgium, Denmark, USA, Korea, and Israel. At least 39 phages passed biobanking QA/QC processes and were classified as having therapeutic potentials (17). Also, 14 unique phages are locally produced with several batches made that have passed QA/QC and approved for patient use (18). The first Australian produced phage for patient use dated back in October 2022 at Westmead Hospital and complete eradication of the pathogen has been documented after 90 days of follow up (not published). Currently, >30 adults and children were treated with both GMO and natural phages against *P. aeruginosa*, *Mycobacterium abscessus*, *E. coli*, *K. pneumoniae*,

and *S. aureus* through instillation into drains, IV injection, oral and topical applications, and nebulization (17, 19, 20).

Similarly, the assembly of a phage collection at Monash University has been guided by clinical collaborations to focus on clinically impactful pathogens, particularly understudied pathogens with respect to knowledge of their phage biology. Typically, projects would start with PhD or Honors students, who may spend the first ~3-6 months collating a clinically relevant and genomically representative collection of bacterial isolates, followed by phage isolation and biobanking. The focus was initially on *Acinetobacter baumannii* (21, 22), *Enterobacter cloacae* complex, UTI-associated *E. coli*, and CF-associated *P. aeruginosa*. Most clinical isolates originated from hospitals in Victoria, making the collection of hosts and phages geographically defined. Currently, the collection gathers ca. 140 phages, the genome of 20-40% of them being sequenced. So far, only one phage was used to treat a CF patient with lung infection caused by *Bordetella bronchialis* and a five-phage cocktail against *Enterobacter* is ready for treatment as soon as a patient needs it.

The Phage WA Program (Perth, Western Australia, Australia) has also amassed >2000 phages against *P. aeruginosa*, 40 against *S. aureus*, 70 against *Burkholderia* and 250 against *A. baumannii*. Interesting candidates for therapy were fully characterized including host range, WGS, TEM, stability studies, EOP, growth curves, and receptor studies when relevant.

**Belgium.** One of the most recognized European laboratories working on phage therapy since more than two decades is located at the Queen Astrid Military Hospital in Brussels. This laboratory owes around 200 characterized and therapeutically relevant phages, some of which obtained from donors. Currently, 26 individual phages from this collection and six defined phage cocktails, including two commercially available cocktails (PyoPhage and IntestiPhage) produced by Eliava BioPreparations (Tbilisi, Georgia) were used therapeutically to treat > 100 patients suffering from various infectious diseases (23).

**Canada.** The Félix d'Hérelle Reference Center for Bacterial Viruses hosted at the Université Laval (Quebec City) was founded in 1982. The mission of this infrastructure is to collect, store, and distribute reference phages for research and development activities. This Center is not for phage therapy but mostly for research purposes. To date, the Félix d'Hérelle Center contains over 600 reference phages and more than 450 bacterial strains representing almost 70 bacterial genera and 140 bacterial species. The conserved phages have been carefully selected because of their historical, geographical, taxonomic, agricultural, medical, veterinary, or industrial importance. A list of phages preserved in the infrastructure as well as their relevant characteristics are available in a catalog on a public website ([www.phage.ulaval.ca](http://www.phage.ulaval.ca)). Access to the catalog and database is freely accessible to users via this website. Customers can select phages or bacteria directly on the website and then send their request by email. When selecting biological material, a PDF form is automatically generated, and the client must sign the request before transmission. In fact, the form also contains a generic biological material transfer agreement (MTA). This agreement meets recognized biological transfer standards. It should be noted that the Center is also storing additional sets of phage (not on the web site) from a few scientists that have retired to avoid losing key biological materials. Over the past five years (2018-2022), the infrastructure has distributed 1057 specimens to 326 laboratories located in 36 countries. Among the 326

laboratories, 204 were University laboratories, 59 companies, and 63 government organizations. Recent funding will lead to more phage therapy activities associated with the Center in collaboration with the University of Toronto.

