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Short Communication

Access to phage therapy at Hospices Civils de Lyon in 2022: Implementation of the PHAGE*in*LYON *Clinic* programme

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ABSTRACT

Objectives: To describe the PHAGE*in*LYON *Clinic* programme, set up in 2022 to improve access to phage therapy in France using pharmaceutical-grade phages.
Methods: All phage therapy requests received during 2022 were collected prospectively, and reviewed retrospectively to analyse the decision and the patient care pathway (NCT05883995).
Results: Of 143 requests for phage therapy, the indication was confirmed at a multidisciplinary team meeting for 57 (40%) patients. Forty-four patients were infected with bacteria that could be targeted easily by phages in France. Finally, 33 patients were treated, including 26 at the study institution, through a compassionate access programme or in a clinical trial. The main indication were complex bone and joint infections, endovascular infection and lung infection. In order to manage these patients, 172 pharmaceutical phage cocktails targeting *Staphylococcus aureus* and/or *Pseudomonas aeruginosa* were prepared: 57 for local injection and 99 for intravenous injection. During follow-up, 18 (69%) patients showed a favourable clinical evolution, and six (23%) patients required subsequent phage therapy, either with the same phage with greater exposure, or with a different phage from elsewhere.
Conclusions: Implementation of the PHAGE*in*LYON *Clinic* programme in 2022 was associated with groundbreaking access to phage therapy in France.

Introduction

Some bacterial infections are considered to be difficult to treat as they are associated with biofilm or have few therapeutic options. They may be associated with high risk of death, morbidity or loss of function. The world is facing antimicrobial resistance, representing a 'slow-motion tsunami' considered as a multifaceted challenge and a mix of various bacterial infections at the heart of a silent pandemic [1]. In France, 20-year trends have revealed contrasting effects of antimicrobial resistance for each bacterial species [2]. However, in the French population as a whole, the mortality rate per 100,000 attributable to antimicrobial resistance was 9–<12% in 2021 and is predicted to increase to 18–<21% in 2050 ac-

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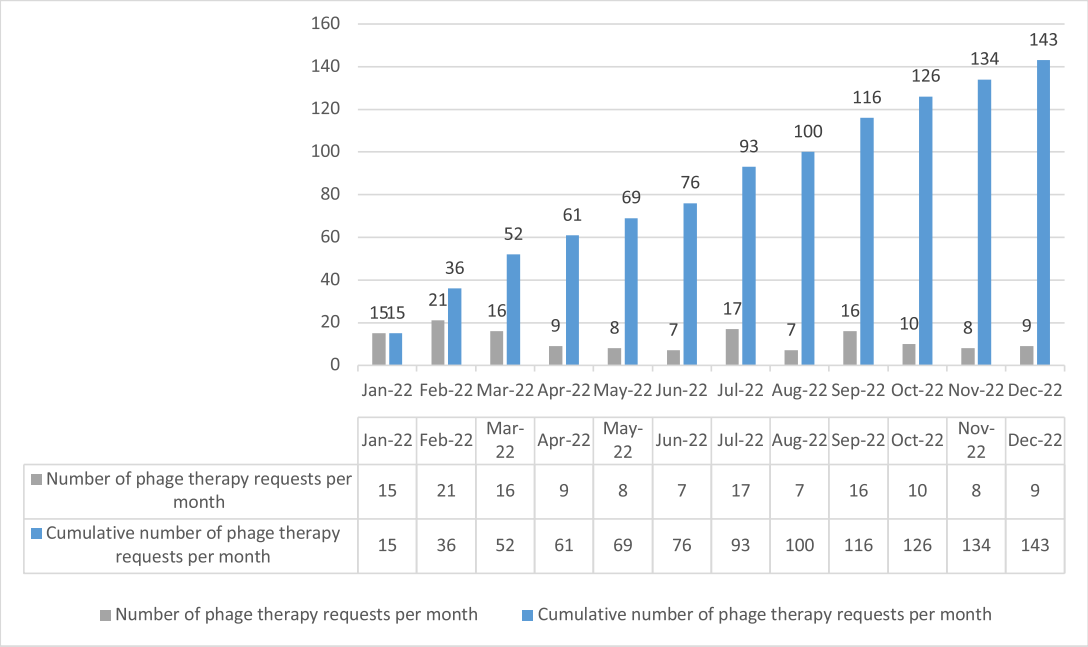


	Jan-22	Feb-22	Mar-22	Apr-22	May-22	Jun-22	Jul-22	Aug-22	Sep-22	Oct-22	Nov-22	Dec-22
Number of phage therapy requests per month	15	21	16	9	8	7	17	7	16	10	8	9
Cumulative number of phage therapy requests per month	15	36	52	61	69	76	93	100	116	126	134	143

Fig. 1. Cumulative number of phage therapy requests [39% made by an external physician, 37% by the patient, 19% by an infectious disease physician from Hospices Civils de Lyon (HCL), and 2% by the patient's family] received by HCL in 2022 through the PHAGE*in*LYON *Clinic* programme.

cording to the results of a global survey, highlighting the worrying trend in the burden of antimicrobial resistance in people aged >70 years in parallel with the overall aging of the population [3].

Virulent (lytic) bacteriophages ('phages' for short) are natural viruses that have the ability to target, replicate in and, in theory, destroy a specific bacterial population. In 2020, the World Health Organization stated that phages are promising non-traditional therapies, and the European Society of Clinical Microbiology and Infectious Diseases created a dedicated study group on their development (ESCMID Study Group on Non-Traditional Antibacterial Therapy) [4].

Phage therapy has existed in the countries of Eastern Europe for decades, and several centres have been created recently, especially as pharmaceutical-grade phages can now be produced and used safely via the intravenous route [5–10]. In 2017, a phage therapy centre dedicated to complex bone and joint infection (BJI) was implemented at Hospices Civils de Lyon (HCL), France through the referral centre [Centre de Référence des Infections Ostéoarticulaires complexes (CRIOAc Lyon); https://www.crioac-lyon.fr/en] [11]. In 2022, the PHAGE*in*LYON *Clinic* programme was launched. This aims to facilitate and reduce the time required to access phage therapy in France to treat relapsing and/or difficult-to-treat bacterial infections that are considered life- or function-threatening. This paper reports on the 1-year experience of the PHAGE*in*LYON *Clinic* programme, the process to access phage therapy in France, and the pathway for patients for whom phage therapy was considered.

Methods

The French Agency for the Safety of Health Products (ANSM) dictates that clinical trials are mandatory for the development of evidence-based medicine. When patients cannot be enrolled in clinical trials, ANSM can consider compassionate use under exceptional circumstances, such as life-threatening disease or if the functional prognosis is highly compromised; the pathway is then managed by a multidisciplinary team. Since 1 July 2021, Haute Autorité de Santé has granted early access authorization for innovative medicines, under the supervision of ANSM, as they have presumed efficacy and safety (Supplementary Figure 1) [12]. This request could be via the 'Compassionate Prescription Framework' (CPF; 'Cadre de Prescription Compassionnelle' in French) or an individual 'Compassionate Access Authorization' (CAA; 'Autorisation d'Accès Compassionel' in French), depending on the off-label use status of a drug that has completed development or depending on the stage of development if the medication is still in development. In 2022, a private company, Pherecydes Pharma (Phaxiam since 2023) developed two phages targeting *Staphylococcus aureus* and four phages targeting *Pseudomonas aeruginosa*. All were available in the CPF, and in May 2022, Phaxiam launched a randomized clinical trial [PhagoDAIR I (NCT05369104)] for *S. aureus* infection of knee and hip prosthetic joints, and acquired the status of CAA for these latter phages.

The PHAGE*in*LYON *Clinic* programme was set up at HCL in 2022: (i) to centralize requests, which were evaluated clinically by experts who had to conclude if there was a relevant clinical indication for phage therapy, at the time of decision, for each patient; (ii) to facilitate and reduce the time needed to access the phages available in France; (iii) to support the prescriber and the patient to obtain phage therapy in the shortest time possible; and (iv) to try to find alternatives to phages if phages were not available (especially if other innovative clinical trials were available), or to find alternatives in the case of phage therapy failure. Evaluations were made during dedicated BJI multidisciplinary meetings at CRIOAc Lyon for all patients with BJI (with infectiologists, orthopaedic surgeons, plastic surgeons and microbiologists), and during multidisciplinary meetings dedicated to phage therapy (with infectious disease specialists, microbiologists and pharmacists) for all patients.