**France.** Félix d'Hérelle was certainly the first scientist who started to collect diverse phages in the early 20th century while working at Pasteur Institute in Paris. However, it remains unclear whether the phages he isolated were formally organized in a collection *per se*. d'Hérelle was involved in the early commercialization of phage products during the 40's-50's, which was subsequently passed to pharmaceutical companies up to late 80's when their production was discontinued. During this period, a parallel supply of therapeutic phages was established for French and overseas physicians and their patients at Pierre Nicolle's enteric reference laboratory at Pasteur Institute, which primarily focused on phage typing (see Kirchhelle et al. in this issue). Therapeutic phage production was moved to Lyon in the 1970s from where it continued into the 1980s (24, 25).[5] Former employees of Pasteur Institute during the 1990s recall that they isolated phages on demand from medical practitioners still aware of the benefit of phages (personal communication to LD). In the early 21<sup>st</sup> century the renewed interest in phage therapy led to the re-initiation of a research program on phages at Pasteur. This activity has generated the isolation of novel phages infecting *P. aeruginosa*, *E. coli*, *K. pneumonia*, and Spirochetes (26-29). Phages infecting *E. coli* (over 100 isolates) and *K. pneumonia* (over 60 isolates) have not been yet formally deposited in the national collection of microorganisms. More broadly in France, during the past decade, phages infecting different bacterial species have been isolated mostly by academic laboratories but also a few companies. More detailed information can be found on the web site of the French phage network ([www.phages.fr](http://www.phages.fr)). Currently, the public-funded project Phag-One located in Lyon led to the isolation of dozens of phages infecting strains of *S. aureus* or *E. coli* with the aim to increase the access to therapeutic phages.

**Georgia.** On its website, the renowned George Eliava Institute of Bacteriophages, Microbiology and Virology claims to have one of the most important bacteriophage collections in the world. The Eliava phage collection currently hosts over 1000 phages active against human, plant, and animal bacterial pathogens (<https://eliava-institute.org/phage-collection/?lang=en>). Since the 1930s, thousands of patients have benefited from phage therapy at Eliava. The spin-off company Eliava BioPreparations is currently producing six standard bacteriophage products that are commercially available (<https://phage.gr/products/?lang=en>) as well as several custom products on demand, for use in human health, veterinary medicine, and environmental care.

**Germany.** The therapeutic use of phages in Germany dates back to the 1920s with commercial preparations marketed from the 1930s onwards (7). After 1945, phage marketing continued on both sides of the Iron Curtain with phages also being used for mass-prophylaxis by the East German state (30). Presently, there are no phage products commercially approved in Germany and all therapeutic phage use is performed under the Article 37 of the Declaration of Helsinki of the World Medical Association (31). Since 1986, the Leibniz Institute DSMZ has been collecting phages. Initially, the phage collection included only the most significant phages described in literature especially for teaching or pure academic purposes but has since been developed to better serve DSMZ's role as a service supply culture collection registered in the WFCC Directory (<https://wfcc.info/membership/memberlist>). DSMZ phage collection efforts were boosted by

the WHO release of its first global survey report on the dramatic emergence of bacterial multidrug resistance (32). As of November 30, 2023, the DSMZ phage bank holds 608 phages targeting many bacterial species, including ESKAPE bacteria. The search for suitable phages can be performed upon justified request by physicians, but delivering phages requires a material transfer agreement that excludes their direct therapeutic application. The institutional focus on maintaining open network avenues towards translational research has given rise to major phage therapy projects such as Phage4Cure (<https://phage4cure.de/en/>), EVREA-Phage (<https://www.dzif.de/en/projekt/evrea-phage>) and PhagoFlow (<https://www.phagoflow.de/en/>). Other therapeutic phage banks in Germany include the Bundeswehr Institute of Microbiology (IMB) in Munich, focusing on multi-drug resistant (MDR) *Klebsiella pneumoniae* strains (<https://www.instmikrobiobw.de/forschung-entwicklung/forschungsschwerpunkte/>) and the German Federal Institute for Risk Assessment (BfR) in Berlin (<https://www.bfr.bund.de/en/home.html>) working on potential application in veterinary medicine.

**Israel.** The Israeli Phage Bank (IBP, <https://www.bacteriophage.news/database/israeli-phage-bank-ipb/>) was established in 2015 with the isolation and characterization of its first phage, EFDG1, targeting *Enterococcus faecalis* at the Dental Medicine Faculty of the Hebrew University (33). The IBP now holds > 500 phages, targeting >35 bacterial species, including human, animals, and plant pathogens as well as environmental bacteria. Additionally, a well-characterized bacterial strain is defined as a “reference strain” for each single phage. The Israeli Phage Therapy Center (IPTC) was established in 2018 from a collaboration between the Dental Medicine Faculty of the Hebrew University and the Department of Clinical Microbiology and Infectious Diseases at Hadassah-Hebrew University Medical Center. IPTC employs selected phages from the IBP collection for therapeutic applications. For example, the *P. aeruginosa* phage PASA16 has been used to treat 16 patients in Israel and worldwide (34-36). Beyond human phage therapy at IPTC, IBP is involved in phage-based initiatives spanning veterinary medicine and agriculture.

**Poland.** The Department of Phage Therapy from the Hirsfeld Institute of Immunology and Experimental Therapy from the Polish Academy of Sciences in Wroclaw owes an extensive collection of 872 phages infecting 16 different bacterial species. For instance, 303 phages target *E. coli* strains and 124 target *K. pneumoniae* (37). To enable the continuation of phage therapy after Poland joined the European Union, the institute opened its own Phage Therapy Unit (PTU) in 2005. PTU's admits patients for phage treatment according to a clinical protocol approved by an independent bioethics committee (<https://hirsfeld.pl/en/structure/iitd-pan-medical-center/phage-therapy-unit/>).

**Switzerland.** Several groups from different geographical parts of Switzerland hold phage collections. The Lausanne University Hospital (CHUV) has a collection of >300 sequenced virulent phages targeting mainly *P. aeruginosa*, *S. aureus*, *K. pneumoniae*, *A. baumannii*, and *E. coli*. This collection has first been gathered at the University of Lausanne (UNIL) starting in 2010 and entrusted to the CHUV in March 2021 to be used in the frame of a phage therapy program currently in development. Three *P. aeruginosa* phages from this collection were recently purified at the Queen Astrid Military Hospital (Brussels, Belgium) and used to treat a patient suffering from a pan-resistant spondylodiscitis in Lyon, France (38). In addition, an extensive collection of phages that mostly infect the strains *E. coli* K-12 and *P. aeruginosa* PAO1 has been established at the Basel University. A subset (i.e. 69 phages out



of several hundreds) of the *E. coli* phage collection has been characterized and referred to as the “BASEL phages” (39). As the BASEL collection contains representatives of the major groups of phages infecting *E. coli*, it can be used to learn more about the different groups of phages to extrapolate to other individual phages which might be used, e.g., for therapeutic purposes. The purpose of this phage collection is therefore not to be a repository of phages for direct therapeutic use but rather to be a resource for basic research in molecular microbiology. The GENPH collection at the University hospital of Geneva (HUG) has around 100 sequenced and characterized phages against clinically relevant *K. pneumoniae* strains, amongst which high-risk MDR clones from worldwide epidemiology, and hypervirulent strains (for instance capsular types K1 and K2). It also possesses a few *P. aeruginosa* phages. The polytechnic federal school of Zürich (ETHZ) originally owned a wide range of phages targeting foodborne pathogens such as *Listeria spp.* and *Salmonella spp.* (>100 phages). This collection extended also more recently to pathogens such as *S. aureus*, *E. coli*, *K. pneumoniae*, and *Enterococcus spp.* for a total of ca. 275 phages, including few genetically modified phages (40). The Bern University Hospital owns a collection of 12 *S. epidermidis* phages, some of which have been collected and isolated from the human skin microbiome (41).

**United Kingdom.** The only publicly available phage collection that currently exists in the UK is held at the National Collection of Type Cultures (NCTC) by the UK Health Security Agency (UKHSA). Due to its close historical association with the UK’s reference laboratories for phage-typing, the NCTC has a collection of over 100 phages (*Campylobacter jejuni*, *S. aureus*, and *Streptococcus agalactiae*) that were deposited between 1950 and 1992 (<https://www.culturecollections.org.uk/products/bacteria/bacteriophages.aspx>). In addition, the Leicester Centre for Phage Research (LCPR) started in early 2023 is working towards establishing a new UK phage biobank (<https://le.ac.uk/research/centres/phage-research#:~:text=The%20Centre%20for%20Phage%20Research,prevent%20and%20treat%20bacterial%20infections>). An additional Citizen Phage Library (CPL) at the University of Exeter has gathered around 200 phages isolates from environmental samples collected by members of the public with phages that target *E. coli*, *P. aeruginosa*, *A. baumannii*, and *K. pneumoniae* (<https://www.citizenphage.com>).