During 2022, phage therapy requests at HCL were collected prospectively and answered. These were analysed retrospectively. Data collection methods for patients treated at HCL are detailed in Supplementary Table S1.

Results

Phage therapy requests

Demographics

In 2022, 143 requests for phage therapy were made to HCL (Fig. 1). The majority of requests came from France (92%), but some were received from the USA (n=2), Canada (n=1), Israel (n=1),

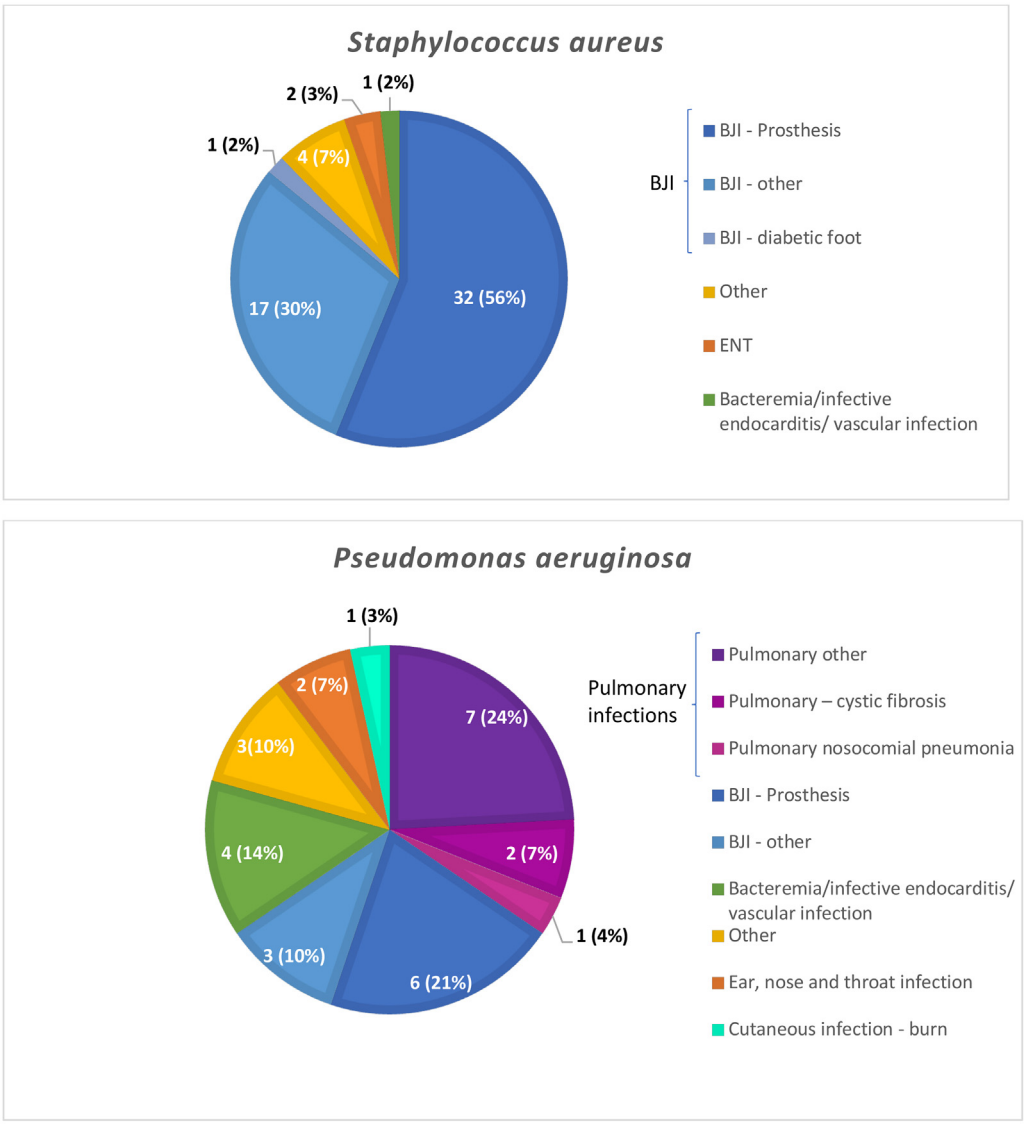


Fig. 2. Proportion of the different types of infection due to the two most prevalent bacteria in patients for whom a phage therapy request was