**United States of America.** The US has many phage libraries. The ATCC’s has 341 authenticated phage products, while additional phage banks are based at various universities (University California San Diego (UCSD), Yale University, Texas A&M University as instances), Army research centers (i.e. NAVY Medical Research Center and Walter Reed Army Institute of Research (WRAIR)), and at phage companies (e.g., Adaptive Phage Therapeutics). Many of these libraries are expanding rapidly to cover the ESKAPE pathogens and others as requests are received for (e.g., *Stenotrophomonas maltophilia*, *Burkholderia cepacia*). Some of these emerging libraries are very advanced, such as the SEA-PHAGES library for Actinobacteriophages gathering >15,000 isolates. However, so far, only a few libraries contain virulent phages suitable for phage therapy (<https://phagesdb.org/>).

### **Centralization of phage collections – dream or reality?**

Our noncomprehensive selection of extensive phage collections is indicative of the significant research and clinical interest on bacteriophages. However, the range of described initiatives also highlights the difficulties faced by researchers and clinicians when it comes to rapidly

sourcing effective phages – as well as inefficiencies involved in establishing and maintaining multiple potentially redundant phage bank infrastructures. Moreover, producing phages for therapeutic purposes may also be very challenging in various countries. Could greater centralization of phage collections cut through these Gordian knots?

Although attractive in terms of improved accessibility, availability, and management, the centralization of therapeutic phage collections seems difficult to implement at present. In 2009, an effort was made to create a central phage bank at the DSMZ in Germany dedicated to collecting phages with application potentials. Contributors, however, were scarce and the concept was eventually abandoned. A more recent centralization effort has occurred in the case of IPATH at the University of San Diego, which assembled an international registry involving researchers who have phage libraries for *B. cepacia* in the US, Canada, Israel, and other countries. However, since phage therapy is still not established as a routine clinical practice, it is currently difficult to convince either public or private bodies making the required substantial investments to create or maintain centralized national or continental infrastructures. This situation may well change because of the ongoing rise of antimicrobial resistance (AMR) and the outcomes of numerous ongoing clinical trials of bacteriophages. Ahead of any such centralization, important questions about how to store, to characterize, and to access phages need to be resolved, as does the necessary question of the long-term financial costs of maintaining such an infrastructure, including qualified personnel.

With the burden of drug resistant bacterial infections continuing to rise (42), there is a widely recognized need to widen access to effective antibacterial treatments. Phages could be one of these alternative treatments. International agreements such as the 2010 Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from Their Utilization have tried to create clearer and more equitable demarcations of property (43). However, most phage banks remain located in the Global North and fees to access their contents can be unaffordable to researchers in low-income settings. A second major question surrounds the format of storage. Advances in artificial intelligence for the development of *in silico* models for predicting phage-bacteria interactions (44-48), as well as the development of cell-free phage production systems (49, 50), may eventually enable to dispense with having to store the phage particles (alongside its bacterial host) in favour of a databank of genomes, at least for major pathogens. Such a shift of storage practices would raise complex legal issues relating to intellectual property and would also require the implementation of best practice guidelines in line with the means and methods available, such as those of the OECD for Biological Resources Centers (<https://www.oecd.org/sti/emerging-tech/oecdbestpracticeguidelinesforbiologicalresourcecentres.htm>).

In Europe, the recent initiative from the European Directorate for the Quality of Medicines and HealthCare (EDQM) to establish a general chapter on phage therapy active substances and medicinal products for human and veterinary use in Pharmeuropa 35.2 ([https://www.edqm.eu/en/home/-/asset\\_publisher/wQkauHDDLDSk/content/public-consultation-on-new-general-chapter-on-phage-therapy-active-substances-and-medicinal-products-for-human-and-veterinary-use-in-pharmeuropa-35.2](https://www.edqm.eu/en/home/-/asset_publisher/wQkauHDDLDSk/content/public-consultation-on-new-general-chapter-on-phage-therapy-active-substances-and-medicinal-products-for-human-and-veterinary-use-in-pharmeuropa-35.2)) and from the European Medicines Agency to establish scientific guidelines for the quality, safety, and efficacy of bacteriophages as veterinary medicines (<https://www.ema.europa.eu/en/quality-safety-efficacy-bacteriophages-veterinary-medicines-scientific-guideline>) will be of crucial help to

establish such best practices guidelines. However, further international coordination with partners beyond Europe will also be necessary.

Whatever the modalities, such centralized banks could also represent a tremendous opportunity to develop phage research in new directions. Indeed, access to information such as geographical location, date of collection, and type of samples could enable detailed study of phage and bacterial evolution, using phylogenetic analyses for example, or in-depth exploration of phage-bacteria interactions as a function of specific and/or conserved parameters. Centralizing information on characterized phage-bacteria pairs from different environments and times, would undoubtedly be also a formidable tool for scientific research. With interest in phage therapy at an historical high, the time to create sustainable, interconnected, and equitable phage bank infrastructures is now.

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### **References**

1. Brives C. Pluribiosis and the never-ending microgeohistories. In: Brives C, Rest M, Sariola S, editors. *With Microbes*. Manchester: Mattering Press; 2021. p. 247-67.
2. Uruburu F. History and services of culture collections. *International Microbiology*. 2003;6:101-3.
3. Gallay-Keller M. Conserver et exposer les microbes au tournant du XXe siècle. Le cas de la première collection microbienne de l'Institut Pasteur. *Revue d'anthropologie des connaissances*. 2021;15(15-3).
4. Strasser BJ. *Collecting Experiments: Making Big Data Biology*: University of Chicago Press; 2019.
5. Clark WA, Geary DH. The Story of the American Type Culture Collection—Its History and Development (1899–1973). *Advances in applied microbiology*. 17: Elsevier; 1974. p. 295-309.
6. Lee V. *The Arts of the Microbial World: Fermentation Science in Twentieth-Century Japan*: University of Chicago Press; 2021.
7. Kirchhelle C. The forgotten typers: the rise and fall of Weimar bacteriophage-typing (1921–1935). *Notes and Records*. 2019.
8. Summers WC. Bacteriophage Therapy. *Annual Review of Microbiology*. 2001;55:437-51.
9. Kirchhelle C, Kirchhelle CEM. Northern Normal – Laboratory Networks, Microbial Culture Collections, and Taxonomies of Power (1939-2000). *ESTS*. 2024.
10. Summers WC. The strange history of phage therapy. *Bacteriophage*. 2012;2(2):130-3.
11. Zinder ND, Lederberg J. Genetic exchange in Salmonella. *Journal of bacteriology*. 1952;64(5):679-99.
12. Smith D. Culture collections over the world. *International Microbiology*. 2003;6(2):95-100.