received at Hospices Civils de Lyon in 2022. Notes: BJI, Bone and Joint Infection; ENT: Ear, nose and throat infection.
Notes: BJI, Bone and Joint Infection; ENT: Ear, nose and throat infection.

Germany (n=1), Switzerland (n=1), Luxembourg (n=1), Monaco (n=1) and Italy (n=1). Thirty-two percent (n=45) of the requests came from the Auvergne-Rhône-Alpes region (8 million inhabitants) where CRIOAc is located, but more requests (n=62; 44%) came from other regions of France. Detailed information is not available for the origin of 33 (24%) requests.

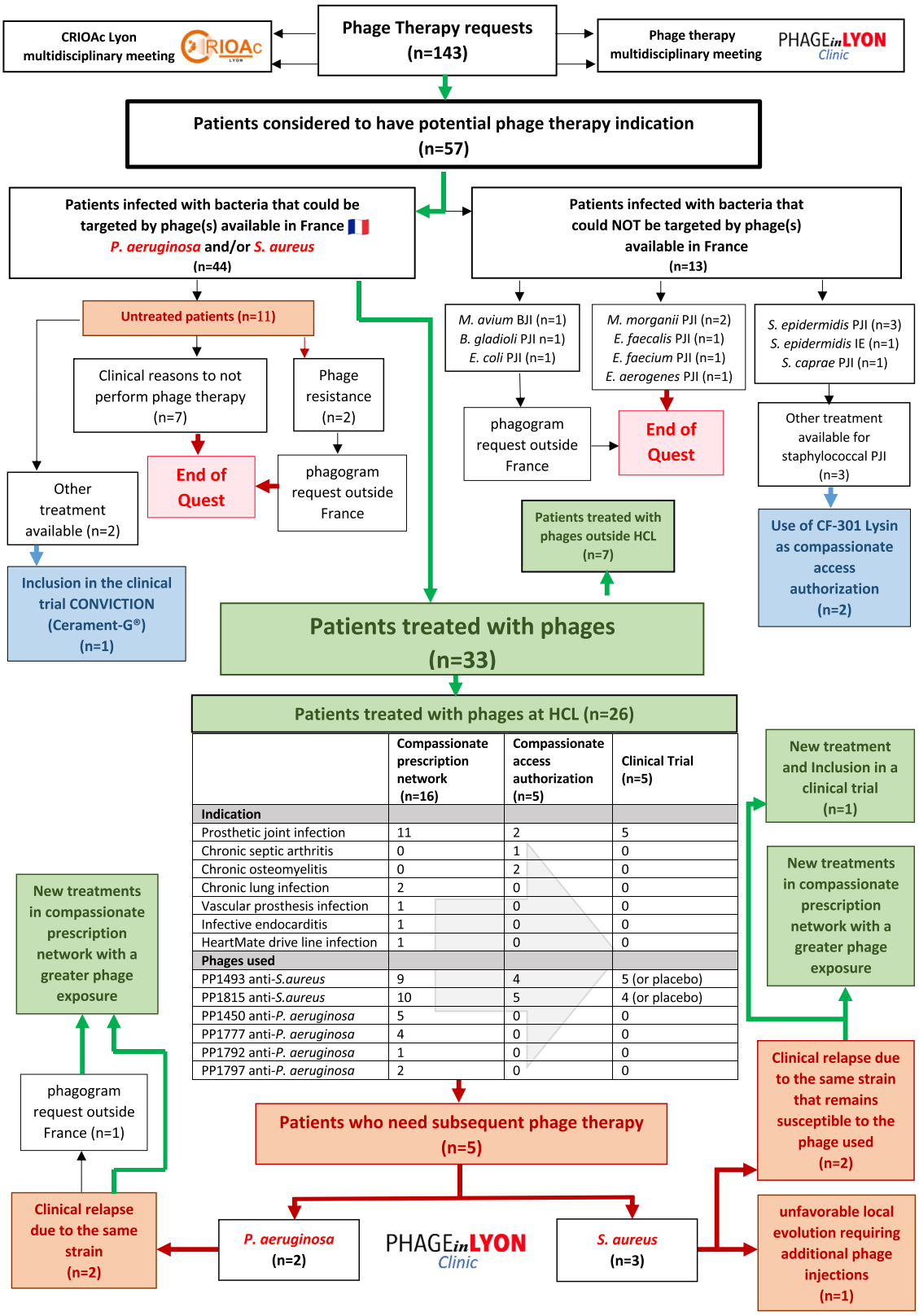
Infectious diseases and bacterial pathogens

The type of infection and type of bacteria involved are presented in Table 1 and Supplementary Table S2. Unsurprisingly, the most common indication for a phage therapy request was BJI (61%), including knee and hip prosthetic joint infection (PJI); followed by pulmonary infection (10%), including cystic fibrosis, pneumonia and other pulmonary infection; urinary infection (5%); and bacteraemia/infective endocarditis/vascular infection (4%). *S. aureus* was the most prevalent bacteria involved in the infections, affecting 35% of cases, followed by *P. aeruginosa*. Fig. 2 shows the proportions of these two bacteria in the different types of infection. Of note, 73% of the infections were due to a single bacterium.

Among the 143 requests for phage therapy received in 2022, 57 (40%) were considered to be indicated for phage therapy at the time of discussion in multidisciplinary meetings. Their pathways are presented in Fig. 3.

Thirteen cases were infected with bacteria that could not by targeted by phage(s) available in France and were not treated (Fig. 3). Of note, some patients with coagulase-negative staphylococci PJI, for whom no phages were available, were ultimately treated with CF-301, a phage-derived enzyme, as compassionate use under arthroscopy, as described previously [13].

Forty-four patients with an indication for phage therapy were infected with bacteria that could be targeted by phages available in France [i.e. *S. aureus* (n=28) or *P. aeruginosa* (n=16)]. To determine whether or not the phages developed by Phaxiam were active, isolates were sent to Phaxiam to perform the phagogram, as described previously [14]. Eleven patients remained untreated. Interestingly, one patient with osteomyelitis and an indication for phage therapy was finally included in a clinical trial evaluating antibiotic-loaded bone substitutes [CONVICTION clinical trial (NCT04805164)] [15].



	Compassionate prescription network (n=16)	Compassionate access authorization (n=5)	Clinical Trial (n=5)
Indication			
Prosthetic joint infection	11	2	5
Chronic septic arthritis	0	1	0
Chronic osteomyelitis	0	2	0
Chronic lung infection	2	0	0
Vascular prosthesis infection	1	0	0
Infective endocarditis	1	0	0
HeartMate drive line infection	1	0	0
Phages used			
PP1493 anti-*S.aureus*	9	4	5 (or placebo)
PP1815 anti-*S.aureus*	10	5	4 (or placebo)
PP1450 anti-*P. aeruginosa*	5	0	0
PP1777 anti-*P. aeruginosa*	4	0	0
PP1792 anti-*P. aeruginosa*	1	0	0
PP1797 anti-*P. aeruginosa*	2	0	0

Fig. 3. Pathway from the request for phage therapy through the PHAGE*in*LYON *Clinic* programme in 2022. Note: (i) among the 11 untreated patients with clinical reasons not to perform phage therapy, four were lost to follow-up, two had disease progression and one had a clinical situation that was finally considered to be too complex to consider phage therapy. (ii) Primary phage resistance was detected in two patients infected with *Pseudomonas aeruginosa*, and phagogram requests were organized (shipment of the strain) and performed outside France, but no active phages were found. (iii) Phages PP1493, PP1815, PP1450, PP1777, PP1792 and PP1797 were provided by Phaxiam Therapeutics.