13. Kirsop B, Sncath PHA. The current status of culture collections and their contribution to biotechnology. *Critical Reviews in Biotechnology*. 1984;2(4):287-314.
14. Rasmussen N. *Gene Jockeys: Life Science and the Rise of Biotech Enterprise* is a book by Nicolas Rasmussen. Johns Hopkins University Press: Baltimore; 2014.
15. Malik KA, Claus D. Bacterial culture collections: their importance to biotechnology and microbiology. *Biotechnology and Genetic engineering reviews*. 1987;5(1):137-98.
16. Pendleton JN, Gorman SP, Gilmore BF. Clinical relevance of the ESKAPE pathogens. *Expert review of anti-infective therapy*. 2013;11(3):297-308.
17. Lin RC, Sacher JC, Ceysens P-J, Zheng J, Khalid A, Iredell JR, et al. Phage Biobank: present challenges and future perspectives. *Current Opinion in Biotechnology*. 2021;68:221-30.
18. Khatami A, Foley DA, Warner MS, Barnes EH, Peleg AY, Li J, et al. 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. *BMJ open*. 2022;12(12):e065401.
19. Fajardo-Lubian A, Venturini C. Use of Bacteriophages to Target Intracellular Pathogens. *Clinical Infectious Diseases*. 2023;77(Supplement\_5):S423-S32.
20. Bosco K, Lynch S, Sandaradura I, Khatami A. Therapeutic Phage Monitoring: A Review. *Clinical Infectious Diseases*. 2023;77(Supplement\_5):S384-S94.
21. Altamirano FLG, Kostoulias X, Subedi D, Korneev D, Peleg AY, Barr JJ. Phage-antibiotic combination is a superior treatment against *Acinetobacter baumannii* in a preclinical study. *EBioMedicine*. 2022;80.
22. Gordillo Altamirano F, Forsyth JH, Patwa R, Kostoulias X, Trim M, Subedi D, et al. Bacteriophage-resistant *Acinetobacter baumannii* are resensitized to antimicrobials. *Nature microbiology*. 2021;6(2):157-61.
23. Pirnay J-P, Djebara S, Steurs G, Griselain J, Cochez C, De Soir S, et al. Retrospective, observational analysis of the first one hundred consecutive cases of personalized bacteriophage therapy of difficult-to-treat infections facilitated by a Belgian consortium. *medRxiv*. 2023:2023.08. 28.23294728.
24. Grimont P, Grimont F, Lacut J, Issanchou A, Aubertin J. Treatment of a case of endocarditis caused by *Serratia* with bacteriophages. *La Nouvelle Presse Medicale*. 1978;7(25):2251-.
25. Nicolle P. A propos de la thérapeutique par les bactériophages. *Bulletin de l'Académie nationale de médecine*. 1979;163(1):58-60.
26. Henry M, Bobay L-M, Chevallereau A, Sausseureau E, Ceysens P-J, Debarbieux L. The search for therapeutic bacteriophages uncovers one new subfamily and two new genera of *Pseudomonas*-infecting Myoviridae. *PloS one*. 2015;10(1):e0117163.
27. Dufour N, Clermont O, La Combe B, Messika J, Dion S, Khanna V, et al. Bacteriophage LM33\_P1, a fast-acting weapon against the pandemic ST131-O25b: H4 *Escherichia coli* clonal complex. *Journal of Antimicrobial Chemotherapy*. 2016;71(11):3072-80.
28. Lourenço M, Osbelt L, Passet V, Gravey F, Megrian D, Strowig T, et al. Phages against Noncapsulated *Klebsiella pneumoniae*: Broader Host range, Slower Resistance. *Microbiology Spectrum*. 2023:e04812-22.
29. Schiettekatte O, Vincent AT, Malosse C, Lechat P, Chamot-Rooke J, Veyrier FJ, et al. Characterization of LE3 and LE4, the only lytic phages known to infect the spirochete *Leptospira*. *Scientific reports*. 2018;8(1):11781.