Thirty-three patients received phage therapy in 2022, accounting for 60% of patients treated since phage therapy commenced at HCL in 2017 [11,14,16–19]. Among the 33 treated patients, seven were treated outside HCL and 26 were treated at HCL, thanks to the set-up of the PHAGE*in*LYON *Clinic* programme. Details for these 26 patients are presented in Fig. 3. Most of them presented with a PJI, and all of them were treated with phage cocktails: 19 were treated with phages targeting *S. aureus*, five were treated with phages targeting *P. aeruginosa*, and one was treated with both, with modalities and routes of administration that were decided in multidisciplinary meetings.

Patients treated with phage therapy at HCL

Among the patients treated at HCL, most were male (n=16; 61.5%) and the mean age was 65 years. The main indication was BJI (n=21; 80.8%), followed by bacteremia/infective endocarditis/vascular infection (n=2; 7.7%) and pulmonary infection (n=2; 7.7%). The average time from referral to the first dose of phage therapy was 22 days. Most patients were treated with phages that target *S. aureus* (n=19; 73,1%), and six (26.9%) received phages that target *P. aeruginosa*. One patient was treated with both phages; of note, this patient had received phage therapy previously (in 2021) and was treated for a recurrent infection. To manage these patients, 172 pharmaceutical phage cocktails were prepared by the hospital pharmacist in a sterile cabinet: 57 were used for local injections (10 during surgery, 47 during sonography) and 99 were used for daily intravenous injections. The outcome of each patient will be presented in subsequent papers (case reports and case series). Globally, focusing on the bacteria targeted with phages, at follow-up, 18 (69.2%) patients had a favourable clinical evolution after treatment, and eight (30.8%) patients had a recurrent infection or an uncontrolled persistent infection. One patient treated for life-threatening endocarditis died due to rapid progression of the infection during phage therapy. Three patients died due to reasons that were not related to the infection. Three of 18 patients with an initial favourable course experienced the occurrence of a new infection due to another bacterium at the treated site without isolation of the initial pathogen treated with the phages. Five patients required subsequent phage therapy – some with the same phage but with greater exposure (i.e. additional injections with the same concentration), or with a different phage from elsewhere (Fig. 3). The average follow-up of patients with a favourable clinical evolution was 10.6 months (range 2.7–21.4 months). Eight patients were considered to have an uncontrolled persistent or relapsing infection, with the average delay between phage therapy and relapse of 5.8 months (range 0.3–18.2 months).

Discussion

Since implementation of the PHAGE*in*LYON *Clinic* programme in 2022, phage therapy in France has made groundbreaking progress. Among 143 requests for phage therapy received at HCL in 2022, 33 patients were treated through a compassionate access programme or through a clinical trial (Fig. 3). The main indication was complex BJI, and only phages targeting *S. aureus* and/or *P. aeruginosa,* were used. Of note, some patients with potential indications for phage therapy received alternative innovative treatment [13,15]. Most patients responded well to phage therapy, but some needed subsequent phage therapy with greater exposure [20].

The main conditions that facilitated access to phage therapy in France were as follows. First, phage production is, of course, critical, and a French company (Phaxiam Therapeutics) decided to invest in phage therapy in France many years ago. Phaxiam developed phages that target *P. aeruginosa,* and performed its first clinical trial in burn patients in 2019 [21]. Phaxiam also developed phages that target *S. aureus* [22], and launched a clinical trial in patients with PJI in 2022. Close to France, the Queen Astrid Military Hospital in Belgium also has a programme of phage production, which was established in 2017 [9]. This makes importation of phages from Belgium possible, under the supervision of ANSM. The second point is the expertise acquired by CRIOAc, which highlighted the importance of multidisciplinary management to personalize the decision for each clinical situation, and to validate the indication for phage therapy if the patient had a life- or limb-threatening clinical situation and if it was considered that the patient would gain benefit from phage therapy [11]. Dedicated multidisciplinary team meetings were held to decide, when there was an indication for phage therapy, which phage could be used, which route of administration, and at what dilution and dose. The third point is the creation of the dedicated programme for authorization for early access to medicinal products in France. This greatly facilitated improvements in development under the supervision of ANSM, and facilitated access to innovative medications in France, including phage therapy [12]. Of note, similar programmes for development of phage therapy are ongoing in other countries, such as Magistral Phage Preparation in Belgium [23], the Special Access Scheme in Australia [8], and the Expanded Access Scheme in the USA [24].