30. Leupold FG. Die Geschichte des VEB Serum-Werk Bernburg von 1954 bis 1990 unter besonderer Berücksichtigung biogener Arzneistoffe. 2018.
31. Willy C, Bugert JJ, Classen AY, Deng L, DÜchting A, Gross J, et al. Phage Therapy in Germany—Update 2023. *Viruses*. 2023;15(2):588.
32. WHO. Antimicrobial resistance: global report on surveillance. Geneva: World Health Organization; 2014.
33. Yerushalmy O, Khalifa L, Gold N, Rakov C, Alkalay-Oren S, Adler K, et al. The Israeli phage bank (IPB). *Antibiotics*. 2020;9(5):269.
34. Onallah H, Hazan R, Nir-Paz R, Brownstein MJ, Fackler JR, Hopkins R, et al. Refractory *Pseudomonas aeruginosa* infections treated with phage PASA16: A compassionate use case series. *Med*. 2023;4(9):600-11. e4.
35. Sharma A, Ruch B, Alwatari Y, Gupta A, Albuquerque F, Cotterell A, et al. Dissection of External Iliac Artery During Pediatric En bloc Kidney Transplant: Successful Rescue and Reimplant. *Experimental and clinical transplantation: official journal of the Middle East Society for Organ Transplantation*. 2022;20(5):526-30.
36. Paul K, Merabishvili M, Hazan R, Christner M, Herden U, Gelman D, et al. Bacteriophage rescue therapy of a vancomycin-resistant *Enterococcus faecium* infection in a one-year-old child following a third liver transplantation. *Viruses*. 2021;13(9):1785.
37. Coffey A, Buttner C. *Bacterial Viruses: Exploitation for Biocontrol and Therapeutics*: Caister Academic Press; 2020.
38. Ferry T, Kolenda C, Laurent F, Leboucher G, Merabishvili M, Djebara S, et al. Personalized bacteriophage therapy to treat pandrug-resistant spinal *Pseudomonas aeruginosa* infection. *Nature communications*. 2022;13(1):4239.
39. Stamatiou K, Vagnarelli P. Chromosome clustering in mitosis by the nuclear protein Ki-67. *Biochemical Society Transactions*. 2021;49(6):2767-76.
40. Du J, Meile S, Baggenstos J, Jäggi T, Piffaretti P, Hunold L, et al. Enhancing bacteriophage therapeutics through in situ production and release of heterologous antimicrobial effectors. *Nature Communications*. 2023;14(1):4337.
41. Valente LG, Pitton M, Fürholz M, Oberhaensli S, Bruggmann R, Leib SL, et al. Isolation and characterization of bacteriophages from the human skin microbiome that infect *Staphylococcus epidermidis*. *FEMS microbes*. 2021;2:xtab003.
42. Murray CJ, Ikuta KS, Sharara F, Swetschinski L, Aguilar GR, Gray A, et al. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *The Lancet*. 2022;399(10325):629-55.
43. Scott D, Berry D, editors. Genetic resources in the age of the Nagoya Protocol and gene/genome synthesis. Report and analysis of an interdisciplinary workshop. 2018: University of Edinburgh.
44. Delattre R, Seurat J, Haddad F, Nguyen T-T, Gaborieau B, Kane R, et al. Combination of in vivo phage therapy data with in silico model highlights key parameters for pneumonia treatment efficacy. *Cell Reports*. 2022;39(7).
45. Zhou F, Gan R, Zhang F, Ren C, Yu L, Si Y, et al. PHISDetector: A tool to detect diverse in silico phage–host interaction signals for virome studies. *Genomics, Proteomics and Bioinformatics*. 2022;20(3):508-23.
46. Yukgehnaish K, Rajandas H, Parimannan S, Manickam R, Marimuthu K, Petersen B, et al. PhageLeads: rapid assessment of phage therapeutic suitability using an ensemble machine learning approach. *Viruses*. 2022;14(2):342.
47. Edwards RA, McNair K, Faust K, Raes J, Dutilh BE. Computational approaches to predict bacteriophage–host relationships. *FEMS microbiology reviews*. 2016;40(2):258-72.

48. Beckler DT, Thumser ZC, Schofield JS, Marasco PD. Reliability in evaluator-based tests: using simulation-constructed models to determine contextually relevant agreement thresholds. *BMC medical research methodology*. 2018;18:1-12.
49. Brooks R, Morici L, Sandoval N. Cell Free Bacteriophage Synthesis from Engineered Strains Improves Yield. *ACS Synthetic Biology*. 2023;12(8):2418-31.
50. Liyanagedera SB, Williams J, Wheatley JP, Biketova AY, Hasan M, Sagona AP, et al. SpyPhage: a cell-free TXTL platform for rapid engineering of targeted phage therapies. *ACS Synthetic Biology*. 2022;11(10):3330-42.

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[1] The National Archives UK, FD 1/985, Medical Research Council – National Collection of Type Cultures (28.05.1920); NCTC did not absorb all collections but became the lead organization in a consortium of collections, from 1947 Britain also attempted to coordinate microbial collection efforts across the British Commonwealth; TNA FD1/2482 Extract from Medical Research Council Minutes (21.11.1947).

[2] Researchers such as Nobel Laureate Joshua Lederberg also frequently corresponded with phage bank directors such as Pierre Nicolle (Paris), E.S. Anderson (London), Theo Scholtens (Utrecht), and Kaare Lilleengen (Stockholm) on ways to work with phages and observations regarding lysogeny and phage resistance, Joshua Lederberg Papers, National Library of Medicine.

[3] Ongoing research by Claas Kirchhelle.

[4] See also ongoing research being conducted by Claas Kirchhelle.

[5] Ongoing research by Claas Kirchhelle.