Thanks to all these innovations and experience acquired in France since 2022, more patients have access to innovative therapies in the field of severe bacterial infections. Of note, for BJI, the development of other non-traditional antibacterials, such as lysins, and the evaluation of particular devices in clinical trials, such as antibiotic-loaded bone substitutes, will help to determine which innovation is the most appropriate for each clinical situation. With greater access to phage therapy in France, more patients will be treated through a compassionate access programme, based on expert evaluation, and more clinical trials will be undertaken to specify which clinical situations are relevant for phage therapy. Part of the PHAGE*in*LYON *Clinic* programme will now have greater access to phages produced by different companies and different academic structures in Europe and beyond, under the supervision of French healthcare authorities, to develop the use of injectable pharmaceutical-grade phages in France.

Centralization of phage therapy requests at national level for each clinical indication that seems to be relevant for phage therapy is an important step. Based on the experience acquired with complex BJI, relapsing PJI in patients for whom prosthesis explantation could be associated with loss of function is relevant. *P. aeruginosa* relapsing lung infections, with or without cystic fibrosis or bronchectasiasis, and ventilator-associated pneumonia also seem to be relevant indications. Finally, patients with endocarditis are also good candidates, especially patients with relapsing prosthetic valve endocarditis for whom surgery could be associated with a high mortality rate. Requests for phage therapy are also centralized in other countries, such as in Australia with the STAMP protocol [8].

Finally, this study found positive results for the efficacy of phage therapy that need to be confirmed by future comparative clinical trials. Before this step, better knowledge of phage pharmacokinetics is required, as few data are available in this field [25]. In addition, better knowledge about optimal exposure and the most appropriate route of administration is required [20,25].

Conclusion

Development of the PHAGE*in*LYON *Clinic* programme in 2022 made groundbreaking progress in access to phage therapy in France. This important milestone in access to pharmaceutical-grade phages was possible thanks to: (i) funding by the French health ministry of expert centres such as CRIOAc; (ii) the development of

private and academic structures that have the ability to produce such phages in France and Belgium; (iii) the national programme of French authorities to improve access to innovative medications, and creation of the CAA pathway; and (iv) the creation of phage therapy multidisciplinary meetings at HCL. Through the multidisciplinary members of the ESCMID Study Group on Non-traditional Antibacterial Therapy, it will be possible for connections to be made between academic and private players, making pharmaceutical-grade phages more accessible (meaning that more phages could qualify for, and be enrolled and reimbursed in a compassionate access programme) and more evaluable for the most relevant clinical indications more than one century since their development by Felix d'Herelle in France.

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Competing interests: TF was investigator coordinator of the PhagoDAIR I Study (funded by Phaxiam; contract with Hospices Civils de Lyon), performed a retrospective cohort study funded by Phaxiam (Retro-PJI; contract with Hospices Civils de Lyon), was investigator coordinator of the CF-301-108 clinical (study funded by Contrafect; contract with Hospices Civils de Lyon), and was investigator coordinator of the CONVICTION Study (promoted by Hospices Civils de Lyon, with the support of Bone Support). SR was investigator of the PhagoDAIR I Study (funded by Phaxiam; contract with Hospices Civils de Lyon), was investigator of the CF-301-108 clinical (study funded by Contrafect; contract with Hospices Civils de Lyon), and was investigator of the CONVICTION Study (promoted by Hospices Civils de Lyon, with the support of Bone Support). The other authors report no competing interests.

Ethical approval: The local ethics committee fully endorsed the approach.

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Author contributions: TF designed the PHAGE*in*LYON *Clinic* programme, managed all the patients, designed the study, and led the multidisciplinary CRIOAc and phage therapy meetings. MLB performed the retrospective collection of the data, and participated in the design of the study. TB prepared phage therapy for all patients, and participated in the phage therapy multidisciplinary meetings. CK and TRG managed the bacterial strains and participated in the multidisciplinary meetings. TP, SR, FA, FV, CJ, SL and CB participated in the CRIOAc multidisciplinary team meetings, and were involved in patient care.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijantimicag.2024.107372.

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